IBD: From Pathophysiology to Personalized Medicine

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IBD: FROM PATHOPHYSIOLOGY TO PERSONALIZED MEDICINE

Oxford, Great Britain
March 29 – 30, 2019

Scientific Organization:
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Scientific Co-Organization:
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F. Powrie, Oxford (Great Britain)
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* = Posters of Distinction
Session I

IBD pathophysiology and genetics
Poly-genetics in IBD: An overview

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The primary goal of genetic studies over the last 20 years has been to better understand pathogenic mechanisms in IBD. In this regard they have been successful. The advent of genome-wide association scanning technologies has particularly accelerated the discovery of new loci associated with susceptibility to Crohn’s disease and ulcerative colitis, now numbering well in excess of 200. Most are shared between CD and UC, but it is a point of interest that many of the loci conferring larger effect sizes are phenotype-specific. In Crohn’s disease it was genetic studies that highlighted the key role that defects in cellular innate immunity make to disease pathogenesis, as exemplified by association with variants in NOD2 and autophagy genes ATG16L1 and IRGM. Intriguingly defects in epithelial barrier genes are UC-specific. Among signals shared between CD and UC are many that implicate subtle abnormalities in regulation of T cell responses and perhaps B cells as well, and an important role for the IL23R pathway. Both innate and adaptive immune pathways are implicated, with a number of lines of evidence suggesting that an abnormal response to microbes (most likely components of the intestinal microbiota) increases susceptibility to IBD. Detailed fine mapping studies to pinpoint causal genes and causal variants, combined with careful functional analyses, are providing a more granular view of the pathogenic mechanisms that thereby lead to IBD. This work is facilitated by the availability of large panels of IBD patients who can be recalled by genotype or phenotype for downstream study – such as the UK IBD Bioresource.
How genes shape the microflora

Philip Rosenstiel
Institute of Clinical Molecular Biology and 1st Department of Medicine, University Hospital Kiel, Germany

The human intestine along its entire length harbours region-specific bacterial communities, which can be regarded as a separate organ modulating metabolism and immune responses of its host. Maintaining the structure of this ecosystem is a major task of the intestinal epithelium, which serves as the primary interface. The constitution of the intestinal ecosystem shows a strong self-regeneratory capacity (resilience), which restores the host-microbial equilibrium even after catastrophic external perturbation. Such events include acute infection/inflammation, dietary life events (e. g. phases of malnutrition) or antibiotic treatment. Impairment of this host-microbial balance has been implicated in human inflammatory bowel disease (IBD). It has been suggested that genetic IBD risk variants may – at least in part – act through their function to shape and maintain intestinal microbiota and function. I will discuss evidence for such molecular mechanisms and set a particular focus on their function for dynamics of community acquisition early in life and for resilience processes after external stressors (antibiotics, amino acid malnutrition and acute inflammation). Recent studies have highlighted the role of the crosstalk between innate immune pathways and autophagy/ER stress responses in intestinal epithelial cells for host-microbial interplay. Evidence for sustained molecular deregulation of epithelial gene expression and inflammatory responses has been presented in IBD, which is even conserved ex vivo in organoid cultures. It is, however, unclear whether and how signals of the microbiota modify such long-term response patterns of the epithelial lining. An impact of microbiota signals on epigenetic reprogramming during early “windows of opportunity” in postnatal development has been suggested, which in turn could modify long-term properties of microbiota. Together with polygenic risk variants, such defined epigenome-bacteria interactions could reflect important factors in IBD pathogenesis. Finally, I will discuss the potential clinical impact resulting from diagnostic access to host-microbiota interplay (e. g. genome, epigenome, microbiome) in inflammatory bowel disease.
Microbes and environmental factors

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The pathogenesis of the inflammatory bowel disease (IBD) involves an activation of the gastrointestinal immune system toward the gut microbiota in genetically susceptible hosts and under the influence of the environment. The microbial community in the human gastrointestinal tract is fundamental to the health and is under the influence of both environmental and genetic factors. Loss of the fragile equilibrium within this complex ecosystem, termed dysbiosis, is involved in numerous pathologies, including IBD. Patients with IBD exhibit an altered gut microbiota composition with notably a decreased abundance of anti-inflammatory bacteria such as Faecalibacterium prausnitzii. F. prausnitzii notably stimulate a newly identified regulatory T cell subtype (DP8a) which amount is also decreased in patients with IBD. We also observed an alteration in the fungal microbiota composition in IBD and recently showed that bacteria from the Enterobacteriaceae family have an impact on the effects of fungi in colitis context. Among the mechanisms by which the gut microbiota impacts the host functions, metabolites produced or modified by the gut microbiota are important actors. We showed that aryl hydrocarbon receptor (AhR) metabolites produced from the transformation of tryptophan by the gut microbiota that is key players in intestinal homeostasis is altered in patients with IBD. Moreover, environmental factors such as a high-fat diet can reproduce the same effect on this microbiota function with impact on both metabolic syndrome and susceptibility to inflammation.
Session II

Epithelial cell biology and stromal cells in IBD
Type I interferon signaling and antimicrobial peptides

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Type I interferons (IFNs) have been amongst the first identified cytokines and played in the last decades a major role in the treatment of various diseases including chronic viral disorders and certain malignancies. Only in the last years certain key functions of these crucial immune mediators have been identified. Type I IFN has also been studied in various immune-mediated disorders including IBD such as ulcerative colitis with rather mixed but mainly negative results. It became evident in the last years that type I IFNs have the capacity to worsen immune-mediated processes, SLE-like disorders reflecting such one example.

Intestinal epithelial cells (IECs) are crucially involved in the regulation of immune responses in the gastrointestinal tract. Paneth cells reflect specialized IECs and have the capacity to produce large amounts of antimicrobial peptides and thereby shape also the intestinal microbiota. We recently investigated the role of type I IFN receptor (IFNAR1) in intestinal inflammation. For this purpose we used mice with conditional deletion of Ifnar1 in IECs. The role of IFNAR1 was also studied in models of DSS colitis and colitis-associated cancer induced by DSS together with azoxymethane (AOM). Ifnar1+/+ mice exhibited increased numbers of Paneth cells. Furthermore, these mice showed an increased tumour rate in the AOM/DSS model. Tumour formation was dependent on the intestinal microbiota and assessment of the gut microbiota demonstrated significant differences between various mouse strains (Ifnar1+/+ and Ifnar1+/−). These studies highlight that type I IFN plays a crucial role in the interplay between IECs, immune cells and the intestinal microbiota. Type I IFNs might critically regulate Panceth cell biology and affect intestinal inflammatory events and associated cancer.
Subtypes of epithelial cells and their function

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Advances in single-cell technologies have provided an opportunity to examine the contribution of rare populations of human intestinal mucosal cells to the pathogenesis of IBD. We used a combination of single-cell RNA-sequencing (scRNAseq), spatial and functional mapping to chart the interplay between epithelial, mesenchymal and immune cells in mucosal inflammatory lesions in IBD. We described new mesenchymal cell states hallmarked by expression of distinct transcriptional determinants, functional ontology pathways and geographical location. These included the mesenchymal crypt niche cell marked by expression of SOX6 and an IBD associated activated mesenchymal population expressing factors capable of fuelling inflammation and fibrosis. Examination of human colonic epithelia identified trajectories of differentiating progenitors and novel goblet cell pathways contributing to barrier breakdown in UC. We identified a new colonic epithelial cell subtype competent for luminal pH sensing. Analysis of colonic inflammatory immune cell behaviour defined the extent of heterogeneity present during remodelling in IBD and highlighted both common and cell specific features of immune populations that define inflammation in the distal colon. Our results provide avenues for design of novel genetic and lineage tracing models to interrogate specific molecular pathways dysregulated in IBD. They also provide a foundation to investigate the influence of genetic risk factors and microbe mucosal mutualism at a cell by cell level.
Regulation of cell death in gut homeostasis and inflammation

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The human gut harbors an enormous number of bacteria. While these bacteria are usually harmless and even support our body in absorbing nutrients, they can cause severe intestinal and systemic diseases if they invade the bowel wall in an uncontrolled way. To prevent the access of bacteria to the bowel wall, the gut is coated with a thin layer of epithelial cells, which form a barrier to the external environment. It is becoming more and more clear that intestinal epithelial cells are highly specialized cells with important functions for innate immune defense. The cellular processes that establish and maintain epithelial barrier functions and gut homeostasis are largely unknown. Inflammatory bowel disease (IBD) is the most prevalent chronic intestinal disease that affects an estimated 5 million people worldwide. The disease is characterized by phases of chronic inflammatory flare ups and increased epithelial cell death interspersed with periods of resolution with no detectable inflammation. The current understanding of the triggers of chronic inflammation on the one hand and the ensuring tissue responses that lead to resolution and homeostasis on the other hand is limited. Central to restitutive processes in the gut is the control of epithelial cell death in an inflammatory environment, which enables the reestablishment of the tight junctions, prevents microbial translocation, reinstates normal tissue function and shuts down inflammation. Emerging evidence points to a crucial role of necroptosis, autophagy and pyroptosis, besides apoptosis, as important modes of programmed cell death in the intestine. Moreover unlike apoptosis, necroptosis is an inflammatory form of cell death that releases inflammatory alarmins into the tissue causing influx of immune cells, inflammatory cytokine release and further tissue destruction.
Session III

Innate immunity
How nutrition and the maternal microbiota shape the innate immune system

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Mucosal surfaces of mammals are densely colonized with consortia of microbes from different taxa. The intestinal microbiota is strongly personalized and influenced by the host environment, including nutrition as one of the main shaping factors. On the other hand, members of the microbiota can metabolize dietary components that can reach the bloodstream and central body tissues. It is believed that the fetus in utero is sterile and colonization with a significant biomass of microbes starts after birth. The unborn fetus is nevertheless exposed to a multitude of metabolites originating from the commensal microbiota of the mother that reach systemic sites of the maternal body. These metabolites (which depend on the taxa colonizing the mother and her nutrition) can be followed in vivo from mother to her offspring in experimental systems using non-radioactively labelled microbial metabolites and high-resolution mass spectrometry. Transient colonization techniques used exclusively during gestation, where live microbes are cleared from the maternal intestine and her offspring are born germ-free, show that the maternal microbiota shapes the innate immune system and other organ systems of the newborn mammal, independently its own microbes derived from postnatal colonization.
Interleukin-22 protects intestinal stem cells against genotoxic stress

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Environmental genotoxic factors pose a serious and constant peril to the genomic integrity of cells at barrier surfaces with the environment. They can induce mutations that, if they occur in epithelial stem cells, contribute to malignant transformation and cancer development. Genome integrity in epithelial stem cells is closely guarded by an evolutionary conserved, cellular response pathway, the DNA damage response (DDR). The DDR culminates in either transient cell cycle arrest and DNA repair or elimination of damaged cells by apoptosis. Here we show, that the cytokine interleukin (IL)-22 produced by group 3 innate lymphoid cells (ILC3) and $\gamma\delta$ T cells is an important rheostat of the DDR machinery in intestinal epithelial stem cells. Using a new mouse model allowing for the sporadic inactivation of the IL-22 receptor in colon epithelial stem cells, we demonstrate that IL-22 is required for an effective initiation of the DDR following DNA damage. In consequence, stem cells deprived of IL-22 signals and exposed to carcinogens escaped DDR-controlled apoptosis, contained more mutations, and were more likely to give rise to colon cancer. We identified metabolites of glucosinolates, a group of phytochemicals contained in cruciferous vegetables, to be a commonplace source of genotoxic stress in intestinal epithelial cells. Glucosinolate metabolites are ligands of the aryl hydrocarbon receptor (AhR) and AhR signaling in ILC3 and $\gamma\delta$ T cells controlled their production of IL-22. Mice fed with diets deprived of glucosinolates produced only very low levels of IL-22 and, consequently, the DDR in epithelial cells of mice on a glucosinolate-free diet was crippled. Collectively, we identify a homeostatic network protecting stem cells against perils to their genome integrity by AhR-mediated “sensing” of genotoxic components contained in diets. AhR signaling in turn ensures on-demand production of IL-22 by innate lymphocytes directly regulating components of the DDR in epithelial stem cells.
Dendritic cells in gut homeostasis and inflammation

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Complex interactions between the intestinal epithelial barrier, microbiota and host immune system are tightly regulated to maintain intestinal homeostasis. Such interactions must maintain the balance between effector immunity against pathogens and unresponsiveness against commensal microorganisms; breakdown in this balance might precipitate the onset of intestinal disorders, such as inflammatory bowel disease (IBD). Dendritic cells (DC), due to their abilities to induce inflammatory responses and tolerance in response to pathogenic and commensal bacteria, are key in maintaining intestinal homeostasis. Our laboratory and others have identified that retinoic acid (RA), metabolized from the dietary Vitamin A, is essential to imprint DC with tolerogenic properties as well as the ability to induce gut-homing tropism on lymphocytes.

Here I will discuss the immunological influence of some dietary compounds and their metabolites acting on DC imprinting. In particular, I will discuss the role of RA in regulating gut DC function and homing properties. I will also discuss some unpublished data from our own lab showing the role of cholesterol sensing on intestinal DC-mediated immunity and the function of IBD-risk genes on myeloid cell function.
Immunometabolism in Crohn’s disease

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Inflammatory bowel disease results from a complex interplay of environmental and genetic risk factors leading to aberrant and chronic activation of the intestinal immune system. The different immune cells within the intestinal milieu engage distinct metabolic signatures. No longer seen as a secondary consequence of cell differentiation and activation, metabolic regulation has emerged as a key driver of multiple facets of the immune response. Emphasising this, we recently discovered the function of a previously uncharacterised, Crohn’s risk gene known as chromosome 13 open reading frame 31 (C13orf31), that we have renamed ‘FAMIN’ (fatty acid metabolism-immunity nexus) and reveal to be a critical controller of immunometabolic function. Rare single-nucleotide variation in FAMIN has been identified as a cause of early-onset Crohn’s disease, as well as systemic juvenile idiopathic arthritis. A common FAMIN variant has also been associated with increased risk to both Crohn’s disease and leprosy. We uncovered that FAMIN serves as a rheostat for the synthesis and oxidation of endogenous fatty acids. In doing so, FAMIN supports a novel immunometabolic pathway that is essential for macrophage ATP production and generating mitochondrial reactive oxygen species. These processes have critical implications for bactericidal activity and early innate immune responses, but also determine resilience to endotoxin stress. Furthermore, we demonstrate that the common and rare risk variants, encoding FAMIN (p.I254V) and FAMIN (p.C284R), cause hypomorphic and complete loss of FAMIN function respectively. Thus, we have identified a central regulator of macrophage metabolic function that determines the risk of Crohn’s disease.

References:

Session IV

Adaptive immunity
Regulation of intestinal autoimmune responses: Lessons from human monogenic diseases

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Mouse models have provided considerable insight into the mechanisms that build an efficient gut barrier and maintain intestinal homeostasis. Whether and how these mechanisms operate in the human intestine is much less well known. In order to address this question and to establish the spectrum and hierarchy of genes essential for development and maintenance of the human intestinal barrier, we have initiated the genetic dissection of a large cohort of patients with intestinal inflammation and/or autoimmunity, in whom disease severity and very early onset (<6 years) are suggestive of Mendelian inheritance. Our multistep approach combines targeted next generation sequencing, whole exome sequencing and functional validation studies. Analysis of the first 350 patients provides evidence for a key role of innate immunity in maintaining colonic homeostasis while precise regulation of adaptive immune responses seems central to maintain small intestinal homeostasis. Taking advantage of recent results, I will focus on the role of the JAK1-STAT3 pathway in the control of intestinal autoimmunity and show how targeted therapy may improve disease outcome.
Role of B and T cells in intestinal homeostasis and inflammation

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The adult gut is typically colonized by a diverse collection of eubacteria but also archaea, viruses, phages and eukaryotic microorganisms. As a whole, this collection of microorganisms is referred to as intestinal microbiota. Animal and human studies have documented critical roles of the microbiota in metabolism, development, immune function and pathogenesis.

One of the most apparent outcomes of microbial colonization is to induce development of the immune system including B and T cell responses. We are tracking microbiota-triggered changes in the intestinal B and T cell compartment by lymphocyte repertoire sequencing.

Our results suggest that in humans and mice, changes in the B cell / antibody repertoire largely rely on the diversification of memory B cells. Consistently, the clonal composition of the IgA repertoire is preserved despite major changes in the microbiota during antibiotic treatment. Thus, a limited number of B cell clones might be sufficient to create antibodies targeting a diverse spectrum of microbiota and to establish symbiotic microbiota-host interactions.

To extend these observations to the T cell compartment, we have modified the adoptive transfer colitis model. Transferring identical sets of T cell clones into individual recipients revealed the impact of T cell clonality for microbiota-triggered intestinal pathology and compartment specific expansion of distinct T cell clones. These results offer insights into the coordination of microbiota-directed B and T cell responses and the regulation of intestinal homeostasis.
Transcriptomic signature of CD8+ T cell exhaustion in IBD

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The course of Crohn’s disease (CD) and ulcerative colitis (UC) varies dramatically between patients, but reliable prognostic markers are not available. This hinders clinical management because treatment strategies that would be suitable for patients with indolent disease will inevitably undertreat those with progressive disease. Conversely, strategies that would appropriately control frequently-relapsing, progressive disease will expose patients with more quiescent disease to risks of unnecessary treatment.

We have shown that hypothesis-free inspection of CD8 T cell transcriptomic data from patients with active, untreated IBD can identify thousands of genes whose differential expression results in 2 distinct patient subgroups being detectable. Patients in these subgroups were clinically indistinguishable at enrolment, but subsequently experienced contrasting disease courses; characterised by differences in the time to first relapse and the number of treatment escalations required over time. More recent work has shown that this gene signature is due to inter-patient differences in T cell exhaustion; the phenomenon by which effector T cells progressively lose their ability to respond to antigens. T cell exhaustion was originally reported as a consequence of chronic viral infection, but can also occur with persistent auto-antigens. Consistent with being less able to mount recall responses to disease-related antigens, patients with more T cell exhaustion had milder disease, characterised by a longer time to first flare and fewer flares over time.

We have recently developed, optimised, and independently validated a whole blood qPCR-based classifier – designed to identify the IBD1 and IBD2 subgroups – that can reliably predict prognosis in patients with CD or UC at diagnosis without the need for cell separation. This qPCR-based classifier has performance characteristics that compare favourably to prognostic biomarkers currently in use in oncology, and should be sufficient to guide therapy from diagnosis in CD or UC. This represents an important step towards personalised therapy in IBD.
Host microbe interactions in the intestine: New therapeutic strategies for the treatment of immune-mediated diseases

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The gastrointestinal (GI) tract is home to trillions of commensal bacteria that play an important role in nutrition, immune system development and host defence. In inflammatory bowel disease (IBD), a chronic debilitating disease of the gastrointestinal tract, there is a breakdown in the healthy dialogue between our body and our microbial residents resulting in chronic immune attack in the bowel. In this presentation I will review key host and microbial pathways that maintain intestinal homeostasis and discuss how understanding these pathways may provide new therapies for the treatment of chronic inflammatory diseases.
Special Session
Oral Poster Presentation 1

Common gene expression signature between Crohn’s disease and other fibrotic disorders reveals enhanced fibrotic pathophysiological pathways in terminal ileum

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Introduction: Fibrosis, a main characteristic of Crohn’s Disease (CD), is shared by various disorders. We cross-examined differentially expressed (DE) genes in CD and four other fibrotic disorders (FD): Idiopathic pulmonary fibrosis (IPF), systemic scleroderma (SSc), chronic kidney disease (CKD) and liver cirrhosis (LC) in order to identify common fibrotic signatures and to investigate tissue-specific processes.

Methods: Expression data from nine CD, two IPF, one SSc, one CKD and one LC microarray datasets (Gene Expression Omnibus) were examined independently, to avoid bias due to different experimental conditions, using bioinformatics analysis (GEO2R). Two separate groups (CDvsFD) were created containing combinations of datasets (SuperExactTest). These contained the significant (p < 0.05) DE genes from at least seven out of nine CD datasets and at least four out of five FD and their intersection provided a gene signature for pathway analysis (Reactome). Finally, network analytics and visualisation were applied to two tissue-specific, gene co-expression networks constructed by all the genes expressed on human terminal ileum and sigmoid (NetworkAnalyst) to detect and visualize differential clusters of function.

Results: Among all CD datasets, seven common DE genes were detected (CXCL1, ICAM1, PHLPP2, ZKSCAN1, ATP9A, NCF4, CACNA2D1). The intersection of at least seven out of nine CD and at least four out of five FD datasets, showed 241 common DE genes contributing to 12 pathways associated with fibrosis and 17 with inflammation/immune response. Tissue-specific co-expression networks revealed 122/241 genes expressed on the terminal ileum and only 32/241 on the sigmoid. Regarding signalling pathways, nine fibrosis- and six inflammation-related ones were featured on terminal ileum, while only one fibrosis- and five inflammation-related on sigmoid.

Discussion/Conclusion: Our bioinformatics analysis highlights common molecular mechanisms among CD and fibrotic disorders as possible therapeutic targets and/or biomarkers and suggests that pathophysiological and fibrotic mechanisms behind tissue-specific CD progression are mainly located on terminal ileum.
Oral Poster Presentation 2

Colorectal cancer development is driven by STAT3 activation through IL-6 and IL-11 in cancer-associated fibroblasts and correlates with prognosis of CRC patients

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Introduction: Cancer-associated fibroblasts (CAFs) can influence the tumor microenvironment (TME) and the growth of tumors. However, the role of CAFs in the development of colorectal cancer (CRC) is incompletely understood.

Methods: We quantified the pSTAT3 expression in CAFs of human colon cancer tissue using a tissue microarray of 375 colon cancer patients, immunofluorescence staining and digital pathology. Emerging imaging technologies (light sheet fluorescence microscopy, raster-scanning-optoacoustic mesoscopy, multiphoton microscopy) were used to evaluate the in situ distribution of CAFs in COLVI reporter mice. We performed a comparative gene expression profiling by whole genome RNA-sequencing of fibroblast subpopulations (COLVI+ vs. COLVI-) upon STAT3 activation under different conditions (IL-6 vs. IL-11). Moreover, in loss- and gain-of function experiments using genetically modified mice with COLVI-specific STAT3 targeting we evaluated the role of STAT3 signaling in fibroblasts during colorectal development.

Results: The analysis of pSTAT3 expression in CAFs of human colon cancer tissues revealed a negative correlation of increased stromal pSTAT3 expression with the survival of colon cancer patients. In the loss- and gain-of function approach we found a critical role of STAT3 activation in fibroblasts during colorectal tumorigenesis in vivo. The comparative gene expression profiling of fibroblast subpopulations upon STAT3 activation revealed the regulation of transcriptional patterns associated with fibroblast activation, cytokine signaling and angiogenesis. The blockade of pro-angiogenic signaling significantly reduced colorectal tumor growth in mice with constitutive STAT3 activation in COLVI+ fibroblasts.

Discussion/Conclusion: In conclusion, our work demonstrates a critical role of STAT3 in CAFs in CRC, suggesting that strategies interfering with STAT3 activation in CAFs or its downstream signaling might evolve as future therapeutic targets in CRC.
From genetic discovery to precision IBD: The road ahead

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The very large IBD case-control cohorts amassed thus far have primarily been used to perform GWAS, or genome-wide hypothesis testing; stringent statistical thresholds to minimize false positives are applied to test specific genetic variants for disease association. Novel uses for these high-quality, large case-control datasets can now be applied for Precision Medicine purposes. First, the reference case-control datasets can be used to continually refine polygenic risk scores, which use several hundred to thousands (the larger number of loci invariably includes some false positive associations) of primarily common genetic variants to triage disease risk in currently unaffected individuals. Combined with other datasets (plasma protein analytes, ASCA or ANCA antibodies), increasingly refined prediction for early disease interception purposes may be on the horizon. Second, through single cell sequencing approaches (scRNASeq), we have defined heterogeneity within ileal Crohn’s disease, driven by an inflammatory mononuclear phagocyte (inf. MNP) module. This inf. MNP module is anchored by inflammatory macrophages and mature dendritic cells, but also includes activated T cells, Tregs, IgG-producing plasma cells, and activated stromal cells (endothelium and fibroblasts). An exciting future possibility is testing whether the cellular modules defined by scRNASeq can be applied back to the case-control datasets to more accurately subset and prognosticate disease course. An additional, likely required component includes interval tissue- and blood-based expression analyses, with key clinical parameters efficiently captured with high efficiencies, in large sample sizes. Given the plethora of new classes of agents to treat IBD, it is incumbent upon the IBD research community to rapidly define key unifying metrics to accelerate Precision IBD in the immediate, near-term. Longer term, more precise cellular and molecular definitions of treatment-refractory patients will most efficiently inform development of novel classes of therapies to meet currently unmet medical needs.
Session V

**Immune sensing and microbiota**
Microbe-derived factors as regulators of the mucosal immune system

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A high density of microbes inhabits the intestine, helping with food digestion, vitamin synthesis, xenobiotic detoxification, pathogen resistance and immune system maturation. Crucial for human health, communities of commensal bacteria benefit in return from a nutrient-rich environment. Host-microbiota mutualism results from a long-term co-adaptation. At barrier surfaces, immune cells distinguish harmful from commensal bacteria and tolerate non-self organisms at close proximity to the mucosa; gut inhabitants have developed strategies to ensure beneficial conditions in their preferred niche. So far, the complex molecular dialogue of host-microbe mutualism remains elusive.

*Helicobacter hepaticus* is a member of the mouse microbiota that colonizes the lower intestine without inducing immune pathology. However, when there is a host mal-adaptation such as the absence of the anti-inflammatory cytokine interleukin-10 (IL-10) or its receptor IL-10R, *H. hepaticus* triggers aberrant IL-23-driven intestinal inflammation. This response results in major changes in the intestinal innate cell compartment, with the accumulation of inflammatory macrophages. Relying both on a bacterial trigger and on an immune defect, *H. hepaticus*-induced colitis in the context of IL-10/IL-10R axis deficiency shares many features of human inflammatory bowel diseases (IBD). In our study [Danne *et al.* Cell Host Microbe. 2017;22(6):733–45], we questioned the interactions between *H. hepaticus* and intestinal macrophages that promote mutualism. Our results show that *H. hepaticus* produces a large polysaccharide that triggers IL-10 production without a corresponding inflammatory response in macrophages. Moreover, *H. hepaticus* polysaccharide specifically induces an anti-inflammatory gene signature *in vitro* and *in vivo*, including transcriptional factors known as repressors of immune activation. This anti-inflammatory program depends on the TLR2/MSK/CREB pathway, which might be crucial to maintain mutualistic relationships at the intestinal interface.
Exposure to microbiota early in life protects from inflammatory pathologies later in life

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The etiology of chronic inflammatory pathologies, such as allergy, diabetes, IBD or neurodegenerative disease, remains complex. Accumulating evidence show that perturbation of the immune system before weaning imprints the intestine with an increased susceptibility to allergy and IBD in adulthood. However, how perturbations in the host-microbial symbiosis early in life impacts the immune system later in life remains unclear. We demonstrate that exposure of mice to microbiota before and during weaning induces a vigorous immune reaction that is limited to this time window. This weaning reaction is necessary to prevent pathological imprinting and involves the generation of regulatory T cells through bacterial antigens, short chain fatty acids and retinoic acid. Mice that have not experienced a weaning reaction develop a broad deregulation of immune responses in adulthood, and thus increased susceptibility to diverse types of immune challenges.
Precision editing of the gut microbiota through host factors

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The development of the germ theory of disease and Koch’s postulates were milestones in our understanding of microbial-induced diseases. In the past decade, we have come to appreciate that many non-infectious diseases involve a significant microbial component. Changes in gut microbiota composition have been observed in malnutrition, obesity, autoimmunity, HIV enteropathy, necrotizing enterocolitis, and inflammatory bowel disease (IBD). In many setting the microbiota is not merely an innocuous bystander but acts as a driver of disease. These findings spawned an interest in developing novel, microbiota-based intervention strategies for non-infectious diseases. The field has now matured to a state in which mechanistic studies on functional microbe-microbe and host-microbe interactions are needed to establish causal relationships and to define the exact microbial contribution to disease and to identify molecular therapeutic targets. In this lecture, I will provide a conceptual overview on factors that control the composition and function of the gut microbiota during homeostasis and inflammatory diseases, with a particular focus on the intersection of microbial and host metabolism. Furthermore, I will provide an example of how my lab has leveraged mechanistic insights to develop microbiota-based intervention strategies for inflammatory diseases of the intestinal tract.
Regulation of inflammasome responses

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Danger signals that can activate innate immune responses arise in many common inflammatory diseases. The appearance of danger signals and their recognition by innate immune signaling receptors has been linked to the pathogenesis of various diseases, and a better understanding of the mechanisms of sterile inflammatory processes may thus guide the development of novel therapeutic approaches to treat inflammatory diseases.

One of the key innate signaling receptor involved in the recognition of danger signals is the cytosolic Nod-like receptor family member NLRP3. NLRP3 can be activated by numerous danger signals that include crystalline and aggregated substances as well as conditions under which cells loose intracellular potassium. Active NLRP3 induces the assembly of an inflammasome which triggers caspase-1 mediated posttranscriptional activation of IL-1b family cytokines and induces an inflammatory pyroptotic cell death.

Pharmacological interference with NLRP3 activation has proved to be successful in a variety of preclinical models of inflammatory diseases, validating NLRP3 as an attractive pharmacological target. Our knowledge about NLRP3 structure and activation mechanisms remains incomplete, which represents a challenge for drug design and development. In this presentation recent advances in our understanding of NLRP3 activation and regulation will be discussed.

