EUROPEAN PARLIAMENT

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A
ECONOMIC AND SCIENTIFIC POLICY

Economic and Monetary Affairs

Employment and Social Affairs

Environment, Public Health and Food Safety

Industry, Research and Energy

Internal Market and Consumer Protection

Workshop on Advanced Therapy Medicinal Products

MEETING DOCUMENT

EN

2013

Workshop on Advanced Therapy Medicinal Products /Meeting Document

DIRECTORATE GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

WORKSHOP

Advanced Therapy Medicinal Products

Brussels, 20 February 2013

MEETING DOCUMENT

ЕВРОПЕЙСКИ ПАРЛАМЕНТ PARLAMENTO EUROPEO EVROPSKÝ PARLAMENT EUROPA-PARLAMENTET
EUROPÄISCHES PARLAMENT EUROOPA PARLAMENT ΕΥΡΩΠΑΪΚΟ ΚΟΙΝΟΒΟΥΛΙΟ EUROPEAN PARLIAMENT
PARLEMENT EUROPÉEN PARLAIMINT NA hEORPA PARLAMENTO EUROPEO EIROPAS PARLAMENTS
EUROPOS PARLAMENTAS EURÓPAI PARLAMENT IL-PARLAMENT EWROPEW EUROPEES PARLEMENT
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EURÓPSKY PARLAMENT EVROPSKI PARLAMENT EUROOPAN PARLAMENTTI EUROPAPARLAMENTET

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

Workshop on Advanced Therapy Medicinal Products

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

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

SHORT BIOGRAPHIES OF EXPERTS

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

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, Head of the Laboratory of Pediatric Immunology, University of Louvain (BE)

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, 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)

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, Scientific Director, EURORDIS (European Organisation for Rare Diseases)

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, 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)

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, founder and Chief Executive Officer of Areta International, member of the Management Committee of Assobiotec, the Italian biotechnology industry association; (IT)

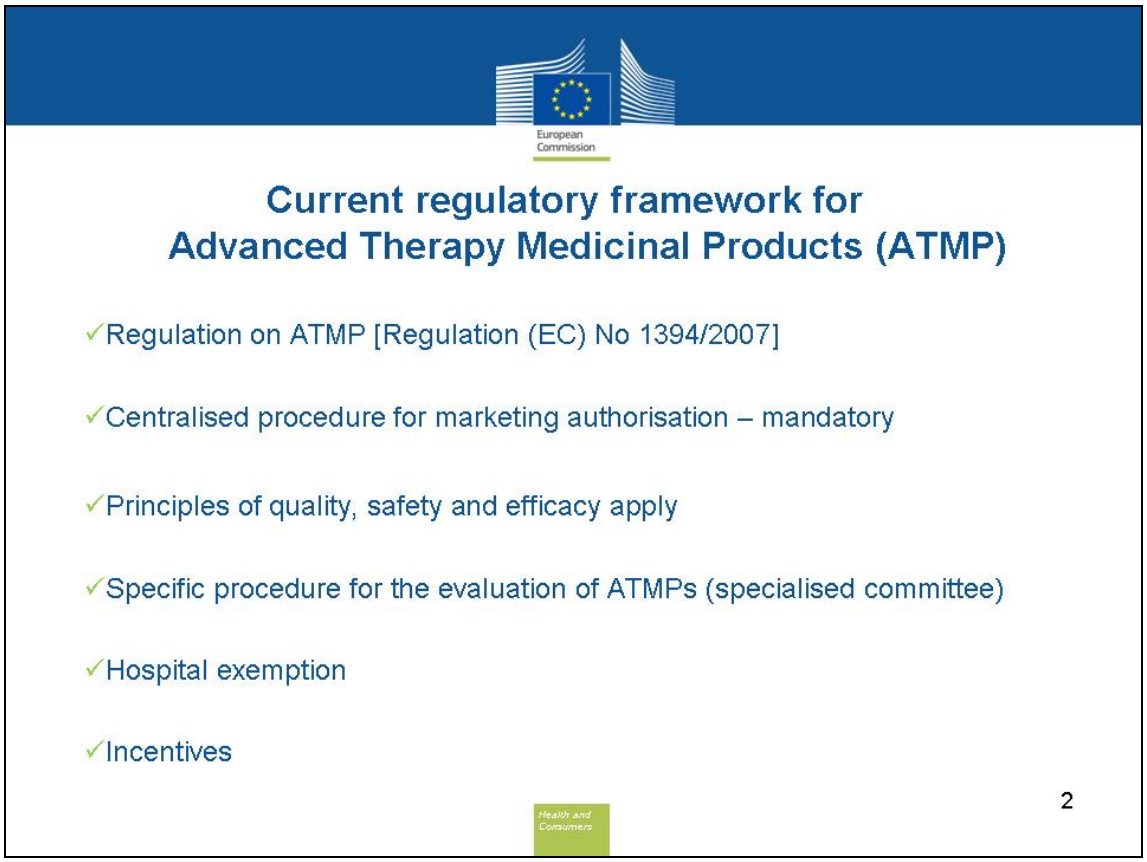
Dr Maria Luisa Nolli holds a degree in Biological Sciences from the University of Pavia and a Ph.D from the Université Libre de Bruxelles. She is the founder and Chief Executive Officer of Areta International, an Italian biotech company dedicated to the contract development and manufacturing of innovative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

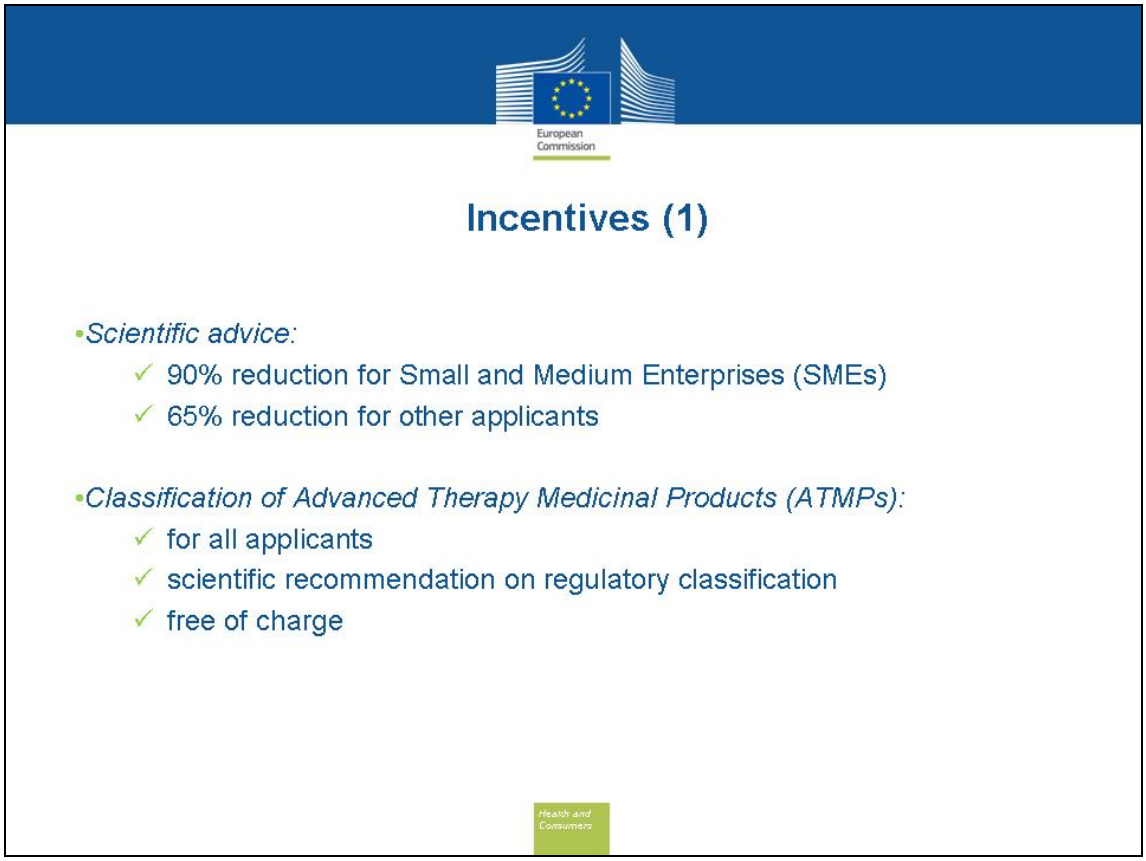
Dr Nolli has developed industrial experience as a scientist and group leader in the field of Cell Biology and Immunology working at the Lepetit Research Center (Dow Pharma). Since 2007, she is also CEO of HO.p.e. s.r.l, a spin-off of the State University of Milan, for the development of an innovative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

