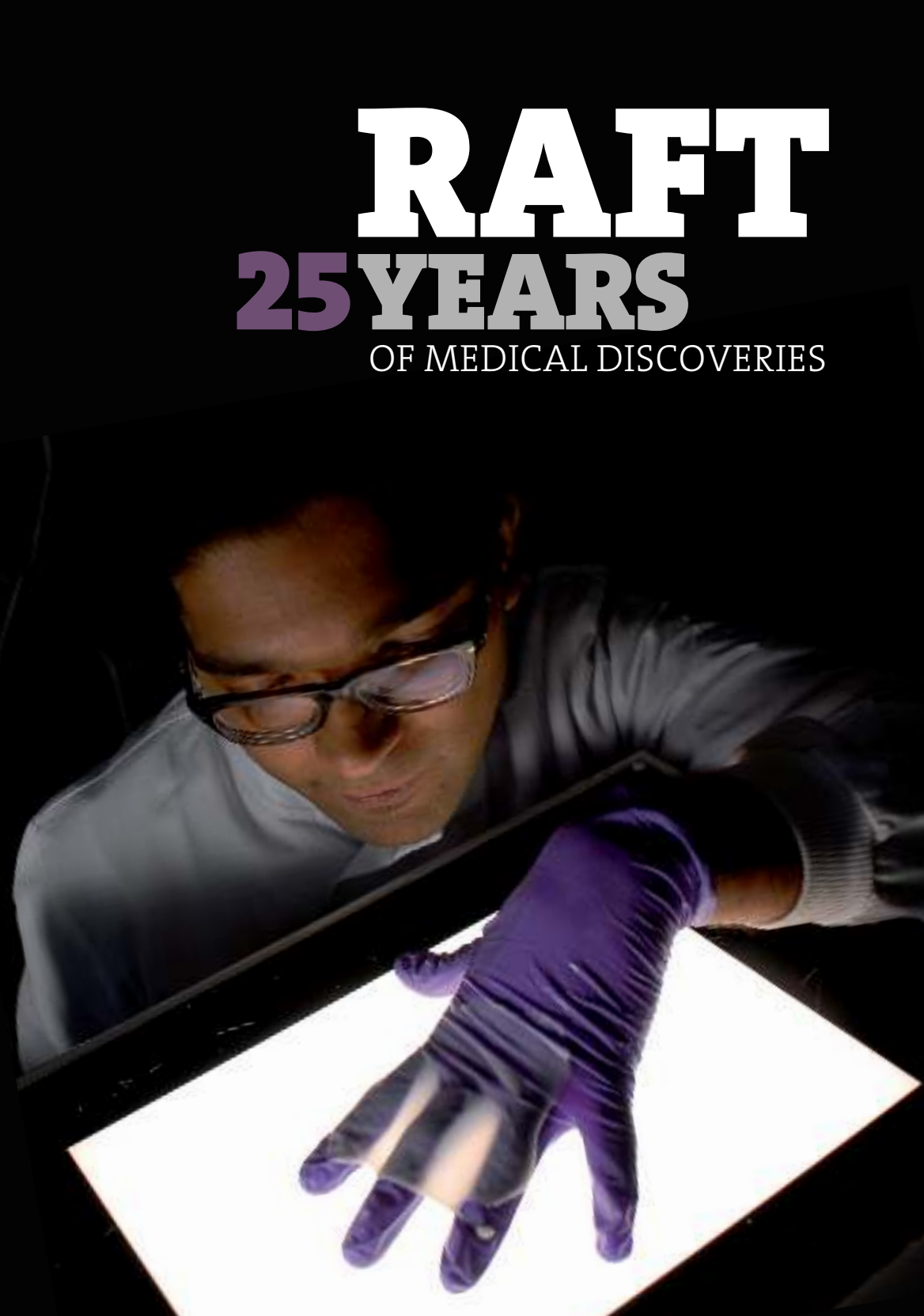
RAFT

25 YEARS

OF MEDICAL DISCOVERIES



The proof is in your hands.

Between these pages you will find confirmation of the amazing success RAFT medical research institute has had over the past 25-years.

RAFT's team of researchers are problem solvers; they consult surgeons and patient groups on the needs of patients – people – and produce innovative medical solutions by carrying out good quality science. Our aim is work with the best in the world to ensure that the people we help are the recipients of the very best and most up-to-date knowledge available.

RAFT works with clinicians and patients; it works with scientists and influencers but our most important partners are those who take an active role in supporting our work – through donations, time, expertise and support. Without them – without you – none of this would be possible.

This book outlines how RAFT's accomplishments have changed the way wounds are treated and have set the benchmark for surgeons worldwide. In it you will read how many of the treatments and practices that are common place today have their origins in RAFT. You may have already been the recipient of RAFT's research without realising it.

Our education programme has created a strong foundation of scientific curiosity and delivery amongst young surgeons and scientists. For example, many of the leading consultant plastic surgeons in the world have trained with RAFT.

While this book highlights the achievements of the last 25-years, RAFT is now thinking about the next quarter of a century. As well as continuing research on areas of clinical need that still need problems solved, we are actively looking at how we can deliver more for people and how we can continue to make a difference.

The proof is in your hands.

Dr Elena Garcia

Dr Yazan Al Ajam

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OF MEDICAL DISCOVERIES

RAFT: 25 years of medical discoveries (1st edition)

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Executive Summary

RAFT is an innovative medical research institute which has a solid 25 year history of delivering success. From the first day it was founded, what has consistently set RAFT apart from other research institutes is an environment where clinicians and scientists work together to bring results from the laboratory bench to the patient's bedside. All our research begins with people and ends with people. Our mission is to solve the everyday problems that face anyone that has suffered a serious injury and come up with a practical solution as an answer.

The institute was established in 1988 by four plastic surgeons working at a UK leading burn centre who wanted to do more for their patients. They were frustrated by what they saw as the lack of continuous collaboration between clinicians and scientific researchers.

A small office in Mount Vernon Hospital, on the outskirts of London, was the birth place of a charity which has since made a significant difference in the fields of restoring skin, repairing tissue and recovering movement and which continues to do so today. We focus on programme results and meet important needs.

Working with leading scientists, surgeons and institutions, RAFT's research has changed the lives of millions of people who have suffered a major injury. RAFT's education programme has allowed young scientists and surgeons to bring fresh thinking into problem solving, whilst provide an important training ground for some of the leading clinicians in practice today.

The quality of the science conducted at RAFT has been internationally recognised at conferences and in published papers. In fact, at one medical conference there was a complaint that RAFT's research was dominating the conference. We take that as a compliment, as well as a sign of how much we have achieved.

This book highlights how RAFT has been instrumental in pioneering the treatment of wounds and major injuries. Amongst our achievements, RAFT has:

- Developed a therapeutic air bed now used in most intensive care units in the world
- Led the way in preventing pressure sores
- Created a national network of skin banks
- Pioneered the early diagnosis of *Staphylococcal toxaemia* in children.

These are only four achievements in a list of nearly 100 that are explained in this book. For us it is not the number of accomplishments that are important, but the knowledge that they have changed the way people with serious injuries have been treated. We know that the quality of life for those affected by burns, injuries, skin cancer, etc has been improved due to RAFT's research. What greater legacy can we ask for in our 25th year?

The book also highlights the importance of our education programme and the impact it has had on the surgical community. At time of printing, we will have appointed our 54th Surgical Research Fellow. These young surgeons give up two or three years of their lives to carry out research for RAFT and the training they receive ignites a life long commitment to research after they leave. A significant number of the leading Consultant Plastic Surgeons practising today have passed through RAFT's doors and still work with us.

Despite a quarter of a century of achievement, RAFT is still striving to do more. We currently have new projects looking at:

- Growing bone to avoid the need for hip replacements
- Improving the reconstruction of breasts after breast cancer – so as to lessen the hospital time for women who have had a mastectomy
- Personalised facial reconstruction using 3-D printing
- Improving the man-machine interface for prosthetic limb wearers so as to make prosthetic limbs more user-friendly and function more like a limb.

We are also in the process of creating a global presence with long term collaborative partnerships around the world, based on the same three principles that has guided RAFT throughout the last 25 years:

1) Meeting clinical need and solving real clinical problems
2) Clinicians and scientists working closely together to come up with solutions
3) Doing research that will get to patients in the quickest time possible.

All of this work would not have been possible without the many people who have helped RAFT's research become a reality – scientists, surgeons, patients, donors.... The list of who has helped us over the years would be too long to reproduce here but the principle remains as true today as it was in 1988. This is a collaborative effort and we hope that you will be inspired to join us in that collaboration.

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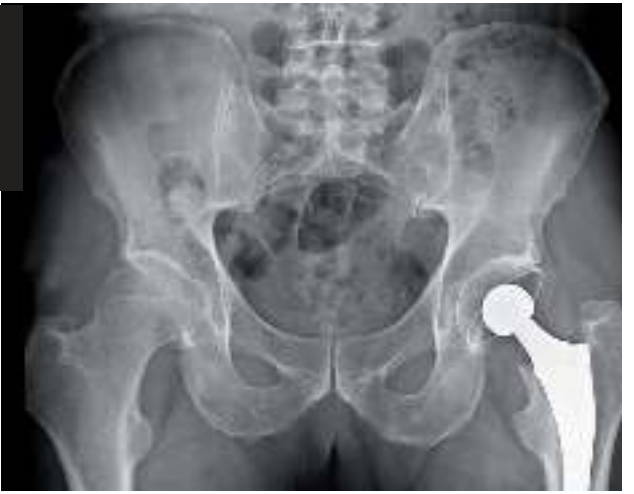
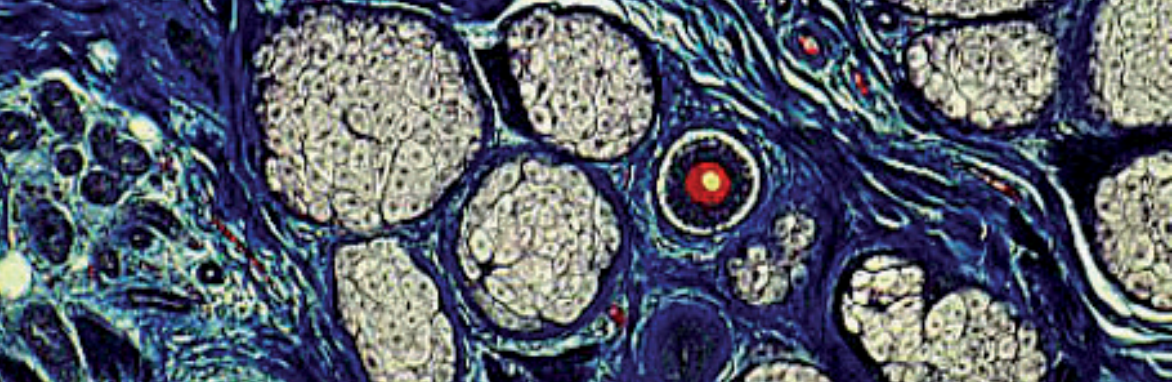
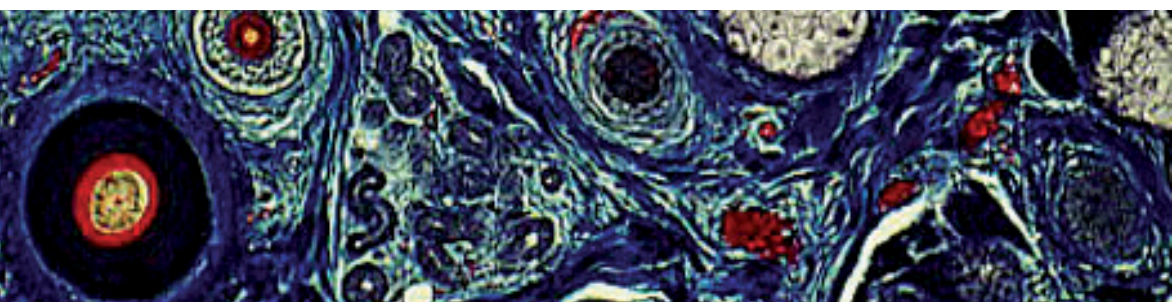
– Professor Roy Sanders


Dr Elena Garcia







Appreciation and Thank-You

We at RAFT would like to thank all of those who have made this book – and the work contained inside – possible.

A most hearty thanks and appreciation must go first to the founders of RAFT; consultant plastic surgeons Mr Roy Sanders, Mr Brian Morgan, Mr Douglas Harrison and Mr Paul Smith. Without their time, effort, personal funds and foresight, RAFT would not be here today.

Professor John Scales, the first director of research, and Sir Robin Chichester-Clark, first chairman of the charity, helped establish the values and pace of research which continue on today.

Thank you to RAFT's Chief Patron, HRH The Duchess of Kent, who has always been an inspiration, especially during RAFT's early years.

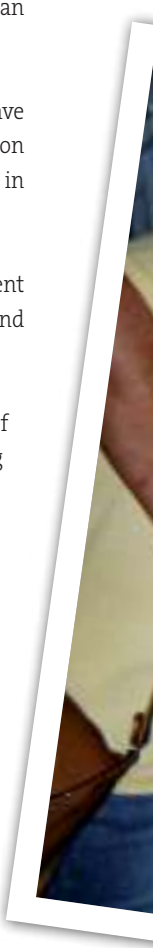
RAFT has had the good fortune to have amazing patrons and trustees over the years who have helped us stay successful. They are too numerous to mention by name, but special mention must be made of Michael Garston, who was instumental with the Leopold Muller Estate in providing RAFT with our building and laboratories.

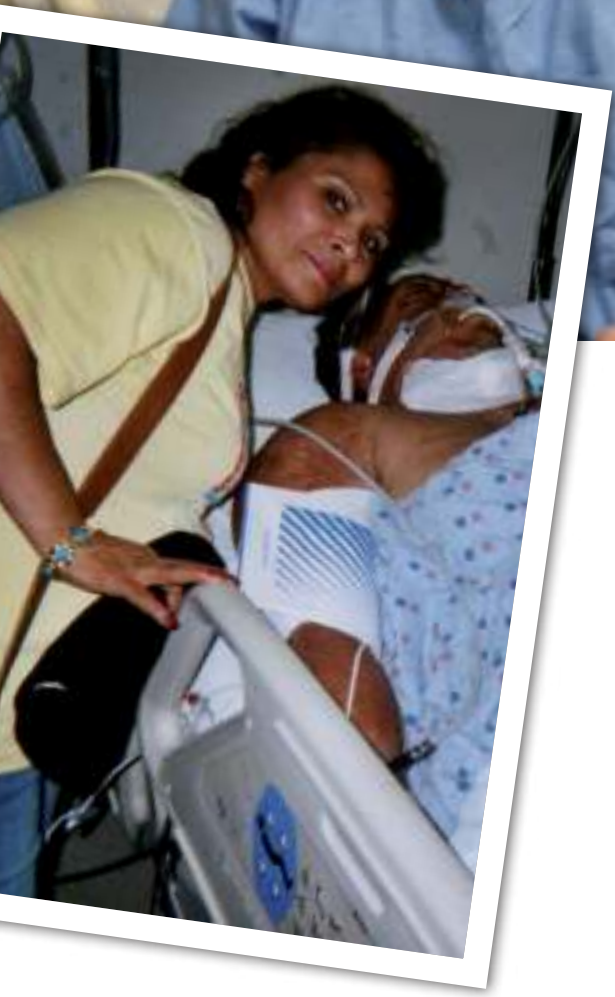
As a charity, which operates without any government support, RAFT is completely dependent on our donors who, big and small, have made all our work possible. Patients – people – around the world who will never know you by name, thank you for making their lives better.

It would be, however, neglectful on our part not to make special mention by name of some of the key donors who have been with us for most of RAFT's journey. These include: Kirby Laing Foundation; Childwick Trust; Garfield Weston Foundation; The Henry Smith Charity; Alan Gaynor Fellowship; Lord and Lady Ashcroft; the London Fire Brigade, and 76 year old Bob Jenkins who has run 18 marathons for RAFT.

Thank you to all of those organisations who have worked in collaboration with RAFT. These include universities, NHS medical centres and international research centres of excellence.

And last but not least a special thanks to all the surgeons and researchers who have put RAFT's values into medical research practice.





Hovercrafts, levitation and the amazing birth of RAFT

You could say it all started with trying to making a patient float in midair. The path which ultimately led to RAFT began when Mount Vernon Hospital in Northwood, England, became a plastic surgery and jaw injury centre in 1953. A burns unit was soon established as well. And with it came the idea of making patients float in midair, according to one of RAFT's founders Professor Roy Sanders.

At that time many burn patients died of sepsis (a whole-body inflammation) because of infection of the burn. To reduce infection, the burnt areas were exposed to the air to dry the injury, which was then less vulnerable to infection.

However, if the burn went around most or all of the body, the side laid upon became wet and remained so due to the massive moisture seepage from the wound. In addition, heat loss was rampant in burn patients.

To get around these two conditions, patient rooms were kept hot to reduce heat loss and to dry the burn more quickly. A so-called Mini Desert was developed and tested on several patients at Mt Vernon. The burns dried more quickly and heat and weight/water-loss was less. Nonetheless wetness and infection still occurred.

Dr John Scales, a biomedical engineer working at the Royal National Orthopaedic Hospital Stanmore, was attending a fair and saw a table-tennis ball being supported on a jet of water. He wondered whether the human body could be supported in a similar manner.

About the same time the hovercraft was being developed and Scales made the link to propose that a body could be supported on an upturned

hovercraft that had been converted into a bed.

Through various stages of development, and with the assistance of Mr Les Hopkins – designer of the flexible skirt of the Hovercraft – a bed was created on which a body could be 'levitated'.

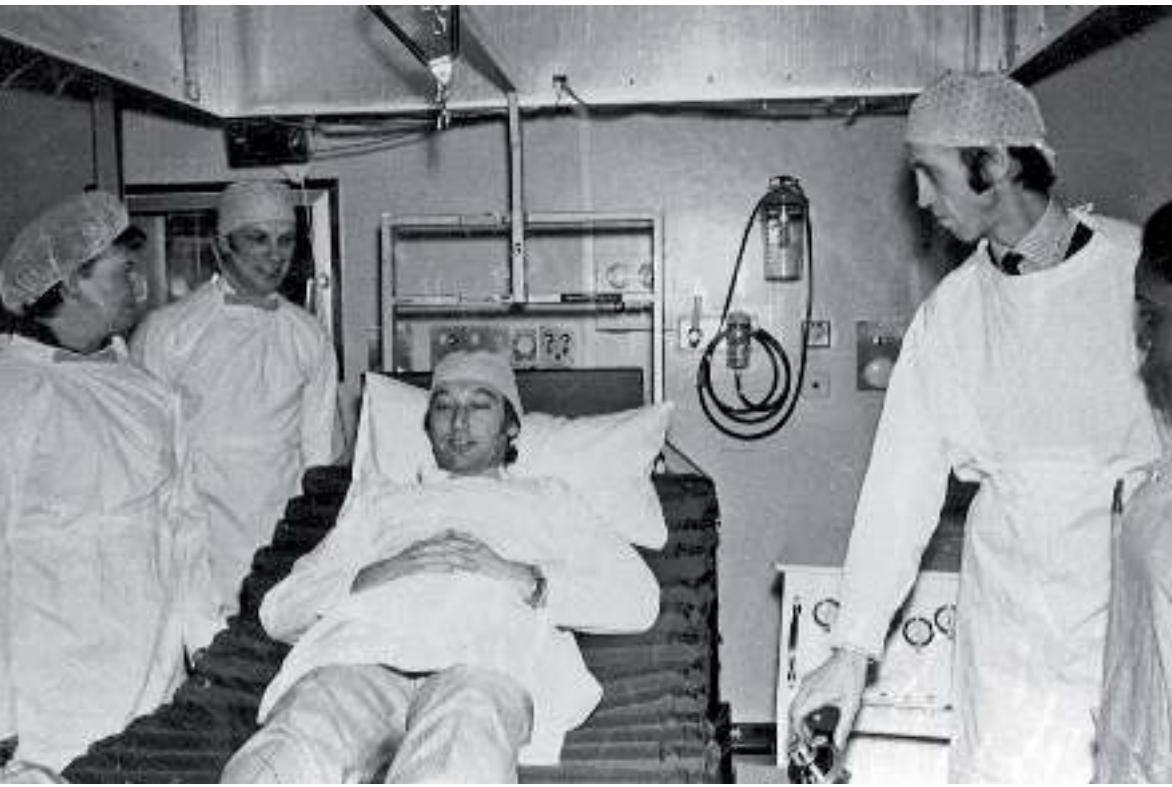
"At this time I was working in orthopaedics at the RNOH when one Saturday afternoon I was walking in the grounds from one ward to another, and heard a massive noise coming from a shed," says Prof Sanders. "I went in to see what was happening and discovered Dr Scales and the prototype of the bed with someone being floated on air. My acquaintance with Dr Scales and air support systems began."

The Medical Research Council supported a limited trial of the bed, and two burnt patients were successfully treated under the supervision of Mr Muir and Dr Scales. The MRC and the National Research development Council funded further development and the MRC supported a further clinical trial of the bed on burnt patients at Mt Vernon Hospital.

"I was working then as a registrar in plastic surgery at MVH, and Mr Muir offered me the appointment of research assistant for two months. I took it and we treated eight patients successfully," he says.

"Hopkins then had the idea of enclosing the skirts of the hovercraft to reduce the air flow but to allow the support of a body by the principle of displacement rather than compression. Scales, Hopkins and I spent all our spare time at Stanmore developing and testing these low-air-loss beds."

The National Research Development Council and the Regional Health Authority agreed to



Professor Roy Sanders (right) with fellow researchers.

fund the construction of a new burns unit at Mt Vernon Hospital. It included another development of that time, the Laminar Air-Flow Enclosures, which had been designed to reduce infection in patients undergoing joint replacement. The MRC agreed to fund a two-year trial of the Hoverbeds and the other two experimental low-air devices .

"I was appointed consultant, Richard Barnett and Jim Khursandi were appointed research registrars, and two research assistants were funded. The grant was for £250,000, a fund administered by the MRC," says Prof Sanders.

"There had been a small departmental fund into which various small donations made by patients were paid. I suggested to the head of the centre that it should be established as a registered charity. It became the Mount Vernon Reconstructive Plastic Surgery Trust. The trustees were the consultants," says Prof Sanders. "Mr Brian Morgan and I put the fees derived from our private patients undergoing treatment for burns or microsurgery into the trust in order to fund the books, journals and surgical instruments for which the BPMF or NHS would not pay."

Adam Topping, Jamie Shelton and Prof. Sanders

Dr Scales retired and was looking for somewhere to continue his research into the development of a 'Phantom', a device resembling the human body which would give information as to pressures developing between bodies and support surfaces which caused bedsores.

"I suggested he should come to occupy a small laboratory space on the plastic surgery corridor and accept the appointment as our unpaid director of research. He accepted, brought limited research funds and a research assistant."

RAFT BEFORE THE NAME

"The funds in the MVHRPS Trust started to accumulated, but the title was cumbersome so Scales and I sought a better acronym," says Prof Sanders. "We first considered GRAFT but thought the rescue meaning within RAFT had a better connotation, subsequently finding The Restoration of Appearance and Function Trust to fit the acronym."

The purpose of the Trust was to be the apposition of Surgery and Science on the same site so that surgeons might present their problems, benefit from the expertise of scientists experienced in the relevant fields, and to train young surgeons in the scientific process. Funds though were not available for this in the beginning and Mr Hamish Laing , RAFT's first Surgical Research Fellow, was funded by Prof Sander's private practice income.

Mr PJ Smith had at that point joined the staff and he related the sequence of events to an acquaintance, Mr Patrick McNamee. The friend became very interested in the fact that the consultants had put in their own money to support the Trust. He then formed a group willing to take forward the support of the concept of RAFT, most importantly including Sir Robin Chichester-Clarke who became its chairman.

A PLACE TO CALL HOME

It was soon desirable in order to house the existing research and develop other possibilities, to have a dedicated building on site at Mt Vernon Hospital.

"A friend of mine, Mr David Acland, told me of The Leopold Muller Bequest which he thought we should apply for and if we did he, as one of the administrators of the trust, would support our application. An application was made and a grant of £750,000 was forthcoming: £500,000 for a building and £250,000 for brains."

Prof Scales was entrusted with the design of the building. The NHS Trust under Mr Stephen Ramsden the CEO, was strongly supportive, and the Regional Health authority agreed to the provision of a site at a peppercorn rent, with the understanding that if the plastic surgery service for any reason was to be relocated, equivalent accommodation would be provided on the new site.

The RAFT laboratories should include provision for fund raising, administration, histology, cell biology and molecular biology as well as for the biomedical engineering of the Phantom. A prefabricated building was planned and constructed in short time.

Dr Claire Linge was appointed as team leader of cell biology and Dr Jorg Kupsch as team leader of Molecular biology. Dr George Wilson, a senior scientist in The Gray Laboratory was appointed to lead the oncology work. Professor Scales, as director of research, led the research on the Phantom and Professor Colin Green accepted the role of Deputy Director of Research.

Thereafter the team grew with the addition of other scientists, PhD students and MD Research Fellows.

"We had many projects going on, that was our strength," says Prof Sanders, "this diversity of research."

After some years, Professor Scales took the Phantom work back to The Royal National Orthopaedic Hospital, and Prof Sanders succeeded him as Director of Research, a role he held until retiring in 1999.

"I felt that my role at RAFT was to enable other people to do research," he says.

"Before RAFT, plastic surgeons were held in contempt; very little research was being done by plastic surgeons at the time. I thought research was very important. I had benefitted enormously from doing a science degree and I was lucky; I serendipitously got into research through John Scales."

He says that projects were chosen based on patients needs, which fitted into his vision of joining science with surgery, to train young surgeons in research.

"At one point we were producing more doctorates than the Department of Surgery at University College London Hospital."

When looking back, Prof Sanders says that he sees RAFT's most lasting impact came from the facial palsy work, the air support system, and the molecular biology of wound healing research.

"I'm proud, too, that we published negative results. There are a lot of blind alleys in research."

When asked about what lasting legacy RAFT has had, Prof Sanders thinks for a moment before speaking.

"RAFT became known internationally as one of the greatest centres of research relating to plastic surgery."

Burns and Skin Grafts

Someone in the UK is accidentally burned or scalded every two minutes and at least 12 patients a day are admitted to hospital for several days as a result of a burn injury. Many of these patients will require skin grafting and plastic surgery following the injury.

Skin grafting is the process where a layer of skin or cells is taken from a 'donor' site and placed over the burn wound to help it heal. There are many different types of skin graft, and though this technique has been in use for at least 200 years, there is still a huge amount of work needed to improve both the grafting technique and materials used.

From designing a synthetic skin substitute, to trying to understand why wounds sometimes don't heal, in this section we explore some of the ways in which RAFT has helped improve burn therapy and skin repair.

Growing skin in the lab

Keratinocytes are the protective cells which make up much of the outer layer of our skin. When a wound is sustained, keratinocytes are some of the first cells which arrive on the scene, helping to repair and rebuild the damaged skin.

Keratinocytes are amazing cells; from a tiny 3cm piece of skin the cells can divide rapidly to produce a sheet of cells large enough to cover an adult within just three to four weeks. Scientists first developed a reliable method of growing these cells in the laboratory in 1975, and the first large burn wound on a patient was treated in 1981.

However, there are many problems associated with using these cells in grafting. Over the years RAFT researchers have worked tirelessly to solve problems which are not only associated with keratinocyte grafting, but also with other more traditional skin grafting techniques. Some of these projects are outlined as follows.

PRODUCING SKIN CELLS FOR USE IN GRAFTING

"I can grow keratinocytes like nobody else!" says former RAFT research assistant James Shelton proudly. And indeed, that is no mean feat; keratinocytes are notoriously hard to grow.

While at RAFT, one of Jamie's side-projects was to grow keratinocyte layers in the lab, to be used in skin grafting by plastic surgeons at nearby Mount Vernon Hospital. But although Jamie started in 1997, and by then the technique of culturing keratinocytes had been around for almost 20 years, the process was still regarded as technically very difficult.

"It's like a personality issue," says Jamie, "they are just really hard to grow. You can have two people using the exact same method, but for some reason they will grow well for one person, but not the other."

Jamie explains that growing keratinocytes involved taking a small biopsy of healthy skin from a badly burned patient, then culturing them in 20 or so culture flasks over two or three weeks.

"Normally for laboratory work you don't want the cells growing too tightly together," he says, "but for grafting, we let them grow in a sheet right across the bottom of the flask. We then developed this 'hot wire' technique to take the top of the flask off, and used a sterile piece of gauze to peel off and transfer the layer of cells."

The cells could then be taken straight over

Left: Young Afghani girl burned during an attack on her village

to surgery and used to cover the burns on the patient, which in turn helped their wounds to heal and recover. Although other hospitals at the time were also using this technique, it was still relatively uncommon as it was so difficult to do.

"The technique is more widespread now," says Jamie, "but at the time, few places were able to do this. RAFT was special because not only was it a research centre, but it also had such close links with the surgeons and was also physically situated very close to the hospital."

The technique was constantly being improved, and new research findings at RAFT were continuously being fed back into the process. For example, a new method of cell transfer using a membrane was developed (which is explained next), allowing for a better chance of the graft working. This project is a beautiful example of how research at RAFT has directly helped patients.

"We used to help maybe six patients a year in this way; they were very badly burned and very ill. It was a great thing for me to be able to do, it was good to be part of something that delivered to the patients," says Jamie, accurately summing up how everybody at RAFT still feels.

EVALUATING A NOVEL DELIVERY SYSTEM FOR LABORATORY-GROWN SKIN GRAFT CELLS

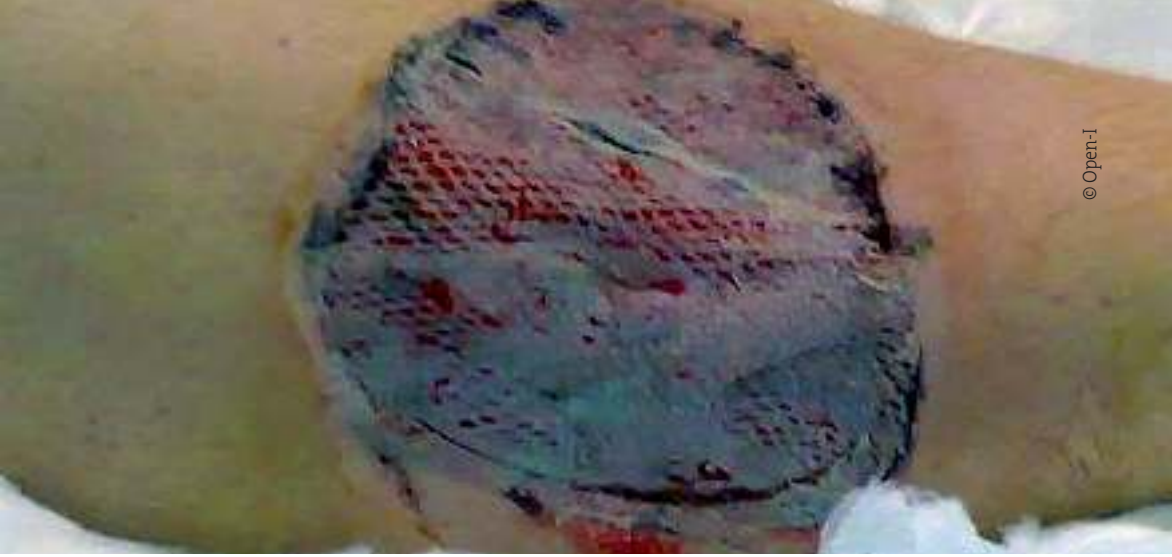
Use of keratinocyte cells grown from the patient's own skin are a useful alternative to skin grafting when a patient has suffered from extensive burns. However the cells can take weeks to grow while the patient has to wait, and also are very fragile and liable to blister once applied to the wound.

In 1997 researchers at RAFT took a further step forward in solving these problems. Using the RAFT model of wound healing, the researchers showed that if keratinocytes were grown on a special type of hyaluronic-acid membrane, fewer cells were needed to achieve a successful graft.

Whereas before, doctors had to wait several weeks to grow enough cells to cover large wound areas, using the new method, cells grew within the supportive membrane, and could be used much earlier for grafting. The grafts were also easier to handle and required less preparation time during the actual procedure.

The researchers at RAFT were first to test this method in a properly controlled and appropriate model, and the paper has been cited many times since, including by a book of wound management guidelines for nurses. RAFT researchers later went on to successfully use this method to treat a male patient who had sustained severe burns.

A report on this ground breaking use of a novel form of skin graft was published in the prestigious medical journal *The Lancet*, heralding a new era for use of biomaterials in wound healing.



Skin graft on arm

Improving skin grafting techniques

Skin grafting can be thought of as the transplantation of skin, either from one area of the body to another on the same patient, or from a separate donor to a patient in cases when the patient's injuries are so severe they do not have enough healthy skin themselves.

The grafts can be 'full thickness', that is, when the full width of skin is used, or 'partial thickness', where a just thin layer of skin is 'peeled' from the donor site and used as a graft.

Grafting is a fundamental technique of plastic surgery, yet there are still many ways it can be improved, and surgeons and researchers at RAFT have contributed to this in many ways.

DEMONSTRATING THE IMPORTANCE OF THE DERMIS IN SUCCESSFUL SKIN GRAFTING

Keratinocyte cell sheets are incredibly fragile when applied to a wound during grafting, and often can blister or refuse to 'take', that is, stick to and integrate into the wound. Scientists thought that perhaps one of the problems was because the grafted cells did not have a supportive and nourishing 'dermis' structure to grow on, as they would normally have in healthy skin. This concept was not new; it had in fact been suggested as early as 1869! Yet it was not until 1993 that a research team at RAFT finally confirmed that this really was the case.

Using the novel laboratory model which had been developed at RAFT, the researchers were able to compare in minute detail two different types of graft, one where keratinocyte cells were applied to the wound with a supportive dermal structure, and one where they were applied to the wound alone.

After three weeks it was obvious, the grafts applied with the dermal structure was revealed by microscope to be much more 'durable' and less fragile than the cell-only graft, and the wounds were much better healed. This paper was a major step forward in helping to improve keratinocyte grafting on wounds.

The work has since been cited many times over, in reviews and books discussing clinical advances of keratinocyte grafting. The use of a supportive dermal base layer is now considered to be essential when grafting with keratinocytes.

MAPPING NERVE AND BLOOD VESSEL GROWTH IN NEW SKIN GRAFTS

As part of an on going set of pioneering studies on the newly developed laboratory model of wound healing at RAFT, in the mid- to late- 1990s the charity helped to fund research investigating how nerves and blood vessels grow into keratinocyte-based skin grafts.

Keratinocyte grafts are used to cover wounds in burn therapy, but they can sometimes fail. By finding out how nerves and blood vessels grow into the grafts, more can be done to try and improve their success rate.

As part of their studies the researchers used a cutting-edge technology of the time, called confocal laser scanning.

Confocal scanning microscopes are able to take a series of very high resolution pictures through layers of tissue in the laboratory. This method had never before been used to study wound healing after grafting, and for the first time researchers were able to follow the pattern of blood vessel and nerve growth through the tissue in intricate detail.

The studies confirmed that similar to other wound healing studies, blood vessels must grow first, before nerves also then can begin to grow into the graft. Blood vessel and nerve growth only appeared under areas where the keratinocyte layer had survived, suggesting these cells help to play a central role in wound healing. This research funded by RAFT contributed essential knowledge to the field of wound healing.

LIMITING DAMAGE TO CELLS STARVED OF OXYGEN

Skin and cells used during grafting treatments of wounds can be harmed by the reduced level of oxygen they receive. This damage is called 'oxidative stress', and is thought to be in part caused by the production of harmful molecules, called free radicals, which occur when oxygen levels are low.

Free radicals are atoms or groups of atoms with an odd (unpaired) number of electrons and can be formed when oxygen interacts with certain molecules. When weak bonds split, free radicals are formed. Free radicals are very unstable and react quickly with other compounds, trying to capture the needed electron to gain stability.

Once formed these highly reactive radicals

Top to bottom: Dr Jorg Kupsch, Karen Price and Dr Claire Linge

can start a chain reaction, like dominoes. Their chief danger comes from the damage they can do when they react with important cellular components such as DNA, or the cell membrane. Cells may function poorly or die if this occurs.

During the late 1990s and early 2000s research at RAFT concentrated on understanding the underlying mechanisms of this damage, and finding potential new ways to prevent it. In two interesting studies, a PhD student completed research showing that cells may be able to better survive blood supply interruption if they are first prepared using certain protective proteins.

The huge importance of this work to the research field is illustrated by the fact that between them these two papers have been cited by other scientific publications a whopping 650 times since they were published in the early 2000s!

Awaiting treatment after suffering burns

INVESTIGATING THE STRUCTURE OF BURN SCARS

Painful hypertrophic scars affect around 30% of all patients who suffer severe burns. They are thought to develop as a result of overproduction of too much scar tissue, but there is still a lot researchers don't understand. Unfortunately these scars can be difficult to study because their characteristics tend to vary a great deal from person to person.

Part of the anti-scarring research carried out at RAFT has involved trying to characterise the different types of hypertrophic scars seen in patients who attended the Mount Vernon Hospital Burns Unit.

Following healing of their burns, patients were followed-up at a dedicated scar clinic every three months. Scars were documented using a number of criteria, including assessment of size, shape, hardness, colour, pain, itching, and sensitivity. Biopsies of scar tissue were also assessed under the microscope.

The researchers then developed a standardised method of assessing the scars, which ensured their findings were reproducible and easily comparable to others findings.

One of the most interesting findings of this study was that only 9% of patients with hypertrophic scars were completely symptom free, while almost half felt pain and nearly all felt itching. Microscope studies showed that hypertrophic scars had an increased level of proteins which are associated with pain receptors, and that these proteins were far less organised and more diffuse in scar tissue, compared to normal skin.

These results were subsequently presented at many national and international meetings, and have helped in the further study and investigation of hypertrophic scarring both at RAFT and elsewhere.

Donor skin placed on wound

A NATIONAL NETWORK OF SKIN BANKS

Patients who suffer from very large burn injuries may need a skin graft to help close their wounds. Ideally the skin used in the graft is taken from the patient, but sometimes the patient is too badly injured and does not have enough healthy skin to use.

