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DNA/RNA therapies for Wilson's disease

Julien Baruteau

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Great Ormond Street Institute of Child Health, University College London, UK

Metabolic Medicine, Great Ormond Street Hospital, London, UK

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PLAN

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- **Landscape of gene therapies**
- **Disclosed projects on Wilson's disease**
- **UCL/ICH expertise**
- **Translation Medicine**

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Liver directed gene therapy

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An overview

Gene Therapy, is it worth trying?

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HUFFPOST

TECH 14/12/2017 10:34 GMT

Gene Therapy Achieves 'Mind Blowing' Results By Curing Haemophilia A

'I now have hope for my future.'

The Guardian UK edition

Stunning gene therapy breakthroughs are a riposte to our truth-tarnished times

Robin McKie

The liver, organ of choice

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- Highly vascularised
- Fenestrated endothelium
- Tolerogenic properties

Gene Therapies

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Replacing a mutated disease-causing gene with a healthy copy

Strategy?

Gene addition

Non-integrating

Non viral

- « Naked DNA »
- Mini-circle

- Liposome
- Nanoparticle
- Exosome

RNA / DNA

Viral

- Adeno-associated virus (AAV)
- Adenovirus

Integrating

Viral

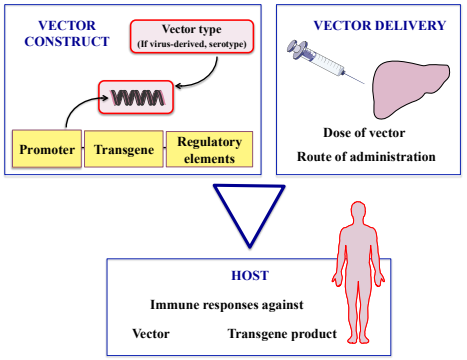
- Retroviral
- Lentiviral

DNA

Gene editing

- Zinc finger nuclease
- TALEN
- Piggyback transposase
- CRISPR/Cas

Factors influencing gene transfer



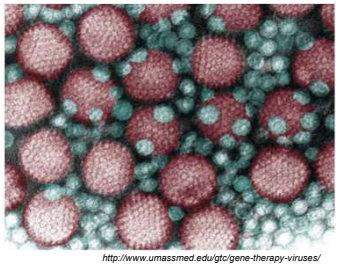
Baruteau, J Inherit Metab Dis, 2017;40,497-517

TECHNOLOGY LANDSCAPE: STRATEGIES OF DELIVERY

	Non viral	Retrovirus (lentivirus)	Adenovirus	Adeno-associated virus
Derived from pathogenic virus	No	Yes	Yes	No
Size of transgene	No limit	8 kb	7.5 kb	4.7 kb
Insertion to host genome	No	Yes	No	Rarely
Achievable titre	High	Low	High	High
Long-lasting transgene expression	No	Yes	Yes	Yes
Target dividing and non-dividing cells	Yes	Yes	Yes	Yes
Safety issues	No	Insertional mutagenesis	Inflammation	Insertional mutagenesis

ADENO-ASSOCIATED VIRUSES

- ***Parvoviridae***
  - Single stranded DNA
  - Small 22nm diameter
  - 12 WT serotypes
  - >>100 AAV variants
- Advantages
  - **- Not pathogenic**



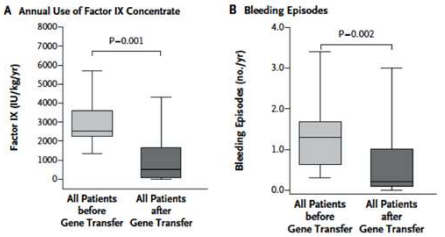
http://www.umassmed.edu/gtc/gene-therapy-viruses/

Asokan, Mol Ther, 2012; 20:699-708

Haemophilia B

Phase I/II clinical trial St Jude/UCL

IV peripheral injection
AAV8-LP1-hFIXco



Persistent increase of plasma F.IX after >7 years of follow up

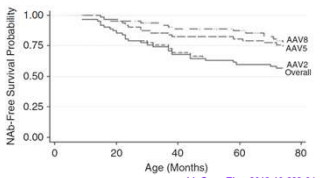
Nathwani, N Engl J Med 2011;365:2357-65
Nathwani, N Engl J Med 2014;371:1994-2004

