New mechanisms and expanded indications for biologic therapies: a perspective on immunology research and development

Over the past decade, the introduction of biologic therapies has had a profound impact for millions of patients with immune-mediated arthritides, inflammatory bowel diseases and plaque psoriasis. Today, five anti-Tumor Necrosis Factor (TNF) therapies are approved in the United States and many countries around the world, and innovations in the TNF class continue more than a decade after the initial approval. Several other biologic therapies targeting distinct immune cell receptors or cytokines have been approved for immunologically mediated diseases, and many promising new biologic medicines are in various stages of clinical development.

By Dr Susan B. Dillon

In this article I will provide an overview of some of the current trends influencing the development of new biologics for immune-mediated and inflammatory diseases including 1) the continued clinical development of biologics targeting TNF-α; 2) new mechanisms in inflammation that are being explored in clinical trials and 3) recent advances in the application of new biologic therapies to an expanded list of indications with high unmet medical need.

Continued development of TNF biologics for immune-mediated disease

Since the initial approval of infliximab (REMICADE®) for Crohn's disease in 1998 and the subsequent approvals of etanercept (ENBREL®) and adalimumab (HUMIRA®) for rheumatoid arthritis (RA) in 1998 and 2002, respectively, the development of anti-TNF biologics has continued. Infliximab is now approved for 15 indications in the US (**Table 1**)[1]. In 2009, golimumab (SIMPONI®), a human monoclonal antibody (mAb) with once-monthly subcutaneous (SC) dosing received approvals for RA, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Another agent, certolizumab (CIMZIA®) was also approved for RA in 2009, bringing the total number of approved anti-TNF therapies to five agents (**Table 2**)[2-5]. Thus, it has been firmly established that TNF is an important pathogenic mediator in a number of autoimmune and inflammatory diseases, a fact that was not fully appreciated before

Table 1: Infliximab approved indications[1]

DATE	INDICATION
1998	Crohn's disease – luminal and fistulising
1998	Rheumatoid arthritis signs and symptoms (MTX failures)
2000	Rheumatoid arthritis structural damage (MTX failures)
2002	Rheumatoid arthritis physical function (MTX failures)
2002	Crohn's disease maintenance (luminal)
2003	Crohn's disease maintenance (fistulising)
2004	Rheumatoid arthritis signs and symptoms, x-ray progression, physical function (MTX naïve)
2004	Ankylosing spondylitis signs and symptoms
2005	Psoriatic arthritis signs and symptoms
2005	Ulcerative colitis
2006	Pediatric Crohn's disease
2006	Psoriatic arthritis structural damage
2006	Psoriatic arthritis physical function
2006	Chronic severe plaque psoriasis
2006	Ulcerative colitis maintenance
Phase III	Pediatric ulcerative colitis

Indications refer to approvals from the Food and Drug Administration (FDA) for the US only

the era of anti-TNF biologic therapies. Even with these advances, however, there is still great potential for further innovations with the TNF class.

In RA, approximately 60% of biologic naïve patients with an inadequate response to disease modifying anti-rheumatic drugs (DMARDs) (depending on the specific patient population, therapeutic, trial design and other variables) achieve a 20% improvement in disease activity according to the American College of Rheumatology criteria (ACR20) with anti-TNF treatment[6], and even fewer (less than 20%[7]) achieve clinical remission, defined as maintenance of an ACR70 response for at least six months. This, and the fact that many patients lose response over time, has prompted research into the identification of biomarkers to predict the likelihood that an individual will have both an initial and durable response to anti-TNF therapy. A variety of potential demographic, clinical, radiological, blood, genetic or synovial tissue markers has been studied. High local (synovial) and systemic levels of TNF-α appear to be correlated with good clinical response although validation by further studies is needed[8,9].

Molecular profiling and genetic association studies have potential for identification of markers which predict response to treatment. While these approaches have produced tantalising results, published studies to date have been small and remain to be prospectively validated in large clinical cohorts[10-12]. The paradigm of identifying responder populations may also be applicable to inflammatory bowel diseases, where gene expression signatures have been identified that correlate to TNF-α response and non-response in ulcerative colitis (UC) patients treated with infliximab[13].

