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DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A
ECONOMIC AND SCIENTIFIC POLICY

Economic and Monetary Affairs

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Advanced Therapy Medicinal Products

WORKSHOP

EN

2013

Advanced Therapy Medicinal Products

EUROPEAN PARLIAMENT

DIRECTORATE GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

WORKSHOP

Advanced Therapy Medicinal Products

Brussels, 20 February, 2013

PROCEEDINGS

Abstract

This report summarises the presentations and discussions at the Workshop on "Advanced Therapy Medicinal Products", held at the European Parliament in Brussels, on Wednesday 20 February 2013. The aim of the workshop was to exchange views on the opportunities and challenges related to advanced therapies for the future of healthcare. The workshop was hosted by MEP Ms Glenis WILLMOTT (S&D, UK) and MEP Mr Alojz PETERLE (EPP, SL), Co-chairs of the Health Working Group within the ENVI Committee.

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LIST OF ABBREVIATIONS

ATHP	Advanced Therapy Hospital Procedures
ATMPs	Advanced Therapy Medicinal Products
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
DG SANCO	Directorate General for Health and Consumers
DNA	Deoxyribonucleic acid
EC	European Commission
EMA	European Medicines Agency
ENVI	Committee on Environment, Public Health and Food Safety
EP	European Parliament
EU	European Union
GBM	Glioblastoma Multiforme
GDP	Gross Domestic Product
GMP	Good Medical Practice
GTP	Good Tissue Practice
HTA	Health Technology Assessment
MEAs	Managed Entry Agreements
MEP	Member of the European Parliament
PDCO	Paediatric Committee
SME	Small and Medium-sized Enterprise

EXECUTIVE SUMMARY

On 20 February 2013, the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament held a workshop on "Advanced Therapy Medicinal Products". The workshop was hosted by Ms Glenis WILLMOTT (MEP) and Mr Alojz PETERLE (MEP), Co-chairs of the Health Working Group within the ENVI Committee.

In his opening statement, Mr Peterle highlighted that the field of Advanced Therapy Medicinal Products (ATMPs) is developing at a fast pace and is offering growing hope for patients and society as a whole. Introducing the aims of the workshop, Mr Peterle stated that the focus of the discussion would be on the challenges and opportunities of advanced therapy treatment and on technology transfer from research to the market. In addition, Ms Willmott emphasised that personalised medicine is the future of healthcare, and therefore is an area deserving particular attention by regulators.

Ms Sabine JÜLICHER, Head of Unit (Medicinal Products - authorisations, EMA) at DG Health and Consumers then introduced the position of the European Commission on the regulatory framework for ATMPs. Explaining the main provisions of the Regulation on advanced therapies (Regulation (EC) No 1394/2007), Ms Jülicher emphasised the role of incentives, which aim to avoid hindering product development with disproportionate fees as well as to facilitate access to scientific advice and classification of ATMP marketing authorisation applications, especially for Small and Medium-sized Enterprises (SMEs). She also stressed that a public consultation is ongoing to collect stakeholders' views on the current regulatory framework, which will feed, together with the information provided by the European Medicines Agency (EMA), into an upcoming report by the Commission on the application of the Regulation.

The first part of the workshop provided an overview of the opportunities and challenges of advanced therapy treatment for the future of healthcare. Prof. Stefaan VAN GOOL, Head of the Laboratory of Paediatric Immunology at the University of Leuven, started his presentation by explaining the potential of cell therapy in the treatment of certain cancers, in particular malignant glioma. He then highlighted the role of academic hospitals in the development of innovative treatments based on immunotherapy, which are increasing the survival rates of patients. However, in his view, the current regulatory framework, including the hospital exemption foreseen in the Regulation, is not adequately supporting the possibilities for medical progression and the accessibility to innovative cures in Europe. Adapted rules should be foreseen for what he defined as "Advanced Therapy Hospital Procedures", taking into account today's clinical reality of a high personalisation of treatment, and the specific role played by academic hospitals in this specialised niche of medical development.

After that, Dr Jacques MALLET, Director of "Recherche Emérite" CNRS at the Institute for Brain and Spinal Cord (ICM), Adjunct Professor at the University of California at San Francisco (UCSF) and Member of the French Academy of Sciences, focussed on gene therapy, which involves the alteration of gene expression in order to prevent, halt or reverse a pathological process. Despite several challenges, related for example to premature clinical trials or the lack of systematic studies on an industrial scale, gene therapy has already proven to be successful in the treatment of certain diseases, including congenital blindness, leukaemia, Parkinson's and psychiatric problems. In his final remarks, Dr Mallet also explained the importance of using physiologically relevant animal models, such as pigs, for the further development of gene therapy.

Dr Monica ENSINI, Scientific Director of the European Organisation for Rare Diseases (EURORDIS), concluded the first part of the workshop by introducing the point of view of patients. Patients, in particular those affected by rare diseases, are very much aware of the opportunities offered by ATMPs and are directly involved in the medicinal products life-cycle, from basic research and clinical trials to regulatory centralised procedures and access to treatment. By participating in the various EMA Committees, patients provide the views and real life experience of those who are directly affected by regulatory decisions. Hence, Dr Ensini called for the nomination of a patient representative also on the EMA Committee on Advanced Therapies (CAT). She then concluded her presentation by highlighting patients' priorities for the development of ATMPs, namely the need to promote an early dialogue between regulators and industry, to provide specific financial support, to adapt regulatory procedures to the fast progress of science and, ultimately, to facilitate access to effective and affordable ATMPs.

In the discussion that followed, Dr Christian K. SCHNEIDER, Chair of the EMA Committee for Advanced Therapies, highlighted the significant potential of advanced therapies, with many ATMPs currently in the research and development pipeline and a high number of marketing-authorisation applications expected in the next years. He also stressed the challenges for the CAT not to over-regulate these products, whilst at the same time ensuring their efficacy and safety.

The second part of the workshop focussed on technology transfer from research to the market. In his presentation, Dr Panos KANAVOS, Reader in International Health Policy at the London School of Economics, outlined the costs for making advanced therapies available to patients. Although evidence is still scarce, data from the United States indicate that the cost of innovation, e.g. the cost of bringing a new molecule onto the market, is very high. This innovation cost includes what Dr Kanavos referred to as the "dynamics of attrition", meaning that a large number of firms engaged in drug innovation have failed or have been acquired over the past fifty years. Also, the lengthy process for regulatory approval implies costs and can therefore represent a barrier to the entry of a product on the market. In his opinion, the regulatory process should therefore be streamlined. Synergies with Health Technology Assessment (HTA) should also be explored, which could help policy makers analyse the clinical and cost effectiveness of advanced therapies.

In the last presentation, Dr Maria Luisa NOLLI, founder and Chief Executive Officer of Areta International, highlighted the role of SMEs, which account for 99% of all companies in the field of advanced therapies. Starting from the experience of her small business, Dr Nolli explained that SMEs are ideally placed in the highly innovative field of ATMPs because of their flexible and creative approach, fast decision-making process and the possibility to benefit from public funding. Dr Nolli also highlighted that a new business model is emerging, from "one size fits all" drugs for the mass population to a more personalised and patient-specific approach. In this context, SMEs provide a bridge between basic research and industry and foster exchange and collaboration with hospitals, which are increasingly important for the clinical development of advanced therapies.

1. LEGAL AND POLICY BACKGROUND

Advanced therapy medicinal products (ATMPs) are novel medicinal treatments for human use based on genes, cells or tissues. Gene therapy, somatic cell therapy and tissue engineered medicinal products can provide treatment for various diseases, including cancer, muscular dystrophy, neurodegenerative diseases (e.g. Alzheimer's disease) and genetic disorders in general, as well as tissue or organ reparation after injuries or burns.

In particular, although the definition of gene therapy has become now quite broad, gene therapy works by inserting a "recombinant" gene (i.e. a stretch of DNA that is created in the laboratory) into cells, in order to replace a mutated gene. Somatic cell therapy medicines contain cells that have been manipulated to change their biological characteristics and subsequently introduced into a tissue in order to treat a disease. Finally, tissue-engineered medicines contain cells or tissues that have been modified so that they can be used to repair, regenerate or replace tissue[1].

This emerging field of biomedicine has enormous potential for patients and industry, with the main developers being Small/Medium-sized Enterprises (SMEs) or academic institutions and hospitals. However, some challenges also exist, including how to ensure that patients have access to safe and efficient products that meet well-defined scientific and technical requirements.

To address the complexity of this innovative and fast-expanding area, the EU adopted, in 2007, a specific Regulation on advanced therapies (Regulation (EC) No 1394/2007)[2]. The Regulation aims to establish a harmonised approach within the Community, in order to promote the free movement of ATMPs as well as the competitiveness of European companies in this field, while ensuring the highest level of health protection for patients. Although the main principles of quality, efficacy and safety apply as for other medicinal products, the Regulation acknowledges that a number of ATMPs actually lie at the border of traditional medicine as they combine biological materials, such as tissues or cells, and chemical structures, such as metal implants. Therefore, the Regulation introduces some specific technical requirements adapted to the particular characteristics of ATMPs.

In addition, the Regulation establishes a centralised procedure for marketing authorisation. A key role in this regulatory framework is played by the Committee for Advanced Therapies (CAT) within the European Medicines Agency (EMA)[3]. In particular, with its multidisciplinary scientific expertise, the CAT is in charge of assessing requests for authorisation of ATMPs and of delivering scientific recommendations on ATMP classification. The marketing authorisation procedure is mandatory for all ATMPs and is managed by the Agency in consultation with the European Commission, which takes the final decision on granting or refusing a marketing authorisation.

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1 European Medicines Agency (EMA) website: http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000504.jsp&mid=WC0b01ac058050f347 .

2 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), OJ L 324, 10.12.2007, p. 121–137.

3 See CAT page on EMA website: http://www.emea.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&mid=WC0b01ac05800292a4

Recognising the important role played by hospitals in this framework, the Regulation includes a limited possibility for derogation to the centralised procedure through the so-called "hospital exemption", which can be applied in case products are prepared and used on a non-routine basis by a medical practitioner in a hospital[4]. In this case, products are not regulated at the EU level, but authorised by competent authorities in Member States.

With the aim of promoting the competitiveness of SMEs in ATMP research and development, the Regulation also provides special incentives for small businesses, for example in the form of fee reductions for scientific advice and for marketing authorisation. In addition, specific rules exist to address the evaluation and certification of quality and non-clinical data developed by SMEs[5].

The application of the Regulation on advanced therapies is currently under review by the European Commission. A public consultation has been launched, and will be open until 31 March 2013, to collect stakeholders' views on this matter[6]. The results of the consultation, as well as information collected from the EMA and other sources, will feed into a report by the Commission, which will be published in mid-2013.

[4] Art 28.2 of Regulation (EC) No 1394/2007.

[5] Commission Regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises (Text with EEA relevance), OJ L 194, 25.7.2009, p. 7–10.

[6] See public consultation paper on the Regulation on Advanced Therapy Medicinal Products: http://www.ec.europa.eu/health/files/advtherapies/2012_12_12__public_consultation.pdf.

2. PROCEEDINGS OF THE WORKSHOP

2.1 Introduction

2.1.1 Welcome and opening – Alojz PETERLE (MEP) and Glenis WILLMOTT (MEP)

Mr Alojz PETERLE, Member of the Environment, Public Health and Food Safety (ENVI) Committee and Co-chair of the Health Working Group, welcomed the attendees and the speakers to the workshop. In his introduction, he highlighted that the field of Advanced Therapy Medicinal Products (ATMPs) is developing at a fast pace and is offering growing hope for patients and society as a whole. Therefore, in his view, this is an area deserving particular attention by regulators.

Mr Peterle reminded the audience of the aims of the workshop, stating that the focus of the discussion would be on the challenges and opportunities of advanced therapy treatment and on technology transfer from research to the market. He then introduced the co-chair, Ms Glenis WILLMOTT, who emphasised that personalised medicine is a promising field and is the future of healthcare. She mentioned that legislation on ATMPs is already in place at the European level, and that the first speaker from the European Commission would provide an overview of the current regulatory framework.

2.1.2 The current position of the European Commission. Incentives for advanced therapy medicinal product development in Europe, Ms. Sabine JÜLICHER (EC)

Ms. Sabine JÜLICHER, Head of Unit Medicinal Products- authorisations, EMA. DG SANCO, EC

Introducing her presentation, Ms Jülicher stated that she would provide an overview of the current legislation on ATMPs, as well as an outlook for the future. She highlighted that the main legal text in this field is Regulation (EC) No 1394/2007[7], which came into force in 2008 and has been applied for four years.

In general, Ms Jülicher stressed that the same legislation as for the other medicinal products applies to ATMPs, in particular as regards the principles of quality, safety and efficacy. However, some elements are specific to ATMPs, including a centralised procedure for marketing authorisation and a specific procedure for the evaluation of such products. These procedures are managed by the Committee on Advanced Therapies (CAT) at the European Medicines Agency (EMA)[8]. Also, she explained that a "hospital exemption" is foreseen in the Regulation, providing hospitals and Member States with an opportunity (under narrow conditions) to authorise an advanced therapy without going through the mandatory centralised procedure at the European level.

[7] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), OJ L 324, 10.12.2007, p. 121–137.

[8] Committee of Advanced Therapies (CAT) website: http://www.emea.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&mid=WC0b01ac05800292a4.

Ms Jülicher then focussed on the incentives that are enshrined in legislation to facilitate progress and development in this area. First of all, incentives take the form of scientific advice provided by the EMA on the design and conduct of certain parts of pharmacovigilance and risk assessment. This is normally subject to costs, but reductions are foreseen for SMEs (90% reduction) and for other applicants (65% reduction), in order not to hinder development by disproportionate fees. Another incentive is the availability, free of charge, of an instrument for the classification of ATMPs, which provides applicants with scientific recommendation on regulatory classification.

Some incentives are specific to SMEs, in particular for the certification of quality and non-clinical data, which encourages an early dialogue between innovative industries and the EMA. Finally, Ms Jülicher mentioned a fee reduction for marketing authorisation, which was granted to SMEs and hospitals under condition of public health interest, but which has been phased out at the end of 2012.

In conclusion to her presentation, Ms Jülicher highlighted the next steps in the regulatory framework. The European Commission has recently launched a public consultation to collect stakeholders' views on the implementation of the current Regulation, which will run until the end of March. The results of the consultation, as well as the information collected from the EMA and other sources will feed into an upcoming report by the Commission on the application of the Regulation, which should be published by mid-2013.

2.2 Part I: Advanced Therapy Treatment: The Future for Healthcare

2.2.1 Cell therapy challenges, Prof. Stefaan Van Gool (BE)

Prof. Stefaan VAN GOOL, Head of the Laboratory of Pediatric Immunology, University of Louvain

Prof. Van Gool started his presentation by providing an overview of cancer incidence in Europe. He explained that, overall, cancer incidence is still increasing, in particular for certain types of cancers, such as melanoma and thyroid cancer. Even for childhood cancer the incidence is on the rise. However, Prof. Van Gool highlighted that children with cancer today have more chances to be cured than in the 50s and 60s. In adults, malignant glioma or glioblastoma multiforme (GBM), which is a type of brain tumour, is still causing the highest number of years of life lost in adults compared to all other cancers. This is in spite of advances in modern surgery, chemotherapy and radiotherapy.

Despite these alarming trends, Prof. Van Gool explained that it is in the area of malignant glioma that innovative treatment and ATMPs are being developed, particularly in the form of dendritic cell-based immunotherapy. In essence, cancer immunotherapy attempts to stimulate the immune system to reject and destroy tumours. Dendritic cells are harvested from a patient and matured in the laboratory. The matured cell is then injected back into the skin of the patient and moves to the lymph nod. Here, the immune cells are stimulated to circulate into the blood to fight the cancer cells. In this context, Prof. Van Gool also acknowledged the work on dendritic cells of Prof. Ralph Steinman, one of the recipients of the 2011 Nobel Prize in Medicine.

Prof. Van Gool went on to explain that research in immunotherapy has been translated into clinical practice and has helped improve the survival rate of patients affected by GBM. Immunotherapy has also been integrated within primary treatment, i.e. chemotherapy and radiotherapy. In this case too, survival rates have improved and patients have been gaining years of life. Thanks to these successes, more and more patients are being referred to the clinic in Leuven - from other Belgian hospitals and from abroad. Finally, Prof. Van Gool highlighted the fundamental role played by pre-clinical research, which feeds clinical work with the conduction of smaller clinical trials that are then applied as primary treatment to larger patient groups.

In the second part of his presentation, Prof. Van Gool focussed on the challenges of the current EU regulatory framework in the field of ATMPs. In particular, he invited the audience to re-read the definition of "hospital exemption", which means "preparation of ATMP on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient". In this respect, Prof. Van Gool highlighted the possible confusion with other EU regulations. If a product falls under the hospital exemption, he noted, it should also fall under Directive 2004/23/EC[9] and the Good Tissue Practice (GTP) framework, which allows clinical trial material. However, the hospital exemption implicitly excludes clinical trials. As regards clinical trials, investigation medicinal products should be regulated under the Good Medical Practice (GMP) framework, which, in his view, is also a problem. Finally, he noted that both hospital exemption and the GTP framework are regulated by Member States.

Despite being in favour of the hospital exemption, Prof. Van Gool emphasised that the "non-routine" basis should be omitted since there are niches where hospital exemption procedures could be used on a regular basis. He then explained what he meant by niches, i.e. patients with low incidence clinical situations who need a multidisciplinary and complex treatment in a highly specialised medical centre. In his opinion, a better definition for hospital exemption would be Advanced Therapy Hospital Procedures (ATHP). This definition would reflect the need to face the clinical reality of a high personalisation of treatment, as well as the need for specific rules, which are different from industry and pharmacy rules. ATHPs should not require marketing authorisations, but rather licences of activity under the control of Member States.

