

# Crohn's disease: beyond antagonists of tumour necrosis factor



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In the past few years, antagonists of tumour necrosis factor have resulted in unforetold therapeutic benefits in Crohn's disease, but the magnitude and duration of responses are variable. New agents are therefore needed. Their development has benefited from advances in the understanding of the pathophysiology of this disease. Uncontrolled activation of the acquired immune system has an important role, and lymphocytes, cytokines, and adhesion molecules are broadly targeted for therapeutic intervention. With increasing evidence of an implication of the innate immune system and the intestinal epithelium, the therapeutic paradigm is also shifting from mere immunosuppression to the reinforcement of the intestinal barrier. We review mechanisms of actions of new drugs and the efficacy and adverse events from data from clinical trials. We discuss future directions, including new strategies with optimum endpoints.

## Introduction

Crohn's disease results from a dysregulated response of the mucosal immune system to intraluminal antigens of bacterial origin in people who are genetically predisposed to this disease.<sup>1,2</sup> The traditional view of the pathogenesis of Crohn's disease is that intestinal inflammation is mediated by cells of the acquired immune system, with overly aggressive activity of effector lymphocytes and proinflammatory cytokines.<sup>1,2</sup> Emerging evidence suggests that disease development implicates a dysregulated dialogue between the intestinal microbiota and components of both the innate and adaptive immune systems.<sup>3,4</sup> The host response to the intestinal microbiota can be categorised into three basic components: the intestinal epithelium, innate immune cells of the myeloid lineages (eg, monocytes, dendritic cells, and granulocytes), and adaptive immune cells (B and T cells) (figure 1). Models with defects in each of these components have been associated with pathogenesis of inflammatory bowel disease in mice.<sup>3,4</sup>

Investigators have long sought to identify a micro-organism that causes inflammatory bowel disease. The present theory suggests a breakdown in the balance between putative species of protective versus harmful bacteria—a notion that has been termed dysbiosis.<sup>5</sup> Recent studies emphasised the potential importance of adherent invasive *Escherichia coli* in the initiation and maintenance of inflammation in Crohn's disease.<sup>6,7</sup> However, our understanding of the microbial flora is still incomplete. Metagenomic and computational analyses of the so-called microbiome might provide a foundation to achieve a more accurate understanding of the relevant, functional diversity of the flora in the context of inflammatory bowel disease.<sup>4,8</sup>

The intestinal epithelium, which is considered to be part of the innate immune system, has an active role in maintenance of mucosal homeostasis. Epithelial cells form a tight, highly selective barrier between the body and the intraluminal environment. Failure of this barrier can result in intestinal inflammation, most likely through

activation of the mucosal immune system.<sup>1</sup> In human beings, the importance of the epithelial barrier in disease predisposition is supported by the finding of abnormal intestinal permeability in first-degree relatives of patients with Crohn's disease.<sup>4,9</sup>

The innate immune system is the body's non-specific defence against pathogens. It is regarded as the first line of defence that reacts to the chemical properties of the antigen.<sup>1</sup> Evidence of the role of the innate immune system comes from the identification of *nucleotide-binding oligomerisation domain containing 2 (NOD2)* as a susceptibility gene for Crohn's disease.<sup>10,11</sup> Individuals who are either homozygotes or compound heterozygotes for any one of the three germline variations of *NOD2* that are commonly identified have as much as a 40-fold increased likelihood of developing ileal Crohn's disease. The *NOD2* protein is an intracellular receptor for a component of the bacterial cell wall, and is expressed in macrophages, dendritic cells, intestinal epithelial cells, and Paneth cells, providing specific support for the long-held hypothesis that Crohn's disease results from a genetically dysregulated host immune response to luminal bacteria.<sup>4</sup> Furthermore, natural antimicrobial peptides, such as defensins, are expressed in an *NOD2*-dependent manner, and patients with this disease

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## Search strategy and selection criteria

We did a computerised search of English and non-English language publications listed in the electronic databases of Medline (source PubMed, from 1966 to March, 2008), the Cochrane Library, and Embase (from 1980 to March, 2008). We searched for the terms: "Crohn's disease", "inflammatory bowel disease", "treatment", "biological therapy", "cytokine", "T-cell", "adhesion", "growth factors". We also hand-searched abstracts from the yearly meetings of Digestive Disease Week between 2003 and 2007, and the United European Gastroenterology Week between 2003 and 2007, and references from review articles and published trials to identify additional articles.

