IBD 2014: Thinking Out of the Box
Mesenchymal stem cell. Colored scanning electron micrograph (SEM) of a human mesenchymal stem cell (MSC). MSCs are multipotent stromal (connective tissue) cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), and adipocytes (fat cells). The youngest, most primitive MSCs can be obtained from the umbilical cord tissue. Magnification: x3000 when printed 10 centimeters wide. (Steve Gschmeissner/Science Photo Library)

Portraits, photos on pages 32 and 33 and photos for the poster prizes on page 23

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IBD 2014: Thinking Out of the Box

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In previous years and decades significant progress has been made in understanding the etiopathogenesis and treatment of inflammatory bowel diseases. Despite significant progress in better understanding the pathogenesis of Crohn’s disease and ulcerative colitis curing these diseases has not been yet possible. There is still a great need for therapeutic advances.

Optimization of treatment by improved collaboration of physicians with different scientific and medical background and participating in care of IBD patients is to be expected. In addition, there are opportunities for advances through more intensive cooperation between researchers in basic science and clinical researchers, allowing new findings to be implemented quickly “from bench to bedside” to directly benefit patients.

Various new therapeutic approaches to inflammatory bowel diseases are already in development due to new pathophysiological discoveries. Apart from that, the objective of the international Falk Symposium 192 in Paris was to expand our intellectual horizons, look at the big picture and learn from other disciplines by “thinking out of the box”.

The breadth of interest in a critical reassessment of established pathways and the search for new, potentially also unconventional strategies and scientific approaches is shown by the high number of more than 1200 participants from over 60 nations. This is the largest attendance of any event so far in the international Falk Symposium series. It underscores the demand to broaden our view and also to take new, yet unestablished paths to realize long-term progress in the treatment of Crohn’s disease and ulcerative colitis.

Prof. Dr. Axel Dignass
Frankfurt (Germany)
“We have to learn to leave our usual thinking patterns behind and look in new directions to find innovative approaches for research and development of new treatment options in inflammatory bowel diseases,” stressed A. Dignass, Frankfurt (Germany), at the opening of the Falk Symposium 192 in Paris. Bringing basic research scientists and clinicians together while also involving other disciplines and attempting to achieve momentum for new strategies in the diagnostic approach and above all the treatment of inflammatory bowel diseases (IBD) was one of the main goals of this symposium.
Microbiome – Pathogenetic factors and the goal of new therapeutic approaches

The range of topics was extraordinarily broad. For example, new findings were discussed on the interaction of environmental factors and the intestinal microbiome, the role of which has long been underestimated for digestive health and consequently also for the development of chronic (bowel) disease. Current findings already indicate potential new treatment options that aim to normalize dysregulated intestinal flora.

Finding its way into headlines in particular is the concept of fecal transplantation, a procedure that has primarily been tested as treatment for Clostridium difficile-associated diarrhea but could also be therapeutically meaningful for IBD.

Fibrostenosing Crohn’s disease – How does fibrosis arise?

Another focus of the symposium was the development of fibrosis, a not uncommon phenomenon especially in Crohn’s disease. The underlying reasons for the development of fibrosis that ultimately may lead to fibrostenosing Crohn’s disease are still not fully understood. Therapeutic measures remain predominantly surgical procedures.

“Fibrosis in Crohn’s disease may ultimately develop similarly to the development of a pulmonary or hepatic fibrosis. Therefore, we should investigate whether the treatments developed for these diseases may also be helpful in Crohn’s disease,” explained A. Dignass.

Progression of disease is not predictable

A medical challenge for the management of Crohn’s disease and ulcerative colitis is also the high variability in disease progression.

The therapeutic significance of phosphatidylcholine is also being investigated. It is a physiological component of cell membranes and an important component of the intestinal mucus. Early trials support the therapeutic benefits and effectiveness of phosphatidylcholine, especially for ulcerative colitis.

“The question of how underlying genetics may be involved in the management of inflammatory bowel diseases and how we can reach the point of realizing the so-called omics-oriented personalized therapy based on the genetic predisposition is a hot topic,” said A. Dignass.
not be predicted in the individual case and can vary considerably. As stated by A. Dignass, “there are patients that are in remission for years, while others show a persistently high level of disease activity and chronic active courses of disease including progression despite extensive treatment.”

However, until now, it has not been possible to predict the course of the disease in an individual case (figure 2).

Still, even if patients have been largely stable in the long term, the possibility of the occurrence of disease complications must always be taken into account. What this means in real terms was illustrated by A. Dignass through examples of two patients with initially stable Crohn’s disease.

One of the two women became pregnant, whereupon the gynecologist ordered immunosuppressants to be discontinued, resulting in a flare with high disease activity.

In a second case, a patient with otherwise clinical remission, complained of increasing abdominal pain and weakness. An abnormal decline in the hemoglobin level without detectable bleeding was detected and no active disease and no increase of inflammatory parameters. During a careful examination, an adenocarcinoma of the small bowel secondary to Crohn’s disease was ultimately discovered.

“Such complicated progression is often difficult to treat in practice and there are no clear recommendations or standard practice derived from guidelines,” explained A. Dignass (figure 3).

