



Research Strategy

Mission Statement

- Restore promotes and provides research into the treatment of burns and similarly life-changing wounds with particular emphasis on scarring.
- Our objective is to lessen the burden, physically and psychologically, of abnormal scarring on the individual and society as a whole.

Our Challenges & the Benefits

- The emphasis of our research is rooted in the everyday challenges faced by medical and nursing staff working with patients in Burns and Plastic Surgery Units. It is driven by constant feedback from patients and the issues that concern them.
- Our philosophy is to identify the key factors causing poor wound healing using clinically relevant models, investigate these in the laboratory using cutting-edge techniques, and then to improve patient outcomes through the findings. We are seeking improvement in the morbidity, and particularly scarring, of burns and similar wounds.
- Concomitant themes to our work include the prevention of burns and psychological support after injury
- The benefits of our research will include the reduction of the physical and emotional burden of scarring with all the attendant benefits of a healthier patient able to engage more fully in all aspects of their life.
- Our research is directed at achieving a national, collaborative approach as indicated by our track record of projects with a range of Burns Centres and Universities
- We target the widest possible target audience for our findings as indicated by the diversity of our publications and presentations both nationally and internationally
- The themes of our work sit harmoniously with current governmental interest in fibrotic diseases, preventative public health, stem cell research, genomics and proteomics, and the use of human models of disease.
- We aim to nurture the development of research skills in our staff and facilitate their lifelong interest in the prevention and treatment of burn injuries.

Why are we funding research?

Scarring within the skin is a frequent outcome after burn injury. It can be disastrous to those afflicted. As well as the physical symptoms it can produce – pain, itching, recurrent infections and occasional limitation of movement – the unsightly appearance can stigmatise and marginalise an individual from society. Scarring can trigger low self-esteem and even psychological illness. Millions of people have significant scars from all causes. The financial cost of treating these and the wounds that trigger them runs into hundreds of millions of pounds. Such scars can be medically improved but never eradicated – currently,

there is no drug that can eliminate scarring. More globally, the lessons learnt at a molecular level in the skin may be useful in the treatment of other significant conditions in which *fibrosis* is a key feature such as Alzheimer's disease, heart attack, cirrhosis and lung fibrosis. By funding research into key topics such as the molecular causes of burns that lead to scars and the psychological outcome of scarring, we are in a unique position within the United Kingdom.

Our Key Research Areas

- The basic molecular mechanisms involved in wound healing that lead to scarring in order to drive the development of anti-scarring treatments.
- Supplemental but complementary themes of our research include the development of robust outcome measures of scarring, both physical and psychometric, which are vital to monitor treatment. As a corollary of this, we aim to assess existing anti-scarring treatments which, as a generalisation, have often been introduced with incomplete evidence of efficacy.
- Our key wound healing paradigm is that of the burn injury, but we are informed from a variety of wound healing models.
- With full ethical approval, we have always strongly encouraged the investigation of wound healing and scarring in human subjects. Moreover, this methodology has met with much enthusiasm from our patients and trial subjects.
- Our work has already been successful, and we continue to support research in the following spheres:
 - development of reproducible and well-tolerated models of thermal and mechanical scarring in human subjects
 - global analysis of the molecules associated with these models using advanced genomic and proteomic techniques
 - analysis of stem cell production in significant burn injury as a source of potential regenerative rather than fibrotic repair
 - tissue engineering approaches to permit the more rapid assimilation of skin substitutes
 - validation of physical and psychometric scarring tools that have widespread applicability
- We initially focussed on clarifying the relationship between injury and scarring in human volunteers, the objective being to achieve an understanding of the processes which lead to scarring. We observed the mechanics at a cellular level of burn injury and the migration of white cells into the zone of injury. We then attempted to control cell migration through drug manipulation and also physical manipulation of the wound environment. The benefits were marginal and we have gone on to consider different ways of manipulation of, and to look at the role of blood vessel stem cells in, burn injury. In particular we are exploring the molecular changes in the early wound environment, both at a blueprint (RNA) and effector (protein) level.
- Our current specific focus is in two areas:
 - *"The molecular effect of cooling on human burns"*. Cooling an acute burn injury appears to reduce pain and inflammation. Ongoing inflammation has been shown to increase the likelihood of a burn going on to produce excessive scarring. In a completely novel human burn model, we are investigating using a global, genomic approach which molecules seem to be protective in cooled, as opposed to uncooled, skin that has been burnt. Our rationale is that these molecules may reduce inflammation and scarring if ultimately applied to the acute burn.
 - *"Vascular repair with adult and umbilical cord blood samples."* The ability to repair and grow new blood vessels is a fundamental step in early wound

healing. We are investigating how successfully isolated stem cells can be chemically triggered into producing new blood vessel networks. This leads us to the exciting new vista of creating an intrinsic circulation in artificial skin substitutes before they are applied to the patient with a large burn injury. Currently, the slow speed with which a new circulation is established is an impediment to the perfect integration of such 'synthetic skin'.

