Tailored Therapies for IBD: A Look into the Future

Symposium 213
Milan (Italy), October 5–6, 2018
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Tailored Therapies for IBD: A Look into the Future
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Successful long-term management of Crohn’s disease or ulcerative colitis requires an understanding of the factors that underlie complex clinical presentations, and also requires treatment to be tailored to the particulars of each patient’s situation and most pressing pathogenic factors. However, these steps are not possible without first taking a global view of the entire functional network of IBD pathogenesis. This network includes both genetic predisposition and environmental factors, while the microbiome and the immune system also play crucial roles.

However, these individual factors do not arise independently, but rather are tightly intertwined. As a result, it is also necessary to pay attention to the interactions between the individual players in this functional network. The implications of these insights for clinical practice were the topic of discussion by international experts at Symposium 213 convened by the Falk Foundation e.V. in Milan (Italy).

One point of consensus in these discussions was the fact that going forward, the central question for planning treatment will no longer be whether a step-up or top-down strategy is preferable. There is no doubt that the current standard therapy will retain its established importance. However, it would be helpful to complement this standard therapy by identifying predictive strategies and biomarkers that could then be used to predict both the likelihood of success and the potential side effects of the available treatment regimens.

Going forward, it will be more necessary than ever to take patients’ pathophysiological phenotype and clinical presentation into account when planning treatment strategies. Treatment algorithms will also need to incorporate patients’ specific risk factors, genetically predispositions, and the pharmacokinetic properties of the selected drugs in order to tailor treatment to be targeted and personalized.

The management of IBD is thus on the cusp of a paradigm shift. Incorporation of the parameters described above is causing a shift away from traditional, hypothesis-driven biomedical research and toward data-driven clinical trials. This shift is in turn powering the development of personalized therapy and of precision medicine for the management of Crohn’s disease and ulcerative colitis.

Scientific organizers
Prof. S. Danese, Dr. A. Armuzzi, Prof. A. Dignass and Prof. P. Gionchetti
**Targeted therapies for inflammatory bowel disease: a look into the future**

Inflammatory bowel disease (IBD) is well-known for being an incredibly heterogeneous set of disorders, so it is no surprise that one-size-fits-all treatment is often not the right choice for a patient’s individual situation. Going forward, therapies will be much more oriented toward the individual characteristics of each patient’s disease. In fact, it may even be necessary to come up with new definitions of Crohn’s disease and ulcerative colitis at some point in the future that differentiate the conditions based on the phenotype and determinant factors of each patient’s disease. This topic was the focus of Symposium 213 convened by the Falk Foundation e.V. in Milan (Italy).

To date, more than 200 genes have been identified as candidate genes for the pathogenesis of IBD. However, the analysis of simple genetic markers is far from sufficient to characterize IBD. Of even greater importance are the genetic signatures in the mucosa, as well as the signaling pathways and the regulatory mechanisms which are controlled by these pathways. As V. Annese, Dubai (United Arab Emirates) explained, “these parameters have even more explanatory power.” These expression profiles will therefore likely provide a major contribution toward characterizing patients, assessing their prognosis, and predicting the therapeutic potential of different treatment regiments on a patient-by-patient basis.

![IBD overview diagram](modified from Fiocchi C. Dig Dis. 2014; 32, Suppl 1:96–102)
Is it time to redefine IBD?

Nonetheless, even genetics only represents one of many factors that play a major role in the manifestation and individual character of Crohn’s disease and ulcerative colitis. The course of the disease can also be modulated by epigenetic parameters, the activity of different immune factors, the composition of the microbiota as well as by various environmental factors. In light of this complexity, V. Annese thinks it may be time to redefine IBD in a manner that incorporates both these factors and the patient’s clinical presentation. A system of this nature would need to differentiate between several different forms of the disease, for example:

– fistulizing Crohn’s disease
– stricturing Crohn’s disease
– Crohn’s disease with perianal complications
– and a form of the disease that does not respond to anti-TNF strategies.

It will also be necessary to differentiate different clinical presentations of ulcerative colitis. V. Annese provided several examples of such differentiation, including a form of ulcerative colitis refractory to pharmacotherapy, a form that does not respond to anti-TNF treatment, and a delayed-onset form of ulcerative colitis. As V. Annese pointed out, “differentiating these forms of the disease will lead us to different treatment strategies which focus on each patient’s individual situation.”

