How can we pool our resources, infrastructures and expertise to accelerate new therapeutics for patients
Outline

• Drug discovery for common diseases is very inefficient
• Problem in rare diseases
• Opportunity in rare diseases
• What have we been doing in SGC?
• What have we been doing in Oxford more broadly?
• 3 exemplars
• What we would like to do with Birmingham and nationally...... then internationally
Drug discovery for common diseases is very inefficient

• Too costly
• Too risky
• Too slow
Problem in rare diseases

• 350 million patients

• Half are children

• 30% do not reach age of 5

• 6-8 years for diagnosis

• 95% have no FDA approved treatment
Opportunity in rare diseases

• Pharma investing increasing resources (Pfizer, Sanofi, Takeda/Shire.....)
  • Many are monogenic.......higher probability for clinical success
  • Accelerated approval
  • Tax credits
  • Insights into more complex diseases
  • Can secure ROI in more common/ most debilitating subset

• Genetic insights: Genome England

• Patient groups increasingly desperate/ committed

• UK has more investment funds per head than any other country in Europe
What have we been doing in SGC?

• Pooling resources......share risk

• Working with several pharmas to generate novel, high quality, early discovery tools, for novel or ‘intractable’ genes/ targets......drive innovation

• Sharing all tools, data, knowledge freely........crowd source science

• Releasing everything immediately........reduce duplication and wastage
What have we been doing in Oxford more broadly?

Oxford Rare Disease Centre (Matthew Wood and Kay Davies): focus on innovation, collaboration, translation, quickly

• > 250 PIs working on > 350 diseases

• collaborations with
  • academics/ clinicians across the world
  • several pharmas
  • numerous patient groups
  • many investors
Open tools accelerate science, proprietary programmes, translational studies and enterprise...........ultimately patient benefit

GSK informs SGC about Mitsubishi compound

Oxford and Harvard start collaboration

Co-publication of BRD4 inhibitors
  - JQ1, SGC/ Harvard, NUT
  - I-BET, GSK, inflammation
  JQ1 distributed to 100+ labs

BRD4 linked to
  - AML (Nature)
  - MM (Cell)

Filippakopoulos et al, Nature 2010 (Dec)

Growing interest in industry:
Pfizer/ SGC produce another BET inhibitor

GSK carries out first in man (for published indication)
Gene, structure, inhibitor, preclinical PoC, clinical molecule from industry........clinical PoC

**Gene**

FOP genetic linkage discovered in Oxford: kinase

A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva

**Mechanism**

Structure solved and mutations mapped

Gain of function

**Preclinical**

New inhibitor

Preclinical PoC

**Clinical candidate**

Clinical molecule identified

Potent and selective

Saracatinib

FOP genetic linkage discovered in Oxford: kinase

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Gain of function

New inhibitor

Preclinical PoC

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Potent and selective

Saracatinib
Strategies for LoF metabolic disorders

- Substrate Reduction
- Functional Bypass
- Pharmacological chaperoning
- Accumulation
- Deficiency
- Functional Bypass
Lysine Metabolism

- DHTKD1 (MIM 245130)
- ALDH7A1 (MIM 266100)

Galactose Metabolism

- Pyridoxine dependent epilepsy
  - ALDH7A1 mutations
- Classic galactosemia
  - GALT mutations

Glyoxylate Metabolism

- Pyridoxine dependent epilepsy
- Classic galactosemia
- Primary Hyperoxaluria

Therapeutic targets for substrate reduction therapy

- Upstream targets to be inhibited
Early discovery tools generated........HTS underway

AASS inhibition is therapeutic target
- ALDH7A1 substrate accumulation is pathological driver
- Metabolite analysis in mice suggests major pathway via saccharopine (Pena IA 2016 BBA)
- Naturally occurring AASS mutations are benign (Houten S 2013 OJRD)

Tools generated
- Proteins
  - LKR, SDH, full-length, mutants
- Structures
  - apo, holo SDH domain
- Assay
  - fluorescence activity, DSF
- Chemical matters
  - Structure of AASS-SDH + Pro
  - Structure of AASS-SDH + Pro analog
- Knockdown
  - siRNA knockdown of AASS in patient fibroblasts
  - reduced metabolite accumulation & rescued phenotype

Ongoing studies
- CRISPR-cas9 zebrafish model
- HTS with NIH-NCATS
What we would like to do with Birmingham and nationally......internationally

• Build national network/ infrastructure for gene to clinical POC

• We are happy in Oxford to generate early reagents for novel genes and targets using our resources (freely available)

• We wish to translate, develop and commercialise derivatives of these by working with
  • Pharmas
  • Patient groups
  • Charitable and Government funders
  • Investors

• Preferably in open manner........to ensure therapies are affordable