Keywords: Inflammasome, NLRP3, pyroptosis, IL-1b
Macrophage IL-10 signaling is required for the therapeutic efficacy of anti-TNF in IBD

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Introduction: Macrophage IL-10 signaling plays a critical role in the maintenance of a regulatory phenotype that prevents the development of inflammatory bowel disease (IBD). We have previously found that anti-TNF monoclonal antibodies act through Fcγ-receptor (FcγR) signaling to promote repolarization of proinflammatory intestinal macrophages to a CD206+ regulatory phenotype. The role of IL-10 in anti-TNF induced macrophage repolarization has not been examined.

Methods: We used human peripheral blood monocytes and mouse bone-marrow-derived macrophages for studying IL10 production and CD206+ regulatory macrophage differentiation. To determine whether the efficacy of anti-TNF was dependent on IL10 signaling in vivo and in which cell type we used the CD4+CD45Rbhigh T-cell transfer model in combination with several genetic mouse models.

Results: Anti-TNF therapy increased macrophage IL-10 production in an FcγR dependent manner in vitro and in vivo, which caused differentiation of macrophages to a more regulatory CD206+ phenotype in vitro. Pharmacological blockade of IL-10 signaling prevented the induction of these CD206+ regulatory macrophages and diminished the therapeutic efficacy of anti-TNF therapy in the CD4+CD45Rbhigh T-cell transfer model of IBD. Using cell type specific IL-10 Receptor mutant mice we found that IL-10 signaling in macrophages but not T-cells was critical for the induction of CD206+ regulatory macrophages and therapeutic response to anti-TNF.

Discussion/Conclusion: The therapeutic efficacy of anti-TNF in resolving intestinal inflammation is critically dependent on IL-10 signaling in macrophages.
Predicting endoscopic response in ustekinumab-treated patients with Crohn’s disease using multi-omics

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Introduction: Ustekinumab has been approved for CD, though predictive biomarkers of response are lacking.

Methods: Inflamed colonic (n = 25) and ileal (n = 22) biopsies were retrieved prior to first ustekinumab administration in patients with active CD, in addition to sorted circulating CD14+ and CD4+-cells (n = 39). RNA was extracted, and RNA sequencing performed. Proteomic analysis was performed on baseline serum samples (n=86) using OLINK Proseek inflammation. Genotyping data was generated using Immunochip (n = 38). All described omics layers were integrated and analysed using Multi-Omics Factor Analysis (MOFA). Strongest omic layers in terms of variance contribution to endoscopic response (≥ 50% in SES-CD by w24) were identified. Dimensionality reduction and feature extraction from the strongest -omic layers were performed followed by predictive modelling on the top ranked features. Cross-validation using distinct test and training sets was performed for the ensemble and individual classifiers, as an internal validation to avoid over-fitting.

Results: MOFA identified 19 latent factors (LF), with 3 LFs correlating with endoscopic response at w24. The genomic and CD14 transcriptomic layers contributed significantly to the prediction of endoscopic response. Predictive modelling revealed a 10-feature CD14 transcriptomic panel predicting endoscopic response at w24, with an accuracy of 98%. In contrast, classification performance based on 10 randomly selected features resulted in a drastic drop in accuracy (66%). Only 2 of the 10 features exhibited significant correlation with baseline faecal calprotectin, and 1 with CRP, suggesting that this panel is not a simple surrogate of baseline inflammation. From the genetic risk burden, we identified a 15-gene panel which could classify (accuracy 96.6%) the patients based on endoscopic response.

Discussion/Conclusion: Through multi-omic data integration, we discovered pathways contributing to ustekinumab response, and identified a 10-feature transcriptomic and 15-feature genomic panel predicting endoscopic response to ustekinumab standard dosage. Further validation in larger and independent cohorts is warranted, as well as its ustekinumab specificity.
Session VI

Optimizing clinical therapy: A look at IBD and beyond
Optimizing classical immunosuppressive agents in IBD

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The role of thiopurines as monotherapy as a steroid sparing maintenance agent Crohn’s has been called into question based on the RAPID and AZTECH European studies. On the other hand its clinical and mucosal beneficial role in combination with anti-TNF is well established. Infliximab drug concentrations are higher and anti-drug antibody titers are lower in the face of combination therapy which could explain the benefit of combination therapy. A post hoc analysis of SONIC trial confirmed that the benefits of combination are indeed driven by higher drug concentrations. Thus, the question remains as to whether the benefits of combination therapy outweigh the risks associated with thiopurines such as malignancies and infections.

In an attempt to minimize the added risk of combination over monotherapy, efforts have been made to use the lowest dose of thiopurine as possible to still maintain the pharmacokinetic benefit of combination therapy. It has been demonstrated that a 6-thioguanine level of at least 125 pmol/8 x 10^8 RBCs is associated with lower rates of anti-infliximab antibodies. However with adalimumab studies have shown that the ideal 6-TGN level is indeed > 235 8 x 10^8 RBCs which was the level that was originally shown to be associated with optimal thiopurine responses when used as monotherapy. This ideal cut point was supported by a pediatric study (n = 92) that suggested that the odds of a therapeutic response were five times higher in patients with 6-TGN > 235 (95% CI: 2.6–9.7; p < 0.001). Osterman et al.’s 2006 meta-analysis of 12 studies, which included these two studies, crystallized this tenet, showing that patients with 6-TGN levels > 230–260 were more likely to be in clinical remission (OR = 3.27 [1.7–6.3], p < 0.001). Studies that have followed over the last decade have supported these findings. On the other hand, the metabolite 6-methylmercaptopurine (6-MMP) has been linked to hepatotoxicity in a dose-dependent fashion, usually observed with levels > 5700 pmol/8 x 10^8 RBCs. Thiopurine metabolism in up to 20% of patients has been shown to be skewed toward excessive production of 6-MMP, and a high 6-MMP/6-TGN ratio can be used to determine a patient’s risk profile.

Stratifying patients based on age and gender to decide on whether mono or combination therapy with thiopurines is appropriate will help to mitigate risk and improve efficacy of IBD treatment options.

**Interpretation of Thiopurine Metabolite Levels**

<table>
<thead>
<tr>
<th>6-TGN and 6-MMP Scenario</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-TGN &lt; 235, 6-MMP &lt; 5700</td>
<td>Check for compliance; if compliant dose escalate</td>
</tr>
<tr>
<td>6-TGN &gt; 235, 6-MMP &gt; 5700, normal LFTs</td>
<td>Maintain dose and monitor LFTs</td>
</tr>
<tr>
<td>6-TGN &gt; 400, 6-MMP &gt; 5700</td>
<td>Dose de-escalate</td>
</tr>
<tr>
<td>6-TGN &lt; 235, 6-MMP &gt; 5700</td>
<td>Consider switching therapy</td>
</tr>
</tbody>
</table>
Optimizing anti-TNF therapy in IBD

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Despite the development of new biologic therapies and small molecules, anti-TNF agents remain one of the mainstays of IBD therapy. Their efficacy data are still among the best when considering clinical and endoscopic remission both in Crohn’s disease (CD) and ulcerative colitis (UC) and they remain first line in specific clinical scenarios including perianal CD and acute severe UC. When positioning IBD therapies one has to consider efficacy, safety, practicality and cost and there is ongoing effort to optimize all this attributes for anti-TNF agents. There is an increasing body of evidence supporting their earlier use to improve outcomes and change the natural course of Crohn’s disease (CD). New therapeutic strategies such as treat to target and tight control (including therapeutic drug monitoring) are pushing up the ceiling of their efficacy. Ongoing studies will also determine the optimal induction regimen for subcutaneous formulations. There is also hope in the development of anti-TNF biomarkers that could lead to precision medicine. Regarding safety, recent breakthrough has occurred in prediction of anti-TNF immunogenicity that could help to select patients who require or not combination therapy. Most of anti-TNF side effects are mitigated by applying simple prevention guidelines and their absolute risk is low and no new red flag has appeared in the long term safety registries. It is expected that the advent of biosimilars will significantly reduce the cost of anti-TNF agents allowing their broader availability over the world. Anti-TNF therapy is here to stay in IBD and many questions are to be answered regarding their optimization more than 20 years after the publication of the landmark infliximab trial establishing their efficacy in CD.
Optimizing clinical therapy with new IL-12 and IL-23 cytokine blockers

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Anti-IL-12 and anti-IL-23 cytokine blockers represent a novel therapeutic strategy for chronic inflammatory disorders including Crohn’s disease, ulcerative colitis as well as psoriasis and psoriasis arthritis. Thus, adding on one hand another option in daily clinical practice and on the other hand complicating the selection process. In general, anti-p40 (ustekinumab) has been approved for Crohn’s disease and phase III data are available for ulcerative colitis indicating efficacy. Remarkably, ustekinumab has been proven to be effective even in TNF-antibody refractory disease courses suggesting that ustekinumab is a good option in TNF-antibody failure patients. Still, it would be desirable to have a biomarker predicting response to one or the other treatment option. However, which other patients might benefit? A significant number of patients on TNF-antibodies develop psoriasis-like lesions that can become a challenge for the dermatologist. However, introduction of ustekinumab provided an alternative strategy that equally solved the skin manifestation and at the same time kept the underlying intestinal disease under control. Is this equally true for other extraintestinal manifestations? This question is getting increasingly important, since a relevant number of patients presents with extraintestinal manifestations. Anti-p40 seems to be effective in peripheral arthritis but not in axial spondylarthropathy. Thus, in patients with Crohn’s disease and an axial spondylarthropathy a TNF-antibody should be the preferred choice whereas in peripheral arthritis ustekinumab provides an alternative option. In addition, although the data on side effects for anti-p40 strategies are still comparably sparse, there is evidence suggesting that in particular infectious complications are lower when compared to TNF-antibody treatment. Consequently, in the presence of comorbidities or in the elderly population the primary choice might become anti-p40.

When focusing on the pathomechanism behind the anti-p40 strategy it is apparent that due to the nature of the antibody (directed against p40), it is neutralizing both, IL-12 and IL-23. Experimental data suggest that the neutralization of IL-23 is sufficient to control intestinal inflammation. In fact, phase II clinical trials provide first evidence that the selective blockade of IL-23 is equally effective. This is of particular interest when looking across our borders to psoriasis where selective blockade of IL-23 was even more effective than dual principle provided by the anti-p40 strategy. Thus, an exciting challenge will be the direct comparison in a clinical study of anti-p40 versus anti-19 strategies.

In summary, already in the absence of a good biomarker, a substantial subpopulation of patients can be identified where anti-p40 might be the preferred strategy. However, this will not the substitute the need for biomarkers that will serve to direct and support our medical decisions.
References:


Session VII

Emerging clinical therapies in IBD: Efficacy and safety
Advances in our understanding of the pathophysiology of IBD suggest a central role of the gut microbiota in genetically predisposed individuals. This makes the manipulation of the gut microbiome a potentially promising endeavour in the treatment of IBD. Early efforts to affect the microbiota using probiotics or prebiotics have largely been disappointing, but these have been limited by products lacking bacterial diversity and concentration. Faecal Microbiota Transplant (FMT), by contrast, involves the transfer of potentially an entire dense colonic microbial community. Data concerning the use of FMT in IBD are accumulating and signals are encouraging. There were early reports of FMT in IBD in small case series, but now this technique has been used in randomised controlled trials. The STOP-COLITIS study is a study of FMT in ulcerative colitis and is currently recruiting patients in the UK. There is more limited data for FMT in Crohn’s disease and pouchitis. Mechanistic studies centred around the randomised studies offers the opportunity to understand in more detail the impact of the gut microbiota on the host.
Targeting immune cells: Integrin and JAK blockers

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Monoclonal antibodies targeting necrosis factor alpha (TNF), leukocyte integrins, and interleukin (IL) pathways are mainstays of therapy for moderate-to-severe Crohn’s disease (CD) and ulcerative colitis (UC). Optimization of TNF-antagonists through combination therapy and therapeutic drug monitoring, development of selective inhibitors of lymphocyte trafficking, and recognition of early treatment of high risk with CD are the most important concepts that have emerged over the past decade. However, new advances are forthcoming.

Vedolizumab a monoclonal antibody directed towards the α4β7 integrin, has demonstrated efficacy for induction and maintenance of clinical remission in both UC and CD, however the relative efficacy of vedolizumab to other treatments is unknown. Results of a randomized comparison to adalimumab in active results are expected this year. Recently a subcutaneous formulation of vedolizumab has shown highly similar results to the intravenous formulation in randomized controlled induction trials conducted in both UC and CD. The safety profile of vedolizumab is excellent, making it a platform therapy for future combination therapy strategies. Etrolizumab, a monoclonal directed towards the beta-7 integrin and PF-00547659, an anti-MadCam antibody, have demonstrated promising results in Phase 2 UC studies. Etrolizumab is being evaluated in a large phase 3 program that includes a direct comparison to infliximab induction therapy.

However, monoclonal antibody therapy has important limitations. Many patients are primary non-responders ics or lose response due to sensitization, intolerance, or “mechanistic escape”. Furthermore, monoclonals must be intravenously or subcutaneously dosed, which may compromise both patient acceptance and cost-effectiveness.

Orally administered small molecule drugs hold promise for the treatment of IBD. Multiple inhibitors of Janus kinase (JAK) are being developed and tofacitinib was recently approved for treatment of moderate-to-severe UC. Depending on the selectivity of the JAK inhibitor for certain TYK proteins, different pathways mediated by interferons, interleukins, and colony stimulating factors, can be targeted. Selective JAK inhibitors are being studied for the treatment of both UC and CD. Although the initial safety experience with tofacitinib has been for the most part favourable, an increased risk of infections, particularly of herpes zoster, has raised concern regarding the risk-benefit profile of these drugs.

This talk will review recent data regarding the role of anti-integrins and KAK inhibitors in both CD and UC.

We therefore conducted a systematic review and meta-analysis of all randomized placebo-controlled trials (RCTs) evaluating JAK inhibitors for IBD to determine their pooled efficacy and safety relative to placebo.
Targeting immune cell: Integrin and JAK blockers

Gert Van Asssche
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Biologics have changed the treatment paradigms for IBD 20 years ago. Anti-TNFs have been added to our treatment armamentarium first. These agents are broad inhibitors of T-cell activation. More recently a selective integrin inhibitor, vedolizumab, was introduced. Newer, mostly less selective, oral anti integrins, have been developed and have shown efficacy in ulcerative colitis (UC). A new class of small molecules, the Janus kinase (JAK) inhibitors, has shown efficacy both in Crohn’s disease (CD) and in UC. We will discuss the two different classes and their current and future place in therapy.

Anti-integrins block the transgression of immune cells, mainly lymphocytes, into the target tissue, the gut. The anti-α4β7-integrin monoclonal, vedolizumab, is selective for the gut since the addressin ligand of α4β7-integrin, MadCam1 is only expressed in significant amounts in the Gut. The precise mechanism of action of vedolizumab in gut inflammation has not been fully elucidated, but the compound is efficacious in UC and CD, particularly in maintenance. Since there should be no extra-intestinal side effects, the safety profile holds promise. In the absence of active comparator, head-to head trials, comparing vedolizumab to anti-TNFs, a clear answer on which agents to use as standard first line cannot be given. The clinical features of the patient will drive these decisions. Recently, evidence has been provided for the efficacy of the oral SP1-R blocker ozanimod in UC. The mechanism of action for this compound is less selective for the gut but it offers the advantage of oral intake.

JAK inhibitors, also small molecules for oral intake, target the signal transduction from the immune cell membrane to the nucleus. JAKs are universally implicated in immune regulation, hematopoiesis and host defense. They always come in heterogenous pairs, heterodimers of JAK1, 2 3 and Tyk 2, and the compounds in development have a different affinity for these individual molecules. Therefore their efficacy and safety will most likely be less generic than that of anti TNFs for instance. Tofacitinib is now licensed for the use in ulcerative colitis and filgotinib and upadacitinib are being tested in CD and UC. The safety and efficacy of these compounds relative to other immunosuppressive small molecules, such as steroids and azathioprine, and biologics, has not been well studied and will determine their place in therapy.
Anti-fibrotic agents in IBD

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Crohn's disease (CD) and is characterized by the frequent occurrence of fibrosis and subsequently the need for surgery due to stricture formation. Up to two thirds of patients with CD may develop either a structuring or penetrating disease course within 10 years after diagnosis (1). Up to 80% of all CD patients undergo surgery at least once during the course of their disease (2, 3). In half of these patients intestinal obstructions and strictures are the indication for surgery. Subsequently, intestinal fibrosis is the reason for resective surgery in approximately one third of all CD patients (4). Fibrosis is less frequent in patients with ulcerative colitis (UC), however, mucosal fibrosis occurs also in UC patients and contributes to a loss of function of the colon. It is still unclear which factors induce fibrosis in some patients and not in others. Epithelial-mesenchymal transition (EMT) is involved in the pathogenesis of intestinal fibrosis. It represents a process in which disaggregated epithelial cells reshape with increased mobility and changed metabolic functions (5). To develop effective anti-fibrotic drugs, fibrosis needs to be viewed as a pathological process distinct from inflammation.

At present, there are no approved or effective anti-fibrotic therapies for CD or UC. Therapy of fibrosis is complicated by the fact that a wound healing response is essential in IBD. Therefore, anti-TGF therapies are not very promising. Another important problem for the development of anti-fibrotic therapies in both CD and UC is the lack of clinical trial end points. Prof. Florian Rieder from Cleveland together with ROBARTS as well The International organisation for the study of IBD (IOIBD) have started initiatives to define such clinical end points or imaging end points for fibrosis studies in CD. In lung fibrosis, pirfenidone has been studied in several clinical trials and approved in this indication (6). As αv integrins can activate matrix-bound latent TGF and αvβ6 integrin plays a role in EMT (see above) specific antibodies against αvβ6 integrin are studied in lung fibrosis. As circulating mesenchymal cells express the CXCR4 chemokine receptor antagonizing antibodies against this receptor have been tested and show promising activity. Specific inhibition of Smad3 by SIS3 does not affect Smad2 phosphorylation but completely blocks activation of Smad3 and has beneficial effects in diabetic nephropathy (6).

Further therapeutic options are second generation and wide spectrum tyrosine kinase inhibitors. They inhibit growth factor receptor signalling thus reducing fibrosis in animal models and some patients with tumor associated fibrosis. PPAR inhibitors had beneficial effects in lung, liver and kidney fibrosis. LDE223, an inhibitor of hedgehog signalling has been beneficial in bleomycin-induced fibrosis. Further treatment strategies tested in various fibrotic diseases are inhibition of specific molecules by microRNAs.

However, clinical developments for anti-fibrotic agents in IBD are just at the starting point. We will most likely see a number of respective clinical trials starting in the next years.
References:


Session VIII

Personalized medicine: Concepts in IBD
Biomarkers and genetic approaches

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In this talk, I will discuss the potential and pitfalls for using genetics to drive personalised medicine in inflammatory bowel disease. I will discuss the history of IBD locus discovery, and how researchers measure the variance explained by these loci and establish their power to predict disease (both in terms of predicting case vs control status, and predicting Crohn’s disease vs ulcerative colitis diagnosis). I will also discuss the issues that make genetic screening challenging to implement in practice, and situations where genetic risk prediction may provide useful information (e.g. in guiding decisions around colectomy in ulcerative colitis). Next, I will talk about the potential role of genetics in identifying different subtypes of disease, and discuss research into the correlation between genotype and disease outcome in IBD. I will also discuss new advances in the pharmacogenomics of IBD (i.e. how genetics can predict treatment response), and the potential for genetics to inform IBD treatment. Finally, I will discuss the future research that will be required to translate genetics into clinical practice, as well as the potential for using genetics to identify non-genetic biomarkers.
Immunological markers and molecular endoscopy

Raja Atreya
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Advances in understanding the underlying immunopathogenic mechanisms of IBD have led to the development of biological therapies, which selectively inhibit crucial mediators of the inflammatory process. The optimized clinical use of these agents in IBD remains unclear, however, as suitable predictive biomarkers for response are lacking. Validated and applicable biomarkers could help positioning respective biologic treatments as first choice therapy, but also in case of refractoriness. Such an approach may provide a basis for personalized medicine in IBD. Possible mechanistic reasons that might confer the variable response to biologic therapies in IBD are therefore a clinical important subject of investigation.

Several studies have indicated that mucosal expression of the targeted molecule may affect response to treatment. In vivo molecular endoscopy with topical application of a fluorescence labelled anti-TNF antibody has demonstrated that the expression of mucosal membrane-bound TNF (mTNF) at baseline is associated with clinical efficacy of subsequent anti-TNF therapy in Crohn’s disease. It is expected that such targeted in vivo molecular endoscopy will assist in optimizing the risk/benefit ratio of treatment in IBD patients. Furthermore, controlled studies showed that high pretreatment mucosal expression of oncostatin-M is associated with failure of anti-TNF therapy in IBD, while colonic tissue levels of granzyme A and integrin alphaE identified ulcerative colitis patients who are most likely to benefit from etrolizumab, an antibody directed against the beta7 subunit of the integrins alpha4beta7 and alphaEbeta7. Recent evidence suggested that the local immune cell infiltrate is an essential factor in driving molecular resistance against therapy. In particular, IL-23 produced by macrophages has been identified as a key regulator of molecular resistance in anti-TNF therapy. One may therefore envision that sequential biologic therapies may lead to sustained clinical response in IBD patients.
Individualized management of IBD: A look into the future

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The management of IBD remains unsatisfactory for many patients due to the wide heterogeneity of clinical phenotypes, outdated step-up treatment approaches and the lack of association between pathophysiology and treatment selection.

Even with the currently available treatments, it appears that outcomes could be improved significantly when smarter algorithms are introduced. There is a lot of room for improvement at the level of disease course prediction, institution of the best (most effective and safest) treatment modality and/or combination of treatments and more optimal use of surgical interventions. Therapeutic efforts should shift from the management towards the prevention of complications.

The course of IBD can be reasonably predicted based on phenotypic characteristics and the combinations of genetic and serological markers as recently demonstrated in the paediatric RISK cohort. Transcriptome analysis of circulating CD8 cells predicts rapid need for treatment escalation. Patients with predicted complicated disease course should be treated with the best available treatment up front. Evidence with anti-TNF agents suggested that perforating complications could be prevented with this strategy whereas fibrostenotic complications could not.

Event with the most potent treatment combinations at hand, mucosal healing and symptomatic remission is rarely attained in > 50% of patients, which calls for more creative approaches. Besides optimization of the pharmacokinetics and prevention of anti-drug antibody formation, combinations of drugs targeting different mechanisms should be considered. Potential options include Jak-inhibitors with integrin antibodies, anti-TNF with anti-p19 antibodies and microbial interventions before/during antibody treatment in order to improve responsiveness. In the same line of thinking early resection of irreversibly damaged bowel segments followed by effective recurrence prevention should be considered.

Ideally, treatment should be selected based on the phenotypic and multi-omics profile of every individual patient. The first datasets offering guidance in this regards focused on microbiome profiles (for vedolizumab), presence of oncostatin M (for anti-TNF) and genotyping (predicting immunogenicity). Evidently, much more exploration is needed that includes more omic layers using big data analysis. These models will then need validation in prospective clinical trials. Although such efforts may take a long time before they lead to practice change, the initiatives for personalized medicine offer invaluable perspectives for a better outcome for IBD patients.
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POSTER ABSTRACTS

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Validation of the CUCQ questionnaire with stoma extension in patients with acute ulcerative colitis in the CONSTRUCT trial

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Introduction: There are no validated quality of life tools that are suitable for assessing patient quality of life in acute severe ulcerative colitis. The purpose of this work was to develop and concurrently validate a patient reported outcome measure suitable for such patients, within the context of the CONSTRUCT trial.

Methods: We developed and piloted a new questionnaire suitable for patients with severe ulcerative colitis. We developed the questionnaires in three stages: item generation by reviewing the literature of previously validated questionnaires and by consultation with patients and experts; initial development of the questionnaires in the CONSTRUCT cohort sample; and definitive validation of the questionnaires in the CONSTRUCT trial sample. We undertook psychometric analysis to examine the underlying dimensions of the scale, internal consistency and validity.

Results: We developed the Crohn’s and ulcerative colitis questionnaire (CUCQ) for patients who had not undergone surgery; and the CUCQ with stoma extension (CUCQ+) for surgery patients. We had 1240 patients in our development sample and 270 patients in our validation sample. The internal consistency of the CUCQ was excellent (Cronbach’s alpha > 0.8). The data did not exhibit any floor or ceiling effects. Principal components analysis indicated that there were 4 main factors. The CUCQ scores achieved significant correlations with the two generic health-related quality of life scales demonstrating good construct validity.

Discussion/Conclusion: The CUCQ is a useful tool for assessing quality of life in patients with acute severe colitis.
Infliximab or ciclosporin for steroid-resistant acute severe ulcerative colitis? Results of a pragmatic randomised trial and economic evaluation (CONSTRUCT)

Introduction: Infliximab and ciclosporin are of similar efficacy in treating acute severe ulcerative colitis, but there has been no comparative evaluation of their relative clinical and cost effectiveness.

Methods: Between May 2010 and February 2013, 270 patients were recruited to this open-label, parallel-group, pragmatic randomised trial from 52 hospitals in England, Scotland and Wales. Consentin patients admitted with severe colitis who failed to respond to intravenous hydrocortisone within about five days, were randomised in equal proportions to: intravenous infliximab at zero, two and six weeks; or intravenous ciclosporin for seven days followed by oral ciclosporin for 11 weeks. Primary outcome was quality-adjusted survival – the area under the curve (AUC) of scores from the Crohn’s and Ulcerative Colitis Questionnaire (CUCQ) completed by participants at baseline, three and six months, then six monthly over one to three years. Data analysis was blinded. Economic evaluation was nested within the trial. Qualitative interviews were conducted with 23 participating professionals, and twice each with 20 participants.

Results: There was no significant difference in: quality-adjusted survival [analysable data from 121 participants (90%) in each group; mean difference in AUC/day 0.0297 favouring ciclosporin; 95% confidence interval (CI) from -0.0088 to +0.0682, p = 0.129]; EQ-5D scores; SF-6D scores; colectomy rates (55/135 infliximab vs. 65/135 ciclosporin, OR = 0.741, 95% CI: 0.457 to 1.202, p = 0.223); time to colectomy; patients experiencing serious adverse reactions (11.9% vs. 7.4%); serious adverse events; or deaths (infiximab 3 vs. ciclosporin 0, p = 0.247). Total NHS costs were lower for ciclosporin (mean adjusted difference £5,632, 95% CI: £8,305 to £2,773, p < 0.001). Interviewed participants spoke more positively about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked giving intravenous ciclosporin.

Discussion/Conclusion: There was no significant difference between ciclosporin and infliximab in clinical effectiveness, but total cost to the NHS was higher for infliximab.
Crohn’s and ulcerative colitis questionnaire-8 (CUCQ-8), a valid and quick quality of life measure in IBD

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Introduction: Most of the disease-specific quality of life (QoL) measures for inflammatory bowel disease (IBD) are lengthy and time consuming. None has been established for routine use in clinical practice. We designed this study to develop a short QoL measure in IBD.

Methods: A 32-item questionnaire, the Crohn’s and ulcerative colitis questionnaire-32 (CUCQ-32) was developed by reviewing the literature and consultation with patients and experts. Construct validity was carried out using the Short Form 12 (SF-12) and the EuroQol 5 dimensions (EQ5D) questionnaires and two disease severity measures (Simple Clinical Colitis Activity Index (SCCAI) and the Harvey-Bradshaw Index (HBI)). Test-retest analysis was done by asking patients to complete the CUCQ questionnaire twice in a period of two weeks.

Results: Data were obtained from 205 patients with IBD who completed the CUCQ-32. Psychometric analysis showed that Cronbach’s $\alpha$ was 0.88, item-total correlations were good and there was no ceiling or flooring effects. Stepwise regression identified 8 items that accounted for more than 95% of the variance in the CUCQ-32. The resulting CUCQ-8 demonstrated good internal consistency (Cronbach’s $\alpha = 0.84$); had good reproducibility (intra-class correlation coefficient $= 0.94$); was well correlated with the EQ5D ($r = 0.58$), the Short Form-12 ($r = 0.65$ for physical component and $r = 0.63$ for mental component); was responsive to change (responsiveness ratio was 0.64, p value < 0.05).

Discussion/Conclusion: CUCQ-8 is a short questionnaire, which has the potential to be an efficient tool for assessing the QoL of all patients with IBD in clinical practice.
Clinicians' knowledge about the ionizing radiation of the common investigations used in inflammatory bowel disease

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Introduction: Patients with inflammatory bowel disease (IBD) are at risk of high radiation exposure due to repeated radiologic investigations. This study aims to assess the clinicians and IBD nurses' awareness about ionizing radiation and its consequences.

Methods: This is a prospective questionnaire based study of doctors and IBD nurses' awareness about ionizing radiation. Participants from Singleton, Morriston, Princess of Wales and Neath Port Talbot hospitals were asked to complete a hard copy multiple choice questionnaire to assess their knowledge of the commonly used investigations in IBD patients: plain abdominal X-ray, Barium follow through, CT scan and MRI.

Results: 49 participants (20 consultants, 28 trainees, 1 IBD nurse) completed the questionnaires. The mean score for all the participants was 4.7 out of 10. There was no difference in the mean score between consultants and registrars. 30% of participants achieved a score of 50% or more. 47% of the participants had attended a training course about ionizing radiation; there was no difference in the outcome between those who attended and those who did not attend; 13% of participants knew that abdominal CT is equivalent to 3 years of natural background radiation; 25% of them knew that a cumulative effective dose above 75 mSv is regarded as a high exposure and the patient is at risk of developing cancer.

