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Innovations in Medical Technology

Regenerative medicine and human tissue engineering

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Human tissue engineering and regenerative medicine in general (e.g. the use of “smart“ biomaterials that promote self-repair of damaged tissues) offer tremendous promise for improved patient treatment, faster recovery, improved prognosis and a more biologically favourable situation where the body can be stimulated to heal itself.

There is a huge amount of research being undertaken worldwide in all areas mentioned in this overview (and others) and a huge interest in the potential of tissue engineering/regenerative medicine.

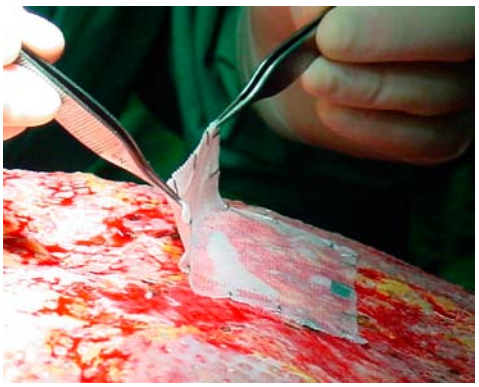
However, there is still currently a lack of effective regulatory framework on a European basis. Such future legislation must be designed in such a way that it allows research and innovation in the field to flourish and the prospect of a timely return on research investment to be realised, whilst at the same time ensuring risks to patients are minimised and that equitable access to treatment can be attained.

What are regenerative medicine and human tissue engineering?

Regenerative medicine and human tissue engineering are rapidly developing new interdisciplinary fields in medicine. They are typically characterized by a convergence of disciplines such as advanced materials science, cell biology, biochemistry, engineering and medicine. Regenerative medicine is a wider term that encompasses human tissue engineering and comprises a range of technologies that seek to help the body repair and restore itself. A definition currently put forward by the US National Institutes of Health (NIH) is:

> *Regenerative medicine/tissue engineering is a rapidly growing multidisciplinary field involving the life, physical and engineering sciences that seeks to develop functional cell, tissue, and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or ageing.*

A human tissue engineered product is currently defined as



A product that:

