Gene therapy for common single gene disorders

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Treating single gene disorders – new developments

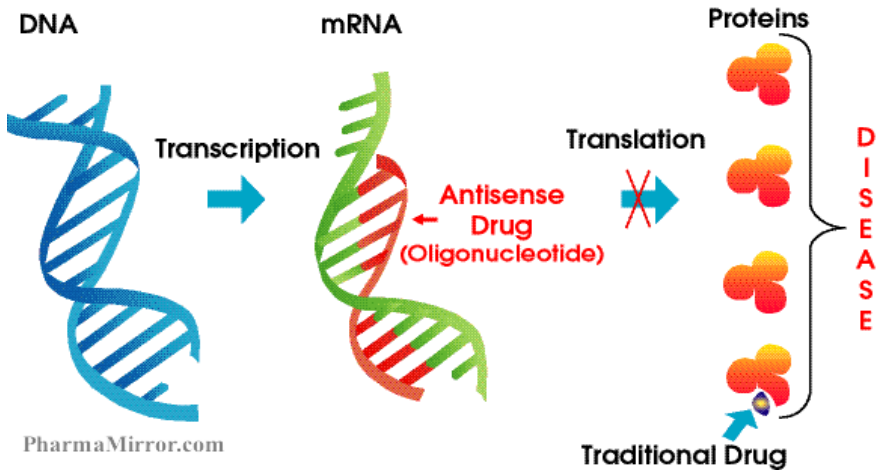
- Spinal muscular atrophy (SMA)
- Dystrophinopathies (Duchenne and Becker muscular dystrophy)
- Cystic Fibrosis
- Haemophilia

Three hopes of treating single gene disorders

1. Treatment based on an understanding of the gene function and pathways involved
2. Cell therapy
3. Therapy on a genetic level
    I. Gene therapy
    II. Gene editing
    III. Gene silencing

Therapy on a genetic level

- **Gene therapy**: Introduction of a normal/functional exogenous gene
- **Gene editing**: Correct a pathogenic gene using molecular methods
- **Gene silencing**: Target at levels of protein expression by using short RNAs, ASO and epigenetic alterations



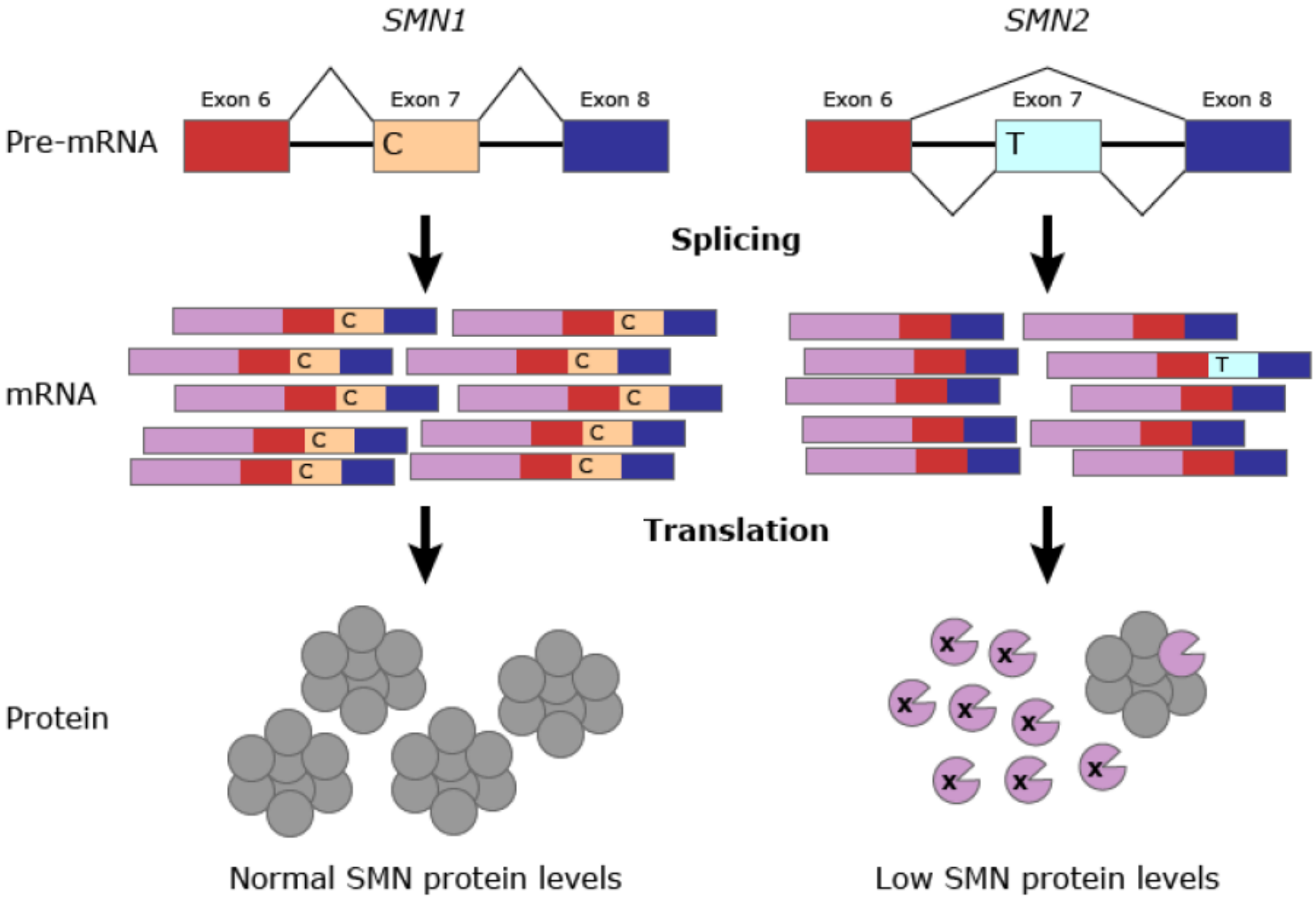
Spinal muscular atrophy (SMA)

