European Commission

Towards nanotechnology-based osteochondral reconstruction

Outline of proposals
for EC policy in research and innovation

Report from the InnovaBone clustering workshop (13.XI.2014),
the associated Stakeholder Day (14. X.2015) and refinement exercise (10.XII.2016)

Research and Innovation

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Directorate-General for Research and Innovation

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Report from InnovaBone project actions:

- *the Clustering workshop (Brussels, 13 November 2014)*
- *the Stakeholder day (Brussels, 14 October 2015)*
- *and the Refinement exercise (10 December 2016)*

Research and Innovation

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Τί εὔ κολον: Τὸ ἄ λλῳ ὐ ποτίθεσθαι
(Θαλῆ ς)

What is easy? To advise others
(Thales)

Executive summary

This report stems from two meetings "Clustering day", and "Stakeholder day", delivering a fresh perspective on EC-funded nanotechnology-based osteochondral research and innovation, based on diverse approaches from tissue engineering, biologically-inspired processes and systems, and biomaterials.

During the "Clustering day", eight EC funded projects were involved, with the participation of 44 experts from 22 countries. The meeting included (i) the presentation and discussion of the main achievements, reached by the 8 highlighted projects, (ii) the outline of essential future research prospects and (iii) the identification of key policy recommendations for future research innovation in the short-, medium- and long-term. Furthermore, during the Clustering day a survey has been submitted to participants. The preliminary survey results, addressing best practices developed by the existing research framework and key EC-funded projects in the field, have been reported in this publication. The results set the stage for a multileveled, strategic discussion leading to a series of possible policy priority interventions for the future.

The second meeting was the "Stakeholder day". During this meeting nearly 60 participants representing stakeholders, dealing with the matter, were debating. Three main categories of stakeholders participated to the debate (i) actors representing patients with arthritis/rheumatism, health professional and scientific societies of rheumatology of all the European nations, with the aim of engaging more patients in EU policies and priorities; (ii) actors representing European materials producers, exposing the major trends and networking in the EU Materials R&D community; (iii) actors explaining potential European grants for research and innovation in nanotechnology, medical device industry, biomaterials.

Recommendations are summarised in this publication, in which authors identify and offer experts' insights in the field, useful to a large number of different kinds of stakeholder communities, including research communities, NGOs, industry, policy-makers, end-users, associations and civil society organisations.

Preface

Promoting good governance on nanotechnology research projects, internally among partners as well as externally - between consortium and key stakeholders, such as EC policy-makers, industry, civil society organisations - is crucial. The main objective of this publication is a meaningful communication, aiming at creating a dynamic relationship and a fruitful exchange between stakeholders dealing in nanotechnology research on tissue engineering. The publication concerns tissue engineering and disciplines based on biologically-inspired processes and systems to improve osteochondral diagnosis, therapy, repair and reconstruction. Good governance on nanotechnology research and innovation is based on dynamic and consistent expert communication efforts, aiming to foster inclusive processes bringing all key actors working together, in the same direction, avoiding dispersion of energies. Thus, expert communication is required to establish sound and clever methods to identify key priorities. Stakeholders in the sector are diverse and variegated, and it is particularly important for policy-makers anticipating how to meet the needs of industry and civil society organisations of end-users.

Experts convened at the InnovaBone Clustering Day and Stakeholder Day workshops with the specific aim to create an outline of new ideas and possible future policy actions about nanotechnology-based research, leading to innovation in the field of osteochondral reconstruction. Valuable insights from this collaboration regarding potential forthcoming actions for the stakeholders' community are presented and discussed in this publication. On the one hand, the Clustering Day workshop, which was based on a range of best practices developed by European-funded projects, delivered a fresh perspective on EC-funded research in the field, and enabled a ranking of possible policy priority interventions. On the other hand, the Stakeholder day was organised to enhance stakeholder participation in the process and to include the collaboration of patient organisations, European initiatives like the European Technology Platform for Advanced Engineering Materials and Technologies (EuMaT), and others.

The broad panoply of ideas stemming from these two events, the Clustering and the Stakeholder Day, is shaped in the form of different sets of proposals, which will hopefully inspire stakeholders to face new challenges, as well as to establish and intensify synergies and dialogue for shaping the future in the field of biomaterials for tissue regeneration and bone reconstruction.

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INTRODUCTION

This report aims at summarising the results obtained in the framework of the EU funded project InnovaBone. More specifically, it is based on the achievements of two distinct meetings, organised by InnovaBone partners, on 13th November 2014 and on 14th October 2015.

These two meetings have been organised with the specific purpose of bringing together stakeholders to identify innovative ideas, proposals and relevant actions that address nanotechnology-based research and innovation on osteochondral reconstruction at the EU level.

There were two aims:

a. Discuss current and future nanotechnology research and innovation

b. Promote responsible, cutting-edge research and innovation in this field, through an inclusive approach combining experts and stakeholders including scientific community, industry, policy-makers, NGOs, civil society associations and end-users.

The first meeting – Brussels 13 November 2014

The workshop entitled "InnovaBone *Clustering day"* brought together experts and participants from EC-funded projects on a wide variety of fields (listed in the appendix).The initiative aimed at using the extensive knowledge of the experts to contribute to policy implementation concerning biomaterials and tissue regeneration. The event was promoted by InnovaBone project consortium with a focus on novel biomimetic strategies for osteochondral regeneration.

The second meeting-Brussels 14 October 2015

The event was conceived for the benefit of stakeholders and was part of a two-day conference organised by InnovaBone aimed at sharing the results obtained during the project on the topic of biomaterials for bone regeneration.

Conference attendees included scientists, representatives from patient associations, health professionals, policy-makers, industrial players and citizens. A number of stakeholders designed different scenarios on the applicability of the InnovaBone results, ensuring on the one hand, better healing solutions, and on the other hand, maximising business opportunities. InnovaBone (founded under FP7) to some extent, achieved one of the key goals highlighted and boosted by Horizon 2020. In fact, InnovaBone is a clear example of Responsible Research and Innovation (RRI) implementation. RRI implies that societal actors (researchers, citizens, policy makers, business, associations, etc.) work together during the whole research and innovation process to better align both the process and its outcomes with the values, needs and expectations of society.

The report is organised as follows: in the first session, participating projects and stakeholders are introduced; in the second session, the two meetings (clustering day and stakeholder day) are explained in detail, the third section, illustrates the methodology used to work together (included the survey) and in the last part, conclusions and proposals for the future are presented.

1. WHY? SETTING THE SCENE

The need for this publication emerged after the first successful meeting, the "Clustering day". At that time, the 13th November 2014, a number of different projects were invited to participate to InnovaBone's workshop. As a follow-up to the second meeting, the "Stakeholder Day", which took place on the 14thOctober 2015, the publication was integrated and accomplished. A refinement exercise took place until late 2016, on remote basis, through the different authors.

The potential impact of nanotechnology on healthcare is immense and has ushered a new era aptly labelled as 'Nanomedicine' in view of the potential benefit in various diseases, which are currently untreatable. Nanomedicine aims to develop novel and superior materials for diagnostic, therapeutic and preventive application and nanotoxicity provides for the necessary safety assessment of nano-products. To recognize the therapeutic value of a medicinal nano-product and avoid potential risks associated with its use are two-sides of a coin, aimed at the achievement of the same goal, i.e., the improvement of human life (Raffa, et al., 2010)[1].
The importance of developing novel approaches for bone repair is underscored by the heavy burden on health care costs and patient suffering caused by traumatic, osteoporotic and osteolytic metastatic bone lesions. To address these health and social challenges the largest number of stakeholders is required to be involved, in order to try to be representative of the whole society.

This is the reason for implementing and sustaining research programs in terms of multi-actor and multi-stakeholder projects. Both meetings organized by InnovaBone consortium were done in the spirit of sustaining this type of solution and looking for a deep understanding of the best ways to build collaborations and capitalize experiences. Obviously, collaborative efforts presume that individual actors are one among many stakeholders whose activities are truly interdependent. With a domain focus, needs and interests

[1]Raffa.V., Vittorio, O Riggio, C., and Cuschieri, A. (2010) Progress in nanotechnology for healthcare. Minimally Invasive Therapy & Allied Technologies. Volume 19, Issue 3, 2010 pagg 127-135

are not defined in terms of a single organization but in terms of the interdependencies among the stakeholders who are affected by an issue and claim a right to influence its outcome[2] (Trist, 1983). The participation of other EU-funded projects before and stakeholders then, helped InnovaBone consortium as well as all the other participants to make the framework clearer, understanding needs and potential valuable inputs each organization could express. In each specific domain and particularly when dealing with healthcare services' innovation, none of the stakeholders acting alone can solve the problem. Furthermore, purposeful actions by any stakeholder may profoundly influence the ability of the others to achieve their goals[3] (Dewulf et al., 2005).
The success of the two events was based on the ability to make different actors work together, since each stakeholder can apprehend only a portion of the problem, but by pooling perceptions, greater understanding of the context can be achieved. In this way, the Clustering day as well as the Stakeholder day serve as catalyst of perceptions, ideas and prospects coming from different points of view never explored before.

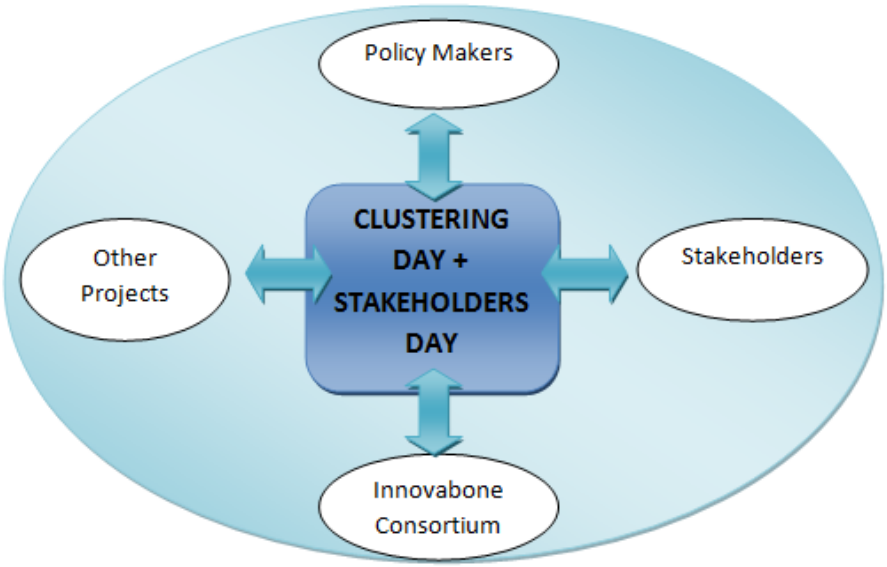

Fig. 1Clustering day and Stakeholder Day: InnovaBone Meetings.

[2] Trist, E.L. (1983). Referent organizations and the development of interorganizational domains. Human relations, 36(3), 247-268.

[3] Dewulf, A., Craps, M., Bouwen, R., Taillieu, T., and Pahl-Wostl, C. (2005). Integrated management of natural resources: dealing with ambiguous issues, multiple actors and diverging frames. Water Science & Technology, 52(6), 115-124.

The idea behind the first event was to bring together a large number of European funded projects, dealing with the same research subject. In fact, InnovaBone is a project of excellence, potentially able to have a great impact thanks to the niche results, but it remains crucial to share knowledge and expertise as well as to have a major perception of what the others achieved in the same scientific area.

So basically, a clustering activity with the main aim of promoting networking at a European scale, future collaborations, but also participation to education activities, workshops and conferences, discussion on common interests, and sharing of best practices, seemed to be the best way to bring experts and stakeholders all together for a serious and stimulating debate. Furthermore, it is a European priority to encourage synergies and complementarities between countries as well as sectors, in order to define a solid knowledge and advance a shared vision towards nanotechnology-based research in the sector of osteochondral reconstruction, in this specific case. So, the "clustering day" seems to be totally in line with the EC objective of increasing openness at all stages of the research lifecycle and thus ensuring that science serves innovation and growth, as then confirmed by the Open Science initiative[4], Horizon 2020.

In fact, the "Clustering day" has been organized in the spirit of increasing open access to publicly funded research results and promotes a range of facilities for knowledge sharing between academics as well as practitioners in the sector. Promoters of the event are fully convinced that providing researchers with tools and workflows for transparency, networking, collaboration, dissemination and transfer of new knowledge is the only way to solve important social and health issues, concerning our society. In fact, the only way to make science more responsive, both to socio-economic demands and to those of European citizens, in order to better address the societal challenges, is to define inclusive processes aimed at promoting diversity in science across the European Union and at the same time trying to open it to the general public and to stakeholders.

[4] For further information on Open Science
https://ec.europa.eu/programmes/horizon2020/en/h2020-section/open-science-open-access

Summarising the lesson learnt from a number of Seventh Framework Programme projects, activities, methodologies and outcomes in the sector of nano- and advanced biomaterials is an attempt to foster the sharing of expertise and know how, networking of relevant projects and actors.

What prompted InnovaBone consortium to organise the conference is summarised in the following points:

- To strengthen the collaboration outside the consortium for potential future opportunities;
- To understand and increment the sustainability of the project;
- To create a debate on the shared interests;
- To discuss about future trends and to give some suggestions to the EC for the future subjects and research areas tackled by Horizon2020, especially for the future programmes to promote the European policy on R&D till 2020.

It is not easy to achieve a plan in order to generate the desired sustainability of the project, and somehow ensure a return on investment at a European level by multiplying the benefits that the assimilation of best practices can provide. This is particularly true in Research and Innovation domain, where very often the market is not promptly ready to finalise, produce and commercialise the new product or service. The sustainability of project outcomes may be difficult to anticipate and to describe. So, it is crucial that participants do not take for granted the capacity of the project to continue its existence and functioning beyond its end.

One of the aims of this first event, the "Clustering Day" was actually to explore the terrain for future prospects, in terms of sustainability and innovation transfer, for InnovaBone project as well as for the other projects. In fact, through a clustering activity, the purpose was to enable a mechanism of "innovation transfer", namely a process of adaptation and/or further development of innovative results of a project, their transfer, piloting and integration into public and/or private systems, companies, and organizations[5].

[5]https://ec.europa.eu/research/innovation-union/pdf/b1_studies-b5_web-publication_mainreport-kt_oi.pdf

Behind this effort of sharing new knowledge there is the main certaintythat better modes of coordination across the economic actors involved will enhance productivity, output and innovation rates.

The creation of a space for sharing and participation of project results, was actually conceived to improve the sustainability of these European funded projects, which implies the use and exploitation of results in the long term, as we are conscious of the fact that a project can be considered as sustainable, only if its outcomes continue after the end of EU funding, and if results have an impact on society.

The eight projects participating at the "Clustering day"[6]:

1. INNOVABONE;
2. BIOTINET;
3. HYDROZONES;
4. LIFELONGJOINTS;
5. OPHIS;
6. RAPIDOS;
7. REBORNE;
8. THE GRAIL.

Putting together these eight projects, all dealing with nano- and advanced biomaterials, is also an excellent starting point for a concrete dialogue concerning the application of their results in medicine for the benefit of the whole society, and nevertheless for the European industrial competitiveness. The selected European projects represent interdisciplinary expertise and an inter-sectorial approach, so potentially they are able to meet the needs of society, to tackle challenges, and to foresee future trends and transformation in their specific domain. As nanotechnology is becoming more deeply embedded in today's life, awareness about its potential opportunities and drawbacks should be increased to reach the whole society.

For this reason, it is crucial to create a credible and uniform discourse within the scientific community, to enable communication, broadening of audience and setting up appropriate actions to be implemented for reaching target audiences, namely decision makers in the sectors.

[6] For further information on the projects see chapters 2, 2.1 participating projects

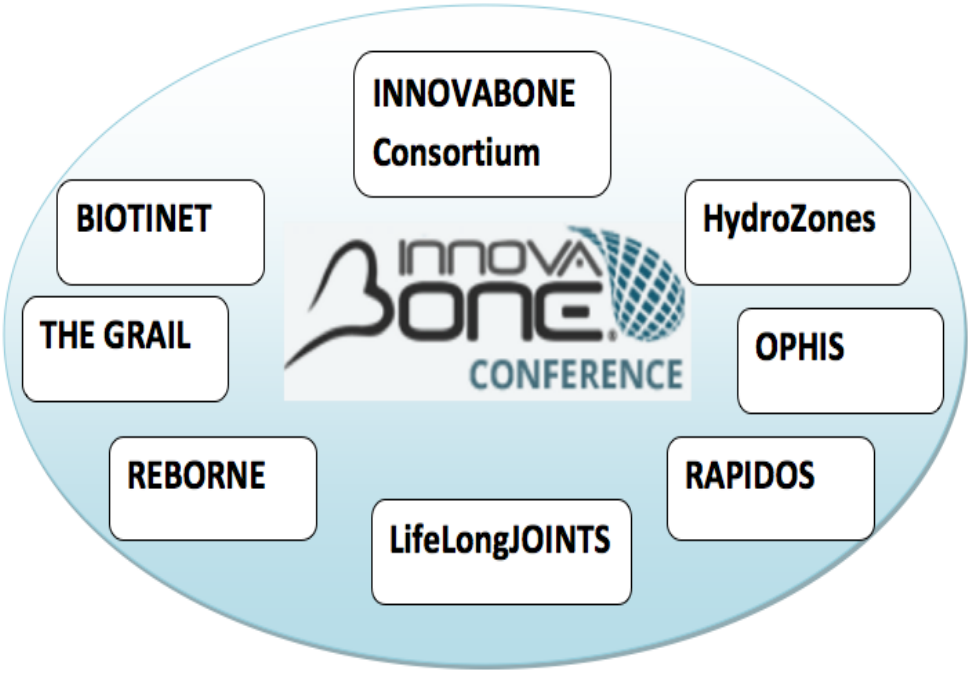

Fig. 2Clustering day.

The first meeting what such a success that InnovaBone Consortium decided to replicate and to extend the invitation to a certain number of stakeholders. The EC funded projects' partners realized that creating a network of experts, would enable different stakeholders to make their voice heard, and to draft a more precise portrayal of society in their different aspects. This is a useful point not only for researchers, who in this way are able to move from needs to solutions, but also for policy makers, who could design new policies based on the citizens' demand (demand- driven services). In this way policy makers are in fact able to set up the right environment for researchers, as well as for the market.

Departing from the requirement of a major inclusion of different societal actors, InnovaBone consortium organized a second meeting, the "Stakeholders day", held on 14th of October 2015.

