A cure for Crohn’s?

Dr Fabio Cominelli is directing a programme of research into the underlying causes of inflammation in this debilitating gastrointestinal disease, with a central focus on dysfunctional immune system response and new treatment paradigms.

Can you elaborate on the idea that an autoimmune response is a major causative factor for Crohn’s disease (CD)?

CD is a chronic inflammatory condition of the intestine that can affect the entire gastrointestinal tract. The proposition is that this leads to an abnormal interaction between the intestinal immune system and luminal antigens, including commensal flora and dietary factors. Although Crohn’s is not considered a classical autoimmune disease, evidence of the presence of autoantibodies and extra-intestinal manifestations points to a role for autoimmune mechanisms, at least in a subgroup of patients.

What led you to work in this area of research?

I am a physician-scientist with clinical training in gastroenterology and basic research, and expertise in mucosal immunology and cytokine biology. Exposure to role models, mentors and patients affected by this condition led to me applying my expertise in an effort to find a ‘cure’ for CD.

Are cases of CD often misdiagnosed?

In certain individuals diagnosis is delayed due to confounding factors. Often, adolescents with chronic gastrointestinal symptoms who are diagnosed with irritable bowel syndrome are later diagnosed with CD and inflammatory bowel disease. It is also frequently misdiagnosed in underdeveloped countries, due to limited access to healthcare and advanced technology.

Can you explain the four separate projects that comprise your current research programme?

Our central hypothesis, that a deficit in intestinal innate immunity may play a pathogenic role in CD, challenges the traditional paradigm that this condition is caused by an overly aggressive immune response against the commensal flora.

Our first two projects deal with the role of the nod2 gene in the pathogenesis of experimental ileitis. Projects three and four are focused on understanding the role of critical innate immune cells, such as dendritic cells and macrophages, in intestinal inflammation, and their interactions with the intestinal epithelium.

How comparable are the mouse models you are using with CD in humans?

The SAMP 1Yit/Fc mouse model of CD-like ileitis has many similarities to the disease in humans with regard to histopathological features, location of disease (terminal ileitis), chronicity of intestinal lesions and extra-intestinal manifestations. The approach we are using to study this model is to combine antibody blockade experiments and genetic deletions. This allows us to precisely investigate the role of specific genes and transcription factors in the pathogenesis of CD-like ileitis.

You have had a successful career exploring cytokine biology; can you outline some of your major findings in this area and how they contribute to your current research project?

Over the years, our group has made important discoveries in the field of intestinal cytokine biology and leukocyte trafficking. These studies have provided the foundation for developing novel treatment modalities for patients affected by this disease. Current ongoing projects are following up on these discoveries to understand the role of novel cytokines and adhesion molecules in the pathogenesis of chronic intestinal inflammation.

Apart from the associated honour and prestige, can recognition in the form of awards such as the Outstanding Investigator Award, which you received in 2002, be a significant boost to a scientist’s career in other ways?

Receiving a scientific award for a major contribution to a specific field of research, in my case mucosal immunology and inflammatory bowel disease, has allowed me to become an opinion leader and to develop international collaborations. Many students and postdoctoral fellows come to our laboratory to pursue rigorous training in this field of research.

Some of your research has laid the foundations for clinical trials using anti-cytokine therapy. How have these progressed?

Monoclonal antibodies against tumour necrosis factor and adhesion molecules such as α4β7 have been approved by the Federal Drug Administration for the treatment of patients with inflammatory bowel disease. Many other new drugs are under investigation as future therapies. Our experiments, and also the contribution of many laboratories around the world, have provided the foundation for these advances.

How do you hope that your work will contribute to the treatment of Crohn’s disease?

We are pursuing novel hypotheses for the pathogenesis of chronic intestinal inflammation using a highly relevant mouse model of experimental CD. Based on our findings, we hope to develop novel treatment modalities that challenge the traditional paradigm, with the ultimate goal of developing a ‘cure’ for at least a subgroup of patients affected by this devastating disease.
A new hypothesis for the **pathogenesis** of Crohn’s disease

Using a unique animal model of chronic ileitis, research at **Case Western Reserve University** in Ohio aims to understand the key molecular mechanisms that cause Crohn’s disease. Their findings so far have overturned current thinking about effective treatment approaches

**CROHN’S DISEASE (CD)** is a chronic inflammatory bowel disease affecting 1 million individuals in North America and several million more worldwide. The incidence of CD is known to be increasing and there is currently no cure. As the disease’s main symptoms are severe abdominal pain, fever, diarrhoea and fatigue, it can initially present as an isolated acute gastrointestinal upset, meaning that diagnosis is often only made after repeated medical consultations. CD can affect any part of the gastrointestinal tract, or indeed the whole of it. It can cause ulcers to form on the lining of the tract, and in some cases these ulcers penetrate through the intestinal wall, creating fistulas – tunnel-shaped structures that can then act as an unpleasant link between parts of the intestine, or between the intestine and other organs. Moreover, the intestinal epithelium no longer acts as a barrier between immune cells and luminal bacteria, so significant infections can result. A further complication of the disease is that scarring of the gastrointestinal wall from ulcers or swelling due to inflammation can cause intestinal blockages and therefore extreme discomfort.

