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Vírus e Outros Vetores em Ensaios Clínicos

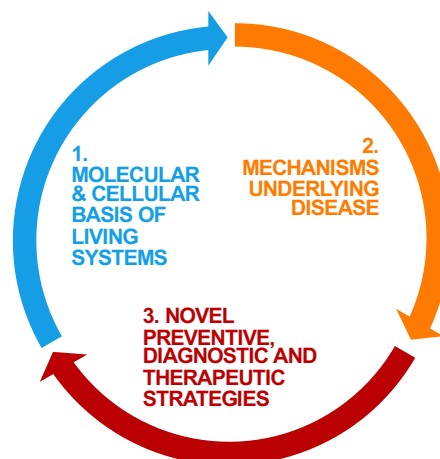
Ana Paula Pêgo
nBTT – nanoBiomaterials for Targeted Therapies
INEB – Instituto de Engenharia Biomédica
I3S – Institute of Research and Innovation in Health
apegno@ineb.up.pt

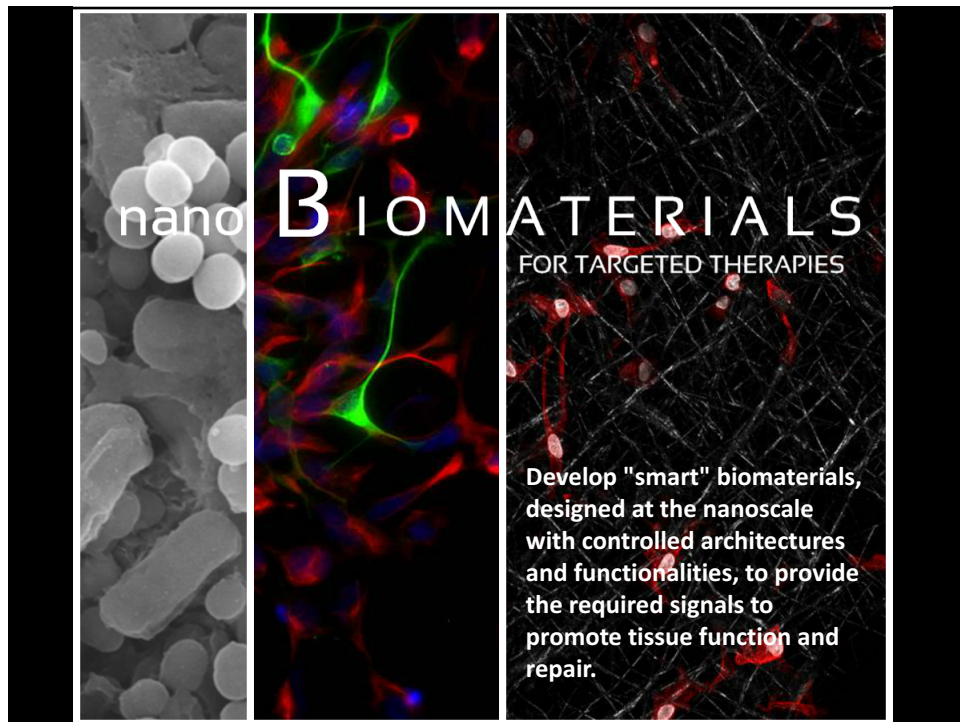
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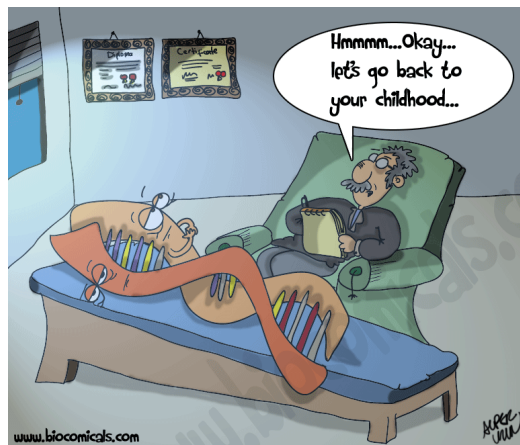
Simpósio CEIC 2016
Ensaios Clínicos: novos desafios, papel social e centros de ensaio
Lisboa – Novembro 22, 2016

Multidisciplinary approach to disease: From basic science to translation





Gene Therapy nucleic acid delivery



From DNA to Protein

DNA

mRNA

Protein

<http://slideplayer.com/slide/4194156/>

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Gene therapy


Nucleic Acids as therapeutic **agents**

Strategy that can provide the genetic information required to produce specific therapeutic proteins, increase their overall expression levels or downregulate its expression in target cells, thus correcting or modulating specific pathologies

