Rare metabolic diseases: the miglustat experience

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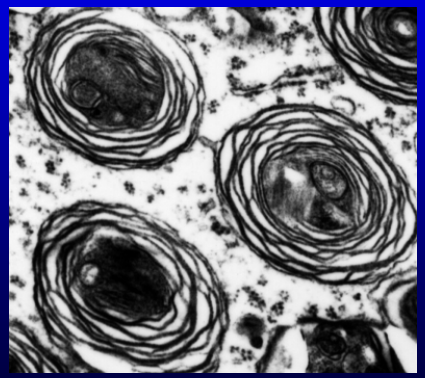
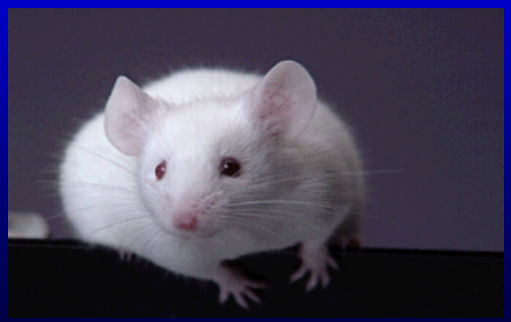
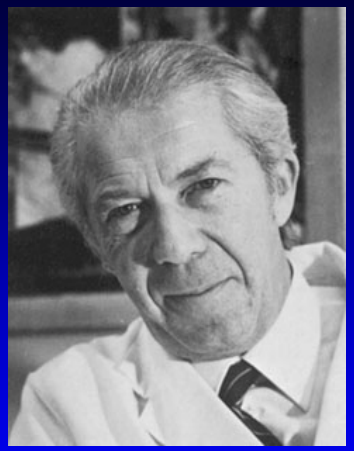




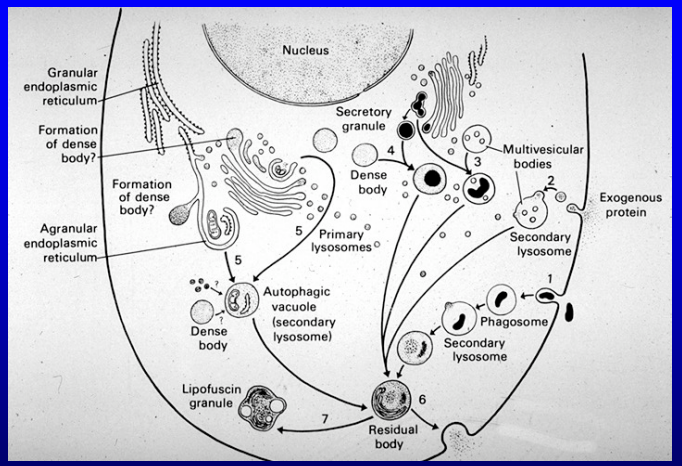


The lysosome is an organelle involved in degrading and recycling macromolecules

Christian de Duve

The Nobel Prize in Physiology or Medicine 1974

"I have been privileged to contemplate many marvelous aspects of the structural and functional organization of living cells. In addition, we have the deep satisfaction of seeing that our findings do not simply enrich knowledge, ***but may also help to conquer disease".***



Functional roles of Lysosomes

- Macromolecule degradation, sorting and recycling
- Endocytosis and vesicular trafficking
- Exocytosis and membrane repair
- Cell death (release of cathepsins)
- Clearance of phagocytosed material
- Ion compartmentalization and signaling
  (calcium - NAADP receptor, iron, zinc, copper etc.)

