Angioscaff – At its half way point

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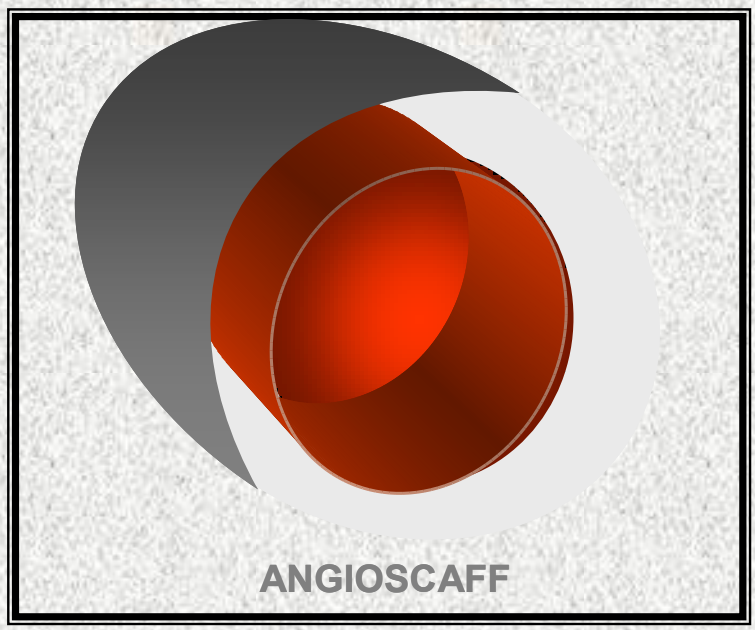

Angioscaff is a major collaboration initiative funded by the 7th framework programme of the European Commission.

Coordinated by Professor Jeffrey Hubbell from the Ecole Polytechnique de Lausanne, the partnership brings together more than 30 groups from leading European and Israeli academic centers, small companies and the large pharmaceutical industry.

ANGIOSCAFF creates bio-responsive, bioactive and injectable materials capable of carrying therapeutics, which can be used for tissue regeneration in humans. The work has been divided into seven interlocking but distinct strategic areas. The specific strategies being implemented are: (1) Radical innovations in state-of-the-art biomaterials (2) Design and production of advanced bioactive scaffolds enabling internal growth of tissue and the site specific delivery of bioactive signaling factors, that control cell differentiation (3) Injectable biomaterials and effective delivery device design that can induce angiogenesis in the body (4) Development of bioresorbable, highly porous, and structurally sound tissue-engineered scaffolds (5) Functionalized biomaterials that have direct influence on cell behavior (6) Bioactive scaffolds with broad applicability for complex tissues

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ANGIOSCAFF is creating and validating bioresponsive, bioactive and injectable materials capable of carrying therapeutics, which can be used for tissue regeneration in humans.

The new materials are responsive to cell-associated environmental signals, such as extracellular proteases and endoglycosidases and generate bioactivity by virtue of bound peptides or recombinant adhesion molecules and growth factors.

The partnership is therefore designing and implementing:

- *Radical innovations in state-of-the-art biomaterials.*
- *High-performance biomaterials inspired by natural processes.*
- *Biomaterials that control cell differentiation*
- *Injectable biomaterials that can induce angiogenesis in living organisms.*
- *Bioresorbable, highly porous, and structurally sound tissue-engineered scaffolds.*
- *Functionalized biomaterials that have direct influence on cell behavior.*
- *Bioactive scaffolds with broad applicability for complex tissues.*
- *Advanced bioactive scaffolds enabling internal growth of tissue and site-specific delivery of bioactive signaling factors.*
- *Effective peptide and nucleic acid delivery devices.*

ANGIOSCAFF

Advances achieved since the beginning of the project

Since the beginning of the project we have developed a set of seven novel biomaterials tuned to combine with bioactives, which possess and transmit various patterns of spatio-temporal biofunctionality.

We have selected and compared materials produced during year 1 and the first part of year 2 and have produced biofunctionalised scaffolds containing growth factors, ephrins, adhesion molecules and genes for delivery into specific target areas.

The first stage of characterisation of similarly functionalized materials has now been completed and the materials are being assesed for regenerative stimulation in degenerative disease models.

We initiated the first series of validation studies *in vitro* in angiogenic, skin, bone, cardiac, neurological and skeletal muscle models to specifically assess their regeneration and repair stimulating capacities. This has enabled us to address the important question as to whether different materials will be able to produce similar angiogeneic and regenerative responses *in vivo*.

The first *in vivo* tests have revealed striking and unique results for the repair of skin, bone and skeletal muscle tissues with selected materials, while the more complex neurological and cardiac tissues require further study and optimization.

The novel materials generated so far have demonstrated high impact, thus laying the groundwork for the final two years of the project that aim at the generation of regenerative therapeutics.

What has been delivered so far?

- Fibronection fragments which have been tailored to contain growth factor binding areas endearing the material with both structural and biostimulatory characteristics

- A Hyaluronic acid- hydrogel click chemistry system consisting of a cross-linkable growth factor binding fibronectin fragment has been developed.

- We have produced new guanidium-modified Hyaluronic acid hydrogels for application as nontoxic, biodegradable, nonviral gene delivery vectors.

