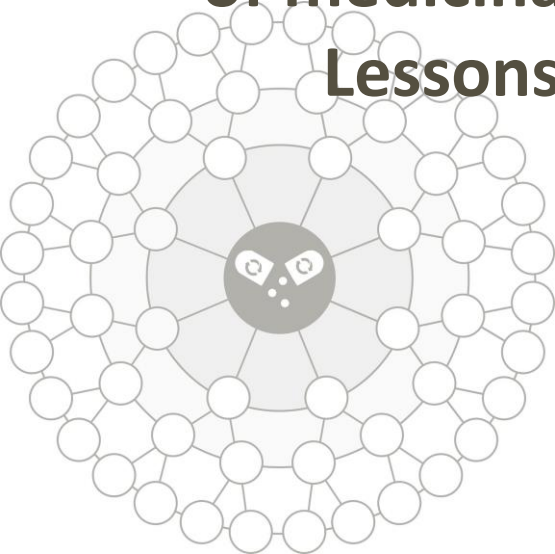


Application of in-silico technologies for the repurposing of medicinal products in rare paediatric diseases: Lessons from a case study in heart failure



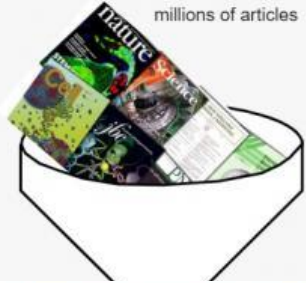
Oscar Della Pasqua

Chair Clinical Pharmacology & Therapeutics

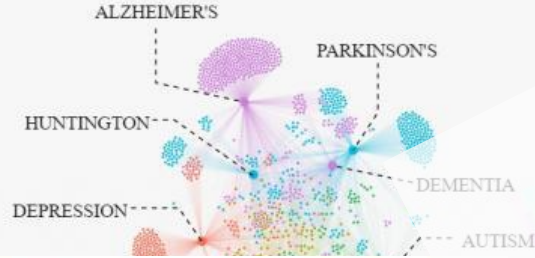
Chair Repurposing Therapeutic Innovation Network (TIN)

Scientific literature

millions of articles











Network medicine



Approval of
novel or
repurposed
medicine










DRUG REPOSITIONING (DR)

DISCOVERY

- ★ Knowledge-based DR 
- ★ Activity-based DR 
- ★ *In silico* DR
 -  Molecular docking
 -  Transcriptional signatures
 -  Network analysis
 -  Data mining
 -  Machine learning
 -  Similarity analysis

