MRC Technology
Centre for Therapeutics Discovery

fast-tracking discovery and development of novel drugs from academia

Dr Duncan Young
Business Development Manager

Warwick, January 2014
Forming partnerships to drive early stage scientific research to the patient

ACADEMIC AND NON PROFIT Institutions

MRC heritage

established 2000

CHARITY status

120+ staff

New PARTNERSHIPS

PHARMACEUTICAL BIOTECHNOLOGY Markets

MRC

£500m+ income

400+ licences

18+ start ups

12+ drugs

£40bn+ revenue

120+ start ups

18+ drugs

400+ licences

£500m+ income

120+ staff

New PARTNERSHIPS

PHARMACEUTICAL BIOTECHNOLOGY Markets

MRC heritage

established 2000

CHARITY status
Creating partnerships...

- Actively seeking collaborator scientists and institutions
- Sharing our expertise and capacities in technology transfer
- Joint early-stage academic drug discovery partnerships
- Promoting our capabilities globally
... to deliver new drugs

- **Tysabri:**
  - A Medicine for Multiple Sclerosis
  - A therapeutic antibody developed by Biogen-IDEC Elan
  - Humanised by MRCT

- By end March 2012
  - > 68,000 patients under treatment
  - > 99,000 patients treated in total
  - > 47,000 patients treated for more than 2 years
The Centre for Therapeutics Discovery

- Resource for MRC drug discovery translational research collaboration
  - In response to Pharma focus on later stage in-licencing
  - Established in 2005 with £9.5m MRC investment
  - Assay development, screening, medicinal chemistry to Pharma standard
  - Proven antibody humanisation expertise

- Relaunched with an external ‘Call for Targets’ in 2009

**Academic Targets**
- Antibody
- Small molecule
- Strong rationale
- Unmet need

**Partnerable Projects**
- Humanised Antibody
- Lead molecules
- Disease efficacy
- Pharma-ready
- Res.Tools

CTD
UNMET HEALTHCARE NEEDS

FORMING PARTNERSHIPS

RESEARCH

PATIENT

SHARING RISK AND REVENUE

MRCT

PHARMA / BIOTECH
Adding Value: Scientific Development

Collaboration:
- Assay Development and Screening
- Medicinal chemistry
- Antibody humanisation and affinity maturation

Academic and Non Profit Institutions

Pharmaceutical Biotechnology Markets
Drug Discovery Biology - Capabilities

- State-of-the-art equipment and robotics to perform wide range of assays
- Develops robust ‘industry standard’ assays suitable for HTS
- Conducts screening of large diverse compound collections
- Validates hits and provides starting points for “Hit-to-Lead” chemistry
- Supports medicinal chemistry programs and confirms activity in secondary and functional cell-based assays
Medicinal Chemistry Group - Capabilities

- Triages screening ‘hits’ and conducts synthetic medicinal chemistry to develop SAR and improve ‘drug-like’ properties.

- Analytical chemistry expertise and in-house ADMET assays eg microsomal stability, permeability etc

- Generates tool compounds for further validation of target

- Generates potent, selective and ‘drug-like’ lead compounds that are active in relevant in vitro and/or in vivo models for partnering.
Structure-Based Drug Discovery

Liganded and APO

Crystal structure assessment, selection and preparation

Binding site identification and evaluation of druggability
Size, shape, exposure, flexibility, interaction potential

Homology Modelling
Consider identity, similarity, and gaps - particularly around binding site
Antibody Humanisation

- Mouse antibodies are readily accessible
  - Easier to characterise and select mouse Abs in murine models
- Antibody humanisation is a reliable and reproducible process
  - It significantly reduces the risk of immunogenicity
  - It has been validated in the clinic and on the market
- Offers rapid development of therapeutic potential of an antibody
- CTD capabilities in antibody affinity maturation and engineering
2010
Approved therapeutic antibodies

Mouse
OKT3
Bexxar
Zevalin

Chimeric
Rituxan
Remicade
Reopro
Simulect
Erbitux

HUMANISED
Actemra
Avastin
Campath
Herceptin
Lucentis
Mylotarg
Raptiva
Soliris
Synagis
Tysabri
Xolair
Zenapax
Cimzia

Fully Human
Humira
Vectibix
Stelara
Simponi
Ilaris
Prolia
De-risking the target
Tools to confirm target association in disease
Compound library, diversity sets and pharma links
**MRCT Compound Collection**

- **Diversity set:** 130K+ diverse commercial and proprietary compounds
  - Library contains clusters of up to 20-30 compounds per template
  - Instant SAR from MTS
  - Lipinski compliant
  - Filtered for Toxicophores

- **Focused sets**
  - Kinase library (9k compounds)
  - Targeted ion channel library (4k compounds)
  - Natural products library (2k compounds)
  - PPI helix mimetics subset (14k compounds)
  - ~2,500 pharmacologically active compounds and approved drugs

- **Collaborations with Pharma**
  - AZ – 100K compounds
  - GSK – GPCR deorphanisation
Collaboration

Case Studies

Transglutaminase 2 antibody
Small molecule neuroscience programme
Anti IL25 ligand antibody

Adding value in Therapeutic Discoveries

Academic and Non Profit Institutions

Pharmaceutical Biotechnology Markets
Case Study: Transglutaminase 2 antibody

Dr Tim Johnson, University of Sheffield

Leading clinician with specialism in kidney fibrosis

Transglutaminase 2 plays key role in fibrosis

Cross links collagen in ECM

Kidney fibrosis major cause of organ failure and complications in diabetes/hypertension