Discussion/Conclusion: The knowledge about ionizing radiation doses among IBD specialists is poor. Training is needed to improve the awareness about the benefit versus the risk of ionizing radiation.
Can the inflammatory bowel disease biologics registry lead to improved quality of care?

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Introduction: A Registry is a systematic collection of data about a disease or diseases. For some years there has been a desire amongst the gastroenterology community to develop a comprehensive Registry of patients with inflammatory bowel disease (IBD). However, there has been no coordinated national approach. In this study, we will review the grounds behind setting an IBD registry; suggest a methodological approach, and the ways to maintain its continuity.

Methods: We searched the PubMed, Embase and PsycINFO databases for articles describing the development and/ or evaluation of one or more of the registries in IBD. We assessed these registries using a standardized checklist.

Results: There have been several registries of biological therapy in Crohn’s disease like TREAT registry for Infliximab®, Registry study for Adalimumab®, the Rotherham IBD management software, and the Inflammatory Bowel Disease Information System (IBDIS). The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHN) has established a registry of paediatric IBD in late 1990s but it was only maintained for a few years. Recently the UK IBD registry was established following the second round of the UK IBD audit, and the launch in February 2009 of the National IBD Service Standards.

Discussion/Conclusion: In summary, having a successful IBD registry will ensure efficient patients monitoring and follow up. It will also support data collection for audit and research purposes. However, any registry should be tailored for individual users’ needs to ensure their engagement and participation. A few difficulties associated with setting a wide IBD registry may include lack of clinicians’ participation or interest, costs related to setting and maintaining the registry, providing enough time to use the registry and data quality assurance.
Systematic review of the clinical disease severity indices for inflammatory bowel disease

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Introduction: Clinical disease severity indices are increasingly being used in choosing treatment and monitoring response of patients with inflammatory bowel disease (IBD). Our aim is to systematically review the clinical disease severity indices in IBD and to appraise their measurement properties and methodological quality.

Methods: We searched the PubMed, Embase and PsycINFO databases for original articles describing the development and/or evaluation of one or more of the measurement properties of clinical disease severity used in IBD. We assessed these properties (e.g., internal consistency, reliability, validity, responsiveness) using a standardized checklist.

Results: We examined the full text of 142 articles that we deemed potentially eligible and identified 22 clinical disease severity indices in IBD. No clinical disease index has met all the required measurement properties. All of the validation studies were not descriptive enough to allow assessment of their methodology.

Discussion/Conclusion: Although commonly used in multiple clinical trials, none of the clinical disease severity indices in IBD had all the required measurement properties. Further validation studies are required.
Immunomodulatory interactions between cyclin-dependent kinase inhibitors (p21 and p27) and tumor suppressor gene p16 in patients with ulcerative colitis

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Introduction: Ulcerative colitis (UC) and non-specific colitis (NSC) are inflammatory disorders with some common genetic, immunological and environmental factors involved in the pathogenesis. Cyclin-dependent kinases (CDKs) are deregulated in IBD, cancers and etc. by silencing of the p16⁵⁴, p21, p27 and other mechanisms.

Methods: The immunohistochemical expression of p16, p21 and p27 was evaluated in 19 patients with UCs. Data compared with clinical and pathological parameters of investigated patients.

Results: Data shown that eleven cases had strong positivity for p21 and 27, and eight were with low expression (p > 0.05, NS). Twelve cases shown expression for p16. After analysis we found that in patients with UC and dysplasia the numbers of p21- and p27-positive cells were significantly more as compared to cases without dysplasia (χ² = 2.44; p = 0.033). p16 expression was correlated to the low expression of p21 in all positive samples (χ² = 4.12; p = 0.019) and also tended to correlate with low expression of p27 (χ² = 1.25; p = 0.066).

Discussion/Conclusion: The study is evaluating the tissue expression of p16, p21 and p27 in patients with UC, in order to identify the relation between these biomarkers and their impact for dysplasia development. Our results suggest that cell-cycle inhibitors p16⁵⁴, p21 and p27 were may play an important role in development of UC and dysplasia changes and were related to progression of the diseases and risk for malignant transformation.
An IL-1-dependent IL-23 inflammatory monocyte signature correlates with disease severity and treatment response in patients with inflammatory bowel disease


The pathogenesis of inflammatory bowel disease (IBD), Crohn’s disease (CD) and ulcerative colitis (UC) is caused by dysregulated innate and adaptive immune responses that drive tissue chronic relapsing inflammation.

An extreme form of dysregulated immune responses that present with infantile onset IBD is caused by biallelic loss-of-function (LOF) mutations in genes that encode IL-10 or its receptor IL-10RA and IL-10RB. Mice that lack the p19 subunit of IL-23 are protected from developing colitis despite IL-10 signalling defects, indicating that IL-23 represents a critical pathogenic factor.

In humans IL-23p19 is a therapeutic target for the treatment of IBD. Still, the cellular sources, networks and regulation of IL-23 production in humans is poorly understood, but is required to identify those patients that would benefit most from these novel treatment options and is necessary for the development of alternative cytokine targeting therapies to extend established therapeutic approaches that are only effective in subgroups of patients with IBD, such as anti-TNF therapy.

Here we investigate the relationship between IL-10 and IL-23 in a modelled response towards relevant microbe derived stimuli in adult patients with IBD and healthy controls. We describe a tightly IL-10-regulated inflammatory gene signature that upon deregulation in the absence of IL-10 signalling induces an IL-1-dependent IL-23 producing monocyte population. By integrating IL-10-regulated gene expression profiles from peripheral blood mononuclear cells (PBMC) derived from patients with IBD, a single cell RNA sequencing (scRNA-seq)-derived gene expression profile and monocytes cytokine analysis at the protein level we generate an inflammatory transcriptional signature that reliably stratifies patients with IBD into active and inactive disease subgroups, that identifies patients with IBD with distinct clinical features and that predicts non-responsiveness to anti-TNF therapy. Together these results may assist in the identification of those patients with IBD that benefit most from IL-23p19 or IL-1 targeting therapeutic approaches.
The hepatobiliary disorders in patients with IBD and their correction

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Introduction: Extraintestinal manifestations (EIM) are common in IBD, affecting up to 35% of the patients. We investigated hepatobiliary disorders in patients with IBD and the effect of phosphotidilcolin in improvement of the liver function in patients with IBD.

Methods: 42 patients were enrolled in the study with a mean age of 39.9 ± 4.8 years, 32 (76.2%) woman 10 (23.8%) men. Ulcerative colitis (UC) was diagnosed in 33 (78.6%), Crohn’s disease (CD) was diagnosed in 9 (21.4%) patients. Liver disorders were diagnosed by detecting of the enzymes, liver steatosis was assessed by ultrasonography, liver stiffness (LS) was measured by Shear Wave Elastography (SWE). 16 (38.1%) patients had increased levels of ALT (68.4 ± 6.9) mmol/l and AST (72.1 ± 5.4) mmol/l, hyperbilirubinemia (32 ± 2.9) mkmol/l was in 12%, hypercholesterolemia (6.4 ± 0.5) mmol/l was in 37% of the patients. Dysfunction of the gall bladder had 25 (59.5%), bile slag 18 (42.9%), fatty liver had 13 (31.0%). LS was increased in the group with steatosis (7.7 ± 1.2) kPa (F1), in the group without steatosis fibrosis was not observed (4.2 ± 0.5) kPa (F0). Additionally to the basic therapy with mesalazine, phosphatidylcholin 2 capsules three times a day was prescribed for 3 months.

Results: After 3 months of the therapy the normalization of AST, ALT, GGT, cholesterol levels (p < 0.05) was observed. LS decreased from the average initial value of (7.7 ± 1.2) kPa to (5.9 ± 0.8) kPa (p < 0.001), accordingly from F1 to F0 on the Metavir scale score of liver fibrosis.

Discussion/Conclusion: In our study 50% of the patients with IBD had biliary pathology, 30% had liver disorders. Additional inclusion to the basic therapy of the IBD phosphotidilcolin improves liver function, decrease liver stiffness and is effective in prevention of the hepatobiliary disorders.
Autoimmune sclerosing cholangitis and ulcerative colitis in 6-year-old boy – A case report

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Introduction: Autoimmune liver disease often has characteristics of both primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH), the condition called autoimmune sclerosing cholangitis (ASC). Its incidence is approximately 0.1/100,000 children. Since there are no diagnostic criteria for making the diagnosis, ASC is diagnosed with the co-existence of clear clinical criteria for AIH and PSC. Immunosuppressant drugs influence the lobular inflammation, but cholangiopathy is resistant to immunosuppression and has a direct influence on the disease course. In 75% of patients the disease is connected with inflammatory bowel disease, mainly ulcerative colitis (UC). In this paper we describe the boy with ASC and UC.

Methods: The disease started at the age of 3 with swelling of the ankles with high AST-O titre which was considered to be reactive arthritis; after penicillin therapy, all symptoms disappeared. At the age of 4 bloody stools appeared. Blood test showed high inflammation parameters (SE 59, CRP 6.1) with high transaminase and cholestatic enzymes levels (AST 682, ALT 428, GGT 451, AP 608) and normal bilirubin levels. Colonoscopy revealed inflammation from hepatic flexure to terminal ileum with histopathological confirmation of Crohn's disease. On MRCP narrowing of segmental bile ducts pointed to PSC. Ursodeoxycolic acid, azathioprine and prednisone were started with excellent clinical and laboratory response. At the age of 6 control colonoscopy showed pancolitis with histopathological findings of ulcerative colitis. Liver biopsy was made; histopathology showed active inflammation partially modified by anti-inflammatory therapy that affects both hepatocytes and bile ducts as a part of AIH/PSC overlap syndrome. Prednisone was reintroduced along with ursodeoxycolic acid and azathioprine; therapy induced clinical and laboratory remission.

Discussion/Conclusion: The diagnosis of AIH/PSC overlap syndrome in children is not easy to establish, especially in preschool children. Nevertheless, it must be considered in chronic liver disease in combination with inflammatory bowel disease.
Dose-dependent differential effects of vedolizumab therapy on adhesion of regulatory and effector T cells

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Introduction: Vedolizumab has emerged as an important pillar of treatment in inflammatory bowel disease (IBD). However, for unknown reasons, not all patients respond to vedolizumab treatment. Earlier studies suggested decreased response rates in the highest compared with lower dosage groups.

Methods: The α4β7 expression on different human leukocyte subsets, as well as the binding efficacy of different concentrations of vedolizumab to these cells were analysed via FACS. Functional effects of different concentrations of vedolizumab on the adhesion of different leukocytes to MAdCAM-1 were analysed using dynamic in vitro adhesion assays.

Results: We found a preferential binding of vedolizumab to regulatory T cells (Treg) at low concentrations of vedolizumab that shifted to a preferential binding to effector T cells (Teff) at clinically relevant concentrations. Both cell types were equally bound at higher concentrations. Consistently, at clinically relevant concentrations, dynamic adhesion of Tregs to MAdCAM-1 was increased compared to Teffs, but no difference was noted at high concentrations. Additionally, dose-dependent differences in the binding of vedolizumab to other leukocyte subsets consistent with functional effects in dynamic adhesion assays could be demonstrated.

Discussion/Conclusion: Our findings support a dose-dependent differential binding of vedolizumab to different leukocyte subpopulations. This suggests that clinical efficacy of vedolizumab therapy might be explained by more pronounced effects on Teff compared with Treg homing. Moreover, they offer an explanation for earlier findings in dose-ranging studies and might help to establish approaches for individualized optimization of vedolizumab therapies in IBD patients.
A blood-based prognostic biomarker in inflammatory bowel disease

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Introduction: The course of Crohn’s disease (CD) varies substantially between affected individuals, but reliable prognostic markers are not available in routine clinical practice. Previously, we have described a transcriptional signature identifying two subgroups of patients that is detectable within peripheral blood CD8 T-cells at diagnosis, correlating with subsequent disease course. In order to translate this work to the bedside and overcome the technical challenges of separating cell populations, which would not be possible in a routine clinical setting, we developed a whole-blood qPCR-based biomarker that can re-capitulate the CD8 subgroups. Here we describe the development, optimisation and validation of this biomarker.

Methods and results: From a training cohort of 69 newly-diagnosed IBD patients, we simultaneously obtained a whole-blood PAXgene RNA tube and peripheral blood CD8 T-cell sample. Gene expression in both samples was measured by microarray. After detecting the CD8 transcriptional signature and identifying its correlation with prognosis, statistical modelling was used to identify a transcriptional classifier in whole-blood gene expression data that could re-capitulate the CD8 findings. This was subsequently optimised into a multi-gene qPCR assay. Independent validation of this biomarker was established using a second, independent cohort of 84 newly-diagnosed patients, which confirmed that the subgroups had significantly different disease courses (HR = 3.34, p = 0.0003 for time to treatment escalation). We now propose to conduct the first ever biomarker-stratified trial in inflammatory bowel disease to determine whether this biomarker can deliver personalised medicine in CD.

Discussion/Conclusion: We have developed, optimised and validated a whole-blood qPCR classifier that is able to predict disease course from diagnosis in IBD patients. This represents a major step towards personalised therapy and is currently under investigation in the PROFILE trial, the first biomarker-stratified trial in inflammatory bowel disease.
Therapeutic fecal microbiota transplantation controls intestinal inflammation through IL-10 secretion by immune cells

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Introduction: Alteration of the gut microbiota (dysbiosis) has been associated with different gastrointestinal disorders. Restoration of normobiosis by fecal microbiota transplantation (FMT) is considered a promising therapeutic approach, even if the mechanisms underlying its efficacy are at present largely unknown. Here we sought to elucidate which were the functional effects of therapeutic FMT administration during experimental colitis on innate and adaptive immune responses in the intestinal mucosa.

Methods: Experimental intestinal inflammation was induced through DSS acute administration. Intestinal microbiota manipulation in colitic mice was achieved by therapeutic fecal microbiota transplantation from both normobiotic and dysbiotic donor mice. The composition and metabolic function of the gut microbiota were assessed through 16S rRNA sequencing and metabolomic analyses. Phenotype and function of intestinal adaptive and innate immune cells were analyzed by flow cytometry. IL-10 functional involvement was evaluated by injection of the anti-IL-10R blocking antibody.

Results: We show that therapeutic FMT reduces colonic inflammation and initiates the restoration of intestinal homeostasis through the simultaneous activation of different immune-mediated pathways, ultimately leading to IL-10 production by innate and adaptive immune cells, including CD4+ T cells, iNKT cells and antigen presenting cells (APC). This, in turn, results in the decrease in the proliferation of mucosal CD4+ T cells and in the reduction of the ability of dendritic cells, monocytes and macrophages to present MHCII-dependent bacterial antigens to colonic T cells.

Discussion/Conclusion: These results demonstrate the capability of FMT to therapeutically control intestinal experimental colitis and poses FMT as a valuable therapeutic option in immune-related pathologies.
Vaccination strategies for IBD patients

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Introduction: Several vaccinations are recommended in patients with Inflammatory Bowel Disease (IBD), especially in those on immunosuppressive therapy or in elderly IBD patients. Unfortunately, adherence to vaccination programs is poor. The aim of the study was to test different vaccination strategies with regard to adherence.

Methods: We identified IBD outpatients with indication for vaccination for seasonal influenza and pneumococcus vaccination, (patients on immunomodulator or biotechnologic therapies, patients aged ≥ 65 years, and those with both indications). At start (autumn 2016) patients were verbally informed during visits, on the opportunity to follow recommendation for influenza vaccination. In autumn 2017 all patients were invited to adhere to vaccination by letter addressed to their primary care physician. At the end of the vaccination campaign (January 2018), all patients were interviewed in order to assess adherence to vaccination; reasons for non-vaccination were investigated. A third strategy was employed for vaccination against pneumonia (Prevenar®): patients were informed and directly vaccinated in our unit in collaboration with the Vaccination Centre of our hospital.

Results: Among 1432 outpatients, indication for vaccination programs were given in 341 patients on immunosuppressive therapy, in 100 elderly patients, and 60 patients with both indications. Adherence to verbal invitation for influenza vaccination was low (19.6%), whereas written recommendation directed to primary care physicians did increase vaccination coverage (51.7%). Reasons for non-vaccinating were safety concerns in 65.5%, scepticism about efficacy in 22.3%, forgetfulness in 11.2%, and in 1% vaccination was discouraged by their primary care physicians. Direct proactive strategy vaccinating patients directly in our Unit yielded an 89.67% adherence to pneumococcus vaccination.

Discussion/Conclusion: Vaccination programs based on patients’ collaboration or collaboration by their primary care physicians yielded poor adhesion not. A proactive approach, providing directly the vaccination during outpatients visits reached a considerable success rate and should be offered in IBD centres.
Inflammatory bowel disease patients with detectable anti-infliximab antibodies have a high risk of acute infusion reactions to infliximab

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Introduction: Infliximab (IFX) represents the first effective biologic therapy introduced for the treatment of inflammatory bowel disease (IBD). Development of acute reactions after IFX infusions are associated with immunogenicity and detection of anti-IFX IgG antibodies (Ab) seem to increase the risk of acute infusion reactions.

Methods: The study included 65 patients with IBD (27 with ulcerative colitis and 18 with Crohn disease) evaluated at a tertiary center in North-East of Romania during 48 weeks of treatment with IFX. 35 patients received IFX induction therapy and 30 were on IFX maintenance therapy with mean treatment duration of 10 weeks. Anti-IFX IgG Ab (ELISA) were assessed prior to infusions at weeks 0, 2, 6, 14. Anti-IFX IgG Ab were considered detectable if titers were above 10 U/ml.

Results: During the follow-up, anti-IFX IgG Ab were detected in a total of 12 patients (18.4%) (in none of the patients at week 0, 2; in 5 patients at week 6 and in 12 patients at week 14). Anti-IFX IgG Ab were present in all patients with acute infusion reaction and in only 5 patients without acute infusion reaction to IFX (100% vs. 9.4%, p = 0.01). Patients with detectable Anti-IFX IgG Ab at week 14 had an increased risk of acute infusion reaction (relative risk [RR] = 5.58, 95% CI: 2.1–15.5; p < 0.0005) compared with patients without anti-IFX IgG Ab.

Discussion/Conclusion: Anti-IFX IgG Ab assessment can be used for detecting patients with high risk of acute infusion reaction.
STAT2 signals control the pathogenesis of colitis and intestinal wound healing in mice

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Introduction: Despite being identified over six decades ago, type I interferons remain incompletely understood vis-à-vis their role during chronic intestinal inflammation. A critical challenge stems from the fact that virtually every cell present in the gut can take part in the interferon response. Moreover, although the canonical signaling pathway of type I interferon signaling (STAT1:STAT2:IRF9) has been worked out in detail, recent data indicate that alternative signaling routes where STAT2 plays a more prominent role over STAT1 can take central stage during inflammatory responses. Inflammatory bowel diseases (IBD) are chronic, relapsing, aggravating disorders in which the intestinal homeostasis has been compromised by uncontrolled immune reactions against microbial and environmental cues in genetically predisposed individuals. Whereas STAT1 have recently emerged as a key modulator of intestinal homeostasis, the biology of STAT2 in this context awaits further clarification. We investigated the role of STAT2 in intestinal epithelial cells during IBD and intestinal mucosal healing.

Methods: Experimental colitis was induced in wild-type and in Stat2 knock-out mice. Disease development was followed using high-resolution mini-endoscopy and in vivo imaging. The direct effects of STAT2 signaling in primary intestinal epithelial cells were revealed by studies in three-dimensional intestinal epithelial organoid cultures coupled with RNA-Seq and gene ontology analysis. We employed a colonic wound healing mouse model to address the role of STAT2 signaling during intestinal mucosal restitution. Primary epithelial cells and biopsies from IBD patients were used to validate our findings in patients.

Results: STAT2 signaling was altered in IBD patients and mice with experimental colitis compared to controls. The interferon-induced phosphorylation of STAT2 was time- and dose-dependent in primary human and murine intestinal epithelial cells. Stat2 knock-out mice were more resistant to experimental colitis compared to wild-type controls and demonstrated enhanced mucosal restitution upon colon injury in vivo. In the three dimensional model of murine gut epithelial cell organoids, STAT2 signaling controlled the balance between cell survival and cell death signals. Stat2 knock-out organoids grew faster and were very resistant to cytokine-induced cell death as compared to wild-type organoids. Gene ontology analysis of RNA-Seq results from these experiments indicated that STAT2 signaling controlled sets of genes implicated in wound healing processes and the antimicrobial defense of the gut. We found that IL-20 could modulate the STAT2-dependent actions of type I interferon in gut epithelial cells.

Conclusions: Our present study indicates that type I IFN signals transmitted over STAT2 play critical roles during intestinal homeostasis by regulating the turnover of the gut epithelium and promoting epithelial cell death and inflammation. These results emphasize for the first time a possible use of STAT2 signaling modulators in future therapeutic approaches for IBD patients.

Keywords: experimental colitis; inflammatory bowel disease, wound healing; STAT2.
Inflammatory bowel disease and cardiovascular manifestations – Clinical case

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Introduction: Cardiovascular manifestations of inflammatory bowel disease (IBD) are considered rare. Patients with inflammatory bowel disease (IBD) have an increased risk of vascular complications.

Results: We present the case of a young female patient aged 34, from the rural environment, she admits herself to the emergency room “St. Spiridon” Hospital Iasi complaining about palpitations, deep physical asthenia, dyspnea on average effort, associated with diarrhea (4–7 episodes per day). On clinical examination, the skin and mucosa were pale, the abdomen was distended and tender, BP = 100/70 mmHg, ventricular allure = 90 beats/minute, rhythmic cardiac sounds, grade 3/6 aortic systolic murmur. The abdominal ultrasound examination revealed homogenous liver, with no other alterations. Echocardiography revealed serositis (with a thin layer of pericardium fluid displayed at 12 mm circumferential level), FE = 60%. An exploratory laparoscopy was performed and the macroscopic cobblestone was consistent with Crohn’s disease (CD). Induction therapy using intravenous corticosteroids was initiated and the overall outcome was favourable.

Conclusion: IBD associates multiple cardiovascular manifestations, included myocarditis, pericarditis, cardiac amyloidosis, arterial and venous thrombembolism, which can complicate the course of IBD and can lead to significant morbidity and mortality.
Evaluation of subclinical myocardial damage in patients with inflammatory bowel disease on treatment with biologics

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Introduction: Patients with inflammatory bowel disease (IBD) have an higher risk of cardiovascular disease (CVD) due to chronic inflammation. It has been suggested that inflammation leads to oxidative stress and to an increase in inflammatory cytokines leading to endothelial dysfunction and atherosclerosis. Biological therapies are the mainstay for the treatment of active IBD and can modify the disease activity and also the risk of CVD. The aim of the study is to assess the subclinical cardiac and vascular damage in IBD patients on treatment with biologics.

Methods: Pulse wave velocity (PWV), global longitudinal strain (GLS) and circulating CD34+ cells were evaluated to estimate subclinical cardiovascular involvement in 16 patients with IBD, before (T0) and after (T1) a six-months treatment with biologics (infliximab, adalimumab or vedolizumab). Carotid-femoral PWV was measured by routine methods. GLS was measured by speckle tracking echocardiography. Circulating CD34+ were counted by flow cytometry. In addition, markers of inflammation (ESR, CRP, fibrinogen) and EF% were also evaluated.

Results: At T1, no statistically significant differences were detected as regards ESR, PWV, EF with respect to T0. On the other hand, we have a statistically significant improvement of CRP (p = 0.013), GLS (p < 0.001) and CD34+ (p < 0.001) from baseline. The interdependence analysis performed on the mean percent changes showed a significant correlation between deltaPWV and deltaGLS: as deltaPWV decreases deltaGLS increases, improving ventricular performance.

Discussion/Conclusion: IBD patients have an increased risk of developing CVD, especially when IBD is uncontrolled. Biologics are effective reducing inflammatory status and symptoms/biological compensation, but also CV risk as suggested by favorable change in plasma levels of CRP, circulating levels of CD34+ and GLS values. Data on a larger cohort of patients is needed to confirm these preliminary results and to correlate biologics with improvement of CVD risk.
Fecal calprotectin, is it a good tool to assess response to treatment with TNF inhibitor?

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Introduction: The use of objective therapeutic targets to evaluate treatment efficacy in patients with Crohn's disease (CD) is recommended. Endoscopic mucosal healing is currently the reference, but its use in daily practice is limited by the low acceptability of repeated colonoscopies. Fecal biomarkers are an attractive alternative, including fecal calprotectin, whose reliability as a marker of mucosal endoscopic activity has been widely demonstrated. However, its sensitivity to change under treatment remains poorly evaluated to date. The objective of our study was to evaluate whether the measurement of fecal calprotectin after 12 weeks of treatment with anti-TNF was predictive of a clinical remission.

Methods: This retrospective study included adult patients with CD requiring anti-TNF therapy, with a Crohn's disease activity index (CDAI) > 150 and increased faecal calprotectin (> 100 μg/g). A fecal calprotectin assay was performed before treatment and at 12 weeks. Patients were treated with adalimumab or infliximab monotherapy or combination therapy. Clinical remission was defined as CDAI < 150 with normal CRP without therapeutic intensification and without surgical resection.

Results: A total of 35 patients with CD were included with an average age of 31.1 ± 11.5 years and a median duration of disease of 6 years [0.6–13.5]. There were 28.5% (10/35) of smokers, 17% (6/35) of patients with ano-perineal lesions and 20% (7/35) with a history of intestinal resection. The location of CD was ileal, colonic or ileocolonic in 28.5% (10/35), 11.5% (4/35) and 60% (21/35) of cases, respectively. The phenotype of the disease was inflammatory in 37% of patients (13/35), stricturing in 25.7% (9/35) and penetrating in 37.3% (13/35). 27 patients received an associated thiopurine (77%) and 4 patients (11.5%) corticosteroids. Median CRP and fecal calprotectin levels were 32.3 mg/l [5.2–95.4] and 1250.5 μg/g [247.6–3400.0], respectively. Median fecal calprotectin at week 12 was significantly lower (420.0 μg/g [215.0–1867.0] vs. 95 μg/g [50–123], p < 0.001) in patients with clinical remission. Using a ROC curve (AUC = 0.75), we determined that fecal calprotectin < 250 μg/g was the best predictor of at 1 year (Se = 81.5%, Spe = 72.7%).

Discussion/Conclusion: Fecal calprotectin seems to be a reliable marker for assessing the response to anti-TNF therapy in patients with CD.
Correlation between levels of C-reactive protein and clinical activity in Crohn’s disease

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Introduction: Crohn’s disease (CD) is characterized by flare-ups alternating with periods of remission. The assessment of CD activity is necessary when it comes to determining the therapeutic approach and to predicting the response to treatment. This assessment can be carried out using clinical disease activity indices. Other ways to measure CD activity are endoscopic and histological examination, accurate but invasive. Biochemical markers are widely used in clinical practice in CD to measure inflammation and evaluate disease activity. C-reactive protein (CRP), an acute phase reactant, is one of the most commonly used markers. Its value is often elevated in patients with severe disease. Several studies found a positive correlation between CRP levels and CD activity based on endoscopic, histological and radiological findings or clinical scores.

Aims: To determine the factors associated with an increased C-reactive protein level in Crohn’s disease patients and to look for a correlation between the C-reactive protein value and the Crohn’s disease activity index.

Methods: We prospectively studied 76 Crohn’s disease patients, 65% of whose disease was active at the time of inclusion. C-reactive protein measurement was carried out on all patients. An increased C-reactive protein level was defined as ≥ 5 mg/l.

Results: The median C-reactive protein rate was 45, 75 mg/l (ranging from 1 to 227 mg/l). An increased CRP was found in 41 patients (54%). A high CRP was observed in 63% of patients with active disease with a significant difference compared to those in remission.
By univariate analysis, severity of the flare, leukocyte and platelet count, albumin and Crohn’s disease activity index were found to be associated to elevated C-reactive protein values.
A statistically significant association between the Crohn’s disease activity index score and the C-reactive protein level was found in our study (p = 0.001). The optimal C-reactive protein threshold value that separates patients with moderate to severe disease (Crohn’s disease activity index > 220) from the others was calculated to be 19 mg/l with a sensitivity of 86.4% and a specificity of 66.2%.

Discussion/Conclusion: The C-reactive protein level is correlated to disease activity in Crohn’s disease. Its role seems to be essential in predicting moderate and severe disease activity.
The transcriptomic signature of IL-23 treated lamina propria mononuclear cells is significantly enriched for genes in the Th17 pathway and is overexpressed in active UC compared to inactive UC and healthy controls

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Introduction: Subunits of interleukin-23 (IL-23) and its receptor have been identified in IBD GWAs and functional pre-clinical studies to be a key cytokine in ulcerative colitis (UC). We hypothesised that an IL-23 induced transcriptomic signature in lamina propria mononuclear cells (LPMCs) which would be overexpressed in active vs. inactive UC and healthy controls (HC) and overexpressed in anti-TNFα non-responders vs. responders.

Methods: LPMCs were isolated from colonic biopsies obtained endoscopically from 5 patients with active UC and cultured in the presence or absence of IL-23 for 4 hours. Cells were lysed, RNA was extracted and RNA sequencing performed. Analysis of differentially expressed genes (DEGs) was performed between the untreated and IL-23 treated LPMCs using DESeq2. Using the filter p < 0.01 the DEGs underwent pathway analysis using Ingenuity Pathway Analysis (IPA). Association to clinical phenotypes was performed using Gene Set Variation Analysis (GSVA) enrichment scores in open access data sets of colonic biopsies from UC and HC. (GSE16879 HC = 6, UC = 24; GSE59071 HC = 11, inactive UC = 23, active UC = 74; GSE23597 anti-TNFα responders = 24, non-responders = 7).

