FINAL PUBLISHABLE SUMMARY REPORT

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1. Final publishable summary report

1.1. Executive summary

BIP-UPy, which stands for ***B**ioactive **I**mplantable **P**olymers based on **U**reido**Py**rimidinone*, is a 4 years project co-funded by the European Commission within the Seventh Framework Programme.

The project addresses the need for new biomedical implants which could be easily fine-tuned in terms of bioactivity, biodegradability and mechanical performance depending on their final clinical application.

The final ultimate goal of BIP-UPy is therefore to develop new bioactivated and bioabsorbable polymers designed to stimulate endogenous tissue growthwith specific bioactivities which can be used to provide the required properties to the via targeted biomedical implants thereby targeting the specific clinical needs.

The consortium brings together expertises in the areas of biomedical materials; biocompatibility, bioactivity, mechanical compliance towards tissue for materials & implants, and clinical procedures. Within the BIP-UPy project two bioactive medical implants that aim at improving quality of life of people suffering from intracranial aneurysms and women with Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI) have been manufactured and validated.

A variety polymers based on the UPy chemistry have successfully been prepared in kg-scales according to GMP protocols and have been bioactivated and further processed into meshes using electro-spinning or into a thread using melt-extrusion combined with melt-spinning.

Biocompatibility studies showed no cytotoxic effects of the UPy-based polymers either as electrospun meshes or radiopaque threads. Ex vivo studies, using a vascular bioreactor platform developed within the project, revealed tissue response. In-vivo studies (using small animals) demonstrated that the bioactive implants were biocompatible (non-irritant) and that they induce an appropriate host response. Animal experiments were also conducted to demonstrate bioactivity which modified this response to a less pro-inflammatory phenotype.

Outcomes and results have been widely disseminated by means of communication materials, press, and presentations at scientific meetings or targeted events to give the BIP-UPy solution the necessary visibility and credibility to foster a short-term market uptake. BIP-UPy impacts the biomaterials industry with new biomaterials and new products with future direct economic benefits. It also impacts the society as it lays the foundation for future improved patient outcome, reduced hospitalization time and other treatment-related risks, and will ultimately result in better health and life quality for the patients, as well as in a reduction of healthcare costs.

Finally, the results obtained within the BIP-UPy project open an innovative strategy based on bioabsorbable medical implants that stimulate endogenous tissue restoration; the body's own natural restoration of complex tissue mediated by a bioabsorbable medical device.

1.2. Summary description of project context and objectives

Biomedical implants based on polymer technologies have become an indispensable part of effective modern medicine. They represent one of the most stable markets for polymers in terms of growth. According to the consultancy firm Frost & Sullivan, the total European market for polymers in medical devices (including implants) had revenues of EUR 664.2 million in 2015.

Pelvic organ prolapse (POP) and stress urinary incontinence (SUI) are common pelvic floor dysfunctions affecting millions of women worldwide. The estimated lifetime risk of POP is 30-50% and of SUI 20-40%.

The lifetime risk to undergo surgery for POP or SUI is 19%. It is most frequently seen in women who have had children, are obese or at elder age. The currently used techniques that use implants have been causing high complication rates.

Intracranial aneurysms are life-threatening bulges of the brain's blood vessels. It is estimated that between 1 and 6% of the population may present them, and the associated mortality reaches 50%. At present, the treatment of cerebral aneurysms is mainly based on endovascular implantation of platinum coils (in approximately 80% of the cases) or surgical clipping (in the remaining 20% of the cases). Current treatments involve both high risks for the patient and high costs for the hospital.

The specific objectives of the project are as follows:

- To develop a protocol for easy processable UPy polymer synthesis and manufacturing scale-up, with properties complying with the mechanical and biocompatibility requirements of the defined implants.
- To develop a procedure for polymer bioactivity tailoring to specific targeted clinical needs, integrated into polymer production scale-up protocol.
- To develop industrial processes for manufacturing the medical implants with preserved bioactivity using processable bioactive polymers.
- To develop two medical implants:
    - A bioabsorbable mesh for surgical treatment of pelvic floor prolapse (POP) and stress urinary incontinence (SUI) which will promote sustained tissue regeneration.
    - An endovascular embolic implant with improved fibrogenesis that reduces artefacts in medical imaging.
- To validate suitable sterilisation protocols for the implants made of new bioactive biomaterials.
- To develop long-term predictive in-vitro model systems for biomaterial and implants assessment under near vivo conditions.
- In-vitro and in-vivo testing of the new biomaterials assessing long-term biocompatibility and bioactivity performance-stability.