Optimize treatment before considering escalation

Even in light of the new treatment strategies for Crohn’s disease and ulcerative colitis that are looking ever-more promising for the future, established drugs remain vital for treatment. A. Dignass, Frankfurt (Germany), illustrated this point using ulcerative colitis as an example. He explained that mesalazine is the standard therapy for both inducing and maintaining remission of mild to moderate ulcerative colitis, noting that “we can treat the majority of patients adequately using this drug.”

This is also bolstered by the fact that mesalazine is available in several different pharmaceutical forms, including tablets or granules for oral administration, and suppositories, enemas or foam products for rectal administration. These different forms can even be combined depending on the location of the inflammation. According to A. Dignass, combining different forms of application can increase the effectiveness of mesalazine. “In most patients, we can achieve mucosal healing and durable improvement in their ability to work and quality of life.”

5-ASA interferes with several different cellular regulatory mechanisms

Fig. 2: Mesalazine can interfere at several different levels in the regulatory mechanisms responsible for the pathogenesis of IBD. Source: modified from Campregher C, et al. Best Pract Res Clin Gastroenterol. 2011;25(4–5):538. (Mod.: A. Dignass)
Overview

According to data from the literature, budesonide is significantly more effective than placebo and nearly equivalent to other conventional drugs. However, S.P.L. Travis pointed out that a Cochrane analysis and several other publications have shown budesonide to be much better tolerated than conventional corticosteroids, especially with regard to the side effects that are typical of steroid therapy. He noted that “modern corticosteroids such as budesonide that have low oral bioavailability thus represent a good bridge between standard mesalazine therapy and systemic steroid therapy.”

Ask patients about their adherence to therapy

If treatment turns out to be less successful than expected, first patients need to be asked about their adherence to therapy before treatment is escalated. Strategies for improving adherence can be implemented as early as the prescription process, since it is very likely that patients will have an easier time taking medication once daily instead of at several time points each day.

Patients must also be informed in detail about the importance of adherence to therapy. As A. Dignass pointed out, they should especially be made aware of the fact that robust adherence can greatly improve the effectiveness of their medication. Greater adherence may also help reduce the need to escalate treatment and may help patients maintain their quality of life and ability to work. Moreover, the chemopreventive effects of mesalazine may help prevent the development of colorectal cancer.

Steroid therapy should also be tailored

A differentiated approach is required when administering corticosteroids, as S.P.L. Travis, Oxford (Great Britain), explained. These drugs have been a standard component of IBD therapy since the middle of the previous century. As S.P.L. Travis said, “they are especially well-established for the treatment of ulcerative colitis, since they have been clearly shown to reduce mortality versus patient groups who did not receive steroid therapy.”

Although these drugs are quite effective, the use of such conventional agents is limited due to their side effects, some of which can be quite serious. As an alternative, S.P.L. Travis proposed budesonide, a drug which is also very effective yet is associated with many fewer side effects. Because the oral bioavailability of this corticosteroid is so low, its effects are essentially those of a topical steroid.

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According to S.P.L. Travis, local steroids such as budesonide should especially be the first choice for IBD patients with considerable comorbidities such as diabetes and/or hypertension, osteoporosis or obesity. Moreover, budesonide is generally suitable for IBD patients who are intolerant of conventional steroids or are unwilling to take them, as well as for patients with emotional lability, severe mood swings and/or who are susceptible to depression.

Fig. 3: Oral bioavailability of different steroids (modified from Brattsand R. Can J Gastroenterol. 1990;4(7):407–14)
Symposium 215

IBD: From Diagnosis to Therapy

July 5–6, 2019
St. Petersburg, Russia

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New advances toward biomarkers and targeted therapy

The management of inflammatory bowel disease (IBD) could be vastly improved by the identification of biomarkers that would allow patients’ individual prognoses to be predicted and treatment strategies to be mapped out in advance. Although the real breakthrough in biomarker research has yet to be realized, several important steps have nonetheless been achieved toward the tailored therapy of IBD.