Another challenge that Prof. Van Gool highlighted in his presentation was that the increasing number of rules in the field of advanced therapies implies increasing costs, which in turn mean less translational research and less money for patient care. He warned that this would ultimately lead to reduced access to innovative treatment, fewer chances for cure and less medical progression in Europe.

[9] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells OJ L 102, 7.4.2004, p. 48–58.

In conclusion, Prof. Van Gool mentioned that patients are well aware of developments in the area of ATMPs, and that today's clinical reality of a high personalisation of treatment should be recognised by regulators. He said that fantastic medical progression is possible in Europe, and the specific role played by academic hospitals in translational medicine and development, as well as in conducting innovative treatment, should be acknowledged. In particular, there are niches for which only academic hospitals can develop and conduct innovative advanced therapies. Therefore, Prof. Van Gool highlighted that adapted rules for Advanced Therapy Hospital Procedures are urgently needed and that Europe should keep its current leading position in this field.

2.2.2 Gene therapy challenges, Dr Jacques Mallet (FR, US)

Dr Jacques MALLET, Director of "Recherche Emérite" CNRS, Institute for Brain and Spinal Cord (ICM), Paris; Adjunct Professor at the University of California at San Francisco (UCSF); Member of the French Academy of Sciences

Dr Mallet began his presentation by stating that the principle of gene therapy is quite straightforward: nucleic acids can be introduced to cells to modify gene expression in order to prevent, halt or reverse a given pathological process. This modification can take different forms: it could result in a gene addition to replace an altered, non-functional gene; there could be a gene correction or alteration; or a gene knockdown (also known as RNA interference).

He continued by pointing out that a major challenge in gene therapy is to successfully bring a gene to a given tissue or cell. For example, nucleic acid sequences delivered to circulatory systems or tissues are unable to enter cells and thus exert their function. To do so, nucleic acid sequences have to be introduced in vectors that play the role of Trojan horses. These vectors are, in most cases, derivatives of viruses. However, in these vectors the useless and detrimental sequences of viruses are replaced by therapeutic sequences.

Dr Mallet explained that gene therapy has greatly benefited from the impact of the human genome project. This has facilitated and revolutionised, for example, the identification of the diverse functions of nucleic acid sequences within the genome; the characterisation of genetic diseases, single gene and complex diseases (such as metabolic diseases and psychiatric disease); the diagnostics of many illnesses; and the biology of gene transfer.

Although there have been some significant advances in gene therapy, Dr Mallet explained that some gene therapy failures have also occurred. These have been seen, for example, in clinical trials that were launched prematurely or when the time needed to launch a clinical trial was too long leading to the use of vector versions that were not the most recent. Furthermore, the biology of vectors has not been explored until recently and there is a need for systematic studies at an industrial scale, e.g. to test serotypes, pseudotypes, promoters etc. Biosecurity has also been neglected. Therefore, more "basic" research is still needed in the areas of virology, molecular biology and chemistry, as well as a stronger involvement by industry.

Dr Mallet went on to explain that gene therapy is a multi-disciplinary domain, and its success relies on the optimisation of a multitude of parameters, including a therapeutic strategy (i.e. the choice of therapeutic gene depending on the physiopathology) and the choice of vector. It also depends on the optimisation of a number of factors: vectors in terms of efficacy and biosecurity; cell culture conditions for an ex vivo approach; the expression cassette (that is, the choice of promoter); and the delivery method. This multi-disciplinary nature of gene therapy needs actors in medicine, virology, vectorology and biotechnology.

Dr Mallet then highlighted three recent successes in the area of gene therapy: the work of Jean Bennett and Albert Maguire to reverse near blindness[10]; the work of Dr Carl June and colleagues to treat leukaemia with gene therapy[11]; and the first gene therapy to get EU backing: uniQure's Glybera to treat lipoprotein lipase deficiency[12].

Indeed, he continued, therapeutical gene transfer in the nervous system has enormous potential and a number of therapeutic factors for the nervous system have been identified. Gene therapy can provide prolonged production of such factors, and most importantly, local delivery and production to limit the risk of side effects. Numerous diseases, such as Parkinson's, Alzheimer's and even psychiatric diseases could therefore be treated by therapeutical gene transfer in the nervous system.

Dr Mallet then explained why gene therapy is now gaining ground. It has seen its first successes, and there have been advances in the discovery of potential therapeutic genes and in vectorology. Furthermore, numerous technologies of interest have been developed, and the demand has grown in some countries (for example, in China - the first country to commercialise gene therapy products and with the largest number of patients treated).

A major challenge, however, is the regulation of transgene expression or non-protein based regulation systems. The use of gene transfer as a therapeutic tool requires, in numerous instances, a regulatory system allowing control of the expression of the therapeutic gene. The treatment could then be adapted to the needs of the patients and, should complications arise, the therapy could be interrupted.

In conclusion, Dr Mallet highlighted the importance of relevant animal models to carry out experimentations in laboratories. In particular, he recommended the use of pigs as an alternative to monkeys or mice. He explained that pigs are recognised as excellent disease models in a variety of areas, including nutrition, toxicology, dermatology, diabetes, cancer, eye diseases, cardiovascular diseases, degenerative joint diseases and skeletal growth. It is particularly important to test preclinical genes and cell therapy protocols in animal models that mimic both human pathology and anatomy. In this context, the physical size of pigs is comparable to that of humans, and they are appropriate for the development of new surgical, endoscopic and delivery techniques.

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[10] Albert M. Maguire and Jean Bennett, Gene Therapy for Retinal Disease, F.M. Kirby Center for Molecular Ophthalmology. Available at : http://www.med.upenn.edu/timm/documents/Maguire.GeneTherapy.re3C2.pdf.

[11] June, C.H., Blazar, B.R., and Riley, J.L. 2009. Engineering lymphocyte subsets: tools, trials and tribulations. Nat Rev Immunol 9:704-716. For an abstract, see: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2898&sKey=12cf85b4-2673-4567-86a8-cb21a0e1f2f1&cKey=00df4880-4e2e-4bc1-80e7-4f66437a74c0&mKey=%7b2D8C569E-B72C-4E7D-AB3B-070BEC7EB280%7d.

[12] See: http://www.uniqure.com/news/167/182/uniQure-s-Glybera-First-Gene-Therapy-Approved-by-European-Commission.html.

2.2.3 The voice of patients, Dr Monica Ensini (EURORDIS)

Dr Monica ENSINI, Scientific Director, European Organisation for Rare Diseases

Dr Ensini began her presentation by describing EURORDIS[13], the European Organisation for Rare Diseases. EURORDIS is a non-governmental patient-driven alliance of organisations and individuals active in the field of rare diseases in Europe and beyond. Its mission is to build a strong pan-European community of patient organisations and people living with rare diseases; to be their voice at the European level; and to support them in facing the impact of rare diseases on their lives.

In particular, Dr Ensini mentioned that EURORDIS operates in different "fields of action", including advocacy as well as research and therapies, both of which are particularly relevant to this workshop. She then gave three examples of EURORDIS' advocacy activities in the development of EU legislation, in particular in relation to Regulation (EC) No 141/2000 on orphan medicinal products[14], Regulation (EC) No 1901/2006 on medicinal products for paediatric use[15]; and Regulation (EC) No 1394/2007 on advanced therapy medicinal products[16].

In recent decades, explained Dr Ensini, the involvement of patients in the medicinal products life-cycle has become more important and more necessary. In 2010, EURORDIS conducted a survey[17], which showed that rare disease patients are particularly involved in the areas of basic research, clinical trials and regulatory centralised procedures. In addition, patients' organisations provide two types of support to research, i.e. financial support, with around €100m per year donated in Europe, and non-financial support, which includes providing crucial support in clinical trials. Moreover, patients are very involved in the European Clinical Research Infrastructure Network[18] and the EU Clinical Trials Register[19].

Patients' organisations are also fully embedded in the regulatory procedures, in particular in the European Medicines Agency (EMA) Scientific Committees. For example, since 2000 they have had three members in the Committee for Orphan Medicinal Products (COMP), and since 2007 they have had three members and three alternate members in the Paediatric Committee (PDCO). Additionally, since 2009 they have had two members and two alternate members in the CAT. However, Dr Ensini noted that at the moment the patients' seat in the CAT was vacant and she advocated for the urgent appointment of a new patient representative.

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[13] http://www.eurordis.org/.
[14] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. OJ L 18, 22.1.2000, p. 1–5.
[15] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) OJ L 378, 27.12.2006, p. 1-19.
[16] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) OJ L 324, 10.12.2007, p. 121–137.
[17] See: http://www.rarediseaseday.org/article/eurordis-survey-rare-disease-patient-groups-in-research .
[18] http://www.ecrin.org/ .
[19] https://www.clinicaltrialsregister.eu/ .

Dr Ensini then explained the role of patients in the EMA Scientific Committees, where they have the same roles and responsibilities as Members nominated by National Agencies. However, patients provide alternative and/or complementary views in addition to technical approaches, in particular the views of those that will be directly affected by regulatory decisions. They also disseminate Committee knowledge to other patients and patients' organisations, and increase transparency and trust in regulatory processes, thus facilitating mutual respect between regulators and the community of patients.

The framework of advanced therapies in which patients operate is complex and challenging, continued Dr Ensini. This is due to the area being at the frontier of scientific and technological developments, with high levels of innovation involved. New methods, techniques and tools are needed to assess innovative approaches, and substantial financial and human investment is required. There is, however, market acceptance and penetration in these early days - against a backdrop of regulatory challenges, in particular for SMEs, but also for academia and charities.

Dr Ensini then spoke about patients' priorities for ATMP development. These include, in the first place, early dialogue between all stakeholders; training for academia and industry on procedures and quality requirements for ATMPs; and the promotion of increased financial support from the European Commission for specific projects focused on quality and pre-clinical development. This should be accompanied by conditional approval or "adaptive licensing", which would allow faster access to treatment.

In her concluding remarks, Dr Ensini highlighted the main challenges for ATMPs in the coming years. In particular, the regulatory procedures should be adapted to the fast progress of science. In addition, clear processes for quality assessment should be identified to minimise the risk of failures and boost innovation, and incentives should be provided not only for SMEs, but also for academia, hospitals and charities. Further challenges exist in the implementation of an adapted follow-up system for the assessment of product safety and efficacy, as well as in the promotion as early as possible of access to efficacious and affordable treatments.

2.2.4 First round of questions and answers

With the participation of Dr Christian K. SCHNEIDER (chair) and Dr. Patrick CELIS (scientific administrator), Committee for Advanced Therapies (CAT), European Medicine Agency (EMA, EU)

Ms WILLMOTT proposed to take questions at the end of the second part of the workshop. She then introduced Dr Christian SCHNEIDER and Dr Patrick CELIS from the Committee on Advanced Therapies (CAT) of the European Medicines Agency (EMA).

In his speech, Dr Schneider acknowledged the challenges and opportunities of advanced therapies as highlighted by the previous speakers. He also emphasised that, although only one gene and one cell-based product have been authorised so far, plenty of new products are being developed. In particular, over 380 clinical trials for ATMPs took place in Europe in the past six years. In his view, the legislator was therefore wise to set up the CAT before the materialisation of this "big wave" of new products.

Dr Schneider also expressed some caution on the issue of hospital exemption. Despite recognising the essential role of academic activity, he stressed that hospital exemption could create some problems. In particular, it may become hard to justify why certain products (e.g. tumour vaccines) can be hospital exempted at the national level, whereas similar products developed by small commercial companies are regulated under the EU framework. In this context, the intention of the CAT would be to regulate all ATMPs in the context of the EU legislation, whilst using a proportionate approach and recognising the specificities of these products to avoid over-regulation.

Prof. VAN GOOL took the floor to highlight that, although regulators are obliged to work within a given framework, it would be important to re-think some of the current rules and procedures and to adapt them to the fast developments in this area. He proposed to be innovative also with legislation, which should take into account what is emerging from reality and seize the enormous opportunities that exist in academia to translate research into practice. In his view, innovation at the level of legislation would ultimately result in better regulation and good clinical practice.

Dr Schneider then came back on the issue of hospital exemption to stress that, in his understanding, proof of efficacy and safety is not explicitly required in this case, which may create some risks. Therefore, the exemption should be carefully implemented at the national level so as not to create a kind of “marketing authorisation light” to bypass the EU framework.

Prof. Van Gool finally mentioned that the required evidence of medical efficacy should be adapted to the specific case of ATMPs. In the implementation phase, it is indeed important to keep control of the situation, but in a realistic way and taking into account patients’ expectations.

Dr MALLET concluded this exchange of views highlighting that, with reference to gene therapy, the proof of efficacy is easily demonstrated in the laboratory or hospital. However, one should not forget that the genes are pushed with vectors that are often not safe enough. Legislation should also take this into account and speed up the process of admitting new, safer vectors into clinical practice.

2.3 Part II: Technology Transfer: Bringing Healthcare to the Market

2.3.1 The costs for making advanced therapies available to patients, Dr Panos Kanavos (UK)

Dr Panos KANAVOS, Reader in International Health Policy in the Department of Social Policy, London School of Economics (LSE) and Programme Director of the Medical Technology Research Group (MTRG) at LSE Health

At the beginning of his speech, Dr Kanavos highlighted that advanced therapies are an issue for health policy, but also for broader science and industrial policy. He explained that his presentation would focus on the costs of bringing advanced therapies to the market and to patients, in particular on the costs of innovation and regulation. He would also touch upon the requirements of Health Assessment Technology (HTA), which are hugely important as they link discovery, development and the regulatory process with the way products and treatments are evaluated. Finally, he would talk about the issue of risk sharing and Managed Entry Agreements (MEAs).

Addressing the cost of regulation, Dr Kanavos explained that it takes a long time and significant resources to bring new molecules to the market. Evidence from the USA indicates that it can cost 800 million dollars to bring a new small molecule to the market, which can increase to 1,318 million dollars for biologics. These figures are probably underestimated as, for example, they do not include the costs of approval of the molecules outside the USA.

Dr Kanavos then talked about the cost of innovation and what he defined as the “dynamics of attrition”. 88% of all firms engaged in drug innovation have failed, been acquired or merged in the past fifty years. In particular, plenty of innovative undertakings had been taken over by commercial entities, which had the resources to translate the innovative scientific potential into commercial terms and to take the new molecules to the market.

He also explained that one could look at regulation as a barrier to entry. Although regulation is needed, significant costs and time are involved in taking a new molecule or therapy through the regulatory process. In his view, the process should be improved, made more efficient and streamlined in the interest of patients and society as a whole.

After that, Dr Kanavos linked the regulatory process with HTA, which basically looks at addressing clinical efficacy and cost effectiveness. On one side, the clinical efficacy analysis explores whether a new technology is more effective, just as effective or less effective in comparison to the current standard of care, and what the impact is on quality of life, longevity etc. On the other side, the cost effectiveness analysis aims to understand whether a new technology provides high, low or no value for money. Dr Kanavos finally mentioned that regulators are addressing efficacy, whereas payers and HTA bodies want to achieve cost effectiveness.

Looking at the impact of HTA in a sample of five cases (Scotland, Sweden, Australia, England and Canada), Dr Kanavos explained that the same technology may have a different outcome depending on the jurisdiction, i.e. a technology may be approved in one jurisdiction, whilst being rejected or accepted with restrictions in other jurisdictions. From an economic point of view, different approaches are not a problem per se and can be justified as a reflection of societal choices. However, this may create inequity within the same Union, as patients living in countries that provide full coverage would have an advantage over others.

Dr Kanavos then showed a knowledge curve, indicating three points. Point A represents the level of knowledge for regulators where marketing authorisation occurs and where some basic understanding of the efficacy and safety of a new therapy is provided. Point B represents the level of knowledge for HTA agencies, although they would ideally want a higher level of knowledge - at Point C. The difference in knowledge between B and C is substantial: at point B far less information is available on the value of a new therapy compared to point C. As the cost of a new therapy increases, risks and uncertainties emerge as well.

To address the issue of high costs and high risks, a number of schemes have been developed in the EU over the past few years, including Managed Entry Agreements (MEAs) and risk sharing schemes. Dr Kanavos explained that nowadays there is a proliferation of MEAs taking into account the trade-off between very high costs on one side, and very high uncertainty and risks on the other side.

Dr Kanavos concluded his presentation by summarising his main messages, i.e. that the cost of innovation is high and rising and that the regulatory process can be streamlined and usefully linked with HTA. Finally, he highlighted that the issue of risks and uncertainties will always be present in the area of ATMPs and that choices will have to be made on how to integrate these technologies in the health care system.

2.3.2 The role of small and medium-sized enterprises (SMEs), Dr Maria Luisa Nolli (IT)

Dr Maria Luisa NOLLI, founder and Chief Executive Officer of Areta International, member of the Management Committee of Assobiotec, the Italian biotechnology industry association

Dr Nolli was introduced by Mr Peterle as both a scientist and a businesswoman. She began her presentation by thanking the organisers for the opportunity to talk about the role of SMEs in the development of ATMPs. She then quoted the EuropaBio Healthcare Manifesto 2011-2012[20], which stated that SMEs account for 99% of all companies, two thirds of private sector jobs and 40-50% of GDP in this field. In her view, the role of SMEs is to promote advances in clinical research and translate these into market opportunities, thus building a bridge between basic research and industry.

[20] See: http://www.europabio.org/healthcare/press/europabio-s-healthcare-manifesto-2011-2012-en-route-2020.

Dr Nolli then emphasized that there are real and tangible advantages to being an SME. Small businesses are flexible, usually based on innovation and technology-driven. In addition, they can be (and have to be) very creative when facing unforeseen challenges related to novel types of products. SMEs also benefit from government/public funding to accelerate research, and most importantly, they have fast decision-making processes.