Same underlying molecular mechanism affects heart, liver, lung
Transglutaminase 2: target validation

Staining for collagen deposition in kidney of TG2 knock out mouse

Unilateral Ureteric Obstruction model mimics chronic kidney disease / fibrosis

Transglutaminase 2 knock out has severely reduced fibrosis
Transglutaminase 2: target validation

Infusion of inhibitor into kidney following subtotal nephrectomy in rats

Kidney scarring prevented

Kidney function (creatine clearance) retained

Sham
CrCl = 0.75ml/min

SNx
CrCl = 0.21ml/min

SNx + Inhibitor
CrCl = 0.71ml/min

Johnson et al, JASN 2007
Transglutaminase 2: a successful collaboration

- MRCT funded generation of highly selective, inhibitory antibodies
- Humanised, optimised and fully characterised antibody activities and biophysical characteristics
- Good activity in cellular assays, animal studies ongoing
- Licenced to Pharma in Dec 2013 for multimillion pound deal
- Revenues being shared with Sheffield, and company collaborating with originating laboratory
Case Study: Leucine Rich Repeat Kinase 2 (LRRK2)

**Collaborator:** Prof Dario Alessi, Dundee

LRRK2 is a multidomain protein - little is known about normal function - endogenous substrate unknown.

Mutations in the LRRK2 gene linked to PD and LRRK2 heavily expressed in the substantia niagra pars compacta region of the brain.

G2019S mutation in the Kinase domain is the most common and results in up to 10-fold increased kinase activity.

Increased kinase activity may be linked to degeneration of dopaminergic neurons & **inhibition of LRRK2 may slow/halt the progression of PD**.

Companies known to have a strong interest in LRRK2 and Michael J. Fox Foundation funding a number of projects.
CTD advantage was ability of academic to express active protein

Robust HTS compatible assay rapidly developed and CTD compound library screened, hits validated by collaborator & kinase selectivity determined.

Hits triaged and series selected for chemistry program

Chemistry conducted to obtain:

- Potent inhibitors of LRRK2
- Excellent selectivity against panel of human kinases
- No cytotoxicity in HepG2 cells
- Good in vitro ADMET
- Good mouse PK with CNS exposure

Two patent filed, covering data from over 300 synthesised compounds

Prior to evaluation in relevant LRRK2-dependant cell based assay or in vivo PD model (not available at the time) the compounds were evaluated by 2 different Pharma companies

Compounds passed chemistry & IP due diligence and final agreements signed 2010.

Upfront payment, milestones & royalties negotiated
Anti IL25 ligand antibody

Mouse monoclonal from LMB, Cambridge

Andrew McKenzie’s lab, immune and haematopoietic disorders

Uncovered role of IL25 in Th2 immunity

Supported by data from animal models of asthma

Humanisation and licence within a year

Licence included large investment into lab
Working with the Centre for Therapeutics Discovery

- Shared risk collaboration
- Open ongoing application process
- Ability to work closely with drug discovery scientists
  - Access to missing parts of “drug discovery jigsaw”
  - Access to specialised resources and equipment e.g. HCS, robotics
- Compounds/antibodies/cells re-supplied as ‘research tools’ for further studies

www.callfortargets.org
CENTRE FOR THERAPEUTICS DISCOVERY
WORKING WITH US

Triage Review: 6 per year
Filter Review: 3 per year
Feasibility Project: 6-9 months
CENTRE FOR THERAPEUTICS DISCOVERY
WHAT ARE WE LOOKING FOR?

MRCT Therapeutics Review Team
WHAT ARE WE LOOKING FOR?

Conventional targets

Novel classes and mechanisms

Strong kinase and GPCR expertise
WHAT ARE WE LOOKING FOR?

Confidence in rationale

Confidence in safety

Supporting siRNA, knockout or human primary tissue data

MRCT Therapeutics Review Team
WHAT ARE WE LOOKING FOR?

- Aim to generate value in new intellectual property
- Freedom-to-operate crucial
- Revenue share agreed upfront
WHAT ARE WE LOOKING FOR?

Clear unmet medical need
Access to reagents, assays and models
Funding options
Why projects fail?

**Application process**
- Not talking to us first
- Fostering projects
- Lack of supporting data for role of target in disease
- Target druggability
- Competition and advantage over existing approaches

**Launched projects**
- Reproducibility of key data
- Finding right assay to show target modulation correlates with therapeutic effect
- Funding for the PI
Helping charities to deliver new drugs

- Collaborating with charity funders to fund
- Providing advice on drug discovery projects in portfolio
- Joint ‘Call for Targets’
  - Review by MRCT, Disease experts and patient groups
  - Funding to support early target validation
  - Option to collaborate with MRCT downstream
- Current call: Parkinson’s UK
  www.callfortargets.org/parkinsons/
Helping charities to deliver new drugs

Dementia Consortium

New initiative to support drug discovery and translation for novel therapies for dementia

£3m funding available for collaborative projects with consortium members

www.dementiaconsortium.org
MRCT Centre for Therapeutics Discovery

- Collaborative drug discovery partner
- Medicinal chemistry projects
- Monoclonal antibodies

Next review deadline: 25<sup>th</sup> March

Promising targets with good validation

  - Knockout or siRNA data
  - Primary tissue access
  - SNP associations
  - Access to reagents and secondary assays