- Star-heparin hydrogels have been generated with varied physicochemical properties, which can be used as highly efficient reservoirs and tunable delivery system for pro angiogenic growth factors.

- PLA/Glass composites have been developed which are optimal scaffolds to be used in a bioreactors and can be produced under controlled and reproducible conditions providing a good environment for proliferation of various cell types

- Tailored PEG-Fibrinogen composites have been developed as a cell carrier system and tested in skeletal muscle models, which mediate greater engraftment and survival of the clinical target cells.

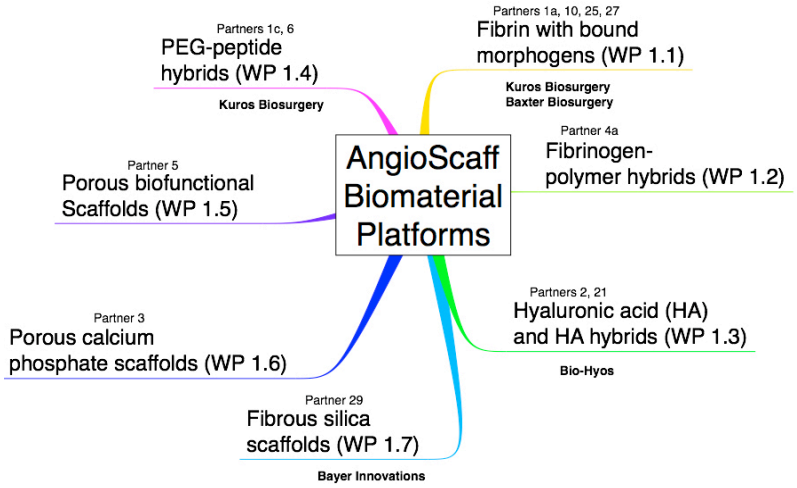
All of these materials are being validated as tissue specific regenerative approaches

How is the partnership achieving so much?

To **garuntee that we exceed our own expectations** we have developed an optimal organisation that can execute with high quality over distant geographic sites.

We capitalize on our combined specialities in different disciplines of regenerative medicine and high quality public and private infrastructures, which allow us to merge our unique and complementary expertise in the field, so that we generate:

Optimised portfolio management



Starting from a catalogue of available biomaterials from the specialist partners, **task teams are created** composed of the materials, morphogen, angiogenesis and tissue specific (cardiac, bone, nerve, muscle, skin), biomechanics and imaging specialists, that target one specific disease.

The teams, which are geographically distant and **from both academia and industry** then define and elaborate the precise portfolio project plan with defined resource needs and milestones against which progress is measured.

The main investigators approve the portfolio projects and an experienced Executive Committee performs final approval.

The portfolio project is then ‘green lighted’

Intellectual capital in a 'can-do' culture

Responsibility for the implementation is then passed entirely to the **highly skilled and motivated young scientists** in each portfolio project team who perform the tasks.

They perform with professionality and responsibility and as such, each team functions with autonomy.

Every 3 months each portfolio project team is then brought together for a virtual management and coordination meeting. Presenting the latest data the team brainstorms, reviews external information that could affect the milestones, measures progress, evaluates possibilities to publish the data and potentially develop the output as an invention or create a company.

All potential barriers to success are monitored and removed and the young scientists encouraged to perform whatever is necessary to achieve the goals.This includes visiting each others locations to implement high tech work which requires local short term visits from the specialists to advance the projects.

Any gaps in skills are corrected with virtual seminars and hands on technical training which complement their local capacity building environment.

Task teams are also expected to think outside of their own immediate sphere and constantly address if their own advances can positively impact the other portfolio projects; if so it should be followed.

Through the constant exchange of know how and advances, every member of every project team becomes highly competent in planning, implementation and the diverse disciplines that are necessary to perform the projects.

Keeping an eye on the bigger picture

Finally we recognise that our endeavours are not about us.

We are aware of the societal and economic issues that our work targets: the human needs and the commercial requirements.

We constantly monitor how our work can be better tailored to fit all the stakeholders requirements so that our knowledge is translated into affordable benefits.

Impact of our work

Age related illness, degenerative diseases, and traumatic injury all create life altering experiences which affect ourselves, our loved ones, our friends and colleagues.

The subsequent diminishment of body functions associated with the illnesses can cause depression and loss of self-esteem. It has been considered essential, based on European policy consistent with human rights principles, that people with disabilities should be treated with dignity, encouraged to have independence, be given equality of opportunity, encouraged to have an active participation, a full citizenship and a high quality of life.

Given the diversity of the illnesses indicated above, their onset can occur at any age: either as a child, during an individual's most productive years, or as an aged person. The trauma frequently results in morbidity, and as a result, patients typically require continuous physical and medical care depending on the illness, severity of manifestation, degree of disability, and location of injury.

The prevalence of degenerative diseases is on the rise because aging population is increasing and this has created the need for biomaterials. 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. While illnesses and degenerative diseases are not the exclusive domain of the aged, they do impact this sector of society the highest with subsequent increased social and economic burdens on the health care systems on which they depend.

In the case of failing organs, the direct healthcare costs of organ replacement are about € 240 billion globally (about 8 percent of global healthcare spending) arising from therapies that keep people alive (such as kidney dialysis), implanted replacement devices, and organ transplants. With a € 240 billion global industry already built on first generation tissue and organ therapy products and substitutes, regenerative medicine has a potential to exceed € 600 billion by 2030.

