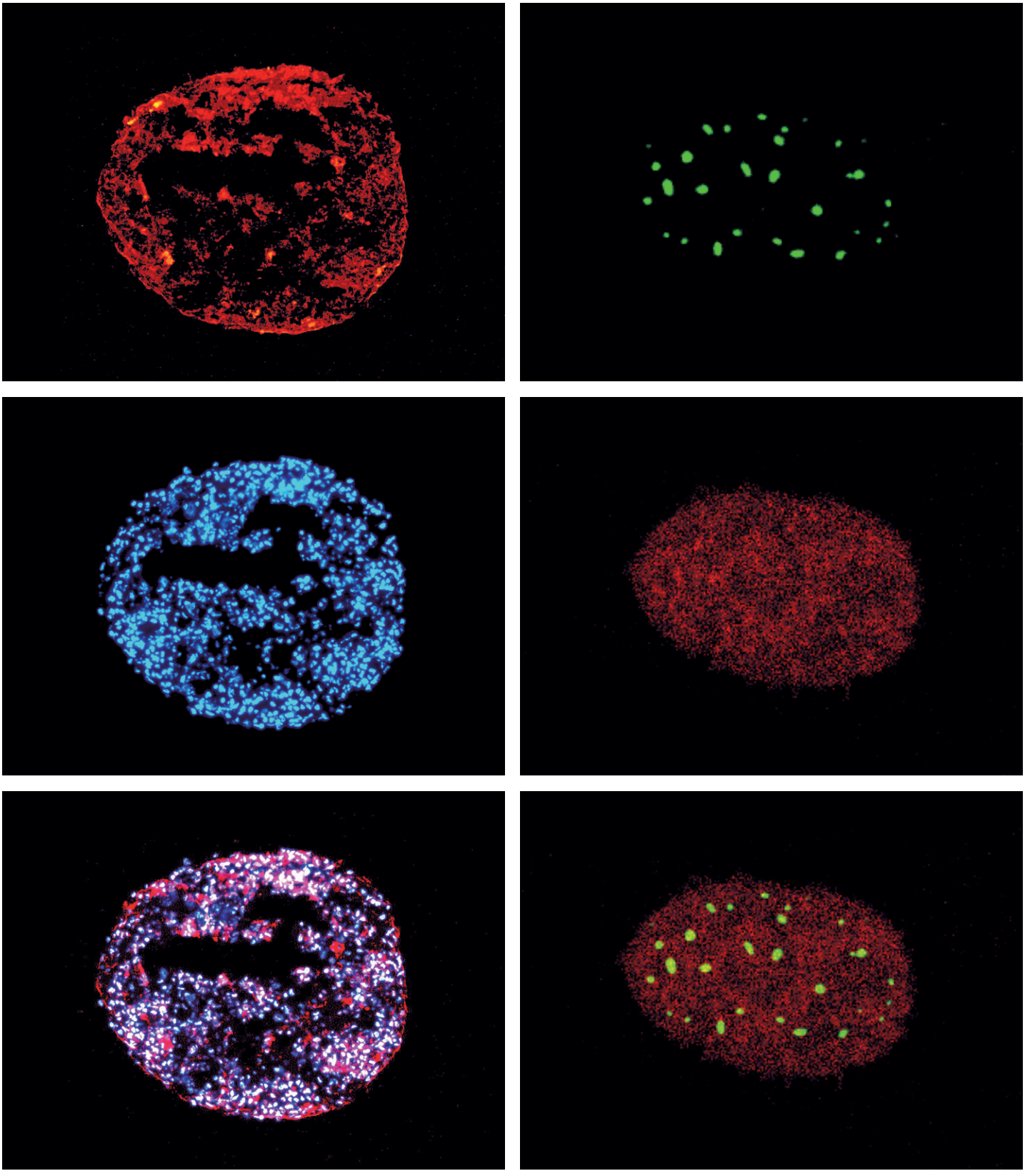
EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

RESEARCH NETWORKING PROGRAMME

REGENERATIVE MEDICINE (REMEDIC)

Standing Committee for the Medical Sciences
(European Medical Research Councils, EMRC)



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Introduction

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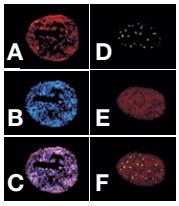
The European Medical Research Councils (EMRC) is the membership organisation for all the medical research councils in Europe under the ESF. Its mission is to promote innovative medical research and its clinical application towards improved human health. EMRC offers authoritative strategic advice for policy making, research management, ethics and better health services.



