Conference Report Editor: Samantha Barton
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Inflammation and immune diseases: what is at the summit?

Inflammation & Immune Diseases Drug Discovery & Development
Philadelphia, PA, USA
14–15 March 2005

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The *Inflammation & Immune Diseases Drug Discovery & Development Summit* held on 14–15 March 2005 in Philadelphia, PA, USA, brought together academics discussing fundamental studies in a range of biological models and industrial scientists describing progress at all stages of drug development. The sessions were characterized by openness and enthusiastic discussion, a willingness to discuss positive progress and also acknowledge where initial high promise (e.g. targeting chemokine receptors) might not yet have been fully realized. Slick organization and three keynote speakers of the highest calibre, Charles Dinarello, David Crossman and Peter Lipsky, contributed to an unequivocally successful event. Key themes were interleukin (IL)-1 biology, application of humanized monoclonal antibodies (MAbs) and novel small molecule inhibitors of signalling pathways [e.g. p38α mitogen-activated protein (MAP) kinase].

Interleukin-1 biology

Our understanding of cytokines in inflammation in general, and the potential for cytokine therapy in particular, owes much to the groundbreaking work performed by Charles Dinarello and colleagues over the past two decades. Application of IL-1 blocking agents, such as IL-1 receptor antagonists (IL-1Ra), has been successful in many diseases, but particularly in systemic inflammatory diseases (e.g. Still's and Muckle-Wells), where more than 100,000 patients have been treated without adverse reactions. The contribution of IL-18, which induces production of interferon-γ (IFN-γ), to inflammation should not be underestimated, and, as well as being a promising target, this cytokine is diagnostically useful: urinary IL-18 levels predict acute renal failure 48 h ahead of creatinine levels. In addition, IL-18 binding protein reduces ischaemic reperfusion injury. The proinflammatory cytokine family continues to grow and IL-32, a cytokine induced by IL-18 and IFN-γ in lymphoid tissue, could be a future target [1]. A striking finding presented by Dinarello concerned the eukaryotic initiation factor (eIF)-5A protein. Levels of eIF-5A increase dramatically during ischaemia and parallel IL-18 levels in the heart. In murine models, eIF-5A-directed short interfering RNAs attenuate lipopolysaccharide (LPS)-induced tumour necrosis factor-α (TNF-α) synthesis, systemically and in the heart, and block neutrophil accumulation in the lung following LPS inhalation.

A key goal of IL-1 antagonism is to block responses at endothelial surfaces, particularly in atherosclerosis, a condition likely to increase in prevalence as obesity and sedentary lifestyles take their toll on ageing Western populations. David Crossman (University of Sheffield, UK) presented an erudite and compelling case, based on animal models and differential gene expression (DGE) studies in humans, that IL-1 antagonism is a highly attractive strategy for treating vascular disease. A DGE screen of tissue derived from patients with ischaemic heart disease revealed a striking upregulation of IL-1α and IL-1β that is not observed in equivalent tissue from patients undergoing, for example, valve replacement. High cholesterol levels were noted in apolipoprotein (apo) $E^{-/-}$ and IL-$1R^{-/-}$ mice fed high-fat diets, but the F1 animal showed strikingly lower levels than the apo$E^{-/-}$ mouse, suggesting IL-1 has a role in the regulation of cholesterol levels. Neointima formation (a new layer of endothelial cells on the intimal surface of a blood vessel graft or vascular prosthesis), studied either using a carotid tie model in mice or balloon angioplasty in pigs [2], is reduced by blocking IL-1 action in either species. A sustained protective effect against neointima formation is achieved if IL-1Ra is administered for several weeks following angioplasty. Reductions in neointima formation in caspase $1^{-/-}$ and $P2X7^{-/-}$ mice, both of which show reduced release of IL-1 from endothelial cells, clinch the argument for targeting IL-1 in atherosclerosis.

