Investigating Potential Therapeutic Targets for the Treatment of Fibrotic Diseases.

Rebekah Jordon[1], Vee Mitchell[2], Carol Austin[2], Celine Legros[3]

[1]University of Bath | St. James's, U.K. BA2 7AY, [2]Eurofins Integrated Discovery | Essex, U.K., CM5 OGS, [3]Eurofins Discovery | Celle-l'Evescault 86600 France

Fibrotic diseases are a major cause of mortality worldwide and there is an unmet clinical need for effective and safe therapeutic treatments. The fibrotic phenotype is the culmination of different pathways converging and influencing each other making the development of an effective treatment difficult. YAP and TAZ are transcriptional regulators that have previously been described to play a role in the activation of hepatic stellate cells (HSCs), the main drivers of extracellular matrix deposition (in particular collagen) in fibrosis1. Previous attempts at inhibiting their activation have been difficult due to their wide-ranging roles in cellular homeostasis, however, a recent discovery has identified dopamine receptor D1 (DRD1) as a fibroblast selective receptor capable of inhibiting their function through downstream cAMP increase2. Metabolic dysregulation and the resulting inflammation is known to be a key driver in fibrotic development. The increased use of fructose in Western diets is believed to be one of the causes of increasing cases of hepatic fibrosis3. Fructokinase inhibitors have already been shown in the clinic to have positive outcomes with NAFLD patients4. The current study investigates the effect of DRD1 agonism on collagen production in HSCs using the well characterised, full, selective DRD1 agonist dihydrexidine (DHX).