Cover pictures:
Mesenchymal stem (stromal) cells differentiating to cartilage (left column) and to cardiomyocyte-like cells (right column). Chondrocyte marker in A is aggrecan (red) and cardiomyocyte marker in D is Nkx2.5 (green). Chondrocyte nuclei in B were counterstained with 4,6-diamidino-2-phenylindole (blue) and the cardiocyte nuclei in E were counterstained with propidium iodide (red). The last images, C and F, represent an overlay of respectively, A&B and D&E. Li W. *et al.*: Bcl-2 engineered MSCs inhibited apoptosis and improved heart function. *Stem Cells* **25**:2118-2127, 2007. AlphaMed Press.

Regenerative medicine, a rapidly evolving and exciting field, can be defined as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. This can be done through a variety of approaches including the replacement of tissue function with synthetic constructs (artificial organs) and using cellular therapies such as stem cells or genetically modified cells to generate new tissues and organs. Today, there is an enormous need for regenerative medicine therapies as is evident, to take only one example, of the high number of heart transplantations, 3500 of which are undertaken worldwide each year[1]. Their number is limited by the lack of appropriate donors and due to the heavy regime, such treatment is not easy to administer to the elderly people who most urgently need it. Less invasive treatment to enable heart regeneration with stem cells would be welcome.

Recent advances in stem cell technologies, including for example the ability to induce human pluripotent stem (iPS) cells, mark a new era for regenerative medicine[2]. Stem cells have an almost unlimited proliferation potential accompanied by an ability to differentiate. Thus, hematopoietic stem cells (HSCs – that give rise to the various blood cell types, including neutrophils and erythrocytes) and mesenchymal stem (or stromal) cells (MSCs – that give rise to many cell types, including adipocytes and chondrocytes) form an essential element in regenerative (or reparative) medicine, including guided regeneration.

This field has the potential to allow either the self-repair of damaged tissues and organs or generation of new tissues and organs to be used in transplantations.

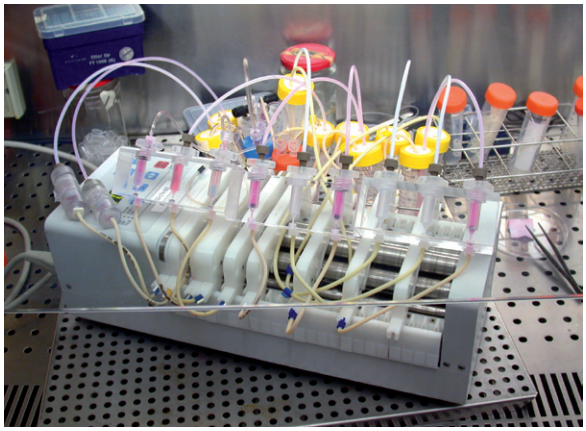


Figure 1. A bioreactor in which naïve or modified stem cells are allowed under controlled circumstances to differentiate and produce extracellular matrix (or resorb or otherwise modify their scaffold) before implantation to the recipient.
Courtesy of Prometheus (Skeletal Tissue Engineering Division) – Katholieke Universiteit Leuven (K.U.Leuven), Belgium.

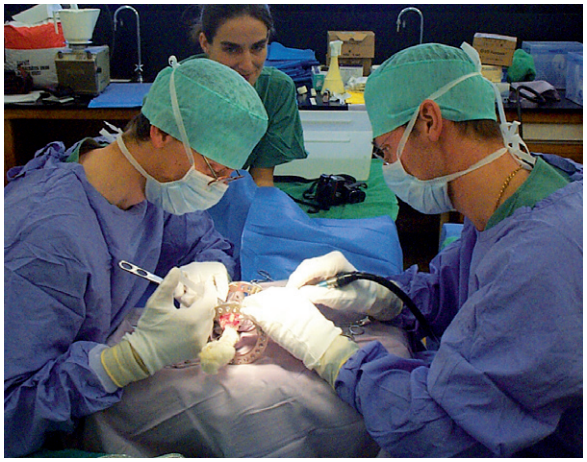


Figure 2. Surgical implantation of a regenerative medicine device is done under aseptic conditions. Courtesy of Prometheus (Skeletal Tissue Engineering Division) – Katholieke Universiteit Leuven (K.U.Leuven), Belgium.