The Economic Impact

Our partnership includes teams working on specific areas of tissue engineering that are associated with clinical targets. *The clinical targets were selected because of their high societal and economic impact.* By translating our knowledge in biomaterials and angiogenesis into clinical targets we put our science to the real test of usefulness. *New biofunctional materials and angiogeneic molecules with therapeutic application will be introduced to the clinic and to commercial development.*

The impact of this is best illustrated by the need for organ transplantation, the major motivation behind regenerative medicine: 25% of patients waiting for an organ donor die before one can be found, and in 2001 there were 12 607 available donors available to help 81 528 patients in need. The stimulation of tissue repair via the use of optimized scaffolds (porous, angiogenic, bioactive and resorbable) that stimulate endogenous cells to regenerate a fully functional tissue should address this problem and decrease related mortality.

The work being performed in Angioscaff is known to have an effect in a broad variety of tissues (soft tissue, bone, neural), through targeting both a general process and a tissue specific process.

Bone tissue

Bone fractures. Most bone fractures are treated. However, approximately. 10 % of bone fractures cannot be treated by standard therapies because the damaged sites are too big. (worldwide around 1.5 million patients per annum and around 600,000 per annum in Europe). Jaw bone surgery and periodontal surgery. Approximately 1.5 million patients in Europe and 4.5 millions worldwide. Bone deficit due to osteoporosis and bone tumours. Approximately 10 million cases annually in Europe, and up to 30 million applications worldwide. Spine lesions being of particular relevance.

Nerve tissue

Neurodegenerative diseases, including stroke and Alzheimer's disease, are the major causes of chronic disability in European communities. With the increasing number of elderly people, coupled with successful treatment of non-neurological causes of chronic illness, the incidence of neurodegenerative disease will increase.

Alzheimer's disease: It has now been reported that the world is on the brink of an Alzheimer's epidemic in which the number of sufferers could quadruple over the next 40 years. It has been speculated by researchers from the Johns Hopkins University that the 26 million people worldwide presently thought to be living with the illness could increase to more than 106 million by 2050.

Stroke: 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.

Spinal cord injury: estimated to be at least 330 000 people living with spinal cord injury (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 to € 2.1 M and have to prepare to spend an average of forty years or more in a wheelchair.

Soft tissue

Progress has been made in the discovery of growth factors that can regulate skin repair (for burns, genetic diseases), but there remain important challenges. Johnson & Johnson has introduced PDGF-BB to the clinic and marketplace, which costs several k€. Adoption in both Europe and the USA has been very limited due to dosage considerations, penetrating less than €150 million/year into a market that is thought to be approximately €5 billion/year deep.

Cardiac tissue

Revascularization of cardiac muscle following myocardial infarction remains a very major challenge of enormous socioeconomic value. Cardiovascular disease remains the number one fatality in the world killing 17 million people each year (and 5 million in the EU-25, accounting for 51% of all deaths) with no indication that this figure is decreasing.

Sport and activity related injuries

In addition to degenerative disorders, other circumstances can induce tissue damage. Among them, occupational injuries and sport-related injuries often cause life-altering conditions.

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 myofibres. 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 end point of Angioscaff is to identify approaches that can be used either alone or in combination to activate tissue repair through endogenous and/or exogenous target cell activation.

Sport and activity-related tissue damage can impair the patients' life as badly as other degenerative disorders.

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, in 2004, occupational injuries in France have 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 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 per year while indirect costs such as loss of wages or workplace disruption costs reach $150 billion. 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.

We are developing approaches to induce tissue repair through the administration of biomaterial and biopharmaceutical compounds bringing hope for any individual suffering from tissue damage.

Tissue regeneration, as opposed to the scarring process, restore a fully functional tissue or organ and allows patients to return to their life, family and occupation.

In the following pages we more information on the scientific advances that have been achieved in the previous two years.

BIOMATERIALS

'Designing the structural, delivery and stimulatory systems'

The six biomaterials indicated above have passed into the validation phases in which their precise bioactivity and regenerative stimulating capacities are assessed in tissue specific degenerative model systems.

The information obtained with the first generation materials has stimulated the incentive to **extend the existing biomaterial platform** to better meet the requirements of the tissues.

The results obtained by testing new biomaterials in angiogenesis and tissue engineering in bone, skin and neuromuscular tissues have catalysed further research, which will improve the **mechanical properties** of injectable matrices, adjust **biofunctionalization,** develop injectable **hyaluronic acid-based** matrixes and conjugate **FN-GBD to starPEG-heparin** hydrogels to produce next generation scaffolds (*Figures 1 and 2*).

