

## Therapeutic potential of targeting inflammation

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On 7–8 September 2012, at Bolton Landing, New York, the International Association of Inflammation Societies (IAIS) hosted a Translational Inflammation Summit which gathered a group of invited specialists from both academic institutions and the pharmaceutical industry for 2 days of intense presentations and discussions.

The goals of the Summit were: (1) to provide participants with the opportunity to present cutting-edge research in inflammatory processes and disorders and discuss means with which to translate these results into therapeutic benefit; and (2) to foster a cross-fertilization of ideas between scientists with different areas of specialty and interest in inflammation research.

The program included a combination of academic and industrial research talks (25 in total), with a focus on potential translational outcomes; there was also focus on unmet medical need in inflammatory/auto-immune disorders and on the future of inflammation research.

The list of 38 participants, with 17 from industry, can be seen in Supplementary Table 1. There were four sessions entitled “Inflammation and Pathology” and three called “Mechanisms in Inflammation”.

The consensus from the participants was that the meeting was valuable, allowing broad thinking and discussion. The participation of both academic and industrial

researchers provided a refreshing perspective for the Summit and allowed its goals to be addressed more easily. It was felt that the opportunity for cross-fertilization of ideas was valuable since both the broad scope and also the gathering of specialists from different “organ systems” were rare features, thereby providing an overview of approaches across disease organ types; the opportunity for the interaction between academic and industrial participants was a unique feature. In addition, the focus on translational research was considered to be of high interest and timely.

### Significance of inflammation vs low profile of its research

John Hamilton (Melbourne) introduced the Summit by defining “inflammation” as the body’s response to damage by pathogens and injury that enables survival and restores tissue homeostasis. He referred to its cardinal signs, noted that it is not a system (like the nervous and cardiovascular systems, for example) or a specific disease, and consists of a diverse range of processes that occupy a central position in physiology and in pathology, highlighting its breadth and ability to provide linkage across pathologies. Inflammation has close ties with both the innate and acquired immune systems. In spite of its association with many chronic conditions, including arthritis, atherosclerosis, cancer, neurodegenerative disease, obesity/type II diabetes, etc., and in spite of the huge market size for anti-inflammatory therapies [e.g. tumor necrosis factor (TNF) blockers], inflammation research per se has a relatively low profile, as judged by the impact factors of “inflammation” journals and the number of attendees at “inflammation” conferences. He suggested that definitions and terminology

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as to what defines “inflammation” can matter, particularly if we are to define the initiating pathogenesis for a particular condition correctly, with its implication for early diagnosis and more effective therapies. He advocated a broad view of chronic inflammatory diseases as incorporating so-called autoimmune diseases, autoinflammatory diseases and those in which the initiating trigger is not well defined but does not seem to involve infection or tissue damage: for example, obesity/type II diabetes, atherosclerosis, neurodegenerative diseases and cancer.

How to redress the disparity between the low profile of inflammation research and the high importance of inflammation to pathology? John suggested a series of ways to enhance the profile and quality of inflammation research: for example, by holding further conferences, the writing of reviews, particularly in high impact journals, establishing cross-disciplinary activities and teams within/between academia and industry, the strengthening of local inflammation groups/societies, attempting perhaps to develop a high impact “inflammation journal”, etc.; funding bodies and industry could be lobbied for support in this endeavour.

### Unmet medical need in inflammatory/autoimmune diseases

Elisabeth Peen (Copenhagen) provided an overview of several inflammatory/autoimmune diseases [rheumatoid arthritis (RA), systemic lupus erythematosus, Crohn’s disease and ulcerative colitis], their current diagnostic criteria, their treatment algorithms and their unmet medical need left by current therapeutic options. She also stated that the unmet medical need among real-life patients is likely larger than that demonstrated among selected patient populations in published clinical trials. From her talk and subsequent discussion, concerning the relationship between modern research developments to their unmet medical need, a number of gaps were identified that should be filled. The following needs with some appropriate constructive recommendations were highlighted.