In Dr Nolli's opinion, the fact that 50% of the ATMPs currently under development are within SMEs shows that these businesses are revolutionising medicine. As a matter of fact, SMEs have an ideal positioning close to hospitals to foster exchange and collaboration on innovative therapies and treatments. She noted that, at the moment, there are not so many ATMPs on the market, and most of these are outside Europe. In particular, the two European products that Dr Nolli cited were Glybera by UniQure (for lipoprotein lipase deficiency) and Chrondrocelect by Tigenix (for cartilage regeneration).

Dr Nolli also highlighted that a new business model is emerging, from "one size fits all" drugs for the mass population (blockbuster drugs) to a more personalised and patient-specific approach ('niche'-busters and/or autologous therapy). In her view, the medical and the business community should be prepared for what she defined as a "revolution", with hospitals playing a more and more important role. In this context, SMEs can be very influential in accelerating the development of advanced therapies and in contributing to transforming them into products. Big industry is becoming increasingly interested as well. In Dr Nolli's opinion, an approach that includes SMEs as a bridge between research and industry is therefore the right model for the future.

Dr Nolli concluded her presentation by introducing her own company, Areta International[21], as an example of a successful SME in the area of ATMPs. Areta International is a biotech company dedicated to contract development and manufacturing of biotechnology products, including cell-based medicines. Areas of activity include pre-clinical development, as well as clinical development of biotechnology products and advanced therapies.

2.3.3 Second round of questions and answers

Before opening the floor for questions, Mr PETERLE noted that the experts' presentations had demonstrated the significant potential of ATMPs, which is an area of fast development and strong specificities requiring particular attention and flexibility by regulators.

A representative from EuropaBio, the European association for bio-industries[22], then took the floor to emphasise the importance of following up the effects of ATMPs on patients in the long term, i.e. of introducing what for traditional medicinal products is known as "pharmacovigilance". As of today no integrated system exists in Europe to ensure such a follow up, irrespective of whether the therapies are developed through hospital exemption or other means.

[21] See: http://www.aretaint.com/.
[22] See: http://www.europabio.org/.

Afterwards, a representative from Cord Blood Europe, the European Association of family cord blood banks[23], asked a question on whether public-private partnerships exist for the development of ATMPs in Europe. She also wondered whether the Commission could do more in this respect and if the EU and the USA are taking different or similar approaches. Finally, she asked Dr Kanavos about the role of insurance companies in the context of advanced therapies.

A representative from a French charity then asked the Commission whether incentives for SMEs would also be available for not-for-profit structures in the future.

Finally, a delegate from the European Alliance for Advanced Therapies[24] commented on the hospital exemption, which might be good for niche markets, but could represent an obstacle for the development of a wider European market. These products should be available for all patients in Europe, not just for patients in specific countries, namely where the hospital exemption is applied.

Addressing some of the comments and questions raised, Dr SCHNEIDER highlighted the role for regulators to ensure safety and efficacy of ATMPs, which in turn means introducing rules and procedures that may increase their costs. However, if we are to offer a balanced and proportionate regulation to stakeholders with less financial capacities, such as universities and SMEs - he wondered - would patients and society be ready to accept a reduced safety data package? He then mentioned that there has been criticism in the literature on the issue of hospital exemption. A product developed under hospital exemption is in the end much cheaper than a product that has been authorised in the centralised approval, as the former does not have to meet the same safety and efficacy trials or the same quality requirements as the latter. The risk is that the market may lean towards hospital-exempted products if Member States do not use this exemption in the spirit of the EU legislation.

After that, Prof. VAN GOOL addressed the question of public-private partnerships, explaining that academic development depends on grant systems, which are mostly insufficient and limited in time. Private initiatives and charities are therefore essential to cover the costs of long-term trials. He mentioned that a balance between academia and industry should be found and that the social finality of academic research for specific niches of patients should be recognised. In his view, the national health system should take over the application of advanced therapies once a certain level of evidence is delivered.

Dr NOLLI then highlighted that pharmaceutical quality needs to be ensured even when a therapy is developed under hospital exemption. The way in which a therapy can successfully become a product is, in her view, a matter of collaboration between hospitals and industry, which at the beginning is usually represented by SMEs. Multinationals become interested at a later stage and promote alliances with - or acquisition of - such SMEs. According to Dr Nolli, this is a winning model.

Dr KANAVOS addressed the question of insurance companies, mentioning that there is significant scope for sickness funds to streamline the regulatory process and data requirements in order to decide on health coverage for ATMPs.

[23] See: www.cordbloodeurope.org
[24] See: www.allianceat.org.

Finally, Ms JÜLICHER took the floor to explain that the Commission is trying to strike the right balance between ensuring product safety and efficacy on the one side, and implementing proportionate rules that do not hinder development and innovation on the other side. Regarding incentives for not-for-profit organisations, she mentioned that the current legislation does not foresee them. However, the public consultation currently ongoing represents an opportunity to express views also in this context. Therefore, Ms Jülicher invited all stakeholders to respond to it. One of her colleagues from the Commission then explained that the current legislation is already foreseeing a certain degree of flexibility, even without contemplating the possibility of “adaptive licensing”. In particular, she mentioned that the level of data requirements provides a possibility for waivers. Also, the level of information required is adapted to the specific circumstances of the disease and of the product. Finally, conditional marketing authorisation and marketing authorisation under exceptional circumstances provide additional flexibility into the standard framework. She concluded that it would therefore be useful to use the existing flexibility measures before introducing new systems.

2.3.4 Conclusions

At the end of the workshop, Mr PETERLE and Ms WILLMOTT expressed their gratitude to all speakers for the very interesting debate and fruitful discussion.

ANNEX 1: PROGRAMME

WORKSHOP

Advanced Therapy Medicinal Products

Wednesday, 20 February 2013 from 13.00 to 14.45
European Parliament, Room A3E-2, Brussels

Organised by the Policy Department A-Economy & Science for the Committee on the Environment, Public Health and Food Safety (ENVI)

AGENDA

13.00 - 13.05
Welcome and opening by Co-chairs of the Health Working Group, Glenis WILLMOTT and Alojz PETERLE, MEPs

13.05 - 13.10
The current position of the European Commission. Incentives for advanced therapy medicinal product development in Europe
Ms. Sabine JUELICHER, head of unit Medicinal Products- authorisations, EMA. DG SANCO, EC.

Part 1
Advanced Therapy Treatment: The Future for Healthcare

13.10 - 13.20
Cell therapy challenges
Prof. Stefaan VAN GOOL, head of the Laboratory of Pediatric Immunology, University of Louvain (BE).

13.20 - 13.30
Gene therapy challenges
Dr. Jacques MALLET, Director of "Recherche Emérite" CNRS, Institute for Brain and Spinal Cord (ICM), Paris; Adjunct Professor at the University of California at San Francisco (UCSF); Member of the French Academy of Sciences; (FR, US).

13.30 - 13.40
The voice of patients
Dr. Monica ENSINI, Scientific Director, EURORDIS (European Organisation for Rare Diseases).

13.40 - 13.55
Question Time
With the participation of Dr. Christian K. SCHNEIDER (chair) and Dr. Patrick CELIS (scientific administrator), Committee for Advanced Therapies (CAT), European Medicine Agency (EMA, EU).

Part 2
Technology Transfer: Bringing Healthcare Research to the Market

13.55 - 14.05
The costs for making advanced therapies available to patients
Dr. Panos KANAVOS, Reader in International Health Policy in the Department of Social Policy, London School of Economics (LSE) and Programme Director of the Medical Technology Research Group (MTRG) at LSE Health; (UK).

14.05 - 14.15
The role of small and medium-sized enterprises (SMEs)
Dr. Maria Luisa NOLLI, founder and Chief Executive Officer of Areta International, member of the Management Committee of Assobiotec, the Italian biotechnology industry association; (IT).

14.15 - 14.40
Question Time
With the participation of Dr. Christian K. SCHNEIDER (chair) and Dr. Patrick CELIS (scientific administrator), Committee for Advanced Therapies (CAT), European Medicine Agency (EMA, EU).

14.40 - 14.45
Conclusions

14.45 Closing

ANNEX 2: SHORT BIOGRAPHIES OF EXPERTS

Ms Sabine Jülicher

Ms Sabine Jülicher holds a veterinary degree from the Free University Berlin and has a postgraduate qualification in food hygiene.

She initially worked in research and later moved to public administration, working both at the national and international level. Ms. Jülicher joined the European Commission in 1999, working in the area of food safety before taking up management functions. She has been Head of Unit in the Health and Consumers Directorate-General since 2008 and is currently in charge of unit D5 - medicinal products, authorisations and EMA.

Prof. Stefaan Van Gool

Prof. Stefaan Van Gool is a pediatric neuro-oncologist at the University Hospital Leuven. He is full professor at the KU Leuven in Belgium and guest professor at the University of Saarland in Germany. Finally, he is senior clinical investigator at the Fund for Scientific Research Flanders.

Prof. Van Gool is chief of the Laboratory of Pediatric Immunology, where he is mentor to 6 PhD students who perform preclinical research in the field of immunotherapy for glioma and immunological characteristics of stem cells, and leads a GMP laboratory to produce the dendritic cell vaccines for patients with malignant glioma. He created the Immunotherapy Platform Leuven in order to link preclinical and clinical work in the translational research program.

Prof. Van Gool is founding member of the Olivia Hendrickx Research Fund and executes the goals of the Herman Memorial Research Fund, the James E. Kearney Foundation and LCH Belgium + Run-for-LCH vzw.

Dr Jacques Mallet

Dr Jacques Mallet holds a PhD in Physical Organic Chemistry from Harvard University. After his Military Service, he joined, as a postdoctoral fellow, the laboratory of Prof. Changeux at the Pasteur Institute in Paris, where his research was focussed on developmental neurobiology.
In 1980, Dr Mallet created a CNRS laboratory at the University of Paris/Orsay, then at Gif-sur-Yvette. In 1995, he created a new laboratory at the Pitié-Salpêtrière Hospital, before joining, in 2010, the Institute for Brain and Spinal Cord (ICM) on the same campus. His laboratory has also been affiliated with Sanofi-Aventis for 8 years. He is now Director of “Recherche Emérite” CNRS at ICM and Adjunct Professor at the University of California at San Francisco.
Dr Mallet’s laboratory pioneering work is related to the fields of: Neurotransmitter’s molecular biology, Psychiatric genetic, epigenetics and gene therapy for nervous system diseases.

Finally, Dr Mallet is Member of the European Academy of Sciences, Brussels, of the French Academy of Sciences, of Academia Europea and of EMBO. He has received several prices including the Prize of the “Fondation de Physiopathologie Lucien Dautrebande” (1993), Belgium, the “Grand Prix” of the French Atomic Energy Commission (2000), the Prize of Neurobiology from the” Fondation pour la Recherche Médicale”, 1983. He has also published over 400 scientific articles in international Journal (H factor over 65), and has filled 40 patents bearing mainly on the use of viral vectors for gene therapy.

Dr Monica Ensini

Dr Monica Ensini holds a PhD in Neurobiology from the University of Pisa and Scuola Normale Superiore of Pisa, Italy. She focused her research studies on the development of the vertebrate motor system during her postdoctoral training at Columbia University, and of the vertebrate forebrain while working at University College and King's College in London and at the École Normale Supérieure in Paris.

Dr Ensini's engagement in the rare diseases field was marked by joining the Italian Telethon Foundation where she was responsible for the scientific review of grants and for the Personal Award Program of the Foundation.

Currently, Dr Ensini is Scientific Director at EURORDIS (European Organisation for Rare Diseases based in Paris). She looks at the challenges of the rapidly evolving technological and scientific advancements relating to their importance and applicability to the rare diseases field with a direct involvement of patients in basic and clinical research.

Dr Panos Kanavos

Dr Panos Kanavos is Programme Director of the Medical Technology Research Group (MTRG) at LSE Health. He has previously been Harkness Fellow in Health Care Policy in the Department of Ambulatory Care and Prevention, Harvard Medical School. He currently teaches Health Economics, Pharmaceutical Economics and Policy, Health Care Financing, and Health Systems Performance Measurement.

As part of its activities, the MTRG conducts research under the auspices of and participates in the European Medicines Information Network, the network for the study of rare diseases, and is a member of the European Health Technology Institute for Socio-Economic Research. It also coordinates the activities of The Patient Academy, an initiative between academia, health care regulatory agencies and patient groups.

Dr Kanavos has acted as an advisor to a number of international governmental and non-governmental organizations, including the World Bank, the World Health Organization and the Organization for Economic Co-operation and Development.

Dr Maria Luisa Nolli

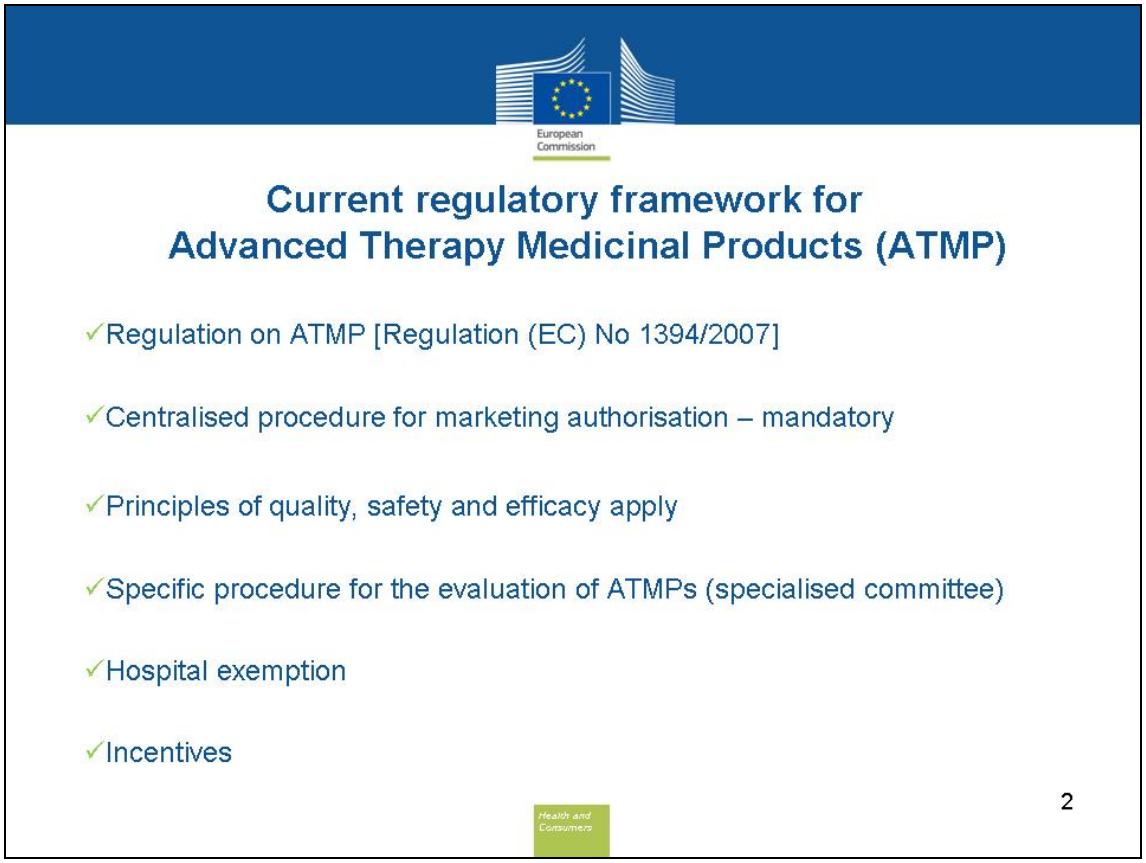
Dr Maria Luisa Nolli holds a degree in Biological Sciences from the University of Pavia and a Ph.D from the Université Libre de Bruxelles. She is the founder and Chief Executive Officer of Areta International, an Italian biotech company dedicated to the contract development and manufacturing of innovative biological drugs and Advanced Therapy Medicinal Products.

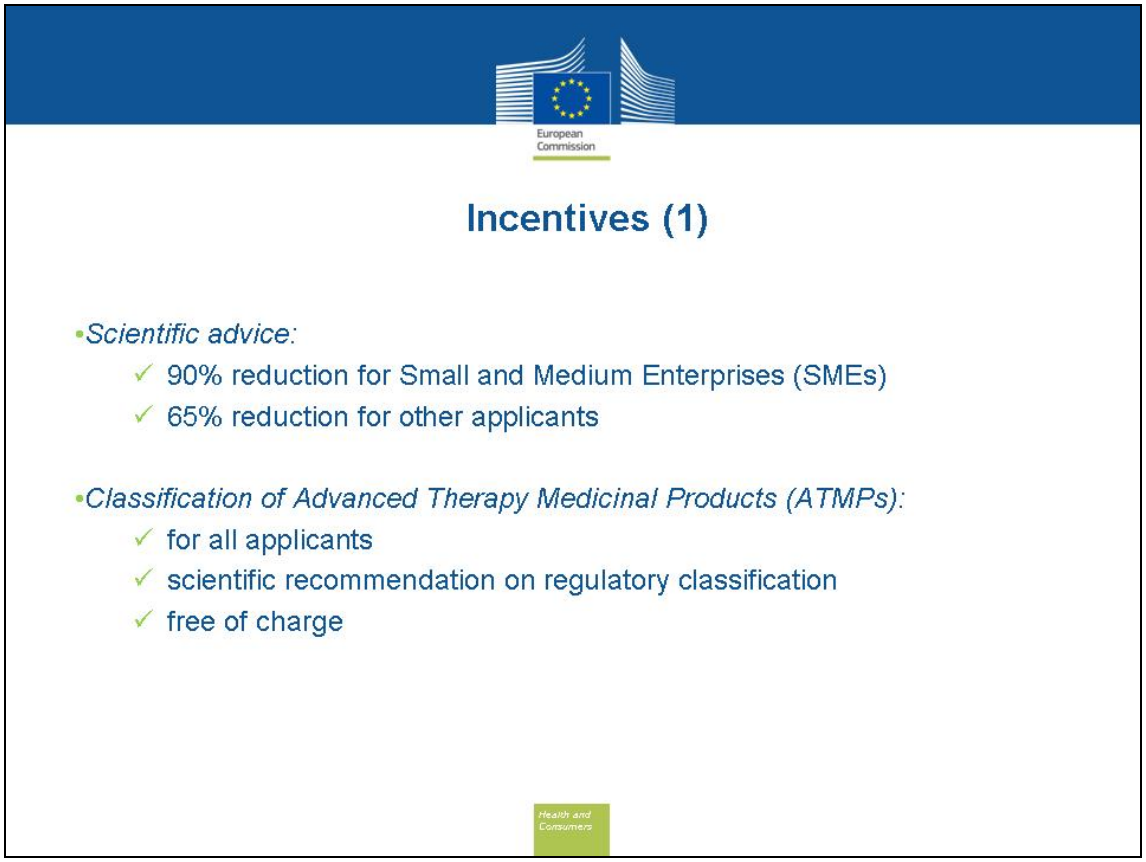
Dr Nolli has developed industrial experience as a scientist and group leader in the field of Cell Biology and Immunology working at the Lepetit Research Center (Dow Pharma). Since 2007, she is also CEO of HO.p.e. s.r.l, a spin-off of the State University of Milan, for the development of an innovative universal kit to ascertain growth hormone abuse for anti-doping purposes as well as for biomedical applications.