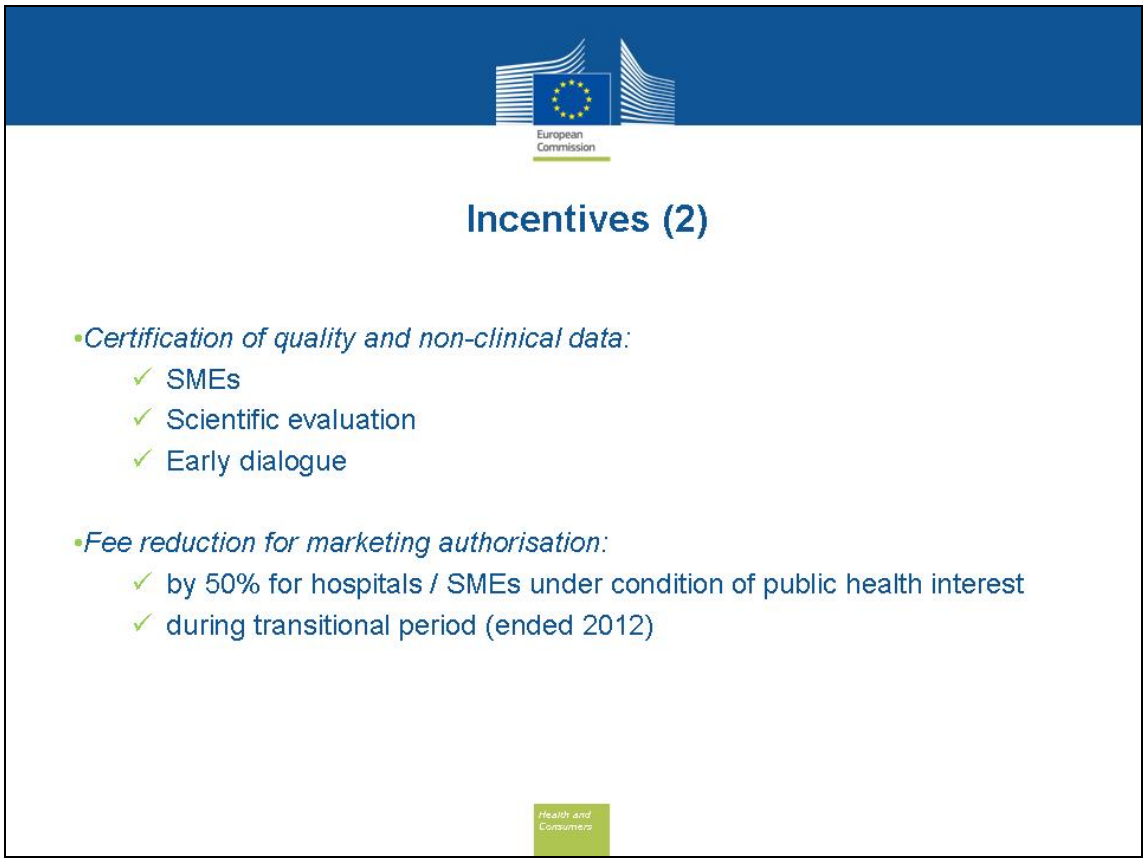
Dr Nolli is member of Assobiotec, the Italian biotechnology industry association, for which she is the representative at EuropaBio and member of the European Federation of Biotechnology.

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

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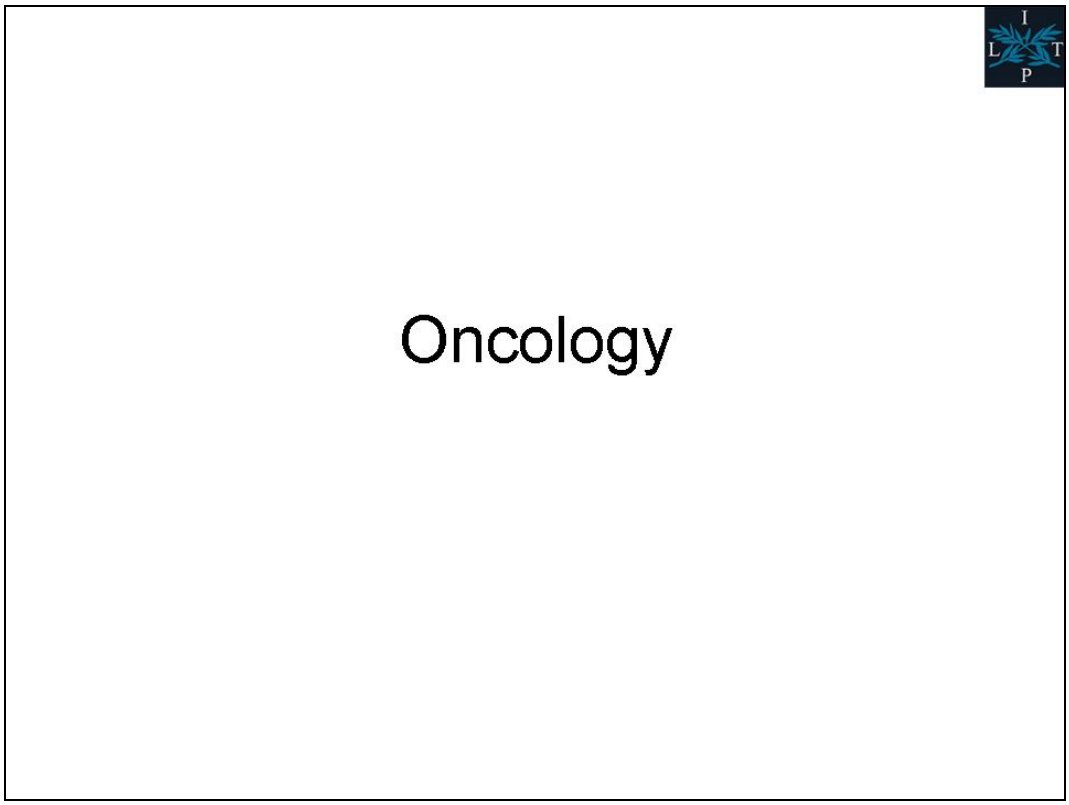
Presentation by Mr Stefaan Van Gool



