

Nanomedicine

Strategic

Research &

Innovation

Agenda

2016—2030

Creating Junctions for Healthcare

Industry

Patient



Disclaimer

This document has been compiled by collaborative work of many people involved in the ETP Nanomedicine and in the ERA-Net EuroNanoMed. The SRIA is the outcome of an in-depth discussion process that took place within the European Nanomedicine Community from mid-2014 until end of 2015. It does not necessarily reflect any individual position or opinion of the authors but shall reflect the general state of the discussion.

The ETP Nanomedicine

Contacts:

ETP Nanomedicine Secretariat (secretariat@etp-nanomedicine.eu)

ERA-NET EuroNanoMed Coordination (enmiicord@agencerecherche.fr or EuroNanoMed3 enm3@isciii.es)

Strategic Research and Innovation Agenda For Nanomedicine 2016 – 2030

Creating Junctions for Healthcare

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Content

Executive Summary	5
1 Introduction.....	7
1.1 Why Nanomedicine	7
1.2 Building on previous strategic documents	7
1.3 Building on previous investments.....	8
1.4 Building on previous achievements.....	9
1.5 Building on a growing community	10
1.6 Rationale of the agenda	11
2 Research and Innovation strategy.....	12
2.1 Objectives.....	12
2.2 Selected diseases	12
2.2.1 Atherosclerosis and other Cardio-vascular Diseases	13
2.2.2 Cancer	14
2.2.3 Neuro-degenerative and other neurological disorders.....	16
2.2.4 Infectious diseases.....	17
2.2.5 Diabetes and Endocrine disorders	18
2.2.6 Arthritis and Osteoarticular pathologies	19
2.2.7 Other diseases	19
2.3 Matching with other Emerging Technologies for Healthcare	21
2.4 Implementation	23
3 Impact	26
3.1 Healthcare and patient's quality of life	26
3.2 Establish a better European biomedical "ecosystem".....	26
3.3 Improved linkages among and to EU authorities and policies	27
4 Long term vision.....	28
5 Acknowledgement.....	29
5.1 Authors	29
5.2 Contributors.....	29
5.3 SRIA dissemination.....	31

Executive Summary

The Strategic Research and Innovation Agenda for Nanomedicine

Nanomedicine – the controlled use of nanotechnologies in healthcare – contributes to a better understanding of and controlled interactions with biological mechanisms at the molecular level leading to new pathways for diagnosis and treatment of human diseases, in line with the global evolution of medicine. In 2005 the European Technology Platform for Nanomedicine (ETPN) published a first Vision Paper, a technology-push strategic document defining the scope of Nanomedicine in Europe and laying thereby the groundwork for the ETPN. The present Strategic Research and Innovation Agenda (SRIA) assesses the state of the art after 10 years and provides the larger nanomedicine community with Research and Innovation priorities for the next 15 years. Integrating innovation aspects into the Strategic Agenda for Nanomedicine is of crucial significance for the further development of Nanomedicine as it emphasizes the efforts of the European Community to tackle the challenges in translation to the market and to contribute to an emerging industrial sector in Nanomedicine.

Europe has recognised the potential of Nanomedicine since an early stage. The 7th EU Framework Program (2007-2014) and the first calls under Horizon2020 together with funding from several Member States raised almost one billion Euros for R&D projects involving researchers, SMEs and industrial companies. Accordingly, the last 10 years have seen deployment of Nanomedicine as a fully-fledged sector within an organised and growing community, with national and European policies for funding research and translation, with structured value chains and finally with the emergence of an industrial and economic sector. As a result of this structuring and the heavy public R&D funding at European and national levels many promising approaches and prototypes for Nanomedicine applications in the areas of therapeutics, diagnostics and regenerative medicine have reached the industrial pipelines and the patient.

Building on these developments the objectives of a Strategic Research and Innovation Agenda for Nanomedicine for the next decade are:

1. to focus on unmet medical needs where Nanomedicine can make the difference by providing currently lacking diagnostic and therapeutic options,
2. to facilitate the matching of nanotechnology features with other Key Enabling Technologies (KETs) for new smart and connected products and devices
3. to optimise the implementation of medical innovations into the healthcare systems by balancing benefit for patients with cost constraints of the healthcare system and industrial return on investment
4. to sustain or even improve competitiveness of European healthcare economy at the global market

To meet these objectives current medical needs in the most important diseases defined by WHO and the ETPN Working Group “Clinical Interface” were matched with nanomedical solutions proposed by the technical working groups of the ETPN. This list was complemented with examples of new medical products, where Nanotechnology is contributing in concert with other Key Enabling Technologies (KETs) to new options for diagnosis and therapy. Together, these data provide a comprehensive overview of the potential impact of nanotechnology on new medical solutions for acute medical needs of patients.

The complexity of nanomedicines and cross-KETs medical applications requires improved communication and collaboration structures of all stakeholders from research, industry and public authorities to adapt existing value chains to the transdisciplinary nature of such products. This not only requires to optimise synergies between different public funding sources coming from Horizon 2020, the European Research and Structural Investment Funds, along with national and regional funding programs of individual Member and Associated States, but also leveraging of this public funding with private investments. Besides such ongoing financial support from public and private sources, the most promising projects and results need cost effective access to appropriate research infrastructures, technical services, regulatory support and especially certified clinical study centres to move more

quickly all along the translation process. The goal is to create a favourable socio-economic ecosystem which enables research groups and SMEs to develop their projects to a Technology Readiness Level (TRL) where global healthcare providers are able to take the lead to deliver the product to patient and market. By installing such professional translation structures which are ready for large industry to connect to and support future product development with reduced investment outlays, Europe will be able to cope with the increasing global competitive pressure. This will not only generate employment opportunities in SMEs, but will also attract or even relocate production capacities of large biomedical companies currently located outside Europe in Asia or even the US. The ETPN will continue to be one of the driving forces behind the implementation of this Strategic Research and Innovation Agenda for the benefit of European patients and healthcare systems.

1 Introduction

1.1 Why Nanomedicine

Nanomedicine as a translational science has the goal to provide cost effective novel therapies and diagnostics using the enabling capacity of nanotechnology applied to medicine. This ambition is based on the fact that nanotechnologies provide the tools for analysis and manipulation of biological processes at the nanoscale, where diseases initiate and progress. The result is an increasingly better understanding of the molecular biology of diseases leading to new targets for more specific and earlier diagnostic and therapeutic treatments. These new options will cause profound changes in future healthcare systems by enabling more personalised, predictive, preventive, regenerative and even remote (tele)medicine.

The introduction of nanotechnologies into medical applications not only requires collaboration of many scientific disciplines but also involvement of different industries such as Pharma, Medical Technology (Medtech), Biotechnology and even Information Technologies (IT). The European Technology Platform for Nanomedicine (ETPN) was established in 2005 by industry and the European Commission as a communication platform to interface such diverse stakeholders for mutual development of new smart and connected medical applications. The members of this platform collectively produced strategic documents and roadmaps defining the scope, R&D topics and translation requirements to be implemented and funded to utilise the full potential of Nanomedicine for the benefit of patients and the healthcare industry in Europe.

1.2 Building on previous strategic documents

This document is the third update of ETPN's strategic publications since the original Vision Paper in 2005, a technology-push strategic document defining the scope of Nanomedicine in Europe and laying thereby the groundwork for the ETPN. The 1st update (Strategic Research Agenda - SRA 2006) and the 2009 Roadmaps focused on industrial needs with two objectives: firstly, to identify translatable trends in research and understand their expected impact on applications, products and markets, and secondly, to fine-tune and target research funding on areas with greater commercial potential and most importantly, where it would help the patient.



Figure 1: Strategic documents published by the ETPN in last decade

The present Strategic Research and Innovation Agenda (SRIA) offers the opportunity to assess the state of the art and to provide the larger nanomedicine community with Research and Innovation priorities for the next 15 years. Integrating Innovation aspects into the Strategic Agenda for Nanomedicine is of crucial significance for the ETPN as it emphasizes the efforts of the European Community to tackle the challenges in translation to the market and to contribute to an emerging industrial sector in Nanomedicine. Furthermore, the current Agenda focuses strongly on unmet clinical needs in selected diseases, highlighting thereby the potential of current and future nanomedical products to provide new, efficient and effective solutions for healthcare.

This document relies to a large extent on data and information collected through consultations with the 160 members of the European Technology Platform for Nanomedicine and 150 researchers from clinical institutions having submitted applications to the EuroNanoMed calls. Additional external sources have also been consulted to complete the set of data and to draw an overall picture for Europe. A constant effort was made along the preparation of the document to make it accessible for audiences with very different backgrounds such as technologists, clinicians, patients and the large public as Nanomedicine is a multidisciplinary issue which addresses a large scope of users.

1.3 Building on previous investments

Europe has recognised the potential of Nanomedicine since an early stage. The 7th EU Framework Program (2007-2014) has invested in:

- 86 projects with a budget of 446 Mio. € funded by the Nanosciences, Nanotechnologies, Materials and New Production Technologies (NMP) programme
- 31 projects with a budget of around 150 Mio. € were sponsored as part of the Health Programme
- 35 projects for the development of Micro-Nano-Systems for a total budget of 135 Mio. € were funded by the programme Smart System Integration Challenge of the Directorate General Communication Networks, Content and Technology (DG CNECT)

Additional projects have been funded through European Research Council, People and the ERA-NET EuroNanoMed. Over **400 industrial partners** (SMEs, Large industry) participated in these projects.

Under the EU Research and Innovation programme Horizon 2020 over 100 Mio. €¹ have already been invested in 2014, the first year of the programme, in 45 nanomedicine-related projects covering the three pillars of Horizon 2020 namely Excellent Research, Leadership in Enabling and Industrial Technologies and Societal Challenges.

