

## WP1 – 4<sup>th</sup> BTCure Workshop on Animal Models



### Meeting Summary

On September 18<sup>th</sup>, 2016 the fourth workshop on Animal Models in Experimental Arthritis took place in Athens, Greece. The workshop was organized by Prof. George Kollias (Fleming) and was funded by the BTCure workshop support. The three day workshop involved BTCure partners from Academia and Industry in addition to external speakers, leaders in their field of expertise.

#### Workshop Aims:

The overall aim of this Workshop was not only to raise discussion among BTCure partners with regard to newly generated data and technologies on established and emerging animal models of RA disease, but also to encourage exchange of emerging knowledge from international experts in the field, and establish new collaborations with both academia and EFPIA. In this context, one of the main responsibilities of the Workshop organizers was to communicate the progress and achievements from within the BTCure network to all partners, but also to endorse participation of external experts in the field of RA, and foster debates and discussions on future research focus and coordinate such efforts for more efficient exploitation of results at an International level.

Over the course of the three day workshop, the following key aims were addressed:

- To discuss emerging knowledge (characteristics, advantages and limitations) from the alternative experimental and/or genetic models not only of rheumatoid arthritis but also of other modalities
- To initiate discussion on the alignment and transfer of knowledge from animal models to human disease and the potential strategies for development of new drugs and therapies
- To learn from the development and advances of the mouse ENCODE project and examine correlations with BTCure and ENSO projects, and extrapolate to initiate discussions on large-scale profiling and metadata integration across platforms and models
- To review the emerging field of non-coding RNAs, with focus on microRNAs and long non-coding RNAs, and their role in RA pathophysiology and treatment
- To up-date BTCure participants on recent research results and advances in the area of Bioimaging technologies and applications in implicated RA tissues and cell types

#### Short Report:

##### Session I – New Animal Models

During this session it once again became evident to all participants how critically important animal models are in advancing our understanding, not only in basic research and disease pathology, but also towards bridging the gap between the bench and bedside. Several mouse models were presented as part of this session, new models that allow further investigation of the signaling pathways involved in skin inflammation (RIPK1, RIPK3, and DAI knockouts) [Pasparakis et al., Univ of Cologne), transgenic animals that are good models to further understand disease pathologies like osteoporosis (Tg5516) and bone fragility (Tg5519) [Douni et al., Agricultural Univ. of Athens], and

models that are good for preclinical trials like TgRANKL and TgA86 [Denis et al., Biomedcode]. Interesting information were also presented on established arthritis models (Tg197 and TNF<sup>ΔARE</sup>), which have been more closely studied and have been found to develop fibrosis in the aortic heart valves and IBD respectively. These models open new insights towards further exploring comorbid conditions. Finally, an interesting talk was given on modelling different aspects of inflammatory joint destruction in mouse models of RA [Pap et al., Univ. Hosp. Münster].

#### Session II – Pathogenic mechanisms and alignment to human disease

In Session II, first the role of Th17 and IL-17 in autoimmune diseases like EAE and psoriasis, was addressed [Waisman et al., Univ. of Mainz]. Interestingly it was also demonstrated that IL17 psoriatic mouse models, also suffer from Heart disease, while IL17A overexpression also leads to bone loss. Furthermore, PGAM5 and MLKL mouse models were presented revealing further information on the pathways involved in liver failure [Becker et al., Erlangen]. The Ikkb/Ripk3 axis was demonstrated as a master regulating signaling pathway of TNF-mediated arthritic disease manifestation [Armaka et al., Fleming]. The final presentation addressed the systemic implications of rheumatic diseases, and the comorbidity risks that RA patients are exposed to. More specifically, the established RA models TNF<sup>ΔARE</sup> and Tg197, have now been demonstrated to serve as models of a common comorbid condition, IBD and fibrocalcific aortic valve disease, and are being further investigated [Sakkou et al., Fleming].

#### Session III – Systems level approaches / the mouse ENCODE

This session commenced with an interesting presentation on the ARE system in relevance to Physiology, Inflammation control and cancer, with specific focus on HuR mutants in this research field [Kontoyiannis et al., Fleming]. The participation of macrophages in RA was then addressed with the example of the STIA mouse model, followed by the involvement of miRs in RA [Perlman et al., Northwestern Univ.]. The data presented, suggest that certain miRs could serve as biomarkers or for disease rescue [Apparailly et al., INSERM]. Coding and non-coding transcripts from mice and men were also shown to be connected to joint inflammation, together with certain miRs [Ospelt et al., Univ. of Zurich]. Finally a systems-level profiling of the Tg197 arthritic synovial fibroblast was presented, leading to a comparison of mouse vs human, demonstrating an overlap between the profiles and indicating a good alignment between mouse and human [Ntougkos et al., Fleming].

#### Session IV – Biomarkers and drug development

First a systems medicine approach of Inflammatory Bowel Disease was presented, describing new humanized animal models to study inflammation with a focus on the NF-κB pathway [Müller et al., Univ. of Manchester]. Mathematical models engaged for the analysis of genomic data generated from the animal models and patient cohorts aim to further our understanding and generate new animal models for studying transduction dynamics in inflammatory diseases. The pharmaceutical approach was then shared, pointing out the importance of biomarkers towards the development of drugs with higher efficacy which can be translated to better patient care in the clinic [Moore et al., UCB]. The idea of inhibiting citrullination in rheumatoid Arthritis has long been discussed, however a novel approach was also described where PAD inhibition appears to provide a novel and realistic

prospect for treating rheumatoid arthritis and other chronic inflammatory diseases [Venables et al., Kennedy Institute of Rheumatology]. The Tg197 RA model is considered an established model for studying the disease and therapies. However, further investigation of gene expression data analysis following Remicade treatment and kinase inhibitor have provided evidence that support further exploration of disease metabolomics and transcriptomics in this model [Karagianni et al., Biomedcode]. Autoimmune disease therapies still remain a challenge and the ultimate goal for their treatment is the development of antigen-specific therapies. To this end antigen-specific regulatory T cells were presented as potential target cells [Verginis et al., BRFAA].

#### Session V – Developments in Bioimaging and Phenotyping platforms

On the last day of the Workshop very interesting presentations were delivered on mouse phenotyping platforms and bioimaging applications [Fuchs et al., GMC]. First a thorough overview of the German Mouse Clinic phenotyping pipelines was presented together with details on the standardized EU phenotyping protocols employed. An interesting statistical computer model of a mouse foot was described based on collected microCT data representations, used to assess bone deformities such as bone erosion [Naylor et al., Univ. of Birmingham]. Finally a novel PET-CT/SPECT in vivo multimodal imaging technique was presented. Through this tool, not only can inflammatory processes and progression of inflammation in the joint be examined in a non-invasive way, but also reversibility of joint inflammation and damage upon therapeutic intervention can be monitored [Hayer et al., Med. Univ. of Vienna].