Results: 112 DEGs were identified including IL22, IFNγ and IL17F which are downstream targets IL-23. Canonical pathway analysis demonstrated ‘Th17 activation’ pathway as the most significantly enhanced. GSVA enrichment scores using the ‘LPMC untreated vs. IL-23’ signature showed a significantly higher score in UC compared to HC in data set GSE16879 (p = 0.006). Furthermore there was significantly greater enrichment in active UC compared to inactive UC and HC in data set GSE59071 (p < 0.00001). However, GSVA enrichment scores calculated on colonic biopsies of patients with UC before commencing anti-TNFα therapy did not show a significant difference between responders and non-responders (dataset GSE16879 p = 0.07; dataset GSE23597 p = 0.1).

Discussion/Conclusion: The IL-23 induced LPMC transcriptomic signature is significantly overexpressed in active UC vs. inactive UC and vs. HC but not significantly overexpressed when comparing anti-TNFα responders vs. non-responders.
GPR35 engages with the sodium potassium pump and promotes intestinal epithelial cell proliferation and oncogenic signalling

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Introduction: Polymorphisms in the orphan G protein coupled receptor GPR35 are associated with increased risk for developing ulcerative colitis (UC) and primary sclerosing cholangitis (PSC), two inflammatory diseases with a high risk of malignant transformation. We studied GPR35 and its UC/PSC risk associated T108M coding polymorphism in order to elucidate its function.

Methods: An unbiased proteomics survey was used to identify protein interaction partners of GPR35. These were confirmed using fluorescence resonance energy transfer (FRET) and co-immunoprecipitation. Based on these findings, GPR35 function was assessed in macrophages and intestinal epithelial cells by rubidium up-take assay, metabolic flux analysis and western blotting. The T108M variant was studied by engineering the polymorphism into human induced pluripotent stem cells which were then differentiated into macrophages. Murine models of colorectal cancer were applied to study the effect of GPR35 on tumourigenesis. Small lipopeptides (pepducins) designed to specifically inhibit GPR35 signaling were then tested as potential therapeutic agents in these models.

Results: GPR35 was found to interact with the α chain of the sodium potassium pump (Na/K-ATPase) and promote its ion transport and Src signaling activity in a ligand-independent manner. Deletion of Gpr35 increased baseline Ca²⁺ to maximal levels and reduced Src activation and overall metabolic activity in macrophages and intestinal epithelial cells (IECs). In contrast, the T108M polymorphism was hypermorphic and had the opposite effects to Gpr35 deletion on Src activation and metabolic activity. GPR35 promoted homeostatic IEC turnover, whereas Gpr35 deletion or inhibition by a selective pepducin prevented inflammation-associated and spontaneous intestinal tumorigenesis in mice.

Conclusion: GPR35 acts as a central signaling and metabolic pacesetter via its interaction with Na/K-ATPase.
Common gene expression signature between Crohn’s disease and other fibrotic disorders reveals enhanced fibrotic pathophysiological pathways in terminal ileum

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Introduction: Fibrosis, a main characteristic of Crohn’s Disease (CD), is shared by various disorders. We cross-examined differentially expressed (DE) genes in CD and four other fibrotic disorders (FD): Idiopathic pulmonary fibrosis (IPF), systemic scleroderma (SSc), chronic kidney disease (CKD) and liver cirrhosis (LC) in order to identify common fibrotic signatures and to investigate tissue-specific processes.

Methods: Expression data from nine CD, two IPF, one SSc, one CKD and one LC microarray datasets (Gene Expression Omnibus) were examined independently, to avoid bias due to different experimental conditions, using bioinformatics analysis (GEO2R). Two separate groups (CDvsFD) were created containing combinations of datasets (SuperExactTest). These contained the significant (p < 0.05) DE genes from at least seven out of nine CD datasets and at least four out of five FD datasets. Their intersection provided a gene signature for pathway analysis (Reactome). Finally, network analytics and visualisation were applied to two tissue-specific, gene co-expression networks constructed by all the genes expressed on human terminal ileum and sigmoid (NetworkAnalyst) to detect and visualize differential clusters of function.

Results: Among all CD datasets, seven common DE genes were detected (CXCL1, ICAM1, PHLPP2, ZKSCAN1, ATP9A, NCF4, CACNA2D1). The intersection of at least seven out of nine CD datasets and at least four out of five FD datasets, showed 241 common DE genes contributing to 12 pathways associated with fibrosis and 17 with inflammation/immune response. Tissue-specific co-expression networks revealed 122/241 genes expressed on the terminal ileum and only 32/241 on the sigmoid. Regarding signalling pathways, nine fibrosis- and six inflammation-related ones were featured on terminal ileum, while only one fibrosis- and five inflammation-related on sigmoid.

Discussion/Conclusion: Our bioinformatics analysis highlights common molecular mechanisms among CD and fibrotic disorders as possible therapeutic targets and/or biomarkers and suggests that pathophysiological and fibrotic mechanisms behind tissue-specific CD progression are mainly located on terminal ileum.
The effects of the remission maintenance therapy in inflammatory bowel diseases on bone mineral density

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Introduction: We studied the relationships between the remission maintenance therapy in IBD and other parameters such as the bone mineral density (BMD) and the localization and activity of disease, BMI, duration of the therapy with steroids or immunosuppressant drugs, levels of the vitamin D deficiency.

Methods: We investigated 32 patients with IBD: 22 patients with UC and 10 patients with CD. The osteoarticular manifestations were clinical, radiological and biochemical investigated and IBD activity was monitoring by CDAI and Powell Tuck scores. BMD was measured by dual energy x-ray absorptiometry (DEXA) of the femoral neck and lumber spines.

Results: The incidence of osteoporosis was significant higher in UC patients (36.36%) comparative with CD patients (20%). The osteopenia was present more frequent in CD (20%). The rheumatic manifestations of UC patients were: pauciarticular peripheral arthropathies (7 cases), polyarticular peripheral arthropathies (3 cases) and only one patient was diagnose with ankylosing spondylitis. CD patients present polyarticular peripheral arthropathies in 2 cases (20%) and ankylosing spondylitis in one case.

We have not found a correlation between BMD and ages, gender or severity of IBD activity, but T-score was correlated with BMI values, C-reactive protein and hypocalcemia. Mean values of BMI was lower in patients with osteoporosis (17.88 ± 4.63 kg/m² in patients with T-score < -2.5 vs. 22.13 ± 6.51 kg/m² in IBD). Also, we not identified a relationship between maintenance therapy of IBD (azathioprine vs. infliximab) and BMD. History of long-term treatment with corticosteroids (in the last 3 years) was associated with less than minus -2.5 values of T-score. IBD patients with an abnormal BMD (15 cases) had a significantly higher rate of Vitamin D deficiency. The localization of IBD and values of clinical disease activity index (CDAI in CD and Powell Tuck Index in UC) were not significantly correlated with T-score, but osteoporosis was present more frequent in patients with CDAI > 150 or large extension of disease.

Discussion/Conclusion: The low BMD, common in remission maintenance therapy in both CD and UC was uncorrelated with the localization, duration and severity of disease. Though low BMI, vitamin D deficiency and long-term treatment with corticosteroids were independents risk factors for osteoporosis, therapeutic option for maintenance of the IBD was not corelated with T-score.
JAK1/3 inhibitor tofacitinib suppresses chronic intestinal inflammation and prolongs epithelial wound healing

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Introduction: Treatment of inflammatory bowel disease undergoes a change to newer agents, from monoclonal antibodies to small molecule drugs. Inflammatory mediators therefore present attractive targets for therapy. JAK1/3 inhibitor tofacitinib is a drug that modulates a panel of proinflammatory cytokines in human T cells, however, the therapeutic effect in colitis is unclear.

Methods: Here, we analysed the inhibitory effect of the JAK protein inhibitor on T cells from patients with ulcerative colitis. Furthermore, tofacitinib treatment was analysed in experimental colitis model and wound healing experiments. Additionally, tofacitinib effects were analysed in in vitro assays.

Results: Treatment of human LPMCs from ulcerative colitis patients with tofacitinib reduced numbers of T cells subsets. Moreover inflammatory cytokine levels in human PBMCs were reduced with tofacitinib. In experimental models, tofacitinib suppressed acute and chronic colitis compared to untreated wild-type mice. Therapeutic treatment with tofacitinib led to reduced numbers of T cells in the inflamed gut and less production of proinflammatory cytokines. Functionally, high dose application of tofacitinib induced apoptosis of intestinal epithelial cells and prolonged mucosal wound healing in vivo compared to low dose application. Thus, our findings suggest that low dose tofacitinib is quite effective in protecting colitis by inhibition of a bundle of cytokines like IL-5, -6, -9, -13 and -17A.

Discussion/Conclusion: A new inhibitory effect of high dose tofacitinib on epithelial cell survival was described that affected wound healing. Low dose application of tofacitinib emerges as an attractive concept for treatment of chronic intestinal inflammation whereas high dose treatment with tofacitinib needs attention due to prolonged wound healing. Our data suggest that specific JAK1/3 inhibition via tofacitinib offers an attractive concept for the future treatment of acute and chronic colitis via immunomodulation and suppression of proinflammatory cytokines in the inflamed mucosa.
Daily enteral nutrition supplements successfully maintain long-term remission in Crohn’s disease: A meta-analysis

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The aim of treatment in Crohn’s disease is to maintain long term remission without side effects of treatment and complications. This is a challenge in practice. Enteral nutrition (EN) is a safe short term treatment to induce remission but long term use data is lacking. A meta-analysis of long term use of EN was carried out. The search revealed 10 studies that met the inclusion criteria. Study periods ranged from 12–60 months with 415 patients given daily liquid enteral nutrition supplements. Out of the 415 there were 317 (76%) in remission at 1 year (p < 0.05 compared to placebo). Enteral nutrition was quite successful in maintaining remission in Crohn’s disease and its efficacy was comparable with immunomodulators.

Introduction: The maintenance of long term remission in Crohn’s disease (CD) without complications is our goal of treatment but is difficult to implement in practice. Enteral nutrition (EN) is a safe and effective short term therapy for induction of remission in CD. There are relatively few studies for long term intake of EN and it is not widely used in this way. This meta-analysis aims to provide stronger evidence by pooling of current data on daily intake of EN to maintain remission in CD.

Methods: A Medline, Ovid and Cochrane database search was carried out from the beginning to current date. We found published studies looking at the efficacy of enteral nutrition (providing up to 50% of daily calorie intake) for the maintenance of remission in paediatric CD. The search criteria were Crohn’s disease, enteral nutrition, maintenance therapy and children. Statistical analysis was done by Chi square test comparing EN to placebo for clinical response to treatment.

Results: Ten studies met the inclusion criteria. There were 4 prospective studies, 4 retrospective studies and 2 studies were randomised controlled trials. Study periods ranged from 12–60 months with 415 patients given daily liquid enteral nutrition supplements. Out of the 415 there were 317 (76%) in remission at 1 year (p < 0.05 compared to placebo). This compares quite favourably with 73% 1 year remission reported with immunomodulators and 62% with placebo (Chande N, et al. 2015).

Discussion/Conclusion: Enteral nutrition is quite successful in maintaining remission in Crohn’s disease. The efficacy of EN is comparable with immunomodulators, but without any of their side effects. However, taste and palatability can limit patients from drinking them and tube feeds may be required. The limitation of this meta-analysis is due to the small sample sizes of the individual studies and their slightly different study criteria. Further studies are needed to compare EN with other maintenance treatments such as biologics.
Crohn’s disease and active pulmonary tuberculosis – A clinical challenge

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Introduction: Crohn’s disease (CD) is an inflammatory disorder characterized by an inappropriate response of immune system. The abnormal host immune response of these patients in association with the immunosuppressive therapy increases the risk for infection.

Methods and results: We present the case of a 42-year-old female patient admitted in our hospital and diagnosed as case of intestinal obstruction. Exploratory laparotomy was performed and diseased resected segments (ileocolonic anastomosis) were confirmed as CD on histopathology. A thorough evaluation of active or latent infections was performed, and the patient was eventually started the anti-TNF therapy regime. Seven months later, the patient began having low-grade fever (37.4–38.0 °C), usually in the afternoon, fatigue, anorexia, productive cough, without respond to medical treatment. A new evaluation revealed a left pulmonary mass which proved to be active tuberculosis. Purified protein derivative tuberculin (PPD) test was strongly positive, and positive cultures for Mycobacterium tuberculosis confirmed the diagnosis. The anti-TB treatment with isoniazid, rifampicin, streptomycin and ethambutol was initiated and shortly after, clinical evolution was worsened by persistent diarrhea (> 20 stools/day), weight loss (10 kg), and mushy stool that occasionally contained mucus, accompanied with periumbilical and the right abdominal dull pain, resulting in developing of malnutrition syndrome due to the side effects of the medication. The intravenous method proved effective and lead to resolution of TB infection.

Discussion/Conclusion: A good interdisciplinary collaboration results with well outcome of patient with resolution TB infection and reduction of CD’s activity. Treatment for TB, if suspected, should be empirically instituted with a full course of anti-TB agents.
Ulcerative colitis patients show a decreased frequency of circulating GPR15+ innate lymphoid cells

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Introduction: The functional characterization of innate lymphoid cells (ILC) in IBD still remains incomplete. A recent study postulated that circulating human ILC precursors are able to migrate into tissue and differentiate in response to local signals (Lim et al. Cell. 2017). This concept might, at least partly, explain the described phenomenon of accumulated ILC subsets in the intestine of IBD patients.

Methods: ILC (lin\textsuperscript{neg} CD127\textsuperscript{+} CD7\textsuperscript{+} lymphoid cells) from the blood or gut tissue of IBD patients or healthy controls were characterized by flow cytometry.

Results: Compared to healthy controls, circulating ILC in IBD patients showed a significantly decreased frequency of the CD117\textsuperscript{+} CRTH2\textsuperscript{neg} CCR6\textsuperscript{neg} subgroup, which shows an ILC precursor-like surface marker profile. In contrast, the systemic fractions of CD117\textsuperscript{+} CRTH2\textsuperscript{neg} CCR6\textsuperscript{+} ILC and ILC2 were unaltered; and the frequency of ILC1 was even increased in UC patients. Only low numbers of CD117\textsuperscript{+} CRTH2\textsuperscript{neg} CCR6\textsuperscript{neg} ILC could be detected in the intestinal mucosa. However, inflamed gut areas of UC patients showed a tendency towards an increased frequency of this precursor-like ILC subset compared to non-inflamed areas. These findings implicate a relevant migration of systemic ILC precursors into the inflamed colonic mucosa of UC patients. Interestingly, a marked frequency of systemic human ILC expressed the colon homing marker GPR15 (healthy controls; mean ± SEM: 24.6% ± 4). However, the GPR15 expression in systemic ILC turned out to be significantly decreased in UC patients. Particular analyses of the reduced fraction of precursor-like ILC in the blood of UC patients also indicated a significantly decreased frequency of GPR15\textsuperscript{+} cells compared to healthy controls, while the expression of beta7 or alphaE integrins was low, but remained stable.

Discussion/Conclusion: Our data support the idea that circulating GPR15\textsuperscript{+} ILC precursors preferentially home into the inflamed colonic mucosa of UC patients in order to undergo local maturation.
Ulcerative colitis: Presentation of 21 observations in a Sub-Saharan Africa hospital

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Introduction: The aim of our study was to determine the socio-demographic, diagnostic and therapeutic aspects of ulcerative colitis (UC) in the Gastroenterology Department of one large hospital in Sub-Saharan Africa.

Methods: This was a retrospective, descriptive study of all UC cases in the Gastroenterology Unit between January 2013 and June 2018. The diagnosis was based on suggestive clinical and endoscopic arguments with a compatible histological aspect. Clinical, biological, endoscopic and histological data were collected, as well as treatment options.

Results: We observed 21 cases, representing a prevalence of 0.87% of inpatients. The mean age of patients was 36 (ranged 18–73) and sex ratio 0.9 (11 females). The mean diagnostic delay was 2.6 years (ranged 4 months to 5 years). The clinical symptomatology was dominated by diarrhea with blood and mucus presence (18 cases). The Litchiger score at admission was 8 on average. Biological inflammatory syndrome was observed in 15 cases (71.4%). During endoscopy, the lesion topography according to the Montreal classification was as follows: 8 cases of E3 (38%), 10 cases of E2 (47.6%). The severity of these lesions was variable with 11 patients (52.4%) at stage 2 of Mayo endoscopic score and 7 patients at stage 3 (33.3%). Extra-digestive manifestations were observed in 9 patients (42.8%). They were mainly articular, cutaneous and hepatobiliary. On the therapeutic side, the step-up strategy was used for all patients. Two cases of death were observed (9.5%): the first in a context of toxic megacolon and the second following a hepatic encephalopathy complicating a PBC at the stage of cirrhosis.

Discussion/Conclusion: UC in Sub-Saharan Africa mainly concerns young adults with a slight predominance of women. The diagnosis is often late. The absence of biotherapy requires close collaboration with surgeons for the management of severe forms.
Is misdiagnosis of Crohn’s disease as ulcerative colitis still possible?

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Introduction: The differential diagnosis of Crohn's disease and ulcerative colitis remains difficult as the clinical symptoms of the 2 digestive diseases are similar. Here we report a case where a patient was initially misdiagnosed with ulcerative colitis.

Results:
Case: The 20-year-old male patient was hospitalized for abdominal pain and bloody diarrhea. Colonoscopy revealed fragile mucosa with exudates all through the colon without any skip areas and the pathological diagnosis was ulcerative colitis and the patient was administered prednisolone therapy for 30 days. However the symptoms did not improve. The patient was readmitted to the hospital because of the increase in the number bloody defecation. A computed tomography scan revealed intestinal wall thickening all through the colonic segments. Infliximab was administered. There was not a clinical and biochemical response at the end of the drug induction period. In the second month, the biologic agent was switched to vedolizumab. There was a slight improvement in the clinical symptoms at the beginning, however, deterioration was seen in the second month of the vedolizumab treatment. The patient was diagnosed as medical treatment unresponsive severe ulcerative colitis with a malnutrition status. Ileal pouch anal anastomosis was planned with three stages. During the first operation, ileum and jejunum walls were macroscopically attached to colon serosa, this warned the surgeon for a misdiagnosis and colectomy and ileostomy were completed. Crohn’s disease was diagnosed in the colectomy specimen. The patient’s symptoms improved rapidly after the surgery. However, the management plan changed, pouch formation was canceled and intestinal diversion was thought to be therapeutic for the residual rectal mucosa. After a period of time, the patient will be evaluated for ileal rectal anastomosis or permanent ileostomy.

Discussion/Conclusion: Eventhough the diagnostic modalities have improved in the recent years in inflammatory bowel disease, there still a place for misdiagnosis which would influence morbidity and mortality rates. In conclusion, patients who are not responding to medical treatments with the development of malnutrition status must be carefully evaluated for other possible diagnosis and the surgery should be planned as three-stage procedure.
**Colonization by *Escherichia coli* Nissle 1917 ameliorates DSS-induced experimental colitis in gnotobiotic mouse model**

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**Aim:** The effect of *E. coli* strains colonization on the development of acute ulcerative colitis (UC) induced by dextran sulfate sodium (DSS) was studied in gnotobiotic mice.

**Methods:** Two-month-old germ-free (GF) BALB/c females were used. Experimental colitis was induced by administration of 2.5% DSS in drinking water for 7 days. At first, originally germ-free mice monoassociated by *E. coli* Nissle 1917 were after weaning (day 21) reassociated by uropathogenic *E. coli* O6K13. At second, originally germ-free mice monoassociated by *E. coli* O6K13 were reassociated after weaning by *E. coli* Nissle 1917. Both groups were administered by DSS. Clinical symptoms – diarrhea, bleedings and enteric rectal prolapse were controlled. Colon morphology, mucin production and tight junction proteins (occludin, claudins, zonulin) were evaluated. The level of cytokines was determined in supernatant of cultivated intestinal pieces of colon descendens. Production of myeloperoxidase (MPO) was determined in colon tissue.

**Results:** Mice monoassociated with *E. coli* Nissle 1917 strain and thereafter re-associated by *E. coli* O6K13 strain developed lower degree of intestinal inflammation in colon than conversely associated group. In this group, tight junction proteins were protected and the level of pro-inflammatory cytokine TNF-alpha and IL-6 production in colon was reduced markedly compared to second experimental group.

**Conclusion:** We conclude that *E. coli* Nissle 1917 colonization protects mice against intestinal inflammation induced by *E. coli* O6K13 strain in DSS model of ulcerative colitis.

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Thiopurine adverse events in patients with inflammatory bowel disease in the United Kingdom IBD BioResource cohort

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Introduction: The inflammatory bowel disease (IBD) BioResource is recruiting patients with Crohn’s disease (CD), ulcerative colitis (UC) or IBD type unclassified (IBDU) from 89 hospitals UK-wide; > 19,000 subjects have been recruited to date. Data have been collected on disease phenotype, treatment, adverse events and treatment response.

Aim: To describe the prevalence of adverse events related to thiopurine exposure among the IBD BioResource cohort.

Methods: A descriptive, retrospective analysis of the IBD BioResource database has been performed to determine the incidence of short and long-term adverse events related to the use of thiopurines in the treatment of inflammatory bowel disease. All patients who have had exposure to thiopurine therapy (azathioprine or 6-mercaptopurine) were included.

Results: 10,092 (57.8%) patients within the IBD BioResource cohort have had some exposure to thiopurine therapy during their disease course, either as monotherapy or in combination with anti-TNF.

9480 patients (94.0%) have been treated with azathioprine (AZA) and 2335 patients (23.1%) have been treated with 6-mercaptopurine (6MP). Of the 9480 patients who have been treated with azathioprine, 4167 patients (44.0%) remain on this therapy. 2369 patients (24.9%) ceased azathioprine due to adverse events. 1723 of the 2335 (73.8%) patients treated with 6MP had previously been treated with AZA and been intolerant. 684 patients (29.3%) ceased 6MP due to adverse events.

The most commonly reported adverse events were nausea and vomiting (9.6%), followed by deranged liver function tests (5.1%), non-specified patient intolerance (2.4%), flu-like symptoms (2.3%) and abdominal pain (2.3%). The incidence of clinically serious side effects was low. Pancreatitis was reported in 2.2% of patients; and leukopenia (total WCC < 3 or neutrophil count < 2) was seen in 379 (3.7%). 83 (0.8%) patients developed lymphoma after a mean of 2.9 years on thiopurine treatment. 27/83 were also on anti-TNF.

Conclusion: We report a large, real world series of patients with IBD treated with azathioprine or 6MP. Thiopurines were ceased due to side effects in 25.1% of patients overall. The incidence of adverse events with 6MP was only modestly higher than in those treated with azathioprine, despite 73.8% having been previously treated with azathioprine. Serious clinical adverse events related to thiopurine exposure were observed but at low frequency.
Efficacy of thiopurine monotherapy in the UK Inflammatory Bowel Disease BioResource cohort

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Introduction: IBD BioResource is currently recruiting patients with Crohn’s Disease (CD), Ulcerative Colitis (UC) and IBDU from 83 hospitals UK-wide. To date > 19,000 patients have been recruited with detailed clinical phenotype data plus serum and DNA, and all will have had Genome-Wide Association Scans ± whole genome sequencing by April 2019. They can be recalled by genotype or phenotype for downstream studies by any investigator.

Thiopurines play a key role in the management of IBD – used either as monotherapy or in combination with other treatments to maintain remission. However, data regarding long term effectiveness are sparse.

Aims: To characterise the long term effectiveness of thiopurine monotherapy among subjects in the IBD BioResource cohort.

Method: IBD phenotype data were extracted by research nurses and clinicians in each hospital site following case note review and uploaded to a Redcap database. Response to treatment was empirically classified as ‘effective’, ‘not effective’, and 5 other categories (‘transient’, ‘partial’, ‘intolerant’ etc.). We sought to identify the proportion of patients in whom thiopurine was effective as monotherapy – in whom (1) treatment was classified as ‘effective’ and (2) there had been no escalation to biologic therapy or need for surgery for the duration of thiopurine therapy. Patients started on anti TNF therapy at thiopurine initiation or undergoing surgery within 1 year prior to thiopurine initiation were excluded since we could not comment on the efficacy of monotherapy.

Results: Data were available on 8296 IBD BioResource subjects (48.3% male) who had been treated with a thiopurine. In 2417 patients (29.1%) thiopurine monotherapy had been deemed to be an effective maintenance treatment – meeting both criteria (1) and (2) above. Long-term effectiveness was higher in UC/IBDU (1531/3485; 43.9%) compared to CD (883/4799; 18.4% – χ² p < 0.0001). 3459/8296 (41.7%) treated with thiopurine were started within 1 year of diagnosis (Fig. 1). Mean duration on drug = 5.9 years (at least 78% of those in whom thiopurine monotherapy has been effective are still on this therapy).

Conclusion: Thiopurines can be effective in producing durable long term remission, particularly in UC. Pharmacogenetic studies will follow. The IBD BioResource is open to all investigators for recall of well characterised patient cohorts.
Fig. 1

Time (years) from diagnosis to thiopurine initiation
Prophylactic effect of *Clostridium tyrobutyricum* on the development of acute intestinal inflammation induced by dextran sulfate sodium. Differential regulation of TNF-α and IL-18 in BALB/c and SCID mice

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One of the promising approaches in the therapy of IBD is administration of butyrate, an energy source for colonocytes, into the lumen of the colon.

**Aim:** The aim of the study was to investigate the effect of butyrate producing bacterium *Clostridium (C.) tyrobutyricum* on dextran sulfate sodium (DSS) induced colitis in mice.

**Methods:** Two-month-old immunocompetent BALB/c and immunodeficient SCID mice reared in specific-pathogen-free conditions were treated intrarectally with live *C. tyrobutyricum* one week prior to the induction of DSS colitis and during oral DSS treatment. Clinical symptoms as changes in body weight, bleeding and rectal prolapse were evaluated. Mucin production, tight junction protein ZO-1 expression, the level of TNF-α and IL-18 were evaluated by ELISA and confocal microscopy. Study was completed by determination of short chain fatty acids in feces of mice by gas chromatography.

**Results:** Intrarectal administration of *C. tyrobutyricum* prevented appearance of clinical symptoms of DSS-colitis, restored normal MUC-2 production and did not change expression of TJ protein ZO-1. The production of IL-18 was dependent on immunocompetency of mice. *C. tyrobutyricum* treatment lead to decrease of TNF-α and IL-18 level in the descending colon of both SCID and BALB/c mice strains. Three-fold increase of n-butyric acid level and two-fold increase of propionic acid level were found in *C. tyrobutyricum*-DSS-treated SCID mice when compared with saline-DSS-treated mice.

**Conclusion:** This study demonstrates that in the DSS model, the severity of inflammatory symptoms depends largely but not exclusively on host immune functions. Thus, *C. tyrobutyricum* protection against destruction of mucosal barrier is equally effective in immunodeficient SCID mice and immunocompetent BALB/c mice. Manifestation of cytokines IL-18 and TNF-α in acute DSS-colitis depends largely on immune cell composition of the mouse host. (Supported by grant 19-08294S of the Czech Science Foundation).
Inflammatory infiltration of CD15-positive cells in endoscopic material of ulcerative colitis and Crohn’s disease patients

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Introduction: The expression of the cell adhesion molecule CD15, also known as Lewis x, was localized on granulocytes and was linked with differentiation of myeloid cell line. CD15-positive cells take part in phagocytosis and chemotaxis. Due to those properties and the significance role of inflammatory cell in the development of ulcerative colitis (UC) and Crohn’s disease (CD), we try to analyze the insensitivity infiltration and the classification of CD15+ cells.

Materials and method: The study group included 34 patients with ulcerative colitis and 8 patients diagnosed with Crohn’s disease. The expression of CD15 was performed by immunohistochemistry and assessed as the membrano-cytoplasmic color reaction in 3 groups of inflammatory cells (percentage of each cells): neutrophils, macrophages and lymphocytes. We also explored the insensitivity of general CD15-positive cells and grouped into 1 – weak, 2 – moderate and 3 – strong.

Results: The group of study consists of 16 female and 18 male in UC, and 2 female and 6 male of CD. The UC lesions were mainly localized in rectum (19/34 cases), sigmoid (8/34 cases) and other (7/34 cases). The Crohn’s disease were observed in small intestine (3/8 cases), caecum (4/8 cases) and rectum (1/8 cases). The infiltration of inflammatory CD15+ cells in UC were weak in 8 cases, moderate in 19 cases and strong in 7 cases. CD15+ lymphocytes were significantly differ in UC and CD (p = 0.040). Neutrophils expressed CD15 antigens were observed in 24 cases in UC as more than 50% of all CD15+ cells. Inflammatory CD15+ macrophages and lymphocytes were showed in 30 and 33 cases as less than 50% of all CD15+ cells. Moreover, those cells also correlated with Geboes score (p = 0.005, p = 0.001, respectively). Infiltration of CD15+ neutrophils and lymphocytes in CD was correlated with localization (p = 0.019, p = 0.022).

Conclusion: Our results showed that infiltration of CD15-positive cells are closely associated with disease activity and localization, and may help to understand inflammatory cell organization in inflammatory bowel disease.
Contrast-enhanced µCT for visualizing and evaluating murine intestinal inflammation

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Aim: To develop a simple and fast method for visualizing and analyzing acute and chronic experimental intestinal inflammation using contrast-enhanced µCT.

