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Advancing the therapeutic potential of the IL-1 family in inflammatory diseases – Meeting report

On October 9th 2018 the Trinity College Dublin hosted a workshop forum at the Royal Irish Academy to discuss recent discoveries and current areas of focus in the field of IL-1 family biology. The aim of this meeting was to further efforts to target the activity of these cytokines in human diseases. Researchers from both academic and pharmaceutical industry backgrounds shared their expertise and insights into the latest developments in what is a field of continued intense basic scientific discovery and emerging drug development.

The early seminal discoveries of Dinarello and colleagues in identifying IL-1 as a soluble endogenous pyrogen can justifiably be cited as one of the defining moments in the genesis of the field of cytokine biology [1]. This work paved the way for subsequent discoveries of evolutionarily related cytokines which are now grouped into the broader IL-1 family consisting of seven agonist ligands (IL-1α/β, IL-18, IL-33 and IL-36α,β,γ) as well as three specific antagonists (IL-1Ra, IL-36Ra and IL-38) and a single anti-inflammatory member (IL-37) [2]. IL-1 family cytokines have been shown to play centrally important, and sometimes instructive roles, in regulating the interface between innate and adaptive immunity [3]. Somewhat paradoxically, they have also been described as often playing dichotomous roles in driving both inflammation and resolution depending on the disease setting [4]. As a result, these cytokines, and in particular, the specific inflammatory responses which they mediate are an area of intense investigation across academic as well as pharmaceutical drug development perspectives.

The rationale for targeting the IL-1 family in human disease is underpinned by the development of inflammatory states in humans suffering from rare monogenic autoinflammatory conditions with genetic defects leading to altered expression/activity of IL-1 cytokines. Indeed, this is validated by the success of biologics to target IL-1, such as Anakinra, a recombinant IL-1 receptor antagonist that binds the IL-1 receptor to impede binding of IL-1β and IL-1α, in conditions known to be IL-1β mediated inflammatory processes [5]. Furthermore, given their apparent prominent roles in driving more common chronic inflammatory diseases, it seems likely that strategies aimed at inhibiting specific IL-1 family member activity may achieve more significant results. This is perhaps best exemplified by the recent CANTOS study, one of the largest phase III clinical trials ever established, investigating the efficacy of the monoclonal anti IL-1β antibody canakinumab,to prevent secondary cardiac events among cardiovascular disease patients [6]. The results of this trial have confirmed the contributory role for inflammation, through an IL-1β mediated process, as an important driving factor in the pathogenesis of atherosclerosis, a concept which has long been suggested through pre clinical studies, opening the door to new even more specific modes of therapeutic intervention among patients.

Against this background, experts with a diverse perspective of IL-1 family biology in various disease settings gathered in Dublin to discuss the potential of targeting this family of cytokines across a range of inflammatory diseases. Specific topics addressed included the apparent dichotomous roles of the IL-1 family in intestinal inflammation and the role of IL-1 family members as mediators of skin inflammation in the settings of psoriasis and atopic dermatitis. Novel insights on the beneficial effects of modulating IL-1 family activity in age related diseases such Alzheimer's disease and Age related Macular Degeneration were also discussed as were recent discoveries surrounding mechanisms which regulate IL-1 family activity, including negative regulatory pathways, cellular metabolism and endogenous protease activity. These findings were placed into translational context with an overview of the current drug development landscape in terms of active clinical programmes aimed at targeting IL-1 family members as well as insight into the complexities of efficient trial design to ensure optimal successful outcomes for patients.

The dichotomous roles of IL-1 family members in intestinal inflammation and homeostasis

A recurrent theme discussed during the workshop was the apparent dichotomous role of IL-1 family members in gut inflammation particularly in the context of inflammatory bowel disease (IBD). Such context dependent roles have been reported for all IL-1 family members to date with the most recent data presented by Tim Denning (Georgia State) highlighting similar findings for IL-36 cytokines. Whether IL-36 can drive proinflammatory or proresolving mechanisms in intestinal inflammation is dependent on the acute or chronic nature of the experimental models employed, as well as the type of pathogenic cellular responses under analysis. While IL-36γ acts to promote epithelial barrier resolution in the innate DSS model of disease, it can also act to enhance pathogenic Th9 responses and restrict Treg function in the gut leading to an exacerbated disease phenotype in a T cell dependent model [7, 8]. The pathogenic nature of IL-36 driven intestinal T cell responses were also

highlighted by Pat Walsh (Trinity College Dublin), who also described how IL-36 cytokines can alter the composition of the intestinal microbiome which may account, at least in part, for the apparent opposing roles of these cytokines in gut homeostasis and inflammation [9]. These presentations addressed the role of IL-36 cytokines in patients with IBD, highlighting the importance of studies on clincal cohorts. Kevin Maloy (University of Glasgow) reported similar findings investigating the role of IL-18 as a key instructive signal in regulating the homeostasis of Th17 cells and the activity Treg subsets within the gut in both the steady and in the setting of inflammation [10]. Further insight was also provided into the role of inflammasome components NLRC4 and NLRP3 as potential activators of IL-1β and IL-18 in response to intestinal infection [11].

