Gastroenterology Symposium

Putting the Puzzle Together: Inflammation and Gastrointestinal Disease

September 16 – 17, 2016

University Hospital Regensburg
Regensburg, Germany

Abstracts

FALK FOUNDATION e.V.

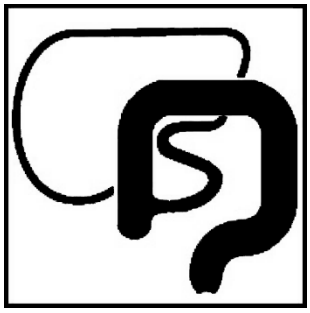
Leinenweberstr. 5
79108 Freiburg
Germany

www.falkfoundation.org

Abstracts of Invited Lectures

Gastroenterology Symposium

PUTTING THE PUZZLE TOGETHER: INFLAMMATION AND GASTROINTESTINAL DISEASE



Regensburg (Germany)
September 16 – 17, 2016

Scientific Organization:
M. Fleck, Regensburg (Germany)
H. Herfarth, Chapel Hill (USA)
G. Rogler, Zurich (Switzerland)
B. Salzberger, Regensburg (Germany)

CONTENTS

Session III

Infections and the GI tract

Session IV

Rheumatic diseases and the gut

Session V

Endocrinology and inflammation

Chair:
R.C. Spiller, Nottingham
R. Tauber, Berlin

Session VI

Inflammation, drugs and cancer

Chair:
A. Vollmar, Munich
A.J.M. Watson, Norwich

Session VII

New treatment options

Chair:
D. Rachmilewitz, Jerusalem
S.R. Targan, Los Angeles

Session I

Hepatitis, pancreatitis and systemic inflammation

The revolution in HCV therapy

Fritz von Weizsäcker
Abteilung Innere Medizin I, Schlosspark-Klinik, Berlin, Germany

Some 170 million individuals worldwide are chronically infected with hepatitis C virus (HCV). The spectrum of HCV-associated diseases ranges from chronic hepatitis to liver cirrhosis and hepatocellular carcinoma. Therapy of HCV-infection is an unparalleled success story in modern medicine. In the late 80s the infection was treated as nonA-nonB-hepatitis with interferon, yielding sustained viral response (SVR) rates of merely 10%. In 1989 the virus was identified and a diagnostic test was developed. Subsequently the structures of key viral proteins were determined, thus enabling the development of small, direct antiviral agents (DAAs). Another breakthrough was the development of HCV replicons, which allow for straightforward testing of DAAs in tissue culture. Up to now a large array of DAAs is available for clinical use. To date interferon-free treatment of most HCV-genotypes is highly effective with SVR rates of > 95% and very few side effects. The aim of eradication HCV infection worldwide seems attainable, provided wide-spread distribution of antivirals and cost control.

Impact of hepatitis C virus NS3/4A and NS5A variants on treatment response

Stefan Zeuzem
Department of Medicine, Goethe University Hospital, Frankfurt/Main, Germany

Due to high rates of viral replication and an error prone HCV RNA polymerase, tremendous variability of HCV has been observed within infected patients (quasispecies) with all single mutations in the entire HCV genome thought to be pre-existing. Similarly, NS3/4A and NS5A RAVs are observed at baseline in patients infected with chronic HCV. The prevalence of baseline NS5A RAVs has been reported to be 6% to 16% using population sequencing (cut off 15–25%) or deep sequencing (cut off 1%), respectively. Interestingly, the prevalence and type of baseline NS5A RAVs may vary by geographic regions. For example, the prevalence of the NS5A M28V in genotype 1a-infected patients was shown to be higher in the United States compared to Europe, 7% versus 0%, respectively. Furthermore, the prevalence of genotype 3 NS5A Y93H varied between 0% and 17% in different geographic regions. A comparison of baseline prevalence of RAVs in Japanese and Western patients showed that the prevalence of Q80L and S122G in NS3, and L28M, R30Q and Y93H in NS5A was significantly higher in Japanese patients than the Western counterparts. Many currently approved interferon (IFN)-free regimens for the treatment of chronic hepatitis C (HCV) include an inhibitor of HCV NS5A. To date, there are four NS5A inhibitors approved for treatment of chronic HCV infection; ledipasvir (LDV), daclatasvir, ombitasvir, and elbasvir. The presence of baseline NS5A RAVs may impact treatment outcome of some NS5A inhibitor containing HCV regimens due to the intrinsic qualities of the NS5A inhibitor, drug pharmacology, or effects of the other compounds within the treatment regimen. To enable comparisons of resistance analyses between clinical trials, standardization of RAV definitions and sensitivity cut offs is needed. Further study is needed to understand the role of RAVs present at frequencies below 15% and whether substitutions without an in vitro susceptibility change to the NS5A inhibitor may dilute a clinical signal by RAVs that do confer reduced susceptibility to the NS5A inhibitor.

Autoimmune pancreatitis – The chameleon of GI diseases

Georg Beyer, Julia Mayerle, Markus M. Lerch, M.D., FRCP*
*Department of Medicine A, University Medicine, Ernst-Moritz-Arndt-University Greifswald, Germany

Introduction
A first description of chronic sclerosing pancreatitis with increased serum immunoglobulin levels was reported by Henri Sarles in the 1960s [1]. The first time the expression 'autoimmune pancreatitis' (AIP) was coined was by the Rostock pathologist Hans Peter Putzke [2] whereas the fully developed concept of the disease entity was formulated in Japan [3]. Initially it was thought that the disease only affects patients in Asia before reports in Europe appeared that reported similar findings and it became obvious that AIP is also found among Caucasians [4].
A large study by Günter Klöppel et al. that included 54 specimens from pancreatic resections collected in Germany, Belgium and Italy, highlighted macroscopic and microscopic features which later found their way into various diagnostic guidelines [5], namely narrowing of the pancreatic duct and common bile duct without upstream dilatation, lack of calcifications or pseudocysts and the dense lymphoplasmacytic infiltrate and periductal fibrosis that can involve the acini. It is noteworthy, that in a number of these cases "granulocytic-epithelial" lesions (GELs) were described, which were later defined as a hallmark of idiopathic duct-centric chronic pancreatitis (IDCP), the histologic description of type 2 AIP [6].

Diagnostic criteria of AIP
The correct diagnosis of AIP remains a clinical challenge. Especially the high prevalence of type 2 AIP in Europe and North America, with its lack of elevated serum IgG-4 concentrations, a broader age spectrum and a higher proportion of mass-forming lesions that mimic malignant disease, prevented a European adoption of early diagnostic guidelines, which were based on the experience in Japan [7].
Currently Japanese and Asian Consensus Criteria include imaging of pancreatic parenchyma and duct appearance, elevated serum IgG-4/autoantibodies and LPSP with IgG-4 positive plasma cells [8] and the American HiSORT criteria involve histology showing LPSP/IDCP, suggestive imaging, elevated serum IgG-4, other organ involvement and response to steroids [9], whereas the Italian criteria [10] include as main characteristics:

- Suggestive radiological features on CT or MRI (no ERCP required)
- Association with autoimmune disease
- Consistent histology (lymphoplasmacytic infiltration and GELs)
- Response to steroid therapy (clinically and on imaging)

The International Consensus Diagnostic Criteria which were introduced in 2011 combine the different approaches and allow to establish the diagnosis of AIP in accordance to regional needs and preferences [11]. For example, ductal imaging is no longer required to make the definitive diagnosis for AIP type 1 as diagnostic ERP is not commonly used in western countries. In equivocal cases it remains, however, a valuable and recommended tool.
But even with these diagnostic criteria and proposed diagnostic work-up the definitive diagnosis of AIP type 2 remains challenging. The group from the Mayo Clinic has

emphasized the importance of histologic proof and championed the use of pancreatic true-cut biopsies [12]. However, this method is still not widely available and the more commonly used EUS-guided FNA has limitations due to the sampling technique [13].

While type 2 AIP (IDCP) is more common in western countries and associated with inflammatory bowel disease, type 1 AIP (LPSP) is part of what is now called IgG-4 related syndrome [14] and can manifest with a plethora of findings in other organs. This makes it the chameleon of gastrointestinal diseases (Table 1).

Previous name	**Effected organ**
Mikulicz's disease	Salivary and lacrimal gland
Küttner's tumor	Submandibular gland
Riedel's thyroiditis	Thyroid
Chronic sclerosing aortitis	Aorta
Morbus Ormond	Retroperitoneum
Autoimmune pancreatitis	Pancreas
Sclerosing cholangitis	Biliary system
Orbital pseudotumor	Orbita
Autoimmune hepatitis	Liver
Multifocal fibrosclerosis	Multiple organs

Table 1: *Organ involvement of type 1 AIP and IgG-4 related disease*

Treatment strategies

The first line therapy for both types of AIP is corticosteroids and virtually all cases show a satisfactory initial response. However, treatment regimens differ greatly between countries. Whereas studies from the United Kingdom and France report fixed prednisolone doses of 30 mg to 40 mg over a period of 4 weeks [15, 16], 1 mg/kg prednisolone for 2–3 weeks was given in an Italian study [17] and is commonly used in Germany. In all of these trials steroids were tapered off over a period of 2–3 months and eventually discontinued. These approaches are similar to those reported from the European centers participating in the largest international follow-up study [18]. Also the relapse rate after a steroid taper or discontinuation was similar to the international average (33% vs. 34%). A study that enrolled 102 patients from several European centers that underwent surgical treatment an overall relapse rate of 26% reported [19] which is comparable to international studies with a relapse rate of 30%.

In the case of relapsing disease most authors repeated the course of steroids with or without steroid sparing drugs. The most commonly used immunmodulator was Azathioprin but also Retuximab has now been employed in individual cases.

When estimating the need for a maintenance therapy or the risk of recurrence it needs to be remembered that type 2 AIP rarely relapses and recurrences are quite common for type 1 AIP.

