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REPORT

Artificial vascularized scaffolds for 3D-tissue regeneration — a report of the ArtiVasc 3D Project

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Abstract: The aim of this paper is to raise awareness of the ArtiVasc 3D project and its findings. Vascularization is one of the most important and highly challenging issues in the development of soft tissue. It is necessary to supply cells with nutrition within a multilayer tissue, for example in artificial skin. Research on artificial skin is driven by an increasing demand for two main applications. Firstly, for the field of regenerative medicine, the aim is to provide patients with implants or grafts to replace damaged soft tissue after traumatic injuries or ablation surgery. Secondly, another aim is to substitute expensive and ethically disputed pharmaceutical tests on animals by providing artificial vascularized test beds to simulate the effect of pharmaceuticals into the blood through the skin. This paper provides a perspective on ArtiVasc 3D, a major European Commission funded project that explored the development of a full thickness, vascularized artificial skin. The paper provides an overview of the aims and objectives of the project and describes the work packages and partners involved. The most significant results of the project are summarized and a discussion of the overall success and remaining work is given. We also provide the journal papers resulting from the project.

Keywords: vascular, skin, bioprinting, 3D, additive manufacturing

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1. Background

Vascularization is one of the most important and highly challenging issues in the development of soft tissue. It is necessary to supply cells with nutrition within a multilayer tissue, for example in artificial skin.

Research on artificial skin is driven by an increasing demand for two main applications. Firstly, for the field of regenerative medicine, the aim is to provide patients with implants or grafts to replace damaged soft tissue after traumatic injuries or ablation surgery. Secondly, another aim is to substitute expensive and ethically disputed pharmaceutical tests on animals by providing artificial vascularized test beds to simulate the effect of pharmaceuticals into the blood through the skin.

To date, it has only been possible to cultivate the upper layers of the skin — the epidermis and dermis — with a total thickness of up to 200 micrometers outside the human body. A complete skin system, however, should also include the subcutaneous tissues having an overall thickness of several millimeters. In order to co-cultivate the hypodermis, blood vessels supplying this tissue are imperative. The aim of the ArtiVasc 3D project was to enable significantly more complex tissues to be cultivated in vitro by developing artificial blood vessels.
2. Introduction

The aim of this paper is to offer a perspective on this large and ambitious project. It aims to disseminate the main findings and achievements of the ArtiVasc 3D project to the wider international academic and research community. The paper provides an overview of the aims and objectives of the project, summarizes the work conducted and highlights some of the most significant achievements with references to published results where possible. The paper offers a critical review of the project and the relative advantages and disadvantages of the large, multidisciplinary, multi-center approach.

The multidisciplinary ArtiVasc 3D project consisted of a consortium of partners from research and industrial institutions across Europe. The project brought together experts in biomaterials development, cell-matrix interaction, angiogenesis, tissue engineering, simulation, design and additive manufacturing to generate bioartificial vascularized skin in a fully automated and standardized manufacturing approach, rapidly and inexpensively. To achieve these aims, ArtiVasc 3D needed to provide a micro and nano scale manufacturing and functionalization technology that would enable the generation of fully vascularized bioartificial tissue capable of the necessary nutrition and metabolism functions (illustrated in Figure 1).

By overcoming these scientific and technical challenges, the project aimed to make a significant contribution to improving and accelerating patient treatment in emergencies and to reducing animal testing to an absolute minimum. The recently completed project was four years in duration starting in November 2011. The project was coordinated by Fraunhofer ILT and involved 20 partners across Europe (see acknowledgments for the full list). The €7.8 million funding was obtained through peer-reviewed open competition from the EU 7th Framework Programme call (FP7-NMP-2010-Large-4, GA no.: 236416). More details about the project can be found in the project website.[1]

3. Project Work Packages

As is typical in large European projects, the research and development required was broken down into a series of work packages (WP) covering three main areas: material development and characterization, process development, and matrix tissue interaction and tissue development. In total, 12 work packages were established as shown in Table 1. Work packages 1, 11 and 12, which are italicized, were largely concerned with the scientific coordination, dissemination and management of the project.