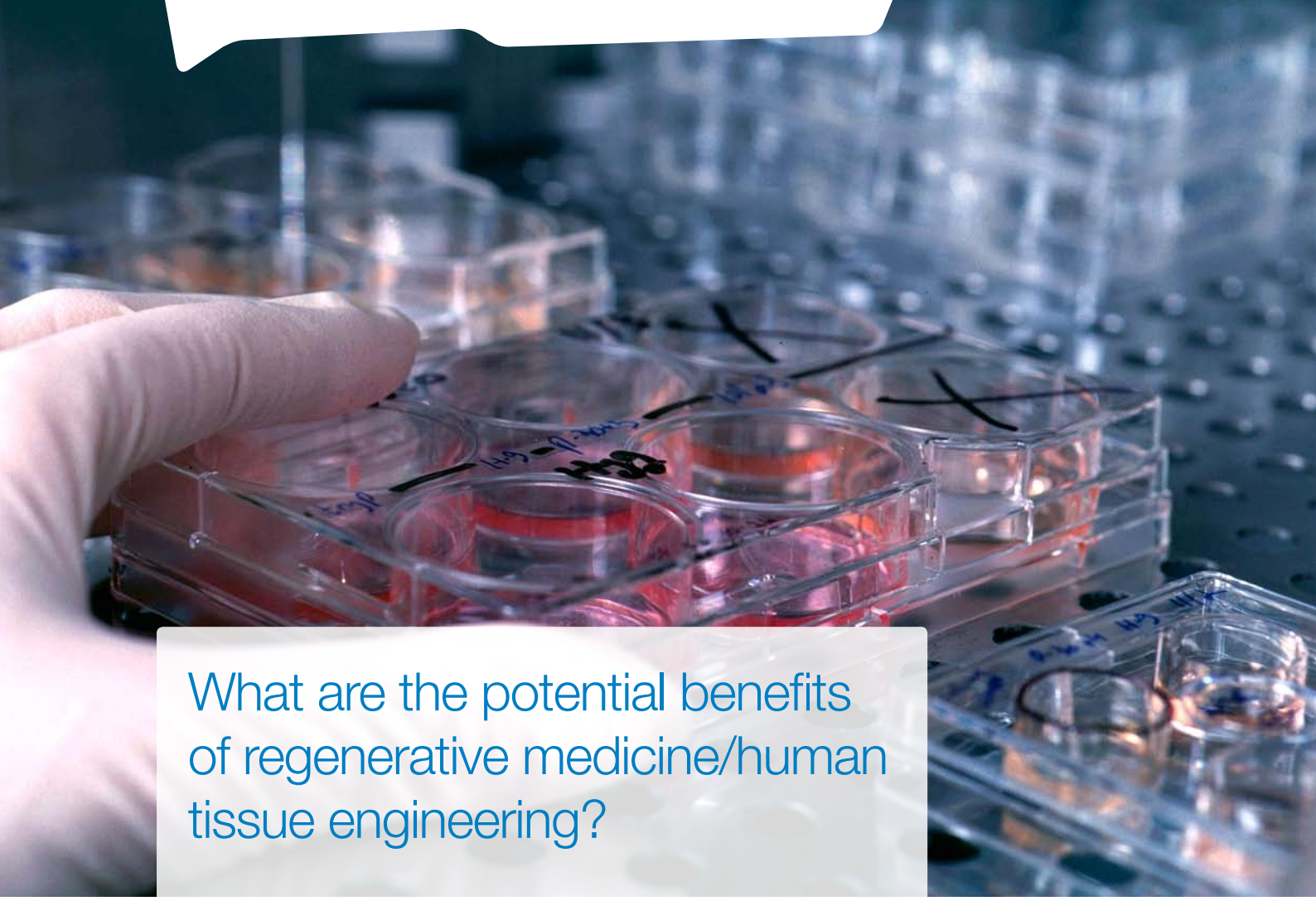
- contains or consists of engineered cells or tissues; and
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A human tissue engineered product may contain cells or tissues of human or animal origin, or both. It may also contain additional substances, such as cellular products, biomolecules, biomaterials, chemical substances, and scaffolds or matrices that help to provide a physical support to the cells/tissues.

In addition to having therapeutic applications, human tissue engineered products can have diagnostic applications where the tissue is made in vitro and is used as a platform for testing drugs and other products.

Human tissue engineering includes the following important areas:

- **Biomaterials:** these may include novel biomaterials that can influence, by physical or chemical means, the organization, growth, and differentiation of cells in the process of forming the desired tissue
- **Cells:** these may be autologous (i.e. from the patient him or herself), allogeneic (from another person), xenogeneic (animal cells), and may be stem cells or cells that have already reached some degree of differentiation
- **Biomolecules:** these may include growth factors, differentiation factors and other key proteins
- **Safety and performance issues:** including characteristics of tissues, identification of minimum properties required of engineered tissues, mechanical signals regulating engineered tissues, and performance and safety of engineered tissues
- **Manufacturing factors:** including cell expansion, three-dimensional tissue growth, the use of bioreactors, cell and tissue storage, etc.
- **Other aspects:** including informatics and data, modelling, quality assurance and clinical data



What are the potential benefits of regenerative medicine/human tissue engineering?

It has been estimated that millions of people worldwide could benefit from regenerative therapies.

Regenerative medicine products are already beginning to change medical practice today. Human tissue engineered skin and tissue engineered cartilage were amongst the first to be used for the treatment of chronic wounds and burns, and joint degeneration and injury, respectively. Other regenerative techniques are being developed to repair bone, the cornea, the bladder and several other common medical conditions.