Humanized monoclonal antibodies: applications in inflammation and immune-related diseases

Peter Lipsky (National Institutes of Health) is the ideal speaker to champion the important role B cells play in autoimmune disease and the application of MAbs in treating inflammatory and immune system-related

1359-6446/05/$ – see front matter PII: S1359-6446(05)03478-1

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diseases. Lipsky stressed that these plasma cells, which secrete the autoAbs that damage tissues directly and indirectly, must not be forgotten. On a lighter note, Lipsky's wry observation that, in the context of differentiation, 'only immunologists could devise T1 and T2 as labels for transitional B cell types' was particularly well judged. Transitional B cells are accepted subsets in murine B cell development, but their unequivocal identification in humans has proved less easy. Nine-colour cytometry defines the human T1 subset as, broadly, $CD10^{++}$, $CD21^{+}$, $CD24^{+}$ and $CD38^{++}$ [3]. T1 levels do not change dramatically following immunization, but plasma cell numbers rise strikingly. Moreover, plasma cell levels correlate with disease activity, with the $CD27^{bright}$ subset of long-lived plasma cells being greatly increased in lupus flares. Rituximab, an anti-CD20 MAb, has positive effects in the treatment of rheumatoid arthritis (RA), where it depletes not only B cell numbers, but also autoAb levels in treated individuals. However, in systemic lupus erythematosus (SLE) patients, rituximab reduces B cell numbers but not anti-DNA autoAb levels. AutoAb-producing cells in RA come from a continuously replenishing pool of $CD20^{+}$ cells, whereas autoAb producing cells in SLE are $CD20^{-}$ long-lived plasma cells that are not recognized by rituximab. Consequently, although B cell numbers are reduced in SLE, the levels of autoAb responsible for tissue damage remain undiminished. Alvin Wells (Lakeshore Medical Clinic, USA) indicated that the specificities of autoAb in patients can be of predictive value; the presence of anti-cyclic citrullinated peptide antibodies consistently predicts development of erosive disease.

As well as rituximab, other humanized MAbs were discussed. Lipsky went on to describe tacilizumab (anti-IL-6), which shows benefit in two RA trials, and a single SLE trial suggests the MAb is safe and ameliorates disease via reductions in levels of IgG3 anti-nucleosome autoAbs and normalization of B cell subsets in treated subjects. Wells presented data on the effects of belimumab, which binds B lymphocyte stimulator, thus reducing circulating B cell numbers: belimumab is currently progressing through Phase I clinical trials. An anti-human IL-12p40 MAb that reduces murine trinitrobenzesulfonic acid-induced colitis and is also at an advanced stage of Phase I trials was described by Trudi Velman (Abbott). Vladmir Vexler (Protein Design Labs) discussed visilizumab, an anti-CD3 MAb that causes a rapid and transient decrease in T cell levels *in vivo* and shows positive effects in ulcerative colitis. Wells and Lipsky separately described an anti-CD154 (CD40 ligand) reagent that proved unsuccessful because of unexpected problems with thrombotic events.

Proinflammatory protein kinase targets

Protein kinases rightly receive considerable attention as therapeutic targets and the components of MAP kinase cascades have been particularly well studied. The p38α kinase is particularly important because it regulates proinflammatory cytokine release in response to extracellular stimuli. Ramon Mohanlal (Vertex) described VX702 [4], which inhibits p38α specifically *in vitro* and, *in vivo*, is active in ischaemic heart disease and reduces myocardial infarct size in animal models. In Phase I trials, VX702 showed a long half-life and reduced LPS-stimulated production of IL-1β, TNF-α and IL-6 in whole blood assays. In Phase II trials, VX702 reduced C-reactive protein levels following angioplasty in a dose-dependent manner. Dipyrazole-based inhibitors of p38α were described by James Monaghan (Pfizer). The prototype compounds are ATP-binding site competitors, they bind active and inactive p38α, block cytokine release and cyclooxygenase (COX) 2 expression *in vitro*, and attenuate collagen-induced and streptococcal cell wall-induced arthritis *in vivo*: Phase I trials are extremely encouraging. A second group of inhibitors, derived by screening a library of some two million triaminotriazine compounds, was outlined by Maria Webb (Pharmacopeia). These compounds show a strong preference for a methylbenzamide group on the triaminotriazine scaffold, with further improvements in potency being achieved by substituting a cyanopyrimidine moiety for the triazine [5]. The lead compounds are ATP-binding site competitors, show strong selectivity for p38α *in vitro* and, when administered orally, inhibit LPS-driven increases in circulating TNF-α levels. Finally, Jim Karras (ISIS) described the development of antisense oligonucleotides (ASOs) bearing 2-*O*-methoxyethyl (MOE) modifications to protect against ribonuclease degradation *in vivo*. When administered intranasally, MOE p38α ASOs attenuate kinase activity in mice challenged with ovalbumin as an aeroallergen [6] and reduce allergen-induced CD86 expression by airway dendritic cells and eosinophils. In chronic asthma, the ASOs decrease the level of mucus in airways and granulocyte accumulation in the lung in allergen-challenged animals. Delivery is a particularly high hurdle for ASOs, but Steven Panzner (Novosom) presented new liposome-based molecules, called 'Smarticles', (www.novosom.com/00inhalt/02smarticles/01smarticles.html; [7]) that might enhance the bioavailability of ASOs in tissues.