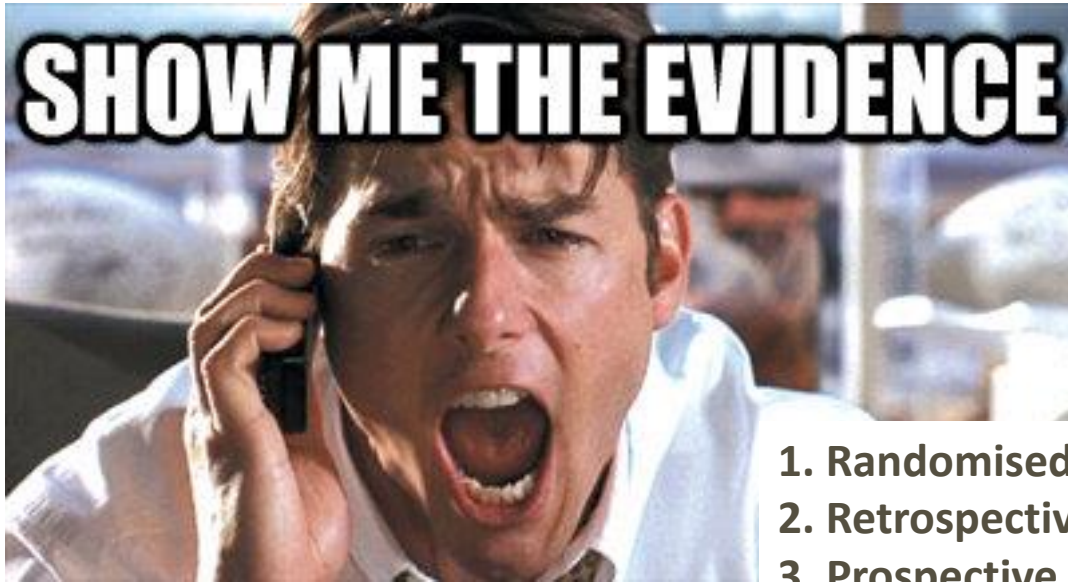


VALIDATION

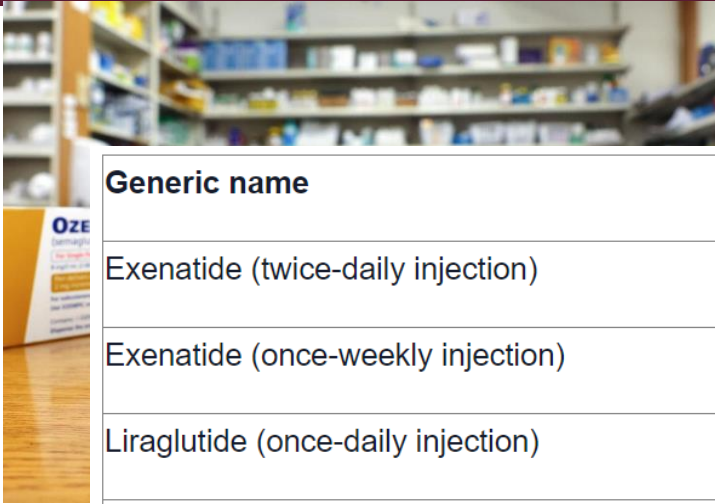
- ★ *In silico* analysis
 -  Retrospective studies
 -  Meta-analysis
 -  Molecular docking
 -  Transcriptional signatures
- ★ *In vitro* analysis
 -  Cell culture studies
 -  Protein signatures
 -  Knock-down gene signatures
- ★ *In vivo* analysis
 -  Xenografts
- ★ *Clinical trials*
 - 



How has the process for evidence generation in clinical research evolved?



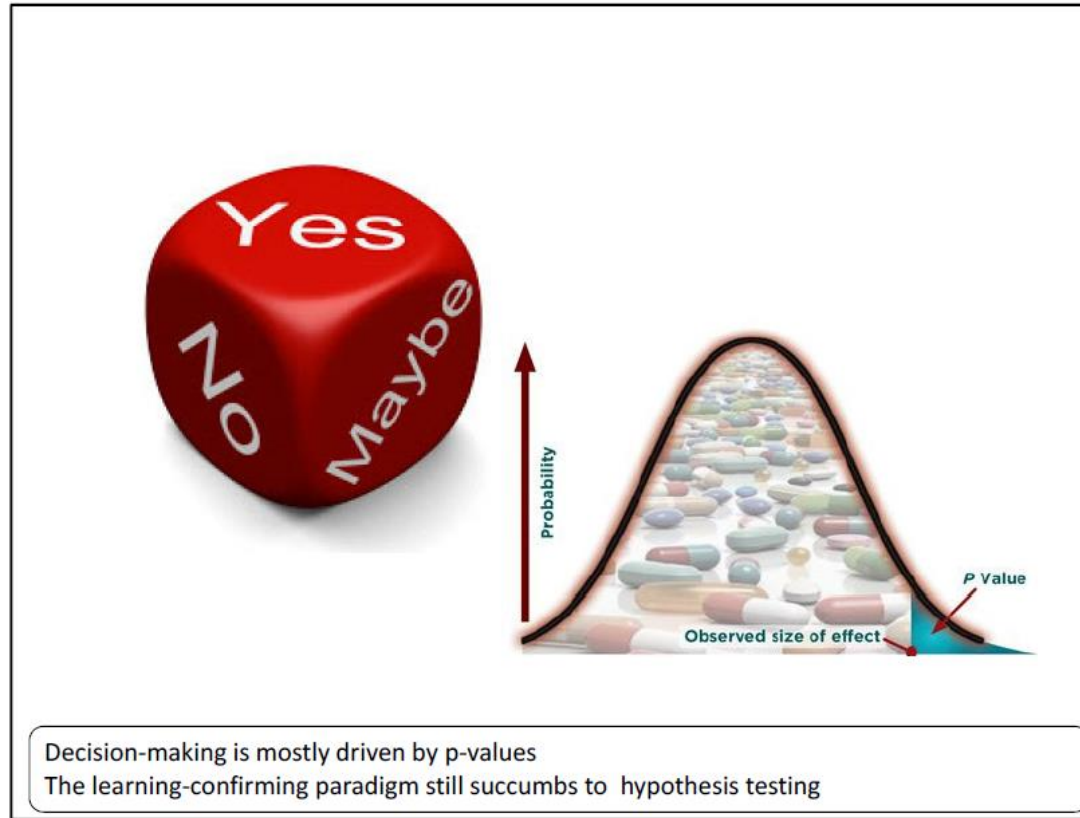
1. Randomised controlled clinical trials
 2. Retrospective observational studies
 3. Prospective observational studies
-

