

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Advances in Management of Crohn's Disease

Talha A. Malik

*Division of Gastroenterology/Hepatology
University of Alabama at Birmingham, Birmingham, Alabama
USA*

1. Introduction

Crohn's disease (CD) is one of two forms of inflammatory bowel diseases (IBD), the other being ulcerative colitis (UC). CD is in fact itself a heterogeneous condition describing a group of closely related disease processes that result from an uncontrolled immune mediated inflammatory response primarily affecting the alimentary tract. CD may affect any part of the gastrointestinal tract and causes transmural intestinal inflammation. It is characterized by flares and remission. CD usually presents with diarrhea, abdominal pain and/or weight loss. Fever, blood in stool, oral ulcers, and/or perianal lesions may also occur. Most patients with CD end up requiring surgery.

In some cases of colitis, the distinction between CD and UC cannot be clearly made despite a detailed evaluation based on a thorough clinical exam, endoscopy, imaging and a biopsy. The term "Indeterminate colitis" is used for these cases. Based on the increasing recognition of the so-called "indeterminate colitis" and the considerable heterogeneity even within the two discrete IBD subtypes, efforts calling for a revisit of IBD classification are under way. In 2000, the Working Party for the World Congresses of Gastroenterology, which had met in Vienna in 1998, published their report in the journal *Inflammatory Bowel Diseases* and proposed the Vienna classification. The Vienna classification attempted to classify CD based on objective variables that included age of onset, disease location, and disease behavior. The Vienna classification classifies CD into 24 disease clusters. Since then however, the Vienna classification has come under criticism due to its lack of clinical applicability, however it is still being used for research purposes. In 2005 Silverberg and colleagues presented the report of the Working Party of the Montreal World Congress of Gastroenterology in which they put forth the Montreal classification of IBD. Montreal classification classified CD largely based on variables chosen by the experts at Vienna except for adding a perianal disease modifier variable. Neither Vienna nor Montreal classification commented on the extra intestinal manifestations of CD though. Extra-intestinal manifestations of CD may include rheumatologic, dermatologic, ocular or hepatobiliary conditions. These have been identified in the Crohn's Disease Activity Index (CDAI) initially introduced as far back as 1979.

It is estimated that approximately 750,000 people in the United States have CD. There is a lot of variation in data with regard to the incidence and prevalence of CD in the US. For example, incidence in the US of CD is estimated at 1 to 6 per 100,000. The prevalence of CD in the US is estimated to be 10-100 per 100,000. There doesn't seem to be a significant

difference in the incidence and prevalence of CD between males and females. The peak age of onset for CD is 15-25 years of age. There seems to be another peak between the ages of 45 and 55. Smoking seems to predispose to CD.

2. Etiology and pathogenesis

The most popular theory regarding pathogenesis of CD considers it to be a result of an uncontrolled immune mediated inflammatory response to a still unknown trigger that occurs in genetically predisposed individuals, primarily affecting the alimentary tract and also involving the intestinal flora.

2.1 Intraluminal factors

Different triggers have been implicated, both external and auto-antigens. External antigens include viruses, bacteria and dietary agents. The most common virus implicated in the pathogenesis of CD is the measles virus. The most common external bacterial agent that has been implicated in the pathogenesis of CD is *Mycobacterium paratuberculosis*. An antigen on a dietary agent may also trigger an uncontrolled immune mediated inflammatory response leading to the development of CD, but no such agent has yet been identified. Auto-antigens that have been implicated in the pathogenesis of CD may be located on non-pathogenic bacteria which constitute the intestinal flora. Similarly it is postulated that a certain antigenic trigger on a yet unknown luminal agent present in the gastrointestinal tract may also trigger an abnormal inflammatory response within the gastrointestinal tract leading to intestinal inflammation.

2.2 Epithelial barrier, innate and acquired immune actors

Despite the lack of definitive knowledge about the potential triggering agents, it is well established that the main mechanism of inflammatory injury is immune mediated and that it occurs in genetically predisposed individuals. There are various mechanisms by which immune mediated injury takes place. It is a combination of the interaction between breakdown in the intestinal epithelial barrier, innate immune system and activation of acquired immune mechanisms. An important factor is abnormal or exaggerated immune response. HLA Class II molecules that are predominantly found on macrophages are considered to be the major mediators of the process of autoimmune injury. They occur in high numbers within the intestinal epithelial cells of patients with active CD. The HLA-Class II molecules are responsible for antigen processing and presentation. HLA-DR molecules seem to play the most active role in this regard. Activated macrophages also secrete pro-inflammatory cytokines including IL-1, IL-6, IL-8 and TNF-alpha within the lamina propria of the intestinal wall. IFN- gamma is also produced and it increases intestinal permeability. There is decreased production of IL-2, IL-10, TNF- beta and TGF-beta, which are down-regulatory cytokines. In patients with IBD, this may explain chronic inflammation. Moreover, direct cell mediated immune mechanisms may also be involved in the immune pathogenesis of IBD. It is postulated that B-cell mediated mechanisms are also important, as there is increased secretion of IgM and IgG classes of antibodies by the intestinal mononuclear cells. Other immune mediators that seem to be involved in the pathogenesis of CD include oxygen radicals, most importantly superoxide molecules. Oxygen radicals are produced by activated neutrophils and they cause further inflammatory injury. Leukotriene Neutrophil Chemotactic Compounds (LNCC) and nitric

oxide also enhance the inflammatory process of IBD by causing vasodilatation and vascular leakage. It has been demonstrated in animal models that the inflammatory process of IBD is enhanced by CD-4⁺ T helpers. This provides evidence for a dominant role of T-cells in the pathogenesis of IBD. Moreover, the effectiveness of TNF-alpha and IFN-gamma antibodies in counteracting T-cell mediated inflammatory damage lends credence to the belief that both TNF-alpha and IFN-gamma are important mediators of the T-cell induced damage in inflammatory bowel diseases.

2.3 Genetic predisposition

Up to fifteen percent of patients with CD may have a first degree relative who also suffers from IBD. Haplotypes associated with CD are HLA-DR1/DQw5 and HLA-DRB3*0301. IBD1 susceptibility locus on chromosome 16 is associated with CD. The NOD2 gene located on this locus undergoes a mutation leading to abnormality in NOD2 protein, which is an intracellular bacterial lipopolysaccharide receptor in monocytes. This mutation is seen in up to fifteen percent of patients with CD. The IBD2 susceptibility locus on chromosome 12 is also associated with CD.

3. Management

3.1 Goals

The historic goal of treatment of CD was to induce and maintain clinical remission. However, it has now become evident that the natural course of disease progression of CD is not positively impacted if focus is laid only on clinical remission. Therefore the goal of treatment of CD has evolved into a broad stratagem. Current goals of medical management of CD include rapid induction and then maintenance of clinical as well as endoscopic remission. This seeks to minimize bowel damage. Other goals of management that are now actively pursued include decreasing rate of complications, hospitalizations, surgical interventions, infections, steroid use, cancer and overall mortality. Moreover, improving compliance and health related quality of life (HRQL) also figure prominently among current management goals. The goals of CD therapy continue to evolve and eventually will include not just minimizing the impact of the disease but perhaps obliterate it altogether. For this purpose, research is ongoing in search of additional biological modifiers. Genetic studies are also being undertaken.

3.2 Approach

Traditionally, a step up approach was applied that involved starting with corticosteroids and evolving to more invasive and newer modalities. Then there was evidence to suggest that top-down therapy might be the best way to achieve the evolving goals of therapy. However, recently there is more support for the accelerated step-up approach.

3.3 Supportive therapy

In regard to diet, there is not a lot of data that suggests a strong link between diet and CD. However some diets that have been suggested to possibly be related to onset as well as increased disease activity and more severe course include diets consisting of red meats. Moreover, diets high in fats and refined carbohydrates also seem to be risk factors for CD whereas fruits and vegetables are perhaps protective. Patients are also advised to make a list

of others foods that seem to worsen their symptoms and to avoid consuming them. Despite a few studies demonstrating benefits of an elemental diet, the risk of malnutrition in patients on it has caused decrease in enthusiasm.

In regard to behavioral management, regular exercise enhances functional capacity of IBD patients. Smoking is strongly associated with CD exacerbations. There is observational data to suggest that NSAID use may increase CD activity. In patients with CD, behavioral counseling and ways to facilitate daily living needs to be ensured.

3.4 Advances in medical therapy

Traditional Therapies have included systemic corticosteroids. They were and are still used for induction of remission in CD. While 5-Aminosalicylates like mesalamine have traditionally been the primary treatment modality in mild to moderate UC but their effectiveness in CD has largely been marginal if any at all. Antibiotics are considered among the most effective and safe therapies used to treat patients with mild to moderately active CD. The antibiotics most frequently used are metronidazole and ciprofloxacin. The most common traditional immune modulators used to maintain remission in CD as well as UC are azathioprine (AZA) and 6-mercaptopurine (6-MP). The role of methotrexate (MTX) appears to be limited to CD.