**Predictive strategies under development**

According to M.C. Dubinsky, New York (USA), the upcoming development of predictive strategies may allow prognosis of Crohn’s disease or ulcerative colitis at a comparably early stage of the disease and may make a vital contribution toward personalized treatment. While IBD represents a group of progressive disorders, the rate of disease progression varies greatly from one patient to the next. It would thus be beneficial to know each patient’s phenotype as early as possible. As M.C. Dubinsky explained, “this would give us the chance to predict the long-term course of patients’ disease and modify their treatment accordingly.” For example, if it were possible to predict early on that a patient has an aggressive form of disease, he or she would be started on an intense course of strong medications as rapidly as possible, despite the greater likelihood of side effects. On the other hand, patients predicted to have a more mild to moderate form of disease could be treated with standard therapies, which usually involve fewer side effects and are more cost-effective. M.C. Dubinsky noted that “we need to avoid overtreating patients.”

**Which biomarkers may have prognostic relevance?**

She then cited patients’ age, specific symptoms, extent of bowel inflammation, and endoscopic findings as markers which may have prognostic relevance for treatment response and even potentially for mucosal healing. Genetic factors, expression profiles, serology and laboratory findings, and stool test results may also be used as additional prognostic factors. Each of these factors is not just important when treatment is initiated: monitoring their changes over the course of the disease can also provide insights into the patient’s prognosis. M.C. Dubinsky then used the example of Crohn’s disease to illustrate how measurement of these parameters can be implemented directly in clinical practice. Although anti-TNF drugs and immunomodulators are most effective when administered early in the course of Crohn’s disease, very few patients actually receive these drugs at this time point. This is due to several reasons, including concerns about potential side effects, the relatively high cost of these drugs, and especially the inability to stratify patients between those who would actually benefit from these drugs and those who would not.
In brief

Using endoscopic findings for prognosis

According to M. Daperno, Turin (Italy), endoscopic findings can also be used for prognosis. The detection of endoscopic lesions with deep ulcerations is associated with a much higher likelihood of requiring colectomy at a later point in time. The recurrence of lesions after surgery is also associated with a greater probability of requiring additional surgery. In contrast, healing of these lesions and (possibly complete) mucosal healing are predictive of a significantly lower risk of surgery at a later time. The prognosis also depends on how completely mucosa have healed, which can be verified using several different scores including the CDEIS (Crohn’s Disease Endoscopic Index of Severity) for Crohn’s disease and the UCEIS (Ulcerative Colitis Endoscopic Index of Severity) for ulcerative colitis. G. Fiorino, Rozzano (Italy), reported that radiological techniques can also be used to assess the course of disease. This is particularly relevant for Crohn’s disease, since imaging procedures are often better tools for gauging the extent of the disease and monitoring emergent complications such as stenoses and strictures.

Treatment primarily based on algorithms

Currently, IBD is treated primarily using treatment algorithms that have been developed over the years, as reported by F. Baert, Roeselare (Belgium). Crohn’s disease is typically treated using corticosteroids, preferably with drugs such as budesonide that have a much lower risk of side effects than conventional corticosteroids. Another option is azathioprine. Should these therapies not provide adequate management, treatment escalation using anti-TNF drugs is indicated. Mesalazine is the main standard therapy for ulcerative colitis. If this treatment is not sufficient, patients may also be given corticosteroids in combination with azathioprine, while patients with steroid-dependent or steroid-refractory disease may be given anti-TNF drugs. F. Carbonnel, Le Kremlin-Bicêtre (France), also suggested methotrexate as an additional potential treatment option. Methotrexate can be administered as monotherapy or in combination with biologics, and can be used in Crohn’s disease for both inducing and maintaining remission. For ulcerative colitis, it appears to be indicated only for inducing remission and is nearly ineffective as maintenance therapy.

As Y. Chowers, Haifa (Israel), pointed out, the lack of biomarkers that could allow clinicians to make a reliable prognosis of a patient’s disease means that they must rely on the existing parameters to the best of their ability. The potential side effects of the available drugs must also be taken into consideration when planning treatment, especially the risks of infection and cancer, particularly lymphoma.

When should patients stop taking certain drugs?

