Gene therapy: the basics (and more)

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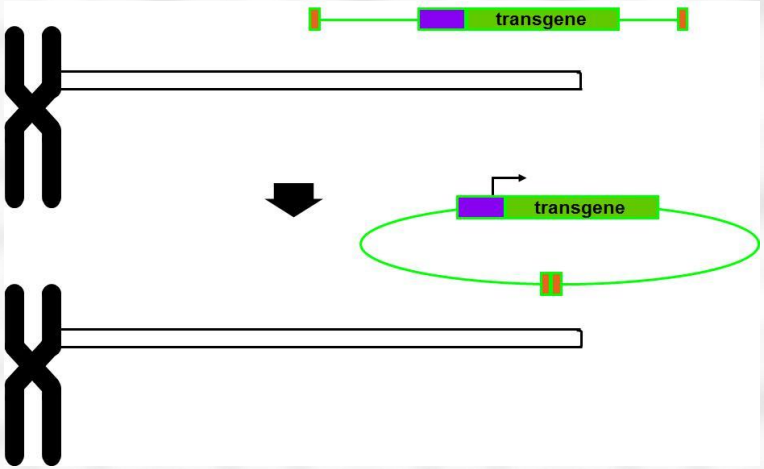
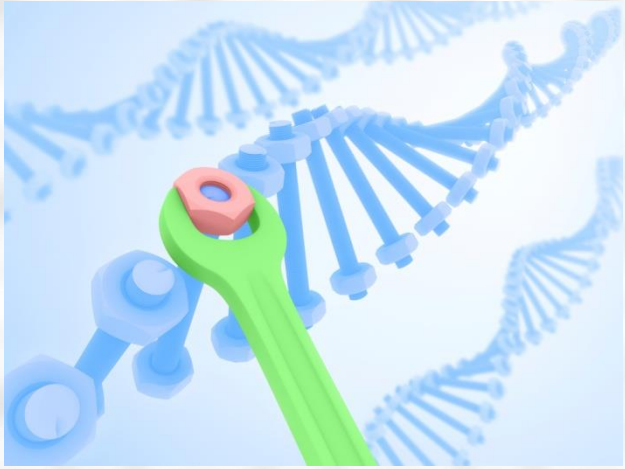
Yáñez lab: Developing safer gene and cell therapy methods

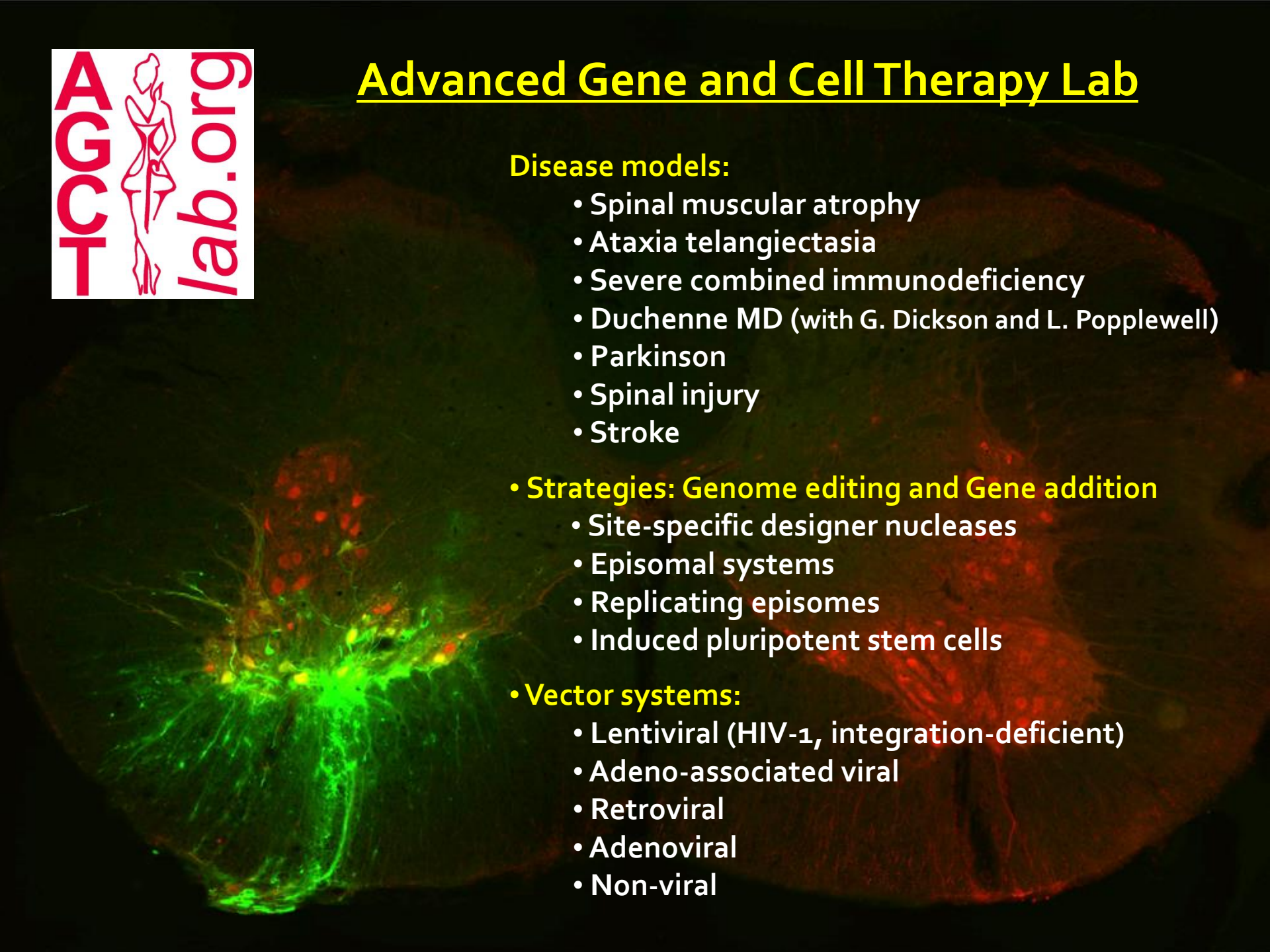
Episomal vectors



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…

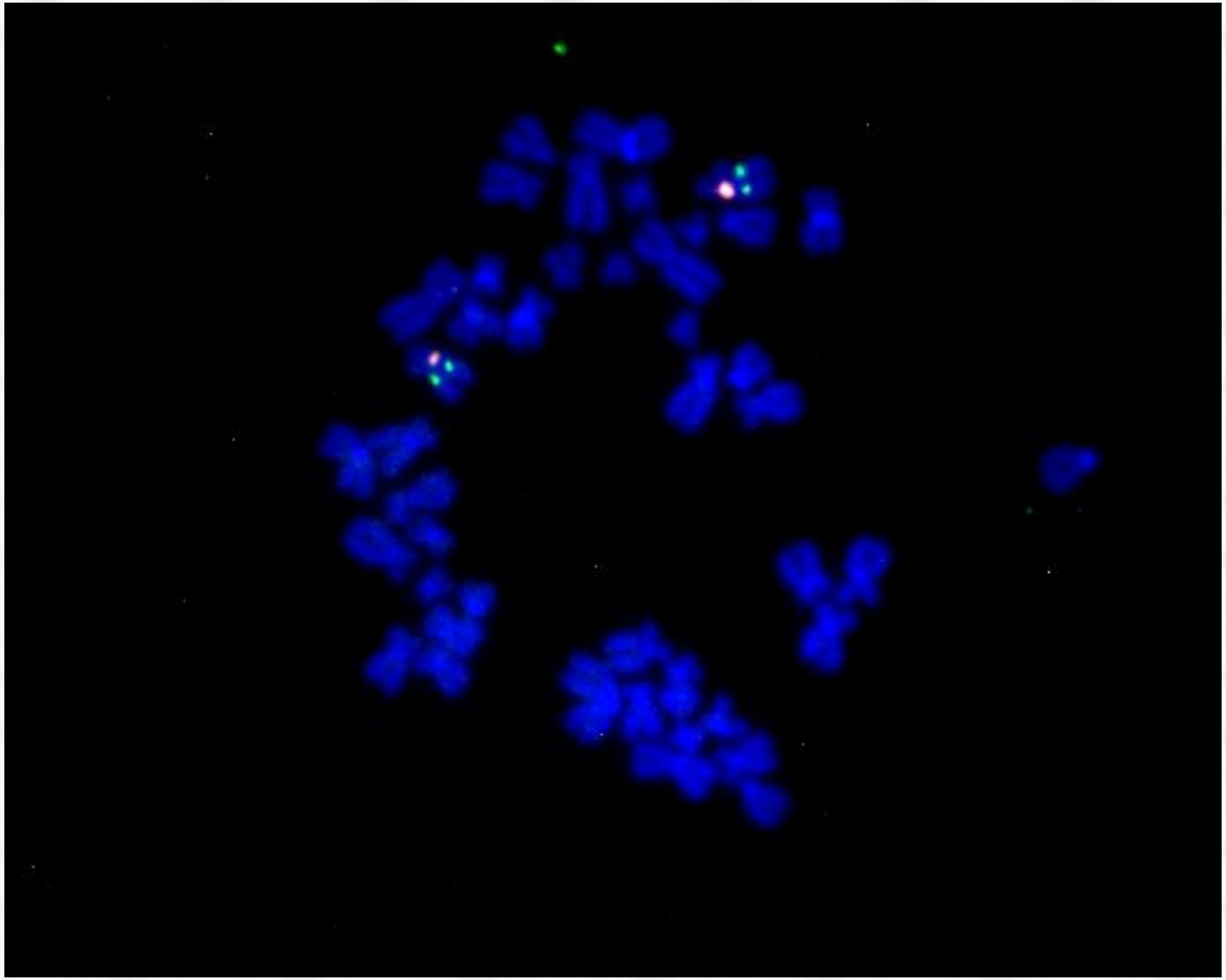
…6,000-8,000 rare diseases, 6% of people, 20% of Health budget…