References:

1. Sarles H, Sarles JC, Muratore R, Guien C. (1961) Chronic inflammatory sclerosis of the pancreas – an autonomous pancreatic disease? Am J Dig Dis. 6:688–98.
2. Putzke HP. (1979) Morphology of acute and chronic pancreatitis (in German). Z Gesamte Inn Med. 34(10):266–71.
3. Yoshida K, Toki F, Takeuchi T, et al. (1995) Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 40:1561–8.
4. Varadarajulu S, Cotton PB. (2003) Autoimmune pancreatitis: is it relevant in the west? Gastroenterology. 125:1557.
5. Klöppel G, Lüttges J, Löhr M, et al. (2003) Autoimmune pancreatitis: pathological, clinical, and immunological features. Pancreas. 27:14–9.
6. Chari ST, Kloeppel G, Zhang L, et al. (2010) Histopathologic and clinical subtypes of autoimmune pancreatitis: the honolulu consensus document. Pancreatol Off J Int Assoc Pancreatol IAP Al. 10:664–72. doi: 10.1159/000318809
7. Chari ST, Longnecker DS, Klöppel G. (2009) The diagnosis of autoimmune pancreatitis: a Western perspective. Pancreas. 38:846–8. doi: 10.1097/ MPA.0b013e3181bba281
8. Otsuki M, Chung JB, Okazaki K, et al. (2008) Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol. 43:403–8. doi: 10.1007/s00535-008-2205-6
9. Chari ST. (2007) Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol. 42 (Suppl 18):39–41. doi: 10.1007/s00535-007-2046-8
10. Frulloni L, Scattolini C, Falconi M, et al. (2009) Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. Am J Gastroenterol. 104:2288–94. doi: 10.1038/ajg.2009.327
11. Shimosegawa T, Chari ST, Frulloni L, et al. (2011) International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 40:352–8. doi: 10.1097/ MPA.0b013e3182142fd2
12. Levy MJ, Smyrk TC, Takahashi N, et al. (2011) Idiopathic duct-centric pancreatitis: disease description and endoscopic ultrasonography-guided trucut biopsy diagnosis. Pancreatol Off J Int Assoc Pancreatol IAP Al. 11:76–80. doi: 10.1159/000324189
13. Pickartz T, Mayerle J, Lerch MM. (2007) Autoimmune pancreatitis. Nat Clin Pract Gastroenterol Hepatol. 3:314–23.
14. Beyer G, Schwaiger T, Lerch MM, Mayerle J. (2014) IgG4-related disease: a new kid on the block or an old aquaintance? United European Gastroenterol J. 2(3):165–72.
15. Church NI, Pereira SP, Deheragoda MG, et al. (2007) Autoimmune pancreatitis: clinical and radiological features and objective response to steroid therapy in a UK series. Am J Gastroenterol. 102:2417–25. doi: 10.1111/j.1572-0241. 2007.01531.x
16. Maire F, Le Baleur Y, Rebours V, et al. (2011) Outcome of patients with type 1 or 2 autoimmune pancreatitis. Am J Gastroenterol. 106:151–6. doi: 10.1038/ ajg.2010.314

17. Frulloni L, Scattolini C, Katsotourchi AM, et al. (2010) Exocrine and endocrine pancreatic function in 21 patients suffering from autoimmune pancreatitis before and after steroid treatment. Pancreatol Off J Int Assoc Pancreatol IAP Al. 10: 129–33. doi: 10.1159/000265945
18. Hart PA, Kamisawa T, Brugge WR, et al. (2013) Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 62:1771–6. doi: 10.1136/gutjnl-2012-303617
19. Detlefsen S, Zamboni G, Frulloni L, et al. (2012) Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: a study of 114 surgically treated European patients. Pancreatol Off J Int Assoc Pancreatol IAP Al. 12:276–83. doi: 10.1016/j.pan.2012.03.055

The role of inflammatory mediators during organ failure in portal hypertension

Alexander L. Gerbes
Medizinische Klinik II, Klinikum der Universität München, Campus Großhadern, Munich, Germany

Inflammation is increasingly being recognized as an important cause of organ failure in chronic liver disease. Acute decompensation of chronic liver disease and moreover, a progress towards acute-on-chronic liver failure (ACLF) have recently been characterized by a large multicenter European study (Canonic). Interestingly, inflammation was found as a trigger for development of ACLF. Likewise, patients with no previous decompensation of liver disease were more prone to develop ACLF than patients who experienced previous episodes. These findings have been interpreted as a protection conveyed by repeated hepatic or extrahepatic infections.
Looking in more detail, pathogen associated molecular patterns (PAMP) as well as damage associated molecular patterns (DAMP) seem to be of major importance. Counteraction of inflammatory signals and limitation of inflammation seem to be equally relevant in this scenario. Gut bacterial translocation has been found of particular relevance for systemic inflammatory response. In liver cirrhosis TLR-10 polymorphisms leading to a functionally impaired limitation of inflammation were just recently reported. In chronic liver disease extrahepatic inflammation and damage have been described in various cells and organs such as astrocytes and adrenal glands, respectively. However, the kidney seems to be particularly vulnerable and of major relevance regarding the overall outcome.
Altogether, inflammation and inflammatory mediators in liver disease are being recognized as a major player leading to hepatic and moreover, extrahepatic organ failure. On the basis of this increased understanding of pathophysiology novel strategies for prevention of organ failure in chronic liver disease may be developed.

References:

1. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome developing in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37.
2. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61(5):1038–47.
3. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. J Hepatol. 2014;61:1385–96.
4. Angeli P, Rodriguez E, Piano S, Ariza X, Morando F, Solá E, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. Gut. 2015; 64(10):1616–22.
5. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes AL, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015;64:531–7.

Session II

Standards and developments of IBD therapy

Aminosalicylates, budesonide and Co: Standards and new approaches

Stephen B. Hanauer, M.D.
Professor of Medicine and Medical Director Digestive Health Center, Northwestern University, Chicago, IL, USA

Aminosalicylates are the foundational therapies for induction and maintenance of remission of mild-moderate ulcerative colitis. Over the past decades the formulations have evolved from salazopyrine to include oral formulations of mesalazine, balsalazide, and olsalazine as well as rectal formulations of mesalazine suppositories, enemas and foams. Clinical trials have demonstrated their safety and effectiveness in a variety of dose-ranges and as mono- or combinations of oral and topical approaches. Their safety profile has been valued for decades and forms a basis of comparison for all other current and potential “first line” agents.

There remain a number of controversies related to aminosalicylates including their (potential) utility for mild or superficial Crohn’s disease, as steroid-sparing agents (e.g. compared to thiopurines), and whether they should be continued in ulcerative colitis subsequent to the introduction of immune suppressives or biologic agents.

The recognized effect of corticosteroids as effective, yet toxic, inductive agents for both ulcerative colitis and Crohn’s disease has led to a quest for effective and safe glucocorticoids devoid of systemic risks. Despite earlier trials with tixocortol pivalate, fluticasone, topical betamethasone, and prednisolone metasulfobenzoate, budesonide has become the preferred compound for enteric formulations as delayed-enteric release for Crohn’s disease and oral colonic release or rectal formulations for ulcerative colitis. While attempts to develop formulations that provide topical without systemic benefits for induction of both Crohn’s disease and ulcerative colitis, budesonide formulations have yet to demonstrate long-term, effective and safe (vis a vis adrenal suppression and systemic glucocorticoid effects) benefits. Furthermore, budesonide has not been effective at prolonging post-operative remissions in Crohn’s disease nor are the clinical benefits “on top of” aminosalicylates proven to have clinically meaningful advantages in ulcerative colitis.

To date, there has been a paucity of other “first line” therapies developed for either ulcerative colitis or Crohn’s disease that meet the standards of safety and efficacy comparable to the experience with aminosalicylates in ulcerative colitis.

Trough level directed therapy in IBD

Ioannis E. Koutroubakis
Department of Gastroenterology, University Hospital of Heraklion, University of Crete, Heraklion, Greece

Recent years a new concept has been developed in order to optimize treatment of chronic inflammatory diseases with anti-TNF monoclonal antibodies by treating patients based on actual exposure to the drug rather than according to a standard dosing regimen.

There is evidence from various studies that the rate of primary nonresponse and non-remission to anti-TNF in inflammatory bowel disease (IBD) ranges between 10% to 40% and 50% to 80%, respectively. The cause of this phenomenon is considered multi-factorial with both pharmacokinetic and/or pharmacodynamic parameters playing a role. The often finding of undetectable or low serum drug concentrations has been attributed to an accelerated (non) immune clearance of the drug in the systemic circulation and/or local tissue. It could be postulated that the absence or loss of response to anti-TNF is associated with adequate serum drug concentrations. Moreover, a hypothesis of a probable shift of the disease from TNF-driven to a non-TNF-driven inflammatory pathway has been suggested. The development of anti-drug antibodies, which is known as immunogenicity, can also play an important role because it has been demonstrated that binding of these antibodies to the anti-TNF drug leads in a faster clearance of drug having as final result less favorable clinical outcomes.

Although a link between serum levels of infliximab or adalimumab, anti-drug antibodies and clinical outcomes in patients with IBD has been suggested by several studies, the interpretation of published data in the clinical practice has been challenging. There are many differences in the used assays for trough levels measurement (ELISA, HMSA, RIA) and their description (mean, median, quartile, cut-off) in relation to various outcomes (loss of response, remission) during the course of anti-TNF therapy.

With an aim to predict the anti-TNF serum levels and to optimize the dose based on serum level, the use of a pharmacokinetic model is considered of great importance. Furthermore, today the cost in IBD therapy is mainly driven by the anti-TNF treatment and a strategy to optimize-personalize therapy and avoid unnecessary treatment is desirable.

Is there a standard approach for post-surgical Crohn's disease?

Axel Dignass, M.D. Ph.D.
Department of Medicine I, AGAPLESION Markus Hospital, Goethe University, Frankfurt/Main, Germany

A majority of patients with Crohn's disease (CD) will require surgical intervention during the course of their disease. Surgical resection is not curative and disease recurrence is relatively common. The decision to pursue surgical treatment for CD is highly personalized. In addition, the pre-operative and perioperative therapies and also the use of prophylactic medical therapy following surgery vary substantially and are also individualized, but adhering to common medical strategies generally used for CD patients. With more medications available, our armamentarium for the postoperative situation has become more complex. In the past, medical maintenance therapy following surgical intervention has not been routinely recommended and patients were frequently treated on demand, with initiation of treatment at the time of symptomatic or endoscopic recurrence. Emerging evidence suggests that early postoperative initiation of medical therapy, especially in high-risk patients may reduce the need for additional operations.

Within the first year of surgery, 70–90% of CD patients develop endoscopic recurrence, increasing to 80–100% within three years. It would be extremely helpful, if the disease course of an inflammatory bowel disease (IBD) before and following surgery could be predicted in order to select the most beneficial diagnostic and therapeutic approaches. However, there are no perfect clinical predictors or markers for the future disease course following surgery in CD patients. Several studies suggest that mucosal cytokine profiles may be helpful to predict the recurrence of IBD. Elevated mucosal concentrations of TNFα, IL-1 and IL-6 in the ileocolonic mucosa have been described as independent predictors for future relapse of IBD. However, the measurement of mucosal cytokine levels is not used in standard clinical care.

