Imperial College London

A Basic Guide to Gene Therapy

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Aims of this Webinar

1. Provide information on key terminology
2. Audience to become familiar with the tools that gene therapist use
3. Audience to gain an understanding of some licensed (or close to licensing) gene therapy treatments

What is Gene Therapy?

Gene Therapy treats, prevents or diagnoses a disease as a result of its recombinant nucleic acid, which regulates, repairs, replaces, ***adds*** or deletes a genetic sequence.

Not covered in this talk:

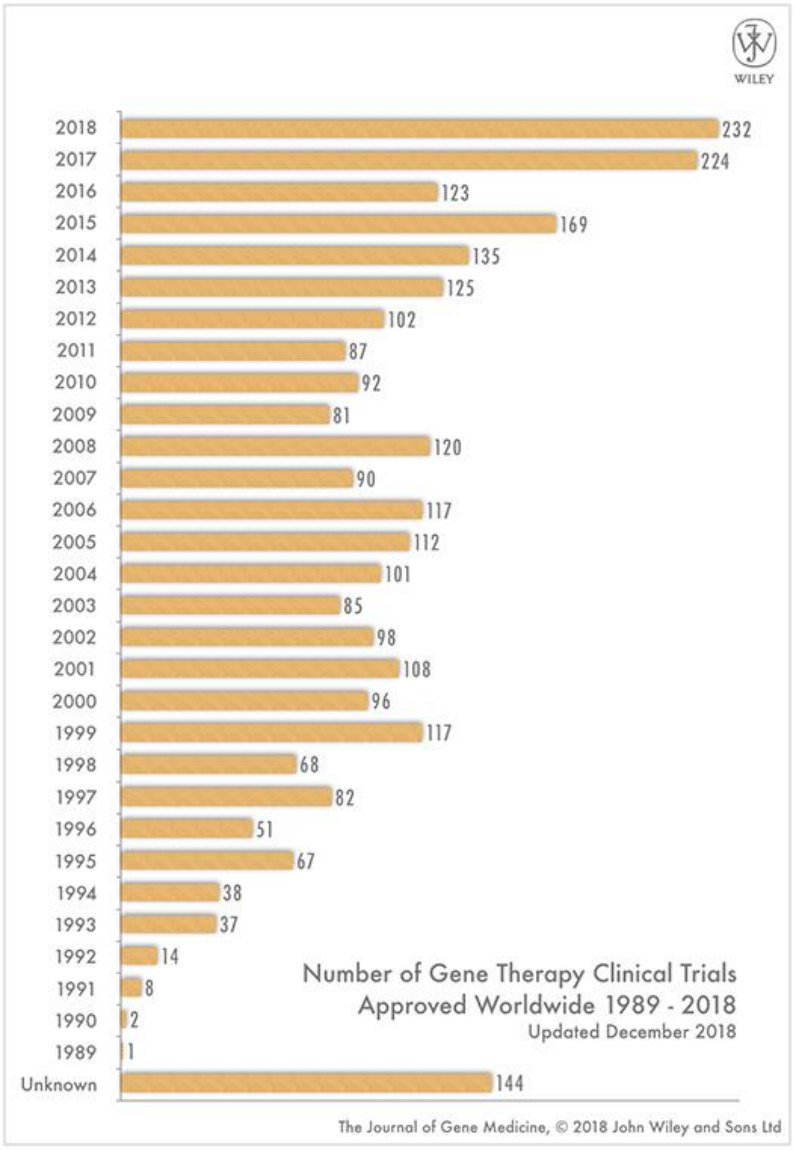
Gene editing
Gene silencing