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Gene Therapy



Gene transplantation to patients with a gene deletion

Gene correction to revert specific mutation in the gene of interest

Gene augmentation to enhance expression of a gene of interest

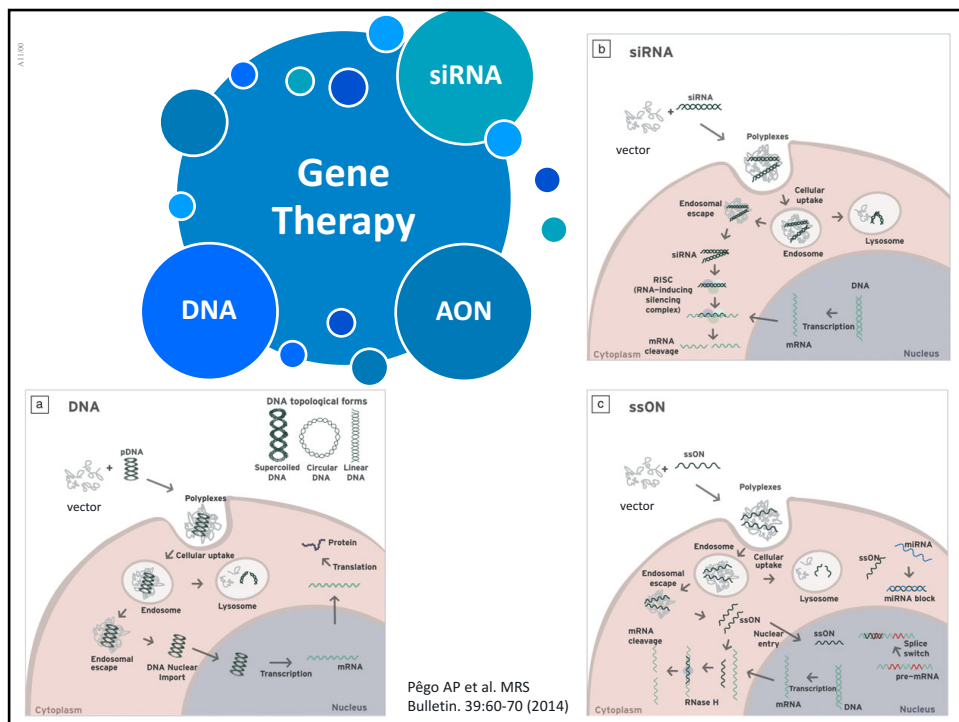
Gene ablation for targeted inhibition of gene expression