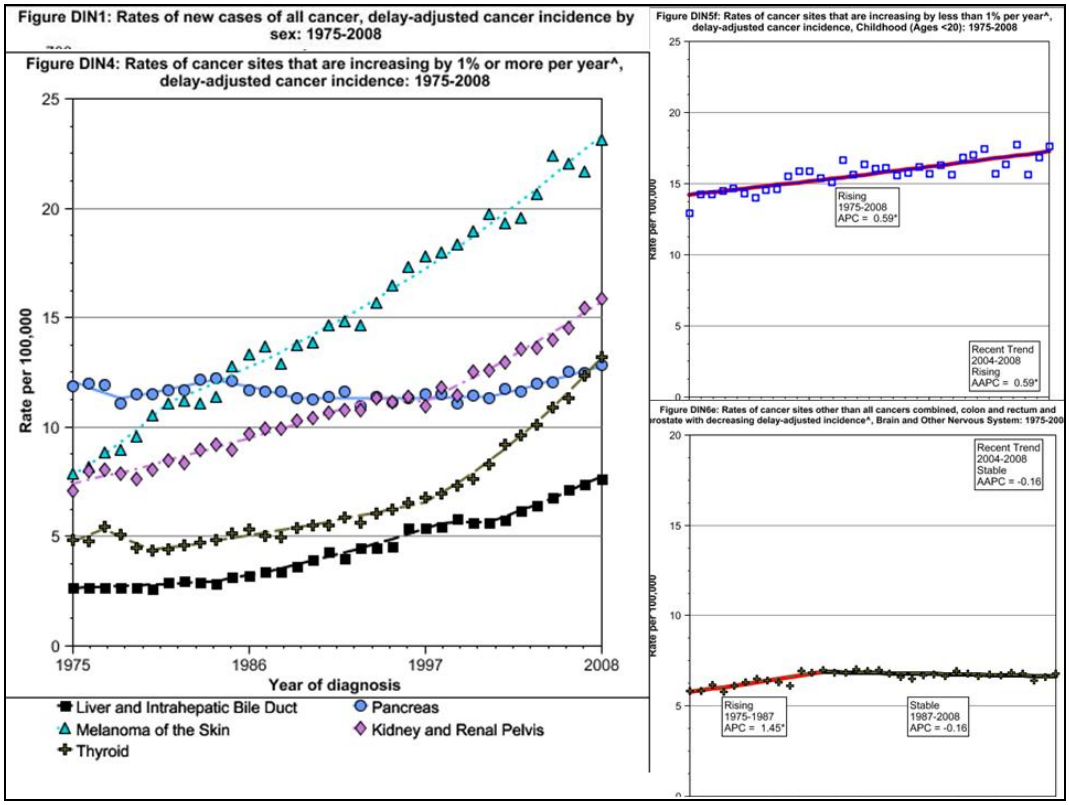
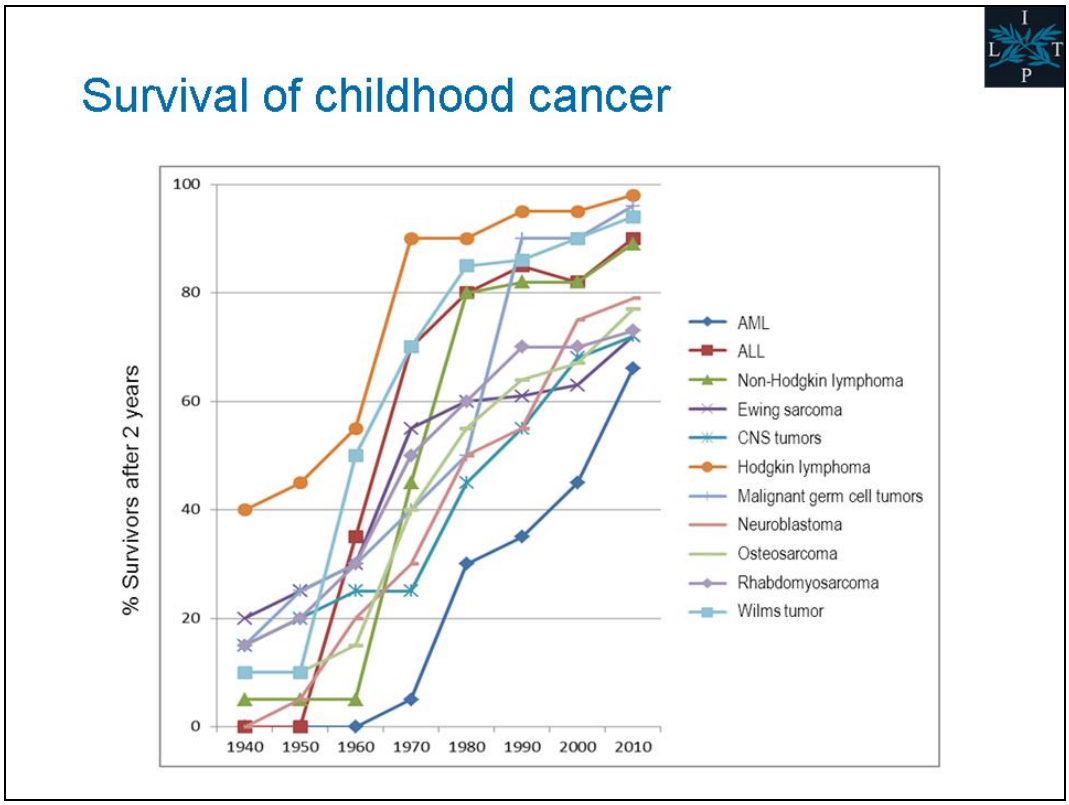
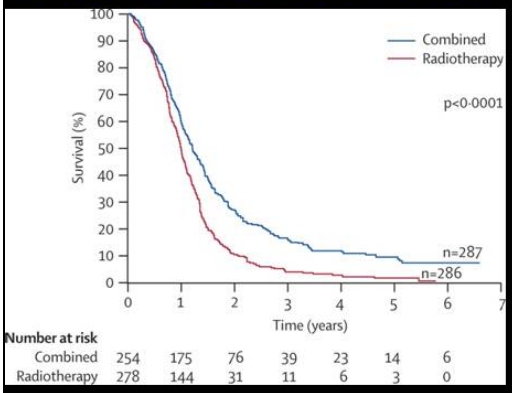
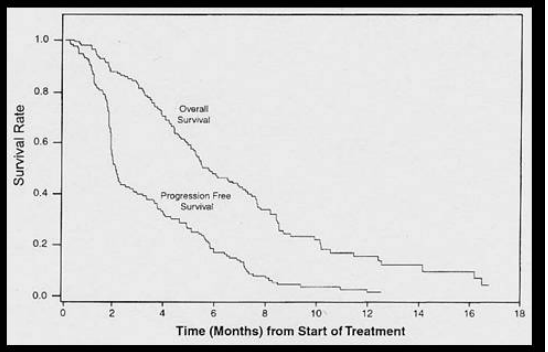


Figure DIN1: Rates of new cases of all cancer, delay-adjusted cancer incidence by sex: 1975-2008
Figure DIN4: Rates of cancer sites that are increasing by 1% or more per year^, delay-adjusted cancer incidence: 1975-2008
Rate per 100,000
Year of diagnosis
1975
1986
1997
2008
Liver and Intrahepatic Bile 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

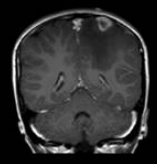

Survival of childhood cancer
% Survivors after 2 years
1940
1950
1960
1970
1980
1990
2000
2010
AML
ALL
Non-Hodgkin lymphoma
Ewing sarcoma
CNS tumors
Hodgkin lymphoma
Malignant germ cell tumors
Neuroblastoma
Osteosarcoma
Rhabdomyosarcoma
Wilms tumor

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



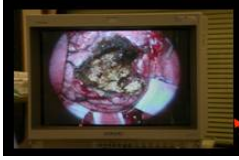


Brada et al. Annals of Oncology 2001;12:259-266



Glioblastoma multiforme: 3 per 100000 adults per year

! High community burden !