### Why does therapy not always work?

If treatment does not succeed as expected, the first question to ask is whether the diagnosis is actually correct. Furthermore, whether the correct medication was prescribed in the optimal dosage and whether it was actually taken by the patient must be checked. The possibility of a superinfection must be considered also and if needed, treatment should be optimized (figure 4).

Despite evidence-based medicine and guidelines, individualized decisions are frequently necessary and, in general, an interdisciplinary gastroenterological-surgical planning of treatment is required, according to A. Dignass.
Why does therapy not always work?

- **Wrong diagnosis, superinfection?**
- **Wrong or suboptimal use of appropriate medications (duration, dosage)**
- **Failure, inadequate effect or unacceptable side effects of medications**
- **Lack of treatment compliance**
In both Crohn’s disease as well as ulcerative colitis, the incidence and prevalence have been increasing for years and globally, according to B. Moum, Oslo (Norway), to a particular extent however in industrialized countries. However, there are relevant local differences in the incidence, which could be attributable to different environmental influences. Nutritional habits, smoking behavior, frequency of antibiotic prescriptions, frequency of appendectomies and additional factors may also play a role. However, it can be assumed that there is not a single individual factor, but rather the interaction of many different factors in our modern life triggering the increasing incidence of IBD (figure 5).

The manifestation of symptoms also varies considerably in Crohn’s disease and ulcerative colitis, and the course of the disease in the individual patient is not yet predictable. Still, there are signs that the progress of the disease in modern days is more favorable in the majority of patients than it was in the 1980’s, for example, which can be attributable to advances in diagnostics and treatment.

Favorable modulation of the microbiome

The research activities in IBD have been recently focusing on the microbiome, according to H. Sokol, Paris (France).

For example, there are increasing signs that disorders of the bacterial colonization of the intestine are significantly responsible for the pathogenesis and may play a role in the recurrence of Crohn’s disease postoperatively. It has been frequently described that the bacterial flora in patients with Crohn’s disease and ulcerative colitis show different profiles than in healthy subjects. It seems reasonable that therapeutic modification of the bacterial flora should be attempted. Theoretically, antibiotic treatment may be considered to effect the primary elimination or reduction of the flora with subsequent restoration of the “normal ecosystem”. However, this approach has so far been unsuccessful. Attempts to treat with probiotics as well as fecal transplantation also have not shown convincing effects.

In the future, H. Sokol therefore suggests instead a favorable modulation of the equilibrium between pro- and anti-inflammatory bacteria – for example, by treating with anti-inflammatory bacteria such as Faecalibacterium prausnitzii. Immune-modulating and direct anti-inflammatory effects have been documented already for this bacterium in vitro as well as in vivo in animal models.

Fig. 5 Inflammatory bowel diseases and nutrition: Unproven connections
Fecal transplantation with IBD

The potential role of fecal transplantation in IBD is so far unclear. The procedure is not new. Reports of its use in patients with severe diarrhea exist from the 4th century in China, according to J. Raes, Brussels (Belgium). In the 17th century, fecal transplantation was adopted in veterinary medicine, primarily to treat horses. There are also reports of Bedouins curing sick camels using feces.

In humans, fecal transplantation was already utilized in 1958. There are 4 case reports on fecal therapy in patients with life-threatening intestinal infections. “Recently, there are increasing numbers of reports again on fecal transplantation,” explained J. Raes. The procedure is primarily tested in antibiotic-associated Clostridium difficile infections that are resistant to treatment. Other potential indications are IBD, obesity, metabolic syndrome, type 2 diabetes and irritable bowel syndrome. However, the path to clinical establishment of fecal therapy could still be long, because “there are still many open questions,” according to J. Raes. These concern the mechanism of action, optimal form of application and especially the safety of fecal transplantation.

Strategies for modifying the altered microbiome

There is no doubt that an altered microbial composition of intestinal flora is involved in the disease processes of Crohn’s disease and ulcerative colitis, according to J.M. Rhodes, Liverpool (Great Britain). The mechanisms may be different in the two diseases. In Crohn’s disease, genetic modifications appear to cause a defect in the innate immune system, which facilitates the invasion of bacteria and especially E. coli in the intestinal wall. In contrast, in ulcerative colitis, environmental factors appear to play a stronger role and modulate the interaction between bacterial components and the epithelial surface (figure 6).

According to J.M. Rhodes, theoretical considerations yield different approaches for modifying the disrupted equilibrium of the intestinal flora:

- Administration of prebiotics, which as vegetable fiber promote the growth of probiotic bacteria in the intestine,
- treatment with genetically modified bacteria as probiotics,
- administration of contrabiotics, for example soluble vegetable fiber, that prevent the interaction of bacteria with the intestinal wall and
- enteral nutrition to reduce the substrate for the microbiome.

Therapeutic trials with prebiotics have so far been disappointing. More promising are findings with probiotics, which have been demonstrated to be significantly maintain remission in ulcerative colitis. There have been few studies of contrabiotics in humans, however, there is good evidence that a fiber-rich diet reduces the risk of developing Crohn’s disease. Only case reports exist in contrast regarding enteral nutrition, such as the case report of a child with Crohn’s disease, in which the microbiome profile “normalized” after enteral nutrition.

Tweaking the paradigm!