Using the versatile genetic information stored within the cell nuclei, from where it is transcribed (copied) and then translated into proteins, is an intelligent way to regulate the repair of cells, tissues and organs. Importantly, regenerative medicine also has the potential to solve the problem of the shortage of organs available for donation compared to the number of patients that require life-saving organ transplantation.

When multipotent stem cells such as HSCs and MSCs are harvested from autologous sources (i.e. using the patient's own cells), immunological rejection and the burden of the use of immunosuppressive (cytotoxic) drugs are avoided. Endogenous stem cells can be activated with proper growth and differentiation stimuli to maintain or augment bodily functions. For example, subcutaneous fat tissue forms an autologous MSC source, which can be simply collected using a needle for fat aspiration. Cells isolated are allowed to expand and then driven to differentiate as such, in tissue engineering devices or bioreactors (Figure 1) before application back to body as cells, tissues or organs, either locally by surgical procedure (Figure 2) or systemically by injection. They help the target site(s) to regenerate so that structure and function are not replaced, but restored.

Another possible application is in wound repair, a complex biological process that occurs during most of our lives. Often, in adults, the wound repair process leads to a once functional tissue becoming a non-functioning mass of fibrotic tissue, more commonly known as a scar. In contrast, injuries that occur during pre-natal development are completely healed, an ability that is lost during adulthood. One approach would be to insert adult stem cells from the patient into a biometric matrix within the wound, recreating the prenatal environment and thus stimulating tissue regeneration[3]. Although, the development of this form of treatment may seem distant, the individual elements of this approach have been demonstrated *in vitro* and *in vivo*.

Furthermore, using HSCs and MSCs raises less ethical concerns than the use of embryonic stem cells for the moment. Autologous stem cells have a known source of origin and as such cannot transmit any new infections or prions to the recipient. Such cells can be used at once or stored in biobanks for eventual future use. The versatility of cell-based therapies can be enhanced by genetic manipulation of the cells in the laboratory, like for example, coding of a missing protein such as a hormone or enzyme which would last for the lifetime of the recipient[4]. For experimental work, markers useful in tracing of the transferred cells can be added to study their long term fate (Figure 5).

As our knowledge advances, the frontiers of regenerative medicine are rapidly expanding. Regenerative medicine provides new insights in areas including cellular proliferation, effects of humoral and matrix signalling on cells, angiogenesis, tissue remodelling, naïve and adaptive immunity and other basic processes in cell biology. Still, regenerative medicine is in its infancy and to advance progress in this important field, national funding agencies from 13 European countries have joined forces to launch a cross-disciplinary Research Networking Programme, REMEDIC, to identify where the frontiers and future needs are in this complex multidisciplinary high-technology field, by networking researchers and clinicians across Europe.

The running period of the ESF REMEDIC Research Networking Programme is for five years from May 2008 to May 2013 (06-RNP-128).

References

1. Chien K. R. Regenerative medicine and models of human disease, *Nature* **453**, 302-305 (2008).
2. Yu J., *et al.* Induced pluripotent stem cell lines derived from human somatic cells, *Science* **318**, 1917-1920 (2007).
3. Gurtner G. C., *et al.* Wound repair and regeneration, *Nature* **453**, 314-321 (2007).
4. Kaye D. M., *et al.* Reversing advanced heart failure by targeting Ca^{2+} cycling, *Ann. Rev. Med.* **59**, 13-28 (2008).

