

BIOMATERIALS FOR HEALTH

A Strategic Roadmap for Research and Innovation

HORIZON 2020

CONTENTS

PRIORITIES FOR R&D AND INNOVATION POLICY	4
BIMATERIALS FOR HEALTH	5
General Technical Challenges	7
Nanostructured Biomimetic Materials.....	9
Bioactive Analogues of Growth Factors.	9
Standardisation	10
Specific Technical Challenges	12
Matrices for Regenerative Medicine	12
Bioinspired Approach for Gene Therapy	18
Matrices for Diagnostics.....	21
Matrices for Cancer and Cancer Diagnostics	24
REGULATORY AFFAIRS	27
Main Challenges	27
Action Plan.....	30
Regulatory Science Framework.....	30
Legislative Actions	31
Regulatory Affairs Actions.....	31
Main deliverables expected by 2020	32
Vision to 2030	32
Regulatory Action plan (2014-2020).....	33
EDUCATION AND TRAINING	34
Curriculum Design	34
Healthcare systems.....	35
Diversity of Degrees and Diplomas	35
Educational resources and strategies.....	35
Disparities between academia and the industrial and clinical sectors.....	35
New private and public funding schemes	36
Policy recommendations for Improved Education & Training in Biomaterials for Health	36
Curriculum Development.....	36
Educational resources and strategies.....	37
Mutual recognition of Degrees and Diplomas	37
SMALL AND MEDIUM SIZED ENTERPRISES (SMES)	39
R&D Institute for Regenerative Medicine	39
Short to Medium term Projects and Initiatives	40
Health Technology Assessment (HTA)	40
Long-term projects	41
Services and Incentives offered by the EMA to SMEs	42
Scientific Advice	42
Scope of scientific advice.....	43
Certification of Advanced Therapy Medicinal Products.....	43

Biomaterials for Health

Regulatory Requests.....	44
Inclusion in the public SME register.....	44
SMEs and Continuous Professional Development (CPD)	45
VENTURE CAPITAL INVESTMENT	47
Venture Capital and SMEs.....	48
Considerations for SMEs in Horizon 2020 Project and VC investment	49
CLINICAL APPLICATIONS	50
Biomaterials for Cardiovascular Disease	50
Biomaterials for the Central Nervous System.....	55
Cerebrospinal Fluid (CSF) Shunts.....	55
Cortical Neural Prosthetics (CNPs).....	55
Drug Delivery	55
CNS Regeneration	56
Neural Stem Cell Encapsulation for Neurotrauma	56
Biomaterials for Orthopaedics	58
First-Generation biomaterials	58
Second-Generation biomaterials.....	58
Third-Generation biomaterials	58
Biomaterials for Diabetes Mellitus	59
Biomaterials for Infectious Diseases.....	60
Biomaterials for Ophthalmological Use	61
Ophthalmic Biomaterials for the Elderly.....	61
Contact lenses and the Artificial cornea.....	61
Drug-Eluting Contact Lenses	61
Biomaterials for Wound Healing	62
Biomaterials for Theranostics & Implant Monitoring.....	62
Biomaterials for Women's Health.....	63
Other Clinical Applications.....	64
CONCLUSIONS	65

PRIORITIES FOR R&D AND INNOVATION POLICY

As part of the Europe 2020 strategy for smart, sustainable and inclusive growth¹, it is intended to re-focus R&D and Innovation policy on the numerous challenges facing society, including amongst others health, demographic change and resource efficiency,

The flagship initiative the “Innovation Union” will foster the development of specific strategic research agendas that are focused on these challenges and there will be an enhancement of joint programming with Member States and regions. There will be improved framework conditions for businesses to innovate and “European Innovation Partnerships” will be launched between the EU and Member States so as to speed up the development and deployment of the technologies needed to meet the challenges identified.

As part of this exercise, the Commission proposal for the next framework programme for research, development and innovation, Horizon 2020, is designed to address these important challenges for Europe through funding excellent science, technology and innovation. Its goal is to create a knowledge-intensive society and to complete the European Research Area as a single market for knowledge. Yet at the same time, the recent financial and economic crisis has highlighted more than ever the need for and the value of researchers and innovators in generating sustainable and long-lasting wealth in Europe, not just as part of economic recovery but also as a foundation for sustainable growth for the future.

Key Enabling Technologies (KETs) are defined by the Commission as : “...knowledge intensive and associated with high R&D intensity, rapid innovation cycles, high capital expenditure and highly skilled employment. They enable process, goods and service innovation throughout the economy and are of systemic relevance. They are multidisciplinary, cutting across many technology areas with a trend towards convergence and integration. KETs can assist technology leaders in other fields to capitalise on their research efforts.”². These technologies – of which materials collectively are a specific example - have been identified as underpinning innovation across all industries and sectors, and the competitiveness and sustainability of the European industrial economy. Their research and development appear across the entire range of industrial research activities from enabling research to applications and demonstration activities, support to materials research can be found throughout the whole Horizon 2020.

¹ Communication from the Commission : “Europe 2020 : A strategy for smart, sustainable and inclusive growth”, Brussels, 3.3.2010 COM(2010) 2020 final

² Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions : “A European strategy for Key Enabling Technologies – A bridge to growth and jobs” Brussels, 26.6.2012 COM(2012) 341 final

BIOMATERIALS FOR HEALTH

In the healthcare field, biomaterials are an example of materials that are entities, surfaces or constructs that interact with specific biological systems. Biomaterials science encompasses elements of medicine, biology, chemistry, tissue engineering and materials science³.

They are derived from nature or else are synthesised in the laboratory using a variety of chemical approaches, at times utilising and integrating metallic components, ceramics or other substances such as pharmaceutical products. In the health field, they become a whole or part of a living structure or biomedical device with the objective of performing, augmenting, or replacing a natural function. They may be non-interactive with their environment, such as is the case for a heart valve, or possess a more interactive functionality such as drug-impregnated stents that release pharmaceutical products¹, or more recently, to facilitate the operation of biomedical devices (BD)⁴ and advanced therapy medicinal products (ATMP)⁵ over prolonged periods of time.

In consistency with the outlook for research into materials, biomaterials should be carried out along the value chain, starting in the laboratory and ending in the clinic - from “bench to bedside” – and by necessity, be multi-sectorial, transverse and cross-cutting.

In individual or “vertical” projects, that is, those conceived at various points along this value chain, research support should aim to increase the Technology Readiness Level (TRL), expectedly from TRL 2 or 3 (e.g. arising from university or ERC/FET supported research) up to level 6 and in some cases even 7. This means that they must therefore be devised not just in terms of their own ultimate composition or biological properties, but also what new product that they will be an integral part of. New biomaterials would be part of new solutions, meaning a focus on “biomaterials for something” rather than on “biomaterials per se”. Adequate integration of biomaterials with their application context is needed to fulfill all the requirements for a functional outcome. Their research and development also requires support to overcome the “death valleys” that exist between the industrial and academic fields, but also with the clinical and regulatory fields, as well as the long path to market. This underpins the need to promote excellence in research and the need to be able to follow research carried out swiftly.

³ Adapted from Wikipedia

⁴ As defined by Directive 90/385/EEC, regarding Active Implantable Medical Devices, Directive 93/42/EEC regarding Medical Devices and Directive 98/79/EC regarding In Vitro Diagnostic Medical Devices.

⁵ As defined by Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (Gene Therapy, Stem Cell Therapy And Tissue Engineering)

Biomaterials for Health

Level	Definition	Explanation
1	Basic Principles Observed and Reported in the Context of a Military Capability Shortfall	Potential scientific application to defined problems is articulated.
2	Technology Concept and/or Application Formulated	Hypothesis(es) generated. Research plans and/or protocols developed, peer reviewed, and approved.
3	Analytical and Experimental Critical Function and/or Characteristic Proof of Concept	Basic research, data collection, and analysis. First hypotheses tested, alternative concepts explored. Initial characterization of candidates in preclinical studies.
4	Component and/or Breadboard Validation in Laboratory/Field Environment	Non GxP laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design
5	Component and/or Breadboard Validation in a Relevant (Operating) Environment	Intense period of nonclinical and pre-clinical GxP research studies involving parametric data collection and analysis in well-defined systems.
6	System/Sub-System Model or Prototype Demonstration in a Realistic (Operating) Environment or Context	Phase I Clinical Trials
7	System Prototype Demonstration in an Operational Environment or Context (e.g., Exercise)	Phase II Clinical Trials
8	Actual System Completed and Qualified through Test and Demonstration	Phase III Clinical Trials
9	Actual System Operationally Proven through Successful Mission Operations	Post Marketing Studies

Technology Readiness Levels as applicable to Healthcare

Specific outputs that would be expected from these individual projects would be expected to develop and/or validate specific biomaterials for use in an eventual **Advanced Therapy Medicinal Product or Medical Device**. Preclinical regulatory affairs would need to be completed taking due account of current good laboratory practice (GLP) and ISO guidelines. Manufacturing processes would also need to be addressed, including up-scaling, good manufacturing practice (GMP), process analytical technology (PAT).

Biomaterials should be characterised with respect to the responses they elicit, such as toxicity, the migration properties and shape of cells, or changes in intracellular signalling pathways. In addition, proposals will be expected to show that the regulatory and IPR strategy is compatible with the overall research objectives.

Education and training activities – either as parts of projects or as the focus of specific initiatives themselves – will be needed so as to help to deliver scientists and technologists who can match the future needs of society and industry. Continuous training – or continuous professional development – will need to be a part of this exercise.

Special attention will need to be paid to the needs of Small and Medium-Sized Enterprises (SMEs) as well as to the ultimate clinical applications of these biomaterials.

General Technical Challenges

The biomaterials that are the subject of proposed research activities in Horizon 2020 are intended to become a whole or part of a living structure or biomedical device with the objective of performing, augmenting, or replacing a natural function. They may be non-interactive with their environment, such as is the case for a heart valve, or as a hip or dental implant which can be desirable in the case because long-term durability or rigidity is desirable.

Alternatively a more interactive functionality may be required such as drug-impregnated stents that release pharmaceutical products¹, or more recently, to facilitate the operation of medical devices (BD)⁶ and advanced therapy medicinal products (ATMP)⁷ over prolonged periods of time. It may be necessary to alter an immune response that already exists in an organism so as to allow for other actions to follow, such as infiltration of a diseased organ with stem cells or other Advanced Therapy products to repair damaged tissue. Collectively, the ability of biomaterials to adapt to their environments in a beneficial manner, referred to as *biocompatibility* will determine the success and that of the therapeutic interventions with which they are associated. This is a major hurdle that will need to be overcome in research for biomaterials for health as it will determine the success and that of the therapeutic interventions with which they are associated. This particular aspect of interactive or *smart biomaterials* is expected to be a major area of growth for research and development activities in Horizon 2020.

For many fields of application, such as in Advanced Therapy Medicinal Products, clinical success requires a proper coupling of the biomaterial with its surrounding environment, able to induce, guide and control a correct cellular response. Ideal platform for this scope have been already identified in bioreactor systems. Three dimensional tissues need specifically designed bioreactor systems whether for achieving successful in vitro model systems, clinically relevant therapies or for moving great research out of the “Death Valley” and into commercially viable solutions.

Currently, the biomedical field relies on the use of “non-smart” biomaterials, that fall under the traditional categories of polymers, metals, ceramics and composites. These only partially fulfill clinical needs by:

- replacing the damaged tissues and organs (i.e. medical implants)
- treating them through a controlled administration of drugs (i.e. drug carriers)
- enabling diagnosis and monitoring (i.e. contrast agents, biosensors).

These biomaterials currently available suffer limitations leading to reduced longevity (medical implants) and lack of biospecificity (biosensing, drug carriers and contrast agents).

⁶ As defined by Directive 90/385/EEC, regarding active implantable medical devices, Directive 93/42/EEC regarding medical devices and Directive 98/79/EC regarding in vitro diagnostic medical devices.

⁷ As defined by Regulation (EC) No 1394/2007 on advanced therapy medicinal products (gene therapy, stem cell therapy and tissue engineering)

Biomaterials for Health

The development of biomimetic and bioresponsive biomaterials is widely recognised as this approach offers solutions for both improved longevity of medical devices and the biospecificity of drug carriers and contrast agents. **This will need to be major focus research and development efforts for the future with innovation being the key to success.** Indeed, the body environment can be simulated by synthetic materials to support tissue repair processes and to facilitate cell-specific recognition processes required to a bio-targeted drug delivery or imaging. Likewise, biomimetic, bioresponsive biomaterials are widely recognised as a pre-requisite for the future implementation of cell-based therapies. Currently, there is no substrate biomaterial able to control their phenotype especially if the cells to be cultured are embryonic and adult mesenchymal stem cells.

The rational design of smart biomaterials cannot be considered unless a better understanding of in vivo perturbation of biological environment, drug delivery, mechanism of biomaterial degradation and fate, namely a deep understanding and control of tissue-biomaterial interaction is investigated. In particular, the importance of controlling any inflammation process has been highlighted in a tissue regeneration context is of paramount importance. Research will also need to focus on biomaterials that can be adapted to non-invasive clinical protocols through the concepts of injectability, self-assembling and bio-responsiveness. This approach is becoming crucial for the diagnosis, management and treatment of critical pathology such as: Neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, Multiple Sclerosis) as well as cardiovascular disorders, cancer, diabetes mellitus, etc.)

Extracellular matrix analogues (EMA) are biomaterials that mimic in various ways the environment around bodily cells, with additional features that lead to desired developments, are obtained through a synthetic route are considered to be the new frontiers of biomimetic/bioactive biomaterials. They will be able to control cell activities and tissue regeneration at nano-/micro-scale level.

Two main categories of EMA have been identified, which originated from a working group within the European Technology Platform (ETP) on Nanomedicines⁸ as essential for the success of biomedical devices (BD) and advanced therapy medicinal products (ATMP) intended for the treatment of disabling and life threatening diseases as well as to foster innovation in and the competitiveness of European industry:

- Nanostructured Biomimetic Materials
- Bioactive Analogues of Growth Factors (Synthetic Pro-Morphogens)

⁸ European Commission, European Technology Platform on NanoMedicine – Nanotechnology for Health, Luxembourg: Office for Official Publications of the European Communities, 2005 – 37 pp. – 21.0 x 29.7 cm, ISBN 92-894-9599-5

Nanostructured Biomimetic Materials.

The development of an advanced biomaterial should aim at controlling the time and spatial scale of both the host reaction and the tissue repair process. These biomaterials should mimic at nanoscale level the features of specific components of the tissue extracellular matrix. Surface (coating and/or covalent attachment of ligands to the surface of the polymers) or bulk chemical modifications of widely used synthetic or natural biopolymers to minimise the non-biospecific adhesion of proteins and cells and to control the response of target cells (cell attachment, migration, proliferation, and differentiation). Several techniques used for micro/nano patterning of surfaces or multifunctional materials such as functionalised micro/nano particles, carbon nanotubes, nanowires have been proposed by the literature. Functionalised nanoparticles can be used for the delivery of a variety of different compounds to tumours. Development of nanostructured biomaterials functionalised with novel targeting and/or effector domains or loaded with different drugs, may lead to production of new powerful multifunctional nanodevices capable of targeting specific cells in tumour tissue and induce cancer regression without causing toxicity. The exploitation of these techniques is often hindered by common issues such as sterility, reproducibility and cost of bioactive compounds when scaled to industrial level.

Bioactive Analogues of Growth Factors.

Synthetic biomaterials based on peptides and peptidomimetics need to be developed to produce cost-effective multifunctional bioactive materials. Nanostructured biomaterials coupled with synthetic morphogens may become therapeutically active biomaterials able to present a specific biochemical signal to either the inflammatory cells or tissue cells in a controllable fashion. In this direction, what is important is the development of bioactivated materials for cell and tissue guidance with a specific control of signal presentation in cell and tissue instructive scaffolds.

This class of product will be based on biomaterials able to vehicle therapeutically active substances and nanosystems to the site of tissue damage without eliciting any immune/inflammatory response. These classes of products can deliver bioactive molecules, tracers and cells to the target tissue in order to favour a stable grafting response.

Other important classes of technical challenges to be met in biomaterial products include:

- *Protective immune-stealth coronas for grafting of transplanted cells to the host tissue.* A specific example would be nanostructured biomaterials that are capable of surrounding pancreatic islet cells during their transplantation and grafting into the portal vein. Currently, after transplantation most of the pancreatic islets are attacked by the host immune system and do not survive in therapeutically suitable numbers in the body. Similar nano-devices could enhance the rate of survival of transplanted stem cells in many clinical applications. Immunostealth coatings for delivery devices can be applied to the surface of delivery devices so as to inhibit any potential immune reaction elicited by the delivery device during the procedure.
- *Myocardial and other nano-conductors.* Electro-conductive nanowires that are not recognised by the immune system could support the early re-establishment of myocardial function following myocardial infarction. Similar structures with appropriately tuned properties can also represent an interesting platform or biological scaffold for neuronal regenerational responses following a wide range of disorders, ranging from spinal cord section e.g. following road traffic accidents to more complex disorders such as motor neurone disease, multiple sclerosis etc..