Extent and severity of disease prior to surgical intervention and severity of early endoscopic lesions following surgery have been demonstrated to predict the symptomatic course of disease after surgery. Therefore, postoperative surveillance has been shown to be helpful to identify patients, who will benefit from early and intensive postoperative medical management. For example, early use of anti-TNFs after surgery has recently been demonstrated to significantly decrease the risk of endoscopic recurrence in patients with multiple previous surgeries, stricturing or penetrating disease. Quitting smoking reduces the post-operative recurrence rate significantly. Several studies have shown a more complicated disease course in patients with perforating disease than in those with non-perforating disease.

Especially in patients with complicated disease courses structured management of IBD patients within a coordinated multidisciplinary IBD team may improve the outcome with improved perioperative and postoperative results. Especially in the postoperative setting, patients should be referred back to their treating gastroenterologists to initiate early follow-up colonoscopy and/or initiation of postoperative medical therapy to avoid a gap between endoscopic recurrence and clinical symptoms.

Azathioprine and methotrexate: Getting dusty?

Hans Herfarth, M.D., Ph.D.
Professor of Medicine, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

For more than 2 decades thiopurines (6-mercaptopurine (6-MP) and azathioprine) as well as methotrexate have been established in the therapy of inflammatory bowel diseases (IBD). Before the introduction of biologics, thiopurines were the preferred approach in patients with steroid dependent IBD. [1] Methotrexate has never been used on a “larger scale” in IBD patients despite 2 successful clinical studies demonstrating its efficacy for induction and maintenance of remission in steroid dependent Crohn’s disease. [2] The low utilization of methotrexate is probably due to several reasons. The methotrexate studies were published in the same time period when infliximab was introduced in the therapeutic armamentarium for Crohn’s disease (CD). The introduction of infliximab went along with significant marketing efforts, whereas methotrexate as a generic drug was not advertised at all to patients or physicians. Also in CD methotrexate has to be applied subcutaneously, which is less favored by patients and also requires some monitoring of the therapy. With the discovery of anti-drug antibodies to biologics and their impact on the overall clinical efficacy, thiopurines and to a lesser degree methotrexate became again en vogue in the setting of combination therapy. [3] Also, due to the risk of hepatosplenic lymphoma as an extremely rare adverse event of thiopurine therapy methotrexate has become a first-line monotherapy or is preferable used in combination therapy in pediatric Crohn’s disease. [4]

Currently several clinical questions in relation to the therapy with either thiopurines or methotrexate are evaluated: The COMBINE trial (ClinicalTrials.gov Identifier: NCT02772965) will evaluate the question of the efficacy of the combination therapy of methotrexate with either adalimumab or infliximab. This study will hopefully clarify why in the COMMIT trial no additive clinical benefit for methotrexate/infliximab combination was observed, which is in contrast to the results of the SONIC study with a significant better clinical benefit of the combination of azathioprine and infliximab compared to single agent therapy. [5] Another important question is if a reduced dose of 6-MP/azathioprine or methotrexate is equally effective as a normal dose in preventing antibody formation and maintaining clinical efficacy of biological therapy. Methotrexate could also represent a unique and affordable maintenance therapy for UC patients in need for an immunosuppressive treatment. The recently published French METEOR trial investigated the clinical efficacy of subcutaneously applied methotrexate 25 mg once weekly as an induction regimen over 16 weeks. [6] The trial failed to achieve the primary endpoint of a combined clinical and endoscopic remission, but showed a significant advantage of methotrexate to placebo for the secondary endpoint of clinical remission only. Several factors might have contributed that the results of this investigator initiated trial are not as clear-cut as one would have hoped for. [4] Currently another investigator initiated study evaluates the clinical value of methotrexate in UC, the US MERIT-UC trial. [7] The primary endpoint of this prospective, randomized, placebo controlled study is the efficacy of methotrexate to maintain steroid free remission over 54 weeks. This trial is still recruiting and the results are expected in early 2018. Hopefully this study will clarify if methotrexate is a viable therapeutic options in patients who fail mesalamine therapy.

References:

1. Schölmerich J. [Indications for immunosuppressive therapy of chronic inflammatory bowel diseases]. Internist (Berl). 1997;38:582–9.
2. Herfarth HH, Long MD, Isaacs KL. Methotrexate: underused and ignored? Dig Dis. 2012;30 (Suppl 3):112–8.
3. Chande N, Marshall JK, Seow CH, et al. New applications for traditional drugs in inflammatory bowel disease: What do cochrane reviews tell us? Inflamm Bowel Dis. 2015;21:2948–57.
4. Herfarth HH, Kappelman MD, Long MD, et al. Use of methotrexate in the treatment of inflammatory bowel diseases. Inflamm Bowel Dis. 2016;22:224–33.
5. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology. 2014;146:681–88.e1.
6. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. Gastroenterology. 2016; 150:380–8.e4.
7. Herfarth HH. Methotrexate for inflammatory bowel diseases – New developments. Dig Dis. 2016;34:140–6.

New concepts for treatment – Lessons learned

Claudio Fiocchi
Department of Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Department of Pathobiology, Lerner Research Institute, The Cleveland Clinic, Cleveland, Ohio, USA

The treatment of both forms of inflammatory bowel disease (IBD), i.e., Crohn's disease (CD) and ulcerative colitis (UC), has continuously evolved since the clinical identification of these chronic inflammatory disorders of the gastrointestinal tract. The pace of this evolution has increased from the very slow one of the 1940's and 50's to the rapid one of the 2000's. Evolution has increased not only its speed but also its numbers, as a constantly expanding number of agents fill up the current therapeutic armamentarium for IBD. However, it is intriguing to notice that some of the very first drugs used for IBD, like sulfasalazine and its derivatives as well as corticosteroids, are still being broadly used today, and here is the first very important lesson: something found to be therapeutically active by educated guess is still being used side-by-side with sophisticated drugs rationally developed based on knowledge of IBD pathophysiology and state-of-the-art technologies. From the 1980's to the 90's the spectrum of agents used for CD and UC substantially expanded to include immunosuppressive agents, antibiotics, probiotics and elemental diets. None of them provided a cure for IBD, but there it becomes obvious that there is always a subgroup of patients who do benefit from any one of those medications, alone or in combination. And here is a second important lesson: every patient or groups of patients respond differently to similar or dissimilar therapies, and there is no "single size fits all" treatment for IBD. Then the late 1990's and the 2000's brought us brand new approaches such as stem cells, fecal transplantation and oligonucleotides, and the biologics. The latter have revolutionized how we treat IBD and what we can expect from modern IBD therapy, not only from the doctor's perspective but also from the perspective of the patients, who are increasingly knowledgeable about IBD treatment by accessing widely available information and take part in therapeutic decisions. Once a therapeutic decision is made, then the expectation arises of a beneficial effect, be it a clinical response or, better yet, a full clinical remission. Unfortunately, the way we define response and remission is still fairly simplistic and unsophisticated, relying primarily on clinical, endoscopic and histological parameters. There is plenty of evidence that all of these are only partially reliable readouts, but we continue to use them not only in daily clinical practice but also even in large multicenter clinical trials. This situation carries another lesson: we are reticent to start using more informative and dependable methods, such a mucosal gene expression profiles, to actually learn whether and to what degree molecular inflammatory patterns have been suppressed or modified. Without adopting more refined methodologies during clinical management we will mislead ourselves as well as the patients, and will postpone the use of additional or alternate therapies.

Major advances in technology go hand-in-hand with better knowledge of IBD, resulting in improved treatment options that can benefit the whole field of IBD. This is also a lesson, one that brings along a corollary question and an appended lesson: have we cured IBD? No and, if so, why not? What is still missing? And the lesson here is that we are still missing a lot of knowledge because of the extreme biological complexity of both forms of IBD. The number of reports on IBD pathogenesis and management

grows exponentially year-by-year, while progress in new treatments proceeds at a much slower pace. We currently know much about the variation of the genetic makeup of IBD patients, we are accepting the astonishing complexity of the environment outside (the diet and xenobiotics) and inside (the microbiota) our bodies to which we must adapt to remain healthy, and we have a reasonable grasp of the immune system and how to manipulate it. But, do we know how these elements come together and impact on each other to determine an outcome of health or IBD? The answer is no, and this answer brings still another lesson. We need to not only accept the amazing complexity of biological phenomena, but also make an effort to organize it to understand it more fully. So, if biological diversity and complexity are intrinsic to IBD, how can we expect to cure CD or UC by intervening on single or a few isolated pathogenic pathways? We can expect some positive results, but we cannot expect a real cure, defined as the disappearance of all disease with no subsequent recurrence. This is obviously a very high stake, but one that can be tackled by adopting new approaches aimed at making sense of biological complexity and diversity. Most IBD experts accept the notion of personalized therapy, but this is only being implemented at a narrow clinical level, and much more “personalization” is needed. And here goes another crucial lesson: only a highly integrated approach can solve the puzzle of IBD, an approach where all putative elements involved with IBD are taken into account, analyzed, integrated, and screened for key controlling factors. These will come down to a selected number of specific genes, proteins, signals, metabolites, etc. that, alone or in various combination, hold the key to the mechanism of disease in each patient. And the lesson here is that this can be done, and can be down today. This can be accomplished by adopting a number of available systems biology and bioinformatics tools that allow integrating massive amount of data and identify the controllers (nodes/hubs) of the disease network(s) that then become the target for therapeutic intervention. So, we have learned many lessons in the therapeutic journey of IBD, but we need to accept the answers to effectively change the way the “see” and treat IBD.

Session III

Infections and the GI tract

Impact of HIV on intestinal function

Bernd Salzberger
Department of Internal Medicine I, University Hospital Regensburg, Regensburg, Germany

HIV associated enteropathy has first been described in the 1990s. Functional abnormalities are clinically characterized by severe weight loss and diarrhea, most prominent in late HIV-infection with severe immunodeficiency.
Infection with the human immunodeficiency virus has a profound impact on gastrointestinal immunity and consequently on intestinal function. This impact on GI-immunity was noted early, but not well and fully understood. Parallel studies in primary HIV-infection and in simian immunodeficiency virus infections demonstrated, that HIV-infection leads to a near complete destruction of gastrointestinal CD4-memory-cells very early in primary infection. This loss of CD4-memory cells leads to bacterial translocation and systemic inflammation also early in the disease. Overt functional changes develop later with morphologic changes in villi architecture, loss of epithelium surface and impaired regeneration.
While some of the clinical features can be reverted with antiretroviral therapy, micronutritient replacement or symbiotics, the repopulation of CD4-cells in the GI-tract is by far not as complete as in peripheral blood. Markers of systemic inflammation remain high in many patients. The immunological changes in these patients are similar to immunosenescence and thus may contribute to more rapid aging as part of HIV-pathogenesis.
HIV-associated enteropathy thus is still an important factor in HIV pathogenesis, even with modern antiretroviral therapy. In addition, it is an important model to study the effects of gastrointestinal immunity on systemic inflammation, intestinal function and aging.