IBD-genes and/or Environmental factors

- Defects in innate immunity, immune regulation, and/or mucosal barrier
- Invasion of bacteria (particularly E. coli) through M cells
- Crohn’s Disease
- Interaction between bacterial components and surface epithelium
- Ulcerative Colitis

Fig. 6 Pathogenesis of inflammatory bowel diseases (J.M. Rhodes, Liverpool)
Fibrosis in inflammatory bowel diseases

Intestinal fibrosis – Excessive wound healing process

An intestinal fibrosis, according to T. Torres Pizzaro, Cleveland (USA), develops through an excessive wound healing process with increased extracellular matrix formation and deposition. In both Crohn’s disease and ulcerative colitis, inflammatory reactions repeatedly occur that can trigger such “excessive wound healing” and as a result an intestinal fibrosis.

“This phenomenon is especially frequent with Crohn’s disease,” emphasized the researcher. Around one third of Crohn’s patients develop such complications in the course of their disease. The central treatment option has so far been surgery, when fibrosis had resulted in strictures and obstructions (figure 7). However, 40% of patients have a relapse within 6 years and within 15 years relevant strictures have again formed in 70% of patients.

Endoscopic dilations in patients with strictures that are under 5 cm should also be considered, though bearing in mind the risk of complications.

Early use of effective therapeutic agents to control the inflammatory reaction is advocated by G. van Assche, Leuven (Belgium): “The intestine is an invaluable organ which we must absolutely preserve in our patients.” Repeated resections necessarily lead to loss of function with the risk of developing a short-bowel syndrome.

In the case of strictures, A. D’Hoore, Leuven (Belgium), argued for an early surgical resection. The intervention is safe, but should only take place after careful patient selection and should be performed in the least invasive way possible, e.g. laparoscopically.

Fig. 7 Clinical presentation of fibrostenosing Crohn’s disease (Pariente B, et al.; Inflamm Bowel Dis. 2011;17:1415–22)
Intestinal fibrosis – Learning from other clinical conditions

The development of fibroses is a frequent reason for surgical interventions in IBD patients, according to G. Rogler, Zurich (Switzerland). Such phenomena are the result of chronic inflammation in other clinical conditions also.

This necessarily provides the chance to learn from the development of new treatment options from other diseases such as hepatic fibrosis.

Potential targets of future therapeutic strategies for hepatic fibrosis, cited by G. Rogler, are active substances that inhibit cell proliferation as well as angiogenesis, fibrogenesis inhibitors as well as active substances that accelerate the decomposition of extracellular matrix. Starting points are offered by inhibitors of growth factors such as TGF-β (Transforming Growth Factor), angiotensin receptor inhibitors, ACE inhibitors, CTGF antagonists, cannabinoid-R1 antagonists and LPA-1 antagonists. In addition, TIMP inhibitors, LOXL-2 inhibitors and a cell-modulating treatment are under development.

In a situation similar to hepatic fibrosis is pulmonary fibrosis, in which comparable strategies are currently under investigation to identify new therapeutic options. Firstly, attempts are made to influence fibroblasts through inflammatory cells and their mediators and, secondly, the messengers formed by these substances are targeted (figure 8).

For pulmonary fibrosis, the first active substances such as pirfenidone, which inhibits the synthesis of profibrotic and inflammatory mediators, has already gone into clinical studies.

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**Fig. 8** Pulmonary fibrosis (Mason RJ, NHLBI Workshop Summary: Am J Respir Crit Care Med.1999;160:1771-7)
As a potential future option for IBD treatment, stem cell transplantation was discussed, among others. Experience from cardiology is already available according to A.M. Zeiher, Frankfurt (Germany). There stem cell transplantation is primarily seen as a therapeutic option for acute myocardial infarctions and in chronic cardiac failure after myocardial infarction.

The hope to be able to stimulate cardiac regeneration is associated with this procedure.

Autologous stem cell therapy is already established for a variety of hematological diseases, according to M. Allez, Paris (France). However, the procedure is not without risks. Mortality averages 1.7% and ranges from 1% to 10% depending on the clinical condition. The cause of death is most often the development of sepsis. Also, with Crohn’s disease, studies have been ongoing for some time on autologous hematopoietic stem cell transplantation, such as the ASTIC trial (Autologous Stem Cell Transplantation International Crohn’s Disease Trial). Potential mechanisms of autologous stem cell transplantation, cited by M. Allez, are the eradication of effector and memory T-cells and practically a reset of the immune system through profound immune suppression.
Mesenchymal stem cell transplantation is also under consideration for Crohn’s disease, according to L. Egan, Galway (Ireland). This uses mesenchymal stroma cells (MSC) that can differentiate into very different cells such as bone and cartilage cells, but also muscle and connective tissue cells (figure 9). First trials with mesenchymal stem cell transplantation were with fistulizing perianal Crohn’s disease, in which 7 of 10 cases could obtain a complete fistula closure. In the meantime, there has been an “explosion” of publications on stem cell therapies with countless positive findings in animal experimental trials. In addition, there is some evidence from multiple small, mostly uncontrolled studies suggesting that it may be a very promising treatment option that may be safe and effective in patients with refractory perianal Crohn’s disease (figure 10). However, there is not yet convincing scientific evidence from larger Phase III trials for this.