Over 50 diseases known that result from defective lysosomal function

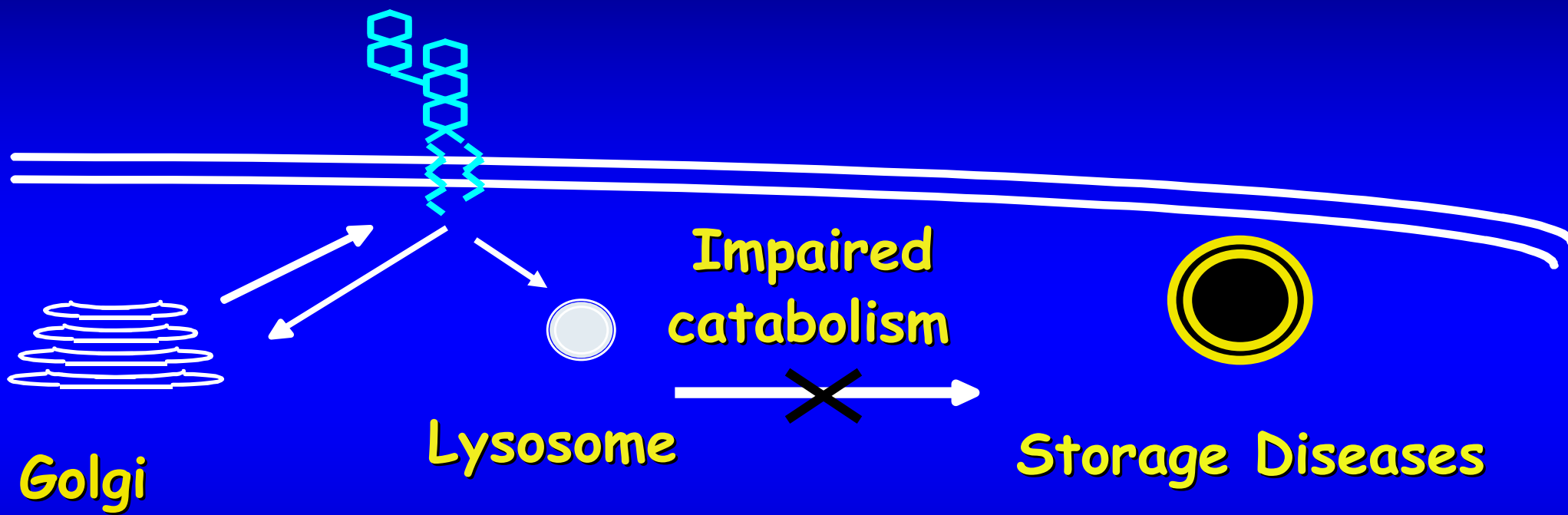
Lysosomal Storage Diseases

- The majority have a neurodegenerative clinical course
- Majority present in infancy/early childhood
- CNS inflammation (microglial/macrophage)
- Visceral organs often involved (spleen/liver)
- Clinical course is highly variable
- Genotype:phenotype correlations limited
- Small increase in residual enzyme major clinical impact

Lysosomal Storage Diseases

Lysosomal storage diseases	1:5000
50% are glycolipid lysosomal storage diseases	1:10000
Gaucher disease (Ashkenazi Jews)	1:450- 1:1000
Gaucher (general population)	1:200,000
Fabry disease	1:40,000
Tay-Sachs (Ashkenazi Jews)	1:4,000
(non-Jewish)	1:300,000
Sandhoff (Jewish)	1:1,000,000
(non-Jewish)	1:309,000
Niemann-Pick type C	1:150,000