1. The pathology of most inflammatory diseases is not well understood; no curative therapy is available, with remission being the best potential outcome at present. It was felt that research involving new drugs and drug combinations may in fact aid in understanding disease pathogenesis and parallel studies of therapeutic strategies in different indications may provide insights into disease mechanisms.
2. Better definitions, including a molecular classification, of each disease is required. Biomarkers are needed to classify disease states, predict outcome and monitor safety; microfluidics technology could assist in this outcome.

3. New therapeutic strategies are needed. Some ideas in this context were raised. The goal of research should be to cure disease and treat co-morbidities, with the ultimate goal being to prevent disease. Early treatment will reduce the extent of tissue damage, but means with which to repair existing damage would also meet an existing need. Local gene therapy may represent a further therapeutic option and special consideration should be given to the long-term safety and long-term availability of therapies used in younger patients who may require life-long treatment.
4. Strategies to encourage the clinical development of personalized medicine are needed. A major impediment to the clinical development of such drugs is the small market size of some patient subpopulations that are not attractive to the marketing departments within the pharmaceutical industry. Means with which to identify patients who may respond to a particular therapy need to be developed; this may require the demonstration of a large disease-modifying effect in identifiable patient subpopulations or alternative medical indications.

### Inflammation and pathology

A number of talks covered the role of inflammation in various diseases.

#### Arthritis

Steffen Gay (Zurich) presented an overview of the role of epigenetics in patients with RA. He pointed out that the dysregulation of micro (mi)RNAs is associated with a number of metabolic and inflammatory pathway disorders. A number of miRNAs implicated in inflammatory arthritis, including miRNA-155, miRNA-203 and miRNA-323, were discussed. In discussion it was suggested that chronic inflammatory conditions may be perpetuated due to epigenetic signals originating with progenitor cells. Paul-Peter Tak (Amsterdam) used RA as an example of the continuum of disease in inflammatory disorders to make the point that identification of individuals with preclinical disease may provide a window of opportunity that could prevent progression towards clinically manifested disease; he also said that a better understanding of disease pathology may enable the recognition of disease onset, which may occur long before clinical diagnostic criteria are fulfilled. More specifically, he referred to a Synoviomics program and resultant biomarkers, epitope spreading of the humoral response against citrullinated peptides, the presence of activated T-cells in lymph nodes during preclinical RA, and the possibility of modifying environmental and

lifestyle risk factors. Yoichiro Iwakura (Tokyo) outlined the role played by interleukin (IL)-17, a C-type lectin receptor, and the complement system in RA models, the last leading to the proposal that CTRP6 is a potential target for RA therapy. Steven Ambramson (New York) presented an overview of what is known about the pathology of osteoarthritis and the contribution of inflammation. The relevance of the C5 component of complement was discussed, as was the observation that a number of inflammatory markers which can be measured in OA serum, such as prostaglandin E<sub>2</sub>, may predict disease progression.

### Nervous system

Trevor Owens (Odense) provided an overview of what is known about the pathology of multiple sclerosis (MS) and the occasional paradoxical results achieved with anti-inflammatory therapies. Despite a number of associations with inflammation, no molecule has yet been proven to be causative. Therapeutic strategies that regulate inflammatory cytokine responses in the CNS can alleviate MS-like symptoms in models; however, interferon- $\gamma$  (IFN $\gamma$ ) and anti-TNF- $\alpha$  therapy increase symptoms in humans. Stephen McMahon (London) reviewed the role of inflammatory mediators in chronic pain and the efforts to use anti-inflammatory therapies to relieve pain. He mentioned that the NGF antagonist, tanezumab, has shown some efficacy in the treatment of chronic OA pain and suggested that chemokines, such as CXCL5 and CCL2, may be worth exploring further. The neutralization of nociceptors appears to reduce signaling between nerve and immune cells; transcriptome analyses may suggest potential therapeutic targets.

### Lung inflammation

Bruce Trapnell (Cincinnati) provided an overview of the role that granulocyte macrophage-colony stimulating factor (GM-CSF) plays in lung inflammation and host defense. Its depletion by autoantibodies or receptor mutations can lead to pulmonary alveolar proteinosis; pulmonary macrophage transplantation therapy in mice appears to show benefit even after 1 year.

