

Identification and Development of Novel Scaffolds for β -Cell Proliferation

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Globally, over 500 million people are diagnosed with some form of diabetes. As countries become more developed, this number is expected to increase. This disease comes with a huge economic cost, an estimated \$825 billion annually, as well as a high individual cost for those diagnosed. Metformin is the most prescribed antidiabetic but has limited efficacy without additional lifestyle modifications. GLP1 modulations, PPAR agonists, glucose absorption blockers, and insulin administration are additional therapies that provide short-term relief to patients but do not treat the underlying cause of diabetes. Recovery of natural insulin secretion through the restoration of beta-cell mass in the pancreas would be a powerful, acute therapeutic for individuals with diabetes. Several small molecule scaffolds have been identified as beta-cell proliferators through targeting DYRK1A; however, these compounds tend to be non-selective or contain severe off-target effects. The Newgard Group at Duke partnered with GNF to screen a 3 million compound library against the Nkx6.1 gene, which is known to regulate beta cell proliferation and insulin secretion. We have partnered with the Newgard group to begin an SAR campaign on one of the top hits, GNF-9228. This scaffold exhibits low micromolar potency in rat and human islets but suffers from incredibly fast metabolism. Forty-eight analogs of GNF-9228 were synthesized with variations to primary site of metabolism. Several of these analogs are conducive to longer metabolic half-lives, but all of these analogs were less potent than the parent compound. Changes at the primary site of metabolism paired with changes at other key sites of the molecule hold the potential to generate an equally potent and metabolically stable molecule. Completion of these studies will lead to an improved *in vivo* active probe and potentially a new therapeutic.