The event was conceived for the benefit of stakeholders and was part of a two-day conference organised by InnovaBone partners to share the latest results obtained by the project on the topic of biomaterials for bone regeneration. Conference attendees included scientists, patient associations, health professionals, policy makers, industrial players and citizens. Furthermore, a number of stakeholders designed different scenarios on the applicability of InnovaBone results, ensuring on the one hand, better healing solutions, and on the other hand, maximizing business opportunities.

The idea behind this event was to create the framework to put all societal actors (researchers, citizens, policy makers, business, third sector organisations etc.) working together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of European society. The "Stakeholder day" in fact, for the InnovaBone consortium represented the main way to conceive synergies between different actors, which have characterised InnovaBone from the beginning and during all the project lifetime, with the main aim of building capacities and developing innovative ways of connecting science to society. Basically, what is defined as a Responsible Research and innovation, RRI[7].

Improving the cooperation between science and society to enable a widening of the social and political support to science and to technology in all Member States is increasingly a crucial issue that the current economic crisis has greatly exacerbated[8].This can only be achieved if a fruitful and rich dialogue and active cooperation between science and society is developed to ensure a more responsible science and to enable the development of policies more relevant to citizens. Rapid advances in contemporary scientific research and innovation have led to a rise of important ethical, legal and social issues that affect the relationship between science and society.

Furthermore, the Stakeholder day has been also a crucial moment for policy makers to be confronted with nanotechnology research from the point of view of researchers, NGOs, SMEs, and industry. Engaging society more broadly in EU research and innovation activities permits to define the role of research and innovation in future scenarios and visions of desirable sustainable futures. It will connect scientists, stakeholders and citizens in building shared understanding, to transmit a clearer message to policymakers who in turn would be able to better respond to societal needs.

In order to increase the relevance of research and innovation policies for society, opening up of the innovation process to social actors, can improve the development process and the quality of the final outcomes of research and innovation in the industrial context, while addressing global societal challenges by fostering better knowledge and innovation co-production with society.

[7]https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

[8]https://ec.europa.eu/programmes/horizon2020/en/h2020-section/open-science-open-access

The Stakeholders day was also organised with two other main aims, firstly building bridges from bench to clinic and secondly to highlight the opportunity of SME growth through EU projects. Different stakeholders participated to the debate, with particular attention to three specific categories: industry – research - organisations dealing with patients. Different actors had the opportunity to share best practices and to keep up on new opportunities for supporting and financing SMEs and further exploiting scientific results.

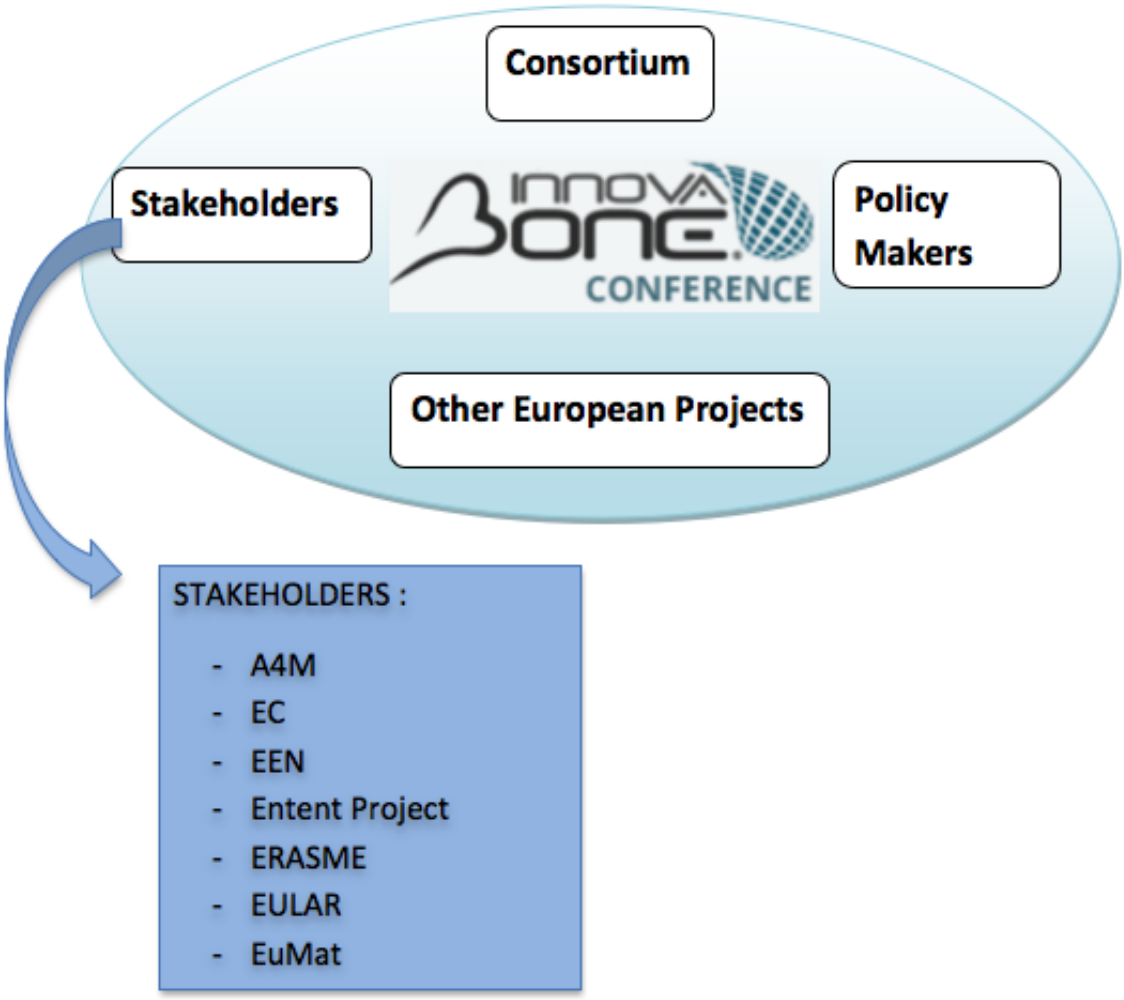

Fig.3 Stakeholder Day

In both meetings, the experts discussed and debated the main outcomes and challenges of their EC funded research. Together with additional experts and EC representatives, they proposed concrete suggestions aimed at promoting good governance in future policy-making. Their exchanges will be a valuable input for future discussion on proposals, actions and activities on nanotechnology

research and innovation in the field, as a line of strategic alignment between technological and societal developments as the ultimate objective[9] of technological assessment.

[9]STOA, Science and Technology Options Assessment, European Parliament (2008).*Technology across borders: Exploring perspectives for pan-European Parliamentary Technology Assessment*, Study of Directorate General for Internal Policies, Directorate G: Impact Assessment, IP/A/STOA/FWC/2008-096/LOT8/C1, PE 482.684.

2. WHO? THE PARTECIPANTS

2.1 PARTICIPATING PROJECTS

INNOVABONE

Novel biomimetic strategy for bone regeneration

InnovaBone aimed to develop optimally performing bio-inspired biomaterials, mimicking the natural physiological processes underlying bone repair. The approach of the project consisted of producing smart bioactive 3D scaffolds to fit within bone lesions, which would then be injected with functional, genetically-engineered, self-solidifying and elastin-like recombinamers (ELRs). The goal was to ensure strong, healthy bone regeneration and to reduce pain and suffering caused by traumatic, osteoporotic and osteolytic metastatic bone lesions. The resulting bioactive, biodegradable scaffolds, ELR - biogels and regenerated bone were analysed and tested with biodynamic assays, to study the effects on bone growth, healing, foreign body reactions, and to assess strength, durability, toxicology, sterilization reaction, eco-toxicology and risk assessment.

The multidisciplinary consortium with its extensive, state-of-the-art expertise consisting of private and public partners, cellular and molecular biologists, immunologists, physicists, bioengineers, and orthopaedic surgeons tackled serious bone lesions with a comprehensive work plan to develop and evaluate a prototype, upscale its production and prepare the final material for clinical phase trials and commercialisation of the dual component product.

Project website: http://www.innovabone.eu/

BIOTINET

Academic-Industrial Initial Training Network on Innovative Biocompatible Titanium-base Structures for Orthopaedics

BioTiNet is a Marie Curie Initial Training Network (ITN) targeted at researchers who will help to develop novel low-rigidity, Titanium-based structures for orthopaedic use. The objective is to improve the overall efficiency of metallic implants in orthopaedic treatment by minimizing the stress-shielding effect, and to promote technical, biological and clinical developments at a pan-European level, for the benefit of all European inhabitants. The novel Titanium-

based structures are meant to meet the end-user/customer requirements of biomechanical and biochemical functionality, and also the material producers' requirement of processing.

BioTiNet ITN an inter-disciplinary, inter-sectoral and multinational initiative, which brought together 12 leading European research groups with state-of-the-art expertise and excellent research infrastructures to provide high-level training in biomedical materials. The research program was designed to deliver young researchers with the most relevant state-of-the-art knowledge and expertise in the biomaterials research field for a career development in line with the scientific, industrial and societal needs and challenges.

Project website: http://www.biotinet.eu/

HYDROZONES

HydroZONES represents an interdisciplinary consortium that adopted a strategy to regenerate, rather than repair, articular cartilage-based on tissue zonal structure and function. Degradable and clinically-used thermoplastic polymers are meant to be applied for mechanical reinforcement of the hydrogels. HydroZONES follows and compares cell-free and cell-loaded hydrogels, comparing chondrocytes and bone marrow-derived mesenchymal stem cells for their efficacy. Three-dimensional printing techniques were employed for the automated assembly of the implants to guarantee reproducibility.

Scaffolds that passed the stringent and well-documented *in vitro* and *in vivo* screening underwent long-term pre-clinical testing in mini-pigs and horses, which set a new international standard for pre-clinical testing of cartilage implants. The defined endpoint of HydroZONES project was the positive long-term pre-clinical evaluation of at least one construct, according to pre-clinical regulatory requirements and GMP standards. Advanced bioreactors were employed for *in vitro* testing of the constructs and results were used as input for realistic *in silico* modelling. The second major aim of HydroZONES was the development of a predictive 3D *in vitro* assay for osteochondral implants, validated against *in vivo* results, along with the hardware to perform the assay.

Project website: http://www.hydrozones.eu/

LIFELONGJOINTS

Silicon Nitride Coatings for Improved Implant Function

LifeLongJoints project aimed to deliver next-generation, functional Silicon Nitride coatings for articulating surfaces and interfaces of total hip replacements (THR) to produce longer lasting implants. It was anticipated that these coatings would significantly reduce the risk of implant failure associated with wear, synergistic wear/corrosion processes and the resultant debris release as well as provide significant economic and societal benefit to Europe and its citizens.

The coatings' suitability in each scenario was assessed against target profiles. In particular, it was important to consider coating performance within each of these applications under adverse conditions as well as those outlined in internationally utilised standards. To accomplish this, cutting-edge adverse simulation techniques, *in vitro* assays and animal models were developed together with a suite of computational assessments to significantly enhance device testing in terms of predicting clinical performance. Data informed new standards development and enhanced current testing scenarios, and provided 5 European enterprises with a significant market advantage.

Project website: http://lifelongjoints.eu/

OPHIS

Composite Phenotypic Triggers for Bone and Cartilage Repair

OPHIS explored the frontiers of knowledge of the effect of nano-structures on tissue regeneration, and led to the de-novo design of active structures able to trigger this process. The project was aimed at developing new, engineered biomaterials for the regeneration of both the osteochondral region and the vertebral body degenerated by osteoarthritis (OA) and osteoporosis (OP). These disabling, degenerative bone diseases have significant economic and societal impacts, and the efficiency of current pharmacologic and implant-based solutions are limited and often poorly tolerated.

These devices developed by OPHIS were based on the unique combination of biological triggers in the form of nanostructured biomaterials, able to mimic the extracellular matrices of either bone or cartilage, and chemical and biochemical cues, able to direct, control and preserve the phenotypes of the relevant cells in their respective histological compartments. Focus was also given to the study of the interactions occurring at the nano-scale level between the implanted

materials and the natural tissues. This information will complement the body of data obtained through clinically reflective *in vitro* and *in vivo* models.

Project website: http://www.istec.cnr.it/index.php/progetti/120-progetti-conclusi/progetti-europei-conclusi/229-composite-phenotypic-triggers-for-bone-and-cartilage-repair-ophis-2011-2014-fp7-nmp-2009-small-3-246373

RAPIDOS

Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs

The goal of the European and Chinese consortium leading the RAPIDOS project was to apply technologies to create custom-made tissue-engineered constructs, to improve the reconstruction of large bone defects in the proximal femur or tibia in orthopaedic surgery, and in cranio-maxillofacial surgery. The difficulty of this challenge lies in the requirements for both complex shape and partial load bearing ability. Rapidos provided innovative high-resolution medical devices made of re-absorbable polymers and calcium phosphate ceramic composites, specifically designed by integrating imaging and information technologies, biomaterials and process engineering, and biological and biomedical engineering for novel and truly translational bone repair solutions.

The use of the Chinese Medicine extract is a safe and a technologically relevant alternative to the intensely debated growth factors. These challenges were advantageously confronted by a strong Eastern-Western collaboration on biomaterials, which allowed the comparison and exchange of the advanced and commercially relevant biomaterials developed, and the parallel development of two precise technologies, stereo-lithography and low temperature rapid prototyping allowing for preparation of custom-made composite scaffolds loaded with unique biologics effectors.

Project website: http://rapidos-project.eu

REBORNE

Regenerating Bone defects using New biomedical Engineering approaches

The main objective of REBORNE was to develop new biomaterials that stimulate bone tissue formation either in combination with adult stem cells or not, for regenerating bone defects in orthopaedic and maxillofacial surgery. The

objectives were to demonstrate that biomaterials and cells are safe and at least equivalent to standard treatments using biological grafts without their drawbacks. Minimal invasive surgery using injectable biomaterials with intrinsic osteo-genic properties were preferred to trigger bone healing.

REBORNE performed clinical trials using advanced biomaterials and cells triggering bone healing in patients. To reach this goal, five clinical studies with 20 patients were proposed in 12 clinical centres spread in 8 European countries. Three orthopaedic trials concerning the treatment of long bone fractures and osteonecrosis of the femoral head in adults or children were conducted using bio-ceramics, hydrogel for percutaneous injection and stem cells from autologous or allogeneic sources. Clinical research also concerned maxillofacial surgery with bone augmentation prior to dental implants and the reconstruction of cleft palates in children. These ambitious clinical targets required research and development efforts from a large consortium of top world-class laboratories, SMEs manufacturing biomaterials, GMP-cell producing facilities and surgeons in hospitals as well as the consideration of ethical and regulatory issues.

Project website: http://www.reborne.org/

THE GRAIL

Tissue in Host Engineering Guided Regeneration of Arterial Intimal Layer

The aim of THE GRAIL project was to design and develop a bioactive and bioreasorbable scaffold that locally regenerates intima growth after endovascular treatment of the obstructed arteries in patients with arteriosclerosis. Arterial obstruction is the cause of a wide spectrum of diseases, disabilities and death, because of induced ischemia in feed arteries of the diseased organs. The purpose of the *in vivo* tissue engineered blood vessel was to offer an alternative treatment for patients affected with this disease. The project aimed at substituting the actual solutions, consisting in rechanneling or bypassing obstructed arteries, with a regenerative, physiological and long-term oriented approach in the therapy of ischemic cardiovascular disease, compatible with today's minimal invasive surgical techniques.

The absorbable bioactive scaffold does not intend to stent the artery; conversely it aims to replace the diseased and stiffened area with a soft and

compliant intelligent scaffold that becomes reabsorbed once its task is completed, leaving a physiologically responsive regenerated tissue. The project aims to merge the single laboratories ongoing work, coordinate it and finalize it to bring it through the whole pre-clinical process, including the whole regulatory work, the animal pre-clinical implants and the design and production of TE device deployment technology.

Project website: http://www.thegrail-project.eu/

2.2 KEY STAKEHOLDERS

A4M

The original initiators of Alliance for Materials initiative, A4M, were six European Technology Platforms with a strong material agenda in their respective strategies. These are: EuMaT, European Technology Platform for Sustainable Chemistry - Suschem, Manufacture, European Technology Platform for the Future of Textiles and Clothing - FTC (textile), European Steel Technology Platform - ESTEP, European Technology Platform on Sustainable Mineral Resources- SMR, integrated by the two main European materials associations: European Materials Research Society - E-MRS and Federation of European Material societies - FEMS.

The main aims of A4M are:

- To create a unique approach including different actors dealing with materials;
- To ensure a Value Chain coverage to improve speedy implementation of innovations in Europe;
- To improve dialogue between industry and research to create synergy and an integrated Materials R&D vision and strategy and make potential innovation valuable;
- To integrate main stakeholders and achieve an effective coordination between different sectors.

Among the fundamental concepts of A4M there is the concept of Value Chain. Value Chain is a key driver of final innovation processes. It acts as guide light integrating actors, resources and strategies in order to deliver a valuable product for the market. It is the reference point from the fundamental aspects of materials science, up to the industrial system, which finally produces or transforms materials into marketable products. The integration of actors along

the Value Chain can make a key contribution to boost the market of European innovations, particularly in case of private and public partnerships dealing with the large societal challenges. This integration will contribute to overcome some limitations existing in today's research and innovation programmes, which are still mostly sector driven. A4M intends to concretely contribute to identify a reasonable identification of the market PULL-PUSH optimal balance. Creating a synergy between academia and industry is the identified path in order to implement a European strategy for valuable innovation. Only together, both of them, academia and industry can design a coherent picture of the future Materials R&D need and strategies and so give form to a so called balanced Innovation.

EASME

EASME is The Executive Agency for Small- and Medium-sized Enterprises, which was set-up by the European Commission to manage, on its behalf, several EU programmes, with the aim of sustaining the growth of entrepreneurial sector in Europe.

One of the implemented programmes is SME Instrument. SME Instrument is the part of the Horizon 2020 programme, which addresses European, or associated countries, SMEs, characterised by:

- An innovative idea;
- A clear ambition to grow at EU/global level;
- Knowledge of the market and of competitors;
- Convincing commercialization plan.

The instrument takes place in three phases, with the aim of transforming disruptive ideas into concrete, innovative solutions with a European and global impact.

- Phase 1. Concept & Feasibility Assessment.
  - Idea to concept (6 months).
  - The European Union will provide €50 000 in funding, and carry out a feasibility study to verify the viability of the proposed disruptive innovation or concept.
- Phase 2. Demonstration, Market Replication, R&D.
  - Concept to Market-Maturity (1-2 years).