If this is the case then donated skin taken from cadavers is sometimes used, either as a temporary measure while the patient's own skin heals, or more permanently to support and help improve the success of grafts made from cells which have been grown in the laboratory.

However, up until the mid-1990s there was no nationally available source of donor skin in the UK. Compare this to the US which already had a national network of 18 skin banks and it becomes apparent the UK was sorely behind in this area.

Two surgical research fellows at RAFT thought this too, and together with consultants from the North London Tissue Bank and Mount Vernon Hospital they published an editorial letter in the prestigious *British Medical Journal*, suggesting that national blood transfusion centres could take on the role of skin banking and distribution.

In the UK at that time only around five locally-based skin banks existed. A national network of skin banks would mean that skin could be quickly and readily available for early treatment of patients, and would also reduce the need for skin donations from relatives or unrelated donors. The authors thought that the National Blood Service was perfectly placed to take on the job, as it already had the appropriate facilities and employees with the necessary skills needed to process the donor skin for storage.

In the late 1990s, four multi-tissue banks joined forces and the National Blood Service started to provide a "single, comprehensive service throughout the whole country." The UK's first national skin and tissue bank was born.

In autumn 2005, the National Blood Service became the only supplier of donated skin in the UK. RAFT researchers obviously can't take all the credit for this, but they certainly helped to raise it as an issue which needed to be addressed. As one of the authors, Michael Machesney says, "We hope that our letter to the BMJ helped to persuade people that the National Blood Service was ideally placed to help with skin banking."

Fire burning out of control on the Deepwater Horizon oil platform in 2010

Burn Treatment and Therapy

Treatment of burns is complicated and involves detailed assessment of the patient and the type, severity and extent of the burn. Shock, infection and scarring can all be serious complications following burn injury and these, too, can require extensive monitoring and treatment. Burn injuries are inextricably linked with plastic surgery, and RAFT has a long history of burns research.

DEFINING THE LINK BETWEEN BACTERIAL WOUND COLONISATION AND SEVERE SCARRING AFTER BURNS

Painful and disfiguring hypertrophic scars are a relatively common complication of burn injury. They usually develop within three months of injury and it is still not fully understood why they develop, although many factors such as race, age, and genetics have been shown to play a role.

In 2007 RAFT surgical research fellow Mr Richard Baker published an important piece of research which showed that colonisation of burn wounds by bacteria could be an important cause of hypertrophic scarring.

There was already a well-known link between hypertrophic scarring and burn wound infection, Richard and his colleagues at RAFT took this idea one step further. By examining case notes of all patients seen at Mount Vernon Burns Unit over a two-year period, he found that as many as 88% of all hypertrophic scars

were colonized by bacteria, compared to just 27% of non-hypertrophic scars.

This important piece of research led Richard to suggest that keeping burns wounds as clean and free of bacteria as possible may help reduce the risk of hypertrophic scarring.

Much more research is still needed to help understand the cause of hypertrophic scarring after burns injuries, but Richard's work at RAFT helped supply an important piece of the puzzle. His paper contributed to the growing amount of evidence linking hypertrophic scarring with bacterial colonisation and has since been cited in several publications, reviews and guidelines discussing hypertrophic scarring cause and prevention.

STUDYING NATIONWIDE BURN TREATMENT PRACTICES

Burns research at RAFT covers a huge variety of areas, from the detailed intricacies of finding out the exact molecular nature of skin healing, to checking up on how well UK hospitals treat burns patients. All research is equally important and all research has something to tell us, something from which we can learn.

In 2007, two RAFT research fellows decided to conduct a study investigating how hospitals in the UK and Ireland use fluid resuscitation to treat patients with severe burns injuries.

Fluid resuscitation is needed when a patient suffers a burn which covers a large surface area of their body. By infusing fluid over a lengthy

US Army nurse treating burn patient

time period as soon as possible after the injury, the patient is less likely to develop burn shock and has a much better chance of survival.

There are many different types of fluid and ways of calculating how much fluid is needed to adequately treat these patients, and it is obviously necessary to monitor current practices, to make sure the best methods are followed.

The RAFT researchers identified all 26 burns units in the UK and Ireland and sent out questionnaires via post asking about their methods of fluid resuscitation. Almost all of the units responded, with reassuring results.

Fluid resuscitation was usually started if the patient had received burns covering 10 to 15% of their body, and two-thirds of units continued fluid resuscitation for 24 to 36 hours. Interestingly, half of the units did not routinely change the type of fluid administered after the initial period of resuscitation, while half did.

The researchers also found that a type of fluid known as 'crystalloid' fluid was becoming increasingly common. The researchers concluded that all in all, fluid resuscitation of burns injured patients in UK and Ireland burns units was fairly consistent. Good news indeed!

The study has since been cited many times. The importance of this study was appropriately recognised that same year, when it was chosen to be included in an international review of the top 90 out of 1000 burns research articles published in 2007, deemed by the author to be "the most important in terms of clinical burns care."

INVESTIGATING HOW ACCURATELY A&E DEPARTMENTS ASSESS BURNS

The Accident and Emergency (A&E) department is often the first port of call if you have suffered a burn, and it is estimated as many as 175,000 people in the UK visit A&Es with burns injuries each year. Adequate initial assessment and treatment of burns at this early stage is often critical to success and recovery of the patient.

In 1991, a RAFT research fellow conducted a review of A&E departments across the UK, to determine how they dealt with burns injuries. The aim was to monitor if the doctors at A&E departments assessed and treated the burns patients in the best and most effective way.

The fellow reviewed the case notes of 100 patients who attended A&E and were subsequently referred to their local specialist burns unit, with some interesting findings.

Perhaps most importantly, it was found that assessments of burn extent in A&E departments were often inaccurate, and made by only one doctor inexperienced in managing burns. The extent of the burn was overestimated in over 85% of patients, leading to inappropriate treatment.

The RAFT researchers suggested that burns training should be improved for doctors in A&E departments, and if possible, patients should be assessed by a team of specialists as quickly as possible. Findings from this research have since been cited several times, including in a systematic review of burn injury in Europe and a textbook of trauma nursing.

HELPING FUND A TRIAL INVESTIGATING ANTIBIOTIC USE IN BURN PATIENTS

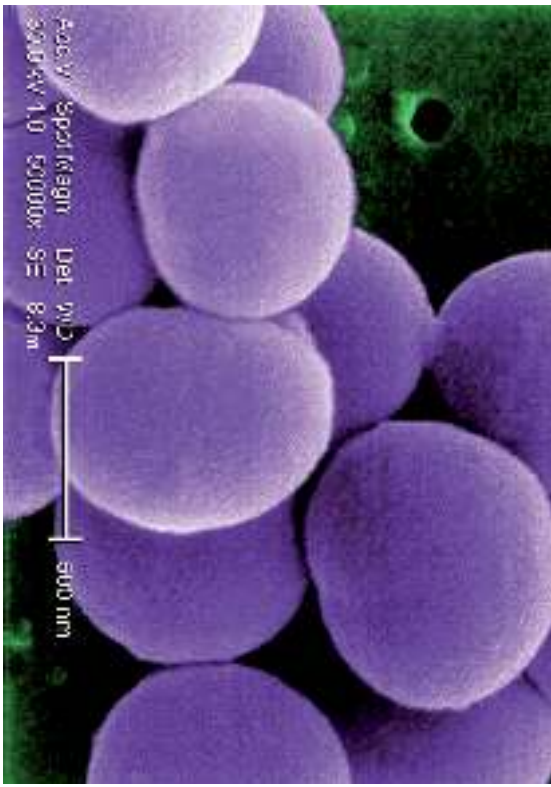
Patients who have suffered from extensive burns may need to be given antibiotics to prevent infection from setting in. Unfortunately it can be difficult to predict how these drugs might act in somebody so badly injured.

Burns patients may often need a higher dose to be sure the drug is effective and the situation can be even more complicated in children. But data can be hard to obtain in these patients, and clinical evidence is often lacking.

In the late 1990s, researchers based at RAFT were involved in clinical trials investigating the best way to give the antibiotic teicoplanin to burns patients. The behaviour of teicoplanin in these patients had previously only been investigated in very few adults and no children, so data was much needed.

The researchers performed a study in 15 adults and five children with severe burns, measuring their blood and burn fluid levels of teicoplanin over several days. Results varied widely between different patients, and it was found that some teicoplanin is lost through the burn in most patients.

In addition, elimination of antibiotic from the body was more rapid in children than in adults. The researchers advised that monitoring of teicoplanin levels in the blood may be necessary in some patients who have suffered burns, a practice which is still recommended in current clinical practice.



HELPING TO IMPROVE EARLY DIAGNOSIS OF STAPHYLOCOCCAL TOXAEMIA IN CHILDREN WHO HAVE SUFFERED BURNS

Toxic-shock syndrome is a rare but life-threatening consequence of infection by a strain of toxin-producing bacteria called *Staphylococcus aureus*. Children who suffer small and otherwise non-serious burns can sometimes be at risk of developing this condition, and some may even die as a result of their injuries.

Twenty years ago the features of burn-induced toxic-shock syndrome in children was not well-recognised, and researchers at RAFT decided to conduct a review of characteristics of the condition in six children.

The children had all developed toxic-shock syndrome after suffering from burns and had attended Mount Vernon Hospital over the past two years.

RAFT researchers suggested that reliable early signals of the condition include a rapidly developing severe fever, with increased heart and breathing rate. There was also a sudden drop in white blood cells, within one to three days after injury. They recommended that treatment needed to be introduced before onset of this shock.

Published in 1993, this study was one of the first to describe the clinical signs of toxic shock syndrome in children suffering from burns and its findings have since been cited in recommendations to clinicians on how to diagnose the condition.

STAPHYLOCOCCUS AUREUS

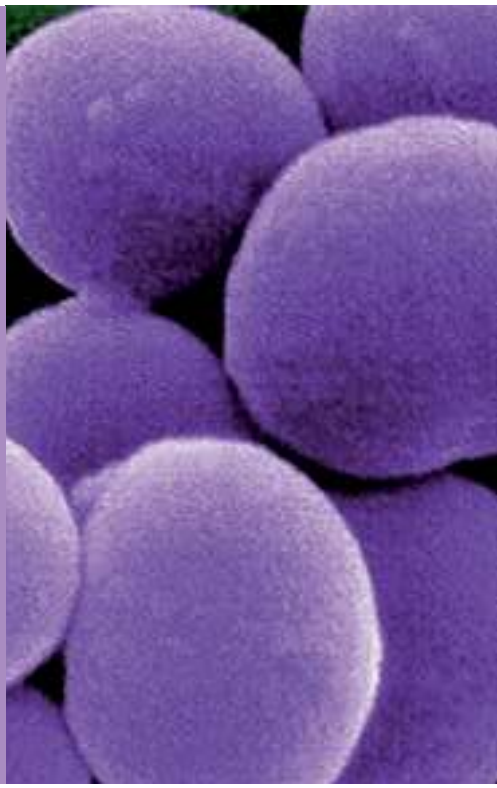
This is a bacterium that commonly colonises human skin and mucosa (e.g. inside the nose) without causing any problems.

It can also cause disease, particularly if there is an opportunity for the bacteria to enter the body, for example through broken skin or a medical procedure.

If the bacteria enters the body, illnesses which range from mild to life-threatening may then develop.

These include skin and wound infections, infected eczema, abscesses or joint infections, infections of the heart valves (endocarditis), pneumonia and bacteraemia (blood stream infection).

The name *Staphylococcus* comes from the Greek staphyle, meaning a bunch of grapes, and kokkos, meaning berry, and that is what Staph bacteria look like under the microscope, like a bunch of grapes or little round berries.



CREATING A PATIENTS BURNS DATABASE

Knowledge is power, especially when it comes to research. Sometimes it is easy to focus on the big achievement and not notice all the small steps, all the hard work and grind which helped the research inch towards that 'eureka' moment.

The creation of a database of burns patients at Mount Vernon Hospital was one of those small, but essential steps. In the early 1990s, researchers at RAFT painstakingly sifted through the case records of all patients admitted to the burns unit at Mount Vernon between 1987 and 1992.

Back then the burns unit served a huge area covering north-west of the Thames, and a total of 774 patients were admitted to the unit during this time. This was a massive job. Data from patient notes including anonymous information about the patient, the type of burn, the type of treatment the patient received, and how well the patient recovered had to be accurately entered into the electronic database by hand.

Preliminary examination of the data revealed some interesting results. From the years 1987 to 1992 the number of patients admitted remained roughly the same, however the average ages of patients reduced from 27 years to just 19 years old.

A positive finding was that more patients admitted in 1992 had received first aid prior to attending the hospital compared to 1987. However, around two-thirds of the all burns patients admitted were male, and the level of burn injuries sustained both at work and at home remained high. This finding highlighted the need for better health and safety education in these areas.

Perhaps even more important, this database served as a 'backbone' for other studies at RAFT, researchers were able to 'mine' the valuable information it held for years to come, searching for elusive answers to other vital research questions.

© DOD

US miltary burn patient

'I would not be here today'

In 1989 I was only two-years-old when a visitor to our house left a box of matches lying around. I found them and somehow I accidentally set fire to my dress. I don't remember doing this, but I do remember the on-going surgeries I have had throughout the years, writes Ferrial Syed.

As a result, I suffered third degree burns and was rushed to Mount Vernon Hospital where I had a number of operations. One of which involved having my right hand fingers and thumb amputated as I was very injured and the situation became life-threatening.

Luckily at the time, RAFT was carrying out research in using skin from dead donors to treat burns wounds. I am told that surgeons used some of my own skin, taken from another part of my body, together with the donor skin to cover my very extensive burns. In order that my body did not reject the donor skin I had to take the drug cyclosporine for quite some time. I was one of the youngest to undergo this procedure and would not be here today if it wasn't for RAFT's life-saving research.

My parents heard that my surgeon, Professor Roy Sanders, co-founded RAFT and as a family we have been in touch over the years. In fact, when RAFT moved into its own laboratories I was lucky enough to be chosen to present a bouquet to the Duchess of Kent, RAFT's royal patron.

In celebrating 25 years of RAFT, I am proud to look back over the years and say I have supported RAFT in fundraising events and in raising awareness of the importance of their research; it's the least I can do for all they have done for me. I recently spoke as a Patron at their Parliamentary Reception in the House of Commons, introducing their latest research in Smart Matrix™, a skin scaffold.

Oftentimes I wonder how less traumatic my recovery would have been if RAFT's Smart Matrix™ had been available at the time of my accident. However, I look forward to the benefits it will give to patients in the future suffering similar traumas to their skin, major burns, military injuries, leg ulcers and so forth.

I am now 26 years old, and am pursuing a career in the medical field myself, as I have been truly inspired by RAFT and my surgeons, am lucky to be here and ever grateful for their skills which saved my life when I was badly burned as a toddler.

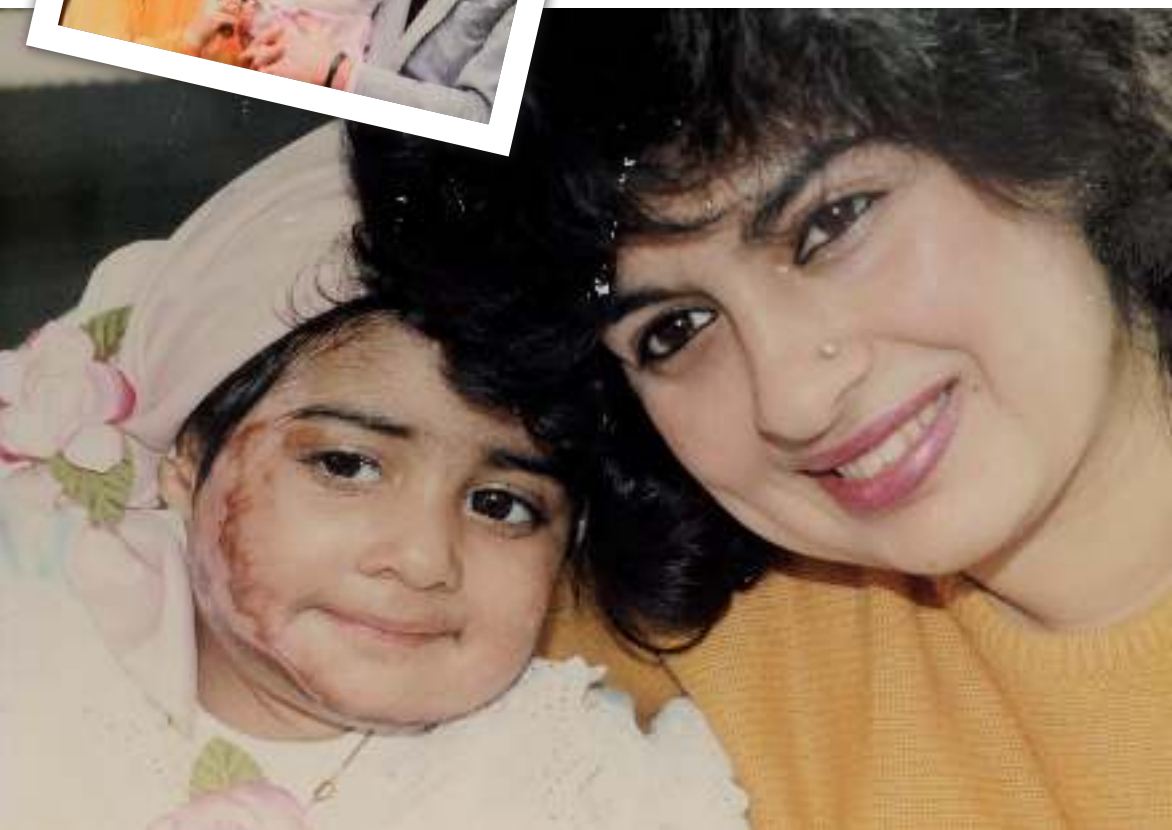
Clockwise from top left:

Ferrial Syed and her father at the House of Commons in 2013

Presenting flowers to the Duchess of Kent at RAFT's opening

Leaving the hospital with her mother

Ferrial and her mother with RAFT founder Professor Roy Sanders



Wound Healing

Bed-testing dummy "Gladys"

Without a doubt one of the greatest contributions made by RAFT's research has been in the field of wound healing. From designing a synthetic skin substitute, to developing new anti-scarring treatments and designing air beds, RAFT has funded wound healing projects in a range of disciplines, from cutting-edge biology to practical engineering.

Pressure sore prevention- RAFT's first success

Not many people have even heard of pressure ulcers. Also known as pressure sores or bed sores, celebrities don't usually campaign for their eradication, and you rarely see new breakthrough treatments reported in the media. But they are a massive problem, as the NHS well knows. As many as one in 20 people admitted to hospital with a sudden illness will develop a pressure ulcer, and the cost to the NHS has been estimated to be as much as £1.4–£2.1 billion (US $2.23-3.35 billion) every year; that's 4% of the NHS budget.

Pressure ulcers can develop when weight is placed an area of skin for a period of time, disrupting blood flow. Starved of nutrients, the skin becomes damaged and starts to break

down. Ulcers are notoriously hard to treat and the worst may need surgery. A particularly unfair aspect of pressure ulcers is that they will most commonly affect vulnerable people; those who are already battling chronic illnesses, are elderly, have limited movement, and must spend a large amount of time lying or sitting down.

WORKING WITH PROFESSOR JOHN SCALES TO DEVELOP THE FIRST THERAPEUTIC AIR BED

The origins of RAFT are inextricably linked with the name of the eminent surgeon-scientist Professor John T. Scales. An orthopaedic surgeon by trade, John Scales is perhaps most well-known as one of the true pioneers of biomechanical engineering, that is, the discipline of using engineers to solve medical problems.

"John Scales just about invented the concept of biomedical engineering," says Dr Duncan Bain, one of the first researchers at RAFT and someone who worked closely with John Scales. "He had realised decades ago that some medical problems were actually engineering problems."

Born in 1920 in Colchester, John Scales completed his medical training at various hospitals in London, and after a two-year stint in the National Service, finally settled at the University College of London Institute of Orthopaedics in Stanmore, Middlesex. Here is where he really started to develop his interest in bioengineering research, first by convincing the university to set up a unit researching the use of plastic in orthopaedic surgery, later by running the first ever university department of biomedical engineering in Britain.

During his time at Stanmore, John Scales was an unstoppable force, collaborating with other researchers to develop a number of world firsts which are standard orthopaedic practice today, including the first Stanmore total hip replacement, and prosthetic replacements for other joints.

The professor's interests were wide-ranging; any medical problem which could be solved by engineering was his aim. He turned his attention to mattresses and the associated problems of pressure ulcers, developing the first ever air beds and other similar 'patient support systems'.

It is at this point that Professor Roy Sanders, a founder of RAFT, enters the picture. Roy was working at Stanmore around the time John Scale's attention had turned to air beds.

"I remember one Saturday afternoon," says Roy, "I went in to this shed which was making an awful racket, asking 'what's going on here?'"

What was going on was John Scales, busy developing a type of 'hoverbed', which used the same technology as a hovercraft, but instead the aim was to physically levitate the patient off the mattress using a giant air fan. It was hoped this would help their wounds to dry out and heal. Roy Sanders was immediately hooked, and started working with John Scales on the 'levitation' hoverbed. "The problem was it was incredibly noisy," says Roy – as you might well imagine.

Soon their attention shifted instead to developing a low-air pressure bed which would help patients at risk of developing pressure sores. Funded by the Medical Research Council, they enlisted the help of a company which specialised in making fans for use in church organs.

"They were the only company which knew how to produce a fan which was quiet, yet powerful enough." says Roy. The resulting air bed technology they developed is still manufactured and universally used today.

Some of the money from the company set up to patent and licence the air-bed technology was also used to set up a very small plastic surgery research charity in a disused ward at Mount Vernon Hospital. This charity was RAFT.

At around this time, John Scales retired from clinical work and Roy Sanders managed to persuade him to join RAFT as Director of Research, to continue his successful work in patient-support systems, which he did for many years.

John Scales died in 2004, and Roy Sanders is still incredibly grateful for the contributions he made to RAFT. Before RAFT, Roy Sanders says "plastic surgeons were held in contempt; very little research was being done by plastic surgeons at the time. I thought research was very important ... I was lucky, I serendipitously got into research through John Scales."

BUILDING A PHANTOM PATIENT

Another scientist drawn into research through the magnetic enthusiasm of John Scales was Dr Duncan Bain, a biomechanical engineer who worked with John Scales at RAFT during the 1990s to develop a patient 'phantom' for testing mattresses and other patient support systems.

In 1989 the government introduced new laws specifying that mattresses must be made of a specific type of flame-retardant material. Although this material was not flammable, John Scales conducted some rudimentary experiments at RAFT which showed this material may not distribute patient pressure as evenly as other materials, and could potentially encourage pressure sore development in patients.

However, there existed no "definitive means of assessing pressure distribution" so it was difficult to truly test the qualities of these new mattresses and materials.

It was decided a patient 'phantom' needed to be built, a model patient which could be used in strictly controlled conditions to test how mattresses and other patient support systems react to patient induced pressure. It was at this point John Scales realised he needed the help of a biomechanical engineer, and called up Duncan Bain.

"I was running a product design consultancy at the time," says Duncan, "and this guy rang me up and asked 'Have you ever heard of pressure sores?' I said no I hadn't, and John says 'Would you like to run a pressure sore programme at RAFT?'"

Duncan found out more about the problem and agreed. "I found out pressure sores were a colossal problem, they were a common cause of death and cost the NHS billions of pounds. Essentially if you stay in one place too long your soft tissues can become compressed or squashed, the blood flow is cut-off and the tissue dies."

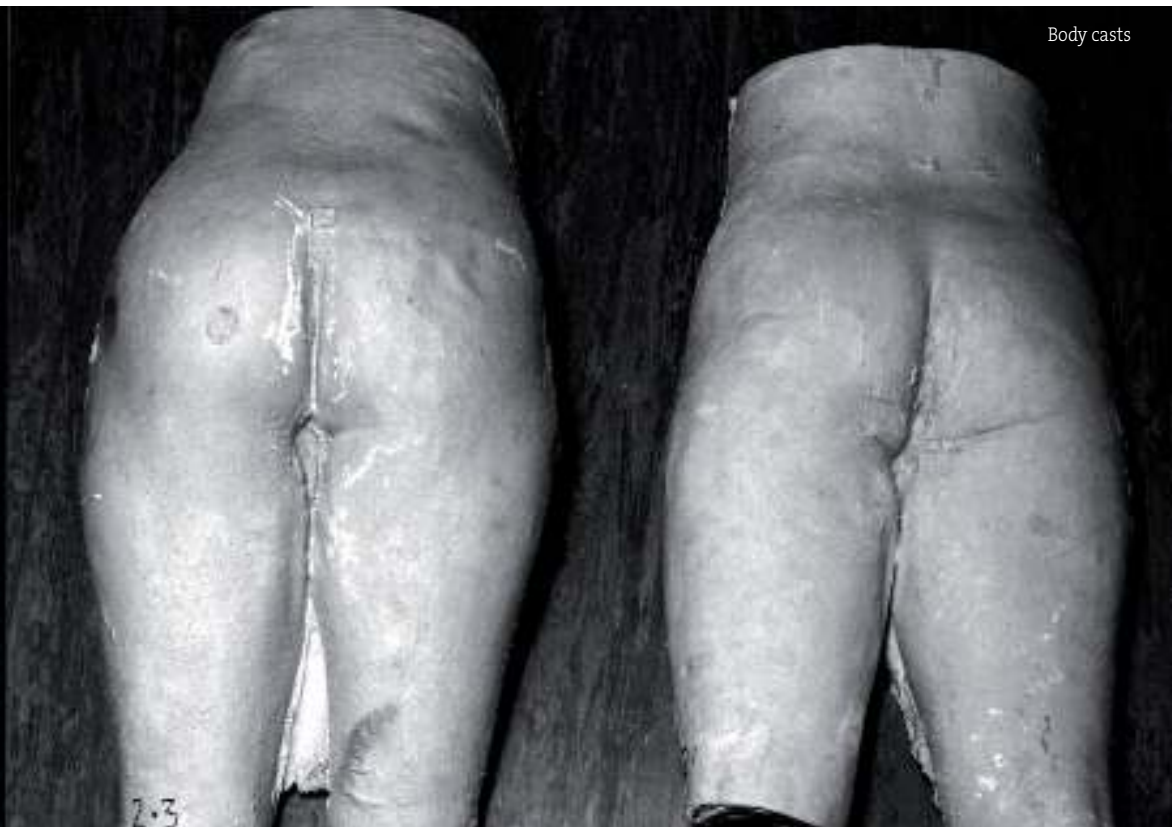
So Duncan handed his business over to a friend to take care of temporarily. "I thought I'd be wrapped-up in a month or two," says Duncan, and headed over to a "semi-derelict wing of the Burns Unit" at Mount Vernon Hospital, where the fledgling RAFT was based.

"My job was to research the problem of pressure sores and first I asked 'what is the problem? What do I have to do to prevent pressure sores?' It became clear that it was a mechanical problem, what was needed was improved beds and mattresses."

But Duncan soon came up against problems.

"There was nothing in the literature," he says, "and there was no methodology for measuring if new mattresses worked. How can you develop something to reduce pressure sores if you can't even test if it works?"

Dr Duncan Bain and Professor John Scales



Body casts

So Duncan, John Scales, and other researchers set about developing a "bed-testing dummy," which they nicknamed 'Gladys'. Their aim was to develop a phantom which was reusable, standardised, and could produce reproducible results.

"We spent a couple of years optimising shapes, sizes, textures of materials." says Duncan. To get the correct dimensions they studied how pressure points develop while sitting and lying down using volunteers.

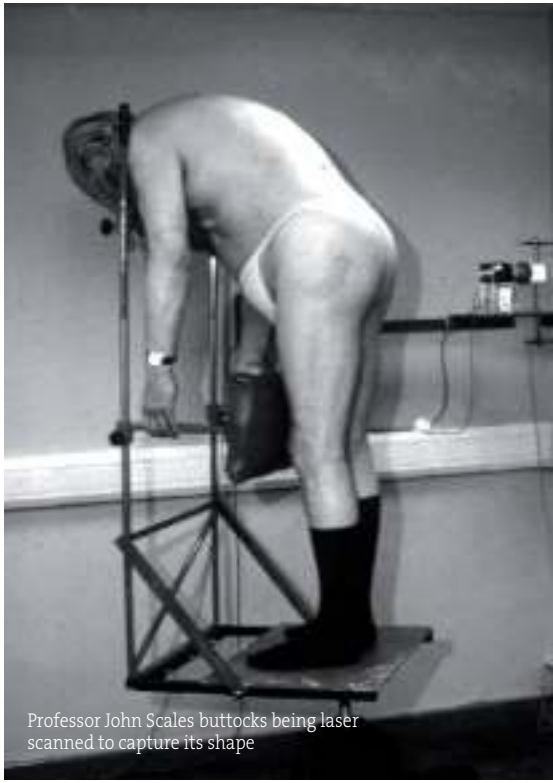
"As many as 70% of pressure sores develop on the bottom," says Duncan, "so we decided we needed to take plaster casts of people's bottoms."

All types of people were used as volunteers; patients, nurses, even models from the local modelling agency. "One of the fundraisers was the wife of a theatrical agent in London and through him we even had a few celebrities lined up to make casts of their backsides for us."

As well as helping science, this would obviously have been great PR for the charity. But it was not to be. "Unfortunately a national newspaper got wind, and ran a story about us on Page 3, right next to the photograph of this naked girl," says Duncan. "They used the headline 'Boffins Want Your Botty'. This was too much for the hospital, and we never got to plaster cast a celebrity's bottom."

But despite the obvious fun to be had in this project, the project also went on to make a real difference to patient's lives. One of the breakthroughs came when the researchers at RAFT realised instead of plaster casting, they could use a laser scanner to produce 3-D images of the patients.

RAFT researchers had recently collaborated with the University College of London using a similar scanner to map facial features of children with cleft lip and palate.



Professor John Scales buttocks being laser scanned to capture its shape

Duncan and his colleagues thought the same technology could be used to scan patients' body dimensions- an easier, more accurate, and perhaps less controversial method than plaster casting. He adapted the scanner so it could be easily used for the body instead of the face and started collecting data.

Eventually they developed a standard body shape and dimensions, and Gladys was born. With a skeleton made of stainless steel and soft tissues made of a special type of silicon, Gladys can be used along with sensors to evaluate how pressure is distributed over new mattresses and beds. Further technology at RAFT was also developed which could measure the spread of heat and moisture through the patient support system, another key risk factor for pressure sores.

Since its development, this RAFT mattress-testing technology has been adopted as the international standard method for testing all new mattresses. After RAFT, Duncan spent 10 years at University College London designing disability equipment and carrying on his pressure research.

Duncan's laboratory became the Medicines and Healthcare products Regulatory Agency (known as the MHRA) centre for testing new mattresses. "The MHRA didn't have in-house expertise for evaluations," says Duncan, "so any new mattress which needed a CE mark [Conformité Européene which literally means "European Conformity] before being marketed in would be evaluated by my laboratory using Gladys and the technology developed at RAFT."

Now running his own consultancy, Duncan and Gladys are still a team. "Mattress companies still come to me today. It seems nobody has come up with anything better – maybe it's about time to reinvent the technology!"

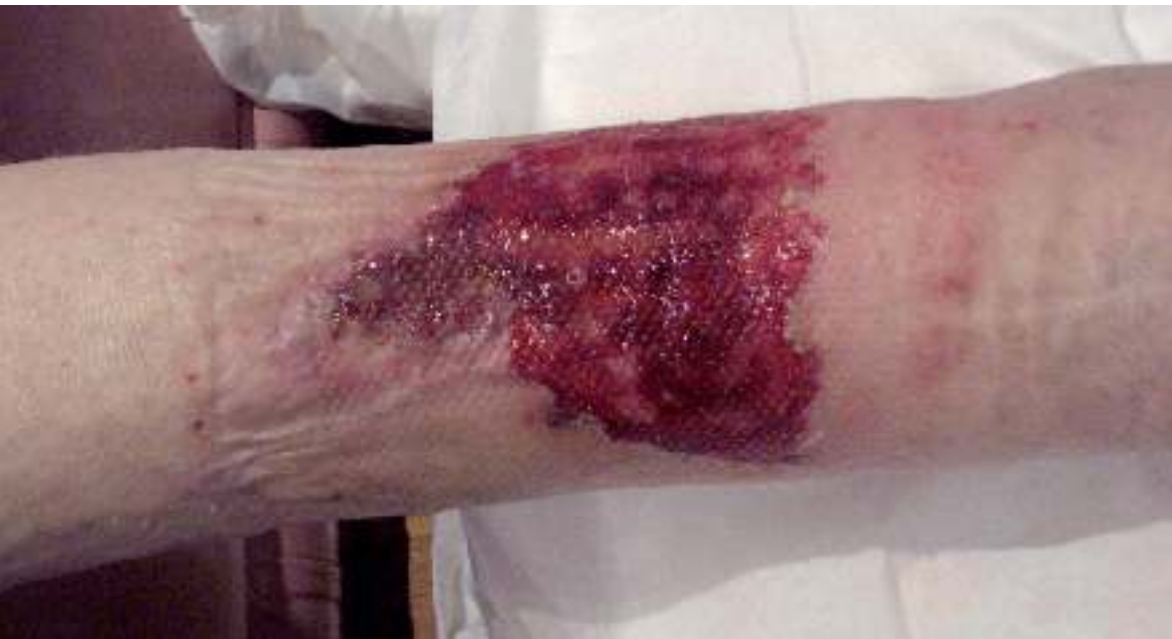
And all of this wouldn't have come about if it wasn't for John Scales and RAFT. "I kind of got carried away while I was at RAFT," says Duncan, "I ended up doing a PhD in biomedical engineering, I became a pressure sore boffin by accident!"

IMPROVING HOSPITAL PRESSURE SORE MANAGEMENT

One of the main aims of RAFT has always been education; to inform surgeons, healthcare practitioners, patients, and anyone else of the most up to date findings, and to help them implement the best methods, the best ways to do things. Increasing knowledge in this way is one of the quickest and most efficient ways to improve patient's lives in real, practical terms.

In the late 1980s and early 1990s, doctors and researchers started suggesting that the best way to reduce the cost and distress caused by pressure ulcers was to prevent them from developing in the first place. In 1991, as part of the pressure sore prevention programme led by Duncan Bain at RAFT, a research nurse was employed to educate, advise and assist with pressure sores in hospitals and the community.

Chronic wounds are extremely difficult to treat



The first aim of the project was to put in place some much needed infrastructure. At the time, the hospital had no way of monitoring how many patients were developing pressure sores while admitted. The research funded by RAFT changed all this, systems were put in place and regular statistics started to be collected. During a preliminary inspection of the hospital as part of the pressure sore programme it was found that as many as 50% of basic mattresses in the hospital had to be condemned due to old age or contamination.

The RAFT programme ensured that a system was set up so all of these mattresses were removed and a mattress monitoring and replacement policy was developed.

Two spin-off projects also followed, helping the vulnerable patients particularly at risk of developing sores. One project investigated how to improve care for patients who have suffered from a type of femur fracture which makes them more at risk of developing sores, and the other aimed to educate GPs and patients in the best ways to help recovery after undergoing surgery for pressure sores.

By 1993 the government had caught up with the research and produced a paper recommending that all hospitals must try to reduce their rates of pressure sores. As was noted at the time, "very few hospitals have recording and audit systems in place which will provide the information necessary to monitor this."

But thanks to RAFT, Mount Vernon Hospital was way ahead – at this point the hospital had developed robust monitoring systems and was assessing patient risk of pressure ulcers within two hours of admission. As noted in the RAFT annual report of 1993, Mount Vernon Hospital was indeed at the "forefront of pressure sore prevention."

Through earlier identification and response to patients at risk, the number of patients developing the most severe type of pressure injuries had substantially dropped, from one in 17 in 1992 to one in 29 by 1993. By focussing on preventative measures for patients who had sustained a fractured femur, the incidence of pressure ulcers in these patients had fallen by as much as 50% in just one year.

The pressure sore prevention initiative had spread throughout the whole hospital, and specialist nurses were placed on many of the wards. Multidisciplinary guidelines were developed along with a hospital-wide rolling mattress replacement programme being initiated. In addition, educational leaflets and structured education for staff, carers and patients were provided on an on-going basis. After three years Mount Vernon took over funding of the pressure sore research nurse and many of these initiatives started through the RAFT project still remain in place today.

DEVELOPING THE MOUNT VERNON FIST TEST

Damaged and old hospital mattresses lose their ability to support the patient properly and lead to increased risk of pressure sores. However as the pressure sore programme at RAFT found out, many hospital mattresses were still being used well past the time when they should have been thrown away.

To address this problem, RAFT gathered an expert panel in pressure sores which included Duncan Bain and others. The panel's aim was to produce recommendations on how to perform regular checks on mattresses, to ensure that they were still functioning.

The subsequently developed Mount Vernon Fist Test is a quick and easy method which can be performed by anyone to evaluate the

Bed test being used to evaluate condition of mattress

condition of a foam mattress. The test involves using clasped hands balled into a fist to place pressure at seven specific points along the mattress, testing its responsiveness. If the base of the bed can be felt at any point then the mattress has 'bottomed out' and it was recommended it should be removed from use immediately.

This simple, cheap and effective test was adopted by hospitals, care homes and NHS trusts nationwide. And although it was later superseded by a newer mattress audit system called Quince (developed by Duncan Bain's team at University College London), some places still operate the Mount Vernon Test today.

Chronic Wounds 101

While some diseases garner the publicity of celebrities wearing ribbons, it is doubtful you will ever see someone at the Academy Awards promoting skin wound awareness.

Indeed, even while the estimate cost of diabetic wounds, pressure sores and leg ulcers in the USA alone will be an estimated $20 billion this year, in the 235 research disease areas that the US National Institute of Health lists, chronic skin wounds does not get a mention.

Part of the problem is that chronic skin wounds are often times seen as a condition from a disease, such as diabetes, or cause from obesity or spinal injuries, and are not seen per se as a major health problem. This is despite the fact that chronic skin wounds are extremely difficult to treat, can take years to heal, and may lead to death.

However, in the paper *Human Skin Wounds: A Major and Snowballing Threat to Public Health and the Economy* by Dr Chandan Sen, Dr Sen states that chronic skin wounds from both funding and medical research reasons need to be treated as a separate condition.