The clinical specific objectives targeted with the new improved bioactive biomaterials are:

- for surgically treated POP and SUI:
    - reduce the rate of serious complications from 10% to below 3%,
- in the treatment of intracranial aneurysms:
    - reduce patient follow-up costs follow-up costs by more than 50%,
    - time of exposure to radiation from 1-3 hours to 10 minutes and
    - aneurysm recurrence from 17-33% to below 5%

1.3. Description of the main S&T results/foregrounds

The main results of the BIP-UPy project can be grouped in the following categories:

a) Biomedical material development

The objectives addressed in this area were the design, synthesis and scale-up of polymers comprising ureido-pyrimidinone (UPy) units that could be processable (thermally or solution based) and that comply with the mechanical and clinical requirements.

At the end of the project, the outputs are:

- Three different UPy polymers successfully prepared in kg-scales according to GMP protocols.

- The chosen UPy-polymers have in vitro mechanical performances which are in line with the targets for the urology mesh and aneurysm implant.
- The UPy-polymers can be easily rendered radio-opaque and can be processed into meshes using electro-spinning or into a thread using melt-extrusion combined with melt-spinning processes.

b) Development of tailored bioactivities and incorporation into the new bioactive implants

Work in this area has been focused on, on one hand, the development of UPy-modified bioactive compounds, mainly peptides, including the design, synthesis and characterization the bioactive compounds; and on the other hand, the development of protocols for the incorporation of the UPy-bioactives into the UPy-polymer materials.

As a result of the work on this area:

- Different UPy-bioactive molecules with the desired bioactivities for the two implants have been successfully synthesized and fully characterized:
  - For pelvic floor implant: antimicrobial and cell adhesion/proliferation bioactivity.
  - For the aneurysm implant: fibrosis induction and cell adhesion/proliferation bioactivity.
- Different strategies for UPy-polymers bioactivation have been defined:
  - For pelvic floor implant: based on a dip-coating approach (in the case of antimicrobial UPy-peptides) and through a premixing approach in the case of UPy-peptides inducing cell adhesion and proliferation.
  - For the aneurysm implant: following a co-extrusion process of UPy-peptides inducing cell adhesion/proliferation and UPy-polymers.

c) Bioactive implants design and processing

The objective in this area has been to develop the manufacturing and sterilization processes to use BIP-UPy bioactive polymers for the two medical implants manufacturing according to implants' design and in view of achieving an optimal performance and therapeutical response.

Main results in this area are:

- Implants' design and specifications set and adapted according to testing results.
- Bioactive meshes successfully manufactured through e-spinning process.
- Bioactive threads processed through melt-extrusion combined with melt-spinning process.
- UPy-based materials can be processed by other processing techniques (i.e. injection moulding), opening the door for their application for other types of implants and applications.
- Demonstrate that bioactive polymers remained chemically stable after being subjected to high temperature processing techniques (145ºC).
- Electron beam has been selected as the preferred method for the sterilization of bioactive materials and the corresponding bioactive implants.

d) Implants biomechanical data

Main target in this area has been to characterise the biocompatibility of the bioactive polymers in-vitro and in-vivo and to generate a strong toxicological and biocompatibility knowledge to verify the safety of the novel biomaterials.

The main achievements in this area are:

- Demonstrate that no cytotoxic effects on cells were found neither with the UPy-based neat polymers nor with the processed electrospun meshes or radiopaque threads.
- Demonstrate that bioactive polymers do induce bioactivity when tested in-vitro.
- Bioactive mesh and thread are biocompatible (non-irritant) in local tissue response experiments performed in vivo (small animals).
- Bioactive mesh does not cause sensitization after being tested in-vivo (small animals).

e) Novel implant's assessment procedures

The goal of this activity has been to characterise the long-term biocompatibility and bioactivity of implants and evaluate their performance in-vivo. Additionally, the consortium has also established implant prototypes clinical procedures testing and validation.