    - Assisted by the EU, the SME will further develop its proposal through innovation activities, such as demonstration, testing, piloting, scaling up, and miniaturisation.
    - Proposals will be based on a business plan developed on phase 1 or otherwise. The EU aims to contribute between €0.5 million and €2.5 million.
- Phase 3. Commercialisation
    - Prepare for Market Launch
    - SMEs will receive extensive support and facilitating access to risk finance
    - Additional support and networking opportunities will be provided by Enterprise Europe Network (EEN).

The SME Instrument is impact oriented. It is focused on finding the best SMEs and not only giving them a grant but also business innovation coaching. Beneficiaries can receive up to 15 days of coaching (3 days at phase 1 and 12 days at phase 2).

The evaluation process is clearly based on three criteria:

- Possible economic impact
    - Commercialisation plan
    - EU/global dimension
    - Knowledge protection
    - Jobs created in Europe
- Excellence in innovation
    - Viable & Disruptive technology
    - Added value
    - Better than existing solutions
- Implementation
    - Credibility of the work plan

ENTENTE PROJECT

The Entente project, funded by the European Commission under the FP7, aimedat strengthening the European knowledge transfer offices in universities, public research organizations and hospitals, and at promoting collaboration between industry and academia in the health sector, through sharing and networking activities among all key stakeholders within knowledge transfer.

Undoubtedly, the generation and spreading of free knowledge is and will remain an essential social role of academic institutes. However, it may not be the most effective approach for transforming academic research into new products and services. Particularly in the health sector, the development of commercially viable products is expensive and time-consuming. For this reason, as well as to avoid problems between partners and to maximise results possibly marketable, it is crucial to understand the legal aspects of a grant agreement in a multi-actor project.

The main aspects to properly manage the Intellectual Property (IP) transfer are three:

- Legal aspects of a grant agreement;
- Consequences for partners;
- Advantages for a Consortium of maximising exploitation of results.

The goal of a grant agreement is twofold:

- Making sure that the IP (background and results) of the beneficiaries is available to all beneficiaries to carry out their tasks under the project and to exploit their respective results.
- Avoiding that the beneficiaries use their IP rights to block each other from either carrying out their tasks under the project or from exploiting their respective results.

Very often complexity is difficult to manage, and IP and exploitation arrangements should seek to balance the research and exploitation objectives of the respective beneficiaries. The best solution to anticipate IP issues and enable exploitation of results is a consortium agreement. The consortium agreement, which represents a management tool throughout the project, should duly specify:

- The background of each of the beneficiaries;
- The availability of access rights on the background;
- Possible transfer of ownership/exploitation rights on particular results to one or more beneficiaries;
- The nature of the access rights.

In conclusion, managing and exploiting results and IP of collaborative research is unavoidably associated with complexity. The Grant Agreement provides a framework, but obviously is not enough to uphold all the partners. It needs to

be complemented with a well-negotiated consortium agreement, taking into account each beneficiary's research and exploitation objectives. In any case, mutual trust and transparency helps managing the complexity throughout the project and it is the best basis for collaboration.

EULAR

European League Against Rheumatism, EULAR, is the organisation, which represents people with arthritis/rheumatism, health professional and scientific societies of rheumatology of all the European nations.

EULAR's mission:

- To improve the treatment, prevention and rehabilitation of musculoskeletal diseases (RMDs);
- To reduce the burden of rheumatic and musculoskeletal diseases (RMDs) on the individual and society.

EULAR in action:

- Advice to policy makers and funding institutions on medical research policies;
- Analysis of RMD research & innovation, identification of gaps, needs and priorities for the future;
- Fundraising for research and innovation in RMDs and support to research projects.

After years of lack of knowledge and awareness of RMDs among decision makers, nowadays, thanks to EULAR's actions, RMDs is starting to be recognised as one of the major chronic diseases, and EU funds for research in RMDs have increased in the last years.

Still a number of challenges remain:

- EU and other international organizations (like WHO) still do not prioritise RMDs vis-à-vis other kinds of diseases;
- The EU's public health agenda is still largely influenced by big actors with different interests;
- Social affairs and employment legislation is insufficient to uphold patients;
- Reluctance to implement specific, comprehensive strategies against RMDs at the EU level.

To face these challenges as well as others, EULAR's main objectives for the next years are:

- To develop strong networks of effective, user led organisations of people with RMDs;
- To ensure the voices of people with RMDs are heard and acted upon by decision makers at the European level;
- To create powerful alliances and collaborations inside and outside EULAR, which make a difference to the lives of people with RMDs;
- To provide support to patient organisations.

In the next two years, EULAR is supposed to increase its influence on a EU level, and assist actions on a national level, towards improving research funding, social policy legislation, and quality of care.

The main EULAR policy goals are based on three axes:

- Research: EU funds match the burden of RMDs; Advice to EU institutions on medical research;
- Social Affairs: Stronger laws on working conditions; Action towards implementation of the EU Disability Strategy and UN Convention;
- Public Health: Collaboration with EU on prevention and management of chronic diseases; Implementation of eumusc.net Recommendations.

NCP BRUSSELS

Impulse Brussels is one of the privileged interlocutors for any beginner or experienced entrepreneur in the Brussels-Capital Region, thanks to a strong expertise and experience in management of European R&I projects.

Horizon 2020 is the biggest EU Research and Innovation programme ever with nearly €80 billion of funding available over 7 years. It is a good opportunity for SMEs to get grants, but at the same time it is crucial to understand if the programme fits well with the specific enterprise strategy.

The programme is particularly suitable in case an enterprise wants:

- To contribute with their unique expertise at a EU level
- To get EU visibility
- To build partnerships
- To scale up the business

On the other hand, in case of:

- The need of funding on a short-term basis
- Fund finalised to create a new company

To understand the kinds of options which are most applicable, the best solution is to hire a consulting service, which in turn enhances innovation management capacities within the company. Consultancy services can be very helpful in:

- Measuring the impact of innovation management on a company's business performance and identifying areas for improving innovation management performance;
- Getting a benchmark which will help to evaluate the competitiveness of a company in terms of innovation;
- Implementing an actionable roadmap to improve the innovation management capabilities and increase competitiveness.

NCPs in Europe (appointed intermediaries between the European Commission and (potential) R&I project participants) follows the entire cycle of the project and obviously without writing the project in place of the applicant, furnishes trustworthy and upstream information, workshops, and specialised and personalised support.

One more instrument supporting SMEs in the European area is EENs (Enterprise Europe Networks). EENs Network helps small and medium-sized enterprises (SMEs) make the most of business opportunities in the EU and beyond.

The main tasks of EENs are:

- Assistance in SME instrument project building & needs analysis;
- Partnership offers/requests (quality checked, valid 1 year);
- Targeted sending of partnership opportunities;
- Brokerage events and company missions (e.g. Medica, Meet In Italy for Life Sciences, BioEntrepreneur, BioMedica, etc.);
- Innovation Management Assessment for innovative SMEs.

SOZIALMEDIZINSCHEOZIALMEDIZINISCHES ZENTRUM OST-DONAUSPITAL

Dr Rainer Kluger is an orthopaedic surgeon at the SozialmedizinischesZentrum Ost–Donauspital, Vienna. He introduced the latest state-of-the-art therapeutic approaches for non-union bone lesions from a clinical perspective to explain the practical implementation opportunities and approaches for InnovaBone partners and external stakeholders. He highlighted the importance of research and innovation aiming at developing novel approaches for bone repair.

Current approaches:

The most used approach at present is bone reconstruction or grafting, which is a method, used to surgically repair bone by replacing the missing bone with substitutes such as human bone or synthetic materials. Bone generally has the ability to regenerate completely, but it requires a small fracture space, if the defect is too large, bone needs material (e.g., scaffold) placed into the defect to start the natural repair process.

- Autologous: the optimal source of bone for grafting is from the patient's own bone; this process is osteo-inductive, which refers to the differentiation of pluripotent cells into bone forming cells that effectively repair bone;
- Allograft: the next best solution is to use bone bank-derived cadaver allografts, even if allografts may also cause infection and require major microsurgical intervention;
- Synthetic: to avoid potential complication with bone grafts, alternative biomaterials have been developed, such as synthetic materials (β-tricalcium phosphate, Calcium carbonate, Hydroxy apatite, etc.). The two last solutions are osteo-conductive processes, which means that these materials encourage bone cells to migrate to the construction site.

Future approach:

The future is in the use of genetic engineering tools to obtain protein-like polymers, based on the human elastin sequence, with absolute control over their molecular architecture and sequence.

3. FOR WHOM

Dialogue needs active and reactive audiences, also called 'stakeholders': these have a vested interest in the performance of nanotechnology and also wield the greatest influence over the long-term role and nature of their organisation. They include staff, advisor committees, the government and the public, the industry, government departments, special interest groups, universities, science centres and science museums, science councils and other research bodies. Stakeholders are people who might want to actively hear and tell things. They tend to resent decisions that are made without their input, as this will virtually guarantee their opposition.

Resuming from chapter 1 (why) the Goals of this publication are:

- Increasing public awareness about nanotechnology and its benefits and risks;
- Improving knowledge about ethical and societal issues;
- Raising awareness of regulatory practices for health and safety issues;
- Initiating dialogue between stakeholders;
- Enabling an informed public debate;
- Increasing awareness about funding, co-ordination and policy for a range of Audiences including the general public, teachers, industry, NGOs, researchers, policy makers and other stakeholders.
- Providing information about research findings and policy to the public;
- Gathering input for future policymaking;
- Attracting younger people into science;
- Exchanging information with partnering agencies/institutions;

To obtain these quite challenging objectives it is crucial to reach the right audiences, with the appropriate messages, in terms of means and language. It is a critical moment for communication on nanotechnology, especially as outreach,

open dialogue and debate are declared to be key elements of the European approach to science and technology.

Nanotechnology has ushered a new era of nano-medicine and life nano-science with very significant potential for more effective therapy of life-threatening or disabling disorders. Nano-medicine, the application of nanotechnology to human healthcare, offers numerous potential pathways to improve medical diagnosis and therapy and even, as in the case of this publication, to regenerate tissues and organs. It can provide personalised yet more affordable healthcare while at the same time offering an improved quality of life for everyone. But Nano-medicine is also a strategic issue for the competitive position of the healthcare industry in Europe.

It is quite clear that social acceptance could come solely from this dialogue and engagement process, which is based on the development of appropriate communication.

But who are the interested audiences? Who is this publication for? The authors are extremely convinced that the sharing of knowledge has two main objectives:

- Collaboration to enhance the potential of European Research outputs;
- Awareness, to disclose nanotechnology and bio mimetic strategies to people not specialised in the matter.

For this reason, the authors through this publication, resuming the workshops outputs, address particularly:

- Policy makers;
- Stakeholders (in particular industry and organisations of patients);
- The scientific community.

The emergence of nanotechnology in society, as well as in the economy, is expected to have significant impacts. Nanotechnology is increasingly stimulating discussion regarding the technical possibilities it brings, particularly in addressing major challenges including, as in the case of the projects discussed during the two events (Clustering day, Stakeholders day), improving patients' health and quality of life.

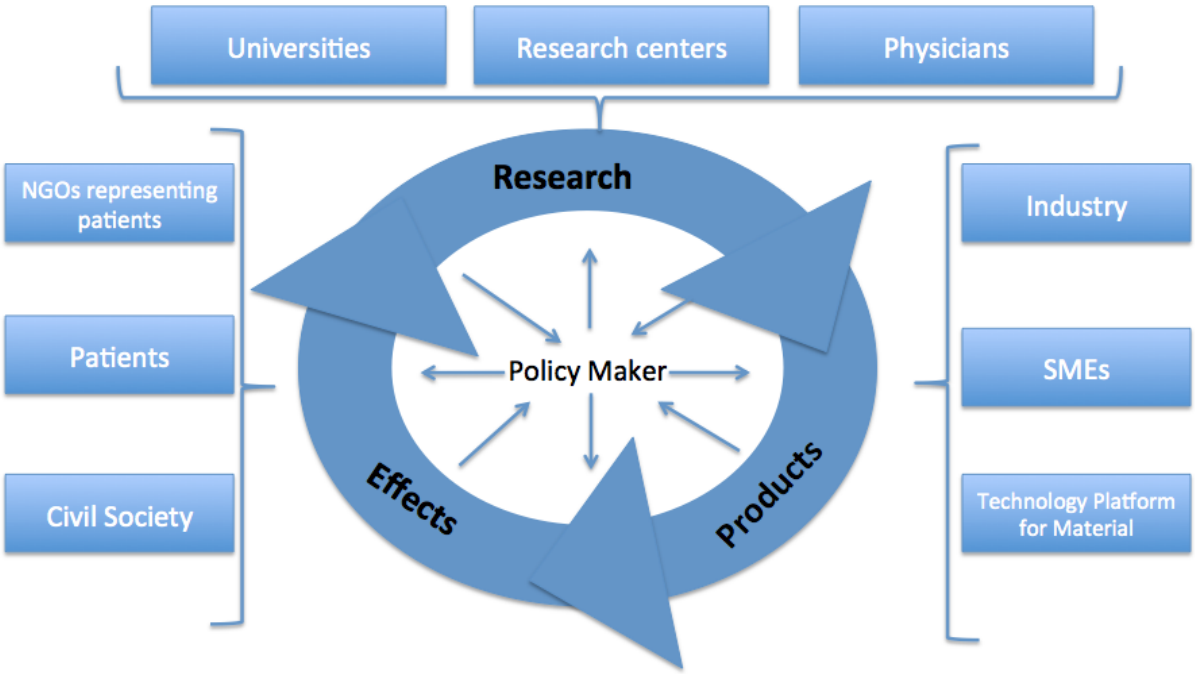

Fig.4 Actors in the field of biomaterials and tissue regeneration.

Authors already highlighted the importance of putting academics and experts working together in the field of nanotechnologies related to health. The link between policy-makers, experts, and practitioners, is extremely important to enable the latter to develop their research in the right institutional ecosystem. Furthermore, at a time when public expenditures are quite controlled to ensure the most efficient use, it is suitable to expose the potential impact of specific research to policy-makers. Indeed, being accurately informed on research results and their impact enables policy-makers to allocate funding correctly.

Research findings can be used as an input to create policies. If researchers and policy-makers cooperate closely to understand specific needs, they can ensure relevance of topics and improve communication, dissemination and implementation of research recommendations.

Bridging the gap between researchers and policy makers needs to work in both ways: on the one hand the comments and experience of both researchers and policy-makers could be brought together to provide a structured set of recommendations for researchers working in the field of nanotechnologies and biomaterials. On the other hand also for policy makers who are strongly invited to use research-based information in the formulation of national or European

policies.Communication flows should go both ways: policy makers should also think of channels to inform academia of major policy questions. This would help make research more policy relevant. Some suggestions in this regard are in the section below.

Today the public is more educated, involved, and concerned about new technologies and industrial processes and their potential effects on human health and the environment than it was 50 or 60 years ago, and as consequence public concern about nanotechnology has increased.

Sometimes new technologies, such as genetically modified foods, are not well accepted by the public worldwide because health agencies did not involve and educate the public and policy makers in the beginning when the technology was being developed, creating misunderstanding and room for manipulating public opinion, in order to use it. If there is a low level of prior awareness of an issue among stakeholders, the process and outputs are likely to differ from those where the stakeholders are better informed about a specific topic or emotive subject.

Public acceptance of nanotechnology is likely to be strongly influenced by the perception of the associated risks. It is therefore essential to establish an appropriate legal and ethical framework for the implementation of nanotechnology in healthcare applications. The adoption of a precautionary approach, based on the use of reliable scientific data, is advisable in order to reduce the level of risk.

Ethical, Legal, and Societal Implications are a crucial aspect for researchers as well as for policy makers. The development of Nanomedicine has led the conviction of many that this field will shape the medicine of the future to a large degree. However, "beyond the technological aspect, important questions in the "meta" domain are open to debate: what will energize, who will guide and to what extent should society channel this revolution in medicine?"[10] (Hunziker, P. chief editor of European Foundation for Clinical Nanomedicine, Basel)

Integration of societal research with nanotechnology development is meant to influence the direction of those kind of investigations, an explicit emphasis ought to be placed on the capacity of the new program's societal and ethical research to influence European nanotechnology development policy.

[10] Hunziker, P. Nanomedicine – Shaping the future of medicine in a context of academia, industry and politics. European Journal of Nanomedicine. Volume 3, Issue 1, Pages 6–6, ISSN (Online) 1662-596X, ISSN (Print) 1662-5986, DOI: 10.1515/EJNM.2010.3.1.6, May 2010

Furthermore, policy-makers must ensure that nanotechnology is developed as a safe consumer product, but also that end-users are provided with correct, comprehensive information without creating futile awareness and in some cases even panic.

Another important point is that many of the governmental regulatory frameworks we have today were conceived 30–40 years ago, when nanotechnology did not yet exist and therefore do not specifically address the unique properties of nanomaterials.

There is a need for increased levels of cooperation between the industries involved, public interest groups, and government parties to find economically viable solutions while still protecting the environment and health. We are looking at the birth of a new industry and beginning to address risk in a way that has not been done with any other developing technology before, that is, well before large amounts of these materials were introduced into the environment or onto consumers. This provides us with a unique opportunity to shape a new, emerging area with a lot of knowledge about environmental health issues that we would ultimately face and avoid the problems that have plagued chemistry in the past.

Finally, the nature of nano-materials and their unique properties accounts for the significant research both in scientific institutions and industry for translation into new therapies embodied in the emerging field of nano-medicine[11]. Obviously, the potential of nano-medicine to make significant inroads for more effective therapies, both for life-threatening and life-disabling disorders, will only be achieved by high-quality life science research, and the expansion of academic-industry partnerships in numbers and types that have become a more prominent feature of the broader landscape of partnerships in biomedical innovation.

A close and synergistic relationship between these sectors is critical to ensuring a robust European biomedical research capacity. Furthermore, the R&D ecosystem in Europe is rapidly evolving to adapt to changes in the healthcare environment.

Still, it is crucial to rise to the practice of creating technology transfer between different actors. The research interdependence between industry and academia, is however a domain which needs regulation and sustain from policy makers, to avoid totally industry-led research and industry guided processes ,while

[11] Raffa V, Vittorio O, Riggio C, Cuschieri A. Progress in nanotechnology for healthcare. Minim Invasive Ther Allied Technol. 2010 Jun;19(3):127-35.

maintaining biomedical research an independent domain of research (once again an ethical prospective).