- *Biomimetic substrates for stem cell pre-clinical handling and transplantation.* Biomaterials that are capable either of preserving the stem cell phenotype or of directing their differentiation into specific desired phenotypes is a key tool for the safe implementation of these cells in a clinical setting. Despite the need to culture these cells in the appropriate numbers required for final clinical application, the substrates currently on the market lead to their uncontrolled differentiation into fibroblast-like cells. Also, the control of the quality of the stem cells isolated from donors is of paramount importance for their transplantation. Biomaterial products capable of facilitating their rapid screening will improve the reliability of any stem cell-based treatment.

Standardisation

A challenge to overcome is the lack of standardisation of the properties of biomaterials as well as a lack of agreement on their “minimal expected performance outcomes”. This problem makes it very difficult to compare data for the various studies that have been carried out. The implementation of a “performance grid” is therefore needed for biomaterials or classes thereof, based on key performance variables and measurements. High-throughput screening could be implemented for identification and optimisation of performance of a biomaterial to meet defined end use criteria such as labelling “for research use or research grade”.

A useful initial step, therefore, would be to develop a centralised repository or database of new materials, or information on where to access the new materials developed with EU funding so that researchers and clinicians can access the material for the purposes of evaluating its biological and clinical usefulness in areas beyond its intended primary application. This would also provide a platform for the development of new composite biomaterials or variants thereof so as to provide a stimulus for potential research programmes. This database should also contain comparative analyses of the results of biological testing of biomaterials from the scientific literature (and clinical trials, where possible) so as to incorporate data on as many of the material properties as possible. Based upon this, it should be possible to formulate, as necessary, standardised protocols for the determination and measurement of the efficacy and safety of new biomaterials, facilitating as it will, the need to establish high throughput test platforms in the future for biomaterials, that comprise standardised testing protocols for ex vivo, in vivo, pre-clinical and clinical testing. The possibility of certifying each modular component of the final product will reduce the time to the market for second generation of products or for different applications.

A second or consequent step to this would facilitate research efforts that are specifically needed to develop multi-functional biomaterials. These are the biomaterials that are capable, by virtue of their own material ingredients or surface properties, of achieving several biological responses simultaneously without additional drug, cytokine or other interventional coating/release. Alternatively, they may help to dampen those that are undesirable such as inflammation, infection, corrosion and issues related to bio and immune compatibility. The development of biomaterial surfaces method through nanotechnology research is expected to play a major role in the future.

Biomaterials for Health

It would therefore mean devising a "label of biocompatibility", which would reflect the state of biocompatibility of a biomaterial after having been tested as a finished product - meaning after appropriate manufacturing, conditioning and sterilisation. This label would therefore permit the fast tracking of an implantable device or therapy to market if the biomaterials used in it are already so labelled. The label would reflect appropriate biomaterials processing (injection temperature, heat treatment temperature etc. as an evolution of ISO 10993 (biocompatibility) in order to give guidance to researchers as to which remaining biocompatibility tests are still necessary in order to bring a final labelled implant to market. The label should not be used as a means to increase the cost of manufacturing, but rather as a tool to assist companies in choosing and facilitating market access for the eventual Medical Device or Advanced Therapy that the biomaterial becomes a part of.

A third step consists of research into smart biomaterials, endowed with all of the properties as alluded to above. This can eventually lead to the regeneration of complete bodily tissue and organs as well as for the building of artificial organs. A major challenge will be to enlist the cooperation of biologists, chemists, physicists and clinicians.

Objective

The creation of a centralised repository or database of biomaterials, with detailed information on their chemical-physical, biological and toxicological properties accessible both to researchers, companies and clinicians for the purposes of evaluating its biological and clinical usefulness in areas beyond its intended primary application.

This will incorporate data on as many of the material properties as possible, allowing for the development of standardised protocols for the determination and measurement of the efficacy and safety of new biomaterials, whether they be single or combination entities.

A label of biocompatibility should be established so as to define the suitability of a biomaterial for eventual use in a Medical Device or Advanced Therapy that the biomaterial becomes a part of, so as to assist companies in choosing and facilitating market access for their products.

The level of safety to be attained with this procedure needs to be specified, reflecting the input of regulators, along with the clinical risk-benefit ratio and level of insurance required. This would be reflected in Health Technology Assessment.

This would be a stand-alone exercise to which individual projects could interact and relate but it would not be a part or subset of such individual projects.

Specific Technical Challenges

Matrices for Regenerative Medicine

In medicine, hundreds of products based on synthetic or natural polymer matrices are introduced for clinical use each year and have had an enormous beneficial effect on patient care. New applications for biomaterials in regenerative medicine have also emerged, most notably when used in combination with cell therapy, tissue engineering, and protein therapeutics. These applications require more than mechanical and chemical versatility from the polymeric matrices; they require cell compatibility based on biomimicry of the extracellular matrix (ECM). The emerging field of bioactive polymeric matrices is therefore defined by design strategies that are focused on tuning the biological and physical attributes of the matrix to achieve specific interactions and responses from cellular systems. In tissue engineering for example, where matrices are used to organise cells hierarchically into tissue-like structures, the architectural and/or molecular cues can be engineered with spatial and temporal presentations that mediate multi-cellular morphogenesis. The challenges of designing complex biomaterial systems have been aided by significant breakthroughs in synthetic polymer chemistry, three-dimensional molecular patterning techniques, and biomimetic rational design approaches that are founded on the basic principles of cell and molecular biology. In the research activities to be funded in Horizon 2020, there is a clear need to develop further those principles that are currently beginning to be applied to engineer cell-compatible biomedical matrices, focusing on biophysical and biochemical manipulations of 3D polymer networks for controlling interfaces at the cellular and subcellular scales.

Current State of the Art

A bioactive matrix is characterised by its ability to control specific molecular interactions at the cell-material interface. These include biological interactions such as receptor-ligand complexes that mediate cell adhesion and mesenchymal migration, bound or soluble molecule interactions facilitating proteolytic biodegradation or transcriptional events that govern cell phenotype, as well as focal adhesion interactions with compliant or rigid substrates to transmit mechanical stresses to cells. Designing the molecular structure of a polymeric matrix to control these spatial and temporal events enables their use for guiding cell response in-vivo and in-vitro. Many features that control cell response, which have been isolated from part of a cell's in vivo microenvironment, can be built into a matrix using a top-down rational design.

Research activities to date have demonstrated that engineered hybrid systems can exhibit biomimetic self-assembly properties, as well as control over physical properties afforded by the synthetic constituent. Many materials have since been modelled on these seminal concepts, including proteolytically responsive synthetic matrices. These and other developments have combined a variety of synthetic polymers and protease substrates – showing that almost any synthetic hydrophilic polymer milieu can be designed to facilitate controlled cellular degradation and invasion. Other biomimetic features isolated from bioactive domains in natural proteins have been used in similar fashion, including cell adhesive integrin-binding domains, controlled release affinity binding domains, and transglutaminase crosslinking domains.

Some applications may require more extensive biomimetic features from the backbone constituents of the biomedical matrix. Certain stem cells, for example, require extensive biochemical stimuli inherent to their natural ECM niche for proper differentiation. These stimuli are difficult to replicate using synthetic biology, and a semi-synthetic approach may appropriately accommodate the discrepancy between the completely natural versus completely synthetic hydrogel microenvironments. The semi-synthetics use proteins or polysaccharides conjugated to low molecular weight hydrophilic polymers as the main building blocks of the hydrogel. The protein/polysaccharide provides biomimetic features and the synthetic polymer provides important control features for regulating mechanical properties, molecular structure, and other physical attributes of the material. One such family of semi synthetic hydrogels is based on the covalent conjugation of linear or branched, nonionic hydrophilic polymers with reconstituted ECM proteins such as fibrinogen, collagen, or albumin. Conjugation in these materials has been achieved by stepwise copolymerisation of the hydrophilic polymers with protein or polysaccharides, Schiff base formation reactions, disulfide bonding, free-radical initiated copolymerisation using peroxides or a fenton reagent, photo-initiated free-radical copolymerisation, or metal-free Click chemistry such as Michael addition. Although less defined than the synthetic ECM analogs, the semi-synthetic ECM matrices are relatively easy to manufacture, can be reproduced in large quantities, and provide a more reliable material compared to natural ECM matrices.

While a top-down approach is beneficial, it has its limitations; for instance, it is difficult to control precisely spatial bioactivity given the structural complexity of natural protein domains. An alternative bottom-up approach provides the opportunity to control hydrogel molecular structure by arranging elementary chemical motifs together to give rise to a system possessing controlled yet complex patterns or gradients of bioactive factors, as well as other biophysical properties. The basis of this methodology is functional chemical features whose structure-function relationships are well characterised, and which are easily to implement into the hydrogel's crosslinking methodology. Some well-established chemical reaction schemes have therefore been recently adapted for the mild conditions often required with in-situ formation of biomedical hydrogels.

Chemical reactions used for immobilisation of reactive macromolecules or localising crosslinking reactions can be performed using tightly regulated light-activated initiation either by traditional photolithographic techniques, or more sophisticated approaches such as multiphoton laser scanning lithography. Photolithography has been widely used for creating patterns in various hydrogels, and more recently, for patterning cell-laden PEG or alginate hydrogels with multiple functionalities using free-radical photopolymerisation. Patterning techniques with submicron-scale resolutions have also been adapted for cell-laden matrices based on the concepts reported using multiphotonic photopolymeriation.

Objective

The interrelationship between the processing, structure, properties and performance of cell-compatible matrices underlie the fundamental design rationale for most biomedical applications. With bioactive matrices, this interrelationship is complicated by a performance criteria characterised by a multitude of molecular interactions at the cell/material interface. Therefore, a high funding priority should be the design of matrices with focus on salient matrix features that give rise to the desired properties most suitable for the biomedical application, including transport properties (e.g. sustained release), tissue interactions (e.g. bioactivity), and chemical stability (e.g. degradability). In principle, these features can be engineered into a cell-compatible matrix; however, there are many challenges in applying these features within bioactive matrices in regenerative medicine. In this context, five important funding properties for regenerative medicine are highlighted:

- Matrices with controlled degradation features,
 - Bioadhesive matrices,
 - Bioactive matrices
 - Matrices that mediate transport (e.g. Controlled/prolonged release of bioactive molecules)
 - Matrices with controlled mechanical properties.
-
- **Novel Biodegradable Matrices:** Biodegradation of matrices is essential for biomedical applications that require controlled reabsorption in-vivo and/or local dissolution to facilitate cell morphogenesis and motility. Matrices have the ability to undergo local or bulk dissolution based on a number of mechanisms (e.g., hydrolysis, proteolysis, disentanglement, or environmental triggers); engineering the spatiotemporal aspects of this presents a challenge. Bulk hydrolytic reabsorption with specific temporal events in the body, such as bone regeneration, can be achieved by controlling the amount of hydrolytically liable crosslinks in the polymer network, resulting in better tissue repair. Cell-mediated hydrogel degradation can provide a more physiological control mechanism for both the removal of the provisional matrix and the liberation of matrix-bound bioactive factors. Strategies using cell-mediated control over degradation employ a peptide-polymer hydrogel design with crosslinking oligomers that are known substrates for collagenases, gelatinases and other matrix metalloproteinases. A large number of oligomer sequences that are known to be responsive to these cell-secreted proteases have now been characterised, and can be synthesised and incorporated into the material design. Other strategies for endowing synthetic polymers with proteolytic biodegradation sites should include the development of *de novo* degradation sites on a synthetic polymer backbone using conventional polymer chemistry. Such chemistries could enable the development of proteolytically degradable synthetic polymer matrices without the use of oligopeptides.

Re-enforcement of a single network with e.g. another network that interpenetrates through the first one can impose further control over mechanical properties and degradability. Normally, implication of physical interactions through hierarchically organised self-association on different spatial scales (sub-molecular, molecular, and supramolecular) result in fibrous networks with the porosity suitable not only for transport of nutrients but also for proper cell-matrix signaling. The examples of such fibrillar matrices include natural fibrin and collagen as well as self-assembling synthetic peptides. Current shortcomings of those networks, however, are their poor mechanical stability and fast *in vivo* degradation. Orthogonal combination of different types of physical interactions (hydrophobic, hydrogen bonding, metal-ligand coordination) or physical and chemical (“click”) cross-linking is the strategy which can first improve mechanical stability of physical networks as well as can provide material resorption both with temporal and spatial control.

- **Novel matrices that are bioadhesive.** Bioadhesion, an important property that allows cells and tissues to adhere to a matrix, has enabled their use as tissue adhesives in surgical repair or as inductive scaffolds for tissue regeneration. While some matrices such as fibrin or collagen inherently exhibit bioadhesive properties, most other natural and synthetic matrices do not. Bioadhesive features can be engineered into a polymer network by using linker molecules that enable covalent or non-covalent molecular interactions between the implant and its surroundings, including for example the cell-adhesive oligopeptides derived from fibronectin’s central cell-binding domains. Cell-adhesion modifications to scaffolds, for example, have been used effectively to promote enhanced osteogenic differentiation of MSCs for 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. Tissue-adhesive modifications to matrices can further improve performance of cell-delivery scaffolds by stabilising the in-vivo location of the graft. Covalent modifications using specific chemistries, such catechol moieties (3,4-dihydroxy-L-phenylalanine, DOPA), may further attenuate the bioadhesive properties of a matrix. In the example of the DOPA moiety, the chemistry was derived from the tethering chemistry that allows mussels to adhere to wet organic surface. In addition to forming strong covalent interactions with nucleophiles such as thiols and imidazoles found in organic substrates (i.e. ECM), these bioadhesive modifications can also participate in the non-toxic crosslinking reaction of the matrix. The effective immobilisation of matrices on the surface of the various organs and tissues may ultimately permit effective local administration of the bioactive payload from the matrix.

- **Novel bioactive matrices.** Bioactivity in matrices is instrumental for materials that are called upon 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 using exogenous growth factors that are delivered with spatiotemporal control [8]. However, matrices do not inherently sequester growth factors and thus fall short of precisely controlling the sustained or localised bioavailability of their payload. In-vivo, growth factor bioavailability is tightly regulated by non-specific associations between the factor and ECM proteoglycans (i.e. glycosaminoglycans, GAGs) through affinity binding domains. Using strategies premised on such non-covalent interactions with polymeric building blocks, design modifications to matrices can be used to improve the localised growth factor availability. These concepts have included short heparin-binding peptide domains that can sequester cell-secreted proteoglycans such as endogenic heparin. Another prevalent approach to sequester bioactive factors within a hydrogel network involves covalent growth factor immobilisation. However, in terms of funding priority, affinity-based linker peptides may be preferred because they circumvent loss of biological activity typically associated with chemical crosslinking of proteins. Temporal control over release of bioactive factors should be realised through the design of linkers that connect a matrix either directly to a growth factor or a growth factor-binding ligand. For example, molecular building blocks containing light-sensitive chemical bonds and incorporated into such linkers will allow the release of a suitable factor on demand. Immobilisation of bioactive factors within a matrix should be accomplished with a spatial control in order to provide surrounding cells with different chemical environment and thus spatially distinguish biological events in the area filled with the regenerating material. This challenging task can be accomplished by using orthogonal and chemoselective chemistries for preparation of homogeneous networks followed by patterning of the prepared matrices in a point or gradient manner.
- **Novel matrices that mediate transport.** Transport of hydrophobic/hydrophilic molecules is an important property of a matrix that can benefit therapeutic techniques requiring sustained drug release or triggered pharmacokinetics. For example, tumour chemotherapy may be far more effective if drug molecules were targeted to and sustained in the tumour site, or if drug is released only after it has been internalised within the cancer cells. Depending on the properties of the therapeutic drug, a matrix's porosity (i.e. mesh size) may be used to regulate the drugs availability by controlling its diffusion through the polymer network. The mesh size of a typical cell-compatible polymer network is no less than five nanometres and far greater than the characteristic size of most small drug molecules. For relatively large protein or peptide drug molecules, the matrix structure and mesh size (~5-20 nm) can be engineered to limit mobility and modulate release kinetics. In order to achieve sustained release of small drug molecules using size exclusion, matrices must employ immobilisation schemes that entrap these molecules in dense physical structures within the network (i.e. mesh size <1nm), including in self-assembled nanostructures, layer-by-layer constructs, liquid crystalline nanostructures and polyelectrolyte complexes. For example, using dense polymer-drug nanostructures that are stable in water at physiological pH levels, drug release is designed only after a pH-triggered transition into a hydrophilic matrix occurs inside the mildly acidic endosomes of tumour cells. This type of triggered release can be highly effective in preventing tumour growth in-vivo using far lower doses than are required with systemic administration of the drug.