Also under current research are treatments such as nerve regeneration for conditions like Parkinson's Disease or Alzheimer's Disease, pancreatic islet cells for transplantation into the liver for diabetes treatment, and regeneration of damaged heart tissue. An ultimate goal will be to build human tissue engineered organs on three dimensional scaffolds such as bladders, livers, hearts, and kidneys. This will entail deep and sustained multidisciplinary collaboration between previously disparate fields such as cell biology, biochemistry, materials science and immunology.

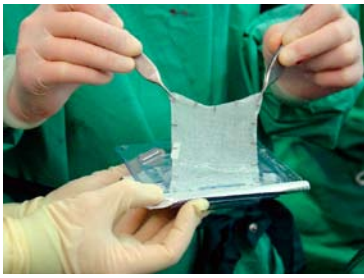
Some regenerative medicine and human tissue engineered treatments

Some of the medical applications and tissue/organs to which tissue engineering approaches are being developed include:

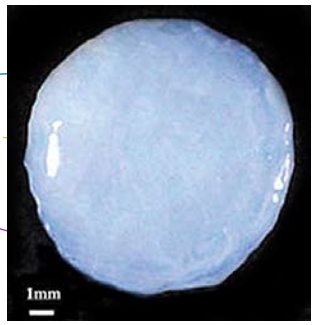
- severe burns
- skin ulcers
- cartilage
- bone, e.g. for facial reconstruction
- tendons
- ligaments
- blood vessels
- myocardial patches
- heart valves
- kidney
- bladder
- liver
- bioartificial pancreas

Some of these developments are further explained in the following examples. These are just a few of the hundreds of therapies under development worldwide for a multitude of conditions and diseases.

Tissue engineered skin



Cells are already being grown on a variety of substrates for the treatment of serious burns or for difficult-to-treat conditions such as diabetic ulcers. They can provide a biocompatible and important physical barrier to fluid loss and infection and assist in the regeneration of the patient's own skin. Treatment of diabetic ulcers in this way often results in much faster healing and greatly improved prognosis for a condition that is often impossible to treat adequately and may sometimes result in amputation.



Tissue engineered cartilage

Degenerative joint conditions are becoming increasingly prevalent with an ageing population and damage may also occur in young patients as a result of sports injuries. Conventional treatments may include partial or total joint replacements but it is possible, in many cases, to replace damaged cartilage with tissue engineered cartilage formed using the patient's own chondrocytes grown on a variety of substrates. This may, in the future, avoid the need for implants for suitable patients.

Tissue engineered bone

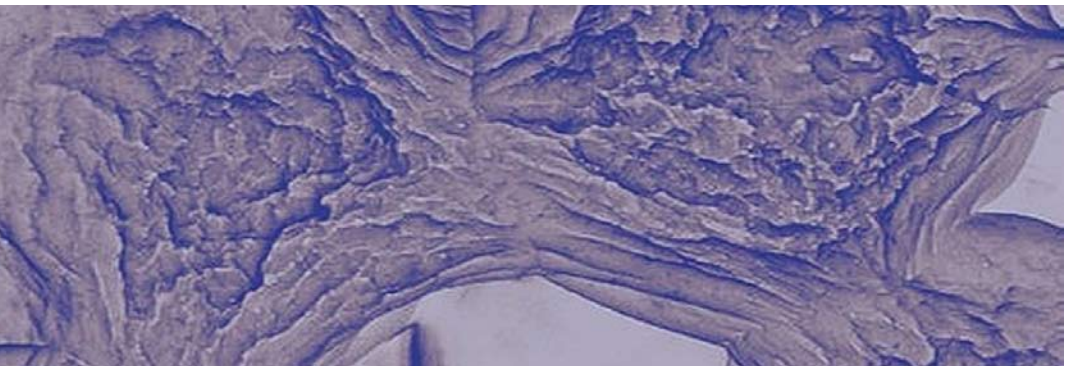
The regeneration of skeletal bone is a major unmet clinical need, e.g. for degenerative diseases and accident victims. The development of new biomimetic materials that provide a suitable microenvironment for cell-matrix interaction and the adhesion and proliferation of differentiated osteocytes (bone cells) is the focus of much research. Research is centred on tissue engineering approaches for new cartilage and bone formation and also on how physical stresses in the body influence tissue development.