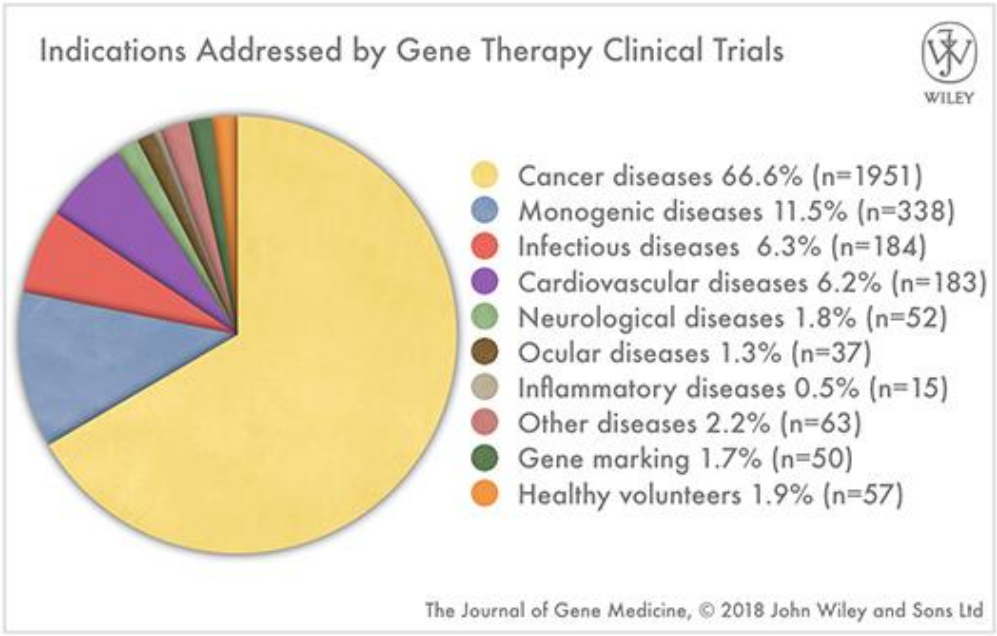
Gene Therapy
Somatic cell therapy (gene modified cells)
Tissue engineered products

Advanced Therapeutic Medicinal Products (ATMPs)

Advanced Therapies

Fast Growing Field + Wide range of Application

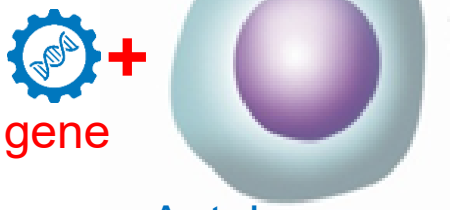




Gene therapy for genetic and acquired diseases

Ex vivo vs *in vivo* Applications

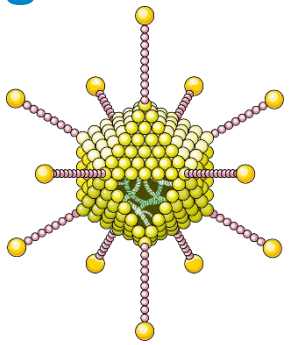
Ex vivo gene modified cells



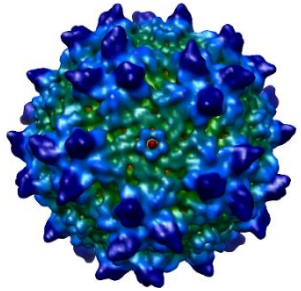
Autologous cells
Allogenic cells

Gene transfer agents (gene transfer vectors)

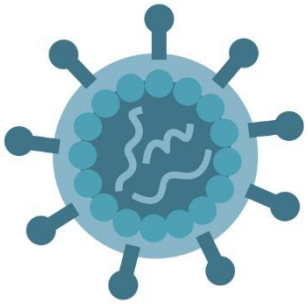
Viral vectors (gene inside)