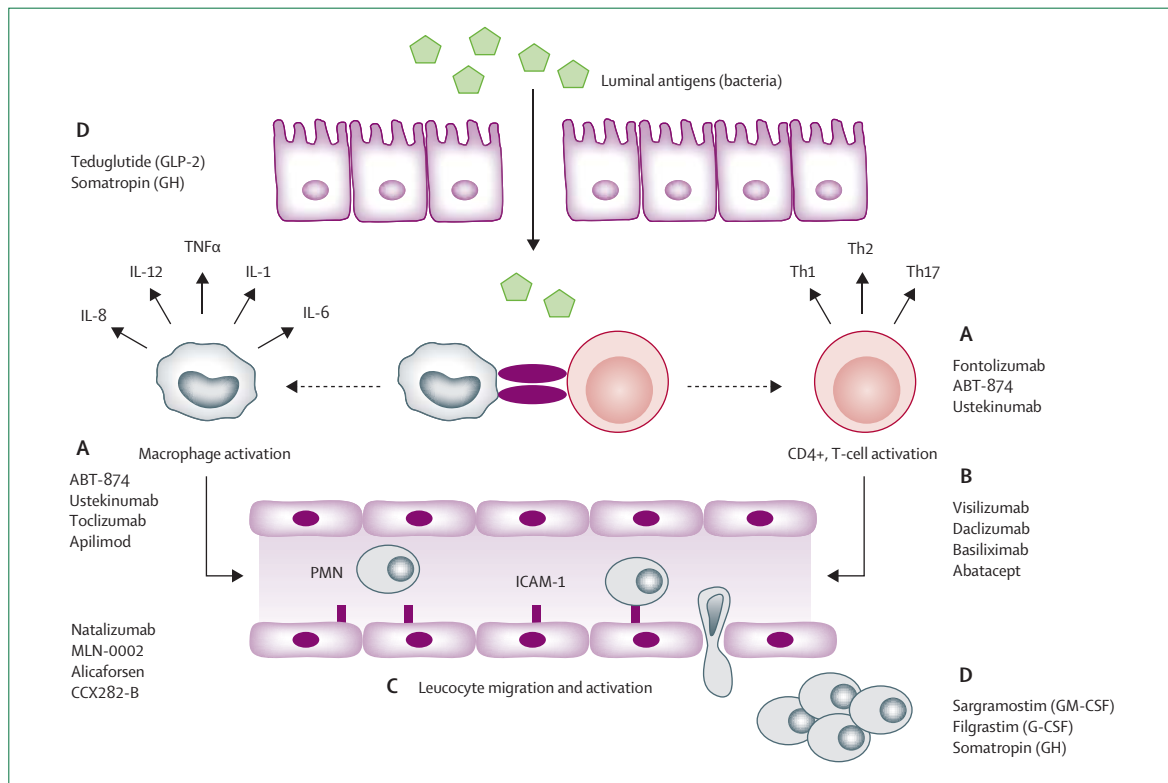
can have reduced defensin production in their intestine,<sup>12</sup> contributing to inadequate microbial clearance.

Adaptive immunity is the most proximate driver of tissue damage that arises in patients with inflammatory bowel disease, although innate immune responses seem to be a prerequisite for the excessive activation of adaptive immunity.<sup>4</sup> Adaptive responses toward a specific antigen are affected by a combination of resident and recruited cell populations. These populations consist of mucosal B cells producing immunoglobulins and a mixture of T cells that are dominated by a T-helper (Th) 1, Th2, or Th17 phenotype, and the coincident presence of regulatory T or B cells.<sup>4</sup> Th1 development is triggered by microbes that stimulate production of interleukin-12p40 and interferon  $\gamma$ , which then activate macrophages and the release of interleukin 1, interleukin 6, and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) (figure 1 and webfigure 1). Classic Crohn's disease has a Th1-type cytokine profile. Another CD4 T-cell lineage (Th17) that is distinct from Th1 and Th2 has now been linked to the pathogenesis of Crohn's disease. In a genome-wide association study involving a North American case-control cohort with this

disease, typing more than 300 000 single nucleotide polymorphisms, an interleukin 23R coding variant was associated with reduced risk of inflammatory bowel disease.<sup>13</sup> Th17-cell development is driven by transforming growth factor  $\beta$  (TGF $\beta$ ) and interleukin 6, whereas interleukin 23 seems to expand and maintain Th17-cell populations. The interleukin-23 receptor consists of the interleukin-23R subunit and interleukin 12RB1, whereas the interleukin-23 cytokine consists of p19 and p40 subunits.<sup>3</sup> In addition to helper-cell activation, evidence in human beings and murine models also suggest a role for regulatory T cells producing interleukin 10 or TGF $\beta$ , or both, in maintenance of intestinal homeostasis<sup>4</sup> (webfigure 1).

