FET Flagship

Statement on the clustering of health topics in Biofabrication, Regenerative Medicine and Medication

The current statement is related to the potential synergies between the following proposals for the new FET Flagship program:

- Human Organ Printing Era (HOPE)
- Organ-on-chip technology: a revolution in healthcare
- European Initiative for Regenerative Medicine
- Sensory Restoration

There have already been preliminary discussions between the core groups of these consortia. There is a strong willingness to further explore these synergies into a common FET flagship initiative under the name Biofabrication for Regenerative Medicine.

The scientific challenge:

All proposals are science-driven initiatives that exploit the potential of innovative technologies in regenerative medicine and biofabrication, for the future of healthcare sciences**.** Bridging personalized medicine and these new technologies is fundamental to achieve a rational roadmap to deliver the dream of long-lasting advanced therapies. Sensory organs will be also targeted as an important application, among others, as they provide excellent systems for such innovative therapies thanks to the mechanical and optical accessibility, and the crystalline structures of the tissues. With these proposals fundamental questions can be answered, such as:

1. What is the level of biomimicry needed to obtain a fully functional tissue or organ?
2. Should we conserve tissue and organ functionality or can we enhance it?
3. Which cells and cell organizations are needed to develop self-sustaining tissues, tissue models and organs?
4. How can we mimic the dynamic environment of healthy and diseased human tissues and organs in *in vitro* models?
5. Can we restore complex functional cell contacts such as neuronal circuits?

Potential for Transformative Change

In addition, the proposals will transform European healthcare and linked markets, creating collaborations with the industrial community by:

1. Developing manufactured functional tissues and organs, thus eliminating transplantation waiting lists;
2. Developing advanced 3D *in vitro* models to better understand pathological mechanisms and advanced therapies for rare and life-threatening diseases;
3. Developing new drugs and enable repurposing of existing off-the-shelf medicines through 3D *in vitro* models, identifying the most effective therapies for patients;
4. Produce tissues and organs generating less immune reaction than donor tissues;
5. Stimulating new regenerative medicine and biofabrication industries;
6. Transforming traditional surgical practice by personalized *in situ* robotic bioprinting of advanced therapies; and,
7. Creating a hub between partners that will guarantee professional knowledge diffusion and democratic access to new regenerative medicine therapies through biofabrication and organ-on-chip technologies;

Biofabrication, organ-on-chip, and Regenerative medicine (RM) are interdisciplinary areas of research, involving physicists, chemists, biologists, clinicians, robotic/mechanical and biomedical engineers, pharmacologists, computer scientists and mathematicians. Recent advances in both areas incorporated many (digital) platform technologies, including additive manufacturing, artificial intelligence, *in silico* modeling, stem cells, microfluidics, microelectronics, and

bioprocessing. Timely advancement of these technologies requires cooperation amongst a range of disciplines, close collaboration between academia and industry, which will be boosted by combining these proposals. Moreover, such an integrated approach will in our view deliver:

1. The first integrated artificial organ biofabrication line as a prototype clinical printing room;
2. Good manufacturing practice (GMP) Robotic 3D bioprinters for use in the operating theatre;
3. Human 3D mini-tissues and -organs for bioreactor-based high throughput automated screening and analysis for toxicity assays, drug development and other relevant industries, working towards personalized drug treatment and testing;
4. An open access database with digital information including models of human 3D tissues and organs to improve strategies and approaches developed for new therapies.
5. European network for basic research, GLP safety testing of biomaterials, GMP production guidelines and facilities, required standardization and quality control strategies for advanced therapies validation and translation;
6. Automatization of procedures and workflows necessary to lower the barrier to market entry for advanced therapies;

Why is this Flagship Necessary?