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

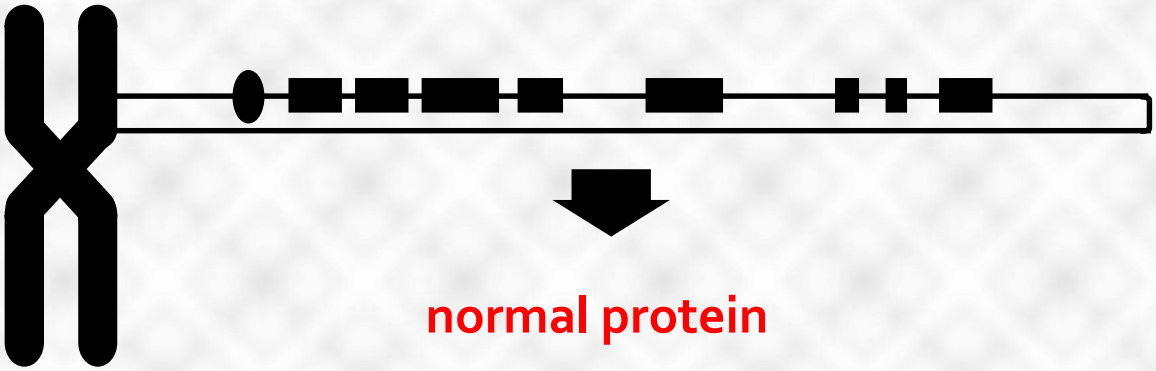
…but 80% of rare diseases are inherited…

…and many are potentially amenable to genetic and stem cell therapies.

All those genes…(the green dots are one of them)

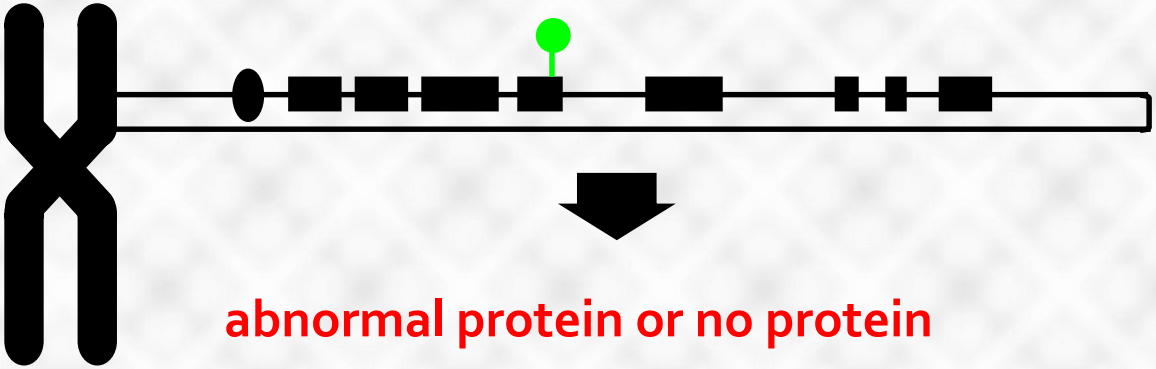


Genes store the info to make proteins



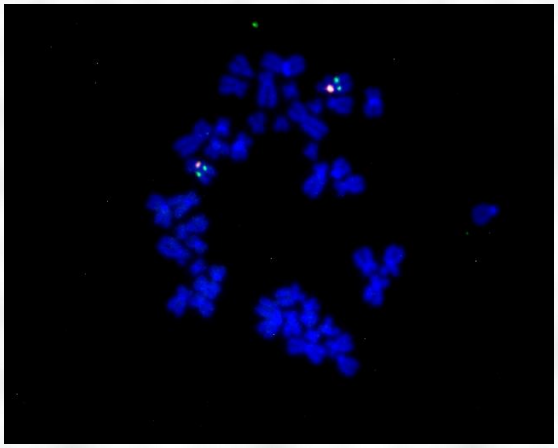
normal gene

normal protein



mutant gene

abnormal protein or no protein



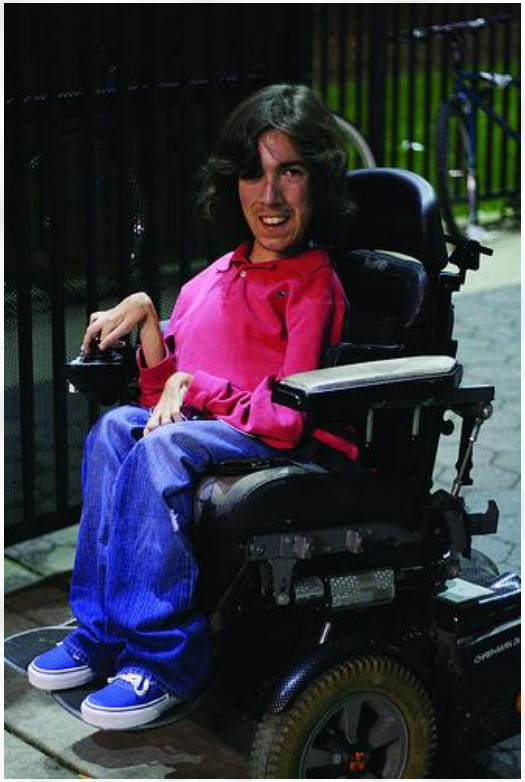
Are all genetic mutations really bad?