Glycosphingolipid Storage Disorders



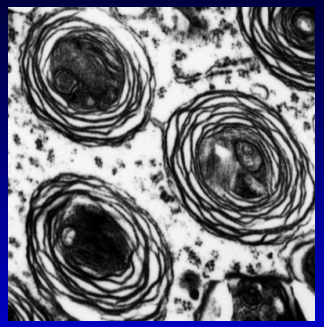
Gaucher

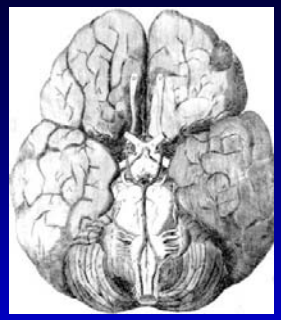
Tay-Sachs

Sandhoff

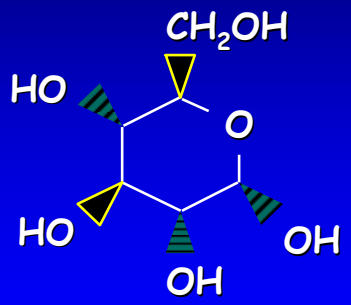
Fabry

GM1 Gangliosidosis

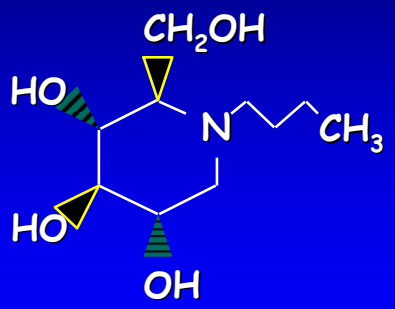
Problem		Therapeutic approach
		
•Genetic defect		*Gene therapy, stop codon read through*
•Enzyme defect		Enzyme replacement, BMT, *chaperones, stem cells*
•Storage of substrate		Substrate reduction therapy (SRT)
•Secondary consequences		*NSAIDS, Ca^{++} modulators*