Newer Therapies are represented by biological immune modulators. Advances made in understanding the pathogenesis of CD have pushed us into the era of biological agents and beyond. The most important biological agents being used today are the TNF-alpha blockers. However, there is a long list of biologics that work by targeting other areas of the entire spectrum of the pathogenesis of CD.

3.5 TNF blockers

The first biologic agent that was approved for CD treatment was infliximab (Remicade). Infliximab is a half murine half human, chimeric monoclonal antibody consisting of an Fc portion as well as a Fab fragment which is active against TNF-alpha. It is administered intravenously, usually every 8 weeks. Infliximab has been found to be effective in inducing and maintaining remission in moderate to severe inflammatory as well as fistulizing CD disease in several multicenter double-blind, placebo controlled trials. The typical induction regimen of infliximab is 5mg/kg intravenously at 0, 2 and 6 weeks followed by 5mg/kg intravenous infusion every 8 weeks. Infliximab also reduces the requirements for corticosteroids, leads to mucosal healing, and reduces complications such as surgical intervention and hospitalization. It has also demonstrated improved quality of life. Initial response rates to infliximab may be as high as 75% but is generally maintained in approximately one third of patients.

Adalimumab (Humira) is a monoclonal IgG1 antibody against TNF-alpha which is fully humanized and has shown promise in the treatment of CD. Adalimumab is administered subcutaneously. Similar to infliximab, adalimumab works as an induction as well as a maintenance medication. The Classic I trial revealed that induction with 160 mg of adalimumab followed in two weeks by 80 mg of adalimumab resulted in over 35 percent of CD patients achieving remission at 4 weeks follow up. The GAIN (Gauging Response in Infliximab Nonresponders) trial was conducted to evaluate response to induction by adalimumab of patients which also included those who had either failed to respond to infliximab or had developed recurrence of disease after an initial response to infliximab. It

was a placebo controlled double-blind trial which revealed that remission rate with adalimumab induction was about 21 percent, and not as good as what the Classic I trial had revealed. An interesting finding was that those patients who had previously either failed to respond to infliximab or had developed disease recurrence actually had decreased remission rate in response to adalimumab than the initial response to infliximab induction. The Classic II and CHARM trials evaluated the efficacy of maintenance with adalimumab. The CLASSIC II trial was a double-blind, placebo-controlled trial and went on for a year. In this trial the investigators maintained initial responders on 40mg of adalimumab every week or every other week or to placebo. After a year of this trial, 79% of the patients on 40mg every other week and 83% of the patients on 40mg of adalimumab every week had achieved remission compared to 44% of the placebo group. The CHARM trial studied 854 patients with moderate to severe Crohn's disease. In CHARM, the 80/40 mg induction with adalimumab had already taken place. The responders to this induction regimen were then randomized to the two maintenance regimens of adalimumab or placebo. These patients were then followed for a year. Forty one percent of the patients who received adalimumab every week were in remission after about a year, whereas 36 percent of those who were on every other week of adalimumab maintenance were in remission. The CLASSIC II and CHARM trials also showed that adalimumab could be used as a steroid sparing agent in order to maintain remission in patients with CD, as most patients on adalimumab in the CLASSIC II trial were off steroids compared to those on placebo. In the CHARM trial, it was seen that the steroid-free clinical remission rates were significantly higher in those patients who received adalimumab versus those who were on placebo. The CHARM trial also revealed a statistically significant decrease in hospitalization in patients who were on adalimumab versus placebo. Adalimumab also helped heal fistulas in patients with CD. At the end of one year, one third of patients who received adalimumab had achieved closure of fistula compared to 13 percent of those were treated with placebo. The CHARM trial was extended for another one year and the end of the additional year, almost 71 percent of the fistulas had healed in patients who received adalimumab.¹⁴

Certolizumab pegol (Cimzia) is a humanized monoclonal agent against TNF-alpha that is comprised of just the Fab fragment and does not contain the Fc moiety. Certolizumab is pegylated by the addition of two polyethylene glycol molecules which increases the half-life as well as its binding affinity to TNF-alpha. Certolizumab pegol is administered once a month subcutaneously at 400 mg dose each time. The induction regimen of Cimzia is 400mg subcutaneously at week 0, 2 and then 4. So far, two placebo controlled, double blind trials have been performed to evaluate certolizumab pegol in CD. PRECISE I (add reference) looked at the effectiveness of induction therapy. Even though a benefit was found in inducing a response with it compared to patients on placebo, the response was not statistically significant. The response to induction was assessed at 2 weeks, 6 weeks and then at 26 weeks. It was noted though that the maximum response occurred in patients who had CRP level higher than 10mg/dl. Patients with high CRP levels were therefore evaluated separately based on a previous post-hoc analysis revealing a greater rate of response in this patient population anyway (add reference). The primary endpoints of this study were the induction of clinical response at weeks 6 and a response at both weeks 6 and 26. In this study, it was demonstrated that 37% of patients with CRP level higher than 10 mg/l experienced response at the end of 6 weeks vs. only 26% in the placebo group. The difference in response at weeks 2 and 26 were not statistically significant

In the PRECISE 2 trial, researchers randomized week 4 responders to certolizumab pegol 400mg every 4 weeks to week 26 or placebo. Randomization was again stratified based on CRP level. It was demonstrated that 64% of the patients responded to induction therapy. This response was maintained in 63% of the intention to treat population up until week 26 vs. 36% who were receiving placebo). In terms of clinical remission at week 26, 48% of the patients on certolizumab pegol achieved it vs. 29% among the placebo group. In the end, stratification by CRP levels did not appear to yield a significant benefit in any of these studies. Moreover, it was noted that the efficacy of certolizumab pegol was not impacted by steroid use or the use of infliximab in the past. But once again, those who had received a TNF blocker in the past had a lower response rate than those who had never received a biologic. The open-label stage of the WELCOME trial was based on CD patients who had been unable to tolerate infliximab or who had developed secondary loss of response to it. The patients received induction with certolizumab 400 mg at weeks 0 and 2. The primary response defined as a decrease in CDAI of 100 was measured at week 6. It was seen that 55% of these patients had responded based on this criterion.

3.6 Adhesion molecule inhibitors

Natalizumab (Tysabri) is a monoclonal antibody against the alpha-4 subunit of integrin molecules which are important mediators of vascular inflammation. Integrin molecules are located on surface of vessels and they play an important role in adhesion and migration of inflammatory cells from the vasculature into inflamed tissue. Natalizumab essentially blocks integrin association with vascular receptors, limiting adhesion and transmigration of leukocytes. Specifically, in CD, natalizumab decreases inflammation by binding to alpha-4 integrin and thus blocking adhesion and migration of inflammatory leukocytes in the gut. Natalizumab has not been studied in patients with UC. Because of the incidence of PML in some cases and in two cases PML leading to death in MS patients who were treated with natalizumab, natalizumab was briefly taken off the market. In order to use natalizumab now in patients with CD, they must be enrolled in the Crohn's disease Tysabri® Outreach Unified Commitment to Health (CD-TOUCH™). Healthcare providers must also register with the program in order to prescribe, dispense or administer natalizumab. Treatment must be reauthorized every 6 months. Natalizumab is available only through infusion centers registered with the TOUCH™ program. Natalizumab is given in a 300 mg dose infused over 1 hour every 4 weeks. It is discontinued if no therapeutic benefit is observed in the first 12 weeks.

Vedolizumab, previously called MLN-0002, MLN-02 or LDP-02, is similar to natalizumab but with some important differences. It is a recombinant humanized anti alpha-2 beta-7 integrin monoclonal antibody, which is undergoing Phase 3 trials to test its efficacy in treatment of UC as well as CD. The alpha-2 beta-7 integrin subunit is relatively specific to the gastrointestinal tract. The Gemini I, II and III (also called the Millennium Trials) are all phase III clinical trials which are being conducted to test efficacy of Vedolizumab in inducing and maintaining remission in patient with UC and CD.

3.7 IL-6 inhibitors

Toclizumab is a humanized monoclonal antibody directed against the receptor of IL-6. An early randomized safety and efficacy trial assessing toclizumab in CD was published in 2004. The trial had 2 treatment arms and one placebo arm with a total accrual of 36 patients. Even though there was a significant difference in serologic and clinical response parameters

between those who received toclizumab vs. placebo at assessment of the induction endpoint assessment, the highest response rate was two out of 10(20%) patients who received toclizumab. No difference was seen in terms of mucosal healing between treatment and placebo groups at 12 weeks.. Due to these less than encouraging results in CD, further clinical trials evaluating the efficacy of toclizumab in patients with IBD have not conducted so far. However, recently, there has been more activity in research assessing efficacy of toclizumab in other autoimmune diseases, most importantly rheumatoid arthritis with several phase II and phase III clinical trials underway.