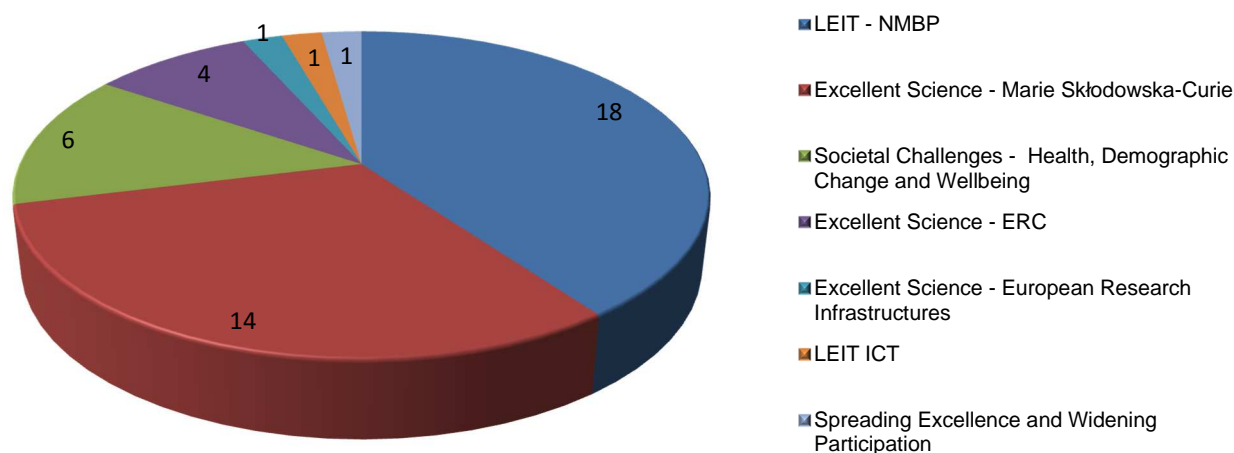


Figure 2: Distribution of nanomedicine-related projects in 1st year of Horizon 2020 (2014)

¹ Source: ETPN Analysis of H2020 Projects with Nanomedicine Relevance



Nanomedicine has also been funded by many Member States via the ERA-NET instrument EuroNanoMed (ENM). The main goal of ENM partners is to foster competitiveness of European Nanomedicine actors through the support of transnational collaborative and multidisciplinary research projects. During the 2009-2015 period, the ERA-NETs ENM I & II have successfully launched **6 joint calls for proposals in line with the strategic priorities of the ETP Nanomedicine**. These joint calls for proposals allowed ENM to fund 51 transnational research projects involving 269 partners from 25 countries/regions participating in the calls, with about 45.5 Mio. € funding from the ENM funding agencies. Altogether, **1327 research groups from more than 25 countries** participated in these calls, in a total of **258 submitted proposals**. The envisioned third phase of EuroNanoMed will focus its efforts on planning, implementing and monitoring joint transnational calls to fund **multidisciplinary translational research projects with market potential**, reinforcing their scope through top-up funding from the EC, inclusion of new partners and close collaboration with ETPN and other European actors in the field.

1.4 Building on previous achievements

The heavy public R&D funding at European and national levels has resulted in many promising approaches and prototypes for Nanomedicine applications in the areas of therapeutics, diagnostics and regenerative medicine.

Area	Nanotechnologies applied to medicine to address medical needs
Therapeutics	<ul style="list-style-type: none"> - Nanotechnologies to cross biological barriers, using nanoformulations, nanoemulsions or nanodevices - “Smart” nanocarriers: Encapsulation of actives into nanodelivery devices / Highly targeted and fast acting drug delivery systems and nano devices for localised drug delivery and release in critical regions / enhanced bioavailability (nanoemulsions) and increased target specificity / - Biocompatible nanoparticles: Lipid/micellar or polymeric nanoparticles to reduce toxicity (biocompatibility) and improve efficacy - Activable nanoparticles providing physical therapeutic effects (crystalline inorganic nanoparticles) - Monitoring of therapeutic efficacy - Theranostic nanoparticles and nanodevices carrying a drug and acting as diagnostic tool: diagnosis and monitoring / active and passive targeting (cancer)
Diagnostics / Imaging	<ul style="list-style-type: none"> - Nano-enabled biomarkers, vectors and contrast agents with high-sensitivity and specificity: functionalised nanoparticles for diagnostics and therapy / Molecular monitoring of markers / Multifunctional contrast agents - Nanotechnologies to cross biological barriers (BBB), using nanoformulations, nanoemulsions or nanodevices - High throughput systems for multiplexed detection of biomarkers of diseases, for optimization of therapy and sensing interfaces - Nanostructured surfaces for biosensors tailored to work within the body, on the body, or out of body - Non-invasive and painless monitoring (diabetes and endocrine disorders)
Regenerative Medicine	<ul style="list-style-type: none"> - “Smart” nanostructured and functionalised surfaces: functionalisation of 2D-3D materials - Scaffolds and nanoparticles for new and advanced therapeutic treatments - 3D printing of cells and biomaterials for implants and/or reconstruction - Intelligent biomaterials/bioactive materials: site specific delivery of active molecules / nanoparticles with spatial and temporal control over the release of biochemical molecules and/or in vivo activation of stem cells / mimic the morphological, mechanical and biochemical environment of tissues / Biomimetic, biocompatible, biocompetent biomaterials - Nanofunctionalisation for increased biocompatibility of implants: polymer coated medical implants to improve biocompatibility

Table 1: Current applications of Nanotechnologies in Medicine

Based on such approaches many potential products already reached the pipeline of Pharma or Medtech companies.

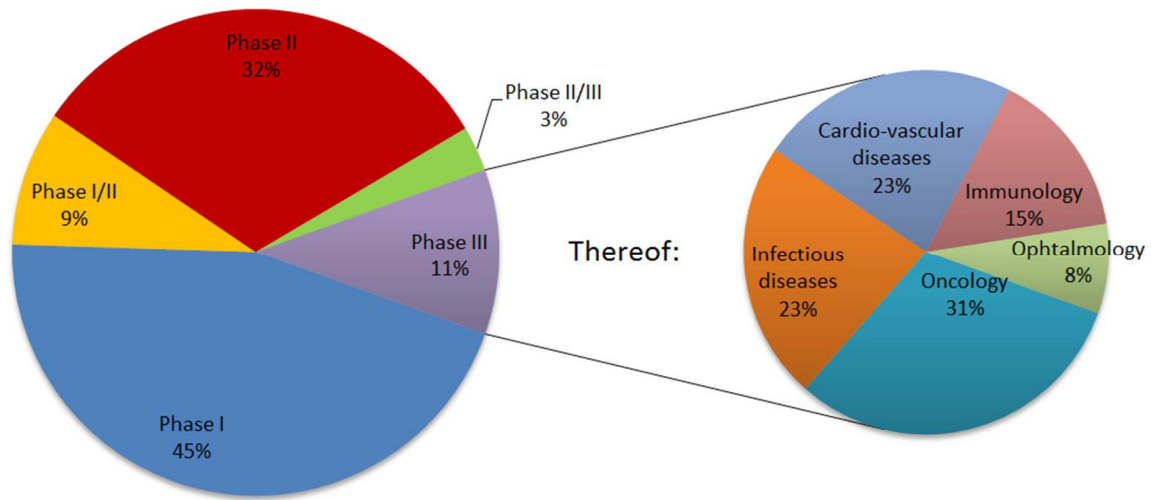


Figure 3: Pipeline of nanomedical products in Clinical stages

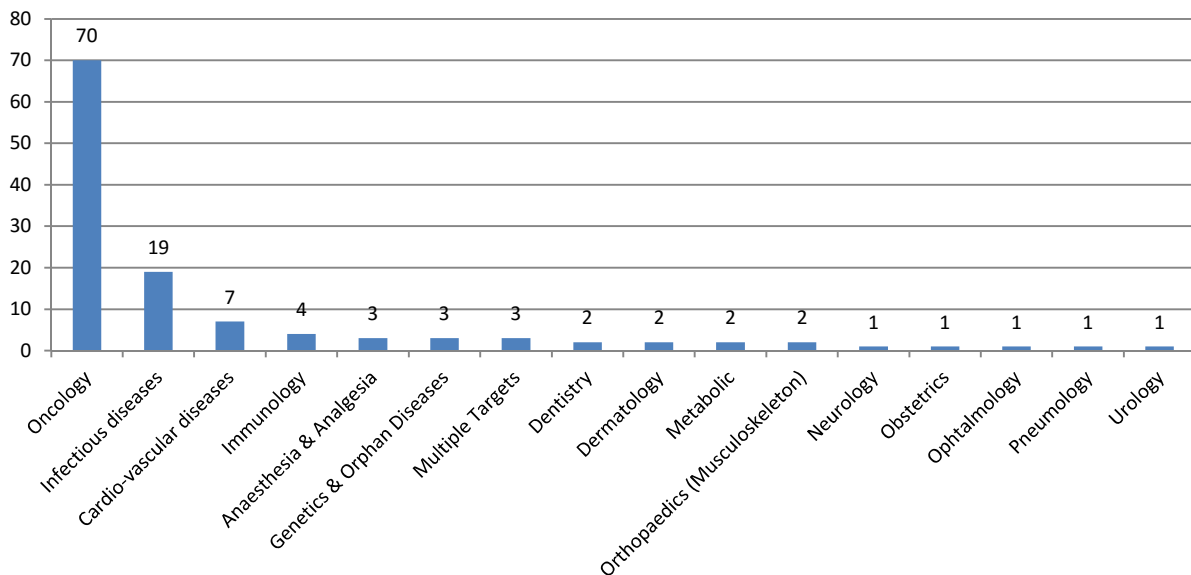


Figure 4: Pipeline of nanomedical products along medical specialties

Further introduction of Nanomedicines into the research and development pipeline of the healthcare industry will not only provide more new innovative approaches for preventive or personalised therapies, but can also restore or repair natural body functions in patients that have deteriorated due to chronic or long term disorders. It also heralds a new age for European **industrial growth** and **competitiveness** and will result in the **wellbeing of European citizens at an affordable cost**. However, unlocking new opportunities in using nanotechnology and other KETs needs to be accompanied by advanced production processes (cross-KETs) implemented at large scale to result in competitive value for the end users.

