Mayo Case 2014-321: TGR5-Targeted Therapies for Cholangiopathies

Problem to be solved

Polycystic liver disease (PLD) and polycystic kidney disease (PD) are genetic pathological conditions characterized by the formation of fluid-filled cysts in the liver and kidney, respectively. Current pharmacological management of these diseases show short-term and/or modest beneficial effects.

Solution

Mayo Clinic inventors have elucidated the underlying molecular mechanisms involved in PLD/PKD pathogenesis andhave identified TGR5 as a target for therapy of these conditions and other cholangiopathies. One of the important contributors into renal and hepatic cystogenesis is elevated intracellular cAMP. A recently discovered ciliary-associated bile acid receptor TGR5 is linked to cAMP signaling. The inventors found that expression of TGR5 is increased in cystic cholangiocytes and renal tubular epithelia. Moreover, activation of TGR5 in vitro and in animal models of PLD/PKD increase cAMP levels enhancing cell proliferation and cyst growth. Importantly, genetic elimination of TGR5 in mice with PLD/PKD decreases hepatic and renal cystogenesis. Together, these data suggest that TGR5 is a therapeutic target for PKD/PLD treatment. Some experimental evidence demonstrated that TGR5 might also contribute to the progression of cholangiocarcinoma and PBC suggesting that TGR5 targeting might have clinical efficacy in these disorders as well.

Stage of Development

Preclinical, a TGR5 antagonist (small molecule, antibody, other) would need to be identified or developed.

Intellectual Property

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