The failure of many patients to initially respond or maintain a response to therapy with an anti-TNF agent has also led to research into the potential of switching within the class. Patients who fail to respond to one or more anti-TNF therapies may respond to another, as was demonstrated by results of the G0-AFTER study of golimumab in RA patients previously treated with one or more TNF inhibitors[14]. More than a third of the patients whose prior anti-TNF therapy had been discontinued due to lack of efficacy achieved an ACR20 response to golimumab.

A recent report of infliximab in the Study of Biologic and Immunomodulator Naïve Patients in Crohn's (SONIC) compared infliximab, azathioprine and the combination of both drugs in patients with moderate to severe Crohn's disease who had not received prior immunosuppressive or biologic therapies. Patients receiving infliximab-containing regimens were more likely to experience clinical remission without the use of steroids and demonstrated improved mucosal healing[15]. Based on this landmark study, the American College of Gastroenterology guidelines on the management of Crohn's disease now recommend infliximab with or without azathioprine as more effective than azathioprine alone in the treatment of patients with moderate to severe Crohn's disease who have failed to respond to first-line steroid or 5-aminosalicylic acid (5-ASA) therapy[16].

Anti-TNF agents have transformed treatment of immune disease. After more than a decade of successful application of anti-TNF treatment in a multitude of inflammatory diseases, we continue to study and to learn more about these drugs. Clinical

investigations are currently under way in new indications and to extend use paradigms in approved indications. Basic research studies continue to define exactly how these agents work to modulate the immune system, and biomarker efforts are in progress to identify predictive markers of response. All of these investigations provide new data to optimise and extend usage of these powerful therapeutic agents.

Targeting new mechanisms in inflammation

The successes achieved with anti-TNF biologics for the treatment of a collection of immune-mediated diseases impacting the joints, intestinal tract and skin have encouraged the search for new therapeutic targets that may impact these organ systems and others that are affected in immunologic disorders. TNF-α is produced by multiple cell types, most notably by macrophages as part of the innate immune response to pathogens and other inflammatory stimuli. In addition to playing an important role in host defence against infection and cancer, TNF-α has many biologic activities that promote inflammation, including increasing the expression of adhesion molecules (ICAM, VCAM) on keratinocytes and endothelial cells[17], inducing the expression of other inflammatory cytokines (such as IL-1, IL-6 and, IL-8)[18], and inducing VEGF expression, which increases angiogenesis at sites of inflammation[19]. All of these activities have the combined effect of increasing migration of circulating leukocytes into local sites of inflammation[20]. **Tables 2-4** provide a list of therapeutic antibodies and receptor fusion proteins with alternative (non-TNF-α) mechanisms that have received approvals in many of the same indications for which infliximab was approved. Rather than discuss the mechanisms for these therapeutics, which are extensively reviewed elsewhere, this report will focus on new mechanisms in clinical development.

Cytokines involved in both innate immune responses and in the regulation of B and T lymphocyte adaptive immune responses, such as IL-12, IL-23, IL-17 and IL-6, have become the focus for new antibody targets. IL-12 was initially identified as a factor involved in several immune activities including the induction of cytotoxic T lymphocytes (CTL) and lymphokine-activated killer cells (LAKs) and the augmentation of natural killer cell mediated toxicity[21,22], and it is now recognised as an important cytokine in driving differentiation of Th1 cells. The hallmark cytokine produced by Th1 cells, Interferon γ, along with TNF-α, play an important role in protecting against infection and in contributing to autoimmune disease pathology. The more recent discovery of the IL-12 family member IL-23 was crucial to the identification of Th17 cells, which also contribute to autoimmunity[23]. The genetic and human translational studies implicating Th1 and Th17 cells in diseases has led to the focus on antibodies blocking the activities of IL-12, IL-23 and IL-17.