<table>
<thead>
<tr>
<th>WP no.</th>
<th>Description of work package</th>
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</table>

4. Material Development and Characterization (WPs 2 and 5)

The overall goal of this section was to provide a new tailored material combination that fulfilled the requirements for soft tissue engineering but was also compatible with additive manufacturing (AM) processes, specifically inkjet printing, stereolithography/multiphoton polymerization (MPP) and electrosprin-
ning, as well as enabling biofunctionalization. The most important challenge of the material development research was not related to a singular parameter, but rather the combination of all of the desired properties within an appropriate combination of materials. Within this WP, the materials were also evaluated regarding their chemical, physical, thermal and mechanical properties as well as fundamental tests of cytotoxicity.

4.1 Objectives of WP2

The overall goal of WP2 was to provide a new tailored material that fulfilled the requirements for soft tissue engineering whilst also being compatible with the combined AM processes and biofunctionalization.

- To design and synthesize 40 chemical structures for blood vessel materials and supporting scaffold materials for 3D AM processes and fiber materials for electrospinning,
- To characterize materials in terms of their chemical structure, thermal and mechanical properties, viscosity, photo-curing behavior, surface functionality and cytotoxicity,
- To adapt polymers for AM and for the needs of blood vessel systems in regard to demands for permeability, mechanical properties and biocompatibility,
- To modify surfaces of polymers to enable biofunctionalization,
- To analyze long-term (1–6 months) behavior of basic materials for the vascular system.

4.2 Objectives of WP5

The overall objective was the biofunctionalization of the artificial vascular structures and of the surrounding fiber matrix obtained from WPs 2 and 4. The biofunctionalization was specifically aimed for the following:

- To minimize cytotoxicity of the biofunctionalized material,
- To control cell adhesion and migration on material surfaces and to stimulate proliferation by binding functional groups to the surface,
- To stimulate neo-angiogenesis,
- To design a process that can be integrated into the proposed combined AM process.

4.3 Highlights

Materials compatible with inkjet printing, stereolithography/MPP for blood vessel generation were developed to fulfill the main requirements. An elastic, photocurable polymer that is inkjet printable and UV-curable was successfully used to build branched porous blood vessels by stereolithography[2]. However, developing an entirely compatible support material proved challenging and was not achieved during the project. Consequently, as inkjet printing necessitates a removable support material, it was not possible to inkjet print vessel structures as envisaged. Additional research was done on gelatin development for additive manufacturing of vessel substitutes [3,4].

To allow endothelialization of those vessels, an inner-surface functionalization was necessary. The University of Stuttgart developed a procedure for coating these vessels with heparin, which allows homogenous cell cultivation[5]. For local functionalization of vessel scaffolds and cell guidance of the surrounding scaffold, localized laser functionalization was investigated[6]. Another aspect was the scaffold material for the surrounding fat. For that reason, two kinds of materials are considered. One kind of materials are electrospun fibres as scaffolds while the other kind are hydrogels filling the pores between the fibres and providing growth factors and allow nutrition of embedded cells[7]. Furthermore, a huge number of electrospinnable materials were tested for their biocompatibility and showed very promising results (INNO). Electrospun meshes have been successfully characterized for their use in adipose tissue generation[8–10].

5. Process Development (WPs 3, 4, 7 and 8)

The overall goal of this section was to develop and demonstrate a combined AM process that integrated the three technologies inkjet printing, stereolithography/MPP and electrospinning to build up the vascularized scaffold utilizing the newly developed materials.

The design of the vascular structures is essential to enable them to replicate human tissue performance. The design and modelling tasks involved physiological simulation and testing to define the optimum vessel dimensions and configuration. This was done through theoretical calculations, physical experimentation and Computational Fluid Dynamics (CFD). To enable AM the design phase needed to incorporate the optimized parameters and produce three-dimensional models that would define the structures. The design tasks involved the creation of a bespoke Computer-Aided Design (CAD) application that could take in physiological parameters, number of branches, skin patch size, vessel diameters, etc. and automatically generate the vessel structure as a solid three-dimensional computer model in a format suitable for AM (e.g., STL file). In
order to integrate with the newly developed combined AM process, computer programs were devised that sliced the CAD model and produced appropriate layer data for each aspect of the AM process. This included image data to drive the inkjet printing steps and vector files to control the stereolithography steps.