Some are irrelevant, others minor…

…and evolution is based on mutations

But it can be very different…

Duchenne muscular dystrophy



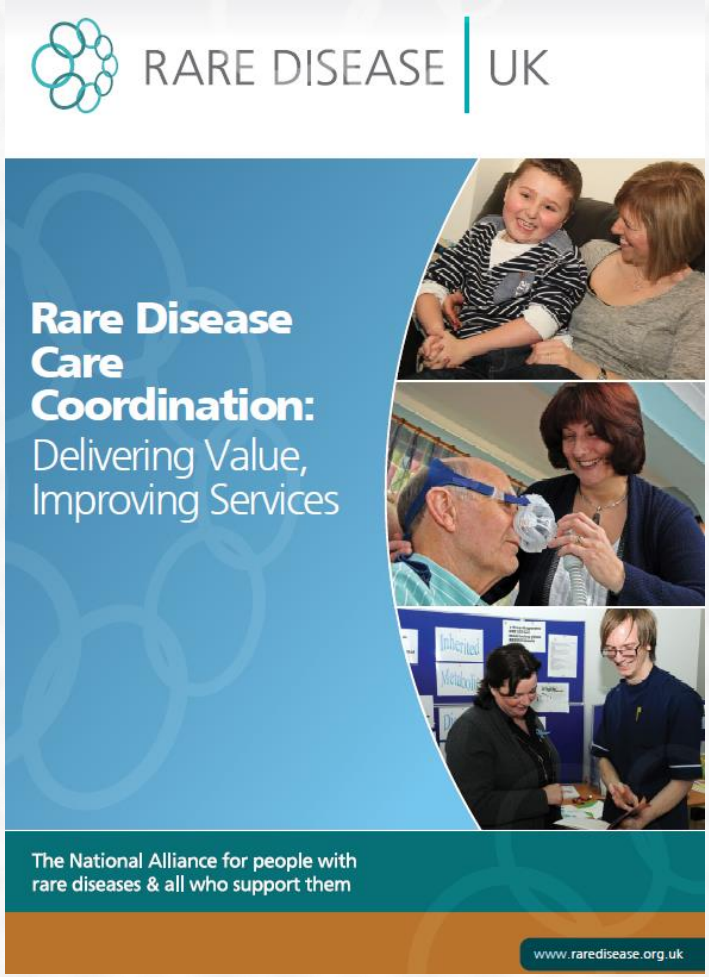
Spinal Muscular Atrophy

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

ORPHA number	Disease name
289157	1-alpha-hydroxylase deficiency
976	2,8-dihydroxyadenine urolithiasis
79154	2-aminoadipic 2-oxoadipic aciduria
391417	2-methyl-3-hydroxybutyric aciduria
391428	2-methyl-3-hydroxybutyric aciduria, classic type
391428	2-methyl-3-hydroxybutyric aciduria, infantile type
391457	2-methyl-3-hydroxybutyric aciduria, neonatal type
391417	2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency
391428	2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, classic type
391428	2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, infantile type

12 hours to read the list

The importance of awareness, diagnostics and coordinated care



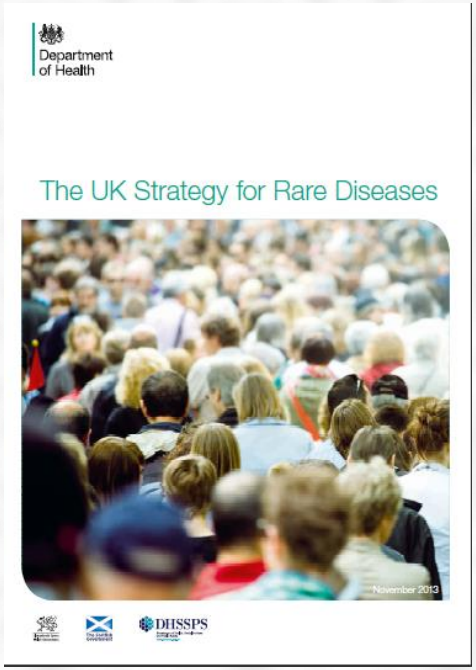
Diagnosis can take 5 years or longer

- 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.

Is there hope? - Politics



EUROPLAN:

- Since 2008 rare diseases are a priority area for action in EU Public Health Programmes

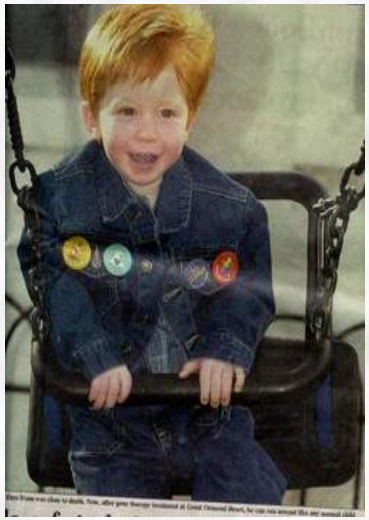
UK Royal College of General Practitioners:

- 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)

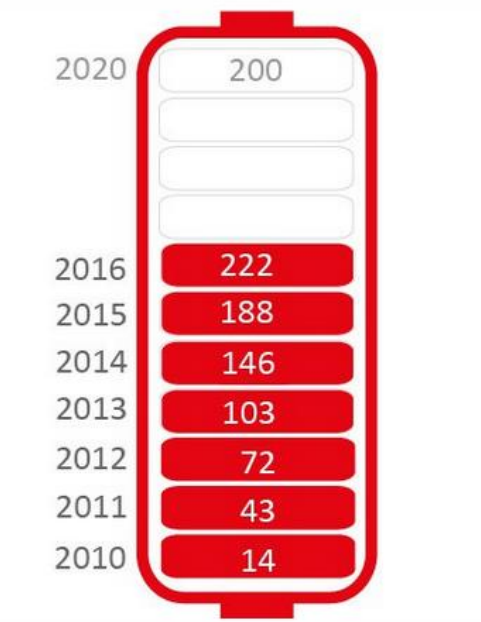
About us

IRDiRC

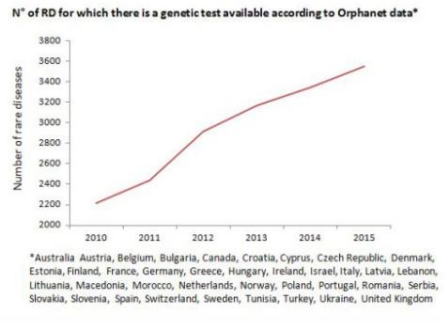
IRDiRC is a consortium of research funding agencies and interested parties acting to accelerate research through collaborations

READ MORE

Objective 2020: 200 new therapies



Objective 2020: identify all genes



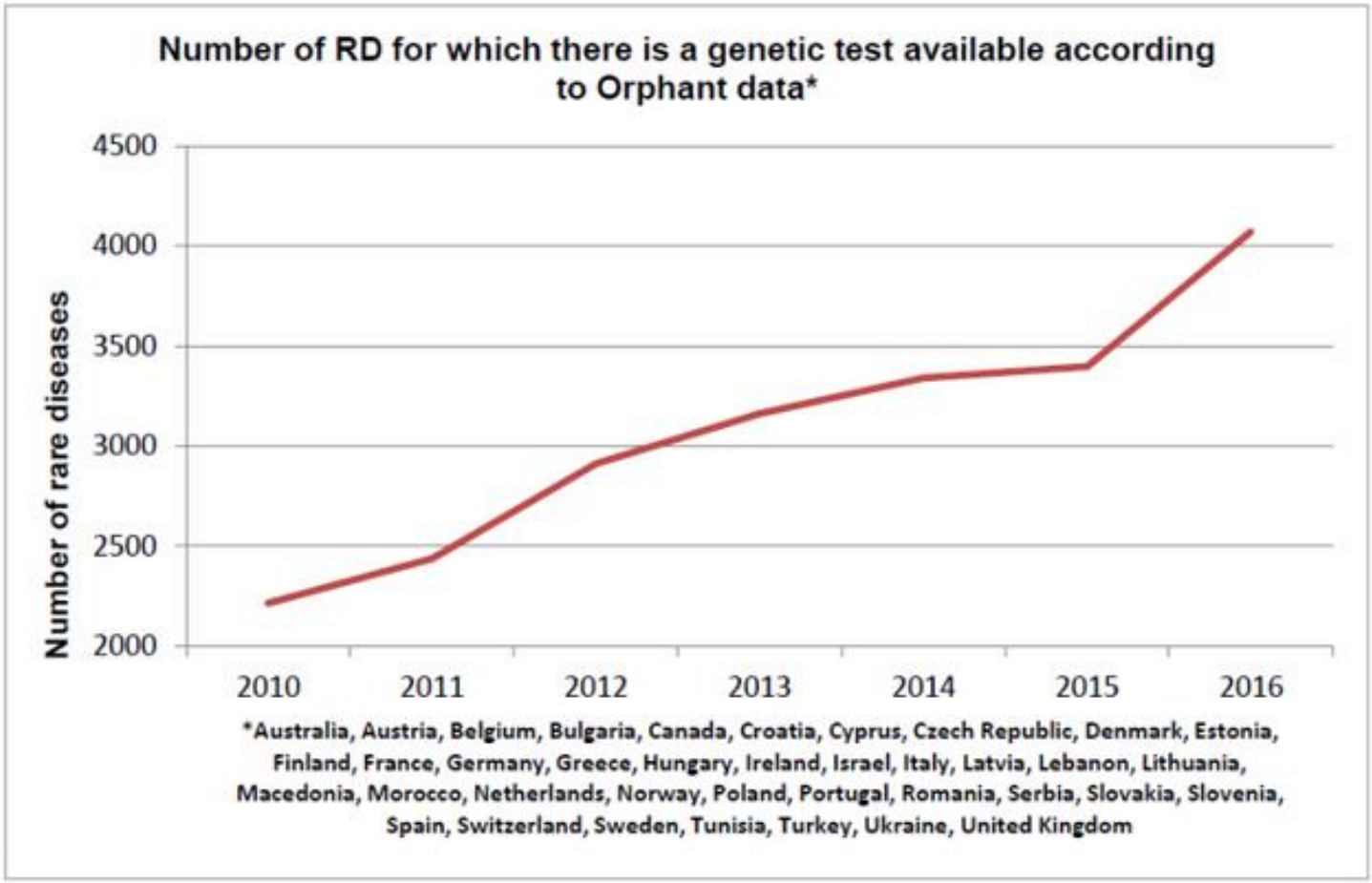
Annual data extracted from Orphanet for 38 countries

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

READ MORE

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.

