Targeting angiogenesis with QM107 as novel therapy for Wet Age Related Macular Degeneration

Key benefits of QM107

- New potent anti-angiogenic peptide that could be used either in combination or as an alternative treatment for patients who do not respond to current therapies e.g. Lucentis or Eylea (25%-45% of patients not responsive)
- Cost effective and scalable chemical synthesis (demonstrated) via eGMP standard production, which presents less challenges than producing antibody based therapies.
- Based on in vivo testing the effective dose range is well within what would be feasible to administer to the human eye and lower than Lucentis (~2µg, while Lucentis is used at 0.5 mg/injection) and Eylea (2mg/ injection)
- Has potential of administration as an eye drop formulation, representing a substantial improvement for patient experience, well-being and comfort.

Background

Age-related macular degeneration (AMD) is a progressive retinal disease that is the leading cause of central vision loss in developed countries, affecting 1 in 10 people older than 50 years. AMD is characterised by abnormal formation of blood vessels (angiogenesis) at the back of the eye. These leak fluid and blood into the ocular tissue eventually causing retinal detachment and vision loss. The pro-angiogenic vascular endothelial growth factor (VEGF) is a major driver of new blood vessel formation in this disease.

- Current therapies block VEGF from stimulating pro-angiogenic responses, whereas QM107 directly targets an endogenous cell surface receptor which stimulates an anti-angiogenic response by reducing vascular permeability and endothelial cell migration.

The Problem

Current therapies which target VEGF:

- Associated with high level of patient non-response and side effects (cardiac infarct, thromboembolic events, microangiopathy etc.)
- Expensive (£ 1000/ injection of Lucentis) and very invasive: They involve injecting antibodies directly into the eyes of patients on a monthly basis
- Evidence that over time (~2 years) their efficacy is lost in 10- 20% of cases and patient’s sight worsens

The invention

- QM107 is a small, stable peptide with potent anti-angiogenic effects which have been demonstrated in various cancer and ocular disease models (Fig.1)
- QM107 does not affect cell proliferation, has a negligible toxicity profile in vitro and based on proteomic analysis has very few off-target effects as well as no effect in cells of epithelial origin
- QM107 prevents vessels leaking at the back of the eye by reducing vascular permeability
- High level of stability: 75% availability at 24hrs at 37 °C in either rat or human serum. Not cleaved by proteases.

QM107 treated mice show ~30% decrease in choroidal neovascularisation

Fig 1. Laser induced choroidal neovascularisation in murine eyes is the gold standard assay for wet age related macular degeneration. Murine eyes are injured by laser burns which stimulate an angiogenic response and this results in the formation of lesions, as visualised by fluorescein angiography. Lesions are greatly reduced 7 days after injury in mice treated with 1µM QM107, 3 days post-injury.

We are seeking collaborators and investor partners to progress towards initiating phase Ib/Ila clinical trial. Inventors are currently preparing a pre-clinical trial toxicology programme in consultation with the MHRA.
Additional Results

- QM107 inhibits choroidal neo-vascularisation in vitro as effectively as Eylea

Efficacy in the murine laser induced choroidal neo-vascularisation (CNV) model. Three laser burns were made to the back of each eye of C57BL6 mice, prior to intra-vitreal injection of 2µl of either PBS or QM107 (at the concentrations indicated) in PBS. Lesions were measured by fluorescence angiography after 7 days and the lesion area calculated using ImageJ. Lesions are substantially smaller in animals treated with QM107 as evidenced in the dose response experiment in n=8 per condition.

- QM107 provides an optimal 50% reduction in angiogenic sprouts from choroid explants

Choroid membranes from C57BL6 mice were seeded into collagen I matrices in the presence of pro-angiogenic factors and tested with several increasing doses of QM107 as indicated in the graph. The formation of angiogenic sprouts from choroid explants was found to be greatly reduced in cultures treated with QM107 between the concentrations of 0.1 to 1.0 µM.

- QM107 is not toxic to Human ECs even at very high doses

The production of Lactate Dehydrogenase (LDH) is a measure of cellular toxicity. We applied QM107 at Human Umbilical Vein Endothelial Cells at indicated concentrations, and measured the LDH release after 24 hours. LDH production remained at baseline in contrast to the positive controls.

Link to inventor’s website: [http://www.whri.qmul.ac.uk/staff-all/staff-research/163-whiteford-james](http://www.whri.qmul.ac.uk/staff-all/staff-research/163-whiteford-james)