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Angiogenesis-inducing Bioactive and Bioresponsive Scaffolds in Tissue Engineering

Rendicontazione

Informazioni relative al progetto

ANGIOSCAFF

ID dell'accordo di sovvenzione: 214402

[Sito web del progetto](#) 

Progetto chiuso

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Final Report Summary - ANGIOSCAFF (Angiogenesis-inducing Bioactive and Bioresponsive Scaffolds in Tissue Engineering)

Executive summary:

ANGIOSCAFF was a partnership of 33 different opinion leaders in regenerative medicine that collaborated from December 2008 to November 2012 on a portfolio of 110 portfolio projects. These projects focused on early stage preclinical development of cutting edge regenerative therapies for the eventual treatment of the major age related and genetic degenerative diseases that result in tissue dysfunctionality and decline in contribution to our society.

Project Context and Objectives:

The context of regenerative medicine

Degenerative diseases represent a significant proportion of chronic, progressive and often fatal diseases with profound human and societal costs for which there are no effective therapeutic approaches and are associated with a progressive decline in tissue function that share many hallmarks of ageing. They create a life-altering experience for the afflicted person, for their partner, parents, siblings, and children. The progressive diminishment of body functions associated with the diseases can cause depression and loss of self-esteem. Given the diversity of degenerative diseases, pathological manifestation can occur at any age: either as a child, during an individual's most productive years, or more frequently as an aged person. There has been an increased prevalence of degenerative diseases with the growing aged population, which has stimulated a growth in the need for effective, affordable and widely applicable therapies. Over the past 50 years, average life expectancy at birth has increased globally by over 20 years, from 46.5 years in 1950-55 to 65.2 years in 2002. Today there are 600 million people in the world aged 60 years or over, and this will double by 2025 and reach 2 billion by 2050. The economic impact of morbidity in this population represents a significant burden, which requires effective and rapid solutions.

The material

Biomaterials are an important part of the medical device industry, and now they are becoming more prevalent as scaffolds in the development of sophisticated therapeutic products, such as sustained drug delivery therapeutics. To date, the choice of scaffold in these applications has largely been dependent on predicated biomaterials, but increasingly, with advancement in biomaterial science, custom scaffolds are being developed with specific properties needed for a particular application. Emerging strategies employ the design of materials that allow release of active factors 'on demand' e.g. enzymatically-triggered release of active factors to optimally meet therapeutic requirements. Design of new materials that meet specific performance criteria is, however, still a challenge. It is currently not possible to freely choose among components that should be assembled/connected into materials. Equally challenging is the development of design principles for new materials based on understanding and quantification of the relationship between the scaffold characteristics - such as molecular composition, morphology and physical properties - and the in vivo outcome.

Defining the bioactive factor

To a large and increasing extent, defining the optimal delivery of bioactive factors is premised on the early processes that occur during development. The reason is that this is when growth, spatial and structural characteristics are defined in the tissue, and a potent mix of factors (materials, cells and growth factors) lays the foundation for a functional tissue during a 9 month gestation, that has to fully functional at birth and remain this way for another 70+ years.

In mammals, once development and growth are completed, many organs such as the brain and the heart, have limited ability to regenerate following acute or chronic damage from trauma or disease. This is despite the fact that these organs have grown in size from birth to adulthood due to the presence of residual stem cells which divide very slowly to permit growth. Such stem cells are found in each organ: the lung, the brain, the skin etc., but they are clearly not normally capable of permitting extensive regeneration. This is because the developmental signalling pathways that were involved in initial building of the prenatal tissues have been switched off or down-regulated to a lower level in cells at the completion of development which has been matched with a number of inhibitory factors (inflammation and scarring) which are required in the adult to ensure adequate protection from the environment following damage and thus the survival of the individual.

The cell

Human tissues can self-repair in response to moderate injuries, but are not able to regenerate when significant loss of tissue occurs in extensive trauma or surgery. Similarly, they cannot sustain repeated cycles of degeneration/regeneration. Reconstructive strategies, such as autologous cell transplantation and injection of progenitor cells yield only modest therapeutic outcomes, mainly because the tissue often presents an inflamed or sclerotic environment that results in poor survival and only modest integration of engrafted cells that are also targets of an immune reaction. Moreover, the in vitro cultivation history of the grafted cells can also negatively affect the efficacy of cell transplantation, although this may be prevented by culturing cells on biomaterials. Among the new therapeutic strategies for several age related and degenerative diseases, stem-cell transplantation is becoming a promising clinical option.

ANGIOSCAFF

The design of bio-interactive therapies is therefore critically dependent on the understanding of how relevant cells interact with natural materials as tissues form and remodel in-vivo, in response to corrective stimuli. The aim is to fabricate the basics of each tissue (then let cells take over), as opposed to hoping that cells will start the process themselves, with the intention to speed them along later, and restore tissue functionality. This requires that sufficient nutrient is provided to the tissue via angiogenesis to enable growth matched with providing tailored stimuli to the tissue itself to enable a complete functional restoration.

Project Results:

High impact results

Portfolio project design and implementation in which 3 to 4 teams were working together on each project within the total project map resulted in 110 different projects ongoing between the partners which generated significant innovations with high impact in the regenerative medicine, degenerative disease field of endeavour. Below we indicate those innovations which will have game changing impact in the short term development of state of the art therapeutics; while we do not report on the extensive amount of insights and fundamental knowledge generated by the partnership which will serve as a long term reinforcement for our continued innovation in this sector.

1 - Biomaterial design

6 biomaterial platforms were generated based on Fibrin, PEG Peptide, Fibrinogen Polymer, Hyaluronic acid, Porous scaffolds or Calcium phosphate. Each material had specific nascent properties which lent itself to application to the different tissues we were aiming to repair. Leveraging the expertise of the biomaterial teams, all of whom had extensive prior knowhow as illustrated in Table 2 we set about optimising their preparation, integrating in biofunctionality and design directly related to the known needs to achieve a tissue functional restoration.