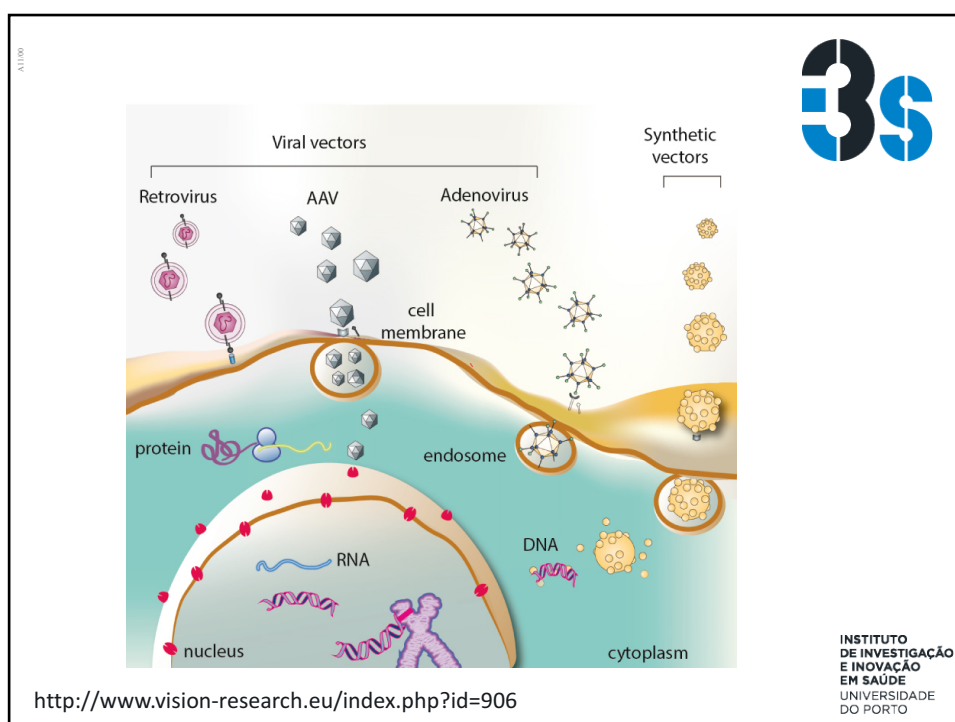
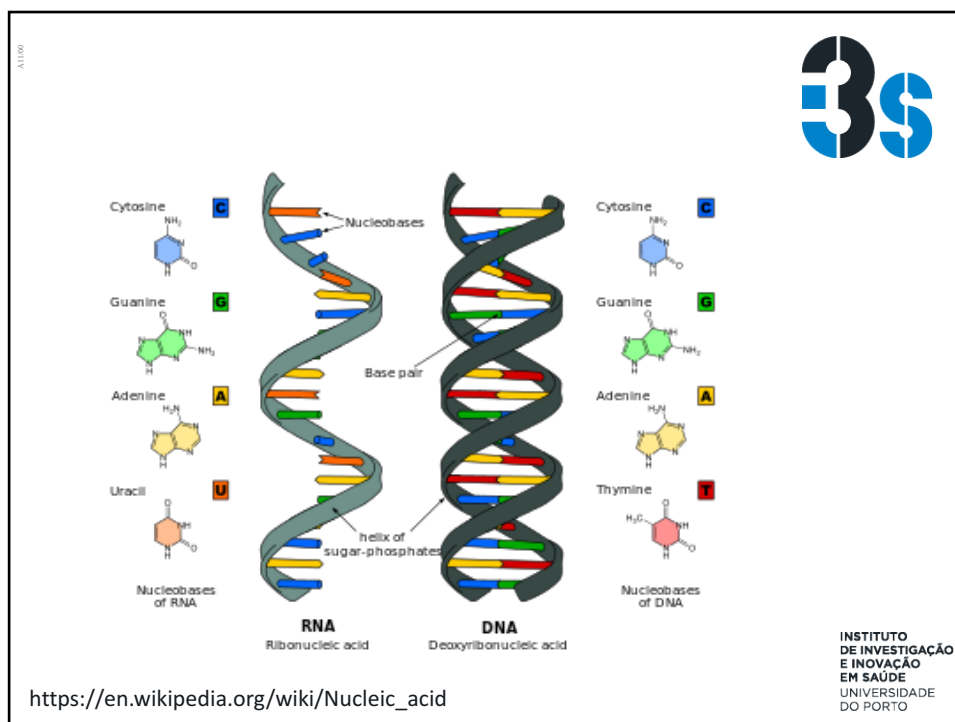
Protein expression ablation

