A Case Study on Collaborative Integrated Project on Metabolic Disorders

Background

The metabolic disorders are defined as a heterogeneous group of conditions characterised by the failure of metabolic pathways, that increase the risk of cardiovascular disease, type 2 diabetes, kidney disease, obesity and other chronic conditions, some of which are the leading cause of deaths worldwide. The metabolic disorders market is thus a growing global market for therapeutics and testing, projected to reach over $120 billion by 2030 with a compound annual growth rate (CAGR) of 7.8%. Melanin-concentrating hormone receptor 1 (MCHR1) plays a key role in regulating feeding, energy metabolism by influencing pathways that affect appetite, body weight, and is considered a potential therapeutic target for metabolic disorders, and significant research has been carried out over the past decades to discover small molecule MCHR1 antagonists as anti-obesity agents. The development of melanin-concentrating hormone receptor 1 antagonists for the treatment obesity, however, has been constrained by off-target safety liabilities. Since, the binding sites of MCHR1 and the hERG channel share common structural features, specifically a hydrophobic region and a basic amino group requirement for high-affinity binding, designing selective MCHR1 antagonists has been

challenging due to potential cardiotoxicity, and the clinical trials of most compounds reported in this class were halted.

Moreover, as the known MCHR1 antagonists contain basic amine moiety, this makes the molecules cationic under physiological conditions, leading to another adverse effect, phospholipidosis. This structural feature thus contributed to both hERG inhibition and cellular phospholipid accumulation, preventing advancement of the earlier compounds.

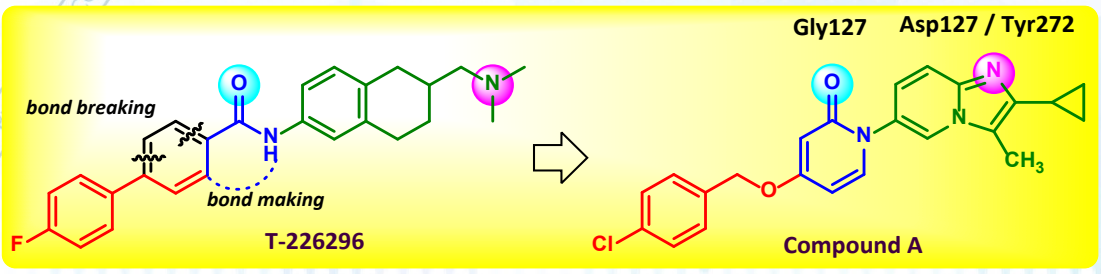
Objective of The Study

To develop novel MCHR1 selective antagonists with improved safety profiles, our collaborative team sought to eliminate the aliphatic basic amine functionality while maintaining receptor binding and activity. The goal was to overcome hERG and phospholipidosis liabilities through rational NCE design and validate these candidates across the integrated discovery pipeline — from design to preclinical candidate delivery.

Mitigating the Challenge with An Example

For a while, drug design efforts focused on identifying MCHR1 antagonists that modify these structural elements to improve selectivity for MCHR1 while minimising hERG affinity. In this regard, the team followed pharmacophore-based scaffold-hopping approach to design new molecules incorporating imidazopyridine and benzimidazole cores in the place of basic amine parts. These scaffolds were devoid of the basic amine moiety but retained essential pharmacophoric interactions within the MCHR1 binding pocket.

Gratifyingly, the following diagram showcases a newly designed compound containing imidazopyridine unit at the right-hand side, that exhibited very low risk for hERG inhibition and phospholipidosis induction, while maintaining substantial receptor binding with the amino acid(s) Asp127 and/or Tyr272 (*J. Med. Chem.*, **2016**, *59*, 1116).