All the underlying design of the materials were already patent protected and owned by the teams themselves; extension of use of the materials and optimisation of their design was defined as the optimal approach for both adding value and generating potential portfolio[s] of intellectual property around each material; secondary IP generated as part of ANGIOSCAFF would be dependent on the underlying IP owned by the scientists and therefore further protect the inventions.

i) Development of the Fibrin scaffolds

We developed a technology to customize fibrin which incorporated bound morphogens within the fibrin meshwork and permitted a controlled release to direct cellular behaviour through a target-specific biofunctionality. This involved generating a transglutaminase sequence bridge that could link the morphogen to the fibrin which would be cleaved in situ by endogenous enzymes.

We could link synthetic peptide or recombinant protein morphogens with the trans-glutaminase sequence (NQEQVSPL: TG sequence) that bound to the fibrin during coagulation under the enzymatic influence of the coagulation transglutaminase factor XIIIa.

Every component of the technology (Fibrin, morphogens, and other parameters such as thrombin, factor XIIIa) were designed to be modifiable depending on target tissues, assay conditions. For example neural cells prefer soft gel, while myoblasts prefer a slightly harder gel.

ii) Development of the Fibrinogen polymer hybrids

The Fibrinogen polymer (composed of a hybrid of Fibrinogen and PEG molecules which are activated by UV light stimulation) had originally been designed as a stand alone material (no morphogens) to be used to enable bone repair; in line with the project strategy, modifications were performed to enable application in other tissues and potentially incorporate morphogens and other cell stimulating factors (chemical entities and hormones). After confirming that the Fibrinogen polymer system permitted extra factors to be included and that these factors could be sustainably released over a 6 hour period we optimised the system by editing the weight of the PEG molecules, and therefore density in the hybrid composition and confirmed biomorphogen release by integrating in VEGF, where we demonstrated that modifications to the hydrogel network structure which alters its density permitted a gradual release from the Fibrinogen Polymer.

iii) Development of the Hyaluronic acid systems

Hyaluronic acid (HA) is a highly versatile naturally occurring extra cellular matrix protein which can be extensively edited for tissue targeting and repair. We developed a novel system consisting of cross-linkable multifunctional HA derivatives, capable of forming a gel in situ in less than 5 min simply by mixing of the two HA solutions. This system could be tailored to address the specific characteristics of the tissue to be targeted.

iv) Development of the PEG-Peptide hybrids

The PEG gel with heparin sites that was already developed (Hybrid materials consisting of heparin and star-shaped PEG) were tailored so that variations in physical characteristics and biomolecular functionalization formed by cross-linking of the amino end-functionalized star-PEG with EDC/sulfo-NHS meant that the heparin component could be functionalized through covalent attachment of cysteine-containing peptide such as cell adhesive RGD peptides, and non-covalent heparin.

v) Development of the Porous scaffolds

Controllable Porous scaffolds based on a slurry to solid transition phase of PLGA/PEG was components was created. Type 1 particle (polymer or ceramic) and Type 2 particle (PLGA/PEG) can be mixed with aqueous carrier, making the type 2 adhere to type 1 particles which following resolidification form strong adhesion bridges between other particles, then the porous structure is stabilized.

vi) Development of the Calcium phosphate scaffolds

First generation calcium phosphate(CaP) ceramics and biodegradable polyactic acid/CaP glass porous composite scaffold (PLA/glass) were engineered by rapid prototyping which produced mechanically resistant and geometrically well defined scaffolds and extracellular matrix like fibred scaffolds. Rapid prototyping consists in the layer by layer deposition of the material in order to fabricate 3D structures according to a predefined design.

2 - Engineered morphogenic biomolecules

To enable the biomaterials developed to be effectively biofunctionalised with the broadest possible spectrum of growth factors (both commercially and non-commercially available) we developed a linker protein which was based on the TG domain linked to recombinant fibronectin (FN) fragments corresponding to the FN 910 domains, wild type FN 910, the structurally stabilized FN 9*10 (mutation at Leu1408 to Pro), wild type FN 10 containing fibrin binding sequence (transglutaminase substrate sequence NQEQVSPL), and a FN fragment with a promiscuous growth factor binding domain (GBD).

3 - Engineered blood vessel growth

Induction of blood and lympho-angiogenesis are critical for obtaining complete functional restoration of damaged tissue. During the course of the project we were able to obtain fundamental knowledge about blood vessels development, develop translational approaches and novel screening platforms to accelerate the design of biomaterial-morphogen combinations.

4 - Innovative imaging

The advances made in developing regenerative approaches necessitated optimized tools for clear pre-clinical demonstration of effect in animal models. Imaging in the preclinical setting is vital to measure and assess tissue repair and has to be comparable to those used in the human clinical setting which are routinely based on using X-rays via a technique termed Microtomography, abbreviated to micro CT, which is used to generate 3D images of the tissue being analysed. An example of a micro CT image is indicated in below.

5 - Soft tissue repair therapy development

From the outset, we aimed to create new soft tissue repair strategies that would address the the shortfalls of existing therapies designed to treat skin burns, trauma, venous insufficiencies and potentially diabetic ulcers (arguably the most difficult to treat of the soft tissue diseases). This predisposed that effort be focused on addressing the correct signalling required via matrix-displayed bioactive factors which would create such advanced therapies.

6 - Bone repair therapy development

We developed practical therapeutic materials for bone repair with materials/biomolecular therapeutics and

used these materials as a quantitative, designed and controllable platform for probing hypotheses regarding the fundamentals of osteodifferentiation, osteogenesis, and bone repair, with an emphasis on the role of angiogenesis in these processes. Our outcomes were both translational (to induce bone repair) and fundamental (to develop material and molecular tools for understanding osteodifferentiation, osteogenesis and bone repair more deeply).

i) Fibrin

The multi- domain fibronectin fragment (FN III9-10/12-14) simultaneously binds integrins and growth factors which were bound the matrix via the FN fragment and evaluated for their retention in fibrin gels and their ability to promote bone repair. Preclinical development indicates the potential for the use of the FN fragment (FN III9-10/12-14) to allow growth factors, in this case BMP-2 and PDGF-BB to be bound to the healing matrices and that the addition of the FN fragment increases bone tissue deposition in calvarial defects through the recruitment of bone progenitor cells.

ii) Fibrinogen polymer

The use of the fibrinogen polymer for supporting bone regeneration was very successful. The hydrogel is easy to use as it is photo-polymerized in situ and appears to degrade almost completely in 8 weeks. The controlled release of matrix bound BMP-2 generates superior bone formation as compared to the material only in both a subcutaneous ectopic bone formation, in which bone marrow with hematopoietic and mesenchymal stem cells was generated, and in cranial defect repair.