In Europe, the existence of various bodies embracing different positions in this field of development of nanotechnology, applied to medicine and health care sectors, is at the same time an opportunity and a challenge to make all the voices heard. In fact, the only way to be the most possible respondent to the societal needs is to create a collaborative and inclusive process of dialogue and exchange of knowledge.

In this respect, the authors, through this publication, try to give their own contribution to deepen the dialogue.

4. WHEN?THE TWO SESSIONS

4.1.THE FIRST MEETING – BRUSSELS 13 NOVEMBER 2014

The meeting brought together experts and participants from EC-funded projects in a wide variety of fields (listed in the appendix), in the workshop entitled "*InnovaBone Clustering day".* The initiative, promoted by InnovaBone project consortium, aimed at taking advantage of the experts' extensive knowledge to foster policy implementation concerning biomaterials and tissue regeneration with a focus on novel biomimetic strategies for osteochondral regeneration.

The agenda was organised as follows:

(i) *Presentation of selected EC-funded research and innovation projects* by the coordinators of BioTiNet, HydroZONES, Ophis, Reborne, InnovaBone, Lifelongjoints, Rapidos and The Grail, highlighting the main results achieved by these other funded projects and by the EC in Europe over the last years;

(ii) *Small roundtable panel group discussions* focused on diverse scientific specific subjects. Building coherently on previous experiences, the participants outlined needed actions for the future, which were presented as key-ideas for future research in the subsequent plenary session.

(iii) *Large roundtable panel group discussions* focused on horizontal cross-cutting issues with the aim to outline needs and prospects for the future, which were presented in the subsequent plenary session as key deliverables in shaping the debate on future research policy needs.

(iv) *Final plenary session* during which the panel discussion on future trends and priorities in the short, medium and long term at the EC level where presented and summarised.

Emphasis was very much put on the endogenous model of technological development[12], aiming for a better interaction between society, science and technology. Nanoscale research development is not isolated from society, and the social value of research-based innovation needs reflective critique, so end-users are crucial. To improve regulatory certainty we need to deepen the current debate between all involved stakeholders, to improve the cognitive basis, credibility, acceptance and conflict-resolving potential of the Technological Assessment[13]; thus, by considering crucial stakeholders as key end users of research and innovation in the field, the overall policy will benefit such an approach.

To support a responsible nano innovation policy, there is a need to widen the participation of affected individuals and groups.

- Firstly, knowledge gaps must be tackled and overcome.
- Secondly, representative, participatory, and deliberative processes must be employed. This methodology aimed to improve access to information, to engage targeted groups in critical reflection and sharing practices[14]
- Finally, it is important to give voice to practitioners and experts, to influence future research policy.

Therefore, the expert meeting was an excellent opportunity to bring together key researchers, previously involved in earlier EC workshops, consultations, and projects together to set up a working meeting to discuss research priorities.

The experts discussed and debated the main outcomes and challenges of their EC funded research. Together with additional experts and EC representatives, they proposed concrete suggestions aimed at promoting good governance in future policy-making.

The participants talked about best practices for further improvement and cross-fertilisation. Firstly, selected scientific issues were proposed to small panel groups for brainstorming, networking, and to discuss future collaborations and new themes and topics in the field for further study.

[12] Van Est R. And Brom F. *Technology Assessment, Analytic and Democratic Practice.* In: Ruth Chadwick, editor. Encyclopedia of Applied Ethics, Second Edition, 2012, Vol. 4, 306-320.

[13]STOA, Science and Technology Options Assessment, European Parliament (2008).*Technology across borders: Exploring perspectives for pan-European Parliamentary Technology Assessment*, Study of Directorate General for Internal Policies, Directorate G: Impact Assessment, IP/A/STOA/FWC/2008-096/LOT8/C1, PE 482.684.

[14]see previous chapters, particularly chapter1 and chapter 3.

Secondly, panel talks on cross-sectorial issues such as standardisation, characterisation, and exploitation were intended to lead to the identification of future challenges for EC policy.

Thirdly, they identified prospects and constraints, such as liability, safety, and regulation, which implied generating a set of realistic options for real policy action (Grunwald, 2003)[15].

The objective of this collaborative effort has been to propose new ideas on how to proceed with future research policy actions, in accordance with the three main priorities of the strategy for smart, inclusive, and sustainable growth[16]:

(1)Delivering Social Benefits,

(2)Economic Relevance,

(3)Concerns on Policy Prospects.

The present deliverable working paper will be a valuable input for future discussion on proposals, actions, and activities on nanotechnology research and innovation in the field, as a line of strategic alignment between technological and societal developments as the ultimate objective[17] of technological assessment.

The Clustering day generated new ideas on how to reach consensus on actions, priorities and prospects. The participants were intermingled into various discussion panel groups across individual areas of expertise and interests, and thus, enabled each participant to provide their particular perspectives and suggestions.

[15]Grunwald, Armin (2003). *Technology assessment at the German Bundestag: 'expertising' democracy for 'democratising' expertise*, Science and Public Policy, volume 30, number 3, pp. 193-198.

[16]European Commission (2012), *EUROPE 2020*, Brussels.
http://ec.europa.eu/europe2020/index_en.htm

[17]STOA, Science and Technology Options Assessment, European Parliament (2008).*Technology across borders: Exploring perspectives for pan-European Parliamentary Technology Assessment*, Study of Directorate General for Internal Policies, Directorate G: Impact Assessment, IP/A/STOA/FWC/2008-096/LOT8/C1, PE 482.684.

4.2. THE SECOND MEETING- BRUSSELS 14 OCTOBER 2015

The event was conceived for the benefit of stakeholders and was part of a two-day conference organised by InnovaBone partners to share latest results obtained by the project on the topic of biomaterials for bone regeneration. Conference attendees included scientists, patient associations, health professionals, policy makers, industrial players and citizens.

Furthermore a number of stakeholders designed different scenarios on the applicability of the InnovaBone results, ensuring on the one hand, better healing solutions, and on the other hand, maximizing business opportunities. InnovaBone project (funded under FP7) to some extent moved up one of the key aspects highlighted and boosted by Horizon 2020. In fact, InnovaBone is a clear example of Responsible Research and Innovation (RRI) implementation. RRI implies that societal actors (researchers, citizens, policy makers, business, associations, etc.) work together during the whole research and innovation process to better align both the process and its outcomes with the values, needs and expectations of society.

The Stakeholder day of InnovaBone conference was organised as follows:

(i) Building bridges from bench to clinic. The main effort of this session was to introduce InnovaBone in its institutional context. Different stakeholders participated to the debate, with particular attention to three specific categories: industry – research - organisation dealing with patients.

(ii) *Growth of SMEs through EU projects.* InnovaBone SMEs, which got the opportunity to grow and increase their turnover thanks to the project. The main aim of this session was to share best practices, to keep up about new supporting and financing opportunities for SMEs and further exploitation of scientific results. This session was in the frame of Open days 2015'- the European Week of Regions and Cities as a side event.

5. WHAT TO DO?

This section addresses the different works carried out by the discussion panels during the Clustering day, to identify future trends, priorities and prospects at various time horizons for future EC research and innovation policy on the osteochondral reconstruction.

5.1 RESEARCH AND INDUSTRY: TRENDS, DEBATE, AND PROSPECTS

Research projects should give substance to the broader objective of activating citizens' role in shaping technological developments, guiding nano-based innovation towards socially robust outcomes.

Experts agreed that the debate should take into account EU identified grand societal challenges (i.e. ageing society), exploring the potential of nanotechnology and nanoscience to solve these multifaceted problems. The common ground of discussion unfolded a multiplicity of choices around nanotechnology from the perspectives of:

- Scientific excellence;
- Innovation and market uptake;
- Regulation.

Experts' discussions focused on three main areas of interest, which also represents the three working groups that were set up:

1. Trends;
2. Debate;
3. Prospects.

5.1.1 TRENDS

The first group focused on "**Mimic natural processes with growth and bioactive factors**". The group was led by Michelle EPSTEIN.

After considerable discussion, we proposed a number of trends in the field. These included the following:

- Personalisation of medical implants by image-directed manufacturing of implants with the ultimate plan to have a stratified approach with personalised devices for patients;
- More effective production of scaffolds;
- Automation of scaffold production;
- Creation and implementation of a common database similar to the gene database;
- Addressing technical issues such as biocompatibility and toxicity problems of nanoparticles;
- Generation of novel *ex vivo* screening models to speed up the validation/selection of most promising advanced materials for further pre-clinical testing;
- Development of tools and instruments to detect, visualise and modify biomaterials;
- Nanoparticles for controlled drug delivery;
- Challenging clinical applications such as cardiovascular operations;
- Important to ensure standardised testing of biomaterials;
- Considering end users, authorities, product liability, EU regulation, and safety;
- Strategies for validating materials;
- Novel anti-microbial metallic surfaces;
- Novel biodegradable metallic implants;
- Considering mechanical and chemical non-compatibility of metallic implants;
- Novel Ni-free Titanium-based shape memory alloys;
- Innovative coatings to improve osseointegration of metallic implants;
- Low modulus metallic implants (beta-type Titanium-based alloys);
- Mimicking natural processes with growth and bioactive factors.

5.1.2 DEBATE

The second group, led by Martha LILEY and Pierre LAYROLLE, worked on the research question:

"**Could modelling work be a way to help predict the behaviour of nanoparticles**?"

Despite evidence that biology systems (cells, proteins) interact with materials in the nanometre range, medical devices containing nanomaterials shave a difficult regulatory pathway until CE mark. These innovative nano-biomaterials are regarded as Class III medical devices requiring clinical trials demonstrating their safety and efficacy. There is also a lack of tools for characterization of nano-biomaterials for quality control of products as well as a limited number of standards to control their interactions with body fluids, cells and tissues. Efforts should be made by regulatory agencies to propose standards that will not hamper the innovation of European SMEs bringing nanomaterials on the global competing market of medical devices.

New quality assurance tools for biological (materials and preparations made from living organisms) are also needed.

5.1.3 PROSPECTS

Serena BEST led the third focus group working on prospects. After a long debate, experts concluded that:

- it is crucial to find ideal features to make the material as safe as possible;
- the creation and the implementation of a common database, similar to the gene database would also be required;
- prioritising clinicians' needs regards NanoMedicine;
- the development of new structures and information exchanges on an International basis.

5.2 FUTURE RESEARCH AND INNOVATION POLICIES

Two main points have been highlighted at this step of the workshop:

- *Drivers and Constraints for future Research*:
  The two main points, touched by experts, have been translational regenerative medicine, and convergence of technologies. This second point of the discussion focused on printing and clinical applications of **bio-printing**;
- *Participation and engagement of civil society organisations (CSOs) and industry*:
  Participation and engagement of civil society organisations (CSOs) and industry are indispensable elements of a responsive policy strategy for nanotechnology. The workshop exercise pinpointed that broad stakeholder involvement would enable robust policies and improve innovation efficiency. The establishment of a **multi-stakeholder clustering platform** involving CSOs, industry and policy makers to advance responsible European policies for nanotechnology would be a desirable and possible outcome of the clustering exercise.

5.2.1 DRIVERS AND CONSTRAINTS

Two main points have been touched:

1. **Translational regenerative medicine**

Development of new materials combining biocompatibility with bio-responsiveness and processability by rapid manufacturing techniques (Biofabrication), e.g. through nano-programmed self-organisation

2. **Convergence of technologies** (printing, quality control/monitoring, bioreactor/culture) for automated production of tissue equivalents.

Bio-printing of tissues and organs started in 2004 in USA. In Europe, there are a limited number of academic laboratories and SMEs involved in the field. The main challenge in bio-printing is to develop bio-inks that sustain multiple cells' adhesion, proliferation, differentiation and tissue remodelling of the 3D constructs.

Clinical application of bio-printing

Medical applications for 3D printing are expanding rapidly and are expected to revolutionize health care (Schubert et al., 2014)[18] Medical uses of 3D printing, both under actual and potential prospects, can be organized into several broad categories, including:

- Tissue and organ fabrication;
- Creation of customized prosthetics, implants, and anatomical models;
- Pharmaceutical research regarding drug dosage forms, delivery, and discovery

The application of 3D printing in medicine can provide many benefits, including:

- The customization and personalization of medical products, drugs, and equipment;
- Cost-effectiveness; increased productivity;
- The democratization of design and manufacturing; and enhanced collaboration.

However, it should be cautioned that despite recent significant and exciting medical advances involving 3D printing, notable scientific and regulatory challenges remain and the most transformative applications for this technology will need time to evolve[19].

5.2.2 ROLES OF RESEARCH POLICY MAKERS, INDUSTRY AND REGULATORY BODIES

While the dialogue process is intended to exchange views and concerns among stakeholders (in the sense of a two-way communication), the exchange is expected to be more effective if participants are, to a certain extent, 'on the same wavelength' with respect to the available information. In other words, in addition to the dialogue meetings themselves, there is a need for the provision of information (in the shape of 'unidirectional' training or education)a platform of exchange envisaging a number of training events, in which each of the stakeholders "educates" the others, by addressing knowledge gaps. The figure

[18]Schubert C, van Langeveld MC, Donoso LA. Innovations in 3D printing: a 3D overview from optics to organs. Br J Ophthalmol. 2014;98(2):159–161

[19] Lee Ventola, C. Medical Applications for 3D Printing: Current and Projected Uses. Pharmacy and Therapeutics P T. 2014 Oct; 39(10): 704–711.

below indicates the multilateral process thanks to which stakeholders may learn from each other.

Multilateral learning process for stakeholders

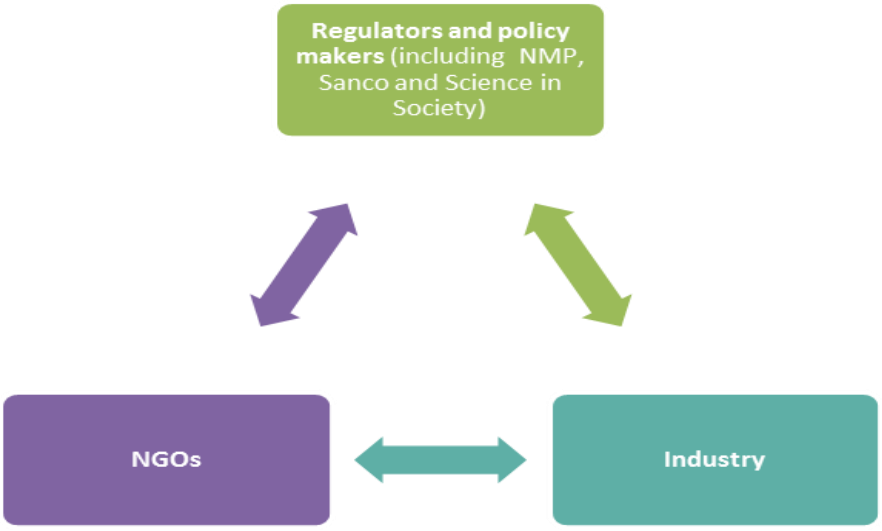

Fig.5 Multilateral learning process for stakeholders

Regulators and policy makers can inform the industry about the state of the regulatory processes and provide a picture of the underlying issues at stake (such as safety concerns). Conversely, regulators can benefit from information sharing with the industry to assess the levels of knowledge already available within the industry and to align regulations to production practices.[20]

CSOs can in turn offer insights on the kinds of values and concerns within different segments of the population, and the way they are prioritised. In doing so, they may broaden the scope of the questions to be addressed during the dialogue meetings. Conversely, regulators and policy makers can assist by promptly providing information on the most updated regulatory and policy processes to date and "open up" the policy making process.

To conclude, dialogue meetings and clustering sessions organised by a multi-stakeholder platform could facilitate the development of a shared vision on the ways in which nanotechnologies may affect Europe and the questions this raises

[20] Particularly here, the issue of equality needs to be kept to the fore. CSOs may be concerned about becoming unwillingly involved in an industrial lobby directed at policy makers. Information exchange needs to remain objective and impartial.

for policy making. In doing so, robust European policies for nanotechnology might or could be enabled, also contributing the Commission's policy strategy for nanotechnology research and innovation. The continuity of the multi-stakeholder platform would also establish cross-links between the various partners and projects involved.

6. HOW? MATERIALS AND METHODS

This section addresses the methodologies applied during the "Clustering Day", based on the input stemming from the preliminary survey results.

The chapter has been divided in three main sections:

- Survey;
- Small Roundtable Discussions;
- Large Roundtable Discussions.

These three tools represent the methodology used during the Clustering Day to facilitate the experts' work defining and analysing new paths for research.

The first section deals with the survey sent to experts before the Clustering day. Questions have been listed and a summary of the answers to the questionnaire has been reported.

The second section deals with the Small Roundtable Discussion session. Several axes of interests have been detected and analysed by experts (Novel Titanium-based structures; Bioactive hydrogels for tissue regeneration, Release of growth factors from biomaterials, Combined drug/biomaterial devices for tissue regeneration; New biomaterials for joint replacements; Nanostructured biomaterials; Biomaterials and cell therapy; Bioreasorbable scaffolds; Novel technology for biomaterials production).

The third section deals with the large Roundtable Discussion session. The work was organised in 5 large panels (Regulatory, standards and safety aspects of medical devices; Exploitation of novel biomaterials in clinics; Industrial production of biomaterials; Stakeholders' needs; Future Challenges in NPM)

The material collected during the "Clustering day" has been used also as a basis for setting up the "Stakeholder Day", held just one year after the first workshop.

6.1 SURVEY

InnovaBone Consortium participated in shaping the future of Nanotechnology and Advanced Materials in Horizon 2020 framework programme for more effective Healthcare. To do this InnovaBone Consortium organised a survey in preparation of the Clustering Day event in Brussels which took place on November 13th, 2014. The event aimed at sharing knowledge, experience and interest in the field of tissue regeneration and biomaterials. This survey lasted for 4 weeks prior to the event and it sought to identify key technological challenges and research priorities to establish a research and innovation agenda for the future. The questionnaire gathered opinions on new nano- and micro- technologies and advanced material themes that may be covered within the 2016-2018 Work Programme. There were 20 survey respondents from InnovaBone, BioTiNet, HydroZONES, Ophis, Reborne, InnovaBone, Lifelongjoints, Rapidos, and The Grail project partners.

Listed Below, the questions with a summary of the answers to the questionnaire[21].

Q1: What are potential vital outcomes from the projects funded through future "nanotechnologies, bio and advanced materials and production" (NBMP) calls?

The main outcome, as indicated in several responses, was the development of new materials, devices, products and systems and the exploitation of novel fabrication technologies for healthcare applications, aimed at improving the health of EU citizens through regenerative treatment solutions, using therapeutic micro- and nano-technologies.