For example, while *Superman* actor Christopher Reeve had a spinal cord injury which led to him getting pressure sores, it was an infected pressure ulcer which killed him, not his spinal cord injury.

While the above information is from the USA, the problem is global that does not seem to be unique to any specific region of the world.

Vulnerable chronic wound patients – far from any Hollywood, Bollywood or London red carpet – include the elderly, stroke victims, patients with diabetes, dementia, those in wheelchairs, bedridden or suffering from impaired mobility or sensation.

A Scandinavia study found that between 50-80% were acquired during a hospital stay and a specific Danish report stated that 58% of open pressure sores were not documented in either the medical records or nurse records. 'Official' given numbers of patients with open pressure sores might then be just the tip of the iceberg when it comes to true figures.

To add insult the injury, the US Centres for Medicare & Medicaid Services has decided that since pressure ulcers "can be prevented in hospitals through the application of evidence based guidelines", it would no longer pay for hospital-acquired skin ulcers.

But tied to this is the number of increased litigation against hospitals and care homes for not preventing open skin ulcers, with settlements favouring long-term care residents in up to 87% of the cases.

LIVING WITH A LEG ULCER

Degrading; smelly; unglamorous; these are just a few of the words that UK resident Mary-Rose Fawkes uses to describe the leg ulcer which not only threatened her leg, but led to a lack of personal confidence and depression.

Mary-Rose was helping her daughter move and she accidentally slammed the car door on her own leg.

Because the wound was triangular in shape, doctors could not stitch it so they tried dressing for two months, hoping it would heal.

"After eight weeks the nurse told me that the wound was getting better, but because I was a

Nurse treating leg ulcer

retired nurse, I knew it wasn't," she says.

During the treatment she was unable to have a bath or a shower in a normal way. The pain was so severe at times that it could only be alleviated by analgesics and sitting with her leg elevated, serving to draw attention to herself when she went out.

"Imagine how it feels to see one's leg being eaten away by a seriously weeping wound which does not heal at all, whatever dressing is applied," she says. "I was now frightened. The future of my mobility was looking bleak.

"It was also most debilitating to know what one 'smelt' and therefore likely to be offensive to other people. All in all, living with a leg ulcer is like being a leper in public and an unattractive aliment in private. It isolates; it depresses."

Mary-Rose says that she was lucky a nurse recommended to her the Lindsay Leg Club as a last resort to get her ulcer healed.

The Leg Clubs are a community-based alternative to the treatment provided by district nurses. The Clubs encourage members to become involved in their own treatment and care, and to share their experiences with fellow members.

Lindsay Leg Clubs serve two purposes. The first is to bring leg ulcer patients together where specially trained NHS nurses can access, clean and apply pressure bandages. The second is members are given the opportunity to socialise.

Many patients with leg ulcers become housebound due to a number of factors. These range from the pain or difficulty in walking; a fear that somebody will bump into their leg ulcer with a shopping cart at a store; and embarrassment of the smell, leaving them uncomfortable at the idea of taking public transportation or even visiting friends.

This causes a downward spiral which can lead to a lack of physical strength, depression and balance issues.

Luckily for Mary-Rose, this did not happen thanks to the care and support she received at her local Leg Club.

"The nurses gave me a test to make sure my circulation was good enough to have a pressure bandage applied, so that healing could begin from the base and not from the surface," says Mary-Rose. "The pressure bandage was re-applied regularly and within eight weeks my leg ulcer was healed.

"Blessed relief! I now have my life and legs back again."

Improving wound healing

Wound healing is a complex process which is still not fully understood. The skin is made up of three main layers, the uppermost epidermis, the middle layer called the dermis, which contains blood vessels, hair follicles and nerves, and the deepest fatty layer called the subcutis, which contains larger blood vessels and nerves.

If these layers become severely damaged by extreme temperature, trauma, chemicals, or sunlight for example, the wound may not heal properly, or may lead to extensive scarring. Luckily there is much which can be done to help wounds heal, as RAFT researchers have found out.

DEVELOPING A NOVEL WOUND HEALING MODEL

All good researchers need effective tools, and when studying wound healing, it can be difficult to find these tools. In the early 1990s, researchers at RAFT spent several years helping to improve this situation by developing a new laboratory model of wound healing.

There were three primary issues they were facing:

- It can take a long time to develop and validate a laboratory model;
- The model must be easy and reliable to use in experiments, and economically viable; and
- Most importantly, it must be proved to have similarities with humans.

Eventually, after much trial and error, the researchers were able to establish a model for studying skin grafting, which further studies proved healed in a very similar way to human skin. The model has subsequently been used for many years by researchers at RAFT and other research institutes, helping to answer specific clinical problems associated with skin grafting.

They were able to study at a very detailed level exactly how wounds heal, and the different structural changes of skin after it has been grafted.

The model is now regarded by scientists worldwide as one of the standard techniques for studying wound healing, and has been invaluable in helping to push forward research and understanding, and developing new treatments for burns injuries.

INVESTIGATING THE WOUND HEALING PROPERTIES OF GREEN TEA AND OTHER NATURAL COMPOUNDS

Some of our most effective pharmaceutical remedies have been 'borrowed' from nature. Aspirin was originally developed from a type of tree bark, digoxin, a heart drug, comes from the foxglove plant. In the mid-2000s, a couple of surgical research fellows at RAFT decided to investigate if any natural compounds might be useful in wound healing.

"It was a side project really" says Ben Klass, one of the research fellows involved. "We already knew that a molecule called TGF-Beta-1 is a major factor involved in wound healing, and we wanted to see if any natural compounds might affect TGF-Beta-1 and its activities on wound healing."

Using a cell-based wound healing model established at RAFT, the researchers investigated several different natural compounds with known anti-inflammatory, anti-oxidant, and potential wound healing effects.

They found that three compounds, a green tea extract known as epigallocatechin-3-gallate, or 'ECGC', an extract from red wine, and a

phospholipid- a naturally produced substance- all had "promising effects" on TGF-Beta-1.

The ECGC research has since been written-up and published, and Ben says that international interest exists around the potential use of this compound in wound healing.

"I still get emails from researchers in China asking about my green tea research," he says. "As you can imagine, green tea is very important over there!"

Ben reports that the phospholipid results were also very promising, and have been taken on by a pharmaceutical company interested in developing the research further. "I loved my time at RAFT," says Ben. "Not only did I gain incredible skills and get to do some really interesting research, but I also got to run a marathon for the charity, and meet some life-long friends!

EVALUATING THE USE OF SUGAR PASTE AS A WOUND DRESSING

One of the earliest pieces of research RAFT helped to fund was a simply-designed study investigating the benefits of packing wounds with sugar paste compared to antiseptics.

Using sugar paste may sound surprising, but honey has long been known to be an effective antimicrobial, and at the time of the study, published in 1990, a special sugar-paste had recently started to be used in wound dressings at some UK hospitals, including nearby Northwick Park Hospital.

Scientists thought the paste could have antibacterial properties similar to antiseptics, but would be more gentle on damaged skin. However few well-controlled studies had been done using current clinical wound dressing practices. So RAFT researchers collaborated with

RAFT has investigated green tea as a wound healing agent

WHY ARE SCIENTIFIC MODELS IMPORTANT?

Scientific models have the aim of understanding, defining, quantifying, visualising and simulating a specific subject.

Models are central in what scientists do, both in their research as well as when communicating their explanations. Models help us to study the characteristics of a cell, a disease process, the human body, or any other entity we may be interested in. In short, models are one of the principal instruments of modern science.

Scientists spend a lot of time building, testing, comparing and revising models, and much journal space is dedicated to introducing, applying and interpreting these valuable tools. Scientists build models to explain how aspects of the real world work.

A scientific model consists of ideas and concepts, and includes some kind of mechanism. In biology, scientific models can take many different forms, including animals, cells, molecules, and even very complex mathematical algorithms or computer software.

The purpose of modelling varies, some models such as the three-dimensional double helix model of the DNA, are used primarily to visualise an object or system, often being created from experimental data. Other models are intended to describe an abstract or hypothetical behaviours or phenomena.

For example, predictive models such as those used to project health outcomes of disease epidemics, generally are based on knowledge and data of phenomena from the past and rely on mathematical analysis of this information to forecast future occurrences of similar phenomena.

In vivo testing refers to when scientists have used an animal or patient model. Animals are used during the research and investigation of human conditions for the purpose of better understanding the problem without added risk to a human being. In vivo testing in animals is a prerequisite step for most drug trials in humans.

In vitro refers to the technique of performing a given procedure in a controlled environment outside of a living organism. The term *in vitro* derives from the Latin language, translating as "in glass".

These tests are usually performed on cells or in test tubes in the laboratory. They are conducted using components of an organism that have been isolated from their usual biological surroundings in order to permit a more detailed or more convenient analysis than can be done with whole organisms.

In vivo and in vitro testing is vital as part of the pre-clinical trials stages, which are used in developing a drug.

Scientists try to explain aspects of the real world by comparing them with models that are based on familiar mechanisms. Scientific models must be testable and they are accepted by scientists only after they have been tried, tested and validated in the real world.

Once models are accepted they allow scientists to communicate and understand each other because they provide a common, shared mental picture of the research.

HONEY & SUGAR

The notion of using sugar to tend to wounds is not a new one.

Ancient Egyptians were not only using sugar and honey on wounds around 4,000 years ago, but also documented their success in the Ebers Papyrus which outlined 147 ways to apply honey to the body.

Legendary Greek physicians Galen and Discorides used sugar in their treatments, calling it Saccharam.

Sugar and honey are still being used in treating wounds throughout the world and in places that might surprise you. The UK's National Health Service uses honey gauze in treating chronic wounds such as leg ulcers and bed sores

Northwick Park and investigated the properties of sugar paste and various types of antiseptics on gauze in wound healing in pigs.

After seven days, the researchers found that the antiseptic gauzes had delayed wound healing compared to sugar paste. They concluded that the sugar paste had performed better than antiseptic gauze, but added that the study was small; and also that the delayed healing could be due to the gauze, the antiseptic or both.

Nevertheless, the researchers recommended sugar paste to be an effective and safe alternative for wounds usually dressed with antiseptic materials. Sugar and honey based dressings are still used in hospitals today, and discussion still rages as to whether sugar is preferable to antiseptics in some cases. Despite its small size, the study conducted by RAFT all those years ago is still cited in books and papers discussing the topic, even today.

LEARNING FROM FOETAL CELLS; FINDING OUT WHY THEY HEAL WITHOUT SCARRING

It is well established that the skin of babies in the womb can heal without scarring, whereas injuries to adult skin will often leave a scar.

In the early 2000s, a team of RAFT researchers embarked on a programme of studies with the aim of learning from foetal skin cells, and understanding why they behave differently to adult skin cells. They hoped they could find clues which might benefit the development of potential new anti-scarring treatments.

By comparing foetal skin cells to adult skin cells in the laboratory, the researchers were able to show distinct differences in behaviour of cells to certain molecules, including TGF-Beta-1. The researchers successfully published many papers helping to describe why foetal cells can heal without scarring, and the search for anti-scarring treatments continues to benefit from this invaluable research funded by RAFT.

Investigating biomaterials

The use of synthetic skin substitutes or 'biomaterials' during grafting and wound healing can help to improve the speed and quality of skin healing, and also act as a barrier to infection. RAFT is lucky to have had significant success in this field.

DEVELOPING A COMPLETELY NOVEL BIOMATERIAL

The RAFT biomaterial research programme originated around ten years ago and early discussions between lead researchers and plastic surgeons had identified an urgent clinical need for a ready-made biomaterial which not only worked well, but was also robust, reliable, and cost-effective.

Smart Matrix™ is the carefully designed product of this research. A specially developed scaffold biomaterial, it helps skin regeneration by encouraging new growth of cells and blood vessels. Every step of Smart Matrix™ research has been funded by RAFT; from first identifying fibrin as a suitable base material , to modifying the structure so it breaks down when no longer needed, and even determining the best storage method.

Student Victoria Tse and Dr Keith Blackwood

Dr Keith Blackwood, a former postdoctoral researcher at RAFT helped to refine and optimise the new biomaterial. When Keith joined the project the basic material had been developed, but a huge amount of work still needed to be done.

"You could clearly see there was something there," he says, "it just needed to be tweaked a bit." Keith spent 18 months running daily tests on the material, gradually optimising and improving the formula.

"We must have tried way over 100 different formulations," says Keith. "It was just a case of sitting down and saying: 'Okay, we need this aspect to be a bit more like this, we need this bit to change'. For example, we knew a porous structure was biologically better, but structurally, it was difficult to maintain. It wasn't making massive leaps, just coming in every day and 'chunking' through it, slowly moving forward, optimising bit by bit."

Now finally all the hard work has paid off. Preclinical studies in the laboratory have shown exciting results. Smart Matrix™ seems to perform well and has a real potential to help patients. Helped by the award of a prestigious government LINK grant to develop a manufacturing process, Smart Matrix™ is now about to enter clinical trials in humans for the first time.

ESTABLISHING THE VALUE OF NEW BIOMATERIALS IN WOUND HEALING

There is no such thing as a 'bad result' in research; even negative findings are necessary. Any knowledge is good knowledge; it all helps to move the field forward and inform doctors on the best available treatments, the best way to help their patients.

One surgical research fellow spent his time at RAFT in the mid-2000s doing just that. The fellow completed a staggering body of research, and published five papers in just five years evaluating the suitability of a relatively new biomaterial, PermacolTM, for use in skin reconstruction and grafting.

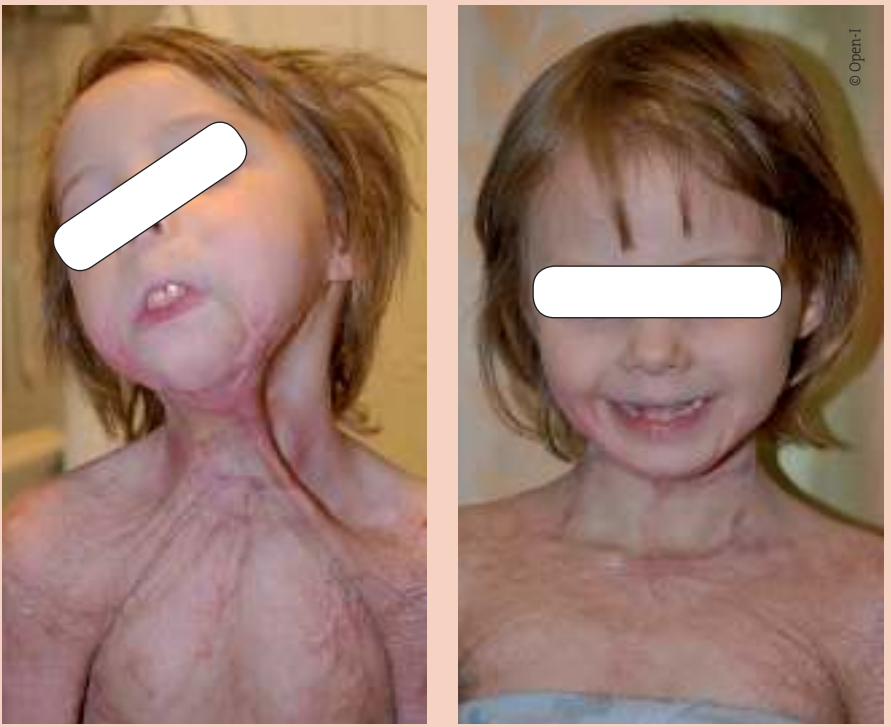
PermacolTM had previously been used for hernia repair, and RAFT wanted to know whether it might also be useful in grafting.

The research was thorough, intensive, and detailed. Just one study, investigating the long-term cellular and immune effects of PermacolTM in a laboratory model took 20 weeks to complete. The results showed that although PermacolTM was well tolerated and safe to use, blood vessels did not readily grow into the material – a necessity if it is to be used in skin repair.

Another study investigated whether a special type of diamond laser could be used to punch little holes in the material, and so encourage blood vessels to grow. The resulting paper states that this method 'proved to be problematic', which is scientific speak meaning it was practically impossible.

Nonetheless, the holes were eventually successfully made, and a further study was completed investigating if they improved blood vessel growth. They did, but only into the holes themselves. The rest of the material was still completely free of blood vessels.

The authors concluded that laser "may not be the optimal method" of increasing the permeability of PermacolTM. All in all, a huge amount of work, which was summed up by just one single sentence in a skin grafting review published by the Journal of the Royal Society in 2009. The journal found it adequate to state merely that the use of PermacolTM for skin regeneration was 'limited'. All that work for one tiny sentence. But a very important sentence indeed when a surgeon needs to decide the best material to use.



This 6 year old girl sustained a 35% TBSA scald injury and subsequently developed a severe neck contracture. She underwent treatment with PDL × 3 prior to release of her neck and coverage with a full-thickness skin graft. Use of the PDL prevented the need to use tissue expanders or even a free flap, to correct this deformity. ©Open-I

BIOMATERIAL BASICS

A biomaterial is any material, natural or man-made, that comprises of (whole or part) living structure.

Biomaterials as a field has seen steady growth over its approximately half century of existence and uses ideas from medicine, biology, chemistry, materials science and engineering.

The range of applications is vast and includes such things as artificial arteries and skin, contact lenses, and dentures. Other biomaterials include certain metals, which might be used in reconstructing bones or joints. For example, metal ball joint sockets can be used in knees or hips.

Preventing Scarring

Hypertrophic scarring, when scars become raised, red, and often painful or itchy can be a traumatic consequence of a burn injury. It has been estimated that around a third of all burn patients will develop hypertrophic scarring as a result of their injuries, and this figure can be 50% or higher for children, who are particularly susceptible to this type of scar.

Unfortunately there is still no single treatment which is considered ideal for healing hypertrophic and other burn scars, and research is still continuing at RAFT to improve this situation. Below are some of the ways RAFT has helped to improve the situation for patients with severe scarring.

RUNNING THE FIRST EVER TRIAL INVESTIGATING INSULIN AS AN ANTI-SCARRING TREATMENT.

Over several years researchers at RAFT carried out considerable work investigating potential anti-scarring treatments which could be applied at the time of injury. Surprisingly, insulin turned out to be one of the most promising treatments in preliminary laboratory experiments. Even more interesting, it appeared to be effective after just one application, making it ideal for use during surgery.

Insulin had been investigated before in the treatment of wounds, but its potential as an anti-scarring agent was unknown. So in the mid-2000s, researchers at RAFT set up and ran a small Phase II clinical trial investigating the safety, feasibility and potential effectiveness of using insulin during surgery to reduce scarring.

A total of 30 patients undergoing breast surgery at Mount Vernon Hospital were recruited to take part in the trial, and half had insulin applied to their incisions during surgery, and half did not. The patients' scars were then assessed at six weeks and three months after surgery. Results were promising.

Insulin was shown to be safe and its use during surgery as an anti-scarring treatment was shown to be feasible. Results also suggested it might have an effect on improving scarring, though a much larger trial was needed. Since then a biotechnology firm has taken on the clinical development of insulin for treating scarring, and the results of a much larger trial are expected soon.

The impeccable quality of the insulin research conducted at RAFT has been recognised nationally with the research team receiving at least two awards, including the prestigious London Biotechnology Network Bio-innovation Award in 2006 for their innovative work on anti-scarring treatments.

WHY CELLS REFUSE TO DIE IN HYPERTROPHIC SCARS

A huge number of different cell types are needed to help heal injured skin. Of all these cells, a type called myofibroblasts are one of the most important.

After injury, myofibroblasts move to the site of the wound and react to special signals. They start producing proteins such as collagen, which help to strengthen the area of the wound. Myofibroblasts are also able to contract, helping to bring the two sides of skin together and close the wound.

Usually these myofibroblasts die off at the end of the healing process, when they are no longer needed. However in hypertrophic and other problematic scars, the myofibroblasts are

APOPTOSIS

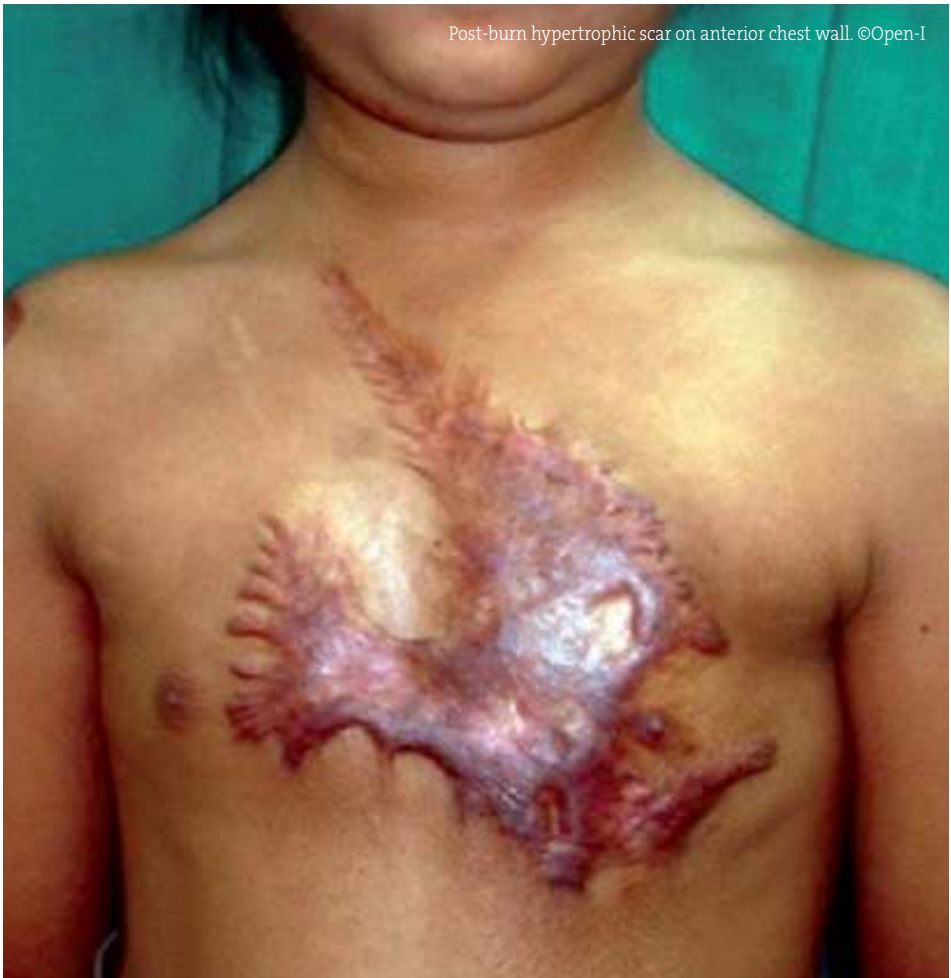
Sometimes known as programmed cell death, is when a cell commits suicide. It involves a controlled sequence of steps in which cells signal self termination.

Apoptosis works to keep the body's natural process of cell division (mitosis) in check.

This process is essential to human development. In the womb our fingers and toes are connected to one another. Apoptosis is what causes the webbing to disappear leaving us with 10 separate digits.

thought to hang around, and stay switched on, producing more and more scar tissue.

It has long been thought that the reason these cells fail to die is because they refuse to commit a form of cell-suicide called 'apoptosis'. But even though many different laboratories had tried to show if, how, and why this was the case, results were still very much undecided. In 2005, researchers at RAFT joined the fray and published an elegant piece of research using



Post-burn hypertrophic scar on anterior chest wall. ©Open-I

different types of scar cells grown from the RAFT bank of patient cells.

The research showed that while a specific form of collagen was able to trigger normal scar cells to undergo apoptosis, hypertrophic scars cells did not react. Digging deeper, they found that the type of collagen in hypertrophic scars appeared to be different, and was unable to trigger the essential apoptosis needed. The team even went so far as to suggest the culprit for this change was a specific molecule which is involved in stabilising the structure of collagen during healing.

There is still much to find out about wound healing, and all the different processes which occur during scarring, however RAFT's research has helped to explain at least part of a very complicated story.

SHOWING FOR THE FIRST TIME THAT THE EPIDERMIS MAY PLAY A ROLE IN HYPERTROPHIC SCARRING

How hypertrophic scars form is still not fully known. The skin is made of two major layers, the dermis which is the deep layer of skin containing nerves, hair follicles and blood vessels, and the epidermis, the protective waterproof outer layer of skin.

Scientists used to think that problems with the dermis was probably to blame for hypertrophic scarring, and that the epidermis was only minimally involved, if at all. That is, before research performed at RAFT proved otherwise.

In the mid-1990s RAFT surgical research fellow Michael Machesney set out to investigate if the epidermis could be involved in hypertrophic scarring.

"Most of the literature of the time discussed hypertrophic scarring as if it was a disorder of the dermis, they did not even consider that the epidermis might also be involved," he says. Using matched samples of hypertrophic scar tissue and normal skin taken from the same patient, Michael was able to directly compare differences between the two samples after growing cells from the skin samples in the laboratory.

"We had samples from 14 patients attending the outpatient clinic at Mount Vernon Hospital and what was great was that I knew the patients, I knew where the samples had come from because I had taken them, and I could make sure they were matched to the same area of the body from the same patient. It was great RAFT was situated close to the hospital and the patients. I could take a biopsy and then take it straight back to the laboratory."

What Michael found when he started studying the skin samples was that cells from the epidermis of the hypertrophic scar tissue produced much higher levels of certain molecules, called keratins, compared to normal skin tissue. These molecules are not normally produced in the epidermis as they are known to be associated with 'activated' cells, that is, cells which divide at a much higher rate than usual.

Michael says: "We knew we had an exciting finding, so we published a short communication paper quickly in the American Journal of Pathology."

His research has since been cited by over 120 other research papers. "We helped to open up a whole new area of hypertrophic scar research," says Michael. "Since our work at RAFT, there is now a large body of research on the epidermis in scar healing, and hopefully we are a step closer to finding a treatment."

Inside the inferno

You're inside a building on fire and the temperature has reached 700 degrees centigrade. Don't try looking for any paper or wood, they're already distant memories. Any plastics in the room have ignited long ago, and aluminium, lead and tin have already passed their melt temperature. A piece of iron in the building's frame work has become red hot and if you grab it with your insulated gloves for support, it will easily bend in your hands.

This is the intense conditions 26 year old London firefighter Richard Richards found himself in – an environment so hot it would make the surface of Venus feel cool by comparison. Even in his protective clothing he knew one thing: if he stayed in the fire a minute longer he'd be dead. He already could feel his body beginning to burn.

Richard, a member of the 'Green Watch' at Wandsworth Fire Station (fire stations have four watches, all colour coded), says the call came in around 10.45pm on 8 January; a three storey terrace house in East Hill was on fire. There was a shop on the ground floor – empty – but there were residents living above. Was everybody out? No one was sure.

Richard was with the second team consisting of four firefighters; they got the word to go inside and join the 1st team.

"The upstairs had been converted into bedsits; it was really confusing inside and real hard to get your bearings," he says. Still, they were there to do a job.

However, once it was determined that all residents were safe outside, 1st team radioed to the others to get out.

"We started moving towards the stairs. The smoke was thick; real thick and it was all pitch black," says Richard. "Even with a torch, you couldn't see a hand in front of your face."

The 2nd team started going down the stairs but ran into an unexpected obstacle. The 3rd team had tried to move a bookcase, but it feel apart in their hands and it now blocked the stair well. Second team started bumping their way back up the stairs, hoping to find another escape route.

"My recollections are a bit hazy, but I remember starting to get hot, so hot. My body was sweating a lot due to the head and exertion, and my sweat had nowhere to go; I was being steamed alive in my own suit. I knew we had to get out or we were dead."

Richard got on his radio and called out to his teammates, but he couldn't hear anyone. He describes it as being "eerily quiet". Where was everyone?

"I was beginning to think that everyone else had either gotten out or were dead. Again, I couldn't see anything so I started to feel around me, trying to touch someone else."

Relieved not to have felt the body of a fellow firefighter, Richard decided to try the stairs again.

"I hit my panic button on my uniform to let them know I was in trouble and went for it. Once I made it to the bookcase, I climbed over it and tumbled down the stairs, knocking myself out in the process."

The green team leader found Richard and tried to pick him up but couldn't; he says Richard felt like a sack of lead and wasn't sure if he was dead or alive. With two other firefighters assisting, they were able to get Richard out of the burning building.

"When I came to, my mask was off and somebody was speaking to me. I wasn't sure what they were saying or much else but I knew I was alive."

All four in the 2nd team had been injured by the fire but Richard was the worse off. At the hospital they discovered that he had third degree burns, and a combination of third and second degree, covering in total around 18% of his body. The worse affected areas were his arms, back of the neck, shoulder blades and upper thighs.

"The first thing they did was to scrape away all the dead tissue and wrapped me up. My brother took a picture of me that now makes me laugh. The bandages were around three to four inches thick; I looked like a mummy."

For the first week Richard had to wear uncomfortable plastic splints on his arms to keep them straight, otherwise his hands would have started curling inwards.

"Between the burns and the splints, I was on constant morphine for the first week. This gave me really strange dreams but the nurses said that this was a normal reaction," he says. "About this time they started then to do the skin grafts, this was more painful than the initial burn," he says.

"To describe it best, if you can remember falling as a kid and getting a skin graze, well multiply the pain about a billion times, it was that painful. The doctors attached the skin with staples; I had around 300 to give you an idea of the size of my skin grafts."

Once he got past the dangerous first week, the hospital figured that he would be there for five to seven weeks – at least. However, thanks to his age, fitness level, diet and general health, he was able to leave the hospital after 19 days.

But being back at home with his fiancée and parent didn't mean he didn't he was finished with the hospital. With the bandages requiring specialised care, doing something as simple as bathing was beyond his abilities so he needed to go back around four to five times a week.

"Right now except for a small part of my chest I'm covered with scars, but I'm really lucky. The doctors told me that they had not had a textbook case like me in a long time and I had the fastest recovery they had ever seen – I feel pretty good about that.

"You hear about a lot of people having infections, I didn't have any. One of the grafts didn't take as well as it should and it had to be replaced; that was as bad as it got."

Richard says that his fiancée was mad – the accident happened three days before her birthday – but not at him or the department. "She - like me - figures something like this goes with the territory of being a fireman. My family was massively worried but very supportive."

Richard is telling this story inside the courtyard of the London Fire Brigade's training centre. As he finishes, a colleague walks by. He asks Richard how much more work they have left on him and Richard holds up his hand. "They got to put another skin graft on here by my thumb," he says.

"You got anymore skin for them to take?" jokingly asks the other firefighter.

"There's not much but I'm sure they'll find a spare patch somewhere," he jokes back.

After his friend leaves he is silent for bit.

"I don't know if it's true but I've been told that no firefighter has been burned as bad as I was and lived to tell the tale," he says, any laughter gone from his voice. "Sometimes it hits me how close I came to dying."

Nerve and Tendon Repair

Tendons and nerves are the supporting structures to the muscular building-blocks of our body. Tendons help hold the muscles in place- connecting them to bone and allowing them to contract and move our skeleton.

Nerves are the electrical wires, sending impulses from the brains to muscles and kick-starting their contraction. Nerve and tendon repair makes up a significant proportion of a plastic and reconstructive surgeon's workload.

From helping people with facial palsy to smile, to enabling people with the debilitating hereditary condition Dupuytren's disease use their hands again, RAFT has improved patient's lives in numerous ways, all connected (excuse the pun) to repairing nerves and tendons.

Facial palsy

Facial palsy is the temporary or permanent weakness of facial muscles, usually due to damage of a facial nerve. There are many different causes of facial palsy, and luckily many people will eventually recover. However for some, it sadly becomes permanent.

Estimations have suggested that there are currently around 100,000 people in the UK living with severe facial paralysis.

Facial palsy is often 'unilateral', that is, it only affects one side of the face. People who have permanent unilateral facial palsy most

Above: Patient with facial palsy

commonly have had it from birth, or have developed it as a complication of cancer. Another common form of facial palsy is Bell's Palsy, the cause of which is still not fully understood.

Symptoms of facial palsy can be painful and incredibly distressing, and patients are forced to contend with a range of physical and emotional difficulties. One treatment option is surgery and plastic surgeons at RAFT and Mount Vernon Hospital have a long history of helping people undergo successful facial palsy surgery.

In fact, Mr Douglas Harrison, one of the co-founders of RAFT, is considered a world-leading expert in facial palsy surgery, with almost 40 years of experience. During his time at Mount Vernon he developed a pioneering surgical technique which became the gold-standard in surgery for unilateral facial palsy. Over the last 25 years, researchers at RAFT have worked with Douglas to help us understand more about facial palsy, and improve surgical treatment for this condition.

UNDERSTANDING HOW TO MAKE A SMILE SYMMETRICAL

The standard surgical treatment for unilateral facial palsy was developed by RAFT cofounder Douglas Harrison and his colleagues over a period of many years from the mid-1970s.

"I was very lucky," says Douglas, "my generation were the first generation to be trained in microsurgery."

Microsurgery is the technique of performing very fine and detailed surgery under a microscope. The technique started to be widely used by surgeons around the early 1970s, and it opened up a range of new treatment possibilities.

Surgeons trained in microsurgery were now able to connect very tiny blood vessels and this meant that they could transfer muscles and reconnect them in other parts of the body much more easily. This was a huge boon for unilateral facial palsy surgery, as the technique requires transplantation and restoration of nerve and muscle to the side of the face which is paralysed.

One of the main aims of this surgery is to give somebody a symmetrical smile, allowing them to show emotion without fear or embarrassment. Other researchers around the world were also developing surgery with this aim.

Some surgeons had developed a popular technique which involved using muscle from the leg, whilst others favoured a muscle near the temples. But Douglas and his colleagues thought a small muscle in the chest, called the pectoralis minor muscle, would do the job perfectly.

"I picked on it because it was a good shape, it was triangular, and because I knew it wasn't that important," says Douglas.

The triangular shape of the muscle allowed for a greater range of the movement in the face, helping patients make the all-important perfect smile.

The surgery Douglas championed involves two stages. First a nerve is taken from the leg and grafted to grow from the side of the face with movement to the paralysed side. Once the nerve fibres have reached the other side of the face, they can then be connected to newly transplanted muscle.

Douglas spent many years developing and perfecting the technique, trying to understand how to get the very best results. Many researchers who were funded by RAFT worked alongside him, helping to optimise and understand the best way to perform this and other types of facial palsy surgery.

TRANSPLANTING NERVES FROM THE LEG TO THE FACE: STUDYING THE STRUCTURE OF NERVE GRAFTS

"We researched so many different ways of improving this surgery." says Douglas Harrison. "I knew I got better results in children and I wanted to know why." So Douglas and his colleagues, including RAFT surgical research fellow Hamish Laing, enlisted the help of researchers at University College London to study samples of nerve grafts at the cellular level, to try and understand why some grafts worked better than others.

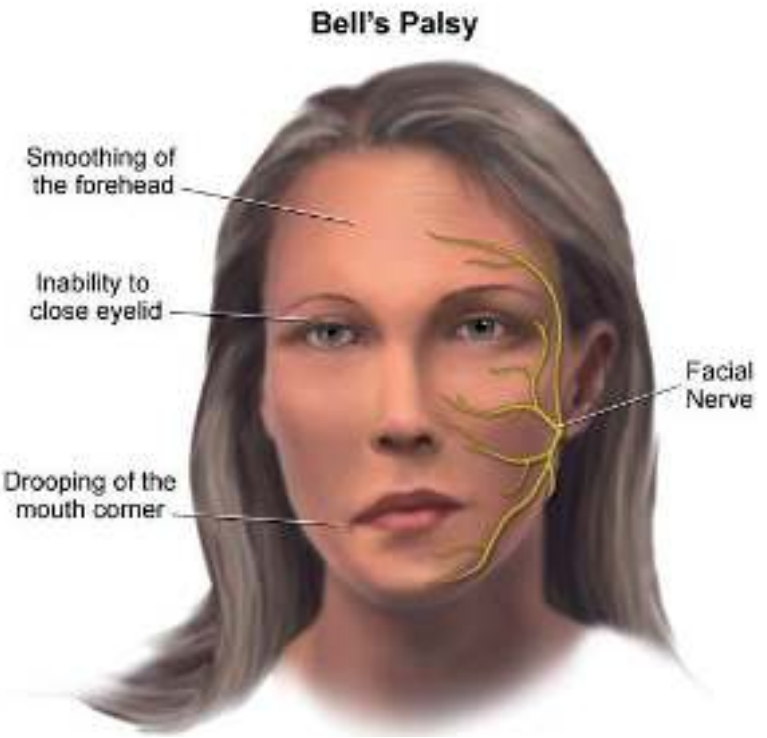
Nerve grafting involves using a 'donor nerve' taken from another part of the body and laying it to form a 'bridge' between the areas where you want the new nerve fibres to grow.

The donor nerve acts like a 'track', along which the new nerve fibres can grow.

For unilateral facial palsy surgery, surgeons at Mount Vernon preferred to use a 20 cm long piece of nerve taken from the leg as a donor nerve.

"Because the nerve was taken out of the leg, the patient ends up with a numb-side of the foot, but it's a lot better to be able to smile!" says Hamish.

Once the nerve is in place, the nerve fibres are left to grow across the graft to the other side of the face .The nerve fibres (called axons) grow at an incredible rate of one or two mm a day, and around six months later, they are ready to be connected to the transplanted muscle. "Douglas Harrison had probably done more facial palsy operations than anyone else in the world at that point." says Hamish of his time working at RAFT in the early 1990s. "It was really brilliant stuff. It was also really good because it meant



we could go in and look at axon growth after so many months, chop off the nerve endings that weren't needed for the surgery, and look at them under the microscope."

The researchers studied nerve graft samples taken from 30 patients aged between 4 and 52 years old. Each patient had undergone the first stage of the surgery and had the nerve grafted under the cheek on one side of their face between five and 15 months earlier.

The molecular studies of these nerve grafts were revealing.

Researchers showed that a large number of axons regenerated through these long nerve grafts. For nerves to work at their best, they must be insulated with a fatty covering called 'myelin'.

The study also showed that many nerve fibres in the graft were not yet covered in myelin, and the researchers suggested that once the nerve graft was connected to the muscle in the second operation, these nerves might then become covered with myelin.

Interestingly, they could find no difference in number and type of new nerve fibres in older or younger patients, or in nerve grafts which had been growing for a shorter or longer time.