Need for further therapeutic advances

Although there have been advances in the treatment of IBD, especially through the introduction of biologics, there is still great demand for further advances according to J.-F. Colombel, New York (USA). Around 30% of patients with IBD already fail to respond to primary treatment with biologics. The number of patients with secondary loss of response to this treatment is also high. Innovative therapeutic approaches could yield a better understanding of the biology of IBD. It is increasingly clear that an imbalance between the pro-inflammatory Th17 cells and the anti-inflammatory Treg cells play an important role in the pathogenesis of IBD. This nurtures the hope of being able to restore the disordered equilibrium using an antigen-specific regulatory T-cell therapy. A study is already underway for patients with refractory Crohn’s disease.

Cytokines in the treatment of IBD

As a potential new approach to treating IBD, the JAK (Janus kinase) inhibitors were presented by S. Schreiber. The first representative, tofacitinib, is already approved in the USA for the treatment of rheumatoid arthritis, but so far not in Europe. However, promising clinical trials already underway for ulcerative colitis and Crohn’s disease show very encouraging initial results and further findings are anticipated.
**Session IV**

**New therapeutic options or new therapeutic strategies for IBD?**

As the rationale for the approach, J. Schölmerich cited observations demonstrating a reduced concentration of phosphatidylcholine in the mucus of patients with ulcerative colitis.

Moreover, smaller trials are showing a beneficial effect in patients with steroid-refractory and chronically active ulcerative colitis. A clear dose-relationship was documented with a clinical efficacy that was comparable to that of mesalazine.

Phosphatidylcholine – Very promising new therapeutic approach

Not all new therapeutic approaches live up to the hopes placed in them, a point made clear by J. Schölmerich, Frankfurt (Germany), with the example of pig whipworm eggs (Trichuris suis ova, TSO). After positive findings in animal studies, initially promising results were seen in 2 first smaller clinical trials in patients with ulcerative colitis and Crohn’s disease. However, this could not be verified in large, multicentric, randomized trials of patients with active Crohn’s disease.

Researchers still have great hopes in the approach using phosphatidylcholine to reinforce the barrier function in ulcerative colitis (figure 11).

New therapeutic approaches in development

There may also soon be new therapeutics in the area of biologics, speculated B.E. Sands, New York (USA). As an example, he cited the integrin antagonist vedolizumab, related to natalizumab, which is already established in the treatment of multiple sclerosis. Natalizumab itself is also effective in IBD, but has the problem of being able to induce a nearly always lethal progressive multifocal leukoencephalopathy (PML). This risk does not exist in second generation integrin antagonists such as vedolizumab and etrolizumab because their specific binding receptors MACCAM are expressed almost specifically in the intestinal mucosa and respiratory mucosa. With the antibody ustekinumab as well as the JAK inhibitor tofacitinib, there are more promising compounds in the pharmaceutical pipeline.

Do not just treat the symptoms

New active substances are not the only way to drive therapeutic success, an optimization of therapeutic algorithms is also necessary, according to R. Panaccione, Calgary (Canada).

![Phosphatidylcholine lamellar bodies](image)

**Fig. 11** Schematic arrangement of phosphatidylcholine in the mucus (W. Stremmel, Heidelberg)

Phosphatidylcholine (PC) and lyso-PC are enriched to more than 90% in the phospholipid fraction of the intestinal mucus (De Schryver-Kecskemeti, J Clin Invest. 1989)
The goal must be not only to treat the symptoms, but to consistently induce healing of the mucosal lesions. If mucosal healing is achieved, more stable remissions, reduction in the need for surgery, an increase in quality of life and the patient's occupational productivity are likely to result.

The other side of the coin is more aggressive therapy may potentially be more likely to have side effects that also could lead to higher costs.

Experiences from rheumatology, where this principle has been followed successfully for years prove that the concept of “treat to target” is nevertheless successful. The procedures for clinical trials could also be optimized, according to J. Panès, Barcelona (Spain). This includes characterizing the patient well “so as not to overlook potentially effective medications in subgroups.”

More biomarkers and predictors would also be desirable to better interpret the data identified in trials and also to be able to develop subgroup-specific treatments.

What future studies should integrate

- **Identification of novel drivers and disease mechanisms**
- **Characterize and predict individual patients’ risk, disease trajectory, and velocity**
- **Novel disease intervention points**
- **Predict patient outcome benefits of long-term continuous therapy**
Even though the majority of patients with Crohn’s disease and ulcerative colitis can be managed well with the established treatment options, there is still need for progress in therapy.

As one of the scientific organizers of the Falk Symposium 192, Professor Dr. Axel Dignass from Frankfurt explains in an interview why in this regard looking beyond one’s current horizon is worthwhile.

Editors:
Professor Dignass, why have you selected “Thinking Out of the Box” as the motto for the symposium?

Professor Dignass:
With respect to inflammatory bowel disease, it makes sense, from my perspective, to leave our current paradigms and to look beyond our own horizons and to learn from other medical specialities and scientific disciplines. We have therefore invited, for example, a cardiologist as speaker, who explained the role of stem cell transplantation in the treatment of cardiac diseases. During this symposium, we have also learned details of the potential role of hematopoietic and mesenchymal stem cells in the management of IBD. We have involved rheumatologists and hepatologists as well, in order to learn how chronic inflammatory diseases in these areas are dealt with. Another focus was on intensification of the exchange with our surgical colleagues with whom we collaborate every day in an interdisciplinary manner. Here, too, the goal is to think beyond current paths and to find means of optimizing cooperation even further.