There was a strong consensus on the need to facilitate the production, scaling up and commercial exploitation of these materials and products, through the active support of SMEs and the development of pan-European links and networks between SMEs and R&D centres (this was mentioned several times). The aim was to create a competitive and leading European market of biomaterials, which would

[21]The symbol: * indicates that multiple respondents replied with similar answers.

deliver more efficient and cost effective technologies to the patient using targeted and personalised therapies, preventive therapies and diagnostic methods.

The development of the knowledge associated with these new nano-technology solutions, and its dissemination through training across Europe, was suggested as a requirement to achieve this goal.

Q2: What topics should be included in the next work programme in the field of "nanotechnologies, advanced materials and production" applied to healthcare?

Respondents suggested several topics for integration and/or development within future work programmes:

- Preventive medicine and advanced diagnostic tools, health monitoring;
- Regenerative medicine, with gene, cell and nanostructure-based therapies, including novel tissue-mimetic (bio-)fabrication techniques and exploitation of nano-based assembly strategies for biomimicry;
- Synthetic biomedical materials mimicking physiological processes and environments, such as "stealth" and smart technologies, with controlled degradation*;
- Development of biocompatible implants with improved recognition and integration with host tissues, including biology of healing;
- Toxicity testing and health assessment of new biomaterials;
- Scaling up the production of biomaterials;

The suggested applications for these topics included:

- Heart valve production;
- Cancer treatment, e.g. breast and prostate cancer*;
- Fabrication of functional human tissue models for cancer research and drug testing;
- Advanced technical textiles;
- *in vivo* organ remodelling and regeneration ("in situ tissue engineering");
- Advanced and implantable sensors

- Development of antimicrobial coatings;
- *in vitro* screening and toxicity models;
- Membrane technology for separation systems and cell encapsulation;
- Imaging and tracking of cells;
- Age-related disorders;
- Minimally invasive surgical treatments;
- Design and production of smart metallic shape memory alloys.

Q3: Which are the main barriers preventing significant breakthroughs in the field of "nanotechnologies, advanced materials and production" for medical use manageable at EU level?

The main identified barrier is the **strict regulatory framework**. The respondents often complained about out-dated regulations and at the same time they moved the urgent need to adapt them to new technologies and challenges. The issues resulting from this regulatory barrier included a high administrative load, the difficulty to change partners during a project, and in the end, regulations leading to the modification of existing devices rather than the development of new ones to facilitate a faster approval and entry in the market. Even if experts recognised the need for rules and strict regulatory frameworks, they asked for a new framework, especially related to new materials.

Ethical and cultural considerations play a role in defining breakthroughs.

Experts also expressed their uncertainty about international standards, which have been defined as not clear enough.

The funding scheme for **clinical trials** was often criticised: project timeframes are too short to allow for thorough clinical trials, which generally require more time than 3 to 5 years. Additionally, clinical trials are expensive. The timescale needs to be adapted to match the funding gap between basic laboratory research and clinical trials.

It is necessary to further develop the collaboration between research and industry, even outside of the healthcare sector, to address the challenges of scale-up manufacturing and industrial sustainability for new products, and to develop investments, both public and private.

The fundamental issues, such as **biocompatibility and toxicity problems** of **nanoparticles**, were raised several times, together with the actual lack of sufficient diversity in the panel of smart materials and devices available. Some respondents argued that the focus is on tissue engineering instead of other fields like gaining deeper knowledge on biologically-inspired processes. Some others indicated the importance of future funding for development of novel materials and exploitation of novel fabrication technologies, to make sure the pipeline doesn't dry out.

Q4: Are the trends, opportunities, and key issues, essential to innovation in the field of "nanotechnologies, advanced materials and production"?

- Yes (70%)
- Yes, but with a different emphasis on particular elements (please specify) (10%)
- Yes, but some essential elements are missing (please specify) (20%)
- No, not at all because… (Please specify) (0%)

Please specify based your answer above.

The respondents considered that the trends, opportunities and key issues described in the reference documents are essential (70% opted for "yes").

Some of them thought that some essential elements are missing (20%) or need to be emphasised (10%), including:

- The development of tools and instruments to detect, visualise and modify biomaterials;
- The generation of novel *ex vivo* screening models to speed up the validation/selection of most promising advanced materials for further pre-clinical testing (hence it should be stated under Q2, see remark there);
- The broadening of functioning technologies in addition to novel and innovative technologies;

- The use of synthetic materials, without biologics, instead of animal-derived products*.

Q5: The present sub-call of the NBMP call for proposals, "Nanotechnology and Advanced Materials for more effective Healthcare", supports research and innovation actions in the areas of:

- **Scale-up of nano-pharmaceuticals production;**
- **Networking of SMEs in the nano-biomedical sector;**
- **Biomaterials for the treatment of diabetes mellitus;**
- **Nanomedicine therapy for cancer;**
- **Biomaterials for treatment and prevention of Alzheimer's disease.**

Please describe further actions required in the area of your expertise, and indicate additional areas not listed above.

In general, the respondents indicated new areas that would require support from Horizon 2020 programme; several areas included **specific actions for biomaterials** (such as biodegradable hydrogels and micro fibrous polymers):

- Biomaterials for regenerative medicine (especially for tissues: several respondents mentioned the cases of fractures, burns, ulcers, or spine injuries);
- Biomaterials for treatment and prevention of osteoporosis;
- Intelligent and stimuli-responsive biomaterials, including injectable materials and biomaterials for 3D printing and bio-fabrication;
- Biomaterials for minimally invasive surgical treatments;
- Biomaterials for cancer detection;
- Biomaterials for plastic surgery applications.

Nanoparticles were evoked for the following actions, in particular, in the case of the development of non-invasive medical methods:

- Controlled drug delivery;
- Challenging clinical applications, such as cardiovascular operations;

- Thin (e.g. antimicrobial) coating for medical devices and prosthesis, such as artificial organs, and systems to bypass or modulate the immunologic response;
- Vectors for gene therapy;
- Novel imaging techniques.

Composite implants that could be used for orthopaedic purposes is a research area with several variations: joint replacements, ligament repairs, shape memory alloys for accurate positioning, biodegradable implants, bio-equivalent mechanical devices with a particular attention to the personalisation of these devices thanks to 3D medical image-based engineering and 3D printing expertise.

The biodegradable characteristic of biomaterials and nanoparticles raise the emphasis on the necessity to develop temporary scaffolds which support cell growth, with applications such as ocular diseases.

Q6: On what body systems might biomaterials and nanomedicines be applied to in the future? Please mark below.

- **Orthopaedics**
- **Cardiovascular**
- **Immunology and infection**
- **Pulmonary / Respiratory diseases**
- **Plastic surgery**
- **Urology / Gynaecology**
- **Endocrinology and metabolic disease**
- **Ophthalmology**
- **Oncology**
- **Dermatology and wound care**
- **Gastroenterology**
- **Neurology**
- **Oto-Rhino-Laryngology(ORL)**
- **Others (please describe)**

The responses to this question are ranked in the following table, by order of popularity (include the **n=number)**

Orthopaedics	95%
Cardiovascular	90%
Dermatology and wound care	80%
Plastic Surgery	75%
Urology/ Gynaecologic	60%
Oncology	60%
Neurology	55%
Pulmonary/ Respiratory diseases	50%
Immunology and Infection	45%
Ophthalmology	40%
ORL (Oto-Rhino-Laryngology)	40%
Endocrinology and metabolic diseases	35%
Gastroenterology	30%
Others: Lymphohematopoietic glands	5%

Table 1. Responses to the question: "On what body systems might biomaterials and nanomedicines be applied to in the future?"

6.2 SMALL ROUNDTABLE DISCUSSION

The first session included 3 minute elevator pitches from the coordinators from InnovaBone, BioTiNet, HydroZONES, Ophis, Reborne, InnovaBone, Lifelongjoints, Rapidos, and The Grail projects to set the stage.

Panellists admitted that a fast and responsible deployment of nanotechnologies will play a critical role in addressing the major societal challenges identified by the EU 2020 agenda. These technologies could help build a smart, sustainable and inclusive growth. Balancing the potential benefits with the risks, the experts tackled a set of research axes ("axes of interest"), in need of careful formulation and consistency.

6.2.1 AXES OF INTERESTS:

Scientific discourse, brainstorming, networking & the forging of new collaborations

- Novel Titanium-based structures: Moderator - Mariana CALIN
- Bioactive hydrogels for tissue regeneration, Release of growth factors from biomaterials, Combined drug / biomaterial devices for tissue regeneration - Chaired by Carlos RODRIGUEZ CABELLO, Willy HOFSTETTER and Maria Pau GINEBRA
- New biomaterials for joint replacements: Moderator - Richard M. HALL;
- Nanostructured biomaterials: Moderator - Anna TAMPIERI;
- Biomaterials and cell therapy: Moderator - Pierre LAYROLLE;
- Bioreasorbable scaffolds: Moderator - Davide DE LUCREZIA;
- Novel technology for biomaterials production: Moderator - Olaf MOLLENHAUER.

6.2.2 WORKING GROUPS:

During the second session of the workshop, the debate identified existing problems and possible solutions, which would have a visible impact on nanoscience and nanotechnology innovation.

The workshop focused on necessary knowledge and the visions that should drive the process of policy-making and decision-taking. Special attention was paid to scientific expectations and to the regulatory systems across the EU member states.

Each working groups delivered a short summary, reported below.

NOVEL TITANIUM-BASED STRUCTURES -CHAIRED BY MARIAN CALIN:

Development of Novel Metallic Biomaterials

The continuous demand for bone replacement and repair is a result of the demographic changes, characterised by a continuously aging of the population and the exponential increase of osteoporotic fractures. Moreover, changing lifestyle habits are increasing the incidence of typically age-related diseases among the younger population. Existing materials for bone repair and replacement do not satisfy all clinical desires. For load-bearing orthopaedic applications, metals have so far shown the greatest potential, owing to their excellent mechanical strength and resilience when compared to alternative biomaterials, such as polymers and ceramics.

A major issue of the commercial metallic biomaterials is the bone-implant stiffness mismatch causing stress-shielding with consequence of tissue loss. An implant must be durable enough to withstand all physiological loads. A suitable balance between strength and stiffness is needed to best match the behaviour of bone and to mechanically stimulate bone growth. The release of toxic metallic species by corrosion and wear is problematic due to inflammatory cascades. Suitable surface states must be created, i.e. tailored surface topographies and chemistry, which enable an optimum osseo-integration. These critical functions of mechanical and biological compatibility must be improved for effectively supporting bone-healing processes and increasing the lifetime of a bone implant. New metallic materials with reduced stiffness, improved biocompatibility and strong surface-tissue bonding are needed to facilitate long-lasting functionality of load-bearing implants.

To increase orthopaedic implants' lifetime, research trends have included the development of new titanium alloys made of nontoxic elements with suitable mechanical properties (low stiffness / Young modulus - high fatigue strength), good workability and corrosion resistance.

Current issues such as stiffness, poor biological compatibility of alloying elements– can we develop low modulus Ti-based implants with appropriate coatings for optimised repair? - through:

- Alloy development: new beta-type titanium alloys (based on mechanical, chemical, biological and electrochemical requirements);
- Thermo-mechanical treatment;
- Structural design;
- Innovative processing;
- Optimised coatings for orthopaedic applications (for both articulation applications and bioactivity);
- Innovative processing to create complex patient-specific implants;
- Development of new geometries of implants which will benefit from the performance and the remarkable properties of metastable beta-Ti alloys.

It is essential to translate the ideas into **commercial products.**

Some of the disciplines involved are: Materials Science and Engineering, Mechanical Engineering, Chemistry, Biomechanical Engineering, Biology, Microbiology, Biochemistry, Mathematics, Physics for ab-initio modelling, and Clinics.

Why is the work needed?

For a reduction in bone resorption and an acceleration of the bone repair.

We need to remember that a bone material that is being replaced and/or repaired is likely to be osteoporotic – therefore, we should not be using materials that have been developed on studies based only on healthy human bone. It would be important to transfer the accumulated knowledge regarding healthy bones to the diseased states.

The continual growth of the world population and the increase in traffic and sport accidents especially for young people, have brought an ever-increasing need for materials especially suited for orthopaedic implant applications.

However, there is also a need for personalised implants developed for younger patients (with sports-related injuries) – to ensure repair and regeneration as a long-term objective for active patients. In fact, revision / re-operation can be particularly damaging for this kind of patients.

Other activities in Europe:

Osteoporosis: million people just in Germany above the age of 50, one in two women and one in five men suffer from osteoporosis– Statistics from "Developing Materials for Replacing and Repairing Diseased Bone" German Trans-regional project funded by DFG.

This program has strong links with Lifelong Implants EU project. There is a possible synergy between this work and "Rapidos" project.

What is necessary at this stage?

- Ability to produce (and understand the influence of) structural hierarchy;
- Understanding the mechanical behaviour of implant structures;
- Optimisation of implant chemistry – either through coatings or alloy chemistry;
- Targeted coating technologies for -Ti alloys;
- Moving towards metallic alloys with no toxic alloying additions;
- Development of optimised porous structures for bone repair;
- Biodegradable alloys (and surface treatments adapted to these – to ensure appropriate degradation times – controlled rates and hydrogen release).

A lot of alloy development is taking place in the Far East. It is important that the EU remains competitive in this area.

Technology Readiness

It varies according to the nature of the developments under consideration. There is a huge potential for commercialisation in the short-term (incremental modifications to design), medium-term (more fundamental changes) and long-

term (visionary and disruptive developments – including sensing, and functional, smart designs).

At the same time, it is necessary to recognise the possible impact of the likely developments in the field of gene therapy and stem cell work. We need to consider whether there will be particular areas of synergy (e.g. drug delivery from smart coatings), but also the emphasis that would need to be made.

BIOACTIVE HYDROGELS FOR TISSUE REGENERATION, RELEASE OF GROWTH FACTORS FROM BIOMATERIALS, COMBINED DRUG / BIOMATERIAL DEVICES FOR TISSUE REGENERATION - CHAIRED BY CARLOS RODRIGUEZ CABELLO, WILLY HOFSTETTER AND MARIA PAU GINEBRA

The groups discussed the following points:

- The aim of tissue regeneration: is it to fabricate biomaterials that closely mimic the target tissue? Or is it to provide simple biomaterials with the capacity of triggering tissue regeneration? This later approach could be accomplished providing the biomaterial with bioactive molecules in order to push/initialise the whole cascade of tissue healing/regeneration events occurring after implantation.

But, is it naïve to initiate something and leave it to nature? There are risks, but sometimes it can be fruitful. Time control and a deep knowledge of the healing process (e.g. inflammation) are needed. This requires studies, both, about regeneration delivered by biomaterials and genetically engineered growth factors.

- The choice of the growth factor/s is critical:
    - Which GF to deliver?
    - How many GF should we deliver? The delivery on one might not be useful. For example. for BMP-2 to work requires blood vessels/vasculature formation;
    - Should they be delivered simultaneously? How to control their release?
- Tools for long-term release:
    - *In vitro* studies;
    - *In vivo*: how to monitor release?

    - Designing systems which activate release at a certain point while the material is degrading;
    - Drug/GF interaction with the material.

- There is a need for *in vitro* tests with pre-defined processes / methods. Cell-mediated release is a possible future option.

- Tests in cell systems should focus on examining degradation products.

- For biomaterials made of hydrogels, providing anchoring points for cells to grow into the gel is important: hydrogels are extra-cellular matrix systems with mechanical properties that favour regeneration, and allow cells to "feel" mechanical signalling. There is a need for studying these hydrogels mimicking materials, especially for bone regeneration applications without excluding other tissues as well.

NEW BIOMATERIALS FOR TOTAL JOINT REPLACEMENTS - CHAIRED BY RICHARD HALL

The group discussed the following points:

- The **main Clinical Challenges and Opportunities for research** that need to be tackled in the next 5-10 years in joint replacement, in its broadest sense, are:

    - Understanding the bone-cartilage interface as a precursor to biological therapies post-joint replacement
    - Designing and delivering spinal implants that allow for more physiologically loading and load partitioning within the spinal complex
    - Greater understanding of controlled differentiation of cells underpinning cartilage and bone.
    - Novel interventions for Osteoporosis including prophylactic use of materials for preventing fractures.

- The role of pre-surgical assessment – identification of different materials specification for instance is:

    - Stratification of the patient population – predisposition to cytotoxic and inflammatory responses, – what works and what doesn't. Profiling of patients in multiple domains.

- Evaluation and validation of *in vitro* tests -testing reflects stratification of the target population.

- Adverse scenario testing is a key issue concerning the more rigorous testing of (orthopaedic) implants
  - What is missing in terms of making adverse scenario testing a reality?
  - What is an adequate representation of the adverse landscape for each of the major joints?
  - Validation of these scenarios and outcomes

- What is the role of nanotoxicity in this TJR and how can the concept be developed within the orthopaedic community.
  - How does the orthopaedic community link with the nanotoxicology community? Links to nanosafety cluster?
  - Neurotox: assessment of neural tissues, particularly in the spine (development of 3D models)

- Why is this research needed now (or when would it be needed)?
  - Public perception of total joint replacement has diminished – safety is a critical issue and the public/patient community needs to ensure that the sector is providing funds for investigating (possible) issues.
  - Development and deployment of tools (computational, biomechanical and biological) that target adverse scenarios in joint replacement and highlight clinical impact if observed to be deleterious. New generation of integrated testing methodologies to surpass current standards, hence inclusion of standards bodies is essential.
  - Novel procedures and biomaterials for the prophylactic treatment of osteoporosis

- What should be the focus of research in this area?
  - Materials/implants focused on the next generation of testing protocols?
  - Research in support of regulation and standards: adverse scenarios
  - Funding for *in vivo* (animal) and phase 1/2 clinical trials.

- Some additional points discussed included:

- Physicians: a lot of progress and developments can be made through training rather than science.
- The need for active external advisers and opinion leaders in projects – validation of the project goals and objectives.
- Replacement optimisation e.g. *in vitro* tests on blood cells of patients
- Tissue engineering: Difficult to manage. Fixation needed for growth. Generate something ex-vivo / implantation / grow inside.
- Patient in situ/rejuvenation. Costs may be an issue?

- Regulations are limiting in that they lag developments in technology. Ensure that projects and new developments have a testing component.

- **Focus of future research:**

  - Material degradation within specific environments, combining technologies to enhance performance, adequate, adverse testing for the population within which the functional implant will be placed. A range of projects is required based on end-goals; medium to large integrated projects with 5 to 15 partners. The inclusion and support of end users is critical in all projects.