Methods: Two colitis models, acute 2% and 3% dextran sodium sulfate (n = 15, female, 8–12 weeks) and a chronic adoptive transfer colitis model (n = 10, female, 8–9 weeks) were established over 9 days or 6 weeks, respectively. Longitudinal measurement of murine intestinal wall thickness and time dependent perfusion was performed on a small animal µCT system (90 kV, 160 µA, FOV: 60 mm, scan time: 17 s, image size: 512 x 512, layer thickness: 118 µm) between 0.5 and 30 min after intravenous bolus injection of an iodine contrast agent. For comparison with contrast-enhanced µCT-imaging findings, weight development, small animal endoscopy, and histological ex vivo analysis were also assessed throughout the experiments.

Results: Murine intestinal wall thickness was significantly increased in inflamed colons of acute colitis at day 9 compared to pre-inflamed state. Perfusion analysis showed a significant remaining contrast enhancement in acute inflamed colons after 20–30 min and the renal medulla at day 9 compared to control mice. In chronic colitis model, an increasing intestinal wall thickness was monitored after 3, 5 and 6 weeks in comparison to control group. A good correlation with endoscopic (r = 0.75, p < 0.0001) and histologic degree of inflammation (r = 0.83, p = 0.04) was found.

Conclusion: Contrast-enhanced µCT is a simple and fast method to visualize and analyze acute intestinal inflammation and to monitor disease progression in experimental models of chronic colitis. According to our findings, one single contrast-enhanced µCT-scan is a valid non-invasive modality to evaluate the degree of colitis in murine inflammatory models.
Pathophysiological roles of plasmacytoid dendritic cell migrating to colonic isolated lymphoid follicles in a murine experimental colitis

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Introduction: Plasmacytoid dendritic cells (pDCs) are involved in the development of autoimmune diseases and inflammatory diseases. Recently, it has been reported that pDCs accumulate in the colon of IBD patients, and the depletion of pDCs alleviates the development of DSS colitis. However, the role of pDCs in the progression of colonic inflammation remains unclear. We have demonstrated suppressive effects of astragaloside-IV (As-IV) and oxymatrine (Oxy) on CCL21-induced pDC migration in vitro and DSS colitis in vivo. Nevertheless, a number of pDCs in the colonic lamina propria (LP) of DSS colitis mice was not affected by As-IV or Oxy. Therefore, we investigated how pDCs migrate in the colonic LP to elucidate their pathophysiological role.

Methods: Matured bone marrow-derived pDCs (BMpDCs) stained with CFSE were transferred into BALB/c mice and then the recipient mice were treated by As-IV (50 mg/kg), Oxy (100 mg/kg) or vehicle. BALB/c mice were given 3% DSS in drinking water for 7 days for acute colitis model. As-IV or Oxy were also given to DSS colitis mice.

Results: In pDC adoptive transfer model, BMpDCs (CFSE+ cells) were largely distributed in both the lateral and inner sites of the isolated lymphoid follicles (ILFs) of vehicle-treated mice, while BMpDCs were distributed in the lateral site of the ILFs of As-IV or Oxy-treated mice. The number of BMpDCs migrated to the ILFs was significantly decreased in As-IV or Oxy-treated mice. In DSS colitis model, pDCs (CD11c+B220+ cells) were almost located in the inner site of the ILFs. However, pDCs were located in the LP and the lateral site of the ILFs in the colitis mice treated with As-IV or Oxy.

Discussion/Conclusion: These findings indicate that pDC migration to the ILFs contributes to the development of the colitis. Suppressor of pDC migration has a therapeutic potential against colonic inflammation and colitis.
Colorectal cancer development is driven by STAT3 activation through IL-6 and IL-11 in cancer-associated fibroblasts and correlates with prognosis of CRC patients

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Introduction: Cancer-associated fibroblasts (CAFs) can influence the tumor microenvironment (TME) and the growth of tumors. However, the role of CAFs in the development of colorectal cancer (CRC) is incompletely understood.

Methods: We quantified the pSTAT3 expression in CAFs of human colon cancer tissue using a tissue microarray of 375 colon cancer patients, immunofluorescence staining and digital pathology. Emerging imaging technologies (light sheet fluorescence microscopy, raster-scanning-optoacoustic mesoscopy, multiphoton microscopy) were used to evaluate the in situ distribution of CAFs in COLVI reporter mice. We performed a comparative gene expression profiling by whole genome RNA-sequencing of fibroblast subpopulations (COLVI+ vs. COLVI-) upon STAT3 activation under different conditions (IL-6 vs. IL-11). Moreover, in loss- and gain-of function experiments using genetically modified mice with COLVI-specific STAT3 targeting we evaluated the role of STAT3 signaling in fibroblasts during colorectal development.

Results: The analysis of pSTAT3 expression in CAFs of human colon cancer tissues revealed a negative correlation of increased stromal pSTAT3 expression with the survival of colon cancer patients. In the loss- and gain-of function approach we found a critical role of STAT3 activation in fibroblasts during colorectal tumorigenesis in vivo. The comparative gene expression profiling of fibroblast subpopulations upon STAT3 activation revealed the regulation of transcriptional patterns associated with fibroblast activation, cytokine signaling and angiogenesis. The blockade of pro-angiogenic signaling significantly reduced colorectal tumor growth in mice with constitutive STAT3 activation in COLVI+ fibroblasts.

Discussion/Conclusion: In conclusion, our work demonstrates a critical role of STAT3 in CAFs in CRC, suggesting that strategies interfering with STAT3 activation in CAFs or its downstream signaling might evolve as future therapeutic targets in CRC.
Dynamics of the level of cytokines tissue of the intestinal mucosa after administration of infliximab and mesenchymal stromal cells

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One of the new promising methods of treatment of ulcerative colitis (UC) is biological therapy using bone marrow mesenchymal stromal cells (MSC). Under the influence of MSC, the imbalance of serum immunoglobulins and cytokines is corrected. However, little has been studied the dynamics of pro- and anti-inflammatory cytokines of the intestinal mucosa under the influence of MSC.

Objective: To determine changes in the level of pro- and anti-inflammatory cytokines in the mucous of the colon (MC) after MSC, infliximab (IFX) and systemic glucocorticosteroids (GCS).

Materials and methods: 96 patients with UC were divided into three groups. The first group of patients aged from 19 to 58 years (Me-29) (n = 36) received anti-inflammatory therapy with the use of the culture of 2 million MSCS/kg. The second group of patients with UC (n = 30) aged from 23 to 60 years (Me-31) received the IFLA in accordance with the recommended scheme. The third group of patients with UC (n = 30) aged 20 to 66 years (Me-36) received GCS. MC biopsy in patients of groups 1, 2 and 3 was performed before and 2 months after appropriate treatment. The content of TNF-α, INF-γ, IL-4 was determined in extracts of the colon mucosa by enzyme immunoassay. The initial level of INF-γ in the 1st group was 1207.6 ± 125.3 pg/tissue levels of TNF-α – 358.67 ± 38.1 pg/tissue level of IL-4 – 541.6 ± 43.7 pg/tissue; in the 2nd group the initial level of INF-γ made up 976.67 ± 101.46 pg/tissue levels of TNF-α – 675.84 ± 76.2 pg/tissue level of IL-4 – 214.8 ± 22.6 pg/tissue; in the 3rd group the initial level of INF-γ made up 237.6 ± 30.1 pg/tissue levels of TNF-α – 251.6 ± 24.6 pg/tissue level of IL-4 made 244.8 ± 23.5 pg/tissue.

Results: In the 1st group of patients with UC 2 months after therapy TNF-α significantly decreased from 358.67 ± 38.1 pg/g tissue to 187.67 ± 18.9 pg/g tissue, INF-γ – from 1207.6 ± 125.3 pg/g tissue – to 499.2 ± 50.2 pg/g tissue (p < 0.05); IL-4 – from 541.6 ± 43.7 to 312 ± 29.8 pg/g tissue (p < 0.05).

In group 2 after therapy TNF-α level decreased to 122.7 ± 10.7 pg/g of tissue, the level of INF-γ decreased to 534.5 ± 48.9 pg/g of tissue (p < 0.05), the level of IL-4 – before treatment was 214.8 ± 22.6 pg/g of tissue; after – 593.54 ± 49.97 pg/g of tissue.

In the 3rd group of patients, TNF-α prior to commencement of active therapy in exacerbation of the disease was 251.6 ± 24.6 pg/g tissue after 2 months of treatment – 418.2 ± 35.2 ng/g tissue (p < 0.05), INF-γ before the start of therapy was 237.6 ± 30.1 pg/g tissue; after 2 months since start of therapy left – 707.6 ± 72.5 pg/g tissue (p < 0.05); IL-4 has changed from 277.2 ± 24.6 ng/g tissue to 400.4 ± 39.8 pg/g tissue (p < 0.05).
Conclusion: Under the influence of MSC there is a gradual decrease in the level of proinflammatory cytokines – INF-γ, TNF-α to 2 months of observation. The level of anti-inflammatory cytokine – IL-4 after the introduction of MSC also decreased, which may be due to the balance of pro- and anti-inflammatory cytokines as the inflammatory activity decreases.
The effectiveness of combination therapy mesenchymal stromal cells and certolizumab pegol in perianal lesions in Crohn’s disease

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Perianal fistulas are common types of fistulas in Crohn's disease (CD). They are difficult to treat, worsen the quality of life of the patient and increase the risk of intestinal resection. Despite the significant effect of anticytokine therapy of fistula form of CD, treatment of this category of patients remains a difficult task, with a high risk of relapse of CD. Mesenchymal stromal cells (MSC), which have immunomodulatory properties and high regenerative potential, are currently also used for the treatment of fistula CD and perianal fistulas of other etiology.

Objective: to compare the effectiveness of combined therapy (local and systemic administration) of bone marrow MSC, the effectiveness of combined therapy of MSC (local administration) and certolizumab pegol (CZP) according to the scheme and monotherapy of CZP according to the scheme of the frequency of healing of simple perianal fistulas in CD.

Materials and methods: 54 patients with CD with perianal lesions were divided into three groups depending on the method of therapy. The first group of patients aged 19 to 58 years (Me-29) (n = 18) received the culture of MSC systematically according to the scheme and locally: 40 million MSC – 4 injection points of 1 ml of physiological solution containing 10 million MSC were administered along the perimeter of the fistula. Then, after 4 and 8 weeks, 40 million MSC were re-introduced into the fistula area. The second group of patients with CD (n = 18) aged 20 to 68 years (Me-36) received MSC locally and anticytokine therapy with CP according to the scheme. The third group of patients with CD (n = 18) aged 20 to 62 years (Me-28) received anticytokine therapy for CZP according to the scheme. The dynamics evaluated the complete closure of the external opening of the fistula. Ano-and rectosigmoscopy was performed 2, 6 and 12 months after the start of therapy.

Results: After 2 months in the 1st group of patients the healing of simple fistulas was observed in 7/18 (38.9%), in the 2nd group the healing of simple fistulas in 14/18 (77.8%) (OR = 5.5; 95% CI: 1.28–23.7; p = 0.043 in comparison with the 1st group) and in the 3rd group in 6/18 patients (33.3%) (OR = 0.26; 95% CI: 0.07–0.97; p = 0.019 in comparison with the 1st group).

After 6 months in the 1st group receiving MSC, the healing of simple fistulas persisted in 6/18 (33.3%), in the 2nd group in 14/18 (77.8%) (OR = 7.0; 95% CI: 1.59–30.8; p = 0.019 in comparison with the 1st group) and in the 3rd group in 5/18 patients (27.8%) (OR = 9.1; 95% CI: 1.99–41.45; p = 0.008 in comparison with the 2nd group).

After 12 months in the 1st group receiving MSC, the healing of simple fistulas persisted in 8/18 (44.4%), in the 2nd group in 15/18 (83.3%) (OR = 6.2; 95% CI: 1.33–29.43; p = 0.038 in comparison with the 1st group) and in the 3rd group in 7/18 patients (38.9%) (OR = 7.857; 95% CI: 1.65–37.4; p = 0.017 in comparison with the 1st group).
**Conclusion:** Combined cell and anti-cytokine therapy of CD with perianal lesions promotes more frequent and prolonged closure of simple fistulas, compared to MSC monotherapy and CZP monotherapy.
Macrophage IL-10 signaling is required for the therapeutic efficacy of anti-TNF in IBD

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Introduction: Macrophage IL-10 signaling plays a critical role in the maintenance of a regulatory phenotype that prevents the development of inflammatory bowel disease (IBD). We have previously found that anti-TNF monoclonal antibodies act through Fcγ-receptor (FcγR) signaling to promote repolarization of proinflammatory intestinal macrophages to a CD206+ regulatory phenotype. The role of IL-10 in anti-TNF induced macrophage repolarization has not been examined.

Methods: We used human peripheral blood monocytes and mouse bone-marrow-derived macrophages for studying IL-10 production and CD206+ regulatory macrophage differentiation. To determine whether the efficacy of anti-TNF was dependent on IL-10 signaling in vivo and in which cell type we used the CD4+CD45Rbhigh T-cell transfer model in combination with several genetic mouse models.

Results: Anti-TNF therapy increased macrophage IL-10 production in an FcγR dependent manner in vitro and in vivo, which caused differentiation of macrophages to a more regulatory CD206+ phenotype in vitro. Pharmacological blockade of IL-10 signaling prevented the induction of these CD206+ regulatory macrophages and diminished the therapeutic efficacy of anti-TNF therapy in the CD4+CD45Rbhigh T-cell transfer model of IBD. Using cell type specific IL-10 receptor mutant mice we found that IL-10 signaling in macrophages but not T-cells was critical for the induction of CD206+ regulatory macrophages and therapeutic response to anti-TNF.

Discussion/Conclusion: The therapeutic efficacy of anti-TNF in resolving intestinal inflammation is critically dependent on IL-10 signaling in macrophages.
Protective effect of *Bifidobacterium longum* spp. *longum* on the development of DSS-induced colitis in mice is strictly strain dependent

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Probiotic bacteria have been proposed for prevention and/or treatment of inflammatory bowel diseases. However, comparative studies of well-characterized strains of the same subspecies for specific health benefits are scarce. Here we compared two *Bifidobacterium longum* spp. *longum* strains for their capacity to prevent dextran sulfate sodium-induced experimental colitis in a mouse model. Nine probiotic candidates – bifidobacterial human isolates – were cultivated with mouse splenocytes and we determined the induced cytokine profile. Based on the different pattern of cytokine induction two *B. longum* spp. *longum* (Bl) strains were selected and they were further analyzed using bone marrow-derived dendritic cells (DC) and human embryonal kidney cells transfected by pattern recognition receptors. We found that cytokine production induced by bifidobacteria is not only species but also strictly strain dependent. Bl 372 induced higher levels of both pro- and anti-inflammatory cytokines in naive splenocytes or DC compared to Bl 7952. Both strains engaged TLR2 receptor but Bl 372 signalization through NOD2 was stronger compared to Bl 7952. In mouse model of DSS-induced colitis, Bl 7952, but not Bl 372, reduced clinical symptoms and preserved expression of tight junction proteins. We conclude that rigorous characterization and careful selection of probiotic strains is crucial in providing beneficial outcome in clinical trials with probiotics in IBD. (Supported by grants 19-02261S and 19-08294S of the Czech Science Foundation).
The functional role of VEGF-R in CD4\(^+\) T cells during the pathogenesis of colorectal cancer

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Introduction: The induction of angiogenesis and tumour angiogenesis are predominantly driven by the vascular endothelial growth factor (VEGF) and its cognate receptor VEGFR-2 [1]. Consequently these two proteins play an important role in the proliferation and survival of tumour cells, which in turn makes them a candidate for targeting cancer [2]. It has been previously shown that anti-VEGF therapy in combination with chemotherapy leads to prolonged overall survival in patients suffering from colorectal cancer (CRC) [3]. But drawbacks of this therapy are that some patients do not respond at all to the therapy or develop secondary resistance [4]. Furthermore VEGF not only impacts the behaviour of endothelial cells but also various types of immune cells, such as T cells, which are essential for the anti-tumour immune response.

Methods: In order to evaluate the functional role of VEGFR-2 in CD4\(^+\) T cells during the pathogenesis of colorectal cancer we generated a conditional knock-out mouse with a deletion of VEGFR-2 in CD4\(^+\) cells.

Results: Surprisingly, we could see in an AOM/DSS model that mice with a deletion of VEGFR-2 in CD4\(^+\) cells have a higher tumour burden and size in comparison to control mice. Moreover we were also able to demonstrate that VEGFR-2\(^{\Delta CD4}\) mice have a reduced T cell infiltration in isolated tumour tissue and in secondary lymphoid organs. Regarding in vitro isolated T cells from VEGFR-2\(^{\Delta CD4}\) mice and VEGFR-2\(^{fl/fl}\) mice we observed similarity with respect to polarization in TH0, TH1 and TH17 cells, T cell differentiation and proliferation under 21% oxygen. However, we observed that cells lacking the receptor have an increase in central memory T cells in TH1 polarized cells in vitro under 1% oxygen. Additionally, VEGFR2-deficiency results in higher CD62L expression of in vitro differentiated T cells, possibly affecting homing of these cells. Furthermore we observed that a lack in VEGFR-2 in T cells leads to a decrease in the expression of OX40 and CD137 costimulatory molecules in TH1 cells in vitro under 1% oxygen compared to the control cells in vitro.

Discussion/Conclusion: Hence VEGFR-2 influences CD4\(^+\) T cells, but further work will be undertaken in order to fully understand the manner in which manner VEGFR-2 affects the T cells in the tumour in vivo. This also might help to better understand the immunomodulatory effect of VEGFR-2 and to further improve anti-cancer therapies in this way.
References:


Advanced optical technologies for label-free analysis of microstructure and biochemistry in IBD tissues ex vivo and in vivo

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Introduction: Common optical technologies such as gastrointestinal endoscopy or bright-light microscopy play a central role in clinical diagnostics of many diseases. However, most conventional techniques as well as certain more advanced methods such as confocal laser endomicroscopy [1] still rely on molecular staining in order to allow analysis of microstructure or biochemical composition of tissues. Here, we present a more advanced approach based on Raman spectroscopy [2] and multiphoton imaging [3], allowing contact-free access to information regarding structure and composition without the use of any biochemical staining procedures.

Methods: Label-free multiphoton microscopy is based on cellular autofluorescence (AF) of endogenous molecules (NADH or FAD) and second harmonic generation (SHG) from collagen I or myosin II. It provides detailed information about tissue morphology such as collagen fibre orientation [4]. Raman spectroscopy on the other hand, relies on inelastic scattering by molecules with specific rotational and vibrational energy bonds [2] and gives access to the composition of certain bio-molecules. Beyond structural analysis alone, multiphoton microscopy enables functional characterization based on AF spectra [5] and polarization properties [6].

Results: In the presented results, it was possible to correlate changes in cellular AF properties with stimulated apoptosis and necroptosis in intestinal organoids. Furthermore, investigations of mucosal wound healing in the colon have revealed a good correlation between collagen signal from Raman spectroscopy and the one from SHG imaging. Finally, a multiphoton endomicroscope has been developed in order to allow successive, label-free, in vivo imaging in the same specimen at different time points [7].

Discussion/Conclusion: New findings regarding the remodeling of connective tissue and significant changes in the concentration of numerous biomolecules were obtained in ex vivo studies, proving the feasibility of the technology. Based on results on acute colitis in an in vivo murine model, it was possible to extract several characteristic
changes of the intestinal muscosa microstructure and the connective tissue around it that allow correct classification of inflammatory tissue response based on label-free, \textit{in vivo} endomicroscopy.

References:


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Refractory Clostridium difficile infection in patient with ulcerative colitis

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Introduction: Clostridium difficile infection (CDI) is a great burden today with a rising incidence in past two decades, especially in hospitalised patients who are taking or have recently taken antibiotic therapy, older population and patients with IBD. It contributes to substantial morbidity and mortality.

Methods: We present here a 49-year-old female patient with quiescent ulcerative colitis she had six years ago who developed CDI. Her ulcerative colitis also relapsed following CDI. She was first treated with antibiotics (metronidazol, vancomycin and fidaxomycin). Consequently to failure of all these therapies she was transferred to University Clinical Hospital Centre for FMT (fecal microbiota transfer). Overal seven FMT have been done to this patient according to the 2017 consensus conference protocol. There were two donors who were not patient's family. She was concomitantly treated with antibiotics (vancomycin and rifaximine), corticosteroids, infliximab, enteral and parenteral nutrition. She was treated with i.v. immunoglobulins during her last FMT and IFX therapy, as well.

Results: Although patient’s clinical condition and laboratory tests (primarily haemogram, albumin and inflammatory markers) fairly improved after FMT, she continued to lose weight and had permanent diarrhoea (up to ten very scanty discharges). Her stool was positive to C. difficile practically every time. Finally, since her refractory UC and CDI caused permanent catabolism and significant weight loss, after six months of conservative treatment colectomy has been performed. She feels well now and she slowly started to gain her weight back. In a few months construction of pouch is planned.

Conclusion: FMT can be treatment option in refractory/reccurent CDI in IBD patient. It is very interesting that in our patient we achieved very significant clinical and laboratory improvement after FMT although she had active UC all the time. We beleive that vicious circle of active UC and CDI was major clinical issue.
Protective role of the Tec kinase ITK in the pathogenesis of inflammatory bowel disease

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Introduction: ITK (interleukin-2-inducible T cell kinase), a member of the Tec family kinases, is expressed in T cells and involved in Th2-type mediated immune responses. Colitis patients can be successfully treated with Cyclosporin A (CsA) but CD patients not. Therefore, we started to investigate the role of ITK in disease pathogenesis of UC.

Methods: Acute and chronic oxazolone mediated colitis was induced in ITK deficient mice and controls. Disease activity was measured by means of body weight, histological and endoscopic score of inflammation activity. Lamina propria mononuclear cells (LPMC) and spleen cells were isolated from these mice. The rate of apoptosis induction after treatment with CsA was assessed via flow cytometric analysis of AnnexinV/7AAD staining. Cytokine concentration (IL6, IL9, IL13, IL17A, TNFα) was assessed using ELISA and the calcium influx was measured.

Results: In the oxazolone induced colitis model, ITK-KO mice are protected against the development of intestinal inflammation compared to control mice. Upon administration of CsA there is a significant induction of apoptosis in LPMCs from control mice as well as a reduction of IL6 expression. Administration of an IL6-mini-circle-vector by hydrodynamic injection technique restores the inflamed phenotype in ITK-KO mice with and without CsA treatment. In the chronic experimental model, CsA loses its effect after four cycles of oxazolone treatment.

Discussion/Conclusion: Our results indicate that in the acute oxazolone induced colitis model, CsA induces enhanced apoptosis in LPMCs of control mice while it loses its protective effect in the chronic oxazolone mediated model. The restoration of the inflamed phenotype after administration of an IL6-mini-circle-vector in ITK-KO mice with CsA treatment underscores our hypothesis that CsA works via ITK.
An exceptional cause of drug-induced inflammatory bowel disease – Ixekizumab

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Introduction: Ixekizumab, a biologic agent known under the brand name Taltz®, is one of the three biologic agents including secukinumab and brodalumab that targets the IL-17 pathway in the pathogenesis of psoriasis.

Case presentation: This is a case report of a 42-year-old woman who was diagnosed at 31 years with cutaneous and nail psoriasis and at 38 years with psoriatic arthropathy treated 5 years with adalimumab. In June 2018, due to recurrence of psoriatic lesions adalimumab was stopped and the therapy with ixekizumab was initiated. The onset of digestive symptomatology (diarrhea, abdominal pain, bleeding) occurred in September 2018; she performed a colonoscopy that reveals pancolic severe ulcerative colitis (endoscopic Mayo score 3). The therapy with corticosteroids and 5-ASA was initiated but after 2 weeks she presented in emergency room for diffuse abdominal pain, accelerated intestinal transit (7–8 chairs/day), fever. Laboratory examinations have revealed the presence of slightly anemic syndrome, leukocytosis, severe hydro-electrolyte imbalances, significantly increased C-reactive protein and hypo-albuminemia. Patient was assessed urgently through CT that highlights the characteristic aspect of toxic megacolon. The patient was initially treated with intravenous corticotherapy, antibiotics, anticoagulants, but with persistent abdominal pain and accelerated intestinal transit. After 3 days, was initiated the therapy with Infliximab in the induction dose, but the day after infliximab clinical and radiological signs of perforation appeared. The patient was transferred to the surgery department where is performed total colectomy with the ileostoma and rectum preservation. Postoperative evolution was favourable.

Discussion/Conclusion: In the literature, have been reported cases of Crohn’s disease (0.1%) and ulcerative colitis (0.2%) in patients treated with Ixekizumab, but this is the first reported case of fulminant colitis with colectomy short time after ixekizumab administration.
Relation between TaqI polymorphism of VDR gene and Crohn’s disease phenotype in Ukrainian patients

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Introduction: Many studies have recognized the relation of TaqI polymorphisms of VDR gene with inflammatory and autoimmune disorders, and the results of these evaluations are often inconsistent. The frequency of the polymorphism in patients with Crohn’s disease (CD) is dependent on ethnicity and vary between different population.

Aim: To determine the frequency of TaqI polymorphisms of VDR gene in affected patients with CD, control group and to study the possible relation of this polymorphism with disease phenotype.

Methods: In this study 38 patients with CD and 28 age and sex matched healthy controls from Ukraine were enrolled. These patients were referred to a Proctology Department of Lviv Regional Hospital during a three-year period (2014–2017). Assessment of VDR gene polymorphism was performed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The genotype-phenotype association for this polymorphism was analyzed.

Results: There was no statistically significant difference in the allele frequencies and genotype distributions of Taq1 mutation of the VDR gene in the patients with CD in comparison to control group. The frequencies of genotypes in the patients with CD were following: TT – 0.368, Tt – 0.447, tt – 0.184; the frequencies of genotypes among the control group were: TT – 0.548, Tt – 0.290, tt – 0.161. It was found that patients carriers of “tt” genotype of a VDR-TaqI had significantly less age at CD onset than a heterozygous carriers of mutation or wild type carriers (p < 0.001) and all patients with “tt” genotype needs surgical interventions. Penetrating behavior of the disease (B3) had 85.7% of the patients with “tt” genotype. One patient with “tt” genotype with structuring behavior of the disease (B2) developed colorectal cancer. Early osteoporosis was revealed in 42.9% of the patients with “tt” genotype.

Discussion/Conclusion: This study provides preliminary evidence for a genetic association between TaqI polymorphisms of VDR gene and CD course and surgical interventions.
Role of R702W and 3020\textit{ins}C mutations of \textit{NOD2} gene in the onset of Crohn's disease and colorectal cancer in patients from Ukraine

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Introduction: Recent studies have shown \textit{NOD2} function deficiency correlates with a notable risk of Crohn's disease (CD) and colorectal cancer (CRC). Most \textit{NOD2} polymorphisms studies in CRC concerning a specific country or region. Despite the evidence from experimental models, population-based studies that have tried to link certain \textit{NOD2} polymorphisms with the increase in the CRC risk give contradictory data. The aim of the study was to determine the frequency of R702W and 3020\textit{ins}C mutations of \textit{NOD2} gene in patients with CD, CRC, and in individuals of control group, and to study the relation of these mutations with the onset time for the diseases.

Methods: The detection of the missense R702W mutation was carried out in 41 patients with CD, in 40 patients with CRC, and in 35 healthy controls from Ukraine. The presence of the frameshift mutation 3020\textit{ins}C was studied in 54 patients with CD, 49 patients with CRC, and in 38 individuals of control group. PCR-RFLP technique was used to identify the mutations. Gene sequencing was subsequently performed to confirm the results obtained by the PCR-RFLP method.

Results: There was no statistically significant difference in the allele frequencies and genotype distributions of R702W mutation in the patients with CD and CRC in comparison to control group. The median age at CD onset in the patients carrying R702W mutation was significantly lower (28.4 ± 1.4 years) comparing with the patients without the mutation (39.4 ± 2.8 years) (\(p < 0.01\)). There was no statistically significant difference of the median age at CRC onset in the patients carrying R702W mutation and in the patients without the mutation. It has been found that the frequency of the minor allele “M” of 3020\textit{ins}C mutation in the patients with CD is significantly higher than in the control group (\(p = 0.01\)). The age at CD onset in women carrying this mutation (23.4 ± 1.5 years) is significantly lower (\(p < 0.01\)) compared to women without the mutation (32.7 ± 2.5 years). There was no statistically significant difference in the allele frequencies and genotype distributions of 3020\textit{ins}C mutation in the patients with CRC in comparison to control group. Only 4.1\% of the patients with CRC carried 3020\textit{ins}C mutation. One patient with CRC was a homozygous carrier of 3020\textit{ins}C mutation and a heterozygous carrier of R702W mutation.

Discussion/Conclusion: The relation between R702W mutation and the early age of CD onset, but not with CRC onset, has been shown. Early age of the CD onset has been associated with 3020\textit{ins}C mutation, but only in the women.
Rac1-mediated maintenance of epithelial integrity in the gut

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Introduction: In our last study we could demonstrate the association between prenylation-dependent epithelial integrity and inflammation in the context of Inflammatory Bowel Disease (IBD) (López-Posadas, 2016). Besides RhoA, we aim at the identification of prenylation targets whose function could contribute to prenylation-regulated epithelial barrier function. Since the subcellular localization of small GTPases critically determines their function, we assessed alterations in membrane-bound proteins in prenylation-deficient intestinal epithelium (Pggt-Iβ⁻¹IEC mice) using mass spectrometry. The observation that Rac1 is shifted from its membrane localization in IECs from Pggt-Iβ⁻¹IEC mice suggests that Rac1 represents a novel prenylation target potentially regulating epithelial integrity in the inflamed gut.