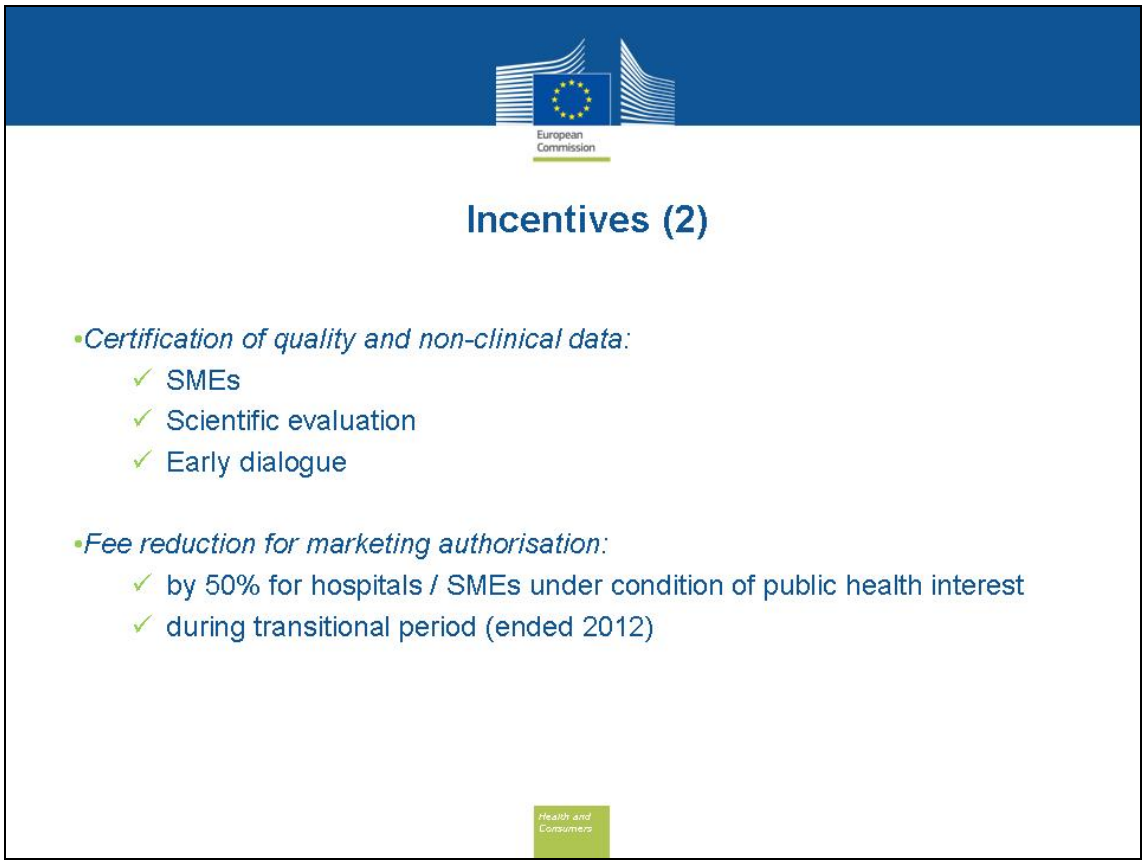
Dr Nolli is member of Assobiotec, the Italian biotechnology industry association, for which she is the representative at EuropaBio and member of the European Federation of Biotechnology.

ANNEX 3: PRESENTATIONS

Presentation by Ms Sabine Jülicher




European Commission
Incentives (1)
•Scientific advice:
✓ 90% reduction for Small and Medium Enterprises (SMEs)
✓ 65% reduction for other applicants
•Classification of Advanced Therapy Medicinal Products (ATMPs):
✓ for all applicants
✓ scientific recommendation on regulatory classification
✓ free of charge
Health and Consumers


European Commission
Incentives (2)
•Certification of quality and non-clinical data:
✓ SMEs
✓ Scientific evaluation
✓ Early dialogue
•Fee reduction for marketing authorisation:
✓ by 50% for hospitals / SMEs under condition of public health interest
✓ during transitional period (ended 2012)
Health and Consumers

Next steps

- Commission report
  - public consultation ongoing (deadline 31 March 2013): <http://ec.europa.eu/health/files/advtherapies/2012_12_12__public_consultation.pdf>
  - information from the European Medicines Agency (EMA)
  - other data sources
- Outlook

Thank you!

European Commission

Advanced Therapies – Major Developments

http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm

Public Health information:

http://ec.europa.eu/health/index_en.htm

6

Presentation by Mr Stefaan Van Gool

UZ LEUVEN | KINDERGENEESKUNDE

Cell therapy challenges
A translational research program for malignant glioma

Stefaan Van Gool, M.D., Ph.D.

Clinical Head Pediatric neuro-oncology UZ Leuven

Full Professor KU Leuven

Senior Clinical Investigator Fund for Scientific Research

Founding member Olivia Hendrickx Research Fund

Guest Professor University of Saarland

Oncology

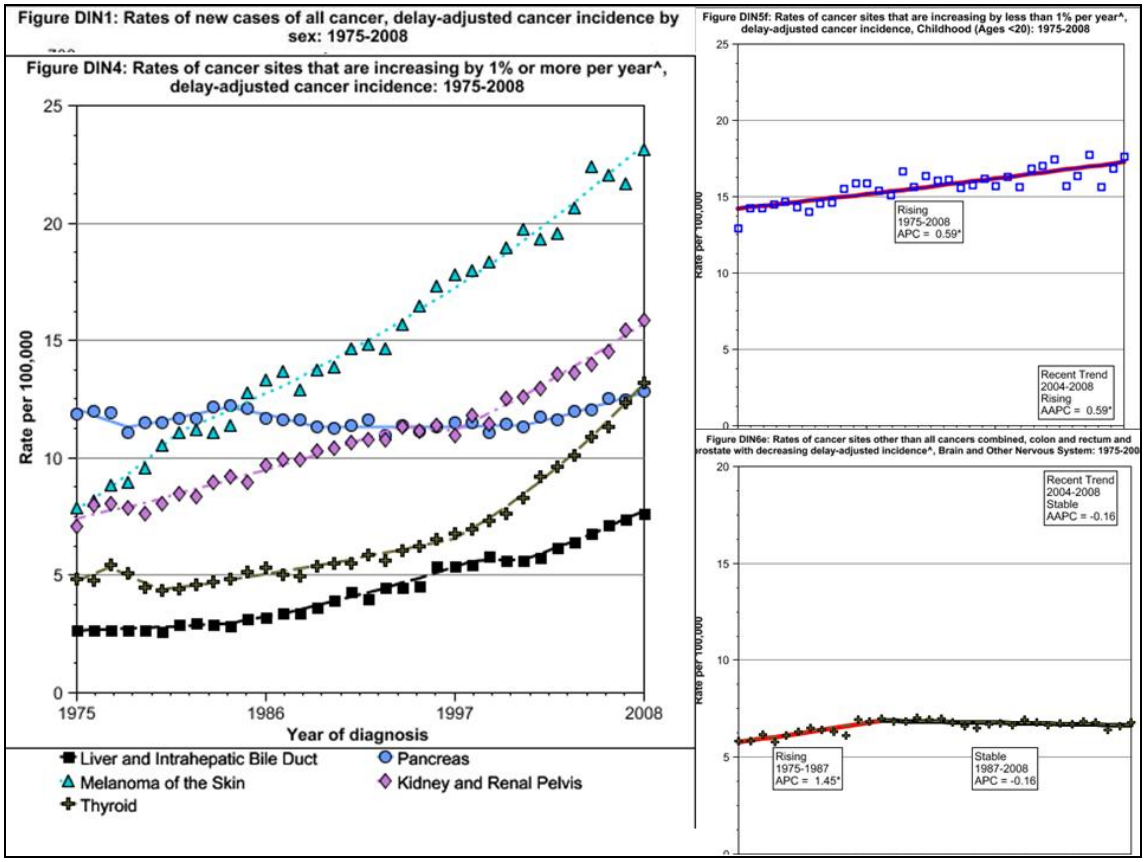
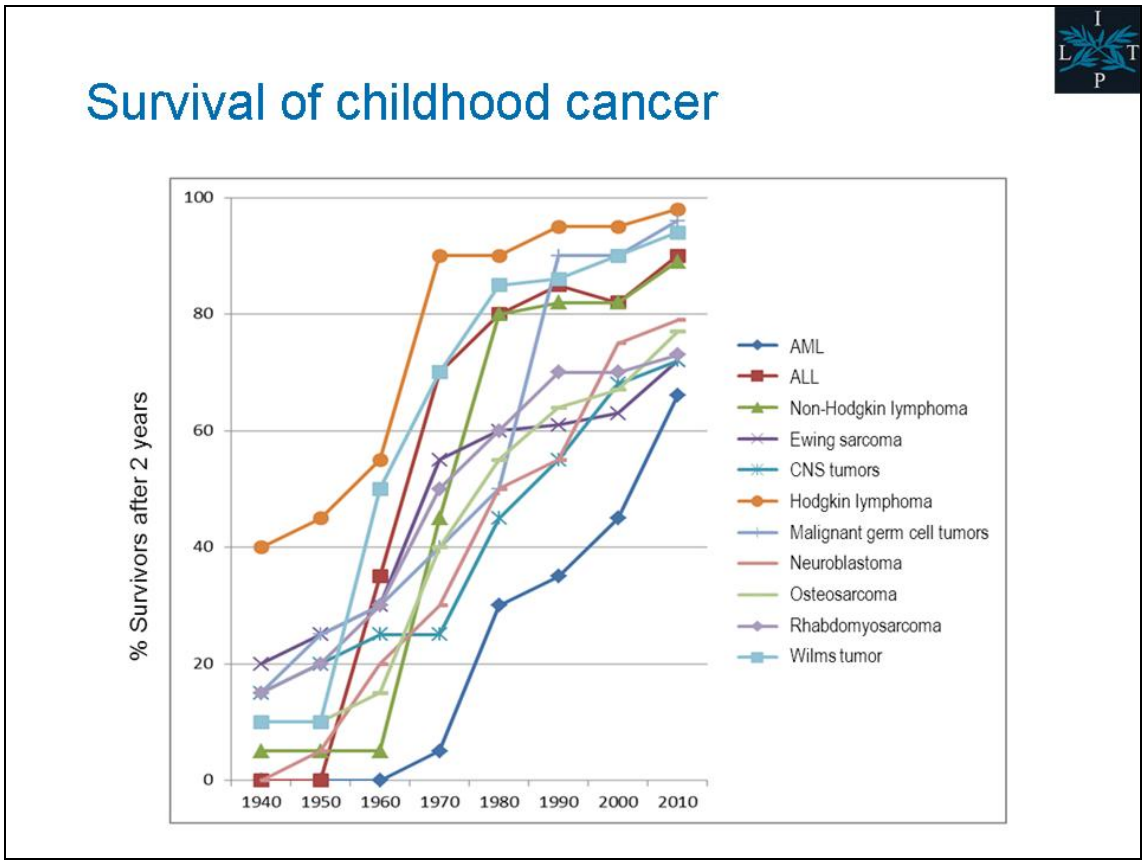
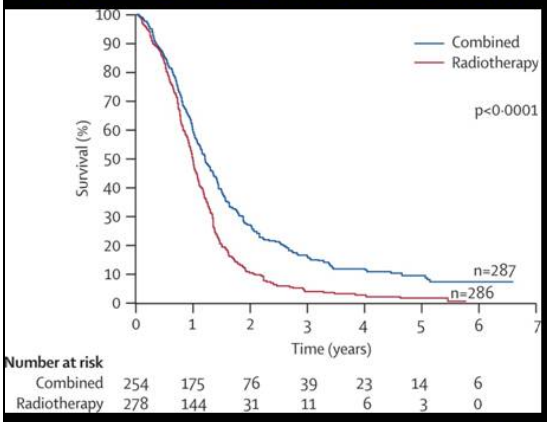
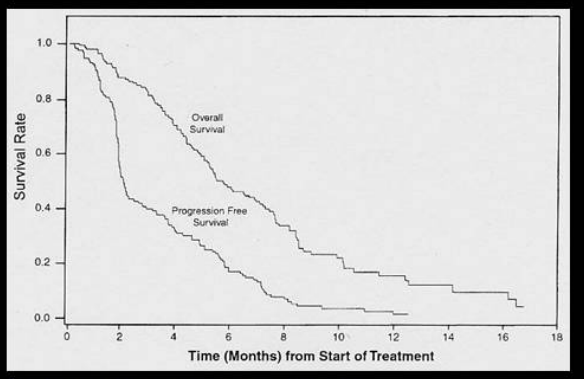


Figure DIN1: Rates of new cases of all cancer, delay-adjusted cancer incidence by sex: 1975-2008
Figure DIN4: Rates of cancer sites that are increasing by 1% or more per year^, delay-adjusted cancer incidence: 1975-2008
Rate per 100,000
Year of diagnosis
1975
1986
1997
2008
Liver and Intrahepatic Bile Duct
Pancreas
Melanoma of the Skin
Kidney and Renal Pelvis
Thyroid
Figure DIN5f: Rates of cancer sites that are increasing by less than 1% per year^, delay-adjusted cancer incidence, Childhood (Ages <20): 1975-2008
Rising 1975-2008 APC = 0.59*
Recent Trend 2004-2008 Rising AAPC = 0.59*
Figure DIN6e: Rates of cancer sites other than all cancers combined, colon and rectum and prostate with decreasing delay-adjusted incidence^, Brain and Other Nervous System: 1975-200
Recent Trend 2004-2008 Stable AAPC = -0.16
Rising 1975-1987 APC = 1.45*
Stable 1987-2008 APC = -0.16

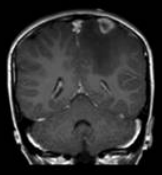

Survival of childhood cancer
% Survivors after 2 years
1940
1950
1960
1970
1980
1990
2000
2010
AML
ALL
Non-Hodgkin lymphoma
Ewing sarcoma
CNS tumors
Hodgkin lymphoma
Malignant germ cell tumors
Neuroblastoma
Osteosarcoma
Rhabdomyosarcoma
Wilms tumor

Stupp R et al. Lancet Oncol 2009;10:459-466





Brada et al. Annals of Oncology 2001;12:259-266



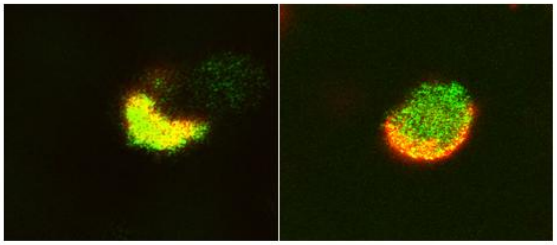
Glioblastoma multiforme: 3 per 100000 adults per year

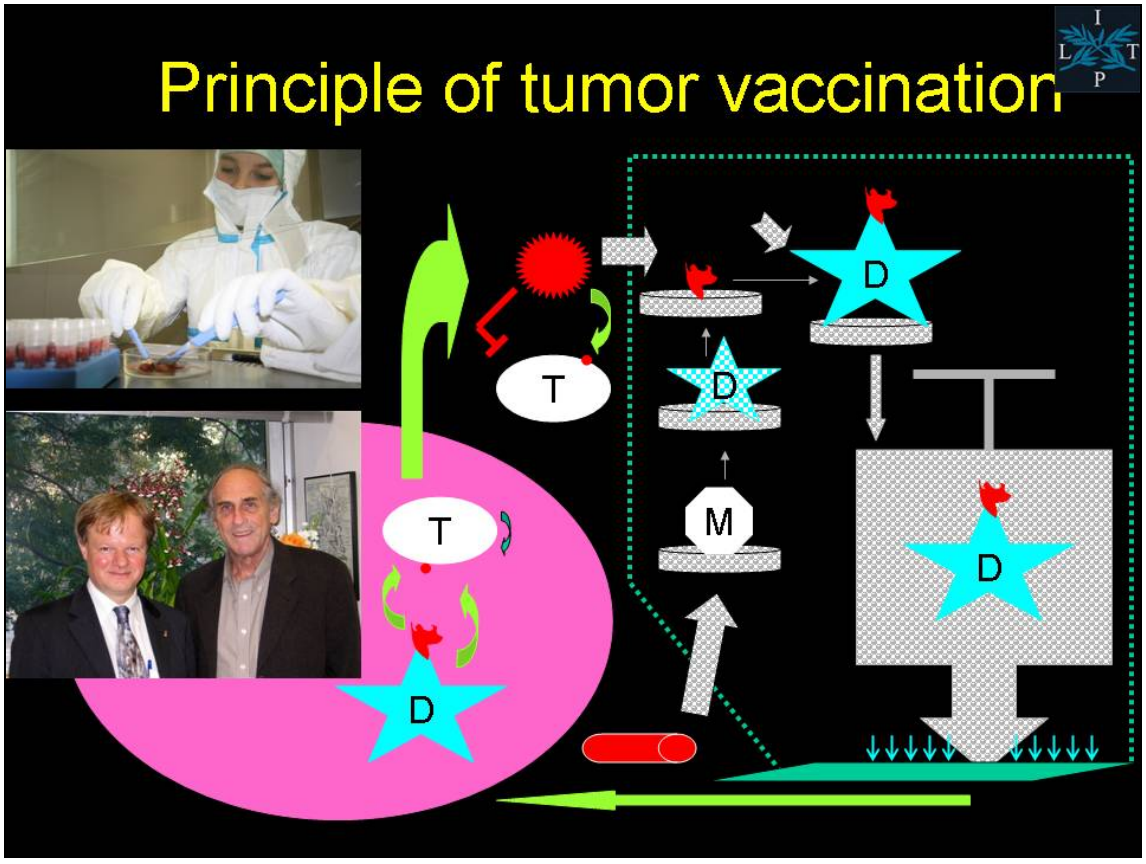
! High community burden !