Over the past decade, the advent of anti-TNF $\alpha$  agent infliximab has changed the way that refractory Crohn's disease is treated. Infliximab rapidly induces and maintains response and remission,<sup>14,15</sup> spares steroids,<sup>15,16</sup> and induces and maintains fistula closure.<sup>17,18</sup> Nevertheless, about a third of patients do not respond at all to this drug, and an additional third has only some response. This finding can be explained by the presence

See Online for webfigure 1



**Figure 1: Overview of therapeutic targets in Crohn's disease: cytokine therapies (A), T-cell blocking agents (B), antiadhesion molecules (C), and growth factors (D)**

The host response to the intestinal microbiota can be categorised into three basic components: the intestinal epithelium, innate immune cells of the myeloid lineages (including macrophages and granulocytes), and adaptive immune cells (including CD4+ T-helper 1 cells). The most crucial environmental factor in the pathogenesis of Crohn's disease might be the luminal flora. Defects in the intestinal innate immune barrier (consisting of several cell types including the epithelial and immune cells), leading to aberrant early innate immune response towards bacterial threats, might start an excessive adaptive immune response dominated by mucosal CD4+ lymphocytes. Classic Crohn's disease has a predominant Th1 cytokine profile that is characterised by interleukin 12 and interferon  $\gamma$ . TNF=tumour necrosis factor  $\alpha$ . ICAM-1=intercellular adhesion molecule-1. GM-CSF=granulocyte-macrophage colony-stimulating factor. G-CSF=granulocyte colony-stimulating factor. GH=growth

of different effector pathways in responders and non-responders.<sup>1</sup> Newer anti-TNF drugs such as certolizumab pegol and adalimumab have similar efficacy to infliximab.<sup>19–21</sup> Patients who have been previously given infliximab who have lost response or become intolerant can respond to alternative biological drugs targeting TNF.<sup>22</sup> However, an overall decrease is noted in the absolute proportion of responses to the second agent, suggesting that some patients who previously responded might not have benefits of targeting TNF.<sup>22</sup> This finding emphasises the need for developing novel biological drugs for the treatment of Crohn's disease.

These advances in our understanding of the pathophysiology of inflammatory bowel disease have led to new therapeutic opportunities (figures 1 and webfigure 1).<sup>2,23</sup> The many therapies being investigated include cytokine and anticytokine therapies, T-cell blocking agents, antiadhesion molecules, and new immunomodulatory strategies (tables 1 and 2). In this review, we will discuss mechanisms of action of new biological drugs, their efficacy, and safety profiles, and will review previous innovative therapies and future directions for treatment of Crohn's disease (table 3).

## Mechanisms of action of novel biological therapies

### T-cell blockade

The T cell is pivotal in orchestration and promotion of the immune response in inflammatory bowel disease. Most therapies for inflammatory bowel disease aim to inhibit T-cell function, block the generation of T-cell pro-inflammatory cytokines, or induce apoptosis of T cells or a particular subset of these cells.<sup>23</sup> CD4+ T lymphocytes recognise antigens that have been processed and are presented in association with a self class II MHC molecule to initiate the immune response.<sup>23,74</sup> After the development of CD4+ T-cell antagonists, such as cM-T412,<sup>24,25</sup> other antibodies have been generated against more specific T-cell subsets: CD3+ cells (visilizumab) and CD25+ (daclizumab and basiliximab).<sup>23</sup> Visilizumab is a non-Fc receptor-binding antiCD3 monoclonal antibody directed against the invariant CD3 $\epsilon$  chain of the T-cell receptor (webfigure 2).<sup>75</sup> Unlike the prototypic murine antiCD3 monoclonal antibodies, which induce T-cell activation by FcR binding and recruitment of antigen-presenting cells, non-FcR-binding antiCD3 monoclonal antibodies do not activate resting T cells and therefore induce less toxic effects from cytokine release *in vivo*.<sup>75</sup>