3.8 IFN- γ blockers

Fontolizumab is a humanized monoclonal antibody fragment that possesses potent binding and neutralizing activity against human interferon- γ (IFN- γ). IFN- γ is a prominent pro-inflammatory effector cytokines. Two safety and clinical efficacy trials assessing the ability of fontolizumab in inducing remission in active CD were published in 2006. They did demonstrate a serologic and mucosal response in the patients who received fontolizumab but there was no significant difference seen in clinical remission between patients on fontolizumab vs. placebo.. In February 2010, results of a placebo controlled Phase 3 trial assessing efficacy of fontolizumab in patients with CD were published. In this trial, a total of 201 patients with Crohn's Disease Activity Index (CDAI) scores between 250 and 450 were randomized to receive an initial intravenous dose of 1.0 or 4.0 mg/kg fontolizumab or placebo, followed by up to 3 subcutaneous doses of 0.1 or 1.0 mg/kg placebo every 4 weeks. At the end of induction phase assessed at 4 weeks, there was no significant improvement in patients who had received fontolizumab. However, during the maintenance period the patient arm that received 1.0 mg/kg intravenous followed by 1.0 mg/kg subcutaneous of fontolizumab group had clinical response and significantly greater improvement in the CDAI score compared with patients who received placebo. But a similar improved response was not seen in the other fontolizumab group. However, all fontolizumab groups had significant improvement in C-reactive protein levels. Adverse event rates were similar in all groups. The significantly low levels of CRP in patients who received fontolizumab suggested a biological effect of fontolizumab on inflammation associated with Crohn's. Further trials are therefore being planned but no trial is currently underway.

3.9 IL-12/23p40 inhibitor

Interleukin-12 (IL-12) and Interleukin-23 (IL-23) are functionally closely associated effector cytokines that seem to play an active role in promoting intestinal inflammation in inflammatory bowel disease. IL-12 and IL-23 are structurally separate but both exist linked to a common subunit p40. IL-12 attaches to the p40 subunit through its unique subunit p35 whereas IL-23 is attached to p40 through its unique subunit p19. Both IL-12 and IL-23 attach to cell surface receptors on T-helper cells to trigger Th1 and Th17 mediated inflammatory cascades respectively. Briakinumab is also a human monoclonal antibody directed against IL-12/23p40 subunit.. Results of a phase II dose ranging and efficacy study published in 2004 demonstrated a significantly higher response in patients on briakinumab (75%) compared to placebo (25%) at the end of 7 weeks ($P=0.03$). (84)A subsequent phase IIb randomized double blind placebo controlled clinical efficacy trial was started in 2007. The trial sought to test safe dose and efficacy of briakinumab in

moderate to severely active CD however it was terminated in April, 2010 without publication of findings. There are no other clinical trials underway testing briakinumab in CD or UC (Abbott ;.Dose Ranging Study Comparing the Efficacy, Safety and Pharmacokinetics of Intravenous Infusions of ABT-874 vs Placebo in Subjects With Active Crohn's Disease . In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00562887>).

STA-5326 mesylate (also called apilimod mesylate) is a small molecule that blocks the release of IL-12 from peripheral blood mononuclear cells. In 2006, results of a safety and dose-ranging study with an accrual of 73 that evaluated oral STA-5326 mesylate (apilimod mesylate) in CD were published. They revealed a remission rate of between 15 and 36% at the end of 4 weeks. Approximately half of the patients demonstrated a decrease in mucosal disease activity. A subsequent phase II dose-ranging randomized placebo control clinical trial assessing the efficacy of oral STA-5326 mesylate (apilimod mesylate) in CD was undertaken between 2005 and 2008, but the results have not been published yet (B.Sands; Synta Pharmaceutical Corp. Study of STA-5326 Mesylate in Patients With Moderate to Severe Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00138840>). Another similar randomized double blind placebo control phase II study that sought to assess peripheral mononuclear and cytokine responses to oral STA-5326 mesylate (apilimod mesylate) was completed in December 2008. The results of this study have not been published yet. There have been no additional studies evaluating STA-5326 mesylate (apilimod mesylate) in CD since then. There are also no studies that have assessed STA-5326 mesylate in UC yet (P.Mannon; Synta Pharmaceutical Corp. Study of STA-5326 Mesylate in Patients With Moderate to Severe Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00234741>).

Ustekinumab, a human monoclonal antibody has specific affinity to the p40 subunit. By doing this, ustekinumab prevents IL-12 and IL-23 from attaching to their cell surface T-helper cell receptors and therefore helps prevent the subsequent inflammatory process. Results of a double blind crossover clinical study assessing efficacy of ustekinumab in moderate to severe CD were published in 2008. They demonstrated a statistically significant difference in clinical response (53%) in patients who received ustekinumab vs. those who were in the placebo arm (30%) ($P=0.02$) by the end of week 6 but this difference was not maintained at the end of week 8 (49% with ustekinumab vs. 40% with placebo; $P=0.34$). It was noted however that when the subgroup of previous non-responders to infliximab were evaluated separately, the difference in clinical response to ustekinumab vs. placebo became statistically significant. Consequently, a multicenter double-blind placebo controlled randomized trial testing efficacy and safety of ustekinumab in subjects with moderately to severely active CD previously treated with TNF blockers was started. This trial is still ongoing with no results published so far. (Centocor Inc;. A Study of Safety and Effectiveness of Ustekinumab in Patients With Moderate to Severe Active Crohns Disease Who Have Been Previously Treated With Anti-TNF Therapy. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00771667>). There are no ongoing trials testing efficacy of ustekinumab involving UC patients.

3.10 Other promising agents affecting cytokines

Thalidomide is a glutamic acid derivative that has historically been notorious for its devastating teratogenic potential, a property most probably linked to its toxic effect on endothelial tissue structures. There is growing evidence that thalidomide in fact also effectively inhibits transcription of TNF among other of its functions that may also be of value in combating intestinal inflammation in IBD. In a retrospective study published in 2007, thalidomide was shown to potentially be an effective in some patients with refractory luminal and fistulizing Crohn's disease. Randomized Controlled Trials testing efficacy of thalidomide in adults with active CD have not begun yet. It is important to note that an RCT conducted in children with CD, testing efficacy of lenalidomide, an analogue of thalidomide in treatment of active CD did not demonstrate any significant benefit over placebo (94). Similarly, despite pre-clinical evidence to support efficacy of thalidomide and lenalidomide in decreasing intestinal inflammation associated with IBD, no maintenance trials have yet been published to justify its safety for use in humans. However, clinical trials are being planned.

RDP58 is an oral d-amino acid decapeptide that has powerful immunosuppressive activity which includes inhibition of TNF synthesis as well inhibition of IFN- γ , IL-2 and IL-12. It has been demonstrated in murine models that RDP58 is extremely effective in reducing intestinal inflammation including histological scores in colitis. RDP58 has also demonstrated variable efficacy in treatment of several inflammatory and presumably autoimmune conditions that include IBD, interstitial cystitis and autoimmune encephalomyelitis. RDP58 has demonstrated ex vivo anti-inflammatory activity in tissue from patients with CD. It has also demonstrated efficacy in vivo murine models.

3.11 Mucosal barrier enhancement/restoration

The intestinal epithelium is a part of the innate immune system of the intestinal tract. It functions as a protective wall that seeks to maintain a balance between the contents of the lumen and the immune cells and matrix that lie on the other side.

Intestinal epithelial cells are the individual units that give rise to this normally impenetrable intestinal barrier by forming tight junctions. Any insult that results in the failure of the tight junctions to keep the contents of the two environments separate is what heralds intestinal inflammation by activating a hyper-reactive acquired immune system made up primarily of effector cells.

Emerging therapies include therapeutic agents that seek to enhance or restore this important protective immune play. Teduglutide is a dipeptidyl peptidase IV resistant glucagon-like peptide-2 (GLP-2) analogue. The manner in which GLP-2 repairs the intestinal epithelium is still unclear. However, it is being tested for its ability to restore the intestinal epithelial barrier. Results of a randomized, placebo-controlled, double-blind trial evaluating efficacy of teduglutide in inducing clinical and mucosal remission in moderate to-severe CD were published in 2010. They demonstrated a significant difference in clinical response and therefore more studies have been planned.

Growth hormone has also demonstrated positive effects on enhancing function of neutrophils. Somatropin, growth hormone, has demonstrated efficacy in repairing the intestinal epithelium in pre-clinical studies. Some early studies have demonstrated that somatropin enhances the innate immune system and repairs the intestinal epithelium through its positive impact on protein synthesis. A phase III study evaluating the efficacy of somatropin in induction of histological healing in children with Crohn's Disease (CD) was

completed. Publication of the results of this trial is still pending CD (L.Denson; Children's Hospital Medical Center, Cincinnati. Trial of Growth Hormone Therapy in Pediatric Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00109473>).