- **Novel matrices with controlled mechanical properties.** The mechanical properties of a cell-compatible matrix can convey important physical cues to cells through mechanotransduction pathways that mediate tissue homeostasis, morphogenesis, cell growth, contractility, differentiation and pathophysiology. With new insights into the mechanical basis of tissue regulation emerging, a number of design strategies have evolved to improve control over a matrix's mechanical properties. One example includes a method for overcoming the inherent limitations of poor mechanical properties (e.g. low strength) using physical interpenetrating double-networks (DN). The DN matrices exhibited extremely high toughness when, for example, they combined a rigid polyelectrolyte gel, poly(2-acrylamido-2-methylpropanesulfonic acid), with a flexible neutral poly(acrylamide) gel. Applying this concept to a cell-compatible and instructive but inherently weak polymer such as reconstituted collagen can help produce matrices with an order of magnitude increase in fracture stiffness while still retaining more than 90% water content. Other hybrid materials that are formed as a result of interactions between ECM derived/mimetic fibrillar or inorganic nanostructures and polymers are also very promising due to the reinforcing nature of the filler to matrix gels can result in unique mechanical properties that also are self-healing if interactions are reversible.

Future Challenges

Many of the early cell-compatible matrices lacked essential features, mainly those that can concurrently control material properties, biodegradation and bioactivity. Material engineering design principles have overcome some of these limitations and with these advances, new applications for bioactive matrices impacted translational research in regenerative medicine. However, the encapsulation of living cells in a cell-compatible matrix is still one of the principal challenges of adapting these materials for further advancing tissue regeneration. Cell encapsulation in 3D matrices has not lived up to its full potential using existing material technologies partly because each type of cell requires its own unique encapsulating microenvironment with cell-specific material properties and spatially controlled bioactive features. Elucidating the specific bioactive requirements of highly specialised cell types (e.g., cardiac, bone, liver) and designing matrices with complimentary spatial features is still an arduous process. **Furthermore, many advanced matrix designs will require more than just one or two of the aforementioned properties to mediate complex biological events such as cellular morphogenesis, differentiation or self-renewal.** Combinatorial and high-throughput (CHT) methods are now available to systematically screen hydrogel scaffolds to identify optimal biomaterial properties. Future study of the regulatory role of niches in maintaining stem-cell fate will utilise scaffolds with multiple gradient presentations of immobilised factors. Overcoming some of these main challenges will help to uncover the vast potential of using cell-compatible, custom designed matrices in basic and applied scientific research.

Objective

Funding will need to be dedicated to advanced matrix designs adapted to individual circumstances, in terms of results that can be realistically achieved, with more than just one or two of the aforementioned properties to mediate complex biological events such as cellular morphogenesis, differentiation or self-renewal in order to achieve the goals set out above.

Bioinspired Approach for Gene Therapy

Most current drugs target proteins that are present at the extracellular border within a tissue or organ. However, smart design of biomaterial based drug delivery systems that can target diseased cells and tissues has become an important tool to increase therapeutic efficiency of these drugs. Future drug conjugates are foreseen to act on the cellular machinery that produces these proteins by acting intracellularly i.e. gene therapy or by delivering active protein at the desired site. With the mapping of the human genome and recent advances in proteomics the number of genes to target, and hence possible diseases, are exponentially growing. The promise of gene therapeutics is, however, hampered by difficulties in the *in vivo* delivery to the targeted cells, and limitations of systemic delivery, which remains to be the biggest challenge to be overcome. In this context, novel biomaterials may offer the revolutionary perspective required to undertake the task of developing novel vectors that can be designed to efficiently target and affect desired genes *in vivo* and can be applied in clinical settings.

Current State of the Art

Gene therapy holds the significance of correcting genetic defects, and there are many nucleic acid-based therapeutic strategies that can be used for gene therapy, including antisense and RNA interference (RNAi) mechanisms. Antisense oligonucleotides are typically 15–30 nucleotides long and block production of the disease-causing protein after complementarily hybridising to their target messenger RNA (mRNA) and degrading the mRNA by activating RNaseH. RNAi is a separate process in which a specific mRNA is targeted for degradation in order to inhibit the synthesis of its encoded protein. Two types of small RNA molecules—microRNA (miRNA) and small interfering RNA (siRNA)—are central to the RNAi function. After delivery into the cytoplasm, the antisense strand of RNAi molecules recruits the corresponding mRNA in a sequence-specific manner to the RNA-induced silencing complex, which is followed by cleavage of the target mRNA, resulting in gene silencing. Both antisense oligonucleotides and RNAi-based therapy target mRNA to inhibit transcription of an overexpressing endogenous gene, resulting in selectively inhibiting the expression of an unwanted protein (downregulation or loss of function). Alternatively, plasmid DNA (pDNA) is also widely used to introduce a normal wild-type transgene into specific cells of the host where the endogenous gene is underexpressing resulting in expression of a deficient protein (upregulation or gain of function).

Currently, enormous success has been achieved to engineer plasmids such that they can be selectively expressed in desired cells (by choosing the promoter sequence) and can stably or transiently express proteins at this site. Clinical advancement has, however, been limited to viral transfection vectors which, though has advantages (to be efficient) also has limitations (side-effects). Today safer and bioinspired delivery technology is needed to overcome current drawbacks of gene therapy.

Within the field of gene silencing technologies, potential of clinical translation has been better. This is due to the fact that synthetic DNA/RNA molecules that could be chemically modified to achieve a desired function were plausible. The siRNA technology has several advantages compared to the classical small molecule drugs.

The design of active siRNA sequence is relatively simple and with the advancement of bioinformatic tools, it is possible to predict the siRNA sequence for almost any gene of interest. However, such nucleic acids technologies also have several disadvantages. First the siRNA technology can only be used for silencing upregulated genes. Oligonucleotides are susceptible to degradation by exonucleases under physiological conditions. Targeted delivery of such therapeutic molecules to the desired tissue has also been limited. Most of these disadvantages are similar to the ones described for the treatments with proteins and monoclonal antibodies but using modified nucleic acids may solve them. It has been demonstrated that it is possible to enhance stability to nucleases by introducing chemical modifications in the nucleic acid structure. These modifications also improve cellular delivery (cholesterol conjugation), reduce off-target effects and can also prevent innate immune activation (e.g. 2'-OMethyl modification). However, there is still a pressing need for further development in order to demonstrate the potential use of nucleic acids as drugs in the treatment of human diseases. Though currently no siRNA-based product is commercially available, nearly 30 clinical trials are being pursued. Recently, the first successful clinical trial with siRNA was demonstrated using nanoparticle composed of partially cationic polymer having a receptor-targeting antibody. This exemplifies the significance of targeted delivery of therapeutic nucleic acids that allow specific and efficient cellular uptake by e.g. receptor-mediated endocytosis.

It is anticipated that solving the delivery problem of nucleic acids will afford a similar or potentially greater level of impact than small molecule drugs for treatment of diseases as predicted by the largest European private-public partnership (Innovative Medicine Initiative⁹).

Objective

Material scientists, chemists and biologists needs to address the problems of nucleic acid therapeutics and should underline different aspects that are the bottleneck for this technology. The biomaterials community should introduce new and innovative methods to find solutions for the delivery problem that are biocompatible and bioinspired. These solutions will be useful not only to improve the therapeutic potential of nucleic acids but also can be applied for small molecule drugs, antibodies etc.

This can be realised by focussing on the following areas :

- **Clinically relevant drug delivery systems**
- **Chemically modified nucleic acids**

- **Clinically relevant drug delivery systems :** Novel methods are imperative for designing drug delivery systems that will provide safe, effective and efficient clinical outcome. This is particularly significant for nucleic acids as its therapeutic potential could only be unlocked by finding solutions to the *in vivo* delivery problem. These materials should improve the therapeutic potential of the drug by providing a step change in delivery solutions of large macromolecular drugs of biological origin, including plasmid DNA, paving the way for new treatments in areas of major medical need, e.g. cancer, diabetes, Alzheimer's disease and rare genetic diseases.

⁹ Council Regulation (EC) No 73/2008 of 20 December 2007 setting up the Joint Undertaking for the implementation of the Joint Technology Initiative on Innovative Medicines

The technology using novel delivery vehicles should be tested in suitable animal models and fine-tuned for successful transition in a clinical setting.

It should take into account factors such as stability, efficiency, safety, immunogenicity, and toxicity aspects that have limited *in vivo* application of biologics in the past. Successful proposal should cut across several disciplines to combine state-of-the-art know-how from complementary areas ranging from material development, *in vitro* and *in vivo* evaluation with preclinical and possibly also clinical experiment planned within the framework of the project.

- **Chemically modified nucleic acids :** Synthetic nucleic acids that overcome the current shortcoming of nucleic acid stability and bioactivity should be addressed with the perspective of fulfilling the need for efficient *in vivo* delivery. **Research proposals should focus not only on chemical modifications of synthetic DNA and RNA nucleotides to achieve biological function, but also should be tailored for a specific biological application.** Progress within the field of chemically modified nucleic acids such as Locked and Unlocked Nucleic Acids (LNA and UNA respectively) is a promising stepping-stone for future development of tailored biologically active therapeutic molecules. RNA/DNA molecules for transient/stable (therapeutic) gene expression and RNA/DNA molecules for gene targeting, as systems based on artificial nucleases e.g. Zinc Finger Nucelases, TALENs and CRISPR/Cas9 RNA-guided nucleases.

The next step within this field is to co-develop such fine-tuned therapeutic molecules with advanced delivery technology since these are intimately linked. This will allow transition of synthetic molecules to real therapeutic application. One of the major advantages for this approach is that, once optimised, this technology could be easily implemented in other biologically relevant settings by simply changing the oligonucleotide sequence and thereby targeting other clinically important genes. Such a contribution will make significant impact within European scientific community and will bring about both social and commercial success.

Matrices for Diagnostics

Biomaterial matrices have made a major impact in many biomedical fields; however, some areas where matrices could be beneficial have been relatively overlooked. For example, biomaterial matrices can impact the fields of biotechnology, pharmacology and biosensors, by providing solutions for large-scale protein production, drug-screening techniques, and individualised chemosensitivity assays. As an example, drug developers can test anti-tumour drugs in-vitro by encapsulating tumour cell spheroids in protease-sensitive, bioactive matrices that more closely mimic physiological tumour growth conditions. Another unfulfilled opportunity for such matrices is in biotechnology, where cell manufacturing and protein production in large scales can be aided by encapsulating microgels that enable suspension cultivation of most anchorage-dependent cell types. Whether the objective is protein production or cell expansion, the use of encapsulating microgels would enable the transition from less efficient roller bottle cultures to efficient industrial suspension bioreactors. Thus, as the field moves to employ new biomaterial designs, it gains the ability to develop sophisticated matrices for these and many other diagnostic and biotechnology application. In the proceeding section, we will highlight the potential impact of bioactive matrices in diagnostics and biotechnology, underscoring the topics for high funding priority in this field.

Matrices for Stem Cell Biotechnology

Human pluripotent and multipotent stem cells (hSC) are of significant interest as a renewable source of therapeutically useful cells. Even as scientists uncover precisely how to manipulate hSC cultures toward directed pathways of differentiation or self-renewal, their routine commercial and clinical applications will still require cultivation and bioprocessing efficiency that cannot be provided by conventional adherent cell culture technologies. **Unquestionably, the development of scalable methodologies for handling hSC necessitates an approach premised on the use of three dimensional (3-D) suspension cultures that are readily adaptable to large-scale bioreactors.** In this context, hydrogel biomaterials may offer the revolutionary perspective required to undertake the prodigious task of developing 3-D bioprocessing technologies for stem cells that can be applied in commercial clinical settings. The biomaterials community is poised to establish a technological foundation for encapsulating biomaterials matrices to be used as a routine, efficient, and scalable solution for hSC bioprocessing.

Stem cells (SC) and induced pluripotent SC (iPSC) are anticipated to become an unlimited cell source for regenerative medicine. Even as hematopoietic stem and progenitor cells (HSC) are already routinely used in the clinic, pluripotent and other multipotent stem cell therapies are expected to provide far more treatment options. The enormous potential of cultured stem cells has already begun to materialise into clinical products likely to reach the market in just a few short years. Cell therapy companies have conducted advanced-stage clinical trials for therapies using human embryonic stem (hES) cells and others are pushing treatments derived from adult stem cells and their precursors. Given this high priority for commercialisation of cell therapy in general and stem cell therapy in particular, one of the toughest tasks facing this field is how to generate the immense numbers of cells required for the eventual treatment of large patient populations. The heterogeneity of stem cell types as well as the numerous areas of application suggests that differential processes are mandatory for their in vitro culture.

Regardless of the advanced stages of some stem cell technologies, a commercial medical delivery infrastructure for stem cell therapies is still very much in its infancy. One major underlying reason for this manufacturing lag is the limited knowledge of stem cell biology, which hampers the development of efficient and commercially viable processes. As researcher begin to understand the exact signalling transduction pathways controlling self-renewal and differentiation of stem cells in more detail, chemically-defined culture conditions will emerge and reduce variability associate with stem cell bioprocessing. Moreover, most stem cells are anchorage dependent, and thus require a surface matrix to be used for bioprocessing. However, culture surface enlargement to ensure efficient and reasonable mass expansion of adherent cells is a central challenge in bioreactor design. The considerable cost with respect to consumables, labour and time as well as the inherent variability in manual processes not only make this option unattractive, but also render it commercially unviable. In this regard, automation and the use of an efficient bioprocess paradigm are imperative for the creation of successful clinical products.

The realisation of stem cell therapies will therefore rely on robust, efficient and reproducible bioprocessing methodology. In this context, stirred tank bioreactors are highly favoured in process scale-up because established culture conditions in lab-scale can often be transferred to much higher volumes with relative ease. However, not all cells can adapt to culture in stirred suspension systems. One of the proposed techniques to enable the growth of anchorage-dependent stem cells in suspension bioreactors is the use of microcarriers. These spherical particles are kept in suspension by stirring or other mixing techniques and provide a massively enlarged attachment surface in a relative small reactor volume due to their high surface-area-to-volume ratio. Unfortunately, solid carriers also impose high mechanical stresses on cells in stirred culture and this can be very detrimental, particularly in stem cell cultivation.

The encapsulation of cells in protective microspheres made from biocompatible hydrogel materials provides an ideal solution to enable the growth of anchorage-dependent cells in suspension bioreactors without mechanical stress-related complications. For more than three decades, hydrogel encapsulation of cells has been performed primarily with hydrogels made from sodium alginate polymers. Formation of cell-laden microgels is easily achieved using alginate by dripping the cell-containing precursor solution into a “hardening” bath of CaCl_2 . Commercial encapsulation devices have likewise been successfully developed for alginate polymers in order to ensure high reproducibility in the generation of beads or hollow capsules. In recent years, there have been some efforts to replace the less biocompatible alginate polymers with synthetic polymer systems that exhibit a lower critical solubility temperature (LCST) at physiological temperatures. LCST polymer show promise in encapsulation mainly because of the mild and rapid character of their reverse thermal gelation (RTG). The most abundant examples of synthetic polymeric biomaterials exhibiting LCST gelation include poly(N-isopropylacrylamide) (pNIPAm) linear and crosslinked polymers, copolyethers such as triblock copolymers of poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG), e.g. the triblock Poloxamers, and others. These materials still require an additional level of chemical crosslinking to avoid dissolution caused by collisions and microeddies in a bioreactor environment. To address this, one could employ a method devised by Cellesi et al. wherein a “tandem” gelation scheme effectively combines rapid LCST gelation and encapsulation of cells with subsequent cytocompatible photopolymerisation.

Objective

Premised on these concepts, the biomaterials community should introduce new and more advanced bioactive hydrogel materials that will improve stem cell bioprocessing. These materials may exhibit fast LCST gelation, photo-initiated chemical crosslinking, and multi-functional protein-like bioactive domains and this should be a criterion for funding decision-taking.

These sophisticated new materials should be exploited for developing bioprocessing methodologies for stem cells, through their encapsulation in microcarriers and subsequent cultivation in commercial suspension culture systems. For example, the rapid gelation kinetics of alginate can be mimicked by the LCST properties of the new hydrogel biomaterials, thus making them suitable for commercial cell encapsulators. Additional covalent crosslinking, based on mild and effective chemical reactions of functionalisation groups on the polymer chains, can form the stable covalent bonds between the backbone macromeres to keep the polymer network intact under hydrodynamic stresses in the bioreactor. The interplay between chemical and physical gelation reactions can be further used to control the mechanical properties of the encapsulating milieu. The combination of controlled mechanical/physical properties, stem cell-specific bioactivity, and ease of processing will help to transform the encapsulating microcarrier hydrogels into a system that can represent a viable solution for commercial stem cell cultivation.