iii) Hyaluronic acid

Hyaluronic acid (HA) hydrogels were functionalized to allow for the attachment of a fibronectin (FN) fragment and loaded with BMP-2. The formed hydrogels were injected subcutaneously into rats to measure bone formation. After 8 weeks we had shown that linking of the cell-adhesive fibronectin fragment resulted in more homogeneously distributed bone tissue (such bone tissue should be less fragile thus excluding the risk of further fracture), which may be due to infiltration of the surrounding pluripotent cells into the corresponding hydrogel material.

iv) Porous scaffolds

The PEG-PLGA-PEG porous scaffolds are very conducive for bone regeneration; they are temperature-sensitive, highly porous, have strong mechanical properties, are biocompatible and degradable. The use of BMP-2 with porous biomaterials were tested for establishing their ability to support bone formation. The scaffolds effectively released BMP-2 in assays, are cell adherent and induced osteogenic differentiation and proliferation. Regeneration of bone in preclinical models is achieved when they were implanted in cranial defect models. The porous biomaterials evaluated in combination with BMP-2 are advantageous for bone healing, with the absence of BMP-2 also inducing significant bone repair, indicating that very low doses of BMP-2 could be used.

7 - Cardiac tissue repair therapy development

Chronic heart failure (CHF) post- myocardial infarction (AMI or MI) is the consequence of a deficit in functional myocardial contractile cells (myocytes), which are not replaced by any of the clinical therapies presently in use. Cardiac regenerative approaches to fill this necessity have been proposed. These regenerative therapies have been mainly based on different versions of autologous cell therapy. Several of them have been clinically tested but most have been proven to be only marginally effective, if at all. Unfortunately, even if their efficacy were to be significantly improved, none of these protocols (including the most promising use of autologous cardiac stem cells) could solve the severe public health problem, have a measurable impact in the everyday clinical setting, or affect the natural course of the disease. Given the high demand in time, human and economic resources, these techniques can only benefit a very small fraction of the candidate patients. Even with improved clinical efficacy, autologous therapies based on extracting cardiac stem cells would fail to satisfy the criteria of affordability, be readily available to treat the acute phase of the disease, and would remain inaccessible for treatment in the majority of clinical centers.

In order to develop effective cardiac therapies and significant improvements in the treatment of injured myocardium, focus was placed on the integration between novel tissue engineering biomaterials and the development of induced pluripotent stem cells (iPS) technology. Injectable biomaterials were considered the best approach to act as cell carriers in the ischemic area, and also prevent associated cardiac remodelling, which would improve cardiac mechanical properties. By utilising a cell-reprogramming technology this would permit us to obtain autologous differentiated cells, such as cardiomyocytes (CMs), directly from somatic tissue which together would address the practical barriers and socioeconomic need.

Induced pluripotent stem (iPS) cells were obtained after neonatal CMs reprogramming which were comparable to murine ES cells in the expression of cardiac associated transcription factors. Microarray analysis of global gene expression in iPS cells derived from the cardiac compartments identified upregulation of genes directly involved in cardiogenesis. Preliminary screening revealed that Fibrinogen Polymers (FP) proved to be the support for the CM-derived iPS, which tested in myocardial infarct models to assess efficacy.

8 - Nervous tissue repair therapy development

Development of regenerative approaches to neural disease focused on traumatic injury to the nervous tissue itself, predominantly manifested as spinal cord injuries in humans, which is where we placed our focus. Recent human clinical work has demonstrated that correct application of stimuli at the site of injury, within hours of the injury occurring, matched with long term rehabilitation can alleviate some of long term outcomes of the injury. The hypothesis is that the initial correct treatment prior to tissue rehabilitation has to be tri-partite. There must be an anti-inflammatory/anti-fibrotic component, as the damaged tissue is rapidly infiltrated by scar tissue which stays and blocks the rejoining of the fibres; there must be an angiogenic component to rapidly restore a functional blood supply to the tissue to permit it to repair and there must be some level of instruction to the undamaged neural tissue to enable them to rejoin with the broken neural networks.

Compared to the four other sectors of application within ANGIOSCAFF, which have all received extensive focus in the regenerative/repair field, in the neural field, this focus of research is very much in its infancy as

concepts and approaches to treating such injuries have had to be reconfigured which meant that conceptually developing therapies would start from a blank canvas.

Initial effort was focused on identifying the best 'soft' biomaterials for the neural tissue itself; adult Dorsal Root Ganglia (DRG) explants were grown on starPEG-heparin gel and different fibrin gels. DRG neurites had an increased length of 50% in both PEGylated fibrin gel and FN-GBD and FN-910-GBD gel when compared with negative control. With the use of heparin gel, the length of DRG neurites increased by an additional 20%.

PEG arrays were used to test different FN9-10,12-14 batches and to demonstrate that high doses of fibronectin fragments showed superior activity, for high capture of the growth factors (10 ng/mL BDNF or NT3) to be tested. These were extended to include the fibrin like hydrogels to generate TG-PEG, to colocalise the fibronectin fragments and the growth factors which permitted the neurites to grow much more radially oriented, compared to hydrogels without neurotrophic factors, where a much more random extension was observed.

An in vivo spinal cord contusion study was performed to analyze cavity formation, the amount of reactive astrocytes, scar tissue formation, and neurite extension. Following pressure injury, growth factor loaded TG-PEG was applied. Histology of the spinal cords revealed that the addition of FN fragments to the gel improves spinal cord recovery.

9 - Skeletal muscle repair therapy development

There are no effective therapies to treat traumatic or genetic skeletal muscle diseases: once the tissue is gone it is impossible to replace. We chose to leverage clinical advances in treating the genetic disease, Muscular dystrophy and the associated models which, like the human disease manifest as progressive muscle wasting, to develop effective muscle treatments. There are, several different therapeutic options that are currently under clinical investigation, including cell transplantation using adult muscle progenitors. These progenitor cells could be transplanted into large animal dystrophic muscle to partially repair the damaged myofibres and clinical trials utilising cell therapies are presently underway. Generating functionally restorative therapies for rare congenital disorders represents the more difficult scenario for restoring muscle, which if performed will permit the rapid development of approaches to restore tissue functionality in the plethora of diseases and traumatic tissue events which damage muscle tissue and prevent the continuation of a long and healthy life.