Another agent that has demonstrated the ability to enhance the innate immune system is the synthetic growth factor Sargramostim. Sargramostim is a granulocyte-macrophage colony stimulating factor (GM-CSF) which specifically stimulates production of neutrophils, monocytes, and epithelial cells. A phase 1 study published in 2009 assessed efficacy of sargramostim in treatment of patients with moderately to severely active CD. The study demonstrated modest benefit with only a few patients experiencing clinical remission. There were no serious reported adverse drug events.

Recently published results of a placebo-control randomized trial that assessed the efficacy of sargramostim in corticosteroid-dependent patients with Crohn's disease demonstrated that it was more effective than placebo in inducing corticosteroid-free remission. It was also demonstrated that treatment with sargramostim was associated with significant improvements in health-related quality of life. Two phase III clinical trials testing efficacy of sargramostim in treatment of moderate to severe CD have recently been completed but results have not been published yet

(Medical Monitor; Genzyme. Efficacy (Induction of Response/Remission) and Safety Study in Patients With Moderate to Severe Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00206674>) (Medical Monitor; Genzyme. Study in Patients With Crohn's Disease Who Are Steroid Dependent, Despite Previous Unsuccessful Attempts to Reduce Steroids Due to Worsening of Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00206596>).

There is evidence for granulocyte colony-stimulating factor's (G-CSF) ability to inhibit effects of T helper 1 cells and of its ability to induce IL-10-secreting regulatory T cells. Filgrastim, a synthetic granulocyte colony-stimulating factor (G-CSF) that specifically stimulates production of neutrophils has also shown promise in early safety and efficacy trials. In a recently published early phase study, the clinical benefit of G-CSF therapy in active CD was tested. The results of the study were important as it was demonstrated that clinical benefit from G-CSF treatment was associated with induction of IL-10 secreting T cells as well as a rise in plasmacytoid dendritic cells in the lamina propria of the inflamed intestinal mucosa. Another phase I study assessing the efficacy of G-CSF in inducing an immune and clinical response in CD patients was recently completed but the results of this trial have not been published yet National Institute of Allergy and Infectious Diseases; National Institutes of Health Clinical Center. G-CSF to Treat Crohn's Disease In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2010 Oct 12]. Available from: <http://clinicaltrials.gov/show/NCT00025805>).

3.12 Intra-luminal targets

While there is no paucity of hypotheses regarding implication of intra-luminal agents as triggers of inflammation, the real advance in devising therapeutic strategies by modulating intra-luminal agents has been the realization that intestinal inflammation seen in CD is actually a result of an imbalance between the intestinal milieu comprising of microbiota,

most likely gut commensals on one side and various components of the immune system on the other. This theory receives more credence with the observation of increased inflammation seen in murine models with defects in any of these components.

Based on the sometimes contradictory observations made, it is very plausible that there are indeed competing and opposing effects of microorganisms in the gut. This dilemma is explained well when one notes that intestinal inflammation is not just the net result of the imbalance between intra-luminal antigens and intestinal immune actors but in fact is also related to the imbalance between the so considered commensal and pathogenic strain of bacteria residing within the intestinal lumens.

Another group of intraluminal actors that has recently garnered the interest of researchers comprises the parasitic helminths. It has been postulated that as development and industrialization became harbingers of improved hygiene, intestinal colonization of people with helminths, a fact of life across the entire globe just a hundred years ago, began to subside. Additionally, it was noted that almost precisely around the same period, there began to occur a substantial increase in the incidence of autoimmune conditions such as inflammatory bowel disease among populations residing in these rapidly industrializing nations. The association between the two phenomena became clearer when evidence of the role of helminths in depressing the intestinal immune reaction also began to emerge. It is now being seen that there seems to be a rapidly rising rate of inflammatory bowel disease among the urbanized populations of several rapidly developing countries whereas their rural counterparts continue to largely enjoy protection from this process. Another theory brought to the fore is popularly termed as the "IBD hygiene hypothesis". It theorizes that immune deregulation occurs early in childhood among populations that are brought up in extremely hygienic environments largely devoid of helminthic colonization. It has been postulated that intestinal helminthic colonizers may actually enhance one's immune regulation processes. Through this mechanism, they may prove to be effective weapons against the various effector cells that are the greatest drivers of the inflammatory cascade representative of CD.

There is also evidence based on murine models suggesting that helminths have a protective effect against the development of colitis. There is evidence based on an open-label clinical trial done on patients with CD that supports the therapeutic role of helminths in these patients. These studies used live ova from porcine whipworm as an oral therapeutic intervention.

4. References

- B. E. Sands: Inflammatory bowel disease: past, present, and future. *J Gastroenterol*, 42(1), 16-25 (2007)
- E. V. Loftus, Jr.: Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology*, 126(6), 1504-17 (2004)
- B. E. Sands and S. Grabert: Epidemiology of inflammatory bowel disease and overview of pathogenesis. *Med Health R I*, 92(3), 73-7 (2009)
- J. R. Korzenik and D. K. Podolsky: Evolving knowledge and therapy of inflammatory bowel disease. *Nat Rev Drug Discov*, 5(3), 197-209 (2006)
- L. Peyrin-Biroulet, P. Desreumaux, W. J. Sandborn and J. F. Colombel: Crohn's disease: beyond antagonists of tumour necrosis factor. *Lancet*, 372(9632), 67-81 (2008)

- F. Scaldaferri, C. Correale, A. Gasbarrini and S. Danese: Mucosal biomarkers in inflammatory bowel disease: key pathogenic players or disease predictors? *World J Gastroenterol*, 16(21), 2616-25 (2010)
- W. J. Sandborn: Current directions in IBD therapy: what goals are feasible with biological modifiers? *Gastroenterology*, 135(5), 1442-7 (2008)
- S. B. Hanauer, W. J. Sandborn, P. Rutgeerts, R. N. Fedorak, M. Lukas, D. Macintosh, R. Panaccione, D. Wolf and P. Pollack: Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*, 130(2), 323-33; quiz 591 (2006)
- W. J. Sandborn, P. Rutgeerts, R. Enns, S. B. Hanauer, J. F. Colombel, R. Panaccione, G. D'haens, J. Li, M. R. Rosenfeld, J. D. Kent and P. F. Pollack: Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med*, 146(12), 829-38 (2007)
- W. J. Sandborn, S. B. Hanauer, P. Rutgeerts, R. N. Fedorak, M. Lukas, D. G. Macintosh, R. Panaccione, D. Wolf, J. D. Kent, B. Bittle, J. Li and P. F. Pollack: Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*, 56(9), 1232-9 (2007)
- J. F. Colombel, W. J. Sandborn, P. Rutgeerts, R. Enns, S. B. Hanauer, R. Panaccione, S. Schreiber, D. Byczkowski, J. Li, J. D. Kent and P. F. Pollack: Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*, 132(1), 52-65 (2007)
- P. Rutgeerts, W. J. Sandborn, B. G. Feagan, W. Reinisch, A. Olson, J. Johanns, S. Travers, D. Rachmilewitz, S. B. Hanauer, G. R. Lichtenstein, W. J. De Villiers, D. Present, B. E. Sands and J. F. Colombel: Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*, 353(23), 2462-76 (2005)
- M. T. Osterman and G. R. Lichtenstein: Current and Future Anti-TNF Therapy for Inflammatory Bowel Disease. *Curr Treat Options Gastroenterol*, 10(3), 195-207 (2007)
- D. K. Podolsky: Inflammatory bowel disease. *N Engl J Med*, 347(6), 417-29 (2002)
- Laurent Peyrin-Biroulet, Pierre Desreumaux, William J. Sandborn and Jean-Frédéric Colombel: Crohn's disease: beyond antagonists of tumour necrosis factor. *The Lancet*, 372(9632), 67-81 (2008)
- V. Leso, L. Leggio, A. Armuzzi, G. Gasbarrini, A. Gasbarrini and G. Addolorato: Role of the tumor necrosis factor antagonists in the treatment of inflammatory bowel disease: an update. *Eur J Gastroenterol Hepatol*, 22(7), 779-86 (2010)
- D. W. Hommes, T. L. Mikhajlova, S. Stoinov, D. Stimac, B. Vucelic, J. Lonovics, M. Zakuciova, G. D'haens, G. Van Assche, S. Ba, S. Lee and T. Pearce: Fontolizumab, a humanised anti-interferon gamma antibody, demonstrates safety and clinical activity in patients with moderate to severe Crohn's disease. *Gut*, 55(8), 1131-7 (2006)
- M. Gandhi, E. Alwawi and K. B. Gordon: Anti-p40 antibodies ustekinumab and briakinumab: blockade of interleukin-12 and interleukin-23 in the treatment of psoriasis. *Semin Cutan Med Surg*, 29(1), 48-52 (2010)
- P. Rafiee, D. J. Stein, V. M. Nelson, M. F. Otterson, R. Shaker and D. G. Binion: Thalidomide inhibits inflammatory and angiogenic activation of human intestinal microvascular