1.5 Building on a growing community

Although the origin of Nanomedicine as a scientific discipline dates back several decades, the last 10 years have seen its deployment as a fully-fledged sector within an organised and growing community, with national and European policies for funding research and translation, with structured value chains and finally with the

emergence of an industrial and economic sector. SMEs play a crucial role in this emerging sector as translation from lab to bedside occurs mainly in such entities. Since 2013, several “big deals” with major multinationals in the pharmaceutical industry have been announced involving nanomedical SMEs, mostly in the US, providing thereby monetary value as economic indicators to measure the impact of Nanomedicine.

The ETP Nanomedicine performed the task to identify key stakeholders in Europe on the *Nanomed Map*², now counting more than 1,700 institutions, directly or indirectly linked to the Nanomedicine Ecosystem. At the national level, beside the efforts done by the EuroNanoMed ERA-NET to coordinate transnational research programs, the scientific and industrial communities created national platforms to gain in visibility and advance on issues such as regulations or reimbursement, which are under the responsibility of national authorities. 15 National Platforms for Nanomedicine nowadays complement the efforts done at the European level by the ETP Nanomedicine.



Figure 5: Screenshot of the European Nanomed Map

The same kind of structuration is happening in other parts of the world, in particular in the USA³ but also in South America or in Asia. Discussions and collaborations at platform levels are key to address global challenges, to foster intercontinental co-operations and to open up new opportunities and markets for European companies.

1.6 Rationale of the agenda

The Strategic Research and Innovation Agenda for Nanomedicine is intended to describe a framework for the fruitful deployment of innovative solutions for healthcare by providing references, strategies and priorities for Research and Innovation as well as for the socio-economic and regulatory ecosystem. The document has been written to reflect the main current and future challenges the European Community in Nanomedicine is facing. The integration of innovation as a full element of the Nanomedicine Strategic Research Agenda shows the importance for Nanomedicine to reach the next steps in the translation process towards the markets.

The Agenda is relevant beyond the Nanomedicine R&I community for:

- **Medtech, Pharma, Biotech and ICT industries** that can draw benefits from nano-enabled technologies having the potential to add value to their existing technologies in connected smart systems for healthcare
- **clinicians and patients** who receive information about possible nanomedical solutions for unmet medical needs
- **regulators** who need early information about nanomedical trends to check the applicability and a possible adaptability of their regulations to future developments
- **European Commission, Member States and investors** to decide where financial support is needed and rewarding the investments
- **Healthcare insurances** to adapt their business models for reimbursement to the paradigm shifts in medicine

A mutual understanding and efficient junctions between all these stakeholders is needed and crucial to ensure the financial viability of the healthcare systems and a competitive nanomedicine economy for the benefit of patients in Europe.

² <http://www.etp-nanomedicine.eu/public/nanomedmap/>

³ <http://www.nanomedicines-alliance.org/>

2 Research and Innovation strategy

2.1 Objectives

After a decade of R&D funding to improve technologies for medical applications the future investments should be further guided by the medical demand and the improvement of the socioeconomic ecosystem for translation. Therefore, the objectives of the Strategic Research and Innovation Agenda for Nanomedicine for the next decade are:

1. to focus on unmet medical needs where Nanomedicine can make the difference by providing currently lacking diagnostic and therapeutic options,
2. to facilitate the matching of nanotechnology features with other Key Enabling Technologies (KETs) such as *Nanotechnologies, Advanced Materials, Micro- and Nano-Electronics, Photonics, Industrial Biotechnology and Advanced Manufacturing Systems* to deliver new and radically innovative cross-KETs medical solutions to patients at affordable cost,
3. to optimise the implementation of medical innovations into the healthcare systems.

Accordingly, this SRIA highlights the contribution of Nanomedicine to meet these requirements in concert with the other KETs and it proposes measures for the adaptation of the regulatory and socioeconomic environment to the speed and complexity of cross-KETs developments.

2.2 Selected diseases

According to the WHO⁴, non-communicable diseases – such as **cardiovascular diseases, cancer and chronic obstructive pulmonary diseases** – account for 80 % of deaths in the European Region. Diseases of the circulatory system (ischaemic heart disease, stroke, etc.) are currently the most important causes of premature death (before the age of 65) in the EU, accounting for nearly 50 % of the total. Cancer is the second leading cause, accounting for nearly 20 % of deaths, while injuries and poisoning are responsible for 9% of deaths. With the ageing population, the risk of cancer is rising; the disease is currently the main cause of premature death in 28 of the 53 countries in the EU, and is predicted to further increase by 2020. Communicable diseases are less frequent in the European Region than in the rest of the world, but with the rapid emergence of **antimicrobial resistance** infectious diseases have become a re-emerging threat⁵. HIV/AIDS remains a major public health challenge in the EU, the eastern part of which has the fastest-growing HIV epidemic in the world⁶.

An extensive survey has been led by the ETPN Clinical Interface working group in collaboration with EuroNanoMed II in order to compile a list of shared unmet clinical needs felt by clinical experts, potentially profiting from nanotechnology-enabled products or processes. The main goal was to focus mainly on the needs more than on the solutions – leaving the latter task to vertical working groups – even though some potential solution already arose from the clinical expert voices.

From the survey it appears that the largest group of diseases for which unmet needs were identified are cancer, neurology, infectious diseases, rehabilitation/aging-related disease and cardiovascular diseases, which constitute together about 70% of the total number of topics. This is well in line with the Horizon 2020 orientation⁷ towards major social challenges in healthcare, both in terms of big killers, like cancer and cardiovascular

⁴ WHO's fact sheet on Leading causes of death in Europe. Information extracted from The European health report 2012: charting the way to well-being: <http://www.euro.who.int/en/data-and-evidence/european-health-report/european-health-report-2012>

⁵ http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf

⁶ <http://www.unaids.org/en/resources/presscentre/featurestories/2012/december/20121205warsaw>

⁷ <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/health-demographic-change-and-wellbeing>

disorders, and of highly disabling disease bringing very heavy social burden, like infectious disease, neurological/degenerative disorders and chronic aging-related conditions.

Considering the groups of prevalent applications, it appears that most of the unmet needs are still in the treatment area (60%), with a still relevant number in diagnostics/monitoring (26%), while theranostic applications – unless considered as precious – are still considered less close to reality than the two previous ones. In several cases, anyway, the monitoring applications are aimed at providing not only a better diagnosis or screening but also the basis for personalised treatments, providing higher quality of life and more efficient use of healthcare resources.

The following sections provide a summary of the medical needs identified through the survey of the ETPN Clinical Interface working group and the solutions offered by Nanomedicine, as identified in the vertical working groups. The analysis is presented in the context of other studies (Bremer-Hoffmann *et al.* *Eur. J. Nanomed* 2015; 7(3):191-202 and Bionest-Leem report, 2013). The report of Bremer-Hoffmann *et al.* elucidates to which extent the field of Nanomedicine in Europe addresses pharmaceutical gaps as identified by the second report on the Priority Medicines for Europe and the World, released by the WHO in 2013⁸. The analysis of 210 Nanomedicine projects/products, including 30 authorised products, 69 clinical trials and 131 drug development projects from 1996-2005, allowed them to identify some challenges that are ahead in order to fully exploit nanotechnology for human health care. The Bionest-Leem report in 2013 identifies the sectors with innovation potential in the field, with a special focus of the French position in the international landscape. The study maps 230 medicinal products and medical devices issued from nanotechnologies, showing that the four most represented therapeutic areas addressed by 70% of these products coincide with the groups of diseases for which unmet needs were identified in our analysis: Oncology, Infectious Diseases, Cardiovascular Pathologies and Orthopaedics.

2.2.1 Atherosclerosis and other Cardio-vascular Diseases

Atherosclerotic Coronary Artery Disease (CAD) is the leading cause of premature death across the globe. It is caused by the formation of an atherosclerotic plaque within the lining of an arterial wall as white blood cells, lipids and fibrous tissue collect and cause a narrowing of the lumen of the artery (stenosis). Over decades of growth the plaque may reach a point at which blood flow through the affected region is heavily restricted, resulting in an insufficient amount of blood reaching the heart, causing pain and discomfort. In serious circumstances, a plaque may rupture and blood clot, causing a blockage in the artery and resulting in a heart attack or stroke.

The formation of arterial plaque is largely asymptomatic and patients are often only diagnosed after suffering from an acute event - heart attack or stroke. Although much research has been undertaken in the cardiovascular field for the pathogenesis of atherosclerosis, there is still a lack of endovascular imaging modalities for early diagnosis, prognosis, acute intervention and monitoring of therapy of the disease, because the current diagnostic paradigms for the non-invasive detection of vulnerable plaques are inadequate.

Another severe medical need exists for the ability to replace parts such as valves or patches or even a whole heart after damage or disease. One problem is the lack of sufficient numbers of donor organs, which can only temporarily be treated with the existing mechanical solutions. Especially children need implants which are able to adapt in size during the growth of the child's body. Currently these children need to go through several surgeries to adapt the size of valves, for example.

The complexity of these pathogeneses made it difficult so far to develop effective therapeutic strategies that are applicable in clinical routine. With 2D and 3D nano- and biomaterials new solutions become available.