(http://www.nhs.uk/conditions/pregnancy-and-baby/pages/newborn-blood-spot-test.aspx)

We need rare disease recognised as a research priority, and large-scale investment in therapy development (like in genomics)

Genomics england

About Us | 100,000 Genomes Project | Taking Part | For Healthcare Professionals | Research | Inc

Home > The 100,000 Genomes Project

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)

(Sanger Institute, Genome Research Limited)

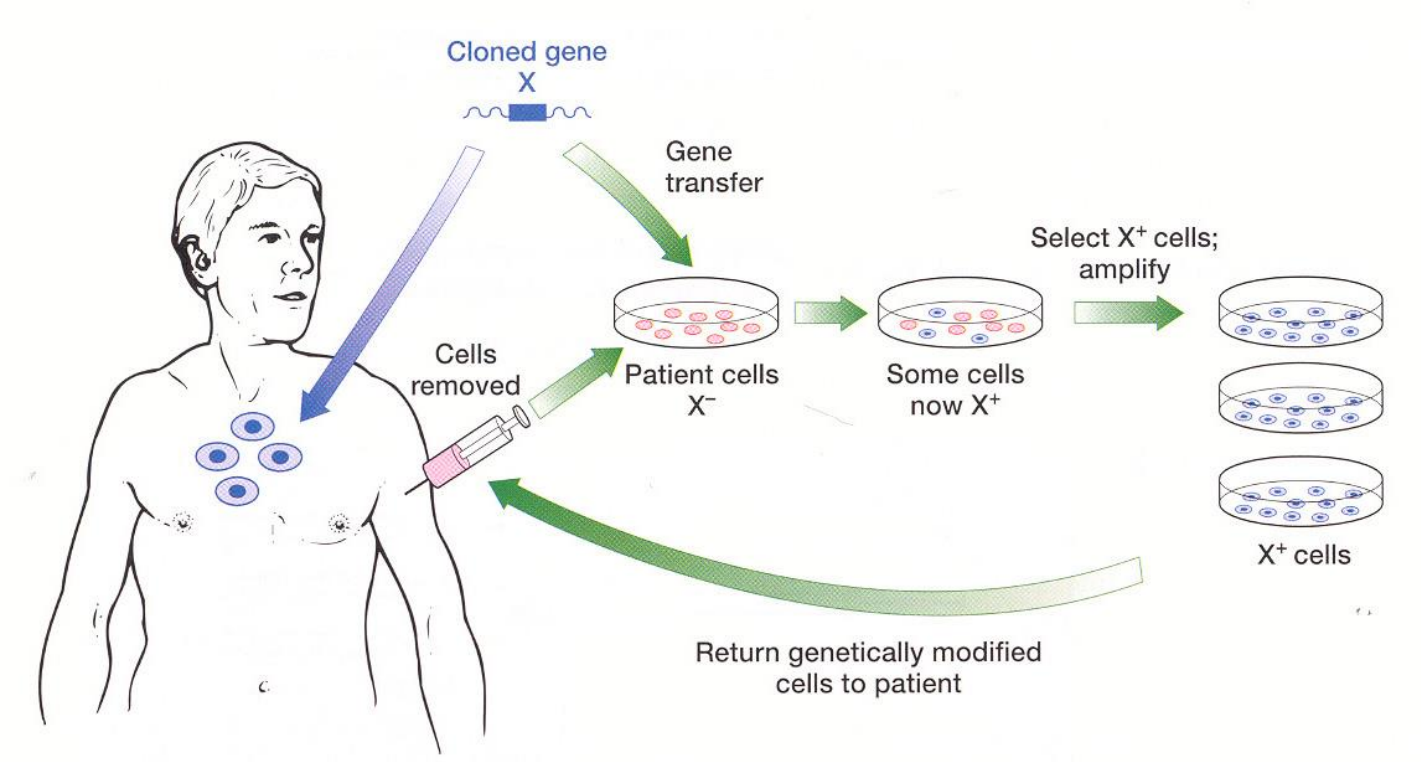
What is gene therapy?

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

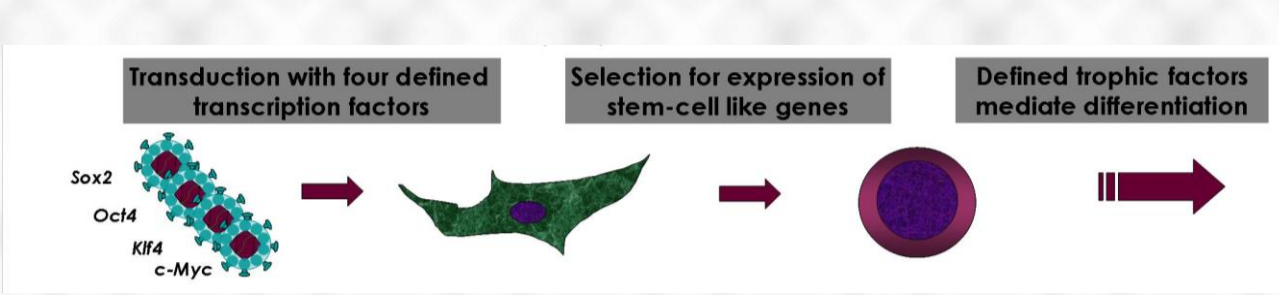
The *in vivo* and *ex vivo* approaches (GM in the body or outside)

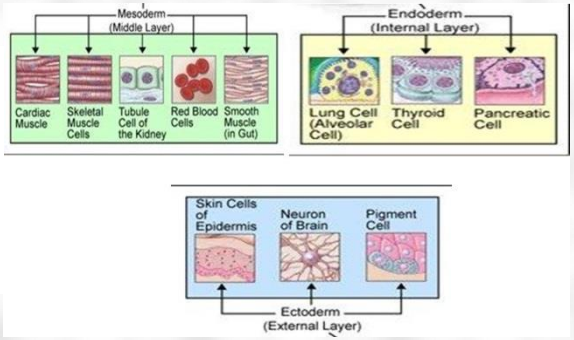


in vivo: **genetic modification of the cells of a patient inside the body**

ex vivo: **cells are modified outside the body before re-implantation**

The promise of (induced pluripotent) stem cells





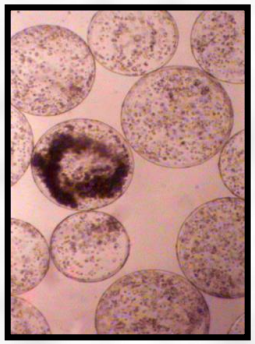
Scientists can take almost any cell from the body (for instance, from a bit of skin), and convert them into a stem cell in the laboratory. Afterwards, these lab stem cells can be corrected (if they were from a patient) and made to produce many different types of cells (muscle, blood, neurons…). In some 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

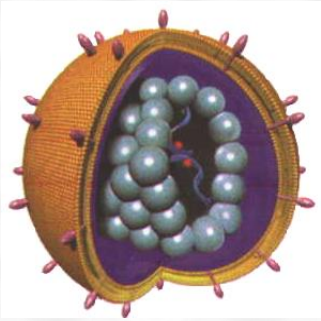
Naked DNA, needs help

Lipoplex/Polyplex (fat/protein packaging)

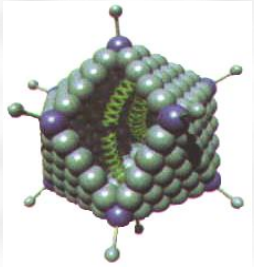


Recombinant Cells (Microencapsulation)