Adenovirus



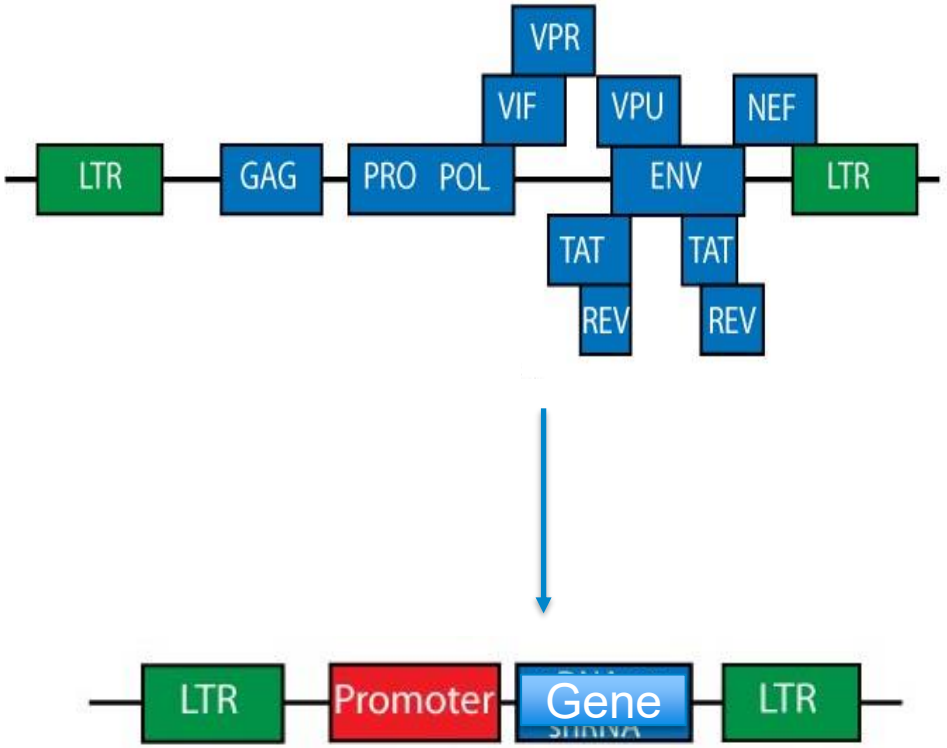
Adeno-associated virus



Lentivirus

Viral vector ≠ Virus

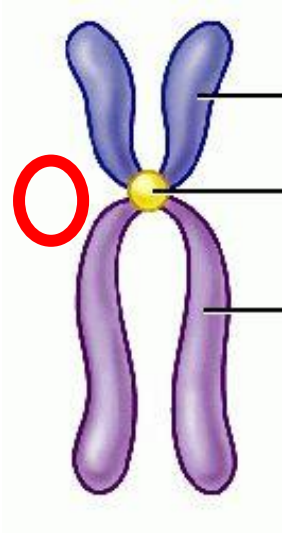
Example:
Lentiviral Vector
HIV most commonly used



Virus
replicating

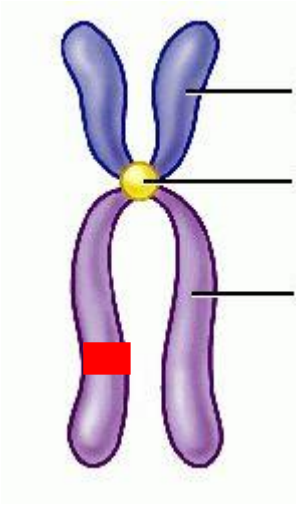
Viral Vector
non-replicating

Integrating vs non-integrating Vectors



Episomal gene addition

Adenovirus
Adeno associated virus
Most non-viral vectors



Chromosomal gene integration (random)

Lentiviral vectors

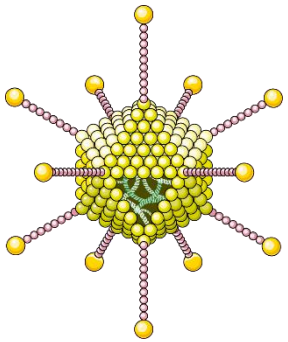
Characteristics

Viral Vectors	*Non-viral Vectors*
More efficient (evolution)	Less efficient (man made)
Most (not all) are immunogenic	Less likely to be immunogenic
Limited packaging capacity	No limit to packaging capacity
Some short, some long duration	Short/moderate duration

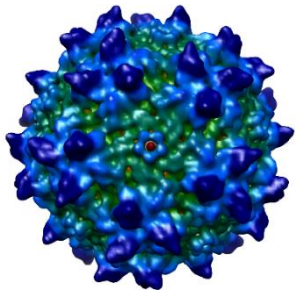
How to choose the right vector?

Steep learning curve!

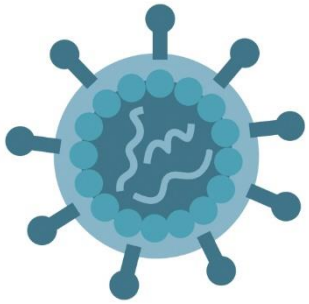
Acute or chronic disease?
Short of long duration of gene expression?
Dividing or non-dividing target cell?
Ex vivo or *in vivo*?
Size of gene?