While most cases of CD are not life-threatening, the condition is generally life-changing. The growth and development of a child with CD can be severely affected until treatment takes effect, and the quality of life for all sufferers is considerably reduced. Treatment in milder cases consists of multiple interventions including medication, dietary changes to avoid foods that appear to trigger CD episodes and, in severe cases, surgery to remove or adjust a part of the gastrointestinal tract is needed. There is clearly a real need to respond to this highly debilitating condition in a decisive way that prevents it from causing major damage.

**SEEKING THE CAUSE OF CD**

A surge in numbers of youths and young adults diagnosed with CD over the last 10 years has given rise to a notion that the disease results from a diet of junk food. However, according to Dr Fabio Cominelli, the
INTELLIGENCE

INNATE IMMUNITY AND EXPERIMENTAL CROHN’S DISEASE

OBJECTIVES
To carry out a programme comprising of four projects and two core laboratories, each of which uses an experimental mouse model of ileitis to examine a facet of Crohn’s disease in humans. The ultimate goal is to conclusively establish the underlying factors that contribute to this debilitating disease, and investigate the hypothesis that the innate immune response to ‘unknown’ antigens in the intestine triggers the condition’s characteristic inflammation.

KEY COLLABORATORS
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FABIO COMINELLI is Professor of Medicine and Pathology, Chief of the Division of Gastroenterology and Liver Disease, and Director of the Digestive Health Institute at Case Western Reserve University (CWRU) and University Hospitals of Cleveland. He is also the inaugural awardee of the Hermann Menges Jr Chair in Internal Medicine. Cominelli is the Principal Investigator (PI) and Director of a National Institutes of Health (NIH) Program Project Grant, studying the role of innate immunity in experimental Crohn’s disease, and two R01 grants focused on the role of cytokines and commensal flora in the pathogenesis of intestinal inflammation. He is also the PI of a T32 Training grant in Digestive Disease Sciences at CWRU, as well as the PI and Director of the newly funded Cleveland NIH Digestive Diseases Research Core Center.

Cominelli has convinced that, when a person has a genetic predisposition to CD, the primary cause is an abnormality in the response of the intestinal immune system cells when they meet certain luminal antigens: “Increasing evidence suggests that a deficit of the intestinal innate immune system may play a causative role in CD,” he explains. As Director of the Digestive Health Institute at University Hospitals of Cleveland, and Principal Investigator and Director of the Cleveland Digestive Diseases Research Core Center at Case Western Reserve University School of Medicine in Cleveland, Ohio, Cominelli is heading up a research programme that aims to discover the mechanisms of this breakdown in normal immune system function that instigate the onset of CD.

The central hypothesis of Cominelli’s programme is that the innate immune response to ‘unknown’ antigens in the luminal space of the intestine triggers the characteristic inflammation found in CD. In the project that he is personally managing within the programme, Cominelli is closely examining the mechanisms of NOD2, as the function of this protein is to initiate signalling that then instigates an immune reaction to muramyl dipeptide (MDP), a molecular compound present in specific bacteria: “Our preliminary data suggest that a dysregulation in NOD2 signalling and intestinal permeability may precede the development of chronic ileitis,” Cominelli explains. “These effects are associated with abnormal dendritic and macrophage function and excessive activation of the adaptive immune system. The resulting proinflammatory effect leads to the chronic inflammatory response characteristic of CD.”

TOWARDS A NEW TREATMENT PARADIGM
To ascertain the interactions that result in intestinal inflammation, Cominelli is exploring NOD2/MDP signaling coupled with lack of integrity of the intestine epithelium caused by the ulcers and fistulas in ileitis, using mice that he has specially bred from an early Japanese strain of accelerated ageing. Cominelli’s strain is the SAMP1 Yit/Fc (SAMP) mouse which, by 10 weeks of age, spontaneously develops a form of ileitis that closely resembles CD in humans. The disease, which is accelerated by luminal bacteria in the ileum, only affects the SAMP ileum and not the rest of the small intestine or colon. The SAMP mice also exhibit extra-intestinal manifestations including periodontal and skin lesions in correlation with bouts of intestinal inflammation. Importantly, the mouse pattern of disease and their responses to selected treatments closely mimic those of humans.

Alongside Cominelli’s project, there are three other projects in the programme. Dr Derek Abbott is running a project that is alternatively investigating whether chronic intestinal inflammation simply results from exaggerated NOD2 signalling. In other programme projects, Dr Klaus Key is running an exploration of the role of myeloid cells in mediating chronic ileitis, and Dr Theresa T Pizarro is studying epithelial-immune cell interactions, specifically the interplay between the intestinal epithelium, dendritic cells and T-regulatory cells. All the projects share a centralised SAMP mouse breeding facility that also provides pathologic and tissue analyses.

Cominelli’s programme has been running for four years now, and he is encouraged by the results obtained so far, which include some key discoveries. He will therefore soon be seeking a renewal of the grant to extend the teams’ investigations further, towards the ultimate goal of rapid translation of the results into new therapies.

At present, CD patients are typically prescribed medications that suppress immune system function. This then exposes them to the risk of contracting additional infections and diseases. The interim results of the programme and its projects have led Cominelli and his colleagues to the view that such treatment is unlikely to be an effective solution, and it may be that medical professionals need to entirely reconsider the basis for this method. Instead, Cominelli proposes a wholly new paradigm: “We believe that stimulation of the intestinal innate immune system, rather than its suppression, is beneficial to prevent or treat early Crohn’s disease. We are now developing novel therapeutic modalities based on the NOD2 gene and probiotics that may accomplish this goal,” he concludes.