- endothelial cells (HIMEC). *Am J Physiol Gastrointest Liver Physiol*, 298(2), G167-76 (2010)
- S. Plamondon, S. C. Ng and M. A. Kamm: Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. *Aliment Pharmacol Ther*, 25(5), 557-67 (2007)
- R. Srinivasan and A. K. Akobeng: Thalidomide and thalidomide analogues for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*(2), CD007350 (2009)
- A. K. Akobeng and P. C. Stokkers: Thalidomide and thalidomide analogues for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*(2), CD007351 (2009)
- D. C. Baumgart, S. R. Targan, A. U. Dignass, L. Mayer, G. Van Assche, D. W. Hommes, S. B. Hanauer, U. Mahadevan, W. Reinisch, S. E. Plevy, B. A. Salzberg, A. L. Buchman, G. M. Mechkov, Z. A. Krastev, J. N. Lowder, M. B. Frankel and W. J. Sandborn: Prospective randomized open-label multicenter phase I/II dose escalation trial of visilizumab (HuM291) in severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis*, 16(4), 620-9 (2010)
- G. D'haens and M. Daperno: Advances in biologic therapy for ulcerative colitis and Crohn's disease. *Curr Gastroenterol Rep*, 8(6), 506-12 (2006)
- T. J. Creed, C. S. Probert, M. N. Norman, M. Moorghen, N. A. Shepherd, S. D. Hearing and C. M. Dayan: Basiliximab for the treatment of steroid-resistant ulcerative colitis: further experience in moderate and severe disease. *Aliment Pharmacol Ther*, 23(10), 1435-42 (2006)
- M. Price, C. S. Probert and T. Creed: Basiliximab and Infliximab for the Treatment of Steroid-Refractory Crohn's Disease. *Am J Gastroenterol* (2008)
- W. J. Sandborn and T. A. Yednock: Novel approaches to treating inflammatory bowel disease: targeting alpha-4 integrin. *Am J Gastroenterol*, 98(11), 2372-82 (2003)
- R. Cianci, G. Cammarota, F. Raducci and F. Pandolfi: The impact of biological agents interfering with receptor/ligand binding in the immune system. *Eur Rev Med Pharmacol Sci*, 9(6), 305-14 (2005)
- S. R. Targan, B. G. Feagan, R. N. Fedorak, B. A. Lashner, R. Panaccione, D. H. Present, M. E. Spehlmann, P. J. Rutgeerts, Z. Tulassay, M. Volfova, D. C. Wolf, C. Hernandez, J. Bornstein and W. J. Sandborn: Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology*, 132(5), 1672-83 (2007)
- D. Soler, T. Chapman, L. L. Yang, T. Wyant, R. Egan and E. R. Fedyk: The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*, 330(3), 864-75 (2009)
- G. Fiorino, C. Correale, W. Fries, A. Repici, A. Malesci and S. Danese: Leukocyte traffic control: a novel therapeutic strategy for inflammatory bowel disease. *Expert Rev Clin Immunol*, 6(4), 567-72 (2010)
- M. Ismail, R. Morgan, K. Harrington, J. Davies and H. Pandha: Immunoregulatory effects of freeze injured whole tumour cells on human dendritic cells using an in vitro cryotherapy model. *Cryobiology* (2010)
- H. Tilg, A. Moschen and A. Kaser: Mode of function of biological anti-TNF agents in the treatment of inflammatory bowel diseases. *Expert Opin Biol Ther*, 7(7), 1051-9 (2007)

- C. W. Thomas, G. M. Myhre, R. Tschumper, R. Sreekumar, D. Jelinek, D. J. Mckean, J. J. Lipsky, W. J. Sandborn and L. J. Egan: Selective inhibition of inflammatory gene expression in activated T lymphocytes: a mechanism of immune suppression by thiopurines. *J Pharmacol Exp Ther*, 312(2), 537-45 (2005)
- S. Buhner, C. Buning, J. Genschel, K. Kling, D. Herrmann, A. Dignass, I. Kuechler, S. Krueger, H. H. Schmidt and H. Lochs: Genetic basis for increased intestinal permeability in families with Crohn's disease: role of CARD15 3020insC mutation? *Gut*, 55(3), 342-7 (2006)
- E. Cario, G. Gerken and D. K. Podolsky: "For whom the bell tolls!" -- innate defense mechanisms and survival strategies of the intestinal epithelium against luminal pathogens. *Z Gastroenterol*, 40(12), 983-90 (2002)
- S. T. Walk, A. M. Blum, S. A. Ewing, J. V. Weinstock and V. B. Young: Alteration of the murine gut microbiota during infection with the parasitic helminth *Heligmosomoides polygyrus*. *Inflamm Bowel Dis* (2010)
- E. Cario, D. Brown, M. Mckee, K. Lynch-Devaney, G. Gerken and D. K. Podolsky: Commensal-associated molecular patterns induce selective toll-like receptor-trafficking from apical membrane to cytoplasmic compartments in polarized intestinal epithelium. *Am J Pathol*, 160(1), 165-73 (2002)
- C. P. Tamboli, C. Neut, P. Desreumaux and J. F. Colombel: Dysbiosis as a prerequisite for IBD. *Gut*, 53(7), 1057 (2004)
- L. J. Egan and W. J. Sandborn: Positioning novel biologic, probiotic, and apheresis therapies for Crohn's disease and ulcerative colitis. *Curr Gastroenterol Rep*, 7(6), 485-91 (2005)
- A. Mathias, M. Duc, L. Favre, J. Benyacoub, S. Blum and B. Corthesy: Potentiation of polarized intestinal Caco-2 cell responsiveness to probiotics complexed with secretory IgA. *J Biol Chem* (2010)
- N. E. Ruysers, B. Y. De Winter, J. G. De Man, A. Loukas, M. S. Pearson, J. V. Weinstock, R. M. Van Den Bossche, W. Martinet, P. A. Pelckmans and T. G. Moreels: Therapeutic potential of helminth soluble proteins in TNBS-induced colitis in mice. *Inflamm Bowel Dis*, 15(4), 491-500 (2009)
- K. Krishnan, B. Arnone and A. Buchman: Intestinal growth factors: Potential use in the treatment of inflammatory bowel disease and their role in mucosal healing. *Inflamm Bowel Dis* (2010)
- J. Jones and R. Panaccione: Biologic therapy in Crohn's disease: state of the art. *Curr Opin Gastroenterol*, 24(4), 475-81 (2008)
- G. Y. Melmed and S. R. Targan: Future biologic targets for IBD: potentials and pitfalls. *Nat Rev Gastroenterol Hepatol*, 7(2), 110-7 (2010)
- N. Saulnier, M. A. Puglisi, W. Lattanzi, L. Castellini, G. Pani, G. Leone, S. Alfieri, F. Michetti, A. C. Piscaglia and A. Gasbarrini: Gene profiling of bone marrow- and adipose tissue-derived stromal cells: a key role of Kruppel-like factor 4 in cell fate regulation. *Cytotherapy* (2010)
- Y. Oyama, R. M. Craig, A. E. Traynor, K. Quigley, L. Statkute, A. Halverson, M. Brush, L. Verda, B. Kowalska, N. Krosnjar, M. Kletzel, P. F. Whittington and R. K. Burt: Autologous hematopoietic stem cell transplantation in patients with refractory Crohn's disease. *Gastroenterology*, 128(3), 552-63 (2005)