CMV colitis – Infectious complication or bystander in IBD

Gerassimos J. Mantzaris, M.D., Ph.D., FEBGH, AGAF
Coordinator Consultant Gastroenterologist, Department of Gastroenterology, 'Evangelismos-Ophthalmiatreion Athinon-Polykliniki' Hospitals, Athens, Greece

Cytomegalovirus (CMV) causes a latent infection in more than 70% of adult IBD patients which does not affect the natural course of disease. However, CMV can be reactivated during treatment with steroids and immunosuppressives (IMS, i.e. thiopurines, methotrexate, calcineurin inhibitors), or because of malnutrition, advanced age, recent surgery, etc. Reactivation can take the form of subclinical CMV infection (slight increase in viral DNA load or a few CMV inclusion bodies detected by H&E staining combined with immunohistochemistry [IHC] in colonic biopsy specimens) or CMV disease (damage to end-organ, e.g. colitis, hepatitis, etc.). The former is common in patients with active IBD, especially ulcerative colitis (UC), but is self-limited and does not need any treatment or withdrawal of steroids or IMS. In contrast, CMV colitis has been associated with a complicated course of UC although its association with flares of Crohn's disease (CD) is less well documented. CMV colitis should be suspected in every UC patient who presents with severe and/or steroid-refractory colitis, and risk factors are severe endoscopic ulcers, intense histological inflammation, and advanced age. CMV colitis is diagnosed by the presence of florid inclusion bodies and > 250 CMV viral DNA copies/mg of tissue by real-time PCR in whole blood. It appears that the use of anti-TNF biologics is not associated with increased risk of CMV colitis. In contrast to CMV infection, the outcome of severe UC complicated by CMV colitis is worse, is associated with increased rates of colectomy and necessitates withdrawal of IMS and treatment with ganciclovir for 2–3 weeks. Risk factors for colectomy are the presence of intense intestinal inflammation, more than 5 infected cells per section counted, and low haemoglobin and albumin levels. Thus, CMV is usually an innocent bystander in active IBD and any screening is not needed before application of appropriate treatment with steroids and/or conventional IMS. However, in patients who are rendered steroid- and/or IMS-refractory CMV colitis should be sought and treated appropriately.

References:

1. Annese V et al. J Crohns Colitis. 2015;9:945–65.
2. Hirayama Y et al. World J Gastrointest Endosc. 2016;8:301–09.
3. Römkens TE et al. World J Gastroenterol 2016;22:1321–30.
4. Rahier JF et al. J Crohns Colitis. 2014;8:443–68.
5. Sager K et al. Aliment Pharmacol Ther. 2015;41:725–33.
6. Zagórowicz E et al. J Crohns Colitis. 2016:1–7, published online March 2016.

Clostridium difficile and fecal transplantation

Gerhard Rogler
Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland

Infectious diseases of the gut are frequently associated with diarrhea and abdominal pain. One example is *Clostridium difficile* infection (CDI). Bartlett et al. first identified *Clostridium difficile* as the major infectious cause of antibiotic-associated diarrhea in 1978 [1]. Clostridia are able to form spores which can survive under very restrictive conditions.
In the past years there has been a constant rise of CDI due to increased use of antibiotics, an older population and more virulent *Clostridium difficile* strains [2]. Treatment of choice is an antibiotic treatment with Metronidazole or Vancomycin orally with primary clinical cure rates of up to 90%. Unfortunately in about 15% the infection reoccurs and the chances of a successful second course of antibiotic treatment are lower [3].
An emerging therapeutic option for the treatment of CDI in recent years (albeit already described several decades ago in the literature) is fecal microbiota transplantation (FMT) and treatment guidelines have been published [4]. In FMT a fecal suspension from a healthy individual is infused into the gastrointestinal tract of another person in an attempt to treat an illness. This treatment has a low complication rate; adverse effects that are most often reported are those associated with a colonoscopy. Furthermore to date no transmissions of infectious bowel diseases has been reported. In a randomized study by van Nood et al. the infusion of donor feces was significantly more effective for the treatment of recurrent CDI than the use of vancomycin [5]. Due to the high efficacy of this treatment and the relatively low rate of adverse effects FMT has gained rising importance in the treatment of recurrent *Clostridium difficile* colitis.
New alternatives to donor dependent FMT are under investigation. Very recently a clinical trial using spores of non-pathogenic Clostridia species, however, has failed to show significant clinical efficacy (vs. placebo).

References:

1. Bartlett JG, Chang TW, Gurwith M, et al. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. New Engl J Med. 1978;298:531–4.
2. Reveles KR, Lee GC, Boyd NK, et al. The rise in Clostridium difficile infection incidence among hospitalized adults in the United States: 2001–2010. Am J Infect Control. 2014;42:1028–32.
3. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. An official publication of the Infectious Diseases Society of America. 2007;45:302–7.

4. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. The official clinical practice journal of the American Gastroenterological Association. 2011;9:1044–9.
5. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. New Engl J Med. 2013;368:407–15.

Infections and GI cancer

E.M. El-Omar
St. George & Sutherland Clinical School, University of New South Wales, Sydney, NSW, Australia

The role of infectious agents in carcinogenesis has commanded significant scientific interest culminating in at least 7 Nobel prizes thus far. Infections can cause cancer by a variety of mechanisms including direct transformation of cells, induction of immunosuppression with consequent reduced cancer immunosurveillance, or by causing chronic inflammation. The latter is now recognised as an essential component of many epithelial cancers by virtue of its combined effects of generating genotoxic by-products and increased cellular proliferation, thus maximising the potential for DNA damage. Perhaps the best paradigm for an infection-induced and chronic inflammation-driven malignancy is gastric cancer. Gastric cancer has a complex multifactorial aetiology but it is now fully established that the key pathophysiological events are largely initiated by H. pylori infection. In genetically predisposed hosts, this infection induces severe gastritis with a consequent hypochlorhydric and atrophic phenotype that facilitates genotoxic damage and neoplastic transformation. The infection leads to malignant transformation through the recognized effects of the mutagenic byproducts and mediators of the inflammatory process but also through the effects of the altered gastric microbiome that thrives in the absence of gastric acid. There is also strong evidence that some of the proteins produced by H. pylori are directly involved in the carcinogenic process. The most understood of these is the cytotoxin-associated gene A (CagA) protein, which acts as an oncogenic protein.
Over the past decade, it has become abundantly clear that the gut microbiota play a crucial role in human health and disease, including several GI cancers. Of these, colorectal and liver cancers are the most important and best understood. It appears that a dysbiotic gut microbiota is a pro-inflammatory risk factor that has a direct impact on the neoplastic process at these two sites. The mechanisms are being unravelled fast and the prospect of preventing such global killers through simple manipulation of the gut microbiota is realistic and palpable. Gastroenterology as a discipline within medicine has never been more exciting.

Session IV

Rheumatic diseases and the gut

The gut microbiota: It's role in rheumatoid arthritis and other inflammatory diseases

R. Balfour Sartor, M.D.
Director Multidisciplinary IBD Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Immune-mediated diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis (RA), spondyloarthropathies (SpA), psoriasis and multiple scleroses share common characteristics, each being complex genetic disorders with strong environmental influences. These disorders have overlapping susceptibility genes, increased incidence of shared disease phenotypes, and recent evidence of overlapping abnormal microbiota profiles. IBD, RA and SpA each have evidence of dysbiosis, with a common decreased diversity of resident gut microbiota and some overlap in intestinal bacterial popuations that are increased or decreased during inflamed states. In IBD, Clostridium subgroups and *Faecalibacterium prausnitzii* are decreased, with parallel expansion of Proteobacteria, especially functionally abnormal (adherent/invasive) *E. coli* strains. Far less consistency results exist for RA and SpA, but it appears that Faecalibacterium species are decreased. Human RA studies suggest strong abnormalities in gut and oral microbiota profiles, with the vast bulk of information available for bacteria and very little for fungi and viruses. As with IBD, uncertainties exist over primary vs. secondary roles for the observed dysbiosis in RA and SpA. Evidence that HLA haplotypes affect intestinal bacterial profiles and that fecal transplants from experimental arthritis transfer phenotypes to susceptible mice suggest a causative role, but there is no evidence that altering the microbiome with probiotics or antibiotics affects human RA. A possible secondary effect is suggested by dysbiotic profiles being associated with disease activity, improving with treatment of active inflammation. Animal models are very helpful in evaluating possible pathogenic mechanisms, which include bacterial regulation of immune function, such as TH17/Treg ratios and mucosal permeability, which affects uptake and systemic distribution of intestinal bacterial TLR ligands and antigens. Some intestinal bacterial antigens can activate autoimmune responses through molecular mimicry with mammalian antigens. This rapidly expanding microbial information has the possibility of guiding development of novel therapies that normalize the associated dysbiosis, as well as biomarkers that can predict clinically important disease subsets, aggressiveness of disease and therapeutic outcomes.

Ankylosing spondylitis and the gut: What is the connection?

Elisabeth Märker-Hermann
Department of Internal Medicine IV, HELIOS Dr. Horst Schmidt-Kliniken, Wiesbaden, Germany

Peripheral and axial spondyloarthritis (SpA) are common extraintestinal manifestations of inflammatory bowel disease (IBD) occurring in up to 10% of patients with Crohn's disease (CD) and ulcerative colitis (UC). Moreover, asymptomatic intestinal inflammation, usually involving the terminal ileum, has been demonstrated in a significant number of patients with ankylosing spondylitis (AS) and other SpAs. Two types of inflammation have been observed in patients with AS: (1) acute inflammation as seen in infectious colitis and (2) chronic inflammation resembling CD. Long-term evolution to overt CD has been described in 7% of patients with initial chronic gut inflammation. The two diseases (AS and CD) show an overlapping set of predisposing genes: The chronic, but not the acute subtype of gut inflammation in AS was shown to be associated with a CARD15 SNP also strongly linked to CD. In AS, in addition to HLA-B27, genes implicated in the Th17 and IL23 pathway and the aminopeptidases ERAP1 and ERAP1 are most strongly linked to the disease.

Several immunologic similarities between gut inflammation in SpA and CD have been described, such as increased expression of the E-cadherin-catenin complex, up-regulation of integrin on intraepithelial T cells, and increased numbers of macrophages expressing the scavenger receptor CD163, supporting the concept that this subgroup of SpA patients may be considered a model for early immune alterations related to CD. T lymphocytes, which were found to be clonally expanded in the gut as well as in the synovium of SpA-patients, play an important role in the regulation of gut innate and specific immune responses.