It is often challenging in clinical practice to decide when to discontinue a therapy that was initially effective but is not delivering the expected positive long-term outcomes. According to I. Dotan, Petah Tikva (Israel), clinicians observe this phenomenon of secondary loss of response all too often. For example, many patients initially respond well to treatment with infliximab, but its effects then begin to taper over time in a considerable number of patients. The annual rate of secondary loss of response to infliximab is 13%, and is even higher for adalimumab at 20%. A patient’s individual risk of this reaction can be estimated using fecal calprotectin levels: two calprotectin measurements above 300 μg/g within the same month are considered to be clear evidence of an impending relapse. However, this does not always mean that the drug must then be discontinued.
Should treatment be optimized instead of discontinued?

According to M. Ferrante, Leuven (Belgium), a much better approach may be to optimize anti-TNF treatment. He proposed dose escalation or switching to a different drug from the same class of medicines as two options. E. Louis, Lütich (Belgium), explained that the decision about whether to discontinue anti-TNF treatment should also take the patient’s history, response to initial standard therapy (or lack thereof), age, and any comorbidities into consideration. In general, the treat to target approach should be pursued for IBD, and the option of de-escalating treatment should always be considered whenever a treatment objective is met. De-escalation is typically associated with both a favorable cost-benefit ratio but also a much greater risk of relapse.

New drugs: integrin antagonists

Among the new drugs available to treat IBD, vedolizumab and ustekinumab are currently the topic of the most discussion. As B.E. Sands, New York (USA), explained, vedolizumab is a humanized monoclonal antibody belonging to the class of integrin antagonists. The drug was approved for the treatment of ulcerative colitis and Crohn’s disease in 2014 after studies demonstrated its clinical effectiveness at inducing remission. This integrin antagonist is indicated for the treatment of adult patients with moderate to severe active ulcerative colitis and Crohn’s disease who do not respond or do not adequately respond to conventional therapy or anti-TNF drugs, or who no longer adequately respond to or do not tolerate such drugs. One of the key benefits of vedolizumab treatment is its steroid-sparing effect. According to S. Schreiber, Kiel (Germany), this drug is also of therapeutic importance for Crohn’s disease, and can induce deep endoscopic remission and mucosal healing in previously treatment-refractory patient populations under certain circumstances.

New drugs: IL-12/IL-23 antibodies

Ustekinumab is a monoclonal antibody that targets the cytokines interleukin-12 and interleukin-23 (IL-12, IL-23), which are thought to play a role in the pathogenesis of Crohn’s disease, as W.J. Sandborn, La Jolla (USA) explained. This drug interferes with the signaling pathways of both interleukins. It can be prescribed to patients with moderate to severe Crohn’s disease if treatment with conventional immunomodulators is not or is no longer adequately effective, or if treatment with TNF blockers is not as beneficial as expected or is not tolerated. As S. Bonovas, Rozzano (Italy), reported, the data available on these relatively new drugs appear to point to a favorable safety profile. However, additional studies, especially long-term studies, are still required for a conclusive analysis. Such studies should focus in particular on the risk of serious infections, opportunistic infections, tuberculosis, and cancer. S. Bonovas thus called for the initiation of more real-world trials, preferably a large-scale registry study that could also capture any potentially-elevated risk of developing cancer. Aside from ustekinumab, M.C. Fantini, Rome (Italy), reported that other anti-IL-23 inhibitors are also being developed to treat IBD, including briakinumab.
The new kids on the block of IBD therapy