⁸ Priority diseases and reasons for inclusions. In: Kaplan W, Wirtz VJW, Mantel-Teuwiwisse A, Stolk P, Duthey B, Laing R, editors. *Priority medicines for Europe and the World – 2013 Update*. Genève: WHO Library Cataloguing-in-Publication Data, 2013:67–165.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<ul style="list-style-type: none"> • Endovascular imaging modalities for early diagnosis, prognosis and acute intervention and monitoring of therapy of the disease, as the current diagnostic paradigms for the non-invasive detection of vulnerable plaques are inadequate. • More adequate therapeutic strategies to improve heart function post-myocardial infarction by regenerating the human heart muscle including the conducting system. • Improved biocompatibility of implantable medical devices / Development of safe and implantable biomaterials as cardiovascular and/or stem cell and drug delivery vehicles. • Late thrombosis: inflammation and endothelium healing delay after angioplasty with drug eluting stent (DES) implantation are of major concern. It has been shown that the polymer coatings and anti-proliferative drugs employed by DES impair stent strut endothelialisation and may induce stent thrombosis. • More adequate <i>in-vivo</i> and <i>ex-vivo</i> regeneration of cardiac tissue (heart valves, heart muscle, conducting system, etc.) • Provision of suitable implants due to donor organ shortage. Currently no ideal solutions for paediatric heart valve replacement or blood vessel substitutes exist, especially in regards to small-diameter grafts, compliance Young's modulus, hemocompatibility, saturation 	<ul style="list-style-type: none"> • Nano-enabled site-specific targeting (drug delivery and monitoring) • Nanotechnology-enabled systems for endovascular theranostics and plaque imaging (therapy, imaging and monitoring) • Intelligent, non-toxic, biodegradable or bioactive materials and implantable devices for compliant vascular grafts, drug eluting stents, medical adhesives and sealants with increased biocompatibility and functionality • Nanostructured sensors for predicting cardiovascular risk, diagnosis, prognosis, and monitoring therapeutic efficacy • Innovative nano-formulations for stem cell recruitment, mobilisation and homing at site of injury • Nano-enabled methods (i.e. highly targeted agents, small drugs, growth factors, cells) and scaffolds for <i>in-vivo</i> and <i>ex-vivo</i> regeneration (heart valves, heart muscle, conducting system, etc) • Nano-functionalisation and modification of surfaces for increased biocompatibility of implants

Table 2: Current medical needs and Nanomedicine solutions for Atherosclerosis and cardio-vascular diseases

The Bionest study identified 20 products issued from nanotechnologies for application in cardio-vascular diseases, with three products on the market since 2011. **Delivery systems and nano-coatings** are the main applications of nanotechnology in this field, the main delivery systems used being emulsions (4 products) and liposomes (3 products). In addition, around 20 FP7 funded research projects and clinical trials addressing cardio-vascular were identified by Bremer-Hoffmann *et al.* Biomaterials play a major role in the research projects under development (11 research projects on biomaterials compared to only two projects on Polymer-based nanocarriers or inorganic particles). Finally, cardio-vascular diseases having a high value of Disability Adjusted Life Years (DALYs), addressing these with relevant and promising FP7 research projects is highly contributing to the reduction of the burden for patients and the economy.

2.2.2 Cancer

Even though the introduction of new treatment options has improved the prognosis of cancer patients over the past years, the disease still represents a major burden with significant medical challenges. Cancer figures among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012⁹, and its incidence has been steadily increasing since 1980. In the Western World and in the US, cancer represents the second leading cause of death after heart-attack. However, the impact in the developing world is growing at an alarming rate. More than 70% of all cancer deaths already occur in low- and middle-income countries and these regions are projected to account for two thirds of all cases of cancer worldwide by 2050 (an increase of 15% since 1975)¹⁰. There are significant regional differences in cancer

⁹ Globocan 2012 - Population Fact sheet. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

¹⁰ Bray, F. et al. Predicting the future burden of cancer. Nat. Rev. Cancer. 2006 6:63-74



prevalence, but the biggest cancer killers worldwide are lung cancer (1.6 million deaths in 2012), liver cancer (745,000 deaths in 2012), stomach cancer (723,000 deaths in 2012), colorectal cancer (693,000 deaths in 2012), and breast cancer (522,000 deaths in 2012)¹¹. In addition to the impact on loss of life, the economic impact of cancer is huge. Currently it is estimated that the disease costs economies across the world an estimated 290 Bio. \$ in 2010, 154 Bio. \$ of which were medical costs¹¹.

There are several treatment options for cancer patients, and the success rates of each treatment vary significantly from one cancer type to another (complete remission, partial response or no response at all). Every possible response to treatment, including a wide variety of adverse reactions (such as pain, infection, blood clotting problems, hair loss, renal toxicity, fatigue, nausea and many others) can be expected with cancer treatment. Most cancer-related deaths occur by the spread of malignant cells to vital organs through a process known as metastasis. As a result, there is a lot of investment in specific treatments to target not only primary tumours, but also those that arise secondarily from metastasis to other organs.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<ul style="list-style-type: none"> • Improved diagnostics and development of novel biomedical technology strategies for early onset cancer detection • Biomarkers for improved diagnostics and imaging • Early and faster detection of circulating tumour cells and metastases • Improved treatment of solid tumours or chemo-resistant cancer • Improved precision and efficacy of radiotherapy, immunotherapy, photodynamic and hyperthermia therapies • Less side effects through more targeted chemotherapy • Stratification of patients for more individualised therapies 	<ul style="list-style-type: none"> • Nanoparticle tracers and contrast agents for fast and efficient means of early stage diagnosis, prognosis, and monitoring disease progress and for quantification of therapeutic agents and concomitant imaging • Minimally invasive endoscope / catheter for diagnostics and therapy • High-throughput screening tools, involving nanostructured sensors with high degree of multiplexing, quick response times for tumour cells or DNA isolation, localisation, quantification, characterisation and sequencing • Nanoparticles and nanoformulations with triggered release for tailor-made pharmacokinetics • Nanoparticles for local control of tumour in combination with radiotherapy • Functionalised nanoparticles for targeted <i>in vivo</i> activation of stem cell production • Engineered theranostic nanoparticles with multimodal imaging and multiple therapy possibilities • Composite nanoparticles for monitoring therapy efficacy • Nano-gels and nano-carriers as contrast agent (radiotherapy precision and efficacy) • High precision optical nano-thermometry for improved nanoparticle-based hyperthermia treatments • New nano formulations for imaging-guided drug delivery of nano-sized systems for personalised therapeutic treatments of tumours • Improved targeted delivery of agents for photodynamic therapy (photoactive nanomaterials) • Enhanced cancer cell targeting through lipidic/micellar nanoparticles • Nano-solutions for the improvement of immunotherapy

¹¹ WEF report: http://www.world-heart-federation.org/fileadmin/user_upload/documents/Advocacy/Resources/Articles_Series_Reports/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf (9th November 2011)

Table 3: Current medical needs and Nanomedicine solutions for Cancer

With 78 products in clinical development or on the market, as identified in the Bionest study (including Abraxane, Doxil, DaunoXome, Evacet, Lipo-Dox, MyCareAssays, NanoTherm), oncology is the first therapeutic area covered by Nanomedicine products. The main developments concern **drug delivery systems**, including liposomes (44 products), micelles (7) and emulsions (6) and a **diverse set of nanoparticles**, gold particles or polymeric particles to reduce the toxicity of harmful compounds used in oncology. The active nanoparticles, imaging markers and theranostic products are composed of metal crystals (gold or iron particles...). The same figures are presented by Bremer-Hoffmann et al, with 45 research projects or clinical trials identified in the field.

2.2.3 Neuro-degenerative and other neurological disorders

Neuro-degenerative diseases include, but are not restricted to, Alzheimer's disease and other dementias such as Degenerative Nerve Diseases, Encephalitis, Epilepsy, Spinal injury, Stroke, Parkinson's Disease, Multiple Sclerosis or Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease).

So far such diseases - thereof many are caused by genetic mutations - are incurable, resulting in progressive degeneration and/or death of neuronal cells. Relations on a sub-cellular level between these diseases are currently under investigation. Discovering these similarities offers new approaches for therapies that could ameliorate many diseases simultaneously.