Potential Impact:

If published figures are to be believed the market average return on investment on industrial Research and Development (R&D) in the life science sector is between minus 2 to minus 7%, which implies that by performing research, companies are in fact destroying their own value. When combined with the well published patent cliff this has resulted in serious questions on identifying where the next cost effective and profitable product is going to come from, being asked. Solutions are not forthcoming and indeed seem increasingly elusive, which has been compounded by the perfect storm of financial recession combined with a socio economic demographic based on an increasing ageing population with tissue degenerative

diseases who spend nearly as much time in retirement as they did working, and cost increasingly more as they age. While published data indicate that new drug approvals maybe holding steady or indeed increasing according to some reports, and this does bode well for confidence in the Research and Development (R&D) and approval process, there does seem to a worrying increase in the reimbursement agencies refusing to buy the therapies as they are not considered to be cost effective for the patient.

While problematic, this is also a unique opportunity to pull together opposing cultures in the life science sector, match them with industry, and generate real value, which leverages the issues that are facing the industry and turn these into market drivers and enablers. In the context of the ageing demographic, the fact that academic research focuses generally on specific issues related to rare or less common diseases (as those with high commercial value are already extensively addressed), there is real strength and opportunity.

Collaborations, joint ventures, and partnerships between industrial and academic partners, simultaneously focusing both on fundamental and translational research is not a new phenomenon. However in the field of degenerative diseases to be treated by regenerative approaches, to create any significant impact, this is the necessary and ideal scenario; not only do the key molecular and cellular triggers for the disease have to be understood, but also their impact on tissue function defined so that potential underlying regenerative mechanisms can be stimulated; insights of which can be rapidly translated into therapeutic reality. Critically, the outcome should be a limitation of the degenerative process, matched with a restoration of tissue function, as opposed to a palliative treatment.

Amongst many diseases, and across tissues, some of the major obstacles to restoring function are shared (angiogenesis, inflammation, fibrosis, stimulation of endogenous cells to repair or replace the damage with exogenous cells) therefore insights can generate therapies for rare diseases with an impact on more common disorders and vice versa. Extended to the development of the therapies themselves, if each underlying technology can be targeted to the underlying problem in one specific disease, it can then be tailored to enable an existing mono-applicable therapy to become multi-applicable. If extended to the global issue of keeping the ageing population operational and contributing to society, such innovations represent the real impact of regenerative medicine research. Whether this is achieved by using chemical entities to stimulate endogenous cells, transferring biological growth factors or attempting to reconstruct the tissue, the outcome remains highly beneficial and lucrative, and low costs should be achievable if the system can be both rapidly tailored and incorporate existing innovations.

Generating knowledge

The single largest impact of the ANGIOSCAFF partnership, has been the enormous amount of insight and volume of fundamental knowledge produced by the partnership, which cannot be valued but only observed in the contractual reports and number of high quality publications generated (total of 89 by the end of the project). The selection of the partnership was based on the criteria of bringing together some of the strongest and most renowned teams working in degenerative disease and regenerative medicine working in Europe and known as opinion leaders around the world. All of them had made extensive prior investments in their sectors and the resources and expertise they brought to the collaboration. Each of the biomaterial teams had made seminal contributions in the field of design and application of polymers as

both experimental tools and human therapeutics.

All of the teams involved in the validation of the novel materials had prior and ongoing clinical trial experience and therefore integrated into the project the constant perspective of real evaluation of approach to be developed as therapy and whether application, patient compliance and the required primary endpoints for success could be achieved. The preceding twenty five pages illustrating the highlights of the collaboration represents a fraction of the results, both negative and positive, all beneficial, generated by leveraging an extensive previous knowledge in the sector into a focused strategy. The more translationally focused outcomes will be moved towards the clinical setting, negative outcomes from tested hypotheses will be used as guidelines to design ones that will be applicable, while many of the positive results represent early stage concepts which will continued to be developed.

This continued development and partnering will occur due to the collegial perspective of the need to develop cures that was held by all the teams, and that the cross fertilisation within the partnership between teams who knew of but had never worked with each other, has laid the foundation for continued collaborations as insights generated. Critically, these same insights are presently being used to establish collaborations with other teams not from the network who can fill a resource hole e.g. large animal modelling or to leverage the outcomes for other application e.g. delivery of biopharmaceuticals, vaccines and chemical entities for other purposes. This is an essential impact due to the complexity necessary to collaborate with teams who are not necessarily of the same expertise; something that happens frequently in regenerative medicine and as such teams are now far more empowered to enter in more complex collaborations because they now have a much deeper understanding of the actual needs and level of understanding of the partners and eventually generate a measurable value as inventions become therapies.

Innovations in regenerative medicine and value adding Intellectual property

Creating tangible outcomes with measurable value in early stage research is not possible; the valuation models used by business development which rely on risk adjusted net present value perceives all innovation which has not entered clinical trial to have a value of zero, as the risk of high attrition dilutes out any accurate measurement.

However, each of the partners brought in a significant amount of prior intellectual property which via the work performed as part of the portfolio projects increased their area of application and future potential value, as tabulated in table 4.

Generating new IP

The partners also filed 4 new patent applications, based on the prerequisites for ensuring that the innovations were 'non obvious' as compared to the prior patents owned, which were as follows:

W Holnthoner, H Redl 'One step method for casting hydrogels for tissue engineering'; application submitted in August 2012.

K Shakesheff 'Injectable compositions comprising polymeric particles and hydrogel' WO2012028881

J Planell 'Nanostructured material, process for its preparation and uses thereof' application number PCT/IB2011/052112

J Hilborn, D Ossipov, O Varghese 'Hyaluronic Acid (HA)- based delivery systems' Application number: WO2010SE50596 20100531: WO2010138074

The patient need and market forces

The future impact for patients and by necessity economic growth for those companies that develop and sell regenerative medicine products as regenerative medical approaches become first line therapeutics has been enhanced by the outcomes of ANGIOSCAFF. The areas of application are broad, as confirmation of application for one disease in one tissue, implies that with modifications the approach can be used for many diseases for that same tissue and by default repurposed to be applicable to other diseases. Below we indicate the sectors, needs and market sizes where the the outcomes of the project will be applicable.