Editors:
Do you hope that this approach will also provide ideas for new therapeutic strategies in inflammatory bowel disease?

Professor Dignass:
I am convinced that we can learn from other disciplines and get inspiration for new therapeutic options. For example, much of what happens in rheumatic conditions is similar to IBD, and there are therapeutic approaches which are quite comparable to biologic therapy. Thus, for
example, the antibody ustekinumab is approved for treatment of psoriasis and psoriatic arthritis and is currently being tested also in Crohn’s disease for clinical efficacy. Another field are fibrotic changes, where for example drugs used in pulmonary fibrosis may possibly have therapeutic relevance in stenotic CD as well.

One further possible approach, which is currently hitting the headlines, is fecal bacteriotherapy by fecal microbiota transplantation, so it seemed a good idea to have this potential form of treatment presented by a microbiologist. Such approaches may in the future result in new relevant therapeutic options in inflammatory bowel diseases.

Editors: At the same time, this indicates that a need for further action still exists. Where are therapeutic advances necessary?

Professor Dignass: We can currently manage approximately 70% of the patients with inflammatory bowel disease well. In about 30% of patients, however, there is a need for therapeutic optimization, either because they do not respond sufficiently to the available drugs, because they develop significant adverse events to the medication, or because clinical efficacy is not sustained in the long term to maintain a stable remission. For these patients, we absolutely need therapeutic advances.

Editors: In what areas is progress most required?

Professor Dignass: We have comparatively little difficulty in the short-term management of active disease. In most cases remission of the disease is easily achieved. It is more difficult to maintain remission in the long term. Especially in this area, we therefore need progress in the future.

Editors: Are there prospects of optimization of established therapies as well?

Professor Dignass: Without doubt, in some cases treatment has not conformed to the long-established evidence-based medical guidelines so far. These guidelines are not intended to oppress physicians’ liberty to treat their patients, and there are certainly many clinical situations, in which a physician may deliberately decide against following the official guidelines. However, medical guidelines are evidence-based recommendations for optimal utilization of available treatment options considering correct dosage, route of application and duration of treatment, and in most cases it seems advisable to follow these guidelines on diagnosis and therapy. It seems evident that if incorrect dosages are administered, the active ingredients are not optimally combined, or treatment does not match the pharmacokinetic profiles of the substances, optimal therapeutic success can hardly be expected. Unfortunately, there are studies showing that insufficient treatment is still a regular occurrence both in Europe and Northern America. For example, there are studies showing that mesalazine, after all the standard treatment for patients with ulcerative colitis, is prescribed in adequate doses only in about every third patient.

Editors: What is the reason for that, and how can the situation be improved?

Professor Dignass: One reason may be that ulcerative colitis and Crohn’s disease are relatively rare conditions, which general practitioners, internists and family doctors are much less likely to face than, for example, hypertension or diabetes. This in turn implies that training sessions on IBD are attended less frequently by this physicians, and that thus knowledge of the optimal therapy is less well-developed and less likely to be up to date than for other, more common diseases. I am therefore convinced that we could achieve therapeutic optimization by intensification of continued medical training. In addition, it seems reasonable that patients in whom the expected treatment success is not achieved should be referred to an experienced gastroenterologist or an IBD center in due time. I also consider the education of patients, e.g. with patient seminars, as very important because also on the patients’ site there are often opportunities for therapy optimization as well – for example by promoting adherence to treatment, which in IBD, as in virtually all chronic diseases, is often still relatively poor.

Editors: What is, in your opinion, the most important message that this symposium should convey?

Professor Dignass: We advocate guideline-based treatment of IBD patients. Despite this general recommendation, however, we must not forget that each patient is an individual in need of a therapy tailored to his or her personal situation. If we make optimal use of the treatment options currently at our disposal, we will undoubtedly be able to manage the vast majority of IBD patients well. For the remaining patients, we continue to search intensively for new treatment options – in the conventional way, but also, as in this symposium, with a view across the border out to other disciplines, which likewise deal with chronic inflammatory diseases.

Professor Dignass, thank you very much for the interview.
The incidence and prevalence of IBD is continuously growing, according to B. Siegmund, Berlin (Germany). Improved diagnostics cannot fully account for this trend. The genetic background also does not sufficiently explain the increase in disease incidence, whereby roughly one fourth of cases arise from a known genetic risk profile. Particularly remarkable is the increase in the incidence of IBD after World War II, which occurred in parallel to continuously improving hygienic conditions. “It can be assumed that the intestinal flora, that is the microbiome, is important to the pathogenesis and maintenance of the disease,” the physician emphasized. The human intestinal metagenome encompasses at least 1000 times more genes as the human genome. In addition, there are experimental findings in animals showing alterations of the microbiome can have considerable pathogenetic importance. Fecal transplantation for ulcerative colitis? Evidence of how important the intestinal flora is and that a fecal transplantation can be helpful for impairments was initially found with the clinical condition of antibiotic-associated, treatment-resistant Clostridium difficile colitis. First trials of treating IBD using a fecal transplantation exist for ulcerative colitis, but a definitive evaluation of the clinical relevance is not yet possible (figure 14).

