Anti-plexin B1 monoclonal antibodies as novel therapeutics

MRC Technology and Max Planck Institutes

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MRC Technology
Forming partnerships to drive early stage scientific research to the patient

ACADEMIC AND NON PROFIT Institutions

MRC heritage established 2000

Not for Profit

140+ staff

DRUG DISCOVERY

PHARMACEUTICAL BIOTECHNOLOGY Markets

MRC

DRUG DISCOVERY

Unmet Medical Need

Therapeutic ANTIBODIES

Small molecules

12 DRUGS in clinical development

4 DRUGS marketed

12 DRUGS in clinical development

Not for Profit

MRC heritage established 2000

ACADEMIC AND NON PROFIT Institutions
MRC Technology current pipeline

Assay Development
- GPR88
  - CNS
  - Internal
- Confidental target
  - Cancer
  - University of Leicester
- CD36
  - Metastatic cancer
  - IRB Barcelona
- CSF-1R
  - Dementia
  - University of Southampton
- Fractalkine
  - Dementia
  - University of South Florida
- Phenotypic screen
  - Dementia
  - ICGEB

Hit Generation
- ULK1
  - Cancer Autophagy
  - MRC
- ALK ADC
  - MRC
  - Cancer
  - Internal
- MALT1
  - Cancer
  - University of Lausanne
- Confidential target
  - Cancer
  - MRC

Hit to Lead
- AB oligomer Ab
  - Alzheimer's
  - University Göttingen
- Confidential target
  - Migraine / pain
  - University Oxford
- Matriptase
  - Osteoarthritis
  - Newcastle University
- MIF inhibitor
  - Inflammation
  - Proximagen
- Confidential target
  - TB
  - University of Manchester
- GalR2 activator
  - Pain
  - University of Bristol
- Netrin-1
  - Bone disease
  - New York University

Lead
- IL17BR
  - Fibrosis
  - MRC
- MNK inhibitor
  - Cancer
  - Southampton University
- EV71 antibody
  - hand, foot and mouth
  - Chinese Acad Science
- PAICS inhibitor
  - Cancer
  - Netherlands Cancer Institute
- IL16 antibody
  - Inflammation
  - Boston University
Plexin B1 as a therapeutic target

- Plexin B1 is a member of a large family of transmembrane receptors that bind to semaphorin ligands
- Receptor-ligand interactions result in alterations in movement and differentiation of cells
- Plexin B1 is a receptor for the ligand Semaphorin 4D
- The Plexin B1-Sema 4D interaction has been implicated in a number of diseases, including multiple sclerosis, osteoporosis, arthritis, cancer, inflammation, neurodegenerative diseases
- We are interested in developing novel monoclonal antibodies that block this interaction with the aim of delivering a new class of therapeutics with particular utility in immune-mediated diseases
Target validation in osteoporosis

- Binding of Sema4D to Plexin B1 on osteoblasts leads to activation of RhoA, which inhibits bone formation.
- Blocking the Plexin B1-Sema4D interaction via Plexin B1 or Sema4D ko or a Sema4D-specific antibody prevents bone loss in an ovariectomized osteoporosis model.
- **Prophylactic and therapeutic benefits shown**
- An anti-Plexin B1 antibody that blocks this same interaction would be expected to have a similar effect.
- **Key advantage**: current osteoporosis therapeutics focused on slowing bone resorption. This therapy would **stimulate bone formation**.

Data from Negishi-Koga et al (2011)
Target validation in cancer

- Mutations in Plexin B1 are found in breast and prostate cancer
- Plexin B1 promotes metastasis in mice with ERBB2-overexpressing breast cancer and invasion in ERBB2-overexpressing breast cancer cells
- Patients with ERBB2-overexpressing breast cancer that have high Plexin B1 expression show poor prognosis
- **Key advantages:** ERBB2 (HER2) resistance to targeted therapies is a significant clinical problem. A Plexin B1 antibody could offer an alternative therapeutic for *trastuzumab-resistant tumours*. Possibility of patient stratification on Plexin B1 expression
Tumour immunomodulatory effects

- Vaccinex anti-Sema4D antibody has shown effects in the tumour microenvironment (TME)
- Suggest that Sema4D expression affects infiltration and distribution of leukocytes in the TME
- Vaccinex antibody shows synergy with anti-CTLA4 and anti-PD1 therapeutics
- Goal to test whether anti-Plexin B1 also has effects on the TME and synergises with other IO therapies
- IO therapies are a commercially attractive area – multi billion $ market

Data from Evans et al. (2015)
An international drug discovery collaboration

Collaborative project goals

- Novel humanised monoclonal antibodies to block Plexin B1-Sema4D binding
- Novel IP position
- Data package to support therapeutic effects in relevant disease models
- Biophysical package to characterise drug-like properties of therapeutic antibodies

MRC Technology

- Independent medical research charity
- Own drug discovery laboratories
- Over 25 years experience in antibody therapeutics and humanisation
- Wealth of commercialisation expertise
- 4 antibody therapeutics on the market
- Self-funded from revenues

Max Planck Institute for Heart and Lung Research

- Prestigious research institute
- High profile translational researcher Professor Stefan Offermanns
- In depth expertise in PlexinB1 biology
- Expertise in variety of disease models (osteoporosis, MS, cancer)
Advantages of the technology

- **Good disease association and target validation** for Plexin B1-Sema4D that has been reported by independent groups, including industry.
- Potential to use the antibodies in **multiple indications with unmet therapeutic needs**.
- **Side effects expected to be low** – Plexin B1 shows restricted expression pattern and Plexin B1 ko mice have no obvious abnormalities (other than bone phenotype). Vaccinex antibodies have been well tolerated in PhI clinical trials.
- **No direct competition** on Plexin B1 target.
- Differentiation from anti-Sema4D may be possible – different expression patterns and Sema4D also binds Plexin B2.
- Potential to gain **novel IP position** on new Plexin B1 antibodies being generated by MRCT.
**Plexin B1 is an emerging, exciting therapeutic target in cancer and immune-mediated diseases**

- Targeting the Plexin B1-Sema4D interaction may have potential in a number of different disease indications, making it commercially attractive
- Generated novel, monoclonal antibodies against this interaction, with the goal of filing IP by the end of 2017
- Demonstrated target validation *in vitro* and *in vivo* disease models using novel antibodies generated by MRCT
- Recent exciting data from Vaccinex suggest an IO effect of blocking Plexin B1-Sema4D
- Strong multi-disciplinary collaborative team combines therapeutic antibody expertise from MRCT and Plexin B1 biology expertise from Max Planck collaborators

- We are interested in finding commercial partners for further collaborations or licencing to explore the potential of our novel antibodies further