e-therapeutics

Network-driven Drug Discovery

FIBROTIC DISEASES: IDIOPATHIC PULMONARY FIBROSIS

BACKGROUND

Fibrosis is the final pathological outcome of most chronic inflammatory diseases. Dysregulated normal tissue repair can result in a progressively irreversible fibrotic response. Fibrosis is defined by the excessive accumulation of fibrous connective tissue and extracellular matrix (ECM) components, such as collagen and fibronectin, in and around inflamed or damaged tissue. The fibrotic ECM component accumulation can lead to permanent tissue scarring, organ malfunction and death. Fibrosis affects nearly every tissue in the body as seen in end-stage liver disease, kidney disease, idiopathic pulmonary fibrosis (IPF) and heart failure.

IPF is a chronic, progressive disease of unknown aetiology that causes lung scarring. The processes mediating lung fibrosis are not completely understood, but it has been suggested that injury of alveolar epithelial cells activates inflammatory cells, which release fibrogenic growth factors that lead to fibrosis. The disease has poor prognosis, a median survival of 3-5 years after diagnosis, and an estimated prevalence of ~20 per 100,000 people worldwide, with ~ 32,000 cases in the UK.

Therapeutic options for patients with IPF are limited. Two drugs are currently approved: pirfenidone, of unknown mechanism of action, and nintedanib, a broad-spectrum tyrosine-kinase inhibitor. Both treatments slightly slow disease progression but they are insufficient in their benefit and the large unmet medical need in the field remains.

THE OPPORTUNITY

e-therapeutics has successfully applied its **Network-driven Drug Discovery (NDD)** platform to identify small-molecule across different areas of disease.

e-therapeutics' platform can be used to discover novel and differentiated hits for subsequent hit-to-lead and lead optimisation.

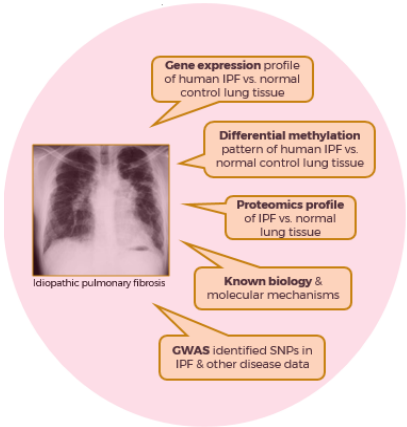
Fibrosis is an area with clear unmet needs, and complex biology, for which the underlying mechanism are not well understood. The use of omics data and network biology analysis could help to discover new drugs.

THE APPROACH

Network-driven Drug Discovery

Our approach aims at developing anti-fibrotic agents by targeting the network of interactions underpinning the disease. Network construction based on both omics data and known molecular mechanisms were used. Focusing on systems level approaches is beneficial for IPF, and fibrotic diseases in general, as fibrosis is a multicomponent disease and a deep understanding of the molecular mechanisms are lacking.