Funded projects should address the principal requirements for 3-D suspension bioprocessing of hSCs in unique biomaterial milieus, possibly through a straightforward cell inoculation into microgels, *in situ* self-renewal and differentiation in the culture system and mild cell recovery into a solution phase. Technological milestones supporting the scheme include scalable protocols e.g. manufacturing large quantities of hydrogel precursor materials, established microgel inoculation protocols and biomaterial-based methods for controlling cell proliferation, differentiation, and cell-to-cell interactions. Using state-of-the-art concepts in materials science, biotechnology engineering, biology, chemistry, and medicine, the expected outcomes from the multidisciplinary research should offer a tangible solution to the growing demand for commercial-scale stem cell bioprocessing practices. This approach has the potential for ground-breaking impact in the transfer of laboratory-based stem cell cultivation techniques to a much broader clinical scale. While there are still many challenges ahead, should this approach be successful, it could lay the foundation for overcoming one of the most enduring challenges in applying stem cells in regenerative medicine.

Matrices for Cancer and Cancer Diagnostics

The incidence rates of cancer have been increasing worldwide for the past few decades, even though the mortality rates have remained either stable or decreased in many countries. Advances in cancer detection techniques and treatment approaches are responsible for reduced mortality; however, even with newer drugs that induce a better response and have fewer side effects, the problem of determining the best individualised chemotherapy regimen still remains largely unaddressed. Tumour cultures from patients diagnosed with breast cancer have been used to identify tumour drug response and to develop customised patient-specific therapies, but the difficulty lies in maintaining the viability of the tissues in culture, as well as their usefulness for the screening of a large number of therapeutic agents.

Despite more than five decades of research on individualised tumour response testing and numerous technological advances in this field, there are still no reliable and effective screening modalities for assessing tumor-specific chemosensitivity in cancer patients. A successful screening assay would need to provide timely and cost-effective input to doctors in advance of determining their first-line regimen. **Once proven effective, the tumour culture diagnostics approach will potentially revolutionise *in vitro* tumor-specific screening in this regard.**

Cancer researchers have made enormous strides in recent years in deciphering the complex molecular basis that is related to cancer initiation and progression. These discoveries provide ideal targets for the development of new anti-cancer drugs that induce better response and have fewer side effects. Active agents are now routinely used to treat patients for cancer (i.e. chemotherapy). Yet, the issue of determining the best chemotherapy agent using simple *in vitro* diagnostic tools still remains unresolved. Over 50 years of research have been invested on developing *in vitro* drug screening techniques in order to improve drug development and patient-specific chemotherapy treatment of cancer. Most efforts have been focused on developing an *in vitro* drug-response assay that can effectively determine the activity of chemotherapy drugs for a specific cancer (i.e. *in vitro* chemosensitivity). Methods for *in vitro* chemosensitivity testing in different patient-specific tumors have been met with mixed results.

One of the major challenges facing this field is the lack of a reliable tumour model system for drug screening and evaluation. Currently, the most commonly used tumour model for anti-cancer drug discovery is two-dimensional (2D) cancer cell cultures. In many aspects, 2D cultures do not mimic the actual microenvironments inside human bodies where cancer cells grow. Cells grown in three-dimensional (3D) culture have different cell surface receptor expression and proliferation, extracellular matrix synthesis, cell density, and metabolic functions than cells grown in 2D monolayers. Biomaterials research has recently uncovered the fact that cancer cells grown in 3D are more resistant to chemotherapy than those grown in 2D culture. A better tumour model system is therefore required to make *in vitro* drug screening more effective and accurate. Three dimensional tissues need adequate oxygen and nutrient supply and controlled conditions to be cultured successfully, achievable only employing specifically designed bioreactor systems.

Given the inherent limitations of current *in vitro* tumour model systems, the biomaterials community can introduce new and more advanced 3-D matrix materials e.g. bioactive hydrogels, cancer nanodevices, that would improve cancer diagnostics. Moreover, these newly developed 3-D cancer models should be demonstrated to correlate with well-established in-vivo cancer models. The potential impact of an effective *in vitro* chemosensitivity assay based on such 3-D cancer models – one that can accurately identify tumor-specific drug response – is enormous. Overcoming the major technological hurdles in this field will enable a rapid penetration of these technologies into standard oncological practice as well as drug development. In the context of patient-specific chemosensitivity, a successful assay would need to provide both timely and cost-effective input to doctors in advance of the initiation of the patient's first-line regimen. For new drug development, the information provided by an *in vitro* assay would be based on cultivation of the human tumour biopsies using simple, proven, and reliable diagnostic techniques. Ultimately, these refined new screening modalities can be used to optimise patient-specific cancer therapy and streamlined drug discovery protocols.

Objective

Many of the problems associated with the various testing modalities can be linked to one of five underlying shortcomings in the present *in vitro* cancer model technologies:

- **tumour dissociation protocols requiring pure homogeneous single cell populations;**
- **time-consuming, labour intensity analysis and long turn-around times;**
- **inadequate 3-D tumour growth model systems,**
- **inability to distinguish between effects on transformed cells and non-transformed cells; and**
- **colorimetric, fluorimetric, or radiometric measurements with high variability.**

Any improvement on the current state-of-the-art in testing modalities will need to address concurrently all of these shortcomings.

Ultimately, an ideal testing method must take advantage of an *in vitro* tumour growth model that in many aspects would resemble an actual tumour *in vivo*, in order to obtain a realistic assessment of the drug's efficacy. At the same time, the tumour growth system needs to be able to differentiate between the transformed cell growth and the non-transformed cell growth in order to minimise any noise from the cancer cell growth signal. The preparation protocol must be straightforward and highly repeatable; preferably this would be done on whole cancer biopsies (un-processed tissue). Moreover, the *in vitro* monitoring of the cancer growth signal should be done without highly variable colorimetric, radioactive or fluorimetric measurements. Finally, the procedure should be accomplished using a cost effective approach.

Projects that fall under the high funding priority should address these principal requirements, using a biomaterial strategy that employs features designed to measure tumor-specific chemosensitivity

without any of the shortcomings of the existing methodologies. Below are a couple of examples of critical parameters for such a system.

A 3-D Tumour Growth Model that Recapitulates the In Vivo Environment

What sets the biomaterials approach apart from the other techniques is its use of a unique tumour culture system, premised on highly sophisticated 3D biomaterials. These culture materials can be developed from both synthetic and biological building blocks, and be used for culturing tissue specimens in a 3D milieu that can easily recapitulate the *in vivo* microenvironment of cells and tissues. The biomaterials components need to provide the matrix with an ability to mimic the *in vivo* culture conditions, while maintaining full control over the material properties.

Selective Non-Transformed Cell Growth

Controlling material properties is particularly important in the application of a biomaterial matrix for *in vitro* drug screening using tumour biopsies, because transformed and non-transformed cells require different features from their 3D culture environment for survival and proliferation. The matrix can provide a precisely defined combination of inductive (i.e. bioactive) and conductive (i.e. structural) features for the 3D culture of tumour biopsies. In this type of a culture milieu, the transformed cells are selectively sustained by controlling the relative inductive and conductive features of the matrix, whereas the survival of the non-transformed cells is minimised. Hence, the selective survival of tumour cells by this rationale is accomplished using simple design features of the biomaterials matrix, including the structural features of the matrix and the layered architectural arrangement of the material.

REGULATORY AFFAIRS

Main Challenges

Regulatory oversight is inevitable for medicinal products and devices that contain smart biomaterials. These products will have risks and costs will be significant. Thus, EU should have a **strategic view on their development and relevant regulations underpinning the EU research Agenda**. The role of regulatory oversight should be critically evaluated according to the principles of regulatory science - and adapted when necessary - balancing the needs of both innovation and health care. **Regulation should not be looked in isolation** but as a factor contributing to the acceptability of the products containing smart biomaterials by the health care system. The requirements for evidence of safety and efficacy do not come only from regulators but also from the end users and payers.

“The challenges of modern product development and globalisation underscore the critical importance of modernising and advancing regulatory science to match advances in basic and applied science and technology”. Major concerns also deal with “anticipating the risk and nature of product-related adverse events and to understand the mechanisms by which these events occur in specific individuals or subpopulations” (both citations from Advancing Regulatory Science at FDA, August 2011¹⁰).

Medical Devices

On 26 September 2012, the European Commission adopted a package on innovation in health consisting of :

- The Communication on safe, effective and innovative medical devices and in vitro diagnostic medical devices for the benefit of patients, consumers and healthcare professionals¹¹
- The Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) N° 178/2002 and Regulation (EC) N° 1223/2009¹²
- The Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices¹³

The new environment in the overall medical devices’ regulatory process has important implications for future Research & Development in the field, including biomaterials.

¹⁰ <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf>

¹¹ http://ec.europa.eu/health/medical-devices/files/revision_docs/com_2012_540_revision_en.pdf

¹² http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

¹³ http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

As a result of this package, several measures would be introduced to ensure the traceability and transparency of the devices, which will have important consequences for biomaterials that may be a part of them. They will be required to bear a European Unique Device Identification (UDI) (identifying specific product type and batch) and all operators must be able to identify all those involved in the supply chain. A number of major questions need to be integrated by future research projects that aim at translational research leading to eventual clinical use. These will concern conformity assessment, surveillance audits, testing and inspections, but also more detailed requirements addressing pre-market clinical evaluation and post-market clinical follow-up. Adaptation of classification rules, risk classification procedures and the reinforcement of clinical evidence requirements all contribute to a more complex regulatory scenario for medical devices in Europe.

The current European databank on medical devices (EUDAMED) will be extended and contain comprehensive information on all economic operators and products available on the EU market, with much information, including some of the foregoing, becoming publically available. This could be improved by having as part of this, a register as part of this of all implanted biomaterials. The establishment of a European biomaterials register would of immense use in tracking the clinical effect of all implantable medicals devices on the market. An example in orthopaedic surgery widely cited by surgeons, is the National Register of Prostheses in Sweden (<http://www.isarhome.org/statements>). The members of the International Society of Arthroplasty Registries have a shared purpose of improving outcomes for individuals receiving seal replacement surgery worldwide.

This will definitely apply to manufacturers of high-risk devices, who will be obliged to publish a summary of key clinical data and an EU portal will be created where all serious adverse events must be reported.

Medicinal Products regulation has been able to integrate major advancements in the use of biomaterials, including the more than 40 nanomedicines currently in the market with routine clinical use. Major problems still exist from the limited experience with exposure to novel biomaterials used in or as pharmaceuticals as well as new evaluation methods, standardisation issues or purposely design assessment for toxicological impact of new biomaterials, providing adequate tools for candidates' selection and translation to clinical trials as well as for final risk-benefit assessment.

Advanced Therapies

Biomaterials are expected also to play major contribution to the whole manufacturing process of pharmaceuticals in particular for the r-H-DNA and high technology ones and for advanced therapies. Of particular relevance has been the Regulation in Advanced Therapies Medicinal Products (ATMP), regarding at Tissue Engineering, Somatic Cell Therapy and Gene Therapy (Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004)¹⁴. The experience of the implementation of current regulation in ATMPs has provided evidence for the need to introduce a number of changes in procedures and rules. Also issues arising from combined ATMPs incorporating Medical Devices need to be adequately considered in the future in order for relevant innovation to be moved through clinical use.

¹⁴ http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

A major part of Horizon 2020 will need to deal with the requirements for translating KETs including biomaterials into the market. Efforts are needed to balance the needs of all stakeholders on a common ground on which to build the future regulatory framework. Assuring conformity with the appropriate regulatory path will be a major issue for a number of research projects from academia and SMEs. **Thereby the current and new framework should consider the need for a concrete action plan of integrative support to academia, regulators and industry, allowing them the opportunity to interact in a better and more efficient manner.** Regulators could play a role of catalysts of such interactions providing for an independent platform where knowledge sharing and formal support can take place.

Action Plan

An action plan should be implemented that encompasses the following three main axes (referred as “action plan 1”, “action plan 2” and “action plan 3” in annex):

- Regulatory Science framework
- Legislative and regulatory actions for medical devices and medicinal products including ATMPs
- Regulatory Affairs actions for promoting innovation access to relevant *fora*

Regulatory Science Framework

Major innovative developments need to be considered in specific areas of medical devices and medicinal products like those related to: devices incorporating nanomaterials; devices manufactured utilising non-viable human tissues or cells; biomaterials intended for use in pharmaceutical manufacturing processes or as part of finished medicinal products, combined products; genetic tests; ingested products; and others with need of better understanding of adequate regulatory requirements. In addition, “regulatory bridges” between Medical Devices, medicinal products and Advanced Therapies require a more in-depth consideration of the appropriate incorporation of new scientific developments into the development process and regulatory path.

Objective

Regulatory requirements should be considered even in those basic-research projects in which new biomaterials are developed from zero. This means that possible applications and their implications in terms of regulation should be set out in detail. Regulatory experts should be involved in basic research activities undertaken by consortia so as to raise awareness of the research decision implications in terms of regulatory path.

Regulation should not be looked in isolation but as a factor contributing to the acceptability of the products containing smart biomaterials by the health care system. A clear regulatory path should be set out as a requirement for proposal to be considered for funding. The requirements for evidence of safety and efficacy do not come only from regulators but also from the end users and payers. This comprises the full value chain from “bench to bedside”, including the manufacturing sector.

It will be necessary to support not only those actions within specific research projects that could contribute to innovation into facilitating access of new products to healthcare, but also to establish a stand-alone framework, that will bring together major relevant entities. The intention is to lead to a new and better methodology for standardisation, safety assessment and clinical evaluation and help to take appropriate stock of innovative scientific advances as and when they occur. This will not in any way replace current systems of regulatory approval.

A calendar and a path to establish a European Consortium with coordination activities financed within Horizon 2020 is therefore proposed.

The proposed action plan should incorporate main stakeholders of the sector including *inter alia* : the relevant services of the European Commission (DG RTD, DG SANCO - Medicinal Products, Medical Devices and Advanced Therapies sectors), the European Research Council (ERC), the European Institute of Technology (EIT), the Joint Research Centre (JRC), the European Medicines Agency (EMA), the European Federation of Pharmaceutical Industries Association (EFPIA), representatives of the Medical Devices Industry, patient organisations, the European Society of Biomaterials (ESB), the European Federation for Pharmaceutical Sciences (EUFEPS), European Society of Clinical Pharmacology, research-based Universities and the Small and Medium-Sized Enterprise Sector.

Legislative Actions

Within the next years and for reference this may be taken to mean the duration of Horizon 2020, a better coordination between existing European institutions will need to be promoted in order to identify critical issues for innovative products and therefore promoting needed updates within existing legislation and/or need for new measures and guidelines.

Objective

In this area, permanent coordination actions between the European Medicines Agency (EMA) and the European Commission Medical Devices sector, as well as integrating other relevant EC and European bodies (ERC, EIT, JRC), are to be considered as highly relevant. Legislative cooperation between European Commission, Council and European Parliament could also be improved through the use of already existing facilitation groups (e.g. the European Parliament STOA group roundtables on new technologies).

Regulatory Affairs Actions

Within existing mechanisms, specific initiatives need to be implemented in order to facilitate much further access to Scientific Advice, including discussion *fora* with EMA, European Commission and other relevant European institutions (European Commission DG RTD, DG SANCO, JRC).

Objective

An important achievement would be to widen the current fee reduction and waiver mechanisms for academia and SMEs, according to existing practices within the medicinal products and ATMPs sectors, and to extend this to the Medical Devices area and innovative combined products. The services of scientific advice and/or protocols provided by EMA should be recognised as an eligible cost for SMEs and End Users and be mandatory for projects going to TRL 4 or beyond.

In tandem with this, funded projects should clearly define whether the target is a Medical Device, an Advanced Therapy, a new drug or otherwise, to ensure a clear exploitation path. The regulatory and financial implications are so different that it cannot be left open to the research progress during the lifetime of projects. Products with similar features - whatever the regulatory regime – should have harmonised requirements.

Main deliverables expected by 2020

- Linking with existing **European Infrastructures**

A highly operational network of European institutions and research infrastructures (academic, industrial, patient organisations, etc.) should be put in place, to provide adequate support for innovation in biomaterials within the European Union and matching the best practices and facilities worldwide.

- Linking through **European Research Networks**

Promoting platforms linking through existing and new research networks, based in the excellence of research and their critical need for clinical use. This and the previous objective should lead a referential position of Europe in Biomedical applications for biomaterials.

- Access points to **regulatory support through national organisations and European bodies**

Due to the complexity of regulatory infrastructure in Europe, notably in the Medical Devices sector, the involvement of national organisations and notified bodies has to be considered along the process. A number of European institutions involved and referred above should take that issue as one of the institutional priorities, strengthening the existence of a pan-European network of competences.

Availability of new scientific knowledge should be enhanced as well as the development of appropriate new tools for fostering biomedical innovation and facilitating access of patients to new technologies, able to solve previously unmet clinical needs.

Vision to 2030

Looking at 2030 for a better integration of the European Union with other areas of the world (USA, China, Japan, etc.) should be considered to be a priority looking at more efficient manners to implement it. This needs to be adequately incorporated already in a number of new actions to start within the current period (2014-2020).