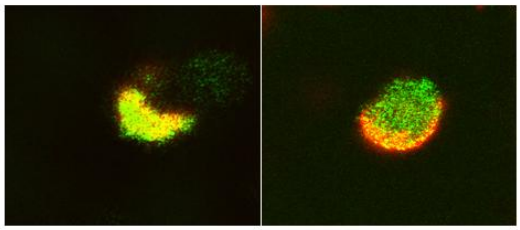


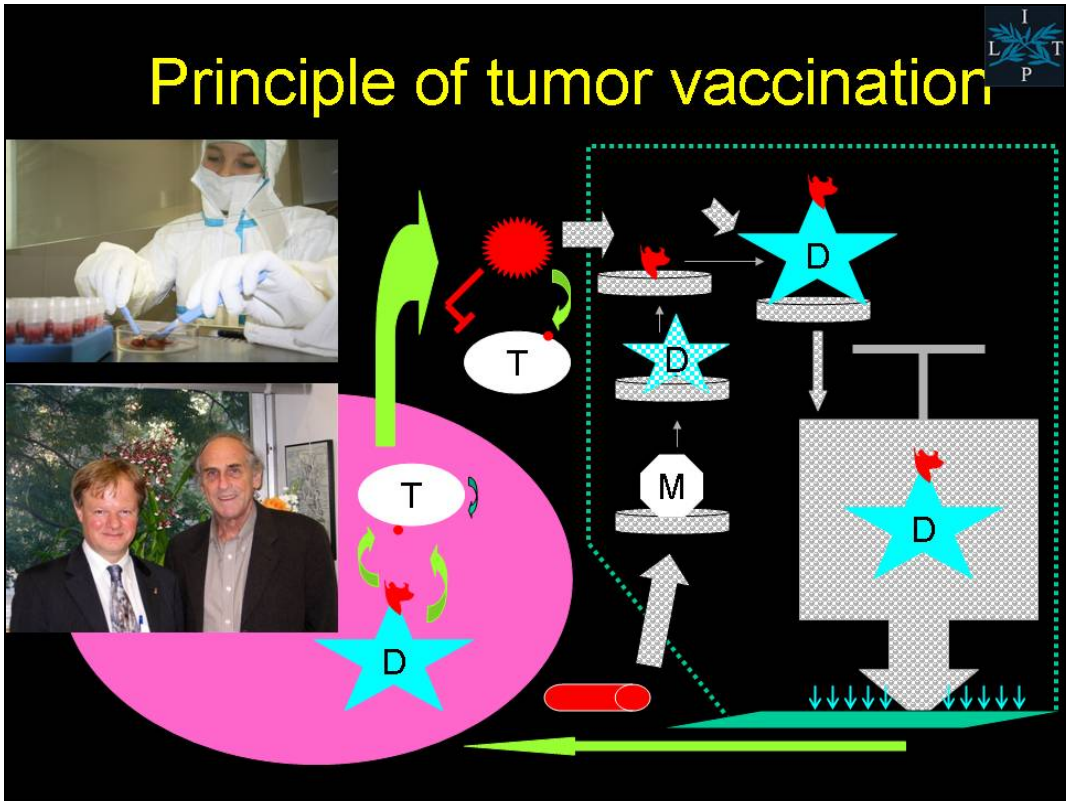
Temodar temozolomide Capsules

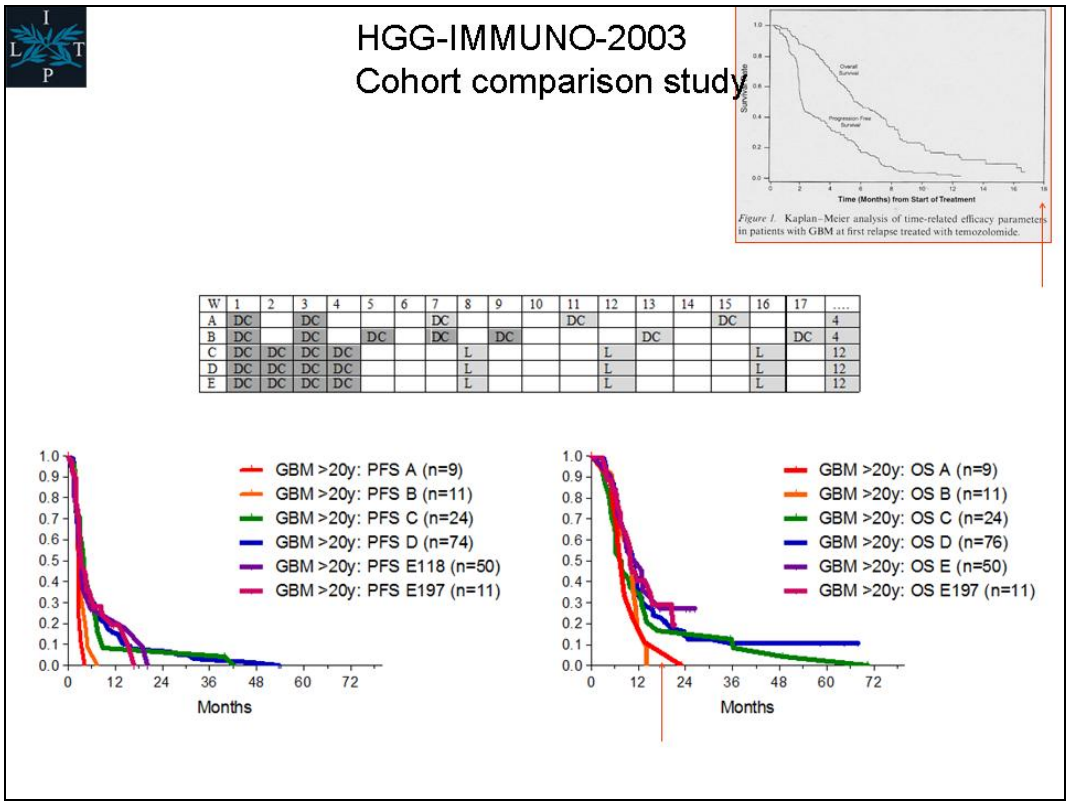
Immunotherapy for malignant glioma

An example

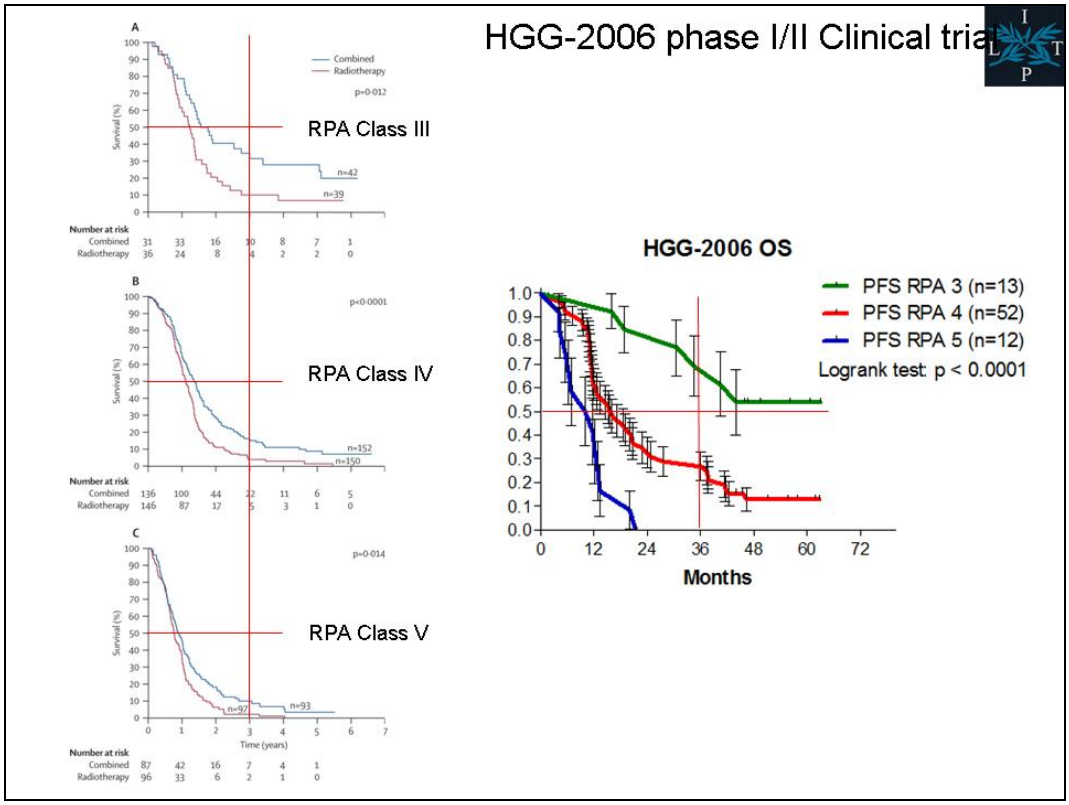
ATMP = DCm-HGG-L

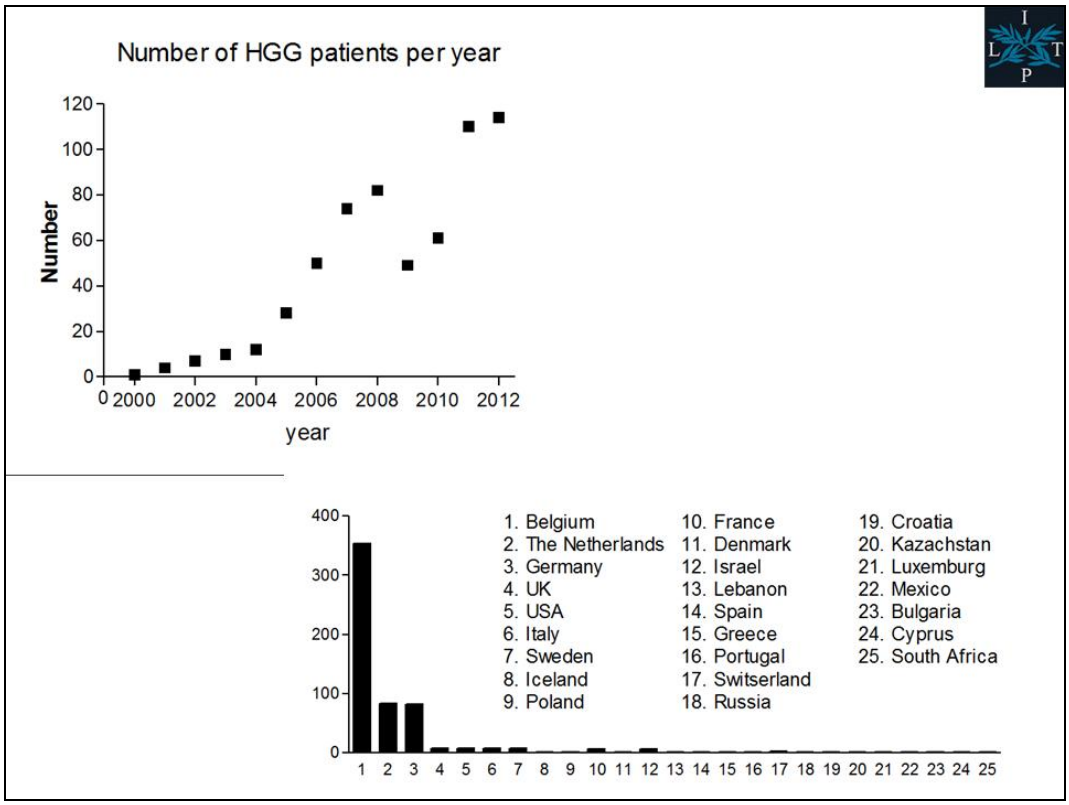


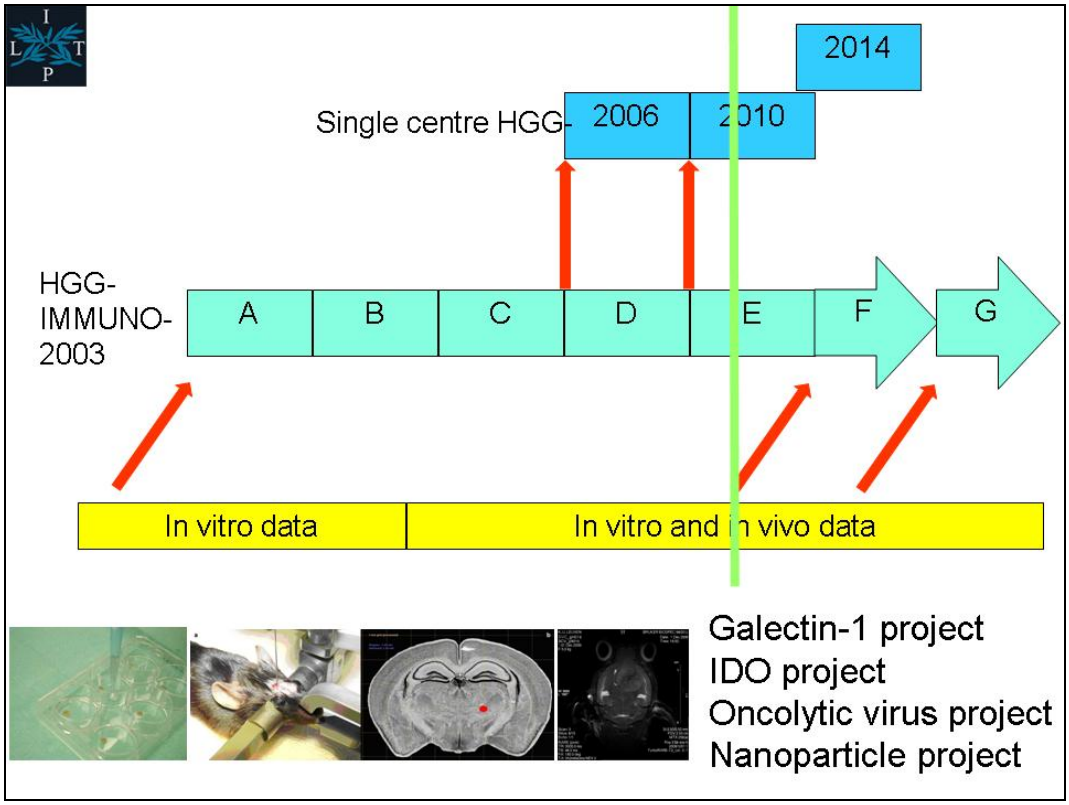


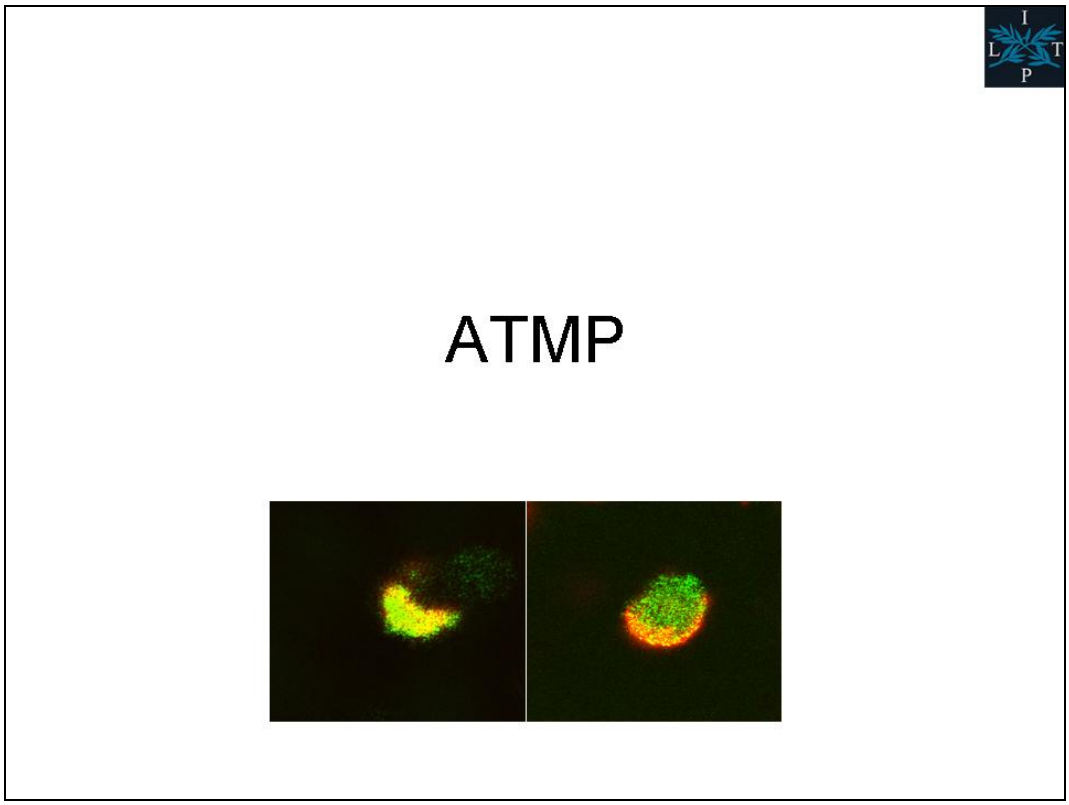


W	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	....
A	DC		DC				DC				DC				DC			4
B	DC		DC		DC		DC		DC				DC				DC	4
C	DC	DC	DC	DC				L				L				L		12
D	DC	DC	DC	DC				L				L				L		12
E	DC	DC	DC	DC				L				L				L		12


HGG-2006 phase I/II Clinical trial
RPA Class III
RPA Class IV
RPA Class V
HGG-2006 OS
PFS RPA 3 (n=13)
PFS RPA 4 (n=52)
PFS RPA 5 (n=12)
Logrank test: p < 0.0001
Months


Number of HGG patients per year
Number
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