Ulcerative colitis

- Mayo score ≥ 4
- Other medications stable for 12 weeks
- No antibiotics in the last 30 days

FMT; n = 27

→ 50 ml enemas 1x/week for 6 weeks

Primary end point:
Remission, Mayo score ≤ 2 in week 7

Placebo; n = 26

Result: No significant difference

Fig. 14 Fecal microbiota transplantation (FMT) and IBD (Moayyedi P, et al.: DDW 2014)
The fact that it is not uncommon for new treatment options to raise hopes that are not sustained during the trial is shown by the example of pig whipworm eggs (Trichuris suis ova, TSO). The use of TSO is based on the idea of being able to influence the regulation of the intestinal defense system.

This treatment appeared hopeful, because TSO are not human pathogens and are excreted again after a few weeks. Recent clinical trials in patients with Crohn’s disease, however, showed response rates under TSO in that were not significantly different compared to placebo. The trial therefore had to be classified as negative and the development of TSO as a treatment for IBD will be probably discontinued for the time being.

**Hope for phosphatidylcholine**

Improved treatment options could potentially be obtained, primarily for ulcerative colitis, by treating with phosphatidylcholine.

The naturally occurring substance has an important function in stabilizing the barrier function of the intestine and there are already early, initially positive study data.

In a double-blind, randomized placebo-controlled trial of 156 patients with ulcerative colitis, who did not adequately respond to mesalazine, a significant improvement in disease activity was shown. The time to becoming symptom-free was significantly shortened by phosphatidylcholine (figures 15 and 16).

The data are promising and should now be verified in a larger controlled clinical trial.
Stem cell transplantation in IBD could represent another new treatment option. The procedure has already been successfully applied for other inflammatory diseases. According to the concept, it should facilitate a “restart of the immune system”.

In first studies of stem cell transplantation for IBD, there was also evidence of a significantly increased risk of infections, which may prohibit a continuation of the procedure for this indication and may restrict its use to a limited number of patients failing all available therapies and suffering from severe disease.

Integrin antagonists as an expansion of biologics treatment

There are already innovations in the foreseeable future in treatment with biologics. Several active substances are close to approval or have been recently approved. These include the integrin antagonist vedolizumab, which prevents the recruitment of inflammatory cells from the blood into the inflamed tissue, and the antibody ustekinumab, which inhibits the two pro-inflammatory cytokines interleukin 12 and 23 and therefore the inflammatory reaction. Ustekinumab acts against the surface markers P40 and therefore inhibits IL-12 and IL-23 (figure 17).

Ustekinumab, according to B. Siegmund, is already approved for the treatment of psoriasis and psoriatic arthritis. Both active substances, it is expected, could soon expand the therapeutic repertoire for patients with difficult, not otherwise controllable clinical characteristics.

IL-12/IL-23

Ustekinumab inhibits

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**IL-12/IL-23**

*Ustekinumab inhibits*

**Fig. 17** New biologic ustekinumab (B. Siegmund, Berlin)
Announcement

Congress Report Falk Symposium 192
with all presentations
(E 192)

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Mesalazine remains the basic treatment

Despite many years of experiences with anti-TNF strategies in IBD, mesalazine is and remains the basic treatment. “It’s no longer just about asking which patients are candidates for an anti-TNF treatment,” said R. Panaccione, Calgary (Canada). “We must also ask who should not be treated with anti-TNF active substances.” If the mesalazine treatment alone is not adequate, then steroids such as prednisolone and budesonide, with significantly fewer side effects, should be considered. If an intensification of treatment is still indicated, then azathioprine, methotrexate or biologics should be considered and used. Surgery should be considered a tool of last resort (figure 18).

Based largely on symptoms
Treats all patients the same
Delays time to a “healing” therapy
Misses window of opportunity for some therapies
Mucosal healing is not achieved in the majority of patients, disease progresses

If treatment with biologics is planned, then the patient’s safety under therapy must also be ensured. The vaccination status must be checked and, if applicable, vaccinations should be administered when appropriate and necessary before starting treatment, when this is clinically possible. Comprehensive laboratory tests including HCV, HBV and HIV serology should be performed and screening for tuberculosis is indicated.

Plea for individualized treatment

“The goal of treatment is to achieve remission for the longest possible term, which requires close monitoring of the disease. We have to get the patients into remission, maintain it and make every effort to effect mucosal healing to avoid long-term complications,” stressed A. Sturm, Berlin (Germany). It’s not about deciding on a step-up or top-down treatment. Patients need individualized treatment strategies, which also can mean that biologics are used quickly when there is a poor prognosis. This strategy is defined in the current ECCO guidelines.

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Delays time to a “healing” therapy
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Fig. 18 Concerns before starting anti-TNF treatment: Limitations of the current step-up treatment paradigm (Rutgeerts PJ.: Aliment Pharmacol Ther. 2001;15:1515-25)
In doing so, introducing not only a clinical remission, but rather a “persistent clinical remission, mucosal healing and even a persistent deep remission” should be attempted. However, individualized treatment must have good drug monitoring also, according to W.J. Sandborn, La Jolla (USA), whereby attention must be given to potentially different pharmacokinetics in individual cases.

Biosimilars – Are they bioequivalent?

According to F. Gomollón, Zaragoza (Spain), innovations are pending through the introduction of biosimilars that are expected in the near future. These are me-too products for biologicals for which the patent protection has expired. In contrast to conventional generics, the active substances may not simply be copied. Rather, with biosimilars, a more complex production process is required, “the process is the product”, according to the physician. Evidence of comparable active substance quality is required, in which the bioequivalence must only be proven in one indication.