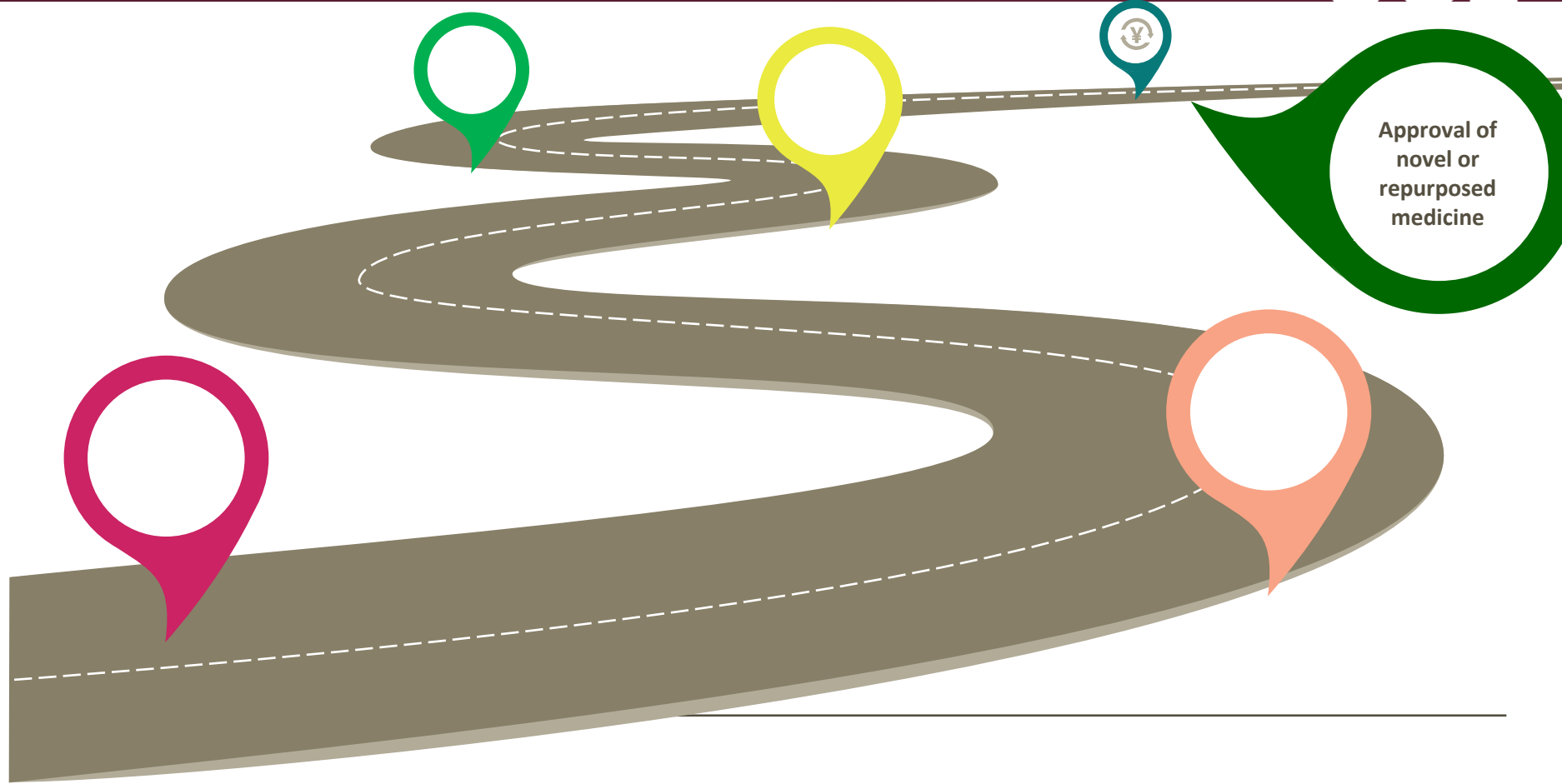


Generic name	Brand or Trade name
Exenatide (twice-daily injection)	Byetta
Exenatide (once-weekly injection)	Bydureon
Liraglutide (once-daily injection)	Victoza
Lixisenatide (once-daily injection)	Lixumia
Dulaglutide (once-weekly injection)	Trulicity
Semaglutide (once-weekly injection)	Ozempic

Diabetes: Semaglutide is a human GLP-1 analogue

Weight loss: Semaglutide is a human GLP-1 analogue




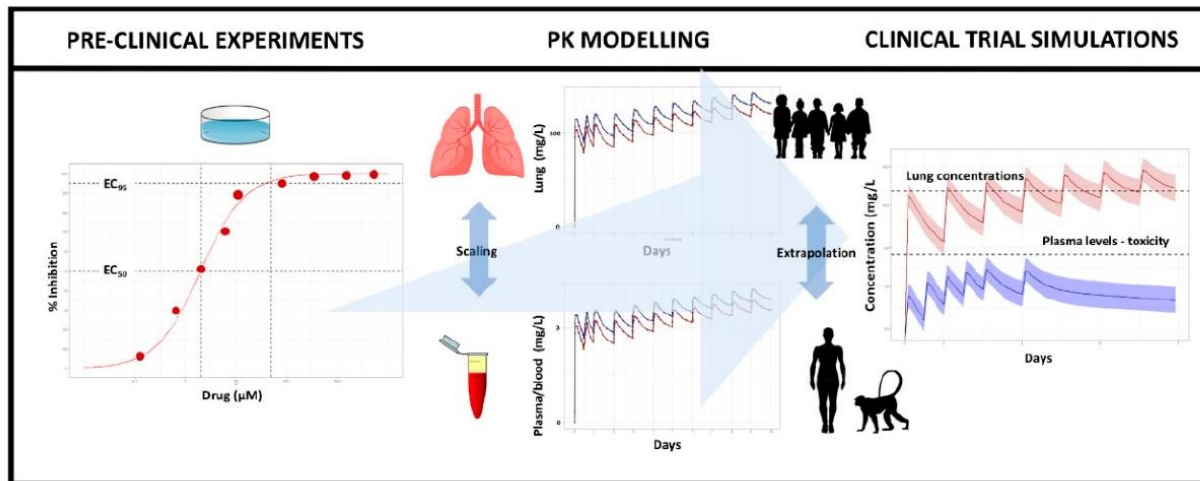


Approval of
novel or
repurposed
medicine

Article

Model-Informed Repurposing of Medicines for SARS-CoV-2: Extrapolation of Antiviral Activity and Dose Rationale for Paediatric Patients