Biallelic mutations (most commonly deletions) of ***SMN1***

Majority show homozygous deletion of exon 7

Results in degeneration of anterior horn cells in spinal cord and motor nuclei in lower brainstem → progressive muscle weakness and atrophy

The effect of the C-to-T transition in exon 7 between *SMN1* and *SMN2* on splicing



Nusinersen – disease modifying drug

Antisense oligonucleotide (ASO) that modifies splicing of the ***SMN2*** to make a full length SMN protein

<u>Approved for treatment in:</u>

- "**Most infants with SMA**"
- Select treatment for children 2-12 years (meet CHERISH criteria)
- Individualised treatment decision in older children/adults or advanced SMA (chronic assisted ventilation)

ENDEAR Trial

- Multicentre double blinded
- Infants 7 months or younger
- Intrathecal Nusinersen vs sham (control group) in 2:1 ratio
- Nusinersen group showed improvement in motor milestones (not seen in sham group) and percentage of infants who died or received assisted ventilation was lower (39 vs 68%)
- Drug safe and approved by FDA and EMA

CHERISH Trial

- Double blinded
- Older children 2 to 12 years
- Eligibility criteria: symptoms after 6 months, could sit independently but not walk, expected life expectancy > 2 years
- After interim analysis, the trial was stopped due to benefit in Nusinersen

Costly - $125 000 per dose

Finkel RS, Mercuri E, Darras BT, Connolly AM et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. ENDEAR Study Group SON Engl J Med. 2017;377(18):1723.
Mercuri E, Darras BT, Chiriboga CA, Day JW et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. CHERISH Study Group SON Engl J Med. 2018;378(7):625.

Gene therapy for SMA

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Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

Duchenne and Becker muscular dystrophy

- X-linked disorders
- Principal symptom: progressive weakness due to muscle fibre degeneration
- DMD: 65 – 80% of mutations are deletions/duplications
- Genotype-phenotype not completely clear
- Mainstay of pharmacological treatment is glucocorticoids

Eteplirseren

Exon 51 skipping drug (ASO to induce specific exon skipping to try and correct the *DMD* reading frame)

- Open label-study of 19 DMD patients received weekly IV administration that showed increased dystrophin without side effects
- Limited data suggests that the drug leads to **increased dystrophin in muscle**

Cirak,S, Arachevala-Gomez, V et al. Exon Skipping and dystrophin restoration in patients with Duchenne Muscular dystrophy after systemic phosphorodiamidate morpholo oligomer treatment, an open-label, phase 2 dose escalation study, Lancet 2011; 378:595

Subsequent placebo-controlled trial assigned 12 patients (ambulatory, 7 to 13 years) to 1:1:1 ratio of weekly IV Etepliseren (30mg/kg; or 50mg/kg) or placebo

- **Etepliseren groups** showed increase in dystrophin positive fibers on muscle biopsy at 48 weeks
- Extension phase of study through 36 months showed continued benefit on six minute walk test and lower rate of loss of ambulation compared to historical group

Mendell JR, Rodino-Klapac LR et al. Etepliseren for the treatment of Duchenne muscular dystrophy, Ann Neurology 2013; 74:637

Ataluren

Oral administered drug

Developed for genetic defects caused by nonsense (stop) mutations

Licensed (EU and UK) as option to treat patients with DMD (> 2 years) caused by nonsense mutations

ACT DMD study: Phase 3, multicentre, 48-week, double blind placebo controlled trial of 228 males with DMD, there was no significant benefit of Ataluren

McDonald CM, Campbell C et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1489

Newer approaches in DMD

- Other exon skipping drugs using an ASO to correct reading frame
- Gene therapy - “micro or minidystrophin”
- Gene editing – CRISPR-Cas in mice models
- Myostatin inactivation