Adenovirus

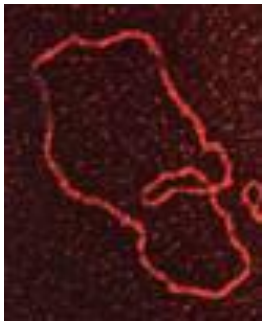


Adeno-associated virus



Lentivirus

+



Non-viral

Manufacturing

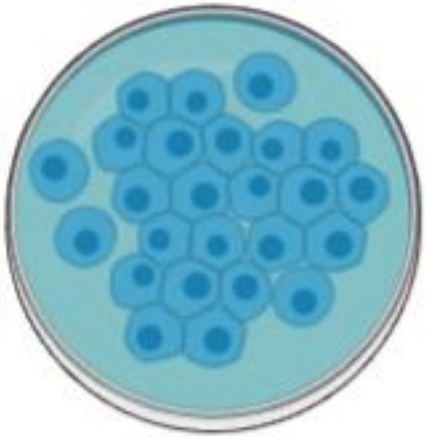
Non-viral vector

Chemical synthesis

Gene

Bacteria as factories

Viral vectors



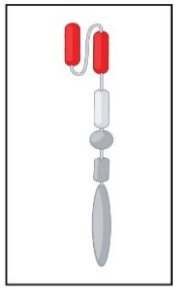
Cells as factories (Producer cells)

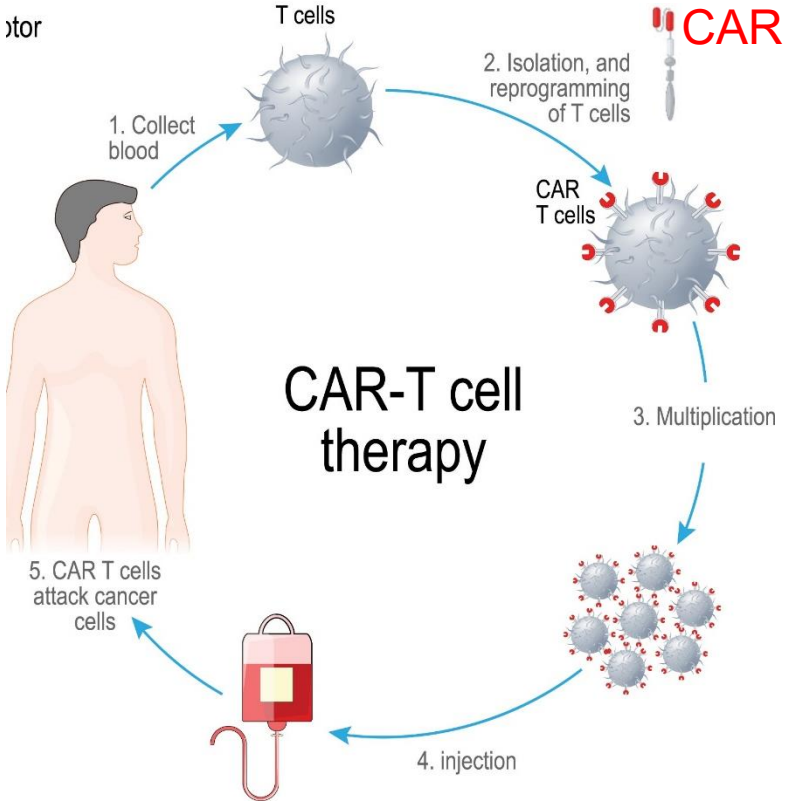
Costs are high – Innovation required

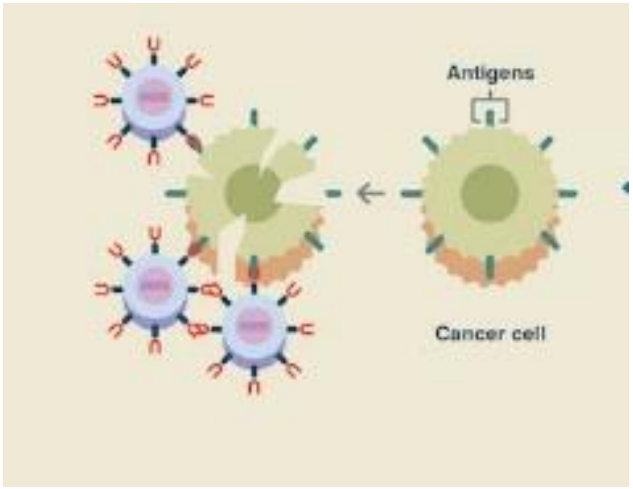
Examples – CAR T cells

- Some tumours make specific protein (antigens)
- Targeting of the immune system to these specific proteins (antigens) can help to destroy tumour cells
- Immune system (T cells) have to be **armed** to recognise the tumour antigen