Federico Romano ^{1,†}, Salvatore D'Agate ^{1,†} and Oscar Della Pasqua ^{1,2,3,*} 

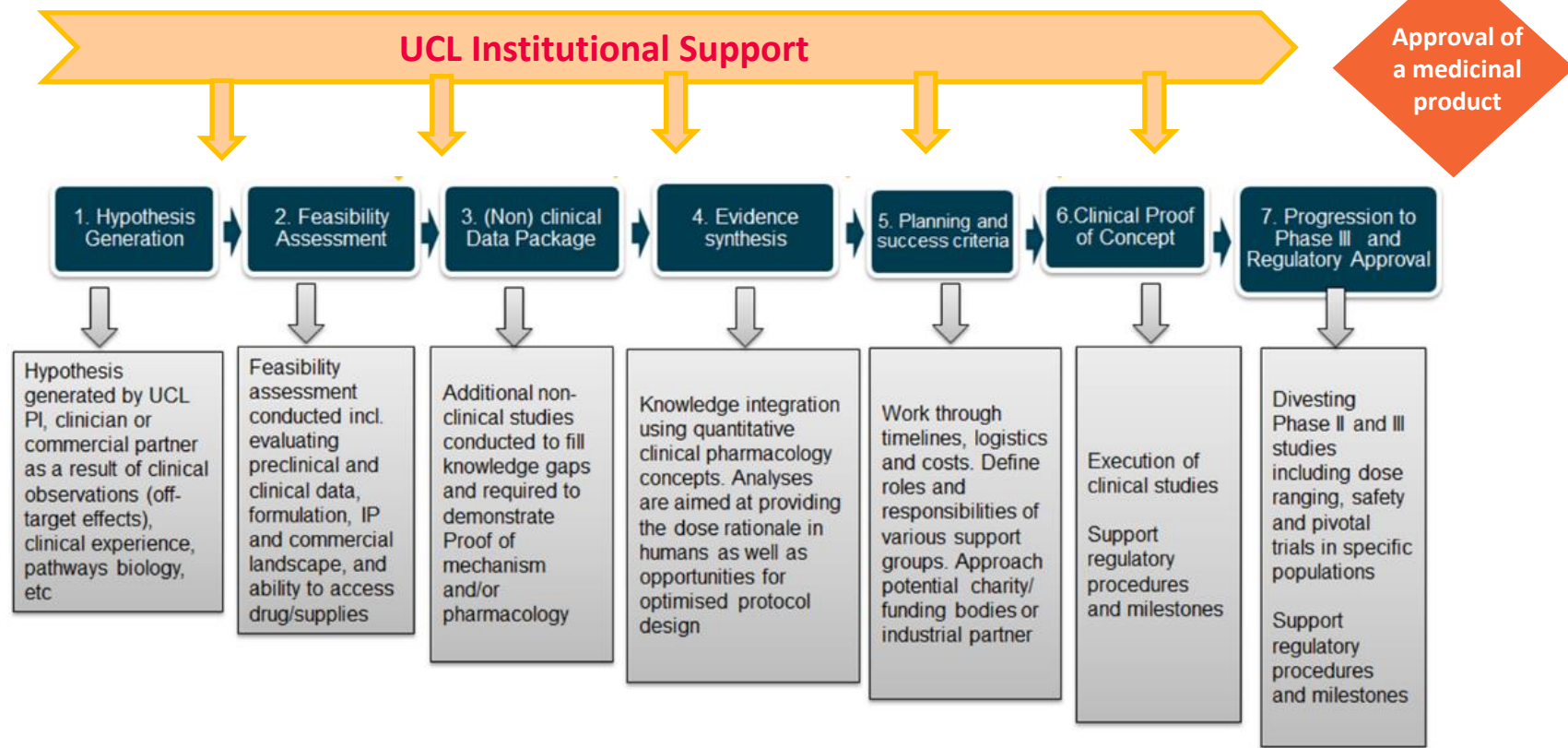


- Rare disease (1-8 / 100,000 children)
- Relevant burden: 15,000 hospitalisations / year in the USA
- Current therapy unsatisfactory: DCM 5y mortality 30-50%
- VAD: morbidity and mortality, burden to families and health systems
- Heart transplant
 - Organ shortage: 15-30% waiting-list mortality
 - Median graft survival ~20y
- Paediatric heart failure therapy: off-label
- Recent advances in adult heart failure (sacubitril/valsartan, SGLT2i inhibitors, vericiguat, ...)

- In the past, heart failure trials in children have failed!
- Reasons:
 - Small and heterogeneous population
(primary myocardial disease versus morphological diagnosis, biventricular versus single ventricle haemodynamics)
 - Poor dose rationale, inadequate formulation/route
 - Poorly defined outcomes
- Can these issues be avoided in the future?