NANO-STRUCTURED BIOMATERIALS - MODERATOR ANNA TAMPIERI

Complete regeneration of diseased hard tissues such as bones and teeth is today a major need, in the perspective of progressive ageing of the population and the requirement of an active life also for the elderly. To achieve this target it is widely accepted that the use of bioactive, bio-reasorbable porous scaffolds with very high mimesis of the host tissues is of pivotal importance. The scaffolds should be designed on the basis of specific clinical needs, and of the specific bony district involved in the disease/pathology.

In respect to the need of mimicking the complex chemistry and structure of bone tissue, new synthesis/manufacturing approaches should be investigated and pursued. Particularly, inspiration by nature is a recent paradigm of increasing relevance and unique to develop complex and smart materials. Bio-mineralization processes are bottom-up processes based on green chemistry, that exploit information inherent to organic macromolecules such as Collagen, to activate self-

assembling of different bio-polymeric blends at the nano-level and 3D organization into macroscopic devices with hierarchical structure. Biomorphic processes are able to transform natural sources (e.g. woods, plants, exoskeletons, coral) into hierarchically organised inorganic products with complex structures with details at the micron scale, which are not achievable by conventional methods.

- Relevant clinical needs for bone regeneration can be broadly identified as:

  - ***Critical size bone defects***.

    Solution: 3D scaffolds with bone-mimicking composition and presenting high open and interconnected porosity ensuring osteo-genesis and rapid colonization by the new bone, as well as adequate strength to bear mechanical loads.

  - ***Extensive segmental and load-bearing bone defects***, which is a still unmet clinical need of huge impact.

    Solution: Biomimetic 3D scaffolds exhibiting enhanced mechanical performance and enabling a very efficient and fast vasculo-genesis, thus requiring:

    - chemical composition ensuring fast osteo-genesis and extensive osteo-conduction;
    - structure able to withstand relevant mechanical loads for activation of physiological mechano-transduction at the cell level;
    - wide, open and pervious pore network, with size relevant for extensive bone and vascular penetration.

  - ***Regeneration of epiphyseal bones*** such as: femoral head and trochanter, or sub-chondral bone, affected by idiopathic disease, trauma or tumour; ***vertebral bodies or any hollow bone defects or cavities***, i.e. bony parts where the implantation of solid scaffolds is difficult or not suitable.

    Solution: Injectable biomaterials with tailored viscosity, osteo-genic and osteo-integrative ability as well as bio-reasorbability. Ability of self-setting *in vivo* with adequate mechanical performance.

  - ***Bone regeneration in patients with reduced endogenous potential*** such as the elderly, patients affected by metabolic diseases, or immunosuppressed.

Solution: Implementation of the scaffold with nano-cues promoting tissue regeneration. Magnetic stimulation by the use of new biocompatible media is among the most interesting and promising approaches.

- **Relevant clinical needs related to cartilage regeneration are related to meniscus and knee joint.**

  Solution: Hydrogels exhibiting chemical and microstructural features able to modulate stem cell microenvironment and enhance cartilage regeneration. Injectability of new hydrogels is a very relevant added value.

- To regenerate defects involving multi-functional anatomical regions, such as *joints* and *periodontium*, biomaterials should exhibit complex structure in order to mimic different anatomical compartments (i.e. in the case of joints: sub-chondral bone, mineralized cartilage, hyaline cartilage; in the case of periodontium: periodontal ligament, alveolar bone, cementum).

  Solution: Hybrid constructs associating mineralised and non-mineralised biomimetic components, acting as triggers for specific cell differentiation and new tissue formation.

- The development of new approaches for **personalised therapies** is an open challenge that will represent a leap forward in nanomedicine. In this respect, smart functionalization can provide biomedical devices with the ability of *selective stimuli responsiveness and of on demand activation*.

  Solution: Polymeric blends to achieve pH or temperature-triggered drug release following specific physiologic states. Chemical doping of inorganic nano-phases to activate specific functions, such as enhanced osteo-genesis, antibacterial effects, or even magnetism. Particularly, the development of new biocompatible magnetic nanophases can be considered as a breakthrough opening new applications in nanomedicine, such as *new magnetically-activated drug delivery systems*, *new cell and gene therapies based on cells magnetization*, *new media for diagnostics*.

- Topics relevant to be developed in the **future actions** are:

***Bone regeneration**:*

- New biomimetic devices with chemical and microstructural features able to modulate stem cell microenvironment to enhance bone regeneration;
- New injectable biomaterials with enhanced osteo-genic, osteo-conductive and bio-resorption properties;
- New implants providing extensive vascularisation in large bone defects; RELEVANT: scaffolds for bone regeneration mimicking the chemical and morphological features of native tissue
- Chemical doping of inorganic nano-phases;
- Biomineralisation process: structural confinement of HA and increase in bioactivity and bio-reabsorbability;
- Self-assembling process to generate hybrid nano-composites;
- Biomorphic transformation to obtain directly 3D bioactive scaffolds;
- New magnetic bioactive completely bio-resorbable scaffolds;

Cartilage regeneration:

- New biomimetic devices with chemical and microstructural features able to modulate stem cell microenvironment to enhance osteochondral regeneration;
- New approaches for meniscus regeneration;
- New approaches for regeneration of knee articular cartilage;
- New hydrogels with ability of cell instruction towards soft tissue and organ regeneration;

Smart scaffolds (magnetic, pH sensitive, functionalization):

- New devices with ability of remote activation for on-demand applications in regenerative medicine and theranostics;
- New smart therapeutic approaches based on stimuli-responsive devices with ability of self-activation following specific physiologic states;
- New bioactive and bio-resorbable magnetic nanoparticles for theranostics of cancer and other degenerative diseases;
- New approaches to reduce biofilm formation in metallic implants;
- New mini-invasive approaches for resurfacing of hip and knee prostheses:

RELEVANT TOPIC: New magnetic biomimetic phase (NO magnetite like system) to be internalised by cells or to be used as transfecting agent or delivery system;

- Magnetic cells for cell therapy;
- Magnetic bioactive drug delivery systems;

BIOMATERIALS AND CELL THERAPY - CHAIRED BY PIERRE LAYROLLE

- What does the issue address?

The biggest priority in Cardio and Osteo-therapy is to do comparative studies that determine the cost-effectiveness of a new cell therapy versus the current standard of care and standardizing.

- What is the state-of-the-art and what are the main scientific challenges?

Developing cost effective cell handling and expansion.

- Which disciplines are involved?

Cell culture experts, (bio) material scientists and surgeons and regulatory agency consultants.

- Critical mass needed
  - 10 partners spread across different disciplines.
  - Clinical applications would need some extension and that is expanded when trials become involved.
- This research is needed because the cost of cell therapy can go upwards from 30 K Euro as it is still experimental medicine, this needs to be decreased if it will be accepted.
- Is it too broad?

No, actually currently it is too narrow. Projects within academics must be expanded and clinical trials broadened to involve more partners across the EU. Blood transfusion units should handle cell therapy in order to democratize regenerative medicine. Private companies will ask too high prices for these advanced therapy medicinal products making them inaccessible to many patients.

- Have recent results been obtained?

Yes, for example Reborne project has piloted the pre-clinical and clinical trial levels that are needed for the expansion of cells and the use of cell therapy in hospitals.

- Related initiatives

Within Europe and the rest of the world, Reborne project has been the first to establish this approach from academics to clinical trials.

- What is needed at this stage?

    - Biomaterials for cell carrier and allowing the expansion of cells.
    - Bioreactors and an efficient production.
    - Biomaterials for injection of cells are currently not good enough, and this is due to cellular encapsulation, there is no attachment, no matrix production or normal cell activity.
    - Must be a hydrogel so that the gas and nutrients exchange can occur and the cells can interact with the gel with normal cell activity.
    - Bio-printing. Polymerisation takes place at a mild condition, with no big pH changes; it is an easy process that doesn't disrupt the cells. Cross linking at physiological conditions, that happens physiologically in a timely manner.

- **TRL7** is a system prototype demonstration in an operational environment within Reborne project. There are other technologies that are at various levels of Technological readiness, depending on their applications.

- Why is this important?

    - The alteration of cells, or treatment, must be done as the surgeon in the surgical theatre, if the cells are augmented by anyone else then regulatory issues become very expensive, people must be adequately trained and acquire authorisation to work with these cells, and quality controls have to be used at all stages.
    - The cost of cell therapy in the industry is astronomical, however if the academic world drives the process of cell therapy evolution, the cost can be decreased.
    - Cell therapy must be invested in by the pharmaceutical industry but performed by academics. Comparative multi-center clinical trials should be performed to convince surgeons and big pharmaceutical companies that cell therapy is the future of medicine. However, the European

Commission is not funding phase III clinical studies involving 150 patients, but prefers to support 'First in man studies' with few patients.

- Regarding the aging population and quality of life issues, new therapies are required.
- Physical properties that can be utilised and developed for correct injection methods and integration, solving key technological problems associated with cell delivery.
- What about allogenic cells and their applicability? They can certainly be used and have recently been published, they are very capable of stimulating the cascade of healing. The population of cells in aging individuals can be exchanged with younger allogenic cells to kick-start the healing process. The allogenic cells then disappear so the problem of them remaining and being immune rejected is not a big issue.

Some additional points discussed included:

- Comparison between standard care and new treatments.
- Regenerative medicine (USA): Screening of molecules that can release in defined time and dosages. Regulation is very tricky and risks have been raised with the use of growth factors in clinical trials. Reprogramming of cells for regenerating tissues may be future treatments but requires more research to avoid tumour growth.
- Robot-very expensive.
- Japan's great developments with robots. Good connection with industry. Transformation of research to product and patent fast(est).
- Lack of connection with industry in Europe.
- Allogeneic cells: disappear and have an indirect effect in bone healing. They may be less expensive and more easily accessible than autologous cells.
- Proliferation at the side. Phase before disappearance. No information on proliferation.
- Future funding in EU member states is delicate. Often decreases of up to 25% are observed and an increasing focus (and dependency) is on EC funding.

BIORESORBABLE SCAFFOLD - CHAIRED BY DAVIDE DE LUCREZIA

Outlook of NBMP technologies

Participants expect NBMP to likely deliver breakthroughs in the field of Regenerative Medicine and to a lesser extent in the field of therapeutics, diagnostics and non-health applications (e.g. food). Main barriers to preventing significant breakthroughs:

- Out-dated regulations;
- Lack of robust and predictive ex vivo tools to evaluate biocompatibility and toxicity;
- Lack of funding for clinical trials;
- Overambitious project objectives;
- Lack of project management flexibility;
- Lack of small-scale GMP compliant manufacturers for NBMP prototyping;
- Lack of training for academic researchers concerning QC, regulatory issues and TT;
- Actions to remove/mitigate barriers;
- Including specific calls for the development of ex vivo models (3D, co-cultures) in close cooperation with EMA and relevant authorities. The ultimate goal is to ensure that deliverables are taken as new standards by the relevant authorities;
- Including specific calls for the development of sensors and imaging techniques for new ex vivo models above;
- Including specific calls for the establishment of a European network of qualified SMEs/institutions for the small-scale GMP production of NM;
- Including specific calls for the establishment of a European network of qualified SMEs/institutions for the *in vivo* tests;
- Introducing consortium flexibility to add/remove partners during project implementation;
- Introducing training for academic researchers concerning QC, regulatory issues and TT;
- Including specific calls for clinical trials for SME NM-based products;
- Explicitly stating whether envisaged results must be breakthrough or incremental;

- Introducing balance between small (<5 partners), short (< 3 years), less ambitious projects and large, overambitious projects with non-attainable objectives.

Agreeing with everything indicated in the survey, but up scaling.

Ideas for new kinds of topics: SMEs making networks, fundamental vs. applied research. To be divided in the funding. Funding to be redistributed according to needs.

NOVEL TECHNOLOGY FOR BIOMATERIALS PRODUCTION - CHAIRED BY OLAF MOLLENHAUER

The groups discussed the following points:

- The additive production of biomaterials is preferable (3D printing, layer by layer);
- Implants and personalised medicine represent the future, but we need the technology;
- Next level of automation, with human labour out of the production process;
- Technology driven by internet, with a shared and structured information, (today, there's a cloud of information about materials, composites, processes, handling methods, etc.);
- New surgery concepts, with new applications of biomaterials;
- There's a lack between the ideas and their application, because big industries are not moving fast enough on new technologies;
- Bringing biomaterials to the market requires more money, not only in R&D; there's a need of new financing models;
- Finally, there's a need to change the way of thinking, from the innovation line to innovation circles: different circles of R&D can touch each other and interact.

6.3 LARGE ROUNDTABLE DISCUSSION

During the Clustering day, cross-sectorial issues were identified and proposed within five large panel discussion groups, to rank issues and prospects and prioritise them for future research policy making.

6.3.1 TRANSVERSAL ISSUES

Large roundtable discussions on Post-project objectives & future trends in NBMP:

- Regulatory, standards and safety aspects of medical devices - Moderator Willibrord DRIESSEN;
- Exploitation of novel biomaterials in clinics- Moderator Michelle EPSTEIN;
- Industrial production of biomaterials - Moderator Martha LILEY;
- Stakeholders' needs - Moderator Laura VIVANI;
- Future Challenges in NPM- Moderator Serena BEST;

6.3.2 WORKING GROUPS

The sessions aimed at making a reflection on the large issues related to key research requirements in conjunction with the end-users' needs and problems. The following dialogues reflect the points of view of industry, patients and explore the future challenges of NPM.

REGULATORY, STANDARDS AND SAFETY ASPECTS OF MEDICAL DEVICES - MODERATOR WILLIBRORD DRIESSEN

A wide range of natural and synthetic biomaterials (e.g. metals, ceramics, polymers, living cell tissue, nanomaterials) is available to use in implantable orthopaedic medical devices such as joint replacements, bone cements/scaffolds, spinal fixation/correction systems, vertebral discs, just to name a few.

Discussion about responses to clustering survey question Q3 "**Which are the main barriers preventing significant breakthroughs in the field of "nanotechnologies, advanced materials and production" for medical use manageable at EU level?"** What will be the consequence of more stringent regulations for the industry, but also for research projects?

Regulations are getting more and more stringent for the industry. Big companies may suffer less compared to smaller sized companies, due to having more resources than SMEs, which do not always have sufficient resources in house. How does this apply to research projects? Do these have sufficient competence and resources?

If there are no standards available for specific R&D applications, there will usually be more burdens to demonstrate compliance to regulations. This is inherent to high risk devices such as innovative orthopaedic implants.

Although standards are 'voluntary', the industry does not usually take the risk of not complying with them. Does this limit the development of new standards? Most standards and scientific publications are not freely available. This may also inhibit the standardization process and thus innovation.

Validated equipment and test methods shall always be used, thus also in research (university) projects. Measuring equipment should be calibrated to assure valid test data. Do research projects include adequate competence for validation/calibration of equipment, which has been developed (thus, not purchased) within the project?

It is, furthermore, strongly recommended to integrate risk assessment and assessment of all applicable standards available for the particular design, early phase the research project.

EXPLOITATION OF NOVEL BIOMATERIALS IN CLINICS- MODERATOR MICHELLE EPSTEIN

The group discussed how synthetic biomimetic biomaterials are becoming increasingly important in regenerative medicine and also how the project's aim is to produce them mimicking the natural physiological processes underlying bone repair. The following list includes the key points and ideas for funding discussed in this round table:

- Focus on medical device production that includes preclinical and clinical studies and Clinical translation
- Focus on studies on the combination of cell therapy e.g. MSCs and biomaterials (but, Cell therapy requires heavy regulation that needs special funding and time)
    - Focus on biomaterials for the following Regenerative indications: heart, skin: plastic surgery, burn patients, vertebral discs, bone, and cartilage
    - Focus on producing artificial organs, i.e. simulate organs such as bladder, heart, trachea, vessels, liver, kidneys, lung, patches for the heart for arrhythmias and CHF, e.g. biological pacemakers, and cornea with e.g. biogels
    - Develop equipment/devices and sensors, e.g. equipment/devices/sensors for implants made of ceramics, metal, etc.

- Artificial Extracellular matrix/matrices with biomimetic materials instead of animal or human based acellular materials for cellular repopulation, e.g. synthetic materials, hydrogels with and without embedded cells
- More studies on 3D cell systems
- Develop *In vitro* 3D models for clinical screening/stratification
- Study how to create vasculature for biomaterials to ensure oxygen and nutrients to the tissues
- Improve surgical applications/new surgical concepts, i.e. how to apply the new materials
- More studies on up-scaling the manufacture of biomaterials
- Focus on the type of biomaterials, e.g. mechanical properties like hard-soft substrates will influence cell differentiation and stimulate stem cells with instructive biomaterials
- Focus on tissue printing technology
- Study the structure and functional aspects of biomaterials
- Produce new types of biomaterials with gradients
- Focus on Biomaterial printing
- Nanomedicine
- Food packaging and processing and water treatment
- Filter/remove pollutants from water and air
- Produce new and improved dental implants
- Produce new antimicrobial surfaces for metal or other implants
- Produce new diagnostic biomaterials for imaging, contrast agents, and tumour detection
- Produce special sensor systems for in situ surgery and long-term monitoring for measuring oxygen, CO_2, etc.
- Produce artificial materials that are immunologically inert and do not cause clustering of cells. Hydrogels are especially good surfaces for implanted medical equipment/devices even electrodes
- Produce drug carriers, e.g. Hydrogels as carriers and drug delivery systems-nanotubes
- Produce biomaterials for personnel care items
- Produce combinations of drug – biomaterial + antibiotics, bone osteoclast and inhibitors, anti-cancer, etc.
- Stimuli-responsive biomaterials- change in pH, oxygenation for drug release
- Synthetic biology technology for producing biomaterials
- Nanoparticles that are able to target, penetrate cells, function, and can then be easily removed

- Bone biomaterials that are injectable, porous, strong, elastic, biodegradable into bone adapted with time
- Application processes
    - Innovation ideas to the market need approximately 7 years
    - Funding opportunities for product development that is closer together and connected with R&D projects, e.g. new opportunities for current projects to apply for progress projects- from innovation to the next level
    - When necessary, clinical trials for biomaterials with/without cell therapy requires more than 6 million Euros and therefore, there is a need for large projects
    - Suggestion: when a grant is almost completed for proof of concept, it is placed in a priority line for applications from projects that are already running, i.e. priority line for successful NBMP projects with sufficient funding for further clinical studies, regulations, etc.
    - Financing could provide a percentage of and funding range projects based on the TLR
    - Small projects on database generation; especially of failures and access to negative results
    - EC should facilitate innovation and favour enterprises, especially small enterprises
    - Force companies to stick with R&D and option to go to product development vs. marketing

INDUSTRIAL PRODUCTION OF BIOMATERIALS - MODERATOR MARTHA LILEY

The group discussed how to stimulate the translation of fundamental projects towards industrialisation/clinical application.