Tissue engineered peripheral nerves

When a peripheral nerve is severed, e.g. in an accident (a very common injury amongst young males in particular), a gap between the severed nerve ending may remain that is too wide to be treated by conventional microsurgery or that would mean “sacrificing“ an existing functional nerve in a nerve graft. There is considerable research under way to identify suitable biomaterials that could provide a conduit to enable regeneration-promoting Schwann cells to grow in a guided manner to bridge such injuries.

Tissue engineered cornea

Tissue engineering corneas is a challenge as the cornea is avascular, i.e. it has no blood supply and receives its physiological needs from lachrymal fluids at the front and from the aqueous humor at the rear. Because of the need for donor corneas for transplant and the rejection that sometimes occurs, much research is under way to characterise the interaction between the cells constituting the cornea and suitable scaffolds, e.g. a biocompatible but non-biodegradable hydrogen. Possible approaches include using the patient’s own limbal cells (where these are still available) or donor limbal cells to colonise the substrate.

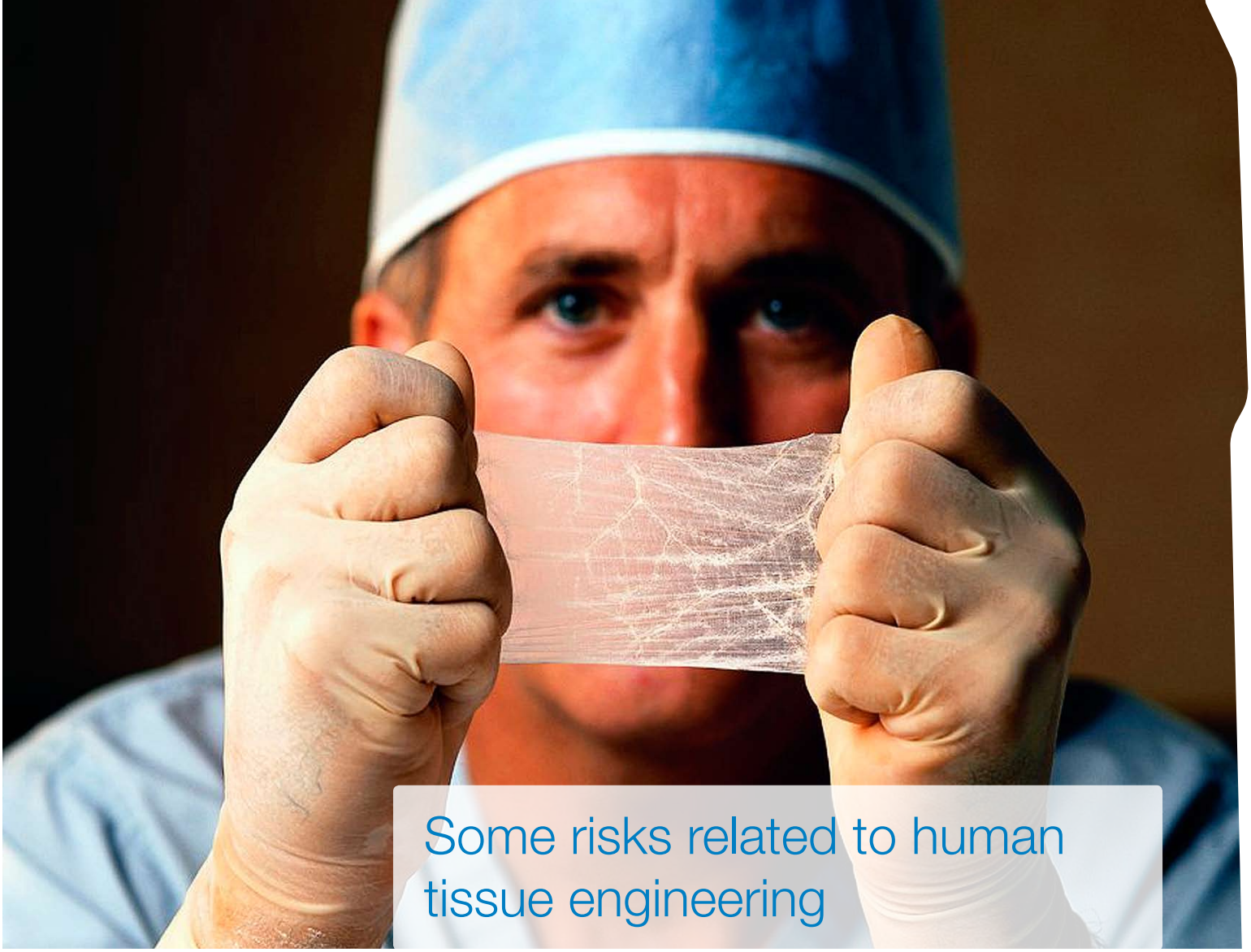


Tissue engineered blood vessels

The development of tissue engineered blood vessels is one of the most exciting current challenges in reconstructive medicine. A variety of approaches are in research and development using both synthetic biopolymer scaffolds and biologically-derived matrix materials. Both entail the incorporation of both smooth muscle cells and vascular endothelial cells into a tubular scaffold so as to establish a structure analogous to that of a native artery. For blood vessels, one particularly important characteristic is the ability to respond to changes in blood pressure in an appropriate manner. Despite the intensive research, solutions are likely to take a number of years to reach the market as, with bioengineered organs, a number of differentiated cell types and three-dimensional structures are involved which provide considerable scientific and medical challenges.

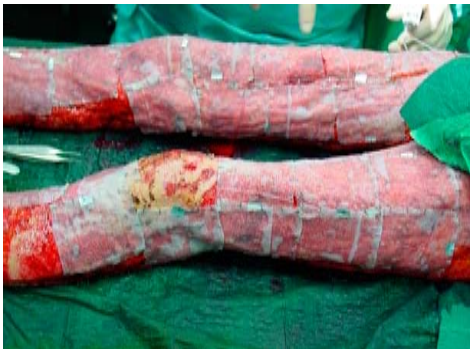
Myocardium

There are a number of therapies in development aimed at regenerating or repairing the heart myocardium. These range from well-advanced research on cell-therapy regeneration of myocardium to earlier stage research on developing tissue engineered myocardial patches.