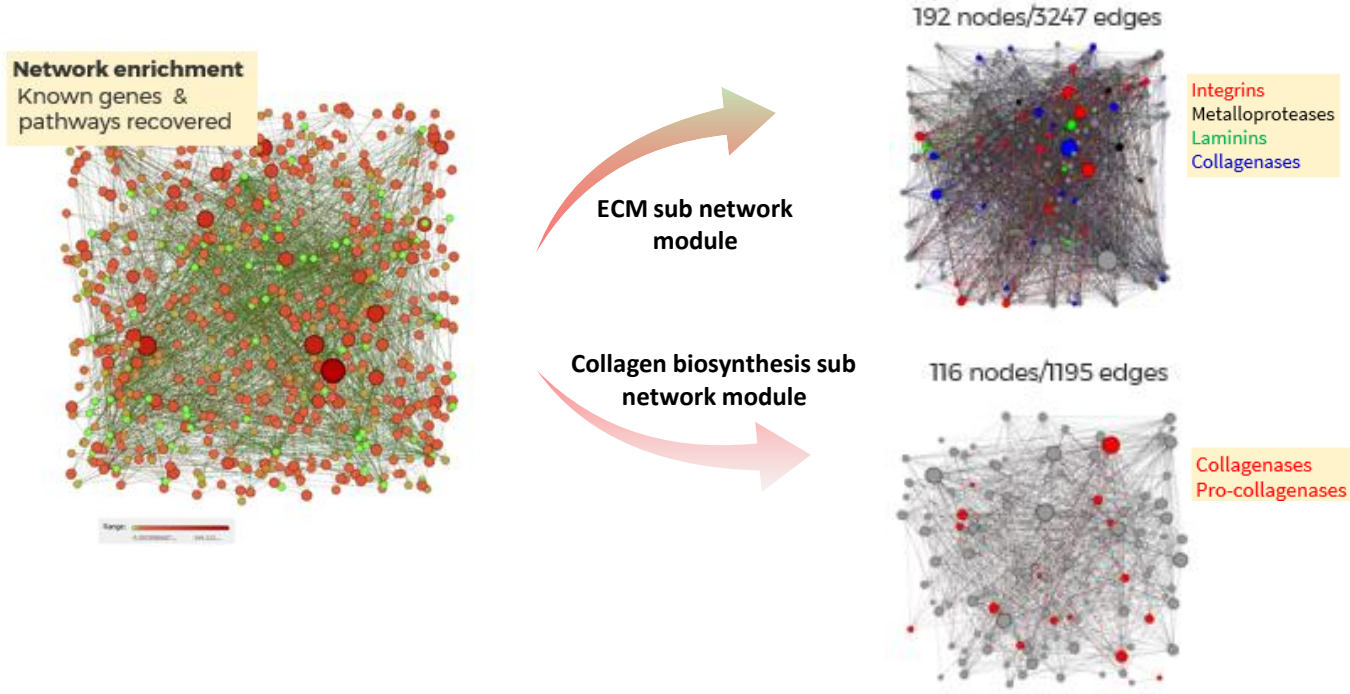
Disease network modules were extracted from patient's data, and network analysis showed that known biology was embedded on those networks. These disease related networks can be analysed to identify and extract sub-modules related to specific disease biology (*e.g.* extracellular matrix sub-network, collagen biosynthesis sub-network). Cell type specific mechanisms can be identified by constructing networks with data from specific IPF cell type (*e.g.* fibroblasts, macrophages, etc).



Examples of use of omics data for network construction

Example of data driven IPF network module

Examples of IPF network extraction submodules



ACTIVITIES

Network Analysis

Using our proprietary NDD platform for network analysis, we can identify potential active compounds with desirable physicochemical characteristics for *in vitro* testing.

Analysis of the networks constructed using IPF, lung tissue transcriptional data yielded a list of compounds that includes: known compounds used to treat IPF, such as nintedanib and pirfenidone, along with compounds with various mechanisms of action that are being clinically tested elsewhere, and novel compounds (not shown in the example listed below) which could form the basis for medicinal chemistry programme if proven to be active in phenotypic assays.

A	B	C	D	E	F	G
flag	Compound ID	Footprint Overlap	Impact	Name	Drug Bank Cate	Mechanism of Ac
81	ETXC000000420736	32	0.155552812	Nintedanib	approved	Fibroblast growth fa
650	ETXC000000696340	27	0.088454178	Pirfenidone	investigational	Unknown
36	ETXC000000002269	10	0.197671957	Troglitazone		Peroxisome prolifer
43	ETXC000000016647	7	0.196595119	Fenofibrate	approved	Peroxisome prolifer
587	ETXC000000242522	4	0.093292178	Mesalazine	approved	Arachidonate 5-lipo:
452	ETXC000000183651	29	0.097555433	Sirolimus	approved; investi	FK506-binding prote

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