Gene therapy: the basics (and more)

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Yáñez lab: Developing safer gene and cell therapy methods

Episomal vectors

Genome editing
Advanced Gene and Cell Therapy Lab

Disease models:
- Spinal muscular atrophy
- Ataxia telangiectasia
- Severe combined immunodeficiency
- Duchenne MD (with G. Dickson and L. Popplewell)
- Parkinson
- Spinal injury
- Stroke

- Strategies: Genome editing and Gene addition
  - Site-specific designer nucleases
  - Episomal systems
  - Replicating episomes
  - Induced pluripotent stem cells

- Vector systems:
  - Lentiviral (HIV-1, integration-deficient)
  - Adeno-associated viral
  - Retroviral
  - Adenoviral
  - Non-viral
What is he talking about???

- What is a rare disease?
- Why are rare diseases important?
- Genes and rare diseases
- Are all genetic mutations really bad?
- Political and research progress
- Need to change research priorities
- How do you do gene therapy?
- Marketed products and pricing
Why are Rare Diseases important?

In Europe, a disease is rare if fewer than 1 in 2,000 people are affected...

...6,000-8,000 rare diseases, 6% of people, 20% of Health budget...

...most rare diseases affect children and 30% of people affected will die before their 5th birthday...

...but 80% of rare diseases are inherited...

...and many are potentially amenable to genetic and stem cell therapies.
All those genes...(the green dots are one of them)
Genes store the info to make proteins

- Normal gene
  - Normal protein

- Mutant gene
  - Abnormal protein or no protein
Are all genetic mutations really bad?
Some are irrelevant, others minor...
...and evolution is based on mutations
But it can be very different...

Duchenne muscular dystrophy

Spinal Muscular Atrophy
A list of Rare Diseases (6,000 to 8,000 of them)

<table>
<thead>
<tr>
<th>ORPHA number</th>
<th>Disease name</th>
</tr>
</thead>
<tbody>
<tr>
<td>289157</td>
<td>1-alpha-hydroxylase deficiency</td>
</tr>
<tr>
<td>976</td>
<td>2,8-dihydroxyadenine urolithiasis</td>
</tr>
<tr>
<td>79154</td>
<td>2-aminoadipic 2-oxoadipic aciduria</td>
</tr>
<tr>
<td>391417</td>
<td>2-methyl-3-hydroxybutyric aciduria</td>
</tr>
<tr>
<td>391428</td>
<td>2-methyl-3-hydroxybutyric aciduria, classic type</td>
</tr>
<tr>
<td>391428</td>
<td>2-methyl-3-hydroxybutyric aciduria, infantile type</td>
</tr>
<tr>
<td>391457</td>
<td>2-methyl-3-hydroxybutyric aciduria, neonatal type</td>
</tr>
<tr>
<td>391417</td>
<td>2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

12 hours to read the list
The importance of awareness, diagnostics and coordinated care

Diagnosis can take 5 years or longer

- Lack of awareness among professionals
- Lack of validated diagnostic tests

Care at Centres of excellence that should:

- Coordinate care
- Have adequate caseload for expertise
- Not depend on a single clinician
- Arrange for transition from children’s to adults’ services
- Engage with people with rare conditions and their families
- Be research active
- Educate and train medical professionals
- Be members of international networks of excellence.
EUROPLAN:
• Since 2008 rare diseases are a priority area for action in EU Public Health Programmes

UK Royal College of General Practitioners:
• Rare Diseases are a clinical priority (2012-2015)
• “This programme focuses initially on Motor Neurone Disease but it will provide generic tools and learning across the spectrum of Rare Diseases.”

UK strategy for rare diseases (November 2013)
• “The UK Strategy aims to ensure no one gets left behind just because they have a rare disease…”
• Three out of the four home nations have developed an implementation plan for the UK strategy (not England yet)
Is there hope for Rare Diseases? - Research

Successes in gene therapy clinical trials:
• Spinal muscular atrophy
• Several Immunodeficiencies
• X-linked Adrenoleukodystrophy
• Haemophilia B
• (Leukaemia, not a rare disease)
• ...

International Rare Disease Research Consortium (IRDiRC, 2011), goals for 2020:
• Diagnostics for most rare diseases
• Cure for 200
• Vision updated for 2017-2027: Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention (1,000 new therapies approved)
International Rare Disease Research Consortium (IRDiRC)

About us

IRDiRC is a consortium of research funding agencies and interested parties acting to accelerate research through collaborations.

Objective 2020: 200 new therapies

- 2020: 200
- 2016: 222
- 2015: 188
- 2014: 146
- 2013: 103
- 2012: 72
- 2011: 43
- 2010: 14

Objective 2020: identify all genes

Follow the progress towards developing a diagnostic test to identify most rare diseases by the year 2020.

*Annual data extracted from Orphanet for 38 countries

http://www.irdirc.org/
International Rare Disease Research Consortium (IRDiRC)

http://www.irdirc.org/
We need treatments, loads of them!