### Psoriasis

James Krueger (New York) outlined what is known about the disease mechanisms and therapeutic options for psoriasis. Transcriptome analyses showed >4,000 genes that may be regulated in disease; the IL-23/IL-17 pathway

appears to be particularly relevant based on clinical trials with neutralizing antibodies.

### Metabolic disease

Ajay Chawla (San Francisco) presented evidence that inflammation may serve as an adaptive response to metabolic stress. The link between obesity and the immune system appears to be the reallocation of nutrients stored in fat tissue that fuels the IL-4-driven alternative activation of macrophages in adipose tissue and governs body temperature maintenance.

## Resolution of inflammation and therapeutic approaches

A series of talks was devoted to the inhibition of inflammatory processes and diseases.

Charles Serhan introduced a group of molecules comprising resolvins, protectins and maresins, in particular the short-lived resolvins, RvD5 and RvD1. Such molecules contribute to the resolution of inflammation as an active process; incomplete resolution may mediate the transition of acute inflammatory events to a chronic state. Resolvins appear to act in a similar manner to glucocorticoids. Vibeke Strand (Palo Alto) reviewed clinical experience using biological therapeutics with respect to the relationship between immunogenicity, efficacy and safety, none of which can be easily predicted. A number of factors that influence immunogenicity were listed; differences in immunogenicity between biological agents may become increasingly relevant as biosimilar products enter the market. Immunotolerance induction regimes have been successfully implemented to improve long-term efficacy. Bing Yao (MedImmune) presented some MedImmune data on anti-cytokine antibodies in clinical development for the treatment of severe asthma, namely anti-IL-5 $\alpha$  receptor and anti-IL-13. Results from these studies may provide new insights into the pathogenic mechanisms involved in asthmatic disorders. William Westlin (Celgene Avilomics Research) gave an overview of the data associated with the Celgene Bruton's tyrosine kinase (Btk) inhibitor, CC-292, currently in clinical development. Btk occupancy by CC-292 correlates with Btk inhibition, cytokine production and disease-modifying activity in RA models. Alan Esekowitz (Abide Therapeutics) shared his views on the challenges within industry to innovation in drug discovery and the opportunities to nurture alternative approaches. Corporate culture often determines a company's ability to support innovation and nurture creative solutions, though size may also play a role. Abide Technologies has focused on identifying serine hydrolases with potential as therapeutic targets using covalent probes to detect inhibition of

enzymatic activity. Neil Graham (Regeneration Pharmaceuticals) provided an overview of a number of therapeutic agents that block Th2 pathways and have been investigated in patients with severe asthma, such as antibodies to IL-4, IL-5 and IL-13. Jose-Carlos Gutierrez-Ramos (Pfizer Inc.) summarized the positive data for some Pfizer drugs in development for inflammatory disorders (e.g. inflammatory bowel disease), namely the JAK-3 inhibitor, tofacitinib, and anti-MadCAM antibody (PF-00547659).

### Cytokines and inflammation

Some of the talks dealt with the role of certain cytokines in driving inflammation.

Pierre Miossec (Lyon) summarized the contribution that IL-17 makes to the chronic inflammation in RA patients by inducing the expression of other pro-inflammatory cytokines and other molecules involved in joint damage, such as the E3 ubiquitin ligase, synoviolin. By intervening early in the IL-17 pathway, the cycle of chronic inflammation and synovial damage might be avoided; the direct elimination of synoviocytes by apoptosis at later stages of disease might also slow or prevent further joint damage. George Hajishengallis (Philadelphia) presented data showing that Del-1, by its regulation of IL-17, may mediate local tissue homeostasis, and its loss of function with ageing plays a central role in the development of periodontitis, for example. Del-1 may also play a role in the link between periodontitis and other disorders such as RA. John Hamilton discussed the development of the concept that GM-CSF can be considered as a pro-inflammatory cytokine, rather than as a hemopoietic growth factor, with support provided by recent clinical trials in RA involving its targeting or that of its receptor by neutralizing antibody.

### Leukocyte populations and inflammation

There was a series of talks which focused on the role of leukocyte populations.