GSK and Prosensa announce primary endpoint not met in phase III study of drisapersen in patients with Duchenne muscular dystrophy.
Bogdanovich S, Krag TO, Barton ER et al. Functional improvement of dystrophic muscle by myostatin blockade. Nature. 2002;420(6914):418
Bengtsson NE, Seto JT, Hall JK, et al. Progress and prospects of gene therapy clinical trials for the muscular dystrophies. Hum Mol Genet 2016;25:R9
Nelson CE, Hakim CH, Ousterout DG et al. In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy. Science. 2016 Jan;351(6271):403-7

Cystic Fibrosis

- Mutations in *CFTR* – deficient or defective function in CFTR, and anion channel present in epithelial cells
- Standard symptomatic treatment and CFTR **modulators**
- Benefits of these drugs stimulated search for additional modulators

CFTR Modulators

- Aim to improve production, intracellular processing and/or function of the defective CFTR protein.
- Indication and efficacy of these drugs depend of the CFTR mutation in individual patient

Patient with gating mutations – carry at least one copy of G551D mutation or another gating mutation (with any other CFTR-disease causing mutation)

- Age 12 months or older – **Ivacaftor monotherapy**

Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis

Steven M. Rowe[1], Sonya L. Heltshe[2,3], Tanja Gonska[4], Scott H. Donaldson[5], Drucy Borowitz[6], Daniel Gelfond[6], Scott D. Sagel[7], Umer Khan[3], Nicole Mayer-Hamblett[2,3], Jill M. Van Dalfsen[3], Elizabeth Joseloff[8], and Bonnie W. Ramsey[2,3]; on behalf of the GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network

Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and Cystic Fibrosis Patient Registry Data

Gregory S. Sawicki[1], Edward F. McKone[2], David J. Pasta[3], Stefanie J. Millar[3], Jeffrey S. Wagener[4,5], Charles A. Johnson[4], and Michael W. Konstan[6]

F508del homozygotes – also known as Phe508del or delta F508

- Age 2 to 11 years – lumacaftor-ivacaftor
- ≥ 12 years – tezacaftor-ivacaftor

ORIGINAL ARTICLE

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del

Jennifer L. Taylor-Cousar, M.D., Anne Munck, M.D., Edward F. McKone, M.D., Cornelis K. van der Ent, M.D., Ph.D., Alexander Moeller, M.D., Christopher Simard, M.D., Linda T. Wang, M.D., Edward P. Ingenito, M.D., Ph.D., Charlotte McKee, M.D., Yimeng Lu, Ph.D., Julie Lekstrom-Himes, M.D., and J. Stuart Elborn, M.D.

Patient **with residual function mutations** – for patient with at least one residual function CFTR mutation (with any other CFTR disease causing mutation)

- Age 1 to 11 years – Ivacaftor monotherapy
- Age ≥ 12 years: Tezacaftor-ivacaftor

Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. N Engl J Med 2017; 377:2024

Triple combination

- Promising new strategy is using tezacaftor-ivacaftor with additional CFTR corrector to further promote F508del CFTR protein processing, trafficking and function
- In late stages of clinical trials
- Two correctors VX-659 and VX-445 when independently added to tezacaftor-ivacaftor bring level of chloride transport in human bronchial epithelial cells >50% in homozygous F508del cells, approximately same level achieved with ivacaftor in G551D mutated cells

Davies JC, Moskowitz SM, Brown C et al. VX-659-Tezacaftor-Ivacaftor in patients with Cystic Fibrosis and one or two Phe508del alleles. N Engl J Med 2018; 379:1599

Haemophilia

X-linked inherited coagulation factor deficiencies

- Haemophilia A (factor VIII deficiency)
- Haemophilia B (factor IX deficiency)

Conditions amenable to gene therapy

Factor replacement therapies have dramatically improved care (require only small amount of CF to change clinical phenotype)

Studies for haemophilia A – focus on vectors

2017 study

- 9 men with baseline factor VIII levels < 1% were enrolled into 3 dose cohorts
- AAV5 containing a B-domain deleted factor VIII gene
- Observed sustained factor VIII activity at therapeutic levels for 1 year in 7 men with severe haemophilia after single does infusion with decrease in rate of bleeding episodes
- Mild increase in hepatic transferases were common

Haemophila B

2017/2018 studies

- Introduced a hyperactive gain-of-function missense mutation (FIX Padua; R338L) known to increase level of expression of FIX through an AAV to 10 men with Haemophilia B with baseline factor levels < 2%
- Lower dose used as previous trials using same method resulted in host-anti-viral immunity
- Mean steady state FIX expression was 33.7%, mean annualized bleeding rate reduced from 11.4 to 0.4 events/year

Other approaches in Haemophilia

Targeting endogenous anticoagulant protein

- Shown that co-inheritance of a prothrombotic mutation leads to less severe clinical phenotype
- Drug example: Fitusiran, an ASO use to reduce expression of antithrombin (*SERPINC1)*

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