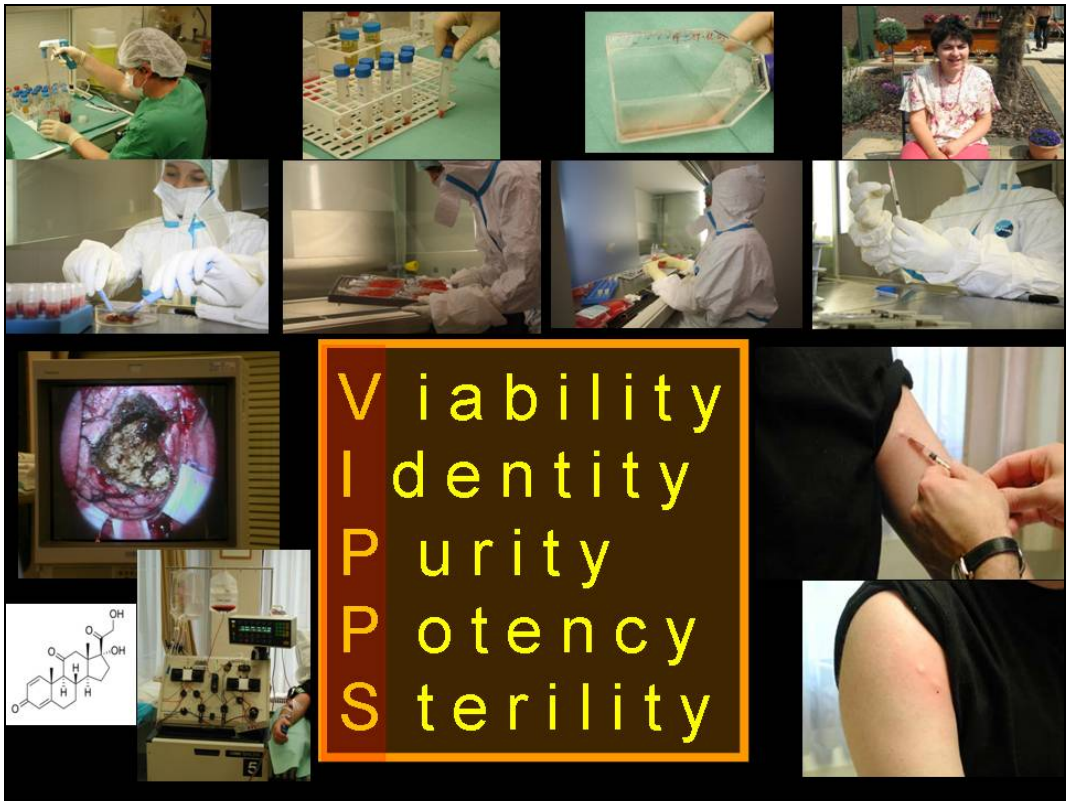
- **ATMP** means any of the following medicinal products for human use:
  - a gene therapy medicinal product ad defined in Part IV of Annex I to Directive 2001/83/EC
  - A somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC
  - A tissue engineered product
- **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



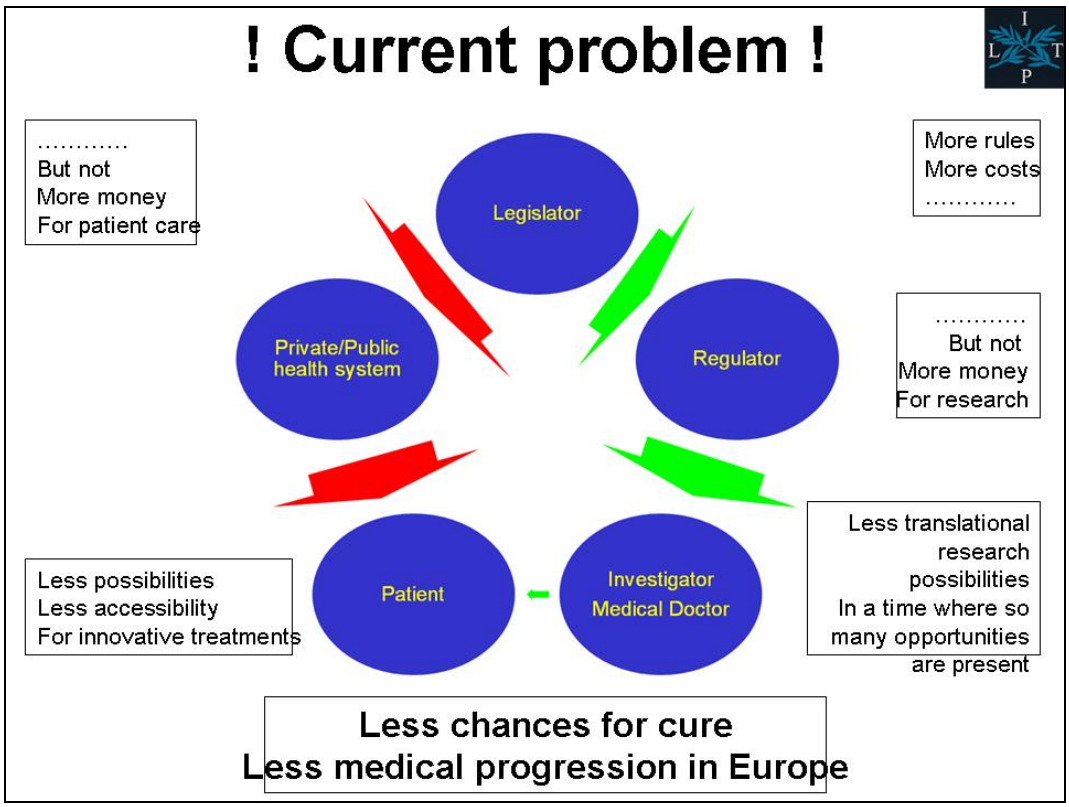
ATHP in academia for specific niche indications

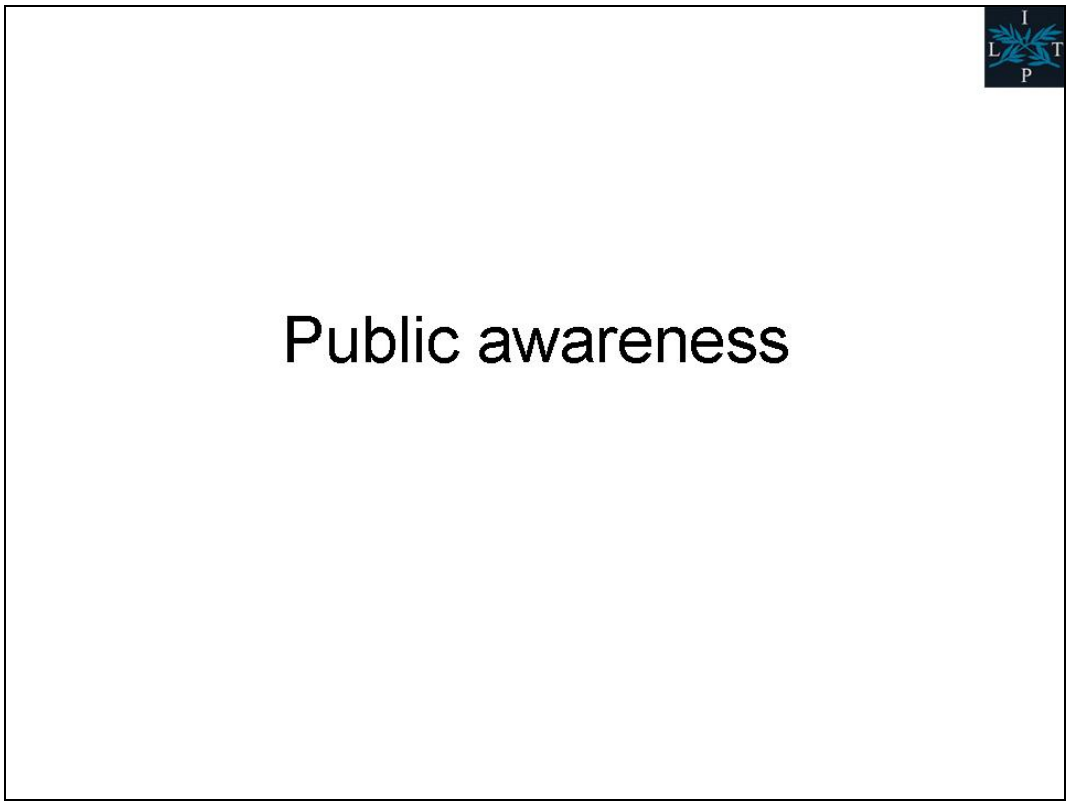
~~***Advanced Therapy Medicinal Product (ATMP)***~~ *prepared according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made 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 !
.....
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
Patient
Investigator Medical Doctor
Less possibilities
Less accessibility
For innovative treatments
Less chances for cure
Less medical progression in Europe


