FET Consultation - template FET Flagships

About you

HOPE (Human Organ Printing Era)

1. *What is your background? Are you submitting this proposal as an individual, or do you represent a community or institution?*

I, Jos Malda, president of the International Society for Biofabrication (ISBF), am submitting this proposal for a FET flagship initiative on behalf of the European ISBF Board members, Juergen Groll, Lorenzo Moroni, Will Shu, Giovanni Vozzi, and myself. We represent a pan-European multidisciplinary community of leading academic and commercial research teams in the field of bioprinting, biofabrication and biomanufacturing, as well as robotics, engineering and information technologies. Our core group is based in approximately 20 countries including the Netherlands, Germany, United Kingdom, Italy, France, Sweden, Austria, Romania, Switzerland, Finland, and consists over 50 researchers and professionals. Colleagues in our affiliated partner countries include Australia, New Zealand, Israel and Turkey.

What is the challenge and the vision?

2. *What is the grand S&T challenge and its underlying vision and what are the main objectives your initiative would address? Why is this a grand S&T challenge and what makes it a "game-changer"?*

Every day, an average of 16 people die in Europe and 22 in the US due to shortage of donor human organs. Our vision is to solve, once and forever, this shortage of organs for transplantation. To do this, we need to transform traditional surgical practice by inventing robotic bioprinting and integrating **information communication technologies** to provide a customisable implant that is robust and successful. Since the first human organ (kidney) transplantation in 1954 (Josephe Murray, Nobel Prize 1990), considerable research efforts have been committed to finding alternatives to treat the millions who are dying while waiting for donor organs. The challenge is not trivial and many avenues have been explored. In particular, xenogenic and allogeneic grafts have been exhaustively investigated and while human donor tissue is used in combination with immunotherapy, there are still more patients waiting for donor tissue than the ones who are being cured.

We aim to deliver what tissue engineering promised in the 1990s; a real-world solution to the challenges faced by people on waiting lists for organs. Our team believes that the post-diagnosis period is a time of action rather than acquiescence. Using the patient's own cells and anatomy to generate an information signal, an artificial tissue/organ – such as kidney, liver or pancreas – will be fabricated using a fully automated bioreactor system. The use of 3D bioprinting, which was by itself recently classified by Gartner Inc. as an information technology, is central to our approach to precisely build known cellular constructs that are fully vascularized. This approach will, besides better engineered tissues and organs also yield valuable personalised *in vitro* 3D test models. The assembly line of the 3D bioprinted tissue or organ replacements will be incorporated into a bio-factory, located on site at the hospital where the transplantation takes place. It is our opinion that the generation of this personalised, highly complex product, would only be possible with effective imaging and information communication technology systems. Moreover, these developments will also fuel the development of the mass-personalisation of test- and prognostic-models.

The HOPE initiative will impact on the quality of life of millions of Europeans by providing personalized solutions. It will also impact on healthcare costs regarding treatments of patients with failing organs, *e.g.* dialysis, etc. Drug-induced organ toxicity accounts for 30% of all drugs that fail prior to reaching the market. For example, nephrotoxicity accounts for 2% of failures in the preclinical stages and 19% of all failures in Phase III. Currently, cell-culture based toxicity models are not predictive. While of the thousands and sometimes millions of compounds that are screened and assessed initially only few will receive approval, the estimated costs of each successful drug is estimated to be €2.6 billion. *In vitro* biofabricated tissue and organ models could thus potentially save several €100M in the development costs of a new drug by providing effective screening prior to the start of animal trials.

Biofabrication of tissue and organs is a direct manifestation of the ongoing **Third Industrial Revolution** (Economist, 2012), which is driven by the exponential successful utilisation of additive manufacturing technologies. The human body is perfectly suited to customisable manufacturing, with every individual having a unique structural and biochemical makeup. Automated manufacturing will assist in fulfilling the regulatory requirements by standardised manufacturing. This seismic shift in manufacturing towards mass-personalisation comes at a time that cell transplantation technologies, particularly the recent research in induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) allow reproducible and expandable cell sources from people of every age. Imaging equipment have also undergone a revolution over the past decades, becoming faster, more accurate and able to accumulate large quantities of data. Together with increased information and communication technology data, 3D bioprinting can be combined with other established and emerging IT technologies to deliver a complex solution to one of humanities greatest challenges.

3. *What are the main technologies, including digital technologies, which your initiative will advance?*

3D bioprinting is a truly interdisciplinary area of research. It involves computer scientists, physicists, biologists, clinicians, robotic/mechanical engineers and chemists. In this respect, 3D bioprinting is a field that brings different researchers together, and coalesces many recent (digital) platform technologies, such as stem cells, nanomedicine, artificial intelligence and additive manufacturing. A grand challenge for 3D printing enhances cooperation further, since then all members of the research team are closely working towards the same goal from different perspectives.