Visilizumab induces apoptosis selectively in activated T cells, and it is much more effective in this respect than are murine antiCD3 monoclonal antibodies (webfigure 2). Two antibodies against the interleukin-2 receptor (CD25)—namely, daclizumab and basiliximab, have been studied to mimic the activity of cyclosporine, which acts by disruption of the calcineurin pathway. Additionally, because interleukin 2 induces steroid resistance, blockade of this receptor should in principle

### Blockade of T-cell differentiation or activation

Instead of depletion of a particular T-cell subset, another approach has been to block steps in T-cell development by targeting cytokines and molecules that are involved in T-cell differentiation and activation (webfigure 1).<sup>23</sup> Interleukin 6 is a pleiotropic cytokine that is released in response to interleukin 1 and TNF $\alpha$ , with central roles in immune regulation and inflammation.<sup>76</sup> Accordingly, interleukin 6 offers an attractive target to interrupt inflammation in inflammatory bowel disease at several points. Increased serum concentrations of soluble interleukin 6R were detected in the active stage of inflammatory bowel disease.<sup>77</sup> Tocilizumab (formerly atilizumab) binds to both the membrane-bound form and the soluble form of human interleukin 6R with high affinity and specificity.<sup>28</sup> Fontolizumab is a humanised antibody directed against interferon  $\gamma$ , which is a key Th1 cytokine driving expression of MHC class II on antigen presenting cells, increasing chemokine secretion and activating macrophages, lymphocytes, and endothelial cells.<sup>76</sup> Because of the proinflammatory role of interleukin 23,<sup>3</sup> attention is now being focused on molecules specifically targeting the interleukin-23 p19 subunit in addition to developing drugs—such as apilimod mesylate (STA 5326), ABT-874, and ustekinumab (CNTO 1275)—which block both interleukin-23 and interleukin-12 activities.<sup>32,34,78</sup>

T cells need both antigen-specific and costimulatory signals for their full activation (figure 2).<sup>79</sup> ch5D12 blocks the CD40/CD40L costimulatory pathway; CD40 belongs to the TNF receptor family.<sup>79</sup> On the basis of a second T-cell surface molecule that is homologous to CD28—CTLA-4 (CD152), which has a 20-fold higher affinity for the CD80 and CD86 ligands than does CD28—abatacept has been developed (figure 2).<sup>79</sup> Another selective costimulation blocker, belatacept (LEA29Y), was designed by substitution of two amino acids in the abatacept CD80/CD86-binding domain to increase avidity to CD86 and provide the potency needed for immunosuppression in transplantation.<sup>79</sup> It has not yet been tested in inflammatory bowel disease.

### Resetting T-cells

Patients with Crohn's disease receiving allogeneic bone-marrow transplants for unrelated disorders had extended remission of their Crohn's disease, providing evidence of the role of bone-marrow T cells (either T-helper or regulatory T cells) in this disease.<sup>80</sup> Although not curative, reconstitution of a normal T-cell balance by autologous haemopoietic stem-cell transplantation resulting in the elimination of all circulating T cells has been used to treat a range of autoimmune, T-cell driven diseases,<sup>23</sup> including multiple sclerosis and rheumatoid arthritis.<sup>81</sup> In theory, a transplant conditioning regimen would ablate aberrant disease-causing immune cells, whereas haemopoietic stem cells would regenerate an

