GUI29: NASH target discovery

Novel fibrotic NASH targets with high clinical translatability

Our comprehensive NASH database in combination with our proprietary **streaMLine *preDict*** algorithm enable identification of novel NASH targets involved in fibrosis resolution. Selected targets are rapidly validated in our preclinical NASH model using specific stellate cell directed knock-down tools for detection of fibrosis resolution.

Identifying novel NASH targets with our StreaMLine *preDict* platform

The Gubra NASH database contains more than 500 preclinical and clinical tissue samples covering the full spectrum of NASH and fibrosis development. The database includes biometric data, RNAseq, scRNAseq and histological data (e.g. NAFLD Activity Score fibrosis stage).

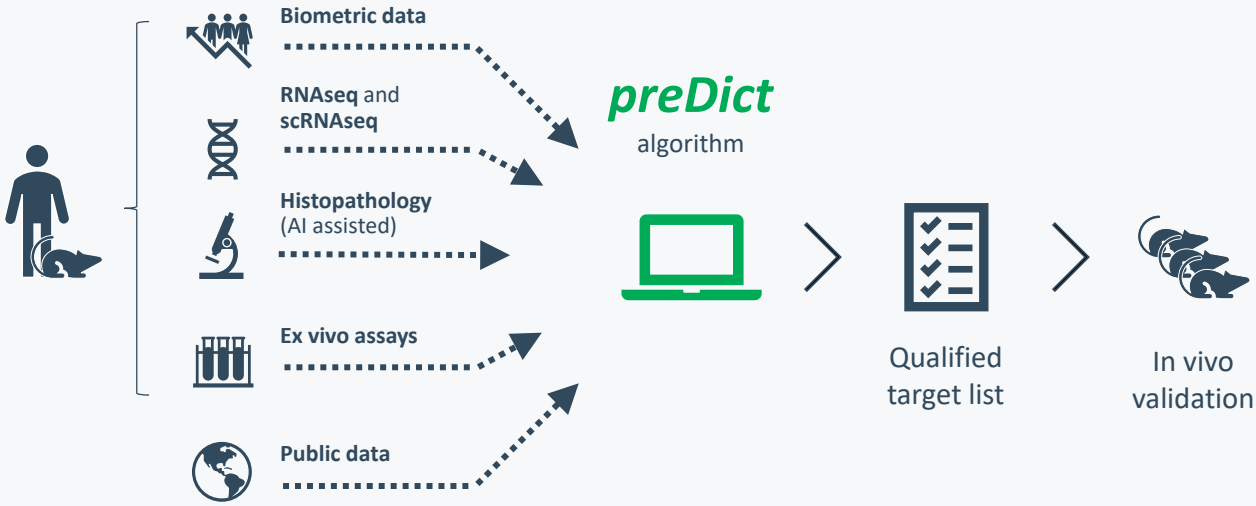
Using **streaMLine *preDict***, we have identified a short list of qualified targets driving fibrosis development or regression. Targets are qualified based on various parameters including gene expression correlation with fibrosis, cell type specific expression (e.g. stellate cells), safety and human translatability.

Key project features

- NASH database with more than 500 preclinical and clinical NASH samples.
- Advanced identification of novel NASH targets by our proprietary **streaMLine *preDict*** algorithm.
- Fast in vivo validation of novel targets in our clinical translatable rodent NASH models.
- Established techniques to knock-down targets expressed in several liver cell types – including stellate cells.

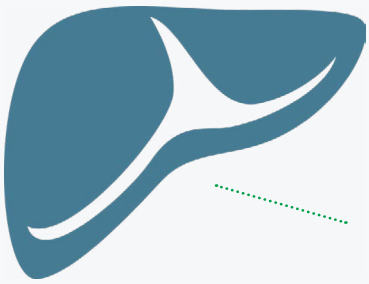
1. NASH data base
Our NASH database includes an enormous amount of data end-points from our preclinical rodent models of NASH and from clinical NASH samples.

2. PreDict algorithm
The ***preDict*** algorithm identifies and qualifies targets based on a unique approach that takes various parameters into account, and rank targets according to their "preDict score".



3. Qualified target list
Our top 20 targets include several classical drugable targets (e.g. receptors) as well as non-classical targets which are drugable by e.g. siRNAs.

4. In vivo validation
Novel targets are validated in our industry golden standard biopsy-confirmed DIO-NASH fibrotic mouse model and other NASH models.