For the AM process development, the first task was to test the new materials for their suitability for inkjet printing and to define the optimal printing parameters. Secondly, MPP was adapted with regard to the developed material and the desired scaffold structures by developing appropriate beam guidance and optics. Thirdly, the materials were tested for their suitability in the electrospinning process and to define the process parameters. Further work involved the development of a process-strategy and concept for combining inkjet, MPP and electrospinning and then to examine the co-action of all three production technologies. This required a test rig including all three technologies to be produced, as well as the development and generation of the necessary machine control code enabling process-integration and optimization.

5.1 Objectives of WP3

The overall goal was the modelling and design of a vascular system that effectively delivers O₂ and other nutrients from the circulating blood flow to the surrounding tissue. Specific objectives were:

- To investigate the nutrient permeation within the vascular system to the cells,
- To identify the requirements for the blood flow through the system and provide an informed design specification,
- To develop design tools for generating 3D CAD models of optimum vascular systems (see Figure 2)[11,12],
- To translate 3D models into an appropriate data format for the proposed AM process.

5.2 Objectives of WP4

The overall goal was to develop a combined AM process that integrates inkjet printing, MPP and electrospinning to work as one single process. Specific objectives were:

- To deliver machine specification for building a working process module in WP7,
- To iteratively adapt and optimize the process for each process technology in cooperation with material development,
- To develop a strategy for combining these three technologies in one process,
- To build a test rig where the combination of the technologies can be examined and developed further.

Figure 2. The user interface for the automated generation of vessel designs.

5.3 Objectives of WP7

The overall goal was to develop the integrated machine prototype encompassing the developed processes through a set of pre- and post-processing steps. Specific objectives were:

- To establish the machine prototype specifications for the machine demonstrator,
- To develop prototype solutions for the production module, combining inkjet printing, MPP and electrospinning and modules for necessary pre- and post-processing steps,
- To manufacture and implement the integrated machine prototype,
- To set the prototype into service, commissioning, parameters tuning and equipment adjustment.

5.4 Objectives of WP8

The overall goal was to demonstrate and test the prototype process and equipment resulting from WP7. Specific objectives were:

- To demonstrate the fulfilment of requirements for the scaffold generation,
- To make fully functional scaffolds for analysis,
- To produce scaffolds for biological applications.

5.5 Highlights

The three AM processes have been installed and extensively characterized. By using UV-curing it could be demonstrated that vessels with different geometries and sizes could be generated either by MPP with dimen-
sions in the micron range or by stereolithography with dimensions in the mm to cm range (see Figure 3)[2,13].

Figure 3. Vessel structure created using stereolithography.

Material development for inkjet printing proved to be very challenging. It was possible to demonstrate the printing of flat structures successfully. However, the development of a support material necessary for multi-layered structures that was water-soluble and yet did not mix with build material proved impossible during the project.

The goal of process combination was realized within a manufacturing chain containing inkjet printing units, stereolithography or MPP-module and UV-curbing unit working under inert gas atmosphere (see Figure 4). Electrosprining was not integrated into this machine but a separate electrosprinning module exists (INNO, UNISA) and it can be combined by using a container transport system.

Figure 4. Prototype modular production unit (Fh-IPA).

6. Matrix Tissue Interaction and Tissue Development (WP6, 9, 10)

The overall objective of this WP was to achieve a detailed understanding of the characteristics and functions of vascular cells in contact with novel materials to optimize the establishment of composite vascular systems. This included the interaction of perivascular cells, with endothelial cells and the underlying extracellular matrix (ECM). Additionally the interaction between adipocytes and electrosprun or biological matrices will be investigated.

The vasculature is characterized by a composite structure of functionally distinct cells like pericytes (PC) and endothelial cells (EC) in the vessel wall, specialized ECM layers (vascular basement membrane, interstitial matrix) and contacts with surrounding tissues. This WP defined the effects of novel materials on the phenotype, behavior and receptor-mediated signaling of vascular cells with a focus on perivascular and endothelial cells to improve maturation and stability of engineered vascular structures. In parallel adipocyte interactions with electrosprun and biological scaffold materials was analyzed.