Targeting IL-1 family cytokines in dermal inflammation

A common feature of several monogenic autoinflammatory conditions resulting from altered IL-1 cytokine activity has been the manifestation of often severe inflammatory episodes in the skin. Such observations have underscored efforts to investigate IL-1 family members as potential targets for more common skin conditions such as psoriasis and atopic dermatitis (AD). Using an elegant mouse model of spontaneous eczematous inflammation [12], Padraic Fallon (Trinity College Dublin) presented data analyzing the relative roles of all IL-1 family cytokines as mediators of type 2 dermal inflammation in the setting of AD. Seamus Martin (Trinity College Dublin) described how IL-1 family cytokine activity can be modulated through proteolytic cleavage by neutrophil derived proteases in the setting of psoriatic inflammation. The activity of IL-36 cytokines is of particular relevance in this regards given their reported roles as orchestrators of psoriatic inflammation [13].

Emerging areas of investigation in IL-1 family biology

In addition to the tissue specific disease settings described above, several attendees described more recent discoveries on IL-1 family biology with broader implications for understanding and treating human disease. As critical regulators of inflammation, several distinct mechanisms to control IL-1 family responses have evolved to restrict inappropriate inflammatory responses. Leo Joosten (University of Nijmegen) provided an update on the most recent advances in understanding the role of negative regulatory IL-1 family receptors, IL-1R8 and IL-1R9, describing how they can potentially play a novel role as co-receptors for immunosuppressive IL-1 family members IL-37 and IL-38 [14]. In the emerging field of immunometabolism, Luke O'Neill (Trinity College Dublin) described recent advances on the interplay between IL-1β expression and activity and its regulation by metabolic intermediates of the Krebs cycle. The recent identification of specific mechanisms through which succinate can sustain IL-1β expression through stabilization whereas itaconate can suppress IL-1β expression through modulating the activity of the transcription factor Nrf2 is opening new horizons with regard to how IL-1 family activity may be modulated in a therapeutic setting [15, 16]. Similarly the identification of how chloride channels play a central role in NLRP3 activation through mediating ASC oligomirization as described by David Brough (University

