1. Osteoarthritis: New Horizons for Treatment

In a session dedicated to new treatment options for osteoarthritis (OA), two talks focused on promising results from phase 2 clinical trials. Yusuf Yazici (NYU School of Medicine, USA) presented week 26 interim analysis from a randomized, double-blind, placebo-controlled, phase 2 study using the novel WNT pathway inhibitor (SM04690) to treat knee OA (NCT02536833). Knee OA is characterized by deformation of the joint due to degradation of articular cartilage and bone remodeling, leading to narrowing of the joint space, pain and disability. The morphogen Wnt has been implicated in the pathogenesis of OA, with increased levels found in degenerated cartilage. This can cause progenitor cells to differentiate into osteoblasts, resulting in ectopic bone formation. The rationale of this trial is that by blocking Wnt signaling using SM04690, progenitor cell differentiation within the joint will be shifted away from bone formation and towards cartilage generation. 455 subjects with knee OA were enrolled and received a single intra-articular injection of either 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo in the most painful knee. Safety, tolerability and efficacy outcomes were periodically assessed, and knee radiographs were taken at baseline and week 26 to measure change in medial joint space width (mJSW). SM04690 appeared well tolerated with no reported serious adverse events. Odds of mJSW improvement, de

2. Neutrophil Aging: An Inflammatory Impact

In the Innate Immunity session, Andrés Hidalgo (Fundación Centro Nacional de Investigaciones Cardiovasculares, Spain) gave a fascinating translational overview of diurnal (daily) aging in neutrophils. Neutrophils are the most abundant myeloid cells in blood and their number, phenotype and function are temporally influenced in a process called neutrophil aging. In mice and humans, the number of neutrophils in the blood stream increase during the day and decrease at night as they are cleared. During this circadian oscillation, ‘fresh’ newly released neutrophils progressively undergo phenotypic changes including the upregulation of certain surface markers, a reduction in cell size, and altered nuclear morphology. Aging is thought to be triggered by multiple factors including exposure to external cues in the bloodstream and cell-intrinsic mechanisms via expression of clock genes. The processes that drive aging are still being elucidated. However, it is clear that as a neutrophil’s morphology and phenotype change, so does its function. For example, unlike fresh neutrophils, aged neutrophils express high levels of the integrin subunits CD11b and CD49d, enabling them to bind to inflamed endothelium. It is postulated that a shift in inflammatory properties of neutrophils during the day might coincide with when the host is most likely to encounter microorganisms. This explanation implies a nearly evolved means of protection, although it might also leave the host immunologically vulnerable when the number of neutrophils are low, or at risk of inflammatory disease if their number, or activity becomes abnormally high. In fact, several chronic diseases including rheumatoid arthritis, are known to present exacerbated symptoms during the early morning. The incidence of cardiovascular events also peak at this time, and it is tempting to speculate that the circadian rhythms of neutrophils at this time are somehow related. Exploring the specific relationship between the circadian control of immune components, such as neutrophils, and inflammatory processes is an active research area.
Perhaps this will enable a better understanding of the pathophysiology of disease, and establishment of the optimal temporal window for therapeutic intervention.

3. Immunogenicity of Therapeutic Antibodies

The use of therapeutic antibodies to treat cancer and immunological diseases has become an extremely important strategy. Unfortunately, many patients develop antidrug antibodies (ADAs) that can diminish therapeutic potency and elicit an allergic response. This is because most therapeutic antibodies are either chimeric or humanized, meaning they consist of non-human regions that the host immune system reacts towards. However, Bernard Maillelé (CEA-Saclay, France), presented data showing how ADAs can be anticipated. The immunogenicity of antibodies is largely driven by the presentation of antibody-derived peptides by antigen presenting cells (APCs), which then stimulate specific CD4 T lymphocytes. Maillelé has devised a strategy to identify CD4 T cell epitopes associated with anti-CD20 rituximab (Rtx) and anti-TNFα infliximab (Ifx) - two common antibodies used to manage inflammatory diseases such as rheumatoid arthritis. First, dendritic cells (DCs) were isolated from healthy donors and loaded with either Rtx or Ifx to act as APCs. CD4 T cells derived from healthy donors were then exposed to the antibody-treated DCs to create antibody-specific CD4 T cell lines. Many T cell lines were raised for each antibody, and investigated for their peptide recognition to create a detailed map of the T cell epitopes for Rtx and Ifx. Second, to assess the utility of antibody-specific T cell epitopes identified from healthy individuals, their ability to stimulate a T cell response in patients who have previously developed ADAs from Rtx or Ifx was tested. Two-thirds of the epitopes identified in the initial screen were able to elicit a T cell response in ADA patients. This encouraging overlap indicates that the strategy can be used to predict the immunogenic origin of ADA and, in the future, might be used to anticipate an ADA response in antibody-naïve patients to guide treatment. This strategy could also be used to engineer de-immunized therapeutic antibodies by removing or masking potentially immunogenic epitopes. This work was done in the frame of the large European IMI project ABIRISK.