Scope and Aims

Bringing regenerative medicine from *bench to bedside* is a complex process covering basic, patient-oriented and public health research with regulatory and ethical considerations, and involving various actors including pharmaceutical and biotechnology companies and competent regulatory authorities. REMEDIC aims to put in place a network to facilitate the transfer of knowledge among basic researchers, clinicians and industrial partners, gather information on the current regulations, standards and patents in regenerative medicine and map the current technical research and development resources (see Box 1 on page 5 for a summary of the aims). REMEDIC is led by a Steering Committee composed of a Chair, Vice-Chair and 11 other members representing the national organisations that support the programme and these members, all of whom are researchers in the field of regenerative medicine, have the primary objective of ensuring that the high-level scientific objectives outlined below are achieved. They are also responsible for the management of the programme activities and the promotion of these activities as widely as possible within the larger community of regenerative medicine and within their own country, ensuring that their communities benefit from REMEDIC.

With regard to the research objectives, there will be a particular focus on mesenchymal (stromal) stem cells (Figure 3) and their differentiated derivatives. These cells, endogenously recruited, freshly isolated or expanded *in vitro*, should be able to replace, restore, repair or regenerate tissues. Understanding the basic biology of cell differentiation, blood and lymphatic vessel development and nerve in-growth (Figure 4) are essential for achieving these ambitious aims. Such cells can be implanted on the surface or within intelligent, drug-releasing and bioresorbable scaffolds, which melt away and are *in toto* replaced by regenerated tissue[1]. Biomaterial-guided tissue regeneration and nano surface technologies can be used to regulate matrix-cell interaction. Currently, hot topics in the field are cartilage repair and bone biology – with applications for diseases such as arthritis and osteoporosis and various types of bone and joint trauma, like for example hip fractures and knee injuries. There are many other applications that range from neurological, ophthalmological and otorhinolaryngological to gastroenterological and cardiological applications. Cell therapy, and if appropriate, in combination with existing (minimally invasive) surgical procedures, forms an important research objective.

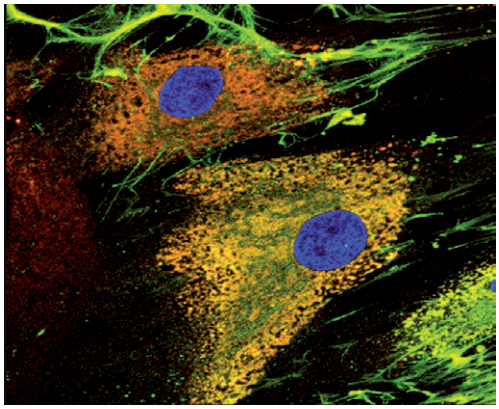


Figure 3. Stromal cells and their differentiated derivatives: Mesenchymal (stromal) stem cells (blue nuclei) containing heat shock protein (granular orange cytoplasm) editing collagen produced to the extracellular matrix (green fibres). Courtesy of Professor Yrjö T. Konttinen.

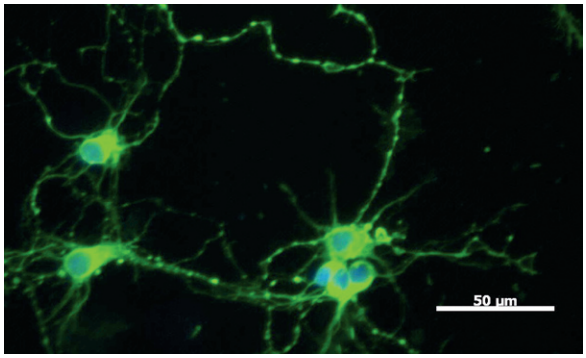


Figure 4. Basic biology of nerve in-growth: Cortical neurons in fluorescence microscopy after staining with anti-Tau antibodies (green) and DAPI (blue nuclei). *Tau is a neuronal microtubule associated protein found predominantly in nerve fibres and DAPI is a fluorescent stain that binds strongly to DNA.* Courtesy of Dr. Ana Paula Pêgo.

As the regenerative medicine field has developed and expanded so rapidly, the view of the field is somewhat hazy, so clarification of the unmet needs of society, academia and companies (pharma and biotech), is necessary to focus interest and funding towards the most important and achievable goals.

Furthermore, as gene, cell therapies and hybrid products have been introduced in a rapid succession, there is need to collect and analyse the rules and standards, which regulate the development, application and marketing of regenerative medicine.