- Approved for T2DM 2012-2017
- Mandatory investigations on cardiovascular (and renal) outcomes - positive surprise
- Trials in HF population (with or without T2 DM): 25-26% reduction in mortality / worsening HF (Dapagliflozin 2019, Empagliflozin 2020)
- ESC adult HF guidelines 2021: Dapagliflozin or Empagliflozin recommended as standard therapy for HFrEF
- 2021-2022: also beneficial for HFpEF
- Safe (adults + children)
- Children
 - approved 10-18y with T2DM
 - used off-label for GSD Ib, HF, CKD

Critical Path to Drug Discovery and Development





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TRANSLATIONAL RARE DISEASE CENTRES

To transform rare disease translational research in the UK



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[HOME](#) > [OUR STRATEGY](#) > [RARE DISEASE](#)

Joint translational funding from Action Medical Research and LifeArc

Published on 27 April 2023



Grants, funding and support for academics

Translational Rare Disease Centres

£40 million to build on the UK's rich, rare disease research base. (Closed to new applications)

Joint funding call: Funding for Epidermolysis Bullosa

LifeArc and DEBRA Austria in joint call for projects to develop therapeutics for any type of Epidermolysis Bullosa - apply by 10 September 2023

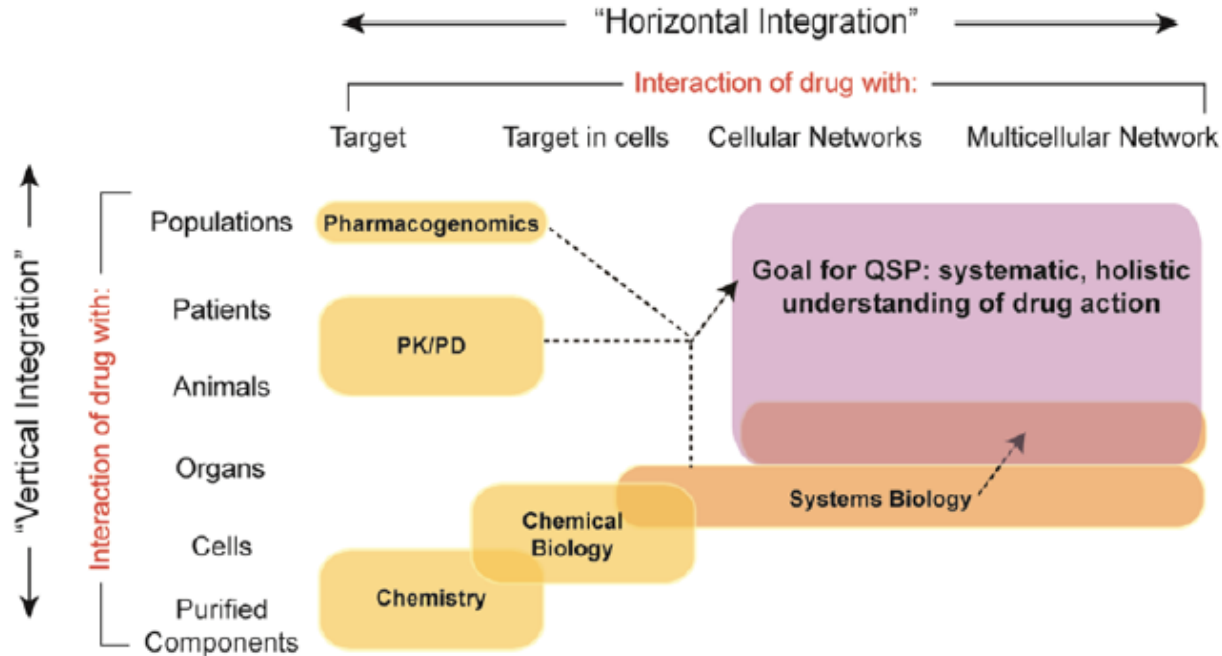
LifeArc Gene Therapy Innovation Fund

£5m annual fund for gene therapy technologies, which includes support from the world-class network of Innovation Hubs for Gene Therapies

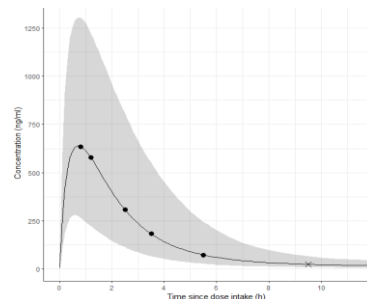
LifeArc & GOSH Charity Fund

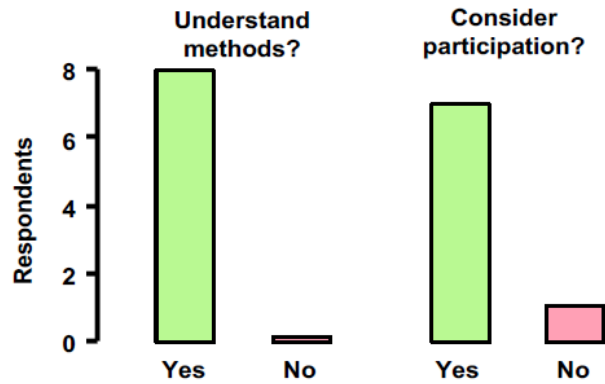
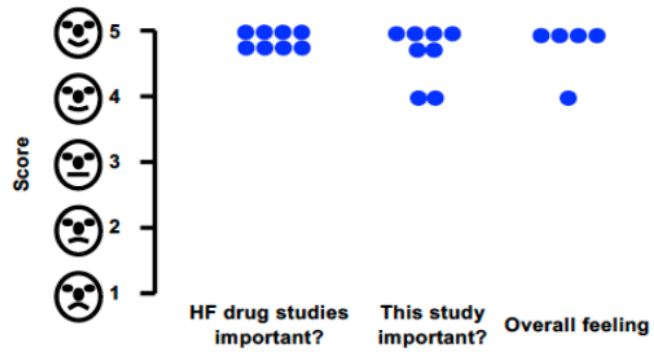
Joint funding scheme for GOSH researchers to drive their discoveries towards new tests and treatments for childhood rare diseases