Methods: Taking advantage of an inducible intestinal epithelial cell conditional knock out mouse model, specific for Rac1 (Rac1⁻¹IEC mice), we analysed the functional consequence of rac1 deletion within IEC’s for the maintenance of the intestinal homeostasis in the gut.

Results: rac1 deletion within IECs in adult mice led to a dramatic body weight loss and increased intestinal permeability, measured in vivo by FITC-Dextran transmucosal passage. Using a small intestine and colon “enteroid/organoid” culture system we demonstrated that disrupted epithelial integrity in the absence of rac1 represents an epithelial-intrinsic defect. Interestingly, the intestinal phenotype in Rac1⁻¹IEC mice is not associated with decreased cell proliferation (Ki67 qPCR and immunohistochemistry) or induction of cell death (Cl.Caspase3/TUNEL staining). However, we have identified an effect concerning the differentiation of the secretory lineage of IEC’s, such as Goblet and Tuft cells.

Discussion/Conclusion: Our data show that rac1 regulates intestinal epithelial integrity in a cell death/proliferation independent manner. Our preliminary observations suggest that rac1 might be a key element for epithelial cell differentiation in the gut.
Infliximab therapy and tight disease monitoring during pregnancy for Crohn’s disease patient with high disease activity

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Introduction: Most of patients with inflammatory bowel disease (IBD) are affected during their peak reproductive years, when many female patients affected by Crohn’s disease (CD) want to have children [Van der Woude CJ et al. 2015]. Antitumor necrosis factor (anti-TNF) therapy has been a major advance in the treatment of inflammatory bowel disease (IBD) by improving rates of mucosal healing, steroid-free remission, and decreasing rates of hospitalization and surgery [Michael G. Kattah et al. 2018]. Always question is about the possible disease effects in pregnancy, as well as the risks of fetal exposure to the biological therapy.

Aim: To report the case of young women who became pregnant while receiving Infliximab.

Case report: A 18-year-old woman, presented with CD of ileocolonic extension and fistulising behaviour (Montreal Classification A2, L3, B3), diagnosed in 2016. The patient was treated with infliximab (Remsima®) (5 mg/kg) since September 2016. In September 2017 patient became pregnant (first gestation), CDAI was 217. In January 2018 (Graviditas in sept 24), she was admitted to hospital with an exacerbation of CD to undergo a perianal abscess drainage. She presented fever, perianal discharge, pain, and discomfort; haematocrit 29.4%, haemoglobin 9.9 g/dl, and C-reactive protein (CRP) 301 mg. Antibiotic therapy was prescribed with metronidazole and ceftriaxone. After one week the patient presented significant improvement of symptoms, CRP 40 mg. After discharge patient continued therapy with metronidazole. She maintained the biological therapy until the 20th week of gestation, with tight disease activity monitoring. The baby was born in 30 week of gestation, by C-section, without complications. The vaccines were postponed for 6 months. 1 month after childbirth, she restarted therapy with infliximab (CDAI = 89).

Conclusion: The data showed that infliximab therapy is effective and safe for CD activity control during pregnancy and early breastfeeding.
Host-microbial crosstalk in the pathogenesis of inflammation and cancer in primary sclerosing cholangitis

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Background: Primary sclerosing cholangitis associated inflammatory bowel disease (PSC-IBD) is characterised by high risk of colorectal and hepatobiliary cancers with poor prognosis. Distinct inflammatory responses and dysbiosis have been involved in PSC-IBD.
We aimed to: 1) assess host-microbial functions in PSC-IBD 2) evaluate whether PSC-IBD-associated pathways affect epithelial transformation.

Methods: Intestinal biopsies and mucosal brushings were collected from patients with PSC-IBD, ulcerative colitis (UC) and healthy controls (HC). 3'RNA sequencing and 16S rRNA sequencing were performed to analyse intestinal transcriptomes and characterise the adherent microbiome. Colonic crypts were isolated from biopsies, seeded onto basement membrane extract and cultured with growth factors to develop organoids. Organoids were stimulated with cytokines for 24 hours and markers of cytokine downstream pathways, stemness and pluripotency were analysed by qPCR.

Results: A distinct transcriptomic profile was identified in the caecal biopsies of patients with PSC-IBD compared to UC and HC, with 890 genes being regulated in PSC-IBD. Amongst differentially regulated genes we found an enrichment of pathways associated with cytokine signalling including IL22 and TGFβ.
We successfully cultured primary intestinal organoids from both groups of patients and HC. Stimulation with IL22 or IFNγ resulted in STAT1 induction, and higher STAT3 induction was observed in PSC-IBD derived organoids. Interestingly, expression of the IL22 receptor, IL22RA1, was induced by IFNγ stimulation in PSC-IBD derived organoids that also over-expressed OLFM4 and POU5F1, both associated with pluripotency and early stages of neoplastic transformation.

Conclusions: The intestinal transcriptomic profile of patients with PSC-IBD shows altered regulation of pathways previously associated with IL22 and TGFβ signalling. Both cytokines have been implicated in cancer pathogenesis. PSC-IBD-associated Th1 responses may result in increased epithelial IL22 responsiveness. Higher expression of the stemness genes OLFM4 and POU5F1, triggered by bacteria and IL22 via STAT3 activation, suggest that microbial-driven IL22 responses may contribute to epithelial transformation.
Common problems in pouchoscopy reports

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Introduction: Flexible pouchoscopy is the most important investigation in patients with any problem within the pouch. It is also important in ulcerative colitis (UC) for colorectal cancer surveillance. Flexible pouchoscopy in the patients with pouch dysfunction is a gold standard for the diagnosis of the reason of the dysfunction. It is cheap, has no need for sedation, is not time-consuming. Endoscopists usually report only abnormal findings. The aim of this study was to determine the lacking parts of the endoscopic reports and if the issue is solved as the experience of the gastroenterologist improved.

Methods: Pouchoscopy reports between 01.01.2010 and 01.11.2018 were reviewed and analysed for the lacking parts and the differences in the lacking parts per year were compared with each other. The gastroenterologists dealing with the UC patients were usually the same during this period of time.

Results: In total, 88 reports were analysed. In the first year the anus and peri-anal area were specifically described in 98% of the reports, rectal cuff in 12%, pouch-anal anastomosis in 44%, pouch body in 45%, pouch inlet in 8%, and pre-pouch ileum in 10%. In the consecutive years, all of the ratios increased. In the last year (01.01.2018–01.11.2018) the anus and peri-anal area were specifically described in 98% of the reports, rectal cuff in 75%, pouch-anal anastomosis in 88%, pouch body in 90%, pouch inlet in 20%, and pre-pouch ileum in 40%. As the experience of the endoscopists increased by time, the description of rectal cuff, pouch-anal anastomosis, pouch inlet and pre-pouch ileum showed a significant improvement.

Discussion/Conclusion: The experience of the gastroenterologist positively effects the proper writing of a pouchoscopy report. Anal and peri-anal area description are the best in our clinic because it is in the flexible sigmoscopy template however the other terms are not placed in the template. So a separate specialized template for pouchoscopy and working with experienced gastroenterologists would improve the quality of pouchoscopy reports.
miR-506 may play a role in a different phenotypic presentation of ulcerative colitis in patients with primary sclerosing cholangitis (PSC)

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Introduction/Aim: Primary sclerosing cholangitis (PSC) is commonly accompanied by ulcerative colitis (UC), mostly localized in the right colon. Impairment of Cl⁻/HCO₃⁻ exchanger (AE2) decreases luminal pH of the colon facilitating the entry of protonated toxic bile salts and sensitizing apoptotic stimuli. Bicarbonate secretion is promoted by release of Ca2⁺ via inositol-1,4,5-trisphosphate-receptor (InsP3R3). Small non-coding miR-506 down-regulates AE2 and InsP3R3. Another target of miR-506 is a sphingosine kinase-1 (SPHK1) that produces sphingosine-1-phosphate, a bioactive lipid involved in immune cell trafficking.

We analyzed the expressions of miR-506 and its target genes such as AE2, InsP3R3, and SPHK1 in colonic tissues of patients with PSC with concomitant UC (PSC-UC) and UC alone.

Methods: Ascending and sigmoid colon biopsies were obtained from patients with PSC-UC (n = 9), UC (n = 10) and controls (n = 8). The relative levels of microRNAs and mRNAs were evaluated by real-time PCR.

Results: There was a significant increase of miR-506 (5-fold, p = 0.03 vs. controls) in the ascending colon of PSC-UC patients, accompanied with downregulation of AE2 (45% reduction, p = 0.05 vs. controls), and InsP3R3 (40% reduction, p = 0.02 vs. controls). No changes in SPHK1 mRNA was observed. In sigmoid colon of PSC-UC the expressions of all investigated factors remained unchanged. On the contrary, in UC patients the expression of miR-506 was substantially suppressed both in the ascending and sigmoid colon (90%/95% reduction, respectively), whereas the SPHK1 expression was noticeable enhanced (4.6-fold, p = 0.04 and 2.8-fold, p = 0.007 vs. controls, respectively). In contrast to PSC-UC group, AE2 and InsP3R3 mRNA levels were comparable to controls.

Discussion/Conclusion: A different phenotypic presentation of colitis in PSC may be related to miR-506 expression. In ascending colon of PSC-UC the upregulation of miR-506 may result in the failure of bicarbonate secretion, while in UC a downregulation of miR-506 may lead to enhanced production of sphingosine-1-phosphate that is involved in inflammatory responses.
Diagnostic delay in Crohn's disease as a cause of complicated disease course – A case report

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Introduction: Clinical presentation of Crohn's disease (CD) may vary substantially from patient to patient; often symptoms are subtle. Atypical presentation may lead to diagnostic delays. It is well known that delays in diagnosing CD have great influence on quality of life, they can affect the natural history of the disease and are associated with the development of complications and consequent bowel resection. In this paper we present the girl in whom the diagnosis of CD has been made with substantial delay and with numerous complications.

Methods: The girl was initially admitted at the age of 14 because of short stature and delayed puberty (height 138 cm, z-score -3.18; body mass 26 kg, z-score -3.89, BMI 13.68, z-score -3.2), along with sideropenic anemia (Hb 88, Htc 31.8%) without any other symptom. Growth hormone deficiency was diagnosed and substitutional therapy was started. The next hospitalization was 1.5 years later because of the significant weight loss, abdominal pain, diarrhea, pain in the left hip and fatigue; she had palpable mass in the left part of the abdomen. Laboratory test revealed elevated CRP and SE rate (142.8 and 45, respectively), with sideropenic anemia (Hb 74, Htc 31.8%) and hypoalbuminemia. On MSCT iliopsoas abscess was seen. In spite of polyantimicrobial therapy her general condition deteriorated. Surgical resection of descending colon and drainage of the abscess were made. Postoperative course was complicated with the development of septic shock and jejunal perforation; the V.A.C. Therapy System Dressing was used for closing the abdominal wall. After clinical stabilization, upper and lower endoscopy along with MREC revealed Crohn's disease of the whole colon and the biggest part of small bowel. Infliximab was started at the age of 17.5, 42 months after initial presentation with suboptimal clinical and laboratory improvement.

Discussion/Conclusion: Early diagnosis and therapy prevent complications development in CD.
Predicting Outcomes For Crohn’s Disease using a molecular biomarker: PROFILE trial recruitment update

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Introduction: The course of Crohn's disease (CD) varies substantially between individuals, but reliable prognostic markers do not exist. This hinders disease management because patients with aggressive disease are undertreated by conventional 'step-up' therapy (in which treatment is gradually escalated in response to refractory or relapsing disease) while those with more indolent disease would be exposed to unnecessary treatment-related toxicity if a more aggressive 'top-down' approach was indiscriminately used. We have previously developed and validated a prognostic transcriptional biomarker and the PROFILE trial will assess whether this biomarker can improve clinical outcomes by appropriately matching therapy to disease course. This represents the first the biomarker-stratified trial in inflammatory bowel disease.

Methods and results: This biomarker-stratified trial will compare the relative efficacy of 'top-down' and 'accelerated step-up' therapy between biomarker-defined subgroups of patients with newly diagnosed CD. 400 participants from ~50 UK centres will be recruited. Subjects within each biomarker subgroup (IBDhi or IBDlo) will be randomised (1:1) to receive one of the treatment strategies until trial completion (48 weeks). The primary outcome is the incidence of sustained surgery and steroid-free remission from the completion of induction treatment through to week 48. Secondary outcomes include mucosal healing, quality-of-life assessments and surrogate measures of disease burden including number of flares, cumulative steroid exposure, number of hospital admissions and number of Crohn's-related surgeries (assessed hierarchically). Analyses will compare the relative benefit of the treatment strategies in each biomarker-defined subgroup, powered as an interaction analysis, to determine whether the biomarker can accurately match patients to the most appropriate therapy. At the time of writing, 40 sites have been opened around the UK and 65 participants randomised. Recruitment is ongoing and the most up-to-date recruitment data will be available for presentation at the Falk Oxford meeting.

Discussion/Conclusion: We have developed, optimised and validated a whole-blood qPCR classifier that is able to predict disease course from diagnosis in IBD patients. This classifier is currently under investigation in the PROFILE trial. If clinical utility of a stratified treatment approach is demonstrated, this would represent a major step towards personalised therapy in IBD.
Germline *de novo* mutation in immune checkpoint regulator PTPN2 causes very early onset autoimmune enteropathy by aberrant activation of JAK/STAT pathway

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Introduction: Monogenic intestinal disorders represent naturally occurring experimental models to decipher the network of pathways regulating homeostasis in the gut. We investigated a girl, born from non-consanguineous parents, who had developed at the age of 3 months autoimmune enteropathy characterized by secretory diarrhoea, severe villous atrophy with prominent T cell infiltrates and serum antibodies against the 75 kD epithelial antigen harmonin.

Methods: Whole exome sequencing was performed on DNA from the patient and both parents. Functional validation of the identified PTPN2 mutation was performed by overexpressing WT or C216G in HEK293T cells expressing a luciferase reporter gene under the control of STAT3 transcriptional response elements (TRE) by luminescence or western blotting. JAK/STAT activation was evaluated *in vitro* in patient’s B cells immortalized by Epstein Barr virus and in PTPN2 KO Jurkat cells.

Results: We identified a *de novo* PTPN2 loss of function mutation (c.646T>G; p.C216G) in a child with early and severe enterocolitis. Overexpression of wild-type PTPN2 alone led to a significant downregulation of STAT3 TRE activity over control following IL6 stimulation while the mutant form of PTPN2 did not repress the STAT3 reporter gene. Moreover, ectopic expression of WT-PTPN2 significantly decreased IL-6 induced STAT3 phosphorylation, while the C216G-PTPN2 mutant failed to do so. Accordingly, patient’s cells and PTPN2 KO cells displayed increased cytokine-induced STAT3 phosphorylation.

Discussion/Conclusion: Our study identifies human PTPN2 deficiency as a novel cause of autoimmune enteropathy and highlights the need of a tight regulation of the JAK STAT pathway to preserve intestinal homeostasis.
Ruxolitinib as tailored treatment for severe enterocolitis caused by STAT3 gain of function mutation

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Introduction: Autoimmune enteropathy, a severe condition often resistant to immunosuppressive treatment, can be caused by monogenic mutations in immune genes. Herein, our goal has been to identify the underlying gene defect in a 25-year-old woman with early onset enterocolitis in order to provide targeted therapy.

Methods: Whole exome sequencing was performed on DNA from the patient and both parents. Functional validation of the identified Signal transducer and activator of transcription 3 (STAT3) mutation was performed using luciferase reporter assay. STAT3-dependent transcriptional response was studied in vitro in B cells immortalized by Epstein Barr virus, treated or not by the JAK1/2 inhibitor ruxolitinib. Clinical symptoms, intestinal histology, intestinal T cell infiltration and mRNA expression of SOCS3, a STAT3-dependent target, and of cytokines were compared before and during oral treatment by ruxolitinib.

Results: A novel STAT3 gain of function (c.1201A>G; p.N401D) was identified in the patient with severe enterocolitis. Accordingly, patient’s cells displayed increased cytokine-induced STAT3 transcriptional activity, which was reverted by ruxolitinib. Oral treatment of the patient with ruxolitinib reduced STAT3-dependent transcription in intestinal tissue and achieved rapid clinical remission. Complete histological recovery was observed after 7 months of monotherapy with ruxolitinib.

Discussion/Conclusion: Ruxolitinib appears to be a therapeutic option for severe enterocolitis associated with STAT3 gain of function mutations.
Colitis on CT – Does this mean inflammatory bowel disease?

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Cross sectional imaging with CT scanning is commonly used to assess the abdomen for a variety of abdominal symptoms. Subsequently, findings of colitis on CT is a frequent indication for lower gastrointestinal endoscopy. The outcomes of performing colonoscopy for colitis reported on CT examinations is not clearly known.

Methods: A retrospective, single centre study was performed on patients with the indication of ‘abnormal imaging’ referred for a colonoscopy. Data was collected using the endoscopy software audit tool over a 12-month period (September 2017 to August 2018). Patients who had undergone an imaging modality other than CT and those with an overt colonic polyp or mass on CT were excluded from the analysis. Analyses were performed using chi-square and student t-test.

Results: 249 patients (183 CT [73.5%], 66 CTVC [26.5%]) underwent a colonoscopy for CT evidence of mural thickening (218 [87.6%]), fat stranding (88 [35.3%]), inflammation (104 [41.8%]) or local lymph nodes (37 [14.9%]); median age 68 (IQR 53–79); median time from CT to endoscopy 33 days (IQR 12.5–56.5). Initial indication for CT examination: abdominal pain 112 (45.0%), change in bowel habit 39 (15.7%), malignancy 32 (12.9%), PR bleeding 13 (5.2%), weight loss 9 (3.6%) and other 44 (17.7%).

53 (21.3%) patients had completely normal lower GI endoscopy. 111 (44.6%) had uncomplicated diverticulosis, 11 (4.4%) diverticulitis, 20 (8.0%) haemorrhoids and 37 (14.9%) colorectal polyps. 20 patients (8.0%) had endoscopic evidence of colitis and 21 (8.4%) had a malignant colorectal tumour. All patients with malignancy found at endoscopy had evidence of focal or circumferential thickening reported on CT.

Table 1. Comparison of endoscopic diagnoses according to CT features.

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 53)</th>
<th>Colitis (n = 20)</th>
<th>Malignancy (n = 21)</th>
<th>*p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>63.6</td>
<td>54.4</td>
<td>69.5</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Time to endoscopy (days), mean</td>
<td>45.3</td>
<td>24.5</td>
<td>24.9</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Mural thickening (%)</td>
<td>48 (90.1)</td>
<td>19 (95)</td>
<td>20 (95.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fat stranding (%)</td>
<td>14 (26.4)</td>
<td>12 (60)</td>
<td>9 (42.9)</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Inflammation (%)</td>
<td>16 (30.2)</td>
<td>12 (60)</td>
<td>9 (42.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Lymph nodes (%)</td>
<td>4 (5.7)</td>
<td>8 (40)</td>
<td>11 (52.4)</td>
<td>&lt; 0.00006</td>
</tr>
</tbody>
</table>
Discussion/Conclusion: Colitis on CT scan correlates poorly with endoscopic colitis occurring in only 8% of patients in this study. The correlation improves in younger patients and with shorter interval between CT scan and endoscopy. One in five patients had completely normal endoscopy and over 90% had a benign diagnosis. Radiological reporting of fat stranding was an independent risk factor for endoscopic colitis. Anaemia and raised CRP helps identify those at higher risk of malignancy whilst raised CRP alone shows a trend towards identifying those with true colitis. We conclude that the findings of ‘colitis’ on CT does not imply inflammatory bowel disease in the majority.
The interleukin-22 transcriptional programme is activated in human colonic inflammation and associated to anti-TNFα primary non-response in Crohn’s disease

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Introduction: Interleukin-22 (IL-22) is an effector cytokine regulated by IL-23, a key player in IBD pathogenesis and target of novel biologics. Preclinical studies suggest a protective role for IL-22 in the context of acute intestinal injury and an inflammatory one in chronic inflammation. Little is known though about its role in human IBD.

Methods: Considering that the only tissue responsive to IL-22 is the intestinal epithelium, we generated colonic organoids (colonoids) from biopsies taken from healthy controls (n = 4) and treated them with IL-22, or other cytokines relevant to IBD pathogenesis (TNFα, IL-17A, IFNγ). Whole transcriptome profiling was performed using the Illumina platform. Association to clinical phenotypes was performed with gene set variation analysis (GSVA) by testing for enrichment of the generated IL-22 transcriptional signature (top 50 upregulated transcripts) in our own (controls: 6, UC: 16) and reposited datasets (GSE59071 and GSE16879).

Results: The IL-22 transcriptional programme was the second largest based on number of differentially expressed genes (DEG) induced in human colonoids by IBD relevant cytokines (IL-22: 1251, IFNγ: 1310, TNFα: 716, IL17A: 245, filtering on FDR < 0.01). Most of the transcripts regulated by IL-22 were shared with the other transcriptional programmes (79% of DEG) while in hierarchical clustering IL-22 clustered closely to TNFα and IL17A. Among the most highly enriched GO terms for all four cytokines were ‘cytokine-mediated signalling pathway’, ‘cytokine production’, ‘response to wounding’, ‘regulation of cell adhesion’ with concordant activation across conditions (upregulation).

All transcriptional signatures, including IL-22, were enriched in active inflammation regardless of phenotype (UC, colonic CD). Enrichment for the IL-22 and TNFα transcriptional profiles prior to starting anti-TNFα therapy was associated with primary non response in CD (area under the ROC curve: 0.88, p = 0.007 and 0.87, p = 0.009 respectively) but not UC.

Discussion/Conclusion: We identify, for the first time, striking transcriptional similarities between IL-22 and other pro-inflammatory cytokines known to drive IBD. We show that the IL-22 regulated transcriptional programme is active in the context of human colonic inflammation and, importantly, enriched in those CD patients who failed anti-TNFα induction. Our findings highlight the therapeutic potential of IL-22 targeted personalised medicine approaches for human intestinal inflammation.
The Inflammatory Bowel Disease (IBD) BioResource: Progressing from genetics to function and clinical translation in Crohn’s disease (CD) and ulcerative colitis (UC)

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Successes in IBD genetics provide an opportunity to further understand pathogenic mechanisms, develop new treatments and test the ‘personalised medicine’ paradigm. Achieving these stepping-stones require access to large cohorts of genetically and clinically well-characterised patients with CD and UC. To facilitate such research, the UK IBD Genetics Consortium and the NIHR BioResource launched IBD BioResource in 2016 to expedite functional/immunological characterisation of IBD-associated variants and the clinical translation of recent genetics advances.

The aim of IBD BioResource is to build a national platform of individuals with CD or UC (25,000) and to generate detailed genetic and phenotypic data to facilitate downstream translational research. The Main cohort comprises individuals with established CD and UC. Both clinical data – surgery, macroscopic extent, medication and co-morbidities – and self-reported phenotypes – IBD and general health questions and family history – are collected, alongside plasma, serum and DNA samples. The latter are undergoing whole genome sequencing at the Wellcome Trust Sanger Institute. The Inception cohort recruits individuals newly diagnosed with IBD and provides a more detailed sampling, unconfounded by drug treatment or effects of surgery. This includes stool, biopsy tissue and whole blood for RNA. This cohort offers a unique resource to undertake ‘omics’ studies and facilitate research into determinants, predictors and biomarkers of IBD disease course and treatment response. The IBD BioResource panel can be accessed by any investigators with ethically approved proposals and may comprise a range of studies from access to existing data or samples or recall of genotype-selected participants to donate further samples, to trial of novel therapies.

We aim to give an overall update to the scientific community about the current state of the project, which will be 3 years into its ambitious task and over 19,000 participants. This will include an update about the UK hospitals currently open and recruiting, the number of patients recruited, key achievements and milestones reached and also a flavour of the downstream studies which are in the pipeline.
Complex management of the patients with fistulating Crohn’s disease complicated with intraabdominal abscess

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Introduction: The management of the Crohn’s disease with enterocutaneous fistula complicated with intraabdominal abscess is complex and requires a combination of therapeutic and surgical approach. There is still a notable lack of data in this field.

Case report: We have report a 23-year-old patient who suffered from active small bowel CD fistulizing form with a concomitant abdominal abscess. In anamnesis congenital atresia of the rectum, followed by several surgical interventions. In 2017 in the paraumbilical area, involving postoperative scar, two fistulas appeared. In 2018 patient was charged with symptoms of acute abdominal pain, increased body temperature, leukocytosis, high levels of CRP and calprotectin. CT scan – abscess 54 x 43 x 42 mm in the right iliac area, thickening to 12 mm of the wall of the ileum 15 cm from the ileocecal valve, lymphadenopathy, enterocutaneous fistulae were visualized. Due to the high risk of perforation of the intestine, colonoscopy was not performed. Therapy with meropenem 3 g/day, mesalazine 3 g/day was not effective, fistulae debit was 200 ml/day. Ultrasound guided, drainage of the abscess of the abdominal cavity was performed. Positive dynamics was achieved. Mesalazine 3 g/day and metronidazole 1500 mg/day was administered. After removing of the drainage tube in a 1 month no signs of abscess in the right iliac area on CT scan.

In a 3 months positive clinical (body temperature is normal, pain is absent, stool 2–3 times a day, increasing weight – plus 5 kg) and laboratory dynamics (decreasing of the calprotectin and CRP levels). The fistula debit was 5 ml/day. Therminal ileus was proved endoscopically and histologically. Mesalazine was increased up to 6 mg/day. Right hemicolecetomy, resection of the therminal ileum with fistula is planed.

Discussion/Conclusion: Combined therapeutic and surgical treatment in patients with CD fistula and intraperitoneal abscess is effective.
QT interval prolongation and inflammatory bowel diseases

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Introduction: Various conditions associated with inflammatory bowel diseases (IBD) such as long-drawn inflammation, dyselectrolytemia, medication side effects are independent risk factors for QT interval prolongation. Whereas prolonged QT interval is associated with malignant ventricular arrhythmias, it is important to risk stratify this subset of patients. Our objective was to evaluate the prevalence of abnormal QT interval prolongation (defined by a QT interval of > 0.45 s in men and > 0.47 s in women) in an IBD population.

Methods: Our study included 61 male patients and 79 female patients with IBD, hospitalized between 1st of January 2017 and 31st of July 2018. Patients diagnosed with a cardiac disorder before the study, were excluded. QT intervals were measured from the electrocardiogram, and corrected QT (QTc) interval was calculated from lead II using Bazett’s formula. Body mass index was determined for each patient.

Results: Of 140 patients, 42.62% (26 of 61) males and 49.37 (39 of 79) females had a prolonged QTc interval. Patients with IBD having a prolonged QTc interval had a higher body mass index than those with a normal QTc interval (29.5 ± 6.7 vs. 25.9 ± 5.7, p = 0.007).

Discussion/Conclusion: Our study demonstrates that patients with IBD are at a higher risk of developing QTc interval prolongation.
Elderly patients with inflammatory bowel disease (IBD) are less likely to persist on anti-TNF therapy compared with younger patients. Data from the Sicilian Network for Inflammatory Bowel Diseases (SN-IBD)


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Introduction: Elderly patients with IBD are frequently difficult to treat because they are at increased risk for severe adverse events when treated with immunomodulators or anti-TNF therapies. Moreover, little is known about their response to biological treatments. The aim of this study was to compare persistence on therapy during the first course on anti-TNF treatments in IBD patients over 60 years of age with that of younger IBD patients.

Methods: Data of consecutive IBD patients > 60 years of age at their first course of anti-TNF treatment from January 2013 to June 2018 were extracted from the cohort of the SN-IBD and compared with patients ≤ 60 years of age. Information on gender, type, duration and extension of disease, and familiarity were analysed.

Results: Eighty-one patients with Crohn’s disease (CD; M = 43) (median age 64 [range 61–80] years) and 43 patients with ulcerative colitis (UC; M = 29) (median age 65 [61–77] years) were included and compared with 204 patients (M = 119) with CD (median age 39 [18–59] years) and 143 with UC (M = 77) (median age 40 [18–59] years). Persistence on therapy was significantly higher (log-rank p < 0.0001) in younger CD patients for every kind of anti-TNF therapy as well as in younger UC patients on i.v. anti-TNF therapy (p = 0.002). On univariate regression analysis, persistence was significantly associated with younger age (p < 0.0001) in CD and with younger age (p = 0.004) and with i.v. vs. s.c. administration (p = 0.02) in UC.
Discussion/Conclusion: In this large cohort of anti-TNF naïve elderly patients we showed for the first time that elderly patients with CD or UC were significantly less likely to persist on therapy within the first 12 months of treatment because of more frequent secondary failures and AE. The only predictor for treatment persistence was a younger age for CD and a younger age and the use of i.v. anti-TNF agents in UC.
Tolerance of infliximab infusions without premedication in pediatric patients with inflammatory bowel disease

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Introduction: Infusion reactions (IRs) are the most common adverse events associated with the use of infliximab for inflammatory bowel disease (IBD). Antipyretics, antihistamines, and corticosteroids have been used to prevent the development of IRs, but their efficacy is not known. There are not guidelines for using premedication in children with IBD.

Methods: Medical charts of children with IBD treated with infliximab infusion, between January 2009 and January 2018 were collected. Diagnosis, age, sex, number of infusions with infliximab, symptoms, blood pressure, heart rate during the infusion, were recorded.