Besides neuro-degenerative pathologies, further neurological disorders such as the disruption of central or peripheral nerves caused by injuries remain incurable resulting in permanent loss of body function as in paraplegia, leading to disabilities and heavy social burden.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<ul style="list-style-type: none"> • Early diagnosis and monitoring systems to improve personalised treatments at earlier stage • <i>In vivo</i> diagnostic imaging of brain diseases such as brain ischaemia, stroke, brain tumours and neuro-inflammation • Improved pharmacokinetics and targeted drug delivery and ability to cross the blood-brain barrier (BBB) • Define the impact of extracellular matrix on the progress of neurodegenerative diseases in order to identify new therapeutic targets • New therapeutic approaches that can interrupt disordered protein aggregation, deliver functional neuroprotective proteins and alter the oxidant state of affected neural tissues • Regeneration of central/peripheral nerves damage 	<ul style="list-style-type: none"> • Diagnostic devices and biosensors based on engineered nano-systems • Nano-contrast agents, economically competitive for enhancement of conventional imaging modalities (MRI, molecular imaging, PET, etc.) • Biospecific contrast agents inhibiting immune response • Biodegradable and biocompatible semi-invasive nano-devices for controlled drug delivery / Delivery of anti-inflammatory drugs to manage cellular and tissue response • Nano-formulations / Surface functionalisation of nanoparticles with peptides for highly targeted drugs for crossing the Blood-Brain Barrier (BBB) • Site specific delivery of neuro active molecules • Intracerebral shunts with antimicrobial coated catheters to reduce cell and bacterial adhesion • Imaging-coupled bioactive agent delivery • Functionalised biomaterials / Intelligent biomaterials such as improved hydrogels (bioscaffolds) to promote the generation of revascularisation • Peripheral and central nerve regeneration by combination of biopolymers, functionalised biomaterials and intraluminal micro/nanostructures mimicking the properties and physical dimensions of the nervous tissue • 3D scaffolds for neural stem cell encapsulation • Biocoatings to minimise long term adverse reactions from host tissue



	<ul style="list-style-type: none"> • Intraluminal microchannels or fibres to promote the gap repair mimicking the different fascicles and the average myelinated axons per nerve • Porous biomaterials with high biocompatibility and targeted biodegradability mimicking the mechanical properties of the nerve • Image guided implantation of advanced nano-electrodes for stimulation, inducing regeneration in neurodegenerative diseases, combined with intelligent feedback loops using nano-sensors • Improved Neuroprosthetics
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Table 4: Current medical needs and Nanomedicine solutions for Neuro-degenerative and other neurological disorders

Bremer-Hoffmann et al identified 10 FP7 funded research projects on **Alzheimer disease and other dementias**, whereas no clinical trial or product on the market is mentioned. The same applies for the Bionest study, which only mentions the importance of the nanotechnologies for regenerative medicine in this field. **Neuropsychiatric conditions** as well as **sense organ diseases** seem to be more advanced in the R&D chain, with 9 authorised products identified by Bremer-Hoffmann et al.

2.2.4 Infectious diseases

With the rapid emergence of antimicrobial resistance, globally as well as in Europe, infectious diseases such as tuberculosis have quickly become a re-emerging threat in Europe. The infectious illnesses of most concern for Europe are tuberculosis (particularly its drug-resistant forms), HIV/AIDS and other sexually transmitted diseases, and hepatitis. Tuberculosis accounts for over 40% of all mortality from communicable diseases and is the most common cause of death among people living with HIV/AIDS.

Beside multidrug resistance, the great challenge related to infectious diseases is the need for fast, accurate diagnostics to control epidemics and pandemics which is particularly acute in developing countries, where no deployed health system guarantees access to central laboratories and highly skilled professionals.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<ul style="list-style-type: none"> • Fighting multidrug resistance bacteria • Improving controlled release of antibiotics • Need for fast, accurate diagnostics to control epidemics and pandemics • New vaccines 	<ul style="list-style-type: none"> • Polymeric nanoparticles (nano-bubbles, biodegradable polymer, hydrophilic biopolymers, Proteins) targeting multi-drug-resistant bacteria • Tools to reduce spread of hospital acquired infections / Improved preventive measures (nanocoatings, nanofiltration) • Nanocoatings of implants / Efficient strategies based on nanotechnology to disrupt and prevent biofilm formation associated with a number of infectious diseases and implant-associated infections • Controlled release strategies for antibiotics in order to achieve local drug delivery, more efficient use of antibiotics and dose-control • Nano-formulation of antibiotics for enhanced bioavailability and increased target specificity • High-throughput screening diagnostics tools, involving nanostructured sensors, with high degree of multiplexing, high sensitivity and quick response times • Vaccines using solid lipid nanoparticles

Table 5: Current medical needs and Nanomedicine solutions for Infectious diseases

With 37 identified products for infectious diseases, Bionest reports that most of them are anti-infective agents coupled to nano-particulate vectors (18 products) and prophylactic vaccines (17 products). A large number of vaccines combined to nanocarriers are being developed with liposomal formulations or nano-emulsions. The functions provided by nanotechnology to the vaccines are the protection of antigens against degradation, graduated liberation of the antigen, increased antigen exposure time vis-à-vis the antigen presenting cells and lymphocytes and an increased immunogenicity via an "adjuvant" activity. Nanomedicines developed as part of FP7 focus on infectious issues for which pharmaceutical treatments are ineffective or will soon become ineffective, as is the case for antibacterial resistance and pandemic influenza.

2.2.5 Diabetes and Endocrine disorders

Endocrine disorders are often complex, involving a mixed picture of hyposecretion and hypersecretion because of the feedback mechanisms involved in the endocrine system. Both types of Diabetes Mellitus are chronic, metabolic diseases characterised by elevated levels of blood glucose (or blood sugar), which over time leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves.

WHO projects that Diabetes will be the 7th leading cause of death in 2030. Moreover, Diabetes is a disease which deeply affects patients' quality of life and can even lead to severe secondary illnesses such as blindness and neuropathies. The urgency of new strategies to fight Diabetes, which becomes a pandemic disease and leads to a significantly shorter life expectancy (10 years in Type 2 Diabetes Mellitus, >20 years for Type 1 Diabetes Mellitus), and to high costs for health systems, is undeniable.

Bremer-Hoffmann et al identified 5 FP7 funded research projects on diabetes using different approaches (biomaterials, lipid based- and polymer based nanocarriers) whereas no clinical trial or product on the market is mentioned. Bionest study only identifies 5 products for metabolic diseases, and no reference is made to Diabetes.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<ul style="list-style-type: none"> • Improved non-invasive glucose monitoring and insulin administration, possibly in a close-loop configuration • New administration routes of insulin • Transplantation of pancreatic islets without immune suppression • Improved implantation strategies to ensure cell engraftment and <i>in vivo</i> long-term function 	<ul style="list-style-type: none"> • Non-invasive and painless monitoring of glucose level in the blood and application routes for insulin delivery / Continued Insulin and glucose measurement by nano enabled devices • Nanotechnologies for insulin delivery into the nose or lungs (spray technologies) • Functionalisation of 2D and 3D materials for spatial and temporal control over release of biochemical factors for artificial pancreas (biomimetic, biocompetent, immunostealth biomaterials) • Nanotechnologies to deliver immunoprotection and to minimise immune response against transplanted cells/tissues / Immune protective nano-coatings • Encapsulation and monitoring of labelled islet transplants • Synthesis of biocompatible materials for nanoparticle preparation. Ex linkage of squalene to insulin to obtain nanoparticles

Table 6: Current medical needs and Nanomedicine solutions for Diabetes and Endocrine disorders

2.2.6 Arthritis and Osteoarticular pathologies

Osteoarticular pathologies, or rheumatic diseases, are a group of conditions like arthrosis, arthritis and related musculoskeletal disorders, of which osteoarthritis is the most frequent.

Arthritis is the destruction of cartilage, articular structures and subchondral bone. Behind cancer and cardiovascular diseases, rheumatoid arthritis (RA) and osteoarthritis (OA) are the most prevalent global diseases. In Europe, there are 3 million RA and 70 million OA patients. Given lifestyle changes and ageing of the population, the number of arthritic patients is expected to increase, resulting in enormous medical and socioeconomic challenges.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<p>Needs in arthritis:</p> <ul style="list-style-type: none"> • Ability to detect the onset of the disease as early as possible, including improvement of the existing immunoassays • Monitor the disease progression and define when a treatment should be initiated • Need for more efficient therapies, safer drugs, better delivery systems avoiding serious complications including infection, hepatitis or bone marrow suppression 	<ul style="list-style-type: none"> • Mimic the morphological, mechanical and biochemical environment of tissues • Nano-formulation of biologicals (peptides, proteins, nucleic acids) • 3D Printing of nano-biomaterials for stem cell immobilisation at site of injury • Bacterial free nanomaterials for implant materials and surfaces to avoid implant infections • Soft nanomaterials for bone regeneration, Rheumatoid Arthritis and Crohn's disease • Imaging of nanoparticles labelled white cells
<p>Needs in orthopaedics:</p> <ul style="list-style-type: none"> • Improved regeneration of bones with osteo-inductive, angiogenic and nerve-regenerative properties • Easy monitoring systems for assessment of bone and cartilage regeneration 	<ul style="list-style-type: none"> • Biospecific contrast agents for imaging coupled agent delivery for assessment of bone regeneration during treatments (ex.: delivery of combined materials with osteo-inductive, angiogenic and nerve-regenerative properties for osteoporosis, osteocarcinoma) • 3D printing & bioactive scaffolds (cells and biomaterials) to induce bone, joint and tissue regeneration • Smart prosthetics / Biomimetic cartilage implants disposing of a zonal structure and disposing of high stability and high water content

Table 7: Current medical needs and Nanomedicine solutions for Arthritis and Osteoarticular pathologies

2.2.7 Other diseases

In addition to the big “killers” or diseases with major impact on the European society identified in the previous sections exploiting the characteristics of materials at the nano-scale represent unique means to enable innovative solutions for clinical needs identified in other medical domains. The survey of the ETPN Clinical Interface working group in collaboration with EuroNanoMed II showed that further medical sectors such as gastroenterology, dermatology, gynaecology or urology could benefit from nano-based solutions, however with different intensity. We choose to select in the following table the nanotechnologies addressing the clinical needs in Gastroenterology and dermatology incl. wound healing for which advances nanomedicine are in the pipeline.

Rare diseases are a complex mix of pathologies affecting 30 million people in Europe. More than 6.000 different diseases exist, 80% of them are of genetic origin. Focusing in the mentioned genetic origin may lead to common therapeutic platforms for similar orphan diseases. Relatively common symptoms and absence of specific

diagnosis systems in many cases lead to misdiagnosis. The EC actively leads the International Rare Disease Research Consortium (IRDiRC) with the main objective to achieve two main goals by the year 2020, namely to deliver 200 new therapies for rare diseases and diagnostic tools for most rare diseases. Nanomedicine should be a key technology to contribute to these ambitious objectives. From the translational point of view, treatments for rare diseases will benefit from the consideration of being an orphan drug, with an easier and less costly access to clinical testing, paving the way for other nanomedicines adoption.