Imino Sugar NB-DNJ



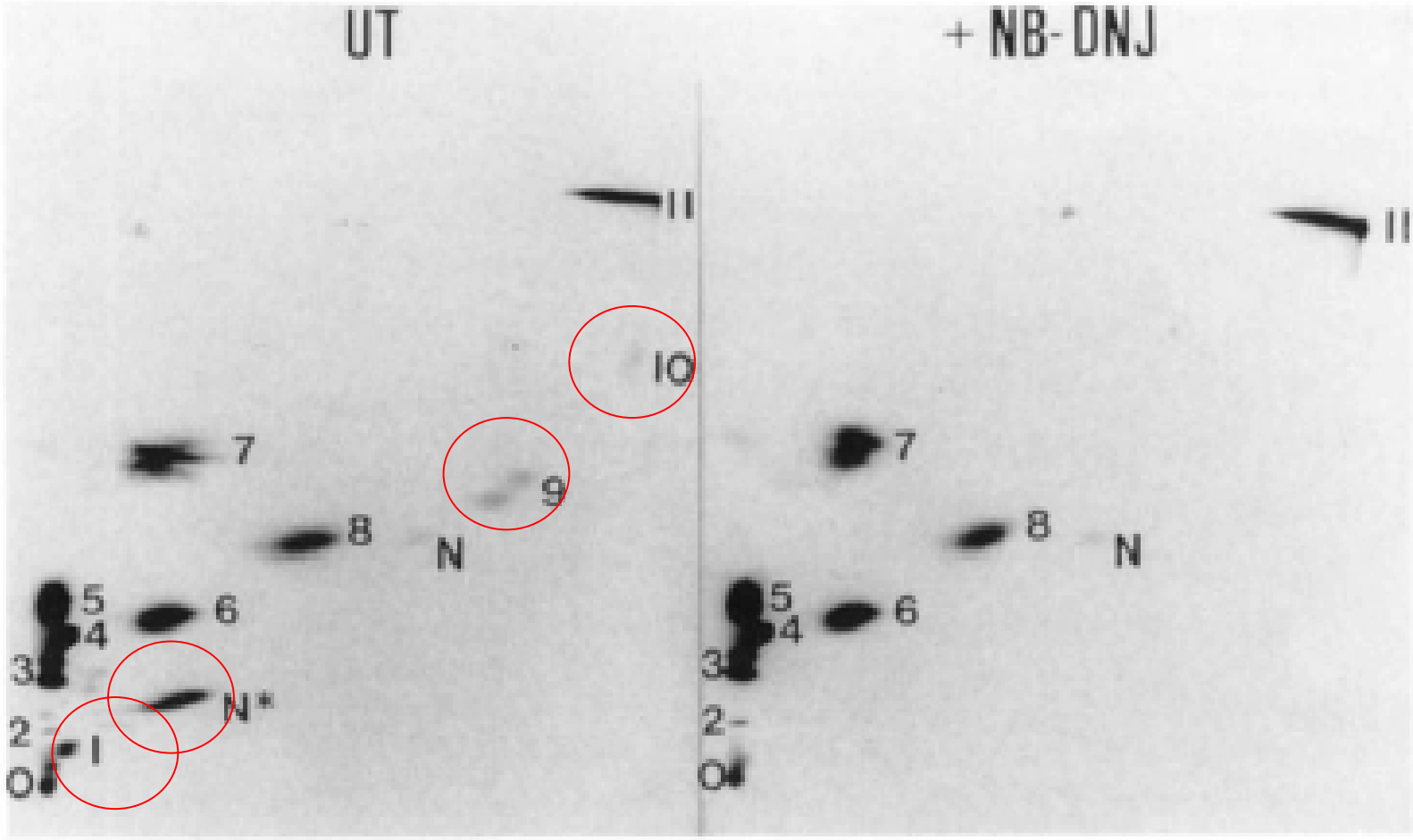
α-Glucose



NB-DNJ

- Derived from natural products (plants/fungi)
- Water soluble, orally available, not metabolised
- Developed (Monsanto) as anti-viral in 1980s (HIV)
- alpha-glucosidase inhibitor

Serendipity: novel discovery in 1993



Platt et al, 1994, JBC, 269, 8362-8365

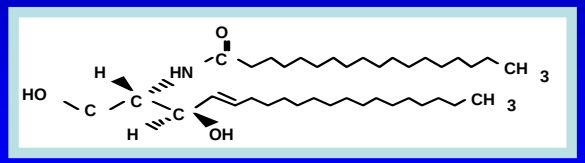
Inhibition of glycosphingolipid biosynthesis

L-Serine, Palmitoyl-Coenzyme A

↓

↓

Ceramide

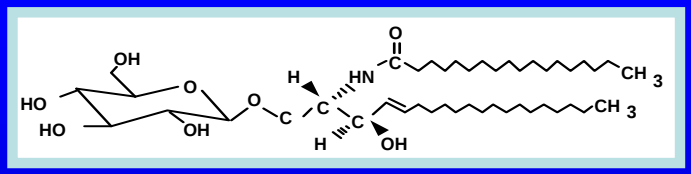


UDP-Glucose

UDP

UDP-Glucose: N-acylsphingosine glucosyltransferase

← ***N*B-DNJ miglustat**



Glucosylceramide

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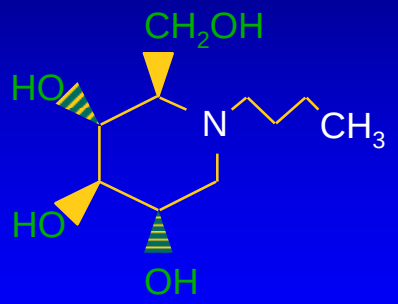
Lactosylceramide

↓

Ganglio- series | **Lacto(neo)- series** | **Globo- series**

Imino Sugar NB-DNJ (miglustat)



NB-DNJ (miglustat)

- Proof of principle in an *in vitro* model of Gaucher disease
- GSL depletion well tolerated long-term in mice
- Proof of principle in mouse models with CNS disease

(Tay-Sachs, Sandhoff & GM1 gangliosidosis)

In our favor….