Project funding:

It was considered that current funding instruments were lacking and that new approaches to funding projects and consortia would be beneficial for the translation to industry/clinical application. Two possibilities in particular were proposed:

The project should have industrialisation integrated into the concept from the beginning. For projects going from fairly early-stage materials through to phase 1&2 trials, clinics would have an important role to play in the project consortium. The possibility to stage projects, so that *successful fundamental projects would*

have access to funding for additional translational stages (with minimal additional paperwork), would be very positive in translating results to industry/the clinic.

Competitive grants would also be stimulating for research. In these grants, several competing teams would be funded in a first phase. In a second (translational) phase, just one successful team/concept would be funded.

It was also considered that including clinical panels in projects would be a valuable tool for ensuring their translational potential.

Quality assurance tools:

The group felt that there is a need for new tools in quality assurance. In R&D, there is an increasing emphasis on the production of personalised implants, for example, using additive manufacturing in the operating theatre. However, this presents particularly difficult problems in terms of quality control, characterisation and reproducibility. New quality assurance tools and techniques are required to address these issues.

New quality assurance tools for biologicals (materials and preparations made from living organisms) are also needed.

Project topics for translation:

The following topics for projects were felt to be cross-cutting themes that would facilitate translation and address unmet needs:

- low-cost (and low-infrastructure) sterilisation techniques
- training in the use of new biomaterials
- new surgical tools for use with new biomaterials

STAKEHOLDERS' NEEDS - MODERATOR LAURA VIVANI

By definition, stakeholders are any group or individual who is affected by or can affect the achievement of an organisation's objectives (Freeman, 1984)[22].Every stakeholder has the potential to contribute to the definition of needs and priorities by bringing their own experience and perspective into the process of choice. The problem is when demand or/and supply-side stakeholders are excluded from governance and consequently from the strategic choice process, therefore losing

[22] Freeman, R. E. 1984. Strategic management: A stakeholder approach. Boston: Pitman

voice, sight, direction and control of service provision. This problem is known as marginalisation of stakeholders and it can assume diverse levels of intensity. To solve this problem academics as well as institutions are implementing a number of actions.

In the continuity of stakeholder theory, much of the current literature on (corporate) governance and business looks at how organizations involve their stakeholders at different decision-making levels (Carroll 2004[23]; Clarkson 1995[24]; Freeman & Reed 1983[25]).

On the other hand, the European Union as well as the United Nations have invested widely in the implementation of multi-stakeholder projects.

In fact, the European Commission designing Horizon 2020 promotes inter- and trans-disciplinary solutions, which cut across the multiple specific objectives of the programme. Furthermore, Horizon 2020 promotes Responsible Research and Innovation (RRI). 'Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view on the (ethical)acceptability, sustainability and societal desirability of the innovation process and its marketable products(in order to allow a proper embedding of scientific and technological advances in our society)'' (von Schomberg, 2011)[26]. It implies that societal actors (researchers, citizens, policy makers, businesses, third sector organisations, etc.) work together during the whole research and innovation process to better align both the process and its outcomes with the values, needs and expectations of society.

The importance of identifying key stakeholders is crucial to conduct a successful project and to design future research agendas.

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[23] Carroll, A. B. (2004). Managing Ethically With Global Stakeholders: A Present and Future Challenge. Academy of Management Executive, 18[2], p. 114-120.

[24] Clarkson, M. B. E. 1995. A stakeholder framework for analyzing and evaluating corporate social performance. Academy of Management Review, 20: 92-117.

[25]Freeman, R. E. , & Reed, D. L. (1983). Stockholders and stakeholders: A new perspective on corporate governance. California Management Review, 3.

[26] von Schomberg (2011) The quest for the "right" impacts of science and technology. An outlook towards a framework for responsible research and innovation. in: (eds M.Dusseldorp, R. Beecroft) "Technikfolgen abschätzen lehren. Bildungspotenziale transdisziplinärer Methoden". Springer Verlag pp394.

A wide range of stakeholders should be involved in project activities with the aim of fostering research respondent to real needs and making suggestions for the future. The list of stakeholders might include actors of different nature, such as:

- European Institutions;
- Investors such as: banks, grant-making trusts, business angels; and financial stakeholders like private Foundations and Charities;
- Public Institutions such as national, regional and local governments;
- Public Administrations;
- Local communities;
- Users and/or consumers, in particular patients and practitioners organisations;
- European, National, and local associations, third sectors, non-profit organisations, NGOs;
- Implementing agencies;
- Industry;
- Universities, Research centres, think tanks;
- SMEs.

Fig.6 EU Multi-stakeholder Project

In a successful EU project, it is important to take stakeholders' needs into consideration for a significant impact on society. It is a good practice to draft a stakeholder map, which in turn would ensure the more suitable partners in one's Stakeholder Engagement Approach. Indeed, mapping is a crucial step to understanding who the key stakeholders are, where they come from, and what they are looking for in relation to your project. Each participant in a consortium should make its best effort to outline a stakeholder engagement strategy processing the following steps:

1. Identification of potential stakeholders: listing relevant groups, organisations, and people;
2. Studying and understanding stakeholder perspectives, issues and relevance;
3. Drawing links and relations between objectives and other stakeholders.

It is important to rank stakeholder relevance and refer to a shortlist of groups that can be reached during the lifetime of a project. During the initial stages of the project, stakeholders are involved in compiling existing knowledge, identifying the challenges, potential harms, risk pathways and assessment methods emerging from activities. In this way, partners are able to move in the proper direction, giving voice to actors potentially affected by the project.

However, throughout the entire project, it is a crucial exercise to continue ensuring participation. The effective engagement of stakeholders might be assured through workshops, events, info/training sessions and clustering activities. These kinds of activities enable actors to provide suitable answers to EU citizens' demands, reducing at the same time incertitude and information asymmetry. Stakeholders can sustain the project beyond the EU funding by: supporting further steps of the research and innovation process, raising awareness on the potential of scientific results and acting as a community of potential users leveraging on the innovation demand. In the specific field of nanotechnologies and regenerative materials, which are both extremely interesting topics to InnovaBone partners and the other participants of the event, it is a priority to follow closely the activities of some specific platforms, namely:

- Nanofuture European Technology platform;
- Nanomedicine European Technology platform;
- European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO);
- EULAR;

- NEWGEN Cost action;
- EuMaT European Technology platform;

All of them participated at the Stakeholder Day .

FUTURE CHALLENGES IN NBMP- MODERATOR SERENA BEST

NBMP represents a major step towards the "future" of the field, but this working group recognised that it is essential to understand, and to take into careful consideration, all of the possible implications of research and development in this area. The future challenges of NBMP fall into several different categories including materials aspects and issues related to the development of appropriate biological evaluation protocols in the areas of both *in vitro* assessments (e.g., their shape, their size etc.)and *in vivo* assessments in terms of their therapeutic effects, but the potential toxicity of nanoparticles as well.

The working group considered a number of different aspects of NBMP and these are:

- Nanoparticles;
- Nanomedicine;
- Nanostructured materials.

Each of these categories has their own challenges and issues to address. These will now be addressed in more detail.

Nanoparticles

These may be introduced either intentionally or unintentionally and can enter the body through ingestion, inhalation, and absorption or through minimally invasive delivery or larger scale surgery. Key questions to address include:

- What do we understand by the term **nano** in this context?
- What effect does particulate shape have?
- Is the toxicity of a given type of particle generic or do materials behave differently according to the system they are in?

These issues were recognised in the last few years and a **NanoSafety cluster** was formed. The NanoSafety Cluster tries to determine toxicity and risk of **nanoparticles** to humans and to the environment and provides a mechanism for

data management: including the creation and the implementation of a common database.

A range of other important questions have also been raised around the production, use and measurement of nanoparticles including

- Can standard operating proceedings be developed?
    - *In vitro* things may seem fine – but we need to check *in vivo* whether they accumulate and if so, whether they are safe
    - e.g., in oncology applications, they may be injected in a local area, but where will they actually end up?
- How can they be manufactured safely?
    - Talking to industry can be problematic, since there is a disincentive to reveal production information in case of issues.
- How can tests be standardised (from the regulatory stand-point) ?
    - Can we develop better models for *in vivo* characterisation
    - Can we differentiate between "good" and "bad" particles.
    - Are we considering single doses or multiple doses (appropriate for treating chronic conditions)
- How can we ensure that nanoparticles be used safely?
    - What will be the long-term effects?
    - Will there be degradation products?

Nanomedicine

Nanomedicine has many possible applications, such as: imaging, drug-delivery, diagnostics, cell transfection (deliberately introducing nucleic acids into cells).

Two examples are shown below:

(1) It is possible to move cells using magnetic hydroxyapatite particles (20 – 30 nm) and also to use endocytosis to allow cells to take up the nanoparticles. Looking towards the future it is important to identify the key features to make the material as safe as possible.

(2) Surface functionalization (peptides, etc.) to encourage specific cell-scaffold interactions is now becoming increasingly important. There is a great deal of interest at the research laboratory-level, but sterilisation is also an important issue. Hence it is important to think through the life cycle and treatment (including sterilisation) and the effects of these treatments on the material.

These applications raise new issues about testing, not just for the specific therapeutic benefit, but also for further-reaching effects and optimisation of the systems being used.

- Which other materials might be possible carriers?
- "Standard" particles are needed to test the effects; small particles are very active and tend to aggregate.
- Control of handling and consistency are essential.
- How are these "medicines" made and characterised?

Nanostructured materials

The ideal implant material is probably one that will perform its required function and then degrade over time. For a material to be used as a biomaterial, it must have a property known as "**biocompatibility**". This means that when it is placed for its intended use, it is compatible with the surrounding tissues and does not cause any adverse reactions.

There have been a number of developments of nanostructured materials over recent years including substituted apatites, glasses and glass ceramics and biodegradable polymers (both synthetic and natural) and coatings. These materials are often used in bulk form but their mode of action designed to deliver therapeutic benefits to the tissues at the sub-micron scale. It is possible that these materials may provide the therapeutic activity in tissue repair (as opposed to nanomedicine), but avoid the potential issues of nanotoxicity.

Over-arching issues

Communication, Dissemination and Risks

It is important to speak to regulators as soon as possible in order to ensure that the standard methods are accepted and to get them on board to understand the materials that are proposed to be used. Other important steps are the development of new structures, databases and information exchanges, on an international basis. Following several examples of major implant failures, companies may be concerned about commercialisation due to the increased threat of litigation. This situation may impede progress and the development of new ideas, leading to incremental changes rather than radical step-changes. However, in the future it is also necessary to prioritise clinicians' needs and stop developments that are going in the wrong direction.

It is also necessary to discuss the NBMP Challenges with a larger community. There is the need to provide fundamental definitions to aid communication since people speak different languages and use contrasting vocabularies in the different scientific communities.

One of the major issues in scientific publishing is that negative outcomes are often difficult to publish. There needs to be a database available for the community to ensure that all the outcomes, good and bad, are available to researchers in the field.

Recommendations:

The group concluded that there are many issues that need clearer definition and that it is necessary to have a meeting to develop further these aspects. A number of ideas and highlights came out of the discussion including issues under the following headings:

Database

An important future challenge is to create a database similar to the gene database where it should be easy to add information. A support action is running currently to think about the quality of the data that should go into the database. Some initiatives in this direction have been made but it would be useful to know

- How far these have gone, how to characterise and produce the data.
- Do the members know who the "community" is? The community is very large, with lots of different fields contributing.

Modelling work

Could modelling work be a way forward to help predict the behaviour of nanoparticles? However, this raises the question of whether the *in-vitro* and *in-vivo* models are good enough at the moment. More models need to be developed to make accurate predictions as close as possible to human situation and in order to do that, a strategy has to be defined. Is it possible to develop accelerated tests? Modelling on its own is not sufficient to provide the whole picture and experimental data are necessary to support the modelling results.

There is somewhat a "chicken and egg" situation –there is a need for very simple systems initially, upon which developments might build. Although, in fact, it might be suggested that incremental improvements on things that do not work very well is not the best way forward. The materials that have most potential still need to be identified and this issue has to be addressed rapidly for further studies.

Ensuring that we are addressing the real issues – and public perception of nanoparticles

There are a number of questions related to this.

- It is necessary to define what we should actually be worried about;
- Are nanoparticles dangerous?
- A perfect example of is asbestos, known to be very harmful for health, although there are chronic effects of materials that we don't yet understand;
- Factors such as long-term use and concentration are important.

The unknown always worries us but do the worries influence the questions that scientists are asking? – Are they testing the right things?

- It is essential to know the bulk chemical toxicity but, it is also important to know the effect of size;
- Should we be doing something about this?
- Chronic low levels are an issue as is the time that it takes for the tissue to react. We appear to be in danger of preventing work on materials before we even know whether or not they are dangerous (or if they have an adverse effect);
- The "cost/benefit" factor has to be taken into consideration;
- A toxic treatment may lead to an extension of the duration of life in a terminally ill patient.

Translational aspects are relatively weak –One theme of the discussion is whether the potential benefits and risks are being sufficiently emphasised. In fact, it is necessary to take them into the clinic and track the follow-ups, but there may not be effective mechanisms in place to allow this to be done effectively. There may well be some beneficial elements that are not being used by scientists for fear of potential issues and risks – this raises the question of whether all dangers can actually be avoided.

A shortlist of well-defined recommendations were:

1) What the research and innovation policy-makers *must* do right now. Proposals which are regarded as "urgent, well-defined and necessary" belong to this class.

2) What the research and innovation policy-makers *should* do in the near or medium-term future. Ideas belonging to this middle field are regarded as "useful rather than necessary, important but not crucial".

3) What the research and innovation policy-makers *could* do later. Suggestions in this field were deemed important by some, but not by all the group members.

7. SO WHAT?

7.1 THE RESEARCH CHALLENGES

This section aims to resume and schematize the discussion. In fact if in the previous section, the methodology has been described, this section is totally consecrated to the contents.

As already mentioned in first section, i.e. "why", one of the major objectives of this publication is to reach policy makers.

The reality is that European countries cannot be regarded as featuring among the big players in nanotechnology yet. The authors are deeply convinced that the only way to advance is through collaboration (multi stakeholder approach).

In fact, biomaterials are revolutionising many aspects of preventive and therapeutic healthcare. They are already playing an important role in the development of new medical devices, prostheses, tissue repair and replacement technologies, drug delivery systems and diagnostic techniques. With huge potential quality-of-life benefits for all, biomaterials are the focus of major research efforts around the world. Progress in this field requires a multidisciplinary approach, where scientists (chemists, physicists, mathematicians, biologists and medical doctors), interact with engineers, materials producers and manufacturers.

Moreover, the nature of the challenges is such that finding solutions often demands an investment of skills and resources that are beyond the capabilities of a single organisation, or even of a single country. Collaborative research is thus the key to achieving breakthrough results likely to bring leadership in the global marketplace.

Furthermore Europe still represents one of the most advanced cultural, technological and industrial environments where materials science and technology is at the highest international levels. Nevertheless Europe is less able, compared to others, to benefit and transform new scientific knowledge into economic value. Due to its fundamental enabling role, materials science and technology is, by definition, one of the best engines for speeding up this transformation process and

proving the importance of industry/research coordination and integration, in creating economic wealth and social well-being[27].

Today nano-based technology and advanced materials are not at their infancy anymore. But the major achievements have been obtained at a lab-scale. At the moment the general challenge is to concentrate the resources to create novel production processes as part of a complete value chain of products. This is how it has been done in InnovaBone project, as well as in other EU projects.

For all of these reasons, and with the final prospective to give some valuable advice departing by an inside perspective, authors defined several key actions. These key actions are quite defined in their content and scope.

The key actions have been divided into two kinds:

- Short term key actions;
- Medium long term key actions.

[27]EuMAT (2015) Strategic Research Agenda.

7.2PROPOSALS FOR FUTURE R&I EC POLICIES IN THE FIELD: KEY ACTIONS IN A NUTSHELL

Overall, the following recommendations stem as the main outcome from the Clustering day and the Stakeholder day efforts. Altogether, they frame a structured set of actions shaping the **"Outline of Proposals for Research and Innovation Policies in nanotechnology-based tissue reconstruction"**. Full details expanding each different action are provided accordingly in the following paragraph, which illustrates which ideas, proposals and actions the policy makers community in the field *must, should or could* develop.

SHORT TERM

Action 1

The development of **new sterilisation methods**- The sterilisation of devices and materials for clinical application often requires the use of techniques based on expensive infrastructures: gamma radiation sterilisation or ethylene oxide sterilisation are two examples. This is particularly the case of devices/materials based on biologicals. The availability – or the lack - of these infrastructures acts as a significant brake on biomaterials development. Alternative methods of sterilisation, with low infrastructure costs would enable biomaterials developments.

Action 2

New surgical instruments- The acceptance of new materials and devices may require the use of new or modified surgical procedures. An opportunity to develop specific surgical instruments to facilitate these new surgical procedures would enable translation of materials/devices from the lab to the operating arena. This can be accomplished through the functionalization of the surfaces of the instruments to enhance the interaction between the tissue and surgical tool.

Action 3

Rapid Prototyping Technologies-Design and function of the interfaces between biomaterials and biosystems are of crucial importance with respect to topography, surface-chemistry and surface-physics including their effects on microbiological, cell biological and biomolecular reactions.

Action4

3D printable bio-photopolymers- The treatment of bone defects remains a challenging problem. In a high number of orthopaedic surgical procedures a bone substitute is necessary.

Action 5

Smart Biomaterials- Stimuli-responsive materials, sometimes referred to as "smart" or "intelligent" materials, prepared from thermo-responsive, light-responsive or pH-sensitive basic raw materials have gained widespread interest in biomaterials research.

Action 6

Characterisation techniques for 3D tissue scaffolds-Next generation tissue scaffolds are an advanced medical device using a special form of engineered biology for e.g. minimum invasive joint repair, personalised drug delivery or 3D diagnostics.

Action 7

Comprehensive study on the chemical and mechanical signals that lead to the regeneration of bone- Regeneration of tissues comprises at least two main fields: the adequate mechanical support of growing cells and the correct signalling through chemical and mechanical stimulation of such growing cells. These "fields of work" arise from the own biology of regenerating bone and its natural pathways. Great effort has to be made in the characterization of the best 3D structure and composition of the supporting material but also and, maybe more importantly, the signals that are introduced in order to stimulate and enhance bone formation. These signals should comprise not only the formation of bone on the surface of the implant (osteo-conduction) but also the ability to induce local stem cells to differentiate into bone cells (osteo-induction) and produce their own extracellular matrix, ending with the regeneration of the defect.

