Opportunities and challenges in non-clinical development

-Academic Perspective

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Opportunities

The identification of new therapeutic targets

The usage of Advanced Genomic Technologies

Sanger sequencing | **Whole genome sequencing** | **Exome sequencing** | **mRNA sequencing** | **Long-read sequencing**

The identification of novel pathogenic variants (genes, mutations)

The NEW ENGLAND JOURNAL of MEDICINE

100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care — Preliminary Report

The 100,000 Genomes Project Pilot Investigators

2183 families with 161 undiagnosed disorders

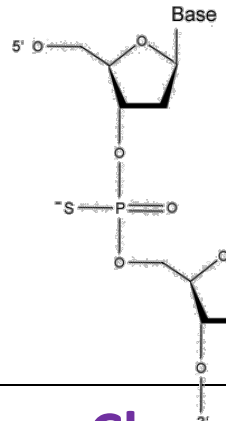
Genetic diagnosis yield: 25% of probands

25% had immediate ramifications for clinical decision making

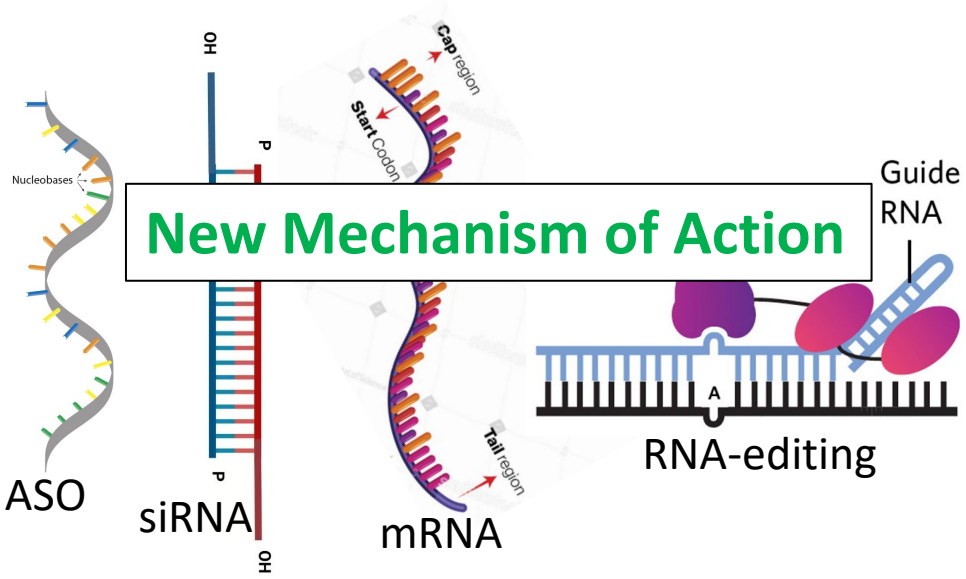
Genomics england

Opportunities

New Platform Technology

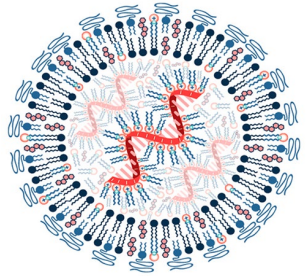


New Chemistries

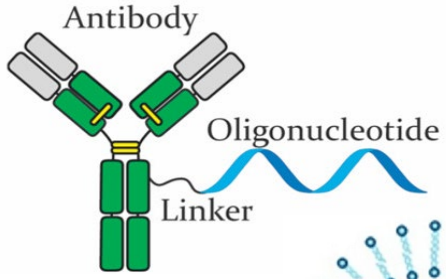


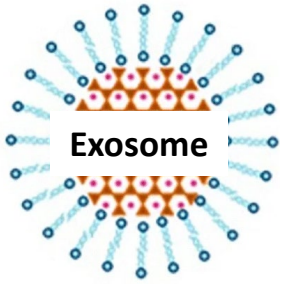
New Mechanism of Action

Lipid Nanoparticle



New Delivery System



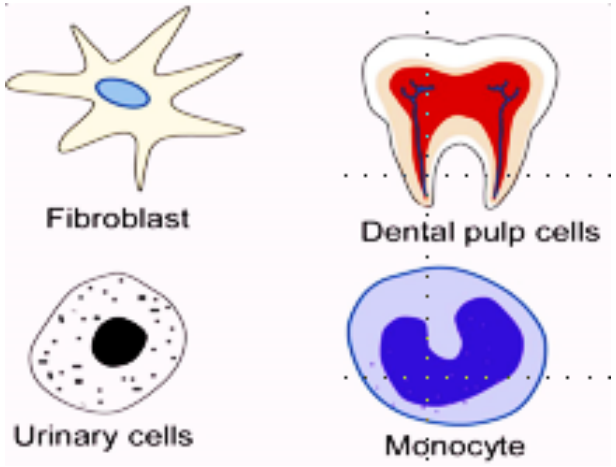


- Next-Generation RNA Technologies
- Academic-led start-ups

Opportunities

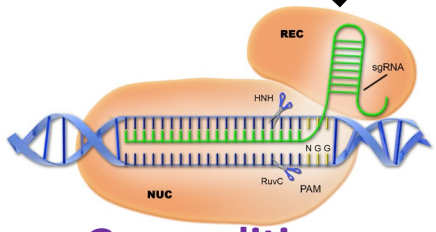
New Model System

Somatic cells
(skin, blood, urine, tooth)