A central pillar for translational medicine

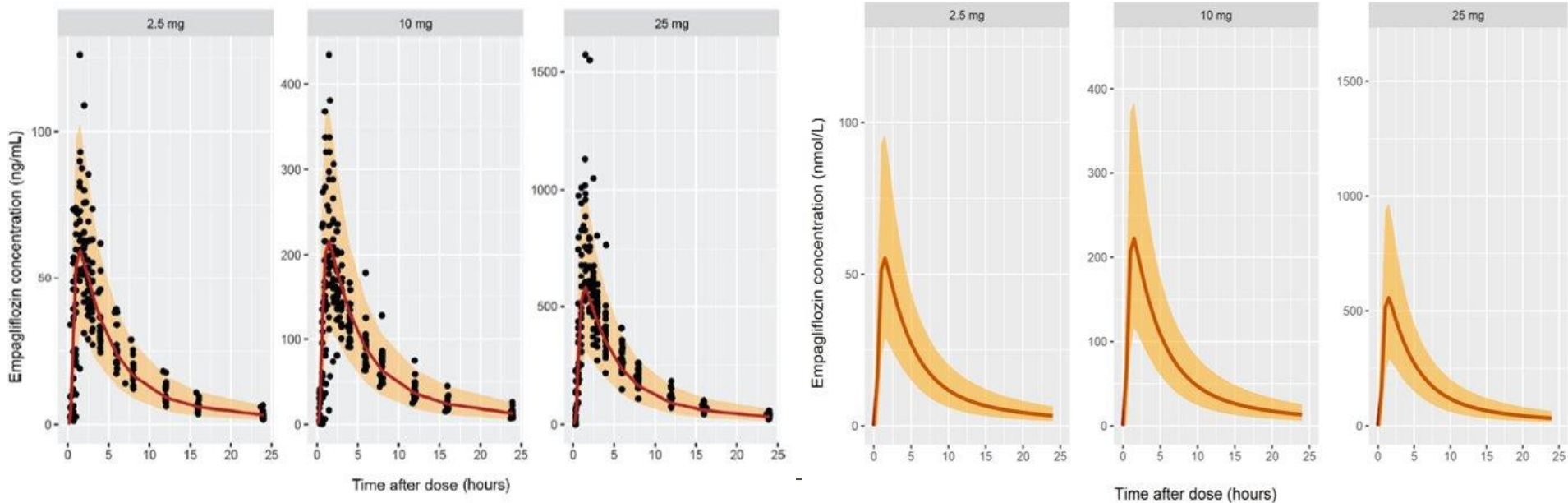


- Patient involvement (survey)
- Define the dose rationale (range)
- Optimised evidence generation
 - In silico modelling and simulation
 - Clinical protocol design and dosage form evaluation
 - Cross-over PK trial in 12 children at GOSH, London, UK
(*4th best children hospital worldwide, one of the biggest HF and HTx programs worldwide*)
 - 1^{ary} outcome: Pharmacokinetics
 - 2^{ary} outcomes: Safety, efficacy markers
 - Adaptive design for pivotal efficacy study including dynamic Bayesian borrowing
 - Age-friendly formulation development (< 6 years old)