Results: 9 patients aged 7.2–14.5 years (mean age 11.7 years) at the time of diagnosis were treated with infliximab during this period. 5 patients were females and 4 males. 7 patients were diagnosed with Crohn’s disease and 2 (females) with ulcerative colitis. The mean age at the time of beginning of biologicals was 13 years (9.1–15.8). During this period were performed 208 infusions of infliximab. All infusions were completed without premedication. Systolic, diastolic blood pressure and heart rate were within normal range for age. All patients were treated with 5 mg/kg/8 weeks after initial schedule. Two patients, 1 with Crohn’s and 1 with ulcerative colitis, were treated with 5 mg/kg/4 weeks after the 9th and 11th infusion respectively, because of poor response and low drug levels without antibodies. One patient felt transient discomfort during 2 infusions (13 & 27th) and 1 other patient had a middle rash and discomfort during the 9th infusion. Both patients were without symptoms after 1/2 hour and continued the infusion without problem.

Discussion/Conclusion: In our population patients with inflammatory bowel disease treated with infliximab without premedication had a good response in the treatment, without adverse events or severe IRs. Prospective, well designed studies are needed to answer for the necessity of premedication in patients with IBD treated with infliximab.
CD4-positive T-helper cells in endoscopic material of ulcerative colitis and Crohn’s disease patients

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Introduction: The expression of CD4 molecule was observed in about 90 percentage of T-helper cells that are involved in the regulation and modulation of the immune response. CD4+ T-helper cells are activated by antigen presenting cells (APC) and secrete cytokines, e.g. IL-2 and IL-3. The aim of study was to identify CD4+ T-helper cells in tissue material obtained from ulcerative colitis (UC) and Crohn’s disease (CD) in correlation to clinic-pathological features.

Materials and method: The study group consists of 34 patients with ulcerative colitis and 8 patients diagnosed with Crohn’s disease. The mean age of patients was 38 years old of UC and 31 years old in CD. The activity of diseases were examined according to Geboes score in UC and to Brennan classification in CD. The expression of CD4+ T-helper cells was performed by immunohistochemistry and assessed in cytoplasmic color reaction classified into 1 – weak, 2 – moderate and 3 – strong.

Results: The group of study consists of 16 female and 18 male in UC, and 2 female and 6 male of CD. The UC lesions were mainly localized in rectum (19/34 cases), sigmoid (8/34 cases) and other part of intestine (7/34 cases). Crohn’s disease was observed in small intestine (3/8 cases), caecum (4/8 cases) and rectum (1/8 cases). According to Geboes classification, we observed score 2 in 10 cases, score 3 in 13, score 4 in 5 and score 5 in 6 cases. We showed 2 cases in score 2 and 6 cases in score 4 based on Brennan criteria. The infiltration of CD4+ T-helper cells in UC was weak in 17 cases, moderate in 9 cases and strong in 7 cases and was significantly associated with Geboes classification (R = -0.360; p = 0.001). Moreover, CD4+ T-helper cells in CD were observed as weak infiltration in 5 cases, moderate in 2 and strong in 1 case.

Conclusion: Our study showed that CD4+ T-helper cells actively take part in the disease activity in ulcerative colitis.
Chronic intestinal inflammation induced by a viral cell death regulator

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Introduction: A plethora of viruses is present in the intestinal microflora therefore
viruses are currently discussed as a potential causative trigger for the development of
inflammatory bowel disease. A number of viruses, belonging to the family of
Herpesviridae or Poxviridae, express homologues to cellular FLIP proteins, which are
important regulators of host cell death in intestinal epithelial cells (IECs). In this study
we analysed the consequences of viral Flip (vFlip) expression in IECs in mice on
intestinal homeostasis and cell death and the ability of viral FLIP to compensate for
cellular FLIP (cFLIP).

Methods: We used different mouse strains, either constitutively expressing vFlip in
IECs or expressing vFlip and/or lacking cFlip in IECs after Tamoxifen injection. Body
weight and survival were monitored and histology, gene expression and protein levels
were analysed.

Results: Surprisingly, mice constitutively expressing vFlip in IECs were characterized
by chronic intestinal inflammation accompanied by loss of Paneth cells, increased cell
death and altered NFκB signalling. Additional blocking of the alternative NFκB pathway
attenuated mucosal inflammation and Paneth cell loss induced by vFLIP. Moreover, in
the inducible model, expression of vFlip in IECs reduced cell death and counteracted
loss of barrier integrity induced by cFlip deletion.

Discussion/Conclusion: Our results show that a single viral protein is able to disrupt
epithelial homeostasis and to initiate chronic intestinal inflammation in mice. Moreover,
vFLIP alters NFκB signalling and is partially able to acquire functions from the cellular
regulator cFLIP, suggesting that viruses are able to deregulate host cell death
pathways by interfering with cellular proteins. Since the general impact of viruses on
intestinal homeostasis and disease development is not fully understood, this study
might help to improve our understanding of the viral influence on intestinal homeo-
stasis, cell death, barrier function and disease pathogenesis in humans.
Characteristics of inflammatory bowel disease patients with pseudopolyps

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Introduction: Extensive course increases the incidence of pseudopolyps as a consequence of a severe disease. Pseudopolyps are detected during endoscopy in patients with inflammatory bowel disease (IBD). Aim of the study is to define phenotypic characteristics of these patients and endoscopic characteristics of pseudopolyps.

Methods: Retrospective medical records and endoscopic findings of patients with IBD and pseudopolyps, with report of pseudopolyps at least at one endoscopy for each patient, diagnosed and followed up between 01.01.2010 and 01.10.2018 at Katip Çelebi University and Atatürk Teaching and Research Hospital. Demographic findings, extent of IBD, pseudopolyp size, number and time interval of presentation of pseudopolyps from diagnosis were recorded.

Results: Eighty five IBD patients with pseudopolyps were analysed. Sixty-seven patients were diagnosed with ulcerative colitis (UC). 55% of them were male, earliest detection interval from the diagnosis was 6 months. The time interval clustered around 24 and 36 months. 89% patients had prednisolone history whereas 67% patients had azatiopyrin and 22% patients had biologic agent history. All of the patients with the biologic treatment history had pseudopolyps more than 15. Three patients underwent total colectomy and ileal pouch anal anastomosis surgery due to medical treatment resistant bleeding from pseudopolyps. Two patients who underwent surgery for refractory ulcerative colitis were diagnosed as colon carcinoma incidentally in the colectomy materials. The most prevalent segment was transverse colon, the second mot prevalent segment was descending and sigmoid colon. 45% of the patients had extra-intestinal findings especially artropathy.

Discussion/Conclusion: The presence of pseudopolyps is a marker of more aggressive IBD with more flares. They are mostly located in the transverse colon and usually appear independant of the time interval from the diagnosis. Biologic treatment is more prevalent than the general IBD population. They have two main issues; bleeding and their presence can obscure the ability of finding dysplastic lesions. Pseudopolyps may be a sign of need for a more frequent and rigid clinical and endoscopic follow up in IBD patients.
The study of key molecules of biological pathways of ageing in patients with ulcerative colitis and horizons of innovative therapy

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Older-onset ulcerative colitis (UC) is more common than Crohn's disease, with rates higher in elderly men than women.

**Introduction:** The aim of the study was the search of key molecules of pathways of UC in the elderly and the development of the roadmap for innovative therapy of UC.

**Methods:** The study included 38 patients (60–75 years old, female – 11, male – 27) with UC E1 (n = 26), UC E2 (n = 12), S2–3, grade 2–3. QoL measured by the IBDQ. Diagnosis based on medical history, laboratory tests for UC, gas-liquid chromatography for the characterization of microorganisms in stool, colonoscopy with biopsy. Proteomic analysis was made in colonic mucosa (1–2DE, MALDI-TOF/TOF-MS, PathCards database). Treatment of UC S2 (Group 1, n = 27) included 5-ASA 1 x 3 g/day + budesonide MMX 1 x 9 mg/day for 8 weeks, UC S3 (Group 2, n = 11) – infliximab 5 mg/kg i.v. at 0, 2, and 6, then every 8 weeks + resveratrol 100 mg/day 4 weeks. Control group (CG) – 20 persons (30–40 years old, female – 6, male – 14) with UC E1 (CG1, n = 13), UC E2 (CG2, n = 7), S2–3, grade 2–3, who took the same therapy without resveratrol. Characteristics were summarized as frequencies, mean ± SEM. Mann-Whitney test, chi-square tests, Fisher’s exact test were used.

**Results:** Clinical response achieved in 77.8% patients (Group 1, p = 0.0007 vs. CG1), 45.4% patients (Group 2, p = 0.0005 vs. CG2), remission – in 22.2% patients (Group 1, p = 0.0008 vs. CG1), 54.6% patients (Group 2, p = 0.0005 vs. CG2). It has been registered the decrease of HIFα (81.8% vs. 42.8%), TNFα (54.5% vs. 28.6%), IL-6 (72.7% vs. 28.6%), IL-22 (63.6% vs. 42.8%) and the increase of IL-10 (90.9% vs. 28.6%) in colonic mucosa in Group 2 vs. CG 2. The reduction of anaerobic colonies in stool were noticed after 4 weeks of infliximab + resveratrol therapy.

**Discussion/Conclusion:** Results of the study allowed to analyze the role of anaerobic microorganisms, hypoxia-mTOR-HIF-1α-Th17 and IL-6-STAT3-HIF-1α-Th17 pathways in colonic mucosa as potential targets for the treatment of UC in the elderly.
Inhibiting interleukin-36 receptor signaling reduces fibrosis in chronic intestinal inflammation

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Introduction: Intestinal fibrosis is a frequent and severe complication of IBD whereas effective therapeutic treatment is missing. Intestinal fibroblasts are key mediators of fibrosis and are known to strongly react to the family of IL36 cytokines in a proinflammatory context.

Methods: We analyzed intestinal tissue from IBD patients by histology for fibrotic alterations and immunohistochemistry for the localization of fibroblasts and levels of IL36R ligands. RNA sequencing was performed from human and murine primary intestinal fibroblasts upon IL36R ligand stimulation. Chronic colitis was induced in Il1rl2⁻/⁻ mice and littermate controls by repeated administration of DSS or TNBS. Antibodies against IL36R were injected into wildtype animals during the course of chronic DSS or TNBS administration (preventive setup) or into animals with established chronic colitis (therapeutic setup). Bone marrow cells from Il1rl2⁻/⁻ animals were transplanted into wildtype animals and chronic colitis was performed.

Results: We found elevated levels of collagens including collagen type VI in IBD patients compared to controls. In fibrostenotic tissue from CD patients higher levels of IL36A correlated with a higher number of alpha-SMA⁺ fibroblasts. IL36R stimulation in human and murine intestinal fibroblasts induced genes that regulate tissue remodeling and inflammation as well as direct collagen type VI expression. Genetically- or antibody-mediated inhibition of IL36R signaling resulted in marked inhibition of intestinal inflammation and fibrosis in chronic mouse models, but bone marrow cells from Il1rl2⁻/⁻ animals did not prevent intestinal inflammation and fibrosis.

Discussion/Conclusion: Blockage or defective IL36R signaling reduces chronic intestinal inflammation and fibrosis in vivo. Interference with IL36R signaling could serve a potent strategy for prevention and treatment of intestinal fibrosis in IBD patients.
The TLR9 agonist cobitolimod induces anti-inflammatory effects and balances the Th17/T-reg cell response in ulcerative colitis

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Introduction: The DNA-based oligonucleotide cobitolimod (DIMS0150) is a toll like receptor 9 (TLR9) agonist and has demonstrated clinical efficacy and a favourable safety profile in inducing clinical remission in patients with active ulcerative colitis (UC). To gain a deeper understanding of its mechanism of action, we analyzed the efficacy of cobitolimod in an experimental colitis model and in peripheral blood or mucosal immune cells of UC patients.

Methods: The immunomodulatory effects of rectally applied cobitolimod were evaluated in the dextran sulfate sodium (DSS)-induced colitis model. Isolated peripheral blood or mucosal immune cells from UC patients were incubated with cobitolimod in vitro and IL-10 and IL-17 expression was determined by quantitative PCR, ELISA and flow cytometry. Furthermore, histological slides from colon biopsies of steroid refractory UC patients that participated in two randomized, double-blind, multicenter clinical trials with local application of cobitolimod were analyzed by immunohistochemical staining for IL-10, FoxP3 and IL-17 expressing cells.

Results: Cobitolimod treatment ameliorated DSS-induced colitis, as it significantly reduced the disease activity index and endoscopic colitis grade and increased the body weight of the mice. Th17 cells and proinflammatory IL-17A, IL-17F, and IL-6 cytokines in intestinal specimen as well as IL-17 in the serum were significantly decreased after cobitolimod treatment. Peripheral blood or mucosal immune cells from UC patients incubated with cobitolimod, demonstrated significantly decreased IL-17 and increased IL-10 expression compared to controls. Quantitative immunohistochemical analysis of colon biopsies from UC patients taken before and four weeks after local cobitolimod treatment, clearly indicated a significant induction of IL-10+ and FoxP3+ and a pronounced reduction of IL-17+ mucosal immune cells, which were not observed in the placebo group.

Discussion/Conclusion: Local administration of the TLR9 agonist cobitolimod modulates the immune response in a mouse model of colitis as well as in UC patients by modulating the Th17/T-reg imbalance in intestinal inflammation.
GPR15/GPR15L as potential therapeutic targets in inflammatory bowel disease

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Introduction: T lymphocytes have been shown to critically contribute to the pathogenesis of IBD. Replenishment of intestinal T cells takes place in a process called “gut homing”, leading to extravasation from the blood stream to the lamina propria. The G protein-coupled receptor 15 (GPR15) has been shown to regulate such trafficking to the colon. Recently, its ligand GPR15L has been deorphanized and characterized as a chemokine secreted by the epithelium.

Methods: Human and murine colon cancer cell lines were analysed for mRNA expression of GPR15L. GPR15L expression in colon samples from patients with IBD was correlated with cytokine expression and clinical data. Co-expression of GPR15 and integrins was studied on T cell subsets from the peripheral blood of healthy donors and patients and the functional effects of GPR15L on T cell adhesion were studied in dynamic adhesion assays. GPR15L knockout and transgenic mice were used in the acute dextran sulfate sodium (DSS) colitis model and characterized by endoscopy, IVIS in vivo imaging, histology, immunohistochemistry, flow cytometry and qPCR.

Results: GPR15L expression in colon cancer cell lines was induced by TGF-β. GPR15L mRNA expression in colon tissue from IBD patients showed a negative correlation with disease activity and proinflammatory cytokines. Low levels of GPR15L expression were associated with early development of flares. High co-expression of GPR15 and α4β7 integrin was found on peripheral blood CD4+ T lymphocytes and dynamic adhesion assays demonstrated enhanced α4β7 integrin-dependent adhesion of CD4+ T lymphocytes to MAdCAM-1 upon GPR15L treatment. GPR15L transgenic mice showed reduced severity of acute DSS colitis compared with wild-type mice, whereas disease was exacerbated in GPR15L knockout mice. Consistently, pro-inflammatory cytokines and Th17 cell markers were increased in knockout mice.

Discussion/Conclusion: Collectively, our findings support an important regulatory role of the GPR15/GPR15L axis in IBD highlighting it as a potential future therapeutic target.
Frequency and characteristics of extraintestinal manifestations in inflammatory bowel disease in children – Single-center experience

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Introduction: Inflammatory bowel disease (IBD) is an important entity in pediatric gastroenterology with increasing incidence. Basically systemic disease, with gastrointestinal symptoms predominantly, may also present with extraintestinal manifestations (EIMs) either as first and only or associated sign of the disease. EIMs can present in different organs but are most commonly seen in joints, skin, bones, eyes, liver and other. Awareness of EIMs leads to earlier detection and more successful treatment of IBD.

Methods: The data were collected retrospectively from medical records of IBD pediatric patients in University Hospital Center from 2011–2016. 56 patients were enrolled, 32 males, 24 females, aged from 3–18 years (mean 13.14, median 14 years). There were 33 patients with Crohn's disease, 19 with ulcerative colitis and 4 with undetermined colitis. The patients with EIMs resulted as therapy side effects were excluded.

Results: Twenty patients, 35.7% of the total were presented with EIMs (median age of appearance was 13 years). 5 patients had more than one EIM. The most common was peripheral arthritis (in 9/56 patients) and aphthous stomatitis (5/56). The other EIMs were erythema nodosum (3/56), autoimmune sclerosing cholangitis (3), pancreatitis (3/56), episcleritis (1/56), primary sclerosing cholangitis (1) and nephrolithiasis. 16 children had EIMs before the diagnosis of IBD, in 6 patients EIMs were confirmed at the time of diagnosis and in 5 patients EIMs developed after the diagnosis was confirmed. EIMs were more common in male (85%) than in female patients (15%) as in patients with Crohn's disease (55%) compared to ulcerative colitis (37%) and undetermined colitis patients (7%).

Discussion/Conclusion: In our group of 56 patients we observed that every third child presented with at least one, and some with more than one EIM. Our data follow the results from the literature and show the importance of EIMs in total morbidity of pediatric IBD. We emphasize the importance of proactive diagnostic workup directed to early detection and treatment of EIMs, aiming to better outcome and prognosis of pediatric IBD.
Risk factors for complicated disease in pediatric patients with inflammatory bowel disease

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**Introduction:** The natural course of inflammatory bowel diseases (IBDs) can range from a quiescent course with prolonged periods of remission to aggressive, incapacitating disease requiring intensive medical treatment or surgery. Predicting which patients are more susceptible to developing complicated disease is important when choosing treatment strategies. The aim of our study was to analyze the clinical risk factors associated with complicated disease course, defined as need for surgery or failure of conventional treatment and start of biologic agents, in paediatric patients with IBD.

**Methods:** Single-centre retrospective study including children and adolescents with IBD, treated in the Department of Gastroenterology and Hepatology at the University Paediatric Hospital “Prof. Ivan Mitev”, Sofia for the period March 2011–October 2018. We analyzed the following variables: gender, age at diagnosis, presenting symptoms, duration of symptoms before diagnosis, disease localization and severity, presence of extraintestinal manifestations. Disease phenotype was assessed according to the Paris classification. Chi squared, Fisher’s exact or Mann Whitney test were used where appropriate, p-value < 0.05 was considered statistically significant.

**Results:** Totally 91 children were included in the final analysis – 51 with ulcerative colitis (UC) and 40 with Crohn’s disease (CD). The median age of the participants at IBD diagnosis was 14 years (range 2–17 years). The median follow up was 36 months (1–180 months). In UC patients, presence of extraintestinal manifestations was the only variable associated with complicated disease course (p = 0.036). In CD patients male gender (p = 0.018), longer duration of symptoms before diagnosis (p = 0.08), upper gastrointestinal involvement (p = 0.037) and presence of perianal disease (p < 0.001) were associated with complicated disease course.

**Discussion/Conclusion:** The identification of clinical risk factors for complicated disease is an essential step in the development of individualized treatment strategies in paediatric patients with IBD.
**Clostridium difficile infection in a patient with ulcerative**

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**Clinical case**
Male patient, 36-year-old, ulcerative left-side colitis, diagnostic in September 2016, clinical remission treated with mesalazine (Salofalk® 2 g/day)

**Symptoms**
Watery diarrhea (8–10/day), with blood, weight loss (6 kg/7 days), abdominal pain

**Physical exam**
Febrile, dehydrated, pale, abdomen painful to deep, palpation at all quadrants

**Lab results**
- Hemoglobin 11.5 g/dl
- Leukocytes 12.3 x 10⁹/l
- Platelets 462 x 10⁹/l
- CRP/Procalciton 25 mg/dl I 0.35 ng/ml
- Calprotectin 535 µg/g
- Clostridium toxin A, B positive

difficile

**Colonoscopy**

**Treatment**
Rehydration, vancomycin 125 mg/6 h, orvagil 500 mg/8 h, Bulardi capsules 500 mg/12 h
Therapy
Salofalk® 4.5 g/day, Salofalk® rectal suspension 4 g/60 ml every evening/2 months – continue, Salofak® suppositories, Bulardi caps 500 mg/12 h

Conclusion: Patients with ulcerative colitis are more prone to infections with Clostridium difficile. The infection can cause the progression of the disease.
Lymphocyte activation gene (LAG)-3 on T cells is a potential therapeutic target in ulcerative colitis

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Background: LAG-3 is a negative co-stimulatory receptor on T lymphocytes, and its expression identifies activated lymphocytes that may contribute to the initiation or persistence of inflammation. Therefore, we investigated LAG-3 expression in blood and tissue from patients with ulcerative colitis (UC) and examined subsets of cells expressing LAG-3 to determine their potential role in disease.

Methods: Flow cytometry was performed on blood and inflamed and non-inflamed colonic biopsy samples from patients with UC (n = 42) and controls (n = 9). Immunohistochemistry was used to quantify LAG-3+ cells, and correlate this with disease activity. Cytokine production from mucosal LAG-3+ cells was determined using flow cytometry and RT-PCR.

Results: The frequency of LAG-3+ cells in peripheral blood was negligible (< 0.5%), regardless of disease activity in patients. However, in the lamina propria, the frequency of LAG-3+ T lymphocytes was markedly increased in active UC compared with uninfamed and controls (p < 0.0001 and p = 0.001, respectively) and correlated positively with endoscopic score (UCEIS, p = 0.004, r = 0.43). LAG-3 expression was enriched on effector memory and CD161+ T cells. LAG3 mRNA levels were also increased in active disease (p = 0.003 and p = 0.008, respectively) and correlated with the histological Nancy score (p < 0.001, r = 0.68). Mucosal LAG-3+ T cells demonstrated robust production of IFNγ (p = 0.04) and IL-17A (p = 0.01) when stimulated ex vivo compared to LAG-3- cells, with lower amounts of IL-10 detected (p < 0.06). In patients undergoing treatment for UC, the number of LAG-3+ cells decreased in patients who responded to therapy (p < 0.0001, n = 11), but remained elevated in non-responders (p = 0.058, n = 12).

Conclusion: LAG-3 expression is not altered in circulating blood. However, mucosal expression is increased in inflammation and normalises after successful treatment. Although some reports suggest LAG-3+ cells have mainly regulatory functions, in human IBD, LAG-3+ cells are mainly effector memory cells and predominantly produce IFNγ, IL-17A and low levels of IL-10. Therefore, depleting LAG-3+ cells is a promising strategy for IBD that merits further clinical investigation.
Effect of dextran sulfate sodium treatment on germ-free mice colonized with mucosa-associated bacteria of ulcerative colitis patients

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Gut microbial colonization in ulcerative colitis (UC) patients is significantly different from the microbiota in healthy population.

We colonized germ-free BALB/c mice by gavage of colon biopsy from three patients with active UC. The shift in microbial community during its transferring from humans to mice was analyzed by Illumina MiSeq sequencer. Acute colitis was induced by drinking of 2.5% dextran sulfate sodium (DSS) solution for 7 days and disease activity was evaluated by clinical colitis scoring, histopathological grading and cytokine analysis.

None of the human-microbiota-associated (HMA) mice developed colitis spontaneously. When treated with DSS, HMA colonized mice developed colitis only in F4 generation. Compared to the DSS-resistant earlier generations of colonized mice, the F4 generation have increased abundance of Clostridium difficile and decrease abundance of C. symbiosum in their cecum contents measured by denaturing gradient gel electrophoresis and DNA sequencing.

In summary, we found that mucosa-associated bacteria from colonic biopsy of UC patients can increase susceptibility to DSS-induced colitis, although they are not able to induce spontaneous colitis in gnotobiotic mice. We showed that change in relationship between specific potentially deleterious and commensal bacterial species is important for increase of sensitivity to colitis. (Supported by grant 19-08294S of the Czech Science Foundation).
Estrogen receptor alpha contributes to T-cell-mediated colitis by influencing T-cell functions

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7Equal contribution

Introduction: More than 75 percent of autoimmune disorders are characterized by increased prevalence in females, indicating two most important factors accounting for the gender-bias in autoimmune diseases are genetics and sex hormones. Many studies have shown that estrogen can modulate the immune system; however, its roles in autoimmune diseases are obscured and it is still unclear whether estrogen influences Th cell differentiation.

Methods: To study how estrogen receptor alpha (ERα) contributes to T cell differentiation and gender biased autoimmune diseases, we generated tissue specific CD4-Cre ERαfl/fl mice, in which ERα is specifically deleted in T lymphocytes. T cell transfer model of colitis was used to clarify how ERα in T cells contributes to colitis development. RNA-seq was applied to identify ERα-regulated genes in T cells.

Results: We found that ERα expression in T cells was essential for the induction of T cell dependent colitis by influencing T cell activation, proliferation, and Foxp3 expression.

Discussion/Conclusion: Our data showed that ERα expressed in T cells plays an important role in T cell-mediated inflammation in a colitis disease model.
IFN-STAT1-MLKL axis drives necroptosis during gastrointestinal inflammation and infection

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Introduction: Interferons (IFNs) are potent immune-modulatory cytokines that are expressed by intestinal epithelial cells (IECs) in response to inflammation and infections. It has just recently been identified that interferons induce Mlkl gene transcription by activation of STAT1 and mediate necroptosis. Further studies demonstrated that epithelial necroptosis is an endogenous trigger of spontaneous intestinal inflammation in mice with many features of human Crohn’s ileitis. These previous data suggest a role for necroptosis in the pathogenesis of human gastrointestinal diseases.

Methods: IFN/STAT1 pathway was evaluated in mice with ileal inflammation and Crohn’s ileitis patients. Organoids were used to characterize the effects of IFNs on primary IECs and to evaluate pharmacological perturbation by Solu-Decortin and Tofacitinib. Additionally, IFN/STAT1 pathway was investigated during gastrointestinal infection.

Results: Here we demonstrate that CD patients display elevated levels of IFN-λ, especially in areas of severe inflammation and Paneth cell death suggesting that IFN-λ is linked to disease activity and associated with Paneth cell homeostasis. In mice, we show that IFNs promote Paneth cell depletion caused by STAT1-MLKL mediated necroptosis negatively controlled by caspase-8. Mice lacking caspase-8 are highly sensitive towards gastrointestinal inflammation and infection associated with lethality of these mice. Deletion of STAT1 ensures the survival of these mice during the early phase of gastrointestinal infection with a milder course of disease based on decreased epithelial cell death and increased epithelial integrity. Finally our data suggest that pharmacological inhibition of JAK/STAT signaling by Tofacitinib or Solu-Decortin attenuates expression of Mlkl, blocking STAT1-MLKL mediated necrosis and Paneth cell death.

Discussion/Conclusion: Collectively, our results strongly implicate a pathophysiological role for IFNs during inflammation by compromising Paneth cell homeostasis and during infection by mediating epithelial cell death and loss of barrier function. Hence IFNs should be considered as a new and promising target for future therapeutic intervention during gastrointestinal inflammation and infection.
Determination of intestinal resection in patients with ulcerative colitis using intraoperative mini-γ-quantum differentiation of tissues

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Introduction: Defining the border of resection of the intestinal area in patients with Ulcerative Colitis (UC) remains a problem of the final stage of the operation before the formation of the anastomosis, since it is very difficult to accurately determine the line of pathological ulcerative lesions and normal mucosa. At the final stage of the operation, after the part of the intestine was removed, before the formation of an anastomosis in patients with UC, the boundaries of the resection were determined using the proposed method of intraoperative mini-γ-quantum differentiation of tissues (V. Sulyma, V. Gaponov, V. Kravchenko, L. Mescheryakov; 2001).

Methods: Taking into account presence of different numbers of microelements in normal, inflammation and neoplastic cells where proposed using of well-known photoelectric effect for early differential diagnostic with fixation of received results in the form of physical size. In case of light-striking of cells with its losing of negative charge appears photoelectric effect, which is strictly individual for normal cells as well as for inflamed cells, non-malignant growth cells and malignant growth cells. Absorption of γ-quantum in case of energy spectrum of radiation from hundred keV to several MeV appears as a result of incoherent scattering by electrons of oxygen, carbohydrate and hydrogen atoms and characterized by low «k» absorption coefficient:

\[ J_1 = J_0 e^{-kL} \]

Where,
- \( J_1 \) – intensity of γ-quantum behind the object of investigation, hertz;
- \( J_0 \) – intensity of γ-quantum in front of the object of investigation, hertz;
- \( k \) – absorption coefficient, 1/sm;
- \( L \) – layer thickness of γ-raying object of investigation, sm.

Results: Were received follow results of measuring of material and registration of absorption coefficients and microelement’s characteristic radiation in initial intensity in patients with intestinal pathology (for 60 sec.):

<table>
<thead>
<tr>
<th>Energy, keV</th>
<th>Inflammation ulcerative tissue</th>
<th>Polyp</th>
<th>Cancer</th>
<th>Normal tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.6</td>
<td>up to 0.19</td>
<td>0.21</td>
<td>0.22</td>
<td>0.15</td>
</tr>
<tr>
<td>17</td>
<td>up to 1.7</td>
<td>1.9</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>5.9</td>
<td>up to 21.0</td>
<td>26.0</td>
<td>31.0</td>
<td>16.0</td>
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</tbody>
</table>

Discussion/Conclusion: Thus, it’s proved that change of intensity of absorption of low-frequency γ-radiation by the tissues’ cells is universal and give us possibility for differentiation in case of normal tissue and inflammatory ulcerative processes in intestine before forming anastomosis in surgical treatment patients with UC.
The complexity of treatment tactics in patients with severe ulcerative colitis in the presence of extraintestinal manifestations of the joints

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Introduction: Ulcerative colitis (UC) is an ulcerative-destructive lesion of the mucous membrane of the colon, which in some cases is manifested as extraintestinal lesion of the joints. Conducting drug therapy using Mesalazine (Salofalk®), which has an effective effect in the normal course of UC, has difficulty in patients with its severe forms in the presence of extraintestinal manifestations on the part of the joints. Particular difficulties arise in the preparation and conduct of surgical interventions in patients with severe forms of UC and the manifestation of extraintestinal joint damage in this case.