Outstanding posters

On the occasion of the Falk Symposium 192 “IBD 2014: Thinking Out of the Box” awards were given for 3 posters:

1. Backert, Erlangen-Nuremberg (Germany), won first prize for his work on the effect of STAT-3 activation in CD4+ lymphocytes on the epithelial barrier function during an infectious colitis.

Second prize was awarded to K. Papamichail, Leuven (Belgium), for studies on prediction of a persistent clinical remission after completing an infliximab treatment for Crohn’s disease.

Third prize was given to A. Viola, Messina (Italy), for research work on Crohn’s disease in older patients.
Prefer budesonide adverse prednisolone

E. Louis, Liège (Belgium), also argued for effective disease control already at an early stage in Crohn’s disease. This changes with the progression of the disease and the risk of developing serious complications, such as the formation of strictures, increases significantly. “This is why we cannot wait too long to use highly-effective therapeutic agents. On the other hand, we must absolutely be aware of overtreatment. The optimum treatment is the safest treatment that induces and maintains a steroid-free deep remission within one year after diagnosis,” said E. Louis. Treatment with mesalazine is initially indicated. This may apply to patients with Crohn’s disease as well. Though lacking clear proof of effectiveness using larger trials, experience in clinical practice shows that mesalazine treatment is effective and sufficient in many Crohn’s patients. If this is not the case, then prednisolone can be used to treat, which leads to remission in up to 92% of cases. The success rate is also very good for the administration of budesonide, a locally active steroid that has significantly fewer side effects than prednisolone (figures 19 and 20).

“Budesonide is effective according to Cochrane analysis, and leads to significantly fewer steroid-related side effects” said E. Louis. Around 50% of Crohn’s disease patients with ileocecal localization are able to control their disease activity well using such a strategy and do not need immunosuppressives or biologics.
**Accelerated step-up treatment**

In patients with signs of a high risk of complications, E. Louis recommended an accelerated step-up treatment instead of the conventional procedure. For this, azathioprine continues to be of significant therapeutic value, according to J. Cosnes, Paris (France). The immunosuppressant can also significantly contribute to reduce steroids during treatment. It is clearly indicated in moderate to severe Crohn’s disease and moderate to severe ulcerative colitis, particularly in steroid-dependent patients.

An accelerated step-up treatment is also indicated in perianal Crohn’s disease as well as after a surgical intervention, according to S. Ghosh, Calgary (Canada). Corticoids are inadequate or even ineffective in these situations, so the patients require immunosuppressants and/or biologics for disease control.

**Integration of “omics”: The future for IBD?**

Similar to other clinical conditions, the “omics” also play a central role in IBD, according to C. Fiocchi, Cleveland (USA), in his “Special Lecture”. For IBD, the genome, microbiome, the exposome and the immunosome are of crucial importance, with close links among each other and intersections between individual areas (figure 21).

“Each of these components must still be considered individually, because there can be large differences between patients with heterogenic clinical characteristics,” the researcher emphasized.

Previously it was assumed that the links of genotype and phenotype lead to the development of the disease, so in the meantime a paradigm shift has occurred in the understanding of pathogenesis. It is clear that susceptibility genes constitute a genetic predisposition that forms the basis for elevated disease predisposition.

However, diet, microorganisms in the environment and also the intestinal flora have an effect. These are factors that influence the innate as well as the acquired immune system and could lead to the formation of tolerance or chronic inflammation. Which path is taken is ultimately decisive for whether triggering, progressing and remodeling of the disease result. In reality, the connections are still considerably more complex, where C. Fiocchi postulates an “IBD interactome”, a network of any number of influencing factors that all participate in the pathogenesis of IBD and control the individual course of disease.
Tandem Talk: Abdominal abscess in a Crohn’s patient

The procedure for handling an abdominal abscess in a Crohn’s patient was discussed in a tandem talk between F. Carbonnel, Paris (France), and W.A. Bemelman, Amsterdam (The Netherlands). The researchers presented a case report of a 17 year old man who visited the clinic due to abdominal pain and fever. Two years before, Crohn’s disease had been diagnosed in the terminal ileum.

The patient received budesonide for 3 months, which is how a persistent remission had been induced. The man had suffered diarrhea again for one month and had lost 10 kg of body weight in a short time. Further testing, including an abdominal CT, showed a thickening in the terminal ileum as well as an abdominal abscess 4 cm in size. The speakers were in agreement that one should not wait too long for surgery in such a case because otherwise formation of a fistula is a concern.

Tandem Talk: Proctocolectomy for refractory distal ulcerative colitis?

A. Spinelli, Rozzano (Italy), argued for a proctocolectomy in the case of refractory distal ulcerative colitis. He based his recommendation on the considerable psychological strain for the patient. The intervention that assumes a very careful patient selection can generally effect a significant and persistent improvement in quality of life. The proctocolectomy also averts the not negligible risk of carcinoma.

E.F. Stange, Stuttgart (Germany), argued against an overly hasty proctocolectomy. He advocated instead for intensifying the medicinal treatment with exhaustion of modern biologics as well in order to preserve the patient’s colon. If the proctocolectomy appears unavoidable, then the decision for such an intervention should only be made in a specialized center and should be made jointly in an interdisciplinary manner by surgeons and internists.

