Fibrosis: Mechanisms and New Treatments
Alderley Park 25th/26th April 2018.

Dr Graham Wallace
Institute of Inflammation and Ageing
University of Birmingham

President, International Association of Inflammation Societies

Delegates from the UK, Europe and the USA gathered at Alderley Park for a meeting on Fibrosis: Mechanisms and New Treatments hosted by the British Inflammation Research Association (BIRAs). Fibrosis now kills more people that cancer; half of all of idiopathic pulmonary fibrosis (IPF) and non-alcoholic steatohepatitis (NASH) patients die within 3-5 and 10 years respectively. As such, fibrosis is an essential target for the development of new therapeutics, a process that will be facilitated by an increased understanding of the mechanisms that drive fibrosis in different organs. The rate of fibrosis progression is variable with rapid and slow development of disease. Regression of fibrosis, particularly of the liver, is possible if the underlying cause i.e. alcohol or hepatitis C virus is removed. Studies in patients undergoing bariatric surgery showed a decrease in liver fibrosis and the increasing incidence of nonalcoholic fatty liver disease in children is indicative of the challenges facing Western societies due to increasing levels of obesity and development of metabolic syndrome. The meeting highlighted current research investigating the mechanisms driving fibrosis and identified novel targets for potential therapeutics.

Gisli Jenkins (Nottingham) led off by describing a major role for lung epithelium in IPF, a progressive condition with a 5 year survival rate of 25-30%. Prof Jenkins indicated that damage to the epithelial layer begins 20-30 years before the development of IPF with 75% of patients being ex-smokers. A worrying prospect is that smoking can drive IPF even if an individual has given up many years ago. Serum biomarkers including surfactant protein D, and matrix metalloproteinase 7 (significantly higher in patients with progressive disease than in patients with stable disease) that can be used to predict disease progression and death were described. The pivotal role of the epithelium in the pathogenesis of IPF is apparent from the identification, at gene level, of an association between IPF susceptibility and SNPs in or near several epithelial genes (A-kinase anchoring protein 13, mucin 5B and desmoplakin). Activation of TGFβ1 by αvβ6 integrin is a key process of fibrogenesis and research from Prof Jenkins' lab has uncovered multiple aspects of the signalling pathways that are evoked in an autocrine loop whereby TGFβ1 induces epithelial αvβ6 expression resulting in the increased generation of further active TGFβ1.

Richard Marshall (GSK) gave a panoramic view of drug discovery for fibrotic diseases from an industry perspective and highlighted the use of "omics" to provide better targets for therapy. Again, the need for drug development within the field was indicated; IPF is the number one cause of lung transplant referrals in both the UK and the USA. The need to develop better methodologies for patient stratification was highlighted – clinicians need to be able to intervene therapeutically at a point when disease progression can still be modified.

Identification of rapid versus slow progressors within the patient population will facilitate treatment. New technologies used to detect biomarkers were discussed including measuring volatile organic compounds in exhaled breath, PET-ligand development and even the use of social media for in silico drug trials.

Tim Radstake (UMC Utrecht) introduced the role of the immune system in fibrosis development, discussing the role of dendritic cells in systemic sclerosis (SSc). Fibrosis is not observed in SSc patients in the absence of inflammation and circulating levels of inflammatory markers have been found to be predictive of disease progression. CXCL4 (upregulated in plasmacytoid dendritic cells) was identified as a very early biomarker for fibrosis development in SSc. pDC numbers are low in the blood of SSc patients. Furthermore, expression of Runx3 in pDCs is low, which may be a result of hypoxia, exhibited as Reynaud's Syndrome. Mice lacking Runx3 in DC exhibit increased skin inflammation and fibrosis, further implicating this pathway. CXCL4 drives pDC into diseased tissue and potentiates the response to innate immune receptors, this places CXCL4 as a link between inflammation and fibrosis potentially through its ability to cause transcriptome imprinting.

