Immunomodulation 3/10/05 19:45 Page 19

IMMUNOMODULATION emerging from obscurity into a major therapeutic class

While not initially apparent, immunomodulation is high on the pharma agenda if recent deal making is a valid indicator. This article discusses the potential of immunomodulation to rise from the relative obscurity of adjuvants in vaccines to mainstream therapies that can be used across major disease areas such as cancers and viral infections.

By David Gee

Four of the biggest deals announced so far this year, forged between pharma and biotech, were based around immunomodulation technologies. These deals have ranged from single products for single indications, to deals within marketing territories and even full-blown company acquisitions. They have covered various disease areas including cancer, vaccines, and antivirals for HIV and HPV.

These transactions topped out with the $570 million licensing deal between Novartis and Anadys Pharmaceuticals in June this year covering hepatitis B and C. Coley Pharmaceuticals struck a $515 million licensing deal with Pfizer to develop a cancer product in March. At the end of April GlaxoSmithKline acquired Corixa for $300 million gaining a portfolio of immunomodulators and finally another March deal between 3M Pharmaceuticals and Takeda formed a joint marketing agreement covering Japan and Asia for a potential topical treatment for cervical high-risk human papillomavirus (HPV) infection and cervical dysplasia. When seen in isolation, what is not immediately apparent is that all these revolve around immunomodulation technologies.

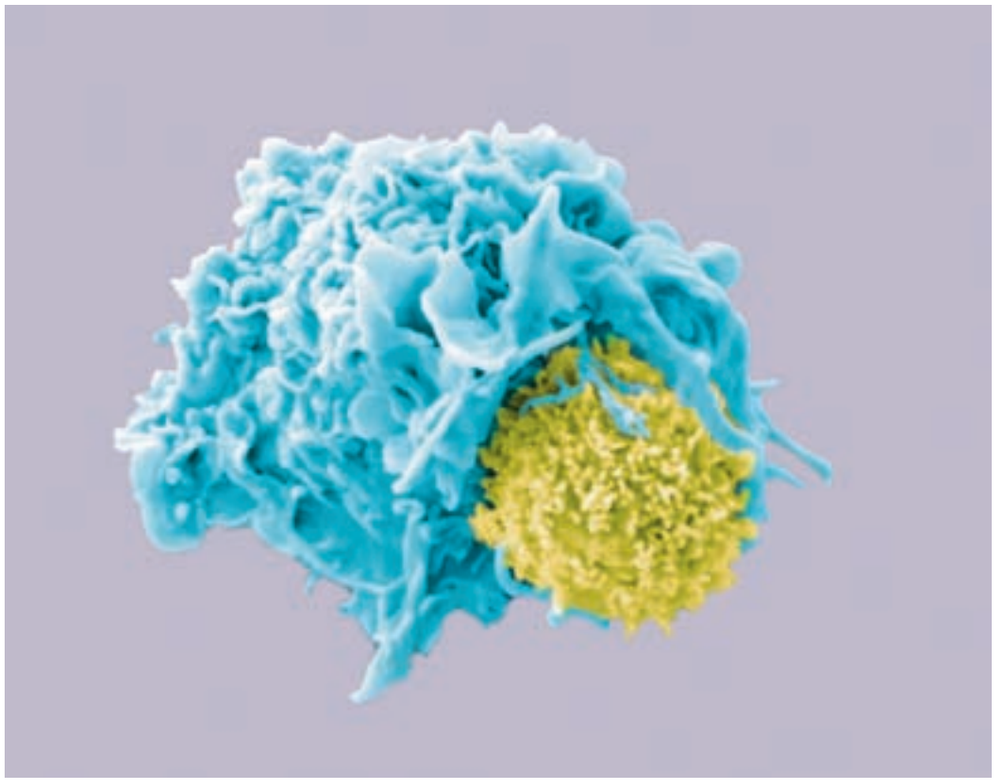
These deals have undoubtedly created a hidden momentum in the area of immunomodulators and are unlikely to be the last. There is still a series of pharma companies yet to enter the game on this scale, meanwhile only a limited number of biotech companies are stepping up to the plate with new technologies and approaches to this aspect of immunotherapy. The majority of new immunomodulators in development are complex molecules that act as Toll-Like Receptor (TLR) agonists. As such, it is likely that while further deals based around immunomodulation technologies will inevitably be struck, only few opportunities exist to acquire true novelty in terms of new mechanisms of action and to progress to small molecules. Thus, the opportunities for major plays in this emerging area, such as that seen by GSK and Pfizer, are currently limited.

When looking over these deals and recent developments in the field it is evident that immunomodulatory technologies are evolving. However, what has yet to fully emerge are the deals and technologies around small molecule immunomodulation.