Safety issues: immune response

Preimmunisation

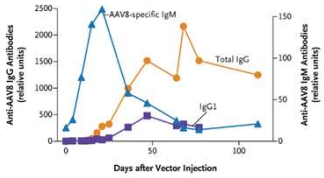
	Human	Non-human Primates
AAV2	30-60%	
AAV8	15-30%	100%

Calcedo, Front Immun 2013;4:1-7



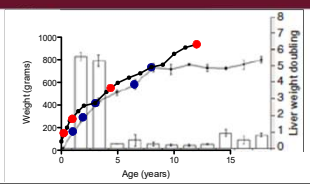
Li, Gene Ther 2012;19:288-94

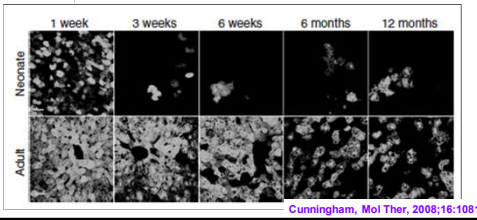
Acquired immune response



Nathwani, N Engj J Med 2011 ;365:2357-65

LOSS OF EPISOMAL TRANSGENE



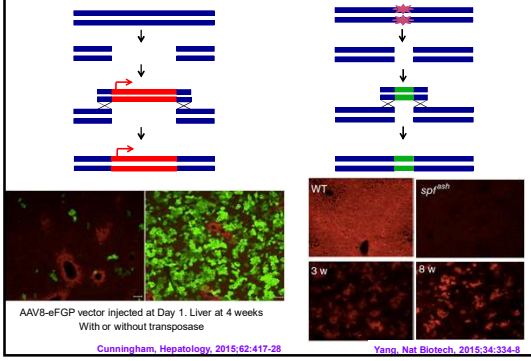


Cunningham, Mol Ther, 2008;16:1081-88

Alternative approach: Native gene repair

Transgene insertion (Piggyback transposase)

In situ gene correction (CRISPR/Cas9)



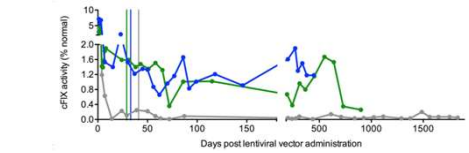
AAV8-eFGP vector injected at Day 1. Liver at 4 weeks
With or without transposase

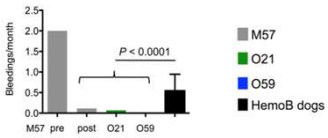
Cunningham, Hepatology, 2015;62:417-28

Yang, Nat Biotech, 2015;34:334-8

Integrating (Lentiviral) vector

In vivo GT in Haemophilia B in dog



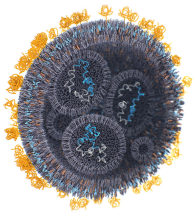


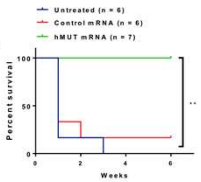
- Long term efficacy
- No evidence of genotoxicity in tumor-prone mice

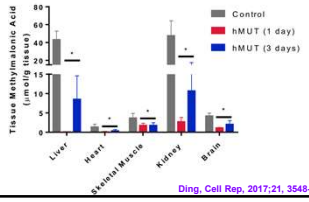
Cantore, Sci Trans Med, 2015;7:417-28

mRNA therapy

- Moderna Therapeutics
- Indications: Methylmalonic & propionic acidaemias
- **Liposome**