IL-12/IL-23

IL-12 and IL-23 cytokines are heterodimeric proteins (p35/p40 and p19/p40, respectively) that bind to a common receptor subunit, IL-12Rβ1, via their

Table 2: Biological therapies approved for rheumatoid arthritis[1-5,79,80]

	Certolizumab	Golimumab**	Etanercept**	Infliximab**	Adalimumab**	Abatacept	Rituximab	Actemra
Structure	Pegylated Fab	Human mAb	Human TNF-α-receptor/IgG1-Fc fusion protein	Chimeric mAb	Human mAb	Human CTLA-4/IgG1-Fc fusion protein	Chimeric mAb	Human mAb
Target	TNF-α	TNF-α	TNF-α, TNF-β	TNF-α	TNF-α	CD80, CD86	CD20	IL-6 receptor
MOA	Blocks TNF-α activity	Blocks TNF-α activity	Blocks TNF-α and TNF-β (LT) activity	Blocks TNF-α activity	Blocks TNF-α activity	Blocks T-cell costimulation	Depletes B cells	Blocks IL-6 activity
Route	SC injection	SC injection	SC injection	IV infusion	SC injection	IV infusion	IV infusion	IV infusion

Certolizumab (Cimzia); Golimumab (Simponi); Etanercept (Enbrel); Infliximab (Remicade); Adalimumab (Humira); Abatacept (Orencia); Rituximab (Rituxan)
*SC = subcutaneous; IV = intravenous; MTX = methotrexate. Indications refer to approvals from the FDA for the US only. ** Also approved for Psoriatic Arthritis and Ankylosing Spondylitis*

Table 3: Biological therapies approved for psoriasis[1-3,30,81,82]

	EFALIZUMAB*	ALEFACEPT	ETANERCEPT	INFLIXIMAB	ADALIMUMAB	USTEKINUMAB
Structure	Humanised mAb	Human LFA-3/IgG1-Fc fusion protein	Human TNF-α-receptor/IgG1-Fc fusion protein	Chimeric mAb	Human mAb	Human mAb
Target	LFA-1	CD2	TNF-α, TNF-β	TNF-α	TNF-α	IL-12/23p40
MOA	Blocks T cell activation and trafficking	Blocks T cell function, Induces T cell apoptosis	Blocks TNF-α and TNF-β (LT) activity	Blocks TNF-α activity	Blocks TNF-α activity	Blocks IL-12 and IL-23 activity

*Efalizumab (Raptiva); Alefacept (Amevive); Etanercept (Enbrel); Infliximab (Remicade); Adalimumab (Humira); Ustekinumab (Stelara). * withdrawn in 2009*
Indications refer to approvals from the FDA for the US only

shared p40 subunit; however, each cytokine signals through a distinct receptor subunit (IL12Rβ2 and IL23R, respectively) to elicit IL-12 or IL-23 mediated cellular responses (**Figure 1**). Both cytokines are secreted by antigen presenting cells in response to inflammatory stimulus or infection. IL-12 is required for naïve CD4+ cells to differentiate into a Th1 phenotype, which is characterised by robust production of interferon γ Th17 activation is promoted by multiple cytokines, including IL-23, and is characterised by the production of several cytokines including IL-17A (IL-17), IL-17F and IL-22[24,25]. IL-23 signalling is essential for reinforcing the Th17 phenotype since Th17 cells are considered to represent an 'unstable' state and can transition to other 'Th' phenotypes upon certain stimulation conditions[26]. Regardless, Th17 cells have been associated with a variety of immune-mediated disease pathologies. Indeed, genetic variants of the shared IL-12/23p40 subunit (ie, IL-12B) and the IL-23 specific receptor, IL-23R, are associated with increased susceptibility to psoriasis and Crohn's disease[27-29].