Viral



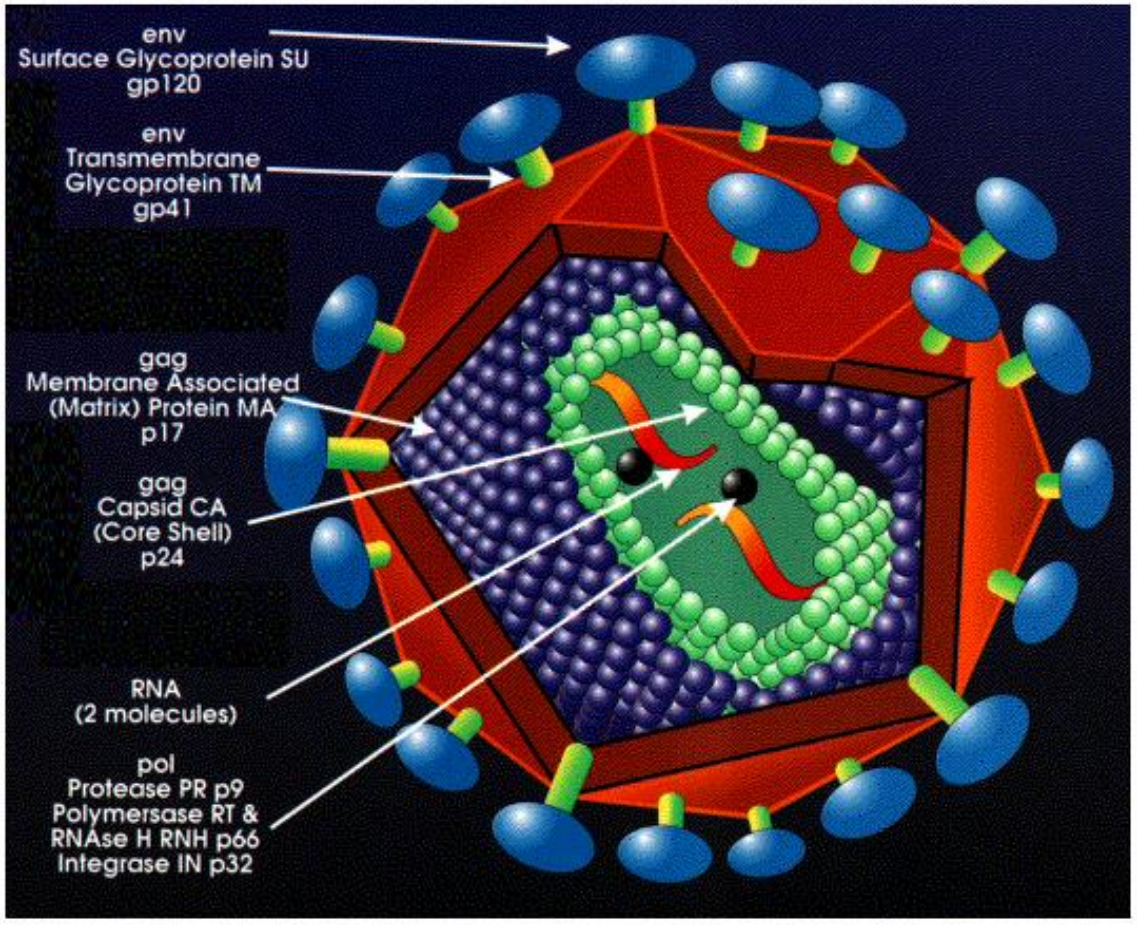
Retroviral vectors (like HIV made safe)



Adenoviral vectors (common cold)

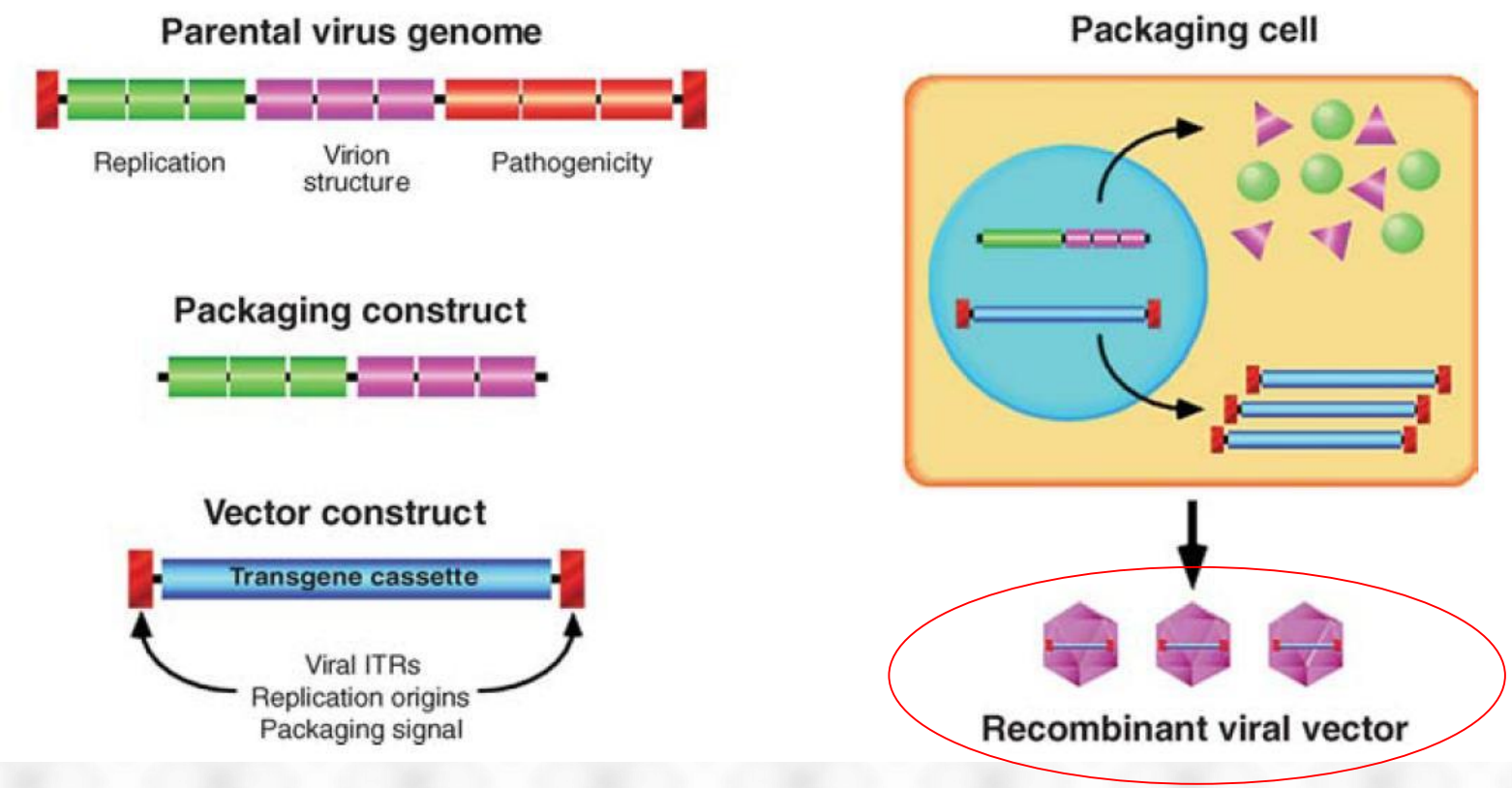
Adeno-Associated Virus vectors (AAV, very important for Duchenne)

Viruses are gene carriers (we hijack them in the lab to carry genes)



(http://biology.kenyon.edu/slonc/gene-web/Lentiviral/Lentivi2.html)