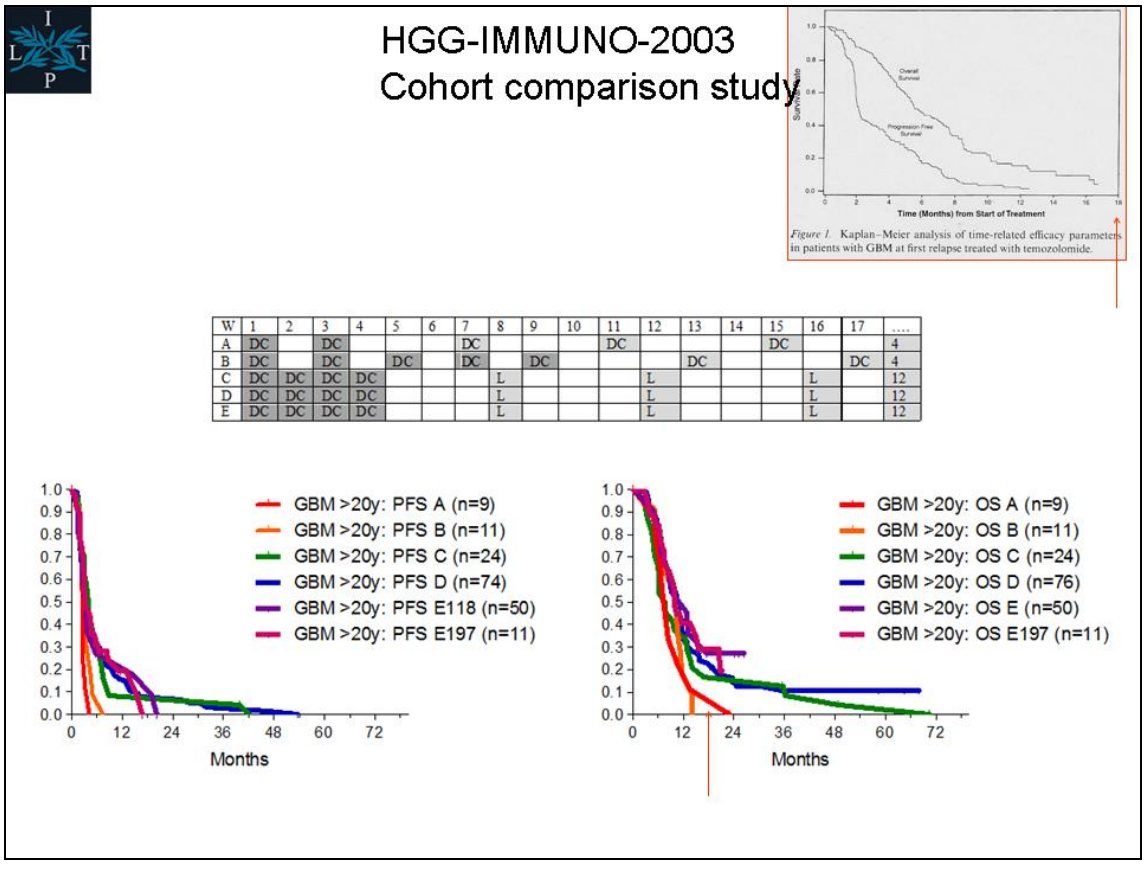
Immunotherapy for malignant glioma

An example

ATMP = DCm-HGG-L







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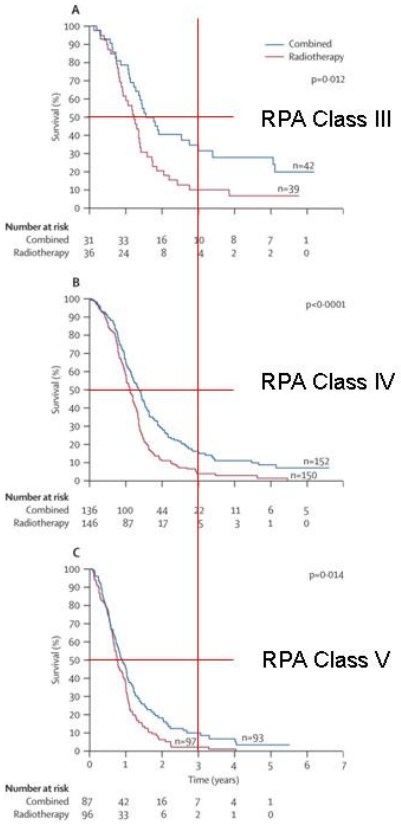
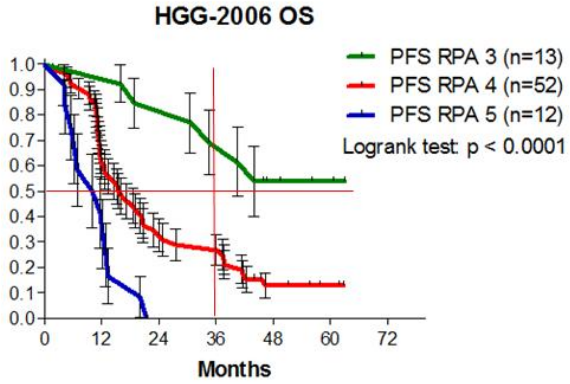
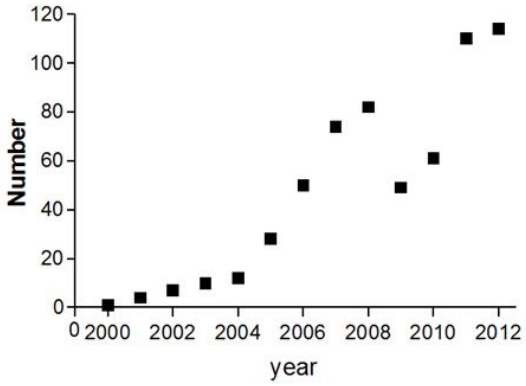
B	DC		DC		DC		DC		DC				DC				DC	4
C	DC	DC	DC	DC				L				L				L		12
D	DC	DC	DC	DC				L				L				L		12
E	DC	DC	DC	DC				L				L				L		12

HGG-2006 phase I/II Clinical trial

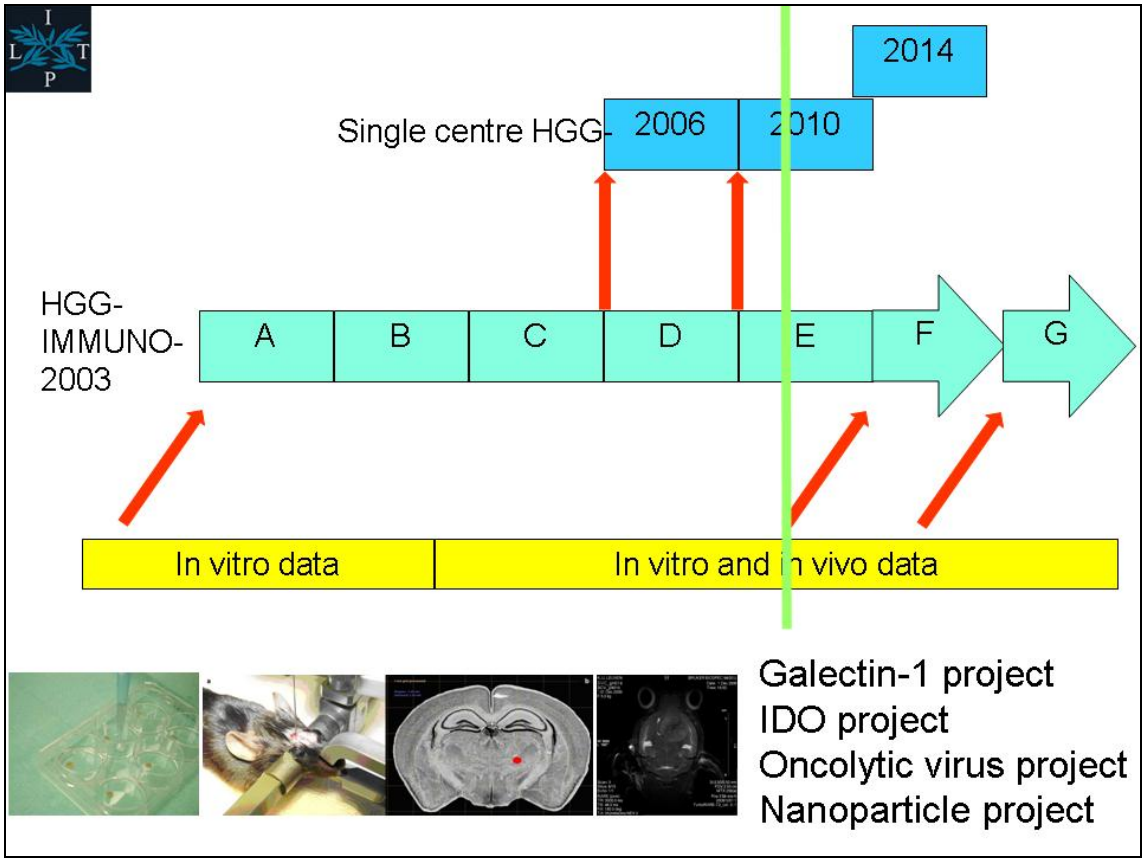


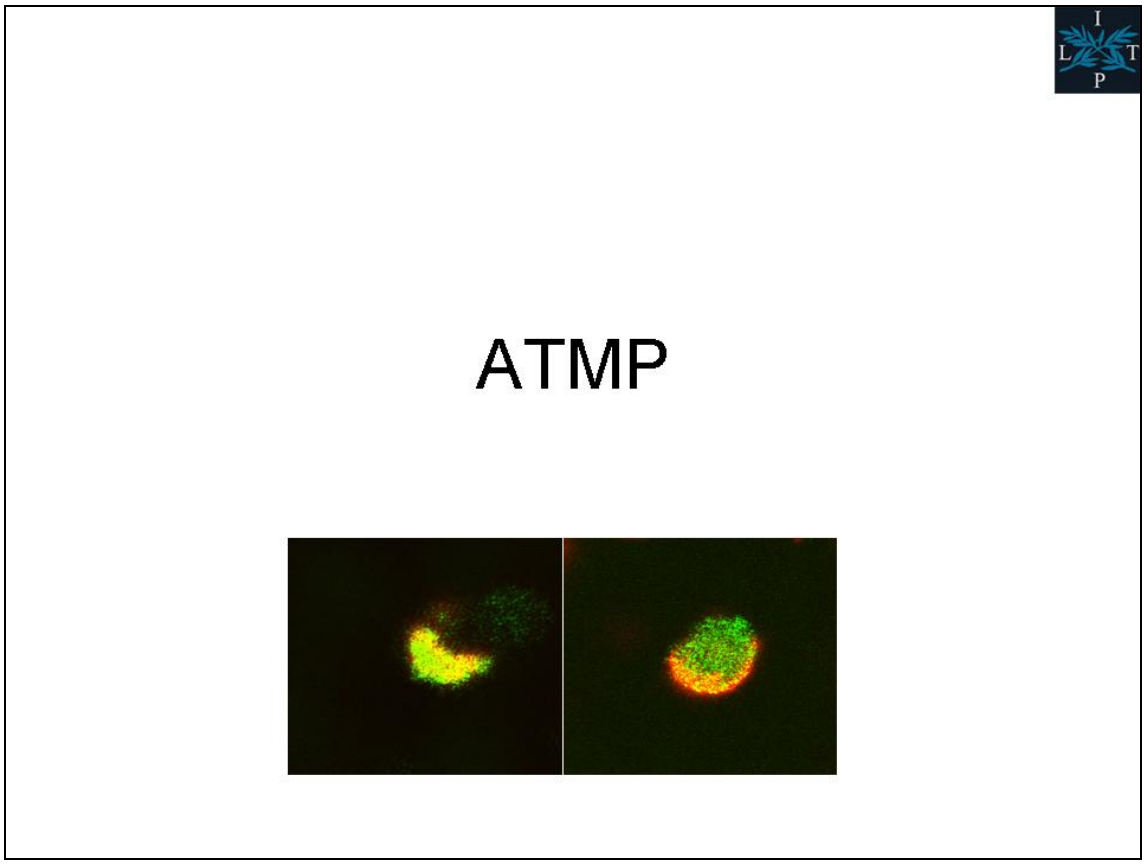


Number of HGG patients per year



1. Belgium
2. The Netherlands
3. Germany
4. UK
5. USA
6. Italy
7. Sweden
8. Iceland
9. Poland
10. France
11. Denmark
12. Israel
13. Lebanon
14. Spain
15. Greece
16. Portugal
17. Switserland
18. Russia
19. Croatia
20. Kazachstan
21. Luxemburg
22. Mexico
23. Bulgaria
24. Cyprus
25. South Africa


2014
Single centre HGG-
2006
2010
HGG-
IMMUNO-
2003
A
B
C
D
E
F
G
In vitro data
In vitro and in vivo data
Galectin-1 project
IDO project
Oncolytic virus project
Nanoparticle project


ATMP

Regulation 2007/1394/EC

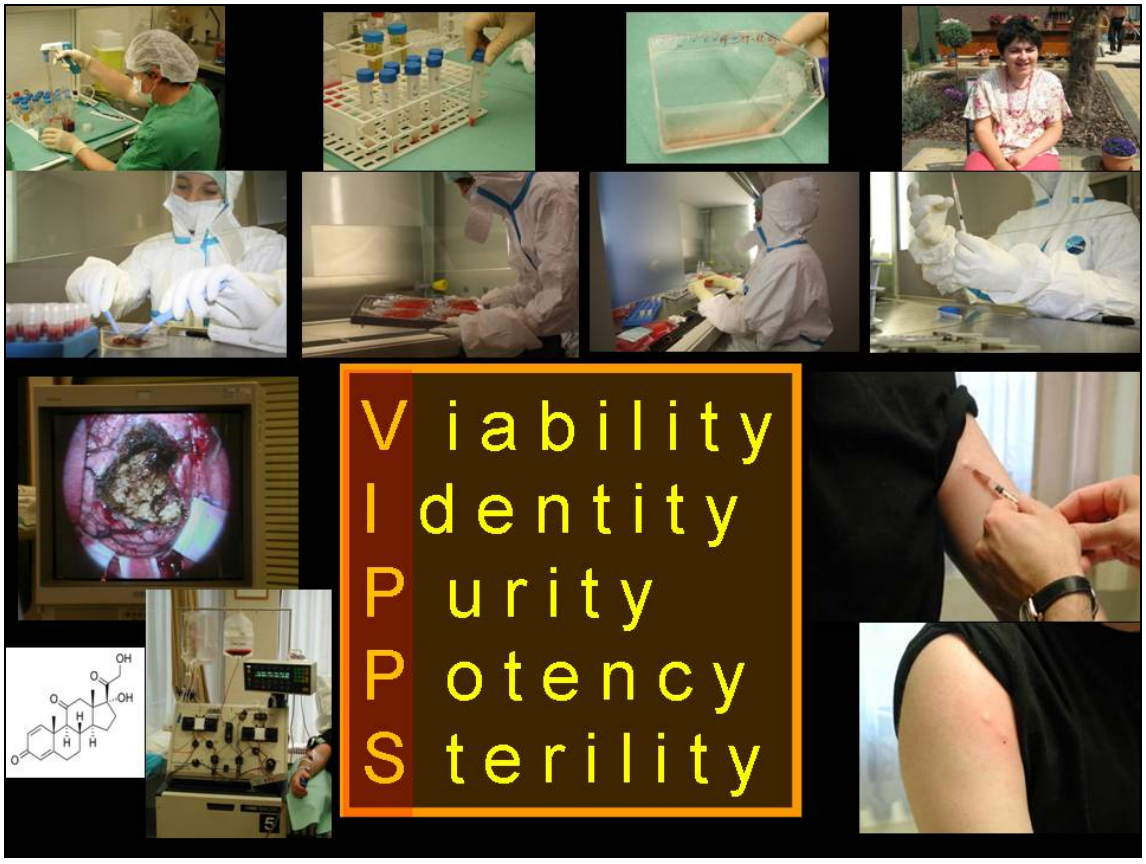
- **ATMP** means any of the following medicinal products for human use:
  - a gene therapy medicinal product ad defined in Part IV of Annex I to Directive 2001/83/EC
  - A somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC
  - A tissue engineered product
- **Engineered** means substantial manipulations, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.
- **Hospital exemption** means preparation of ATMP on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient