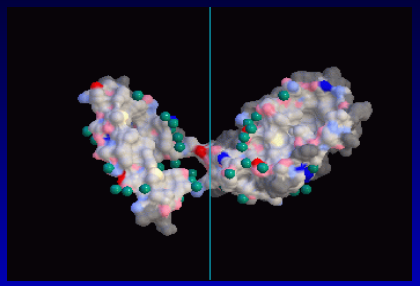
- Pre existing toxicology and DMPK data in multiple species
- Pre existing clinical safety data at high dosage (HIV studies)
- A metric ton synthesized
- 1 drug to treat multiple diseases
- A small company wanting to develop it (Oxford GlycoSciences)
- Key opinion leaders who believed in the concept/data/approach (Prof. Tim Cox & Prof. Bryan Winchester

Clinical trial

- Disease with no CNS involvement
- Clinically relevant end points (consensus)
- Surrogate disease markers/biochemical markers
- An effective therapy to compare SRT with
- Expectation that clinical changes will be manifest within 1 year

Type 1 Gaucher disease (glucocerebrosidase deficiency)

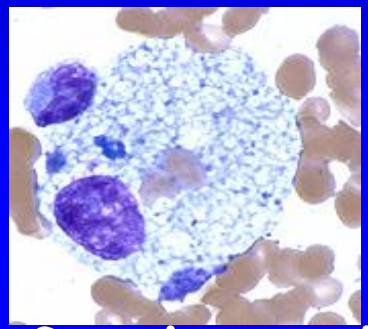
- Standard of care: Intravenous enzyme replacement therapy (ERT)
- Increase choice for Gaucher disease clinical management with an oral drug?



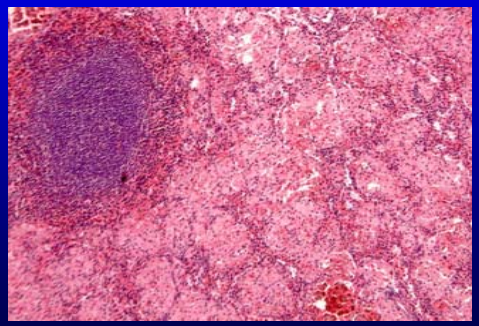
Cytokines

Cathepsins

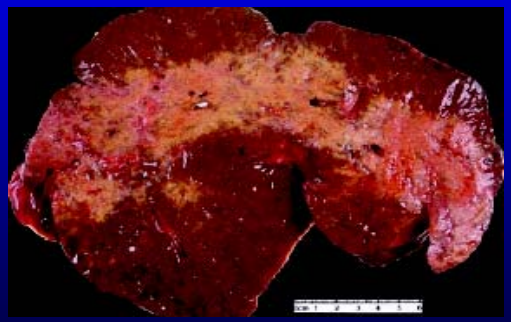
Chitotriosidase



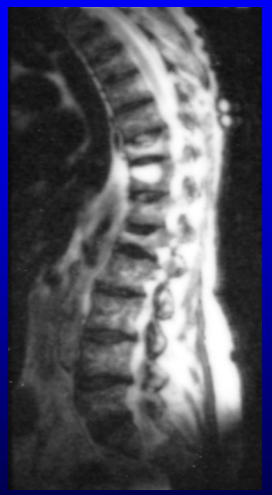
Gaucher cell



Spleen



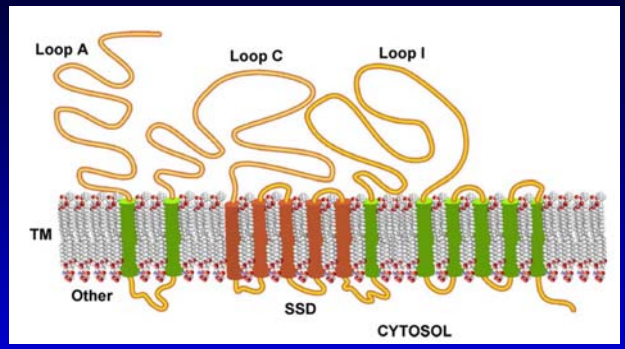
Liver



Bone marrow

- Trial based on 28 patients
- 1 year open label trial
- **Trial data positive (Cox et al, Lancet 2000)**
- EMEA approved 2002
- FDA approved 2003
- Requirement for post-marketing surveillance
- Drug transferred to Actelion, Basel
- *10 Years from first data to EMEA approval*

