



CURRENT CLINICAL APPLICATIONS OF STEM CELLS

Who was there?

More than 50 attended this one-day EuroStemCell workshop at the Royal Society in London. The Academy of Medical Sciences had circulated the programme to its Fellows, ensuring that a large proportion of the audience were eminent research-active clinicians and policy formers.

The talks

The opening talk by **David Linch** (University College London) covered the history of bone marrow transplantation. He pointed out that transplantation of stem cells has been in routine clinical use for over 40 years. There are 10 million volunteers on the bone marrow register and there is an 80% chance of a good match for Caucasians requiring a transplant. He highlighted the initial failures at the start of allogeneic transplantation: 414 out of 417 patients died in the initial studies. The growth of transplantation as a successful treatment has gone hand in hand with the development of the field of cellular immunology.

David Linch pointed out that in the current regulatory climate it is questionable whether the early bone mar-

row transplantation studies would ever have gone ahead. In addition, treatments that have been routine for many years are now being subjected to more stringent regulatory guidelines and as a result the cost of treatment is increasing. In the British national health system there is a ceiling on the cost of treatment that is approximately £35,000 per Quality of Life Year. Cost will be a general issue for future stem cell therapies.

Mohammadreza Mirbolooki of the University of Alberta described progress in pancreatic islet transplantation for the treatment of type 1 diabetes. He made a convincing case for the efficacy of this treatment, although he highlighted the problems of limited donor material, the short survival time of islets *ex vivo*, and the cost of treatment. 80% of grafts continue to function after 5 years. Islet cell transplantation from a living donor has now been carried out.

Mirbolooki pointed out that islet cell transplantation is a very young field: Paul Lacy performed the first pancreatic islet cell transplant in 1972 and the Edmonton protocol is only 6 years old. He explained that the next steps are

to conduct multicentre trials, to be able to use a single donor per recipient, to improve graft tolerance, and to find new sources of donated islets.

Nagy Habib (Imperial College London) described the cultivation of CD34 positive cells from blood, called 'omnicytes', that have multilineage differentiation potential. He described his initial experiences of transplanting the cells into adult human liver. His goal is to be able to replace liver transplantation with a treatment based on the patient's own cells that yields more material and is less invasive. He pointed out that adverse publicity surrounding a liver transplant received by celebrity alcoholic in the UK had led to a sharp decline in donated organs in the UK.

Omnicytes grow rapidly in culture but reach a plateau at day 10. Their gene expression profile differs from other CD34 positive cells in the blood. In the right culture conditions 40% of omnicytes produce insulin; these cells can restore blood glucose levels in mice in which insulin production has been blocked. Omnicytes also express liver markers and can repair liver damage in mice. A phase 1 clinical trial in a patient with

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liver insufficiency is underway. Nagy Habib's talk demonstrated how quickly a research-active clinician can get promising new stem cell treatments into clinical trials, given the right setting.

The remaining talks covered transplantation of cultured epidermis and cornea. The early methodology for repairing skin with autologous cultured epidermis was developed in the 1970's. Commercialization commenced in the 1980's with the advent of the biotechnology sector; however, it rapidly became clear that large scale grafting of burns victims is a very costly treatment with very few patients, which limits its suitability as a commercial product. Over time the technique has been successfully extended to other epithelia, in particular the cornea, and has been developed as a vehicle for gene therapy. The different speakers shared their experiences of working in different countries, with different legal and funding constraints.

One issue raised was the problem of communication between scientist and surgeon, since cultured epidermis is very fragile and if not handled with care during transplantation it is easily destroyed. It is no coincidence that **Yann Barrandon** (Lausanne) ran a highly successful transplantation programme when working in Paris with a military hospital where the doctors were used to taking orders. He felt that it is important to improve the basic grafting methodology to allow development of adnexal structures, such as hair follicles and sweat glands, and for this he is using minipigs as an experimental model.

Steve Boyce (Cincinnati) benefits from the support of a non-profit organisation, the Shriners Burns Hospital, which is devoted to the care of children with burns injuries. He grafts keratinocytes that have been cultured on a sponge and has made step-wise efforts to improve grafts by removing mouse cells and

foetal bovine serum. He has found that vitamin C promotes basement membrane development and he introduces autologous fibroblasts to improve graft quality. He is currently investigating ways of incorporating melanocytes into the grafts with the goal of re-pigmentation. He said that in the US regulatory framework cultured grafts are a device, not a biologic, and that xenotransplantation guidelines were published in the US in 2003.

Colin Song (Singapore) reported that the average successful take of cultured epidermal grafts is 60%. He uses a mixture of auto and allogeneic cells. He said that as a consequence of their faiths Hindus and Buddhists were not happy with use of bovine collagen as a graft substrate and described his experience of Biobrane and Tegaderm polymer supports. He considered Biobrane too expensive, but had good results with Tegaderm. An important resource for his work is a human skin allograft bank. Initial coverage of burned patients with cadaver skin reduces the mortality rate from 45% to 16% and reduces hospital stay by about 10.2 days.

Al Lane (Stanford) described a lethal form of the skin blistering disorder epidermolysis bullosa. His

goal is to correct the gene defect in cultured keratinocytes and then graft the cells onto patients. He discussed the lengthy and complex regulatory hurdles involved in going from proof of concept to treatment. One problem is that the regulations are being developed at the same time as the treatment protocols. Many scientists and clinicians are unable or unwilling to spend the time required to overcome these problems, because they erode research output.

Michele De Luca (Venice) described his experiences of treating an adult patient with nonlethal junctional epidermolysis bullosa. After overcoming many obstacles and starting treatment, all gene therapy in Italy was halted for a time. He and the patient have developed a mutually supportive relationship over the years and have been involved in fund raising for research. Michele De Luca also discussed his success in using cultured limbal cells to repair damaged corneas. In this protocol patients receive autologous grafts rather than cadaveric corneal transplants. Michele De Luca highlighted the retrospective requirement for new lab facilities to satisfy government regulations, leading to increased cost and no patient benefit.

Summary and conclusions

- All treatments discussed involved adult stem cells.
- Pioneers, sometimes cavaliers working in an ethical vacuum, play an important role in the development of new therapies.
- Regulations introduced after a treatment is in routine use increase cost and reduce ability to perform treatments.
- Treatments improve and evolve as a result of progress in the underpinning science.
- Donor registries are extremely valuable.
- Money and time are limiting factors, particularly for 'niche treatments' involving small numbers of very sick people.
- There is a need for centralised GMP/grafting facilities and international harmonisation of regulations.
- The time from proof of concept to clinical application needs to be born in mind.
- Cell transplantation, gene therapy and biomaterials are inter-related areas.
- Stem cell therapies often do not need to achieve 100% repair: for example, a 5% increase in serum albumin levels can benefit a patient with liver failure.