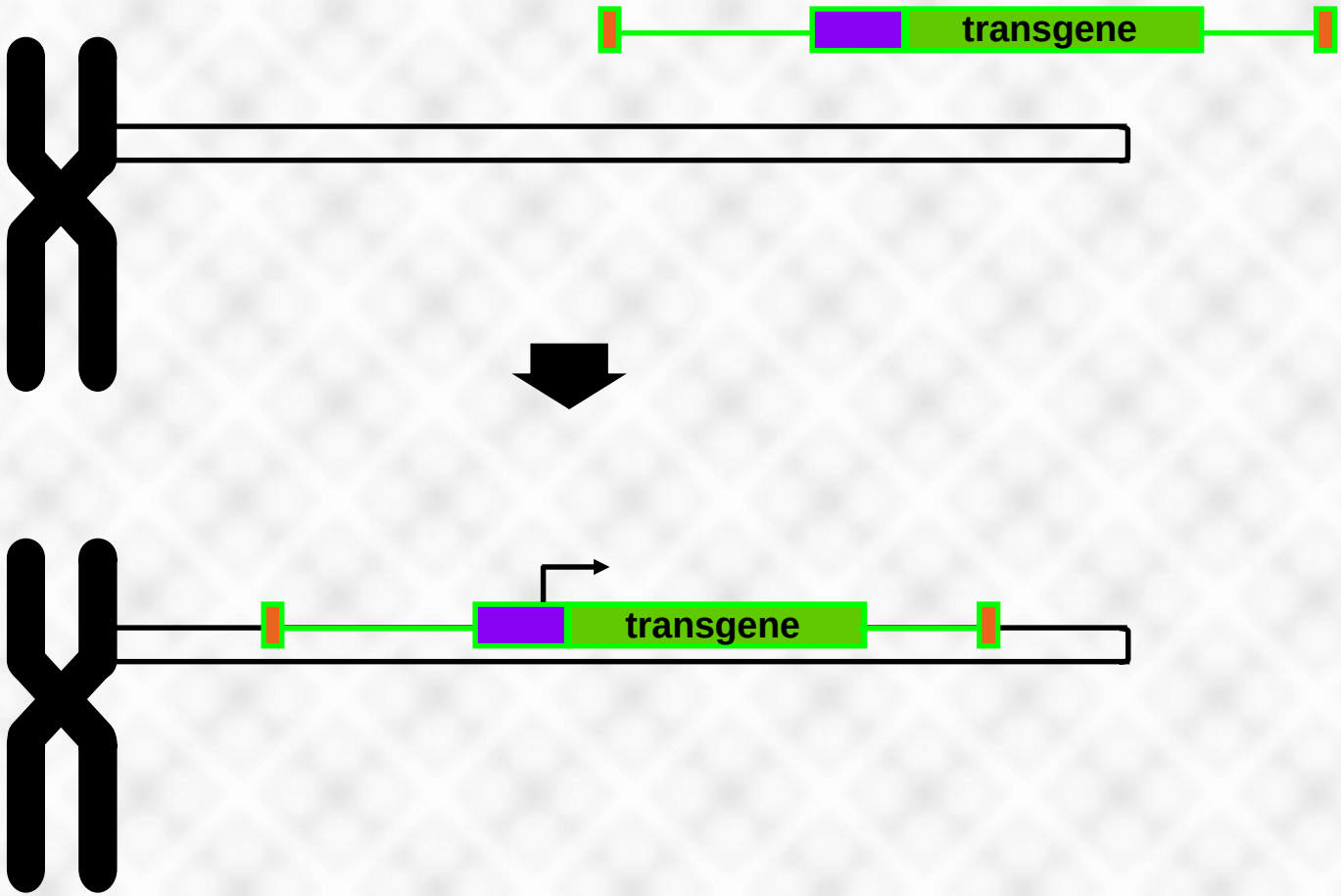
Viral vectors: how we make them (a lab cell produces them for us)



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

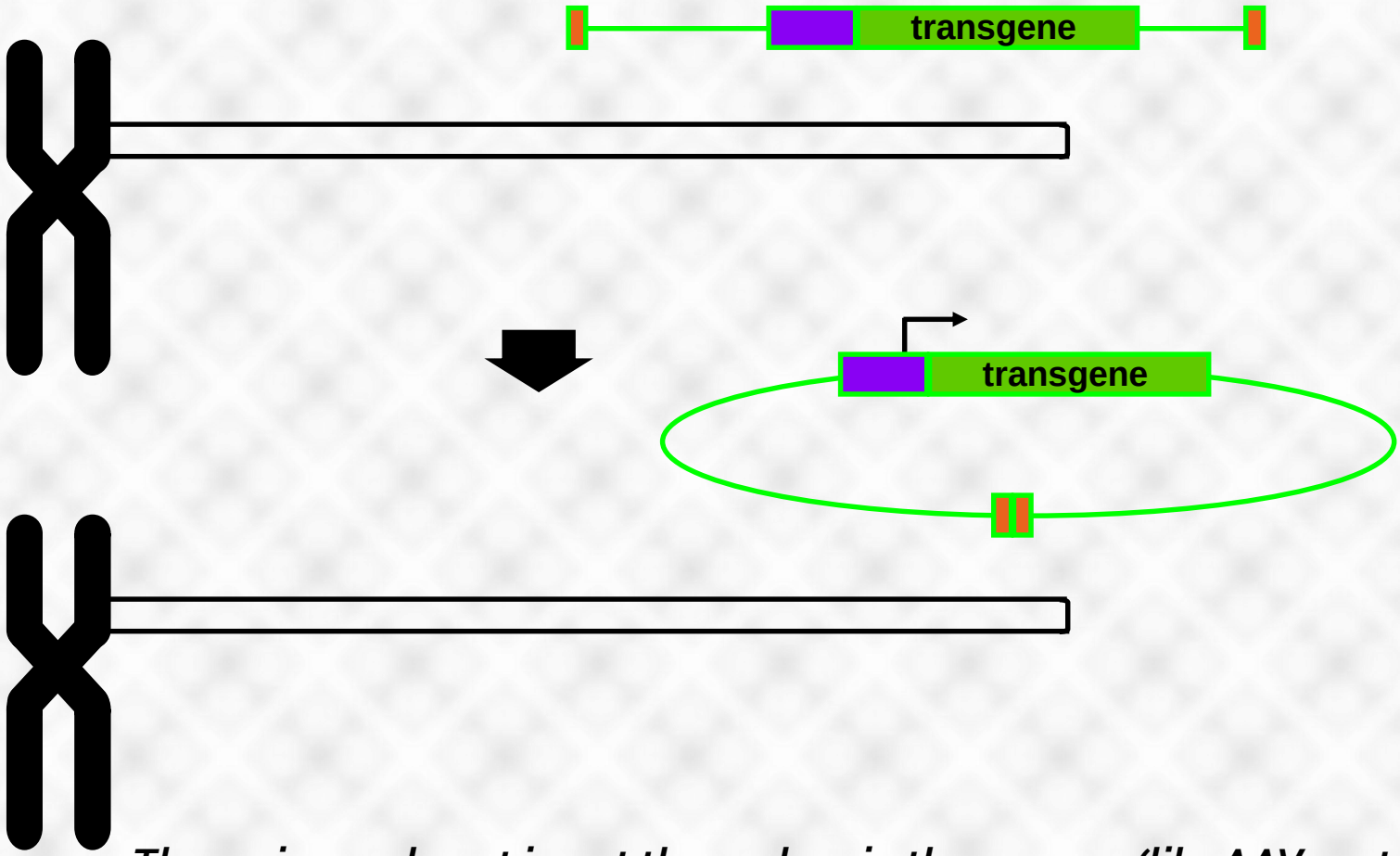
(Verma and Weitzman, Annu Rev Biochem 74, 711-738, 2005)

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



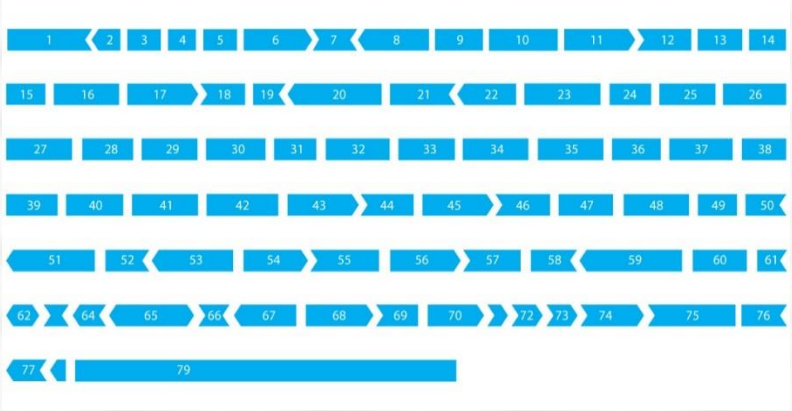
These viruses insert themselves in the genome; this could be a problem