Scientific and commercial competition from the United States and Asian countries in advanced therapies, *in vitro* models and biofabrication requires that Europe not only provides resources to maintain technological competitiveness, but also to strategically invest in this quickly developing area. The clustering would build on Europe's track record of stem cell biology, biofabrication, engineering, advanced material science, and GMP manufacturing of medical therapies. Europe is already in a dominant position in stem cell biology, biofabrication, engineering and advanced material science and is home to many of its pioneers. Our initiative will capitalize on ongoing success and demonstrate European technological superiority and leadership.

Advanced therapies are expected to develop into a 5 billion Euro industry in 2016, with a yearly growth rate of 13.0% over the next 10 years, with biofabrication playing a pivotal role in this growth. The global market for bioprinting reached $263.8 million in 2015. The market should reach $295 million in 2016 and $1.8 billion by 2021, growing at a compound annual growth rate (CAGR) of 43.9% from 2016 to 2021. Despite of some promising regenerative medicine strategies already clinically used, in most cases their development is still a "black box" of complex information. We aim at tackling this information gap while improving biofabrication technologies that have a pivotal role in most of the stages of these novel strategies. This will allow large scale articulation of information between the EU partners promoting a faster and efficient development of functional advanced functional therapies.

In addition, organ-on-chip technology is in its infancy, but is also developing extremely rapid. Organ-on-a-chip and microtissues have been identified by the European Pharma-Industry as an essential requirement to reduce animal testing in the drug development cycle and improve early stage rejection of unsatisfactory compounds. This has the potential of reducing drug development costs by 1B Euros each new molecule.

Why is it good for Europe?

The combined consortia are comprised of European leaders in all major fields working towards advanced therapies, organ-on-chip, and biofabrication, from healthcare, academia, and industry. These technologies have been already identified as an important future industry, exemplified by recent significant investments in countries like the U.S., Japan, Canada, and China. Hence, the project will directly:

1. improve European healthcare, and the lives of ageing European citizens;

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2. guarantee citizens access to the new regenerative therapies and personalized medicine;
3. Activate structural exploitation of research results dynamics in order to maximize the impact of scientific activities and stimulate the growth of derived innovative value chains;
4. standardize academic research and commercial production of fabricated therapies;
5. lead the development and convergence of biofabrication, organ-on-chip and regenerative medicine;
6. create coherence within the rapidly emerging biofabrication industry;
7. stimulate the cosmetic, pharmaceutical, agriculture, food and robotic industries.

What would it take to do it?
A comprehensive and broad approach based on a Responsible Research & Innovation (RRI) paradigm, as offered by the synergy of the proposals, is necessary to bring vision and common goals to the efforts of such interdisciplinary efforts. Enabling the integration of advanced therapies into existing and emerging technologies is required for leadership in the success and intelligent exploitation of advantages offered by this rapidly growing multidisciplinary community. We want to connect biofabrication specialists with clinicians to define unmet medical needs and select fast and long-term clinical objectives for regenerative medicine. We want to interface with other emerging therapies (e.g. gene therapy, optogenetic therapy, stem cells and medical devices) to bring biofabrication at the forefront of regenerative medicine. Only with such a catalytic framework as a FET flagship, we can bring together a broad and critical mass of experts generating momentum to provide a continuous and concrete development of the different advanced therapies for tissue and organ regeneration.

What could be the role of ICT?
Data management and communication tools are gradually becoming mainstream among the different experts working in advance therapies. Despite these advances, significant work is needed to articulate different levels of information with increased simplicity and accessibility for a wider number of experts. Biofabrication requires a high level of automation for patient specific and large scale production. Functional databases with non-invasive and non-destructive imaging, testing and monitoring of biofabricated tissue and organs (sensors and imaging) are essential parts of quality control. Furthermore, image processing, machine learning, and wireless communication technologies provide exciting opportunities for real-time enhancement of these therapies from the operating theatre to the patient's home. Also juridical and economical aspects have to be considered in order to simplify the development of innovative process that could be derived from our activities. As consequence, it is imperative for the project to be combined with other established and emerging IT, electronic, mechanical, and material technologies, considering also juridical and economic issues, to deliver a complex solution to one of humanity greatest challenges.