Regulatory Action plan (2014-2020)

Year	Action 1 Regulatory Science	Action 2 Legislative/Regulatory (guidelines) path for medicinal products, medical devices and ATMPs	Action 3 Regulatory Affairs path (promoting innovation access to relevant fora)
2014-2015	<ul style="list-style-type: none"> • Working group in Regulatory Science issues for Biomaterials (start 2013) • 2020 Roadmap for Regulatory Science in Biomaterials 	<p>Identification of critical issues for innovative products (update needed within existing legislation and/or need for new legislation) and establishment of an action plan for future updates.</p> <p>Use an independent platform to facilitate scientific knowledge sharing between innovators and Regulators of the relevant regulatory framework</p>	Work plan on facilitation of access to Scientific Advice including discussion fora with EMA, European Commission, other relevant European institutions (European Commission DG RTD, DG SANCO)
2016	Establishment of a European Consortium for Regulatory Science in Biomaterials (European Commission - DG RTD, DG SANCO – Medical Devices & Medicinal Products, ATMP, European Research Council, European Institute of Technology, Joint Research Centre, European Medicines Agency, EFPIA, representatives of the Medical Devices Industry, Patients Organisations, European Society for Biomaterials, EUFEPS, European Society of Clinical Pharmacology, Universities and Research Centres)		
2016	Start of Consortium (funding through Horizon 2020)		
2017			
2018			
2019			
2020	End of funding		

EDUCATION AND TRAINING

The need for and imminent arrival of smart Biomaterials for Health poses particular challenges in the field of education and training needs to respond to these challenges, which in some ways are unprecedented, in that it requires a combination or merging of research efforts both from a clinical perspective and that of a more fundamental, or laboratory-based nature. In other respects, it puts into sharp focus those challenges that already exist concerning medical education and training as a whole in Europe as well as in the wider world. These challenges affect not just medical graduates themselves and those in related professions, but also in terms of the required deliverables in the form of faster and greater benefits for patients.

The main obstacles relate to :

- curriculum designs that lack sufficient opportunities for interdisciplinarity as well as the possibility of research as a long-term career option,
- educational resources and strategies that need to be modernised so as to reflect new developments and challenges related to health care,
- healthcare systems that could be made more attractive for medical researchers,
- mutual recognition of degrees and so as to facilitate more effective international collaborations, while at the same time maintaining the highest possible clinical and quality standards.
- co-operation between academia and the industrial and clinical sectors
- the need for new private and public funding schemes that channel sustainable support into education and training programmes for medical researchers,

Curriculum Design

It might initially appear that the absence of research into the medical curriculum is more than compensated for by the dearth of researchers at PhD level in medical-related disciplines as well as by the great heterogeneity that often exists in individual countries within their own medical curricula. Nevertheless, this lack of disciplinarity reduces the comparability of medical degrees and diplomas between different countries, as well as opportunities for collaboration with these very other fields of knowledge with strong and not-so-strong links to medicine, such as different fields of biotechnology on the one hand, as well as business and management, social sciences, regulatory affairs and economics on the other.

Furthermore, the structure of – particularly undergraduate - medical degree courses is such that there is little or no time dedicated to the acquisition of research skills. This is certainly in contradiction to the post-graduate sphere, where major emphasis is placed on carrying out research and eventually publishing the results of these activities, in order to acquire credibility in a given therapeutic field. This is the norm in most if not all PhD programmes, where the requirement to publish peer-reviewed articles prior to defending a doctoral thesis has become increasingly popular across Europe, ranging from the highly advisable to mandatory.

Healthcare systems

Healthcare systems have a simple objective : to provide individually tailored resources and facilities that are dedicated to the health and well-being of the community at large. The enormous costs incurred in maintaining these services at an adequate level, not to mention keeping abreast of the latest technical and scientific developments intended for use in the population at large, leave little time for research activities as part of their remit. Nevertheless, research activities need to be tailored to operating within the constraints of healthcare system management which in turn need to become more user-friendly to research activities.

Diversity of Degrees and Diplomas

Great diversity of post-graduate qualifications in the medical research field exist within Europe. These take various forms, such as PhD (doctor of philosophy), DSc (doctor of science), MD (doctor of medicine), MSc (Master of Science) and parallel MD-PhD programmes. Whereas a great deal has been achieved in the medical field with the recognition of basic or primary medical degrees by member states of the EU, this has yet to be extended to the post-graduate field, where the mutual recognition of degrees is not at all automatic. This makes it difficult for medical doctors, particularly those with specialist qualifications as well as researchers in various medical-related disciplines to move freely between countries and to pursue a pan-European research career. These disparities in training standards often mean that specialist training acquired in one country is not recognised in others, leading to knock-on adverse effects related to salaries and social security and thereby make the exchange of professionals between countries even more difficult.

Educational resources and strategies

The major challenge that impedes the arrival of new smart biomaterials that facilitate the deployment and use of new therapeutic interventions is that none of the required educational and training resources are ever to be found in one single location. Not only are the required skills wholly of a scientific or medical nature, but there is also a need for economic, business management, IPR protection and administrative and regulatory expertise. At the same time, there is an ever-increasing need to comply with the highest research ethics standards and applicable regulations affecting both data protection, the use of any human specimen collections hosted therein and products that have implication for health and human services.

Disparities between academia and the industrial and clinical sectors

Perhaps the most important obstacle of all is the existence of time and human resource constraints within the clinical world as well as insufficient participation of researchers from other organisations and even closely related backgrounds in hospital-based research. This means that the right people do not get to work in appropriate new key domains work on the right ideas, duplication of existing efforts, inadequate usage of time and resources, all of which results in lost opportunities to improve European healthcare systems and place Europe at a sustainable pole position in key healthcare domains.

New private and public funding schemes

A shortage of funding as well as excessive duplication of efforts with the little resources available underlies all of the foregoing. In many countries, cutting-edge research facilities and infrastructures are largely the privilege of a few and therefore inaccessible to most physicians and scientists in training due to costs and other related issues. Furthermore, information about those resources and facilities that are adequate at national and pan-European level is often disperse and scant.

Policy recommendations for Improved Education & Training in Biomaterials for Health.

Whereas research is the basis for many if not most PhD programmes, especially in those related to Biomaterials, the acquisition of research skills needs to become an integral part of training, both at undergraduate and post-graduate level for medical students and for doctors. The degree of PhD should be given the same career merit as specialist training for doctors, which needs to incorporate hands-on, problem-based and systems-based approaches along with top-notch theoretical science-based training. Educational systems need to develop this combined approach which would offer more opportunities for candidates and increase the diversity in the choice of thematic modules and institutions. This would result not just in greater mobility and career choices, but also in practical skills acquired, facilitating a better response to the challenges that lie ahead.

Curriculum Development

Whether they are part of an MD or PhD programme, research curricula need to associate practical problem-solving systems-based approaches that are based upon solid scientific training in the health sciences.

These curricula need to be ambitious and to take account of the essential multidisciplinary nature of biomaterials research. This might also comprise modules in physics, chemistry, economics, regulatory affairs, ethics, management, business administration and law, as well as in those disciplines traditionally associated with biomaterials research.

Amidst the global explosion of information and greater accessibility to knowledge, on an ongoing basis, educational institutions could consider revisiting their role and leveraging on participatory technologies and other resources and approaches to better train medical researchers for the global interdependent context in which we live. Continuous professional development programmes for senior medical researchers as well as medical doctors should also become part of this exercise.

Educational resources and strategies

Mobility in terms of geography and interdisciplinarity need to be encouraged from the earliest possible stages in research careers. Common and internationally accepted principles regarding research integrity can help to devise appropriate principles for in and in this regard, existing programmes such as the Marie Curie Actions and the ERASMUS Student Exchange programme should be continued and expanded. Furthermore, pan-European organisations should be encouraged to establish common principles and sets of guidelines based on good practices and consensus. These would comprise European University Association (EUA), the Organisation for PhD Education in Biomedicine and Health Sciences in the European System (ORPHEUS), various divisions within the European Science Foundation as well as those of the European Institutions.

Mutual recognition of Degrees and Diplomas

A major objective for Europe should be the mutual recognition of degrees and diplomas. This should be based upon commonly developed standards for their global recognition, along with the development of Pan-European career-tracking schemes that can support the development of world-class quality standards in the field of biomaterials research.

A first step would be to develop a pan-European career-tracking scheme so as to support the development of world-class quality standards for Biomaterials. This will support and consolidate the classification and standardisation the different types of new and emerging biomaterials, as well as the excellence and overall competitiveness of European research institutions, as well as of researchers and their mobility within the EU. The development of common evaluation tools, reflecting both clinical and industrial needs so as to deliver required products of the highest possible standards to the bedside as soon as possible would be the first step in this process, leading to full harmonisation in the recognition of degrees throughout the EU. This has already commenced under the Irish Presidency of the Council of the European Union with the launching of the European Qualifications Framework (EQF). This aims to bring a common European reference to the national qualifications of different countries to enable individuals and employers to better understand and compare academic levels in different education and training systems. It will also ensure that education and training leading to qualifications that are referenced to the EQF are supported by robust quality assurance arrangements.

These might comprise making all evaluation criteria for MD-PhD public as devised above and that PhD jury panels for programmes within the biomaterials necessarily consist of :

- scholars and experts from institutions outside the home institution of the PhD candidate,
- at least one medical doctor, not necessarily a PhD holder and a well-recognised expert in a field pertinent to the PhD thesis under evaluation,
- a PhD holder who is also well-recognised expert in a field pertinent to the PhD thesis under evaluation,
- co-supervision of PhD programmes in Biomaterials by a medical doctor and a PhD holder as above,
- publication in peer-reviewed publications of the results of PhD research, filing of patents and other certification of such research in biomaterials, complying with recognised international quality standards.

Co-operation between academia and the industrial and clinical sectors

Academic institutions that offer degrees and diplomas related to medical research in all its forms, whether clinical or non-clinical, should develop more numerous and more active connections with public and private stakeholders, be they in their immediate regional environment or worldwide. These would comprise large and small industry, health care institutions, regulatory bodies, public administrations, research institutes and all other stakeholders with an interest in the research and production of biomaterials for health.

This co-operation may take whatever forms are required in order to achieve the common goal of appropriately-trained researchers in the field. This can range from formal didactic educational courses, e-learning, work placements and training programmes tailored to provide experience of future working environments, laboratory or field research joint projects, joint workshops, student and staff exchanges or joint publications. Existing initiatives, such as PharmaTrain, a part of the Innovative Medicines Initiative which aims to implement new and reliable standards for high-quality postgraduate education and training in Medicines Development with global impact and GRIP (Global Research in Paediatrics, which has similar aims for paediatric clinical pharmacology) will act as valuable references. Formal or informal groupings of academic and industrial concerns, or “technology clusters” that provide for the exchange of personnel, know-how and technical expertise as necessary within academic, clinical and industrial settings can also be considered.

Objectives

The educational and training challenges posed by the need for new smart biomaterials for health reflects the challenges that face education in medical research as a whole. The key challenges revolve around two main issues : a heterogeneous career progression system that does not take account of the interests of those participating in it and a corresponding lack of career development, as well as its inability as of yet to face the new challenges that confront it.

These comprise curricula design, the need for more modern strategies and resources, a closer involvement of healthcare systems and public bodies in medical research, a closer collaboration between industry and academia and greater mutual recognition of degrees and diplomas in the field of medical research.

Yet there is also a need to involve other stakeholders, such as other professions and disciplines linked to law and economics and to take into account current demographic, social and epidemiological changes, posed by an ageing population, increasing demands for even more scarce resources, etc. There will be a need for better governance structures, policy measures on a wider scale than before and a better allocation of resources. All stakeholders need to play a proactive role and to consolidate those improvements already in place.

SMALL AND MEDIUM SIZED ENTERPRISES (SMES)

Most of the research and development activities for biomaterials for health are performed at start-up companies and at SMEs that build on very specialised technical knowledge. This can be divided into three separate levels :

Levels of biomaterial research			
	Description	Objective	Characteristics
1	Concept phase (TRL¹⁵ level 1-2)	Generation of innovative biomaterials for innovative applications	low number of industrial partners, regulatory agencies and clinicians required (more in the position of an advisory board).
2	Product development phase (TRL¹ level 3-4)	Realisation of innovative ideas to product application	More important role of industrial partners in the project plus clinicians for pre-clinical phase (animal testing), certification aspects have to be resolved.
3	Clinical approval & certification phase (TRL¹ level 5-6)	Clinical (regulatory) approval & certification phase	High impact of industry, regulatory agencies, clinical trial centre & academia for accompanying scientific evaluation => essential for market introduction.

For these companies, collaboration with their peers in adjoining technical fields is a prerequisite for further development of their own technologies with a view to clinical application. The design of their final products should be driven by the specific clinical applications and by joint ventures. In this way, SMEs (and large companies) should specialise in the process optimisation of manufacturing and assembling of specific yet different components for the final product. Technical and clinical advancement in the field of regenerative medicine will therefore be driven in particular by these start-ups and SMEs, so any collaborative efforts at EU level should facilitate the participation, contributions and integration of these entities. Speed of biomaterial development and access to capital are essential requirements for SMEs, so any measure that will facilitate both will contribute to their further growth and success must be considered. In this respect, well aligned and transparent regulatory approval procedures at the EU level, also in comparison to regulation in e.g. the US and Asia, are essential to remain competitive at a global level.

R&D Institute for Regenerative Medicine

In addition to the many collaborative efforts (exchange of researchers, networking activities, formal cooperation of consortia in virtual institutes in projects aimed at clearly defined objectives) a real, physical institute on R&D and translation of regenerative medicine could further boost the development of the field in the EU. Currently we see the development of these dedicated institutes in the various member states. Also increased collaboration with existing large scale consortia and initiatives in e.g. the US (CIRM may serve as an example) or Asia is needed.

¹⁵ Technology Readiness Level

Short to Medium term Projects and Initiatives

The role of the SMEs and Industries in the field of biomaterials has to be implemented and sustained to bridge the gap – the so-called “Death Valley” - between research activities carried out in laboratories and the use of end products of which biomaterials are a part, in a clinic setting. To this end, it is necessary to take appropriate measures to cluster different SMEs with different but closely related specificities and specialisations into broad sectors. The creation of such hubs of excellence should help to focus and drive the downstream of product development towards the market. The involvement of the SMEs on the development of biomaterials would benefit from the financing of EU projects that present a medium to low risk on the materials production and on the material specifications. The risk analysis performed on the biomaterials developed represents a fundamental aspect to predict, to some extent, the potential of these biomaterials to reach the market. Project consortia that deliver a product ready to enter a clinical trial should have the possibility to obtain financing for a “continuation project” that launches this phase and speed up the product’s arrival at market.

This might be conditioned to suggestions made by a panel of evaluators to the required consortium (not necessarily the same than the original project) and the tasks to be fulfilled.

Health Technology Assessment (HTA)

A crucial matter for the route of Medical Devices and Advanced Therapies from laboratory to manufacturing and thence to market is the economical evaluation of their possible clinical use. The financial profile of companies becomes highly attractive when reimbursement from healthcare organisation has been made or is probable. Thus, a specific evaluation of possible modifications to the health systems organisations, savings, as well as patients, clinical and social benefits must be made and SMEs can and should be at the forefront of these initiatives. The addition of patient groups into project consortia alongside SMEs could represent a major advantage in attaining this objective.

The need for health technology assessment (HTA), and (or) “horizon scanning” preliminary procedure, is mandatory for new biomaterials, especially when included in Advanced Therapy procedures. **This should be examined at an early research stage as part of a proposal.** The biomaterials already proposed for osteochondral lesions, for example, greatly increase the costs of knee surgery. It is probable that the use of collagen-based biomaterials could improve disease management and reduce the overall healthcare burden of disease, but HTA is necessary for a clear demonstration of this aspect. This process is similar for Medical Devices. Generally speaking, nanomaterials used as “drugs” (combined with pharmacological substances) or industrialised materials (cartilage or collagen) are often made economically attractive for third payer by “private” assessments. A public and transparent appraisal is acknowledged, while HTA methodology is present in many countries and regions of Europe, even harmonized by EunetHTA¹⁶ network. The accurate economical evaluation of possible savings, together with patient benefits, will make biomaterials more attractive, as well as the financial profile of SMEs that are responsible for their research and development. A major problem related to high-quality, innovative materials is because their implementation is not economically viable, especially in an area where the SMEs represent 80% of the market, which is about 10% of the market overall.

¹⁶ EUnetHTA - European Network for Health Technology Assessment

Long-term projects

In the field of long-term projects, where high-risk is counterbalanced by high-gain, the role of SMEs might not be focused so much on the production and marketing of the product but on the development of standards, on the regulatory issues connected with the development of the projects and solve the issues related to issuing of marketing authorisations. In this sense, the guidance of EU authorities seems necessary and it would be appropriate to expand and extend the range of services currently available to SMEs from the European Medicines' Agency so that they can fulfil this role more efficiently.