Current medical needs	Added-value of Nanotechnologies / solutions offered by Nanomedicine
<p>Needs in Gastroenterology:</p> <ul style="list-style-type: none"> • Reliable and minimally-invasive diagnostic tools for large-scale screening • Efficient treatment for inflammatory bowel disease • Liver regeneration, pancreas regeneration 	<ul style="list-style-type: none"> • Nanoformulations to cross intestinal barrier • Nanoparticles and nanoformulations for personalised and controlled drug release
<p>Needs in skin diseases and wound healing:</p> <ul style="list-style-type: none"> • Reliable and competitive tools for early screening and diagnosis • Non-invasive treatment of melanoma and non-melanoma cancers • Regeneration of skin, grafts (auto, allo, xeno) for management of chronic wounds and ulcers induced by ageing, vascular disorders, rare diseases, etc. 	<ul style="list-style-type: none"> • Carbone derivatives nanostructure (Fullerene, Nanotube, Nano-shell, Efficacy improvement of API; Toxicity reduction of API) • 3D-tissue printing of materials and living cells on a micro- and nanoscale to enable printing of complex functional tissue on a large scale • Inorganic/organic nano-carriers for loading with photosensitizers for Photodynamic Therapies (PDT) • Highly hydrophilic polymer coated medical implants to improve biocompatibility, lubrication, or reduce the wear in prosthesis • Lipid nanoparticles for vehiculation of biological molecules for wound healing
<p>Needs in rare diseases:</p> <ul style="list-style-type: none"> • Improved diagnostic systems to overcome misdiagnosis of rare diseases • New, more efficient and less costly drugs for treatment of rare diseases to alleviate diseases symptoms • Development of advanced therapies for correction of genetic defects to get a potential cure for genetic related rare diseases 	<ul style="list-style-type: none"> • Nanotechnology enabled diagnostic systems for more accurate ex vivo detection methods (i.e. mutation screening) • Identification and use of novel biomarkers in integrated screening systems for genetic rare diseases • Nanotechnologies for improved formulation of small molecules for palliative care of symptoms or to regulate disease progression, to avoid rapid clearance, inactivation and/or to promote specific interactions with targeted organs/systems/cells • Nanoformulation of biologicals to protect the cargo against inactivation and to cross significant biological barriers. Enzymes and siRNA are promising biomolecules to be formulated for rare diseases • Novel biomaterials, scaffolds and nanoformulated promoters for cell therapy, to get faster and safer cell cultures and engineered tissues and to allow cell transplantation to the patient

Table 8: Current medical needs and Nanomedicine solutions for other diseases

2.3 Matching with other Emerging Technologies for Healthcare

So far nanotechnology has mainly impacted pharmaceutical applications, because it provides a large variety of carrier systems which help to deliver and target drugs with low solubility or high toxicity in an unprecedented way. To exploit the full potential of nanotechnologies for diagnostic or regenerative applications its special features need to be integrated with other enabling technologies. Based on current research, economic analyses of market trends and their contribution to solving societal challenges *Nanotechnologies (N-T)*, *Advanced Materials (AM)*, *Micro- and Nano-Electronics (MNE)*, *Photonics (PhT)*, *Industrial Biotechnology (I-B)*, *Advanced Manufacturing Systems (AMS)* have been identified as the EU's **Key Enabling Technologies (KETs)**. They are characterised as 'knowledge intensive technologies associated with high R&D intensity, rapid innovation cycles, high capital expenditure and highly skilled employment. They enable process, goods and service innovation throughout the economy and are of systemic relevance.

Whilst each of the KETs individually already has huge potential for innovation, their cross-fertilisation is particularly important as combinations of KETs offer even greater possibilities to foster innovation and create new markets. The concept of 'cross-cutting KETs' refers to the integration of different key enabling technologies in a way that creates value beyond the sum of the individual technologies. **'Cross-cutting KETs have therefore the potential to lead to unforeseen advances and new markets, and are important contributors to new technological components or products.'**

The integration of nanotechnology with other KETs is deemed to be of highest benefit to the following healthcare fields:

- Devices and systems for targeted diagnostics and personalised medicine
- More efficient and less invasive therapies
- Smart systems and robots for healthcare services

Table 9 lists the potential areas of industrial interest relevant for Cross-cutting KETs in the Health domain and more specifically in Nanomedicine (partially based on References: European Commission Key Enabling Technologies and Cross-cutting Key Enabling Technologies, RO-cKETs, Roadmap for cross-cutting KETs activities in Horizon 2020, November 2014). It aims to help the Commission to identify the most promising areas of innovation for cross-cutting KETs that address clear industrial and market needs in a broad number of industrial sectors. The study focused on identifying potential innovation areas of industrial interest, implying Technology Readiness Levels of between 4 and 8.

The integration of nanotechnologies with other KETs into smart devices not only creates big challenges for the involved scientific R&D communities but also for the related industries, especially SMEs, which will mainly provide the multi-KETs innovations for the connected smart medical solutions. To assure that the new solutions meet medical standards scientific progress in emerging technologies needs to be matched in an **Open Science** approach with industrial strategies addressing clinical, patient and societal needs. Platforms such as ETPN will provide the necessary communication tools to enable the matchmaking of all stakeholders involved.

Legend for the KETs table on next page:

Nanotechnologies	N-T	Photonics	PhT
Advanced Materials	AM	Industrial Biotechnology	I-B
Micro- and Nano-Electronics	MNE	Advanced Manufacturing Systems	AMS

Potential areas for cross-cutting KETs	Specific technical/industrial challenges (mainly resulting from gaps in technological capacities):	KETs involved
Targeted molecular imaging diagnostics and/or focused therapy	<ul style="list-style-type: none"> - Development of targeted molecular imaging techniques - Development of new and innovative tracers or contrast agents for in vivo (imaging) diagnostics - Improvement of tracers or agents efficiency of targeting - Improvement of tracers or agents biocompatibility 	AMS, AM, PhT, MNE, N-T , I-B
Minimally-/non-invasive devices for diagnostics and/or focused therapy	<ul style="list-style-type: none"> - Miniaturisation for lower invasiveness - Surface functionalisation and "biologicalisation" of instruments to increase biocompatibility 	AMS, AM, PhT, MNE, N-T , I-B to a lower extend
Technologies to identify and validate biomarkers for diagnosis and predictive personalised medicine	<ul style="list-style-type: none"> - Identification of new diagnostic markers specific to diseases 	AM, N-T , I-B, AMS, MNE, PhT
Portable Point-of-Care devices and test kits for instant diagnosis based on microfluidics, biosensors and/or arrays	<ul style="list-style-type: none"> - Substitution of analytical labs by point-of-care in vitro diagnostic tests 	AMS, AM, PhT, MNE, N-T , I-B
Multiplexing devices for in vitro diagnostics	<ul style="list-style-type: none"> - Design and development of integrated multifunctional devices with a broad range of applications for improving in vitro diagnostics - Development of reliable, cheap, fast and multiplexed highly sensitive detectors providing high content results from a single sample - Identification of new diagnostic markers specific to diseases 	AMS, AM, PhT, MNE, N-T , I-B
Implantable devices for medicine	<ul style="list-style-type: none"> - Miniaturisation for lower invasiveness - Surface functionalisation and 'biologicalisation' of instruments to increase biocompatibility - Delivery of macro (bio) molecules - Development of nano- or micro-scale devices for drug delivery (e.g. micropumps) 	AMS, AM, MNE, N-T
Improved delivery systems, surface coatings and coating techniques for drugs	<ul style="list-style-type: none"> - Improvement of conventionally fabricated tablets by new delivery systems as well as surface coatings and coating techniques achieved through optimised formulation research 	AMS, AM, N-T , I-B
Bioengineered tissues (including organs) for regenerative therapies (and for autologous transplantation in case of organs)	<ul style="list-style-type: none"> - Development of novel cell culture techniques - Development of targeted drugs to trigger and control stem cell differentiation - Use of biomaterials as carriers for ligands stimulating cell membrane receptors and on controlled release of bioactive compounds - Chemical modification of existing biomaterials to obtain new generation of healing dressings - Chemical modification of existing biomaterials to obtain scaffolds for in-vitro cell culture or tissue engineering - Validation of product manufacturing processes in regenerative medicine, including scale-up and manufacturing (process optimisation) - Proof of long term efficacy and safety in regenerative medicine 	AMS, AM, N-T , I-B
Functionalised and connected surgical tools	<ul style="list-style-type: none"> - Real time tissue analysis and feedback to surgeon - Precise 3D-positioning and force feedback - Combination within vivo imaging techniques - Robots for (automated) precision surgery - Micro-robots for minimal invasive surgery - Decision-support system to help surgeons during interventions 	AM, MNE, N-T

Table 9: Potential areas of industrial interest relevant for Cross-cutting KETs in the Health domain

2.4 Implementation

Improving collaborative structures for stakeholders

The White Paper published by ETPN in 2013 has already highlighted the need for improving translation of nanomedical R&D into innovative medical products. As a result, the EU-Nano-Characterisation Lab, 3 pilot lines for GMP manufacturing of Nanomedicine and the constitution of a Translation Advisory Board in the framework of the ENATRANS Coordination and Support Action have been launched. However, further efforts and structures need to be established, because healthcare is a highly regulated area where many stakeholders are involved in the value chain from research to product.