Gene therapy strategies: episomal vectors

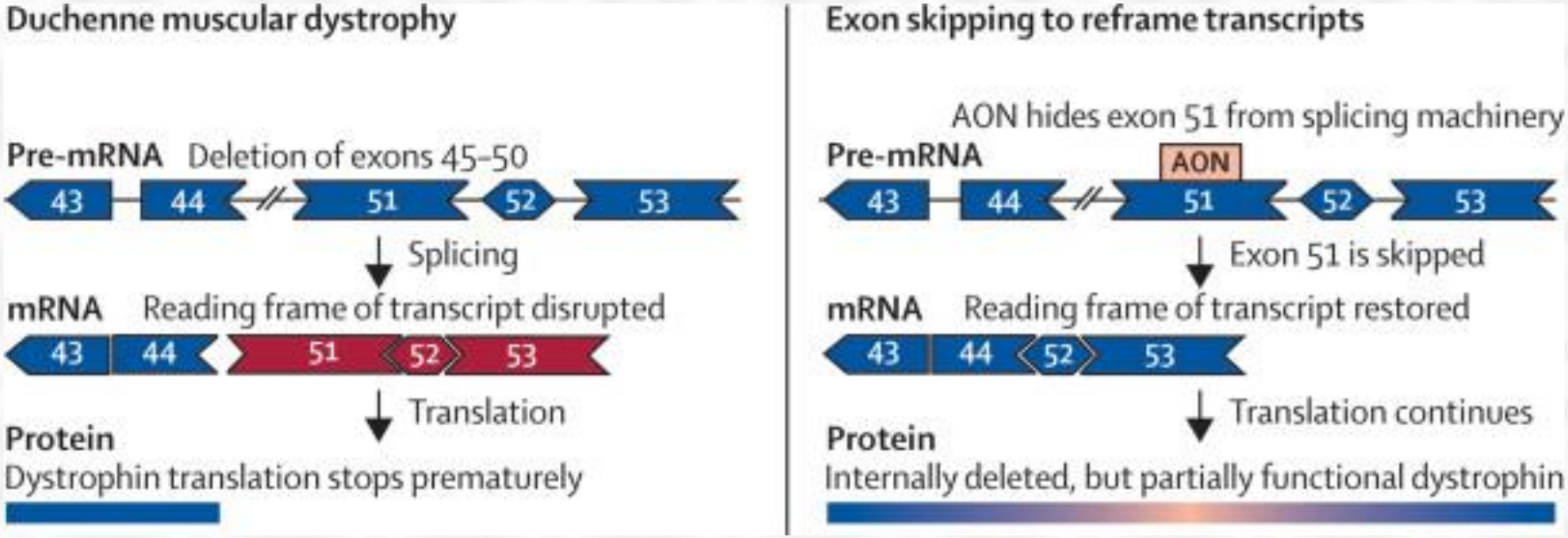


These viruses do not insert themselves in the genome (like AAV vectors)

Exon skipping in Duchenne muscular dystrophy

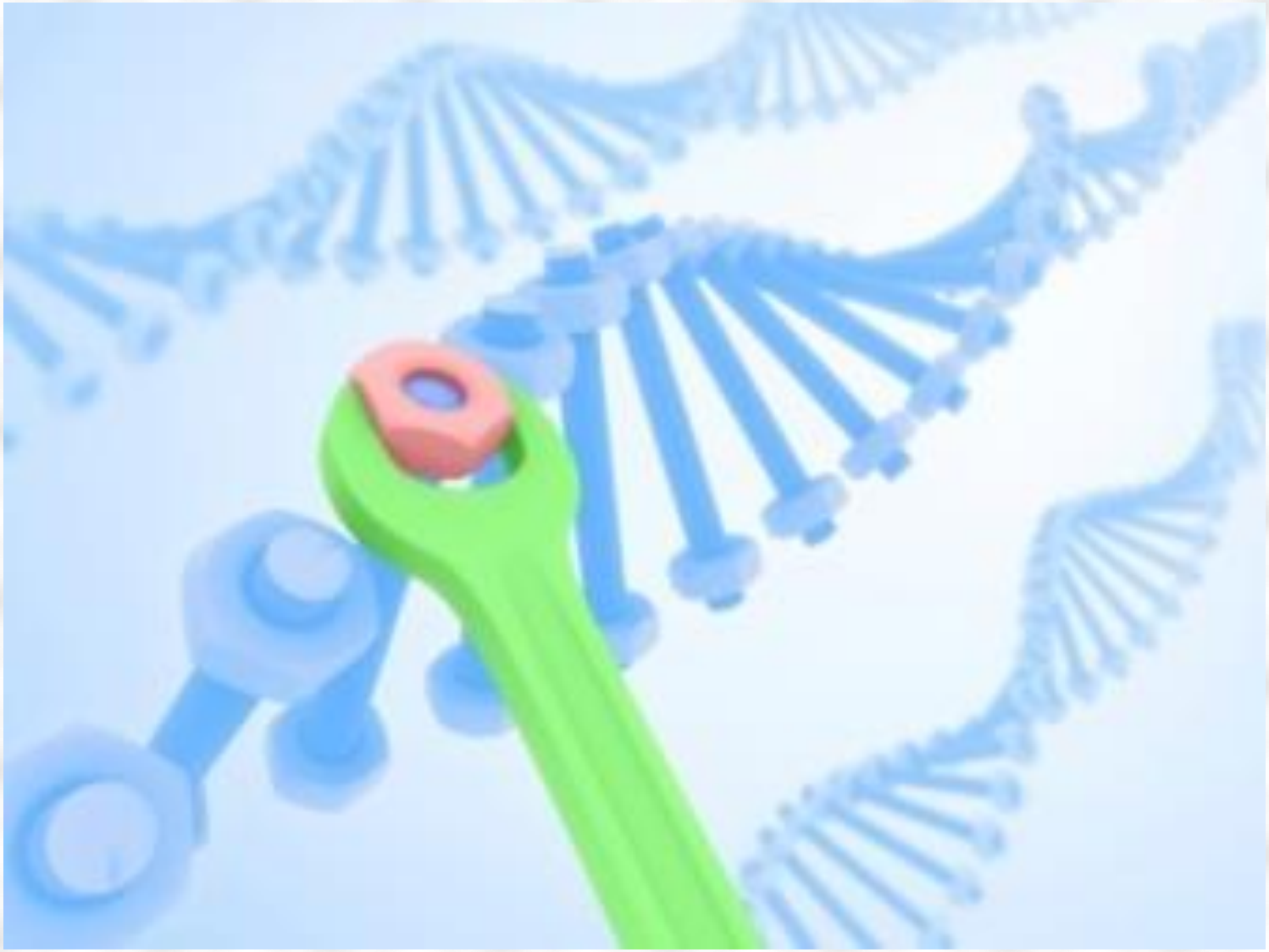


(http://www.musculardystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/)