Some risks related to human tissue engineering

Human tissue engineered therapies represent a move away from “traditional“ medical device and pharmaceutical technologies. Very often, the tissue engineered solution is geared towards an individual patient rather than a standard product being aimed at a wide and differing population of patients. This brings a number of new challenges for both manufacturers and regulators. For example:



- with an autologous tissue engineered treatment, the product is a “one-off“ for a particular patient. The focus therefore moves from a traditional large production run situation to one where strict quality and risk management principles must be applied to the process of collecting, multiplying and differentiating cells, incorporating those cells with a scaffold, producing a three-dimensional tissue engineered construct and transporting and reimplanting the resulting product into the patient within a critical timescale
- safety in sourcing cells and tissues, especially allogeneic materials
- how clinical performance and in-vivo biological responses can best be assessed
- follow-up studies with patients to monitor viability, performance and safety of the tissue-engineered product

Proposed new EU Regulation

Currently, a new Regulation is being developed at European level on Advanced Therapy Medicinal Products (ATMPs) and it is proposed that this should cover human tissue engineered products as well as gene therapy and cell therapy which are already covered under medicinal products legislation.

Eucomed is actively involved in the debate as to how to develop this Regulation, and in the possible additional development of other existing Directives, e.g. the Medical Device Directive (93/42/EEC) to accommodate certain aspects related to tissue engineering and regenerative medicine.

However this legislative process evolves, Eucomed is convinced that a risk management-based approach is necessary that will maximise patient safety in this important new area of medical technology, whilst allowing scope for the rapid innovation that is taking place throughout Europe and taking account of the patient-specific nature of the products.

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