At the end of the project, the outputs are:

- A pre-clinical in-vivo protocol to validate the non-bioactive and bioactive mesh implants through in-vivo experiments in multiple animal models was established.
- In-vivo functionality tests on large animal model (sheep) that revealed that UPy-mesh is suitable for pelvic floor repair. The mesh supports and substitute's regeneration of tissue without obvious inflammatory or other graft related complications were detected. Additionally, UPy-bioactive mesh (cell adhesion induction) showed modulation of the host response towards a lesser pro-inflammatory profile and increased collagen deposition was demonstrated.
- A protocol to validate UPy-thread implants under simulated clinically relevant environment was also set. Radiopacity, mobility through catheters, curling into aneurysm models and mechanical occlusion of flow into these aneurysm modelss were satisfactory.
- Two novel long-term mechanical and bioactivity performance assessment platforms were developed and successfully optimized according to relevant clinical environment. Bioactive aneurysm implant did show strong indications of neo-tissue formation directly around the coil, despite being only cultured for one week.
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1.4. Potential impact and main dissemination activities / exploitation of results

BIP-UPy project was born with the aim of impacting the biomedical sector delivering an innovative strategy towards in-situ tissue-engineering and therapy through the development of medical implants that promotes a body response.

BIP-UPy is expected to bring implant manufacturers and clinicians the freedom to design long-term implantable devices using ready-to-use biomedical polymers with desired bioactivities tailored to a variety of specific applications, thereby avoiding any implant post-processing or pre-surgery surface preparation steps to implement bioactivities.

BIP-UPy project has impact at different levels: industry, medical and social level. How BIP-UPy contributes to each of them is detailed below:

a) European biomaterials industry competitiveness

BIP-UPy exploitation will have a direct impact on the participating companies' competitiveness and on their target markets, strongly related to the biomaterials industry; a preferential market positioning; increase their proprietary technologies/products; new internal R&D capability building; enlarged material/product/service portfolio to be offered to their customers and to increased business economic benefits.

b) Medical sector

Incorporating bioactivities is an innovative therapeutical approach to achieve a given body response. Bioactivities tailored by the developed implants will act strictly on a local basis, because bioactive peptides are attached to the polymer backbone. Therefore, they might not be washed away by body fluids and consequently, would not exert their effect distally. This kind of therapy can replace the use of external pharmaceuticals.

c) Social impact: *improving the quality of life of patients due to improved therapeutic outcome*

The improvements of the bioactive BIP-UPy implants will result in a greater health gain as a result of a reduction of post-implant complications compared to current standard treatments. BIP-UPy implants have an improved functionality and optimized compatibility with the body and will result in an increase in health-related quality of life.

In the case of pelvic floor dysfunctions, current treatments mainly based on non-biodegradable meshes are causing high complications with important rates of re-surgery need. For the intracranial aneurysms, BIP-UPy implants will result in a simplification of the patient follow-up as, for instance, no hospital in-take will be necessary and the radiation dose will be reduced as CT scanning or MRI become the best option for patient follow-up (instead of angiography, the current treatment).

Furthermore, through all dissemination activities, which will expand beyond the project duration, BIP-UPy has and will continue to raise awareness of the BIP-UPy project and its outcomes as the ultimate goal of the project is to benefit the European society as a whole, in terms of better healthcare treatments, cost reduction and an improved quality of life of the patients. Dissemination activities are considered essential to give the BIP-UPy the necessary visibility and credibility towards European citizens and to facilitate market uptake. However, BIP-UPy consortium has been also very aware of not raising too early expectations as BIP-UPy implants needs still some further testing and validation before they can be commercialized.

Dissemination activities have been intensified during the second half of the project, once results on the bioactivity and in-vitro/in-vivo assessment have become available. Presentation of project achievements at remarkable conferences has been carried out by different partners. Moreover, different communication materials to raise awareness on the objectives, benefits and main results of the BIP-UPy project have been prepared, targeting different audiences: this includes general leaflet and video for citizens' awareness; posters presentations addressed to the scientific community and scientific publications for both the medical and scientific community.

Regarding exploitation, the consortium has followed a clear strategy since the beginning of the project, based on reviewing and fine-tuning project results in view of fitting project's development and the exploitation interests of the different partners. Apart from discussing results in the different general meetings, an Exploitation Strategy Seminar (ESS), led by an expert consultant appointed by the European Commission, was carried out at month 30.

1.5. Address of project public website and relevant contact details

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