Finally, microbial dysbiosis in the gut is emerging as a common component in various inflammatory disorders including IBD and SpA. Decreased numbers of Firmicutes, a major phyla of gut commensals, especially the species Faecalibacterium prausnitzii and Clostridium leptum have been found in various inflammatory disorders including SpA and IBD. Recent findings are consistent with the hypothesis that genes associated with AS act at least in part through effects on the gut microbiome.

Several of the novel cytokine directed biologic therapies target IBD as well as the SpAs, whereas others are efficient in SpAs only and may lead to flares in IBD patients.

Whipple’s disease mimicking seronegative rheumatic diseases

Martin Fleck
Klinik und Poliklinik für Rheumatologie/Klinische Immunologie, ASKLEPIOS Klinikum Bad Abbach, Bad Abbach, Germany

Whipple's disease (WD) is a chronic infectious systemic disease caused by the bacterium Tropheryma whipplei (TW) that is widely spread in our environment. Children may present an acute primary infection, but only a small number of people with a genetic predisposition subsequently develop clinically overt WD. Classic WD affects middle-aged men and is characterized by gastrointestinal and general symptoms including marked diarrhoea (with serious malabsorption), abdominal pain, prominent weight loss, and low-grade fever [1]. However, WD might also manifestate as chronic infection without typical GI symptoms. WD can be the cause of chronic inflammatory joint or spine disease frequently misdiagnosed as seronegative rheumatoid arthritis or HLA-B27 negative spondyloarthritis as well as undifferentiated connective tissue disease or vasculitis. The diagnosis is based on the clinical picture and typical histology revealing foamy macrophages containing periodic-acid-Schiff-(PAS-)positive material, or positive findings of TW-DNA in tissue samples, synovial fluid, cerebrospinal fluid or other specimens by PCR analysis. Long-term (up to one year) antibiotic treatment is required resulting in rapid improvement and clinical remission in the majority of WD patients. However, primary or secondary treatment failure as well as an immune reconstitution syndrome might occur [2].
Analyzing a cohort of 20 WD patients of our tertiary Rheumatology Center at the Asklepios Clinic Bad Abbach, several important lessons could be learned:
i) GI symptoms are absent in a substantial number of patients and musculoskeletal symptoms may be predominant, ii) exclusion of WD once during the course of the disease is not sufficient, iii) immunosuppressive therapy may “unmask” the presence of TW, iv) biopsies of the lower GI tract may be required to establish the diagnosis, v) PCR analysis should be performed if histologic findings are inconclusive [3].

References:

1. Barth et al. Lancet Infect Dis. 2016;16:e12–21.
2. Puechal, Ann Rheum Dis. 2013;72;797–803.
3. Lehmann et al. Scand J Rheumatol. 2016; Epup Jul 11:1–5.

Redistribution of energy: Novel targets of intervention

Rainer H. Straub
Department of Internal Medicine I, University Hospital Regensburg, Germany

Factors relevant to energy regulation in the body influence every physiological and pathophysiological pathway. The tinniest event in cell physiology needs energy-rich fuels, typically in form of glucose, fatty acids, or amino acids yielding ATP. E.g., folding of stretched amino acid chains in the endoplasmic reticulum to native proteins needs 6 ATP molecules [1]. A person living a sedentary way of life with 1.80 m and 85 kg needs 10,000 kJ (2388 kcal) per day, which is facilitated by hydrolyzation of 200 moles of ATP. A *Tour de France* bicyclist might need 30,000 kJ (7165 kcal) a day, and a person with sepsis might spend up to 20,000 kJ (4776 kcal) during 24 hours.

Energy regulation in the body and in every cell is a critical physiological determinant of life, and energy availability always represented the strongest evolutionary pressure [2]. Two organs (or organ systems) the brain and the immune system – dominate energy regulation in the body. During evolution, both organs developed a sophisticated memory to save energy. The two organs are selfish in that activation of one of these systems blocks energy distribution to the other and to the rest of the body. Central to dominance is insulin resistance, an adaptive evolutionarily positively selected catabolic program of the brain and the immune system. The brain uses hormones of the pituitary gland and the sympathetic nervous system to redirect energy to the brain and activated muscles, but this blocks the immune system. The immune system has its own pathways using proinflammatory cytokines to block the brain and voluntary muscular activities.

If a patient develops a **chronic inflammatory disease** (CID), the immune system becomes activated and it dominates energy regulation in the body. Unfortunately, the brain is under its continuous influence leading to *sickness behaviour* with all consequences such as fatigue and even major depression, loss of appetite with anorexia and malnutrition, reduced libido, withdrawal of social contacts and loneliness, and others. In flare-ups of the disease but also during drug-controlled intervals of relatively low inflammation, the activated immune system influences energy redistribution. Typically, this can be observed as an increase in the resting metabolic rate (RMR) and a parallel decrease in physical activity-induced energy expenditure (PAEE). I call the extra costs of the activated immune system “undesirable”, because a patient would rather spend his free energy for desirable activities. In conjunction with an activated energy-demanding immune system, psychological stress (the stress of chronic illness), anxiety (the stress of living a shorter and harder life), disease-induced loneliness, chronic pain, chronic sleeping problems, sometimes higher involuntary muscle activity (e.g., in chronic obstructive pulmonary disease), and often regular smoking induce extra energy expenditure. These extra bystander costs further reduce physical activity and desirable actions.

Physicians treat patients with CIDs by inhibiting inflammation and immune system activity. However, this is only one part of the problem because the extra costs outside the immune system are usually not respected. An integrative approach, using a multitude of techniques from different disciplines, needs to define the immune system and

non-immune system extra costs of patients with CIDs. With an integrative understanding and therapy, life quality of patients with CIDs will increase because they can spend extra energy for desirable activities. This lecture delineates an integrative approach to detect extra energy expenditure by physicochemical and other methods.

References:

1. Hartl FU, Hayer-Hartl M. Nat Struct Mol Biol. 2009;160:574–81.
2. Straub RH. The origin of chronic inflammatory systemic diseases and their sequelae. Elsevier, 2015.

Session V

Endocrinology and inflammation

Is diabetes an inflammatory disease and should it be treated like that?

Andreas Schäffler
Department of Internal Medicine III, University Hospital, Justus-Liebig-University, Giessen, Germany

It is a well-known clinical observation that inflammatory diseases are accompanied by metabolic implications such as hyperglycemia, insulin resistance and increased fatty acids. On the other hand, metabolic diseases have inflammatory implications. There is a chronic and low-grade state of inflammation in obesity and type 2 diabetes. Physiological insulin resistance during infection or inflammation re-distributes glucose and fatty acids to immune cells.

What is the evidence from clinical studies using anti-inflammatory approaches to treat patients with type 2 diabetes mellitus?

Basically, TNF plays an important role in insulin resistance in rodents. Blocking TNF in rodents reverses obesity-related diabetes. There are no state of the art clinical studies showing convincing evidence of an anti-diabetic potential due to underpowered cohorts and short duration of the studies. Only one single study over 6 months showed a 10% improvement of fasting glucose levels in 40 prediabetic obese patients.

Diacerein belongs to the chemical group of anthranoids. Although the mechanism of action is unknown, diacerein decreases the levels of TNF and of IL1β and has therefore been used in rheumatic diseases. Diacerein has potent effects on insulin secretion and glycemic control with a reduction of HBA1c level by 1.6%.

IL-1 receptor antagonists such as anakinra (a recombinant human IL-1 receptor antagonist) have also been studied in diabetes. Anakinra was able to improve glycemia, inflammation and insulin secretion. Two additional studies in patients with impaired glucose tolerance or prediabetes demonstrated positive effects of anakinra on beta cell secretory capacity. Since anakinra requires daily injections and often causes adverse effects at the injection site, humanized antibodies against IL1β have been developed. Each of these antibodies had beneficial effects in patients with type 2 diabetes. However, studies were either underpowered or showed only little improvements of glycosylated HBA1c levels, probably due to low pre-study levels.

Inhibition of the IKK/NFkB pathway might also be of benefit in insulin resistance. Salsalate improves insulin sensitivity, insulin secretion and glycemic control to a moderate extent of 0.4–0.5%. Salsalate also has effects in prediabetic patients and in drug-naive type 2 diabetic patients.

There is upcoming evidence of potential benefical effects of CCR2 antagonism in diabetes.

Obesity causes an increased flux of fatty acids into muscle and liver with an accumulation of DAG in these organs. DAG activates specific isoforms of protein kinases, that are PKC T in muscle and PKC E in the liver. These isoforms cause an inhibitory phos

phorylation of IRS-1 and the insulin receptor itself leading to insulin resistance. Weight reduction by diet, physical activity and bariatric surgery remove ectopic fat and are able reverse diabetes. Most interestingly, PKC-isoform specific inhibitors such as FGF-21 might represent new drug targets.

Finally, targeting ectopic fat is more close to the pathophysiology of diabetes than anti-inflammatory therapy.

Does fat cause inflammation? Metabolic syndrome and NASH

Stefano Bellentani[1,2]
[1]Gastroenterology and Hepatology Service, Clinica Santa Chiara, Locarno, Switzerland
[2]Centro Studi Fegato, Fondazione Italiana Fegato, AREA Science Park-Basovizza Campus, Trieste, Italy

Nowadays non-alcoholic fatty liver disease (NAFLD) is becoming the most common chronic liver disease both in adults and children, and is the second indication to liver transplantation in USA.
Its prevalence involves 25–30% of the general population. The highest prevalence rates are registered in the Middle East and South America, the lowest in Africa. In Europe and North America approximately one every four adults in the general population has NAFLD. NAFLD prevalence varies from 16% in lean individuals to 76% in obese; it is higher in men, in patients with type 2 diabetes mellitus, metabolic syndrome or hyperlipidemia, and in Hispanic subjects. Natural history of NAFLD has different clinical entities: simple steatosis, Nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and HCC. HCC could develop in NASH patients also without the presence of cirrhosis in more than 43% of the cases. Due to the coexistence of visceral obesity, insulin resistance and dyslipidemia, NAFLD is considered to be the hepatic manifestation of the metabolic syndrome. Steatosis is a reversible condition, whose major determinants are lifestyle habits: diet and physical exercise. NAFLD progresses to NASH in 30% of the cases. We don't yet know when NASH becomes irreversible in the progression towards fibrosis and cirrhosis. The responsible of the passage between NAFLD and NASH could probably involve the so-called organokines, such as adipokines, myokines and hepatokines, all proteins with both paracrine or/and endocrine activities.

Mediators derived from fat tissue and their impact on systemic disease: Treatment targets in the future?