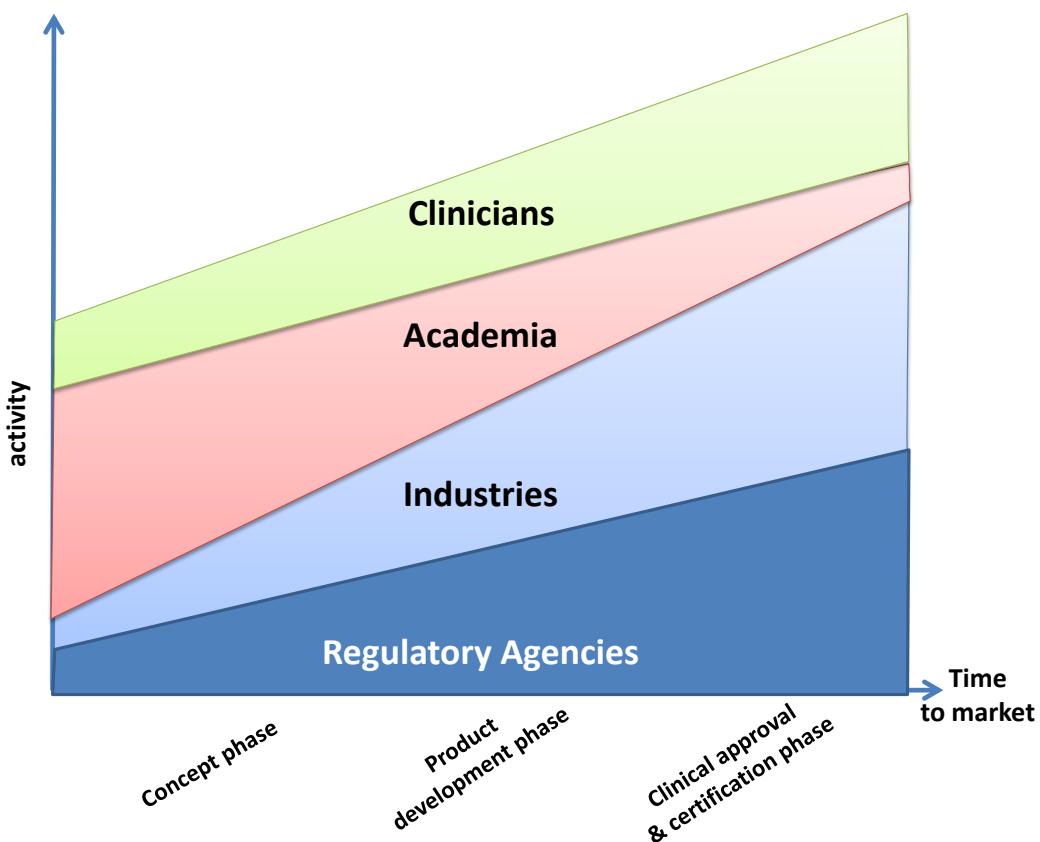


Fig. 1 : involvement of the various stakeholders in in biomaterials research

Services and Incentives offered by the EMA to SMEs

Because biomaterials for health will find application in Advanced Therapy Medicinal Products (ATMPs) and Medical Devices, which are regulated (and will be regulated) at European level and because they are often developed by SMEs, these innovative companies may benefit from the pooling of scientific expertise at EU level. This comes in the form of financial and scientific incentives available from European Medicines' Agency (EMA), comprising a substantial 90% fee reduction for scientific advice, so as to encourage SMEs to seek advice from the EMA on all issues relating to the development of new medicinal products, with a view to maximising the chances of a successful marketing authorisation. The scientific advice thus received can and should form part of Grant Award Applications. Therefore, as well as bringing the necessary research and innovation expertise to projects, SMEs can facilitate the acquisition of the required regulatory advice needed for a successful project and an eventually successful Marketing Authorisation Application.

The EU incentives offered by the Agency apply to both the human and veterinary sectors, and for the human sphere, these include:

- Regulatory, administrative and procedural assistance from the Agency's SME office;
 - Fee reductions for scientific advice, scientific services and inspections
 - Fee exemptions for certain administrative services of the EMA;
 - Deferral of the fee payable for an application for marketing authorisation or related inspection;
 - Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
 - Certification of quality/non-clinical data for advanced therapy medicinal products (ATMPs) intended for human use;
 - Translations of the product information documents submitted in the application for marketing authorisation;
 - Waiver of the MedDRA licensing fee when registering with EudraVigilance. This is only available for micro- or small enterprises and not for medium-sized enterprises;
 - Inclusion in the public SME register.
-
- *For innovation in human medicines: iftsecretariat@ema.europa.eu*
 - *For innovation in veterinary medicines: vetapplications@ema.europa.eu'*

Scientific Advice

At any stage of development and irrespective of eligibility to use the centralised procedure for marketing authorisation, sponsors can request scientific advice from the EMA for both human medicinal products. SMEs are particularly encouraged to initiate an early dialogue with the Agency before submitting a Grant Award Application, to obtain scientific advice. This helps the applicant to ensure that the appropriate tests and studies are carried out within a potential project, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing authorisation application. Such major objections can significantly delay the eventual marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the Agency's advice, therefore, increases the probability of a positive outcome.

For human medicinal products, scientific advice is given by the EMA's committee for medicinal products for human use (CHMP) on the recommendation of the scientific advice working party (SAWP-H).

Guidance on how to put together a request for scientific advice for these products is available on the Agency's website. Detailed information on how to apply, including a template for notifying intent of submission, submission deadlines and details of the programme for EMA-FDA parallel scientific advice are available on the EMA website.

The Agency offers assistance to applicants in putting their scientific advice requests together through free pre-submission meetings. SMEs are strongly recommended to request a pre-submission meeting or teleconference at the time they notify their intent to file the request.

Scope of scientific advice

Scientific advice should be sought on the tests required to support an application for marketing authorisation for a medicinal product in the areas of:

- quality (chemical, pharmaceutical and biological testing);
- non-clinical/safety (toxicological and pharmacological tests);

It is also now possible for sponsors to approach the EMA and National Health Technology Assessment (HTA) bodies in parallel to discuss scientific advice/protocol assistance. HTAs provide information to decision makers about the clinical effectiveness, cost effectiveness and broader impact of medicines, medical technologies and health systems. Sponsors considering such parallel requests are advised to contact the scientific advice secretariat (scientificadvice@ema.europa.eu). This would have implications for the eventual impact of a scientific proposal. EMA scientific advice can also be given parallel to the FDA scientific advice or combined with advice from an HTA body.

Certification of Advanced Therapy Medicinal Products

As an incentive to develop Advanced Therapy Medicinal Products (ATMPs), an SME can submit to the EMA, the results of studies carried out within a Grant Award Application to demonstrate the quality and non-clinical safety of ATMPs and their components and request evaluation and certification of the data, independently of any MAA. Although not legally binding, the certification procedure should facilitate the evaluation of any future application for clinical trials and marketing authorisation based on same data.

The certification procedure for ATMPs, which is open exclusively to SMEs, provides a mechanism for companies to receive scientific feedback on quality and non-clinical data generated during the course of development. As such, it provides support for companies seeking to attract investors for the continued development of their product or to license out their technology and is highly recommended in the context of Grant Award Applications.

The aim of certification is to facilitate dialogue between SMEs and the regulators ideally at an early stage in development and is complementary to the scientific advice process. Whereas, scientific advice provides feedback on future development proposals and protocols, certification provides a scientific evaluation of experimental data already generated with the product and its components. Through certification, companies can receive a “snapshot” of their data evaluated to the current review standards for marketing authorisation. Companies can then seek scientific advice on how to resolve any deficiencies that may have been highlighted during the certification assessment.

An SME can submit an application for certification containing either quality data alone or both quality and non-clinical data at any time during the development process of an ATMP. The process can be repeated as development proceeds. The procedure for certification consists of a 90 day review by the CAT with the possibility to request clarifications on the data submitted during the review.

Regulatory Requests

Scientific advice is restricted to purely scientific issues. Regulatory requests should be the subject of separate advice from the EMA and can be sent to the SME office.

The major need is to shorten the regulatory processes. This means doing right things at the right time which is a major challenge for the developers, especially for SMEs. When the regulation is tuned to the products containing smart biomaterials, **it should be considered as a continuous process following closely the product development**. The development of most innovative products containing biomaterials is carried out in SMEs rather than in large established companies. The fact that companies that have scarce regulatory expertise are operating within the most complex regulatory framework may create bottlenecks in the translational phase, i.e. between the discovery and clinical development phases.

In general, the most effective regulatory tool therefore is the scientific advice that increases the predictability of the final regulatory requirements and improves the likelihood of a positive outcome. EMA scientific advice can also be given parallel to the FDA scientific advice or combined with advice from an HTA body. Scientific advice is given to companies that will seek for it and that are able to formulate relevant questions.

As well as the SME office, the EMA has also established an **Innovation Task Force (ITF)** to facilitate the early contacts with SMEs and offers informal free-of-charge Briefing meetings with applicants. These cover regulatory, technical and scientific issues arising from the development of innovative medicines, new technologies and borderline products. **These meetings are intended to facilitate the informal exchange of information and the provision of guidance early in the development process.**

The ITF arranges these meetings within 60 days of receipt of a valid request from an applicant. The discussions are led by experts from the Agency's network, working parties and committees, with the best available scientific expertise being represented. **Briefing meetings are intended to complement and reinforce existing formal regulatory procedures**, such as "Advanced Therapy Medicinal Product (ATMP) classification and "certification, designation of orphan medicinal products and scientific advice.

Inclusion in the public SME register

Access to the fee reductions and deferrals outlined above will be subject to the applicant company's SME status being assigned by the EMA and remaining valid on the date that the fee falls due for the relevant application or procedure. Financial incentives cannot be applied retrospectively.

If a product is out-licensed to another company during a procedure, the SME office at the EMA should be informed immediately. If the company licensing in the product does not meet the SME criteria, there will be no further access to the provisions of the SME regulation with effect from the date of the licensing agreement. Any fees shall no longer be subject to fee deferral pursuant to article 5 of the SME Regulation.

SMEs and Continuous Professional Development (CPD)

A significant number of tools, computational, mechanical and increasingly biological, used for implant testing are developed within SMEs who face specific challenges in terms of:

- investment in new service & products (finance and people);
- the necessary broad expertise with which to add value to and diversify from the core products; and,
- personnel retention due to uncertain career paths

whilst at the same time being the key element in intervention testing process. The issues around added value may be tackled through a combination of specific continuous professional development in the context of a focused research project – what could be termed an SME-focused Marie Curie Scheme employing persons with 3-6 years research experience (i.e. to doctoral level), based in SMEs but with access to academic support within leading research groups. This could be effected through a small number of ESRs and focused training which would award credit in line with the ECTS. Such a scheme would attract high value researchers into the SME environment, allow effective translation from the academic to industrial base and allow the SMEs to focus on developing structures for career progression and training. In any case, greater flexibility than in previous schemes will be required.

Objectives for the SME sector

- Promote collaboration with peers in adjoining technical fields,
- Promote clustering of SMEs with different specificities and specialisations into special interest groups or sectors, generating hubs of excellence to drive the downstream of the product development towards the market
- Promote SME collaboration with academia, research institutes, large industry into specialised networks, public-private partnerships,
- Promote collaboration with existing large scale consortia and initiatives e.g. US or Asia (China, Japan),
- Promote greater access to capital :
 - Develop a novel business model between partners of projects, supported by experts that can be subcontracted on a greater
 - Make Calls for Proposals more “development oriented” rather than “research oriented”, thus promoting SME/Hospitals collaboration, giving product design a place of importance, including SMEs (or entities recognised as subcontractors) with testing accreditations as mandatory partners, asking for risk analysis and regulatory dossiers configuration
- Extend the range of services offered by regulators to SMEs
- Enhance access by SMEs to Commission funding so as to cover expenses related to infrastructural outlays e.g. clean rooms, etc. as well as other Commission programmes that facilitate guarantees and counter-guarantees for financial intermediaries (e.g. guarantee organisations, banks, leasing companies) to help them provide more loan and lease finance to SMEs,
- Assign specific roles to SMEs in research and innovation projects :
 - Short to medium term actions : production and marketing of biomaterials, act as interface with regulators, assume responsibility for user-friendly IT tools for a given clinical application, including product design, functional simulation, manufacturing processes, etc.,
 - Long term action : assist on the development of industrial standards, regulatory issues related to the development of biomaterials,
- Allow projects that were successful in the preclinical phase by delivering a product ready to enter a clinical trial (or first testing in humans) to obtain additional financing by launching calls for “Continuation projects” for these clear success stories, to overcome the “Death Valley” and reach the market.

VENTURE CAPITAL INVESTMENT

Attracting venture capital investment into biomaterials research in the future presents a particular series of challenges that will need to be addressed in the context of Horizon 2020 and can be divided into a number of levels.

Overall profit margins from venture capital investments do not always generate great returns. This is particularly true in the case of biomaterials for health, which find major application in Medical Devices and Advanced Therapies, since market entry is restricted and takes a long time. Even after achieving this, maintaining that market acceptance can equally become a major long-term exercise. Building profitable growth can often take years of investment, therefore making any decision to invest seem daunting.

In the next level, biomaterials are but an integral and smaller part of an eventual Advanced Therapy and Medical Device. These are naturally positioned at the back end of the product-delivery-value chain, beginning with an initial prototype of a biomaterial and ending with a viable commercial product, which is very expensive and time consuming. The industry is required to operate as a low margin business in the case of medical devices, but in the case of Advanced Therapies, it remains to be seen if this in itself would become a high margin commercially attractive business, if the commercial claims made prove to be sufficiently strong and well documented with acceptable side effects and meet a long-term medical need.

The industry is dominated by a handful of large Original Equipment Manufacturers. This is a natural consequence of being exposed to the very strong general price pressures that are to be expected in a highly competitive market, as well as more specific concerns related to differences in reimbursement decisions that are taken at a purely national level, which fragments the market further and making entry into it more difficult. This is compounded by the fact that it often requires large-scale clinical trials, which are expensive undertakings and have a failure rate estimated to be between 30 and 50%. Technical risks such as these, which are aggravated by an incomplete understanding of both how the relevant body system works and the effect of the therapy on it, can live with a company for a very long time. Another complicating factor is the ever-present risk that in the case of failure, either due to innate technical flaws or the arrival of a newer smarter competitor, leading to the entire value of a company disappearing overnight.

Matching the stages of “Technology Readiness” to the initial stages of technology investment under H2020 is critically important in order to ensure that H2020 can deliver a series of VC investible technologies over the next 10 years, which will in turn lead to the creation of more SMEs in Europe over the next decade or which will improve the commercial prowess of existing SMEs. For this reason, clear value-added milestones in the form of definable progress in terms of concrete results will be needed in Call texts. This might constitute proof of concept, building a prototype, or make a market study or to protect an IP with the target of licensing or transfer the technology, which could be a medical device, a new treatment, some active principles, etc.

Biomaterials for Health

At the present time, venture capital funding is focussed now only on large and long-term commercial opportunities, characterised by otherwise unmet clinical needs in large niche markets. There seems to be little hope for investment in biomaterial development, where the main therapeutic interest is in a final product, of which the biomaterial is but an integral and sometimes non-functioning part. Strong IPR protection seems to be an absolute must, covering the biomaterial itself, its destination product and/or production with freedom to operate in a niche field. Smaller patent portfolios may need to be licensed out to larger industrial players.

Venture Capital and SMEs

Much attention needs to be focussed on the role of SMEs. The context of innovation in the biomaterials and medical products fields has strongly evolved in recent decades. The classical framework of the development of a technology in academia that created a start-up putting a product on the market is no longer the case, since the innovation environment has become much more complex with several start-up and SME profiles with different business models now in existence.

Several start-ups exploit a single technology coming from an academic laboratory. These start-ups usually develop the technology until the point they are sell to a bigger company. Usually these start-ups benefit from the use of their parent university laboratories and facilities. Due to an uncertain future for this kind of company, 50% close their doors after 5 years, if they are not absorbed by a bigger player in the meantime, so investment in these companies is risky.

Another type of start-up is that with big capital resources, from exploiting several technologies and putting rapidly some secondary products one the market (e.g. Tigenix, Cardio 3 BioScience, Carmat). These start-ups become rapidly SMEs with great innovation and research potential. Funding these companies is also not without risk, but this is proportional to the gains to be made in case of success. These companies need big amounts of funding but the perspective of becoming leaders in their market field are significant.

The last type of company is the well-established SME that turns out classical products but still with a good potential for innovation. These companies are more financially stable as their business does not depend solely or largely on a capacity to innovate. Funding innovation projects coming from these companies often makes a pragmatic investment. The innovation products coming from these companies are usually not revolutionary ones but answers to a therapeutic need and have a good market penetration.

It is important to support the first profile of start-ups to get access to capital, joint ventures or other kind of liquidities allowing them to get the necessary competencies to growth and develop their products until its marketing authorisation.

The second model of start-ups and the SMEs are of course focus on processing, regulatory and quality issues, marketing and commercialisation. However, most of them have structured research services adapted to put product on the market (as these researchers know quality and regulatory issues related to this specific market).

