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Fenobam: Old drug, new tricks from serendipity to target-based drug discovery

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Introduction: Phenotypic Drug Discovery (PDD) has been the cornerstone of Drug Discovery (DD) for decades. In many instances, the pharmacological activity of molecules was tested without knowing the mechanism of action (MoA) and/or the drug target. An extreme case of a serendipitous finding via PDD is the story of Fenobam [Swinney DC, 2013], where the objective was to identify a better anxiolytic agent than the then standard-of-care, Benzodiazepines, which have serious use limitations including sedation, drug dependence, and respiratory depression, as well as risk of death upon abrupt cessation of therapy. Active in a variety of animal models and taken into phase I clinical trials (PI CTs), mixed efficacy and poor pharmacokinetic properties killed the program. The mechanism was deemed interesting but a better drug than Fenobam was needed in the absence of MoA data. Fenobam was a very simple, drug-like molecule and ended up in chemical libraries.

Method: A Roche high-throughput screen (HTS) was conducted in the context of a program looking to discover mGlu5 receptor inhibitors, and Fenobam was an HTS hit. Fenobam and other potential mGlu5 inhibitors were tested in various *in vitro* (Kd=31.14±4.1nM; IC50 0.058±0.002μM; both n=3) and *in vivo* assays (range of behavioral models), as described in Porter et al [2005].

Results: Fenobam was found in an HTS to act as a selective mGlu5 inhibitor. As it turns out, Fenobam had been in preclinical models of anxiety in the 1960s and PII CTs in anxiety patients in the 1980s by McGill University laboratories. The interesting potential of the mGlu5 receptor as a target was realized by numerous companies including Addex, Novartis and BMS.

Conclusion: Fenobam was discovered as an atypical anxiolytic agent with demonstrated PII CT efficacy, of the unknown pharmacological target. The compound was later discovered at Roche to act as a potent and selective non-competitive inhibitor of mGlu5. In this case, findings from a PDD effort which yielded Fenobam were invaluable for a target-based DD (TBDD) on mGlu5. Following serendipitous discovery through Roche HTS, the pre-existence of preclinical and clinical data was a giant advantage for an early DD program, which allowed the linkage of a drug target to existing published data not known to be mGlu5-related. Such data is not usually available at such an early project stage. PDD still has its place but in the majority of cases, we want to understand the MoA and go after defined target mechanisms (i.e. TBDD).

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