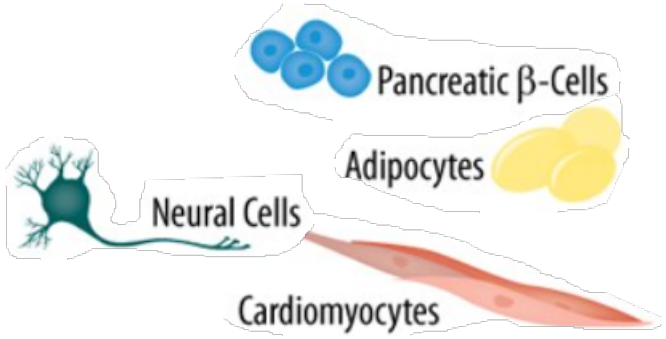
Reprogramme

iPSCs

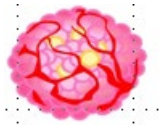


Gene editing

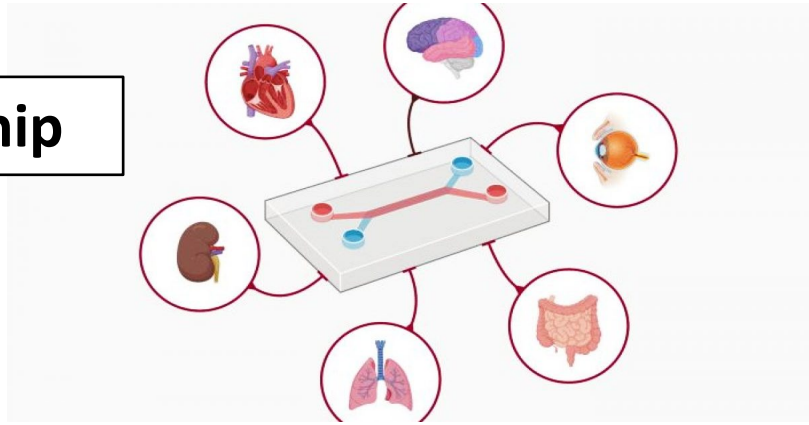
2D models



3D models (organoids)