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

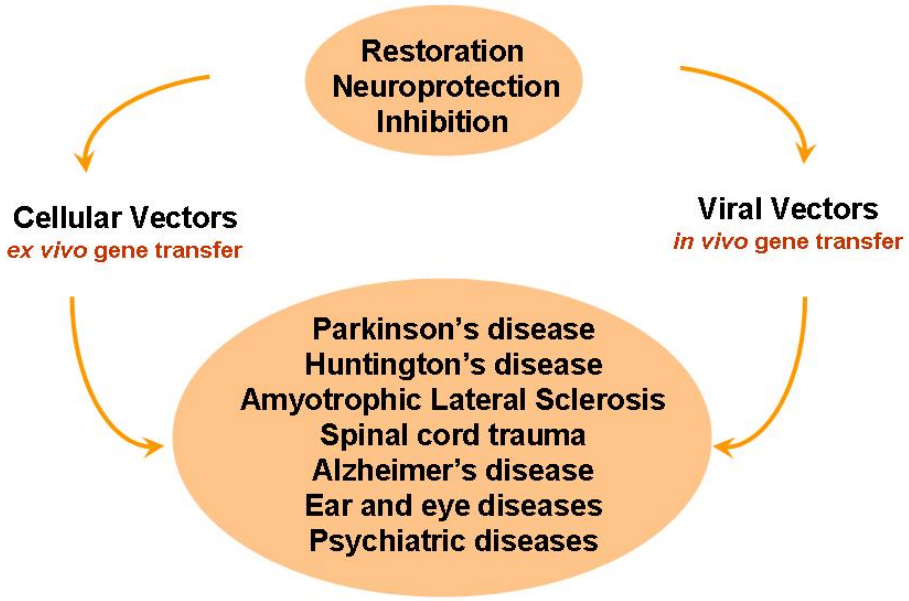
A number of therapeutic factors for the nervous system have been identidied.

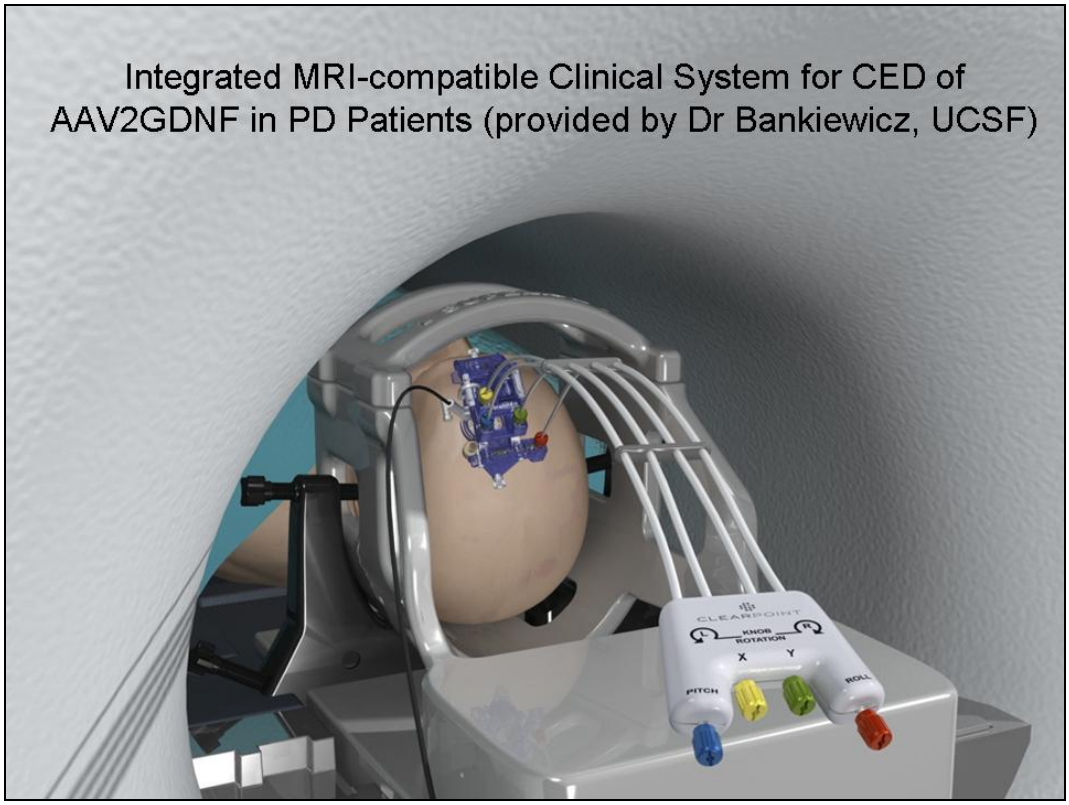
But, no possible systemic administration.

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

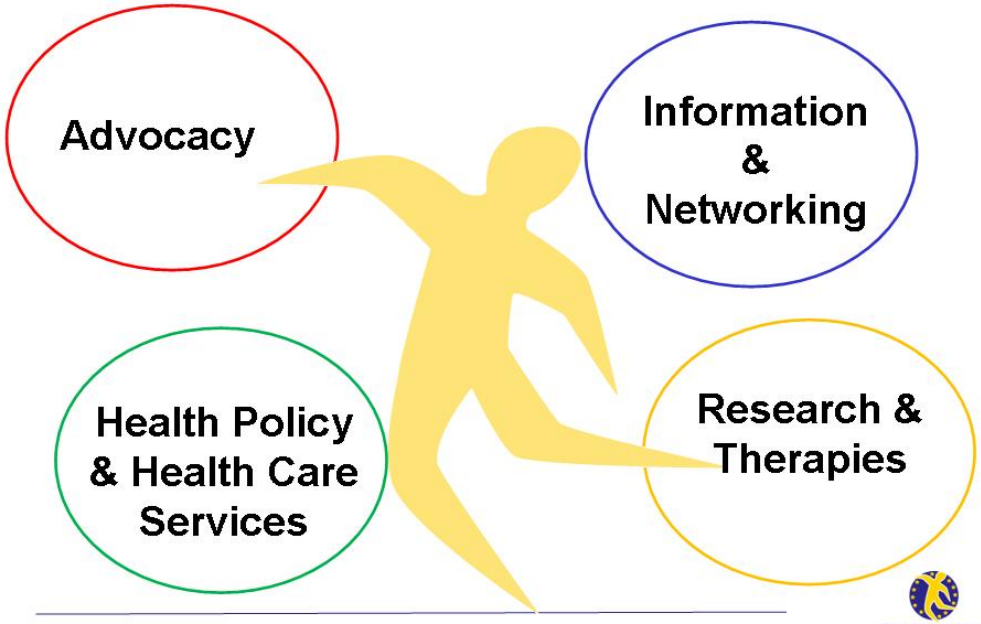
EURORDIS : KEY FIGURES

- 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

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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

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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

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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

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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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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.