Another new development in the treatment of IBD presented at the symposium is inhibitors of Janus kinases (JAK), which are a family of cytoplasmic tyrosine kinases that activate the intracellular JAK-STAT signaling pathway. According to R. Panaccione, Calgary (Canada), JAK inhibitors are small molecules that bind to receptors on the cell surface and induce their dimerization. Several members of the class of JAK inhibitors are currently in clinical development, including peficitinib, upadacitinib and filgotinib. Tofacitinib is the most mature of these drugs, and is already approved in Germany to treat moderate to severe ulcerative colitis. The advantages of JAK inhibitors include a rapid onset, a steroid-sparing effect, the absence of immunogenicity, as well as the convenience of oral administration. Although many of these drugs are already being used to treat other indications, in R. Panaccione’s opinion extensive long-term data is still required before their suitability for IBD can be conclusively determined. Another option for expanding the therapeutic spectrum of IBD is anti-adhesion molecules such as natalizumab, which has already been in clinical use for many years to treat multiple sclerosis. As S. Ghosh, Birmingham (Great Britain), explained, this drug belongs to the class of integrin antagonists and thus represents an alternative to vedolizumab. Other members of this class of drugs are also in clinical development; of these, S. Ghosh highlighted etrolizumab, abrilumab, and AJM300. A number of other strategies are also being pursued to design anti-adhesion molecules, including receptor-ligand blockers, allosteric inhibitors, and inhibitors of transcription-translation pathways. According to B.G. Feagan, London, (Canada), work is also progressing on the development of sphingosine-1-phosphate receptor modulators such as fingolimod, which is also already being used to treat multiple sclerosis. Modulation of S1P receptors is also expected to elicit a therapeutic effect in patients with Crohn’s disease or ulcerative colitis.

Pharmacological antifibrotic strategies

The development of drugs that inhibit the fibrotic processes in Crohn’s disease has also raised the hopes for new advances in the treatment of IBD. According to G. Rogler, Zurich (Switzerland), fibrosis is a relevant issue in Crohn’s disease because it is associated with a high risk of complications. This is reflected by the finding that approximately two-thirds of Crohn’s patients develop strictures and stenoses within 10 years of diagnosis. The majority of these patients then require surgery to treat these complications. Unfortunately, anti-inflammatory drugs do not inhibit fibrosis, and antifibrotic agents have not yet become available for IBD. G. Rogler stressed that “the development of fibrosis remains an unsolved problem, especially for Crohn’s disease.” To confront this issue, specific models are currently being developed to test drugs already in use for other indications. One example of these drugs cited by G. Rogler is pirfenidone. Furthermore, MMP9 antibodies are also currently under development in the hope that they may help prevent fibrosis.

Non-pharmacological interventions as additional options

When conservative therapy fails to control the disease, surgery is often the only option, as A. Spinelli, Rozzano (Italy), pointed out. However, surgery must also be tailored, and physicians must determine beforehand whether laparoscopy is sufficient or whether open surgery is unavoidable. As A. Spinelli pointed out “a targeted, personalized approach is required for surgery as well.” This approach must start well before the operation itself by ensuring that the patient has an optimal nutritional status. The surgery must also be scheduled for the optimal time point, which requires taking the patient’s needs and plans into consideration. The operation itself should be as minimally-invasive as possible. According to S.R. Steele, Cleveland (USA), this is especially the case for operations intended to treat perianal Crohn’s disease. In these cases, the approach is completely dependent on the patient’s individual situation. Surgery should typically be combined with conventional therapy, an approach which often taxes the patience of both doctors and patients.
Cancer patients with IBD present a special challenge in treatment management

Some clinical scenarios represent an additional hurdle to managing IBD. One example of this is treating patients with a history of cancer. According to L. Beaugerie, Paris (France), there is general consensus that immunosuppressive therapy should be discontinued in patients who develop cancer, or at least postponed until the cancer is under control. Exceptions to this rule can only be justified if it is the first instance of a form of cancer known to be less aggressive, such as basal cell carcinoma or controlled, HPV-related cervical dysplasia. However, L. Beaugerie noted that the required anticancer therapy can be expected to exacerbate IBD in these patients. This phenomenon has been especially observed in cases of breast cancer treated with docetaxel, renal cell carcinoma treated with sunitinib and sorafenib, as well as in patients with various forms of cancer treated using novel immunotherapy strategies. It is generally recommended that immunosuppressive treatment be discontinued for two to five years in cancer patients unless they have high disease activity and no other therapeutic alternatives. In these cases, it is also very important to work closely with the patient’s oncologists.

