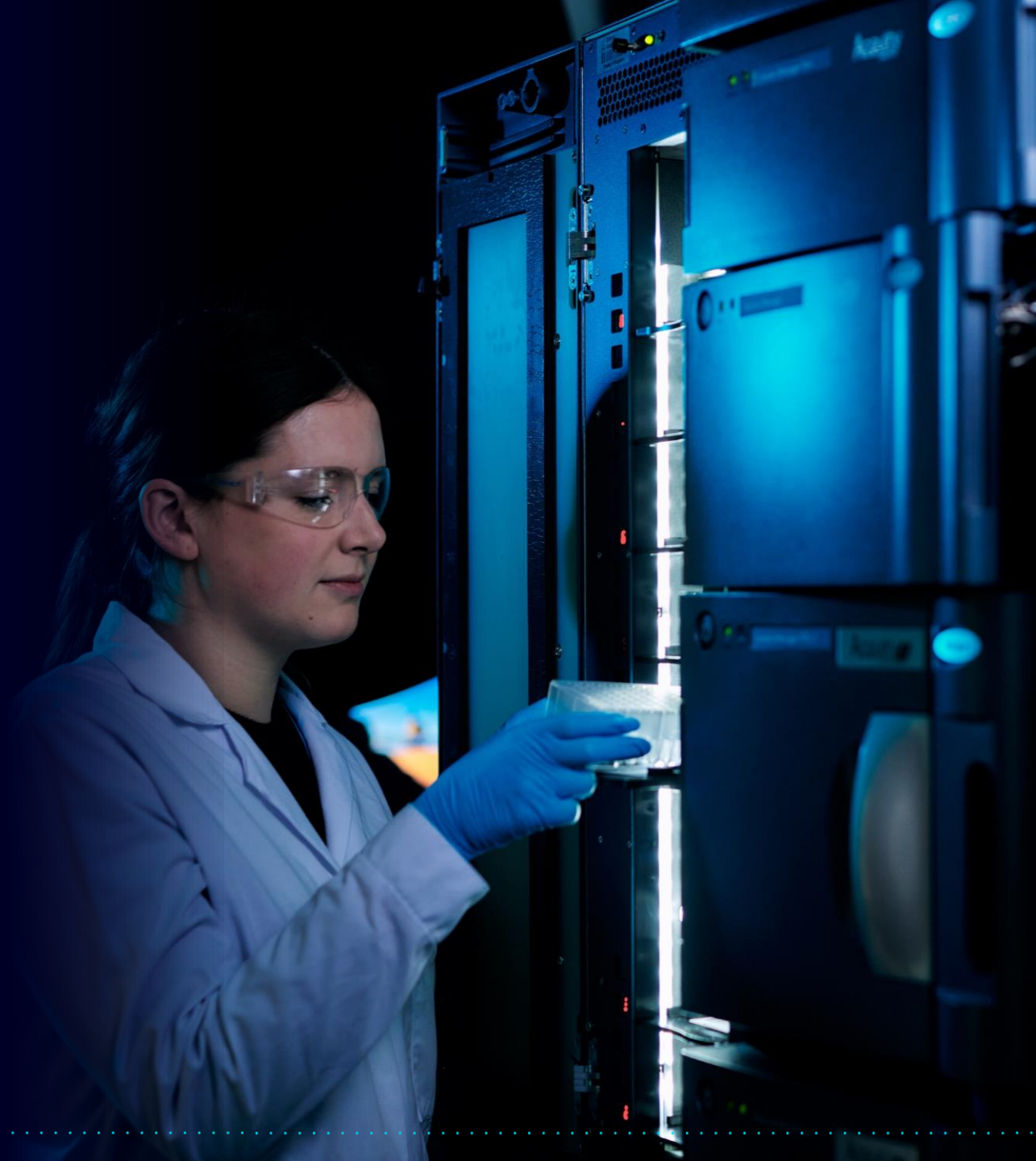
CANCER RESEARCH HORIZONS

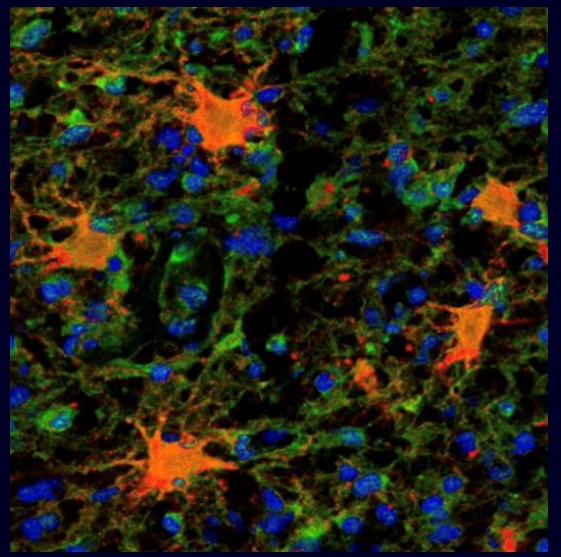
FURTHER FASTER TOGETHER

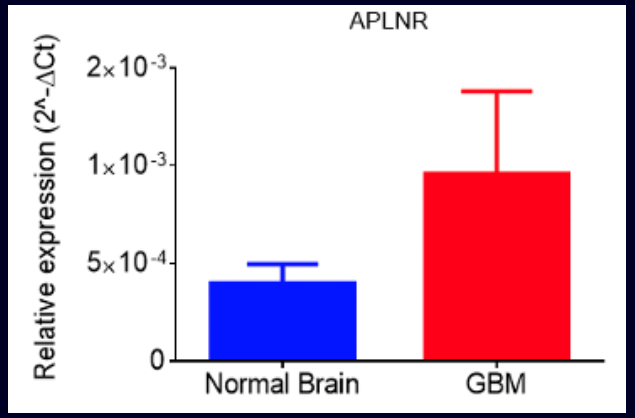
COLLABORATION OR LICENSING OPPORTUNITY: NOVEL APELIN RECEPTOR ANTAGONIST



EXECUTIVE SUMMARY

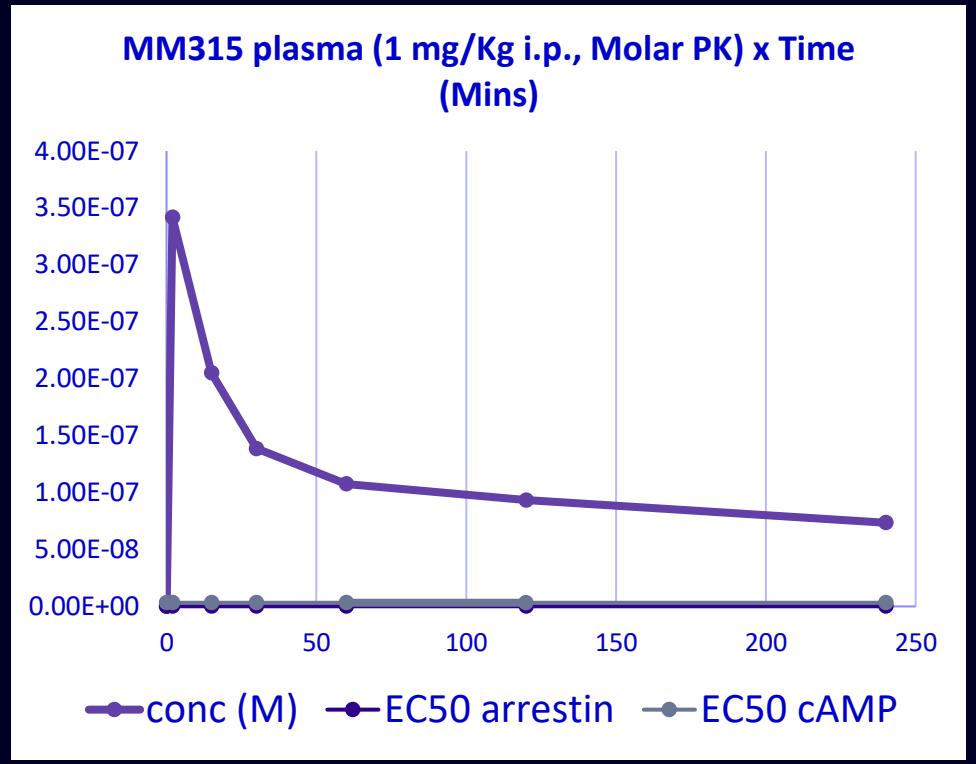
- Target Statement
  - Apelin (GPCR) receptor antagonist peptide for use as a single agent or in combination treatment for Glioblastoma (GBM) or other Apelin dependent tumor therapies
  - Status: lead compound MM315 identified
- Competition
  - None
- Key highlights
  - Apelin receptor is over expressed in all excised human GBM tumor samples
  - MM315 is a potent competitive antagonist at the Apelin receptor: 2.4 nM affinity (pA2=9.55 for β-Arrestin, pA2=8.48 for cAMP)
  - MM315 shows in-vivo efficacy, significantly extending survival in intracranial orthotopically implanted mice
  - Potential for synergy with temozolomide and radiation therapy
- Timeline to next gate decision
  - Rat PK package (underway), and 6 months to complete an *in vivo* GBM comparison with radiation/temozolomide in rats





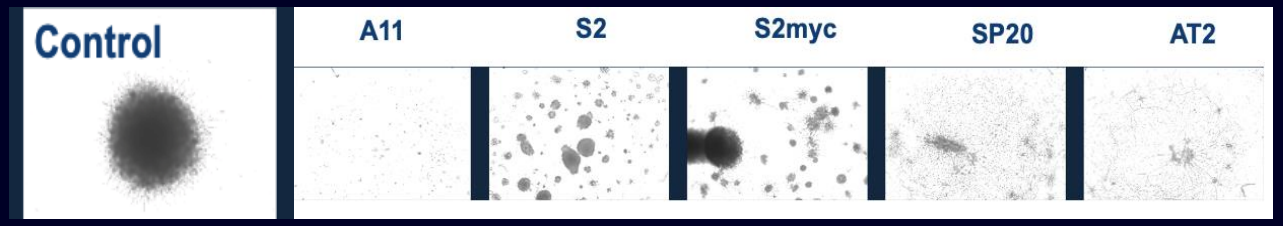
MM315 ANTAGONIST OVERVIEW

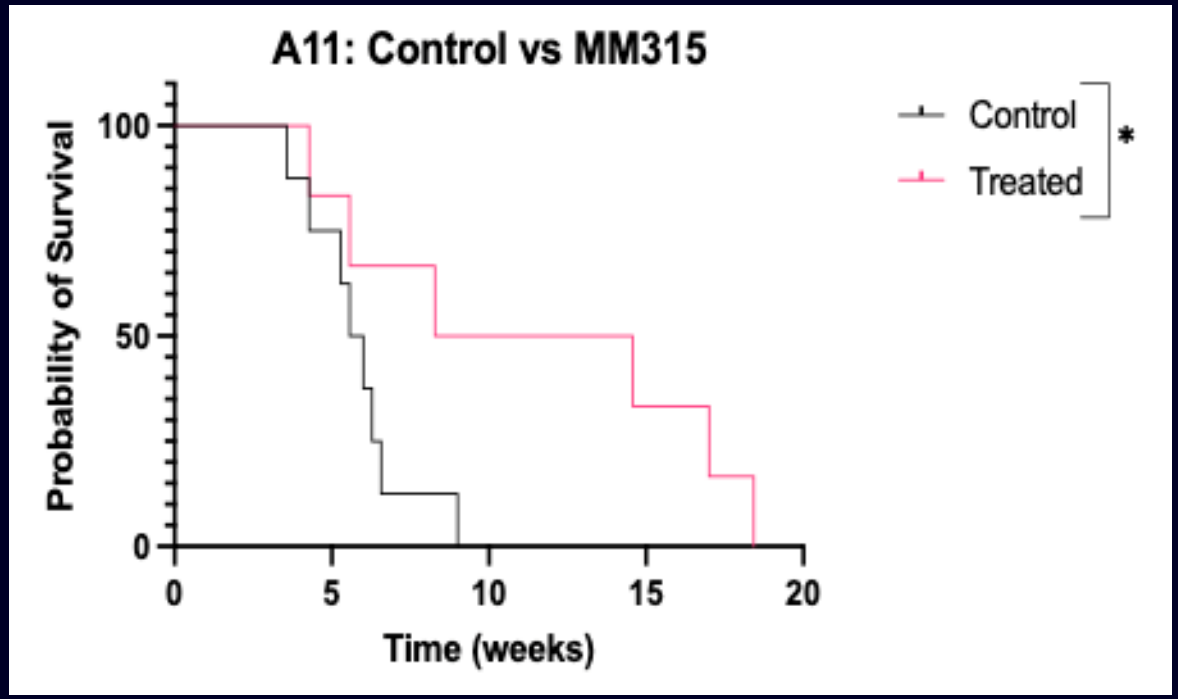
- Potent (β-Arrestin K_B = 0.28nM) and selective Apelin receptor antagonist, water soluble, excellent PK (mouse)
- Structurally-enabled and extensively-elaborated, with well-understood SAR
- Demonstrated therapeutic potential in orthotopic models of glioblastoma
- Well tolerated in-vivo (mouse)
- In vitro and in vivo data packages available
- Biochemical and cell-based assays fully developed
- Patents covering MM315 and a diverse series of linear analogs have been filed in CRUK's name and are at national/regional phase



APELIN EXPRESSION & MM315 IN-VIVO EFFICACY: GBM

- Apelin expression is driven by tissue hypoxia and is known to promote tumor growth by direct stimulation of the tumor cell migration and metastasis. There exists a subpopulation of highly plastic self-renewing cancer cells that retain the ability to expand ex vivo as tumourspheres, induce tumour growth, and have been implicated in radio- and chemo-resistance. MM315 disrupts sphere formation and migration in GBM cell lines.
- Apelin receptor antagonist inhibits appearance of neurological symptoms and extends survival in an intracranial orthotopic mouse model of glioblastoma





MM315 KEY COMPOUND DATA TABLE

Molecular Weight	1969.15 Da
Binding (hApelin expressed CHO cells), and Functional Data (DRx β-Arrestin, DRx cAMP)	2.4nM, pA2=9.55 (antagonist), pA2=8.48 (antagonist). No agonist response up to 100µM
Mouse PK **IV** (Tmax (min), Cmax(ng/ml), Auc ng/min/ml, T1/2 (min), Kel (Lambda_z,$^{min-1}$)	2.0, 9860, 153000, >160, 0.004
Mouse PK **IP** (Tmax (min), Cmax(ng/ml), Auc ng/min/ml, T1/2 (min), Kel (Lambda_z,$^{min-1}$)	2.0, 673, 121000, >331, 0.002
Plasma Protein Binding (mouse)	80%
Plasma Stability (mouse) T1/2 (min)	>120min
Metabolic Stability S9 Fraction (mouse) T1/2 (min)	49min
Solubility	Good aqueous solubility
Cell toxicity (HepG2)	IC_{50}=20.3µM
Selectivity (1uM, 44 targets)	>50% KAPPA(55%), M1(53%), V1A(87%)

SUMMARY AND NEXT STEPS

- High quality candidate identified with positive in-vivo data
- Clear path to the clinic
    - rat PK package underway
    - 6 months to complete in vivo GBM comparison with radiation/temozolomide in rats
    - 6 months to deliver in-vivo safety package (rat) and deliver >100g
    - 6 months to perform two species toxicology package
    - planning for phase 1 clinical trial underway
- Patents covering the lead peptide and a series of linear compounds have been filed in CRUK's name and are at national/regional phase
- Available for collaboration/partnership or licensing
- Contact Jonathan Brown: jonathan.brown@cancer.org.uk