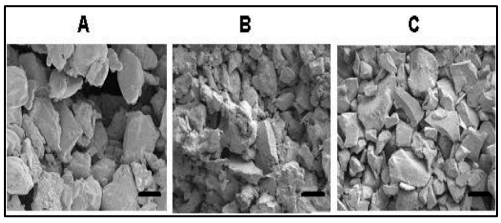


Figure 1. Microstructure of injectable, mechanically stable matrixes. *(A)PLGA/PEG; (B) PLGA/PEG + (B) glass (melt blend); (C) PLGA/ PEG + G5 glass (powder blend)*

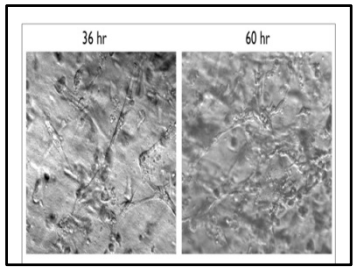


Figure 2. Endothelial cell morphology over time on new generation star-PEG-heparin gel. gel. *Cells attach to gels, have no sign of toxicity and start forming tubes.*

ENGENEERED MORPHOGENS

'Delivering the correct signals'

- To induce angiogenesis and desirable angiogenesis-associated morphogenetic processes in the target tissues we have generated growth factors-containing scaffolds such as: Fibrin-binding and cys-containing VEGF-A and VEGF-C and fibrin-binding PlGF; Fibrin-binding and cys-containing VEGF-syndecan; Wild-type, fibrin-binding and cys-containing TGF-β1 and TGF-β3; Fibrin-binding PDGF-AB; Wild-type, fibrin-binding and cys-containing IGF-1; Fibrin-binding BMP-2.

- Second generation ephrin-modified scaffolds (TG-EMP peptides, *Figure 3*) were generated by incorporating ephrin peptides into fibrin gels in the presence of serum components and cells. In particular, TG-EMP-A2 peptide activated EphA2 receptor signalling preferentialy in fibrin matrix-bound form and TG-EMP-B4 retained inhibitory potential in free form. TG-EMP-A2 could be efficiently incorporated in PEG-based gels and used for EphA2 receptor signaling activation in 2D and 3D cell cultures.

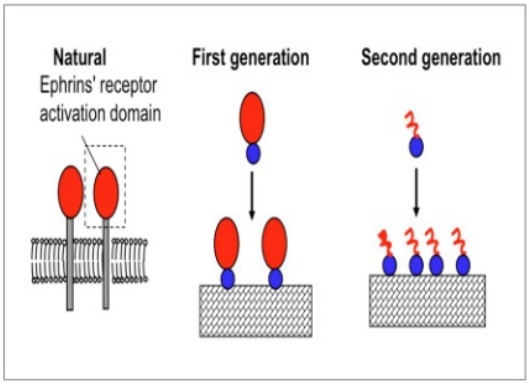


Figure 3. Schematic of ephrin-modified scaffolds. *The whole recombinant ephrins activation domain is tagged for scaffold incorporation in the first generation scaffolds, whereas only small synthetic ephrin peptides are tagged in the second generation scaffolds*

- Controlled delivery of VEGF and Ephrin peptides improved the functionality of mesenchimal stem cells and endothjelial progenitor cells in 3D culture, where cells also showed changes in gene expression, including chemokine receptor and growth factor genes.

- Fibronectin fragments supported the isolation and expansion of human bone marrow-derived mesenchimal stem cells more efficiently compared to the full-length protein. The most efficient fragment comprises the CBD and the GBD.

ANGIOGENESIS

'Feeding the regenerating tissues with an effective blood supply'

- We have determined the range of matrix components and the degradation rate of different matrix compositions in vivo to define how hydrogel composition controls the duration of growh factor release to meet the long term goal of delivering VEGF locally by hydrogels.In the context of lymphangiogenesis, we found that fibrin-binding TG-VEGF-C with a matrixmetalloprotinase (MMP)-degradable sequence improved lymphatic endothelial cell proliferation and capillary formation compared with wildtype VEGF-C. In vivo, TG-MMP-VEGFC drove efficient functional lymphatic regeneration.

- Low dose growth factors (VEGF-A and PDGF-BB) delivered in FN fragments with approproate integrin ligands induced enhanced wound healing and angiogenesis in vivo. The signaling through the growth factor receptors was enhanced and prolonged. Thus FN III9-10/12-14 act in synergy with growth factors and the synergy was mostly dependent on the integrin $\alpha_5\beta_1$ (*Figure 4*). Along similar lines, the covalent integration of VE-cadherin in a fibrin matrix increased ring formation of endothelial cell lines.

- We have established a powerful Zebrafish model that will allow rapid and minimally invasive screens for different biomaterial/morphogen combinations in vertebrates (*Figure 5*). Furthermore endothelial cell progenitor migration towards SDF-1 was increased by a new starPEG-heparin hydrogel, which resulted in increased cell infiltration, vessel formation, matrix remodelling and angiogenesis in vivo (*Figure 6*).

Preliminary results have also shown that TG-VEGF121 activated fibrin matrix at low concentrations of VEGF121 were most effective in reducing tissue necrosis on day 7 post surgery in the rodent epigastric flap model. Finally neovessel formed in vivo upon co-transplantation in mice of clonogenic mesenchymal progenitors from different tissue sources (human postnatal bone marrow, human postnatal muscle, human cord blood) and human endothelial cell lines in mice, whereas the angiogenic potential of the progenitor cells alone was limited.

This system revealed that endothelial cells can introduce a specific spatial pattern in an otherwise isotropic distribution of differentiating mesenchymal progenitors.