Collection of information on the available equipment and methods used in regenerative medicine has not yet been performed. Due to its inter-disciplinary nature and relevance in many fields of medicine, the need for clean room space and excellent clinical research centres is very high. For the latter, the European Clinical Research Infrastructures Network (ECRIN), will serve as a useful resource centre[2]. Some of the technologies and procedures are so specialised that individual groups and centres cannot maintain them all. REMEDIC will gather information on these current technical R&D resources for the research community.

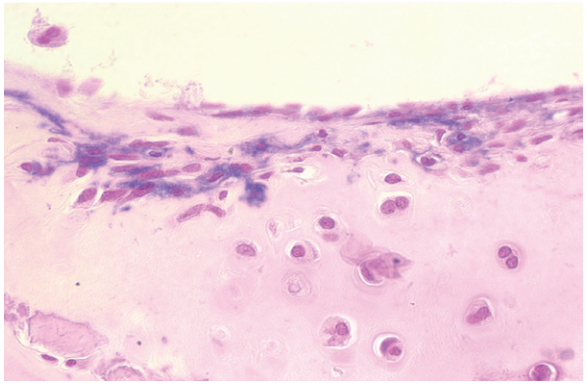


Figure 5. The violet cells are rat mesenchymal stromal cells, which are transgenic for the human placental alkaline phosphatase, in the knee joint of a bone marrow-transplanted, marker tolerant rat knee. Odörfer K. I. *et al.* Marker tolerant, immunocompetent animals as a new tool for regenerative medicine and long-term cell tracking, *BMC Biotechnol*. **7**:30 (2007).

Another key aim is to network institutions, laboratories and companies across Europe to generate collaborations to define and develop research projects at the frontiers of this field and potentially implement them through joint grant applications either during the course of REMEDIC or shortly afterwards. Building such consortia takes time and the activities of the programme should ensure that partners with the relevant experience and technological expertise are linked together.

Box 1:

REMEDIC Aims

1. To facilitate the exchange of ideas and know-how across disciplines in the area of mesenchymal (stromal) and other stem cells;
2. To review the regulatory laws, rules and standards governing the use of regenerative medicine;
3. To map the unmet population, academia and company needs in regenerative medicine and the current R&D resources (e.g. instruments, analysis techniques);
4. To assist researchers in the field of regenerative medicine in preparing cross-disciplinary coordinated research projects.

References

1. ESF-EMRC Scientific Forward Look on Nanomedicine, Chapters 2.1.3 & 4.2.1 (2005). www.esf.org
2. ECRIN (www.ecrin.org) is one of six research infrastructures identified by the European Strategy Forum on Research Infrastructures (ESFRI) in the biomedical domain. http://cordis.europa.eu/esfri/home.html

In order to achieve the aims outlined above, the following activities will be undertaken during the duration of the programme:

• **Workshops** – it is envisaged that there will be a workshop each year of the programme, either stand alone or as part of a larger conference for added synergy, focusing on key aspects of mesenchymal stem cells, their differentiated derivatives and potential clinical applications. The first workshop on Heart Regeneration took place on 15-17 August 2008 in Helsinki, Finland.

• **Short-term (up to 15 days) and exchange (from 15 days up to 6 months) visits** – a particular emphasis will be placed on these visits, to allow researchers to share expertise and techniques in this multi-disciplinary field. Applications will be open to the community of researchers in the field, as long as the proposed research is relevant to the aims of REMEDIC.

• **Reviews** – state-of-the-art reviews based on analysis of literature and patent databases will be prepared for peer-reviewed journals.

• **Rules and Standards** – a review of the regulatory laws, rules and standards governing the use of regenerative medicine will be prepared and made available on the dedicated website.

• **Mapping of needs and available resources** – this will be undertaken within the first two years of the programme and made available for the regenerative medicine community.

• **Internet platform** – there will be a dedicated internet platform to act as the main tool for distribution of information on REMEDIC, its advancement and results. It will also serve as a resource to the entire community, including for example a register of future project partners for joint proposal applications. Dissemination of information is aimed not only at the research community but also at the public, authorities and other key stakeholders.

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