Britta Siegmund
Medizinische Klinik für Gastroenterologie, Infektiologie, Rheumatologie, Charité – Universitätsmedizin, Campus Benjamin Franklin (CBF), Berlin, Germany

For a long time fat tissue has been considered to serve exclusively as energy storage. Several discoveries led to a fresh view on this compartment. First, mediators released by the fat tissue were identified to contribute to tissue homeostasis and furthermore participate in the regulation of the immune system. For example our group could identify leptin as a critical regulator for intestinal inflammation. Similar data were described in parallel for other inflammatory conditions as well as for different fat tissue-derived mediators. Second, the fat tissue architecture revealed milieu-specific structural and cellular changes that we only start to understand. Here, draining lymph nodes from an area of chronic inflammation have been characterized by an increase in the number of surrounding adipocytes that in parallel decreased in size. This hyperplasia of adipocytes can equally be observed in the creeping fat of Crohn's disease. Remarkably here is the unique cellular composition that is not only dominated by regulatory macrophages but also presents with memory T cells underlining the working model of a second barrier. This unique compartment is being shaped by translocalizing bacteria which suffice to stimulate cells within the stromal compartment as well as adipocytes. Last, fatty acids within the inflammatory or tumor environment have been shown to modulate the immune response. Here, oleic acid is of particular interest, since it can mediate a strong inhibitory effect on T cell proliferation mediated by cells of the myeloid compartment. In summary, the fat tissue has turned from a sole energy provider into a complex tissue that interacts in many networks with inflammatory as well as tumorigenic diseases. Hence it seems feasible that the more detailed understanding of this network might ultimately result in novel therapeutic strategies.

Mesenteric lymphatic changes in Crohn's disease

Gwendalyn J. Randolph, Jean-Frederic Colombel
Department of Pathology & Immunology Washington University School of Medicine St. Louis, USA and Department of Gastroenterology, Icahn School of Medicine, New York, USA

Early pathological descriptions of Crohn's disease argued for a potential defect in lymph transport; however, this concept has not been thoroughly investigated. In mice, poor healing in response to infection-induced tissue damage can cause hyperpermeable lymphatic collecting vessels in mesenteric adipose tissue that impairs antigen and immune cell access to mesenteric LNs, which normally sustain appropriate immunity. To investigate whether analogous changes might occur in human intestinal disease, we established a 3-dimensional imaging approach to characterize the lymphatic vasculature in mesenteric tissue from controls or patients with Crohn's disease (CD). In CD specimens, B cell-rich aggregates resembling tertiary lymphoid organs (TLOs) impinged upon lymphatic collecting vessels that enter and exit LNs. In areas of creeping fat, we observed B cells and apparent innate lymphoid cells that had invaded the lymphatic vessel wall, suggesting these cells may be mediators of lymphatic remodeling. Although TLOs have been described in many chronic inflammatory states, their anatomic relationship to pre-established LNs, has never been revealed. Our data indicate that, at least in the Crohn's disease-affected mesentery, TLOs are positioned along collecting lymphatic vessels in a manner expected to impact delivery of lymph to LNs. It is furthermore possible that the structural alterations to human collecting lymphatic vessels render them obstructed or permeable in a manner similar to the outcomes described in mice infected by Y. pseudotuberculosis or dogs that have been treated to have elevated output pressures in LNs. We speculate that this, in turn, may promote leakage of chylomicrons that could drive the genesis of creeping fat in CD.

Session VI

Inflammation, drugs and cancer

Inflammation and colon cancer – Harnessing the immune system in diagnosis and treatment

B. Jung
Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

Colorectal cancer (CRC) remains deadly due to metastatic disease and there is a fundamental gap in understanding how CRC metastases form. The inflammatory cytokine transforming growth factor-beta (TGFβ) promotes metastatic CRC at later stages and TGFβ inhibitors are in early phase clinical trials, but focusing on TGFβ alone may not be effective without considering the role of its superfamily member, Activin, which also has prometastatic actions mechanistically distinct from TGFβ. Preliminary studies indicate that Activin and TGFβ are complexly intertwined and need to be interpreted as a unit and further that tumor stroma potentiates metastatic Activin/TGFβ signaling. Ultimately, given their importance in metastatic disease, both Activin and TGFβ pathways are attractive putative targets. Despite several studies investigating TGFβ blockade in the setting of solid tumors including CRC, to date no benefit has been shown. This might be due to the complex interplay of TGFβ with other pathways, such as Activin, and the multifunctional character, where inhibition could theoretically not only lead to beneficial anti-metastatic effects, but simultaneously have detrimental effects of loss of growth suppression at least in a subset of patients. Recently, we reported that in an APC driven murine model of CRC global inhibition of TGFβ signaling leads to an autoimmune response, wasting and shorter survival. Therefore, caution is warranted with regards to TGFβ inhibition in unselected CRC patient cohorts. Biomarkers identifying patients with disrupted TGFβ signaling and a better understanding of pathway interconnectedness are needed before we can fully envision treatment strategies. We have additional evidence that the role of Activin in metastatic disease is underappreciated. Activin signaling appears to be an equal participant in TGFβ superfamily pathway signaling with no lesser effects than TGFβ. While TGFβ-directed therapeutics are clearly not appropriate for all CRC patients, there are sub-populations which would benefit from this approach. To implement this approach, biomarkers to stratify patients are needed and we propose that p21 localization could be such a biomarker. We support a novel view of Activin as a co-conspirator with TGFβ in a closely interconnected system, with net Activin and TGFβ signaling promoting metastasis. The mechanistic understanding of the Activin/TGFβ cross-regulation together with the translational component is highly significant and it shows great promise to improve clinical care for CRC patients in the near future.

5-ASA and immunosuppressants and colon cancer: Is there a role in colorectal cancer prevention?

W. Schmiegel
Medizinische Universitätsklinik, Ruhr-Universität Bochum, Germany

Colorectal cancer is the second most common GI cancer worldwide. More than 1,2 million patients are diagnosed with colorectal cancer every year, and more than 600.000 die from the disease. The prognosis varies according the stage at diagnosis. Thus the 5-year relative survival of patients diagnosed with colorectal cancer is about 90% for patients with localised stage, 65% for patients with regional spread, and 10% for patients with distant tumour spread. Most cancers arise from adenomatous polyps. This process is associated with well characterised genetic changes the so called adenoma-carcinoma sequence.
One of the factors with evidence for a role in tumour formation is prostagladin E2. It is well known that aspirin influences the prostagladin metabolism. Epidemiolgical studies strongly suggest a protective role of aspirin on colorectal cancer incidence and mortality. This is supported by secondary analyses of cardiovascular prevention trials. Thus in a pooled analysis aspirin use was associated with a reduction of CRC incidence by 25% and CRC mortality of 39%. The effect was even higher if only users > 5 years were included. Furthermore several randomised studies using colorectal adenoma recurrence as a surrogate have been performed. In a meta-analysis the adenoma-recurrence rate in the aspirin arms was 17% lower than in the placebo-arms, restricting the analysis to advanced adenomas the effect was larger with 28%. However the use of aspirin is not without risks with GI- and intracranial bleeding being the most serious side effects. In a recent model calculation the use of aspirin was associated with a positive benefit-risk ratio for men and women aged 50 to 59 years whereas the risks were higher than the potential benefits for older age groups. However more data is needed before the use of aspirin should be considered for primary prevention of colorectal cancer. Furthermore it is unlikely that the effect would be large enough to influence recommended screening intervals.
COX-2 inhibitors have also been shown to reduce the adenoma recurrence rate. However due to the cardiovascular risks these substances should not be used for prevention. Other substances with immunmodulatory effects like vitamin D or statins have not been shown to be effective in CRC prevention.
Patients with inflammatory bowel disease have an increased CRC-risk. One of the risk factors in these patients is uncontrolled inflammation. Recent analyses have shown that the cancer risk has decreased in recent years. This is at least partly explained by better control of inflammation in IBD patients. There is some data on the protective effect of 5-ASA on cancer development. There is less data on the potential role of thiopurines and TNF-α antagonists.

Biologic therapy and paradoxical inflammation

Stephan R. Targan, M.D.
F. Widjaja Family Foundation, Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

In attempting to understand the pathobiology of mucosal inflammation to smartly define targets for biologic therapy, results from both animal models and assessing the level of a particular protein/cytokine in the mucosa has been the historical approach. More recently, using this approach, there have been paradoxical responses in Biologic trials in Crohn's disease. A major example of this has been the attempt to block the IL-17 pathway. The blockage of the IL-17 pathway has been very effective in psoriasis, however, trials in Crohn's disease showed there was a subset of patients who flared. One such study showed preliminary evidence that demonstrated different genetic variants of the TNSF15 gene related to differential expression of TL1A showed response or flaring related to TNSF15 variants.
Mouse models testing the level of TL1A levels on the outcome of IL-17 blockade, supported the findings in human studies. A second study using a mouse models with or without an engineered defect in epithelial barrier also showed different outcomes of IL-17 blockade. Finally, even if a dominant pathway such as been suggested with TL1A/DR3 is selected for biologic targeting, targeting the ligand or the receptor may not be equivalent. In fact, studies in mouse show differential outcomes on inflammation if TL1A (inhibition) or DR3 (no effect/increase) are targeted. These findings emphasize it is time for precision medicine approaches in developing biologics to treat inflammatory bowel diseases.

Session VII

New treatment options

Bile acids in the treatment of biliary, hepatic, and intestinal disease

Alan F. Hofmann, M.D.
University of California, San Diego, La Jolla, CA, USA

In the Eastern world, bile from diverse animal species was long considered to have therapeutic value, whereas in the Western world, therapeutic agents were derived from plants. The National Cooperative Gallstone Study (US), a placebo-based, double-masked trial, confirmed the original Mayo report that chenodeoxycholic acid (CDCA) ingestion induces the slow dissolution of cholesterol gallstones. Ursodeoxycholic acid (UDCA), a Japanese development, was soon shown to also induce gallstone dissolution, and UDCA rapidly replaced CDCA because of its lack of toxicity. Despite the established safety and efficacy of UDCA for gallstone dissolution, gallstones are largely managed by laparoscopic cholecystectomy at present because such surgery provides a rapid and permanent cure for all types of gallstones. UDCA can be used to prevent gallstone formation in patients undergoing rapid weight loss after bariatric surgery.

UDCA was shown to improve biochemical parameters in primary biliary cirrhosis/ cholangitis (PBC), and pooling of French, Canadian, and American data showed that UDCA increased survival. Obeticholic acid (OCA), the 6α-ethyl derivative of CDCA, was envisioned by R. Pellicciari in Italy, as a potent FXR agonist. OCA was shown to improve biochemical parameters in PBC patients unresponsive to UDCA, and OCA is now marketed for this purpose. OCA diminishes fibrosis in NASH, and large studies in which efficacy will be assessed by changes in liver biopsy histology are in progress. Primary sclerosing cholangitis (PSC) does not respond to UDCA, but improvement in biochemical parameters has been achieved with 24-norUDCA, a homologue of UDCA. NorUDCA differs from natural bile acids in that it is secreted into bile in part in unconjugated form, undergoes cholehepatic shunting, and induces a bicarbonate-rich hypercholeresis. Bile acid synthesis from cholesterol involves a multi-enzyme pathway. The extremely rare inborn errors of bile acid biosynthesis and conjugation are now identified by mass spectrometry and treated successfully by ingestion of primary bile acids. Cholic acid is now approved by the FDA as a therapeutic agent.