Chimeric antigen receptor







CAR T cells – 2 licensed products

Licensed 2017/2018

B cell lymphomas
Significant improvements in survival rates
Some side effects
Relapse rates? – Time will tell

Future challenges:

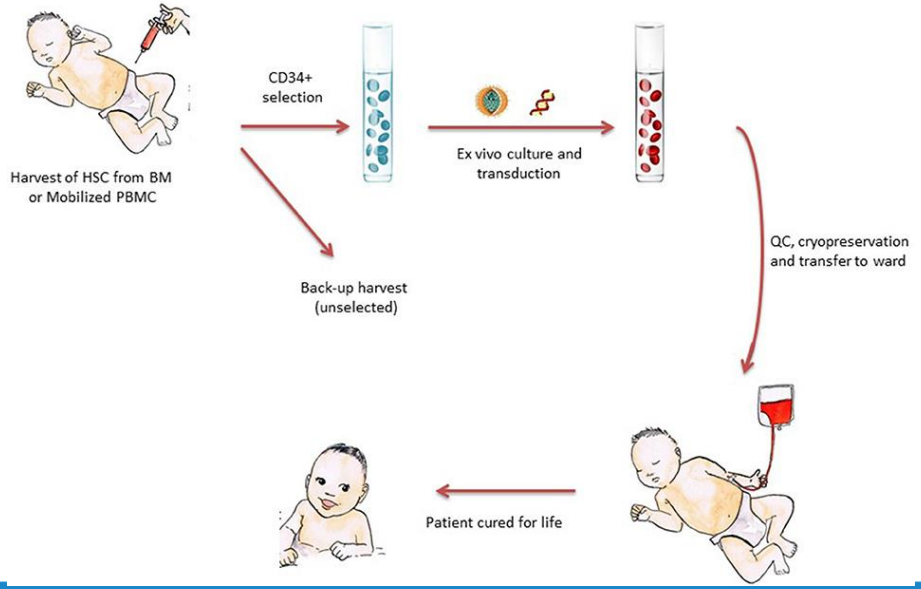
Allogenic vs autologous cells
CAR T for solid tumours

Examples – Immuno deficiencies

Defective immune system due to various genetic defects

ADA-SCID one form of the disease

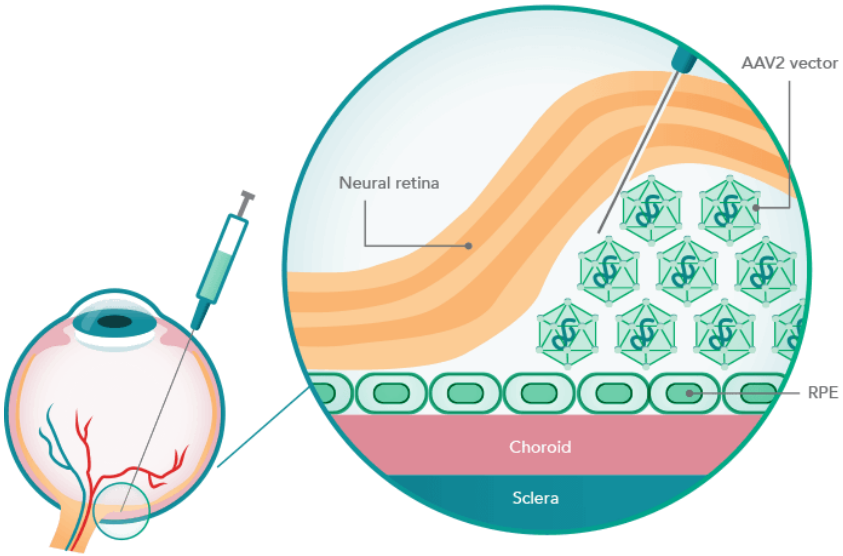
Correct genetic defect in hematopoietic stem cells