Biopharma and pharma therapeutic delivery

Innovations in biomaterial development have been the driving force behind advances in sustained-release technology for injectable therapeutics, particularly for biodegradable drug polymers that can be used as depots and implants which could increase patient compliance by decreasing side effects and reducing the amount of therapeutic that has to be administered. Patient compliance to therapy significantly impacts therapeutic efficiency health outcomes and healthcare budgets, with a world wide importance.

Virtually all medicines are highly sensitive to changes in available concentrations of bioactive substance, which affects the efficacy, safety and tolerability of the therapeutic. The route of administration and local presentation of a therapeutic at the site needed therefore has a significant effect on its therapeutic concentration within the body.

'Patient noncompliance with therapy regimens is often thought to be the single greatest threat to successful treatment in chronic conditions. Low rates of adherence to treatment substantially contributes to increased levels of mortality, as well as accelerated disease progression, which in turn results in hospitalization or other costly procedures that ultimately place an economic burden on healthcare budgets' (source Datamonitor 'innovations in drug delivery') while the World Health Organisation has stated that lack of compliance to therapeutic treatment 'is a worldwide problem of striking magnitude' and that 'the consequences of poor adherence to long-term therapies are poor health outcomes and increased health care costs.'

The delivery route and mode of presentation is thus driven by more than simple patient acceptability, as the properties of the therapeutic (such as its solubility, duration of need to elicit an effect and level of metabolism) determine optimal administration routes.

Advanced and affordable therapeutic delivery systems, which can be designed and tailored for a direct

personalized medicine with drug specific release profiles represent value maximizing approaches for the generation of 'best in class therapeutics'. This design opens new opportunities to develop new therapeutics and the repositioning/reformulation of existing ones, maximizing value for large pharma looking to stay viable. The total therapeutic delivery market is in the region of 82bn EUROS.

Optimising drug delivery improve pharmacokinetics and pharmacodynamics by enhancing therapeutic stability, the therapeutic efficacy and half-life in the patient. Advanced targeted delivery system will increase patient compliance; preserving the pharmacological action; reducing toxicity, and the antigenicity of the agents administered. Importantly, and as demonstrated in ANGIOSCAFF, it also reduces the amount of therapeutic that would have to be administered greatly reducing the medical costs that would have to be reimbursed, while simultaneously increasing efficacy.

In the context of therapeutics that did not pass during development, there is the potential to readdress their application through combination with therapeutic delivery systems to extract value from the costs of development. Furthermore for therapeutics that proved to be efficacious and value generating, potential reformulation generates the opportunity to extend patent life, destroy competing generics and maintain market share. This can be performed for the primary targets, and for maximum value extraction by repositioning the drug in other therapeutic areas: the market has numerous examples of this being performed as a value adding strategy (Glivec, Thalidomid, Viagra, Exubera).

Within ANGIOSCAFF, two delivery systems were successfully generated; one which linked a selection of structural biomaterials to any selected factor via a promiscuous growth factor binding domain which was demonstrated to be highly effective in a number of tissue systems in eliciting significant tissue repair and a second which could effectively deliver any kind of therapeutic directly into a cell. Both are poised to have played a significant role in what has become a very complex healthcare market.

Soft tissue repair

The application of the successful soft tissue repair developed as part of the project is incredibly broad. Soft tissue regenerative medicine targeting the epithelia and epidermis is designed for patients who have poor therapeutic alternatives, with obvious high social and clinical impact. This includes epidermal, ocular and mucosal diseases which have a large range of clinical manifestation.

For instance, in Italy there are approximately 6,000 patients/year receiving a corneal graft from organ donors. Only a fraction of them would require regenerative medical treatment. Those patients, however, have severe symptoms, loss of vision, poor alternative therapy and can even undergo eye bulb removal. For those patients, tissue restoration means cornea functionality and complete recovery of visual acuity. In the case of total destruction of the corneal surface, a clinical situation that requires regeneration of both corneal and conjunctival epithelia, there are no available therapies. When applied to bilateral ocular surface lesions, the technology developed in this project would determine an extraordinary improvement of the quality of life: patients who are virtually blind could resume a normal life-style. Similarly, patients with large oral lesions often need complex surgical procedures. The proper restoration of such surgical lesions is however hampered by the lack of an epithelial replacement, leading to severe pain and discomfort for the patient. Such patients would enormously benefit from the availability of technologies that restore or

replace the epithelia.

In 2009, European sales of skin replacements and substitutes and active wound repair modulators totaled approximately 340 million EUROS, with skin replacements and substitutes accounting for 48% of sales and active wound repair modulators accounting for the remaining 52% of sales. Wounds that do not heal within three months are often considered chronic. The vast majority of chronic wounds can be classified into three categories: venous ulcers, diabetic, and pressure ulcers. A small number of wounds that do not fall into these categories may be due to causes such as radiation poisoning or ischemia.

Diabetic ulcers (DUs) are a devastating medical problem and possibly the most difficult soft tissue to demonstrate primary endpoints being reached as part of therapeutic development. There are 26 million diabetics in the US and that number is growing. As a result, 1.5 million DU's are being treated annually in the US alone. In Europe there are 20 million diabetics, and of these, 1.0 to 1.4 million have DUs. The US diabetic foot ulcer market is 2.6 billion EUROS and growing. The European market for DU's is also ~2.6 billion. The cost of failure to treat DU's is often amputation, a decreased quality of life and over ~35,000 in associated medical costs³.

Less life threatening disorders such as scar contractures following burns, dermatitis, psoriasis and potentially rarer diseases such as Epidermolysis Bullosa all represent significant patient need and product potential.

Within ANGIOSCAFF we used traumatic tissue damage as the model for demonstrating that biofunctionalised materials offers potential and can be developed into an effective therapy, which can be used to treat all of the above clinical needs.

Bone repair

The global orthopedic market is growing at 10% per year and anticipated to reach \$50 billion by 2016. In Europe alone the market is expected to reach 10 billion EUROS in 2016. In China specifically, the worlds second largest market, its worth approximately 14 billion EUROS per year, with 13% of this being for implantable devices.