Hepatocytes

- Abundant cell type in the liver.
- Targetable with e.g. GalNAc-siRNA or AAV-shRNA based delivery.

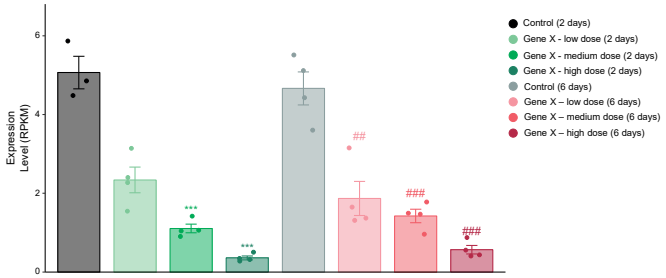
Stellate cells

- Relative rare cell type in the liver.
- Stellate cells drive fibrosis development.
- We can efficiently knock-down NASH targets expressed in stellate cells (see data below).

Knock-down of a stellate specific gene in DIO-NASH mice

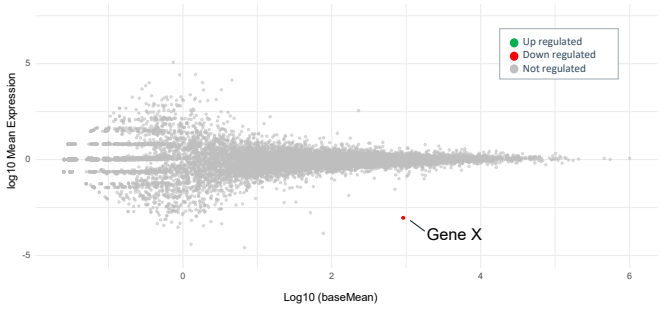
Efficient knock-down of target genes in stellate cells enable us to target fibrosis in NASH.

Dose-dependent knock-down of stellate target gene



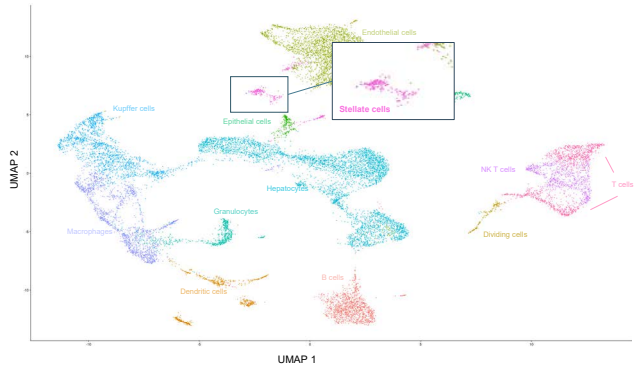
RNAseq analysis of mRNA levels of gene X shows an efficient and dose-dependent knock-down. **/##: p < 0.01, ***/###: p < 0.001 compared to Control.

Specific knock-down of stellate target gene



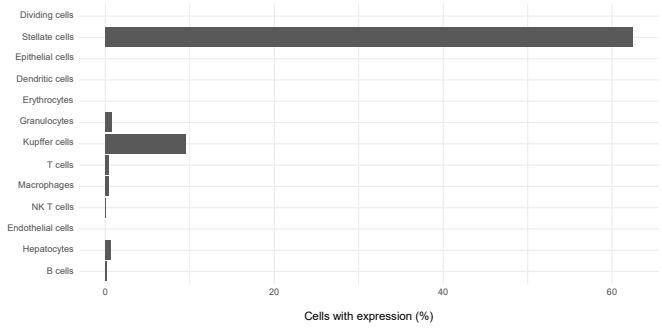
Global gene expression analysis of RNAseq shows that gene X is the only significant regulated gene which demonstrates the specificity of the applied knock-down technology.

Stellate cells identified by scRNAseq



Single cell RNAseq (scRNAseq) analysis of liver from DIO-NASH mice shows identification of all key liver cell type including stellate cells

scRNAseq profile of stellate specific gene



Single cell RNAseq (scRNAseq) profile of gene X in liver from DIO-NASH mice shows that gene X is primarily expressed in stellate cells.

Why choose Gubra?

- Proven track record with identification of new disease targets and new peptide drugs. The most advanced are currently in clinical development with pharma partner.
- All projects are led by professional project leaders with strong scientific backgrounds and project management experience.
- All data are generated in-house to ensure high data quality, integrity, speed and flexibility.
- AAALAC accredited in vivo facility