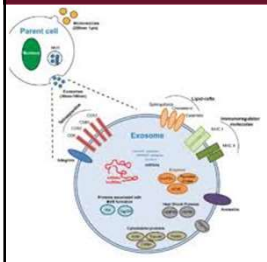


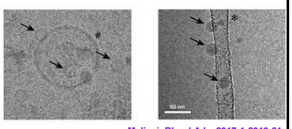




Ding, Cell Rep, 2017;21, 3548-58

Exosome / Exo-AAV





Meliani, Blood Adv, 2017;1:2019-31

Exosome

- mRNA or protein delivery
- Crossing Blood brain barrier

Exo-AAV

- Increase of transduction
- Protection against antibodies

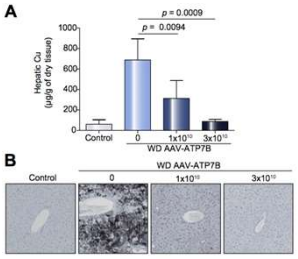
Gene therapy for Wilson's disease

What do we know?

ATP7B KO mouse recapitulates the human phenotype

Transduction of 40% hepatocytes reverses the phenotype

Efficacy of lentiviral (Roybal et al, Gene Ther 2012) & AAV (Murillo et al, J Hepatol 2016) vectors in mice



Murillo et al, J Hepatol 2016 ;64-419-26

AAV Gene therapy

Vivet Therapeutics

- Development stage: toxicology studies in 2018, trial planned for 2019
- Vector
  - Engineered AAV Anc80 serotype
  - Liver specific promoter
  - MiniATP7B transgene
- In mice
  - Normalisation of survival
  - Effect maintained >1 year
  - Effect maintained in mice with advanced liver disease
  - Reduces Copper content in liver and brain

Ultragenyx

Early research and development stage.

Liver-directed gene therapy

at Great Ormond Street Institute of Child Health, UCL

Building up a translational platform

Indications

Urea cycle defects as first programmes: OTC and ASL deficiencies

Expertise

Strategies
AAV, lentiviral vectors, exosome, liposome, exo-AAV
Gene editing with TALEN and CRISPR/Cas9

In-house development of specific testing
Immunoassays
Potency assays

Interaction with regulators
MHRA: innovation office, scientific advice
EMA: orphan designation, protocol assistance

HORACE trial

Halting Ornithine transcarbamylase deficiency with Recombinant AAV vector in ChildrEn

- AAV-LK03 capsid
- First in children liver-directed GT

General remarks about translational medicine

Patience, patience, patience

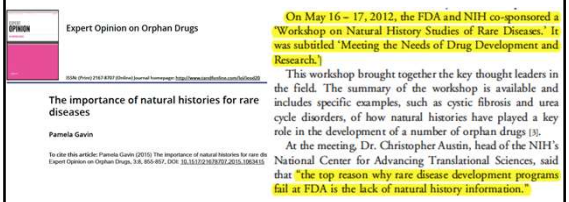
Access to gene therapy from 1st patient to market authorisation

Glybera®, Uniqure: **8 years** (1st trial 2005, approval 2012)

Strimvelis®, GSK: **14 years** (1st trial 2003, approval 2016)

Luxturna®, Sparks Therapeutics: **12 years** (1st trial 2007, approval 2017)

Natural history study



Expert Opinion on Orphan Drugs

The importance of natural histories for rare diseases

Pamela Gavin

On May 16 – 17, 2012, the FDA and NIH co-sponsored a 'Workshop on Natural History Studies of Rare Diseases.' It was subtitled 'Meeting the Needs of Drug Development and Research.'

This workshop brought together the key thought leaders in the field. The summary of the workshop is available and includes specific examples, such as cystic fibrosis and urea cycle disorders, of how natural histories have played a key role in the development of a number of orphan drugs [3].

At the meeting, Dr. Christopher Austin, head of the NIH's National Center for Advancing Translational Sciences, said that "the top reason why rare disease development programs fail at FDA is the lack of natural history information."

- Characterise sub-population of interest for a first-in-man trial
- Knowledge of natural evolution under standard of care
  - Clinical score of severity
  - Biomarkers
- Involve patients in the design !!!

Development strategy

- **Target**: where are the most unmet needs?
- Reliable **animal model**
- Anticipate **manufacturing** early
  - Scalability
  - Characterisation: purity, potency, stability
  - Reproducibility

CONCLUSION