David Mosser (College Park) focused his presentation on the anti-inflammatory properties of regulatory macrophages that in this way appear to promote homeostasis. Following their development upon Fc receptor stimulation, their administration was able to inhibit experimental autoimmune encephalomyelitis (EAE) and lipopolysaccharide-induced lethality, suggesting a novel therapeutic strategy for autoimmunity/chronic inflammation. Filip Swirski (Boston) summarized the contribution extramedullary hematopoiesis makes to the development of atherosclerotic lesions. A significant splenic red pulp monocyte reservoir

was defined arising from IL-3- or GM-CSF-dependent clonal expansion of precursors. Klaus Ley (La Jolla) outlined some of the inflammatory processes in the aortic wall that contribute to the development of atherosclerosis. These were proposed to involve a MHC-II-dependent interaction between T cells and CD11c<sup>+</sup>-aortic myeloid cells that results in IFN $\gamma$  expression followed by foam cell formation. The inhibition by a functioning IL-27-dependent pathway appears to be mediated by reduction in IL-17 production. Lionel Ivashkiv (New York) provided insights into the transcriptional mechanisms that regulate cytokine production, particularly TNF and IL-6, in RA synovial macrophages; IFN $\gamma$  appears to play a central role in this process by increasing the magnitude and extending the transcriptional kinetics of cytokine production, utilizing epigenetic mechanisms to maintain active promoter complexes; possible therapeutic strategies were indicated. Frederic Geissmann (London) gave an overview of the possible relationship between fat metabolism, innate immunity and the activity of macrophages. His observations suggested that the response of macrophages (innate immune system) to high-fat dietary stress is a homeostatic reaction, and that diseases associated with a high-fat diet might be counteracted by targeting macrophages.

### Future perspectives

In addition to detailed discussion and incisive questions covering the specific topics, a number of “general” points arose with relevance to translational outcomes across the board, as well as to the profile of inflammation research. Besides the common issues facing industry/clinical academia with respect to efficient drug development for any disease, such as the need for early disease detection, disease definition, patient stratification to identify responders, and safety issues (see above), the conditions in which diverse systemic inflammation plays a significant role may in fact have overlapping mechanisms linked with this inflammation—as an example, such inflammation may provide the rationale for the associations between RA, cardiovascular disease and periodontitis. As a corollary, parallel studies in different inflammatory/autoimmune indications may provide insights into such disease mechanisms.

As regards what might be done to raise the profile of inflammation research with respect to journal impact factors, it was suggested that citations can be built up for “inflammation” articles by the publication, for example, of reviews, consensus statements or guidelines that are likely to be frequently cited, and also by establishing strategic alliances with professional societies with reasonably sized memberships. Researchers who work on topics related to

inflammation come from a variety of areas and they often do not consider themselves inflammation researchers—they probably do not belong to a professional inflammation society. Inflammation is so cross-disciplinary that, in order to draw interest, the focus for conferences/workshops may need to be on quite specific areas, and dialogue encouraged between those interested in, say, signal transduction, innate immunity and acquired immunity. A separation of inflammation from immunology may not be beneficial although an improvement in the profile of “inflammation” within the immunology community may be productive. A better understanding of the different mechanisms and interactions between inflammatory networks is needed, and more interdisciplinary communication is required at professional meetings. Interestingly, it was suggested that industrial researchers are often more accustomed to recognizing cross-disciplinary relationships, whereas academic researchers are often focused on a single disease.

The consensus was that similar forums should be held in the future with possible modifications being the pairing of perspectives from academia and industry on selected topics as well as the pairing of “bench” and “clinical” topics. Other constructive options were put forward such as the idea that a portion of a future program could be devoted to defined “hot” topics. Discussions emanating from future

meetings could evolve into compendium reviews on specific topics in high-ranking professional journals, clinical practice guidelines or recommendations to regulatory bodies. Industry attendees relished the opportunity to hear the latest research approaches to many diseases presented with outcomes in mind while academics appreciated the opportunity to present and discuss possible outcomes from their research, as well as to become informed about industry perspectives and therapeutic issues. The Summit reinforced the relevance of “inflammation” for many major diseases.

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