6.1 Objectives for WP6

The main objective was to achieve a detailed understanding of the characteristics and functions of vascular cells in contact with novel materials to optimize the establishment of composite vascular systems. This included perivascular cells, essential for the mutual interactions of endothelial cells to the underlying ECM and surrounding tissues. Additionally, the interaction between adipocytes and electrosprun or biological matrices was investigated. Specific objectives were:

- To define and modify the effects of novel materials and specific ligands regarding to adhesion, proliferation and differentiation on individual vascular cells with a focus on pericytes, endothelial cells and adipocytes,
- To realize the efficient endothelialization of the artificial vascular systems,
- To evaluate the interaction of adipocytes with electrosprun or biological matrices,
- To transfer the knowledge from the murine system to human systems.

6.2 Objective for WP9

The overall objective of WP9 was the development of a vascularized composite graft using the example of vascularized skin by the achievement of the following specific objectives:

- To develop in vitro fatty tissues and compare them to non-scaffold and scaffold-based models,
- To combine this fat layer with a dermal and
6.3 Objective for WP10

The overall aim of this work package was to validate the biofunctionality of the delivered scaffolds and composite grafts. Specific objectives were:

- To evaluate the biocompatibility of electro-spun scaffolds and artificial vascularized raw material,
- To validate the functionality of cell seeded composites and their combination,
- To validate the usability of the artificial vascularized skin as a pharmaceutical test system,
- To validate the usability of the artificial vascularized skin as a tissue graft.

6.4 Highlights

A three-layered vascularized skin will consist of at least four or five different kinds of cells in co-cultivation. All those cells will interact. Therefore, mechanisms and interaction effects have to be studied. Additionally, all cells must be available from the same species, in this case from human. However, until the beginning of this project some cells e.g. pericytes had only been characterized from mice. Therefore, scientists had to establish protocols for the isolation of human pericytes. They characterized human pericytes in comparison to mouse pericytes[14]. In the end, they achieved stable human pericyte populations. Co-cultivation of pericytes and endothelial cells was analyzed as well. A cultivation medium that supports both cells was found.

The second aspect was the build-up of fatty tissue. After development of isolation and cultivation protocols, the optimized surrounding material was tested. Scientists chose a hydrogel from hyaluronic acid and gelatin for the cultivation of adipocytes (see Figure 5)[15–19].

The integration of the vascular system into the fatty tissue is the last challenge in the project. The first experiments in the newly developed bioreactors are ongoing and results are expected in October 2015.

Figure 5. Newly developed bioreactor for vascularized fat cultivation (Fh-IGB, Unitechnologies).

7. Overall Results

In order to achieve the desired properties, the scientists in this project combined the freeform AM methods of inkjet printing and stereolithography (or MPP). With these combined processes, the researchers were able to achieve a very fine resolution for the construction of branched, porous blood vessels with layer thicknesses of about 20 microns. The researchers used mathematical simulations to develop data for the construction of branched structures. This data should create the conditions so that branched structures can be generated which allow uniform blood supply to a given size of skin patch. The use of the acrylate-based synthetic polymer developed in the project permits the scientists to construct these optimized vessels with a pore diameter in the order of hundreds of microns. Compared to conventional methods, the ArtiVasc 3D process provides the general conditions to produce branched and biocompatible vessels in this size range for the first time.

The development of an artificial, three-layered perfused skin model was ambitious and pioneering but this project has developed a 3D Printing process for the production of artificial blood vessels using innovative materials. The project has laid the foundation to cultivate a full-thickness skin model to a much greater layer thickness than previously possible.

One of the biggest challenges the project ArtiVasc 3D faced was to develop the right material for the production of artificial blood vessels. For them to be used in the human body, these vessels must have the correct mechanical properties and biocompatibility as well as full processability. Indeed, endothelial cells and pericytes must be able to colonize the artificial blood vessels.
At the time of writing, the project has generated 26 conference presentations (2 pending), 15 journal publications (with 5 in press or under review) and a PhD thesis. Many more are currently in progress.

8. Discussion

The results of ArtiVasc 3D are shaping the future. A toolbox has been developed that can respond flexibly to diverse materials, shapes and sizes. These results can be viewed as a precursor to a fully automated process chain for the production of artificial blood vessels that can be integrated into existing lines. Another highlight of the project is the successful breeding of adipose tissue in a novel bioreactor. The combination of the fatty tissue with an existing skin model allowed the production of a full-thickness skin model that has a thickness of up to 12 millimeters.