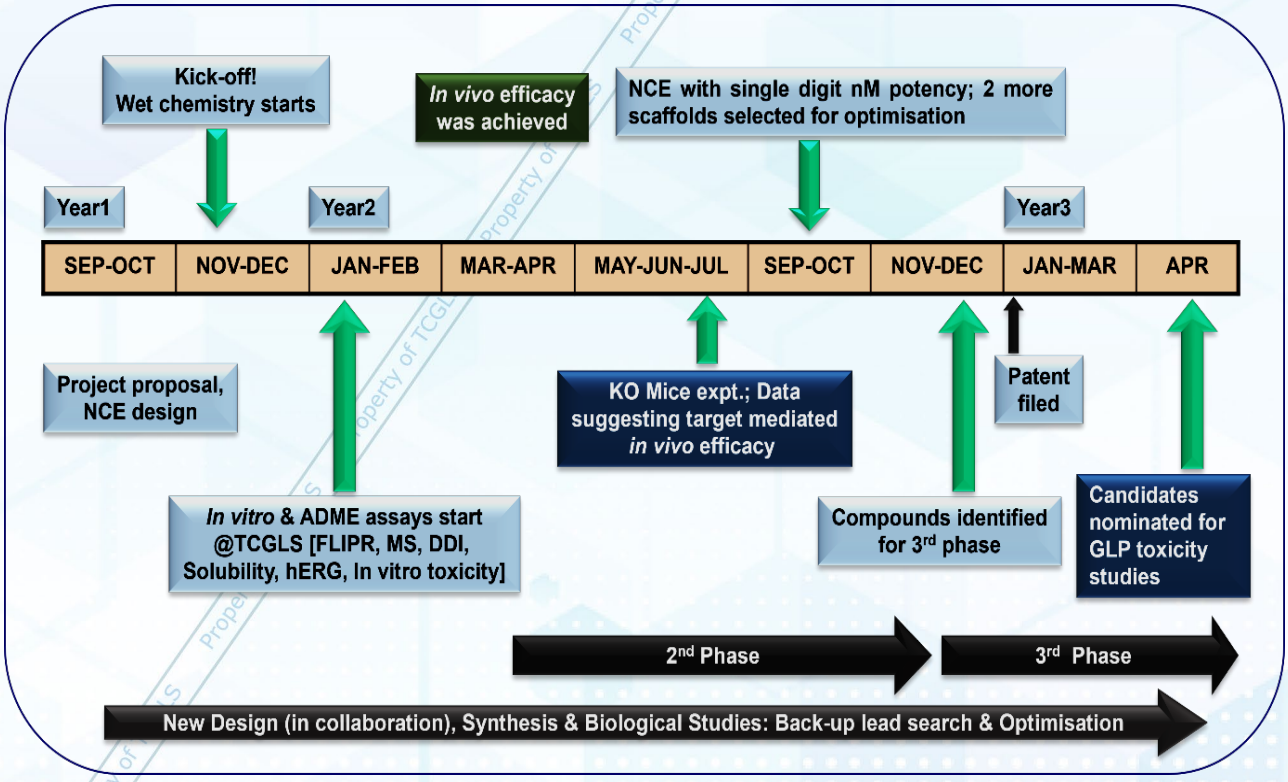
The selected parameters of the **compound A**:

- Binding IC_{50} (hMCHR1) = 26 nM
- Functional IC_{50} (hMCHR1) = 23 nM
- %F = 58; Cl_{int} = 312 mL/h/kg; C_{max} = 313 ng/mL
- T_{max} = 2h (PK @ 0.1 mpk IV and 1 mpk PO in rats
- *In vivo* efficacy = 8.6% body weight reduction @ 10 mpk PO (2-week repeated dosing using DIO F344 rats)
- Safety = exhibited low potential for hERG inhibition and phospholipidosis induction

< Medicinal-Chemistry >

Schematic Representation of The Workflow Towards Delivering PCC

The project followed a stepwise workflow, combining medicinal chemistry, *in vitro* assays, ADME-PK, and *in vivo* efficacy studies delivering preclinical candidate in <2 years:



Project Snapshot: Initiation → NCE design → *In vitro* & *in vivo* validation → Lead optimisation → Candidate nomination → Patent filing (*WO 2013105676 A1*)

< *In-Vitro*-Pharmacology >

< DMPK >

< Safety-And-Toxicology >

Conclusion

This fast-follower programme demonstrates the successful example of an integrated project executed at TCGLS and how TCGLS can help to transform ideas into solutions for better health through an innovation mindset, enabling technologies, and a collaborative approach.

Thus, spanning medicinal chemistry, synthesis, *in vitro* assays, DMPK profiling, *in vivo* studies, safety toxicology, and thereby preclinical candidate nomination—TCGLS can offer service from project initiation to preclinical candidates, culminating in patent-protected outcomes.

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