Arianne Van Koppen (TNO) gave an insightful presentation detailing how the factors that drive fibrosis begin to influence progression before overt signs of fibrosis develop. This is an important finding as it may pave the way for predicting who will develop fibrosis and also early treatment. Using a model of bleomycin-induced lung fibrosis, fibrosis development was studied over time with and animals were sampled weekly. Within the first three weeks, 95% active fibrosis genes from the lung were also present in the kidney, indicating the presence of a generic fibrosis signature. This signature also coincided with the peak of leukocyte activation. Over 50% of genes identified in a model of NAFLD, the LDLr-/- Leiden mouse, which is prone to NASH, obesity and hyperlipidaemia were found to overlap with human NASH. In this model fibrosis develops from week 18, with all mice having fibrosis by week 30. Samples were collected at 12 weeks when no overt signs of fibrosis were evident and were analysed to compile a molecular signature of a pre-fibrotic state. This signature was modified by a high fat diet. Treatment with OCA-FxR agonist modified this early signature and also reduced hepatosteatosis and hyperlipidaemia when given at 24 weeks.

On the second day the theme changed to potential therapeutic targets. Alison McKinnon (Edinburgh) discussed a role for galectins, particularly galectin-3 in IPF, which is raised in BAL fluid from patients. Macrophages are a major source of Gal3 which recruits monocytes and drives M2 polarisation. In $Gal3^{-/-}$ mice fibrosis in lung, liver and kidney models is greatly reduced. In the liver Gal3 promotes the expansion of hepatic progenitor stellate cells. Therapeutic administration of TD139, a Gal-3 inhibitor, with some activity also towards Gal-1, was reduced fibrosis in a bleomycin-induced model. This compound has also undergone a first in man study, administered as a dry powder inhaler to IPF patients. Plasma biomarkers associated with IPF were reduced in response to TD139. Clinical trials are ongoing to test inhibitors of Gal3.

Tim Johnson (UCB) discussed tranglutaminase-2, an enzyme which is inactive until triggered by calcium. TG2 forms irreversible crosslinks with protein including binding latent TGFβ to the extracellular matrix and is a principal enzyme in controlling TGFβ maturation. TG2 is raised in kidney fibrosis and its inhibition improves streptozotocin and bleomycin-induced mouse models of kidney and lung fibrosis. Prof Johnson described the generation of a new antibody inhibitor of TG2 that show promise in model systems. By targeting a molecule such as TG2 that is fundamental to the fibrotic process these inhibitors may have broad utilisation. Again, Prof Johnson stressed the need for explotory biomarkers to monitor the efficacy of new therapeutics.

Jonathan Fallowfield (University of Edinburgh) again identified the scale of fibrotic liver disease, with the numbers of patients presenting increasing year-on-year. He particularly highlighted the growing incidence in children, with up to 80% of obese children now diagnosed with NAFLD. Dr Fallowfield also discussed the importance of patient stratification, as some patients progress quickly to fibrosis, whilst others do not. Macrophages were described as having a positive or negative effect on fibrosis in mice and are an important cell type to be considered. Macrophage depletion during injury results in less scar formation, whereas macrophage depletion during recovery results in less scar resolution indicating the complex biology of fibrosis development and macrophage phenotype. Furthermore a significant role for hepatic stellate cells and novel pathways of their activation was discussed. The need for a combined therapy approach targeting different aspects of the fibrotic response was highlighted as the way forward to deal with this complex process, as was the ability to target therapies to specific organs for example through the use of vitamin A-coupled liposomes.

These excellent plenary presentations were backed up by equally excellent short talks selected from the abstracts submitted. The topics ranged from the role of platelet-monocyte aggregates, hydrogel delivery systems and “scarless“ regeneration in the uterus following menstruation. There was a good display of high quality posters on many aspects of fibrosis that generated significant interest and discussion at coffee and lunchtime sessions. The poster prizes were awarded to Phoebe Kirkwood (Edinburgh) for her work on endometrial regeneration and Sara Namvar for her work on

There were several informative and detailed talks from our exhibitor/sponsors on model systems of fibrosis, phenotypic profiling and growing liver tissue in a dish. All provided fresh thought for the audience in regards to how we investigate and model fibrosis going forward. BIRAs would like to thank all our sponsors in particular RedX Pharma for their support and contributions to the meeting.