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ON RESTORING TISSUE FUNCTION IN RARE AND AGE RELATED DISEASES

# A common apothecary cabinet

IN part one of this editorial series, Jöns Hilborn and David Sassoon, the co-ordinators of the Biodesign and Endostem projects, illustrated the brighter future that regenerative medicines can provide (Pan European Networks; Science and Technology 06 '2090…or 2020?'). In this second part of the series, we present the different components of the therapeutic product (the material, the cells, and the growth factors) and how they will be combined and tailored to treat both rare degenerative diseases and more common age related and traumatic disorders.

## Commonalities

Degenerative diseases represent a significant proportion of chronic, progressive and often fatal diseases with profound human and societal costs for which there are no effective therapeutic approaches. They are also associated with a progressive decline in tissue function that share many characteristics of ageing, and they create a life-altering experience for the afflicted person and their family, representing the progressive diminishment of body functions which can cause depression and loss of self-esteem.

Given the diversity of degenerative diseases, pathological manifestation can occur at any age: either as a child, during an individual's most productive years, or more frequently as an aged person. There has been an increased prevalence of degenerative diseases with the ageing demographic.

Over the past 50 years, average life expectancy at birth has increased globally by over 20 years, from 46.5 years in 1950-55 to 65.2 years in 2002. Today, there are 600 million people in the world aged 60 years or over, and by 2025 this will double, eventually reaching two billion by 2050. The economic impact of morbidity in this population represents a significant burden, which requires effective and rapid solutions.


## The material

Biomaterials are an important part of the medical device industry, and are now becoming more prevalent as scaffolds in the development of sophisticated therapeutic products, such as sustained drug delivery therapeutics.

To date, the choice of scaffold in these applications has largely been dependent on predicated biomaterials, but increasingly, with advancements in biomaterial science, custom scaffolds are being developed with specific properties needed for a particular application. Emerging strategies employ the design of materials that allow the release of active factors 'on demand' to optimally meet therapeutic requirements.

The design of new materials that meet specific performance criteria is, however, still a challenge. It is currently not possible to freely choose among components that should be assembled/connected into materials. Equally challenging is the development of design principles for new materials based on the understanding and quantification of the relationship between the scaffold characteristics – such as chemical composition, morphology and physical properties – and the *in vivo* outcome.

It has become clear that the native extracellular matrix (biological glue that surrounds cells) supplies critical signals to initiate or sustain cellular functions within the tissue which are favourable to tissue repair. It is not surprising, therefore, that many of the novel matrix materials in use or under development are designed to mimic the characteristics of this matrix.

## Bioadhesion

One such characteristic is bioadhesion, which is an important property that allows cells and tissues to adhere to biomaterials and has enabled their use as tissue adhesives in surgical repair or as inductive scaffolds for tissue regeneration. Bioadhesive features can be engineered into a biomaterial in order to facilitate interactions between the implant and its surroundings.

Cell-adhesion modifications to scaffolds have also been used effectively to promote enhanced bone repair, to provide an essential foothold for neurite outgrowth in axonal regeneration, and to understand the regulatory role of mechanotransduction in stem cell fate determination.

Engineering this type of bioactivity is instrumental for materials that are called on to mediate specific biological events in the body based on endogenous cell recruitment, local morphogenesis, and controlled cell differentiation. Many of these events can be induced by using exogenous growth factors that are delivered with spatiotemporal control.

However, most materials do not inherently sequester these growth factors and thus fall short of precisely controlling their sustained or localised availability. *In vivo,* growth factor availability is tightly regulated by nonspecific associations between the factor and extra cellular matrix. Using strategies premised on such interactions with scaffolds, design modifications to materials have recently been used to improve the localised growth factor availability, with remarkable results in their ability to mediate tissue repair.

## Defining the bioactive factor

To a large and increasing extent, defining the optimal delivery of bioactive factors is premised on the early processes that occur during development. The reason is that this is when growth, spatial and structural characteristics are defined in the tissue, and a potent mix of factors (matrix, cells and growth factors) lays the foundation for a functional tissue during a nine-month gestation, that has to be fully functional at birth and remain this way for another 70+ years.

In mammals, once development and growth are completed, many organs such as the brain and the heart have a limited ability to regenerate following acute or chronic damage from trauma or disease. This is despite the fact that these organs have grown in size from birth to adulthood due to the presence of residual stem cells which divide very slowly to permit growth.

Such stem cells are found in each organ: the lung, the brain, the skin etc., but they are clearly not normally capable of permitting extensive regeneration. This is because the developmental signalling pathways which were involved in the initial building of the prenatal tissues have been switched off or down-regulated to a lower level in cells at the completion of development which has been matched with a number of inhibitory factors (inflammation and scarring) which are required in the adult to ensure adequate protection from the environment following damage and thus the survival of the individual.

The best evidence that developmental signalling pathways are down-regulated once organogenesis has been completed is the fact that many organs can regenerate when still in a developmental state. For instance, the prenatal spinal cord will regenerate perfectly after severing and there is a precise stage in late development when regeneration no longer occurs.

Similarly, prenatal mouse digits regenerate perfectly if amputated when *in utero* and skin wounds heal perfectly without scarring if the damage is similarly performed *in utero.* This loss of ability is likely due to changes within the cells of the organ themselves.

There is still significant support needed for, and performed within, fundamental research which can continue to identify the best possible bioactive factors and other environmental stimuli that can be combined with the biomaterials to provide the correct information and environment to the target cell.

## The cell

Human tissues can self-repair in response to moderate injuries, but are not able to regenerate when significant loss of tissue occurs in extensive trauma or surgery. Similarly, they cannot sustain repeated cycles of degeneration/regeneration.

Reconstructive strategies, such as autologous cell transplantation and the injection of progenitor cells yield only modest therapeutic outcomes, mainly because the tissue often presents an inflamed or sclerotic environment which results in poor survival and only a modest integration of engrafted cells that are also targets of an immune reaction. Moreover, the *in vitro* cultivation history of the grafted cells can also negatively affect the efficacy of cell transplantation, although this may be prevented by culturing cells on biomaterials. Among the new therapeutic strategies for several age related and degenerative diseases, stem-cell transplantation is becoming a promising clinical option.

Presently, there is a focus on the use of engrafted stem cells as therapeutics which are best complemented by advancing our understanding of the basic biology of stem cell activation. The potential successes and applications of engrafted stem cells needs to be matched with those aimed at mobilising endogenous stem cells whose limited regenerative potential can probably be restored with the correct stimuli.

As stated above, injury or disease often produces inappropriate re-patterning of the tissue culminating in scar tissue formation (fibrosis), inadequate blood vessel creation, or chronic inflammation; none of which are beneficial. Therefore we anticipate that the cell of choice for regenerative medicine may be exogenous and/or endogenous, depending upon the specific pathological situation.

For example, this could be a cell which is transplanted at low numbers (isolated from the patient, developed as an iPS, or obtained from potential donors) in a bioactivated scaffold, and that upon integration activates the endogenous cells to hybridise with the implant and restore function in the degenerating tissue.

## Summary

The rational design of bio-interactive therapies is critically dependent on the understanding of how relevant cells interact with natural materials as tissues form and remodel *in-vivo,* in response to corrective stimuli. The aim is to fabricate the basics of each tissue (then let cells take over), as opposed to hoping that cells will start the process themselves.

Biodesign and Endostem are investing significant effort, with the support of the EC via the Seventh Framework Programme in defining the optimal combinations for combining cell, biomaterials and factors for creating tomorrow's therapies today.

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