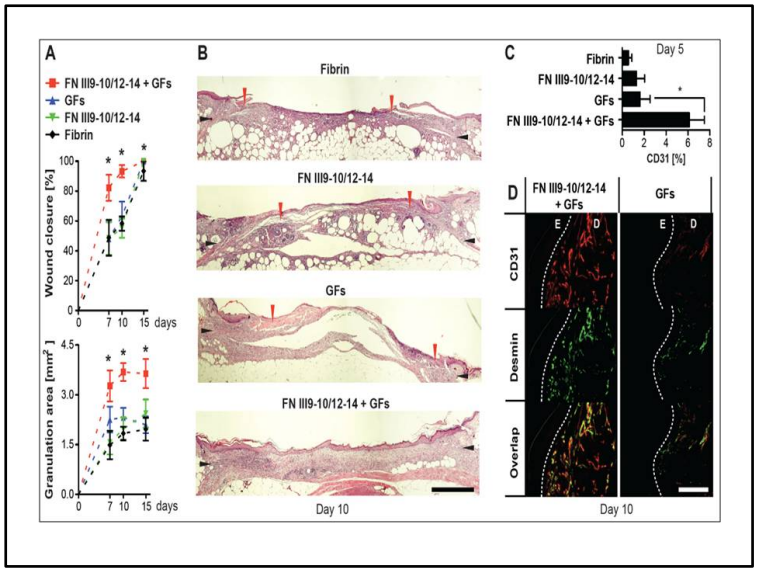


Figure 4: Growth factors synergise with fibronectin fragments to enhance wound healing and angiogenesis. *After wounding, wounds were filed with fibrin matrices functionalized with or without FN III9-10/12-14 and GFs (VEGF-165 and PDGF-BB).* ***A****) Wounds where GFs have been delivered using FN III9-10/12-14 closed more rapidly and contained more granulation tissue, compared to fibrin only.* ***B****) Representative histology of wounds at day 10. Black arrows indicate the wound edges, red arrows indicate the end of the new epithelium (haematoxylin and eosin staining, scale bar = 1mm).* ***C****) Enhanced recruitment of CD31+ endothelial cells within the wounds when GFs were delivered with FN III9-10/12-14.* ***D****) Greater blood vessels formation within granulation tissue when GFs were delivered with FN III9-10/12-14 (E = epidermis, D = dermis, scale bar = 0.2mm).*

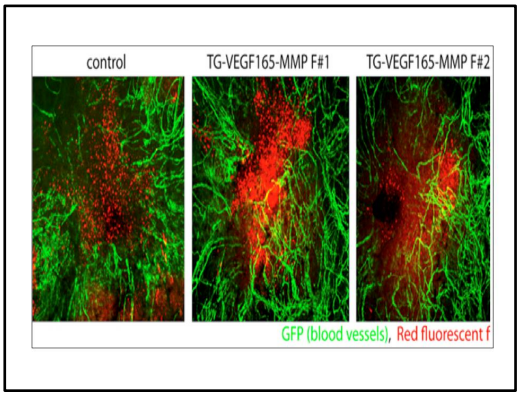


Figure 5: Confocal stacks of control fibrin gel (left panel) and two TG-VEGF165-MMP/fibrin gel implanted fli:GFP fishes *(central and right panel). Angiogenesis toward and within the gel (red) can be observed (in green, GFP positive vessels); the presence of VEGF into the gel induces higer levels of angiogenesis compared to control.*

Preliminary results have also obtained from a single donor suggest that a selective medium supports $CD133^{+}CD34^{+}$ mesenchymal stem cells from liposuction material. Mature endothelial cells in whole human blood have been detected, magnetically isolated and characterized by flow cytometry.

BONE REPAIR

'Repairing the skeleton'

- Using subcutaneous or cranial implantation models of bone formation, we have compared by Micro-CT and by histology various scaffolds produced by AngioScaff laboratories. Below is an example of osteogenesis induced by BMP-2 complexed with PLGA/PEG (*Figure 6*).

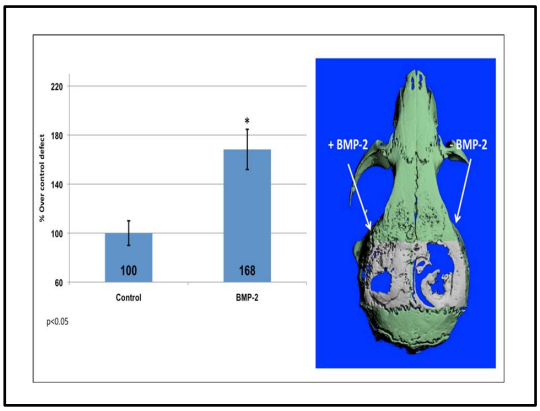


***Figure 6: Bone formation induced by BMP-2 complexed with PLGA/PEG in cranial Implantation**. BMP-2 induced significantly greater bone formation than the empty control*

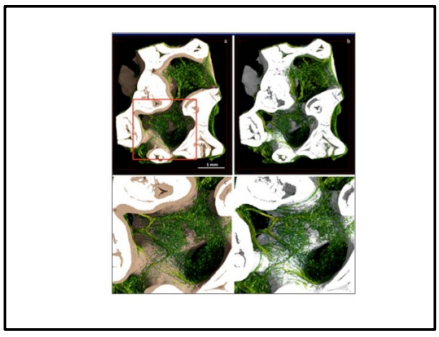


Figure 7: Example of microCT imaging of a bone section

- A spinal fusion model in rabbits was used to address whether a limited vascular network in different implants may correlate to lack of bone formation and non-fusion. Osteoprogenitors in combination with fibrin, HA, PLA +/- osteoconductive materials +/- VEGF were evaluated in a heterotopic model aiming to find a novel concept for bone regeneration.We are also testing polylactic acid/glass/calcium phosphate scaffolds in combination with Platelet-derived growth factors and stromal cells to assess cell recruitment patterns for bone regeneration. Imaging, including high resolution, three-dimensional X-ray synchrotron radiation microtomography (microCT) is used to generate 3-D representation of angiogenesis, bone formation and scaffold degradation (*Figure 7*).