The Frost and Sullivan market report on 'Biomimetics inspired by Nature' stated 'In recent times, the orthopedics and sports injury markets are undergoing a transition as there has been an increase in demand for the adoption of biologically active treatments. This would mean that the industry would shift from the use of traditional, passive, highly invasive metallic devices to more advanced, bioactive and nano biomimetic devices. This trend may be seen from the fact that osteobiologics, in particular bone grafting related products, is one of the fastest growing segments within the orthopedics market⁴. The report also indicated that biostimulatory approaches had the highest probability of success and level of attractiveness for the market.

The reason for the sustained global market growth is due to:

- An increase in the ageing population. From 2012 to 2020, this growth rate was expected to reach 3.1 per cent as the baby boomers become 65 years old. The total population, in comparison, is growing at a rate

of 0.9 per cent. However, this rate is expected to decrease to 0.8 percent by 2020. The aging population has been very active and hence there has been constant stress to their bodies. Orthopedic surgeries are performed on people of all ages, but many of the degenerative conditions that lead to the need for surgery affect people in middle age or later in life.

- The improving medical infrastructure and consequent rise in diagnosis rates in emerging markets in Asia, Africa, and Latin America also present growth opportunities.

- The number of overweight people worldwide is expected to increase by 44 per cent between 2005 and 2015. As the risk of orthopedic related disorders is more in overweight people, this trend is expected to fuel demand in the global orthopedic medical devices market.

Within the orthopedic sector, approximately 15 companies control 95% of the world's market in orthopedic medical devices, which includes novel biomaterials, however the market is very fragmented in which each market Tier is controlled by its own market forces based on price differences or quality; nonetheless the sector as a whole is investing in innovation as basic patents of most orthopedic devices and implants have expired, leading to genericisation and commoditisation. Thus 'continued innovation' or value additions such as improvement of materials is becoming very competitive and perceived of high value.

While the non medical device sector is also targeting this market (in 2012 there were 5 NCEs in development for fractures, 5 for spinal fusion, 4 for bone repair, 3 for bone regeneration and 1 for osteo induction) the biomaterial sector is considered to be the future. In 2011 the orthopaedic biomaterials market was worth about 14.5% of the global orthopaedics market and sales of biomaterials are expected to grow about 10% annually and could surpass 10 billion EUROS in 2016.

Present state of the art products are based upon materials sciences implants made of metals combined with biological substances for better incorporation in the natural bone. In addition, re-absorbable materials in implants that fulfill their function during a period of time and then gradually undergo re-absorption are emerging. Growth factors alone such as BMP2 are also considered as products, however in the context of large bone defects, efficacy is questionable.

Currently, the highest focus sector, and one that was developed in ANGIOSCAFF involves materials implanted with growth factors rendering it bioactive that stimulate cellular. When commercialised, these are likely to revolutionise the orthopedic sector, but is very dependent on combination products being approved by the authorities.

Heart repair

In the Western world alone presently there are over 9 million people suffering of heart failure where the treatment available (with the exception of heart transplant) are only palliative. Yearly, more than a million new patients join this group. Extended to the rest of the world which has witnessed a significant increase in cardiac disorders the future impact of the data generated is large.

The Frost and Sullivan report 'Advances in cardiovascular therapy': stated

'A fundamental driving force in the cardiovascular therapeutic field is the realization that pharmaceuticals

can only go so far in the treatment of cardiovascular diseases. With increasing complexity of the genetic makeup and the role of multiple factors in the etiology of cardiovascular diseases, there has been a drive to think beyond the ordinary and consider the use of technologies such as tissue engineering and stem cells in managing cardiovascular diseases and leading to treatment of the disease. '

The prevention and amelioration of pathological cardiac remodelling as a consequence of acute or chronic ischemic heart, myocardiopathies due to inflammatory, infectious or genetic causes is an immediate requirement. The average life-span after the first episode of heart failure for these patients is of approximately 5 years. By 2016 the annual global market for all cardiovascular products is estimated to reach 160bn EUROS, with the top ten companies estimated to possess half of that market. Critically, cardiac disease and myopathies are global issues.

Due to its prevalence and its disabling long term sequels, Ischemic Heart Disease (IHD) is a critical challenge for the health care systems of the developed world and increasingly also for developing countries. In each the EU and USA, over 1 million acute myocardial infarctions (AMI) are treated annually. Angioplasty, combined with stent implantation and new pharmacological regimes, when applied promptly, has been successful in re-establishing the perfusion of the ischemic myocardium and has reduced significantly post-AMI early mortality, which now stands at greater than 10%. Despite the remarkable reduction in early mortality, these new therapies do not recover the injured tissue or the cells lost and fail to prevent the subsequent degenerative process of cardiac remodeling which ultimately leads to Chronic Heart Failure (CHF). Paradoxically, the reduction in early mortality due to AMI has aggravated an epidemic of late CHF, which is now suffered by greater than 12 million patients in the EU and the USA, with approximately 500,000 new patients added every year. Post-MI CHF is a terminal disease with an annual mortality rate of approximately 18% after the first episode (average life-span approximately 5 years), for which the only curative treatment is heart transplantation.¹⁻⁴ This treatment is available only to a minute fraction of candidate patients due to donor scarcity, cost, and the requirement for long-term immunosuppression⁵ with its many deleterious effects. The fact that the worldwide number of annual heart transplants peaked in 1994 at 4,429 cases and has steadily decreased since then to about 3,000 annual cases underscores the need to develop a myocardial regeneration protocol which could restore myocardial function to an unlimited number of patients.

The outcomes of the Cardiac work achieved in ANGIOSCAFF, exceeded our expectations. The insinuations of the data indicate that an 'off the shelf' cardiac repair strategy is both feasible and affordable.