Throughout the four years of research, the researchers have faced many challenges that were not expected in the beginning. At the beginning, researchers defined specifications that were to be met at the end of the project. Those specifications ranged from material properties for processability, such as viscosity and material interaction, to the biological requirements, such as biocompatibility and elasticity. The material scientists met 9 out of 10 of those requirements. Nevertheless, the development of two biocompatible materials able to print next to each other and to dissolve one of these materials afterwards (i.e., a support material) was unfortunately not possible within the timeframe. This influences the build-up of blood vessels within the combined automated process. Nevertheless, researchers found alternative routes to generate porous branched vessel structures by using stereolithography and produce linear porous vessels by using electrospinning or dip coating. Thus, new technologies have been established to achieve the final goal of porous vessels.

While engineers worked on vessel generation, another group of chemists and biologists worked on the endothelialization of those vessels. It took a lot of effort, a huge number of materials and protocols to define the best protocol for endothelialization.

In parallel, biologists and chemists broke new ground in the field of fat tissue generation. The biggest, and up until now unavailable, third layer of the three-layered skin model. They developed protocols for isolating cells and gained knowledge in handling of adipose tissue derived stem cells and mature adipocytes. In the end, they could successfully demonstrate cells growing in hydrogels developed within the ArtiVasc 3D Project. It is still challenging to find the right cultivation media allowing not only adipocytes but also pericytes and endothelia cells to grow under co-culture conditions. Biologists together with engineers developed a bioreactor that can be perfused with media to provide nutrition to all cultivated cells.

Since not only fatty tissue was the goal of the project but also three-layered skin, the biologists tried to develop a dermal and epidermal tissue from existing protocols on top of the adipose tissue. In stainings, they were able to show the formation of all three layers. Analysis of the expression of typical tissue marker is still under investigation.

The final aim to build up a genuinely vascularized artificial skin remains a big challenge. Due to unforeseen challenges coming from the material and process development and a tight project plan, some steps towards the vascularized tissue are still open. Up to now, we have demonstrated the three-layered skin without vessels. By using stereolithography as the build-up strategy, branched porous vessels are available today. The integration and function of these available endothelialized vessels has to be demonstrated. We expect neo-angiogenesis from those porous blood vessels containing endothelial cells and pericytes, which would be a real benefit for the nutrition of the thick fatty tissue because more natural and reliable processes are expected. However, this will most probably be a challenge for future research projects. The original plan in ArtiVasc 3D foresaw the generation of an elastic, branched blood vessel system, to provide a scaffold for endothelial cell and pericyte organization. Since we found that just a hollow channel in the middle of a hydrogel could be used as a supply channel, we could imagine different strategies for nutrition supply and vessel organization without having a static scaffold wall. By just using functionalized hydrogels that contain growth factors, those factors could be released by time dependent or by photo-induced degradation of the hydrogel. This would add the fourth dimension (time or 4D) to the 3D printing technology and could induce cell organization and blood vessel formation with time. Nevertheless, the generation of a branched blood vessel scaffold is necessary for other applications such as blood vessel replacement. The other reason for such a scaffold is the connectivity to the natural tissue in case of implantation in the future. This will not be possible with those self-organized vessel systems.
The successful conquest of the third dimension need not be confined to the skin, however. The ArtiVasc 3D project has also laid the foundations for future developments in three-dimensional tissue engineering. By using the principle of blood circulation with artificial blood vessels, medical engineers will be able to build larger structures such as whole organs in the future. For full skin cultured in vitro, there are a variety of applications: quick assistance for large-area skin injuries such as burns or after tumor resection as well as a replacement model that would make animal testing in the pharmaceutical industry unnecessary.

Whilst some of the objectives were not fully achieved, the project has produced a significant number of scientific findings and technical innovations. It is our view that these achievements could not have been made by the individual partners working in isolation. This kind of large, multidisciplinary, multi-institution project poses some practical, logistical and managerial challenges. Some of the pros and cons are summarized in Table 2. However, the authors hope that the achievements of the project illustrate that it was productive and successful and forms a valuable and significant contribution to the research in tissue engineering and bioprinting. We encourage other researchers in the international community to develop multidisciplinary and multi-institutional projects where the combination of expertise and facilities can achieve more than the sum of the parts.