- P. H. Carter and Q. Zhao: Clinically validated approaches to the treatment of autoimmune diseases. *Expert Opin Investig Drugs*, 19(2), 195-213 (2010)
- B. Ngo, C. P. Farrell, M. Barr, K. Wolov, R. Bailey, J. M. Mullin and J. J. Thornton: Tumor Necrosis Factor Blockade for Treatment of Inflammatory Bowel Disease: Efficacy and Safety. *Curr Mol Pharmacol* (2010)
- W. J. Sandborn and S. B. Hanauer: Antitumor necrosis factor therapy for inflammatory bowel disease: a review of agents, pharmacology, clinical results, and safety. *Inflamm Bowel Dis*, 5(2), 119-33 (1999)
- D. W. Claussen: Remicade (infliximab). *Gastroenterol Nurs*, 21(6), 256-9 (1998)
- E. Ricart and W. J. Sandborn: Infliximab for the treatment of fistulas in patients with Crohn's disease. *Gastroenterology*, 117(5), 1247-8 (1999)
- A. Kornbluth: Infliximab approved for use in Crohn's disease: a report on the FDA GI Advisory Committee conference. *Inflamm Bowel Dis*, 4(4), 328-9 (1998)
- B. G. Feagan, W. Reinisch, P. Rutgeerts, W. J. Sandborn, S. Yan, D. Eisenberg, M. Bala, J. Johanns, A. Olson and S. B. Hanauer: The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol*, 102(4), 794-802 (2007)
- C. R. Selvasekar, R. R. Cima, D. W. Larson, E. J. Dozois, J. R. Harrington, W. S. Harmsen, E. V. Loftus, Jr., W. J. Sandborn, B. G. Wolff and J. H. Pemberton: Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg*, 204(5), 956-62; discussion 962-3 (2007)
- R. Rau: Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. *Ann Rheum Dis*, 61 Suppl 2, ii70-3 (2002)
- S. Schreiber and W. J. Sandborn: CLASSIC-I study the efficacy of adalimumab. *Gastroenterology*, 130(6), 1929-30 (2006)
- L. Peyrin-Biroulet, C. Lacombe, X. Roblin and M. A. Bigard: Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol*, 13(16), 2328-32 (2007)
- W. Afif, E. V. Loftus, Jr., W. A. Faubion, S. V. Kane, D. H. Bruining, K. A. Hanson and W. J. Sandborn: Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*, 105(5), 1133-9 (2010)
- N. Goel and S. Stephens: Certolizumab pegol. *MAbs*, 2(2) (2010)
- T. A. Winter, W. J. Sandborn, W. J. De Villiers and S. Schreiber: Treatment of Crohn's disease with certolizumab pegol. *Expert Rev Clin Immunol*, 3(5), 683-94 (2007)
- W. J. Sandborn, B. G. Feagan, S. Stoinov, P. J. Honiball, P. Rutgeerts, D. Mason, R. Bloomfield and S. Schreiber: Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*, 357(3), 228-38 (2007)
- S. Schreiber, M. Khaliq-Kareemi, I. C. Lawrance, O. O. Thomsen, S. B. Hanauer, J. Mccolm, R. Bloomfield and W. J. Sandborn: Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med*, 357(3), 239-50 (2007)
- W. J. Sandborn, S. Schreiber, S. B. Hanauer, J. F. Colombel, R. Bloomfield and G. R. Lichtenstein: Reinduction with certolizumab pegol in patients with relapsed

- Crohn's disease: results from the PRECiSE 4 Study. *Clin Gastroenterol Hepatol*, 8(8), 696-702 e1 (2010)
- G. Hutas: Golimumab as the first monthly subcutaneous fully human anti-TNF-alpha antibody in the treatment of inflammatory arthropathies. *Immunotherapy*, 2(4), 453-60 (2010)
- D. Shealy, A. Cai, K. Staquet, A. Baker, E. R. Lacy, L. Johns, O. Vafa, G. Gunn, 3rd, S. Tam, S. Sague, D. Wang, M. Brigham-Burke, P. Dalmonte, E. Emmell, B. Pikounis, P. J. Bugelski, H. Zhou, B. Scallon and J. Giles-Komar: Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor alpha. *MAbs*, 2(4) (2010)
- S. Mazumdar and D. Greenwald: Golimumab. *MAbs*, 1(5), 422-31 (2009)
- R. D. Inman, J. C. Davis, Jr., D. Heijde, L. Diekman, J. Sieper, S. I. Kim, M. Mack, J. Han, S. Visvanathan, Z. Xu, B. Hsu, A. Beutler and J. Braun: Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum*, 58(11), 3402-12 (2008)
- G. Hutas: Golimumab, a fully human monoclonal antibody against TNFalpha. *Curr Opin Mol Ther*, 10(4), 393-406 (2008)
- V. Cortez-Retamozo, N. Backmann, P. D. Senter, U. Wernery, P. De Baetselier, S. Muyldermans and H. Revets: Efficient cancer therapy with a nanobody-based conjugate. *Cancer Res*, 64(8), 2853-7 (2004)
- J. J. Hulstein, P. G. De Groot, K. Silence, A. Veyradier, R. Fijnheer and P. J. Lenting: A novel nanobody that detects the gain-of-function phenotype of von Willebrand factor in ADAMTS13 deficiency and von Willebrand disease type 2B. *Blood*, 106(9), 3035-42 (2005)
- N. Deckers, D. Saerens, K. Kanobana, K. Conrath, B. Victor, U. Wernery, J. Vercruysse, S. Muyldermans and P. Dorny: Nanobodies, a promising tool for species-specific diagnosis of *Taenia solium* cysticercosis. *Int J Parasitol*, 39(5), 625-33 (2009)
- S. H. Bakhtiari, F. Rahbarizadeh, S. Hasannia, D. Ahmadvand, F. J. Iri-Sofla and M. J. Rasae: Anti-MUC1 nanobody can redirect T-body cytotoxic effector function. *Hybridoma (Larchmt)*, 28(2), 85-92 (2009)
- A. Y. Lam, E. Pardon, K. V. Korotkov, W. G. Hol and J. Steyaert: Nanobody-aided structure determination of the EpsI:EpsJ pseudopilin heterodimer from *Vibrio vulnificus*. *J Struct Biol*, 166(1), 8-15 (2009)
- S. Magez and M. Radwanska: African trypanosomiasis and antibodies: implications for vaccination, therapy and diagnosis. *Future Microbiol*, 4, 1075-87 (2009)
- R. B. Abderrazek, I. Hmila, C. Vincke, Z. Benlasfar, M. Pellis, H. Dabbek, D. Saerens, M. El Ayeb, S. Muyldermans and B. Bouhaouala-Zahar: Identification of potent nanobodies to neutralize the most poisonous polypeptide from scorpion venom. *Biochem J*, 424(2), 263-72 (2009)
- K. Vandenbroucke, H. De Haard, E. Beirnaert, T. Dreier, M. Lauwereys, L. Huyck, J. Van Huysse, P. Demetter, L. Steidler, E. Remaut, C. Cuvelier and P. Rottiers: Orally administered *L. lactis* secreting an anti-TNF Nanobody demonstrate efficacy in chronic colitis. *Mucosal Immunol*, 3(1), 49-56 (2010)

- N. Nishimoto: [Anti-interleukin-6 receptor antibody therapy--from bedside to bench]. *Nihon Rinsho Meneki Gakkai Kaishi*, 29(5), 289-94 (2006)
- H. Ito, M. Takazoe, Y. Fukuda, T. Hibi, K. Kusugami, A. Andoh, T. Matsumoto, T. Yamamura, J. Azuma, N. Nishimoto, K. Yoshizaki, T. Shimoyama and T. Kishimoto: A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology*, 126(4), 989-96; discussion 947 (2004)
- A. Venkiteshwaran: Tocilizumab. *MAbs*, 1(5), 432-8 (2009)
- J. S. Smolen, D. Aletaha, M. Koeller, M. H. Weisman and P. Emery: New therapies for treatment of rheumatoid arthritis. *Lancet*, 370(9602), 1861-74 (2007)
- R. N. Maini, P. C. Taylor, J. Szechinski, K. Pavelka, J. Broll, G. Balint, P. Emery, F. Raemen, J. Petersen, J. Smolen, D. Thomson and T. Kishimoto: Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum*, 54(9), 2817-29 (2006)
- F. J. Dumont: Fontolizumab Protein Design Labs. *Curr Opin Investig Drugs*, 6(5), 537-44 (2005)
- W. Reinisch, D. W. Hommes, G. Van Assche, J. F. Colombel, J. P. Gendre, B. Oldenburg, A. Teml, K. Geboes, H. Ding, L. Zhang, M. Tang, M. Cheng, S. J. Van Deventer, P. Rutgeerts and T. Pearce: A dose escalating, placebo controlled, double blind, single dose and multidose, safety and tolerability study of fontolizumab, a humanised anti-interferon gamma antibody, in patients with moderate to severe Crohn's disease. *Gut*, 55(8), 1138-44 (2006)
- W. Reinisch, W. De Villiers, L. Bene, L. Simon, I. Racz, S. Katz, I. Altorjay, B. Feagan, D. Riff, C. N. Bernstein, D. Hommes, P. Rutgeerts, A. Cortot, M. Gaspari, M. Cheng, T. Pearce and B. E. Sands: Fontolizumab in moderate to severe Crohn's disease: a phase 2, randomized, double-blind, placebo-controlled, multiple-dose study. *Inflamm Bowel Dis*, 16(2), 233-42 (2010)
- P. C. Van De Kerkhof: Novel biologic therapies in development targeting IL-12/IL-23. *J Eur Acad Dermatol Venereol*, 24 Suppl 6, 5-9 (2010)
- X. T. Lima, K. Abuabara, A. B. Kimball and H. C. Lima: Briakinumab. *Expert Opin Biol Ther*, 9(8), 1107-13 (2009)
- P. J. Mannon, I. J. Fuss, L. Mayer, C. O. Elson, W. J. Sandborn, D. Present, B. Dolin, N. Goodman, C. Groden, R. L. Hornung, M. Quezado, Z. Yang, M. F. Neurath, J. Salfeld, G. M. Veldman, U. Schwertschlag and W. Strober: Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med*, 351(20), 2069-79 (2004)
- R. Burakoff, C. F. Barish, D. Riff, R. Pruitt, W. Y. Chey, F. A. Farraye, I. Shafran, S. Katz, C. L. Krone, M. Vander Vliet, C. Stevens, M. L. Sherman, E. Jacobson and R. Bleday: A phase 1/2A trial of STA 5326, an oral interleukin-12/23 inhibitor, in patients with active moderate to severe Crohn's disease. *Inflamm Bowel Dis*, 12(7), 558-65 (2006)
- G. G. Krueger, R. G. Langley, C. Leonardi, N. Yeilding, C. Guzzo, Y. Wang, L. T. Dooley and M. Lebwohl: A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med*, 356(6), 580-92 (2007)