Muscle repair

The outcomes of the work performed in combining biofunctionalised scaffolds with cells and the total muscle repair obtained provides a ground breaking approach that could be used to treat the following:

Muscular dystrophies: The inability to produce dystrophin and other proteins usually linking the cytoskeleton to the membrane and the ECM in muscle causes several genetic diseases collectively known as muscular dystrophies. Duchenne Muscular Dystrophy (DMD), the most common and one of the most severe forms, is due to mutations that affect the X-linked DMD gene and affects 1 in 3,500 newborn boys

and there are 800 new cases annually in the EU. The burden for DMD healthcare in Europe is 75,000 EUROS/annum/patient, amounting to an annual bill of 60 million euros; an effective treatment will therefore be of significant economic benefit to the EU. The stem cell therapy itself for DMD has been estimated to cost approximately 300,000 euros per patient (G.Cossu personal communication); this would be extremely cost effective in both contributing to reducing the health burden and generating novel marketable products, which together will give socio-economic benefits to the EU community. The potential cost saving to the health care systems, given that DMD patients can live into their 40s, is over 5.5 million per patient, while the value given to the patient and their families is immeasurable. Being the most common, DMD has been so far the most studied form of MD and thus it may serve as a paradigm for new treatments. However it is unlikely that a topic treatment may be effective in all patients' muscles that are affected in this form. Nevertheless, treating selected target muscles, such as the dorsal muscles in children (to prevent lordosis), intercostal muscles (to enhance ventilation) and the hand muscles in adult patients (to maintain motility) may result in great benefits for the patients and increased quality of life and partial independence. In addition, less common forms, such Oculo-Pharyngeal (OPMD), Becker dystrophy or distal (DD) muscular dystrophies are restricted to few specific muscles, even though they compromise the autonomous life and in some cases (OPMD) are lethal due to the inability of patients to swallow food and even liquids. These forms represent ideal target for a topic treatment also because cells may be derived from non-affected muscles (e.g. thigh) and thus would not require genetic modification nor immune suppression for the patient as in the case of heterologous cells.

Urinary Incontinence (UI): This is an extremely common problem, and has a significant impact on quality of life, the vast majority of those who experience the condition do not undergo treatment, in part due to cost, embarrassment, or fear of risky surgical procedures. There is therefore a very strong demand for less costly, less invasive and more tolerable, discreet, nonsurgical UI therapies. UI is due to both age-related muscle degeneration and to iatrogenic lesions in young women due to epiphysectomy during delivery. Trials with myoblasts injections are ongoing but the low engraftment of cells injected in saline solutions lowers efficacy. The global UI therapeutics market was worth approximately 2.5 billion euros in 2009. In 2001 the market was valued at 1.4 billion euros and it grew at an approximate CAGR of 7.8% from 2001 to 2009. The global UI therapeutics market is expected to reach 3.4 billion euros by 2017 growing at a CAGR of 3.5%. Existing therapies simply do not repair the non or dysfunctional tissue.

Surgical management of malignant lesions of the oro-facial region: Tumors of the splanchnocranium often require demolitive surgery. Patients survive but with mutilations that severely limit their normal life functions and usually abolish their social life. Plastic reconstruction is major challenge and could be enormously helped by the possibility of developing in situ, artificial muscles, as the proponents have demonstrated to be possible by combining biomaterials and stem, at least for the small Tibialis anterior of the mouse (Fuoco et al in preparation). The possibility of combining this novel approach with ongoing bone and teeth reconstruction would immensely help this challenging novel therapeutic strategy

Hysterectomies: According to the U.S. Dept. of Health and Human Services, 25% of all women (16 million) suffer from fibroid symptoms, leading to 250,000 annual hysterectomies - a highly invasive surgery with many side effects. The problem is so widespread that a third of all U.S. women have undergone hysterectomy by age 60, with fibroids being the most common reason. In 2006, combined sales of products for the treatment of the three most common benign conditions affecting the uterus

(Endometriosis, fibroid tumors, and menorrhagia) were totaled approximately 415.6 millionUSD; reaching approximately 760.3 USD million in the year 2010. The hysterectomy process removes a significant portion of the tissue, which results in extensive remodelling and debilitation; processes that could be both optimised and decreased in time with a highly effective muscle restoration therapy.

In addition, less traumatic and life threatening or altering issues, such as hernia repair which is the most common surgical procedure performed, can also be treated easily with such an approach, reducing scar formation, restoring tissue integrity and decreasing the possibility of repeat herniation

Neurological repair

Neurodegenerative diseases, including stroke, spinal cord injury and Parkinson's disease, which could be treated with tissue repair approaches, are the major causes of chronic disability in European communities with a market size estimated to reach 17 billion euros by the year 2014. With the increasing number of elderly people, coupled with successful treatment of non-neurological causes of chronic illness, the incidence of neurodegenerative disease is increasing. Approximately 1% of people over 65 years of age are likely to develop a neurodegenerative disorder.

Europeans suffer nearly one million strokes each year, highlighting the need for efficacious therapy and the tremendous market potential for effective stroke therapy. Between 15-30% of ischemic stroke victims are permanently disabled and 20% require prolonged institutional care. As a result, stroke is one of the most common causes of long-term serious disability and represents an economic burden similar in scale to myocardial infarction, the symptoms of which could be treated using vascular repair and neurostimulatory therapies to potentially restore function.

Spinal cord injury is estimated to affect at least 330 000 people (paraplegia and tetraplegia) with over 15 000 new cases reported each year. In two-thirds of cases, road accidents are the cause of injury, with sporting accidents making up another 10%. Most occur at a young age: average age of 19; about 80% of males with spinal cord injuries are aged 18-25 years. The cost of treatment and aftercare for sufferers is phenomenal: the average lifetime costs directly attributable to spinal cord injury for an individual injured at age 25 range from 0.45 M EUROS to 2.1 M EUROS and have to prepare to spend an average of forty years or more in a wheelchair. It is known that stimulating angiogenesis and preventing fibrosis as soon as possible after injury, using locally administered morphogens and factors directly into the site of damage, immediately after the accident (followed by rehabilitation) will significantly increase the possibility of the patients retaining motor function.

Treating Parkinsons Disease (PD) with conventional drugs and newer innovative therapies such as deep brain stimulation and/or the use of Apomorphine or DuoDopa® cost between 8000 and 40,000 Euro a year per patient treated. Indeed in the UK the total cost of PD is estimated to be between 449 million and 3.3. billion pounds annually. Thus any therapy that can reduce disability and dependency on expensive drugs that only offer symptomatic benefit would be a major breakthrough. Regenerative therapies, likely involved cell transplantation with the neuromorphogen/material complex or morphogen/materials alone will not only reduce the costs of care in the short term but also in the long term by altering the natural history of treated disease. and significantly reduce patient morbidity and mortality and be highly cost-effective.