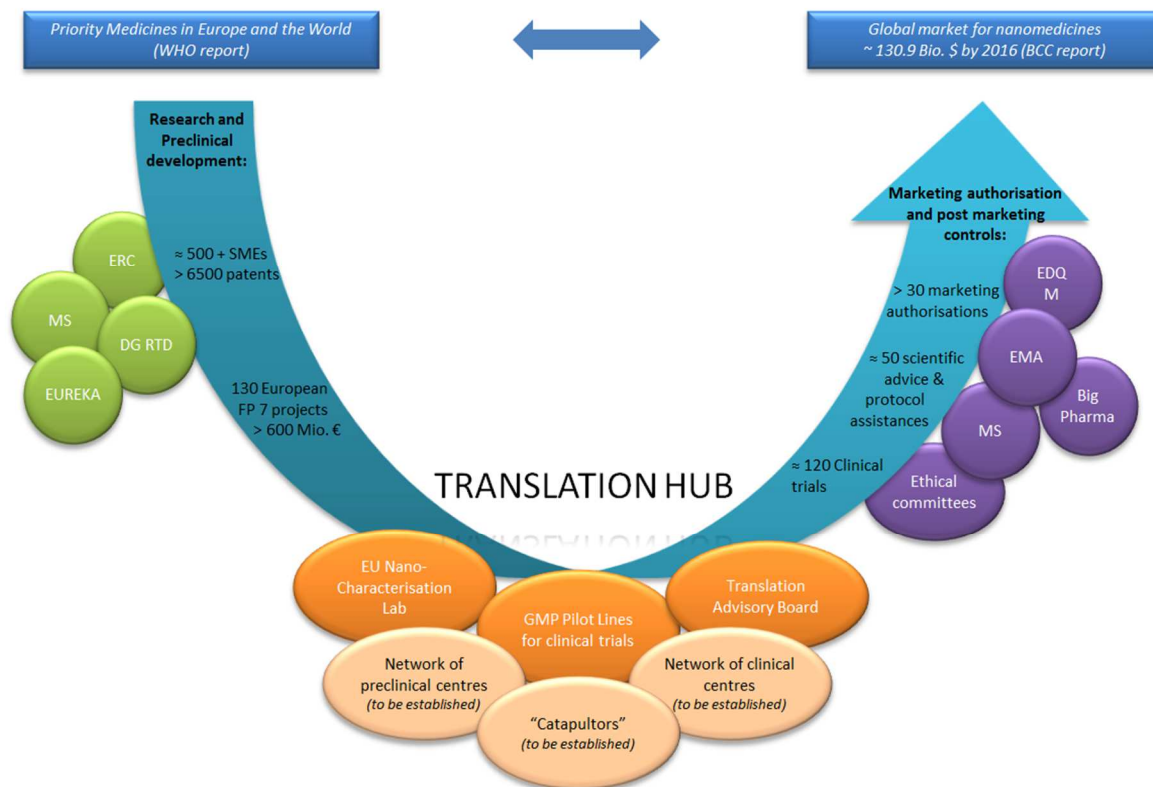


Figure 6: Translation Hub to create junctions between medicine, technologies, markets and the ecosystem¹²

To improve and accelerate translation of early research results into marketable products ready for clinical use it is necessary to:

- further set up effective communication and collaboration structures involving researchers, SMEs, industry, clinicians and regulators to align scientific progress and emerging technologies with industrial strategies addressing societal and medical needs,
- efficiently support the most promising projects and results by providing them with ongoing financial support and advice at all stages through showcasing them to large industry and investors,
- enable cost effective access to appropriate research infrastructures, technical services, regulatory support and especially certified clinical study centres to move more quickly all along the translation process.

¹² Source: Bremer-Hoffmann et al. Eur. J. Nanomed 2015; 7(3):191-202

A new innovative approach to increase the maturity of R&D projects for translation is the “**Catapultor**” concept. The aim is to prepare start-ups for investors by elaborating a comprehensive business development plan with in-depth information about market and clinical requirements, regulation and reimbursement standards, and timely financial and management plans. In addition, new topics such as the increasing demands to investigate the ecotoxicology and the quantitative and qualitative assessment of long-term impact of new nanomedicines have to be considered to address concerns that may hamper the adoption from the general public and to facilitate their contribution to the healthcare systems of the future. Such a business plan will increase the chances to attract investors and the success rate significantly.

The overall goal is to enable research groups and SMEs to develop their projects to a Technology Readiness Level (TRL) where global healthcare providers are able to take the lead to deliver the product to patient and market. To achieve a smooth transfer, industry needs to participate and monitor progress of the projects applying industrial standards at all levels of the value chain from proof of concept and building of a prototype through completing regulatory toxicity testing up to obtaining authorisation for clinical trials.

Leveraging public and private investments

Healthcare products are highly regulated, their research and innovation development periods are lengthy and production processes include complex assembly methods which often reflect an extremely high financial risk. In addition, life cycles of products in Medtech are very different from Pharma because they are much shorter, of about 2-3 years vs 10-12 years in Pharma. Considering this and both current and potential financial constraints, both in the public and private spheres, it is essential to **mobilise and ensure synergies between different public funding sources** coming from Horizon 2020, the European Research and Structural Investment Funds, along with national and regional funding programs of individual Member and Associated States. In particular, ongoing activities in many different regions of Europe reflect an enormous financial commitment from both public and private stakeholders that offer great potential for future economic growth and development, when properly interfaced with one other.

Industry should leverage these public and private commitments with cash and/or in-kind contributions and corporate investments to generate and manage a critical mass of R&I investments to fill their pipeline with KETs based medical applications. **Agreed key performance indicators** have to assess and monitor progress and investments along the value chain. This makes the case for a partnership built on corporate **Responsible Research and Innovation** (RRI) and trust among all stakeholders. A greater transparency of the research and translation process of Nanomedicine-based medicines and treatments will ensue, while at the same time rewarding innovation and generating enhanced industrial competitiveness.

Enabling socio economic benefit

New technologies such as Nanotechnology can generate scepticism among the public perception as their nature can be seen as complex and difficult to explain. A fair and balanced judgment can therefore be a daunting exercise which can lead to their rejection despite bringing new benefits.

In addition, Europe is faced with a renewed challenge to create jobs, stimulate industrial growth and generate economic welfare. To withstand these challenges, the **social and economic environment** needs to support innovation so as to maintain and improve a significant share of the global market which generates the required **revenue** to develop new products. **Key factors** to keep this economic cycle running between top class research and large industries are an up-to-date educated and trained workforce, applied research institutions and SMEs, and patients who will need new medical treatments. Communication interfaces such as the ETPN, national platforms or hands-on formats such as a translation advisory board need to be extended, whereby:

- SMEs can obtain the necessary advice, guidance and feedback from users for further product development from the wider healthcare industry and from clinicians,
- the healthcare industry can obtain rapid access to a highly skilled workforce,

- patients can receive open, objective and unbiased information regarding the benefits and possible risks of new nano, biomaterial and ICT based medical interventions,
- different stakeholders can co-ordinate their communication activities so as to foster an integrated approach regarding benefits and risks of new technologies. This can increase investments and improve private and public acceptance of their products,
- researchers are informed about industrial, regulatory and clinical requirements.

These activities will establish an appropriate socioeconomic environment which will:

- **accelerate the translation** process and market introduction of nanomedical products by opening up bottlenecks along the value chain,
- **optimise financing** by providing better access to public and private investment sources,
- **create sustainable growth and jobs** in the European Union by supporting the creation and maintenance of SME-based supply chains,
- **address health, demographic change and wellbeing** challenges faced by European citizens with innovative and safe medications.

This will support and boost the development and deployment of advanced nanotechnology-based diagnostic and therapeutic interventions. The result will be a **breakthrough in delivering better healthcare solutions** at the bedside.

3 Impact

3.1 Healthcare and patient's quality of life

Nanomedicine has the potential to improve incrementally existing medical solutions in reformulating for instance well-proven drugs for a better targeting or solubility, with a positive, but probably moderated impact on existing medical treatments or routines. But working on a multidisciplinary basis at the nanoscale also opens up radically new opportunities to target the biological origins of diseases leading to a disruptive approach in healthcare applications. The corresponding impact on both the patients and the economy will be further augmented by the use of combinational products integrating multiple Key Enabling Technologies and tailored to respond to current trends in medicine, the 4P medicine:

- **Predictive:** early diagnostics based on genome analysis or biomarkers give patients more chances to search for options to prevent onset of disease and thereby avoiding cost-intensive medical interventions;
- **Preventive:** a deeper knowledge and understanding of human – but also bacteriological and viral - biological mechanisms allow to start a therapy or change a lifestyle before the occurrence of pathologies, notably by using nano-vaccines;
- **Personalised:** each disease of a patient is a unique case which has to be specifically identified, treated and followed up. A personalised approach avoids side effect and increases efficacy;
- **Participatory:** the increasing use of precision medicine based on genomic data, sophisticated biomarkers and lifestyle information increasingly involves the patient in the decisions to be taken and encourages the dialogue with healthcare professionals rather than a “hierarchical” relation.

Based on these trends and the underlying “big data” management paired with connected technologies in smart devices more efficient and thereby shorter durations of therapy can be deployed. In addition, the chance to cure chronic diseases such as diabetes based on the emergence of **smart nano-engineered biomaterials**, which offers unprecedented possibilities in terms of **self-healing** or replacement of damaged organs in patients will have a major impact, because it would at best alleviate if not remove heavy and long term burdens on patients and healthcare systems. Therefore, one anticipated socio-economic impact in the context of healthcare is the ability to provide new innovative healthcare interventions at an affordable price so as to sustain a high level of health and well-being in the population. This progress will therefore not only benefit patients, but will also alleviate the pressure on healthcare systems resulting from demographic change.