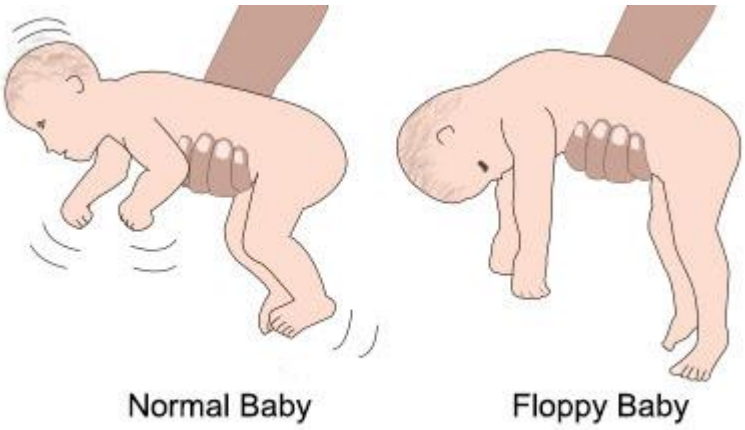
Strimvelis – licensed in 2017
Cure for life, but very expensive
Treatment only in one centre in Italy

Examples – Blindness

Leber's congenital amaurosis
Inherited disorder causing progressive blindness
Subretinal injection to replace the defective gene in the retina
Not a cure, but improvement in vision



Examples – SPINAL MUSCULAR ATROPHY (SMA)

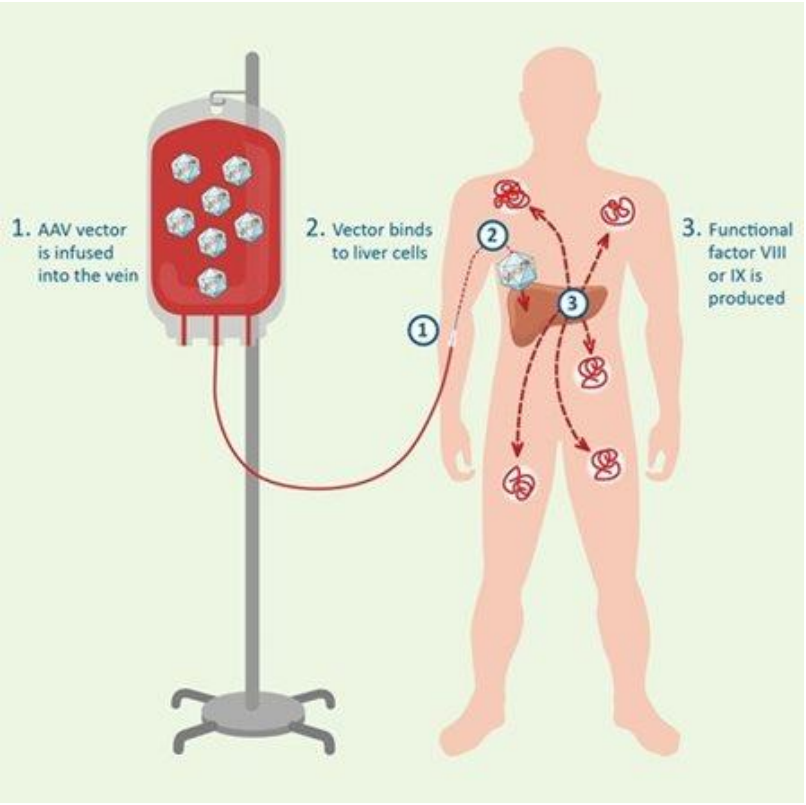


Inherited neurological disease
Rapid loss of motor neurones function
>95% dead at 6 months

Zolgensma (approved in 2019)

Injected intravenously
Improvement in motor function (not a cure)
Most expensive drug ever approved