The human mAb ustekinumab (STELARA®) was recently approved for the treatment of moderate to severe plaque psoriasis[30]. By binding to the p40 subunit that is shared between IL-12 and IL-23, ustekinumab has a dual mode of action that inhibits both cytokines from binding and signalling their cognate receptor complexes (**Figure 1**). In two randomised, placebo-controlled Phase III trials (PHOENIX 1 and PHOENIX 2) in patients with moderate to severe plaque psoriasis, ustekinumab demonstrated significant efficacy and a favourable safety profile, with more than two-thirds of patients treated with ustekinumab achieving a 75% improvement in their Psoriasis Area and Severity Index (PASI 75) compared with less than 10% of patients receiving placebo[31,32]. These results were achieved with maintenance dosing of either 45mg or 90mg delivered SC once every three months, following an initial 2 SC doses of either 45mg or 90mg in the first month. Recent results from the open label, long-term extensions of these trials have shown that PASI 75 responses are maintained over a period of up to

Table 4: Biological therapies approved for inflammatory bowel diseases[1,3,5,83]

	NATALIZUMAB	CERTOLIZUMAB	INFLIXIMAB	ADALIMUMAB
Structure	Humanised mAb	Pegylated Fab	Chimeric mAb	Human mAb
Target	α4-subunit of α4β1 and α4β7 integrins	TNF-α	TNF-α	TNF-α
MOA	Inhibits α4-mediated adhesion of leukocytes	Blocks TNF-α activity	Blocks TNF-α activity	Blocks TNF-α activity
Approved indications	Crohn's disease	Crohn's disease	Crohn's disease and UC	Crohn's disease

Natalizumab (Tysabri), Certolizumab (Cimzia); Infliximab (Remicade); Adalimumab (Humira). UC = ulcerative colitis. Indications refer to approvals from the FDA for the US only

three years with continued maintenance dosing[33]. Ustekinumab treatment of plaque psoriasis can lead to a remarkable resolution of histological features of psoriasis lesions including cutaneous inflammation and T-cell infiltration with minimal effects on the systemic immune system[34,35]. These important studies confirm the pathophysiologic role of the p40-containing cytokines IL-12 and IL-23 in plaque psoriasis. IL-12 and IL-23 are also implicated in inflammatory bowel diseases[36], arthritis[37] and other immune-mediated diseases. The relative contribution of each cytokine to human immune-mediated diseases is not yet known, while many studies in mice suggest that IL-23 is the major pathogenic mediator. This question will be addressed through clinical studies of IL-23 specific antibodies currently in early development.

IL-17

IL-17 blockade is an attractive therapeutic strategy for autoimmune diseases based on the wealth of data in animal models and human translational studies that implicate Th17 cells in pathology. Numerous tissue cells including epithelial cells and fibroblasts express IL-17 receptors and innate immune cell populations (ie, T cells and CD3+ invariant natural killer T cells)[38] also produce IL-17, providing additional mechanisms for IL-17 mediated inflammation in the local tissue environment. IL-17 signalling leads to the production of a wide spectrum of cytokines and chemokines, including IL-1beta, TNF-α, IL-6 and G-CSF[39], which further drives the influx of inflammatory cells, in particular neutrophil infiltration into the lung[40]. IL-17 plays a role in normal host defence against certain types of bacterial, fungal and viral infections[41], and the effects of therapeutic blockade on risk of infection is not yet known. Anti-IL-17 AIN457 (Novartis) and LY2439821 (Lilly) and anti-IL-17 receptor monoclonal antibodies (AMG 827; Amgen) are in development for a variety of diseases including RA[42], psoriasis[43], PsA[44], AS[45], uveitis[46] and Crohn's disease. Both LY2439821 and AIN457 have reported efficacy in proof of concept studies in RA[47,48].

