

Beacon Discovery

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Unlocking drug development opportunities in 350 GPCRs, including 120 orphans

Employing its deep understanding of G-protein coupled receptors (GPCRs) the Beacon Discovery team has delivered more than 20 compounds into clinical development over the past two decades, and is now working with partners to unlock the therapeutic value of challenging receptors in this class.

Although more than 350 non-olfactory G-protein coupled receptors (GPCRs) are present in the human genome, only 135 are targeted by currently approved drugs. Beacon Discovery believes there are significant untapped opportunities among these 135 targets, and even more within the remaining >200 GPCRs, including 120 orphans, that have not been successfully targeted to date.

"GPCRs are exceedingly important as therapeutic targets; indeed, some 30% of all approved drugs target them," said Sunny Al-Shamma, President and CEO of Beacon Discovery. "Our objective as discovery scientists is to identify novel molecules to modulate these receptors and address disease".

"We have a particular focus on GPCRs for which the endogenous ligand remains unknown. These so-called orphan GPCRs provide significant opportunities for drug development to address a broad spectrum of unmet medical needs".

Beacon Discovery was launched in 2016; however, its founding team of five scientists guided the drug discovery arm of GPCR-focused Arena Pharmaceuticals for more than 15 years.

When Arena pivoted to focus on its clinical assets and ceased early discovery efforts, the department heads in in vivo pharmacology, screening and in vitro pharmacology, medicinal chemistry, computational sciences and CNS discovery founded Beacon, acquired the early-stage GPCR research portfolio, and were able to retain a team of highly experienced scientific staff who have contributed to more than 75 peer-reviewed publications in the past 15 years.

Concept to clinic

Beacon Discovery works as a GPCR drug discovery incubator (Fig. 1), building its business by developing an internal pipeline of projects as well as providing its GPCR expertise to external collaborators through multiple discovery partnerships with pharma and biotech companies.

Beacon has collaborated on orphan GPCRs with companies that include Takeda, Janssen, Boehringer Ingelheim and Escent Pharmaceuticals. Al-Shamma said the forefront of GPCR research has moved from traditional orthosteric receptor-ligand interactions toward understanding allosterism, biased ligands and persistent signaling. "We have extensive experience in this emerging science; the revolution in GPCR structural biology has enabled significant advances in both biophysical methods and computational modelling of receptors."

Beacon has built a GPCR incubator at its company

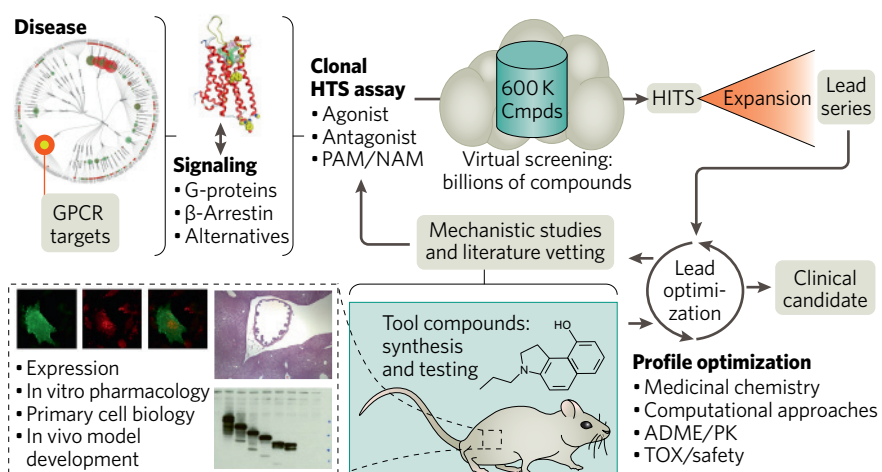


Fig. 1 | Beacon: a fully integrated GPCR drug discovery incubator. ADME, absorption distribution metabolism excretion; GPCR, G-protein coupled receptor; HTS, high-throughput screening; NAM, negative allosteric modulator; PAM, positive allosteric modulator; PK, pharmacokinetics; TOX, toxicity.

headquarters in San Diego, integrating all aspects of drug discovery under one roof, including a broad array of high-throughput screening and targeted assay platforms addressing emerging GPCR biology, a diverse collection of 650,000 screening compounds, state-of-the-art computational approaches, and extensive in vivo pharmacology and medicinal chemistry capabilities.

Recognizing the pitfalls

"What distinguishes us is our years of experience with GPCRs, which allows us to recognize potential problems and pitfalls and avoid them. We've overcome countless challenges in orphan receptor assay development and screening. In the process we have developed expertise in efficiently discovering selective chemical tools that emerge from such screens and have used these types of tools to elucidate the biology of these completely novel targets," said Al-Shamma.

Many companies avoid orphan GPCRs because they don't know what the receptors do. Beacon tackles them 'head-on'. In a project that resulted in a collaboration with Boehringer Ingelheim, Beacon identified a specific CNS-expressed orphan receptor that could be targeted to treat schizophrenia. Modulating this orphan receptor could provide comparable benefits to currently approved drugs, but without the side effects of existing drugs that often limit patient compliance.

The lead compound for this program is now in preclinical development, and the first clinical trials are intended for 2021.

Target vetting

Al-Shamma expresses concern about the level of questionable findings in the scientific literature regarding GPCRs.

"We often find that novel tool compounds used in publications can be of low potency, not entirely specific for the target of interest and incompletely characterized, therefore we frequently find that activity attributed to a GPCR is in fact off-target," he said. "We've spent 20 years vetting novel GPCR targets internally. We provide our collaborators with the opportunity to look at more extensive data that we can use to significantly bolster the hypotheses behind the target, before we move forward with a full-force drug discovery campaign," said Al-Shamma.

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