The deals

Anadys' deal with Novartis was an exclusive global licence and co-development agreement for ANA975, a toll-like receptor 7 (TLR7) oral prodrug for chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. The deal also covered other TLR7 agonists, with the scope to

Immunomodulation 3/10/05 19:45 Page 20



Coloured scanning electron micrograph showing interaction between a dendritic cell (blue) and a T lymphocyte (yellow), two components of the body's immune system. Dendritic cells are antigen-presenting cells (APCs), which present antigens to T lymphocytes. T lymphocytes recognise a specific antigen, bind to it and produce antibodies or cells to eliminate that antigen. MNLpharma's imino sugar compounds have demonstrated elicit potent immunomodulatory effects, including effects mediated through dendritic cells and macrophages. These effects are harnessed in the development of new immunomodulatory drugs for the prevention and treatment of disease. *Illustration courtesy of Dr Olivier Schwartz, Institut Pasteur/Science Photo Library*

move into other infectious disease indications. The product, currently in Phase I, brings a new immunomodulatory approach to Novartis' antiviral and hepatitis programme.

The Coley/Pfizer global exclusive marketing and development deal covers ProMune (CPG 7909), a toll-like receptor 9 (TLR9) agonist delivered by subcutaneous injection for the potential treatment, control and prevention of cancers in humans. ProMune is a synthetic bacterial oligonucleotide that induces a cytokine response. The programme is currently in Phase II for non-small cell lung cancer, melanoma and cutaneous T Cell lymphoma. Through the deal, Pfizer bolsters its oncology pipeline, currently its second largest area of research investment.

GSK's acquisition of Corixa brings the pharma company an array of immunomodulatory adjuvants for infectious diseases, cancer and allergies. The key product in the deal was MPL, Corixa's lipid A derivative found in gram-negative bacteria. MPL is approved in Europe for use with Fendrix, GSK's hepatitis B vaccine, and is in development with two other late-stage GSK vaccines: Simplirix, a vaccine for genital herpes, and Cervarix, a cervical cancer vaccine that targets the human papillomavirus. GSK's acquisition of Corixa brought in-house existing collaborations with Corixa, and gave it access to other applications of the MPL adjuvant technology.

Finally, Takeda and 3M struck an exclusive joint development and marketing agreement around a topical treatment for cervical high-risk human papillomavirus (HPV) infection and cervical dysplasia. The compound, currently in Phase I development, is part of the family of small molecules that 3M term "immune response modifiers". 3M currently markets Aldara (imiquimod) Cream 5%, an IRM for the treatment of actinic keratosis, primary superficial basal cell carcinoma, and external genital and perianal warts. This is the first small molecule immunomodulator to hit the market, but is currently only used topically, the desirable oral form has yet to emerge.

The history

This new wave of enthusiasm for immunomodulators is coming from earlier successes in the field. There have been a series of immunostimulants, predominantly revolving around cytokines, which have carved large market revenues in tackling acute and chronic diseases. Among others, interferon alpha, which Roche markets under the name Roferon-A, is for the

Immunomodulation 3/10/05 19:45 Page 21

treatment of chronic hepatitis C, hairy cell leukaemia and chronic myelogenous leukaemia; interferon beta, in the shape of Avonex from Biogen, now Biogen Idec, is marketed for the treatment of multiple sclerosis, and Actimmune, an interferon gamma from InterMune, is for the treatment of Chronic Granulomatous Disease, and severe, malignant Osteopetrosis.

However, these early cytokines have well recognised side-effects. The primary cause for these side effects is that cytokines are involved in many signalling processes throughout the body. While administration of a pure cytokine does give a massive signal to the immune system and a beneficial immune response is invoked, such administration creates a major spike in the cytokine blood concentration which initiates other, unwanted, signalling pathways. These pathways invoke side-effects that can include depression, gastro-intestinal distress, nausea, abdominal pain, flu-like symptoms, and injection site reactions.

The technology behind the deals

Despite these side-effects, this class of drugs are highly valued and the clinical needs are clearly defined. Given the nature of the diseases they treat, both chronic and fatal, such side-effects are acceptable. However, removal or even reduction of the side-effects would make chronic treatment, as with hepatitis C or multiple sclerosis, far more tolerable for the patient.