Limited therapeutics: Number of Rare Diseases versus Number of Diseases screened for in newborns

Newborn blood spot test

Every baby is offered newborn blood spot screening, also known as the heel prick test, ideally when they are five days old.

Newborn blood spot screening involves taking a blood sample to find out if your baby has one of nine rare but serious health conditions.

Most babies screened won’t have any of these conditions but, for the few who do, the benefits of screening are enormous. Early treatment can improve their health and prevent severe disability, and even death.

What does the blood spot test involve?

When your baby is five days old, a health professional will prick their heel using a special device and collect four drops of blood on a special card. You can minimise any distress to your baby by cuddling and feeding them, and making sure they are warm and comfortable.
We need rare disease recognised as a research priority, and large-scale investment in therapy development (like in genomics)

The 100,000 Genomes Project

The project will sequence 100,000 genomes from around 70,000 people. Participants are NHS patients with a rare disease, plus their families, and patients with cancer.

(https://www.genomicsengland.co.uk)
What is gene therapy?

Deliberate alteration of the genome or its function to produce a therapeutic benefit
What can you do with gene therapy?

- Introduce a gene
- Make a gene produce more or less protein
- Repair a gene
- Stop a gene from working
- Kill cells
- Vaccinate
The *in vivo* and *ex vivo* approaches (GM in the body or outside)

*in vivo*: genetic modification of the cells of a patient inside the body

*ex vivo*: cells are modified outside the body before re-implantation
Scientists can take almost any cell from the body (for instance, from a bit of skin), and convert them into a stem cell in the laboratory. Afterwards, these lab stem cells can be corrected (if they were from a patient) and made to produce many different types of cells (muscle, blood, neurons...). In some cases these lab-grown cells could be used for therapy in transplants (not clear if this would be useful in Duchenne), but they are certainly useful to study the disease and to test possible therapies in the lab.
Gene therapy vectors (used to deliver genes, otherwise will not enter cells)

**Non-Viral**
- Naked DNA, needs help
- Lipoplex/Polyplex (fat/protein packaging)
- Recombinant Cells (Microencapsulation)

**Viral**
- Retroviral vectors (like HIV made safe)
- Adenoviral vectors (common cold)
- Adeno-Associated Virus vectors (AAV, very important for Duchenne)
Viruses are gene carriers (we hijack them in the lab to carry genes)

(http://biology.kenyon.edu/slnc/gene-web/Lentiviral/Lentiviz.html)
Viral vectors: how we make them (a lab cell produces them for us)

We produce these viruses in the lab, carrying the gene we want

Gene therapy strategies: “uncontrolled integration” (like HIV-type)

These viruses insert themselves in the genome; this could be a problem
Gene therapy strategies: episomal vectors

These viruses do not insert themselves in the genome (like AAV vectors)
Exon skipping in Duchenne muscular dystrophy

(Aartsma-Rus and van Ommen, Lancet Neurol. 2009 8: 873–875)
Exciting times in research: Genome Editing and Stem Cells
Genome editing for gene repair (used to be very difficult)

corrective vector

mutant gene

corrected gene
The future is CRISPR...maybe

Riding the CRISPR Wave

Biologists are embracing the power of gene-editing tools to explore genomes.
CRISPR has made genome editing democratic (much easier)

Pole dancing vaults towards Olympics

One has its origins in Ancient Greece when long jumps were used for vaulting the walls of high-walled cities, the boom of the 1980s. Yet within a decade it looks possible that pole dancing could join pole vaulting as an Olympic sport.

The Global Association of International Sports Federations (GAIMS) confirmed yesterday that it has given observer status to the International Pole Sport Federation (IPSF) in a move which sets out a “clear pathway” towards full Olympic recognition. Patrick Baumann, president of GAIMS, said it was an “exciting time” for pole sports and added: “We will do everything within our means to help them realise their full potential and one day, maybe become part of the Olympic programme.”

With skateboarding making its debut in Tokyo 2020, Katie Coates, president of the IPSF, is cautiously optimistic that pole sports could make the grade by 2024. She held her first meeting with the International Olympic Committee in February and described it as encouraging.

“I’m not saying yes we will be there, I’m not saying no either — there is a good opportunity for us and the sporting bodies are interested in seeing pole sports being recognised because they get people involved,” she said.

“We’re proving everybody has been told again and again that the additional sports that it will be very difficult for us to be recognised as a sport, but this shows us on one achieved...
The problem with the gene therapy market

Glybera (AAV vector, one-off): EUR\textsubscript{1,000,000}

Strimvelis (GM cell, one-off): EUR\textsubscript{594,000}

Spinraza (small-ish chemical): EUR\textsubscript{90,000/dose} (EUR\textsubscript{540,000} first year, EUR\textsubscript{270,000} per year thereafter)
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