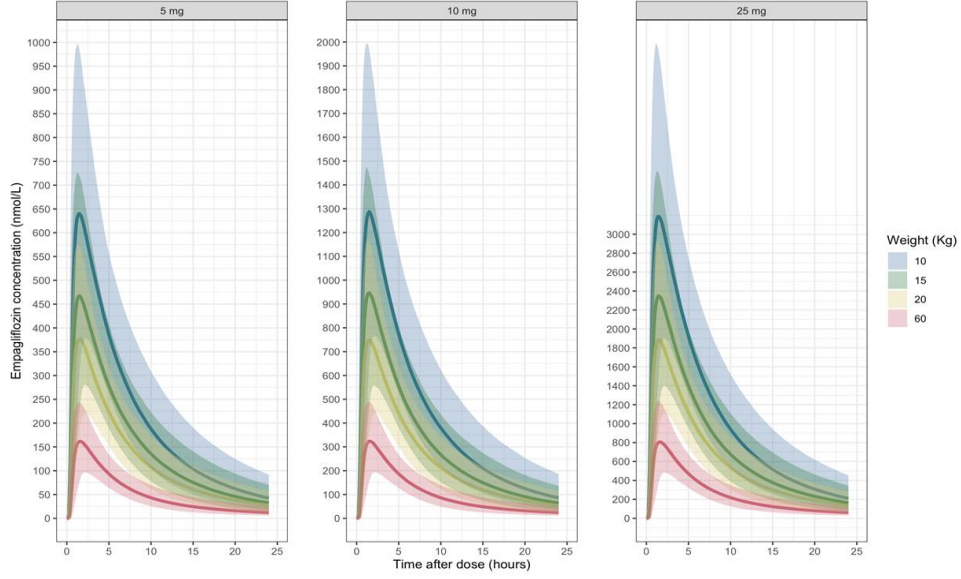
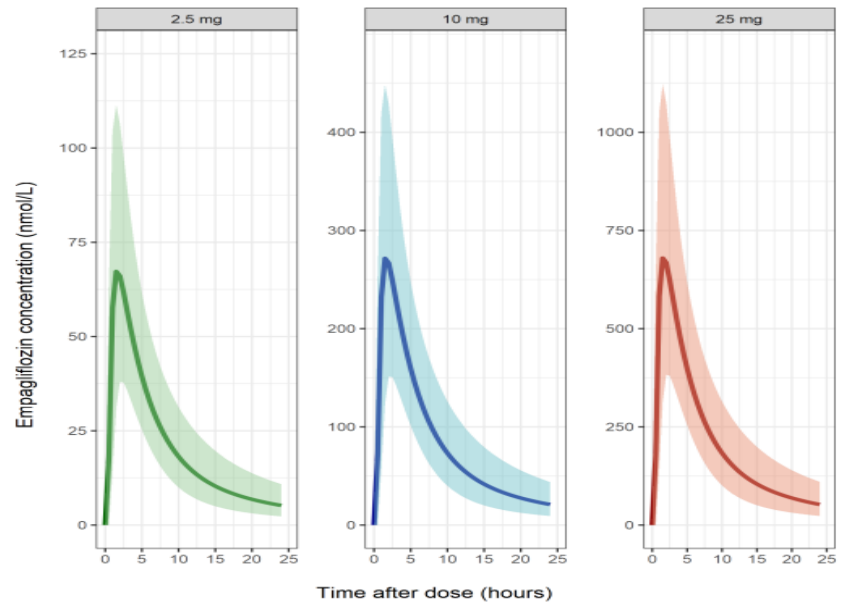




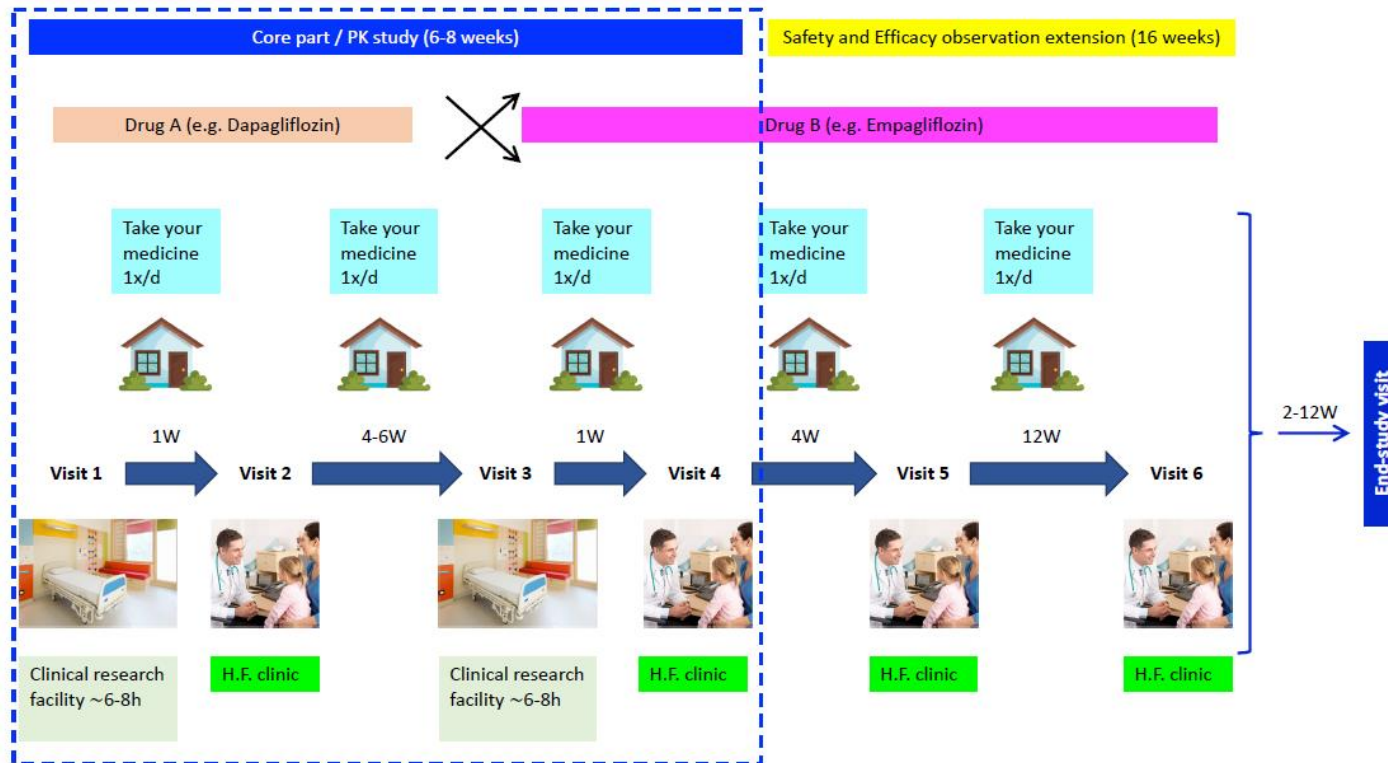
Systematic literature review, selection of a candidate model and reproduction on a virtual population (with similar demographic & biological characteristics)