WOUND REPAIR

'Growing soft tissue'

- We have tested VEGF-isoforms produced in HEK 293 EBNA for angiogenesis in skin repair in the diabetic mouse model. These VEGF-isoforms are biologically active, promote VEGFR-2 phosphorylation, can be covalently bound to fibrin and are retained for prolonged time periods, promote accelerated wound closure in vivo (*Figure 8*). Covalently linked isoforms are superior to soluble VEGFmut in regard to the induction of angiogenesis.

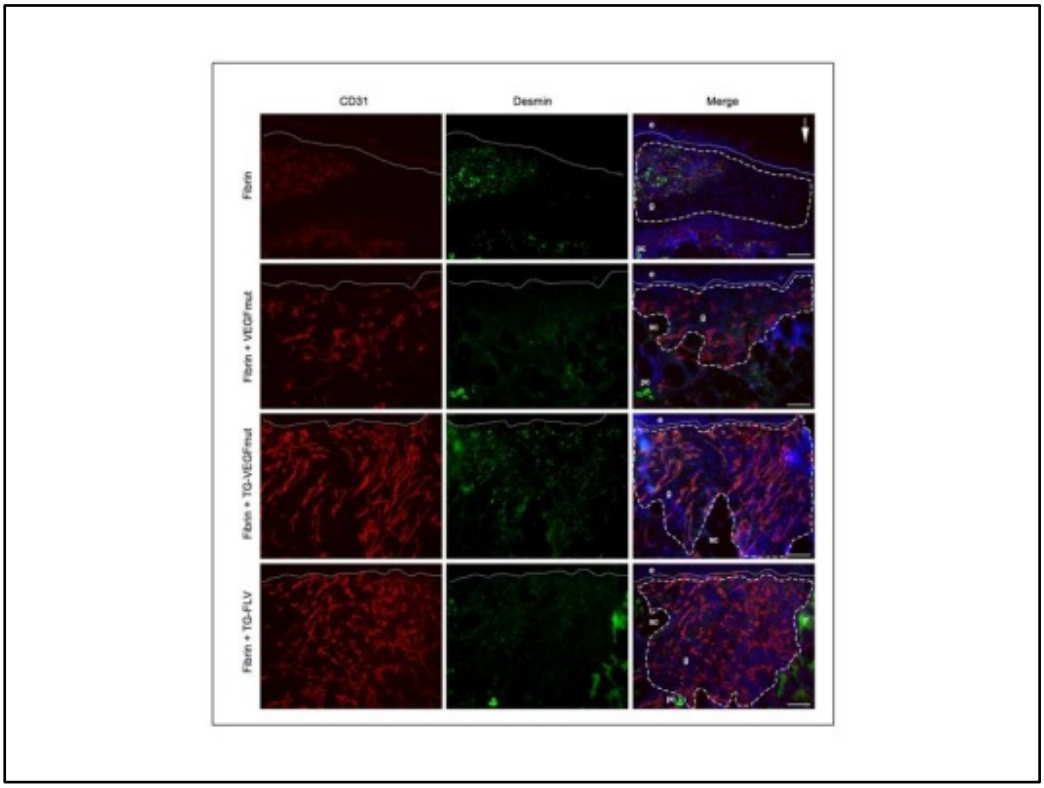


Figure 8. VEGF-isoforms promote angiogenesis in vivo. *Day 10 wounds in the diabetic mouse model*

- Studies on the angiogenic potential of Placenta Growth Factor (PlGF) have progressed. We have mapped the angiogenic capacity of PlGF to its heparin binding site. PlGF is cleaved by plasmin, which induces loss of the heparin binding domain, resulting in reduced chemotaxis, loss of matrix-binding capacity, reduced sprouting capacity and decreased granulation tissue formation after wound treatment in diabetic mice.

NEUROMUSCULAR REPAIR

'Your heart, your muscles, your nervous system'

- We have established two transgenic mouse lines in which endothelial cell-specific and tamoxifen-inducible expression of Cre-recombinase marks endothelial cells. The effect of soluble and immobilized angiogenic factors is currently analyzed using these reporter mice.

- PEG-Fib was able to promote mature well-differentiated myofibers in vitro and also showed well-defined skeletal muscle organization and differentiation in vivo. In mouse models of muscle injury TG-PEG and PEG-Fib caused increased survival of transplanted cells and an overall improvement in cell engraftment. Moreover PEG-Fib enhanced skeletal muscle differentiation of engrafted cells (*Figure 9*).