9. The ArtiVasc 3D Project Partners

1. Aalto University, Finland
2. Albert-Ludwig University of Freiburg, Germany
3. AO Research Institute, Davos, Switzerland
4. International Management Services ARTTIC, Germany
5. Beiersdorf AG, Germany
6. Berufsgenossenschaftliche Kliniken Bergmannsheil [Bergmannsheil Hospital of the Ruhr-Universität Bochum], Germany
7. Fraunhofer Institute for Applied Polymer Research IAP, Germany
8. Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Germany
9. Fraunhofer Institute for Laser Technology ILT, Germany
10. Fraunhofer Institute for Production Technology and Automation IPA, Germany
11. Fraunhofer Institute for Mechanics of Materials IWM, Germany
12. INNOVENT e.V. Technology Development Jena, Germany
13. KMS Automation GmbH, Germany
14. Medical University of Vienna, Austria
15. Unitechnologies SA, Switzerland
16. University of East Anglia, UK
17. Loughborough University, UK
18. Institute for Interfacial Engineering and Plasma Technology IGVP, University of Stuttgart, Germany
19. University of Salerno, Department of Industrial Engineering, Italy
20. Vimecon GmbH, Germany

Table 2. Pros and cons of large, multidisciplinary, multi-partner projects

<table>
<thead>
<tr>
<th>Pros Positive features and opportunities</th>
<th>Cons Negative features and challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Enables multidisciplinary working</td>
<td>• Challenging to set up the consortium and attract all the right partners</td>
</tr>
<tr>
<td>• Well planned projects</td>
<td>• Have to develop the proposal with little or no funding</td>
</tr>
<tr>
<td>• Clear aims and objectives</td>
<td>• Securing competitive funding</td>
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<tr>
<td>• Inclusive approach</td>
<td>• Communication difficulties — language barriers and translation issues</td>
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<tr>
<td>• Shared resources</td>
<td>• Time and cost associated with travel</td>
</tr>
<tr>
<td>• Intellectual stimulation from wide variety of colleagues</td>
<td>• Logistical challenges (e.g. moving materials or equipment around partners)</td>
</tr>
<tr>
<td>• Academic rigour (debate, consensus and internal peer review)</td>
<td>• Tight plans and limited resources</td>
</tr>
<tr>
<td>• Mutual, cross-disciplinary learning</td>
<td>• Time and cost of legal agreements</td>
</tr>
<tr>
<td>• Training and researcher development</td>
<td>• Administrative burden of strictly controlled financial reporting and record keeping</td>
</tr>
<tr>
<td>• Forming new collaborations and future projects</td>
<td>• Unforeseen changes (people leaving, companies coming or going)</td>
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<tr>
<td>• Co-authoring papers</td>
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<tr>
<td>• Wider international dissemination of results (in more languages)</td>
<td></td>
</tr>
<tr>
<td>• Cultural exchange and learning</td>
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</table>
10. Summary of Conference Presentations

The project outcomes have been presented in 28 presentations including Tissue Engineering and Regenerative Medicine International Society — EU Meeting, Genova, Italy, 2014 (3 presentations); EuroBioMat 2015 (4 presentations) and 2013 (2 presentations); 26th European Conference on Biomaterials, Liverpool, UK, 2014 (3 presentations); Euronanoforum, Dublin, Ireland, 2013 (3 presentations); DGBM conference, Erlangen, Germany, 2013 (2 presentations).

Conflict of Interest and Funding

No conflict of interest was reported by all authors. The project was funded by the European Union 7th Framework Programme (FP7-NMP-2010-Large-4, GA no: 236416). Update ArtiVasc3D-Generation of a 3D vascularized skin substitute; Keck M, Gugerell A, Kober J, Engelhart S, Gillner A, Nottrodt N; GA no: 263416; revised (2014), http://www.artivasc.eu

Acknowledgements

This extremely ambitious challenge could only be achieved in an interdisciplinary network. All over Europe, twenty partners from the fields of biomaterial development, tissue engineering, freeform methods, automation and simulation have joined forces under the leadership of Fraunhofer ILT.

References