Initially, certain aspects of basic sciences require improvement. This includes:

- developmental and stem cell biology: stem cell organogenesis and organoids formation, biological self-organisation and *in vitro* self-assembly
- tissue fusion and accelerated tissue maturation, understanding of cell/material interactions
- Structure/material properties of tissue spheroids (biomechanics)
- *in vitro* models of human diseases
- rational design and chemical synthesis of 3D bioprintable biomaterials and hydrogels
- understanding flow processes and rheology at the micrometre (pico-nanolitre) scale
- modelling and computer simulation of bioink rheology and post-printing tissue fusion

These basic science concepts formulate some of the advanced research tools and enabling technologies, such as efficient representation of 3D models, conversion of tomographic data to design file formats, and digital manufacturing tools. Biocompatible inks, photoinitiators and biomaterials form the building blocks for cell patterning, positioning and 2D/3D positioning. Micro and mini-bioreactors for bioprinted tissue and organs are an essential component of an automated biofabrication, and results from basic science in developmental biology and spheroid fusion. Ultimately, these become part of automated biofabricator rooms for organ printing.

Information communication technology is obligatory to integrate all of the various components. Non-invasive and non-destructive imaging, testing and monitoring of bioprinted tissue and organs (sensors and imaging) are essential parts of quality control, including wireless communication technologies. Principles of toolpath programming can optimise cell survival with robotic 3D bioprinters, and programmable self-assembly of bioprinted constructs (4D bioprinting) improves the assembly processes.

The outcomes that HOPE will significantly advance include:

- Tissue/organ printing (kidney, then others – lung, liver, cardiac muscle, thyroid) and the establishment of an organ fabrication line.
- *In situ* bioprinting (printing at the “bedside”)
- Automated biofabrication line of *in vitro* human models of tissues and organs for cosmetic and pharmacological industries
- Personalised predictive diagnostic models

- Body on a chip for drug development and compound screening.

Why is it good for Europe?

4. *Is your initiative relevant for the European industry and what is its innovation potential that would benefit Europe's economy and/or society?*

Our aim is to exploit the potential of biofabrication, which is at the interface of information technology, biology and engineering, as a game changer for the European health sector. We plan to transform European healthcare by developing **new 3D tissue models** and **eliminating organ shortages**, create **new 3D bioprinting industries**, and transform traditional **surgical practice** by personalised *in situ* (at the hospital) **robotic bioprinting**. This extensive 3D bioprinting consortium will deliver significant benefits to both the European and International community, including:

1. **Solving the shortage** of human organs for transplantation through 3D bioprinting and dramatically improving European healthcare
2. Combining surgical **robotics** with **computer-aided** 3D bioprinting (including elements of **artificial intelligence**) to **transform surgical practice** for improvements in surgical treatment and outcome
3. Provide opportunities to the **pharmaceutical industry** by improving drug discovery tools and toxicity assays with 3D bioprinted *in vitro* models of healthy and diseased human tissue and organs, including automated high throughput screening, significantly decreasing animal experimentation.
4. Create **new high tech jobs** based on the strong European tradition in engineering and high technology standards to maintain and enhance **European technological superiority** and competitiveness
5. Create synergies with existing and emerging industries including:
    a. **Cosmetics** (*in vitro* testing models)
    b. **Agriculture** (biofabricated leather and food)
    c. **Space exploration** (using 3D human living tissue and miniorgans as radiation sentinels)
    d. Future **defensive capacity** of Europe. (employing of human 3D tissues and organs for testing effect of biological, chemical and nuclear weapon and development of protective countermeasures)

5. *Are there existing <u>international</u> research initiatives linked to this proposal? How would this initiative position Europe with respect to other regions in the world?*

Our 3D bioprinting European community is vibrant and includes some of the pioneers in the field. There is an existing network especially within the International Society for Biofabrication with a strong European share. This includes the first International Master's degree in Biofabrication. www.biofabdegree.net. This is a funded cooperation between Europe (EACEA) and Australia to provide practical research experience, courses and international mobility for 40 students until 2018. Further, within FP7-NMP projects HydroZONES, Bio-Scaffolds and RAPIDOS, which focus on 3D-printed constructs for cartilage and bone restoration, bridges are built between Europe, Australia and China. Moreover, Centres of Excellence in Additive Manufacturing are opened in Canada, USA, Singapore, South Korea, Japan, Australia. The NIH and DARPA agencies in the USA launched a $100M initiative for organ on a chip and Body on a chip research in 2012. The HOPE initiative would allow Europe to compete in this fast moving research space.

What would it take to do it?

1. *What is the scale of the effort required to reach the objectives and how long will it take to do so?*

The next ten years should be a transformational period for 3D bioprinting and additive manufacturing technologies in medicine and biology. Scientific competition from the United States and Asian countries in 3D bioprinting requires Europe not only to provide enough resources to maintain technological equivalence, but to strategically invest in this field. In this respect, there are many advantages to establishing a strong European product rather than importing methodologies developed under different regulatory requirements.