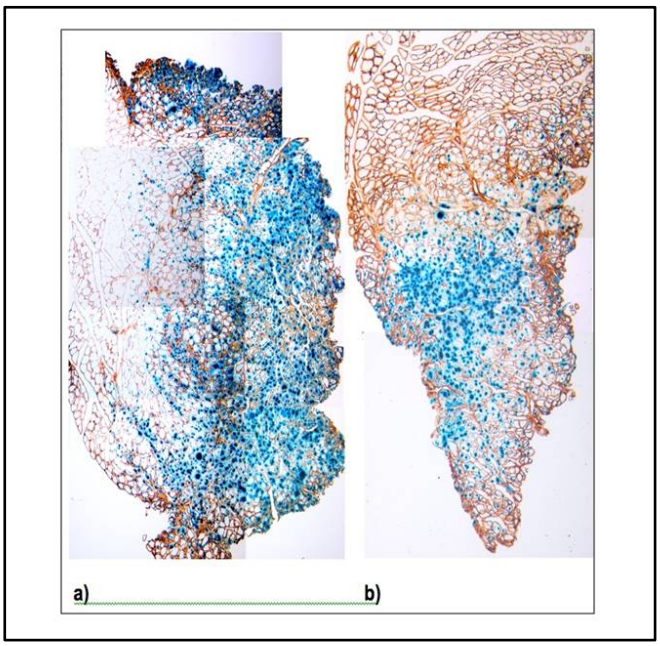


Figure 9. In vivo injection of Mesoangioblast expressing LacZ with (a) or without (b) PEG-Fib. *Remarkable amelioration on cell engraftment and retention into host Antrior Tibialis*

- Neonatal mouse cardiac cells, i.e. CMs, can be reprogrammed and grown in feeder-free conditions to generate iPS cells. CM-derived iPS cells survive, integrate, and differentiate in the host myocardium, significantly improving cardiac function. The results show that iPS cells methodology integrated with tissue engineering approach can ameliorate cardiac function when introduced into an infarcted myocardium.

- For neurological repair, the FN-910-GBD gel gave superior support for the growth of dorsal root ganglia (DRG) neurites. We are continuing the screening by determining the effect of hyaluronan scaffold on the outgrowth of DRG explants. Neurite extension was significantly enhanced by the presence of BDNF in the gel and reached long distances into gels containing FN-9-10, FN-9-10-GBD and full-length fibronectin. Using MACS® Cell Separation System from Miltenyi-Biotec, we are establishing a method to mobilize sufficient amounts of autologous Schwann cell-like cells from rat adipose tissue.

IMAGING

Maximising knowledge generation with optimal regenerative readouts'

- We have demonstrated:
  i) in vitro, the dynamic range of reporter expression and its correlation with changes in mRNA expression;
  ii) in vivo bioluminescence of gene expression using the DBM reference biomaterial;
  iii) a fluorescent angiography procedure that has been optimized to analyze vascular structures in implanted scaffolds and their structural relation with seeded stem cells.

To monitor vascular growth within biomaterials by micro-CT (*Figure 10*) we have found that with water soluble contrast agent we can obtain visualization of entire organs, tissues and major vessels. We generated correct values of vascular density in brain tissue, whereas other tissues (i.e. *M. tibialis anterior*) have leakage of contrast, which can nevertheless be used to study dynamic tissue perfusion by micro-CT (*Figure 11*).

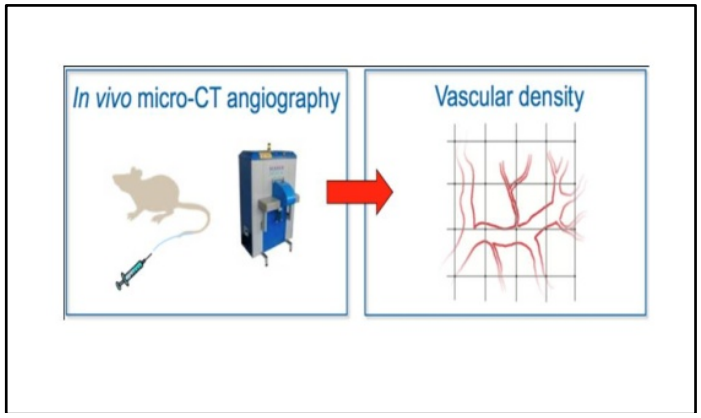


Figure 10: Schematic of in vivo monitoring of angiogenesis

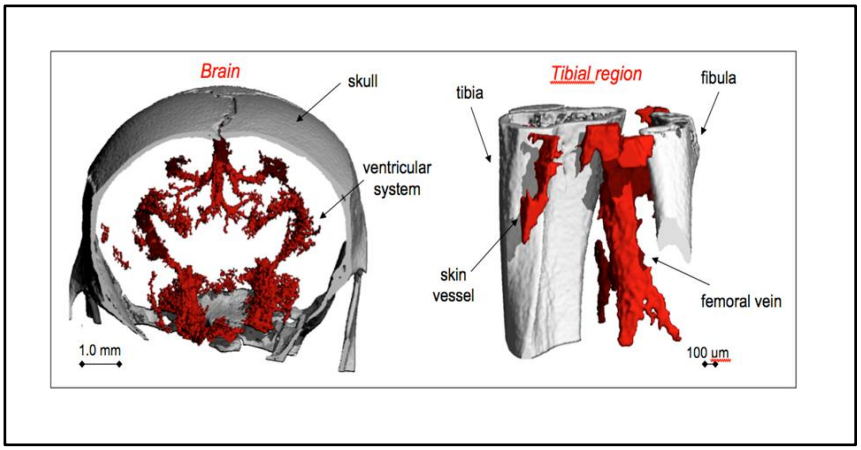


Figure 11: Example of anatomical micro-CT

- We have developed a methodology to import synchrotron data, reconstruct in 3D the vascular network and perform a large-scale computational fluid dynamic analysis using sample-specific geometries.