There had been some discussion between surgeons as to whether the delay required to allow the nerve fibres to reach the other side of the nerve graft affected the quality of the new nerves. Importantly, this study suggested that there was no obvious deterioration of the new nerve fibres up to 15 months after the first operation, with no effect on the success of the operation.

The results of this study were published in the prestigious journal Brain. "It was a very important study," says Hamish, "a rare opportunity to look at nerve growth in vivo [in the body]."

CHANGING THE TEXTBOOKS – DISCOVERING NEW BLOOD VESSELS.

The second stage of facial-palsy surgery involves transferring the pectoralis minor muscle from the chest to the affected side of the face, so the newly grown nerve fibre can be reconnected and used to move the muscle.

To make sure the muscle retains a good supply of blood, the surgeon must carefully cut-out blood vessels along with the muscle to be transferred. However, opinions have been divided on the best blood vessels to take with the muscle during transplant.

In 2004, RAFT researchers published a study which suggested that a previously unrecorded blood vessel "not described in any textbooks" was in fact the best vessel to use.

The researchers showed by photographs that they were able to identify this new blood vessel in 97 consecutive cases, and that it was the major supply of blood to the muscle in as many as 72% of these patients.

This finding has since been recorded in textbooks and reviews, and used to inform the development of other surgeries involving the pectoralis minor muscle. This demonstrates yet another way in which researchers at RAFT and Mount Vernon hospital pushed forward to boundaries of knowledge to help patients.

The type of palsy surgery developed by Douglas and colleagues gave some of the best results ever achieved for this type of surgery.

"I think we have performed over six hundred of these operations now. About 80 or 90% of patients will get some form of movement on the previously paralysed side of the face, and about 60% will get very good movement." says Douglas.

"The great thing about this surgery is that it allows patients to smile spontaneously, in response to emotion. Before, patients would do

their best not to smile, or cover their face. I like to think there are lots of people walking around [who've had this surgery] who you wouldn't even notice there was anything wrong. I like to hope I've made some people happy."

MOVING FORWARD: THE NEXT STEPS FOR FACIAL PALSY SURGERY

As any good doctor or scientist will tell you, science will always progress, and techniques can always be improved. This includes the innovative two-stage facial palsy surgery developed by Douglas Harrison and his colleagues at Mount Vernon Hospital.

Although enormously successful, there can be some variation in the results. In some patients the previously paralysed side of the face may end up underactive, whilst for others the transplanted muscle may become overactive, which pulls the face over to the paralysed side. Surgeons do not know why this happens.

"It is unpredictable when this will happen," says Fulvio Urso-Baiarda, a RAFT research fellow who worked on this problem in the mid-2000s. "It can be the same surgeon, the same day, and still there will be these problems."

"I had a theory as to why this was happening," says Fulvio. He thought it was to do with motor units - and not the sort you find in cars.

In biology, a motor unit is made up of a nerve fibre and the muscle fibres it stimulates to contract. For muscles requiring fine movement, such as around the mouth, one motor unit will be comprised of many nerve fibres connected to just one muscle fibre. This allows for precise and delicate manipulation of the muscle.

However, for muscles which do not require delicate movement, but which need power (such as in the bum!), you may have just a few axons activating a high number of muscle fibres i.e., the motor units are huge, because the nerve is trying to innervate a massive muscle.

"The ability to finely control the muscle is lost, but the gain is ramped right up." Fulvio thought that this might be the problem with the standard nerve grafts used for facial palsy, sometimes the motor units might be too small, sometimes too large, affecting how much the muscle is activated by the nerve.

Essentially, small differences in the size of the nerve used for grafting could lead to massive changes in muscle stimulation.

HIGH-FIDELITY VERSUS LOW-FIDELITY NERVE GRAFTS

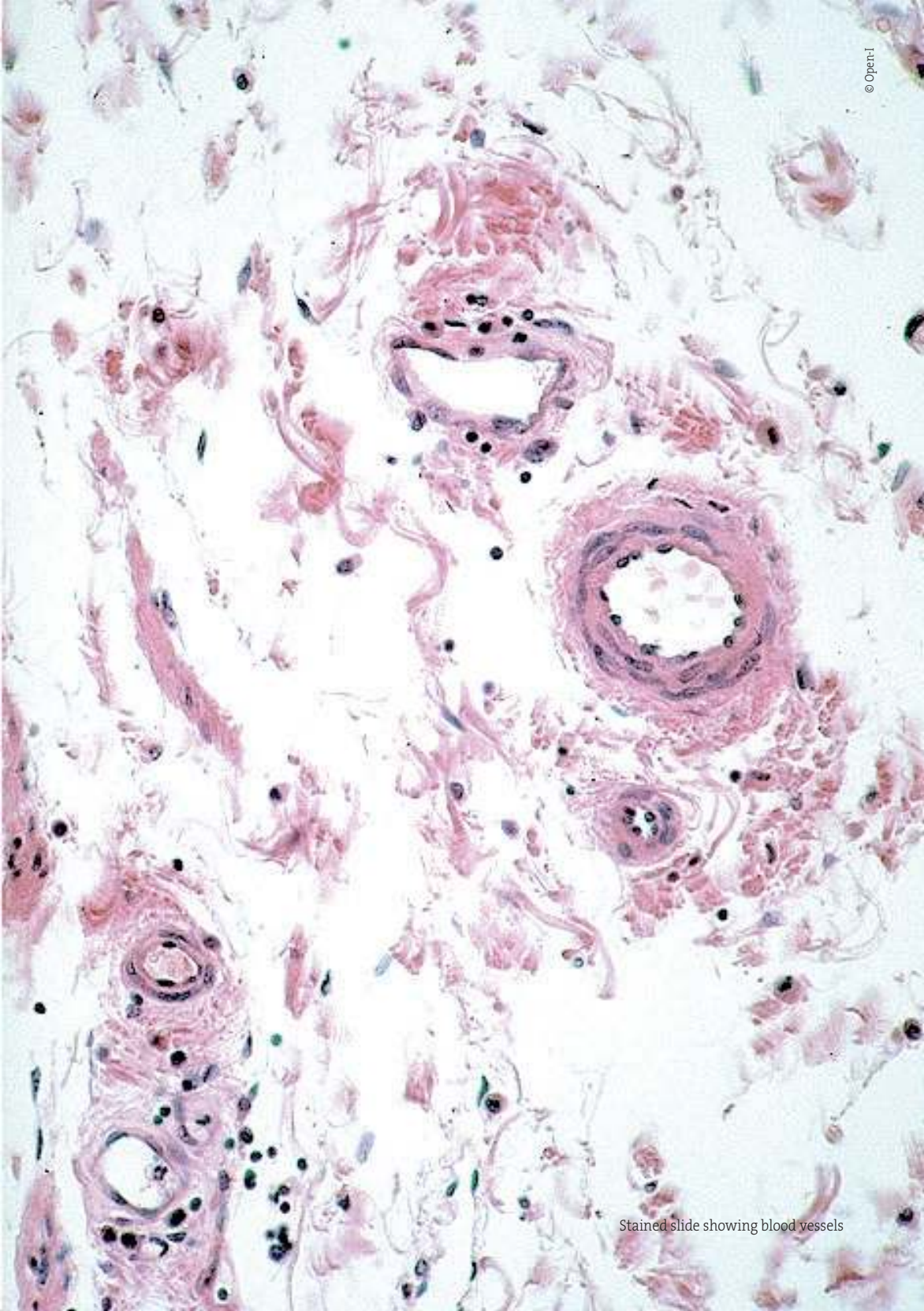
So during his fellowship, Fulvio carried out experiments investigating how different properties of the nerve graft controlled the transplanted muscle in a laboratory model.

"My experiment was comparing the function of big and small nerves in high and low fidelity nerve grafts."

Here, when Fulvio says fidelity he refers to the number of axons allowed across the nerve graft to connect with the muscle- essentially manipulating the size of the motor unit. Low fidelity grafts are smaller with fewer axons attaching to the muscle. High fidelity grafts are larger with a higher number of axons attach to the muscle. This means that the graft is more 'sensitive', and any small change in nerve size can affect function.

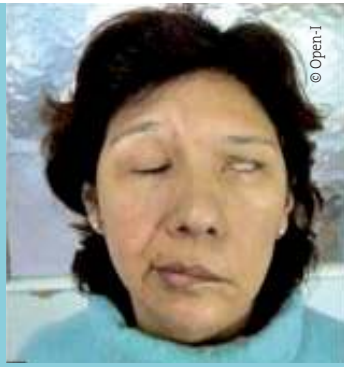
Fulvio found that with larger nerve grafts, how well the muscle functioned was very sensitive to the size of the nerve, whereas with smaller nerve grafts, there was less variability in how well the muscle functioned compared to nerve size.

It is complicated to understand, but the point to keep in mind is that Fulvio had theoretically found a way to standardize the function of nerve



Stained slide showing blood vessels





WHAT IS BELL'S PALSY?

Bell's palsy is an acquired weakness of one side of the face, due to an injury to the facial nerve. The symptoms on the affected side typically include inability to close the eye, to smile, wrinkle the forehead and whistle. Speech may be mildly slurred. Tearing occurs because the eye does not close completely. Taste sensation may be diminished on the front half of the tongue.

In most cases (80%) the condition recedes after three months though for a proportion of sufferers the symptoms can continue for longer and in extreme cases indefinitely.

About 25/100,000 persons per year develop Bell's palsy. The incidence increases slightly with age. There are only minor differences in rates between the sexes and among persons of different race. There is a slightly higher incidence in the winter.

Bells Palsy is the diagnosis when all other possible reasons for paralysis have been discounted and no known cause can be found. It does, however, has numerous potential causes.

It is presently thought that most cases arise from herpes simplex virus infections (the same one that gives you cold sores in your mouth as well as other variants). However, there are a wide variety of other possibilities including diabetes, sarcoid, HIV infection, and various cancers. On the other hand, some possible causes for facial palsy are:

- Bacterial infections such as Lyme disease
- Pressure on the facial nerve possibly due to a cyst or tumour
- HIV
- Middle ear infection
- Facial trauma
- Melkersson-Rosenthal syndrome
- Moebius syndrome
- Guillain-Barre Syndrome
- Sarcoidosis
- Leukemia

Bell's Palsy was named after Sir Charles Bell (1774-1842) who demonstrated that spinal nerves carry both sensory and motor functions and that sensory fibers traverse the posterior roots whereas the motor fibers run through the anterior (Bell's Law).

He also demonstrated that the cranial nerve V was sensory to the face and motor to mastication whereas cranial nerve VII controlled muscles of expression. The eponyms of the respiratory nerve of Bell and Bell's Palsy perpetuate his name.

grafts, to decrease the potential variability in outcome of the surgery.

However, the downside of this technique was that although with smaller nerve grafts the results were more standardised, they were also consistently weaker.

"As a surgeon, you really want to do your best for your patient, you want to make sure you do a graft that works really well, you don't want to start deliberately doing not so well functioning grafts. This was a proof of concept study.

"I knew I was hobbling the results, but I wanted to make them consistent. It shows that as the size of the graft increases, so does variability."

Fulvio sees these results as just the start.

"These results are all from one animal study, it's not really enough to leap straight into humans. I am hoping that this can be a platform for other people to take on this idea, do more animal work, then hopefully human work."

SHOWING ONE-STAGE IS JUST AS GOOD AS TWO-STAGE FACIAL PALSY SURGERY

"I also compared one-stage versus two-stage surgery," says Fulvio.

Standard surgery is performed in two operations which take place around six months apart. The gap is to allow the nerve fibres to grow across the nerve graft and reach the correct place before the muscle is transplanted and connected up to the newly grown fibres.

This is because it is thought that if the muscle is transplanted at the same time as the nerve, it will go a long time without being activated by any nerve and this could irreparably damage the muscle.

Fulvio's preliminary studies in animals suggested there is no difference in success rates if the surgery was performed in one or two stages.

He was one of the first surgeons to investigate one-stage compared to two-stages for this type of surgery. At the same time a group of researchers in Japan were studying the same thing in patients. They showed the same as Fulvio, that one-stage surgery was just as good as two-stage surgery.

"This makes the results very strong." says Fulvio.

Since then, other clinical studies have shown that there is no problem with one-stage surgery. But it might take time before one-stage facial palsy surgery becomes the norm. Fulvio thinks that the majority of surgeons still use two-stage surgery, but there are some who now will do one-stage surgery.

"The stakes are higher in surgery," explains Fulvio. "You don't want to take a punt on people. Slowly ideas may change, but two-stage works very well, so why risk it?"

PROVIDING EVIDENCE THAT BIRTH TRAUMA DOES NOT CAUSE PERMANENT CONGENITAL FACIAL PALSY

Facial palsy is thought to affect around two in every 1000 babies born. The most likely cause of facial palsy in these babies (known as congenital facial palsy) is trauma during birth, for example as a result of using forceps.

Fortunately, the majority of babies born with facial palsy will make a full recovery within the first few weeks or months. However, for some the condition will be permanent, which is obviously traumatic for both parent and child.

It has long been common belief that similar to temporary congenital facial palsy; permanent congenital facial palsy is also most likely caused by some form of trauma suffered around the time of birth.

This can be distressing for the parent, and also for the healthcare practitioner who delivered

Infant with facial palsy

© Dan-i

the baby, and may also lead to medico-legal ramifications.

In 1996 Hamish Laing, a surgical research fellow at RAFT, set out to determine if permanent congenital facial palsy was indeed primarily caused by birth trauma.

Looking back over case notes of some 61 children who had attended either Mount Vernon Hospital or Great Ormond Street Hospital in London between 1983 and 1993, Hamish and colleagues identified 53 who had permanent facial palsy, with no other complicating factors.

Next the researchers wrote to the mothers of each child, asking specific questions about the birth, such as use of forceps, mode of delivery, the baby's birth weight and whether this was their first pregnancy.

Every mother they contacted responded, and the research team were able to carry out detailed statistical analyses to determine if the rate of traumatic births in this group of children was higher than in the general population, as might be expected if traumatic birth was indeed a cause of permanent facial palsy.

Instead, they found that the risk of these children having had a traumatic birth was

no more than for other children, suggesting traumatic birth may not be a primary cause of this form of facial palsy.

This study was followed up by a further study from RAFT in 2000 which performed MRI scans on patients with permanent congenital facial palsy for the first time. Studying these scans, the researchers found that some structures of the brain were abnormal in four of 15 (27%) patients.

This is a much higher proportion than previously thought, and the researchers suggested that problems with the brain may be a much more common cause of congenital facial palsy than previously assumed.

Facial palsy is a complicated condition, and there is still much debate over the true causes and forms of the disease. Hopefully, researchers at RAFT have helped us to understand the condition a little more.

Both RAFT studies have since been cited many times, and Hamish Laing's 1996 study is even referenced in a recent edition of the study guide for postgraduate medical students training to take the Royal College of Paediatrics and Child Health exams to become paediatricians.

Dupuytren's Contracture

Dupuytren's contracture is a relatively common condition affecting the hands. Over 2 million people in the UK have Dupuytren's, and though it can affect anyone, you are most at risk if you are a male over 50 years old, have Celtic heritage, and have a family history of the condition.

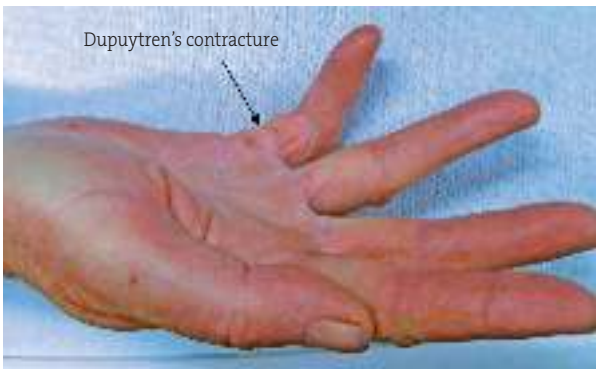
People who develop Dupuytren's may first notice small lumps or nodules under the skin around the palm of their hand which can be painful. The condition can gradually worsen until the fibrous tissue in the hands become so damaged that movement is lost in one or more fingers, which become permanently bent.

This can obviously cause distress, discomfort, and inconvenience for the sufferer. Despite this condition being relatively common there is still very little known about how and why it develops. The best treatment option available for the worst cases is surgery, and even then, the condition often returns.

RAFT has completed a number of successful studies looking into the causes of the disease, and searching for potential new treatments. Twelve papers directly related to the condition have been published by RAFT, each one of them helping scientists to inch a step closer to finding more effective treatments for this debilitating condition.

DEFINING WHICH SURGERY WORKS FOR DUPUYTREN'S

One of the first Dupuytren's studies at RAFT, carried out in the mid-1990s compared the different surgical methods used to treat the condition. Up until the second half of this



century the most favoured way of dealing with severe forms of the disease was simply to amputate the offending digit.

As surgeons' skills and tools improved, less traumatic styles of surgery were developed. But debate continued about the best form of surgical treatment for this condition: do we go in there guns blazing, and force that finger to straighten-up, or do we gently massage and coax it back to its original more comfortable position?

The researchers at RAFT helped to answer this question by studying the outcomes of 188 Dupuytren's operations performed at Mount Vernon between 1980 and 1992. They were able to see clear differences in success rates; a form of treatment during surgery which involves a gentle manipulation of the hand to release the bent finger joints proved to be more successful with less complications post-surgery than more aggressive forms of surgery.

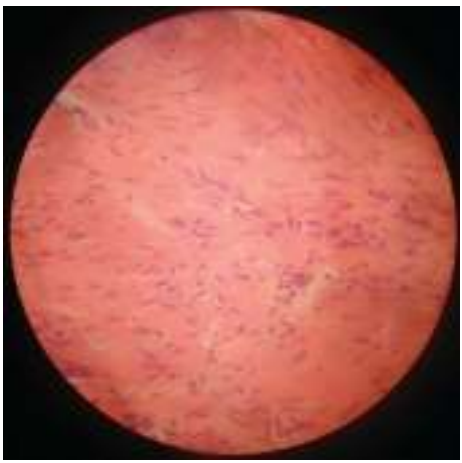
Over the years this gentler type of surgery for Dupuytren's has gradually become more popular, and the research published by RAFT helped to make this happen.

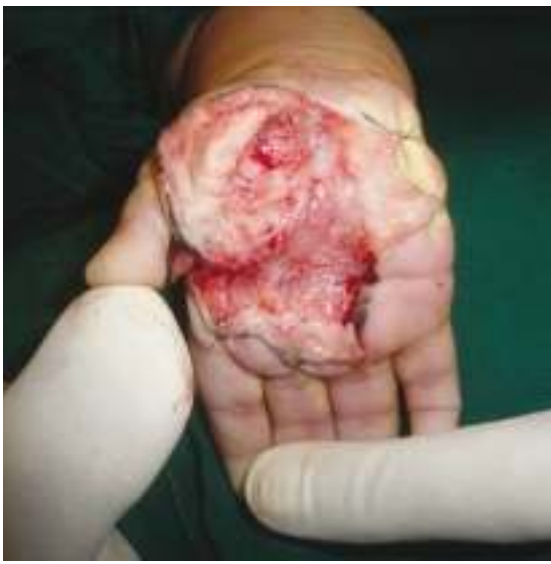
Another important RAFT study again involved searching back though case records of patients who had undergone surgery for Dupuytren's at Mount Vernon Hospital, this time studying a total of 253 patients between 1982 and 1999.

Some patients suffer complications after this type of surgery, and researchers wanted to find out exactly how many did, and why. The great design of this study was that every single patient had exactly the same type of surgery, performed by exactly the same surgeon; an eminent consultant plastic surgeon linked with RAFT, Paul Smith.

Less variability in study methods means higher-quality results. This immediately improved on earlier studies, all of which had involved more than one surgeon and more than one technique.

Using a specially developed disease severity classification system, the researchers found that around 18% of patients (46 out of 253) had complications such as infection or nerve damage during or after surgery, and that patients with severe disease were more likely





(L) High-power view of the histology confirming fibrosis due to Dupuytren's disease found in a four-month-old male child. Only a few histologically confirmed diagnoses are noted in literature. (R) Picture showing the thickened palmar fascia in same child. ©Open-I

to suffer from complications, especially if the finger joint is extremely bent.

The subsequent paper published by RAFT has been cited many times, and other studies have since reported similar findings. This research will help surgeons assess and manage risk for patients undergoing surgery for Dupuytren's.

UNDERSTANDING WHY DUPUYTREN'S COMES BACK

Unfortunately surgery is often not the end of patients' worries, and sadly up to 40% of patients will see their Dupuytren's return within five years. A large part of the Dupuytren's research at RAFT was aimed at trying to solve this problem, and researchers have spent a long time searching for a treatment which could help prevent recurrence of the condition. They have come very close, in fact one potential new treatment investigated at RAFT has made it all the way through to clinical trials. But before trials, comes lab work, and lots of it.

First, researchers needed to set up a model of the disease in the laboratory. A particular type of cell called a fibroblast is responsible for causing many problems associated with Dupuytren's, so they decided to grow fibroblasts from patients undergoing surgery for Dupuytren's.

They then used a variety of techniques to compare the behaviour of cells from affected tissues of the hand with cells from healthy tissue in the same patient. Dupuytren's disease is 'benign' that is, cells do not invade other cells or tissues like some cancers do. Molecular studies at RAFT helped to partly explain why this is, by showing that a gene involved in growth of aggressive tumours called BCL-2 only has low activity in Dupuytren's cells.

Researchers also showed that another gene, c-MYC was highly active in Dupuytren's which had not yet been treated with surgery, but was less active in disease which had recurred after surgery. Importantly, in the patients whose disease came back, the researchers found they could predict how severe the disease would be based on the activity of c-MYC in their cells. This could be very important knowledge when trying to decide the best way to treat a patient with Dupuytren's.

SEARCHING FOR NEW DUPUYTREN'S TREATMENTS

Next the researchers looked for practical ways to stop Dupuytren's returning after surgery. They were interested in a compound, 5-fluorouracil, which had shown some success in preventing scarring problems after glaucoma surgery.

They knew that excess growth of fibroblasts was one of the problems in Dupuytren's, and as 5-fluorouracil stops cells from growing and dividing, they wanted to see what would happen if they applied the drug to the cells from Dupuytren's patients. The results were clear, just one treatment with 5-fluorouracil was enough to stop Dupuytren's cells growing and dividing.

One reason fibroblasts are so troublesome in Dupuytren's is because they produce collagen, a normally useful protein which is needed for healing wounds. However, in Dupuytren's, too much of the wrong type of collagen in produced which leads to formation of 'nodules' in the hand, and contributes to the development of severely contracted fingers.

Exciting experiments at RAFT showed that 5-fluorouracil potently reduced collagen production by Dupuytren's fibroblasts. The researchers concluded from these results: "the clinical implication is that 5-fluorouracil could possibly reduce extracellular matrix production and therefore reduce recurrence of Dupuytren's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THE VIKING DISEASE

Did Dupuytren's contracture come from the Vikings? No one really knows what causes Dupuytren's contracture, but it is well known that it runs in families – 60 to 70% of individuals have a family history of the condition.

Other factors have been suspected for causing Dupuytren's contracture, such as trauma, diabetes, alcoholism, epilepsy, and liver disease, but there is no clear relationship.

While it does affect other population groups, the most common group affected is those who can trace Scandinavian ancestry.

Indeed, a large study of around 1,000 patients conducted in US Veterans hospitals found an incidence of 734 per 100,000 population in whites, 237 per 100,000 in Hispanics, 130 per 100,000 in blacks, and 67 per 100,000 in Asian. In the United States the incidence in white populations is about 3%; in Norway, the incidence is about 30%-40%. The disease is very rare in African Blacks.

In the UK, Dupuytren's was associated for a considerable with those areas in England and Scotland where either the Vikings raided or where they had settlements. With the population now being more mobile, Dupuytren's clusters are not as common.

One story has Dupuytren's contracture coming from a curse against the Scottish piping clan, the MacCrimmons. With their fingers bent so far in their palms, the men could not play the pipes anymore. Interesting, the surname MacCrimmon is believed to be of Norse origin.

disease of the hand." Cautious words but with potentially massive meaning for patients who suffer from Dupuytren's.

This work at RAFT led to a small clinical trial involving just 15 patients undergoing surgery for Dupuytren's at Mount Vernon Hospital.

Each patient had two fingers affected by the condition and during the corrective surgery one finger was treated for five minutes with 5-fluorouracil, the other was treated with an inactive placebo as a control. Patients were then followed-up over the next 18 months.

The results, published in 2004, showed that although 5-fluorouracil was safe and did not delay wound healing as it was feared it might, there was no difference between control and 5 fluorouracil treated fingers in terms of finger joint contraction angles.

These were obviously disappointing results, but not necessarily the end. Research at RAFT has shown that 5-fluorouracil has beneficial effects in the laboratory, and bigger trials are needed to establish without doubt what effect, if any, it has on Dupuytren's in patients.

Until this happens, 5-fluorouracil remains designated in treatment guidelines as an 'experimental' research treatment which has not yet been proven in patients.

But the search for a treatment didn't stop there. In the late 2000s, another surgical research fellow at RAFT looked into the potentially beneficial qualities of a compound called ilomastat, which inhibits a different type of molecule also associated with Dupuytren's, called matrix metalloproteinase (MMP).

The result was two positive publications showing that ilomastat was able to prevent some of the cell mechanisms which caused Dupuytren's when tested in the lab.

Since then, other research groups have published findings which support the RAFT results, and the potential benefits of MMP inhibitors as a treatment for Dupuytren's continues to be investigated.

Tendon Healing

Tendons are strong cords of fibrous tissue which connect muscle to bone. They are made of tough connective fibres enclosed by a protective membrane called a tendon sheath. The tendon sheath keeps the tendon lubricated and able to move. When muscles contract, the tendons must withstand huge force as they pull and move the bone.

To feel just how resilient a tendon must be, simply try pressing your Achilles tendon just above the heel when your foot is flexed, notice how tough it is.

Unfortunately problems can arise if the tendon becomes damaged and ruptures, commonly as a result of sporting injury, trauma, or diseases like rheumatoid arthritis. It is at this point you may need surgery to repair the tendon.

However, tendons are very weak when they are healing, and often a long period of recovery and rehabilitation is needed.

Even after full recovery it is likely that some loss of movement will remain. Over the years, RAFT has published 20 papers helping to understand and improve tendon repair.

EXAMINING TENDON REPAIR

A major complication following tendon repair surgery can be the formation of adhesions, a type of scar, between the tendon and the tendon sheath. This means that the tendon essentially 'sticks' and is no longer able to glide smoothly, so reducing movement.

Studies on patients who undergo surgery to repair a flexor tendon (i.e., the tendons which help to move a body part), estimate that around a quarter of all patients will experience only poor to fair recovery in tendon function as a result of adhesions.

How tendons heal and why adhesions form has long been a subject of debate. Several pieces of research published by RAFT have provided answers which have helped to settle some of these debates, including three papers published in 2003.

"We investigated the cellular mechanisms of tendon repair." says Martin Jones, one of the authors of these papers. Using novel techniques, the researchers studied tendon healing in detail, investigating where the cells involved come from, and mapping the layout of blood vessels in these tendons.

First the researchers developed a new laboratory tendon model; they were then able to use specially labelled dyes to stain different tendon cells so they could watch their behaviour during tendon healing.

Tendon surgery at a
US army hospital

The researchers found that within a single day of injury and over the course of a week, cells from the surface of the tendon and also even sometimes from the tendon sheath migrate to the centre of the tendon, to initiate healing.

This evidence has not only helped us to understand how tendons heal, but may well have implications for cell-seeded tendon constructs – a form of tendon repair treatment currently under development - for the treatment of tendon injuries in the future, according to Martin.

But that is not all. "We also developed a method for staining tendon vascular architecture," says Martin, essentially meaning they looked at the layout of blood vessels in the tendons.

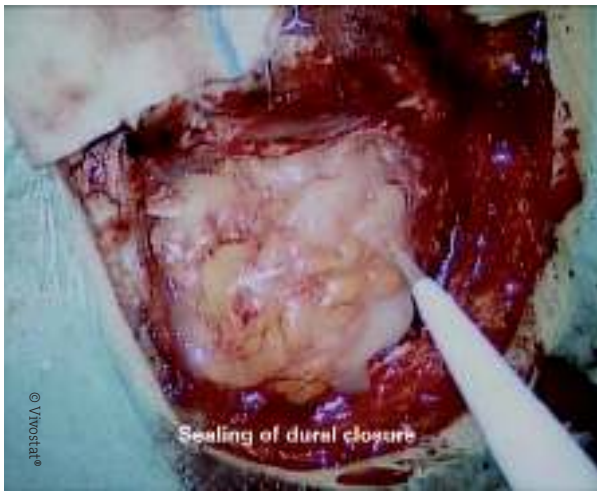
Using a method which preserved all the intricate and delicate detail of the tendon, Martin and his colleagues were able to estimate the tendon vascularity index, that is, the proportion of the tendon which is made up of blood vessels, for different areas of the tendon.

Other studies had suggested that some regions of the tendon might have no blood vessels at all. However, using this more precise method, the RAFT researchers were able to demonstrate that although the number of blood vessels varied in different tendon areas, there were no areas which completely lacked blood vessels. Another chunk of knowledge, and another debate hopefully settled.

"It added further to the understanding of the cellular mechanisms of tendon repair," says Martin.

EXPLORING NEW MATERIALS WHICH MAY REDUCE TENDON SCARRING AFTER SURGERY

Over the years a wide range of experimental compounds have been developed and tested, with the aim of applying them to the tendon healing site during operations to prevent or reduce adhesion formation. As part of the tendon healing project at RAFT, researchers tested the suitability of different compounds which could potentially be used during tendon surgery.



One of the compounds tested was a new type of 'fibrin sealant'.

Fibrin sealants are gel-like compounds which contain clotting factors and can be used to protect and speed repair of surgical wounds.

"Using a rabbit model, we showed that the fibrin sealant significantly reduced tendon adhesion formation compared with controls," says Martin Jones.

The sealant they used was called Vivostat®, a newly developed compound produced by processing the patient's own blood. This gave it an added advantage over other sealants, the majority of which were synthetic or came from pooled human-plasma.

Working in a rabbit model, the RAFT researchers showed that Vivostat® could potentially be useful in tendon repair both with and without post-operative mobilisation of the

tendon. They researchers concluded that should these findings be reproduced in humans, then Vivostat® could potentially help patients who found it difficult to follow the intensive post-operative exercises needed to keep the tendon moving.

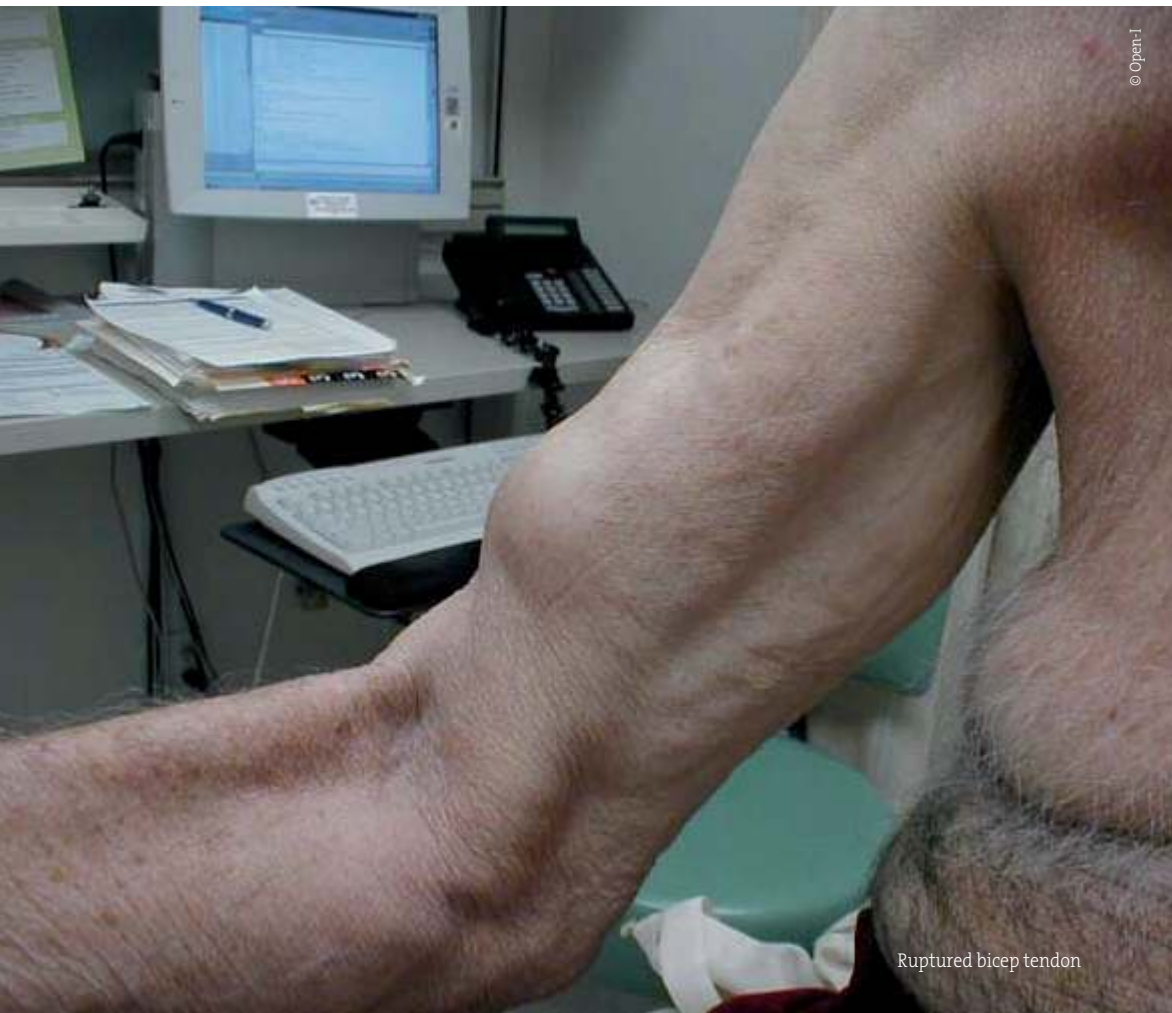
Ten years on, and although Vivostat® is now used in other operations, human data for its use as a sealant during tendon surgery is still sadly lacking.

"I haven't seen it reach the human stage yet." says Martin, "but these things take time." The research produced by Martin and colleagues is published, and has been cited as evidence of potential clinical use, both in books and also by other researchers.

Meanwhile the research (and seemingly the researcher) never sleeps, and scientists at RAFT have been busying themselves developing and testing another novel biomaterial for use during tendon surgery.

Involved in the project was the surgical research fellow Olivier Branford, who won a large lottery-funded grant and a prestigious Royal College of Surgeons fellowship to develop the work.

The initial work was promising and the project even reached the second stage of the prestigious



Ruptured bicep tendon

Medical Futures Awards and Department of Trade and Industry Awards. Although no longer being developed by RAFT, Olivier says that the new biomaterial still "remains an attractive approach to be taken further." And it seems that Olivier's research is already being noticed by other researchers.

SHOWING WHY WITH TENDON HEALING, YOU NEED TO MOVE OR YOU LOSE.

For many years it has been known that movement of the injured tendon after repair surgery can help improve tendon healing and decrease tendon adhesion formation.

For this reason, patients are often asked to carry out various repeated exercises to help mobilise the tendon during recovery. But scientists still don't know exactly why mobilisation helps.

To answer this question, recent RAFT surgical research fellow Olivier Branford developed a new laboratory model system. The system investigated how movement affected tendon healing and adhesion formation, and studied how tendon adhesions were affected by force at both the cellular and the whole adhesion level.

For the first time ever, it was possible to not only visualize, but to also measure local adhesion tissue mechanics. The researchers found that mobilisation altered how the adhesions responded to force and introduced potential points of weakness, which could explain why mobilisation can help disrupt adhesions and improve hand movement after surgery.

Further studies also showed that mobilisation could help favour attachment of 'good' cells to the healing environment while reducing the attachment of 'bad' scar-forming cells from around the outside of the tendon.

Put together, the researchers concluded that the relationship between the mechanical properties and also the cellular environment of tendon adhesions is "complex." But Olivier Branford is hopeful.

"My work has contributed to a change in the approach to the complex problem of adhesion formation. Using these principles we are closer to finding the golden chalice in tendon repair: allowing healing while suppressing adhesion scar formation."

Olivier's words are already starting to ring true. Despite only being published in 2012, this piece of RAFT research has already been used and cited by another team of researchers developing a novel compound to help with tendon repair.

Dr Raina Zarb Adami

RAFT Celebrates 25 Years

Fighting Cancer

Dr Rajiv Grover

Malignant Melanoma

Without a doubt, malignant melanoma was one of the most long-running, innovative, and technically advanced projects at RAFT. Melanoma is usually a form of skin cancer, most often associated with suspect looking moles. In fact around half of all melanomas actually start in normal-looking skin. Melanoma is on the increase; over 10,000 people in the UK are diagnosed with it every year and it is the most common cancer to affect young people aged between 15 and 34 years.

Melanoma is very much "a plastic surgeon's disease," says Rajiv Grover, a former surgical research fellow at RAFT who was involved in the

project. This is because, he says, melanoma can be very aggressive, especially once it spreads through the body. To make sure it is all removed, a very large margin of otherwise healthy skin around the cancer must also be taken, to make sure no disease cells are left.

"This can leave a huge hole in the skin, which may need to be repaired," he says. "The melanoma project was a real corpus of work." He is correct. In over 13 years, no less than 50 melanoma-related papers were published by RAFT. These papers have themselves been cited by other researchers almost 1,200 times. This shows more than anything the quality and impact of the melanoma work carried out at RAFT.

THE EARLY YEARS: SETTING UP THE MELANOMA PROJECT

Haimish Laing came to RAFT in 1991. Not only was he one of the first surgeons to do research at RAFT, he was also directly involved in setting up the melanoma project. Haimish recalls that he got interested in RAFT through the four founding members who were senior consultants at Mount Vernon at the time; Brian Morgan, Roy Sanders, Paul Smith and Douglas Harrison.

At this time RAFT had the good fortune to be based on the same site next to the prestigious Gray Cancer Laboratory, which has since been moved to Oxford. The Gray Laboratory specialised in radiobiology and by 1991 had long been established as an internationally recognised centre of research excellence into cancer radiation therapies.