Niemann-Pick type C disease



- Neurodegenerative lysosomal disorder
- 1:120,000 live births, carrier frequency 1:100
- Ataxia, dementia, speech and swallowing defects, premature death
- In NPC disease there is secondary GSL storage, candidate for miglustat therapy

Clinical evaluation of SRT in Niemann-Pick type C (NPC) disease

- SRT improves survival in the NPC1 mouse (*Zervas & Walkley*)
- SRT in NPC patient improved cellular function (*Lachmann et al*)
- Clinical trial in NPC reported efficacy *(Patterson et al)*
- Stabilisation /improvement in some clinical signs (visual system, swallowing)
- Retrospective surveys: miglustat-treated patients and natural history

EU Commission Approval

- January 2009 (Actelion)
- FDA requested more information 2010
- In USA NPC patients being randomised to treatment by insurance companies.....

The Challenges

- All therapies for lysosomal disorders have been developed in academic labs i.e. industry reluctant to do discovery research
- No rare disease policy in UK to catalyse basic research: Research Councils, Government Agencies, NHS.
- Biotechs will take on drugs post- proof of principle (not big pharma)
- Orphan Drug Act Incentives work but only up to a point
- Regulatory process fails products for rare diseases

Patients in Rare Disease Clinical Trials

- All have established/advanced disease
- Highly variable clinical presentation/age of onset/genotypes
- Small numbers of patients
- Ages vary
- They do not predict outcome in early intervention
- They do not model pre-symptomatic intervention
- If a trend towards stabilisation or improvement seen predicts better outcomes in patients treated earlier
- Choice of endpoints: what can be improved/stabilised in a symptomatic patient? Relevance to QOL?
- Neuronal loss versus neuronal dysfunction?

Falling at the final hurdle

- Lack of rare disease expertise on regulatory panels
- Requests for trial design, patient numbers and questions raised during approval process reveal profound ignorance of rare diseases
- Clinical endpoints are selected pragmatically for new therapies, may not guess/predict appropriate primary end points- is that grounds for approval failure? The primary endpoint dogma is not helpful.
- Statistically underpowered trials inevitable
- Trends in the right direction in pivotal trials enough?
  Role of secondary endpoints/surrogate endpoints/biomarkers?

Ways forward?

- Approve with more flexible criteria for a rare disease (endpoints, trial size, design)
- Post-marketing monitoring requirement to prove statistically that efficacy is achieved in larger population, withdraw if fails to show efficacy
- Specialized panels who have appropriate expertise/knowledge of rare diseases essential

http://www.curetheprocess.org/goals

- streamlined development path to shorten timelines and reduce the financial risk associated with development of rare disease therapeutics.
- More patients with rare biochemical and genetic disorders will get earlier access to specific, effective therapies
- Investment in early stage biotech companies focused on rare diseases
- A new Office with experts trained and knowledgeable in the disease area, will allow for an improved and more specialized FDA review.
- *"No disease is too rare to deserve treatment"*

KAKKIS EVERYLIFE FOUNDATION

Challenges and Potential Solutions

- Traditional criteria for drug approval not appropriate for rare diseases : underpowered and effects likely to be modest
- Lack good biomarkers and natural history data
- Composite clinical scores are not validated e.g. NPC
- Introduce "conditional approval" with post-approval monitoring of safety and efficacy. Lesser burden of proof than common diseases.
- Use n=1 trials where patient closely studied before therapy to prove they have moved from their disease trajectory on therapy

Academic discovery
Biotech-pharma development
Incentives from Orphan Regulation

Urgent re-think of regulatory process/approval for rare diseases