Examples – Haemophilia

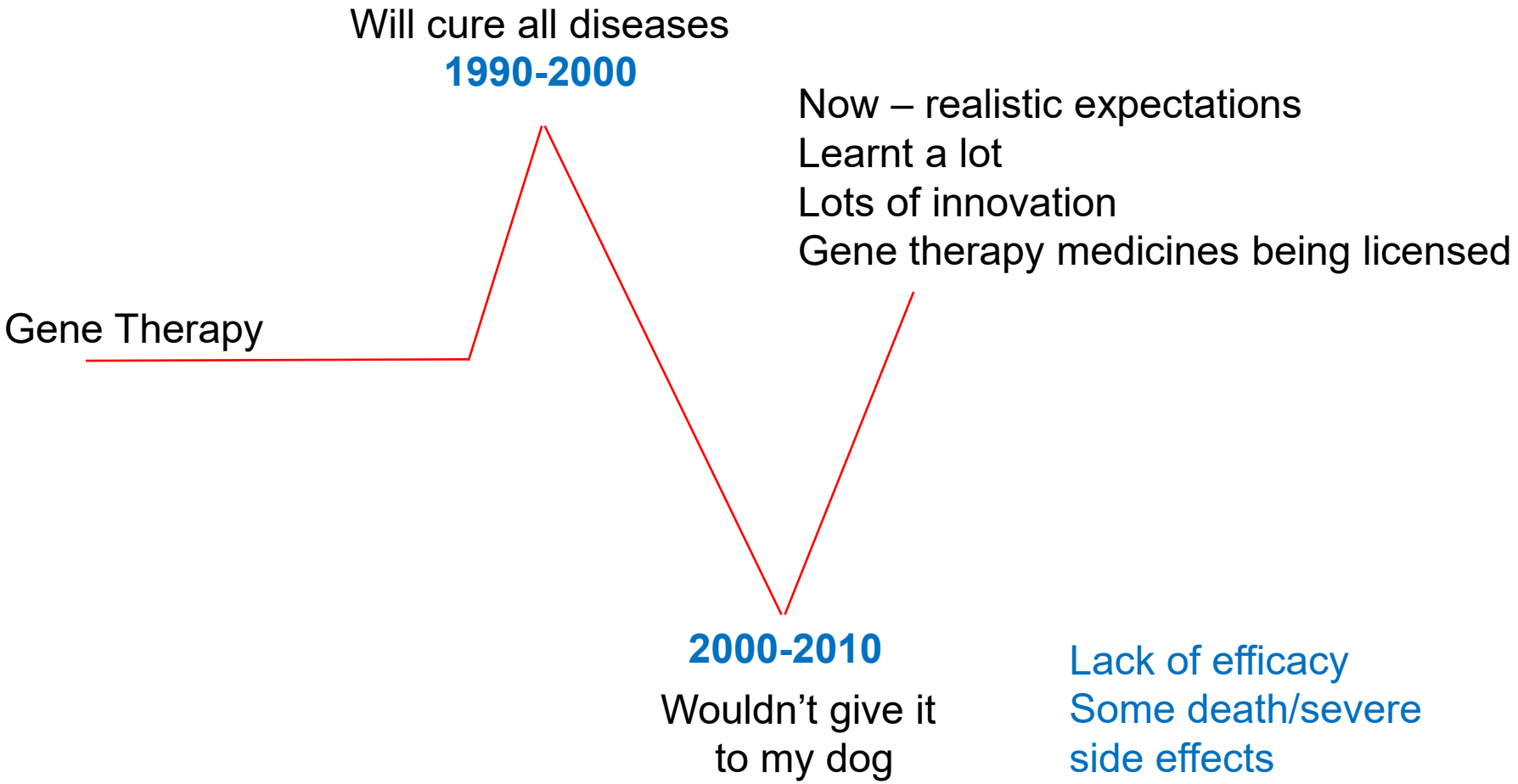


Not a licensed medicine yet,
but several phase 3 trials ongoing

TABLE. Ongoing or Announced Phase III rAAV-Mediated Gene Therapy Trials for Hemophilia A and B

Sponsor	Therapy	Coagulation Factor
BioMarin Pharmaceuticals	Valoctocogene roxaparvovec ("val-rox", formerly BMN-270)	Factor VIII
Spark Therapeutics	SPK-8011	Factor VIII
Pfizer	Fidanacogene elaparvovec (formerly SPK-9001)	Factor IX
UniQure	AMT-061	Factor IX

Problems encountered



Advanced Therapeutics - Headlines

Priority area for the UKs Industrial Strategy

Significant government investments (~£200 M)

- Cell and Gene Therapy Catapult
- 3 Advanced Therapeutic Treatment Centres
- Vector manufacturing

Estimates market growth to $21bn/year worldwide by 2025

£2.5bn of venture capital funding invested since 2012

Skill shortage is a bottleneck to developing gene and cell therapies and for delivery into the NHS

UK Apprenticeship scheme – tackle skill shortage in manufacturing (~ 6000 UK jobs in 2024)

ATTCs/LAT/CGTC working closely together to address skill shortage across various sectors (webinars, e-learning modules, conferences…)

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