"There certainly was quite a lot of cancer research going on at Mount Vernon," says Haimish, "Stanley Dische [at Gray Laboratory] had developed a radiotherapy treatment regimen for head and neck cancer which was based around the doubling time of the cells, giving them better outcomes. I thought it would be interesting to look at the doubling time of melanoma cells."

Haimish teamed up with George Wilson at the Gray Laboratory and went about setting up the melanoma project. Over the years, the Gray laboratory had built up a huge 'library' of cancer samples from patients treated at Mount Vernon Hospital, and Haimish wanted to analyse some of these patient melanoma samples, and then follow-up the case notes of these patients over 10 years to find out what happened.

He also wanted to see if melanoma cell doubling time could be related to aggressiveness of the cancer.

But Haimish had an uphill struggle. This was the first biologically based project at RAFT, and an awful lot of organisation and collaboration with other parts of the hospital was needed.

"There was no infrastructure really," says Haimish. "There was a lot of methodological challenge. After all, I was looking at samples, then trying to follow up case notes from 10 years later."

Haimish spent a lot of time establishing new links between the plastic surgery department at Mount Vernon, RAFT, and Gray Laboratory, and getting scientists and clinicians used to working together – which was fairly unusual in those days.

"There were a few minor conflicts," says Haimish. "The research scientist might say 'I can help you in six months, after I've written this paper,' and the doctor will be saying 'but I need it in three months!' George Wilson could see the relevance of patient focus and could see it was good for scientists AND clinicians."

Managing scientists' and clinicians' conflicting ideas of urgency wasn't the only problem. Haimish also had to persuade hospital

laboratories to part with valuable tissue samples.

"Melanoma samples are very tiny; I was helped by having a very collaborative pathology department who were willing to give up their precious sample."

Gradually everything came together, and Haimish published some interesting studies. Although he found that melanoma cell doubling time was not necessarily related directly to cancer prognosis (that is, how the disease will develop), he did find some potential links between certain melanoma cell characteristics and some clinical features of the disease.

The stage was set, the investigation had begun, and the researchers were on the right path.

FINDING C-MYC: A GENE WHICH COULD PREDICT MELANOMA AGGRESSIVENESS

David Ross was the surgical research fellow who picked up where Haimish Laing left off. He also worked with George Wilson at the Gray laboratory.

His project involved looking at oncogenes, these are genes implicated in the development of cancer. "There was an enormous interest in oncogenes at the time," says David. "George and I wanted to look at a gene called p53 in melanoma. We also thought it would be very interesting to look at another gene called c-Myc."

By this point p53 was fairly well established as an oncogene and a few papers had suggested it might be involved with melanoma, but the role of c-Myc in melanoma was much less well-defined.

"There was some work showing that c-Myc was an oncogene, but we didn't know how it might be involved in melanoma," says David. The activity of c-Myc was thought to affect the rate that a cancer cell divides; the more active c-Myc is, the faster the cell divides. David wanted to find out what this meant for melanoma patients.

David went back to the Mount Vernon library of patient melanoma samples. He used an established technique called flow-cytometry to study the activity of p53 and c-Myc in skin melanoma cells. Flow-cytometry essentially involves suspending cells in liquid then streaming this liquid past detection sensors. These sensors can be used in combination with protein-binding fluorescent dyes to detect tiny amounts of different proteins in the cells.

The great thing about this method is that it can even be used on patient samples which are many years old and which have been stored fixed in paraffin.

"We went back to the pathology lab, dug out the patient samples from about 10 years previously, removed the paraffin [using chemicals] then used flow cytometry to look at levels of p53 and c-Myc in these cells."

David could then look to see if the levels of these genes correlated with disease characteristics. "We were able to analyse samples from cells, then look up the patient histories, it was really interesting work," he says.

David's and his colleagues showed that while p53 may have a role in the development of melanoma, findings with c-Myc were much more striking. They found that high activity of c-Myc could be used as a predictive factor for poor outcome (i.e., more severe disease) in patients with melanoma.

This finding was true for both spontaneously developing (primary) melanoma, and also for melanoma which had spread to other parts of the body (metastatic melanoma).

"We showed c-Myc was associated with outcome," says David. "It was a seminal finding, we had observed an association between oncogene and tumour activity." His studies

CANCER JARGON

Prognosis — The prognosis is the predicted outcome. Prognosis is a prediction of the chance of recovery or survival from a disease. Most physicians give a prognosis based on statistics of how a disease acts in studies on the general population.

Marker — Markers can be used to judge the progress or decline of a tumour. Tumour markers are substances that are released by cancer cells or produced by the body in reaction to a tumour that is present. Normal cells also make these substances, but they are produced in much greater amounts by cancer cells. The most common use of these markers is to follow a known cancer.

Outcome — Outcome is the survival rate which is defined as the percent of people who survive a disease such as cancer for a specified amount of time.

Metastatic and primary disease — Metastatic cancer is cancer that has spread from the place where it first started to another place in the body. A tumour formed by metastatic cancer cells is called a metastatic tumour or a metastasis.

The primary cancer is where the cancer started. If some of the cancer cells break away from the primary cancer and settle in another part of the body this cancer is then called a secondary cancer. Secondary cancers are made up of the same type of cells as the primary cancer.

Oncogenes — A gene that causes the transformation of normal cells into cancerous tumour cells, especially a viral gene that transforms a host cell into a tumour cell.

Prospective — A research study that follows groups of individuals over time, who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) and compares them for a particular outcome.

Retrospective — A research study that looks at medical records of groups of individuals who are alike in many ways but differ, similar to prospective however retrospective studies records rather than individuals.

Personalised medicine — A form of medicine that takes information about a person's genes, proteins, and environment and uses that information to prevent, diagnose, and treat disease. In cancer, personalised medicine uses specific information about a person's tumour to help diagnose, plan treatment, find out how well treatment is working.

also showed that high levels of c-Myc activity were related to other melanoma characteristics, including thickness of the tumour, and the length of time before the cancer returned.

These were exciting findings; if the severity and prognosis of a patient's cancer can be accurately predicted, then more appropriate and targeted treatment can be delivered. But this was also just the beginning of the research.

"Like every good project," says David, "it raised more questions than answers. Now we started asking questions such as 'Can we confirm this? How strong is this association?' We had shown an association between c-Myc activity and melanoma prognosis. But, was it an incidental finding or was it a key player?

"Our finding about prognosis was interesting but also it gave us an insight into how genes affect the behaviour of this cancer. We started to think, what happens if we can manipulate

the activity of this gene? It laid open the path of melanoma research at RAFT for the next 10 years."

New surgical research fellows joined RAFT and moved the melanoma project forward. High c-Myc activity was shown to be a powerful and accurate predictor of poor outcome in many different types of melanoma, including melanoma of medium thickness, melanomas of the head, neck, and scalp, melanomas which grow on hairless skin such as the palms and soles of the feet, and the first ever study of oncogene activity in melanomas which grow under the nails (subungual melanomas).

RAFT researchers also carried out studies into uveal melanoma, which develops in the eye. They again found an association between c-Myc and prognosis for the patient, but intriguingly in these samples a high level of c-Myc activity was associated with an improved patient outcome, in complete contradiction to other melanomas.

Next, the researchers at RAFT took their c-Myc studies one step further, by moving from retrospectively reviewing old patient samples and case notes in the Mount Vernon database, to studying samples taken in the clinic, to see if they could actively predict which patients with melanoma would fair better, based on their levels of c-Myc activity.

Diagnostic samples from a total of 117 patients with melanoma who attended Mount Vernon Hospital in succession between 1996 and 1998 were assessed using flow cytometry. Patients were then followed-up over the next five-years or so.

The study results confirmed their previous findings, and again showed that patients whose melanoma cells had higher c-Myc activity tended to have a worse prognosis.

As this was a prospective study, that is, the patients were followed over time as opposed to looking back and retrospectively reviewing

Uveal melanoma developed in the eye

samples, this study helped to show that c-Myc testing at diagnosis was feasible.

The researchers went on to suggest that c-Myc could potentially be used along with other standard predictive tests (such as measuring melanoma thickness) to help understand the severity of the disease, and tailor treatments for the patient.

Still, the importance of c-Myc in melanoma is by no means established. Other groups have published findings which suggest that c-Myc activity has little value for predicting how the disease will develop.

But this is the nature of exploratory science, to publish your findings as best as you can for others to discuss, dissect, and try to disprove. If after many years, the growing body of evidence is on your side, the scientific community might just start believing your findings to be true.

And, other studies are also being published which agree with RAFT's c-Myc research.

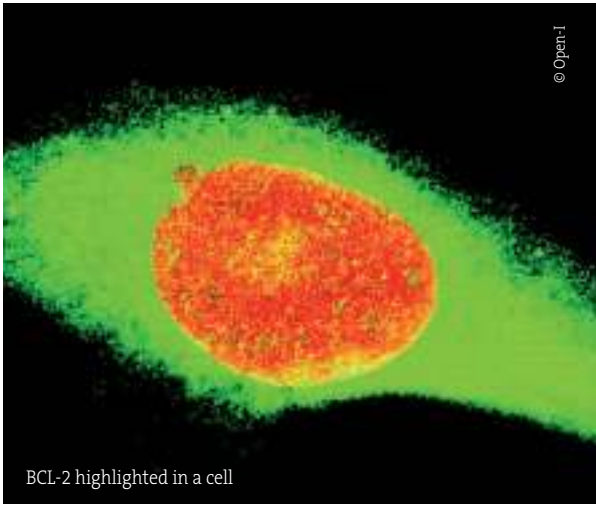
It seems this research has kick-started a valid and important discussion surrounding the role of this gene in melanoma. Almost entirely due to research published through RAFT, c-Myc has earned a mention as a potential predictive signal (or 'marker') for melanoma in books, reviews, and even the US National Academy of Clinical Biochemistry guidelines for the use of tumour markers in malignant melanoma.

RAFT'S ROLE IN THE BCL-2 STORY

Another molecule targeted by melanoma researchers at RAFT was a molecule called bcl-2.

In healthy cells, bcl-2 has an important role in regulating a form of pre-programmed 'cell-suicide' called apoptosis.

This is an essential cell mechanism which prevents potentially cancerous cells from turning into full-blown tumours. Put simply, if a cell appears to be going rogue, perhaps starting



BCL-2 highlighted in a cell

to behave or divide in an out of control or odd manner, then bcl-2 is part of the cell's in-built surveillance system which can trigger apoptosis. This ensures the potentially dangerous or damaged cell shuts itself down quickly.

Every cell is regulated by a balance of different molecules, some which trigger mechanisms leading to apoptosis, and some which inhibit these mechanisms. Cancers can develop when this system becomes unbalanced and cells lose their ability to trigger apoptosis.

Confocal microscopy showing blockage of NFAT translocation by Bcl-2

In this cellular equilibrium of molecules 'for' and 'against' apoptosis, bcl-2 is known to act as a safeguard, helping to prevent healthy cells from entering into apoptosis unnecessarily.

In the early 1990s, new research identified that changes in bcl-2 levels may contribute to the development of some tumours. Surgical research fellow Rajiv Grover followed this research up at RAFT, and in 1996 he published a study which was one of the earliest to report a connection between bcl-2 expression and survival of patients who had metastatic melanoma.

Working with George Wilson at Gray Laboratory, Rajiv looked at 42 tissue samples from patients who had melanoma which had spread to the lymph glands. He found that patients whose cancerous cells produced blc-2 tended to live for a shorter time before dying due to the cancer. As well as being an important study in terms of developing potential new melanoma treatments, it also showed that measuring levels of bcl-2 in patients could also help predict the course of the disease.

Along with other studies, Rajiv's study contributed to a large body of evidence which developed, showing bcl-2 to be important in melanoma. His paper was cited as evidence in over 80 later papers, including several important papers which investigated therapeutic options for melanoma.

One such paper was from a company which went on to develop and test a molecular treatment against melanoma. The treatment used a cutting–edge form of biotechnology called 'antisense'.

Antisense molecules are small synthesised pieces of DNA code which target genes. The company used antisense molecules to silence the gene producing bcl-2 and so reduce levels of bcl-2 in patients' melanoma cells, making them more susceptible to chemotherapy.

The first clinical trials of bcl-2 antisense combined with a chemotherapy treatment in patients with metastatic melanoma were encouraging, slowing the progression of the cancer and improving survival in some patients.

However, a later larger study did not show a difference between patients who had received anti bcl 2 treatment and those who hadn't, and for now the development of this treatment appears to have slowed. Still, it must be remembered that cancer therapy is a complicated business, and more studies may well be needed to truly establish whether bcl-2 therapy can help certain patients with melanoma. RAFT researchers can be proud of their contribution to this story.

TARGETING CANCER WITH MOLECULAR WARFARE: ANTISENSE STUDIES

RAFT also investigated the effects of reducing c-Myc activity using antisense. Resistance to chemotherapy is a big problem when treating melanoma and researchers wanted to see in the lab if reducing c-Myc activity in melanoma cells would make them more susceptible to anti-cancer drugs.

Researchers based at RAFT collaborated with scientists at the Gray Laboratory and also with scientists at Moorfields eye hospital to investigate the effects of using antisense against c-Myc in a range of cells derived from melanomas, including uveal (eye-based) melanoma.

The first study produced by RAFT showed that not only did c-Myc-targeted antisense molecules injected into the cells reduce c-Myc activity, but they also inhibited melanoma cell growth. This is good news when you are trying to stop a tumour from increasing in size.

Antisense research was cutting-edge at the time, and this study was one of the earliest to show that c-Myc antisense could potentially reduce growth of melanoma. Furthermore, through using a clever combination of controls, the researchers also showed that it was this particular antisense molecule which produced the effect, and not just the consequence of adding any old antisense molecule, a point which was the subject of intense debate at the time.

Paul Tulley was one of the surgical research fellows who investigated using antisense to reduce c-Myc activity in melanoma cells from

the eye. Paul worked at Moorfields and at RAFT, growing melanoma cells in the laboratory and then using them to see if c-Myc antisense could block resistance to a chemotherapy drug called interferon.

His work was successful, and in 2004 he published a paper of his findings.

"My studies helped show that c-Myc was involved in chemotherapy resistance in these cells, and that the better c-Myc was blocked by antisense, the increased level of damage chemotherapy was able to inflict on the cell," says Paul.

His and others' work at RAFT contributed to the growing body of evidence from many research groups establishing c-Myc as a potential target in melanoma treatment. Today, 10 years later, the pharmaceutical industry recognises that in melanoma, "Blocking c-Myc may pave the way for new approaches in combination with newly found adjuvant vaccines, immune response modifiers and chemotherapeutics."

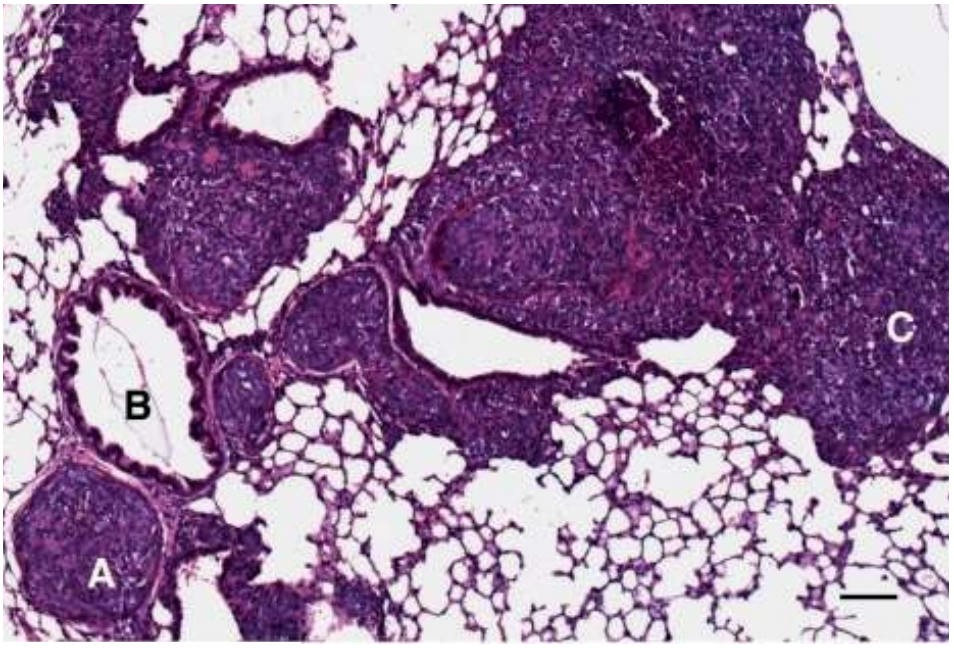
DETECTING METASTATIC MELANOMA: ANTIBODY TECHNOLOGY

Melanoma usually starts in one single area of the body. As the tumour or lesion grows, cancer cells can then spread to different parts of the body. This is called metastastes.

Advanced metastatic melanoma which has spread is very difficult to treat. One reason is because once the melanoma has spread, there is no way of knowing which other parts of the body it has affected.

A large portion of the research conducted as part of the ongoing melanoma project at RAFT was aimed at developing a new method of detecting melanoma once it had spread.

One of the surgical research fellows involved in this research, Stephen Hamilton, explains what they were trying to do.



H&E staining of lung metastasis

Dr Steve Hamilton with RAFT visitor

"Early spread of melanoma can be difficult to detect and our treatment options for many of these patients are limited. We sought to develop new ways of both detecting the spread and targeting treatment to it."

Researchers at RAFT wanted to develop an antibody to detect and treat melanoma in patients. Antibodies are usually produced by the body as part of an immune response to target and bind to bacteria or other foreign objects which have invaded the body.

However, in medicine, researchers are interested in developing special types of antibodies which can detect cancerous or diseased cells in the body. The hope is that just as they stick to bacteria, specially modified antibodies can stick to the cancer cells and act like a flag, so doctors can see where the cancer is in the body. Another aim is that these antibodies could be used to direct anticancer treatment specifically to diseased cells, sparing healthy cells.

When developing antibodies for use in detecting and treating cancer, the key aim is to make the antibody as specific as possible for the cancer cell you are targeting, so it won't stick to healthy cells in the body.

This is a complicated process and RAFT spent over six-years developing an antibody which could target melanoma cells.

Researchers had to start from scratch. First they developed a new laboratory method to generate antibodies targeted to melanoma. Once the basic molecule had been defined, RAFT's team next spent several years refining and improving the function and specificity of the molecule.

Joy Odili was one of the surgical research fellows involved in this part of the project. "My job was to perfect the antibody so it was suitable

for clinical trials," says Joy, "I was tweaking the antibody, re-engineering it to get it to bind [to the cancer cell target] more specifically."

Many improvements were made, from finding which fragment of the antibody worked best, to improving the yield and solubility of the fragment.

Researchers eventually were able to test their antibody in a mouse model, showing that a specially labelled version was able to specifically target and bind to melanoma cells in the body as well as in the lab.

Next they set about improving how well the antibody worked in the body.

They found a way to stop the antibody accumulating in the kidneys and giving off a false signal, and tried using a 'cocktail' of three different antibody fragments gave a better and more accurate signal.

"We improved the antibody significantly," says Joy. "When I finished we had the best antibody we had ever had. It had increased detection in mice, and the next stage was to make it suitable for humans and take it to clinical trials."

Joy says that the antibody got to a point where it needed a real specialist to perfect the antibody for use in humans. RAFT had taken the work as far as it can and it is time for someone else to take over the antibody development.

But, although this specific RAFT antibody has not yet made it to human trials, much of the innovative methods used by RAFT to develop the antibody have since been used by many other groups all over the world to develop similar molecules for other diseases.

In fact, some of the methods developed at RAFT as part of the melanoma antibody project are now regarded by researchers as 'routine'.

Stephen Hamilton sums up the lasting impact of the RAFT melanoma antibody project: "[The work] added to the knowledge base in this particular aspect of cancer treatment, says Stephen. "It showed the potential of antibody-directed therapy in melanoma, though I think it also demonstrated the difficulties and limitations in this particular way of targeting tumours."

Recently an antibody which targets melanoma has been developed by a different group, and has shown promising results in a very small trial involving patients with metastatic melanoma. RAFT was not involved with this work, but papers published by RAFT undoubtedly contributed to moving the field forward to this point, and closer to antibody targeted melanoma treatment becoming a reality.

FINDING OTHER MARKERS LINKED TO MELANOMA PROGNOSIS

Along with the c-Myc and bcl-2, the melanoma prognostic markers discussed above, the RAFT team also identified other potentially predictive markers using the Mount Vernon library of melanoma patient samples.

They found many of these markers after developing a novel method which allowed for rapid high-throughput assessment of molecules in tissue samples. First, a total of 480 samples from 120 melanoma patients were embedded in a single block of paraffin. Then sections were sliced from the block and stained with different chemicals to detect potential new markers.

One such marker identified in this way was a gene called MCAM, which had previously been identified as a predictive marker for melanoma prognosis by another group. When the researchers at RAFT looked for MCAM activity in their melanoma samples, they saw 76 of the 120 specimens were positive. Further studies at RAFT went on to show that MCAM could be an accurate predictor of disease metastases and

relapse in some patients.

The researchers went on to use their novel method to identify several other potential markers for melanoma severity. Some of these markers have since been confirmed by studies from other research groups and may even be potential targets for developing new melanoma treatments.

The high quality of the melanoma science done by RAFT is underlined by looking at the number of RAFT publications included in systematic reviews. A systematic review gathers together results from only very high quality studies to gain an overview of a particular area of science.

In 2009 a systematic review was conducted by academics in the US wanting to evaluate potential new molecules which could be used to predict prognosis in cutaneous melanoma.

The authors conducted the review because they wanted to understand why there were hundreds of studies assessing potential prognostic markers in melanoma, but no molecular markers yet recommended for clinical practice.

Using an electronic publication database, they searched for all of the studies so far published anywhere in the world which investigated prognostic markers in melanoma of the skin. Of the 102 publications they found, just 21 different research groups produced 37 studies that were deemed of a high enough quality to be included in their review. Of these 37 studies, a total of five, that's over 10% of all studies, came from RAFT. This is high accolade indeed.

The authors of the review concluded that all of the markers included in their review (including RAFT's) were worthy of further investigation in larger studies, and also suggested that more studies were needed of this high quality to help with melanoma research and clinical practice.

Other cancers

Melanoma is not the only cancer which plastic and reconstructive surgeons regularly have to deal with. Over the last 25 years RAFT has run successful research programmes into other forms of cancer, including basal cell carcinoma, squamous cell carcinoma, head and neck cancer, and other more rare form of cancers. Just three of the many successful stories from RAFT's research into other forms of cancer are outlined next.

BLASTING BASAL CELL CARCINOMA

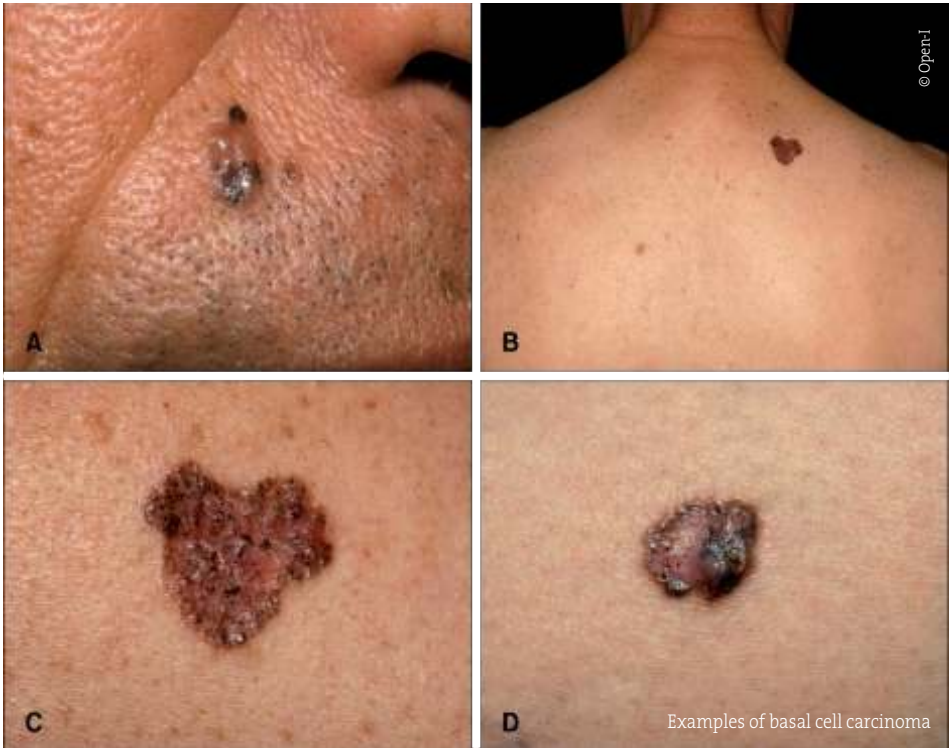
Basal cell carcinoma (BCC) is a non-melanoma type of skin cancer and accounts for over 80% of all skin cancers diagnosed in the UK.

BCC mainly affects people with fair skin, and is commonly caused by sunlight or sunbed exposure. Although it is one of the most common, it is actually one of the least dangerous forms of skin cancer; it grows slowly and rarely spreads to other parts of the body.

However, BCC can still cause discomfort and extensive damage to the skin, especially if it has been left untreated for a long time. Around one in 30,000 people have a rare genetic disease called Gorlin syndrome, which means they are more at risk of developing many BCCs over their lives.

Some patients with Gorlin syndrome can develop thousands of BCC tumours during their lives, mostly on their face, chest and back.

BCC tumours usually look like small lumps or nodules on the skin, and treatment involves



Examples of basal cell carcinoma

physical removal by surgery or other non-surgical methods. The method used depends on a number of factors, including the size and the position of the tumour. Whichever method is used, it is important to make sure that the entire tumour is removed from the deeper and surrounding skin to decrease the risk of tumour regrowth.

A special form of laser, called the carbon dioxide 'vaporisation' laser, has occasionally been used to remove BCCs since the 1970s.

However, improvements in laser technology in the late 1990s meant smaller more portable lasers suitable for use in dermatology clinics could be developed, and interest in their use for treating BCCs was renewed.

At this time there was little agreement on the best way to use vaporisation lasers (which 'blast' the cancer cells, as opposed to cutting them away) to treat BCC. So a RAFT surgical research fellow and other surgeons at Mount Vernon decided to conduct a study to establish the best way to treat BCCs using this laser.

They wanted to find out exactly how much the tumour must be blasted to ensure it never returns. During the study, a total of 35 patients with 51 BCCs who were attending Mount Vernon to have their tumours cut out under local anaesthetic took part. Before having conventional treatment, they first underwent multiple treatments with the laser. Following laser treatment a sample of skin was removed to ensure that all of the tumour had been removed, and to evaluate under a microscope how effective the laser had been.

The researchers found that tumours which were more shallow and were of a certain non-nodular type were the most reliably removed by laser. They also demonstrated that using the

laser was easier and at least three times faster than conventional surgery.

RAFT's team concluded that laser could be very useful for treating some forms of BCC and could form part of a combined approach to treatment of patients with Gorlins syndrome, who may need to have up to 100 tumours removed at each session.

This study was one of the earliest to investigate in detail the types of BCC which would benefit from laser treatment, and the first to investigate the effectiveness of different depths of laser treatment through microscope studies of the treated lesion.

Consequently, other researchers have cited this study as a pivotal early paper on laser treatment of BCC. This research has undoubtedly contributed to evidence for the use of the carbon dioxide laser for some forms of BCC. Clinical guidelines now advise that although it remains fairly uncommon, laser treatment could be effective in treating multiple low-risk BCC.

UNDERSTANDING THE CHARACTERISTICS OF BASAL CELL CARCINOMA IN YOUNG PEOPLE

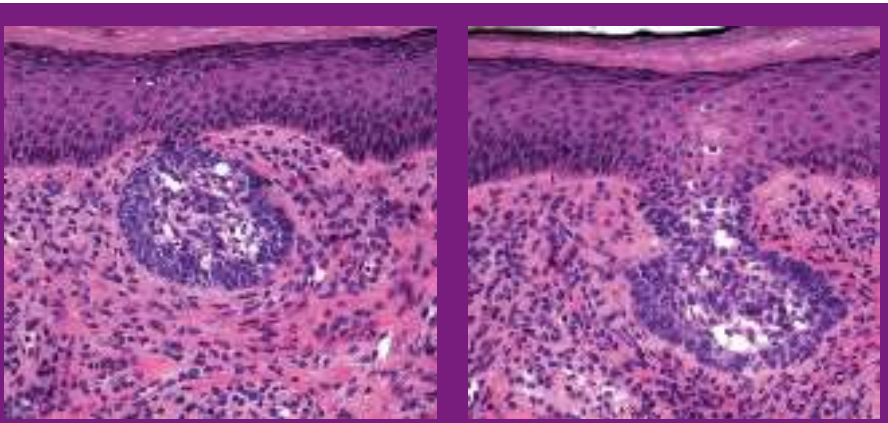
BCC in young people under the age of 35 years is relatively rare. However, doctors in the UK are now seeing more and more younger people with BCC, partly as a result of the increased trend for sunbathing and sunbeds.

For some time doctors have been debating whether young people tend to develop a more aggressive form of BCC which is more likely to come back after having been treated. One large study suggested that a much higher percentage of people under 35 will develop aggressive BCC compared to those over 35.

Still, other studies have not found a difference in the aggressiveness of BCC between younger and older individuals. It is important to understand the characteristics of this cancer in different patients, as this knowledge can then help inform the best type of treatment.

Researchers based at RAFT and Mount Vernon wanted to clarify the characteristics of BCC in younger people and in 2000 they published findings from their own study on the matter.

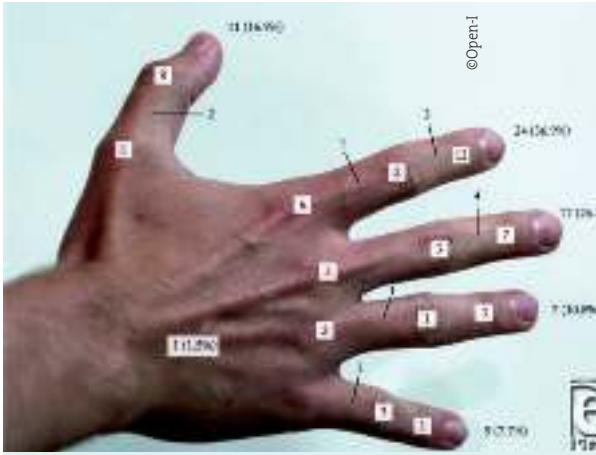
During the study the researchers compared the cellular characteristics of BCC tissue samples from 120 patients under 50 years old with samples from 151 patients over 50 years old. The researchers found no difference in the rate of aggressive BCC with age. They reported that aggressive BCC tumours affected 33% of patients under 50 and 35% of patients over 50.



Superficial spreading basal cell carcinoma

Interestingly, they also noted that younger patients tended to have 'incomplete excision' of their tumour, meaning not all of the cancerous tissue was removed during treatment. They speculated that this could be due to worries about the increased cosmetic impact of larger scars as a result of removing more tissue when treating the BCC, a problem which is particularly worrying to younger patients.

This study from RAFT helped to add to the data showing that BCC in younger patients is not necessarily a more aggressive subtype, and a tendency for the cancer to return may in fact be a result of incomplete removal when being treated. Other studies have since shown similar findings, although the debate is by no means settled. Nevertheless, the study published by RAFT has earned a mention in the evidence-based US national cancer guidelines for treatment of BCC.



Location of giant cell tumour of the tendon sheath. Boxes and lines indicate the number of tumours at each joint and phalanx, respectively. At the tip of each respective digit, the total number is shown with percent of total indicated in parentheses.

PREDICTING THE OUTCOME OF TENDON SHEATH TUMOURS

Giant cell tumour of the tendon sheath is a relatively rare type of tumour which can develop in the tissues surrounding the tendons of the hand, wrist and feet. These tumours can be removed by surgery but will often come back.

In 1998 RAFT researchers conducted a study looking at giant cell tumour samples taken from 41 patients. The patients were then followed-up for about six and a half years. Tumours reoccurred in around 17% of these patients, and the researchers found that low expression of a molecule called nm23 was highly related to the risk of tumour regrowth.

The researchers recommended that a test for nm23 could be performed as an accurate prognostic marker for giant cell tumours of tendon sheath.

Debate still continues over the value of nm23 in the prognosis of this type of cancer, and other researchers have failed to find a link between nm23 and relapse. However, this study has helped to improve knowledge of a rare form of cancer and contribute evidence that nm23 could be important.

The quality of this study was highlighted by its inclusion in a recent systematic review investigating the characteristics of giant cell tumours of tendon sheath, published in 2011. For this study the authors identified all English language studies conducted over the last 30 years.

Any studies which were below par in terms of scientific quality were discounted. They found 21 studies in total and over half were discounted. Just 10 were included in the final review, including the RAFT study.

Of all the studies included, the RAFT study followed up patients for the longest period of time. And it seems that RAFT may have been heading in the right direction. The review concluded that although larger studies were

needed, tumour biology seemed to contribute to the risk of recurrence more than clinical factors such as location or invasiveness.

SKIN CANCER PREVENTION – IMPROVING SUNSCREENS

The RAFT project which has perhaps had the greatest impact on the largest number of people is the sunscreen project. Driven by the fact that levels of skin cancer have risen dramatically in the UK over the last few decades, the researchers at RAFT wanted to investigate exactly how the skin was damaged by sunlight, and what sunscreen did to protect it.

Their findings were not only startling, but have also helped to change the law in both the US and the UK, better protecting millions of people from the deadly risk of skin cancer.

Developing a model to assess skin damage caused by the sun

Perhaps it seems like it should be fairly simple to come up with a way of assessing skin damage caused by the sun, after all most of us are fully aware of the detrimental effects sun can have on our own skin.

But, when it comes to developing an accurate and controlled model system suitable for precisely measuring the exact amounts of damage caused, this is altogether a more complex issue.

To solve this problem, the skin cancer research group at RAFT turned to physics. They decided to use a technology known as 'electron spin resonance spectroscopy'.

Now to explain: when ultraviolet (UV) radiation in the form of sunlight hits the skin in sufficient amounts it can inflict damage to the skin cells. As

Electron spin resonance spectroscopy at RAFT

a cause of this damage, the cells produce highly reactive particles called free radicals. These are potentially very dangerous molecules indeed, as they can react almost indiscriminately with surrounding molecules in the cell, causing havoc to healthy cellular processes.

This form of damage is generally called oxidative stress, as the free radicals undergo a type of reaction with other molecules called oxidation. Cells can produce antioxidants, which react with and mop up the free radicals before they cause damage to the cell. However, if too many free radicals are produced, or the cell can't produce enough antioxidants, then the balance is tipped and cells and tissues suffer.

Electron spin resonance spectroscopy is a sophisticated technique which can be used to measure the levels of free radicals in biological systems such as body tissues and fluids. Researchers at RAFT wanted to use this technique in a relatively new way; they wanted to see if they could measure free radicals and oxidative stress in skin biopsy samples taken from patients.

They devised an experiment where they treated scalp and skin biopsy samples with special chemicals to help detect the free radicals, then subjected these samples to two different forms of radiation, one from UV light and one from red light produced by a ruby laser.

The ruby laser had recently been developed through a collaboration of researchers at RAFT and in Swansea as a novel method for removing hair from skin. RAFT wanted to know if this laser was safe to use on skin without causing formation of free radicals and potential skin damage.

Using different methods of electron spin resonance spectroscopy the researchers showed that although UV light readily caused production of free radicals in the skin samples, the light emitted from the ruby laser did not. They were able to conclude that the ruby laser does not cause oxidative stress to skin cells when compared to UV light.

Not only was this study innovative in that it used special methods of electron spin resonance spectroscopy to detect free radical production directly in skin biopsies, it also showed for the first time that the ruby laser developed by RAFT did not damage skin through free radical production.

The method went on to be adapted and developed by RAFT to test sunscreen protection, and forms the backbone of standard sunscreen testing methods used by commercial companies today. How this was done is described in more detail that follows.

FINDING THAT SUNSCREENS INADEQUATELY PROTECT AGAINST UVA RAYS.

UV rays are invisible rays emitting from the sun, and are also generated from sun lamps and tanning beds. UV rays can be further categorised as UVA, UVB and UVC rays.

UVB causes the most damage to skin. It affects the outer layer and is primarily responsible for sunburn and skin cancer. For this reason sunscreen manufacturers for years concentrated their efforts on protecting the skin from these rays.

UVA is less powerful than UVB, and it was thought that UVA only causes minor skin damage. But research started to show that UVA may also have a role in aging skin and causing skin cancer, and scientists started to suggest that perhaps sunscreens should also protect against UVA.

But, there was no way to directly measure the impact of UVA on skin or to assess protection afforded by sunscreens. Many sunscreens were already claiming they protected against UVA, but was this true?

The skin cancer team at RAFT decided to find out. They adapted their skin model so they could use electron spin resonance spectroscopy to measure the effect of sunlight-levels of UVA radiation on

Sunscreen applied for testing

free radical production in skin biopsies.

They then investigated the protection provided by three high-factor (factor 20+) sunscreens which claimed to have UVA blocking capability. The results were disconcerting. When the recommended amount of sunscreen was applied, UVA produced free radicals were reduced by only 55% in the skin samples. When the more commonly applied level of sunscreen was applied (much smaller than the recommended dose), then the majority of free radical production was only blocked by 45%.

The team calculated that these sunscreens only had a 'free radical factor' of 2. Factor 20 sunscreens are so categorised because after application, your skin can be exposed to the sun for 20 times longer than you normally would be able to before burning.

Burning is an indication of UVB damage and sunscreen factors are therefore essentially a measure of UVB protection. What this RAFT study showed is that when measuring UVA damage, the sunscreen only protected the skin enough to be exposed to sun for twice as long as normal before free radical damage may start to build.

This led to the worrying idea that longer sunbathing afforded by the use of sunscreens could in fact contribute to an increased risk of UVA damage and perhaps even to the increase in skin cancer which has been observed in many countries.

This was ground breaking research and when the study was published in 2003 it caused a media furore, but not always for the right reasons. Many newspapers and websites wrongly suggested that sunscreens were perhaps dangerous, 'caused cancer' and should not be used.