In brief

Many factors influence the outcome of surgery

In any case, about 40% of patients who undergo surgery can expect a recurrence of their complications, as M. Vecchi, Milan (Italy), noted. The risk factors for these complications include having a severe form of disease prior to surgery, poor nutritional status, and comorbidities. The outcome of surgery also depends on the timing of the surgery, not to mention the experience of the surgical team. Hence, the benefits and risks of surgery must be weighed carefully against the continuation of medical therapy. This is particularly the case with fistulizing Crohn’s disease, as P. Gionchetti, Bologna (Italy) and P.G. Kotze, Curitiba (Brazil), explained in a pro/con discussion on this topic. Fistulizing Crohn’s disease is known to be the most aggressive form of the disease, and a medication-only treatment approach is associated with several limitations. Patients therefore typically undergo surgery combined with adjunct perioperative medication using many of the same drugs as used for preoperative medication: corticosteroids, thiopurines, methotrexate, and biologics. M. Vecchi stressed that “the proper choice of perioperative medication can definitely improve the likelihood that surgery is successful.”
A difficult case with prior serious infections

Patients with a history of serious infections present special difficulties for managing treatment. According to J. Lindsay, London (Great Britain), opportunistic infections also pose a therapeutic challenge. Patients treated with high-dose corticosteroids or various biologics are at a much higher risk of such infections, including reactivation of latent infections. For example, tofacitinib is associated with a risk of herpes zoster in patients with a history of herpes virus infections. The risk of tuberculosis reactivation in patients with latent mycobacterial infections is also well known. As F. Gomollón, Saragossa (Spain), pointed out, this hazard must always be considered when patients taking anti-TNF therapy develop complications.

State-of-the-art lecture
“This is the future of inflammatory bowel disease treatment”

It appears that the complex nature of inflammatory bowel disease (IBD) is still frequently underestimated. According to C. Fiocchi, Cleveland (USA), this underestimation is reflected in the way physicians treat these disorders. Until now, the heterogeneity of the pathogenesis and individual clinical presentations of Crohn’s disease and ulcerative colitis has not been sufficiently appreciated.

At present, the primary objective of treatment is to repress the disease by keeping inflammation in check using anti-inflammatory and immunosuppressive drugs. However, according to C. Fiocchi, we can expect the spectrum of therapeutic options to expand greatly going forward.

For example, small molecules that interfere with regulatory processes in a targeted manner are currently in development. Attempts are also being made to develop strategies to modulate the microbiome, and research is also focusing on influencing the immunological processes underlying these disorders. For example, tests are currently being conducted on dietary measures which may be able to alter the microbiome as well as the immunological reactions.

As C. Fiocchi concluded, the ultimate goal of all therapeutic strategies for IBD is to interfere with the regulatory mechanisms that lead to the pathological alterations in the metabolic network and to normalize these mechanisms. Over the coming years, we can expect the number of tools available to physicians to expand greatly. C. Fiocchi suggested combinations of multiple monoclonal antibodies, stem cell transplantation, or even gene therapy as potential future strategies for IBD that are currently rarely or never used.
Building Bridges in IBD

September 13–14, 2019
Brussels, Belgium

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Scientific Organization
I. Dotan, Petah Tikva (Israel)
D. Rachmilewitz, Jerusalem (Israel)
S. Vermeire, Leuven (Belgium)
Poster prizes: awards for young scientists

At the Falk Foundation symposia, prizes are awarded to important research conducted by young scientists. The recipients at Symposium 213 in Milan were:

1st prize: N.M. Noor, Cambridge (Great Britain), for his presentation of the PROFILE study on the use of biomolecular markers in Crohn’s disease

2nd prize: D. Yablecovitch, Tel Aviv (Israel), for his research on the serum marker MMP-9 as a biomarker for the prediction of relapse in quiescent Crohn’s disease

3rd prize: J. Doherty, Dublin (Ireland), for her studies on the effects of vedolizumab on liver function in IBD patients
One of the major challenges in treating inflammatory bowel disease is generating a unique profile for every patient and identifying the specific characteristics that trigger pathogenesis in each individual patient. The development of novel, targeted drugs that allow personalized treatment of Crohn’s disease and ulcerative colitis will only be possible if we understand the factors at the core of this disease, as well as their interactions and interdependence. Prof. Dr. Silvio Danese, Rozzano, discussed this topic in an interview during Symposium 213 in Milan. He explained which factors are already relevant today, and which new strategies can be expected in the future.