IL-6

IL-6 plays a diverse role in immune signalling by binding to IL-6 receptors expressed on the surface of several cell types including hepatocytes, macrophages and lymphocytes. IL-6 also binds to a soluble IL6 receptor that is not anchored to a cell membrane[49], but binds to gp130, found on multiple cell types, to form the functional IL-6 receptor complex. IL-6 has a crucial role in the adaptive

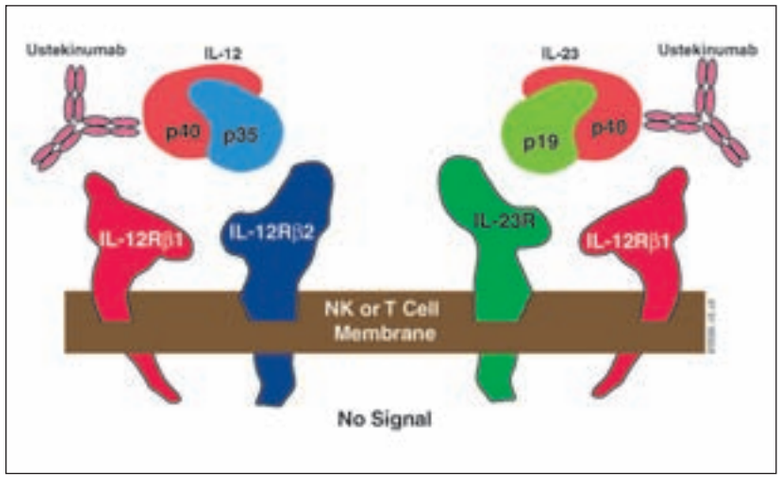

Figure 1
Ustekinumab (STELARA) binds to the p40 subunit of IL-12 and IL-23, thus preventing their interaction with the cell surface IL-12Rβ1 receptor and subsequently inhibiting IL-12 and IL-23 mediated cell signalling, activation and cytokine production (image not drawn to scale)

immune response by influencing both B-cell differentiation to antibody producing plasma cells and, in concert with other cytokines as noted above, can drive development of Th17 cells. Additionally, IL-6 is able to inhibit the production of Foxp3+ regulatory T (Treg) cells that are critical for protecting against the development of autoimmunity[50].

IL-6 is one of the principle stimulators of acute-phase protein production through hepatocytes and is also involved in many local and systemic signaling processes that can contribute to tissue damage and diverse symptomatology of inflammatory diseases including fever, fatigue and anaemia[51,52]. Local inflammation directed by IL-6 can lead to tissue damage through direct signalling and recruitment of neutrophils[53] and the production of extracellular matrix enzymes and turnover[54]. IL-6 signalling has also been implicated in systemic osteoporosis through its regulation of the cellular balance of bone-forming osteoblasts and bone-resorbing osteoclasts[55].

Tocilizumab (ACTEMRA®) is a monoclonal antibody specific for the soluble and cell surface IL-6 receptors and has demonstrated efficacy in reducing signs and symptoms and bone structural damage in adults with RA, including subjects that have had an inadequate response to TNF therapy (**Table 2**)[56,57]. As an alternative approach for abrogating IL-6 signalling, there are new therapeutics in development specific for the IL-6 ligand including ALD518 (Alder/BMS) and CNTO 136 (Centocor Ortho Biotech). As described above for the anti-TNF class, IL-6/IL-6R inhibition may demonstrate efficacy in a broad range of immunologic diseases and is also a promising therapeutic strategy for the lymphoproliferative disorder Castleman Disease[58,59].

Expanded use of biologic immunomodulators in new diseases

Therapeutic intervention with cytokine or immune cell receptor blockade is being studied in an increasing number of immune-mediated and/or inflammatory disorders; some examples of exciting progress in this arena are summarised below.

Systemic lupus erythematosus is an autoimmune disease that affects multiple organ systems including the skin, joints, blood, nervous system and kidneys. Levels of B lymphocyte stimulator (BLys) protein are elevated in lupus and are thought to play a role in triggering activation of autoimmune B cells[60]. Belimumab (BENLYSTA®) is an antibody that targets the BLys protein and thereby reduces the production of autoantibodies. Belimumab met its primary efficacy endpoints and demonstrated a favourable safety profile in two Phase III studies (BLISS-52 and BLISS-76) for lupus[61,62]. This validates the critical role of B cells in SLE and provides the first potential new treatment for lupus in decades. Belimumab was filed with the FDA in June of this year and received a priority review designation by the FDA with potential to reach approval by the end of 2010[63].