More targets

Small molecule inhibitors targeting the two pathways leading to NF-κB activation and Janus kinase 3, which are key regulators of proinflammatory gene expression, were described by Guoging Chen (Amgen) and Maria Webb (Pharmacopeia), respectively. Martin Braddock (AstraZeneca) reviewed alternative strategies for targeting release of IL-1β by antagonism of the P2X7 receptor and described progress with such antagonists in Phase II trials for RA and osteoarthritis, whereas Derek Gilroy (University College London, UK) elegantly revisited the detailed mechanism of action of aspirin, via epi-lipoxins, in inhibiting inflammation [8]. Finally, breathtaking studies using two-photon imaging to track 3D movement of lymphocytes and dendritic cells *in vivo*, presented by Paul Garside (University of Glasgow, UK), challenge us to re-consider what we think we know about the real cellular dynamics of immune responses.

What next?

It is quite clear that no single class of drug will be overwhelmingly superior to all others in combating inflammatory disease. Small molecule receptor and enzyme antagonists will continue to be in the vanguard of new drugs, but humanized MAbs are proving to be excellent therapeutics, with few side-effects. Soluble cytokine binding proteins, exemplified by anakinra, are impressively powerful agents

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with IL-18 and, potentially, IL-32 being probable future targets for this approach. Antisense strategies hold much promise and efforts to improve bioavailability, by enhanced stability or better delivery, will accelerate application of these compounds. Next year will be the tenth anniversary of this conference, and it promises to be just as exciting and informative as this year's event.

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private prescription

Jargon: the twittering of scientists and medics

A thought-provoking tonic on the lighter side

Column by Raymond C. Rowe, AstraZeneca, UK

Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

Galen, the Greek physician who founded experimental physiology and is one of the most distinguished physicians of antiquity, commented in his work *On the Natural Facilities* (written in the second century AD) [1]: 'We, however, for our part, are convinced that the chief merit of language is clearness, and we know that nothing detracts so much from this as do unfamiliar terms.'

I wonder what he would have said about the proliferation and incessant use of jargon in science and medicine today.

Etymology

The word jargon is descended from the old French word 'jargoun', denoting the meaningless chatter and twittering of birds. However, it was not until mediaeval times that it was applied to unintelligible or meaningless talk or writing, and it was not until the mid-1600s that it was applied contemptuously to the language of scholars or the terminology of science [2]. Of course, the word meaningless has to be qualified – meaningless to whom? Jargon might be intelligible to a specific group of people but unintelligible to outsiders and, therefore, can be used to ensure secrecy and conceal the truth. Jargon can be applied across the whole spectrum of language, for example, using long complicated words where smaller simpler ones would suffice, acronyms, abbreviations and initialisms, and metaphors – indeed, anything that causes confusion either intentionally or unintentionally. A limerick that sums this up perfectly is [3]:

Ad-i-ad-o-cho-kin-e-sis
Is a term that will bolster my thesis,
That 'tis idle to seek
Such precision in Greek,
When confusion it only increases.

Incidentally, adiadochokinesis is the ability to perform rapid alternate movements such as winding up a watch.

Medical jargon

Everyone is aware of medics' insistence on using long complicated words to describe, for example, diagnoses and surgical techniques. Indeed, even simple techniques can be jargonized, as so aptly stated by Oliver Wendell Holmes (1809–1894) [4]: 'I know there are professors in this country who 'ligate' arteries.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03463-X