Medicinal product: Dir 2001/83/EC, Dir 2004/27/EC
ATMP: defined in Part VI Annex I to Dir 2001/83/EC

Investigational ATMP: Clinical trials Dir 2001/20/EC
GCP Dir 2005/28/EC; all IMP in GMP
Non-commercial trials; member state authorisation

Regulation 2007/1394/EC; Hospital exemption; implicit no clinical trial
Dir 2004/23/EC includes clinical trial material; member state; GTP

- Confusion
  - If product is under hospital exemption >> product falls to scope of Dir 2004/23/EC (cells and tissues) > GTP framework
  - If product is in clinical trials > IMPs require GMP framework
  - Cells and tissues framework allows clinical trial material
  - Hospital exemption implicitly excludes clinical research
- In both cases: hospital exemption and cells/tissues (GTP): member state to regulate



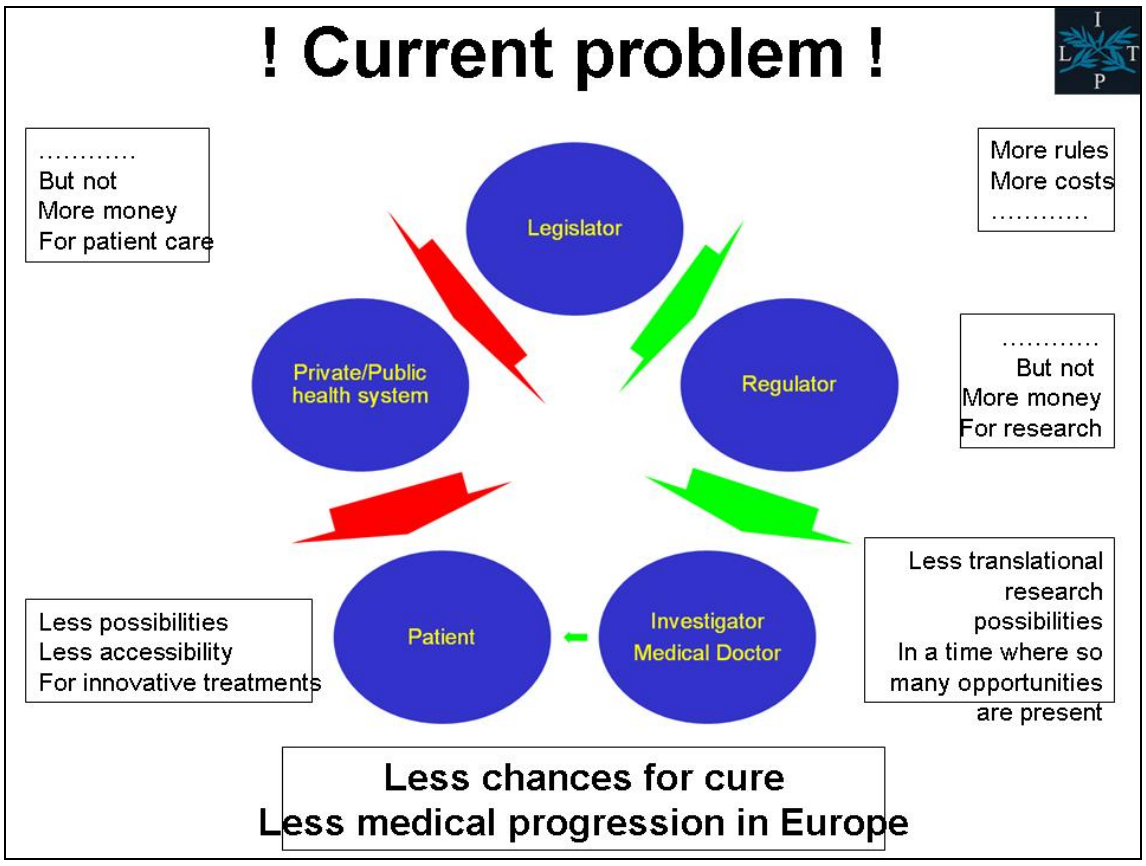
ATHP in academia for specific niche indications

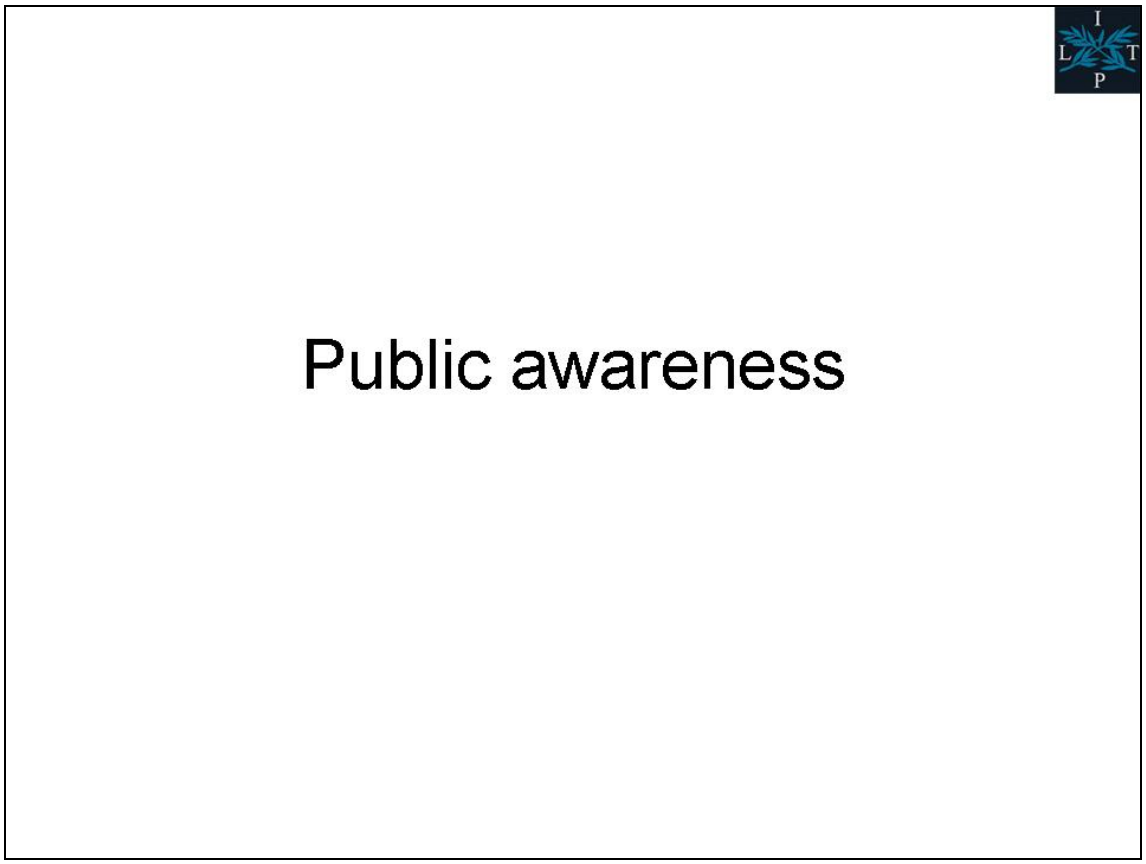
~~Advanced Therapy Medicinal Product (ATMP)~~ *prepared according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient*

Niche*: patients with low incidence clinical situations who need a multidisciplinary complex often multimodal treatment in a highly specialized medical centre and in whom full standardisation needs some flexibility*

Advanced Therapy Hospital Procedures (ATHP)

- *need to face **clinical reality**: small number, personalization*
- *need for **specific rules**, different from industry and pharmacy rules*
- *no need for marketing authorizations, but **licence of activity** under the control of the Member State*


! Current problem !
I L T P
.....
But not
More money
For patient care
More rules
More costs
.....
Legislator
Private/Public health system
Regulator
.....
But not
More money
For research
Less translational research possibilities
In a time where so many opportunities are present
Less possibilities
Less accessibility
For innovative treatments
Patient
Investigator Medical Doctor
Less chances for cure
Less medical progression in Europe


I L T P
Public awareness

Conclusion

- **Fantastic medical progression** is possible in Europe
- Academic hospitals have specific tasks in **translational medicine** and **development but also conduction of innovative treatments**
- There are **niches** for which **only** academic hospitals can develop and conduct **innovative advanced therapies without marketing**
- Adapted rules for **Advanced Therapy Hospital Procedures** are urgently needed
- **ATMP and ATHP are no concurrents**, but both are aimed as innovative treatments for specific medical conditions
- **Europe should keep its current leading position for ATHP**

Presentation by Mr Jacques Mallet

GENE THERAPY CHALLENGES

Jacques Mallet

Institute for Brain and Spinal Cord, Paris
University of California at San Francisco

Worshop on

Advanced Therapy Medicinal Products

European Parliament, Brussels
20 February 2013

THE PRINCIPLE OF GENE THERAPY IS STRAIGHTFORWARD

The introduction of nucleic acids into cells to alter gene expression in order to prevent, halt or reverse a pathological process.

- ✓Gene addition (to replace an altered, nonfunctional gene)
- ✓Gene correction/gene alteration
- ✓Gene knockdown (RNA interference)

Long-term effects following a single treatment

A MAJOR ISSUE IN GENE THERAPY : BRINGING A GENE TO A GIVEN TISSUE/ CELL

- ✓ Nucleic acid sequences delivered to the circulatory system/tissues are unable to enter into cells and thus to exert their function .
- ✓ To do so, nucleic acid sequences have to be introduced in vectors that play the role of Trojan horses.
- ✓ The vectors are, in most cases, derivatives of viruses.
- ✓ The useless and detrimental sequences of viruses are replaced by therapeutics sequences

IMPACT OF HUMAN GENOME PROJECT ON GENE THERAPY

Has greatly facilitated and revolutionized :

- ✓The identification of the diverse functions of nucleic acid sequences within the genome.
- ✓The characterization of genetics diseases, single gene and complex diseases (metabolic diseases, psychiatric disease …).
- ✓The diagnostic of many illnesses.
- ✓The biology of gene transfer (insertion of vectors ….).

FAILURES OF GENE THERAPY

- ✓ Clinical trials launched prematurely, (First SCID-X trial led to Leukemia- like Syndrom in 4 patients).
- ✓ Immunogenicity of the therapeutic factor (F-IX …).
- ✓ Time needed to launch a clinical trial is too long (leading to the use of not updated vector versions).
- ✓ Biology of vectors not studied until recently.
- ✓ Need for systematic studies at industrial scale (e.g. for testing various serotypes/pseudotypes or promoters…
- ✓ Biosecurity neglected.

- ➢ **More « basic » research needed (virology, molecular biology, chemistry ..).**
- ➢ **Stronger implication of industry.**

GENE THERAPY: A MULTIDISCIPLINARY DOMAIN

The success of gene therapy relies necessarily on the optimization of a multitude of parameters, including :

- Therapeutic strategy (choice of therapeutic gene depending on the physiopathology).
- Choice of vector.
- Optimization of vector (in terms of efficacy and biosecurity).
- Optimization of the vector dose.
- Optimization of cell culture conditions for ex vivo approach.
- Optimization of the expression cassette (choice of promoter …).
- Optimization of the delivery method…

To be successful, the multidisciplinarity nature of gene therapy must be taken into account. Actors in various domains must be involved:

- Medicine
- Virology
- Vectorology
- Biotechnology

RECENT SUCCESSES

Jean Bennett and Albert Maguire: Gene Therapy to Reverse Near-Blindness

Sci Transl Med. 2012 Feb 8;4(120):120ra15. doi: 10.1126/scitranslmed.3002865.

AAV2 gene therapy readministration in three adults with congenital blindness.

Bennett J, Ashtari M, Wellman J, Marshall KA, Cyckowski LL, Chung DC, McCague S, Pierce EA, Chen Y, Bennicelli JL, Zhu X, Ying GS, Sun J, Wright JF, Auricchio A, Simonelli F, Shindler KS, Mingozzi F, High KA, Maguire AM.

F. M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, 309 Stellar-Chance Labs, 422 Curie Boulevard, Philadelphia, PA 19104, USA. jebennet@mail.med.upenn.edu

Abstract

Demonstration of safe and stable reversal of blindness after a single unilateral subretinal injection of a recombinant adeno-associated virus (AAV) carrying the RPE65 gene (AAV2-hRPE65v2) prompted us to determine whether it was possible to obtain additional benefit through a second administration of the AAV vector to the contralateral eye. Readministration of vector to the second eye was carried out in three adults with Leber congenital amaurosis due to mutations in the RPE65 gene 1.7 to 3.3 years after they had received their initial subretinal injection of AAV2-hRPE65v2. Results (through 6 months) including evaluations of immune response, retinal and visual function testing, and functional magnetic resonance imaging indicate that readministration is both safe and efficacious after previous exposure to AAV2-hRPE65v2.

Gene therapy leukemia treatment successful

The Associated Press Posted: Aug 10, 2011 4:34 PM ET | Last Updated: Aug 10, 2011 8:46 PM ET 94

Scientists have reported the first clear success with gene therapy to treat leukemia, turning the patient's own blood cells into assassins that hunt down and wipe out their cancer.

They have only done it in three patients so far, but the results were striking: Two appear cancer-free up to a year after treatment, and the third had a partial response (Study led by Dr Carl June, University of Pennsylvania)

Scientists are already preparing to try the approach for other kinds of cancer.

LIPOPROTEIN LIPASE DEFICIENCY

GENE THERAPY

First Gene Therapy Gets EU Backing

Regulators recommend approval of uniQure's gene therapy Glybera.

MARIE DAGHLIAN

The Burrill Report

THERAPEUTICAL GENE TRANSFER IN THE NERVOUS SYSTEM: AN ENORMOUS POTENTIAL

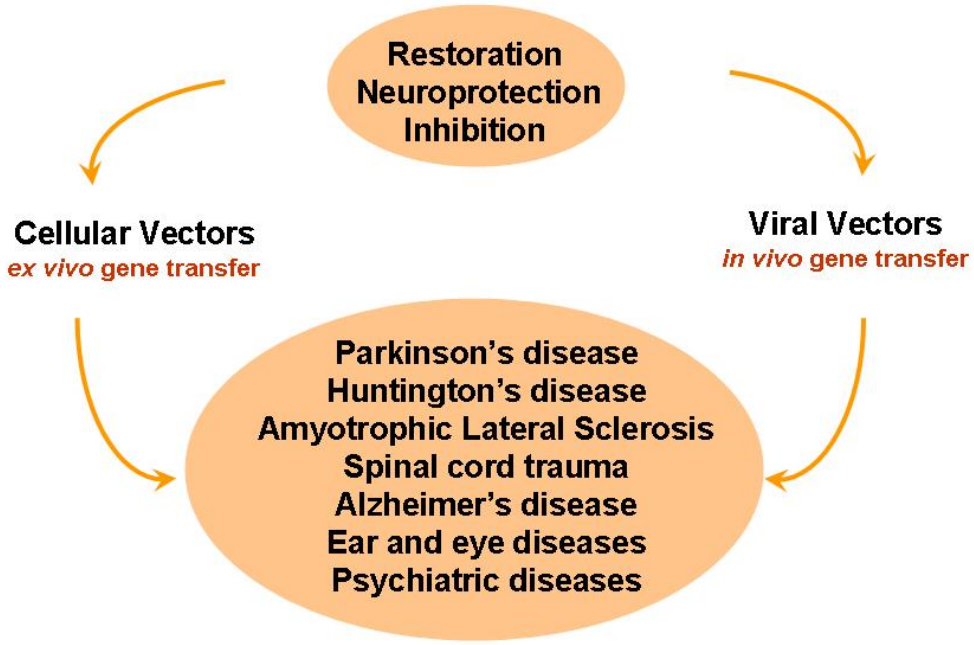
A number of therapeutic factors for the nervous system have been identidied.

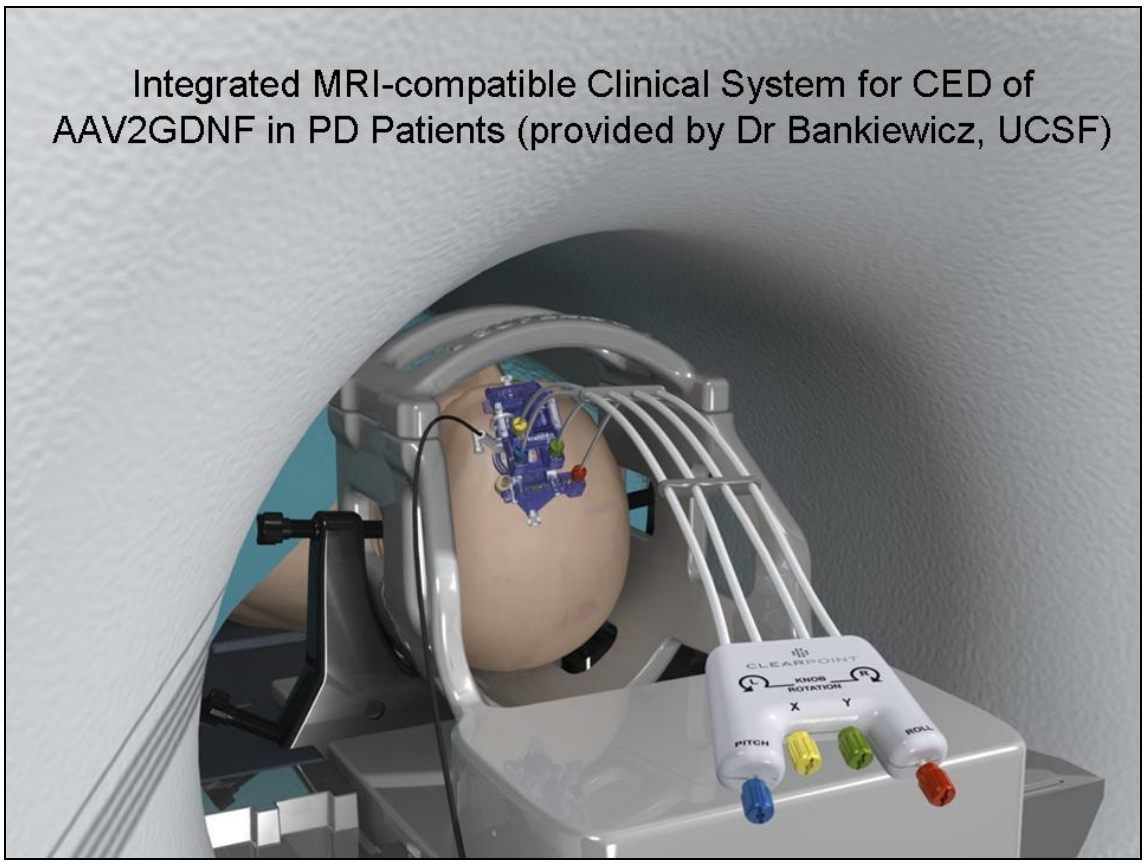
But, no possible systemic administration.