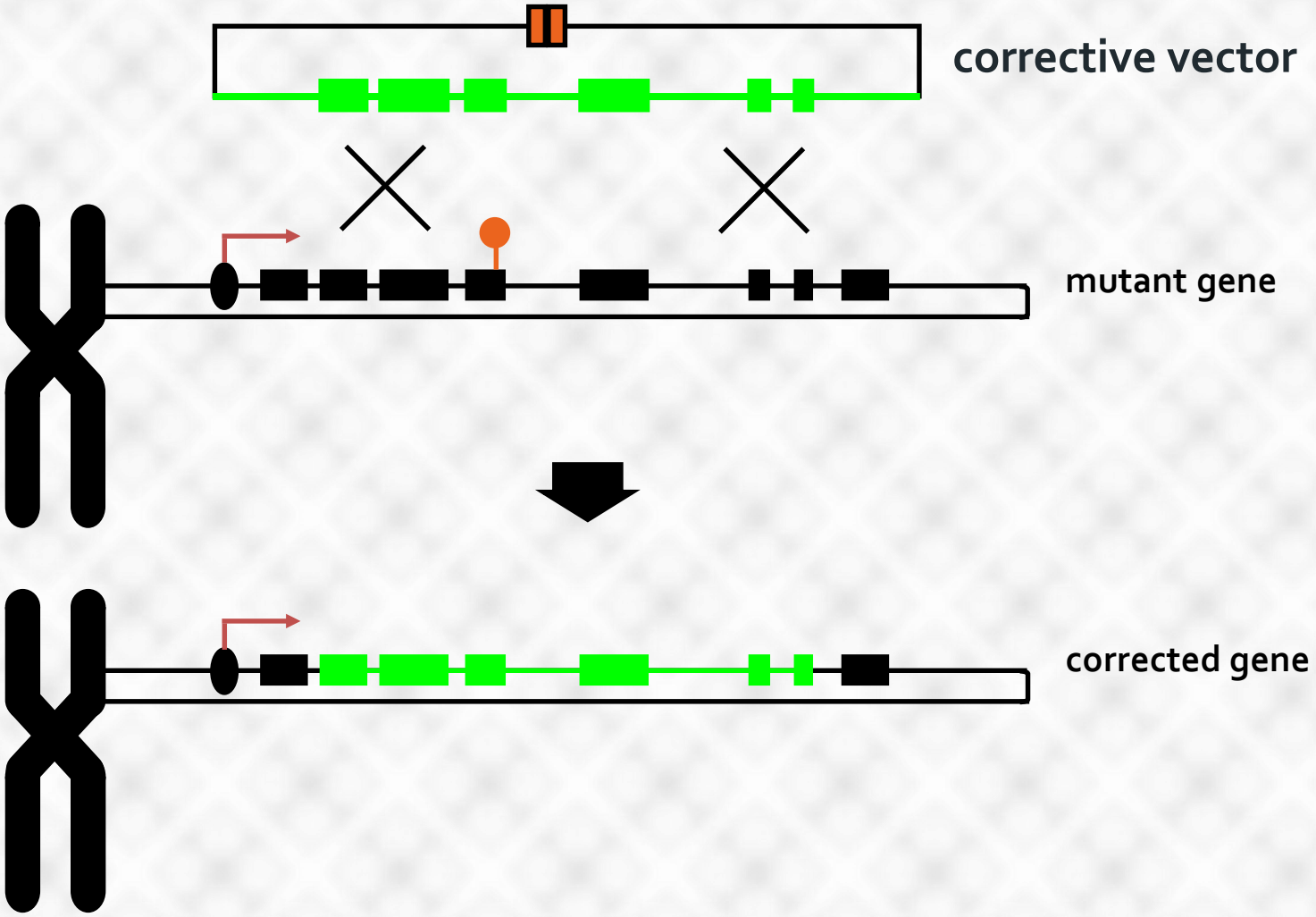


(Aartsma-Rus and van Ommen, Lancet Neurol. 2009 8: 873–875)

Exciting times in research: Genome Editing and Stem Cells



Genome editing for gene repair (used to be very difficult)



The future is CRISPR…maybe

(Nature,10 Mar 2016)

CRISPR has made genome editing democratic (much easier)

3

News

Pole dancing vaults towards Olympics

Sean O'Neill

One has its origins in Ancient Greece when long spears were used for vaulting the walls of besieged cities, the other traces its roots to the strip club 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 (GAISF) confirmed yesterday that it has given observer status to the International Pole Sports Federation (IPSF) in a move which sets out a "clear pathway" towards full Olympic recognition.

Patrick Baumann, president of GAISF said it was an "exciting time" for pole sports and added: "We will do everything within our remit to help them realise their full potential and... one day, maybe become part of the Olympic programme".

With skateboarding making its debut at 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, but I'm not saying no either — there is a good opportunity for us and the sporting bodies are interested in young, trendy sports being recognised because they get people involved," said Ms Coates.

"We're proving everybody wrong. We've been told again and again by the traditional sports that it will be very difficult for us to be recognised as a sport, but that just spurs me on to achieve

Pole dancing has come a long way since it appeared at 1980s strip clubs and has an accepted scoring system. Katie Coates, right, has helped take it towards Olympic recognition, which it may gain by 2024

Given a sporting chance

The Global Association of International Sports Federations (GAISF) gave observer status to six other nascent sporting bodies this month, opening the door to possible Olympic glory.

The World Armwrestling Federation The playground and bar table staple has been dressed up as a sport that the GAISF says tests "power, strength, endurance, technique, strategy, experience and passion".

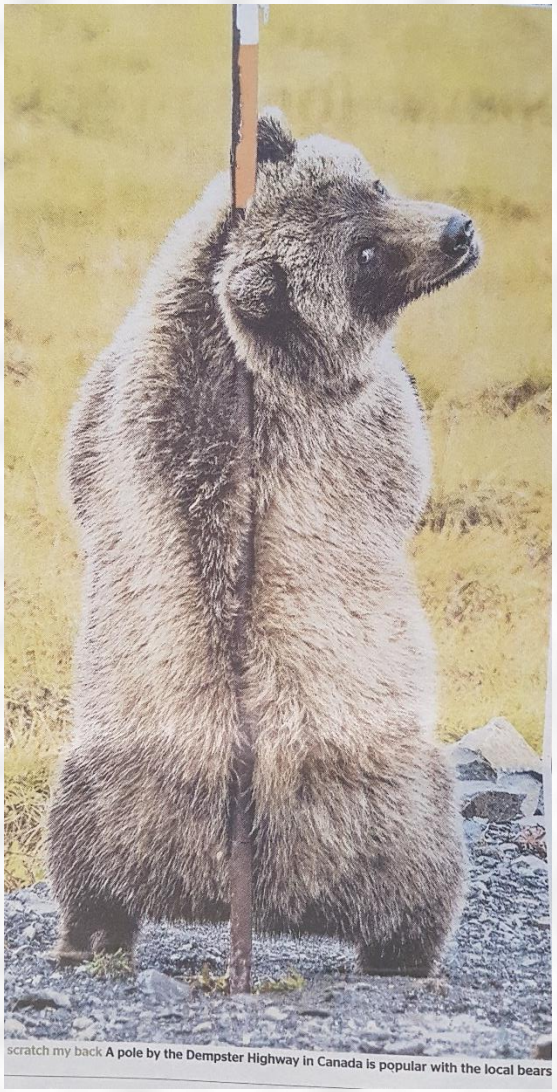
World Dodgeball Association As in the film — two teams of players throw balls at each other and try to avoid being hit themselves.

Federation for International FootGolf Players kick a football into a hole in the manner of golf, just like golf but with bigger balls, no clubs and no requirement for terrible clothes.

International Union of Kettlebell Lifting A body dedicated to trying to turn a tedious gym activity into a sport.

International Federation of Match Poker A variation on the classic card game, but without gambling, thereby removing most of the fun.

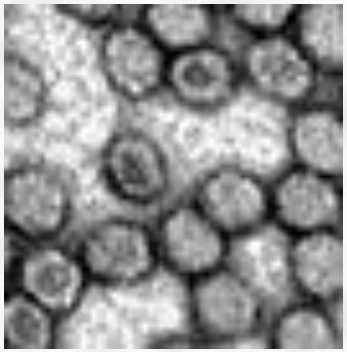
International Table Soccer Federation Yes, the age-old manual arcade game of table football; the GAISF says it helps to "build social cohesion" and is "an extraordinary vector of exchange". Really.



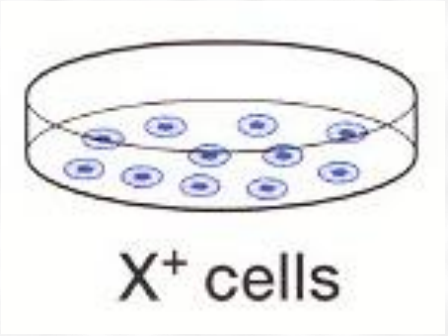
scratch my back A pole by the Dempster Highway in Canada is popular with the local bears

The problem with the gene therapy market

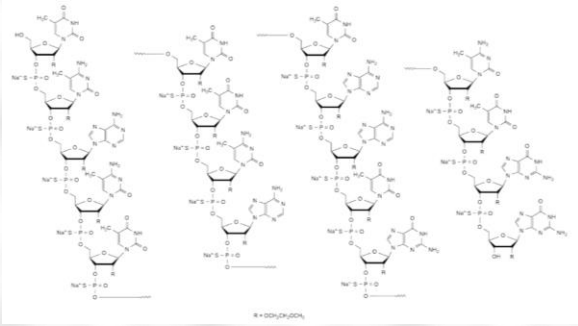
Glybera (AAV vector, one-off): EUR1,000,000



Strimvelis (GM cell, one-off): EUR594,000



Spinraza (small-ish chemical): EUR90,000/dose (EUR540,000 first year, EUR270,000 per year thereafter)



Advanced Gene and Cell Therapy *Lab*-2017

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