  Results in one network indicates the heterogeneity of fluid flow and shear distribution within the different vessels (*Figure 12*). Comparison of in-silico results with in vivo results on many different samples will be made to determine the functionality of the angiogenic process in tissue regeneration.

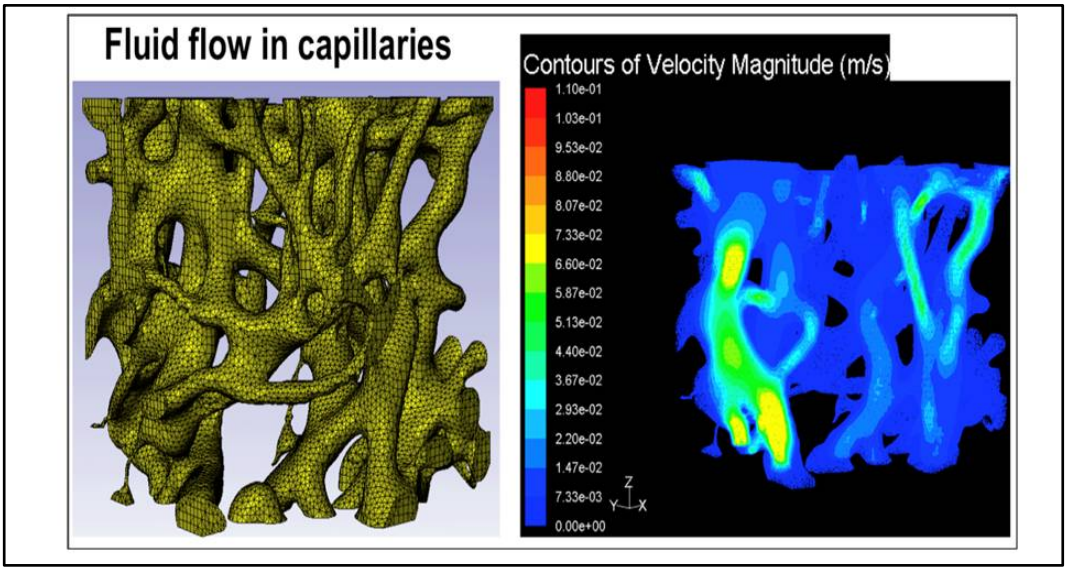


Figure 12: Example of 3D reconstruction of capillary fuid velocity

Angioscaff's partners are…

Team leader	Location
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Erella Livne	Technion Israel Institute of Technology
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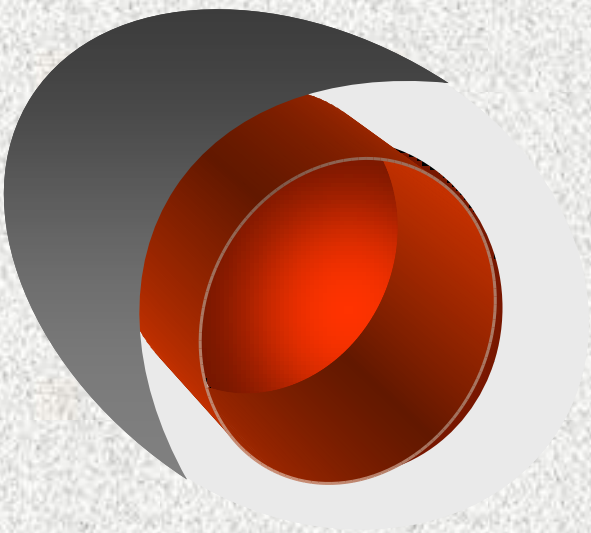
Ralph Müller	Eidgenössische Technische Hochschule Zürich
Sabine A. Eming	Universitaet Zu Koeln
Thomas Eschenhagen	Universitaetsklinikum Hamburg-Eppendorf
Heinz Redl	Ludwig Boltzmann Institute for Experimental and Clinical Traumatology
Ranieri Cancedda	Istituto Nazionale Per La Ricerca Sul Cancro
James Fawcett	The Chancellor, Masters and Scholars of the University of Cambridge
Anders Haegerstrand	NeuroNova AB
Jim Akerblom	Bio-Hyos AB
Nicola Zaghini	Biorigen Srl
Jonathan Dando	Dando Weiss and Colucci Ltd
Paul Kemp	Intercytex Ltd
Edward Currie	Kuros Biosurgery AG
Michael Apel	Miltenyi Biotec GmbH
Andreas Göppelt	Baxter Innovations GmbH
David Farrar	Smith & Nephew plc
Burkhard Fugmann	Bayer Innovations GmbH
Gianluigi Condorelli	Fondazione MultiMedica Onlus
Giulio Cossu	Fondazione Centro San Raffaele Del Monte Tabor
Paolo Bianco	Universita degli studi di Roma, La Sapienza

Angioscaff – At its half way point



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