No company possess all competencies and capabilities to perform all required development and tests. To facilitate the creation of consortiums including all profiles required to put a product on the market is necessary. Particularly in the present as new developments are more and more technical and complex. Projects should all include clinicians and hospitals as they will be the technical and commercial future costumers.

Considerations for SMEs in Horizon 2020 Project and VC investment

In order for SMEs to attract VC investment, they should have a strong underlying patent / IP estate; where possible an accompanying freedom to operate (FTO) report verifying the strength, novelty and inventiveness of the patent estate. Their technologies should be developed at least to design freeze stage with appropriate biocompatibility or DVT testing; preferably have initial first-in-man (FIM) clinical data supporting the technology.

The following should be prepared by an appropriate qualified expert in the target industry sector as part of a Grant Application :

- a forward-looking consideration of the way forward post-Horizon 2020 funding, timelines and costs to get to regulatory approval (e.g., CE mark or FDA 510(k) or PMA approval) and initial product commercialisation/ roll-out in target territories – ideally such a report might be prepared by a future CEO or management team that will lead the start-up of a new SME arising from the H2020 project,
- a clear business plan with strong /defendable business model and clear financial perspectives,
- a global market analysis and competitor analysis report;
- a health technology assessment report as well as economic benefit report;
- a global survey of clinicians, market strategists, payers, hospital administrators and other stakeholders that will address the ability of the technology output to address unmet clinic needs,
- a regulatory report as well as a reimbursement report addressing the likely regulatory path and reimbursement strategies in different territories,
- where relevant a report on where the H2020 funded technology could be manufactured, possible challenges on scale-up and manufacturing, identity of relevant CROs/service providers, sourcing of components,
- where relevant, a survey of patient advocacy groups (likely to be limited to certain disease areas only where such groups exist and are informed and interactive).
- evidence of engagement with or feedback from different market strategists on the perceived benefit(s) and market/product opportunities of H2020 outputs on a global basis,
- where possible, evidence of strategic collaboration opportunities and/or strategic validation of the H2020 technology outputs.

H2020 should provide financial and marketing support to show-case biomaterial technology outputs at relevant international medtech and biotech conferences in Europe and USA. In addition, H2020 such develop showcase events to showcase new emerging technologies on the global stage. Furthermore, H2020 should develop events to showcase new emerging technologies to “recycling entrepreneurs” as well as develop an active database of recycling entrepreneurs which may in the future lead the spin-out of H2020 technology outputs.

Objective

It is therefore necessary to sponsor and organise a large-scale conference to define better the problems as outlined above and suggest ways to overcome them, so as to promote greater venture capital investment into biomaterials research.

Suggested solutions ad interim might be to increase the financial attractiveness of the SME sector by implementing appropriate measures such as those outlined above.

CLINICAL APPLICATIONS

Biomaterials have already demonstrated successful applications in many diseases by means of classical approaches (scaffolds, implants). Nevertheless, in order to progress further in the field of clinical applications move a step further in the field – particularly to meet current disease challenges in an aging population, research, development and innovation in biomaterials will require more interdisciplinary approaches that will allow to design smart-bioresponsive systems with capability of support (classical biomaterial concept/scaffold), drug delivery (where nanomedicine in particular polymer therapeutics, and novel drug delivery hybrid systems could play an important role) and regenerative capability (stem cell therapy).

Taking this into consideration, the main challenges to overcome are:

- To design multifunctional biomaterials offering the 3 requirements (support/drug delivery/stem cell therapy). To learn and understand how to ensemble this hybrid construct to enhance therapeutic output.
- To understand better disease processes so as to be able to design rationally the smart-bioresponsive hybrid constructs, ranging from the initial selection of the polymer to be deployed, up to the combination of bioactive agents (for example, to be released in a controlled manner) and cells to be implemented.
- A smoother and faster transition from laboratory to clinic – the “Death Valley” that must be crossed. To achieve this objective, regulatory requirements (safety issues, risk-benefit, manufacturing: scaling up, batch-to-batch reproducibility, etc.) need to be considered from initial design phase onwards.

Biomaterials for Cardiovascular Disease

Cardiovascular disease is the most frequent cause of death worldwide, with ischemic heart disease being the single most common condition accounting for the death toll. The lifetime risk of developing chronic ischemic heart disease (CIHD) is estimated at 20% in the population over 40 years of age, with 30% and 60% of patients dying after 1 and 5 years of diagnosis, respectively. CIHD currently represents a 1-2% of the overall costs of the healthcare system, and this figure continues to rise every year.

In the European Union alone, this translates into more than 4.3 million people who die every year from chronic ischemic heart disease with direct and indirect costs that exceed €192 billion annually. Furthermore, changes in demography will have a key influence on the epidemiology of cardiac pathologies. It is estimated that of the world's population aged 60 years and over will reach 2 billion in 2050 (three times more than in 2000). Another complication is that according to the WHO, in 2005 there were 2.3 billion people around the world with a body mass in the overweight or obese range. Taken together, this means a huge increase in the numbers of those with chronic ischemic heart disease in the next 40-50 years.

Current available treatment for diseased blood vessels, heart valves and myocardium include: organ transplantation from one individual to another, tissue transfer from a healthy site to the diseased site in the same individual (such as coronary artery bypass with autologous vein and Ross operation) and

replacement by using artificial prosthesis (including synthetic vascular grafts, mechanical and biological valves and left ventricular assist device).

However, each of these methods presents serious limitations: autografts can produce complications at the donor-site; synthetic prostheses present the risk of infection, lack of biocompatibility, limited material durability and they cannot follow the growth in paediatric patients; transplantations are limited by the low number of donors and the need for life-long immunosuppressive therapy. More importantly, all of these treatments do not allow full regeneration and functional recovery, therefore reducing patient's life expectancy and quality of life.

An example of an Advanced Therapy, tissue engineering, aims at the development of biological substitutes that restore, maintain, or improve tissue or organ function, is emerging as an alternative approach to treat cardiovascular diseases. This strategy can potentially offer significant advantages: it can be a permanent solution, a cost-effective treatment in the long term and it does not have any need of supplementary therapies.

Two different tissue engineering approaches can be followed. In the more traditional *in vitro* tissue engineering approach, stem cells are seeded on a preformed scaffold, the tissue is matured *in vitro* in a bioreactor and then implanted in the appropriate anatomic location as a prosthesis; in the *in situ* approach, unseeded scaffolds, functionalized to attract endogenous cells and to control their proliferation and differentiation, are implanted to repopulate and remodel an altered cardiovascular tissue directly in the patient body. If the *in situ* regeneration is the most market-attractive, since biomedical industries prefer technologies that do not involve handling of patient cells, the *in vitro* tissue regeneration is the most convenient and promising therapy for elderly and sick patients, with impaired stem cell function and regenerative capacity. Therefore, both strategies should be investigated to assure market penetration and overall impact.

Promising alternatives for cell replacement therapies are defined populations of resident cardiac stem/progenitor cells (which can be isolated from the adult human heart, expanded *ex vivo*, and show multipotent differentiation ability into cardiac-restricted cell lineages), and human pluripotent stem cells (induced pluripotent stem cells in particular, for which tremendous advances are being made to address their safety concerns). These concerns are summarised below.

Cells being tested for Myocardial Regeneration ¹⁷		
Cell Type	Advantages	Disadvantages
<i>Embryonic Stem Cells</i>	<ul style="list-style-type: none"> • Divide for indefinite periods • Evolve with cardiac myocyte action potential 	<ul style="list-style-type: none"> • Major ethical opposition • Possibility of teratoma formation
<i>Bone marrow stem cells</i>	<ul style="list-style-type: none"> • Feasible and safe in humans • Readily prepared in hospitals • Possibility of "off-the-shelf" use 	<ul style="list-style-type: none"> • Pluripotency uncertain • Limited success in clinical trials
<i>Skeletal myoblasts</i>	<ul style="list-style-type: none"> • Readily obtained • Low risk of tumour formation • Survive and differentiate in human hearts • Align parallel with host cardiac cells • Resistant to ischaemia 	<ul style="list-style-type: none"> • Do not form gap junctions • Ventricular arrhythmias in clinical trial
<i>Cardiac Stem Cells</i>	<ul style="list-style-type: none"> • Cardiac origin • Differentiation into all cardiac lineages • Readily obtained at cardiac biopsy • Clinical trials under way 	<ul style="list-style-type: none"> • Cardiac stem cells isolated from an ageing heart may not sufficiently improve function
<i>Induced Pluripotent Cell</i>	<ul style="list-style-type: none"> • Readily obtained from skin and thus less invasive • Closely resemble embryonic stem cells • Differentiate into all cell lines • Regenerate myocardium in animal studies 	<ul style="list-style-type: none"> • Potential for malignant transformation

Key elements

Both *in vitro* and *in situ* tissue engineering are based on three key elements:

- the scaffold, which serves as a guiding structure for tissue development;
- the cell source from which a living tissue is grown;
- the signals that guide cell behaviour.

As a consequence, the success of tissue engineered replacements depends on a multidisciplinary approach.

In this multidisciplinary approach, biomaterial science and technology play a central role, being based on the study of the interactions between the material and physiological environment. In order to satisfy the requirements coming from tissue engineering applications, the development of biomaterials has evolved through three stages: bioinert materials (first generation); bioactive materials (second generation) and materials designed to stimulate specific cellular responses at the molecular level (third generation). The latter two collectively comprise the *smart biomaterials* for cardiac regeneration.

¹⁷ Rangappa S, Makkar R and Forrester J; J Cardio Phar Ther; Nov.2010

Starting from mid 1990s, an increasing effort has been devoted to the development of biomaterials for cardiovascular tissue engineering and significant advancements have been made. However, several challenges still exist. The complexity of cardiovascular tissue requires careful attention to a large number of design parameters, including scaffold architecture, chemical composition, mechanical properties, biofunctionality, rapid vascularisation, electromechanical coupling with the surrounding tissue. However, most of the studies carried out until now have been focused only on one or two aspects at a time. Moreover, addressing all of the requirements for engineering functional cardiovascular tissues is challenging, because different aspects of design often conflict with each other.

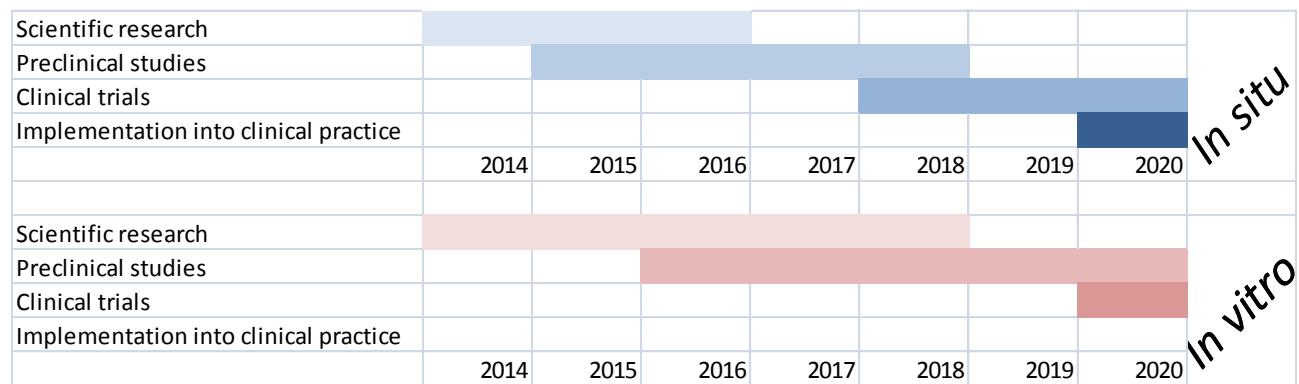
In order to overcome these challenges, suggested actions should include: research projects involving interdisciplinary teams, partnerships between academia and private sectors, improvement of dialogue with end users and stakeholders, creation of European cardiovascular tissue engineering networks.

At the same time a number of more general challenges need to be addressed :

- The development and/or improvement of those biomaterials that are capable of reducing the invasiveness associated with the use of the above interventions without diminishing the high level of clinical care of current and conventional approaches. This would not only improve the results and reduce the cost of the treatment of current patient populations, but would also increase the number of patients who could have access to such treatments, thereby improving their quality of life
- The development and/or improvement of materials capable of achieving :
 - Perfect hemocompatibility, in order to minimise interactions with blood components and to reduce costly and invasive pharmacological treatments;
 - Perfect biocompatibility, so as to increase the durability and lower the risk of rejection of implants,
 - Life-long mechanical resistance: so as to increase durability in those clinical conditions of a critical nature
- Development of materials and therapies capable to deal with some currently unsolved issues, in particular the cure of ischemic myocardium and the cellular regeneration of myocardial scars still represent a challenge.
- The identification and development of therapeutic platforms with a global view so as to take into account the increasingly complex pathologies linked to an ageing patient population.

Last but not least, research projects on cardiovascular tissue engineering can contribute to the upgrade of the relative European Regulation. As a consequence of the uncertainty related to the regulatory patterns to be associated to these new technologies, many working groups have been created at EU level in order to find solutions which can improve/shorten the procedures, without impact on patients' safety. The involvement as consultants in research projects can be extremely helpful for these working groups, in order to understand better the problematic/designs/progresses of these new technologies and to reach consensus on the best possible regulatory patterns.

The roadmap for the translation of cardiovascular tissue engineering strategies into clinical products is illustrated in the figure below. The increase of scientific, regulatory and commercialisation difficulties determines a delay in the timeline of *in vitro* tissue engineering products, with respect to *in situ* tissue engineering products.



Biomaterials for the Central Nervous System

Biomaterials in the Central Nervous System are chiefly used in

- shunting systems for hydrocephalus,
- cortical neural prosthetics (CNPs), i.e. electrical stimulation of the diseased brain
- drug delivery systems in the CNS,
- hydrogel scaffolds for CNS repair, and
- neural stem cell encapsulation for neurotrauma.

Cerebrospinal Fluid (CSF) Shunts

CSF shunt systems are the most common treatment for hydrocephalus, but have a high failure rate. The most severe problems for ventricular catheters are shunt obstruction and infection. Prolonging shunt longevity relies on the improvement in catheter materials. A major technical challenge to be overcome is to develop antimicrobial-impregnated catheters from biomaterials and to modify their surfaces so as to reduce cell and bacterial adhesion, which can lead to a reduction of the rate of ventricular catheter failure. Another approach can be the use of neural prosthetics to improve the shunt performances.

Cortical Neural Prosthetics (CNPs)

Recording-based CNPs hold great promise for the treatment of a wide variety of movement disorders (Parkinson's disease, etc.). However, their long-term performance is often compromised by the formation of glial scar tissue around them. Local administration of anti-inflammatory drugs from microfluidic channels or bioactive coatings of the neural prosthetics, which are derived from biomaterials, therefore have the capacity to manage the cellular and tissue responses in their surroundings and this represents the greatest promise to improve the long-term stability of chronically implanted neural electrodes. An additional opportunity is the seeding of individual-specific (autologous) iPS-derived neurons and/or glial cells within the biomaterial coating the neuroprosthetics for enhancing their fitting and thereby minimizing the long-term aversive reaction of the host tissue.

Drug Delivery

Drug delivery into the CNS is challenging due to the presence of the Blood Brain Barrier (BBB). One strategy to overcome it is local delivery of drug via biocompatible polymers. This approach offers the advantage of local exposure to drugs at therapeutic levels while at the same time eliminating the adverse events associated with systemic drug exposure. This method has been successfully used for treatment of recurrent malignant brain tumours. However, the surgery for polymer implantation is invasive and drug delivery at therapeutic levels over the long term is difficult to achieve, which limits the application of local drug delivery. Systemic drug delivery, in which drug can be repeatedly administered as required, provides an alternative strategy. Penetration through the BBB and reduced systemic side effects can be managed by active targeting. However, systemic exposure to the drug is not avoidable at this stage. Since both drug delivery systems have advantages and disadvantages, the selection of appropriate drug delivery carrier is dependent on the nature and location of the disease.

CNS Regeneration

The big challenge is to develop better hydrogels, which are bioscaffolds used to improve tissue regeneration and CNS repair, owing to their tissue-like mechanical abilities that are conformable to the soft CNS tissue that will surround them. This is a naturally porous structure allowing for cell infiltration, transplantation and axonal outgrowth and the gel assumes this characteristic allowing for this process to continue. The ability to gel *in situ* is an additional, important and desirable property for hydrogel scaffolds so that they can fill conformally the irregularly shaped lesion cavities, avoiding the need for intrusive implantation surgery. What is also needed in the future in addition to this property, is the potential to attach adhesion and/or growth-promoting molecules that promote cell attachment and tissue growth and a capacity for drug/gene incorporation and delivery.