Sarcoidosis is an immunologic disease characterised by the formation of immune granulomas that may target any of several organs, most commonly the lung and lymphatic systems, but infiltration in the skin, and other organs is common[64]. Therapeutic management of sarcoidosis is not well defined, but may involve the use of corticosteroids or other immunomodulators. Improved treatment options are particularly needed for the management of patients who have chronic resistant disease, as well as patients in whom prolonged use of corticosteroids is contraindicated. Although the pathogenesis of this disease is not well understood, both clinical and translational data suggests there may be a role for TNF-α[65] and IL-12/23 p40[66] in sarcoidosis.

At Centocor R&D, Inc we are conducting a Phase II multicentre, randomised, double-blind, placebo-controlled study that will simultaneously investigate ustekinumab and golimumab in patients with sarcoidosis[67]. While the comparative trial is exploratory and not powered to determine superiority between the two treatment arms, the novel study design offers added efficiency towards gathering clinical data on two drugs by circumventing the need to recruit placebo arm patients in two independent studies.

Rilonacept (ARCALYST®), an IL-1 receptor fusion protein, and canakinumab (ILARIS®), an anti-IL-1beta antibody, have both been approved for the treatment of cryopyrin-associated periodic

syndromes (CAPS)[68,69], a group of inherited inflammatory disorders associated with mutations in the NLRPC (CIAS1) gene that leads to excessive production of IL-1[70]. Both agents are also undergoing investigation in other inflammatory metabolic disorders including gout.

Type 1 diabetes (T1D) is a T cell-mediated disease directed towards islet beta cell proteins. In patients with early-onset T1D, therapeutic antibodies directed to the CD3 protein on T cells have shown promise in slowing the loss of function of insulin producing beta cell function and preserving better glucose control[71]. Several anti-CD3 mAbs (Teplizumab (Macrogenics/Lily) and Otelixizumab (Tolerex/GSK) are in Phase III trials[72,73].

While TNF-α inhibitors have not shown a favourable risk-benefit profile in severe persistent asthma[74], many additional cytokine targets are under investigation for asthma, including IL-4, IL-13, IL-5, IL-9, IL-25 and IL-17. These targets have been reviewed elsewhere[75]. The heterogeneity of asthma and the need to identify patients who will best benefit from anti-cytokine therapy illustrates the importance of biomarker research and the trend towards implementation of personalised medicine.

Conclusion: what is on the horizon?

Next generation therapeutics based on new biologic drug platforms beyond monoclonal antibodies include a class of proteins termed 'alternative scaffolds'. These are small proteins that either have an antibody or novel binding domains or can be generated with the diversity and exquisite specificity of antibodies for their antigen. Because of their small size and stability, these therapeutics can be produced in bacteria, they may penetrate into diseased tissues more effectively than antibodies and can be readily engineered to bind more than one target. Several of these molecules are advancing into clinical development, including a nanobody directed to TNF-α[76].

Small molecules that blockade targets involved in intracellular cytokine signalling pathways are a logical extension of current biologic therapies, but to date have been largely unsuccessful due to insufficient potency and toxicity issues. Several oral small molecules directed against the JAK kinases[77] and Syk kinases[78] are currently in Phase II and Phase III development for RA and have shown impressive efficacy in reducing signs and symptoms in early stage trials; however, results of longer-term treatment are needed to assess the effects on structural damage and safety profiles.

The advent of biologic therapies has clearly made a profound impact on the lives of patients with serious immune-mediated inflammatory diseases, and many studies are under way investigating new targets and a broader spectrum of diseases with inflammatory etiologies. The bar for improved clinical efficacy, reduced safety risks, improved patient convenience and reduced cost will increasingly be raised, and will continue to drive innovations leading to new and better therapeutic options for patients. DDW

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