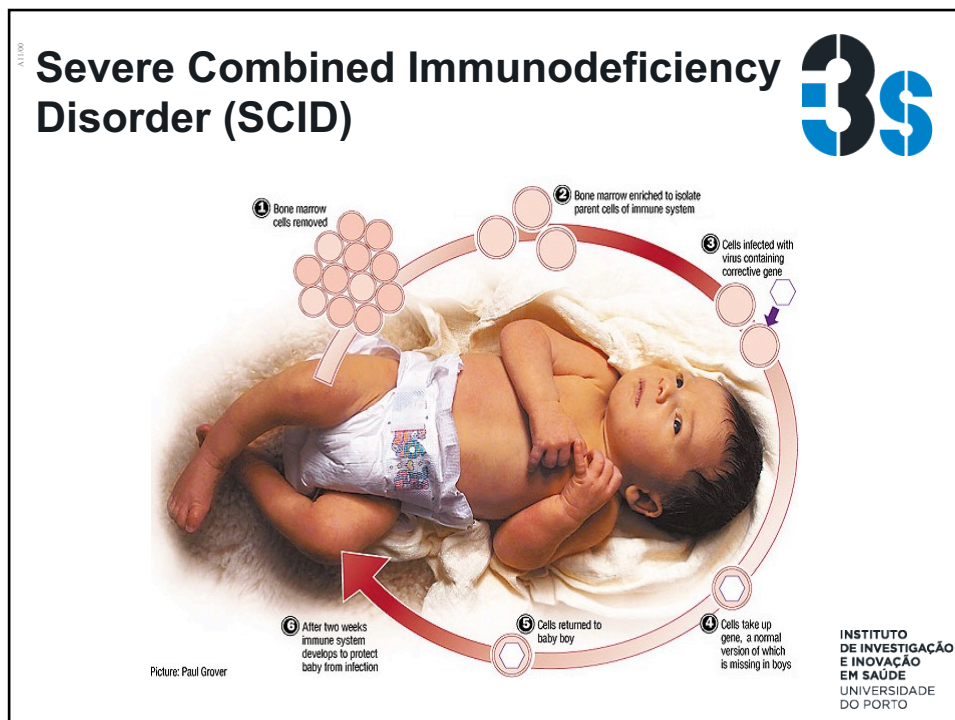
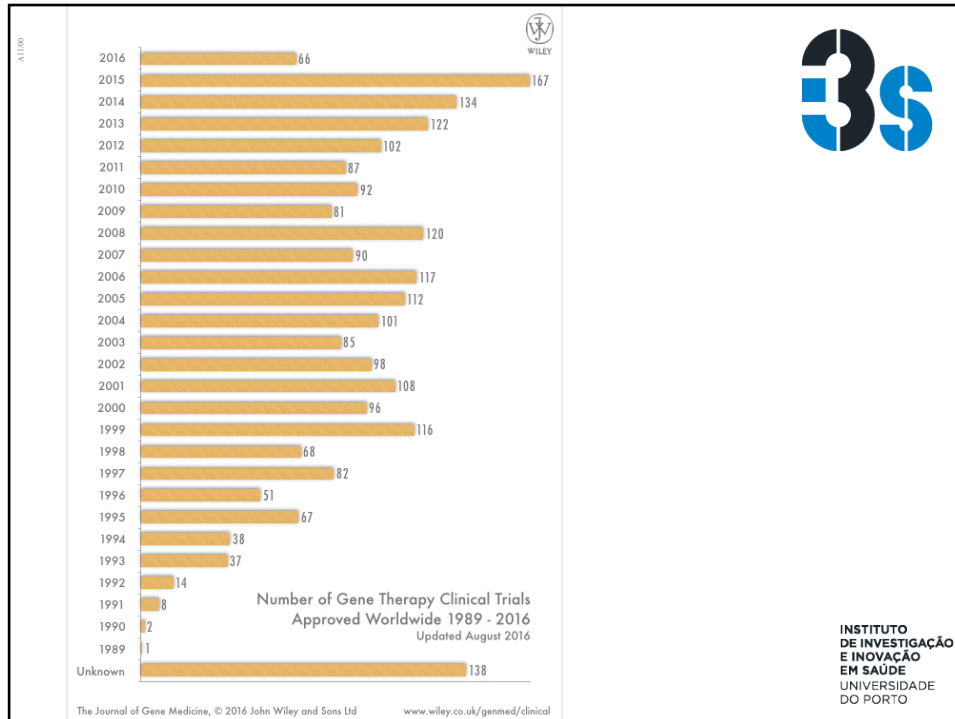
Targeted killing of specific cells by introducing a killer gene