4. Axial Spondyloarthritis: From Bug to Gut and to Disease Phenotype

In a Bench to Bedside session dedicated to axial spondyloarthritis (SpA), Dirk Elewaut (VIB-UGent Center for Inflammation Research, Belgium), discussed the relationship between gut microbial composition and SpA disease activity. Up to 50% of patients with SpA have signs of microscopic bowel inflammation. Furthermore, a significant pathogenic overlap between SpA and inflammatory bowel disease (IBD) has previously been reported. As gut microbial dysbiosis has been implicated in IBD, the relationship between intestinal microbial composition, gut histology, and disease activity in SpA warrants further investigation. A recent study from Elewaut’s team used gene analysis to compare the microbial composition of intestinal biopsy specimens from 27 patients with SpA (14 had microscopic bowel inflammation), and 15 healthy control subjects. The Shannon Index was used to measure microbial diversity, incorporating the richness (number of species), and evenness (relative abundance of species) of each biopsy. The inflamed SpA group showed a greater, but not statistically significant, Shannon Index compared to the non-inflamed SpA tissue and healthy control groups. Interestingly, hierarchical clustering analysis revealed that the inflamed SpA group formed a separate cluster of bacterial community composition compared to non-inflamed tissue. Analysis of specific microbial species revealed that Dialister was significantly greater in inflamed tissue, compared to non-inflamed tissue from patients with SpA, and in healthy controls. This result, if confirmed, suggests that Dialister could be used as a microbial marker of disease activity in SpA. It remains to be seen whether this abundance of Dialister causes, or is a consequence of microscopic bowel inflammation, but perhaps manipulating the gut microbiome may be a promising target for SpA therapy.

5. Tools to Guide Early Diagnosis of Systemic Sclerosis

Systemic Sclerosis (SSc) is a heterogeneous autoimmune disease affecting connective tissue, and is characterized by an accumulation of collagen in the skin and injuries to small arteries. Localized SSc can affect skin on the hands, face and feet, while the systemic form can progress to visceral organs. Prognosis depends on the type and severity of SSc, and ranges from limited morbidity in the mildest cases to significantly decreased lifespan when there is a large visceral component. SSc has no cure, but early diagnosis can help predict development of the disease so it can be treated early to manage symptoms and limit permanent damage to tissue. Two studies were presented in the SSc session that highlighted new tools to help the early diagnosis of SSc. The first study focused on a novel blood test to detect SSc-specific autoantibodies as a means to identify active disease. Gianluca Moroncini (Università Politecnica Marche, Italy) described the identification of a peptide that can be used to diagnose SSc. The peptide is derived from platelet-derived growth factor receptor alpha (PDGFRα), and is recognized by autoantibodies present in patients with SSc. A biosensor-based approach was used to detect SSc-specific anti-PDGFRα autoantibodies in serum, and was able to discriminate SSc patients from healthy controls. This blood test was tested on patients with active disease, and has not yet been tested on early disease. However, these promising preliminary results are hoped to be applied prospectively to individuals suspected of having SSc. If found to be robust, this test could be rolled out for the early diagnosis of SSc.

The second study, presented by Vanessa Smith (Ghent University Hospital, Belgium), used a non-invasive imaging technique called nailfold videocapillaroscopy to measure structural changes in the peripheral microcirculation of 1085 patients with Raynaud’s syndrome. Raynaud’s syndrome often precedes SSc, and is characterized by reduced blood flow to the extremities. Using nailfold videocapillaroscopy to visualize structural changes to peripheral small vessels, atypical capillary networks correlated to a greater extent in patients with SSc-associated antinuclear antibodies (ANA) (40%), than in ANA-negative patients (13%). This inexpensive and reproducible imaging modality could be incorporated into the ‘very early diagnosis of systemic sclerosis’ (VEDOSS) criteria, to help diagnose SSc as early as possible. Perhaps combining the blood biosensor approach with nailfold videocapillaroscopy will facilitate VEDOSS, and provide individuals with the best possible chance of successful disease management.