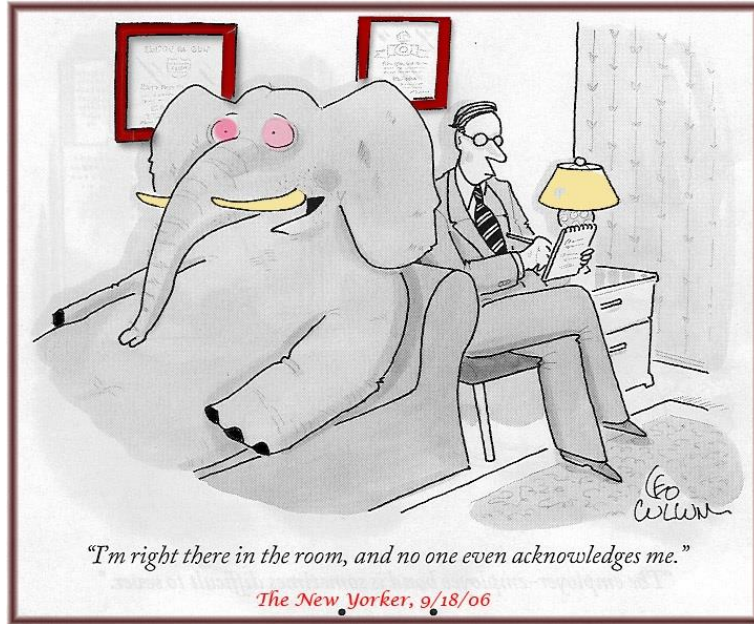
Covariate effects due developmental growth



Protocol – sample size and sampling optimisation



- Accurate identification of unmet needs, check clinical and patient relevance
 - Identification of suitable doses, dosing regimen and formulation
(once daily administration, well tolerated and efficacious in both adults with HF and adolescents with T2DM)
 - Future: not only RCT's!
 - Repurposing is appealing if based on strong scientific rationale
 - M&S is a pivotal instrument to assess the probability of success and mitigate risks
-



- Clear development plan
- Quantitative assessment of the probability of pharmacological success
- Integrated evaluation and prediction of clinical performance
- Evidence generation and (informed) decision making

UCL Institutional Support

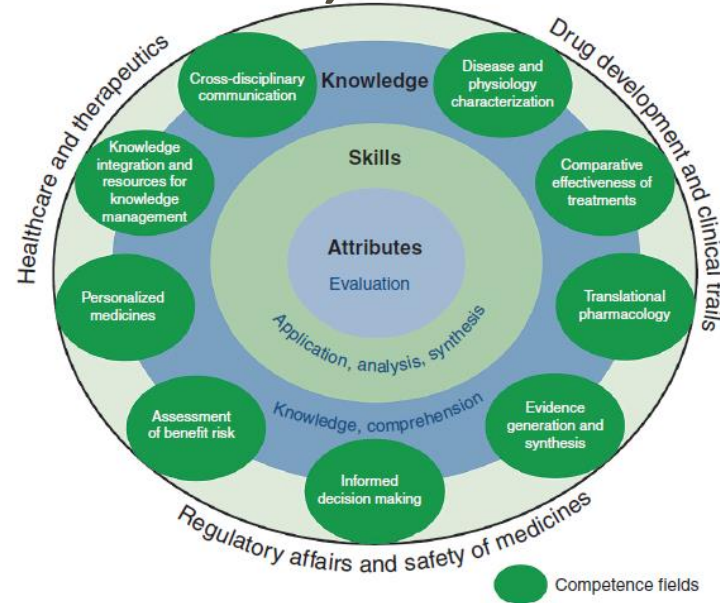
Collaboration, collaboration, collaboration

Training

Development

Collaborations

Partnerships



Vlasakakis et al., CPT:PSP 2013; 2:e40

Pluralitas non est ponenda sine necessitate
("Plurality should not be posited without necessity" (William of Ockham))



OSCAR DELLA PASQUA



SILVIA GRANDONI



SALVATORE D'AGATE



UMBERTO VILLANI

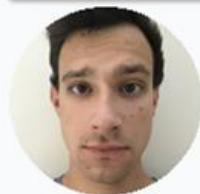


ELISA ALESSANDRINI



SEBASTIANO LAVA

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PIETRO LADDOMADA



ALESSANDRO DI DEO



FEDERICO ROMANO



PAUL HEALY



GIAMMARCO BAIARDI

Research Collaborators, Postdoctoral Fellows, and Graduate Students are Welcome!

Thank you !



The greatest obstacle to discovery is not ignorance, but the illusion of knowledge

by Daniel Boorstin