Delivery of viral or bacterial genes as a form of vaccination

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Gene therapy setbacks

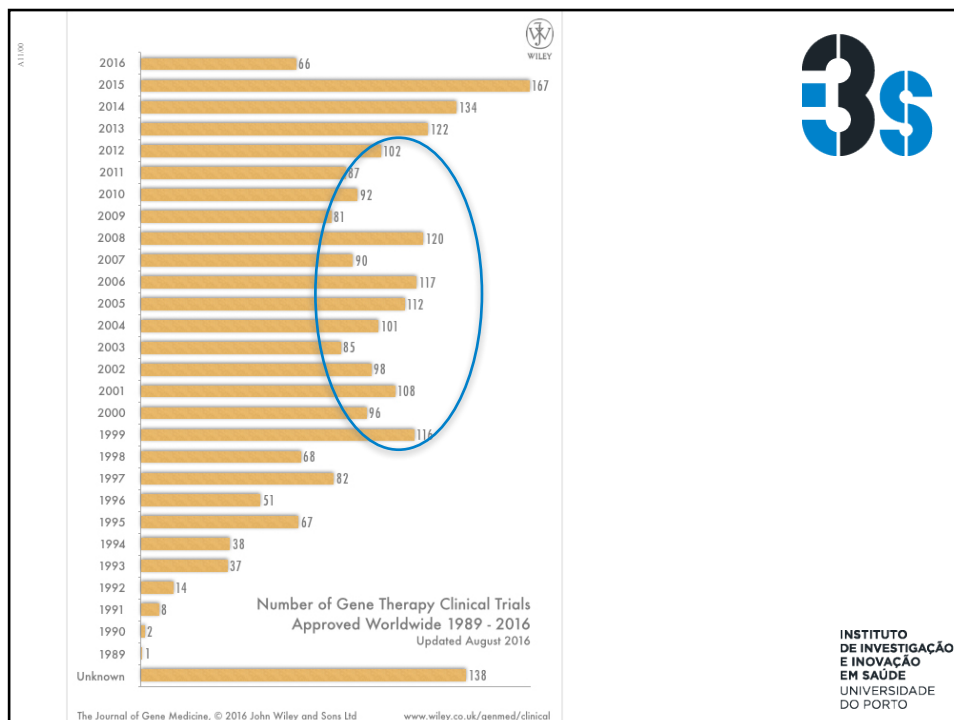


In 1999, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger. Jesse was participating in a gene therapy trial for ornithine transcarboxylase deficiency (OTCD). He died from multiple organ failure 4 days after starting the treatment. His death is believed to have been triggered by a severe immune response to the adenovirus carrier.

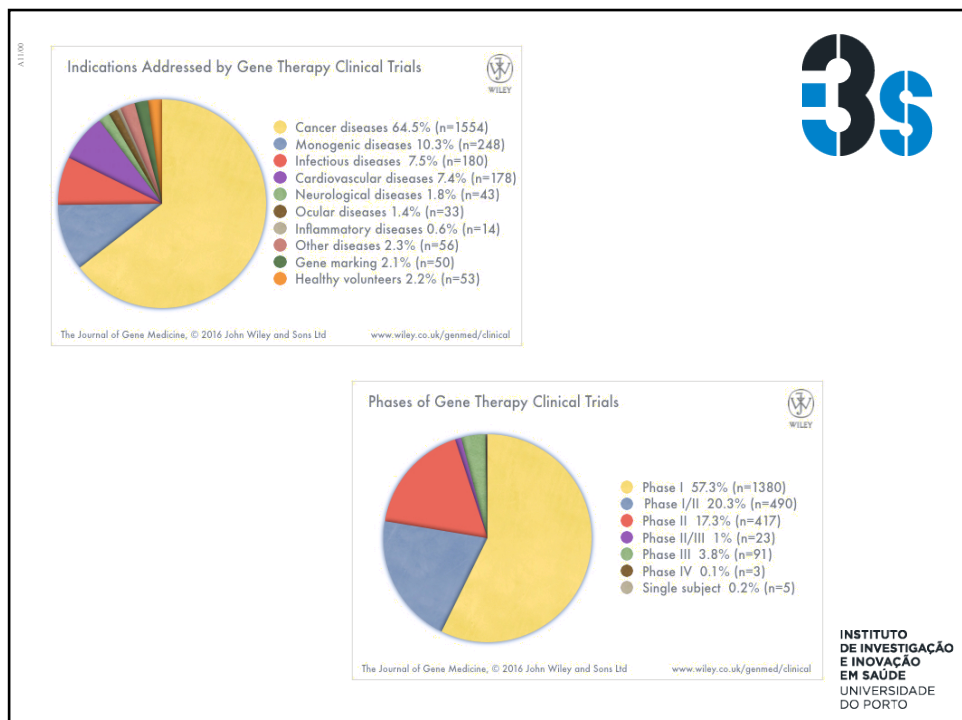
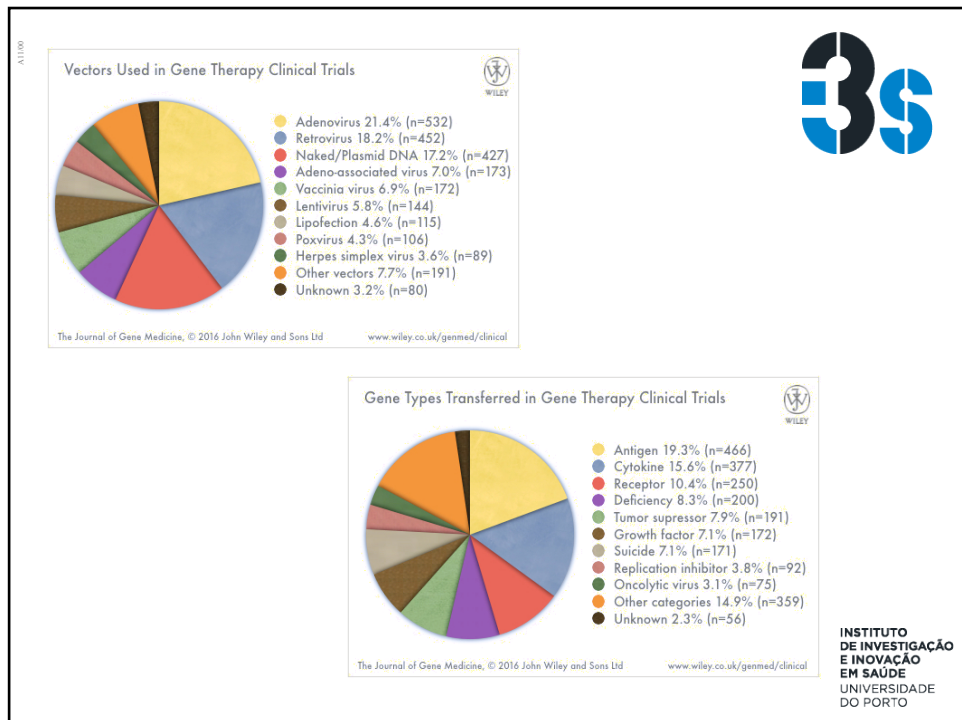
Another major blow came in 2003, when a second child treated in a French gene therapy trial had developed a leukemia-like condition. Both this child and another who had developed a similar condition in August 2002 had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID)