Action 8

Innovative bond repair approach through multi-actor governance - It is necessary to establish cross cutting working groups that will be able to pave the paths for the future of research towards 2020 and beyond. The working group will be shaped developing a cluster model with the objective of bringing together actors from EU funded projects and actors from different fields in a unique multidisciplinary scenario, bringing together competences and new acquired knowledge.

MEDIUM AND LONG TERM

Action 9

New QA tools- In the move towards personalised medicine, there are a number of developments of technologies for the production of made-to-measure implants in the operating theatre. In contrast, very little attention has been paid to methods for the quality assurance (QA) of these devices, fabricated on-site. Similarly, new materials based on biologicals also lack suitable tools for quality assurance.

Action 10

3D personalized regenerative implants for osteochondral-reconstruction-Development of integral approaches for the convergence of bio-printing and/or bio-fabrication, imaging/monitoring and bioreactor technologies for automated and sterile production of tissue equivalents. Personalized medicine should develop and bring to the market new clinical treatments customized to the patient's disease.

Action 11

Non-cell based regenerative approaches for joint regeneration.

Action 12

Materials for regeneration and substitution of neural tissues-Their specific development is needed for addressing both traumatic (for instance, spinal cord injury following road traffic accidents) and non-traumatic pathologies (for instance, Parkinson's disease, etc.).

Action 13

Development of novel strategies for new materials– It combines biocompatibility and bio-responsiveness with the processability by rapid manufacturing techniques, e.g., through nano-programmed self-organization

7.3 PROPOSALS FOR FUTURE R&I EC POLICIES IN THE FIELD: DETAILED DESCRIPTION

SHORT-TERM

1. ACTION

New sterilisation methods- Foster the research on nanomedicine used in imaging, drug-delivery, diagnostics, cell transfection (deliberately introducing nucleic acids into cells). Example: Surface functionalisation (peptides, etc.) to encourage specific cell-scaffold interactions. The main issues are: sterilisation, life cycle and treatment, effects of treatments on the material, small particles are very active and tend to aggregate, control of handling and consistency, characterisation.

Areas for EU investment:

Database

Create a database similar to the gene database, with public access and ability to add information. (A support action is running currently to think about the quality of the data that should go into the database)

Modelling work

Modelling work could be a way forward to help predict the behaviour of nanoparticles. Development of optimised and accurate *in vitro* and *in vivo* models. There is a need for very simple systems initially, upon which developments might build. The materials that have most potential still need to be

identified and this has to be done rapidly for further studies.

It is essential to know the bulk chemical toxicity, but it is also important to know the effect of size. The effects of chronic low levels are an issue that need to be addressed.

2.ACTION

New surgical instruments- The acceptance of new materials and devices may require the use of new or modified surgical procedures. An opportunity to develop specific surgical instruments to facilitate these new surgical procedures would enable translation of materials/devices from the lab to the operating context. This can be accomplished through the functionalization of the surfaces of the instruments to enhance the interaction between the tissue and surgical tool.

3.ACTION

Rapid Prototyping Technologies- Over the last decades, tissue engineering researchers have devoted themselves to seeding cells onto a porous biodegradable scaffold material to direct cell differentiation and functional assembly into three-dimensional (3D) tissues. However, it is extremely difficult for this strategy to be used in creating a branched vascular system or a complex organ regenerative template mimicking the native ones with similar mechanical and biological properties. Therefore, a significant gap came into existence between scientific expectations on the one hand and technological feasibilities on the other hand. Rapid Prototyping (RP), also referred to as additive manufacturing (AM) or solid freeform fabrication (SFF), is a set of manufacturing processes which can deposit materials layer-by-layer until a complex structure with freeform geometry has been built. The integration of Rapid Prototyping

Technologies and tailor made biomaterials possesses the potential to close this gap and to enable the production of hybrid and hierarchic biomaterial structures (including living cells and/or biomolecules) over a range of size scales (i.e. from a few nanometers to a few centimeters).

4.ACTION

3D printable bio-photopolymers- Autologous bone grafting is currently the most frequently used method for bone replacement, although key disadvantages as donor site morbidity with prolonged hospitalization, graft resorption or limited shaping of these grafts have not been solved. Autologous free bone grafting serves as gold standard and shows good osteo-induction and osteo-conduction in the management of smaller bone defects. In larger reconstructions, however, it results in poor osseo-integration and graft resorption caused by deficient blood supply. Other techniques such as microvascular grafts or distraction osteo-genesis appear better suited, but are technically more difficult and sometimes are associated with even more complications. In recent years, alternative therapeutic approaches, such as alloplastic bone replacement materials or growth factors have been developed. Among biomaterials currently under investigation one can find ceramics as well as polymers. Available alloplastic bone replacement materials feature unsatisfying biological and mechanical properties. They are inferior to autologous bone and fail to prove in clinical routine. In this context printable bio-photopolymers (on the basis of already FDA approved material systems) for creating 3D scaffolds/medical products by means of Rapid Prototyping Technologies (e.g. Additive Manufacturing, 3D Printing, Laser Sintering, photopolymerization, Stereolithography, inkjet-based techniques, etc.) must be further tailor made (degradation, mechanical properties, cellular response, osseointegration, etc.) by focusing on the real problems of the clinical

everyday life.

5.ACTION

Smart Biomaterials- Smart materials respond in a dramatic way to very slight changes in their environment. They can respond to environmental cues such as temperature, presence of water, pH, light, ionic strength, the presence of certain substances, illumination, electric or magnetic fields etc. Of special importance, from a biomaterials point of view, may be a change in conformation, change in solubility, alteration of the hydrophilic/hydrophobic balance or the release of bioactive molecules (e.g. drug delivery systems). Selected potential or future applications of smart materials are stimuli-responsive scaffolds in tissue engineering, controlled release drug delivery systems, cell cultivation materials with switchable cell adhesion properties, and materials used for the development of special gene delivery vehicles. Hence, technical skills in the design and manufacture of "smart materials" as well as suitable medical devices are required, thereby acknowledging the specific challenges encountered by the site-specific reactivity of the final medical product.

6.ACTION

Characterisation techniques for 3D tissue scaffolds- Next generation tissue scaffolds are an advanced medical device using a special form of engineered biology, for example minimum invasive joint repair, personalised drug delivery or 3D diagnostics. Their performance is strongly influenced by mechanical properties, surface topography and porosity of the scaffolds. There is a strong need of industry for the development of methods, equipment, metrology, good practice guides and standards to properly characterise

the material, the parts it is made from, as well as the parts themselves. A quality control methodology has to guarantee certain/constant properties of the material to ensure that the scaffolds lead to implants/medical products that meet the respective requirements

7.ACTION

Comprehensive study on the chemical and mechanical signals that lead to the regeneration of bone - Excellent Science to be developed: Get to fully understand the mechanical and chemical signalling that favours the regeneration and formation of bone.

Technology to be produced: simple models that allow to understand one at a time, the effect of each signal.

Societal challenge to be accomplished: Fully understand the biological healing pathways of bone.

8.ACTION

Innovative bond repair approach through multi-actor governance

Excellent Science to be developed: The continuous demand for bone replacement and repair is a result of the demographic changes, characterised by a continuous aging of the population and the exponential increase of osteoporotic fractures. Existing materials for bone repair and replacement do not satisfy all clinical desires. Therefore creation of new materials for bone repair is requested and it could be effective only with a multi-actor approach to target actual needs of end users and aim at a

demand –driven innovation. The cross fertilisation of ideas between different actors with different perspectives and complementary knowledge (universities, research centres, SMEs, manufacturers of large-scale production, practitioners, health care organisations, regulators and organisations representing patients) should lead to innovative solutions that can more likely reach a largely shared and concerted impact. The actions should include activities of coordination to promote a deeper understanding between the different actors, as synergies and coherence is necessary to create high-level products.

It is necessary to establish cross cutting working groups that will be able to pave the paths for the future of research towards 2020 and beyond. The working group will be shaped developing a cluster model with the objective of bringing together actors from EU funded projects and actors from different fields in a unique multidisciplinary scenario, bringing together competences and new acquired knowledge.

Many activities can be suggested to support this aim, such as:

- Consulting stakeholders in apposite and institutional places (creating a number of boards, such as board of partners, advisory thematic boards, etc. with the aim of including different stakeholders);
- Implementing trust to reduce the effect of mutual suspicions about intentions (it is suitable to create a space guided by a combination of actors who would themselves be above the struggles of suspicion and the deadlocks these create);
- Creating mechanisms to implement exchanges (ICT, as well as face to face meetings, conferences, thematic workshops, clustering days);
- Creating mechanisms to implement confidence, through high level of consciousness of each others'

activities (workshops and training);

- Developing common training material and services; international cooperation related to community building, road-mapping, etc.

Societal challenge to be accomplished. All these exercises aim at:

- Developing new approaches to innovation in the context of nanotechnology including stakeholders and end users in the decision making process;

- Reaching out the highest number of actors from different EU funded projects in several areas across the entire society, which have interest in the context;

- Improving competitiveness of the European nanotechnology sector

- Creating open and living discussion tables among researchers, industry, policy makers, and others;

- Facilitating private investment to support research activities beyond the EU fund;

- Bringing consistent impact on the new regulation, e.g. Medical device regulation.

MEDIUM-LONG TERM

9. ACTION

Excellent Science to be developed:

Technology to be produced: Development of integral approaches for the convergence of bio-printing and/or bio-fabrication, imaging/monitoring and bioreactor technologies for automatised and sterile production of tissue equivalents.

Bioprinting/biofabrication technologies enable the controlled three-dimensional assembly of materials and cells into tissue like structures. The automatisation of these processes ensures reproducibility and minimises batch-to-batch variations which is regarded as a key advantage for the control over subsequent maturation of the constructs to functional tissue equivalents. However, at the moment the three most important steps, printing, maturation (meaning in vitro culture in a (dynamic) bioreactor) and the online monitoring of the evolvement of tissue function are technologically not integrated. This imposes significant challenges for sterility of the complete process chain and quality control of tissue maturation.

Societal challenge to be accomplished: Human tissue equivalents for drug testing and therapeutic approaches (cardio-vascular, musculo-skeletal, soft-tissue)

10. ACTION

3D personalized regenerative implants for osteochondral-reconstruction

Biomaterials for repair of osteochondral defects in situ

do not exist yet. They should be injectable for minimal invasive surgery, contain cells or growth factors, setting in situ with high strength and ultimately replaced by normal tissues.

Technology to be produced: Development of integral approaches for the convergence of bioprinting/biofabrication, imaging/monitoring and bioreactor technologies for automated and sterile production of tissue equivalents.

Personalized medicine should develop and bring to the market new clinical treatments customized to the patient's disease. For instance, personalized anatomic regenerative implants produced by 3D printing from medical images, 3D cell constructs, nanotechnology vaccines, etc could be envisioned. However, medical devices customised to patients' needs are out of the scope of CE mark and require a special authorization from regulatory agencies.

Societal challenge to be accomplished: joint damage

11. ACTION

Non-cell based regenerative approaches for joint regeneration. Technology to be produced: application of approaches that do not include cells but other biological cues, such as MSC secretome, or rely on structural biomimicry and tailored morphology to induce regeneration.

Societal challenge to be accomplished: simplify the regulatory burden and enhance the translation towards

the clinic.

12. ACTION

Additive manufacturing technologies allow for the automatised and thus reproducible generation of hierarchical and tissue-like structures consisting of several materials and cells. Such constructs bear great potential for tissue engineering and regenerative medicine, as functional features of tissues may in this way be reachable dramatically more rapidly and evolve through biomimetic placement of the constituents. However, progress in this exciting field is to a large extent hampered by the lack of suitable materials. While there has been significant process, for example in developing hydrogels for tissue engineering, these systems are often not suitable for printing technologies such as robotic dispensing, ink-jet printing or laser induced forward transfer. Hence, there is an urgent need for materials that combine the processability by printing technologies under cytocompatible conditions with biocompatibility and eventually bioresponsiveness. Key challenges are cytocompatible processing conditions (physiological conditions, limited overall viscosity and shear forces) in combination with good shape fidelity and mechanical stability of the produced constructs. One promising strategy to develop materials that meet these demands are multifunctional molecular precursors for the nano-programmed assembly into ordered structures.

7.4 THE IMPACT FOR EUROPE

The European Union faces important challenges for the next decades, from a societal economic and environmental point of view. For this reason it is crucial to create a knowledge-intensive society and to complete the European Research Area as a single market for knowledge. Yet at the same time, the recent financial and economic crisis has highlighted more than ever the need for and the value of researchers and innovators in generating sustainable and long-lasting wealth in Europe, not just as part of an economic recovery but also as a foundation for sustainable growth for the future. In the healthcare field, biomaterials are an example of an important challenge for Europe.

Biomaterials for health will play a major part in shaping the future of advanced therapies and medical devices, as well as in many other applications not yet defined. A number of technical, administrative and clinical challenges exist, all of which need to be dealt with in the coming years.

Adequate integration of biomaterials with their application context is needed to fulfil all the requirements for a functional outcome. Their research and development also require support to overcome the "death valleys" that exist between the industrial and academic fields, but also with the clinical and regulatory fields, as well as the long path to market.

The effectiveness of the dialogue between the different European players that are part of the virtuoso chain strongly linking the fundamental knowledge of material science to the production and transformation of materials into sustainable solutions and products must be improved.

CONCLUSION

This publication has presented the very intensive knowledge exchanges between academics, SMEs, civil society organisations, policy makers and all the other key stakeholders that took place during the two meetings "the Clustering day" and the "Stakeholder day".

One of the main recommendations evincing from this work is that nanotechnologies and advanced materials for more effective healthcare research should be carried out along the value chain, starting in the laboratory and ending in the clinic - from "bench to bedside" – and by necessity, should be multi-sectorial, transverse and cross-cutting.

A coral and collective effort is required to advance in this matter. For this reason authors repeatedly highlighted the crucial necessity of multi actor and multi stakeholder projects. Nevertheless the strong support of policymakers is required to advance all together and guarantee the well being for all the society.

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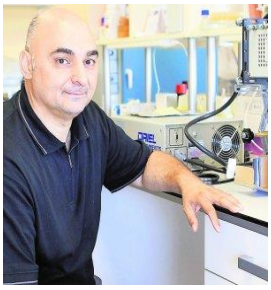

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Moverim founder (2001), Laura has worked intensively for nearly 20 years on EU financial programmes, in particular EU Framework Programmes for research and innovation. Lecturer on European affairs for DG COMM since 2002 , she conceives and organises trainings on management and implementation of EU contracts, EU policies, functioning and strategies. Economist with a Master in Science Communication, Laura is particularly interested on RRI policy implementation and Science Diplomacy. She is. heavily involved in project design phases, negotiation, implementation, dissemination and communication activities. vivani@moverim.eu

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Matteo has been programme officer in converging Nano-Bio-Info-Cogno sciences & technologies and communication outreach at the European Commission since 2003. He has authored 22 books and edited tens of articles, having also designed and developed diverse exhibitions and workshops. Graduated "cum laude" with honourable mention in Natural Sciences at the University of Turin, Italy,he wrote an experimental dissertation on eco-ethology carried out in central Africa at the Kenya Marine Fishery Research Institute of Mombasa (Kenya). Subsequently, he was awarded the title and Medal of "Best in the School" for best curriculum and dissertation by the academic Senate of the University of Turin (Italy). He holds a European Master in Environmental Engineering, issued by the European Association of European Polytechnics of Chambery (France), and an International Master Course in Fats issued by the CSIC of Seville, Spain. He holds a PhD in Environmental Engineering issued by the University of Surrey (England), awarded with honourable mentions by the Centre for Environmental Strategy (Guildford, U.K.) and the University of West Indies (Kingston, Jamaica). He possesses work and research experience in Europe, Asia, Africa and the Americas. matteo.bonazzi@ec.europa.eu

ANNEX

LIST OF ATTENDEES

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ANASTASIA	Silvia	MOVERIM	InnovaBone
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DE MAURO	Alessandro	University of Leuven	
DRIESEN	Willibrord	QSERVE	InnovaBone
EPSTEIN	Michelle	MUW	InnovaBone
ESPANOL	Montserrat	UPC	InnovaBone
FALZETTI	Marco	EuMaT	
FELFEL	Reda	UNOTT	InnovaBone
FOWLER	Tristan	UNIVIE	InnovaBone
FRAUKE	Alves	University of Göttingen	
GAVA	Elisa	Moverim	InnovaBone
GERMINARIO	Michaela	TuTech Innovation Gmbh	Lifelongjoints
GIAZZON	Marta	CSEM	InnovaBone
GIMENO-FABRA	Miquel	UNOTT	InnovaBone
GINEBRA	Maria-Pau	UPC	InnovaBone
GONZALEZ	Constancio	UVA	InnovaBone
GRANT	David	UNOTT	InnovaBone
GROLL	Jurgen	University of Würzburg	InnovaBone
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HATTO	Peter	Ionbond UK	Lifelongjoints
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HILDEBRAND	Gerhard	IBA	InnovaBone
HOFFMANN	Oskar	UNIVIE	InnovaBone
HOFSTETTER	Willy	University of Bern	InnovaBone
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RAINER	Bernd	Easy Software	
RICHARD	Christian	UNIVIE	InnovaBone
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SCOTTILE	Virgnie	UNOTT	InnovaBone
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SOTTILE	Virginie	UNOTT	InnovaBone
STEENSON	Karen	University of Leeds	Lifelongjoints
STOOPS	Giada	Moverim	InnovaBone
TAMPIERI	Anna	ISTEC-CNR	Ophis
TRASCIANI	Giorgia	Moverim	InnovaBone
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This report stems from a set of dedicated workshops run from 2014 to 2016 clustering eight EC funded research and innovation projects delivering a fresh perspective about nanotechnology research and innovation in nanotechnology-based osteochondral reconstruction. This exercise has been promoted in the framework of InnovaBone project, aiming at developing novel biomimetic strategies for bone regeneration. Starting from the critical review of best practices developed by selected European funded projects and research, its main outcome is valuable for EC policy making to the extent that it identified, characterised, discussed and ranked possible future EC research and innovation policy actions in this field at various time horizons. Different recommendations are summed up in this publication, offering an expert insight of this field, considering both activities and prospects from diverse communities of stakeholders, such as research community, industry, policy-makers, civil society organisations.

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