CREATING BREAKTHROUGH DRUGS
TO TREAT BRAIN DISEASES AND COMBAT CANCER

LRP-1: A Key Receptor for Cancer Cells

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Angiochem’s EPiC platform leverages the LRP-1 mediated pathway

- This pathway provides:
  - A gateway to the brain through the LRP-1 at the surface of the BBB
  - Direct access to cancer cells expressing LRP-1
LRP-1
Low-Density Lipoprotein Receptor Related Protein

- Transports small and large molecules (> 40 ligands)
- One of the most expressed receptors at the surface of the BBB
- Over expressed on cancer cells

LRP-1: ~600kDa
(α: 515k, β: 85k)

α2-Macroglobulin
(MW ~ 700 kDa)
apoE
(Apolipoprotein E)
Lactoferrin

MMP9
(Matrix metalloproteinase 9)
RAP
Thyroglobulin

Cell Membrane

TPA
(tissue plasminogen activator)
Angiopep

LRP-1
~600kDa
(α: 515k, β: 85k)
Expressed on cancer cells
- Hypoxia and serum deprivation induces over expression

LPR-1 is essential for cancer cell proliferation, migration, invasion and dissemination
- LRP-1 mediated endocytosis maintains cell matrix
- LRP-1 mediated signalling pathway is responsible for cell de-adhesion and invasion through FAK

* Focal Adhesion Kinase
**LRP-1 Mediated Endocytosis**

**Ligands:**
- Proteinases
- Proteinase complexes
- uPA:PAI-1/uPAR
- MMP-2, -9, -13

Interaction with LRP-1 and internalization

Cancer Cell Membrane

Endocytic vesicle

Receptor recycling

Lysosome

Induces Matrix degradation

Leading to Invasion and migration
Ligands:
- Growth factors
- Integrins

Interaction with receptor

Activation of signalling pathway:
ERK/PI3K and FAK/paxillin

Cytoskeleton architecture

Adhesion complex and dynamics

Cell de-adhesion and invasion
Angiochem’s EPiC Platform
LRP-1 Mediated Pathway

• Identified sequences of amino acids called *Angiopeps* that target LRP-1
  – a library of >100 Angiopeps ranging from 8 to 34 amino acids

• The EPiC technology incorporates an *Angiopep* with a drug moiety to create new chemical entities (NCEs) that:
  – Cross the BBB physiologically and act directly on the brain to treat brain diseases
  – Penetrate cancer cells and release the drug where needed
ANG1005

The first oncology product using the LRP-1 mediated pathway

Angiopep-2  Binding site to LRP-1 receptor
ANG1005 Novel Mechanism: Receptor-Mediated Endocytosis

1. LRP-1 Targeting
2. Receptor interaction
3. Internalization and endocytosis
4. Cleavage and activation

- LRP-1 Recycling
- Endocytic vesicles
- Esterases
- Activation
- Lysosomes
- Induces polymerization of β-tubulin (mitotic arrest) leading to cell apoptosis

Paclitaxel
Angiopep-2
LRP-1
P-gp
Key Conclusions

- **EPiC Platform Validation:**
  Clinical data generated with ANG1005 validate the LRP-1 mediated pathway for the treatment of multiple types of cancers

- **ANG1005 Product Validation:**
  Targeting cancer cell through the LRP-1 receptor is a novel and innovative way to fight cancer