In this context, I. Dotan, Tel Aviv (Israel), stated that currently around 25% of patients with highly active ulcerative colitis and complications undergo a total proctocolectomy with ileoanal pouch placement. The intervention has the advantage that the disease can be theoretically cured and the risk of cancer is averted. The pouch placement avoids a permanent ileostomy and protects the intestinal continuity. Pouchitis occurring after pouch placement is a complication that is not uncommon and frequently presents a great therapeutic challenge.
History of tumor: Pros and cons of TNF blockers and immunosuppressants

Discussed in detail was the question of whether patients with tumors in their prior history can be treated with immunosuppressants and/or biologics in the case of IBD. According to D. Laharie, Pessac (France), these medications are contraindicated, because an elevated risk of malignancy is feared. However, there is no clear evidence of an elevated risk of tumors, not least because patients with carcinoma in their medical histories are excluded from trials. The physician conceded that certainly caution is necessary, if the patient has suffered a malignancy in the last 5 years before adopting an anti-TNF treatment. If the cancer occurred more than 5 years ago, however, an immunosuppressive treatment can also be considered.

Unfortunately, there is frequently no therapeutic alternative in patients with complex progressive IBD, so immunosuppressive treatment must be performed despite the risk of tumor development.

G.J. Mantzaris, Athens (Greece), sees the situation critically. He states that under immunosuppressive or TNF blocker treatment, there is an elevated risk of tumor recurrence and new occurrence of tumors is assumed in any case. This applies primarily to the first 2 years after the carcinoma, but also beyond that. If the administration of immunosuppressants and biologics is unavoidable, then close monitoring of the patient by a multidisciplinary team is essential to ensure early detection of a tumor development.
Incidence and thus also prevalence of inflammatory bowel disease are steadily increasing. However, despite intensive research activities there will be no cure for these conditions in the foreseeable future. Professor Dr. Britta Siegmund from the Charité – Universitätsmedizin Berlin explained in an interview to what extent progress in therapy can nevertheless be realized.

Editors: Professor Siegmund, why do we need new treatment options in inflammatory bowel disease?

Professor Siegmund: For more than 15 years, no fundamentally new therapeutic agents for inflammatory bowel disease have been introduced. Yet we still have a considerable number of patients who do not respond adequately to the available treatment options. Especially for these patients, we urgently need new, more effective and at the same time well-tolerated drugs.

Editors: What is the proportion of patients not responding well to the established therapeutic strategies?

Professor Siegmund: The majority of patients can be managed well with the available therapies. However, in approximately 20–30% of patients we fail to obtain disease remission and maintain it in the long-term. In these patients, therefore, the current treatment...
options are inadequate, and we must continue to work hard to develop new therapeutic strategies.

Editors: Is such treatment progress to be expected in the near future?

Professor Siegmund: We hope that the treatment options in inflammatory bowel disease will increase very soon. Here we also learn from other fields of medicine. Thus, a new treatment option with so-called integrin antagonists, as they are used for example in the form of the drug natalizumab in the treatment of multiple sclerosis, may be expedient.

A second substance is vedolizumab. This drug specifically inhibits infiltration of inflammatory cells into the intestine and will become available as the first new option in IBD in July 2014. We also expect the antibody ustekinumab to be approved rather soon. Similar to the anti-TNF antibodies, this substance inhibits pro-inflammatory mediators in IBD, specifically interleukins 12 and 23, thereby exerting anti-inflammatory activity.

Editors: Is progress in the medium term on the horizon, too?

Professor Siegmund: There are indeed interesting new approaches above and beyond the options described. For example, first smaller studies have provided strong evidence that phosphatidylcholine is therapeutically effective, especially in patients with ulcerative colitis. Phosphatidylcholine appears to strengthen the intestinal barrier function, thus counteracting bacterial invasion and further promoting the healing of existing lesions. Via this mechanism, long-term improvement of the clinical picture is to be expected. This approach is therefore currently being tested in a larger clinical trial. It is a promising option, and we hope that it will find its way into clinical practice. By contrast, attempts to effectively “reset” the immune system in IBD patients by stem cell transplantation are still experimental in character. As a potential new treatment option, direct manipulation of the microbiome with the perspective of possibly being able to induce even a cure of inflammatory bowel disease by “optimization” of the microbiome is currently intensively being discussed. The option of fecal bacteriotherapy is, however, currently being debated. Due to the complexity of the microbiota, this concept requires a differentiated approach, and we must await clinical trials before we can judge the therapeutic relevance of the method.

Editors: What is, in your opinion, the message that this symposium should convey?

Professor Siegmund: We need new therapeutic strategies in the treatment of inflammatory bowel disease. Therefore, we search in many fields of medicine and attempt to elicit what strategies are being pursued in other medical specialties and disciplines and how they may be helpful for IBD as well.

The symposium was designed as a kind of “thinkbox” to discuss with representatives of other disciplines how we may find synergies and establish progress. This is in my opinion a very important approach, since in other diseases, such as pulmonary fibrosis, there are already effective anti-fibrotic therapeutic approaches that might potentially help CD patients as well. We should therefore consistently continue to pursue this path of searching and learning from other disciplines.

Dear Professor Siegmund, thank you very much for the interview.
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Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD

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