Gene therapy offers great potential for the treatment of these diseases :

- Prolonged production of the therapeutic factor
- **Local production**: limitation of side effects

THERAPEUTICAL GENE TRANSFER IN THE NERVOUS SYSTEM





GENE THERAPY : WHY NOW ?

- ✓ First « successes »
  SCID-X, Retinitis Pigmentosa, cancer, lipoprotein lipase deficiency…
- ✓ Advances in the discovery of potential therapeutic genes
  Genome sequencing, System biology, Proteomic…
- ✓ Advances in vectorology
  Non-integrative lentiviral vectors, AAV, gutless adenoviral vectors…
- ✓ Numerous technologies of interest
  ZFP, IVC, In vivo imaging, Delivery methods …
- ✓ Strong demand in some countries
  China is the first country to commercialize gene therapy products and has the largest number of treated patients

A MAJOR REMAINING ISSUE

Regulation of transgene expression

Non-protein based regulation systems

The use of gene transfer as a therapeutic tool requires, in numerous instances, a regulatory system allowing control of the expression of the therapeutic gene.

The treatment could then be adapted to the needs of the patients and, should complications arise, the therapy could be interrupted.

RELEVANT ANIMAL MODELS

- ✓ **Pigs are physiologically relevant model animals**

  Pigs recognized as excellent disease models in a variety of areas, including nutrition, toxicology, dermatology, diabetes, cancer, eye diseases, cardiovascular diseases, degenerative joint diseases or skeletal growth.

- ✓ **Their physical size are more comparable to that of humans**

  More appropriate for development of new surgical, endoscopic and delivery techniques.

  It is specifically important to test preclinical genes and cell therapy protocols in animal models that mimic both human pathology and anatomy.

- ✓ **Lower costs and faster breeding and experimentations as compared to primates and dogs**
- ✓ **Experimentation on pigs, although sensitive, is far more socially and ethically accepted than on primates, dogs or cats**
- ✓ **Validated technologies for genetic engineering are available**
- ✓ **Species of particular interest for veterinary research**

Presentation by Ms Monica Ensini

www.eurordis.org

EURORDIS
Rare Diseases Europe

The voice of patients

Dr. Monica Ensini
Scientific Director
EURORDIS

Workshop on "Advanced Therapy Medicinal Products"
European Parliament , Brussels, February 20th 2013

EURORDIS MISSION

Emilia - Achondroplasia (Photo contest winner 2011)

To build a strong pan-European community of patient organisations and individuals affected by rare diseases

To be their voice at the European level

To help them – directly or indirectly – fighting against the impact rare diseases have on their lives

EURORDIS (European Organisation for Rare Diseases) is the voice of 30 million people affected by rare diseases throughout Europe.

2

EURORDIS
Rare Diseases Europe

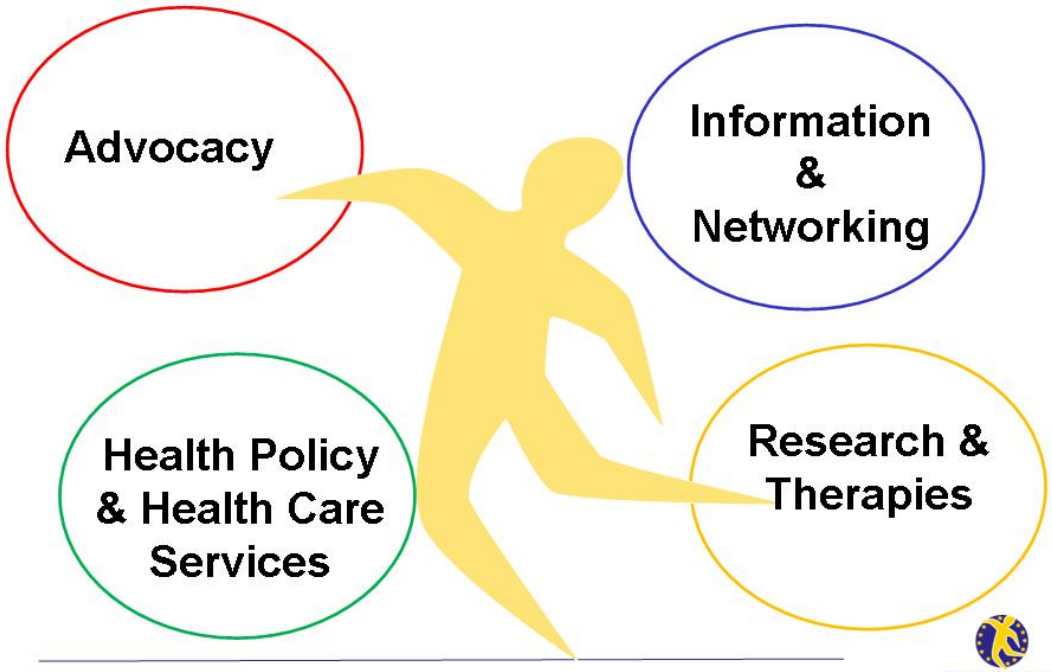
EURORDIS : KEY FIGURES

- Founded 1997
- 51 countries (26 EU countries) represented
- 561 patient organisations are members
- 26 National Alliances
- 35 European and International Federations
- Over 4 000 rare diseases represented
- 29 staff members (Paris, Brussels & Barcelona)
- ≈ 100 volunteers

3

EURORDIS Rare Diseases Europe

EURORDIS FIELDS OF ACTION



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EURORDIS Rare Diseases Europe

Rare Disease Patients' Organisations (RD Pos) and Therapy Development

- RD POs are involved from basic research, clinical trials, regulatory centralised procedures and beyond (access to the treatments) – EURORDIS Survey 2010
- RD POs have a strong willingness for collaboration with researchers
- POs provide two types of support to research
  - Financial : estimation on RD around 100 M€ per year in Europe
  - Non-Financial: identifying needs, creating links between patients, researchers and physicians; crucial support in clinical trials

But….POs have limited budgets

5

EURORDIS Rare Diseases Europe

Involvement of patients in the medicinal products life-cycle

- Basic research
- Clinical trials
- Regulatory centralised procedures
- Access to the treatment
- Pharmacovigilance

6

EURORDIS Rare Diseases Europe

EU Regulations and Rare Disease Patients'Organisations (POs) contribution

Advocacy and development of EU Regulations:

- REGULATION (EC) No 141/2000 ON ORPHAN MEDICINAL PRODUCTS
- REGULATION (EC) No 1901/2006 ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE
- REGULATION (EC) No 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS

7

EURORDIS Rare Diseases Europe

Patients' Organisations in the European Medicines Agency (EMA)

Members (and Alternates), Observers, Experts and Representatives of a specific organisation

- Since 2000 in COMP with 3 Members
- Since 2007 in PDCO with 3 Members + 3 Alternates
- Since 2009 in CAT with 2 Members + 2 Alternates
- Patients' and Consumers' Working Party (PCWP):
- 11 organisations (transparency and dissemination of information, product information, pharmacovigilance, interaction with the EMA and its scientific committees)
- 2 Members in the EMA Management Board

8

EURORDIS Rare Diseases Europe

General role of patients in the European Medicine Agency (EMA)

- Same roles and responsibilities of Members nominated by National Agencies
- Represent patients' benefits/interests
- Provide alternative/complementary views in addition to technical approaches. Particularly, the views of those that will be directly affected by regulatory decisions
- Identify topics which may require or benefit from additional specific patient consultation
- Actively contribute to patient information and communication issues related to medicines

9

EURORDIS Rare Diseases Europe

General Role of POs in therapies development

- Raise ethical issues during the discussion; identify ethical risk factors, propose measures for risk prevention and minimisation measures.
- Disseminate Committee knowledge (when not confidential); pass on information to patients and patients' organisations
- Facilitate and engage dialogue with interested parties and international counterparts
- Increase transparency and trust in regulatory processes
- Develop mutual respect between regulators and the community of patients

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EURORDIS Rare Diseases Europe

Role of patient representatives in the Committee for Advanced Therapies (CAT) (1)

- Representing patients' voice
- Bringing points of view and perspectives on Regulatory procedure
- Link outside POs useful for their specific expertise
- Points of view and real life experience of concerned patients
- Address issues that could concern lay peoples
- Involvement in all the Regulatory process including issues of post-marketing access.

11

EURORDIS Rare Diseases Europe

Role of patient representatives in the Committee for Advanced Therapies (CAT) (2)

As any other member:

- Contribute to all discussions of the CAT
- Voting and taking part in Committee decision
- Possibility to act as Rapporteur, Co-rapporteur or Peer reviewer for marketing authorisation application for ATMPs
- Possibility to act as CAT Co-ordinator for ATMP Classification and Certification procedures
- No disclosure of confidentiality, declare any conflict of interest and abide by the EMA code of conduct

12

EURORDIS Rare Diseases Europe

Framework of Advanced Therapies

- At the scientific and technological frontiers
- High levels of innovation involved
- Novel methods, techniques, tools to assess innovative approaches needed
- Substantial financial and human investments needed
- Market acceptance and penetration in early days
- Regulatory challenges, in particular for SMEs

13

EURORDIS Rare Diseases Europe

Patients priorities of actions for ATMPs development

- Early dialogue between regulators and industry
- Training for academia and industry on procedures and quality requirements for ATMPs
- Financial support from EU Commission (DG-Research, DG-Sanco) for specific projects focused on preclinical development of ATMPs
- Conditional approval or adaptive licensing that will allow a faster access to the treatments (long term monitoring of ATMPs in terms of efficacy, safety and pharmacovigilance requirements)
- Adaptive HTA for a real access to the available ATMPs: costs and reimbursement

14

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CONCLUSIONS

- The challenges for ATMPs in the next years will be:
- The identification and availability of real and concrete incentives during the preclinical and clinical phases of development of ATMPs to minimise the risk of failures and boost innovation
- The implementation and assessment of a follow-up system for safety and efficacy of ATMPs
- The adaptation of regulatory procedures to the fast progresses of science
- An as early as possible access to efficacious and affordable ATMPs
- **Patients want to provide their contribution to this endeavor!**

15

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EURORDIS Rare Diseases Europe

Thanks for your attention

Special thanks to

Dr. Michele Lipucci di Paola
EURORDIS Volunteer
CAT Member

Dr. Maria Mavris
Therapeutic Development Director
EURORDIS

All photos courtesy of the EURORDIS photo contest

Presentation by Mr Panos Kanavos

The Cost of Making Advanced Therapies available to Patients

Panos Kanavos, PhD
LSE Health, London School of Economics

Brussels, 20 February 2013

Outline

- The Cost of innovation
- The regulatory process; why can it be a barrier to entry?
- The requirements of payers and Health Technology Assessment
- Managed Entry Agreements to deal with risk and uncertainty?

2

Cost of Innovation

- R&D spending has been growing at an average compounded rate of 12.3% since 1970, but R&D productivity has been declining
- 60 years of innovation (1950 – 2009) have resulted in 1,222 NMEs:
  - 1,103 are small molecules
  - 119 are biologics
- Cost of bringing a NME onto market:
  - Cost per NME in 2000 for small molecules: US$ 800 million
  - Cost per NME in 2005 for biologics: US$1,318 million
  - The above averages do not include post-approval costs for Phase IV; of obtaining approval outside US; additional labels for new indications
  - Probability of a new molecule emerging from CTs estimated at 21.5%

3

LSE

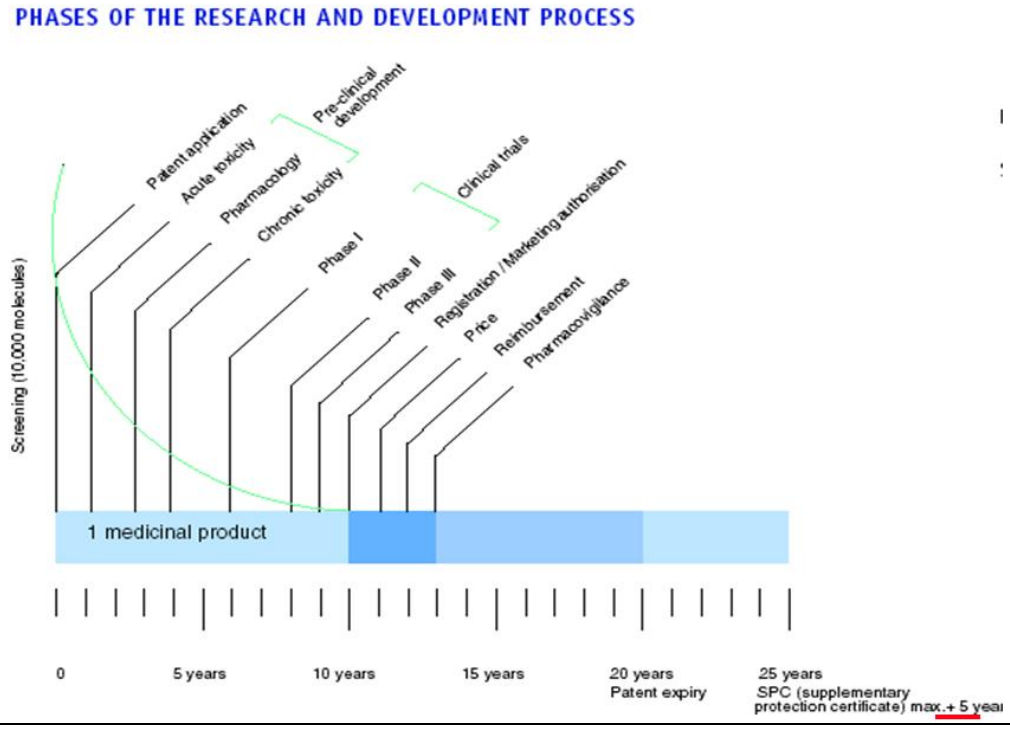
Cost of Innovation – dynamics of attrition

- More than 4,300 firms engaged in drug innovation
- Of these, 261 (6%) have registered at least 1 NME since 1950
- Of these, 32 (12%) have been in existence for the entire 50 year period
- The remaining 229 (88%) have failed, been acquired, or were created by M&A deals resulting in substantial turnover in industry
- Of the 261 organisations only 105 exist today, 137 have disappeared through M&A and 19 were liquidated

4

LSE

The regulatory process: why can it be a barrier to entry?



The requirements of payers and HTA

- Clinical effectiveness
  - Is the new technology in comparison to the current standard of care:
    - More effective?
    - Less effective?
    - Just as effective?
  - If so by how much?
    - E.g. does it improve longevity?
    - E.g. what is the impact on quality of life?