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	Development status	Compound	Manufacturer	Target	Compound class	Clinical efficacy		Biological efficacy (CRP)	References
						Induction	Maintenance		
T-cell blockade	Phase I/II	cM-T412	Centocor, Malvern, PA, USA	CD4 on T-cell surface	Chimeric mAb	No placebo group	NA	NA	24,25
		Visilizumab	PDL Biopharma, Fremont, CA, USA	CD3 on T-cell surface	Humanised Fc IgG2 receptor -non-binding mAb	No placebo group	NA	+	26,27
Blockade of T-cell differentiation or activation	Phase III	Abatacept*	Bristol Myers Squibb, New York, NY, USA	Blockade of CD28 costimulatory pathway	Soluble recombinant fusion protein	Not yet available	Not yet available	Not yet available	NA
	Phase I/II	Tocilizumab	Chugai Pharmaceuticals, Fremont, CA, USA	IL-6 receptor	Humanised mAb	+	NA	+	28
		Fontolizumab/HuZAF	PDL Biopharma, Fremont, CA, USA	Interferon $\gamma$	Humanised mAb	-	NA	+	29-31
		ABT-874/J695	Abbott, Parsippany, PA, USA	IL-12/IL-23, p40	Humanised mAb	+	NA	NA	32
		Ustekinumab (CNTO 1275)	Centocor, Malvern, PA, USA	IL-12/IL-23, p40	Human mAb	+	NA	+	33
		Apilimod mesylate/STA 5326	Synta Pharmaceuticals, Lexington, MA, USA	IL-12/23	Small molecule	No control group	NA	NA	34
ch5D12	Tanox, Houston, TX, USA	CD40 on antigen-presenting cells	Chimeric mAb	No placebo group	NA	NA	35		
Resetting T cells	Phase I/II	Haemopoietic stem cell transplantation†	Northwestern University, Evanston/Chicago, IL, USA	Autologous haemopoietic stem cells	Cell therapy	No placebo group	NA	NA	36
AntiTNF strategies	Phase I/II	Semapimod/CNI-1493	Cytokine PharmaSciences Inc, King of Prussia, PA, USA	JNK and p38 MAP kinases	Synthetic guanlylhydrazone	No placebo group	NA	+	37,38
		Doramapimod/BIRB 796	Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA	p38 MAP kinase	Small molecule (member of the N-pyrazole-N-naphthly urea class)	-	NA	+	39
		Thalidomide	Pharmion, Camberley, UK	Antiangiogenic and anti-inflammatory (TNF $\alpha$ ) properties	Synthetic derivative of glutamic acid	No placebo group	No placebo group	NA	40
Regulatory T-cell modulation	Phase I/II	IL-10	Shering-Plough, Kenilworth, NJ, USA	IL-10	Recombinant human cytokine	-	NA	NA	41-43
		Oprelvekin/IL-11	Wyeth, Madison, NJ, USA	IL-11	Recombinant human cytokine	-	NA	-	44-46
		Lactococcus lactis (LL-Thy12) expressing mature human IL-10	ActoGeniX, Ghent, Belgium	IL-10	Living non-pathogenic micro-organisms expressing IL-10 (TopAct system)	No placebo group	No placebo group	NA	47
Blocking cell recruitment	Phase III	Natalizumab	Elan, Dublin, Ireland	Leucocyte $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins	Humanised mAb	+	+	+	48-56
		Alicaforsen/ISIS-2302	Isis Pharmaceuticals, Carlsbad, CA, USA	Endothelial ICAM-1	Phosphorothioate-modified antisense oligodesoxynucleotide	-	NA	NA	57-62
		CCX282-B	ChemoCentryx, Mountain View, CA, USA	Antichemokine receptor CCR9	Small molecule	+/-	NA	+/-	63,64
	Phase II	MLN-0002/LDP-02‡	Millennium Pharmaceuticals, Cambridge, MA, USA	Leucocyte $\alpha 4\beta 7$ integrin	Humanised mAb	+/-	NA	-	65

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### AntiTNF strategies

In addition to TNF antagonists—such as infliximab, adalimumab, and certolizumab—other antiTNF approaches have been developed to treat inflammatory bowel disease. Mitogen-activated protein (MAP)

kinases, constitute major NF-kB-independent inflammatory signalling pathways from the cell surface to the nucleus. Four major groups of distinctly regulated groups of MAP kinase cascades led to altered gene expression: ERK1/2, ERK5, JNK, and p38 MAP kinase.

Development status	Compound	Manufacturer	Target	Compound class	Clinical efficacy		Biological efficacy (CRP)	References	
					Induction	Maintenance			
(Continued from previous page)									
Enhancing repair	Phase II	Teduglutide/ALX-0600	NPS Pharmaceuticals, Salt Lake City, UT, USA	Intestinal GLP-2 receptors	Analogue of human peptide GLP-2	+	NA	NA	66
		Somatropin/	Eli Lilly, Indianapolis, IN, USA	Intestinal epithelium	GH peptide	+	NA	NA	67
Innate immune stimulation	Phase III	Sargramostim	Berlex (Schering AG), Berlin, Germany	Intestinal epithelium, neutrophils, monocytes	Yeast-derived recombinant human GM-CSF	+/-	NA	NA	68-71
	Phase I/II	Filgrastim	Amgen, Thousand Oaks, CA, USA	Neutrophils	E coli-derived human (G-CSF)	No placebo group	NA	NA	72
Induction of oral tolerance	Phase I/II	Aleqel	Enzo Therapeutics, Farmingdale, NY, USA	Induction of oral tolerance	Autologous colonic extracts	-	NA	-	73
		Opebacan	Xoma, Berkeley, CA, USA	Induction of oral tolerance	Autologous colon-derived antigens	Not yet available	Not yet available	Not yet available	NA