3.2 Establish a better European biomedical “ecosystem”

The global Nanomedicine and biomaterials markets are expected to grow rapidly by about 12.5% per year up to the year 2020, reaching 130.9 Bio. € in 2016 for Nanomedicines and over 100 Bio. € for biomaterials (ref. Bionest Nanomedicine report 2014). To capture the benefit of this growth and to generate and maintain employment, Europe has to face off strong competition from the U.S. and new emerging centres in Asia. By installing professional translation structures which are ready for large industry to connect to and support future product development with reduced investment outlays, Europe will be able to cope with this global competitive pressure. In addition, by providing and managing education and training for research groups and SMEs about translation issues, **a robust SME-based technology supply chain** will be set up that will be ready to feed into the product pipelines of the wider healthcare industry. This will not only generate employment opportunities in SMEs, but will also **attract or even relocate production capacities** of large biomedical companies currently located outside Europe in Asia or even the U.S., because global industries are moving and establishing their activities in the best ecosystem available. Europe can thus become a world leader with a strong competitive edge in creating jobs and generating economic wealth in these highly promising biomedical areas.

3.3 Improved linkages among and to EU authorities and policies

An interface with European and national regulators and standard-setting bodies is crucial for transforming nanotechnology and biomaterial based innovation into future healthcare products. A good example is the EU-Nano-Characterisation-Laboratory (EU-NCL) which started in May 2015. The participation of the U.S. counterpart (US-NCL) in this four year project offers the chance to establish pre-clinical assays on both sites of the Atlantic accepted by both EMA and FDA. Another promising development is the regular meetings of international regulators at the annual CLINAM conference. The mutual sessions do not only foster the communication among the regulators but also offer the opportunity to discuss regulatory issues raised by researchers and companies with the representatives of the agencies. The aim will be to further intensify communication with and among the national agencies to facilitate the harmonisation of regulatory and industrial standards not only at European but also at global prospect. This will open new possibilities for companies to bring products to new global markets and expand their market expectations.

4 Long term vision

Driven by the convergence of Key Enabling Technologies (KETs), the healthcare industries - namely Pharma, Medtech, IVD, Biotech and Digital Medicine - will undergo a **profound transition** in the coming years towards a more collaborative approach. For example, Biotech will deliver better characterised and validated biomarkers which will be utilised by Medtech/IVD to develop new smart diagnostic devices and companion tests used to guide targeted therapeutics produced by Pharma. In addition, IT and digital technologies will increasingly connect all healthcare sectors and technologies. The Big Data approach to merge for example IVD and imaging data of patients with their personal daily body sensor data (e. g. fitness or Quantified-Self trackers) transmitted via internet will revolutionise personalised diagnosis and therapy monitoring. The marriage of multi-KETs smart medical devices with the Digital Single Market will create **new industrial platforms for healthcare**, and Nanomedicine will play an important part in this transition due to the fundamental importance of the nano scale features of drug carrier, medical devices and (bio)materials for regenerative medicine.

The most important future challenges for setting up the new industrial healthcare platforms are:

- to **interface multibillion industries** towards new value chains,
- to **improve manufacturing** of complex smart medical solutions,
- to **accelerate adaptation of the regulatory systems** to the speed of cross-KETs developments towards a “fast but safe track” to innovation,
- to develop **new business models for healthcare providers** adapted to the new precision medicine trends,
- to **embrace doctors, patients and society** in the implementation of new cross-KETs medical options to gain acceptance of these stakeholders.

The ETPN together with the EU Commission, industry associations such as MedTech Europe and EFPIA, and other stakeholders representing SMEs, regions and regulators has worked out a concept on “**Emerging and Strategic Technologies for Healthcare**” (ESTHER) to make Europe the leading place to invent, develop, manufacture and implement smart and cost effective healthcare solutions. The ETPN will continue to be one of the driving forces behind the implementation of this concept for the benefit of European patients and healthcare systems.

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5.1 Authors

- Klaus-Michael Weltring, Member of the ETPN Nanomedicine Executive Board, Bioanalytik Münster e.V., Germany
- Nicolas Gouze, ETPN Secretariat, VDI/VDE Innovation + Technik GmbH, Germany
- Natalia Martin, of the EuroNanoMed II Coordinator, Agence Nationale de la Recherche, France
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5.2 Contributors

ETP Nanomedicine, www.etp-nanomedicine.eu

Created in 2005, the European Technology Platform on Nanomedicine is an initiative led by Industry and set up together with the European Commission to address the applications of nanotechnology to achieve breakthroughs in healthcare. The ETPN is structuring and federating the European Nanomedicine community and leading the communication toward the European Commission and the European Members States.

ETP Nanomedicine Chairs:

- Patrick Boisseau, ETPN Chairman, CEA Leti, France
- Laurent Levy, ETPN Vice-Chairman, Nanobiotix, France
- Didier Letourneur, ETPN General Secretary, INSERM, France
- Philippe Mauberna, ETPN Treasurer, Nanobiotix, France

Chairs and Members of the ETPN Working Groups

- Working Group Nano-Enabled Medical Devices
- Working Group Nano-Enabled Imaging
- Working Group Nano-Therapeutics and Targeted Delivery
- Working Group Nanotechnologies for Regenerative Medicine
- Working Group Business Opportunities
- Working Group Clinical Interface
- Working Group Education and Training
- Working Group Toxicology and Characterisation
- Advisory Group Ethics and Social Impact of Nanomedicine, Public Awareness

EuroNanomed ERA-Net, www.euronanomed.net

EuroNanoMed II is an ERA-NET comprising 20 partners from 17 countries/regions that has been granted for funding through the European Commission's 7th Framework Programme. It will run from November 2012 to October 2016.

The ERA-NET serves as a platform for funding agencies and ministries, to develop joint activities and programmes in order to coordinate high quality research across national borders.

EuroNanoMed II builds on the achievements of its predecessor, the EuroNanoMed ERA-NET, which was funded by the European Commission from 2009 to 2011. Through 3 joint calls for proposals, EuroNanoMed granted 24 transnational research projects on Nanomedicine with a total funding of 25 Mio. € from its partner organisations and an additional 21 Mio. € from the participating project partners.

The aim of EuroNanoMed II is to continue fostering the competitiveness of European Nanomedicine actors through the support of transnational collaborative and multidisciplinary research and technology development projects with participants ranging from academia, clinical/public health communities, and industry (particularly small and medium-sized enterprises). Among the most important activities of EuroNanoMed II are annually launched joint transnational calls for proposals for research groups operating in the EuroNanoMed II partner countries.

ESTHER Task Force

The ESTHER (Emerging Strategic Technologies for Healthcare) Task Force has been set up by the European Commission at the end of 2014 with the aim to produce a comprehensive concept for an Industry-Driven Initiative to support the translation of innovative Key Enabling Technologies with applications in the medical sector. The fundament for the work done within the ESTHER Task Force being the Translation Hub as defined by the ETPN in its White Paper published in 2013, the ETPN Chairman, Mr. Patrick Boisseau, has been appointed by the EC as coordinator of this Task Force, composed of:

- Patrick BOISSEAU, Coordinator, CEA, France
- Serge BERNASCONI, MedTech Europe, Belgium
- Françoise CHARBIT, CEA, France
- Klaus-Michael WELTRING, Bioanalytik-muenster, Germany
- Paul GALVIN, Tyndall National Institute, Ireland
- Martina GLIBER, Institut Mérieux, France
- Christos TOKAMANIS, European Commission
- Heico FRIMA, European Commission
- Maj-Inger NILSSON, European Commission
- Fergal DONNELLY, European Commission
- Andreas LYMBERIS, European Commission
- Bernd REINER, European Commission

5.3 SRIA dissemination

The dissemination of the SRIA is supported by the European project ENATRANS (www.enatrans.eu) as part of its mission to raise awareness about innovation in Nanomedicine.

ENATRANS is led by a consortium of 7 partners belonging to the European Technology Platform for Nanomedicine (ETPN). It has been built to help the translation of innovative projects related to Nanomedicine to successfully go through the different stages of development from the idea to the patients and also improve global knowledge on Nanomedicine.

The key corner stone of ENATRANS is the Translation Advisory Board (TAB) a new instrument to provide free of charge advice and support to ambitious European Nanomedicine projects. First-in-class recognized experts from industry deliver concrete and invaluable advice to drive selected Nanomedicine projects into innovative products for healthcare.

ENATRANS partners: CEA-LETI (Grenoble, France), Nanobiotix SA (Paris, France), Gesellschaft für Bioanalytik Muenster e.V. (Muenster, Germany), Tel-Aviv University (Tel-Aviv, Israel), Fondazione Don Carlo Gnocchi ONLUS (Milan, Italy), TecMinho (Braga, Portugal) and coordinated by VDI/VDE-IT (Berlin, Germany).

Figures

Figure 1: Strategic documents published by the ETPN in last decade	7
Figure 2: Distribution of nanomedicine-related projects in 1 st year of Horizon 2020 (2014)	8
Figure 3: Pipeline of nanomedical products in Clinical stages	10
Figure 4: Pipeline of nanomedical products along medical specialties	10
Figure 5: Screenshot of the European Nanomed Map	11
Figure 6: Translation Hub to create junctions between medicine, technologies, markets and the ecosystem	23

Tables

Table 1: Current applications of Nanotechnologies in Medicine	9
Table 2: Current medical needs and Nanomedicine solutions for Atherosclerosis and cardio-vascular diseases	14
Table 3: Current medical needs and Nanomedicine solutions for Cancer	16
Table 4: Current medical needs and Nanomedicine solutions for Neuro-degenerative and other neurological disorders	17
Table 5: Current medical needs and Nanomedicine solutions for Infectious diseases	17
Table 6: Current medical needs and Nanomedicine solutions for Diabetes and Endocrine disorders	18
Table 7: Current medical needs and Nanomedicine solutions for Arthritis and Osteoarticular pathologies	19
Table 8: Current medical needs and Nanomedicine solutions for other diseases	20
Table 9: Potential areas of industrial interest relevant for Cross-cutting KETs in the Health domain	22

