IL-17BR ANTIBODY
FOR THE TREATMENT OF ASTHMA AND IBD

John Kelly PhD
Associate Director Business Development, MRC Technology

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MRC Technology

- A Life Science Specialist Technology Transfer Company

- MRCT is a charity affiliated to the MRC
  - Encourage commercial exploitation for the benefit of health & wealth

- Since 1998 MRCT has:
  - Filed 400+ patents & granted 400+ licenses
  - Brought in $1+ billion/£600+ million to the MRC Commercial Fund

- Centre for Therapeutics Discovery (CTD)
  - Undertake ‘own risk’ (commercial) drug development projects
  - Work with Biotech/Pharma on collaborative research programmes
Centre for Therapeutics Discovery - Capabilities

- **Assay Development and Screening**
  - Highly diverse experience
  - State-of-the-art laboratories and equipment

- **Medicinal Chemistry**
  - High level of “Pharma” experience
  - Combined 150 years of industry experience, 20 candidates taken into man

- **Therapeutic Antibody Group**
  - World Leaders in Antibody Humanization, 56 humanized, 2 on market, 1 approved, several still in clinic
  - Affinity maturation
  - Biophysical characterization
Antibody Humanization

- Humanizing for 25 years
- MRC’s CDR grafting technology
- Humanized 56 antibodies through collaboration and fee for service
- 2 on market, 3 in Ph3/2 stage development

Pembrolizumab
- MERCK

Vedolizumab
- Eisai
- Takeda

BAN2401
- Biogen Idec
Dr David Matthews
Head of BioTherapeutics, MRC Technology

MRC Technology

IL-17BR ANTIBODY FOR THE TREATMENT OF ASTHMA AND INFLAMMATORY BOWEL DISEASE
### Background IL-17BR

**Member of IL-17 cytokine receptor family**

**Binds IL-25 (IL-17E) and IL-17B**

**Regulates innate and adaptive immunity**

**Upstream of key cytokines – IL4, IL5, IL-9 and IL13**

**Eosinophil infiltration, goblet cell hyperplasia, IgE secretion, mucus production and fibrosis**

**IL-25 is growth factor for T cells and ILCs, other inflammatory pathways**

**IL-17RB in other diseases?**

**Ulcerative colitis**

**Fibrosis**
**BACKGROUND** Chronic inflammatory diseases:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>7MM Sufferers</th>
<th>Unmet Medical Need</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>Airway obstruction, hyper-responsiveness, inflammation</td>
<td>1.5 million</td>
<td>Considerable</td>
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<tr>
<td>Ulcerative colitis</td>
<td>Chronic inflammation colon driven by type II cytokines</td>
<td>300 million</td>
<td>Considerable</td>
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## WORLD CLASS SCIENCE: Dr Andrew McKenzie

**Andrew McKenzie, MRC Laboratory for Molecular Biology, UK**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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<tbody>
<tr>
<td>World class research laboratory</td>
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<td>Strong understanding of type 2 immune responses</td>
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<td>Access to numerous models of asthma and colitis</td>
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<td>Considerable experience of collaborating with industry</td>
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<td><a href="http://www2.mrc-lmb.cam.ac.uk/group-leaders/h-to-m/andrew-mckenzie/">Link</a></td>
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MRCT OPPORTUNITY: VALIDATED TARGET

ANTI-IL-17BR BLOCKING ANTIBODY

- IL-17RB and IL-25 upregulated in patients
- Antibody reduces AHR and UC
- Knock-out mouse shows no adverse effects
MRCT OPPORTUNITY: VALIDATED TARGET

**Immunohistochemistry of bronchial biopsies**

- **Isotype**
- **IL-25**
- **IL-17RB**

**Before**

- A
- B
- C

**24 hrs**

- D
- E
- F

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- Increased IL-25 and IL-17RB expression after allergen challenge in asthma patients
- mRNA expression and histology tracks with severity of disease in mouse model of allergic asthma
- SNP associated with protective role in asthma
MRCT OPPORTUNITY: VALIDATED TARGET

Airways responses of IL-17BR-deficient and IL-25-deficient mice

- Blocking IL-17BR more potent anti-inflammatory than IL-25
- Transgenic expression of human and mouse IL-25 induces type-2 responses and delivery of recombinant IL-25 induces Th2 pathologies
- No adverse phenotype
Specific for IL-17BR

Potent inhibition of IL-13 production

Activity in *in vitro* and cellular bioassays

ANTI-IL17BR BLOCKING ANTIBODY
MRCT OPPORTUNITY: IL-17BR BLOCKING ANTIBODY
MRCT OPPORTUNITY: IL-17BR BLOCKING ANTIBODY
Allergic asthma mouse model

Reduction in pathology and clinical scores

Mouse model of colitis

Reduction in pathology and clinical scores

ANTI-IL-17BR BLOCKING ANTIBODY

In vivo POC
MRCT OPPORTUNITY IN VIVO POC ASTHMA

- Sensitisation:
  - Day 0: Endotoxin cleaned OVA/Alum OR PBS/Alum, i.p.
  - Day 12: Endotoxin cleaned OVA/Alum OR PBS/Alum, i.p.

- Lung Challenge:
  - Days 19-24: 1% normal OVA OR PBS, 20 mins aerosol

- Day 25: Restrainted WBP and tissue collection

Graph:
- Y-axis: Airways Resistance (Fold Increase)
- X-axis: Methacholine Concentration (mg/ml)
- Lines:
  - Black dots: wild type PBS
  - Dark grey squares: wild type OVA IgG1
  - Light grey triangles: wild type OVA Anti-IL17BR D9.2
  - Blue arrows: 500 µg IgG1 Isotype
  - Blue and purple arrows: 500 µg anti-mIL-17BR D9.2
SUMMARY IL-17BR: AN EXCITING UPCOMING OPPORTUNITY

- Rodent blocking antibody against IL-17BR
- Priority patent application, 2012
- Protection for antibodies
- In vivo POC in two animal models
- Building strong data package for licensing
- Humanization completed and being tested *invivo*
- Focus is on ulcerative colitis in first instance
- Interested in feedback, future licensing