DCA and CDCA induce colonic secretion and stimulate colonic motility. In the ileal enterocyte, bile acids induce the synthesis of a protein, FGF19, that travels to the liver and suppresses hepatocyte bile acid synthesis. Thus, ileal dysfunction or resection leads to less FGF19 release and an increase in bile acid biosynthesis; this in turn results in an increased flux of bile acids into the colon, inducing a secretory diarrhea. A subset of IBS-diarrhea patients has impaired FGF19 release leading to a failure of down regulation of bile acid synthesis and diarrhea (work of Julian Walters at the Hammersmith Hospital), thus providing an explanation for idiopathic bile acid malabsorption. FGF19 synthesis is FXR dependent, and OCA improves diarrhea in these patients as do bile acid sequestrants. In short bowel syndrome, bile acid malabsorption is profound, and the compensatory increase in bile acid synthesis is insufficient to restore luminal bile acid concentrations. Improved lipid absorption and weight gain can be obtained by feeding cholylsarcosine, a conjugated bile acid derivative that is non-secretory and resistant to bacterial deconjugation-dehydroxylation. Claims of Austrian

physicians a century ago that bile acids are effective treatment for postoperative ileus have been ignored.

Thus, in the past half century, bile acids and bile acid derivatives have been shown to be safe and effective in the treatment of certain biliary, hepatic, and intestinal diseases. It has been an exciting time for students of bile acid metabolism. And patients with biliary, hepatic, and intestinal disease have benefited.

New aspects of primary biliary cholangitis, primary sclerosing cholangitis and autoimmune hepatitis

Michael P. Manns
Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover, Hannover, Germany
E-Mail: manns.michael@mh-hannover.de

Primary biliary cholangitis (PBC) is a chronic non-suppurative destructive cholangitis with an underlying autoimmune pathogenesis. The chronic inflammatory process targets the small intrahepatic bile ducts. Autoantibodies against acyltransferases of the inner mitochondrial membrane (PDH-E2, BCKD-E2 and OGDC-E2) are the diagnostic hallmark. Ursodesoxycholic acid (UDCA), 13–15 mg/kg bodyweight, is the standard of care (SOC). Response to UDCA means normalization of alkaline phosphatase (AP) or reduction of AP to below twice the upper limit of normal. Responders to UDCA therapy have a long term survival comparable to the normal population: Patients who do not respond to UDCA, so called non-responders, progress and may become candidates for liver transplantation. 20–30 years ago PBC has been a major indication for liver transplantation. However, nowadays it is a rare indication. PBC may recur after liver transplantation and may lead to graft loss. Several new alternative therapies are now under clinical development for PBC, in particular for UDCA non-responders. Among interesting novel drugs are FXR receptor agonists like obeticholic acid (OCA). Significant improvements of AP have been demonstrated for OCA, in particular for UDCA non-responders. Therefore this therapy will soon be approved based on recently published phase 3 data. The therapy is rather safe apart from increase in pruritus in some patients. PBC is not only a liver disease. In up to 25% PBC is associated with extrahepatic autoimmune syndromes like the sicca syndrome as well as gluten-sensitive enteropathy (celiac disease). Recent research efforts also concentrate on the pathogenesis of extrahepatic manifestations of PBC like pruritus and fatigue. These efforts hopefully will lead to innovative therapies.

Primary sclerosing cholangitis (PSC) is a disease of unknown etiology and pathogenesis, the biggest “black box” of modern hepatology. Up to 15% develop bile duct cancer. In addition, the risk to develop pancreatic and colonic cancer is also significantly increased. There is no established medical therapy yet. The use of UDCA is controversial in PSC. UDCA is widely used at a concentration of 15–20 mg/kg bodyweight. Biochemical parameters like alkaline phosphatase improve under UDCA therapy while termination of UDCA leads to an increase in AP levels. High concentrations of UDCA may be harmful. However, AP is still controversial as an endpoint for PSC treatment. Another bile acid analogue, nor-ursodesoxycholic acid (Nor-UDCA), is under clinical development. Promising phase 2 results have been reported recently and phase 3 studies for the use of nor-UDCA in PSC are planned. This drug is under clinical development in PBC and NASH as well. Several competing hypotheses for the pathogenesis of PSC are being discussed. These include aberrant homing of gut primed T lymphocytes to the liver, namely bile ducts, autoimmunity, genetic predisposition, the toxic bile acid hypothesis, and the “leaky gut hypothesis” – just to name a few. Based on these hypotheses several novel therapeutic targets are under clinical development for PSC like FXR receptor agonists, bile acid analogues like nor-UDCA, monoclonal antibodies like anti LOX 2, e.g. simtuzumab, as an anti-fibrotic agent.

Finally, anti-integrin antibodies like vedolizumab, are under investigation. Apart from these novel medical therapies endoscopic treatment of dominant strictures, treatment of bacterial cholangitis and liver transplantation for end stage liver disease are well established.

Autoimmune hepatitis (AIH) has been the first liver disease in which medical therapy was shown to prolong survival. The standard of care is predniso(lo)ne alone or in combination with azathioprine. In patients with cirrhosis predniso(lo)ne may be replaced by budesonide, a topical steroid. Efficacy of budesonide was shown to be comparable to prednisolone while steroid specific side effects are significantly reduced due to the low systemic availability of this topic drug. The endpoints of treatment are normalization of transaminases, ALT and AST, and serum IgG levels. In non-responder patients to steroids with or without azathioprine alternative therapies have to be explored. Mycophenolate mofetil (MMF), tacrolimus and ciclosporine A are widely used as second line therapies. MMF is favored as a second line treatment in the case of azathioprine intolerance. The minority of patients does not respond to first or second line treatment. In those patients failing to first and second line treatments biologicals like monoclonal anti-TNF antibodies (Infliximab) or anti-B-cell antibodies like anti-CD20 (Rituximab) are explored as third line therapy regimen. Hopefully our insights into the pathogenesis of autoimmune hepatitis will be further develop in order to identify new therapeutic targets that allow a more specific and better tolerated therapeutic intervention. So far still 4% of all liver transplantations in Europe and North America are due to autoimmune hepatitis.

Can we treat or reverse fibrosis?

Bernd Schnabl
Division of Gastroenterology, University of California, San Diego, La Jolla, CA, USA

Liver fibrosis, the accumulation of extracellular matrix proteins, occurs in most types of chronic liver disease. Patients with liver fibrosis may progress to cirrhosis with subsequent portal hypertension, hepatic failure and hepatocellular carcinoma. Activated hepatic stellate are the main extracellular matrix producing cell types in the liver. Following their activation activated hepatic stellate cells proliferate, acquire contractile functions and attract other immune cells to the liver [1]. Removing known stimuli of liver injury reduces liver fibrosis and can even lead to regression of cirrhosis in humans [2]. Beyond the cure of the primary liver disease, multiple targets for therapy have been established in preclinical models. These include targeting the activation process of hepatic stellate cells, inhibit fibrogenesis and promote the resolution of liver fibrosis [3, 4]. Although many approaches are effective in experimental models of liver fibrosis, the efficacy of many of these drugs has not been tested in humans. The recently published FLINT trial shows an improvement of hepatic fibrosis in patients with NASH treated with obeticholic acid for 72 weeks [5]. In addition, other currently ongoing clinical trials with promising antifibrotic effects will be discussed.

References:

1. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005;115:209–18.
2. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013;381:468–75.
3. Hartmann P, Haimerl M, Mazagova M, Brenner DA, Schnabl B. Toll-like receptor 2-mediated intestinal injury and enteric tumor necrosis factor receptor I contribute to liver fibrosis in mice. Gastroenterology. 2012;143:1330–40.
4. Iwaisako K, Haimerl M, Paik YH, Taura K, Kodama Y, Sirlin C, et al. Protection from liver fibrosis by a peroxisome proliferator-activated receptor delta agonist. Proc Natl Acad Si. USA. 2012;109:E1369–76.
5. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomised, placebo-controlled trial. Lancet. 2015;385:956–65.

New compounds for IBD treatment

William J. Sandborn, M.D.
Division of Gastroenterology, Department of Medicine, University of California San Diego, La Jolla, CA 92093, USA

New classes of compounds used to treat inflammatory bowel disease (IBD) include anti-integrin therapy, anti-interleukin 12/23 therapy, Janus kinase (JAK) inhibitor therapy, S1P1 modulators, and anti-sense to SMAD7. The monoclonal antibody to α4β7 integrin, vedolizumab, is effective for induction and maintenance of remission in both ulcerative colitis and Crohn's disease, and is currently approved throughout the world for though indications. Other still investigational drugs in this class include anti-MAdCAM1 (PF-00547,659, Pfizer), etrolizumab (anti-β7, rhumab beta 7, Genentech), and anti-α4β7 (AMG181, Amgen). The monoclonal antibody to the p40 subunit shared by both interleukin-12 and -23, ustekinumab, is effective for induction and maintenance of remission in Crohn's disease, and is currently awaiting regulatory approval throughout the world for this indication. The monoclonal antibodies to the p19 subunit unique to interleukin-23, MEDI 2070 and risankizumab, have shown efficacy for induction therapy in Crohn's disease in Phase 2 trials. The pan JAK inhibitor JAK1, JAK2 (to a lesser degree) and JAK3, tofacitinib, has shown efficacy for induction and maintenance of remission for ulcerative colitis in Phase 3 trials, and regulatory filings for this indication are anticipated. The S1P1 modulator, ozanimod, has shown efficacy for induction and maintenance therapy in Phase 2 trials in ulcerative colitis. The anti-sense to SMAD7, Mongersen, has shown efficacy in a Phase 2 trial in Crohn's disease. The role of these new agents as first, second or third line agents in moderate to severe IBD is still evolving.