- Previous research projects, supported by Restore and undertaken by Restore Research Fellows, include:
 - **RNT/0068** 'The role of human bone marrow-derived endothelial precursor cells in the acute human burn', Mr A Fox, Feb 2004 – April 2006, £125,011.
Stoke Mandeville Hospital / Blood Transfusion Service, Oxford
 - **RNT/0069** 'Oligonucleotide microarray analysis of differential gene expression in the cooled early human cutaneous burn wound', Mr Tze Kong, Feb 2004 – June 2006, £95,512
Stoke Mandeville Hospital/ Institute of Molecular Medicine, Oxford
 - **RNT/0342** 'Immunohistochemical and biochemical analysis of wound healing biology in graded-thickness dermal injury', Mr J M Pleat, Mr C S J Dunkin, Feb 2001 – Feb 2007, £160,673
Stoke Mandeville Hospital /Dept of Biochemistry, University of Oxford
 - **RNT/0307** 'Topical Negative Pressure: The effect on human burn wound healing and scar formation', Mr R Caulfield, June 2000 - June 2003, £81,328
Stoke Mandeville Hospital / Dept of Surgery, John Radcliffe Hospital, Oxford
 - **RNT/0381** 'An investigation of the relationship between angiogenesis, protease/anti-protease profile and epithelialization in the active human burn wound', Mr R Caulfield, Sept 2002 – May 2004, £35,664
Stoke Mandeville Hospital / Dept of Surgery, John Radcliffe Hospital, Oxford
 - **RNT/0269** 'A study of angiogenic inhibitory growth factors and inter-individual heterogeneity induction of VEGF in relationship to surgical intervention for breast cancer: significance for breast cancer prognosis and treatment', Miss C Davies, Aug 2001 – July 2003, £75,000 approx.
Stoke Mandeville Hospital / Institute of Molecular Medicine, Oxford
 - **RNT/0239** 'A study of the angiogenic growth factors in relationships in surgical intervention for breast cancer', Miss C Davies, Mrs E Hormbrey
June 1999 – June 2002, £95,000 approx.
Stoke Mandeville Hospital / Institute of Molecular Medicine, Oxford
 - **RNT/0268** 'The effect of topical negative pressure on donor site wound healing', Mr T Adams, Jan 2001 – Feb 2002, £33,500
Stoke Mandeville Hospital/Department of Surgery, University of Oxford
 - **RNT/0307** 'Topical negative pressure: the effect on human burn wound healing and scar formation', Mr T Adams, Sept 2002 – Feb 2003, £30,047
Stoke Mandeville Hospital/Department of Surgery, University of Oxford

Our Grants

- Restore award "*Duke of Kent Plastic Surgery Research Fellowships.*" Typically there are two to three fellows at any one time.
- Fellows must be qualified medical doctors, surgeons or medical students with permission to work and reside in the UK.

- We advertise the fellowships in the British Medical Journal. The application process consists of a review of the candidates' *curriculum vitae* and past achievements. This is followed by an interview conducted by the Internal Review Panel and officers of Restore. Applicants will receive oral feedback after the assessment process is completed.
- There are no restrictions as to where work is carried out, but the Fellow is expected to conduct the majority of their clinical studies at Stoke Mandeville Hospital in Aylesbury, Buckinghamshire. However, the laboratory studies can be carried out any convenient location dependent upon the availability of the scientific techniques used to address the question at hand. In the past, we have forged links with the Universities of Oxford, London and Manchester.
- The research projects to be undertaken by fellows are proposed by our Directors of Research and scrutinised by our peer review process. Our peer review process consists of both an internal and an external peer review panel. The former is composed of those members of our Scientific Advisory Committee with no direct or indirect links to the proposed research project. Professor Sir Ronald Mason is our external reviewer and we are seeking a second external reviewer.
- Each post is for 2 or 3 years commencing on the award of the fellowship and dependent upon whether the researcher submits for the award of a DM/MD degree or a longer PhD/DPhil. We have established informal links with Green Templeton College at Oxford University to enable future fellows to benefit from integration as Green Templeton Fellows into this supportive centre of academic excellence. Fellows are expected to complete their higher degree and disseminate their findings at national meetings and by the publication of papers within peer-reviewed journals. Overlap of tenure is encouraged between Fellows to facilitate the transfer of knowledge and skills.
- A salary is paid on a monthly basis and Restore will pay for reasonable capital costs, consumables, higher degree entry and publication costs in relation to ongoing projects. Recent grants have ranged from £30,000-160,000 and are committed on the basis of full funding for the particular research project.
- To supplement traditional laboratory meetings, there are weekly clinical meetings at which Fellows discuss progress with senior members of the SAC or the Clinical Director. Fellows are obliged to present progress reports to our Scientific Advisory Committee at least three times a year. These reports will be assessed by the Committee, our Directors of Research and the Director of Clinical Studies.
- Our partners include the Buckinghamshire NHS Trust, the National Blood Transfusion Service and the University of Oxford. Past partners have included Cancer Research United Kingdom, Smith and Nephew and Oxford Glycosciences Limited. We are also seeking to develop partnerships with other relevant charities.

Our Timescale

This strategy has been set as of this date and is intended to be reviewed upon completion of each sequential research project and at least every two years.

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