In 2007 a patient died who was receiving systemic immunosuppressive therapy for rheumatoid arthritis and who was enrolled in a gene-therapy trial. This trial was designed to evaluate intra-articular delivery of a tumor necrosis factor α (TNF- α) antagonist, through an adeno-associated virus (AAV) type 2 delivery system, for inflammatory arthritis.

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The first products... ... Gendicine™

Approved in
China in 2003




This virus (adenovirus) is designed to treat patients with tumors which have mutated p53 genes. Gendicine was approved in 2003 by the Chinese State Food and Drug Administration to treat head and neck squamous cell carcinoma.

<http://en.sibiono.com/>

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The first products... ... Oncorine®

Marketed
since 2006 in
China




<http://www.sunwaybio.com.cn/en/product.html>


The multi-center, open, randomized and parallel controlled clinical study with squamous cell carcinoma of head & neck and esophagus showed that curative effect of oncorine® (AAV-5) combined with chemotherapy was superior to chemotherapy alone with good safety profile. Promising data was noted for oncorine® in clinical studies of lung cancer, liver cancer, pancreatic cancer and malignant effusion.


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The first products... ... Glybera®

Approved in Europe since 2012 – used once after approval





Home About Gene Therapy R&D **Products** Investors

Glybera

Glybera® (alipogene tiparvovec) overview

Glybera has been approved for the treatment of lipoprotein lipase deficiency (LPLD), a very rare inherited condition that is associated with increased levels of chylomicrons, particles carrying certain fat in the blood. LPLD is caused by errors in the gene that codes for a protein called lipoprotein lipase (LPL). The LPL protein has an important role in dealing with the fats from the food that we eat. When the LPL protein does not work properly, or there is not enough of it, fat levels in the blood increase dramatically.

Glybera introduces a normal, healthy LPL gene into the body so that it can make functional LPL protein. The LPL gene is packaged in a delivery vector derived from adeno-associated virus (AAV), serotype 1, which has a natural propensity towards muscle cells. As muscle cells are normally the most important tissue contributing to healthy LPL protein production, this particular AAV is very suitable for correction of LPLD. Glybera is administered via a one-time series of small intramuscular injections in the legs.

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The first products... ... Imlygic®

FDA and EMA approved (2016)





IMLYGIC®
(talimogene laherparepvec) SUSPENSION FOR INJECTION
10⁶ PFU/mL and 10⁸ PFU/mL single-use vials

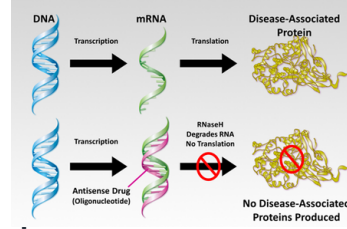
In unresectable melanoma recurrent after initial surgery...