New anti-inflammatory targets in rheumatology

Ulf Müller-Ladner
Justus-Liebig University Giessen, Germany

Owing to the rapidly increasing knowledge in molecular biology and molecular pathophysiology, several novel therapeutic targets have been identified in the various inflammatory rheumatic diseases, of which a substantial number have already been licensed for clinical use or are close to market. In the “flagship” disease *rheumatoid arthritis*, the strongest dynamic is in the field of biosimilars, which, due to their lower price, challenge all established biologics, especially infliximab, etanercept, and adalimumab. In addition, several small molecules of the Janus-kinase inhibitor class, especially tofacitinib, which is already in clinical use outside of Europe and Switzerland, and baricitinib are expected to be licensed in 2017. Aside tocilizumab as interleukin-6 antagonist, several other IL-6 inhibitors have successfully completed phase III trials on their way to market. A novel idea is the inhibition of synovial macrophages by growth factor inhibitors, and specifically mavrilimumab may be available in the upcoming 2 years. Even more progressive is the situation in *psoriatic arthritis*, in which targeting IL-12/-23 (ustekinumab), interleukin-17 (secukinumab) and the PDE4-inhibitor apremilast are within their first period of everyday clinical use. Of note, the close relationship between psoriatic arthritis and inflammatory spondyloarthopathies (e.g. ankylosing spondylitis), has led to the parallel use and partly licensing of these novel molecules also to inhibit inflammation at the vertebral column. More difficult is the situation in the field of connective tissue diseases and vasculitides. Inhibition of B-cell activating factors by belimumab appears only useful for few, single patients and aside rituximab for ANCA-associated vasculitides, few ideas are about to make it to clinical reality. On the other side, several kinase inhibitors are being tested for systemic sclerosis, at present the most challenging disease in the field of rheumatology. Taken together, there are many new ideas emerging resulting in a most interesting and fascinating perios in clinical research in rheumatology.

List of Chairpersons, Speakers and Scientific Organizers

Prof. Dr. Stefano Bellentani
Capo Serviczio Gastroenterologia
ed Epatologia
Clinica Santa Chiara SA
Via Stefano Franscini 4
6601 Locarno
Switzerland

Prof. Dr. Dr. h. c. mult.
Markus Büchler
Klinik für Allgemein-, Viszeral- und
Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 110
69120 Heidelberg
Germany

Jean-Frederic Colombel, M.D.
Professor of Medicine
Icahn School of Medicine
Mount Sinai Hospital
One Gustave L. Levy Place
New York, NY 10029
USA

Prof. Dr. Axel Dignass
Medizinische Klinik I
AGAPLESION
Markus Krankenhaus
Wilhelm-Epstein-Str. 4
60431 Frankfurt
Germany

Dr. Emad M. El-Omar
Professor of Medicine
St George and Sutherland
Clinical School
University of New South Wales
Level 2 Clinical Sciences Bldg.
St George Hospital
Short Street, Kogarah
Sydney, NSW 2217
Australia

Claudio Fiocchi, M.D.
Professor of Medicine
The Cleveland Clinic Foundation
Pathobiology/NC 20
9500 Euclid Avenue
Cleveland, OH 44195
USA

Prof. Dr. Martin Fleck
Klinik und Poliklinik für
Rheumatologie/Klinische Immunologie
ASKLEPIOS Klinikum Bad Abbach
Kaiser-Karl V.-Allee 3
93077 Bad Abbach
Germany

Prof. Dr. Wolfgang E. Fleig
Universitätsklinikum Leipzig AöR
Liebigstr. 18
04103 Leipzig
Germany

Prof. Dr. Ulrich R. Fölsch
Klinik für Innere Medizin I
Universitätsklinikum
Schleswig-Holstein, Campus Kiel
Arnold-Heller-Str. 3 (Haus 6)
24105 Kiel
Germany

Prof. Dr. Alexander L. Gerbes
Medizinische Klinik und Poliklinik II
Klinikum der Universität
München – Großhadern
Marchioninistr. 15
81377 München
Germany

Prof. Dr. Jörg Hacker
Deutsche Akademie der
Naturforscher Leopoldina
Nationale Akademie der
Wissenschaften
Postfach 110543
06019 Halle
Germany

Stephen B. Hanauer, M.D.
Professor of Medicine
Gastroenterology Section
Digestive Health Center
Northwestern University
676 North St. Clair Street
Chicago, IL 60611
USA

Hans Herfarth, M.D.
Professor of Medicine
Division Gastroenterology and Hepatology
Department of Medicine
University of North Carolina
4151 Bioinformatics Bldg.
130 Mason Farm Road
Chapel Hill, NC 27599-7080
USA

Alan F. Hofmann, M.D., Ph.D.
Professor of Medicine (Emeritus)
5870 Cactus Way
La Jolla, CA 92037
USA

Barbara Jung, M.D.
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Department of Medicine
University of Illinois
College of Medicine
840 South Wood Street, MC 716
Chicago, IL 60612
USA

Prof. Dr. Ioannis E. Koutroubakis
Department of Gastroenterology
University Hospital of Heraklion
University of Crete
P.O. Box 1352
71110 Heraklion
Greece

Prof. Dr. Markus M. Lerch
Klinik und Poliklinik für
Innere Medizin A
Universitätsklinikum Greifswald
Ernst-Moritz-Arndt-Universität
Ferdinand-Sauerbruch-Straße
17489 Greifswald
Germany

Prof. Dr. Elisabeth Märker-Hermann
Klinik Innere Medizin IV
HELIOS Dr. Horst Schmidt-Kliniken
Ludwig-Erhard-Str. 100
65191 Wiesbaden
Germany

Prof. Dr. Dr. h. c. Klaus-Peter Maier
Camererweg 12
73732 Esslingen
Germany

Prof. Dr. Michael P. Manns
Klinik für Gastroenterologie,
Hepatologie und Endokrinologie
Medizinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
Germany

Prof. Dr. Gerassimos J. Mantzaris
Department of Gastroenterology
Evangelismos Hospital
45–47, Ypsilantou street, Kolonaki
106 76 Athens
Greece

Prof. Dr. Joachim Mössner
Klinik und Poliklinik für
Gastroenterologie und Rheumatologie
Universitätsklinikum Leipzig AöR
Liebigstr. 20
04103 Leipzig
Germany

Prof. Dr. Ulf Müller-Ladner
Lehrstuhl für Innere Medizin
Schwerpunkt Rheumatologie
Justus-Liebig-Universität Giessen
Klinikstr. 29
35392 Giessen
Germany

Prof. Dr. Martina Müller-Schilling
Klinik für Innere Medizin I
Universitätsklinikum Regensburg
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Germany

Daniel K. Podolsky, M.D.
Professor of Medicine
University of Texas
Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9046
USA

Prof. Dr. Daniel Rachmilewitz
Department of Medicine
Shaare Zedek Medical Center
P.O. Box 3235
91031 Jerusalem
Israel

Prof. Dr. Dr. Torsten E. Reichert
Klinik und Poliklinik für MKG-Chirurgie
Universitätsklinikum Regensburg
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Germany

Prof. Dr. Dr. Gerhard Rogler
Klinik für Gastroenterologie und Hepatologie
Universitätsspital Zürich
Rämistr. 100
8091 Zürich
Switzerland

Prof. Dr. Bernd Salzberger
Klinik für Innere Medizin I
Universitätsklinikum Regensburg
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Germany

William J. Sandborn, M.D.
Professor of Medicine
Division of Gastroenterology
Department of Medicine
University of California San Diego
9500 Gilman Drive, MC 0956
La Jolla, CA 92093
USA

R. Balfour Sartor, M.D.
Professor of Medicine
Gastroenterology & Hepatology
School of Medicine
University of North Carolina
111 Mason Farm Road
Chapel Hill, NC 27599-7032
USA

Prof. Dr. Tilman Sauerbruch
Medizinische Klinik I
Universitätsklinikum Bonn
Sigmund-Freud-Str. 25
53127 Bonn
Germany

Prof. Dr. Andreas Schäffler
Medizinische Klinik und Poliklinik III
Universitätsklinikum
Giessen und Marburg
Klinikstr. 33
35392 Giessen
Germany

Prof. Dr. Wolff Schmiegel
Medizinische Universitätsklinik
Ruhr-Universität Bochum
In der Schornau 23–25
44892 Bochum
Germany

Bernd Schnabl, M.D.
Associate Professor
Division of Gastroenterology
Department of Medicine
University of California San Diego
9500 Gilman Drive
La Jolla, CA 92093
USA

Prof. Dr. Jürgen Schölmerich
Germanenstr. 8b
65719 Hofheim
Germany

Prof. Dr. Britta Siegmund
Medizinische Klinik für
Gastroenterologie, Infektiologie,
Rheumatologie
Charité – Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
12203 Berlin
Germany

Prof. Dr. Robin C. Spiller
Biomedical Research Unit
Nottingham Digestive Diseases Centre
Queen‘s Medical Centre
University Hospital
Nottingham NG7 2UH
Great Britain

Prof. Dr. Rainer H. Straub
Klinik für Innere Medizin I
Universitätsklinikum Regensburg
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Germany

Stephen R. Targan, M.D.
Professor of Medicine
Inflammatory Bowel &
Immunobiology Research Institute
Cedars-Sinai Medical Center
110 George Burns Road, D4063
Los Angeles, CA 90048
USA

Prof. Dr. Rudolf Tauber
Institut für Laboratoriumsmedizin,
Klinische Chemie und Pathobiochemie
Charité – Universitätsmedizin
Campus Virchow-Klinikum (CVK)
Augustenburger Platz 1
13353 Berlin
Germany

Prof. Dr. Angelika Vollmar
Abteilung für Pharmazie
Zentrum für Arzneimittelforschung
Pharmazeutische Biologie
Universität München
Butenandtstr. 5–13
81377 München
Germany

Prof. Dr. Alastair J.M. Watson
Division of Gastroenterology
University of East Anglia
Nuffield Building
Elizabeth Frey Building
Norwich NR4 7TJ
Great Britain

Prof. Dr. Fritz von Weizsäcker
Abteilung Innere Medizin I
Schlosspark-Klinik
Akademisches Lehrkrankenhaus
der Charité
Heubnerweg 2
14059 Berlin
Germany

Prof. Dr. Andreas M. Zeiher
Innere Medizin III
Klinikum der Johann Wolfgang
Goethe-Universität Frankfurt
Theodor-Stern-Kai 7
60596 Frankfurt
Germany

Prof. Dr. Stefan Zeuzem
Medizinische Klinik I
Klinikum der Johann Wolfgang
Goethe-Universität Frankfurt
Theodor-Stern-Kai 7
60596 Frankfurt
Germany

Falk Foundation e.V.

Scientific Dialogue in the Interest of Therapeutic Progress

Symposia and workshops
Over 270 with more than 130,000 international participants since 1967

Continuing medical education seminars
Over 16,000, attended by more than 1.3 million physicians and patients in Germany alone

Comprehensive literature service for healthcare professionals and patients
More than 200 publications

www.falk-foundation-symposia.org
symposia@falk-foundation-symposia.org

Leinenweberstr. 5
79108 Freiburg
Germany
Tel +49 (0)761/1514-0
Fax +49 (0)761/1514-321