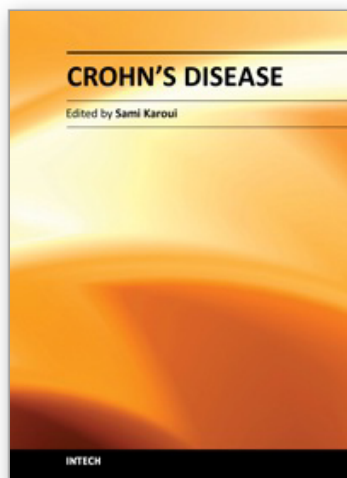
- M. Elliott, J. Benson, M. Blank, C. Brodmerkel, D. Baker, K. R. Sharples and P. Szapary: Ustekinumab: lessons learned from targeting interleukin-12/23p40 in immune-mediated diseases. *Ann N Y Acad Sci*, 1182, 97-110 (2009)
- W. J. Sandborn, B. G. Feagan, R. N. Fedorak, E. Scherl, M. R. Fleisher, S. Katz, J. Johanns, M. Blank and P. Rutgeerts: A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology*, 135(4), 1130-41 (2008)
- S. V. Sitaraman, M. Hoteit and A. T. Gewirtz: Semapimod. *Cytokine. Curr Opin Investig Drugs*, 4(11), 1363-8 (2003)
- I. Dotan, D. Rachmilewitz, S. Schreiber, R. Eliakim, C. J. Van Der Woude, A. Kornbluth, A. L. Buchman, S. Bar-Meir, B. Bokemeyer, E. Goldin, C. Maaser, U. Mahadevan, U. Seidler, J. C. Hoffman, D. Homoky, T. Plasse, B. Powers, P. Rutgeerts and D. Hommes: A randomised placebo-controlled multicentre trial of intravenous semapimod HCl for moderate to severe Crohn's disease. *Gut*, 59(6), 760-6 (2010)
- S. Schreiber, B. Feagan, G. D'haens, J. F. Colombel, K. Geboes, M. Yurcov, V. Isakov, O. Golovenko, C. N. Bernstein, D. Ludwig, T. Winter, U. Meier, C. Yong and J. Steffgen: Oral p38 mitogen-activated protein kinase inhibition with BIRB 796 for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol*, 4(3), 325-34 (2006)
- S. Travis: Advances in therapeutic approaches to ulcerative colitis and Crohn's disease. *Curr Gastroenterol Rep*, 7(6), 475-84 (2005)
- S. Murthy, A. Flanagan, D. Coppola and R. Buelow: RDP58, a locally active TNF inhibitor, is effective in the dextran sulphate mouse model of chronic colitis. *Inflamm Res*, 51(11), 522-31 (2002)
- R. Boismenu, Y. Chen, K. Chou, A. El-Sheikh and R. Buelow: Orally administered RDP58 reduces the severity of dextran sodium sulphate induced colitis. *Ann Rheum Dis*, 61 Suppl 2, ii19-24 (2002)
- C. G. Devry, M. Valdez, L. Gao, J. Wang, K. Kotsch, H. D. Volk, I. Bechmann, R. Buelow and S. Iyer: RDP58, a novel immunomodulatory peptide, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalomyelitis. *J Neuroimmunol*, 152(1-2), 33-43 (2004)
- S. Travis, L. M. Yap, C. Hawkey, B. Warren, M. Lazarov, T. Fong and R. J. Tesi: RDP58 is a novel and potentially effective oral therapy for ulcerative colitis. *Inflamm Bowel Dis*, 11(8), 713-9 (2005)
- W. Liu, B. R. Deyoung, X. Chen, D. P. Evanoff and Y. Luo: RDP58 inhibits T cell-mediated bladder inflammation in an autoimmune cystitis model. *J Autoimmun*, 30(4), 257-65 (2008)
- A. Bourreille, M. Doubremelle, D. R. De La Bletiere, J. P. Segain, C. Toquet, R. Buelow and J. P. Galmiche: RDP58, a novel immunomodulatory peptide with anti-inflammatory effects. A pharmacological study in trinitrobenzene sulphonic acid colitis and Crohn disease. *Scand J Gastroenterol*, 38(5), 526-32 (2003)
- E. Kudlacz, M. Conklyn, C. Andresen, C. Whitney-Pickett and P. Changelian: The JAK-3 inhibitor CP-690550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. *Eur J Pharmacol*, 582(1-3), 154-61 (2008)

- H. Nagai, Y. S. Kim, K. T. Lee, M. Y. Chu, N. Konishi, J. Fujimoto, M. Baba, K. Matsubara and M. Emi: Inactivation of SSI-1, a JAK/STAT inhibitor, in human hepatocellular carcinomas, as revealed by two-dimensional electrophoresis. *J Hepatol*, 34(3), 416-21 (2001)
- K. Yamaoka and Y. Tanaka: Jak inhibitor ; possibility and mechanism as a new disease modifying anti-rheumatic drug. *Nihon Rinsho Meneki Gakkai Kaishi*, 32(2), 85-91 (2009)
- J. S. Fridman, P. A. Scherle, R. Collins, T. C. Burn, Y. Li, J. Li, M. B. Covington, B. Thomas, P. Collier, M. F. Favata, X. Wen, J. Shi, R. Mcgee, P. J. Haley, S. Shepard, J. D. Rodgers, S. Yeleswaram, G. Hollis, R. C. Newton, B. Metcalf, S. M. Friedman and K. Vaddi: Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol*, 184(9), 5298-307 (2010)
- S. Cohen, S. H. Zwillich, V. Chow, R. R. Labadie and B. Wilkinson: Co-administration of the JAK inhibitor CP-690,550 and methotrexate is well tolerated in patients with rheumatoid arthritis without need for dose adjustment. *Br J Clin Pharmacol*, 69(2), 143-51 (2010)
- R. J. Riese, S. Krishnaswami and J. Kremer: Inhibition of JAK kinases in patients with rheumatoid arthritis: scientific rationale and clinical outcomes. *Best Pract Res Clin Rheumatol*, 24(4), 513-26 (2010)
- J. H. Coombs, B. J. Bloom, F. C. Breedveld, M. P. Fletcher, D. Gruben, J. M. Kremer, R. Burgos-Vargas, B. Wilkinson, C. A. Zerbini and S. H. Zwillich: Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*, 69(2), 413-6 (2010)
- A. Suzuki, T. Hanada, K. Mitsuyama, T. Yoshida, S. Kamizono, T. Hoshino, M. Kubo, A. Yamashita, M. Okabe, K. Takeda, S. Akira, S. Matsumoto, A. Toyonaga, M. Sata and A. Yoshimura: CIS3/SOCS3/SSI3 plays a negative regulatory role in STAT3 activation and intestinal inflammation. *J Exp Med*, 193(4), 471-81 (2001)
- T. T. Pizarro and F. Cominelli: Cytokine therapy for Crohn's disease: advances in translational research. *Annu Rev Med*, 58, 433-44 (2007)
- P. A. Carpenter, F. R. Appelbaum, L. Corey, H. J. Deeg, K. Doney, T. Gooley, J. Krueger, P. Martin, S. Pavlovic, J. Sanders, J. Slattery, D. Levitt, R. Storb, A. Woolfrey and C. Anasetti: A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. *Blood*, 99(8), 2712-9 (2002)
- S. Plevy, B. Salzberg, G. Van Assche, M. Regueiro, D. Hommes, W. Sandborn, S. Hanauer, S. Targan, L. Mayer, U. Mahadevan, M. Frankel and J. Lowder: A phase I study of visilizumab, a humanized anti-CD3 monoclonal antibody, in severe steroid-refractory ulcerative colitis. *Gastroenterology*, 133(5), 1414-22 (2007)
- G. Van Assche, W. J. Sandborn, B. G. Feagan, B. A. Salzberg, D. Silvers, P. S. Monroe, W. M. Pandak, F. H. Anderson, J. F. Valentine, G. E. Wild, D. J. Geenen, R. Sprague, S. R. Targan, P. Rutgeerts, V. Vexler, D. Young and R. S. Shames: Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the

- treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut*, 55(11), 1568-74 (2006)
- G. Van Assche, I. Dalle, M. Noman, I. Aerden, C. Swijsen, K. Asnong, B. Maes, J. Ceuppens, K. Geboes and P. Rutgeerts: A pilot study on the use of the humanized anti-interleukin-2 receptor antibody daclizumab in active ulcerative colitis. *Am J Gastroenterol*, 98(2), 369-76 (2003)
- T. J. Creed, M. R. Norman, C. S. Probert, R. F. Harvey, I. S. Shaw, J. Smithson, J. Anderson, M. Moorghen, J. Gupta, N. A. Shepherd, C. M. Dayan and S. D. Hearing: Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther*, 18(1), 65-75 (2003)
- F. H. Gordon, C. W. Lai, M. I. Hamilton, M. C. Allison, E. D. Srivastava, M. G. Fouweather, S. Donoghue, C. Greenlees, J. Subhani, P. L. Amlot and R. E. Pounder: A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. *Gastroenterology*, 121(2), 268-74 (2001)
- D. T. Selewski, G. V. Shah, B. M. Segal, P. A. Rajdev and S. K. Mukherji: Natalizumab (Tysabri). *AJNR Am J Neuroradiol* (2010)
- M. Yildiz, B. Tettenborn and N. Putzki: Natalizumab and Beyond. *Eur Neurol*, 64(4), 236-240 (2010)
- L. Gorelik, M. Lerner, S. Bixler, M. Crossman, B. Schlain, K. Simon, A. Pace, A. Cheung, L. L. Chen, M. Berman, F. Zein, E. Wilson, T. Yednock, A. Sandrock, S. E. Goelz and M. Subramanyam: Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*, 68(3), 295-303 (2010)
- R. W. Olausson, M. R. Karlsson, K. E. Lundin, J. Jahnsen, P. Brandtzaeg and I. N. Farstad: Reduced chemokine receptor 9 on intraepithelial lymphocytes in celiac disease suggests persistent epithelial activation. *Gastroenterology*, 132(7), 2371-82 (2007)
- D. C. Baumgart and W. J. Sandborn: Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*, 369(9573), 1641-57 (2007)
- M. Bayes, X. Rabasseda and J. R. Prous: Gateways to clinical trials. *Methods Find Exp Clin Pharmacol*, 28(10), 719-40 (2006)
- B. Yacyshyn, W. Y. Chey, M. K. Wedel, R. Z. Yu, D. Paul and E. Chuang: A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. *Clin Gastroenterol Hepatol*, 5(2), 215-20 (2007)
- J. R. Philpott and P. B. Miner, Jr.: Antisense inhibition of ICAM-1 expression as therapy provides insight into basic inflammatory pathways through early experiences in IBD. *Expert Opin Biol Ther*, 8(10), 1627-32 (2008)
- S. O. Lopez-Cubero, K. M. Sullivan and G. B. McDonald: Course of Crohn's disease after allogeneic marrow transplantation. *Gastroenterology*, 114(3), 433-40 (1998)
- J. A. Snowden, J. Passweg, J. J. Moore, S. Milliken, P. Cannell, J. Van Laar, R. Verburg, J. Szer, K. Taylor, D. Joske, S. Rule, S. J. Bingham, P. Emery, R. K. Burt, R. M. Lowenthal, P. Durez, R. J. Mckendry, S. Z. Pavletic, I. Espigado, E. Jantunen, A. Kashyap, M. Rabusin, P. Brooks, C. Bredeson and A. Tyndall: Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: a report from the EBMT and ABMTR. *J Rheumatol*, 31(3), 482-8 (2004)

- R. K. Burt, D. Patel, J. Thomas, A. Yeager, A. Traynor, F. Heipe, R. Arnold, A. Marmont, D. Collier, E. Glatstein and J. Snowden: The rationale behind autologous autoimmune hematopoietic stem cell transplant conditioning regimens: concerns over the use of total-body irradiation in systemic sclerosis. *Bone Marrow Transplant*, 34(9), 745-51 (2004)
- R. J. Xavier and D. K. Podolsky: Unravelling the pathogenesis of inflammatory bowel disease. *Nature*, 448(7152), 427-34 (2007)
- P. B. Jeppesen, E. L. Sanguinetti, A. Buchman, L. Howard, J. S. Scolapio, T. R. Ziegler, J. Gregory, K. A. Tappenden, J. Holst and P. B. Mortensen: Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut*, 54(9), 1224-31 (2005)
- A. L. Buchman, S. Katz, J. C. Fang, C. N. Bernstein and S. G. Abou-Assi: Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn's disease. *Inflamm Bowel Dis*, 16(6), 962-73 (2010)
- X. Wang, B. Wang, J. Wu and G. Wang: Beneficial effects of growth hormone on bacterial translocation during the course of acute necrotizing pancreatitis in rats. *Pancreas*, 23(2), 148-56 (2001)
- D. Decker, W. Springer, R. Tolba, H. Lauschke, A. Hirner and A. Von Ruecker: Perioperative treatment with human growth hormone down-regulates apoptosis and increases superoxide production in PMN from patients undergoing infrarenal abdominal aortic aneurysm repair. *Growth Horm IGF Res*, 15(3), 193-9 (2005)
- D. I. Shulman: Gastrointestinal effects of growth hormone. *Endocrine*, 12(2), 147-52 (2000)
- Y. Huang, S. R. Wang, C. Yi, M. Y. Ying, Y. Lin and M. H. Zhi: Effects of recombinant human growth hormone on rat septic shock with intraabdominal infection by *E. coli*. *World J Gastroenterol*, 8(6), 1134-7 (2002)
- J. R. Korzenik and B. K. Dieckgraefe: An open-labelled study of granulocyte colony-stimulating factor in the treatment of active Crohn's disease. *Aliment Pharmacol Ther*, 21(4), 391-400 (2005)
- M. Takazoe, T. Matsui, S. Motoya, T. Matsumoto, T. Hibi and M. Watanabe: Sargramostim in patients with Crohn's disease: results of a phase 1-2 study. *J Gastroenterol*, 44(6), 535-43 (2009)
- J. F. Valentine, R. N. Fedorak, B. Feagan, P. Fredlund, R. Schmitt, P. Ni and T. J. Humphries: Steroid-sparing properties of sargramostim in patients with corticosteroid-dependent Crohn's disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Gut*, 58(10), 1354-62 (2009)
- P. J. Mannon, F. Leon, I. J. Fuss, B. A. Walter, M. Begnami, M. Quezado, Z. Yang, C. Yi, C. Groden, J. Friend, R. L. Hornung, M. Brown, S. Gurprasad, B. Kelsall and W. Strober: Successful granulocyte-colony stimulating factor treatment of Crohn's disease is associated with the appearance of circulating interleukin-10-producing T cells and increased lamina propria plasmacytoid dendritic cells. *Clin Exp Immunol*, 155(3), 447-56 (2009)
- C. Abraham and J. H. Cho: Bugging of the intestinal mucosa. *N Engl J Med*, 357(7), 708-10 (2007)
- N. Barnich, F. A. Carvalho, A. L. Glasser, C. Darcha, P. Jantscheff, M. Allez, H. Peeters, G. Bommelaer, P. Desreumaux, J. F. Colombel and A. Darfeuille-Michaud: CEACAM6

- acts as a receptor for adherent-invasive *E. coli*, supporting ileal mucosa colonization in Crohn disease. *J Clin Invest*, 117(6), 1566-74 (2007)
- C. P. Tamboli, C. Neut, P. Desreumaux and J. F. Colombel: Dysbiosis in inflammatory bowel disease. *Gut*, 53(1), 1-4 (2004)
- D. E. Elliott and J. V. Weinstock: Helminthic therapy: using worms to treat immune-mediated disease. *Adv Exp Med Biol*, 666, 157-66 (2009)
- R. W. Summers, D. E. Elliott, J. F. Urban, Jr., R. Thompson and J. V. Weinstock: *Trichuris suis* therapy in Crohn's disease. *Gut*, 54(1), 87-90 (2005)



Crohn's Disease

Edited by Dr. Sami Karoui

ISBN 978-953-307-811-3

Hard cover, 210 pages

Publisher InTech

Published online 13, January, 2012

Published in print edition January, 2012

In this book, several important points regarding Crohn's disease are discussed. In the first section, we focus on etiopathogeny of Crohn's disease and the recent advances in our overall understanding of the disease - specifically, the role of the gut epithelium, alterations of the epithelial crypts, and the roles of the different cytokines in the pathophysiology of Crohn's disease. In the second section, a diagnosis of Crohn's disease is discussed. Another particular area of focus is in the diagnosis of intestinal tuberculosis, and the role of mycobacterium avium in Crohn's disease. In the third and final section, the management of Crohn's disease is discussed, with a focus on recent evidence-based medicine recommendations.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Talha A. Malik (2012). Advances in Management of Crohn's Disease, Crohn's Disease, Dr. Sami Karoui (Ed.), ISBN: 978-953-307-811-3, InTech, Available from: <http://www.intechopen.com/books/crohn-s-disease/advances-in-management-of-crohn-s-disease>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen