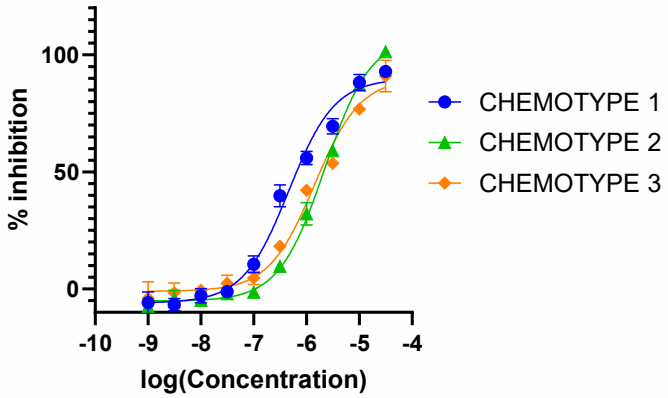
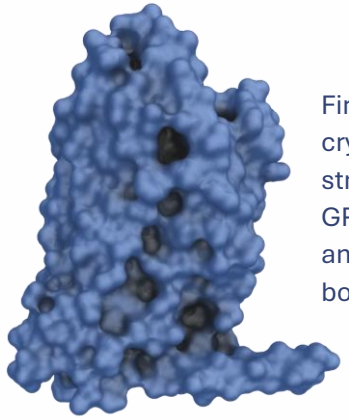
Lead-Like Hits for Challenging Targets: Multiple Novel Chemotypes to Expand the GPR68 IP Estate

Alipheron

As part of the collaboration between Cumulus Oncology and leadXpro to discover high-quality small molecule modulators of the challenging target GPR68, Alipheron's 3D-analogue searching engine for ultra-large chemical spaces (Pharos3D) was incorporated into the programme. Using a high-resolution proprietary CryoEM structure (leadXpro/ Cumulus Oncology), chemical spaces containing billions of compounds were searched for analogues in 3D space against the pharmacophore configuration, delivering a hit rate of 4.8% and identifying 3 discrete novel chemotypes.

hGPR68 cAMP HTRF assay pH6.8





First 2.5 Å cryo-EM structure of GPR68 in an antagonist-bound state.

The success of this project reflects not only the power of Pharos3D as a 3D-analogue search platform, but also the effectiveness of a tightly integrated collaboration model. By combining leadXpro's structural biology and Alipheron's computational expertise with Cumulus Oncology's deep target knowledge and medicinal chemistry capabilities, the team was able to bring their respective strengths to bear to execute successfully on this challenging target.

Cumulus Oncology

Dr. Tilly Bingham, Chief Scientific Officer, Cumulus Oncology

"GPR68 has broad therapeutic potential across various oncology and inflammatory conditions. As leaders in the field, we wanted fast access to novel intellectual property which would enable us to target different therapy areas with bespoke tailored molecules and target product profiles. The Pharos3D approach with leadXpro was fast, delivered high hit rates and the structural insights mean that the hit follow-up is accelerated."

leadXpro

Dr. Luboš Remen, Director of Lead Medicinal Chemistry, leadXpro

"By combining our modern technology platform encompassing advanced protein engineering, structural biology and biophysics with cutting-edge computational solutions, we enable structure-based drug design for membrane protein drug targets - shifting the paradigm from 'make and test' to 'design with intent."