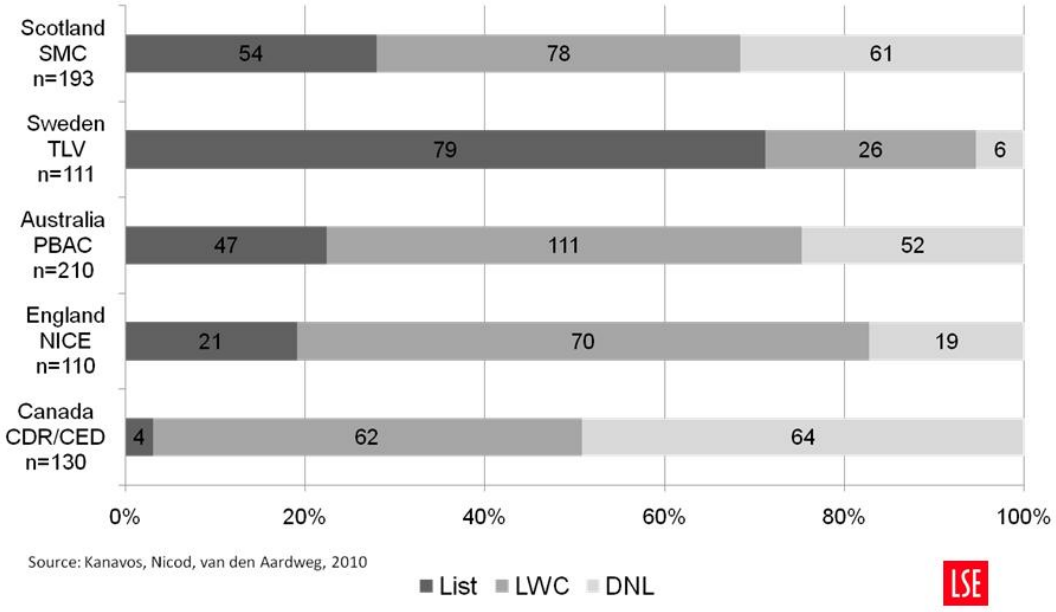
- Cost effectiveness
  - Does the new technology (and its cost) provide
    - Good value for money
    - Poor value for money
    - No value for money

6

LSE

Efficiency: Using HTA in health care decision-making

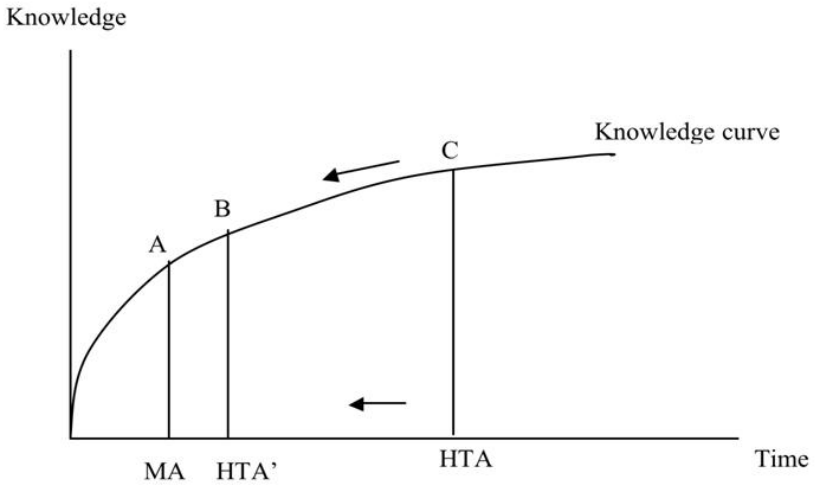
N= 287 drug-indication pairs collected between 2007-2009 in the 5 study countries
Figure represents the HTA recommendations issued in each country



Source: Kanavos, Nicod, van den Aardweg, 2010

The requirements of payers and HTA

The knowledge conundrum



Source: Kanavos et al, 2011, DG Enterprise & EMINet

8

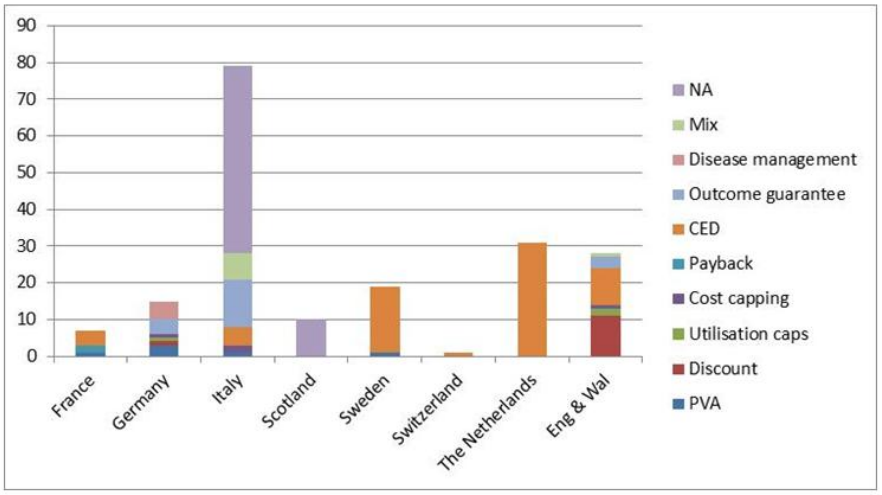
Managed Entry Agreements to deal with risk and uncertainty?

	Right patients	Uncertain clinical value	Low cost effectiveness	Budget overspend
Coverage with ED	Yes	Yes	Yes	x
Conditional coverage	Yes	Yes	Yes	Yes
Outcome guarantee	Yes	Yes	Yes	x
Price-volume deal	x	x	X	Yes

9

LSE

Type of MEAs implemented in Member State countries



Source: Ferrario A, Nicod E, Kanavos P, "Dealing with risk and uncertainties: Managed entry agreements for pharmaceuticals", forthcoming

Conclusion

- The Cost of innovation
  - *High and rising*
  - *The deep pocket argument about affordability*
- The regulatory process; can it be a barrier to entry?
  - *Lengthy time for regulatory approval and costly process*
  - *Adaptive licensing and streamlining*
- The requirements of payers and Health Technology Assessment:
  - *Increased requirements*
  - *risk and uncertainty dominate discussions on value*
- Managed Entry Agreements to deal with risk and uncertainty?
  - *Restrictions to admit new technologies to coverage*
  - *More data requirements to prove benefit*

11

LSE

Presentation by Ms Maria Luisa Nolli

areta international

THE ROLE OF SMALL AND MEDIUM-SIZED ENTERPRISES (SMEs)

Dr. Maria Luisa Nolli
CEO

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SMEs IN THE EUROPEAN UNION

Small and Medium Enterprises account for:

- 99% of all companies (number)
- 2/3 of the private sector jobs
- 40-50% of GDP

EuropaBio. (2011) Healthcare Manifesto 2011-2012

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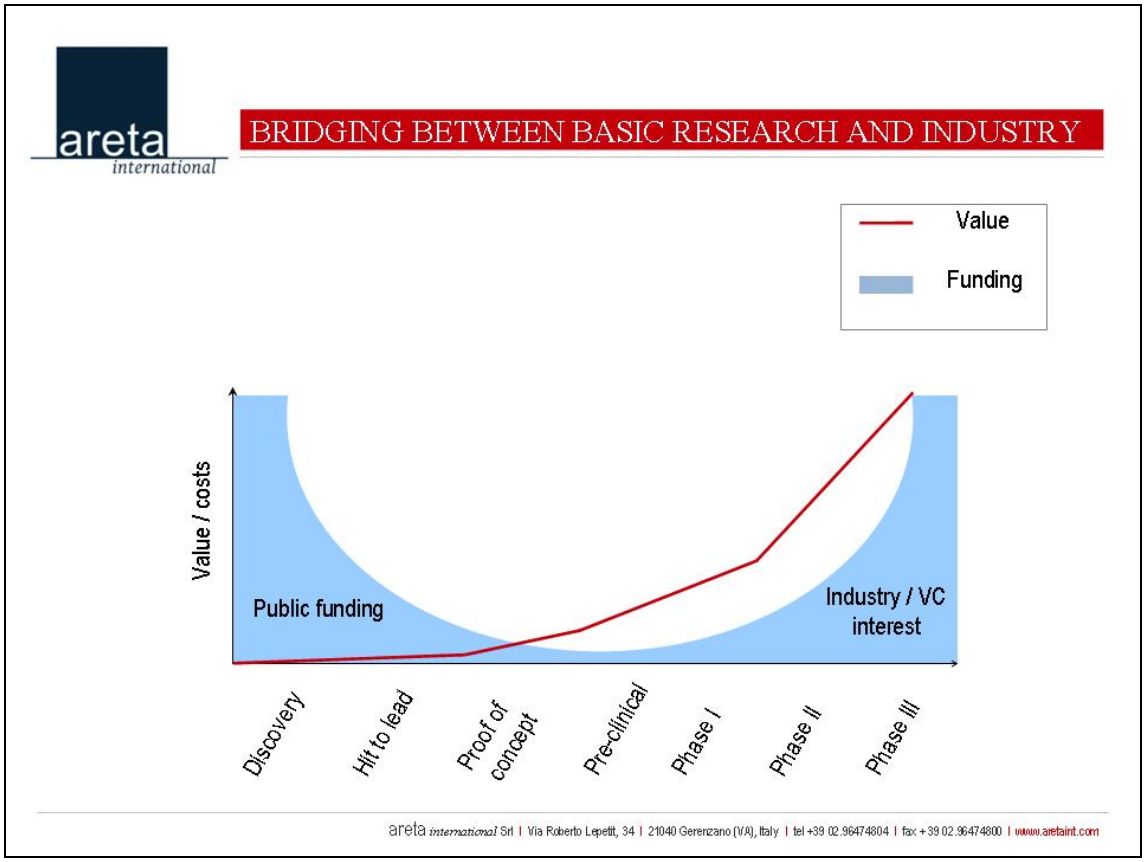
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BRIDGING BETWEEN BASIC RESEARCH AND INDUSTRY
Value
Funding
Value / costs
Public funding
Industry / VC interest
Discovery
Hit to lead
Proof of concept
Pre-clinical
Phase I
Phase II
Phase III
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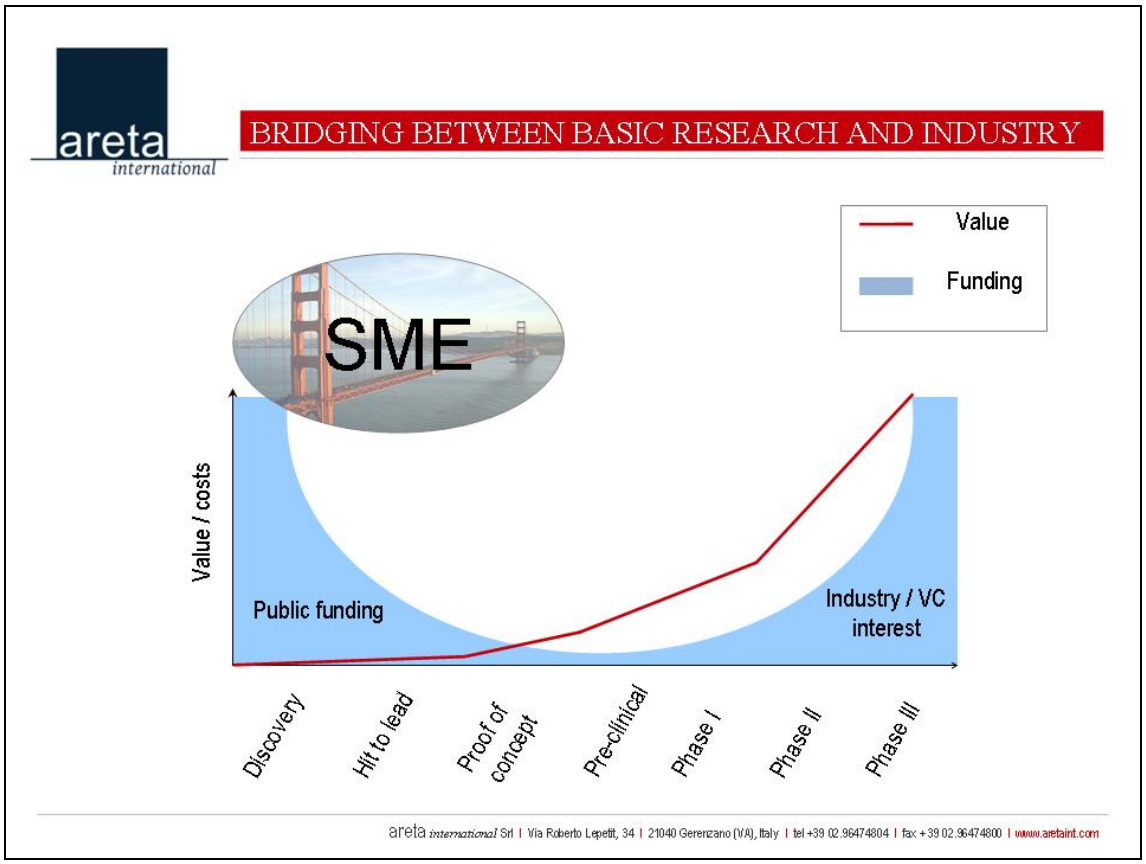
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BEING SME

- Fast decision-making process
- Usually based on innovation and technology-driven
- Can (and have to) be very creative when facing unpreviously seen challenges related to novel type of products
- Represent the excellence of regional clusters
- Can benefit from government / public funding to accelerate research

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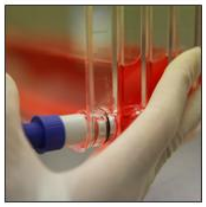
SME AND ADVANCED THERAPIES



- 50% of the ATMPs currently under development is within SMEs
- SMEs can represent the industrial realization of cluster of excellence
- Strong and proficient interaction with academic structures
- Ideal positioning close to the hospitals to foster exchange and collaboration on innovative therapies / treatments

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ADVANCED THERAPY PRODUCTS ON THE MARKET

Name	Company	Description	Countries approved	Indication
Glybera	UniQure	Adeno-associated vector	EU	Lipoprotein lipase deficiency
Chondrocelect	Tigenix	Autologous chondrocytes	EU	Cartilage regeneration
Provenge	Dendreon	Autologous dendritic cells	USA	Prostate cancer
Laviv	Fibrocell sciences	Autologous fibroblasts	USA	Wrinkles treatment (cosmetic)
Hemacord	New York Blood Center	Autologous hematopoietic cells	USA	Immunologic reconstitution
Prochymal	Osiris	Allogeneic mesenchymal stem cells	Canada New Zealand	Graft versus host disease
Hearticell-gram	Pharmicell	Autologous mesenchymal stem cells	S. Korea	Myocardial infarction
Cartistem	Medipost	Umbilical cord-mesenchymal stem cells	S. Korea	Osteoarthritis
Cupistem	Anterogen	Adipose-derived mesenchymal stem cells	S. Korea	Chron's disease

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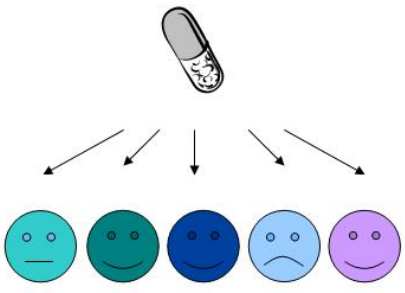
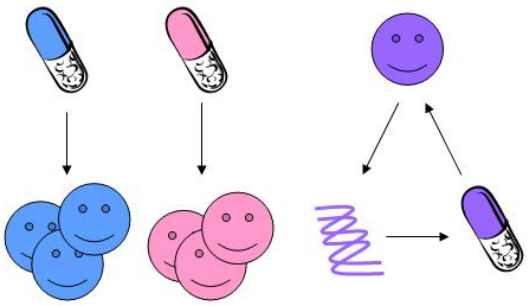
SERVING THE FUTURE OF MEDICINE

From blockbusters...

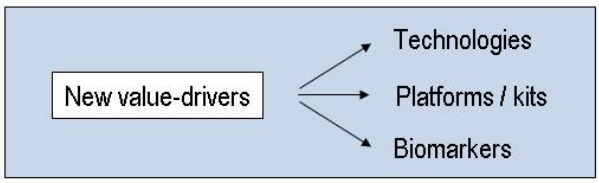


" one size fits all"

...to "niche"-busters and autologous



" the right medicine to the right patient"



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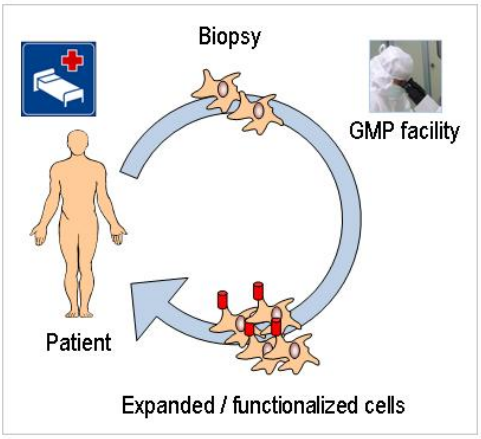
HOSPITAL – INDUSTRY COLLABORATION

Bringing together different sets of skills and expertise
for the clinical development of Advanced Therapies



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HOSPITAL – BIOTECH COLLABORATION

Bringing together different sets of skills and expertise
for the clinical development of Advanced Therapies

Hospital

- Good Clinical Practice
- Patient's management
- Target indications and applications
- Clinical trial protocols

SME
Industrial GMP Facility

- Good Manufacturing Practice
- Scale up – industrialization
- Logistics – Supply chain
- IP management

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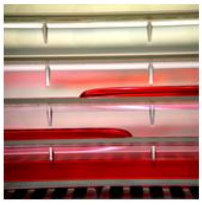
MISSION



areta *international* is a biotech company dedicated to the contract development and manufacturing of biotechnology products and cell-based medicines.

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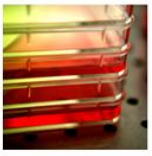
CORE COMPETENCES



- Products from cells
  - Monoclonal antibodies
  - Recombinant proteins
- Cells and tissues as products
  - Tissue engineering
  - Cellular therapy

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HISTORY

1999
Foundation of Areta with private capital, as a spin-off of cell biology labs of Lepetit Research Center (subsidiary of multinational company)

2004
GMP authorization by AIFA (Italian Drug Agency) for a Cell Therapy product for Phase I and II clinical trials

2008
GMP facility revamping: 2X surface area and 4X production capability

2012
Periodic inspection for GMP-compliance, passed with no major observations

2012
Holding F.I.S. acquires a strategic stake in Areta, to strenghten the company's position as the ideal partner for the development of innovative therapies

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WHERE WE ARE TODAY

2013
Experienced Contract Development and Manufacturing Organization, with GMP-inspected facility, authorized to produce investigational drugs of the following categories:

- Cell-based medicines
- Recombinant therapeutic proteins and monoclonal antibodies
- Plasmid DNA for therapeutic vaccination

We can formulate and release the finished dosage, through in-house:

- Final filling and finishing (+ lyophilization)
- Chemical and microbiological analysis

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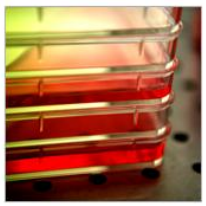
AREAS OF ACTIVITY



- Pre-clinical development: high-quality, GMP-like material for toxicology and non-clinical studies
- Clinical development: supply for Phase I, II and III clinical trials of Biotechnology products and Advanced Therapies

Phase	Pre-clinical	Clinical trials			Large scale
Development stage	R&D	Phase 1	Phase 2	Phase 3	Market

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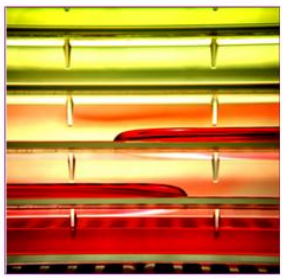
THANK YOU FOR YOUR ATTENTION



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