Despite posing the greatest challenges for tissue repair in the ANGIOSCAFF project, the long term potential to adapt the developed material/morphogen systems similar to that achieved with the heart (iPS cells) and skeletal muscle provides a long term potential therapeutic, that despite its complexity will actually restore function to the tissue.

Sport and activity related tissue damage

In addition to tissue specific disorders indicated above, other circumstances can induce tissue damage. Among them, occupational injuries and sport-related injuries often cause life-altering conditions. Two examples are cited below:

In high intensity sports, hardly a game or championship goes by without a sprain, strain or break. Just before a championship, it is not ideal for a team to lose one of its star players. Strain injuries, which are common in sport, cause the rupture of large myofibril bundles leading to muscle regeneration and formation of scar tissue and new myotendinous junctions at the level of the rupture. To avoid the risk of reruptures, early remobilization is required to induce correct growth and orientation of regenerated myofibers. The problem is to improve the healing process. A lot of the work has initially been in bone, but the more exciting area is the soft tissues. These soft tissues that cushion and hold joints together-tendons, ligaments and cartilage-heal slowly, if at all. Part of the problem is that the blood that helps other tissues heal after injury hardly reaches them. One of the challenges of sport medicine is to reach the tissues that are injured. Thus the problem of sports medicine could find solutions in our project. Indeed, the central goal of EndoStem is to identify molecules that can be used either alone or in combination to activate muscle repair through endogenous muscular or/and vascular stem cell mobilisation and activation.

Sport and activity-related tissue damage can impair the patients' life as badly as other degenerative disorders however none of these traumas receives the same profile as the major life debilitating disease however restoring the capabilities of those injured at work or activities performed in their free time has become a major issue, especially because those injuries have a considerable economic impact. For example, based on the latest data available (generated in 2004 by a French health insurance company), occupational injuries in France alone resulted in a net loss of 48 million working days, which, in other words, corresponds to shutting down a 130,000-people company for one year. In addition, over 6 billion EUROS were spent by insurance companies to compensate those whose injury resulted into life-altering disabilities.

In the United States, direct costs for occupational injuries are estimated to be over 50 billion USD per year while indirect costs such as loss of wages or workplace disruption costs reach 150 billion USD (source: Costs of Occupational Injuries and Illnesses, University of Michigan Press, 2000). In France, direct medical costs incurred after sport injury reach 200 million euros per year, without considering the resulting absence of work, which corresponds to about 4% of total absenteeism (source: British Journal of Sport Medicine, 2008).

If matched with effective pain management, the materials generated in ANGIOSCAFF could offer rapid tissue repair at a very localised level and with likely more effect; the endogenous cells necessary for repair

of the tissue are still local and available, but simply lack the correct stimuli and structure.

Non human-health related markets

While we have naturally focused the potential developments on human healthcare needs, in the context of pure market development, the outcomes of ANGIOSCAFF also have the potential to be developed for both human cosmetic and veterinary sectors, which have stand alone large market values.

(Sources of information: BCIQ, MDDI, Datamonitor, Research and Markets, Forest and Sullivan, Kalorama)

Spin off companies

Two spin off companies were created from innovations that arose from the work performed: The first, Delivery Limited which was based on the delivery technologies created by the team of Jons Hilborn from Uppsala. The technology itself has a very low cost of production and can be engineered to deliver all types of therapeutics (chemical entities, nucleic acids and proteins). The hyaluronic acid component which forms the core of the technology means that the 'payload' of the delivery vehicle is taken into the cell by receptor mediated cytosol intact. As the pharmaceutical field is looking to repurpose existing therapeutics, readdress earlier stage therapies which were abandoned due to inefficient delivery e.g. toxicity due to high dose necessary, or poor effect due to poor pharmacokinetics, and explore new therapies such as siRNA, the potential of the application is very wide.

The second company (originally named Promimetic Limited), renamed to Echino Limited (after the Echinoidea Class of organisms which have the capacity to regenerate limbs and organs throughout their life span) was created based on the combined work of Professor Dror Seliktar from the Technion and Professor Giulio Cossu from the UCL. The capacity to create de novo a completely functional tissue in situ is groundbreaking for soft tissue and the potential applications extremely broad based on the flexible tailoring that forms the core part of the innovation; the fact that both the cell component and the biomaterial component have progressed through clinical trials, means that conceptually the product is de-risked. The largest barrier we face with continued development is dependent on a change in regulatory perspective of combination tissue repair products.

Despite the particularly difficult financial market for hi-tech life science companies and that early stage capital for start up companies is sparse, we aim to keep the companies functional and continue the product development using any source of funding possible so that when the funding markets do become more conducive we can rapidly grow these companies.

Linking with the public: general public and scientific community

The pre-clinical nature of the work being performed decreased the potential to attract stakeholder interest in the work being performed; the prior experience of all the partners involved in stakeholder liaison clearly indicates that interest is only received when clinical testing is publicised. Stakeholders in general have great difficulty in being interested in early stage research unless there is a near short term application, and

observing what other outreach entities perform (Eurostemcell, the Association of Science and Discovery Centres, The European Network of Science Centres and Museums), extensive investment is necessary in the establishment of the outreach activity itself and its continued population with information. This was not designed into the budget of ANGIOSCAFF and therefore these activities were limited by these constraints. The added factor was based on human consumption of media and the rationale behind it, which in the context of hi-tech at a conceptual phase of development is linked to controversy which polarises opinion and fosters debate e.g. the use of human Embryonic Stem Cells. The field of work of ANGIOSCAFF was not controversial.

In addition to the project website, a total of four press releases were made: one referring to the kick off of the project and three highlighting the advances made during in years 2, 3 and 4 of the project, while to the scientific community 86 oral and poster presentations were given in invited seminars, international meetings and congresses.

List of Websites:

<http://www.angioscaff.eu> 

Documenti correlati



Final Report - ANGIOSCAFF (Angiogenesis-inducing Bioactive and Bioresponsive Scaffolds in Tissue Engineering)

Ultimo aggiornamento: 1 Settembre 2013

Permalink: <https://cordis.europa.eu/project/id/214402/reporting/it>

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