Organ-on-chip



Challenges

Chemistry-related toxicity

Efficacy

Dose-related

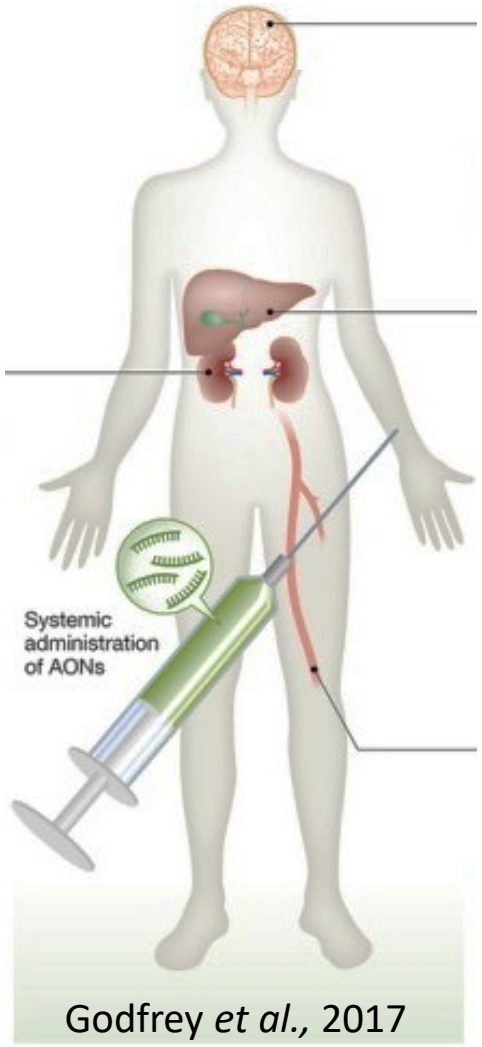
Toxicity

New chemistry and modification

Tissue or cell-targeted delivery

Tissue or Cell-targeted Delivery

Upon systemic administration, up to 18-40% ASOs accumulate in the **kidneys**

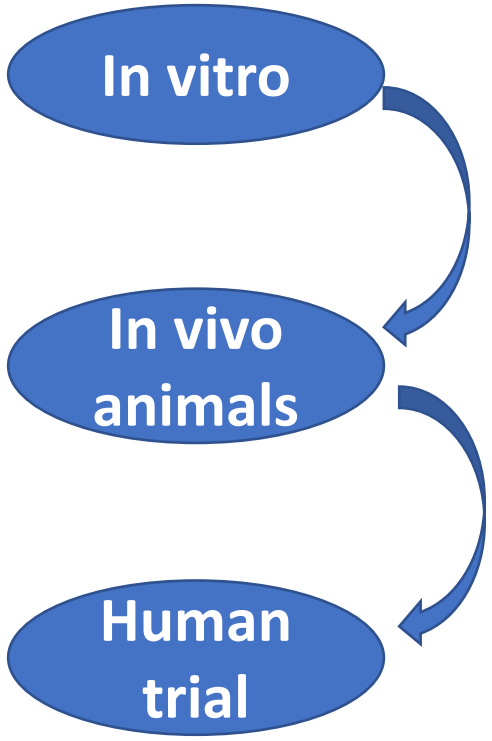


Godfrey *et al.*, 2017

- Hepatocyte-specific delivery: GalNAc-conjugation
- Skeletal muscle-enhanced delivery: anti-TfR antibody-conjugation
- Pancreatic β-cells targeted delivery: GLP1R ligand-conjugation
- Targeted RNA oligonucleotide delivery is required in many other organs, where cell-type specific treatment is required, and to reduce the undesirable exposure of RNA drugs to liver and kidneys.

Challenges

Animal models



- The platform toxicology of many nucleic acid chemistries is already known
- Sequence-related off-target effect is detectable *in silico* and *in vitro* (e.g. by mRNA-Seq)
- Immunoreaction is predictable *in vitro* (e.g. PBMC)
- Efficiency at RNA, protein and functional levels are measurable in *in-vitro* models
- Target sequence is usually human-specific. Unless it is a humanized model, very often RNA oligonucleotides targeting human genes do not target other animal genes

Animal or no animal, that is the question

FDA no longer needs to require animal tests before human drug trials

New law welcomed by animal welfare groups, but others say change won't happen fast

10 JAN 2023 • 5:30 PM • BY MEREDITH WADMAN

https://www.science.org/content/article/fda-no-longer-needs-require-animal-tests-human-drug-trials

"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

'I don't think this is the correct way. Even if they pass the bill, scientists around the world will not follow the new rule.'

'This seems odd logic. While the premise of 'animal models offer false negatives on toxicity studies' is true, the other half of the question is how often are the animal models true positives. How many drugs would have harmed people if not screened out?'

'Typical misleading headline. We can be pretty sure drug companies will want to be sure of safety and animal model accuracy before they progress to expensive human trials. '

Challenges & Opportunities

UCL

RNA-based medicine for ultra-rare diseases

Milasen *– The world's first personalized RNA oligonucleotide therapy*

The NEW ENGLAND JOURNAL of MEDICINE

Kim & Yu et al. 2019

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

Synofzik et al. 2021

Preparing n-of-1 Antisense Oligonucleotide Treatments for Rare Neurological Diseases in Europe: Genetic, Regulatory, and Ethical Perspectives

Matthis Synofzik,[1,2,i] Willeke M.C van Roon-Mom,[3,*] Georg Marckmann,[4,*] Hermine A. van Duyvenvoorde,[5,*] Holm Graessner,[6,7,*] Rebecca Schüle,[1,2,*] Annemieke Aartsma-Rus,[3,*,ii] on behalf of the 1M1M consortium

Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators

Draft Guidance for Sponsor-Investigators

APRIL 2021

FDA *April 2021*

- N-of-1 or N-of-few where no industry mode is available
- Guidance from regulators are needed for academic-lead studies

Opportunities

- More therapeutic targets become available for RNA-based medicines
- Novel chemistries and delivery methods are developed
- More advanced model systems
- More matured regulatory system for clinical translation
- Academic – Industry collaboration

Challenges

- Increased efficacy-reduced toxicity
  - New chemistries
  - Tissue/cells – targeted delivery
- More novel mechanism of action
- Selection of suitable model system
- Guidance on toxicology study
- Clinical trial initiation and support for ultra-rare disease and personalized RNA therapy

Acknowledgement

- https://www.oligotherapeutics.org/
- https://antisenserna.eu/
- https://www.nlorem.org/
- https://www.natahub.org/
- https://www.n1collaborative.org/
- https://www.1mutation1medicine.eu/