**INJECT THE LESION.
TRIGGER AN IMMUNE RESPONSE.
THAT'S THE PRECISION OF IMLYGIC®¹**

IMLYGIC® is the first and only FDA-approved oncolytic viral therapy designed to replicate in cancer cells leading to oncolysis, whereby the release of tumor-derived antigens, virally derived GM-CSF, and replicated IMLYGIC® may promote an antitumor immune response.¹ The exact mechanism of action is unknown.¹

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Clinical trials in Portugal



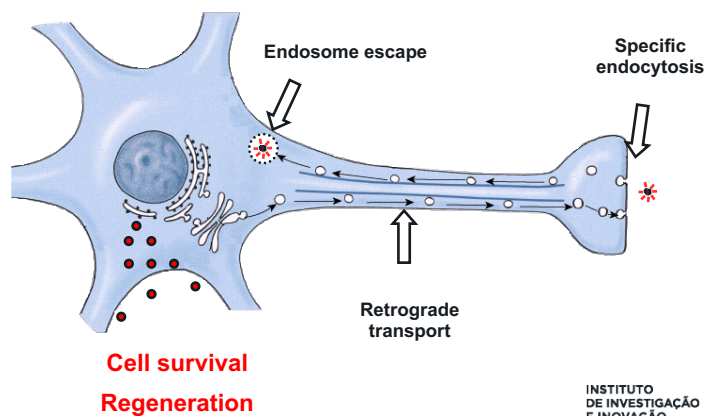
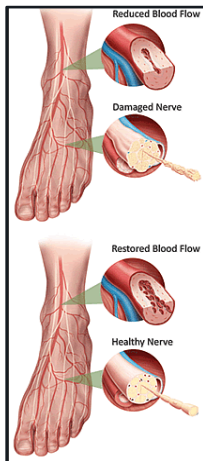
J. Clin Lipidol 2010; 4:350

- 5 ongoing trials involving antisense drugs
 - Safety = 1
 - Phase 2/3 = 2
 - Phase 3 = 2
- Familial Amyloid Polyneuropathy (FAP) (liver; reduce the production of transthyretin)
- Familial Partial Lipodystrophy (liver; reduce apoC-III protein production and to lower triglycerides to treat patients with dyslipidemia)
- Crohn's disease (gut; reduce Smad7 protein levels)

Information obtained @ <https://www.clinicaltrialsregister.eu/ctr-search/search>


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Gene therapy Viral vs non-viral vectors



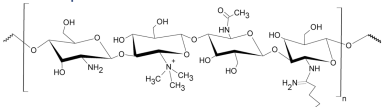
<http://www.provitastore.com/pag.php?id=199940>

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Chitosan-based nanoparticles

- Natural polymer
- Biodegradable
- Biocompatible



TMC, 40 kDA, 16% DA, 38.8% DQ
(fungal origin, provided by Kytozyme)

Gene delivery

- Nonviral Vector**
- Non-invasive**
- Targeted**

Tetanus Toxin C-fragment (HC)

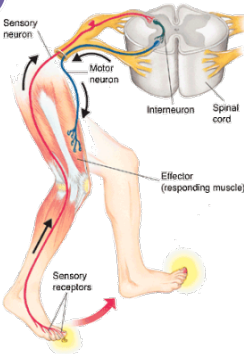
- Non-toxic
- High affinity to GT1b gangliosides (glycosphingolipid)
- Retrogradely transported


GT1b ganglioside

Tetanus toxin C-fragment (HC)