A comprehensive and broad approach to enabling and integrating 3D bioprinting into existing and emerging information technologies is required to be the first to succeed and exploit advantages in this rapidly growing scientific discipline. We anticipate that this consortium will be a 1-billion-euro initiative that will span a decade. In context, the development of tissue-engineered skin by Advanced Tissue Sciences in USA cost $200 million. We intend to build a broader, bigger collaborative effort that promises to deliver an automated approach to a 3D-bioprinted tissues/organs by 2027. While this is significant investment, the cost/benefit of a successful product is quite clear – a large number of people (millions globally) who die waiting for organs require a high-value product (*e.g.* artificial hearts estimated to cost 250,000 USD). This level of expenditure already occurs for people on waiting lists – the treatment of end stage kidney diseases is particularly expensive and amounts to a staggering 7% of all healthcare costs in the USA.

In summary, At the conclusion of the 10-year project, HOPE aims to deliver:

1. An integrated organ biofabrication line as a prototype of future organ biofabrication plant;
2. *in situ* robotic 3D bioprinters for use in the operation room;
3. the development and testing of human 3D mini-tissues and mini-organs for high throughput automated analysis of tested compounds in cosmetic and pharmacological industries, as well as personalised treatment evaluation;
4. a shared bioprinting database on digital models of human 3D tissue and organs;
5. shared databases on biomaterials and hydrogels suitable for bioprinting.

2. *Why is Europe well positioned in terms of skills/expertise and capabilities, including industrial capabilities, to address the challenge and exploit the results? Which are the research communities to be involved?*

Bioprinting is expected to develop into a >billion euro industry over the next 10 years. The HOPE consortium builds on Europe's strong engineering traditions and in particular superiority in precision engineering and advanced material science. The first commercial 3D bioprinters were built in Europe (e.g., Envisiontec, Germany; RegenHU, Switzerland) and numerous additive manufacturing companies (e.g., Layerwise, Belgium; Nanoscribe, Germany) started here. There is a sustained interest in healthcare from some of the best precision engineering companies (Siemens, Germany; Philips, Netherlands) and Europe currently has the world leader in additive manufacturing software (Materialise, Belgium). Europe has successful cell therapy (TiGenix, Belgium) and bio-monitoring companies (BioTek, Germany) and can capitalise on strong European expertise and leadership position in industrial robotics (Kuka, Germany; ABB, Sweden; Staubli, Switzerland); essential for developing *in situ* articulated 3D bioprinters. Moreover, significant pharmaceutical companies with a strong interest in predictable *in vitro* models are present within Europe. Taken together, Europe is unique with its advanced research and industrial technologies all within a small region of the world. Europe is already in a dominant position in this emerging biofabrication technology and HOPE must capitalise on ongoing success and demonstrate European technological superiority and leadership.

3D bioprinting is an incredibly interdisciplinary field, and draws on robotics, materials science, electrical engineering, mechatronics, physics, chemistry, molecular biology, autonomous systems, surgery and cell biology. Our application team comprises leaders in all of these fields, from both academia and industry. HOPE brings together new research fields such as stem cell biology, artificial intelligence, materials science and nanotechnology and combines them with more traditional fields such as mechatronics, software, mathematical modelling, physics and chemistry.

3. Are there existing national or European research initiatives linked to this proposal? What is the added value for such an effort at the European level?

In our opinion, the European 3D bioprinting community is more coherent than our American and Asian counterparts. Many of the global leaders in biofabrication originate from Europe and have built research and development links within the Union. The HOPE initiative complements European Research Council funded projects, including LebMEC, 3D-JOINT, Design2Heal, and CELL HYBRIDGE Further, it also builds on larger consortium projects such as (H2020) FAST, (FP7-NMP) HydroZONES, RAPIDOS and Bio-Scaffold.

There is an exceptional interest in additive manufacturing and 3D bioprinting has the opportunity to attract the most dedicated and intelligent students into the field. Europe has already established the world's first MSc in Biofabrication with Australia that is expected to train 40 students by 2018. Moreover, there are multiple additional local interdisciplinary research consortia focussing on "Biofabrication" with dedicated graduate programs. Our group envisions to extend this and to also provide academic/industrial training at the PhD level.

The increased interest in bioprinting is also reflected in the fact that increasing numbers of sessions during large international conferences on biomaterials, tissue engineering, regenerative medicine and surgery are dedicated to this topic.

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Thus, proposed FET Flagship Project HOPE is very ambitious multidisciplinary project on interface of science and technology which integrates and advances application of information and communication technologies in 3D bioprinting It will stimulate the development of new convergent research discipline 3D biofabrication, will dramatically improve European healthcare, health and well-being of European citizens, and provide strong economic impact by creating new rapidly emerging biofabrication industry and transforming cosmetic, pharmaceutical, agriculture and robotic industries.