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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

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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

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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

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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!**

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Rare Diseases Europe

Presentation by Mr Panos Kanavos

The Cost of Making Advanced Therapies 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

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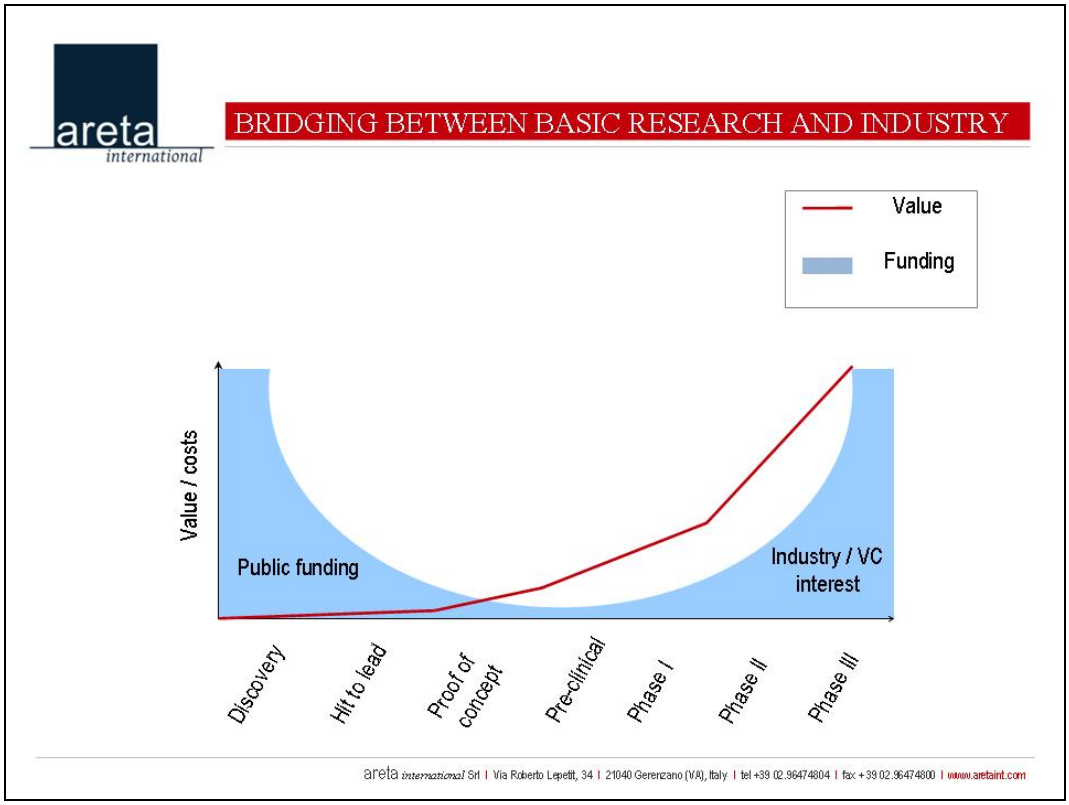
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BRIDGING BETWEEN BASIC RESEARCH AND INDUSTRY
Value
Funding
Value / costs
Public funding
Industry / VC interest
Discovery
Hit to lead
Proof of concept
Pre-clinical
Phase I
Phase II
Phase III
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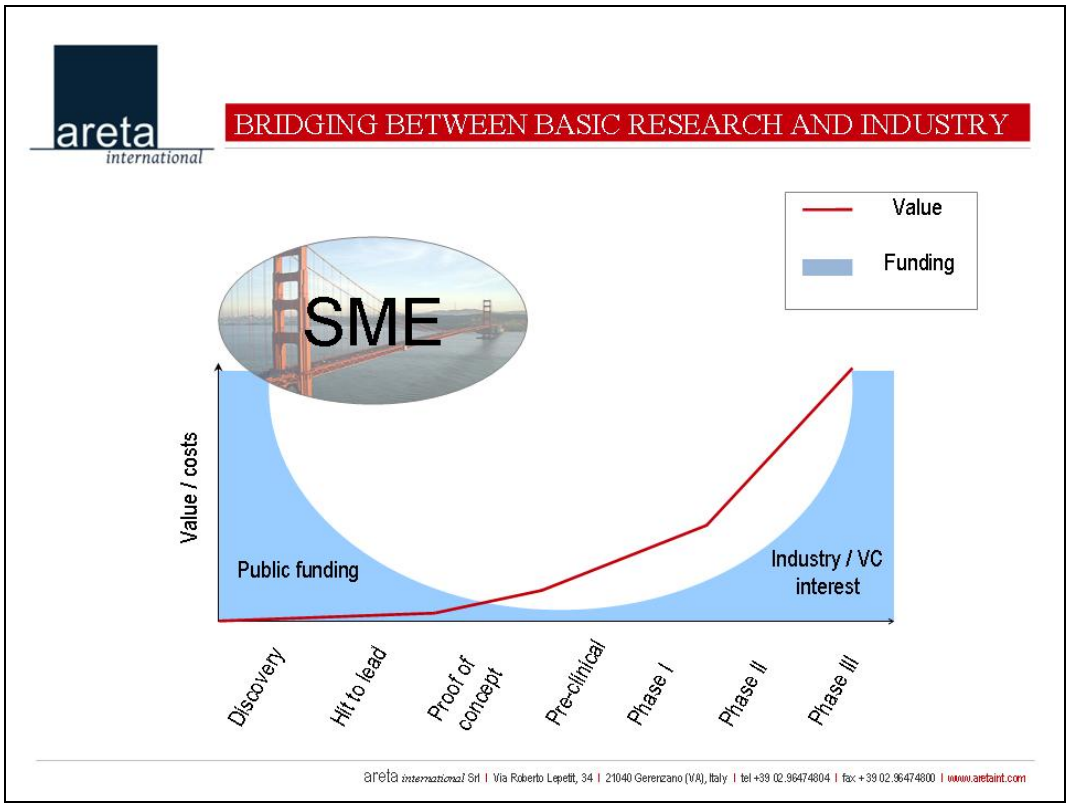
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BEING SME

- 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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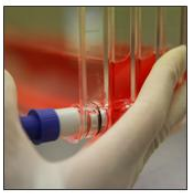
SME AND ADVANCED THERAPIES



- 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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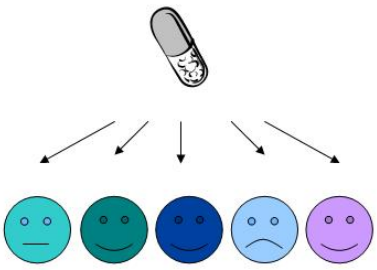
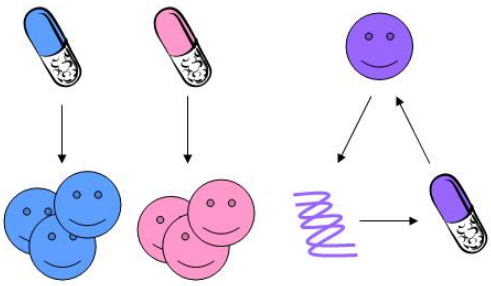
SERVING THE FUTURE OF MEDICINE

From blockbusters...



" one size fits all"

...to "niche"-busters and autologous



" the right medicine to the right patient"

New value-drivers → Technologies; Platforms / kits; Biomarkers

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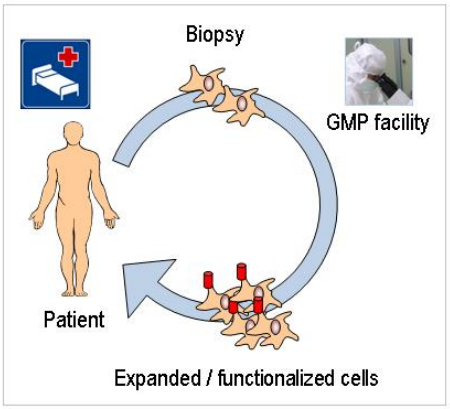
HOSPITAL – INDUSTRY COLLABORATION

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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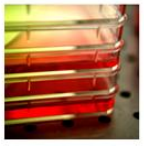
CORE COMPETENCES



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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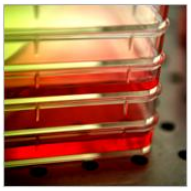
AREAS OF ACTIVITY



- 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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EUROPEAN PARLIAMENT

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A
ECONOMIC AND SCIENTIFIC POLICY

Role

Policy departments are research units that provide specialised advice to committees, inter-parliamentary delegations and other parliamentary bodies.

Policy Areas

- Economic and Monetary Affairs
- Employment and Social Affairs
- Environment, Public Health and Food Safety
- Industry, Research and Energy
- Internal Market and Consumer Protection

Documents

Visit the European Parliament website: **http://www.europarl.europa.eu/studies**

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