**Eds.: Prof. Danese, what steps are needed to establish more breakthroughs in treating inflammatory bowel disease (IBD) in the future?**

Prof. Danese: In light of the increasing number of drugs available for IBD, it will become ever-more important going forward to thoroughly stratify patients. However, apart from the development of innovative drugs with potentially novel mechanisms of action, we need to focus more attention today on optimizing the treatments we currently have and to strive for targeted treatment that is tailored to each individual’s condition.

**Are there any ways treatment could be optimized now?**

Ulcerative colitis and Crohn’s disease are complex and heterogeneous conditions. We thus need to modify treatment to the unique circumstances of each patient. This means using disease activity, the localization of inflammation, and the patient’s needs as guides. However, our tendency as clinicians is to underestimate the complexity of the pathogenesis of IBD and the heterogeneity of potential clinical presentations. This is why we need a treatment approach that takes each patient’s individual characteristics into account. We are currently experiencing a paradigm shift on this topic. Going forward, there will be much more focus on identifying genetically-determined phenotypes that will guide our choice of treatment regimens. In order to optimally tailor treatment to each individual patient, we will also need to take their pharmacokinetic characteristics and specific risk factors into account.

**What needs to happen to make this vision a reality?**

We need to intensify our research efforts so that we can expand predictive medicine into IBD treatment. This concept has already been implemented in practice in several cancer disciplines, for example by tailoring treatment based on different biomarkers. It would be helpful if we could develop a similar concept for IBD that would allow us to directly predict which treatment strategies would be most promising for each individual patient when planning treatment. However, this gap has actually been widening lately. While it is true that we are developing new drugs, we know very little about which patients will actually benefit from these innovations.

**What are the consequences of this situation?**

Overtreatment is a common result when we prescribe these innovative medications to large numbers of patients without knowing which patients will respond to which drug. Some percentage of patients just don’t benefit from them. This creates a greater risk of side effects and also incurs unnecessary expenses, since these innovative drugs are quite a bit more expensive than conventional medicines. This can also result in undertreatment, since the result of high costs is that other patients are not prescribed a drug that they would probably have responded to.
How can we change this situation?

It is well-known that genetic factors play an important role in the pathogenesis of IBD, as do environmental factors. Unfortunately, it remains unclear exactly which genetic predispose patients to Crohn’s disease or ulcerative colitis, and we also don’t know which environmental factors are actually responsible for the manifestation of these disorders. On top of that, we don’t understand the interaction of these numerous factors well enough. This is why we need to keep pushing for breakthroughs in systems biology and to integrate the existing insights into our treatment decisions more deeply. The goal is to incorporate both the patient’s history and his or her clinical presentation into the treatment planning process, in addition to the genetic factors that promote pathogenesis and the epigenetic factors that trigger the onset of the disease. As Prof. Fiocchi pointed out in his state-of-the-art lecture, there are other factors that must also be considered, including the proteome, which means the peptides and proteins involved in the disease, the metabolome, and the new concept of the cytome (the structure and function of cellular systems).

Each of these factors can influence the others, and taken together they form a regulatory network known as an interactome. If we want to understand the foundations of ulcerative colitis and Crohn’s disease, we will need to characterize their molecular subtypes and molecular interactomes in a way that allows us to practice predictive medicine based on the insights we have gained. Once we can identify each patient’s unique disease, we will be able to prescribe them targeted medications that are appropriate for their specific clinical circumstances. We could then predict, for example, whether a patient is likely to respond to immunosuppressants, or whether he or she might be more likely to benefit from anti-TNF treatment or possibly from other innovative new strategies. This is the basis of personalized therapy, and it will give us a stepping stone to greatly improve the treatment of IBD in the future.

Prof. Danese, thank you very much for the interview!
Falk Foundation e.V.

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If we want to attract an audience for new ideas and findings, we need to give people the opportunity to talk about them. Dr. Dr. Herbert Falk had a unique and successful strategy for creating this “space for dialogue.” Since 1978, a globally recognized concept for continuing education in the sciences has developed under the umbrella of the Falk Foundation. This is an achievement that has many voices. Today, we express our gratitude for everything they have done. We look forward to many more years of working to give science a strong collective voice.
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Symposium 215
IBD: From Diagnosis to Therapy
St. Petersburg, Russia
July 5–6, 2019

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Building Bridges in IBD
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