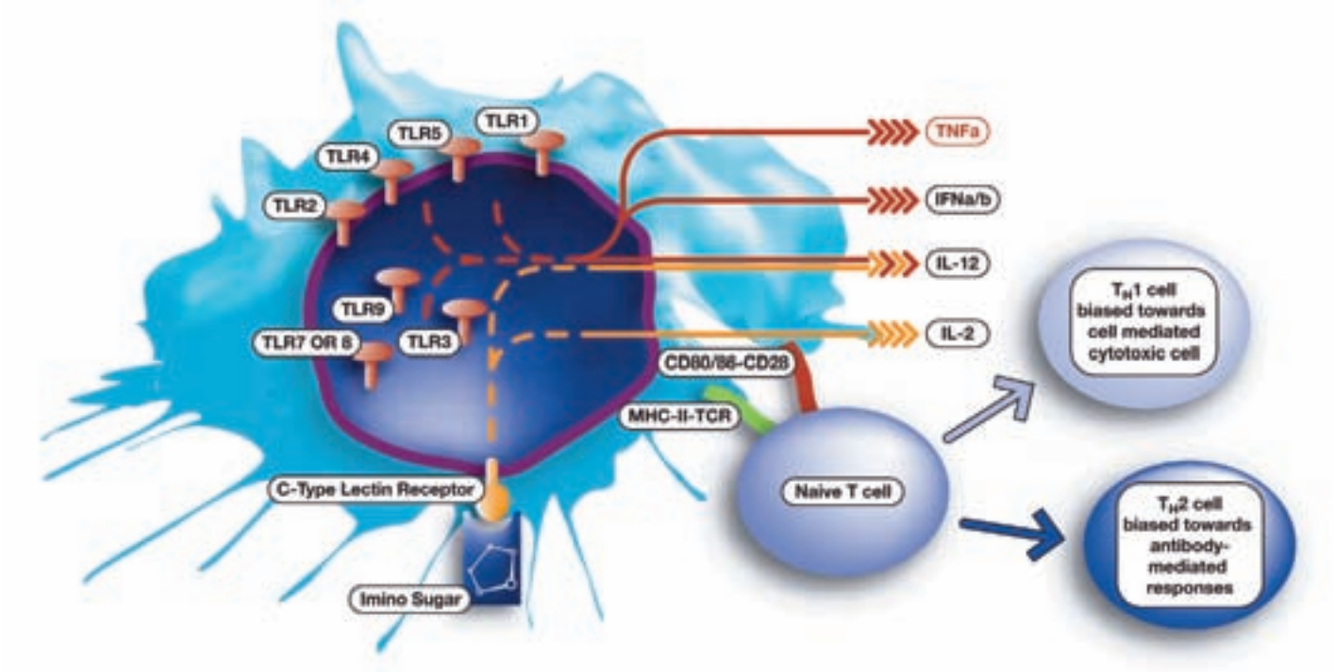
And indeed, the next stage of development in immunomodulation was able to tackle precisely this issue. CpGs, sequences of DNA that mimic bacterial DNA, are able to produce a more controlled release of the body's own cytokines. The deal between Coley and Pfizer on ProMune adopts this technology. ProMune, and other CPG-based drugs, target the toll-like receptor 9 (TLR9) usually found inside dendritic and B cells.

In a natural setting, stimulation of a TLR, either on the surface or inside a dendritic cell, would instigate a full cytokine response. The secreted cytokines act as chemical messengers to modulate an effective anti-microbial immune response.

It is this mechanism that CpG-based drugs exploit to gain therapeutic results. The primary advantage of this approach over injection of pure interleukin is that dendritic cells release a controlled level of interleukin. As a result many of the side-effects seen with interleukin injections do not arise with CpGs, without loss of efficacy.

However, CpGs do activate secretion of TNF alpha, a proinflammatory cytokine that can give

Immunomodulation 3/10/05 19:45 Page 22



Immunopotentiators including adjuvants currently used in vaccines, other adjuvants in development and immunomodulators elicit an effect by stimulation of one or more Toll-Like Receptors (TLRs). These result in beneficial IL-12 release as well as release of cytokines with less-desirable, toxic effects. It is thought that MNL compounds act via C-type Lectin receptors or 'sugar receptors' that the Dendritic Cell uses to identify glycoprotein patterns on cells to identify those that are foreign to the host. Stimulation of these receptors by MNL compounds elicits IL-12 and IL-2 release – a beneficial cytokine profile for immunopotentiators

rise to undesired toxic side-effects. Again, while this is an unwanted side-effect of TLR agonists, it would be acceptable in the treatment of cancer, as is the case for ProMune. However, such an approach may not be appropriate for chronic disease as prolonged treatment may have long-term repercussions.

CpGs have marked an important step forward despite a number of limitations. However, there are still advances to be made in the field above and beyond those that have been subject to these landmark deals.

The acquisition of Corixa by GSK stems from earlier deals with vaccine adjuvants. All these adjuvants are based on MPL, lipid extractions and components of bacterial cell walls. These compounds target TLR4, located on the surface of dendritic cells, which is stimulated by components of the membranes of gram negative bacteria.