NA=not available. IL=interleukin. TNF=tumour necrosis factor. ICAM-1= intercellular adhesion molecule-1. GLP-2=glucagon-like peptide-2. mAb=monoclonal antibody. MAP=mitogen-activated protein. GH=growth hormone. GM-CSF=granulocyte-macrophage colony-stimulating factor. GCSF=granulocyte colony-stimulating factor. CRP=C-reactive protein. \*Phase III trials are in progress in Crohn's disease (abatacept has been approved by the US Food and Drug Administration for rheumatoid arthritis). †Phase II trials are in progress in Crohn's disease (results presented here come from phase I trials). ‡Phase III trials are anticipated in Crohn's disease (results presented here come from phase II trials).

**Table 1: Efficacy of biological agents in clinical trials in Crohn's disease**

contribute to pro-inflammatory response, specific inhibitors, including semapimod and doramapimod (BIRB 796)<sup>37-39</sup> were tested in inflammatory bowel disease. Several therapies, which are presented as TNF $\alpha$  inhibitors, have a more general immunomodulatory effect and are fairly weak inhibitors—such as thalidomide.<sup>40</sup> RDP58 is a decapeptide that is orally available and reduces the activity of TNF $\alpha$ , interleukin 2, interleukin 12, and interferon  $\gamma$ .<sup>23,82</sup>

### Regulatory T-cell modulation

Regulatory T cells function to control the inflammatory process directed by other T-helper cells. Interleukin 10 is one of the prototypic products of regulatory T cells and downregulates activation of Th-cell subsets. Interleukin 10 also inhibits macrophage inflammatory cytokine production including TNF $\alpha$ , interleukins 1 and 12, and T-cell associated macrophage activity. Interleukin 10 has therapeutic effects in several preclinical murine models of colitis.<sup>23</sup>

### Blocking cell recruitment

Most of the strategies detailed above aim to interrupt cytokine activity through the inhibition of pathways promoting cytokine production, or by directly blocking cytokine action. A different approach aims to block leucocyte migration to sites of inflammation by interfering with cell-adhesion molecules.<sup>23</sup> Most leucocytes, including lymphocytes, monocytes, eosinophils, and basophils, express  $\alpha$ 4 integrin adhesion molecules.<sup>83,84</sup> The integrins are a large family of heterodimeric, transmembrane glycoproteins that are capable of mediating both cell-cell and cell-matrix

found adjoined with  $\beta$ 1 and  $\beta$ 7 subunits. Endothelial ligands for  $\alpha$ 4 integrins include members of the immunoglobulin superfamily of adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) (figure 3).<sup>83,84</sup> Inhibitors of selective adhesion molecules interfering with the migration of leucocytes from the bloodstream to the sites of inflammation—a process known as diapedesis—have been developed. Natalizumab and MLN-0002 bind specifically to  $\alpha$ 4 integrins, whereas the anti-intercellular adhesion molecule-1 (ICAM-1) antisense oligonucleotide ISIS-2302 (alicaforfen) blocks the endothelial cell adhesion molecules (figure 3). ICAM-1 binds  $\beta$ 2-integrin leucocyte function-associated antigen-1 (LFA-1). CCX282-B is a drug that targets the chemokine receptor 9 (CCR9), which is a highly specific receptor expressed by T cells migrating selectively to the digestive tract. CCR9-positive cells are recruited into the epithelium of the small intestine because they respond specifically to the CCR9 ligand CCL25 (also called TECK [thymus-expressed chemokine]) expressed by small-intestine cells, and to a lesser extent by colonic cells.<sup>85</sup> Another means to prevent cells from migrating to sites of inflammation uses extracorporeal devices (for instance Adacolumn, Otsuka, Tokyo, Japan) to filter out or lyse leucocytes subsets from whole blood.<sup>86</sup>

### Enhancing repair

Rather than interfering with inflammation, teduglutide, a dipeptidyl peptidase IV resistant glucagon-like peptide-2 (GLP-2) analogue,<sup>66</sup> and somatropin, a growth hormone, can overcome the detrimental effects of the inflammatory process by driving restitution of the

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