Neural Stem Cell Encapsulation for Neurotrauma

While implantation of exogenous neural stem cells remains the treatment of choice for neurotrauma (e.g. spinal cord trauma), it faces serious problems, the most important of which is the host immune response. This occurs in neurodegenerative conditions, such as multiple sclerosis and amyotrophic lateral sclerosis, which requires patients to continue taking medicines for sustained immunosuppression, but which also reduces the viability of implanted stem cells. In addition, when vast amounts of tissues are lost and a cystic cavity is formed, the ability of the implanted cells to reconstitute the tissue and reconstitute the connections is limited. The survival of the cells is also affected due to a large distance (if more than a few hundred micrometres) to the nearest capillary.

An alternative strategy is to improve the cell replacement therapy, by increasing the cell viability and reducing the acute host immune response. This derives from the creation of three-dimensional bioscaffolds that encapsulate neural stem cells. Studies in this area are classified into two categories: *in vitro* studies for evaluating stem cell proliferation and differentiation on the biomaterial scaffold and *in vivo* studies for evaluating the interaction of scaffold seeded with stem cell with the host tissue and the function recovery of the host. Further progress is needed to determine the required properties of the bioscaffold that facilitate implantation of the stems cells *in vivo* and to modulate the host immune response sufficiently well to allow for tissue regeneration to take place.

Objectives

Biomaterials play a role in delivery of drugs and/or bioactive molecules can be used to treat tumour and neurodegenerative diseases, reduce inflammatory tissue response and promote tissue regeneration. Advanced Therapies can be used to treat neurodegenerative diseases and promote tissue regeneration. Hydrogel scaffolds are mostly used for supporting tissue regeneration in the CNS and their potential for tumour therapy is also under exploration.

As each strategy has its own advantages and limitations, several strategies need to be combined for treatment of neurological diseases or injuries. For example, so far the treatments for tumours in the CNS mostly focus on delivery of chemotherapy either locally or systemically to the tumour site. Combined drug delivery, gene therapy and encapsulation of native as well as induced (iPS-derived) neural stem cells into *in situ* gelling hydrogel scaffolds can be used not only to prevent recurrence of surgically removed malignant tumours but also to promote neural tissue regeneration into the cavity at the same time so as to achieve functional recovery. Combination of sustained release of anti-inflammatory agents and neurotrophic factors from CNPs and their coating with iPS-derived neuronal cells may improve neuron-electrode communication, and lead to long-term functional stability of these implanted devices.

Thus, while each strategy shows promising results, the major challenge in biomaterials for health is to achieve desirable combinations of multiple strategies as outlined above which may lead to more successful regeneration and recovery in CNS repair.

Biomaterials for Orthopaedics

As in the cardiovascular field, in orthopaedics, three different generations of biomaterials have been defined¹⁸: bioinert materials (first generation), bioactive and biodegradable materials (second generation), and materials designed to stimulate specific cellular responses at the molecular level (third generation). These generations are chronological, but conceptual, since each generation represents an evolution, which is still ongoing and which is still expected to evolve further, in function of the requirements and properties of the materials involved. This means that at present, research and development is still devoted to biomaterials that, according to their properties, could be considered to be of any of these generations.

First-Generation biomaterials

As well as being among the earliest of the biomaterials for health, intended for use in dental applications, as well as replacement parts of the skeleton, first-generation biomaterials are inert, and developed to serve mainly mechanical and physical purposes. The products based on these biomaterials have demonstrated major therapeutic potential in the diagnosis and treatment of diseases. First-generation biomaterials are characterised by the appearance of a layer of diverse unspecific proteins adsorbed on their surface after implantation. The effect of this leads to a rather nonspecific chemically-mediated signalling process to the cellular environment. The consequence is that a layer of fibrous tissue grows on the material surface, and with time the implant becomes totally encapsulated by such fibrous tissue. The development of bioactive interfaces eliciting a specific biological response and avoiding any fibrous layer has been one of the main driving forces in second generation biomaterials.

Second-Generation biomaterials

The second generation of biomaterials can be considered to have appeared between 1980 and 2000. This was defined by the development of biomaterials' ability to interact with the biological environment so as to enhance the biological response and the tissue/surface bonding, as well as by the development of bioabsorbable materials' ability to undergo a progressive degradation while new tissue regenerates and heals. Functional bioactive materials incorporating various layers or zones with different properties designed to fulfil a specific function are also under development.

Third-Generation biomaterials

Third-generation biomaterials are meant to be new materials that are able to stimulate specific cellular responses at *molecular* level. For these biomaterials, the bioactivity and biodegradability concepts are combined and bioabsorbable materials become bioactive and vice versa. Examples include temporary three-dimensional porous structures that stimulate cells' invasion, attachment and proliferation, as well as functionalised surfaces with peptide sequences that mimic the ECM components so as to trigger specific cell responses. The capability of processing the biomaterials by different technologies, the effect of the processing on the biomaterials properties and on the implants performance should be established. Deliveries of biochemical factors and medicinal drugs, as well as control of cell behaviour through mechanotransduction are some fields of interest.

¹⁸ Hench, L. & Polak, J. 2002 Third generation biomedical materials. Science 295, 1014–1017.

Biomaterials for Diabetes Mellitus

The ultimate goal for all diabetes research is effective long-lasting glucose normalisation for both type I and type II diabetic patients at levels comparable to those achieved by intensive insulin therapy in the Diabetes Control and Complications Trial (DCCT)¹⁹. Despite improvements in insulin pharmaceutical efficacy and delivery methods, this approach has still major limitations that impact significantly on patients' quality of life. Islet transplantation of allogeneic cadaver pancreatic islets into an immunosuppressed recipient is regarded as the most promising alternative to insulin administration, but its use is currently confined by the limited number of available donors and by the side effects of pharmacological immunosuppression. There are alternative cell-based therapy approaches under development that include the use of xenogeneic islets (e.g., porcine) or engineered, immortalised beta cell lines or other cell types. Regardless of the cell source, all these potential cell therapies require immunosuppression or immunoisolation to avoid graft rejection as well as protection from the hypoxic and oxidative stress that occur during the early phases of implantation. There is a consensus among experts that **clinical application of cell therapy for diabetes will depend on immunisolation, immunoprotection and grafting methods as an enabling technologies.**

Whether the cellular therapies comprise patient-specific or "off the shelf" and ready-to-use procedures, two classes of intervention may be identified :

- Delivery vehicles, with cellular elements immobilised within specifically engineered biomaterials, usually within a medical device and which become active once that biomaterial has become degraded and absorbed. Such a biomaterial would possess immunoprotectant properties that would minimise the immune response mounted against transplanted cells and enhance both their survival and functional activity.
- Tissue-Engineered Products that are designed to replace and remodel damaged tissues as part of an *in vivo* process of integration and reconstruction. Three-dimensional scaffolds are needed to fulfil the requirements for mechanical stability as well as structural integrity that mimics that of the surrounding healthy tissue.

¹⁹ "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". N Engl J Med. 1993 Sep 30;329(14):977-86 329 (14): 977-86

Biomaterials for Infectious Diseases

Integrating viral gene delivery with engineered biomaterials is a promising strategy to overcome a number of challenges associated with virus-mediated gene delivery, including inefficient delivery to specific cell types, limited tropism, spread of vectors to distant sites, and immune responses. Viral vectors can be combined with biomaterials either through encapsulation within the material or immobilisation onto a material surface. Subsequent biomaterial-based delivery can increase the vector's residence time within the target site, thereby potentially providing localised delivery, enhancing transduction, and extending the duration of gene expression. Alternatively, physical or chemical modification of viral vectors with biomaterials can be employed to modulate the tropism of viruses or reduce inflammatory and immune responses, both of which may benefit transduction. Biomaterials may be employed to promote viral gene delivery technologies, potentially providing opportunities for numerous applications of gene therapy to inherited or acquired disorders, infectious disease, and regenerative medicine.

Biomaterials are employed in the manufacture of medical devices and implants, as well as contributing to preventing infections associated with them. The devices range from easily inserted and retrieved contact lenses, urinary catheters and endotracheal tubes to surgically implanted cardiac valves, hip joints and coronary stents. All suffer a common problem of device-related infection resulting in morbidity, at least, in the patient, but with considerable mortality also recorded for some devices. The attendant extended hospital care and drug costs impact greatly on health budgets. Increasingly, manufacturers are turning their attention to combating this device infection problem by developing what are variously described as 'antiinfective', 'bioactive' or 'antimicrobial' devices, which usually entails coating them with antiinfective solutions, thereby ensuring their viability on the long term. The development of biomaterials with antimicrobial properties in the bulk, as alternatives to surface coatings, will expand the number of applications of the novel biomaterials to several clinical applications.

Biomaterials are involved in the field of nanomedicines, where novel approaches to drug delivery centre on the development of biomaterial based nanoscale particles or molecules that improve drug bioavailability. This entails a better concentration of drug at the required active site, for a longer period of time and away from other areas, thereby also reducing long term toxicity. This finds application in the treatment of drug resistant infections as well as poverty related diseases such as malaria and tuberculosis.

Biomaterials for Ophthalmological Use

Biomaterials are extensively and increasingly used for the treatment of ophthalmological disorders. In the developed economies of Europe, the need for optimal vision for all, particularly the elderly, require more effective treatments for conditions such as myopia and presbyopia, such as long duration contact lenses. Taken together with corneal implants, biomaterials will play a significant role as part of the research and development efforts needed. With the growing incidence of myopia in the young and the availability of newly introduced extended (overnight) wear contact lenses there will also be a growing tendency to prescribe contact lenses for children of school age.

Safer ophthalmic biomaterials are therefore of increasing importance both to the young and the old. The major challenge to overcome is that there is no existing ophthalmic biomaterial at present that exhibits a satisfactory degree of ocular biocompatibility for long-term use.

Ophthalmic Biomaterials for the Elderly.

This is increasingly linked with the problem of ageing. The ageing process of the healthy tear film is poorly understood because studies of the ageing eye are invariably associated with abnormality – disease, disorder or adverse events. As part of studies of ophthalmic biomaterials a greater knowledge is therefore required of the ageing healthy tear film, with appropriate biomarkers that can be used to identify an early departure from healthy ocular physiology to the pathological state as well as the complications of disease elsewhere – such as diabetes mellitus - that have potentially serious implications for healthy vision.

Contact lenses and the Artificial cornea.

There will be a growing need to design and develop ophthalmic biomaterials – for contact lens and therapeutic ocular bandage use for example – that are more compatible with the ageing eye/ ageing tear film. There would be many advantages in being able to prolong contact lens wear for existing wearers as their age advances and the problems of ocular discomfort due to marginal dry eye lead to discontinuation of wear. Advances in these areas will help to respond to the ultimate challenge in ophthalmic biomaterials: the artificial cornea.

Drug-Eluting Contact Lenses

In addition to conventional contact lens wear there are many potential advantages in the development of contact lens-based ocular drug delivery systems – especially for the older population. As an example, glaucoma is a chronic optic neurodegenerative disease that affects 67 million people worldwide. Its origins involve multiple factors and can lead to a gradual degeneration of retinal ganglion cells, diminution of the visual field and acuity and eventual blindness if left untreated. Many drugs are rendered ineffective in the treatment of this disease due to the inability to effectively deliver and sustain them within the eye. The major obstacle to targeting the eye with therapeutics in general is the presence of various barriers such as the epithelium tear film and the conjunctiva, which control the concentration and entry of solutes into the eye.

Additionally, drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctival absorption, the relative impermeability of the corneal epithelial membrane, and blinking act to reduce the residence time of topically applied molecules. Therefore, it is clear that simpler, more effective method of delivery of drugs, which lead to better patient compliance would have both financial and quality of life benefits. Chronic ocular conditions, such as glaucoma, require long-term pharmacological treatment. Frequent dosing often leads to compliance failures. It is widely recognised that this is an excellent potential application for the use of controlled-release, drug-eluting contact lenses.

Biomaterials for Wound Healing

No models of an artificial nature exist at the present time that can completely replicate normal uninjured skin. Natural biopolymers such as collagen and fibronectin have been investigated as potential sources of biomaterial to which cells can attach and begin the regeneration process, but the process has been hampered by a continuous inflammatory reaction, leading to fibrosis and scarring and an incomplete regeneration process. The first generation of degradable polymers used in tissue engineering have been adapted from other surgical uses, not originally intended for this activity and therefore have drawbacks in terms of mechanical and degradation properties.

This has led to the development of synthetic degradable gels primarily as a way to deliver cells and/or molecules *in situ*, the so-called "smart matrix" technology. Yet in order to achieve complete regeneration, the inflammatory response that has occurred in the first place, has to be attenuated so that the extent of fibrosis and scarring is diminished. The challenge therefore is to identify those cytokines and other molecules expressed during regeneration and incorporate them to create a smart biomaterial-based matrix for use in a skin equivalent. Recent advances in the use of DNA microarray and proteomic technology are likely to aid the identification of such molecules. When associated with other recent advances in biomaterial-based non-viral gene delivery and stem cell technologies, this may also contribute to novel approaches that would ultimately generate a skin replacement whose materials technology was based not only upon intelligent design and the molecules involved in the process of regeneration, but also the biomaterial scaffolds that allow these therapeutic interventions to function.

Biomaterials for Theranostics & Implant Monitoring

Theranostics refers to the combination of disease diagnosis and disease treatment. Biomaterials are highly appropriate tools for theranostic purposes, since they can be easily co-functionalized with diagnostic and therapeutic agents. Many different theranostic materials have been developed recently. These in particular include image-guided nanomedicines, such as liposomes, polymers and micelles, which are submicrometer-sized carrier materials designed to improve the biodistribution and the target site accumulation of low-molecular-weight (chemo-) therapeutics. Upon intra vascular administration, nanomedicines circulate for prolonged periods of time, and they accumulate in tumours and at sites of inflammation via enhanced permeability and retention (EPR) effect. The EPR effect, however, is a highly variable phenomenon, with large differences between different patients and different types of tumours.

Consequently, there is an obvious need to incorporate imaging moieties into nanomedicine formulations, to visualise and quantify EPR, to identify patients presenting with sufficiently high levels of EPR, and to thereby preselect patients likely to respond to EPR-based treatments. The combination of drug targeting and imaging can also be used to non-invasively monitor drug release from nanomedicine formulation, and to longitudinally assess their therapeutic efficacy. Besides for drug targeting, theranostic constructs and concepts also hold significant potential for implementation in tissue engineering. Both the cells and the scaffold materials employed for tissue engineering purposes can be labelled with contrast agents. By using such theranostic tissue engineering materials, non-invasive and quantitative information can be obtained on their localization, resorption, remodeling and function.

Biomaterials for Women's Health

Among the many diseases affecting human health, female related reconstructive surgeries require unique consideration of anatomical and histological structures. Such reconstructive surgeries are warranted following mastectomy, pelvic floor prolapse, and individual forms of genital malformations such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. The aetiology for most female genital malformation is still unknown. Established surgical therapies exist to correct certain malformations, but in complex malformations like cervical and partial vaginal aplasia, there is still no ideal implant that could replace missing or malformed genital tissues. Additionally, many materials used in breast reconstruction have come under fire with product re-calls and formations of excessive granulation tissues. Tissue engineered constructs, designed specifically for the female anatomy, have yet to be fully optimised.

There is a clear need for the creation of tissue-engineered constructs that can suitably replace female-specific tissues. The development of biomaterial-based constructs ranging from the assessment of the *in vivo* biomechanical properties and geometric considerations of breast tissue and urogenital tract tissue should provide a robust and clinically translatable product that can successfully function as a biomaterial replacement in the field of women's health.

Biomaterials for Health

Other Clinical Applications

Body System	Clinical Application of Biomaterials
Skin & connective tissue	<ul style="list-style-type: none">• Artificial skin, sutures, burn dressings• Breast implants, other cosmetic applications• Artificial blood substitutes
Musculoskeletal system	<ul style="list-style-type: none">• Bone, sutures, ligaments, cartilage
Central & Peripheral Nervous system	<ul style="list-style-type: none">• Heart pacemaker• Drainage of AV hydrocephalus or cerebrospinal fluid• Nerve guidance channels
Endocrine system	<ul style="list-style-type: none">• Micro encapsulated parcreas cells (Langerhans)
Cardiovascular system	<ul style="list-style-type: none">• Artificial heart valves, blood vessels (large, small)
Oxygen transport	<ul style="list-style-type: none">• Perfusion equipment
Gastrointestinal Tract	<ul style="list-style-type: none">• Sutures
Genitourinary Tract	<ul style="list-style-type: none">• Dialysis machines, catheters
Intelligent medical devices including electronics	<ul style="list-style-type: none">• Medical diagnosis

CONCLUSIONS

Biomaterials for Health will play a major part in shaping the future of Advanced Therapies and Medical Devices, as well as in many other applications not yet defined. A number of technical, administrative and clinical challenges exist, all of which need to be dealt with in the coming years and by harnessing the facilities available under the proposals for the Horizons 2020 programme. The objectives to be realised are entirely consistent with those set out in the Europe 2020 and Innovation Union programmes, which will lead to a longer – and better - quality of life for European patients and people as a whole.