The company also has in earlier stage development RC-529, a synthetic analogue which emulates MPL. Being synthetic, this is easier, cheaper, and more reliable in manufacture.

An advantage of these MPLs is that they target a receptor on the surface of the dendritic cell. This is an easier target as any drug does not have to pass through the dendritic cell membrane. Additionally, compounds that target internal receptors (such as TLR7), have the possibility to disrupt other pathways within the dendritic cell, which would result in further side-effects.

What's left to explore

It is clear that considerable progress has been made in immunomodulation; both in the sophistication of immunomodulating compounds, and an understanding of the biological principles underlying the discipline. Indeed, from the early days when immunomodulators were only considered a vaccine adjuvants, it is now clear that immunomodulators are moving into the territory of stand alone therapeutics.

Logically, the next stage in the development of the field beyond CpGs would be to move towards orally available small molecules that evade the less favourable proinflammatory cytokine responses. One product, that is part way to the solution, is Aldara (imiquimod), at the centre of the Takeda-3M deal. This is the first small molecule immunomodulator to reach the market. Aldara targets the internal TLR 7/8 receptors and is marketed as a 5% topical cream to treat genital warts (HPV), actinic keratosis and superficial basal cell carcinoma. However, Aldara does still invoke the less desirable TNF alpha response and targets the internal TLR 7/8 receptor.

Moving closer to the solution is a class of compounds called imino sugars. These are orally available, small molecules that target a separate family of receptors on the dendritic cells, sugar receptors that are thought to be involved in detecting 'foreign' sugar patterns on the surface of pathogens. This represents a whole area of

Immunomodulation 3/10/05 19:45 Page 23

immunomodulation yet to be fully explored but which is showing great promise.

While MNLpharma do not disclose the precise mechanism of action (MOA) for these compounds at this time it is known that they invoke immune responses that seem to lack proinflammatory cytokines. Early research indicates that these novel compounds induce both and IL2 and IL12 response, whereas the TLRs commonly produce IL12 only.

MNLpharma is emerging as a key player in the field of immunomodulation using imino sugars. It has two main programmes based on two lead compounds. MNLP462a is an imino sugar that has been selected as an anti-cancer immunomodulator. Its activity as an orally available, small molecule immunomodulator promises use as a broad-spectrum anti cancer agent. On the basis of preclinical studies, the company believes it will have efficacy against a number of different cancers at different stages of disease. The additional advantage of MNLP462a is the promise that it will be well tolerated, allowing it to be used concurrently with other cancer therapy regimens. MNLP462a is expected to enter the clinic towards the tail end of 2006. MNLpharma also has a vaccine adjuvant in development, MNLP24, which acts through the very same receptor system and which is being explored in a number of different vaccine and immunotherapy settings with a number of strategic partners.

While this is early research, it is clear that delving deeper into the mechanisms of immunomodulation is throwing up new possibilities. With more favourable cytokine profiles, it appears as though these sugar receptors may well make better targets than TLRs. Alternatively, this new class of immunomodulators may be found to be synergistic to other types of immunomodulator. Blending various receptor agonists in the development of new vaccines is a concept in research at many vaccine companies and the availability of a whole new set of compounds acting via another receptor group is likely to open up a whole new set of possibilities for immunomodulation.

The pharmaceutical industry consistently prefers small molecules in drug development as they are cheap to manufacture and frequently orally available, but such compounds haven't appeared as quickly as expected in immunomodulation. However, the size of recent deals in the field suggest that the financial drivers for such technologies are building, and there is no doubt limited opportunities for small molecule technologies are there, awaiting development and exploitation.

Thus, the field of immunomodulation is moving from the relative obscurity of adjuvants for vaccines into mainstream therapy and these immunomodulator deals of the first half of 2005 bear witness to this trend. Major pharma's interest is heightening and investments are being made. This is not surprising as this class of compounds have the potential to be used across major disease areas such as cancers and viral infections with minimal interaction or interference with other classes of drugs being used. The concept of 'powering-up' the immune system is an attractive one and will become more so as better classes of small molecule compounds enter the arena and prove themselves in the clinic. **DDW**

David Gee *has more than 20 years' experience within several international healthcare companies serving in sales, marketing, strategic planning and business development roles. He has managed commercial activities for all stages of drug development, from concept to sales and marketing of mature pharmaceutical products. He also has extensive experience establishing research collaborations, in- and out-licensing and M&A. Having held senior management positions with Arexis AB, Pharmexa A/S, Byk Gulden (now Altana Pharma), Mundipharma International (part of the Purdue/Mundipharma/Napp Group), and Argenta Discovery Ltd, he currently serves as Commercial Director for MNLpharma.*