A rapid response article in the *British Medical Journal* written by RAFT emphasized that this new research did not mean people should abandon sunscreens, but also sought to make "the medical profession, sunscreen manufacturers, and those disposed to sunbathe" aware of the limited UVA protection provided by sun creams.

Further studies at RAFT went on to show exactly how UVA damaged skin cells and their DNA, and findings of the research programme, which lasted for over a decade, generated some real, lasting impact.

RAFT's expertise in the field has been recognised worldwide and has even contributed to major changes in both EU and US legislation on sunscreen regarding UVA damage. New rules for how sunscreens are labelled and advertised have been introduced – in the US this is the first change to sunscreen laws for 30 years. In addition, sunscreen manufacturers now routinely use the methods developed by RAFT to test their products.

In addition, data produced by RAFT highlighting the dangers of UVA rays from tanning beds contributed to a change in UK law which banned under 18 years old from using sunbeds, and banned the use of unsupervised coin-operated sunbeds which made it easy for young people to use.

Following the extent to which RAFT's sunscreen findings were initially misrepresented in the media, the charity reaffirmed its belief that it is essential that the public is provided with the latest and most accurate facts in preventing skin cancer. To help with this mission, the skin cancer team also worked intensively with the Save Your Skin education campaign, providing sound scientific advice about skin cancer for young people.

WORKING OUT THE BEST WAY TO APPLY SUNSCREEN

The skin cancer team at RAFT again hit the headlines in 2006 when they published a new study showing that the way people apply sunscreen may in fact affect how well the cream works. Using the UV-skin damage model developed at RAFT, the researchers tested different ways of applying a four-star rated sunscreen with UVA protection to human skin samples left over from plastic surgery operations, and measured how this affected free radical production.

They found that rubbing in sun cream, as the majority of people tend to do, actually may reduce its effectiveness against harmful UV rays. This could be because rubbing in cream spreads it around and causes it to collect in crevices, reducing the thickness of the layer of cream covering most of the skin. The researchers found that applying a thin film of cream across the skin provided the best protection against damage.

Dr Rachel Haywood, the lead researcher of this project, explained the significance of these findings to the BBC news website. "Most people prefer to rub the cream into the skin; they find it more pleasant and comfortable. However, our research shows for the first time that if the cream is rubbed in, the protection is minimal."

This research helped to highlight again the dangers of relying only on sunscreen for protection from the sun, and added to evidence that clothes, hats, and use of shade are also incredibly important in the battle against sun damage.

A spokesperson from a leading cancer charity agreed with RAFT's findings.

"The one message people should take from this research is that you cannot rely on sunscreen alone to protect you from skin cancer. Sunscreen should be the last – not the first – line of defence against the sun's harmful rays."

Dr Rachel Haywood

What does being a RAFT Surgical Research Fellow actually mean?

Over the last 25 years RAFT has been providing trainee plastic and reconstructive surgeons with the opportunity to undertake two precious years of research in a rigorous academic environment. A total of 54 surgical research fellows have passed through RAFT's doors, and many of them have gained high accolades attesting to the excellence of the research they do here. The majority of these research fellows have been awarded a medical doctorate, or MD, for their work at RAFT.

In the UK the MD is awarded to medical doctors who have completed a formal period of research at a respected institute. They must write a thesis and undergo a viva, a form of oral exam, on their findings. This ensures that their research is valid, of good quality, and scrupulously scientific.

Some research fellows at RAFT have also been awarded PhDs and other research awards such as the prestigious Hunterian professorships, annually bestowed by the Royal College of Surgeons to surgeons who have conducted outstanding research.

Rajiv Grover held a surgical research fellow post at RAFT from 1994 to 1996. He was awarded an MD from the University of London for his work. Rajiv looks back at his time at RAFT fondly.

"RAFT gave me the time, salary, and inclination to do research," he says, "It was the time in my career when I had the most freedom." He also explains why he decided to take up a surgical research fellowship with the charity. "RAFT was known to be one of the few places doing cutting edge research [in plastic surgery], and if you were interested in research, RAFT was where to go."

While at RAFT Rajiv worked on the melanoma project. He was interested in the biological complexities of the disease, and how genes such as c-Myc might be involved in melanoma growth and development. This, he says, is another reason why he chose RAFT.

"At the time there were very few [research] papers in plastic surgery that had a scientific approach. Lots of papers were anatomical, but people weren't really doing molecular biology, or applying molecular biology tools to plastic research. Papers from RAFT had real impact because they were real scientific research."

Rajiv's time at RAFT was incredibly productive and in 1998 he was awarded a Hunterian Professorship in recognition of his work on melanoma at RAFT. Rajiv is now well established in clinical practice and still continues to research and publish, with almost 60 scientific papers to his name. He is also president of the British Association of Aesthetic Plastic Surgeons (BAAPS), and has a special interest in improving safety and outcome after cosmetic surgery.

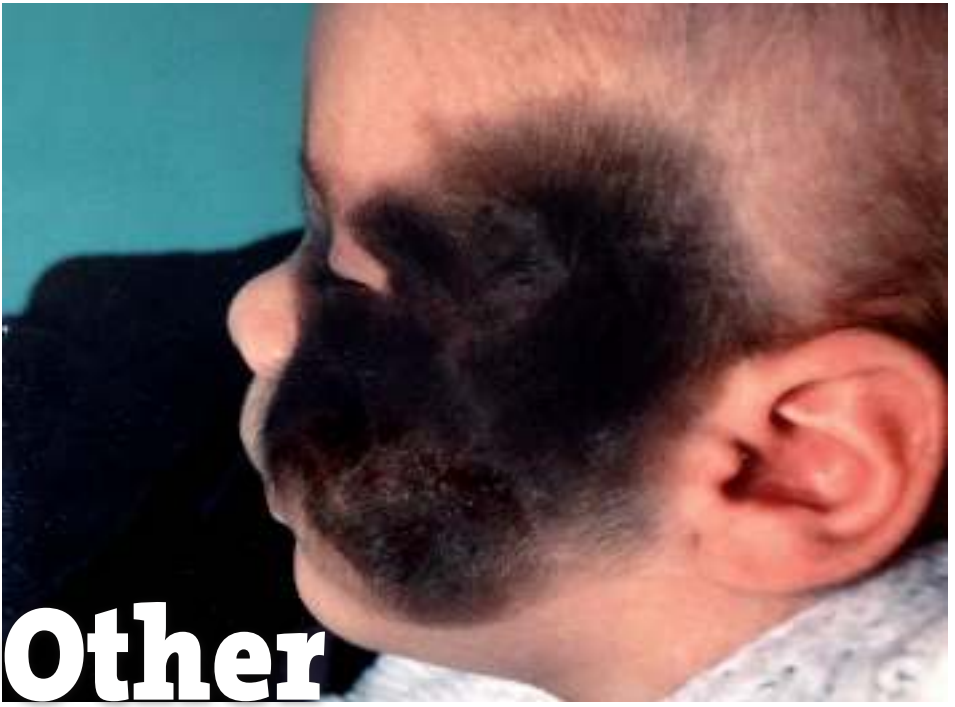
As president of BAAPS Rajiv has had an instrumental role in establishing the UK's first National Institute of Aesthetic Research in conjunction with the Royal College of Surgeons and The Healing Foundation charity. The institute's aim is to address the chronic lack of evidence-driven research in aesthetic surgery. Rajiv credits his time at RAFT as being a driving force for him to set up the institute. "Those two years at RAFT were quite powerful in directing my enthusiasm for research," he says. "Aesthetic

surgery now, is how plastic surgery was 20 years ago. If there was one thing that acted as a good stimulus for this, it probably was RAFT. It made a generation of plastic surgeons look at plastic surgery as a proper academic speciality where scientific method and scientific analysis of outcomes helps patients."

Rajiv's story is just one example of how RAFT has influenced and inspired a generation of surgeons to continue with high-quality, meaningful research. "It changed our lives so we could help our patients," he says, "RAFT trained us in scientific method. We learned to question dogma, to no longer accept the accepted."

RAFT's Roll of Honour Surgical Research Fellows

Raina Zarb Adami
Mo Akhavani
Richard Baker
Chris Baldwin
Kate Beckett
Marcus Bisson
Oliver Branford
Corine Breed
Neil Bulstrode
Nigel Carver
Jagdeep Chana
Sophie Dann
Sinclair Gore
Rajiv Grover
Stephen Hamilton
Paul Harris
Richard Harrison
Nigel Horlock
Barbara Jemec
Martin Jones
Norbert Kang
Loshan Kangesu
Ben Klass
Hamish Laing
Se Hwang Liew
Philip Lim
Michael Machesney
Ian Mackie
Tom MacLeod
Anthony MacQuillan
Dan Marsh
Murdoch McAllister
Catherine Milroy
Anita Mohan
Simon Myers
Hiroshi Nishikawa
Joy Odili
Marc Pacifico
Robert Pearl
Bruce Philp
Matt Potter
Alex Ramsden
Fabrice Rogge
David Ross
Nick Sheppard
Branavan Sivakumar
Adam Topping
William Townley
Paul Tulley
Fulvio Urso-Baiarda
Martin Vesely
Vikram Vijh
Anna Wilson



Other Research Projects

Unfortunately it is impossible to cover all of the research projects funded by RAFT in this book. Below is just a selection of some of the more unusual or smaller projects which have been completed at RAFT over the years.

Laser Hair Removal

There has always been a need for a long-term or permanent method to remove hair. Apart from obvious cosmetic issues, many conditions and surgical procedures are complicated by the presence of unwanted hair. But in the 1990s, the most common methods for removing hair were shaving, waxing, depilatory creams and electrolysis. These methods were time-consuming, often painful and were usually only a short term solution.

Several research groups around the world started to independently work on this problem. After just 18 months of intensive research RAFT came up with a solution – using a type of laser, called the ruby laser, to remove hair. This technique went on to become the standard method for long-term

laser hair removal which was used in hospitals and clinics around the world.

Below are some of the significant achievements RAFT made to the field of in laser research and hair depilation.

DEVELOPING THE FIRST EVER WIDELY-USED LASER HAIR REMOVAL TECHNIQUE

Removing body hair is an issue most of us have had to deal with at some time or another. But for some people having too much body hair, or body hair where they don't want it, is more than just an inconvenience, it can be incredibly distressing.

One patient tells of her harrowing experience with the condition before the introduction of the ruby laser technique. "Excess body hair has made my life a misery for the last 15 years," she says. "This has made me feel very depressed, embarrassed, unattractive and different from 'normal' women. Other people's reactions include distaste, laughter, shock, derision...this has stopped me doing all the normal things which expose your body; no summer holidays, no swimming, no wearing shorts."

Reading these words it becomes apparent just how much patients and doctors needed a new method of long-term hair removal. "If it's successful and available freely, this laser treatment would transform my body – and my life."

Like all good science tales, the story of how RAFT developed the world's first hair depilation laser for wide-scale use is a heady mix of perceptive insight, serendipity, and hard, persistent work.

The insight came from David Gault, a consultant surgeon who ran an active plastic surgery unit at Mount Vernon. David was also a member of the RAFT medical research committee and was involved in many plastic research projects at RAFT, including initiating and supervising the laser project.

David first realised the clinical need for a better solution to long-term hair removal while he was reconstructing ears for children with microtia. This is a condition where the child is born with very small or non-existent outer ears, and the surgeon must use some scalp skin to reform the ear. Sometimes the part of the scalp that is used is hairy, and so David set about finding a way to remove this hair near permanently. "We tried electrolysis," says David, "but it didn't really work."

At that time, fibre optics was a relatively new concept. The first transatlantic fibre optic cables had only been laid a few years before. "I thought, if we can use fibre optic cables across the sea, maybe we can use them to blast hairs."

The serendipity part came along when David met Professor Marc Clement, at that time based at the Swansea Institute of Higher Education. Marc had earlier suffered an unfortunate mishap in the lab. Speaking in 1996, Marc recalls the incident. "Ten years ago I was experimenting with different laser strengths when I inadvertently struck my arm with the laser. I later noticed that the area hit by the laser was completely bald and the hair has never grown back.

"Then about three years ago I met Mr Gault who had developed the theory that laser technology could be specifically designed to remove hair. I pointed out my 'accident' and he was immediately interested."

Next came the hard work. "Professor Clement and his team provided us with a prototype laser," says David, "and we received the backing of the Ethics Committee at Mount Vernon to start clinical testing."

Unfortunately early laboratory tests were disappointing. "We did all the pre-clinical research on rats, but it didn't really work because the rats' hairs were blonde!" However later clinical tests on the first few patients (and even the researchers' own hairs) were extremely successful.

So David and his team at RAFT embarked

on a clinical trial treating 116 patients over 18 months, investigating the feasibility of laser hair removal. RAFT's work received huge national and international publicity, with television stations from as far as Brazil requesting interviews with David and his patients.

After the broadcast of a segment about David's work on Tomorrow's World, a popular programme on UK national TV, RAFT was inundated with calls from individuals desperate for help. Some of these were able to take part in David's trial.

The trial was a success. Most patients had around two laser treatments and hair growth was reduced by almost 60% after six months. Even better the treatment was shown to be relatively pain free, with patients scoring their pain at a level of just 1.26 out of a maximum of 10 on a special scale. The treatment produced no scarring (although it did cause patches of skin pigment loss in some patients), and was shown to be particularly effective in the removal of ingrowing hairs.

RAFT's researchers were cautiously optimistic, they had shown that laser removal of hair was now a realistic treatment option, but they also stressed that many more studies were needed to refine treatment methods and guidelines.

And more studies they indeed did, publishing more than 20 scientific papers over the next four-years. Some of these studies and their findings are described in more detail over the rest of this chapter. However, the scale of this not insignificant scientific achievement almost pales away to nothing when compared to the impact that this research has had on millions of patients across the globe.

EVALUATING THE SAFETY AND EFFECTIVENESS OF LASER HAIR REMOVAL

Once the researchers had established that the laser actually works, they had to do many more studies to ensure that it was safe, and effective. But how do you measure hair? How can you tell if your laser method is improving the situation or making it worse?

This was one of the issues that prompted RAFT researchers to come up with a new way of measuring laser depilation. Hair growth is actually a very complex process, with hair density, colour, growth cycle, length and diameter all playing a part.

The most widely used method of measuring hair growth at the time was actually to physically count the number of hairs before and after treatment. But this method is subject to serious problems. When exactly do you count the hair for example? There will be more hair at three months after treatment than one month after treatment.

So the laser team at RAFT wrote to the *British Journal of Plastic Surgery* suggesting a new, much more simple and more practical method. They suggested that to determine how well the laser treatment worked, researchers just need to ask the patient.

As the researchers explained, what was important for patient satisfaction was not necessarily directly related to the number of hairs remaining, in fact, the most useful method of assessing effectiveness was by gathering the patients' views of how long they thought they remained hair-free.

This new method of measuring the hair removal success has since been used by other studies that wish to assess patient satisfaction with treatments.

Establishing safety is of paramount importance with any new treatment and a number of studies were carried out at RAFT investigating potential damage and side-effects caused by the ruby laser on skin.

One retrospective study investigated how safe it was for patients of different skin colour to use the ruby laser. They found that although the

laser was effective in removing unwanted hair in patients with darker, more pigmented skin, they were more likely to suffer from side-effects such as blistering, and areas of increased or reduced pigment in their skin. As a result it was recommended that these patients use a different sort of laser treatment for hair removal.

INFORMING CLINICAL PRACTICE: WORKING OUT HOW LASER TREATMENT WORKS

A ruby laser uses pulses of light at a wavelength which selectively targets melanin, the pigment which gives hair its colour. The light pulses excite the melanin molecules, causing the surrounding tissue to heat up and become permanently damaged.

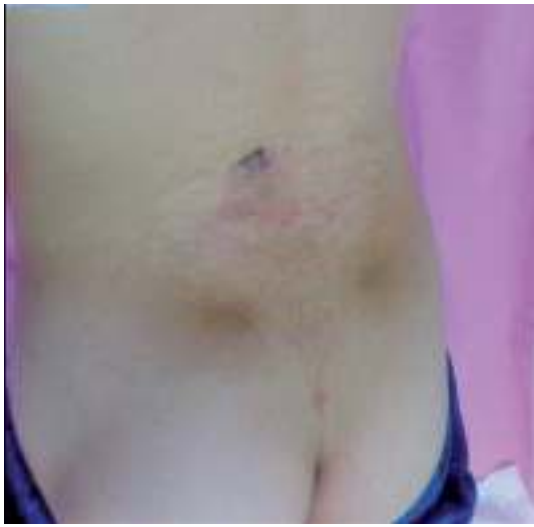
In this way the laser can selectively target the pigmented cells surrounding dark hair follicles, while leaving the paler skin unaffected. But researchers didn't know why for some patients it just didn't work as well. Some would need many treatments to remove the hair, and for others it just wasn't as effective.

The effectiveness of laser therapy is thought to be impacted by many factors, including hair colour and type, the hair growth cycle, melanin content, laser depth, skin properties, and follicle temperature during the treatment. The researchers at RAFT used many creative techniques to investigate the influence of all these parameters on laser effectiveness.

To study if there was any link between laser effectiveness and the hair growth phase, the researchers developed a simple method to gauge the growth phase the hairs were in when they were zapped by the laser.

In preliminary experiments they took skin samples from patients undergoing face-lifts. They were able to show that by plucking a number of hairs from around the laser treatment area and examining their root structure under a microscope, it was easy to estimate the proportion of growing and resting hairs at the time of treatment.

Using this method the researchers were able to show that in fact, in contradiction to the results reported for mice, the growth stage of the hair did not really determine the effectiveness of the laser.



Before and after laser hair removal photographs of a 13 year-old female patient who was admitted to the hospital due to presence of an excessive amount of hair on her lower back which was present since her birth.

In other studies they laid skin samples of different thicknesses on energy meters and measured the power of the laser to penetrate the skin. They showed that although most of the laser's energy was lost within the first millimetre below skin's surface, the maximum depth the laser could penetrate was 14.8mm, with sufficient energy to destroy the whole follicle.

Yet intriguingly, microscopic studies of the samples showed that most laser damage to the hair follicle was sustained at just over a millimetre under the skin, only part way down the hair follicle, in a place called the hair bulb.

Researchers even used thermal camera imaging to measure how hot the hair follicles got during laser treatment. They found exciting results; that the temperatures varied wildly between follicles, some follicles heating up by just five-degrees, others by up to 30 degrees. They concluded that along with other factors, the temperature of the follicle during treatment may well also help determine effectiveness of the treatment.

Other studies at RAFT investigated melanin levels, skin colour, hair depth, skin layer thickness and skin density, producing a wealth of information and helping to inform others on best clinical practice.

USING LASER TREATMENT TO HELP PATIENTS

Once they had established the technique, the surgeons at Mount Vernon were able to use laser depilation to help a wide number of patients. For example, patients who had suffered cancer and were undergoing reconstructive treatment could now be sure of hairless skin grafts.

Another group of patients helped by laser treatment were those with a painful and distressing condition called a pilonidal sinus. Pilonidal sinuses are nasty but rare, and affect 26 in every 100,000 people, and twice as many men than women.

Pilonidal essentially means 'nest of hairs', and people usually develop the condition between the buttocks. It is not clear how pilonidal sinuses develop, but it is thought to have something to do with hairs from the back and buttocks making their way down and working their way in, forming 'tunnels' or sinuses in the skin. These tunnels can become infected, inflamed, and as you can imagine, are incredibly painful. Unfortunately the only way to remove a pilonidal sinus is to cut it out.

Patients with excessive hair growth between their buttocks are more likely to be afflicted by this condition, and as a preventative measure removal of excess hair through creams or depilation is sometimes recommended by doctors.

In 2002 RAFT published a study investigating the practicality and patient satisfaction in using lasers to remove the excess hair from this delicate and embarrassing area. Researchers wrote to 14 patients who had been treated by the ruby or an alternative laser, asking them how they found this treatment.

All patients wrote back and all but one patient said that they would have laser treatment again if required. The patients found it a satisfactory and less embarrassing method of hair removal. However all patients all found the treatment exceptionally painful, and the one patient who wouldn't have it again stated it was because she found the treatment just too painful.

This kind of research is not glamorous, and it isn't easy to raise funds for, but to the patients it helps, it is just as important as RAFT's other, more high profile projects.

Another group of patients RAFT investigated laser treatment for were children. Children

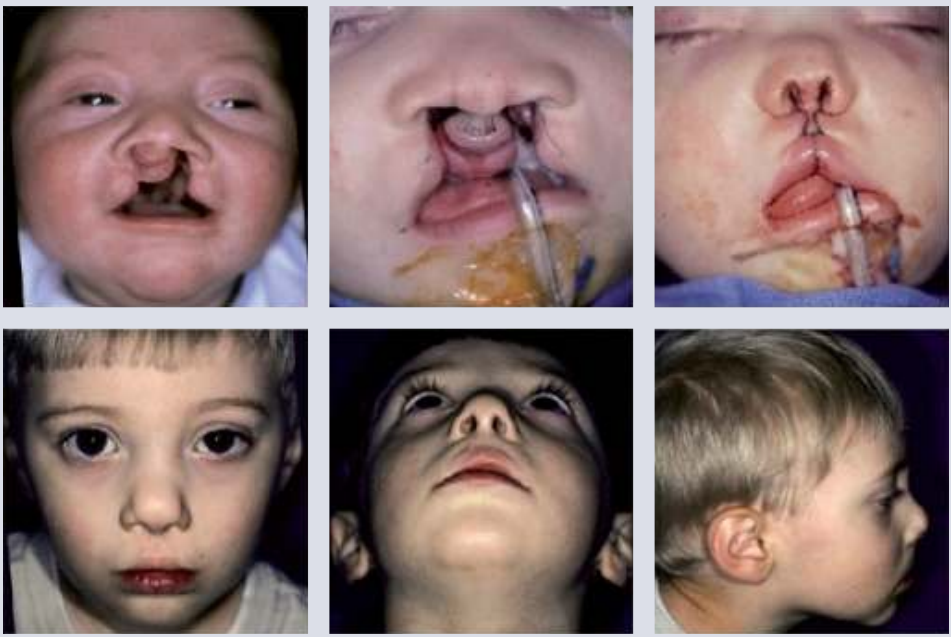
often react differently to treatments and it is always important to make sure any new therapy or method is safe for both children and adults.

In this study, researchers assessed patients under the age of 16 who were undergoing hair removal with the ruby laser. They found that treatment was successful in as many as 25 out of 28 cases, with around 63% of hair still removed at six-months. No scarring or changes in pigment levels were noticed and the pain was manageable. The authors of the study recommended that the ruby laser can be a quick, safe and well tolerated form of hair removal in children.

All of the innovative and informative experiments described in the sections above helped to refine and define the best techniques for successful hair removal using a ruby laser. In 2002 the laser team at RAFT collated all this information to produce definitive guidelines for ruby hair removal, based on the wealth of knowledge gained through their investigations.

These guidelines have since been cited over 80 times by other scientific publications and have either informed or have been incorporated into European and international standard guidelines for safe laser hair removal and care.

Cleft lip and palate



Preoperative image of newborn with bilateral complete cleft lip/palate prior to dentofacial orthopaedic manipulation. Following completion of nasolabial repair and at 2 1/2 years old.

Babies born with clefts have a gap or a split in their upper lip or the roof of the mouth. It is the most common form of facial defect in the UK and around 1 in every 700 babies are born with the condition. The usual treatment option is surgery, and surgeons at RAFT and Mount Vernon have helped to improve this surgery through a series of studies, two of which are described below.

3-D LASER SCANNING TO ANALYSE CLEFT LIP AND PALATE

In the late 1990s a team of researchers at RAFT collaborated with the University College London to carry out an important study, to investigate the use of 3-dimensional (3-D) laser scanning of facial characteristics in children with cleft lip and palate.

The Optical Surface Scanner, recently developed for use in facial analysis, was already known to be accurate and reliable in measuring facial dimensions. But no one before had properly investigated its suitability for analysing characteristics of children with clefts.

Surgeons need a quick and accurate way of analysing facial characteristics in cleft patients to determine the best way to operate, and accurate 3-D images can help them plan the surgery. The RAFT research team scanned the faces of 39 children with cleft lip and palate who were patients at Mount Vernon Hospital and Eastman Dental Hospital in London, and compared these to scans of 25 children without a cleft.

The scanning procedure took approximately 10 seconds and was safe, noninvasive, and well tolerated by children. The researchers found that this method of 3D laser scanning was able to accurately analyse and measure the surface characteristics of the face of children with clefts.

This study, published in 2000 was the first major study investigating live 3-D laser scanning of cleft characteristics. In 2004, it was one of the studies included in a review of facial scanning methods which ultimately recommended that 3-D, rather than 2-D scans should be used to assess cleft-related characteristics.

Since then the use of facial 3-D laser-scanning techniques has been further verified by many more studies, and this initial RAFT study is still routinely referenced by publications from other research groups.

COMPARING GROWTH IN CHILDREN WITH CLEFT LIP AND PALATE

In 2001 RAFT funded a study comparing the growth of facial characteristics in children who had undergone surgery for cleft lip or palate when they were younger. A UK report had recently stated that cleft surgery and care in the UK was lagging behind that of Europe.

The surgeons at Mount Vernon were concerned by this, and decided to see if it was true.

They set out to compare the facial characteristics of 75 children who had been treated for clefts at Mount Vernon with 150 children who had been treated for similar conditions at Rikshospitalet in Oslo, Norway. They used cephalograms, that is, x-rays of the face and skull, to carefully measure any differences in characteristics between the two groups.

The research aim was to discern if there was any difference in the way children grew after receiving different forms of cleft surgery and care, in Norway or the UK. In fact they found that as a whole, there was no difference between the two groups, a promising sign.

There was also some especially good news for the Mount Vernon team, the results showed that the Mount Vernon method actually produced better outcomes than the Oslo method in children who were aged 14-16. The Mount Vernon team could be reassured that they were doing a good job.

Novel ideas

Sometimes it's the little ideas that count. Some of the weird and wonderful ways that RAFT researchers have tackled problems are described in this section.

COUNTING NERVE FIBRES

Counting nerve fibres under the microscope is a tedious, labour intensive and time-consuming job. Some computerised methods have been developed which can be considered 'fully automated', but these methods can be expensive, lack accuracy and are prone to making large errors.

In 2006, Fulvio Urso-Baiarda, a surgical research fellow at RAFT, came up with a compromise between the two methods – a semi-automated system of counting nerve fibres which could combine the speed of the automated system with accuracy of a manual method of counting. The method required only a digital image of the nerve and two widely available software packages.

Before this invention, as many as 8,000 nerve fibres would have to be counted by hand.

"You'd go in," says Fulvio, "and there would be someone sitting on the floor, with all these huge photos, counting all these axons [fibres]. I needed another method. I came up with a cheap form of semi-automated nerve morphometry [studying the structure of nerve fibres]."

Since his method was published, other researchers have been grateful for it too. A recent study comparing automated systems with semi-automated systems such as Fulvio's, found that semi-automated techniques allowed for more "rapid, accurate, and complete assessment" of nerve fibres.

IMPROVING DNA SEQUENCING IN CELLS CONTAINING PIGMENT

Melanoma is an aggressive cancer which usually starts in the skin. For several years RAFT conducted a successful research programme investigating potential new treatments for melanoma, which involved studying in detail the cellular and molecular characteristics of the disease.

To delve further into the genetics of melanoma, cell biologists at RAFT needed to isolate and study the DNA taken from melanoma cells. However they soon came across a difficult problem.

The most common and effective way of studying DNA sequence in detail is by using a method called the polymerase chain reaction, or PCR for short. PCR is a chemical reaction which converts tiny amounts of DNA isolated from cells into sufficient quantities that can be accurately sequenced; a process called 'amplification'.

However, researchers at RAFT found that PCR did not work very well when they tried to amplify the DNA from melanoma cells, and as a consequence it was very difficult to study the genetics of this cancer.

Many melanoma cells originally start out life as skin cells, and some of these cells contain the pigment melanin, the molecule which protects our skin from sun damage. The researchers were able to demonstrate that it was only in the types of cells which contained melanin that the PCR didn't work, and similar to other research groups who had found the same thing, concluded that it was the melanin which was inhibiting the

PCR reaction.

The research team at RAFT went on to develop a novel method for removing the melanin from DNA samples and in 1999 they published a "simple and rapid technique" which removed the melanin and allowed efficient PCR of the DNA in melanoma cells. This RAFT method has since been successfully used by a number of research groups around the world to measure and remove melanin from their own contaminated cells.

MAKING A LEECH LATCH ON

Perhaps somewhat surprisingly, leech therapy is still a valuable tool in modern-day medicine. Throughout history, these small, worm-like creatures which normally reside in rivers and ponds have been used to treat many conditions, from blood clots to headaches.

These days, medical leeches are invaluable to plastic-surgeons, and are not just plucked from the nearest river but are bred in sterile conditions at specialist leech farms. Once applied to the skin, leeches can suck away pooled or congested blood.

This makes them particularly useful in cases where skin reconstruction is needed after burn injury, or in any situation where many tiny blood vessels have been severed and blood may accumulate. But, it is not just a case of leading the leech to blood, because you must also make him drink. Light-hearted as this may sound, getting a leech to attach in the appropriate area can be difficult and time-consuming for all concerned.

In 2002 a surgical research fellow at RAFT published a novel method "derived through desperation" for attaching a leech where it is needed. He describes the case of a 7 year old boy with minor injuries caused by glass which needed to be drained using leeches.

After several attempts to attach the leech, the fellow manufactured a makeshift "leech applicator" using a section of suction tube and

Leeches at work

some surgical tape. The results, as the fellow says, "allowed easy transport and precise placement of leeches," and best of all, "obviates any need to handle the leech itself."

The boy's injuries were effectively treated using this method over three days, and the health of the skin around the injury was successfully maintained.

ESTABLISHING THAT COFFEE AND MICROSURGERY DO NOT MIX

Microsurgery is the art of performing incredibly detailed small-scale surgery under a microscope. Today, as surgery becomes ever more sophisticated, this technique is commonly used in transplant and plastic surgery when very tiny nerves and blood vessels often need to be reconnected.

As you might imagine, microsurgery is an immensely skilful job which takes huge amounts of patience and training.

To give you just a small idea of the level of dedication needed, prior RAFT surgical research fellow, Fulvio Urso-Baiarda describes his own personal experience of learning one particular microsurgical technique.

"During my two years at RAFT I performed around 60 operations under the microscope for my research project. I started off taking eight-hours per operation. By the end I was down to just 2.5 hours!"

Microsurgeons often choose to avoid drinking caffeinated drinks such as coffee on days they are operating. This is to prevent potentially problematic issues with hand tremors, a common effect of excess caffeine intake.

But until Fulvio decided to investigate, the effect of caffeine intake on surgical skill had actually never been properly explored. So Fulvio and his colleagues conducted a scientific study on microsurgical training course students to establish if caffeine really did affect performance.

Each student received either caffeine in the morning and a placebo in the afternoon, or the reverse, and their microsurgical technique was then monitored and scored.

Fulvio found that subjects consuming caffeine in the morning demonstrated significantly improved scores from morning to afternoon, whereas subjects consuming caffeine in the afternoon showed no such improvement.

Taking into account the natural learning curve of each student throughout the day, these

results unfortunately support the view that caffeine does indeed have a detrimental effect on microsurgical ability and alas, microsurgeons must continue to forgo their morning coffee.

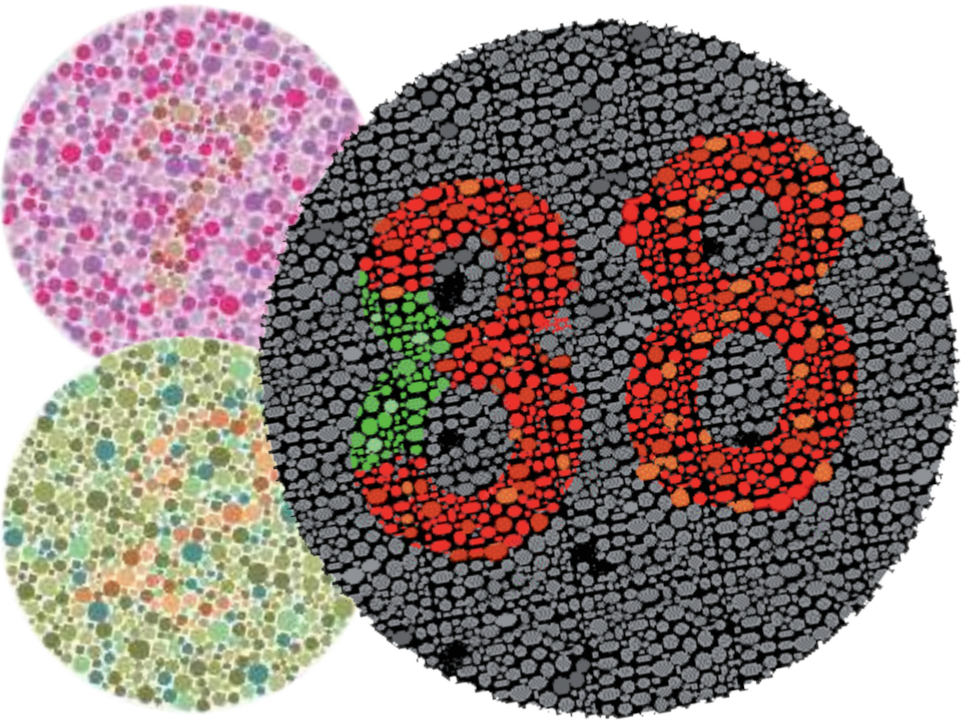
FINDING A SIMPLE SOLUTION TO A 'BLINDING' PROBLEM

Around 2% of the population, mostly males, have red-green colour blindness. People with this condition find it difficult to accurately distinguish colours containing elements of red or green. For example, out of a box of 24 different coloured crayons, a person with red-green colour blindness may only be able to accurately identify the correct colour of just five crayons.

For a researcher in a laboratory, or a diagnostic specialist in a hospital, this can cause problems. Many experiments and diagnostic methods use stains or dyes or different colours to identify the different sorts of cells and structures present in a tissue sample. If you can't tell the difference between these cells, then your research, your job, and even your patient's life could be at stake.

This is why, in 2002, one enterprising colour-blind RAFT surgical research fellow came up with a novel way of manipulating the images digitally, so that all scientists, even the colour-blind ones, can see every detail.

This cost-effective method used software that is already available in all labs and involved no other equipment, making it a quick and easy solution to a very real problem for many lab workers. This new method was quickly written up and published, and has been available to all colour-blind scientists ever since.



Stephen Bell

What it feels like to have a skin graft

My Syndactyly condition, which is a fusion of fingers, was present at birth; I was born with all four fingers fused together on my right hand, writes Stephen Bell, a London-based events manager and planner.

When I was six plastic surgeons did skin grafts to separate my index finger. The other three fingers on my right hand cannot be separated as there is only one bone fused between them. For the graft, skin was taken from the underneath my upper forearm area (near the elbow) and also from the groin area. It was all very painful.

The operation was performed to the best ability of the surgeon, but this particular procedure in time caused tension in the joint area and also lead to the skin graft splitting due to my fingers and hand growing.

Words cannot describe the terrible burning sensation in between the finger joint area of the separation. It felt like my hand and fingers were on fire. There was bleeding as well due to the splitting of the skin graft.

One critique of using skin grafts is that the grafts darken in the years after surgery and become more noticeable. Also, with the skin grafts being harvested from the groin area, the skin may start growing hair[which is one of the reasons why RAFT invented laser hair removal.

WHAT SURGERY WAS LIKE

The surgery itself was pain-free, as I was – thankfully – put to sleep. I remember waking up with the whole of my right hand and arm bandaged up to my elbow area. The separation was not initially visible and I remember it all feeling a little numb (likewise with my groin area, too, where they took a skin graft).

It felt strange and I really wanted to run out

of the hospital as quickly as possible in order to pull off the bandages to see the results. I could not run off anywhere with my parents, family and friends being present, plus of course the health professionals.

To be honest, I was rather tired and lacked the energy to physically move from the hospital bed. Time seem to past quickly, as before I knew it, the results were revealed and I was: thrilled, delighted, pleased, excited and emotional with the successfully separation. YIPPEE!

I now had TWO fingers on my right hand instead of just one big finger of four fused together. The next stop was a trip to a different part of the hospital to get a glove made which would compress and help heal the scars.

Try and visualise an extremely tight rubber glove, multiply the tightness by about a thousand, and then add some itchy skin coloured material for good measure. This was the experience I was going through and it was sheer torture.

I watched two gloves being cut up and stitched together in minutes. Both were identical, with one just a 'spare'. I was asked by both my plastic surgeon and the talented glovemaker, stitcher-lady to wear the glove day and night for six months. When I got home, I completely refused point blank to EVER wear it, as it was horrendous. My parents were not too pleased, but said it was my choice. I have been left with some scars and have actually kept these two gloves as a keepsake.

INSIGHT INTO SCARS AND DISFIGUREMENTS

My personal experience and journey has been: positive, successful, interesting and exciting. I am right-handed and I can do most things with it except for a few exceptions like catching a ball, clenching my right fist, grip wide ojbects, etc. Thankfully I am not in any kind of pain and lead a normal life.

My right hand is a little smaller, than my left, but this is hardly noticeable. My past 35 years have flown by. For some reason it was only when I turned 30 that I suddenly decided to undertake some research to find out a bit more about my fusion of fingers and only then did I discover that it was called Syndactyly' condition.

Over the past four to five years, I have taken a strong interest in raising both the awareness of it and image of positive body confidence.

My six particular personal interests are: visible differences, disfigurements, disabilities, deformities, 'looking different' and scars.

I enjoy encouraging the promotion of: equality, diversity, social inclusion, fairness, acceptance, humanity, tolerance, identity and corporate social responsibility (for all types of personal characteristics, including both visible and hidden impairments). Assisting to improving people's attitude, perception and reactions is fun and fantastic, as are both the challenges and also the coping strategies involved too.

All this has led me to:

- Undertaking presentations at different universities to medical students
- Getting involved with Centre of Appearance Research (The University of the West Of England in Bristol) for their Appearance Matters 5 Conference (July 2012) where photos taken of my Syndactyly condition are part of their Perspectives exhibition.
- Attending the House of Commons (March 2012) as a 'plus one guest' of a Member of Parliament for the All-Party Parliamentary Group on Body Image's (APPG) first ever Body Confidence Awards. I never met so many humble people in all my life.