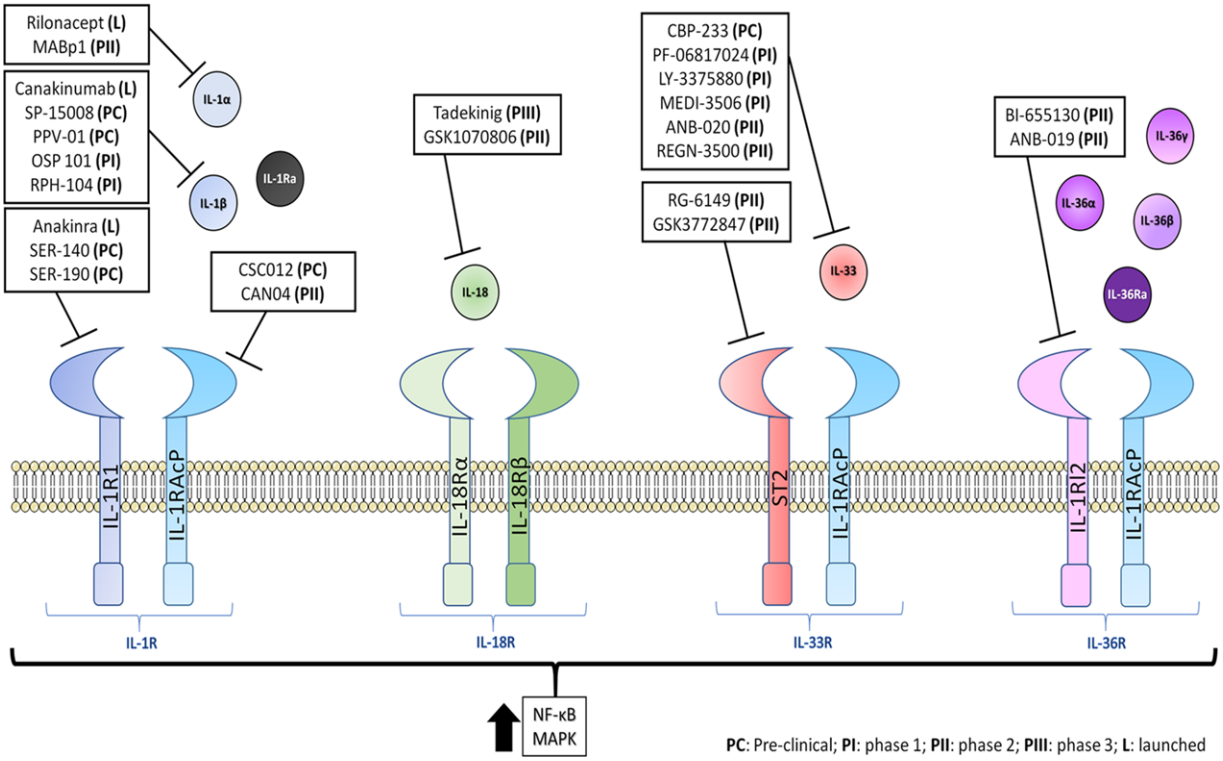

Figure 1. Current therapeutic entities in the clinic and across various stages of development targeting specific IL-1 family members for a range of inflammatory conditions.

of Manchester), has revealed a key step in inflammasome mediated activation of IL-1 family members with direct relevance to a range of chronic inflammatory diseases including neurological disorders such as Alzheimer's disease [17].

Current drug development landscape

Unsurprisingly the IL-1 family of cytokines continues to garner significant attention as possible targets for a wide range of inflammatory conditions. Sarah Doyle (Trinity College Dublin) described a new programme of preclinical validation of the use of recombinant IL-18 as a novel adjunctive therapy for age related macular degeneration offering a possible new therapeutic avenue for a disease which affects millions worldwide [18]. Devon Taylor and Alison Humbles (MedImmune) brought an invaluable translational perspective to the workshop in providing an update on the current clinical drug development pipeline across the pharma sector. While efforts to target the prototypical family member IL-1β have progressed to the clinic in the form of neutralizing monoclonal antibodies eg. canakinumab and the recombinant IL-1R antagonist (anakinra), significant efforts aimed at targeting both IL-18, IL-33 and IL-36 members are also at advanced stages of clinical development for a range disease indications such as asthma, psoriasis and IBD (Figure 1). The difficulties in achieving clinical trial endpoints were also illustrated using the example of targeting IL-1 Receptor 1 in chronic obstructive pulmonary disease as a case study [19]. The requirement for a deeper understanding of patient phenotypes in disease was identified as a necessary step to achieve significant impact in clinical trials. The recently completed CANTOS study was cited as an example of such an approach with continued outcomes being reported with potential significant clinical impact such as targeting IL-1β in certain types of malignancy [20].

Future perspectives

After a full day of comprehensive evaluation of the state of the art in the field of IL-1 family cytokines in inflammatory disease, discussion and discourse continued over a pint of Guinness as is customary in Dublin. The sharing of knowledge and expertise among attendees provided an excellent forum to evaluate current gaps in our understanding surrounding the how, why and where IL-1 family cytokines represent such centrally important mediators of human disease. While the translation of fundamental research discoveries in this area has already yielded significant impacts on patient health, such advances are likely to continue as we understand more about how this family of cytokines act as critical regulators of the inflammatory response.

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Yasmina E. Hernandez-Santana[1,2], Devon K. Taylor[3], Alison Humbles[4] and Patrick T. Walsh[1,2]

[1] National Childrens Research Centre, Our Ladys Childrens Hospital Crumlin, Dublin, Ireland
[2] Trinity Translational Medicine Institute, School Of Medicine, Trinity College Dublin, Ireland
[3] Cancer Biology, Research & Development, Medimmune LLC, One MedImmune Way, Gaithersburg, MD 20878, United States
[4] Department of Respiratory, Inflammation and Autoimmunity, Medimmune LLC, Aaron Klug Building, Granta Park, Cambridge, CB21 6GH UK

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Full correspondence: Dr. Patrick T. Walsh, National Childrens Research Centre, Our Ladys Childrens Hospital Crumlin, Dublin, Ireland.
e-mail: walshp10@tcd.ie