Peripheral administration

- Minimally invasive
- Clinically relevant

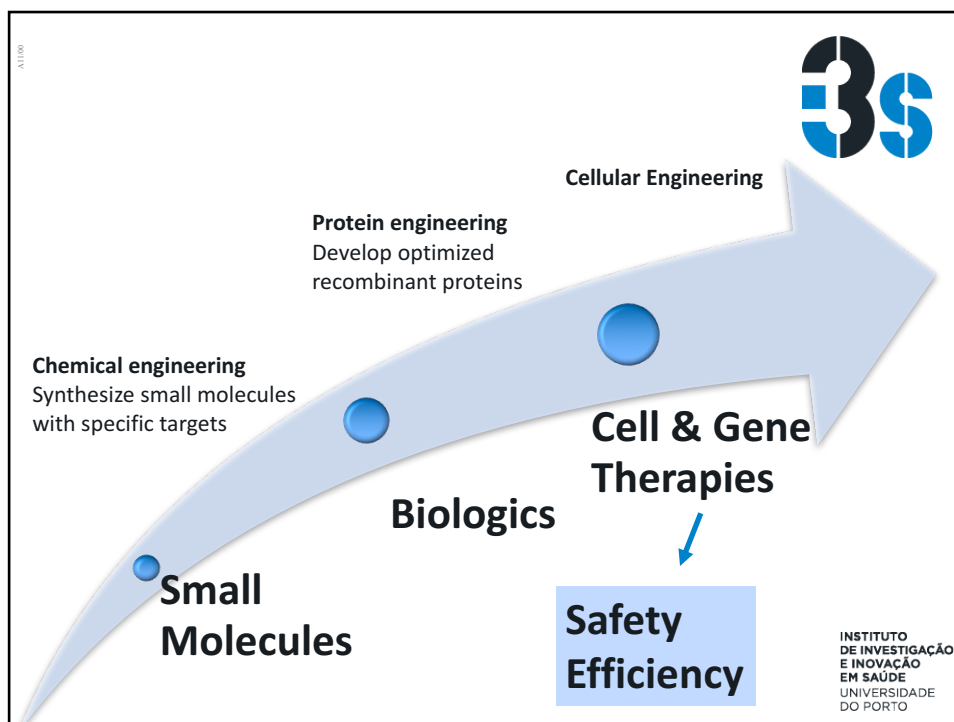




Slides removed by the researcher due to unpublished data.
For complete list of publications from the researcher visit:

<https://scholar.google.pt/citations?user=rF-q6vMAAAAJ&hl=en&oi=ao>
https://www.researchgate.net/profile/Ana_Paula_Pego
<http://orcid.org/0000-0001-5169-328X>

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Challenges

- Historically developed in academic environment without the objective of global commercialization
- Lack of adequate pre-clinical models and of sensitive tools to extensively characterize the product
- Technology transfer and showing comparability highly challenging
- Technology rapidly outpacing both industrial and regulatory questions
- Divergent product classifications/definitions add to complexity in migrating through regulatory pathways on global level

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Challenges



- **Cost of therapies potentially quite high – at least initially**
- **Current health eco-systems**
 - **Are not set up to deliver such complex therapies**
 - **Undervalue gene therapy, reducing incentives to develop and market them**
 - **Not set up to properly fund advanced therapy medicinal products (ATMPs), thus limiting access to few or no patients**

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NEURO TEAM

Isabel Amaral, PhD
Pedro Moreno, PhD
Vicky Leiro, PhD
Sofia Santos, PhD
Carla Gomes, PhD student
Cátia Lopes, PhD student
Ana Sadio, PhD student
Daniela Barros, PhD student
Ana Rita Bento, PhD student
Eva Carvalho, Technician
Teresa Rodrigues, Technician
Ana Spencer, MSc student
Filipe Oliveira, MSc student

FORMER TEAM MEMBERS

Hugo Oliveira, PhD
Liliana Pires, PhD
Joyce Santos, PhD
Daniela Rocha, PhD
Marta Freitas, PhD
Carla Moreira, MSc
Ana Rita Ferreira, MSc
Rita Silva, MSc
Tiago Santos, MSc
Ismael Neiva, MSc
Diana Leite, MSc
Miguel Xavier, MSc
Patrick Kennedy, MSc
Aida Moreira, MSc
Joana Silva, MSc
João Garcia, MS
Daniela Salvador, MSc
Marisa Assunção, MSc

Joana Loureiro, MSc
Joana Silva, MSc
Sara Sousa, MSc

COLLABORATORS

Mónica Sousa (i3S|IBMC)
Maria João Saraiva (i3S|IBMC)
João Relvas (i3S|IBMC)
Mário Barbosa (i3S|INEB)
Maria Oliveira (i3S|INEB)
Pedro Granja (i3S|INEB)
Cristina Barrias (i3S|INEB)
Paulo Aguiar (i3S|INEB)
Maria Lázaro (i3S|bIMAGE)
Paula Sampaio (i3S|IBMC)

Sergio Simões (CNC, PT) /Bluepharma
Domingos Henrique (IMM, PT)
Helena Tomás (U Madeira, PT)
Carlos Duarte (CNC/PT)

Peter Hinterdorfer (Linz U, Austria)
Jesper Wengel (SDU, Denmark)
James Kirkpatrick (Mainz U, Germany)
Herman Mansur (UF Minas Gerais, Brasil)
Eva Chinarro (CSIC, Spain)
Buchard Schlosshauer (Germany)