I am now in the process of looking at the physiological impact of having a visible difference, disfigurement, disability, deformity, scar(s) and/or looking different, and the general public's reactions and perceptions.

Training and education

Training and education was one of the main early aims of RAFT: To train and educate future surgeons, ensuring that the research ethic becomes well and truly established in the plastic surgery and reconstructive field.

In this section we talk about some of the ways that RAFT has helped this to happen, from ensuring around 15% of all plastic surgeon consultants practising in the UK had been trained in research at RAFT, to publishing over 315 research articles – every single one of them pushing the boundaries of human knowledge forward, one step at a time.

Training surgeons of the future

In 1988 research in plastic and reconstructive surgery wasn't the same as it is today. "Plastic surgeons were held in contempt; very little research was being done by plastic surgeons at the time," says Professor Roy Sanders, principle founder of RAFT.

Roy's aim was to change this, to help make sure plastic and reconstructive surgery practice and methods are underpinned by a strong research ethic, to "join science with surgery, to train young surgeons in research."

Above: students being trained at RAFT under the watchful eye of Dr Sorousheh Samizadeh

FUNDING 54 SURGICAL RESEARCH FELLOWS

Perhaps one of the greatest legacies of RAFT has been to contribute the rigorous research training of 54 surgical research fellows over the last 25 years. Over half of these have gone on to become consultant plastic surgeons at leading UK hospitals, and many are still in research.

In 1998, 10% of all consultant plastic surgeons in the UK had received scientific training at RAFT. By 2004, over 16% of all UK plastic surgeons had been trained at RAFT. This is a phenomenal achievement for a research institute which had been going for just over 15 years at the time.

During this review we spoke to 25 former surgical research fellows, researchers and surgeons connected to RAFT. All of them emphasized just how important RAFT had been to them in their career, and how their time had helped them to be better doctors to their patients.

"I was on an immensely exciting project working in a laboratory that was so efficient and dynamic, it was wonderful. I was lucky to have worked with such committed individuals," says David Ross, a surgical research fellow who worked on the melanoma project in the early 1990s.

"My supervisor [George Wilson, who worked in the Gray Laboratory and collaborated with RAFT on the melanoma project] was hugely kind, incredibly gentle and patient, and so unbelievably generous with his time.

"He was able to nurture me from being completely incompetent in the laboratory when I started to being able undertake a complex scientific project. After my project I was able to base my clinical decisions on a much broader perspective of the disease, I learned that it's not necessarily what you see going on with the eye, it's what's going on underneath."

"RAFT taught me so much about research," exclaims Ben Klass, a former surgical research fellow. "I learnt many different research methods, including how to write papers and present at scientific meetings."

Richard Baker, another prior research fellow, agrees. "I developed an ongoing research ethic at RAFT. The charity kick-started a research mind-set in me, which I still feel now, years later. For example, I have just submitted a research proposal for a new clinical trial, and I also have friends from RAFT whom I am sure I will collaborate with in the future."

By teaching surgical fellows the importance of research early in their career, the future of plastic surgery research is secure.

Jamie Shelton, a former research assistant at RAFT put it succinctly. "RAFT is so great because the surgeons that go there have it ingrained in them how important research is, and how important it is to continue having links with research."

"I think the benefits of spending time doing research at RAFT are amplified over the years," says Richard Baker, "as even after you are no longer at RAFT, that research ethic still goes on and yields successful research in areas related to RAFT, and even beyond. I can think of many ex-RAFT fellows who are still producing lots of research, and contributing in other ways too."

HELPING CLINICIANS FIND THEIR SCIENTIFIC FEET

It really seems that from the start RAFT was a hot bed of scientific creativity, and also a very fun place to work. "It was a real golden time," says Duncan Bains, who ran the RAFT pressure sore programme. "We were like a bunch of nutcases, running around just trying to get different things to work."

Surgeons and doctors don't often get the chance to focus purely on research for a couple of years. RAFT was one of the first centres dedicated to plastic and reconstructive surgery

research; it gives talented surgeons the chance to develop research skills they might otherwise have never gained. But this can be a daunting prospect for a young trainee.

Fulvio Urso-Baiarda was a surgical research fellow who worked on the facial palsy project. During his time at RAFT, Fulvio went on to not only conduct some scientifically rigorous and highly technical experiments investigating possible ways to improve facial palsy surgery, but along the way he had to develop whole new ways of doing things.

"I remember the first Christmas, I was going into it [his research project at RAFT] thinking, how am I going to do this? It literally came to me in my sleep, I remember getting up and thinking: 'I can make this work, there are ways round everything. Just focus'."

One such method developed by Fulvio to help him with his project was a way of counting muscle fibres under the microscope. Stains and dyes are often used to distinguish different tissue structures for viewing under a microscope.

Whereas before, researchers at RAFT had to basically 'guestimate' which bits were connected to nerves based on the colour of staining they had used, Fulvio developed a new method he called 'reverse colour coding'.

The method involved applying mathematical transformations to work out the exact amount of specific coloured pixels in computer images of the stained muscle nerve fibres. Fulvio has now published this method, available for anyone to use.

It was this sort of innovative thinking which helped train scientific minds.

"It was fantastic for fine tuning scientific method, a really creative thing. It really encouraged innovation," says Fulvio, of his time at RAFT. "Also it was fun, it gave me a few challenges, a real technical challenge. On top of this I still have friends I made at RAFT, and I'm still publishing."

Fulvio has the same sentiments as many of

Drs Duncan Bain and Graham Nicholson studying pressure sores

the surgical research fellows we spoke to for this review. "It was great. I look back at those two years really fondly."

Ollie Branford, another surgical research fellow echoes these sentiments. Ollie was the first research fellow at RAFT to be awarded a PhD, an accolade which shows the excellent quality of the scientific training at the charity.

"I really learnt about scientific method," says Ollie, "my examiners after my PhD viva [exam] thought that I was a scientist and not a surgeon!" I have gained great understanding of my project area – tissue engineering and cell biology, which are central to research in surgery. I aim to use all these skills and have a strong academic arm to my plastic surgical career."

TESTING NEW TRAINING METHODS FOR SURGEONS

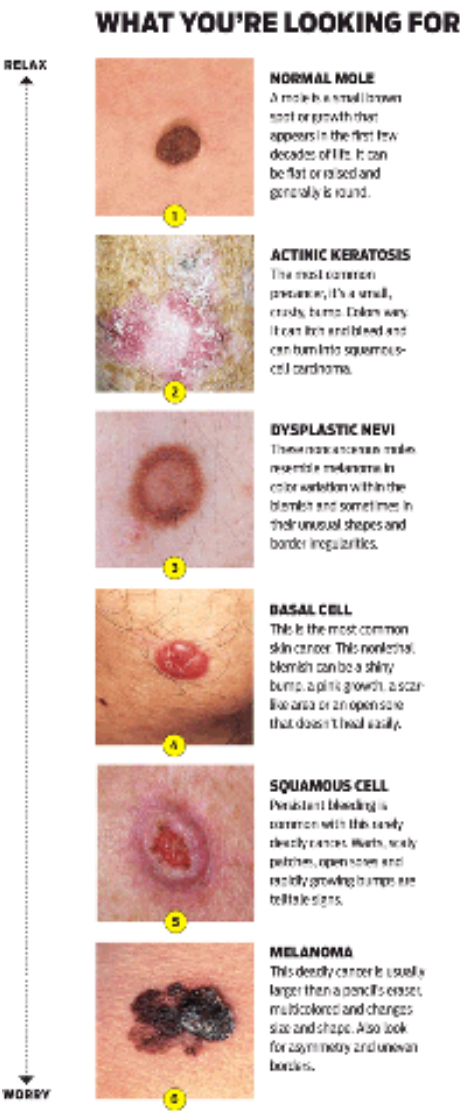
Accurate clinical diagnosis by doctors depends on the reliable recognition of signs and symptoms. Although some skin cancers are easily recognisable when presented by patients in clinic, some are not so easy to diagnose. Developing this expertise comes through experience in seeing patients, traditionally gained through long-term training.

However, some years ago, formal specialist surgical training was generally shortened and replaced with more intensive teaching sessions. This raised concerns as to whether it is possible to 'fast-track' a surgeon's diagnostic skills.

Surgeons based at RAFT wanted to look into these concerns, and so in 2005 they conducted a study at the RAFT-funded walk-in pigmented lesion clinic to assess how the diagnostic skills of two surgical trainees (who were also surgical research fellows at RAFT) improved over a one-year period.

Both trainees had weekly exposure to patients with many different types of skin lesions and regular teaching sessions. During these sessions, feedback was provided about the lesions the trainees had diagnosed, and how accurate their diagnosis was.

The researchers found that during the year, the trainees' rate of diagnostic accuracy improved from 53.3% to 65.0%. During the training period the trainee surgeons saw between 15–20 patients each week, and it was noted that



trainees attending a normal 'appointment-based' plastic surgery out-patients clinic would not see this volume and could take longer to achieve the same diagnostic accuracy.

Perhaps not surprisingly, the biggest improvements for diagnostic accuracy were noted in those cancer lesions the trainees were seeing regularly.

The researchers concluded from this study that the improvement shown by the surgical trainees during their year at the pigmented lesion clinic was a direct result of regular exposure to skin cancer patients and a structured learning programme.

This led the authors of the subsequent paper publishing the results of this study to warn: "The shortening of the specialist training period may affect the acquisition of diagnostic skills by trainees and impact on the confidence with which they commence consultant practice."

This study has since been used as evidence by Australian study which suggests that regional surgical registrars in Australia need closer supervision with regular feedback on their performance.

IMPACTING UK PLASTIC SURGERY RESEARCH

RAFT hasn't just helped patients, but has helped to raise the standards of plastic and reconstructive surgery at a national and international level.

Multi-disciplinary and translational research from the start; RAFT has always been ahead of its time.

Talking to surgeons who have been through the RAFT process, several common themes emerge, which hint at reasons why RAFT has been so successful.

One reason which is mentioned over and again is the close proximity RAFT has to Mount Vernon Hospital, which in the early years was a world renowned centre for burns treatment and also the location of a very good cancer laboratory called the Gray Laboratory.

Paul Tulley, a former surgical research fellow, explains what this meant to him.

"The great thing about RAFT was that it was attached to the plastic surgery unit at Mount Vernon, says Paul. "This unit had been running at least since the Second World War, and it worked well, was successful, and developed good collaborative links with RAFT. It gave RAFT a good source of clinicians, patients, data for databases."

Paul's words adequately sums up the major strength of RAFT, that it was a place where doctors and researchers could collaborate and work to help the patients. The huge resource of patient data and samples available from the long-established hospital has underpinned just about all of the major projects undertaken at RAFT.

Improving links between clinicians and research, which has been one of the fundamental principles of RAFT for 25 years, is today recognised as a major priority in the NHS constitution.

Through links with the hospital and by training surgeons, RAFT was able to emphasise 'bench to bedside' research, also known as translational research.

This essentially means that the science in the lab is done with the direct aim of improving patient's lives. RAFT was especially well placed to aid collaborations between scientists and clinicians, to help find the research that really mattered to the patient.

Sinclair Gore, a former surgical research fellow, talks about this aspect of his time at RAFT.

"It gave me great insight to the working of science within medicine and surgery, and how translational research should be driven. Skills I learnt during that time have been invaluable since. It was also a significant time of personal


Entrance to Mount Vernon Hospital

development and taught me to be a self-starter."

Douglas Harrison, a cofounder of RAFT and distinguished reconstructive surgeon adds his perspective: "We could work with the researchers, and tell them what answer we need. I could just go and talk to someone and say 'I've got this problem, any ideas how to fix it?', and the researcher would say 'yes, yes, we can help you'."

Douglas talks of collaborating with medical physicists in the radiology department of the hospital, to help develop a device for measuring blood flow through muscle grafts during his surgery.

This work was done just prior to the start of RAFT and shows the real multidisciplinary nature of the research ethic surrounding Mount Vernon and RAFT at the time.

Today, cross-discipline science is yet another 'hot-topic', promoted as a way to speed up translational research. Yet RAFT was founded with the core aim of conducting translational and multi-disciplinary research 25 years ago. In this way, the charity has always been ahead of its time.

IMPROVING THE QUALITY OF PLASTIC AND RECONSTRUCTIVE SURGERY

The real impact of RAFT becomes apparent when looking at how the charity has changed the field of plastic and reconstructive surgery research in the UK. This can be seen from the results of a survey carried out by RAFT in 2002.

The survey wanted to "take a 'snapshot' of the state of plastic surgery research activity in the UK at the end of the 20th century," at a time when RAFT had been going for just 12 years.

The survey showed that RAFT was in the top six major institutions where surgical research fellows were based, and was second only to the University College Hospital London for the number of research degrees awarded to trainee plastic surgeons.

Furthermore, RAFT had become one of just four main UK centres for plastic surgery research, next to the prestigious institutes of Cambridge, Blond McIndoe in East Grinstead, and University College Hospital in London. Together these centres employed the vast majority of scientific staff, including 81% of all postdoctoral (i.e., non-clinical) plastic surgery scientists in the UK.

Hunterian Professorships are a prestigious accolade awarded every year by the Royal College of Surgeons to individuals who have made a significant contribution to surgical, anaesthetic or dental science.

The awardee holds this post for a year and during this time is expected to make a series of lectures to the royal college on their work. Many important advances in clinical surgery have first been publicised through these lectures.

It comes as no great surprise that several prior RAFT researchers have been awarded this honour. In 2005 RAFT's annual report noted that "only 12 Hunterian Professorships are awarded each year, and only 25 have ever been given to the speciality of Plastic surgery and this [awarded to Adriaan Grobbelaar] is RAFT's 7th.

It is impressive to think that almost a third of all plastic surgery Hunterian Professorships have gone to individuals associated with RAFT.

Disseminating knowledge

There is no point doing research if the rest of the world doesn't know about your findings. Although competition is necessary to drive forward scientific progression, the core spirit of research relies on collaboration and the sharing of ideas.

Researchers can disseminate their findings in many ways, but two ways they are formally expected to share their research is through writing results up and publishing them in respected journals, and presenting their work at national and international scientific conferences.

PUBLISHING OVER 315 RESEARCH ARTICLES

Looking at the number of peer-reviewed research articles (that is, articles which have been assessed for scientific integrity by experts in the field) which have been published by an institute or laboratory is a good indicator of the success of the research being done there.

Every paper published must bring something new to the scientific field; adding another piece to the jigsaw puzzle.

This is one thing that the experts who review the article check for; that the findings are novel. They also check that the quality of the research is of a high-standard. A total of 317 papers have been published by researchers funded by RAFT over the last 25 years.

That's an average of around one paper published for every month, from 1988 to 2012. This is incredibly impressive for such a small institute and something of which all associated with RAFT should be very proud.

By far the area of research which has yielded the most papers for RAFT has been in the field of burns therapy, skin regeneration and wound healing, with around 70 papers published in this field so far – almost a quarter of all papers published by RAFT.

MEASURING IMPACT: RAFT PAPERS CITED BY ALMOST 8000 OTHER ARTICLES

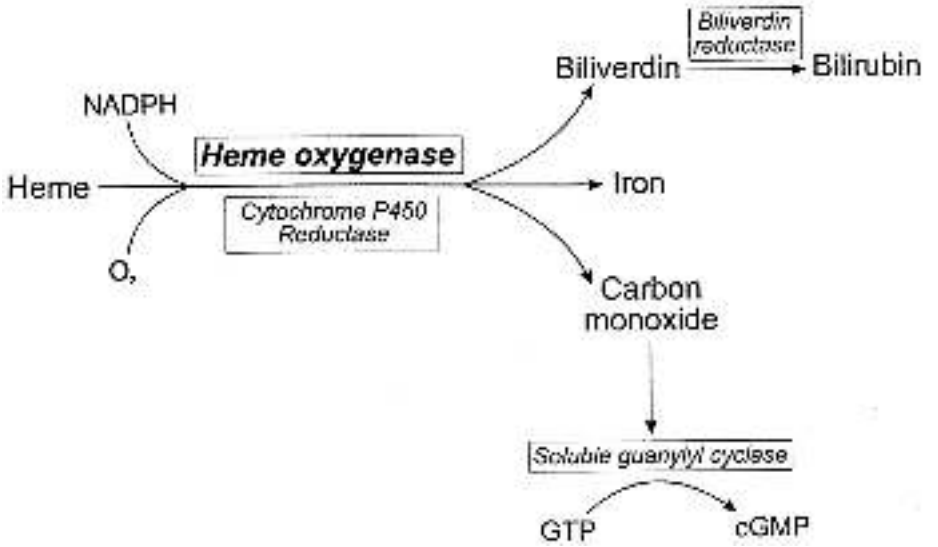
Another way of assessing the quality and relevance of published research is to look at how many times a researcher's paper has been cited (or referenced) and used by other researchers in their field.

Generally speaking, the higher the number of citations, the more impact the article has had on the field, that is, the more relevant and useful other researchers have found it.

But that's not to say that only 'good quality' papers get cited, or 'bad quality' or irrelevant papers are never cited. Often it can take years for the evidence to mount and for the results to be validated by others. Or occasionally a truly ground breaking finding can just be completely missed by other scientists.

Gregor Mendel, the 'father of modern genetics' presented his 'eureka' findings about inheritance a full 35 years before anyone realised what this actually meant. Rumour goes it was because his lecturing style was simply too boring for people to concentrate.

But bearing this caveat in mind, it is a significant achievement that those 317 RAFT research papers have been cited almost 8,000 times already, an average of 26 times per article, by other research articles, books and scientific



reviews. This shows the truly significant impact of the research carried out by RAFT.

The most highly cited RAFT research article was published in 2000 and has since been cited by 400 other articles.

The paper showed results from a study investigating the antioxidant effects of a protein called bilirubin. The RAFT researchers showed that a form of bilirubin found in the heart might be able to protect cells and tissue against damage from lack of oxygen, for example when someone has a heart attack or a transplant.

Bilirubin is produced as a result of the action of a molecule called heme oxygenase. This was one of the first studies to show that bilirubin produced by heme oxygenase could have a protective effect in this medical context.

Over 10 years later, and a large amount of evidence now shows heme oxygenase and its associated molecules act as powerful antioxidants, which could be protective following injury. One recent review has urged that every effort must be made to transfer this research from the laboratory to the clinic.

PRESENTING AT INTERNATIONAL CONFERENCES

National and international conferences are a way for scientists to present their data to the scientific community fast, so their findings can be discussed, debated, and progress as quickly as possible.

Following its launch in 1988 RAFT soon gained a reputation as a major player at the national and international conferences for meetings in plastic and reconstructive surgery.

In 1998, just 10 years after RAFT started, RAFT researchers were noted to have produced 10% of all the papers presented at the European Meeting of Plastic Surgeons. By 2005, at the 9th congress of European Congress of Scientists and Plastic Surgeons, this figure had increased to 25%.

Douglas Harrison, cofounder of RAFT explains what it was like.

"It was almost embarrassing, the number of papers from RAFT which would be presented at conferences. I remember at one international conference in San Francisco somebody telling me a story about how another non-RAFT researcher seemed disgruntled, taking to a

delegate there saying 'We've had so many papers from RAFT, shouldn't we restrict the number they can present?' and the other delegate asked 'Well, are they good?' 'Yes', replied the first. 'Well then, why put a limit on it?'"

REGULARLY REVIEWING CURRENT RESEARCH AND CLINICAL PRACTICES

Sometimes in research, the answer is already out there, but we just don't know it yet.

With the hundreds of researchers, all publishing their findings, sometimes in direct conflict to each other, it can be difficult for a doctor to know what the most up to date research shows, and what is generally accepted as the best way to treat or manage a condition.

This is why researchers and doctors spend time writing reviews. A review is just what it says it is; a review of the findings from all the current studies on a particular topic which have been published.

When a researcher decides they want to conduct a review, they must spend a lot of time and effort searching the published scientific literature databases, and wading through many papers. They must then make sense of all they find, and write about it.

This means that when doctors or other researchers want to know about the most up-to-date expert opinions on research in a specific area, they need just read the review, instead of themselves wading through mountains of papers.

Researchers usually do not publish a review until they themselves have gained significant experience in the field. The number of reviews a researcher has published can be an indicator of their expertise.

Between them, researchers at RAFT have produced over 30 reviews and book chapters based on current research and clinical practice. That's more than one review for each year of RAFT. From the best way to culture keratinocytes, to current clinical treatments for the management of hypopigmentation, RAFT researchers have helped to study and summarise existing research for the last quarter of a century.

Dr Anna Wilson preparing to give a talk

Why do scientists write?

To non-scientists they seem confusing, convoluted and boring. They even seem to lie. You're at the airport, you pick up a copy of *Nature* and expect to see stories of elephant seals. You see anything but. In the latest issue is the 'riveting' article 'Treatment of idiopathic membranous nephropathy' – and by four authors!

However, for researchers and scientists, one of the most important thing they can do is to be published and by a respected journal.

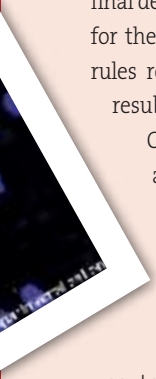
According to former RAFT scientist Dr Keith Blackwood, by being published, it is a sign of validation of your work because it has been reviewed by your peers.

"It doesn't matter what you do – it matters that you *know* what you did," says Keith. You can create something in your laboratory, but can you create it again? Can you then present your results to your peers and have them give you their stamp of approval?

PROCESS OF PEER REVIEW

Usually an article that appears in a peer-reviewed journal will require several months, if not a year, of research, analysing data, writing, editing and reviewing.

The peer-review process can go through two or three rounds of revisions before reaching a final decision about whether to accept the article for the journal. And, each journal has different rules regarding the rejection of an article and resubmission.



One of the main reasons for peer-reviewed articles is to present a more objective research base. Every author has biases, regardless of how hard they may try to remain objective.

Every peer reviewer has biases too. Having a diversity of opinions can help to neutralize the biases that may come up during research and help to keep the findings of the article objective, thus presenting the best possible research for others to build upon

PROCESS OF WRITING

"When you start even considering writing a paper to explain your research, you need to step back and decide how is your work unique?" says Keith. "How does it differ from other research? What have you discovered? What research have you pushed forward? It's very hard to do."

Keith takes a long breath, unsure how to go on. You suspect he is expecting his next sentence to be greeted with laughter.

"You need to take a step back and see the work is trying to say instead of just the data," says Keith. "For example, what is the protein binding trying to say; seeing the holistic view and then seeing how else the work can fit in."

Keith says that all he learned about writing for science journals he learned from his advisor at the University of Sheffield, Professor Shelia MacNeil, who taught that you can never forget your paper is a story, the same elements in any work – such as beginning, middle and end – also has to be your paper.

According to Keith, the beginning has to outline the whole rational of what you're doing, explaining the shortcomings in the current research, what you're hoping to solve and the justification of why you think of what you're going to do will work.

The middle is what most find the easiest to write because in it the data collected is explained and the results shown. "People go into research because they basically like doing research and in the middle is where all of this goes," says Keith.

Where most papers fail is the end, says Keith.

"Too many researchers just regurgitate their beginning, the end is very difficult to write."

He says that a writer needs to have a very good grasp of surrounding papers and an even greater grasp as to what makes your paper unique.

What can make the entire process even harder is if the data is part of a patent.

"You can explain the beginning and the end, but a patent screws up the middle – how we did things.

"If you can't then you're going to have to ask your audience to take a leap of faith," says Keith. "And you know what, scientists don't like taking a leap of faith."

Patient Education and Support

Dr Eileen Bradbury

Helping patients with disfigurement

Around one in every 44 people in the UK are living with significant face, hand, or body disfigurement – that's over one million people. Disfigurement can effect a person's life in many ways; they may have to endure a number of corrective operations, for example, or adapt to a new way of living with their condition.

Yet the psychological effects of a disfiguring injury or condition can often be overlooked. Everybody responds differently, and it can be very difficult to determine the level or type of psychological support they need. RAFT understood that psychological trauma can play a huge toll on a patient, and funded research projects into how best to help these patients.

STUDYING THE IMPACT OF TRAUMA

Dr Eileen Bradbury is a consultant psychologist who specialises in the psychological consequences of conditions such as traumatic injury, disfigurement, and scarring. She has spent her career working alongside plastic surgeons and other health professionals involved in trauma care and treatment.

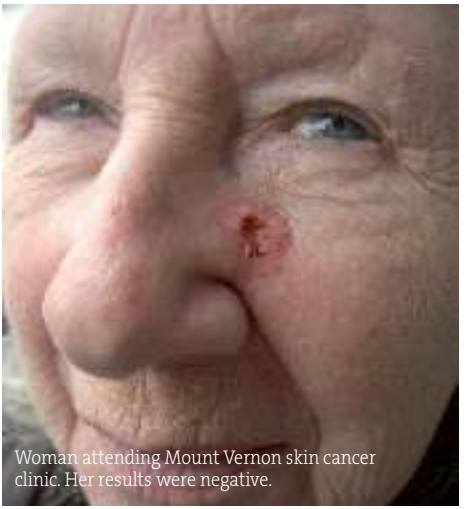
To get her research findings to the health professionals who want to know how to help their patients, Eileen regularly presents her work at scientific and surgical conferences. It was at one such conference that Professor Roy Sanders, RAFT's cofounder and Director of Medical Research, approached her and invited her to come and speak at RAFT.

He also wanted to discuss the possibility of collaboration. For many years, the Plastic Surgery Unit at Mount Vernon Hospital had been treating patients with cleft lip or palate and facial palsy, and a hugely valuable resource of patient data had been collected.

However, no one really knew how the patients who had undergone surgical correction for their condition actually felt. Eileen and RAFT wanted to investigate this, with the ultimate aim of finding better ways to help patients deal with their condition.

RAFT funded a research assistant for the project and over 200 patients with cleft lip or palate who had undergone treatment at Mount Vernon were followed-up and interviewed about their experiences. This took rather a long time as many had finished treatment and moved. But it was well worth the detective work.

Eileen says that a particular strength of her collaboration with RAFT was that she was not "cosseted away" in the psychological community, but was based in a rigorous scientific institution, surrounded by practising surgeons.



Woman attending Mount Vernon skin cancer clinic. Her results were negative.

"It was quite innovative and incredibly exciting for us to be based in the same place as surgeons and scientists from other disciplines." she says. "Everybody was accessible and open to our research. At our annual seminars they would ask incredibly insightful and useful questions."

UNDERSTANDING HOW PEOPLE ARE AFFECTED BY FACIAL PALSY

Of the 108 patients with facial palsy interviewed for this study, 35 had been born with the condition and 73 had developed paralysis after birth as a result of disease or trauma. You might think that most people would cope badly with disfigurement. It is a reasonable assumption, and this is certainly what Eileen thought might be the case.

Indeed, facial palsy undoubtedly brought great psychological and social stress for these patients, and some of their stories were heartrending.

"I caught sight of myself in the mirror and it made me jump," said one, "I thought I was normal from the inside, so why not on the outside?"

However, some unexpected results also surfaced after detailed analysis of the patient responses. "We were quite surprised to find that not everybody does struggle psychologically," says Eileen.

Depression levels in patients were actually slightly lower than in the general population, and levels of anxiety were similar. Interestingly, there was no significant difference in how patients coped regardless of if they were born with facial palsy or acquired it later in life.

"With disfigurement," says Eileen, "everybody must go through a grieving process. If someone has grown up with the disfigurement, the grieving process comes in stages, but it still needs to happen. They may occasionally think 'how might I have looked without this?' for example."

Research at RAFT found that the main reason patients had corrective surgery was to improve appearance. Patients were asked to assess their satisfaction with the surgery, and a specialised questionnaire, the Facial Paralysis Evaluation Profile, was developed by Eileen for this purpose.

The profile requires patients to score from one to seven how satisfied they are with a range of facial expressions and functions, such as eating, drinking, and blinking. This tool has since been extensively used by other researchers in the field. It has even also been used by hospitals to rate their surgical services. A recent study measured the Facial Paralysis Evaluation Profile against other similar available tools, and found it to be the best in terms of validity and reliability.

Using this profile, Eileen found that most patients were satisfied with their surgery, and felt it had been a success. But around 30% were not happy either with the surgery or how it turned out. Patients who were depressed before surgery were more likely to be dissatisfied with the outcome.

Using this knowledge, Eileen recommended that patients should be screened and those who need it receive counselling prior to surgery, to enable them to gain maximum benefit from reconstructive surgery.

FINDING WAYS TO HELP PEOPLE WITH CLEFT LIP AND PALATE

For the second part of the study, 109 patients with cleft lip or palate were interviewed, and again some interesting results emerged.

"We were quite surprised to find that the psychological impact tended to go one of three different ways," says Eileen. "Two-thirds

Children with cleft lips and palates

of patients said they had problems growing up, and when asked whether having a cleft had fundamentally changed them, roughly a third said it had made them less confident, but another third said it made no difference to them at all, and the final third even said it made them stronger and more sensitive."

Patient responses also highlighted this stark difference in psychological outcome. "Having a cleft has put something into me in terms of character. I can accept things that happen in life and fit in with other people," said one patient. "It was a very mundane part of me," says another. "I can't say that it affected me as a person."

But some patients paint a very different picture. "I was whipped away at birth, my father fainted. They had very low expectations of what I could achieve... I was very shy ..."

Through her research Eileen showed that the presence of specific 'resilience factors' in a patient's early life had a large influence on how they viewed their condition.

For example, family relationships were very important, and a supportive family background helped them come to terms with their condition.

However, if patients had pre-existing issues, such as poor support or poor self-esteem for example, then they were much more likely to view the condition negatively. "Once you learn which factors help make someone resilient," says Eileen, "this knowledge can then be used to develop support for those who need it."

THE FAR REACHING IMPACT OF THE RAFT PSYCHOLOGICAL RESEARCH PROGRAMME

Eileen published her work in the surgical press, and presented her findings at relevant conferences. In this way she was able to get her findings out to more of the people who mattered, the plastic surgeons and the people who worked with patients with disfigurements.

"Working with them, I understood what the surgeons wanted to know. In this way the research I conducted with RAFT was very practical. It directly informed and educated surgeons and health workers who had not routinely received a great deal of psychological training, yet who needed to deal with the psychological issues of very distressing injuries."

By increasing awareness of the psychological needs of these patients, and how to meet these needs, Eileen hopes to improve the treatment offered to patients so that they feel better able to face the world.

"It's easy to focus on physical treatment

and forget the enormous psychological and social effects of facial disfigurement and reconstructive surgery. I learned so much from this study about the long-term effects of disfigurement and the ways in which those with disfigurement cope against the odds. I also learned a lot about what patients need from psychologists and surgeons and how those needs could be met."

Eileen's work at RAFT has been far-reaching in a very real sense of the word. After her work with RAFT she went on to collaborate with other surgical/scientific bodies in the UK, the USA and Scandinavia developing measures to assess outcomes following reconstructive surgery, including a project partly funded by the World Health Organisation.

Soon after her work at RAFT had finished, she embarked on a research project in Uganda, looking at how clefts are managed and affect patients in the developing world.

"I used what I'd learned from the research at RAFT," she says, "In Uganda, in small isolated communities, children born with clefts and their families can be ostracised. If a child is born with a cleft, it is sometimes said the mother has been consorting with the devil.

"So I went over expecting a very different attitude and cultural approach to clefts in Uganda compared to the UK. I thought perhaps the mother might be blamed. But actually, the parents still loved and protected their child. They wanted to make their child better.

"Society and the village might have different views, but so much is still similar with our own culture. A mother still loves her child, no matter what. So even in Africa, I was still developing on findings from RAFT. There were still consistencies between the UK and Africa."

"This whole project was invaluable in terms of my clinical work with patients," she says.

"As a clinician, the day you stop learning is the day you take your pension. RAFT gave me a huge opportunity to build on my clinical knowledge.

"The more I've learnt, the more I've understood that each patient has a deeply individual and complex set of needs surrounding their condition. Patients will occasionally say 'How can you understand? You don't have what I have, how can you understand how it feels?'

"I can agree that no, I don't understand how it feels, but if I had their condition, I could only understand how I would feel about it. I still wouldn't be able to understand how they feel. They have to tell me."

LEARNING WHAT EAR RECONSTRUCTION SURGERY MEANS TO ADULTS AND CHILDREN

Prominent ears affect one to two percent of children born in the UK. Non-surgical moulding and splinting can be used to correct the ears within the first six-months of life, but after six-months old, surgical correction is the only option.

Unfortunately it is often not until later in life that the condition can become problematic for the patient. Prominent ears often do not affect hearing, but can have a long-lasting psychological impact if the child is bullied or teased at school as a result.

It is a sad thought that some children will only become bothered by their ears once they reach school and are teased by other children.

In 2005 researchers connected with RAFT, including Eileen Bradbury, conducted a review of 62 children and adult patients who had undergone surgery to correct their ears at Mount Vernon Hospital within the last five years.

They wanted to find out why these patients wanted the surgery in the first place, and

how they felt after they had the operation. The researchers asked the patients to fill out a number of questionnaires which assessed their feelings about the surgery and their condition.

The research found that many adults and children who had ear surgery at Mount Vernon reported reduced self-confidence and over 80% of both children and adults said they had been subject to hurtful teasing about their ears.

However, interestingly, motivations for surgery differed. Children said teasing was their main motivational factor for surgery, whereas the majority of adults said their reason for having surgery was dissatisfaction with their appearance.

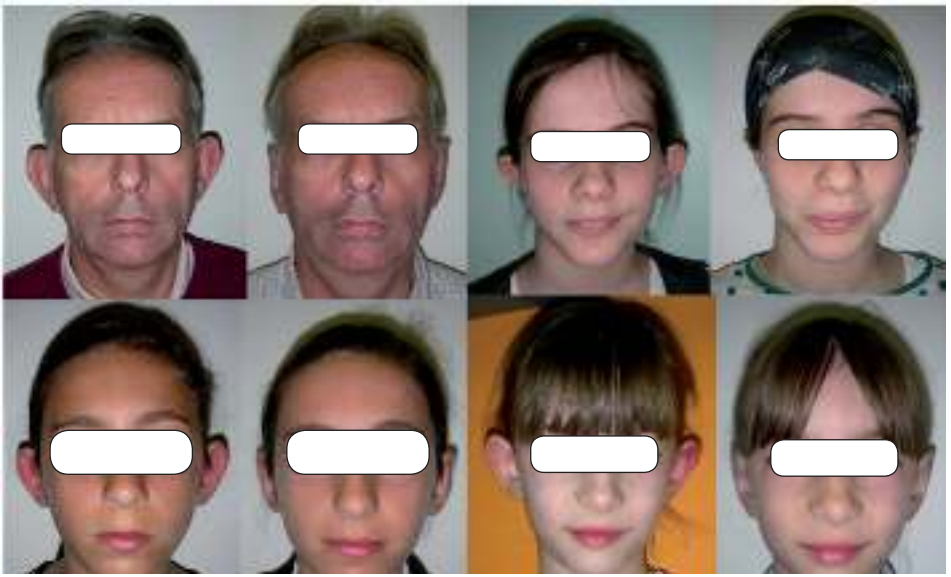
After surgery for ear correction, the majority of patients reported their surgical results as excellent and 91% of children and 74% of adults said their self-confidence had improved. The researchers concluded that ear correction surgery provides significant benefits to the patients' quality of life, despite variations in technical success of the surgery and potential problems for the patient associated with the operation.

In recent years as health budgets have been squeezed, some treatments deemed 'cosmetic' can sometimes be overlooked or labelled as 'not important'. How a treatment impacts a patient's wellbeing is difficult to measure, but can be incredibly valuable when health authorities are considering whether to fund the treatment.

This study was therefore essential for showing the importance of ear correction surgery to the patients who received it, and has since been used as positive evidence for the surgery by influential books, opinion papers, and patient websites.

Perhaps more importantly, this study has also been used to inform NHS policy statements and the Royal College of Surgeons Statement of Position in 2010, recommending that corrective ear surgery continue to be funded.

As it stands today, funding for surgical treatment of prominent ears in the UK varies between NHS trusts. Some may not fund treatment if it



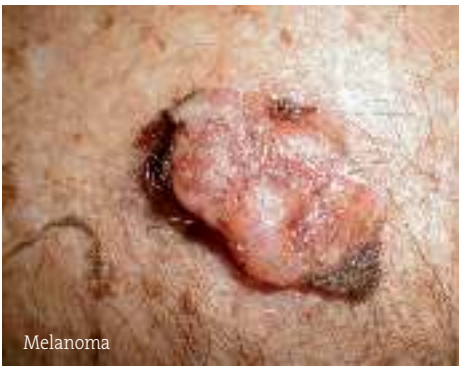
Patients before and after ear reconstruction surgery

is deemed 'purely cosmetic', whereas others will require psychological reports profiling the effect of the condition on the patient.

This is why studies such as the one carried out by RAFT continue to be important, the evidence they provide is vital to fight the corner for people who might not otherwise get the treatment they need.

ENGAGING WITH PATIENTS - SETTING UP A 'WALK-IN' SKIN CANCER CLINIC

In the last half of the 20th century the UK experienced an explosion in the number of patients developing the skin cancer melanoma. In just 20 years, from 1974 to 1994, the number of patients dying from melanoma had risen by a staggering 74%. People under 40 years old were especially affected. Due to the numbers being affected and the black look of melanoma, some were calling it the Second Black Death.


Melanoma


Patient at RAFT walk-in clinic

Something had to be done, and it was around this time that surgeons based at RAFT had the idea of setting up a system for screening patients with suspicious moles. Their aim was to catch melanoma and other skin cancers in patients early, when the cancer was easier to treat and before it had spread.

Studies have shown that if melanoma is caught when it is less than three-quarters of a millimetre thick, chances of patient survival are hugely increased.

So RAFT surgical research fellow Haimish Laing and other surgeons persuaded Mount Vernon Hospital to set up a weekly 'pigmented lesion clinic'. This was a relatively new idea, and the clinic was one of just four in Europe.

The clinic was staffed by RAFT surgical research fellows and operated on a walk-in basis. Patients merely had to get a letter of referral from their GP and they could come to the clinic any time, without an appointment.

This provided a rapid assessment service for patients and those with suspicious-looking moles or lesions (an area of skin damage) were offered urgent treatment to remove it under local anaesthetic. Patients whose moles or lesions were obviously not cancerous were reassured and discharged from the clinic.

The clinic was an immediate success – a total of 1779 patients attended in the first two years alone. The majority of patients were discharged without treatment; however 18% of patients, – almost two patients out of every 10 who attended the clinic – had cancerous skin lesions removed.

Further analysis showed that the thickness of the melanomas removed from these patients were generally thinner than those removed from

patients attending the usual outpatient clinics at the hospital before the walk-in clinic was set up, indicating the pigmented lesion clinic was catching the patients with melanoma earlier.

BY 1996 almost 4,400 patients had attended the clinic, and 290 melanomas had been diagnosed and removed. The number of these clinics throughout the UK had increased and RAFT researchers decided to conduct a study investigating for the first time whether walk-in clinics had a beneficial effect on patients' lives.

It had already been shown that the clinic was picking up thinner lesions, but was this being translated into a better outcome for the patient? The answer was yes.

The researchers showed that early detection through the pigmented lesion clinic not only potentially increased the length of time before patients relapsed and their melanoma came back, but also reduced the number of patients who actually suffered a relapse at all. This was the first time that early detection had been demonstrated to be an effective strategy for improving survival in patients with melanoma.

In 2000 the government introduced a 'two-week rule' stating that patients with some cancers, including melanoma, should be referred to a consultant within two weeks of seeing a GP. By this time the pigmented lesion clinic at Mount Vernon had been wound down, but researchers at RAFT used data they had gathered from the patients who had attended the clinic to produce the first piece of evidence that the 'two-week rule' would have a beneficial impact on patient survival.

The legacy of these walk-in pigmented lesion clinics lives on today, in the form of teledermatology clinics.

"The pigmented lesion clinics were the precursor to teledermatology, which is happening now," says Haimish Laing. "Pictures of patients' lesions are taken using a special lesion detecting camera, and are then sent off to a dermatologist to look at them remotely."

The pigmented lesion clinic at Mount Vernon Hospital directly benefited patients in a number of ways.

Not only did it improve patient chances of surviving a particularly aggressive cancer, but the clinic also brought about wider more indirect benefits, including improved patient education of melanoma through the distribution of leaflets at the clinic, more thorough consultant training by giving them direct exposure to a large number of patient cases, and providing the researchers at RAFT with a huge catalogued database of patient samples to work with.

In the 1990s, a RAFT annual report mentions that the clinic is the "only integrated skin cancer service in England, consisting of an early detection clinic, surgical management of melanoma, subsequent treatment based on prognostic gene testing, and gene therapy and diagnostic research."

And all of it was started with funding from RAFT.

PROMOTING SELF-EXAMINATION FOR SKIN CANCER

Educating patients to self-examine their skin for suspicious moles is an important method to help catch skin cancers such as melanoma in the early and most treatable stage.

This method is especially important if the patient has already been treated for melanoma and may be at risk of the disease coming back. However, it has taken a long time for the exact role of the patient in melanoma diagnosis to be defined.

In 2001 a surgical research fellow at RAFT, Joy Odili, wrote to the *British Journal of Plastic Surgery* describing clinical experience of this

issue over the last nine years at Mount Vernon, the time during which melanoma consultants had been teaching melanoma patients to examine themselves for relapse of the disease.

If the patients found anything suspicious, they were able to refer themselves back to the melanoma clinic at the hospital.

Joy and her colleagues reviewed case notes of 73 patients who had been treated for recurring disease at Mount Vernon Hospital, and found that of these, the majority (41 patients) had actually self-referred themselves back to the hospital after having correctly diagnosed the return of the disease.

In comparison, just five had the return of their disease diagnosed by their GP, and 27 had it diagnosed at a routine hospital outpatient appointment.

The researchers saw this as evidence that the patients themselves were as good as their hospital doctor at diagnosing their disease recurrence. They recommended that teaching patients to examine themselves following melanoma treatment an efficient and cost-effective way of helping to optimize chances of picking up new lesions or recurring disease.

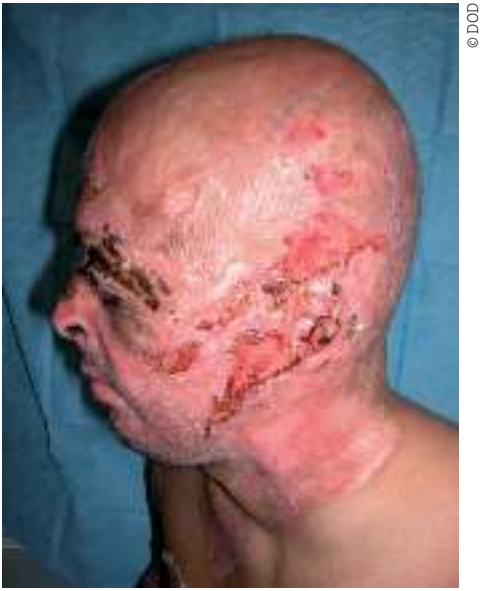
In the revised UK guidelines for the management of melanoma of the skin in 2010, teaching patients to self-examine featured prominently as part of the follow-up for patients who were at increased risk of the disease. It's good to know that by this time, melanoma consultants at Mount Vernon had been recommending self-examination for almost 20 years.

SUPPORTING PATIENTS WHO HAVE SUFFERED TRAUMATIC BURNS

Suffering from a severe burn is not only traumatic at the time, but can also have a serious lasting psychological effect.

The patient not only has to deal with the


Patient being supported after surgery



People forget that burn injuries can affect a person's mental state

after- effects of suffering a serious accident and possibly years of follow-up treatment, but they may also be left with disfiguring scars and other on going problems.

Over the years, RAFT has recognised the importance of addressing the psychological side effects of burn injury in many ways.

One of these ways was in the early 1990s, when surgical research fellows at RAFT ran a dedicated scar clinic for patients attending the Burns Unit of Mount Vernon Hospital.

The scar clinic was recognised by one research fellow as being particularly useful in the support of patients, as it "gives patients time to air their fears and feelings as well to seek further advice in an unhurried atmosphere." The fellow went on to say that the success of the clinic at Mount Vernon "suggests the need for such a clinic in all burns units." Several specialist scar clinics exist today at NHS hospitals across the UK.

What drives Vaibhav?

It is not by random chance that this review of RAFT's 25 years' worth of accomplishments is ending with PhD student Vaibhav Sharma. Like all the other surgical fellows, researchers, PhD and MSc students who went before him, he is linked to the beginning of RAFT with his same commitment, drive and passion that the founders had.

For 26 year old Vaibhav, this journey began in Dubai where he was born.

"I have known for some time that I have wanted to run my own medical research company in Dubai, specialising in diabetes research since the disease is rampant there and in India," says Vaibhav. "But how do you do such a thing?"

Vaibhav went to Manipal University in Dubai where he completed a BS degree in biotechnology. He thought that having an MSc Industrial Biotechnology would complement his first degree so he looked for a programme that he could complete in a year, figuring he could go straight into the industry. Vaibhav figured wrong.

"I did my MSc at Newcastle University in northern England and thought that would be

it. On returning to Dubai I quickly learned how hard it would be to find work."

During a six month period he had only two job interviews. With one the intended project never got off the ground; with the second he says he gave the worst interview of his life. With no options in Dubai, Vaibhav decided to return to the UK where he knew the lay of the land.

"I applied everywhere, with RAFT being one of them. I had never heard of them before, there wasn't an opening, but I had nothing to lose."

One of RAFT's researchers though was involved in a serious bicycle accident and there was a sudden opening. Vaibhav got the job.

"I was put on the team working on RAFT's skin scaffold Smart Matrix™, with my job centred on the manufacturing and optimising of it. I worked with Drs Julian Dye and Keith

Blackwood, learning a tremendous amount from them."

Vaibhav decided then to pursue a PhD in protein-based scaffolds and RAFT offered to fully fund it, with his course leader Prof Chris Mason at University College London.

"In a nutshell what I'm doing is research to improve the mechanical strength of Smart Matrix™ and to improve its interaction with cells," says Vaibhav. "Smart Matrix™ will revolutionise wound healing – wounds will never be treated the same way again. It is exciting to be part of this project."

For Vaibhav, working at RAFT fits in perfectly with his 'big picture' of running his own institute.

"At RAFT, like in the real world, you need to learn how to work on a fixed budget. This means you need to plan ahead. At universities, you never think about this, you just buy what you need.

"At a university, too, you tend to work only with people in your own speciality; here I work with people with different expertise. Besides scientists, I work with fundraisers, with accountants, even with the communications officer; you really learn the big picture on how an institution works. This is one of the main things I'm going to take away with me.

"At RAFT, too, in the research side we have a surgeon and she can tell you exactly what a patient needs. In a university research department, you are far removed from patients and from medical staff. You can only assume."

However, RAFT's small size can be a double-edged sword. "On the research side we are all specialists in our own field. This can give you a broader perspective; on the other hand, this can be a problem when you need help."

Vaibhav laughs at what he's about to say. "I know this sounds like some sort of pat answer but it's true. For all of us at RAFT we get a tremendous amount of satisfaction from working here because we know everything we do is to benefit patients."

Above: Dr Elena Garcia, Dr Raina Zarb-Adami, Vaibhav Sharma, Niroshehaa Ragunathan and Nimesha Patel

Current Projects

RAFT is continuing to push the boundaries of research, while adapting to a very changing economic and scientific world.

What many university, non-profit and profit research institutes are finding is that funds are no longer available to move medical research projects into – and through – all the clinical testing stages.

Pharmaceutical companies are also going through a transition stage due to many high-profit products, such as Viagra, reaching the end of their patent protection. While in the past these companies were more willing to fund early-stage clinical trials, this is no longer the case, wanting products to be proven in latter-stage testing before they get involved.

The end result is a tremendous amount of excellent research not moving beyond this basic stage due to a lack of funds. This ever increasing gap between research institutes, pharmaceuticals – and patients – was referred to as 'the Valley of Death' by RAFT CEO Leonor Stjepic at the BioDundee Conference 2013 held in Scotland.

In looking at this situation, RAFT was left in a quandary. RAFT's *raison d'être* is to bring needed research to patients, but without pharmas to pay for clinical trials – which RAFT is not set-up to do – vital projects were either hitting a dead-end, or moving at less than a snail's pace.

Above: Mike Ferguson – University of Dundee, Ken Duncan – Bill & Melinda Gates Foundation and RAFT CEO Leonor Stjepic at BioDundee Conference

Leonor decided then to take a radical approach to overcome this problem by setting up a for-profit company which would buy the research and fund the clinical trials. When trials end and the product is sold on, a set percentage of the profits will then be channeled back into the charity. The end result could someday be a completely self-supporting charity.

While on the medical charity side RAFT is unique in taking this approach, in other areas such as agriculture research this method has been tried and proved.

For scientists, however, there is one problem with this approach and that is the patent process. While in the past RAFT took a self-imposed 'high road' and released information, depriving itself of millions of pounds (such as with laser hair removal), RAFT is now keeping research much more confidential until patents are approved. Because this can be a long process, while the work is there, papers are not being published at the rate they once were.

RAFT though is continuing on with the excellent research it has produced over the last quarter of a century, with projects that have a strong potential of changing forever the way wounds and injuries are treated around the world. Here is a look at this work.

Breast Reconstruction

At RAFT we are working toward a reliable, safe and consistent method of breast restoration. A faster and more efficient process lessens the time needed for recovery and increases patient wellbeing. Risk to patients is reduced, as it the cost of repeated hospital admissions.

- Breast cancer is the most common form of cancer affecting women in the world
- 49,000 new cases are diagnosed in the UK each year
- 1 in 8 women will be diagnosed with breast cancer in their lifetime
- 40% of women diagnosed with breast cancer undergo a mastectomy

There are two types of surgery for breast cancer:

- Breast-conserving, which involves removing just the cancerous lump, and
- Mastectomy, which involves removing the whole breast

RECONSTRUCTION

Reconstruction to recreate the breast is now offered routinely on the NHS, alongside mastectomy, for all breast cancer patients.

There are lots of positive results from having breast reconstruction. For example, the patient won't have to wear an external breast form (prosthesis); when wearing clothes the patient's appearance will be similar to before their mastectomy; and psychologically a breast reconstruction can help to restore self-confidence, feelings of femininity, attractiveness and sexuality.


Fat that has been removed

There are two main avenues for breast reconstruction:

- Prosthetic, where artificial implants are used, and
- Autogenous, where a woman's own tissue, from elsewhere in the body, is used

Both methods have their benefits and drawbacks, but with the new breast settling down and taking its final shape and size, contour defects and asymmetry can become an obvious problem in either method. In these cases, fat transfer can be used to improve the shape of the breast. Fat is removed from the fatty layers of the buttocks, abdomen or thighs, purified and re-injected into the problem area.

While an extremely promising method of reconstruction, fat transfer is plagued with unpredictable results. The body can reabsorb between 20% and 90% of the transferred fat, leading to multiple re-operations for patients as well as unreliable outcomes.

Dr Anna Wilson

Studies have shown, however, that stem cells within the fat are the key to successful fat transfer, and results are much improved when stem cells are added to fat before it is re-injected. The stem cells increase the chances of fat survival within the reconstructed breast by encouraging the growth of new blood vessels and developing into mature fat cells themselves.

RAFT's Surgical Research Fellow Anna Wilson, along with Dr Sorousheh Samizadeh and in collaboration with The Royal Free Hospital have commenced a project which aims to improve reconstruction.

RAFT is improving the current outcomes of fat transfer using the following strategies:

- The time/cost-efficient isolation of stem cells, and their use with purified fat and scaffolds, reduces the chance of the body reabsorbing the re-injected fat, thus reducing the number of operations required.

Since the project began at the beginning of 2013, we have already halved the time taken to isolate the stem cells from the fat. Further reduction will mean that the patient can undergo the fat removal and transfer in just one operation, instead of two.

- The use of a biological scaffold, in conjunction with stem cells, provides the framework and physical filler for the new breast. The scaffold encourages the necessary blood supply needed for the injected cells to grow, multiply and develop into mature cells, seamlessly filling the defective area. Once the scaffold has done its job, it will dissolve into the blood stream.

RAFT's Breast Cancer research is focussed on finding an efficient way of isolating stem cells from fat, creating an "off-the-shelf" material so the stem cells can then be used by surgeons in the operating theatre quickly and efficiently.

3000 year old prosthetic toe found on an Egyption mummy. There is very little difference between this and modern day prosthetic limbs.

Bionic Limb

This project aims to give more movement, control and comfort to patients with prosthetic limbs.

- Every year there are more than 5,000 lower limb amputations in the UK due to disease. That's more than 100 every week.
- In addition, there are about 300 new traumatic upper limb amputations in the UK annually. The number has increased as military personnel return injured from conflicts around the world.
- More than 60 babies are born in the UK every year without part of one or both arms or hands due to congenital conditions.
- Worldwide, many tens of thousands of ordinary people have lost a limb due to war, accident or disease.
- Not only do these amputations cause enormous suffering, but they have a significant economic impact on the individual, and on society as a whole.

Kenneth Carey demonstrating to RAFT how difficult it is to put on an artificial limb


Dr Yazan Al Ajam

When an arm is amputated, the simplest form of reconstruction is an artificial, or prosthetic limb which is usually attached to the body using a socket, straps and harness. It is very difficult, however, to secure a prosthesis in this way, and most patients experience additional problems which include chafing, ulcers and pain.

Most prosthetic limbs are controlled with a cable and harness system, or by signals which are picked up my electrodes—wires that are stuck onto the skin surface of the amputation stump. The electrodes detect electrical signals in the remaining muscles of the amputation stump which can then be used to control electric motors in the prosthesis.

Unfortunately, skin surface electrodes are unreliable and non-intuitive. For example, to open and close a prosthetic hand, the user must actually think "bend or straighten elbow" to make it happen. And rotation is nearly impossible—making it extremely difficult to use a key in a door or start a car's ignition.

As a result of all of these issues, actual use of the prosthesis is poor and 80% of patients stop wearing this kind of prosthesis within two years.

Other prototypes being developed are prohibitively expensive, require an extremely specialised team of surgeons to install, and have not solved the basic problems of wearer discomfort.

RAFT is developing a completely new way to deliver electrical signals from the body to the prosthesis—placing electrodes inside the limb itself, and connecting the limb to a metal rod which acts as an extension of the existing bone. The metal rod channels the electrical signals to the artificial limb, and with RAFT's further research this system will provide stable and reliable control which aims to utilise the 32 muscles in the arm, an eight-fold increase on the muscles used in current prostheses.

As the user thinks "open" "close" or "rotate", the limb does exactly that: it's the next generation of prostheses which not only improves the use of the limb, but is cost effective.

RAFT'S PROGRESS

We tested the concept of using the metal rod as way to transmit muscle signals out of the body. Not only does the metal rod efficiently attach the prosthesis to the body, but we thought it was the ideal way to convey electrical signals from the muscles to the artificial limb.

RAFT was right.

So far, we have succeeded in transmitting signals from a single muscle. RAFT's laboratory models have demonstrated that these signals can be reliably transmitted without deterioration in the quality of the signal. Further research is now needed to deliver the signals from all of the muscles and to translate this device into something that we can use in people.

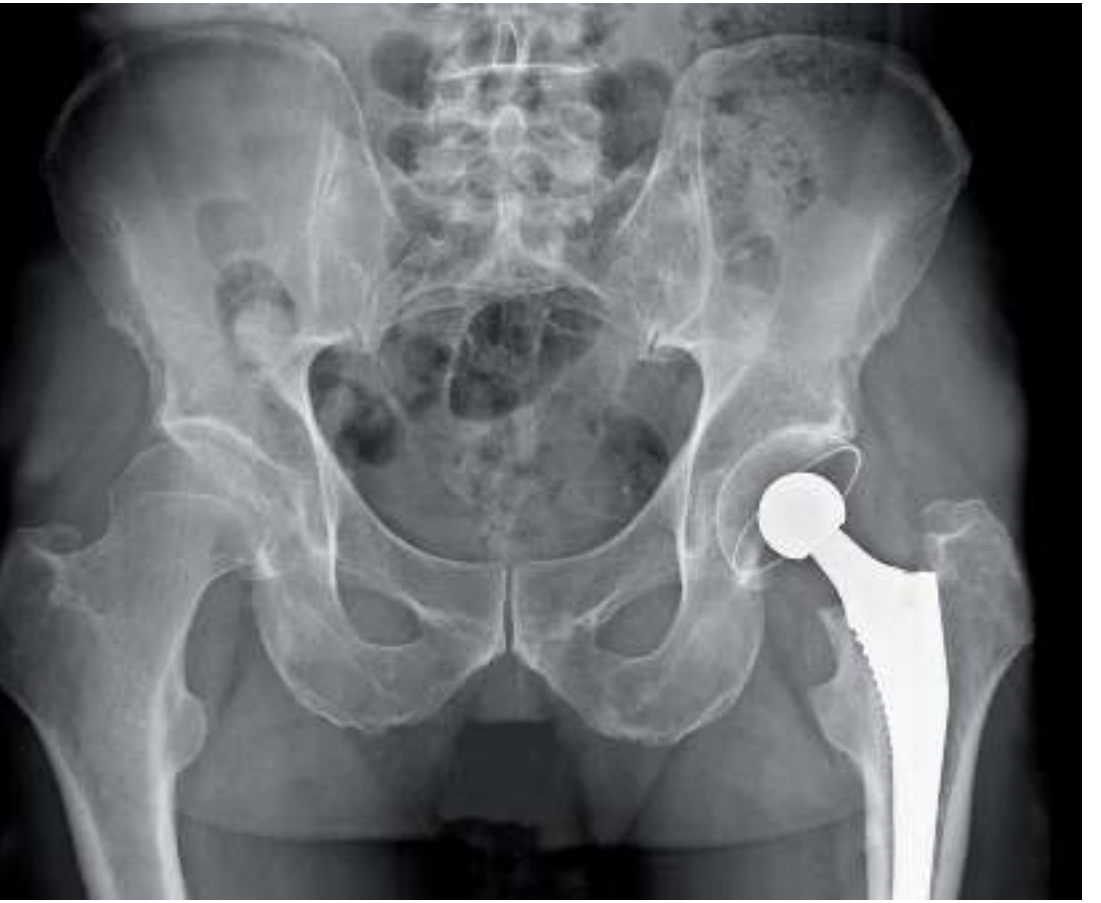
1. Although we focused on the signals from one muscle in the initial phase, we detected some interfering signals from adjacent

muscles. We need to modify the electrode design to reduce this interference, and we need to perfect the interface to maximise the number of muscles which send signals to the artificial limb, ensuring that the connections themselves are robust and watertight.

2. We need to design and test the transfer of electrical signals from the metal rod to the artificial limb and back again, and ensure that battery power is maintained.
3. We need to design and test the mechanical coupling to ensure the safe and robust attachment of the prosthesis, building in necessary fail-safe mechanisms in case of accidents.
4. Once we have a functioning device, we will conduct lab-testing to assess function and longevity, addressing any issues that develop.
5. We will test the final design in a controlled environment to gauge how the device will work in people. We will measure muscle signals in laboratory models for three to six months, allowing us to further identify potential issues and modify our designs before progressing to clinical trials with human amputees.

Limb attached to stump with titanium rod

Prosthetic limb being tested by the US military



Artificial hip in place

Growing Bone Programme

There is an urgent need to grow bone inside the body to improve the outcome for patients who require surgical implants such as hip or knee replacements, says RAFT's Dr Elena Garcia.

Growing bespoke bone inside the body improves lives in situations like these:

- Even after successful surgery, replacement joints in the hip and knee and erode and loosen over time, and in many instances this erosion causes pain and makes walking difficult
- Weaknesses in the supporting structure of the mouth, jaw, and teeth can make eating and chewing painful.
- Bone cancer patients, people with bone fractures, and back surgery patients

THE PROBLEM

Currently, in cases like these, patients may have up to three options. Depending on the severity of the condition, fewer options may be available.

None of these options guarantees success:

1. The transfer of a piece of bone from another part of the body. This is extremely painful, and some patients do not have enough quality bone to transfer.
2. Transplantation—using somebody else's bone—has a high infection risk and uncertain results due to the necessary mixture of bone.
3. Artificial bone substitutes are difficult to integrate with existing bone, and require additional plating which can be subject to further wear and erosion.

THE SOLUTION

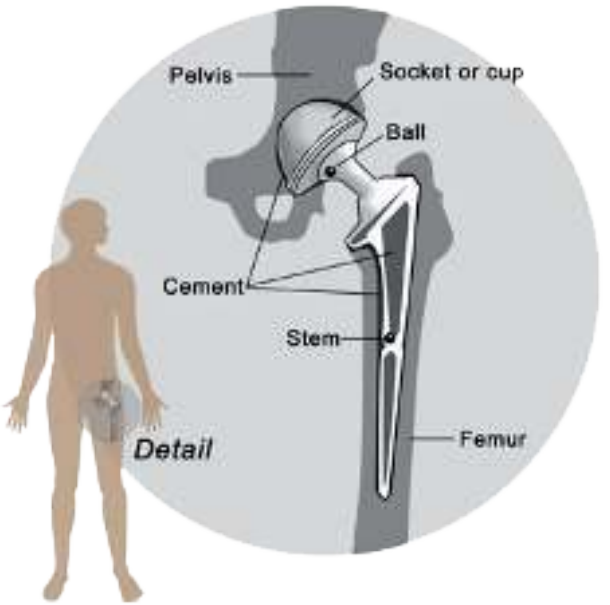
Growing the patient's own bone—inside the body—is the ideal solution. RAFT's research is bringing this process closer to reality.

RAFT's team of dedicated surgeons and scientists has a track record of delivering working solutions to patients. Our successful skin scaffold, Smart Matrix™, was developed at RAFT to encourage the body to heal wounds in the quickest possible time. We plan to apply the same concept for regenerating bone by seeding the scaffold with stem cells and calcium phosphate, the building block of bone.

RAFT has partnered with Professor Gordon Blunn at UCL, an expert in the field of orthopaedic surgery, and also joining the team are Dr Mia Woodruff, Dr Keith Blackwood and Professor Dietmar Hutmacher at Queensland University of Technology in Australia, and Dr Simon Cool and Professor Victor Nurcombe at the Institute of Medical Biology in Singapore.

Coupled with RAFT's own expertise in scaffolds, these collaborations bring together the very best of knowledge needed to take this work forward, and by connecting our worldwide networks of surgeons and patients we have confirmed the real need for this research and work.

As with all of RAFT's projects, we plan to build on our findings. We are planning to look at remodelling bone for birth defects and injury, and we will test the same principles for other tissue and organ regeneration.



The Future

QUT's new Science & Engineering Centre

Twenty-five years ago the clinics RAFT worked with were a two-minute walk away; now they can be halfway across the world.

In early 2014, RAFT will send Dr Elena Garcia and PhD student Vaibhav Sharma to the Queensland University of Technology in Australia for six months. In late spring Surgical Research Fellow Anita Mohan will be based at the Mayo Clinic in the USA to work on RAFT's breast cancer reconstruction programme.

"To continue to make a real difference in wound healing, our researchers need to be placed where they can learn from and work with the best," says CEO Leonor Stjepic. "To accomplish this, RAFT is taking a global view."

This change in approach is also seen as making financial sense as well. Sharing costs with other institutions – for example UCL and a facial reconstruction project – will allow funds to be used more effectively.

In addition to these centres, RAFT is in early stage discussions with universities and research

Mayo Clinic

organisations in the UK and overseas. Our criteria – to solve clinical problems and work with the rest.

This change is not being seen without its fair share of difficulties to overcome.

Although it is not uncommon for some industries such as petroleum to take a global business view, it is for medical research organisations. RAFT's approach, however, has always been to lead from the front and this is no exception.

"RAFT founder Prof Sanders said that his role at RAFT was to enable other people to do research, my role is exactly the same," says Leonor. "To achieve this, 25 years ago it made perfect sense for Prof Sanders to set up RAFT as a local medical research institute. In today's global world, for me to enable RAFT's team to do its finest work and carry on the vision of RAFT's founders, it now makes perfect sense for us to see ourselves as international."

RAFT Awards

Our research scientists and teams are regularly awarded major prizes and honours in recognition of their pioneering work.

DATE	PRIZE	RESEARCHER
October 2012	AMRC (Association of Medical Research Charities) – Best practice in medical and health research peer review	
March 2012	BJN (British Journal of Nursing) – Innovation Award	*Julian Dye* *Roland Renyi* *Ellie Lindsay*
2012	National Council For Work Experience Awards – Finalist in Charity Sector	
February 2009	Hunterian Professorship awarded by The Royal College of Surgeons of England	*Mo Akhavani*
2009	Winner of the Health Investor Award	
November 2008	Charles Clarke Prize Winner – Best Postgraduate Research Presentation – Pearce Gould Visiting Professor Meeting, UCL Department of Surgery. Winner ECSAPS Prize 2008 – Best Presentation	*Sophie Dann*
September 2008	12th European Conference of Scientists and Plastic Surgeons	*Sophie Dann*
July 2008	Poster Prize Winner (2nd), Tissue & Cell Engineering Society, Nottingham University	*Sophie Dann*
May 2008	Journal of Hand Surgery Prize – best paper presented at the British Society for Surgery of the Hand – Spring Meeting	*Mo Akhavani*
April 2008	Royal Colleges – McGregor Medal for distinction in the final plastic surgery specialist examination	*Marc Pacifico*
December 2007	NHS National Technology Awards – Diagnostics & Therapeutics Category	*Claire Linge*
October 2007	'British Oncological Association Young Investigator of the Year' – NCRI Cancer Conference (Birmingham, UK)	*Daniel Marsh*
February 2007	BAPRAS Paton-Masser Memorial Fund Award for work on 'alpha v beta 6 – a novel target for therapy and diagnosis in squamous cell carcinoma'	*Daniel Marsh*
December 2006	LBN Bio-Innovation Award 2006	*Claire Linge*
December 2006	Hunterian Professorship awarded by Royal College of Surgeons of England	*Matt Potter*
November 2006	The Patrick MacNamee Prize for best publication	*Marc Pacifico*

November 2006	AMRC Certificate of Best Practice in Medical & Health Research Peer Review	*RAFT*
April 2006	Commendation Smith & Nephew Award for Medical Technology	*Claire Linge & Richard Baker*
April 2006	First Prize Mills & Reeve Innovation Award for Medical Technology	*Norbert Kang*
April 2006	Third Prize Boult Wade Tennant Innovation Award for Medical Technology	*Norbert Kang*
2006	Health Enterprise East Award	*Richard Baker*
November 2005	Journal of Hand Surgery Prize – best paper presented at British Society for Surgery of the Hand Autumn Meeting.	*Bill Townley*
September 2005	9th European Conference of Scientists and Plastic Surgeons for best presentation	*Bran Sivakumar*
July 2005	John Calder Prize awarded by The British Association of Plastic Surgeons	*Sinclair Gore*
June 2005	Hunterian Professorship awarded by Royal College of Surgeons of England	*Matt Potter*
December 2004	American Society for Laser Medicine & Surgery 25th Annual Meeting – one of best student/resident papers in Dermatology/Plastic Surgery section	*Matt Potter*
June 2004	Hunterian Professorship awarded by Royal College of Surgeons of England	*Addie Grobbelaar*
September 2004	Royal Colleges – McGregor Medal for distinction in the final plastic surgery specialist examination	*Stephen Hamilton*
February 2003	Mentor Prize for best publication in British Journal of Plastic Surgery	*Marcus Bisson*
November 2002	Scholarship from the Keystone Symposia Fund for meeting on 'Antibody-Based Therapeutics for Cancer' – Alberta, Canada	*Vandana Joshi*
July 2002	Best basic science paper presented by a Trainee at Summer British Assocation of Plastic Surgeons 2002	*Rick Harrison*
March 2002	Best poster prize for Hertfordshire University, Industrial Symposium	*Mark Beckett*
March 2002	The Schering-Plough Young Investigator's Award	*Joy Odili*
February 2002	Best Industrial Placement Student, Hertfordshire University	*Charlotte Vigor*
January 2002	Hunterian Professorship awarded by The Royal College of Surgeons of England	*Joy Odili*
October 2001	Mentor Prize for best paper in British Journal of Plastic Surgery in 2001	*Rajiv Grover*

September 2001	Prize for best presentation at the ECSAPS Conference, Helsinki	*Joy Odili*
October 2000	Prize for best presentation at the ECSAPS Conference, Paris	*Neil Bulstrode*
June 2000	Prize for best presentation at the Melanoma 2000 Conference, Milan	*Joy Odili*
March 2000	Hunterian Professorship awarded by The Royal College of Surgeons of England	*Martin Vesely*
July 1999	John Calder Prize awarded by The British Association of Plastic Surgeons	*Caty Milroy*
June 1999	European Association of Plastic Surgeons (EURAPS)	*Rajiv Grover*
August 1998	European Tissue Repair Society Award	*Paul Harris*
August 1998	Societe Francaise de Microcirulation Award given by 20th European Conference on Microcirculation	*Martin Vesely*
1997/98	Sylvia Lawlor Prize in Oncology awarded by The Royal Society of Medicine	*Jagdeep Chana*
1997/98	Alan Edwards Award in Surgical Oncology awarded by British Association of Surgical Oncology and the British Association of Cancer Research	*Jagdeep Chana*
August 1997	European Tissue Repair Society Award	*Paul Harris*
June 1997	British Medical Laser Association Award	*Nigel Horlock*
1996/7	Hunterian Professorship awarded by The Royal College of Surgeons of England	*Thurloshan Kangesu*
1996/7	Hunterian Professorship awarded by The Royal College of Surgeons of England	*Rajiv Grover*
May 1996	European Association of Plastic Surgeons (EURAPS)	*Rajiv Grover*
1995	Amgen Roche Oncology Award and Young Investigator of the Year	*Rajiv Grover*
1995	Aesculap Prize in Plastic Surgery awarded by The British Association of Plastic Surgeons	*Rajiv Grover*
1995	European Travelling Fellowship awarded by Federation of European Cancer Societies	*Rajiv Grover*
1995	UK Travelling Fellowship awarded by British Oncological Association	*Rajiv Grover*
October 1995	Frank Cort Plastic Surgery meeting	*Rajiv Grover*

RAFT also received 16 further prizes between 1988 & 1999.

© London Fire Brigade

At RAFT we are so proud of our strong relationship with London Fire Brigade; without their on-going support and interest in our research work, RAFT wouldn't be where it is today.

London Fire Brigade has been involved in RAFT's 25 year journey, helping us in a variety of different ways, such as having us as a beneficiary at their annual Carol Service, their World Rescue Challenges and working with us on the water station at the Virgin London Marathon.

Mr Ron Dobson CBE QFSM FIFireE, has been hugely supportive of RAFT since becoming Commissioner in 2007, having made several visits to RAFT with some of his fellow colleagues as well as attending various events hosted by us.

It is an honour to work with the London Fire Brigade team, and we look forward to many more years doing so.

LFB
LONDON FIRE BRIGADE

Glossary

Apidose
Adipose tissue, or fat, is an anatomical term for loose connective tissue composed of adipocytes. Its main role is to store energy in the form of fat, although it also cushions and insulates the body.

Antimicrobial
An antimicrobial is an agent that kills microorganisms or inhibits their growth.

Apoptosis
Also known as programmed cell death. A type of cell suicide in which a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells. Apoptosis is the process of programmed cell death (PCD) that may occur in multi-cellular organisms.

Bilirubin
Bilirubin is a yellowish pigment found in bile, a fluid made by the liver

Biomaterial
A biomaterial is any matter, surface, or construct that interacts with biological systems.

Collagen
Collagen is the most abundant protein in mammals, accounting for around 30% of the protein content of the human body. It is often considered to be the glue that holds the body together.

Crystalloid
Crystalloid solutions contain small molecules that pass freely through cell membranes and vascular system walls. These solutions are useful as fluid expanders and are stored at room temperature. The crystalloid solutions are a useful source for electrolytes and a temporary source of fluid volume.

Epigallocatechin-3-gallate
Epigallocatechin-3-gallate is the most abundant catechin in tea and is a potent antioxidant.

Fibrin
Fibrin is a fibrous, non-globular protein involved in the clotting of blood.

Hyaluronic acid
Hyaluronic acid is a viscous slippery substance that lubricates the joints, maintains the shape of the eyeballs, and is a key component of connective tissue.

Hypopigmentation
Hypopigmentation is the loss of skin colour.

Marker
Markers can be used to judge the progress or decline of a tumour. Tumour markers are substances that are released by cancer cells or produced by the body in reaction to a tumour that is present. Normal cells also make these substances, but they are produced in much greater amounts by cancer cells.

The most common use of these markers is to follow a known cancer. In this setting a decrease in the level of a tumour marker may be a sign that a tumour is decreasing in size, whereas an increase in the level could mean a tumour is progressing.

Metastatic and primary disease
Metastatic cancer is cancer that has spread from the place where it first started to another place in the body. A tumour formed by metastatic cancer cells is called a metastatic tumour or a metastasis. The primary cancer is where the cancer started. If some of the cancer cells break away from the primary cancer and settle in another part of the body this cancer is then called a secondary cancer. Secondary cancers are made up of the same type of cells as the primary cancer.

Myofibrolasts
Myofibrolasts are spindle shaped cells with characteristic contractile proteins that contribute to the wound healing process.

Nephropathy
Nephropathy means damage to or disease of a kidney.

Phospholipod
Phospholipids are a class of lipids that are a major component of all cell membranes as they can form lipid bilayers.

Staphylococcus aureus
Staphylococcus aureus is a bacterium that is a member of the Firmicutes, and is frequently found in the human respiratory tract and on the skin.

Syndactly
Syndactyly is a condition wherein two or more digits are fused together.

Teledermatology
Teledermatology is a subspecialty in the medical field of dermatology

Prognosis
In the simplest term, the prognosis is the predicted outcome. Prognosis is a prediction of the chance of recovery or survival from a disease. Most physicians give a prognosis based on statistics of how a disease acts in studies on the general population.

Oncogenes
A gene that causes the transformation of normal cells into cancerous tumour cells, especially a viral gene that transforms a host cell into a tumour cell.

Outcome
Outcome is the survival rate which is defined as the percent of people who survive a disease such as cancer for a specified amount of time.

Personalised medicine
A form of medicine that takes information about a person's genes, proteins, and environment and uses that information to prevent, diagnose, and treat disease. In cancer, personalised medicine uses specific information about a person's tumour to help diagnose, plan treatment, find out how well treatment is working.

Prospective
A research study that follows groups of individuals over time, who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) and compares them for a particular outcome.

Retrospective
A research study that looks at medical records of groups of individuals who are alike in many ways but differ, similar to prospective however retrospective studies records rather than individuals.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Dr Sorousheh Samizadeh working with placental cells

Dr Khwaja Islam, Ex Laboratory Manager at RAFT

Sophie Dann, Ex Surgical Research Fellow, and Amir Taheri, Ex Research Assistant

Who is RAFT?

We are medical researchers, surgeons, fundraisers and support staff working together as a team, but with a global perspective. If RAFT didn't exist, it would need to be invented.

We are academic collaborators, donors, patient groups and volunteers who believe in the work of RAFT and we only work with the best.

We are a forward looking organisation. Our vision is to be world recognised in wound healing through the application of research, and our future projects are pointing us in this direction.

We have seen many changes in the past 25-years, but one thing that has always remained constant is our mission: We get our research to patients to transform major wound recovery.

We ask you now, come join in our success.

www.raft.ac.uk

raft

Lab manager Richard Ellis

Dr Anna Wilson

"At RAFT it was fantastic for fine tuning scientific method, a really creative thing, it really encouraged innovation. Also it was fun, it gave me a few challenges, a real technical challenge"

Mr Fulvio Urso-Baiarda

"I know this sounds like some sort of pat answer but it's true. For all of us at RAFT we get a tremendous amount of satisfaction from working here because we know everything we do is to benefit patients"

PhD Student Vaibhav Sharma

"We started to think, what happens if we can manipulate the activity of this gene? It laid open the path of melanoma research at RAFT for the next 10 years"

Mr David Ross

"RAFT changed our lives so we could help our patients, it trained us in scientific method. We learned to question dogma, to no longer accept the accepted"

Mr Rajiv Grover

"RAFT became known internationally as one of the greatest centres of research relating to Plastic Surgery"

Professor Roy Sanders

"I was one of the youngest to undergo this procedure and would not be here today if it wasn't for RAFT's life-saving research"

Ferrail Syed

"If RAFT didn't exist, we'd have to invent it" *Mr Norbert Kang*