Methods: We have considered ways to optimize treatment tactics in patients with severe forms of UC with extraintestinal manifestations on the part of the joints in the preparation and conduct of surgical interventions. The treatment regimens for patients with UC were studied using the effective drug Mesalazine (Salofalk®), with the additional use of specific anti-inflammatory treatment of the affected joints.

Results: The use of combined treatment regimens for patients with UC on the background of extraintestinal articular manifestations in the preparation and conduct of surgical interventions to remove the affected areas of the intestine, which included mandatory therapy with Mesalazine (Salofalk®) and specific drugs aimed at reducing the manifestations of joint pathology, reduced activity as UC and its articular extraintestinal lesions. This therapy allowed subsequent radical surgery to be performed in patients with severe UC.

Discussion/Conclusion: The observations confirm the need for the use of combined treatment regimens for patients with UC and its extraintestinal articular manifestations in the preparation and conduct of surgical interventions.
Inactive plasma matrix Gla protein and biochemical parameters in patients with ulcerative colitis

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Introduction: Matrix Gla protein (MGP) is investigated as an important inhibitor of vascular calcification, and its inactive form has been connected with endothelial dysfunction, increased arterial stiffness and elevated cardiovascular risk in general. Inflammatory bowel disease has also been increasingly associated with cardiovascular risk and endothelial dysfunction, in addition with chronic inflammation. Therefore, aim of this study was to investigate inactive plasma MGP levels in patients with ulcerative colitis in comparison to control group, while additional goal was to investigate association of plasma MGP levels with disease activity and other biochemical parameters.

Methods: In this study 35 patients with ulcerative colitis were enrolled and paired with 35 control subjects matched in age, gender and BMI. ELISA kit (Phoenix Pharmaceuticals, Phoenix, USA) was used for plasma MGP measurement, while other parameters were measured using standard biochemical procedures. Detailed clinical information and anthropometric measurements were obtained from each participant.

Results: Ulcerative colitis patients had significantly higher plasma MGP values in comparison with control group (599.4 ± 120.5 vs. 532.6 ± 98.8 pmol/l, p = 0.013). Furthermore, plasma MGP showed positive correlation with faecal calprotectin (r = 0.393, p = 0.019) and hsCRP (r = 0.413, p < 0.001), while association with total cholesterol, LDL, HDL, and liver enzymes was not found. Positive correlation was found between plasma MGP and BMI (r = 0.340, p = 0.004) and waist circumference (r = 0.369, p = 0.001) as well. Finally, when described parameters were modelled in multiple linear regression analysis adjusted for age, sex and BMI, faecal calprotectin remained in significant association with plasma MGP (β = 0.11, SE = 0.04, p = 0.037).

Discussion/Conclusion: Results show that plasma MGP levels are elevated in patients with ulcerative colitis, and that it may play a role in complex pathophysiology of ulcerative colitis and its complications. However, further research is necessary to clarify the findings of this study.
Dynamics of secretion of immunoglobulin A in the serum of patients with Crohn's disease on the background of basic therapy

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Introduction: Blood serum secretory immunoglobulin A (SIgA) is the additional component of immunological protection of intestinal mucosa.

Methods: 38 patients with recurrent Crohn's disease (CD) aged 21–70 years (38.5 ± 1.7 years) were examined. The patients were divided into two groups: I – 12 patients with an isolated lesion of colon (31.6%), II – 26 patients with lesion of colon and small intestine (68.4%). The control group – 20 healthy volunteers, average age is 26.2 ± 8.3 years. Serum SIgA was determined by ELISA test. Statistical data analysis was performed using the software "STATISTICA 10.0“ (StatSoft, USA).

Results: The increase in the average concentration of SIgA in the group of patients with CD was recorded, which amounted to 9.5 ± 0.9 μg/ml, which is 3 times higher than the values in the healthy group (p < 0.05). Changes of SIgA concentration in serum did not depend on localization of pathological process: with colon lesions and combined lesions of the small and large intestines, the average SIgA values were: 8.3 ± 2.3 μg/ml and 10.1 ± 0.9 μg/ml (p < 0.05 compared with the control group). In patients with moderately severe disease course, SIgA serum concentration was 6.4 ± 1.4 μg/ml, with severe course it increased 1.7 times and amounted to 10.9 ± 1.3 μg/ml (p < 0.05). A direct link was also established between the indicator being studied and the duration of CD. Thus, during the first attack of CD, the increase in serum SIgA concentration averaged 8.7 ± 4.5 μg/ml the group, which was 2.8 times higher than the values in the control group. With a disease duration of 1–5 years, the average serum SIgA level increased to 10.1 ± 3.4 μg/ml, exceeding the control values by 3.3 times; at 5–10 years anamnesis the maximum 4-times increase in SIgA 12.9 ± 5.7 μg/ml (p < 0.05) was recorded. Upon reaching remission of CD, the concentration of SIgA decreased to the level of values in the control group – 3.1 ± 0.2 μg/ml.

Discussion/Conclusion: The results confirm the involvement of components of adaptive immunity in the initiation and maintenance of the inflammatory process in the intestine at CD.
Dynamics of changes in alpha and beta defensins in serum and feces during the course of treatment of ulcerative colitis

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Introduction: Secretion of antimicrobial peptides (AMP) (defensins) by the cells of the intestinal wall is aimed at activating the innate immune mechanisms, however, the conjugation of their levels with the course of inflammatory intestine diseases and dynamics during treatment remains unclear.

Methods: 63 patients with ulcerative colitis (UC) were under examination: 18 (29%) patients (group 1) had proctosigmoiditis, 24 (38%) (group 2) had left-sided colon lesions, 21 (33%) (group 3) had pancolitis and comparison group – 16 healthy volunteers. The content of defensin alpha in blood and defensin beta in feces was determined by ELISA test before and after 12 weeks of the course of treatment. All patients received therapy with 5-ASA (Salofalk®) in standard doses.

Results: The dependence between AMP content in blood and the Rachmilewitz and Mayo-Schroeder indices (r = 0.67, r = 0.75, p < 0.05), the AMP concentration in feces and endoscopic markers of colon inflammation (granulations, vulnerability, in-depth mucosal lesions), Rachmilewitz and Mayo-Schroeder indices (r = 0.75, r = 0.62, r = 0.82, r = 0.82, r = 0.80, p < 0.05), respectively. When clinically endoscopic remission of UC was achieved, a decrease in defensin alpha was recorded in group 1 from 471.8 ± 9.9 ng/ml to 170.6 ± 4.6 ng/ml by 2.8 times, in group 2 from 853.5 ± 19.5 ng/ml to 164.7 ± 5.7 ng/ml 5.2 times and in group 3 from 479.3 ± 16.8 ng/ml to 177.5 ± 8.6 ng/ml in 2.7 times (p < 0.001). Unidirectional changes were also recorded for defensin beta: in group 1, concentration decreased from 218.5 ± 8.2 ng/g to 60.4 ± 8.5 ng/g by 3.6 times, in group 2 from 210.8 ± 4.3 ng/g to 100.2 ± 7.5 ng/g by 2.1 times and in group 3 from 261.7 ± 9.2 ng/g to 87 ± 4.3 ng/g, which is 3 times lower than the level at relapse of UC (p < 0.001). In all groups, the level of defensins remained elevated: the defensin alpha content 2.3 and 2.5 times (p < 0.05), the defensin beta 1.9 to 3.1 times (p < 0.05) exceeded the average level of healthy.

Discussion/Conclusion: Elevated levels of AMP preserved after achieving clinical and endoscopic remission of UC, may have significant biological significance.
Cellular senescence of CD4⁺ T cells in the adaptive immune response against inflammatory bowel diseases

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Introduction: Induced by regulation of p53/p21 and p16INKa/retinoblastoma pathways, cellular senescence is mostly considered a protective mechanism against cancer development [1]. Lately, the role of cellular senescence in the immune function during aging is emphasized [2]. For example, aberrant CD4⁺ T cells can lead to inflammatory bowel diseases (IBD) [3]. The onset of IBD is common in elderly, potentially affected by an inefficient CD4⁺ T cells function [4]. Therefore, the molecular mechanism of cellular senescence on CD4⁺ T cells during inflammation needs to be investigated.

Methods: In order to study the role of cellular senescence in CD4⁺ T cells in inflammation, we employed p21 deficient mice (Cdkn1a⁻/⁻) and then subjected them to TNBS acute model.

Results: Interestingly, the knockout mice lost less weight and developed milder colitis compared to the wildtype mice. When investigating the immune infiltration in lamina propria (LP), we observed higher relative numbers of macrophages, but less dendritic cells in p21⁻/⁻ compared to the control mice. Moreover, relative gene expression showed downregulated Tbet and IFNγ expression in the LP of knockout mice. We further investigated the polarization of p21-deficient CD4⁺ T cells in vitro. Th1 polarization experiments showed that p21-deficient T cells produce less IFNγ and mature into effector/effector memory T cells in the detriment of central memory. Furthermore, T cell polarization led to less living p21-knockout cells compared to the control cells. Daily analysis of wildtype CD4⁺ T cells during Th1 polarization revealed that p21 is upregulated after two days of stimulation, influencing the production of effector and memory T cells and regulating cell death.

Discussion/Conclusion: In conclusion, p21 affects Th1 cell polarization of CD4⁺ T cells and leads to less colitis in mice models. Our data lay the foundation in understanding the mechanisms through which cellular senescence modulates inflammation.
References:


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Is there a difference between patients with ulcerative colitis diagnosed in the emergency department and outpatient clinic?

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Introduction: Some patients with UC may be diagnosed in the emergency department. The aim of this study was to determine the clinical characteristics and outcomes of the patients who were diagnosed with UC in the emergency department compared with those who were diagnosed in the outpatient clinic.

Methods: From 2012 to 2018, medical records were reviewed for patients diagnosed with UC. Patients were divided into two groups those diagnosed in the emergency department (ED) and in the outpatient clinic (OPD). We investigated demographic and clinical characteristics such as disease behaviour and location. We also compared clinical outcomes including the use of biologics and bowel resection surgery during the follow-up period.

Results: Overall, 65 UC patients were included in the study (male 65%, mean age 34). There was no significant difference in age, sex and follow-up period between groups. The length of the diseased colon segment was longer in the ED group. Surgical intervention and biologic treatment were more prevalent in the ED group.

Discussion/Conclusion: This investigation revealed that UC patients diagnosed in the ED had more complicated disease compared with those who were diagnosed in the OPD.
Pseudomyxoma peritonei in a patient diagnosed as Crohn’s disease initially

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Introduction: Many malignant or inflammatory processes cause abdominal lymphadenopathy (LAP), and computed tomography (CT) has become the primary modality for its detection. LAP is defined as retrocrural nodes greater than 6 mm in short axis, upper abdominal nodes greater than 10 mm, and pelvic nodes greater than 15 mm. Here we present a patient diagnosed as Crohn’s disease initially and suspected to have a different diagnosis due to abdominal LAPs irrelevant with the endoscopic signs. Pseudomyxoma peritonei (PMP) is an uncommon “borderline malignancy” generally arising from a perforated appendiceal epithelial tumour.

Results:
Case: A male patient with abdominal pain admitted to our hospital and diagnosed as Crohn’s disease due to intraabdominal LAPs and aphtheous lesions in the terminal ileum. However, the size of the abdominal LAPs were irrelevantly bigger than the expected sizes seen in Crohn’s disease. He did not have any peripheral LAPs and he underwent surgery for the resection of the 30 mm abdominal LAP. The histopathologic diagnosis was PMP.

Discussion/Conclusion: Reactional abdominal LAPs can be seen in Crohn’s disease however the clinician should be keen for a misdiagnosis if the LAPs are irrelevantly larger than the expected size.
Extraintestinal manifestations in patients with inflammatory bowel disease: Experience from a tertiary center

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Introduction: Inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) and Crohn’s disease (CD), affect mainly the gastrointestinal tract. Nevertheless, extraintestinal manifestations (EIMs) may occur before or after IBD diagnosis. The aim of the study is to investigate the epidemiological and clinical features of IBD patients who experience EIMs.

Methods: We performed a retrospective analysis of consecutive IBD patients who attended the outpatient IBD clinic in our center between September 2017 and September 2018. Demographic and clinical data concerning IBD characteristics and EIMs were collected and analysed using SPSS v24.

Results: Overall, 188 IBD patients were included (89 UC, 84 female) with mean age (SD) 48.7 ± 12.5, mean age (SD) at disease diagnosis 36.3 ± 14 and mean disease duration (SD) 12.6 ± 8.7. Of these, 21.3% of patients had at least 1 EIM and 3.2% had more than one EIM. In 13% of patients EIMs have occurred before IBD diagnosis, whereas in 87% EIMs followed IBD diagnosis. The EIMs that were reported were 20.2% musculoskeletal, 5.3% cutaneous, 2.1% ocular and 1.6% hepatobiliary. There was no significant correlation between the presence of EIMs and sex (p = 0.62), age and age at diagnosis (p = 0.983 and p = 0.432 respectively) and disease duration (p = 0.154). The proportion of patients with EIM was significantly greater in CD patients (35.4%) as compared to those with UC (12.4%) (p < 0.001). Smoking status (p = 0.287), BMI (p = 0.667), CD phenotype (p = 0.207), UC extent (p = 0.431) and prior IBD surgery (p = 0.123) were also not correlated to the presence of EIMs. However, patients with EIMs were more often hospitalized (p = 0.021). Musculoskeletal manifestations were significantly greater in CD as compared to UC patients (28.3% vs. 11.2%, p = 0.004), while cutaneous manifestations were most commonly found in patients with perianal CD (p = 0.002).

Discussion/Conclusion: The greater proportion of EIMs occurs after IBD diagnosis and are associated mainly with CD patients.
Differential expression of Th-related cytokine receptors in human colonic subepithelial myofibroblasts among IBD patients and healthy controls

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Introduction: Fibrosis, although more clinically significant for Crohn’s disease (CD), may occur in both forms inflammatory bowel diseases (IBD). Subepithelial myofibroblasts (SEMFs) are key players in fibrogenesis, as they are able to produce excessive quantities of extracellular matrix components. The study’s aim was to investigate whether SEMFs isolated from patients with IBD differentially express Th-related cytokine receptors compared to healthy controls.

Methods: SEMFs were isolated from endoscopically-obtained colonic biopsies from healthy controls and IBD patients (CD and UC: CD-SEMFs, UC-SEMFs), were cultured and total RNA was extracted. Cytokine receptors mRNA expression was assessed by reverse transcription quantitative (RT-q) PCR.

Results: Unstimulated SEMFs had a basal expression of most cytokine receptors studied. Regarding the Th1-related receptors, both CD- and UC-SEMFs had downregulated levels of IL1R1 (CD: 0.43-fold, IQR 0.31–0.51; UC: 0.15-fold, IQR 0.15–0.16) and TNFRSF1A (CD: 0.39-fold, IQR 0.38–0.51; UC: 0.27-fold, IQR 0.25–0.29), but differentially expressed IL12RB2; CD-SEMFs had downregulated levels, while UC-SEMFs upregulated (CD: 0.59-fold, IQR 0.48–0.6; UC: 1.46-fold, IQR 1.44–1.51). As to Th2-related receptors, only UC-SEMFs were found with downregulated mRNA levels for IL4R (0.24-fold, IQR 0.22–0.25) and IL13RA2 (0.23-fold, IQR 0.16–0.26). Concerning the Th17-related receptors, IL17RA was downregulated only in CD-SEMFs (0.58-fold, IQR 0.5–0.78), while both CD- and UC-SEMFs presented with reduced levels of IL23R (CD: 0.4-fold, IQR 0.28–0.43; UC: 0.58-fold, IQR 0.57–0.59). Finally, regarding the Treg-related receptors, CD-SEMFs expressed reduced levels of IL10RA (0.4-fold, IQR 0.32–0.55) and IL10RB (0.53-fold, IQR 0.39–0.65), while UC-SEMFs of TGFBRB2 (0.48-fold, IQR 0.34–0.63) and IL10RB (0.54-fold, IQR 0.5–0.59).

Discussion/Conclusion: Our data suggest that SEMFs might be the link between the inflammation and fibrosis, as they were found positive for most of the studied Th-related cytokine receptors. In CD-SEMFs, Th1- and Th17-related cytokine receptors appear to be downregulated, while UC-SEMFs were characterized by reduced levels of Th2-related cytokine receptors.
A vedolizumab-specific 4-gene colonic signature accurately predicting future endoscopic remission in patients with inflammatory bowel disease

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Introduction: Vedolizumab, a monoclonal antibody targeting α4β7 integrin, has been approved for the treatment of both Crohn’s disease (CD) and ulcerative colitis (UC). Due to the increasing availability of therapeutic compounds in inflammatory bowel disease (IBD), predictive biomarkers are urgently awaited in order to help clinicians decide between anti-TNF, vedolizumab or other therapies.

Methods: We obtained inflamed colonic biopsies from 31 patients (20 UC, 11 CD) prior to initiation of vedolizumab. Similarly, inflamed colonic biopsies (15 UC, 9 CD) were collected from 24 patients initiating anti-TNF therapy. RNA was extracted and RNA sequencing performed. Using randomized generalized linear modelling (RGLM), a predictor for vedolizumab-induced endoscopic remission (absence of ulcerations at month 6 for CD; Mayo endoscopic sub-score ≤1 at week 14 for UC) was identified in a randomly generated test cohort (n = 20) and validated in 11 independent samples. Through unsupervised consensus clustering, we validated the marker in a publicly available microarray dataset (GSE73661), and studied vedolizumab specificity in the anti-TNF treated cohort.

Results: Forty-four genes (25 down, 19 up) were significantly differently expressed between future vedolizumab remitters and non-remitters. Using these 44 differentially expressed genes as input for the RGLM modelling, we identified a 4-gene signature which could accurately split remitters and non-remitters in both the discovery (accuracy 90.9%, p = 0.02) and validation (100%, p = 0.006) set. Using the same 4-gene signature we could accurately discriminate prospective future remitters from non-remitters in a publicly available microarray data set of 13 open-label vedolizumab treated UC patients (84.6%, p = 0.02). In contrast, this 4-gene signature was not predictive for anti-TNF induced endoscopic remission (62.5%, p = 0.65).

Discussion/Conclusion: We identified and validated the first, vedolizumab-specific predictive 4-gene expression signature which may guide treatment strategy in IBD patients with colonic involvement.
Predicting endoscopic response in ustekinumab-treated patients with Crohn’s disease using multi-omics

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Introduction: Ustekinumab has been approved for CD, though predictive biomarkers of response are lacking.

Methods: Inflamed colonic (n = 25) and ileal (n = 22) biopsies were retrieved prior to first ustekinumab administration in patients with active CD, in addition to sorted circulating CD14+ and CD4+-cells (n = 39). RNA was extracted, and RNA sequencing performed. Proteomic analysis was performed on baseline serum samples (n = 86) using OLINK Proseek inflammation. Genotyping data was generated using Immunochip (n = 38). All described -omic layers were integrated and analysed using Multi-Omics Factor Analysis (MOFA). Strongest -omic layers in terms of variance contribution to endoscopic response (≥ 50% in SES-CD by week 24) were identified. Dimensionality reduction and feature extraction from the strongest -omic layers were performed followed by predictive modelling on the top ranked features. Cross-validation using distinct test and training sets was performed for the ensemble and individual classifiers, as an internal validation to avoid over-fitting.

Results: MOFA identified 19 latent factors (LF), with 3 LFs correlating with endoscopic response at week 24. The genomic and CD14 transcriptomic layers contributed significantly to the prediction of endoscopic response. Predictive modelling revealed a 10-feature CD14 transcriptomic panel predicting endoscopic response at week 24, with an accuracy of 98%. In contrast, classification performance based on 10 randomly selected features resulted in a drastic drop in accuracy (66%). Only 2 of the 10 features exhibited significant correlation with baseline faecal calprotectin, and 1 with CRP, suggesting that this panel is not a simple surrogate of baseline inflammation. From the genetic risk burden, we identified a 15-gene panel which could classify (accuracy 96.6%) the patients based on endoscopic response.

Discussion/Conclusion: Through multi-omic data integration, we discovered pathways contributing to ustekinumab response, and identified a 10-feature transcriptomic and 15-feature genomic panel predicting endoscopic response to ustekinumab standard dosage. Further validation in larger and independent cohorts is warranted, as well as its ustekinumab specificity.
The first anti-TNF-specific biomarker guiding therapeutic decision in IBD

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Introduction: With the expanding therapeutic armamentarium for IBD, biomarkers predicting efficacy are urgently needed.

Methods: We prospectively included 35 (discovery) and 19 (validation) consecutive IBD patients with active disease (both CD and UC) initiating anti-TNF therapy, as well as 22 patients initiating ustekinumab and 51 patients initiating vedolizumab. Whole blood expression levels of OSM, TNF, TNFR2 and TREM1 (total and transcripts separately) were measured prior to start of therapy using qPCR, and mucosal gene expression in inflamed biopsies using RNA-sequencing. Endoscopic remission was defined as an SES-CD ≤ 2 at week 24 for CD and a Mayo endoscopic sub-score ≤ 1 at weeks 8–14 for UC.

Results: Baseline whole blood TREM1 expression was significantly downregulated in future anti-TNF healers (p < 0.001, both discovery and validation cohort). ROC-statistics showed an AUC of 0.78 (p = 0.001), resulting in post-test probabilities of 77.1% and 90.0% for endoscopic remission and non-remission, respectively. A similar accuracy could be observed in mucosal TREM1 expression (AUC 0.77, p = 0.003), which outperformed the accuracy of serum TREM1 at the protein level (AUC 0.58, p = 0.31). Whole blood TREM1 expression did not significantly correlate with CRP (spearman ρ = -0.08, p = 0.38), faecal calprotectin (spearman ρ = -0.06, p = 0.64) or serum TNFα (spearman ρ = - 0.15, p = 0.63). OSM, TNF and TNFR2 were not differentially expressed in whole blood (p = 0.09, p = 0.13, p = 0.24, respectively), whereas they were at the mucosal level (p = 0.007, p = 0.02, p = 0.008, respectively). The whole blood TREM1 predictive signal was anti-TNF specific, as no changes in expression were seen in ustekinumab and vedolizumab treated patients, neither in whole blood (p = 0.82, p = 0.53, respectively), nor in tissue (p = 0.24, p = 0.10, respectively).

Discussion/Conclusion: We identified and validated low TREM1 as a specific predictor for anti-TNF induced endoscopic remission. These results can aid in the selection of therapy in biological-naïve patients, but should be confirmed in a randomized trial prior to translation into daily clinical practice.
Upregulation of IL-17-related pathways in affected colon from ulcerative colitis compared to Crohn’s disease

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) can both affect the large intestine but harbour key differences in the type of inflammation. Underlying molecular differences might guide therapeutic decisions. We aimed to elucidate the molecular networks in inflamed colonic biopsies from newly diagnosed CD and UC patients.

Methods: Patients naïve for biologicals and immunosuppressives, and without previous IBD-related surgery were prospectively included within 6 months after diagnosis (PANTHER study). We collected serum and inflamed colonic biopsies from 31 CD and 21 UC patients. All biopsies underwent single-end RNA sequencing. Co-expression networks (adj. p ≤ 0.1) were identified with WGCNA (R). A panel of 91 serological inflammatory proteins (O LINK) was tested for correlation with co-expression clusters.

Results: We found 21 co-expression clusters, of which 4 were upregulated in UC, and 3 in CD. Genes within UC-upregulated clusters (I to IV) were mainly involved in (a)granulocyte adhesion/diapedesis, and in the role of IL-17 in psoriasis. CD-upregulated clusters (V to VII) were enriched for mitochondrial dysfunction. Three clusters significantly correlated with serological marker levels: IL-6 with CD/UC cluster VIII, CDCP1 with CD/UC cluster IX, and IL-17A with UC cluster I (r = 0.57, adj. p = 0.10). The latter cluster was enriched for protein ubiquitination, known to be regulated by IL-17A. Of note, IL-17A serum levels were higher in UC than in CD (p < 0.001). Moreover, IL-17A tended to positively correlate with UC clusters II and III, of which cluster II contained IL-17A and IL-23A, both significantly increased in UC versus CD.

Discussion/Conclusion: In newly diagnosed CD and UC patients, we found common and distinct gene expression profiles, such as upregulated IL-17 pathways in UC. Higher mucosal expression of these IL-17 pathways correlated with higher serological IL-17A. These differences potentially affect drug target identification and therapeutic decision making, and emphasize the need for studies on the role and potential blockade of IL-23/IL-17 pathways in UC.
Primary immunodeficiency and inflammatory bowel disease: What is the main area of cooperation?

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Introduction: The aim of the research is a comprehensive study of the structure of colon microbiota in the mucosa of the colon in patients with PID, CVID and UC in different phases of the disease course.

Methods: The research included 19 patients with primary immunodeficiency (PID), 28 with common variable immunodeficiency (CVID) and 32 with ulcerative colitis UC (22 with relapse and 10 with persistent remission of the disease), control group – 20 healthy volunteers. Estimation of microbiota was performed by bacteriological seeding faeces, hydrogen breath test (HBT) with lactulose. Content of short-chain fatty acids (SCFA) and microbial lipid markers (MLM) in feces and colon mucosa was determined by gas-liquid chromatographic and gas chromatography-mass spectrometry (GC-MS).

Results: HBT showed a 4.5-, 8- and 11-fold increase in hydrogen production on a 150th minute study. SCFA showed a 6.9- and 11-fold decrease in propionic and butyric acids, mainly in patients with PID and UC: 0.2 ± 0.1 mg/g, 0.14 ± 0.03 mg/g and 0.04 ± 0.02 mg/g, respectively. Microbiological analysis showed a decrease in titers of E. coli, bifido and lactobacilli, bacteroids on average 4.6 ± 0.8 Lg. The conditionally pathogenic microflora was represented by hemolytic strains of E. coli, Clostridium spp., Klebsiella spp. and Candida fungi in titers > 10^6. MLN GS-MS results showed a 4.5-, 3- and 5-fold increase in total bacterial load in patients with PID, CVID and UC, respectively, which was represented by resident anaerobic microflora: Streptococcus mutants, Bacteroides fragilis, Clostridium difficile, Candida albicans and glabrata. In patients with UC, production of hydrogen normalized in the stable remission phase, the total bacterial load was reduced by a resident anaerobic microflora, the production of propionic and of butyric acids increased to subnormal levels.

Discussion/Conclusion: In patients with PID, CVID and UC, markers of colon excess growth with an increase in resident anaerobic microflora are recorded during the relapse period, a significant decrease in SCFA production is noted. Patients with UC in the phase of persistent remission have normalization of intestinal flora and production of SCFA.
Primary immunodeficiency and ulcerative colitis: Is it important gut microbiome?

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**Introduction:** A prospective pilot study of the relationship between the protein profile and the gut microbiota in patients with primary immunodeficiency (PID) and ulcerative colitis (UC).

**Methods:** The research included 22 patients with PID and 29 with UC (18 with relapse and 11 with persistent remission of the disease), control group – 18 healthy volunteers. Gut microbiota was assessed by the content of short-chain fatty acids (SCFA) and microbial lipid markers (MLM) in the feces and colon mucosa, as determined by gas-liquid chromatography and gas chromatography-mass spectrometry (GC-MS). The mucosal protein profile (MPP) was assessed using isoelectric focusing (SDS-PAGE, 2DGE). Mass spectrograms were obtained using MALDI-TOF-MS/MS (Bruker, USA).

**Results:** SCFA showed a 9- and 11-fold decrease in propionic and butyric acids, mainly in patients with PID and UC: 0.2 ± 0.02 mg/g, 0.04 ± 0.01 mg/g, respectively. MLN GS-MS results showed a 4.5- and 5-fold increase in total bacterial load in patients with PID and UC, respectively, which was represented by resident anaerobic microflora: Streptococcus mutants, Clostridium difficile, Candida albicans and glabrata. Results of PPP in biopsy specimens of the colon mucosa in patients with PID were detected: 1, 2, 4 okkludin, kininogen 1, interleukin-1B, interleukin-8, B2-glycoprotein, heat shock protein 27, apolipoprotein C-III. In patients with UC – NF-κB, alipoprotein C-III, TNF-α, interleukin-2 and 8 were presented. In patients with UC in the stable remission phase, the production of propionic and of butyric acids increased to subnormal levels. Proteomic profiles were dominated by accompanying proteins: a-enolase, b-defensin-1, cathepsin D.

**Discussion/Conclusion:** In patients with PID and UC recorded an increase in resident gut microbiota, reducing the SCFA production in relapsed disease. During remission of UC, the gut microbiota and SCFA production normalizes, specific components of the MPP disappear.
Infection rates in patients with inflammatory bowel disease in long-term vedolizumab treatment

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Introduction: Vedolizumab (VDZ) has shown both efficacy and safety in the treatment of active moderate to severe ulcerative colitis (UC) and Crohn’s disease (CD) in the Gemini trials and in real world studies. We aimed to assess the incidence of infections in patients who received long-term VDZ either as first line biologic treatment or after they lost response to anti-TNFs.

Methods: This was a retrospective analysis of prospectively acquired data in patients with UC or CD who have received VDZ for at least 14 weeks and were either biologic-naïve or anti-TNFα-exposed. VDZ was administered according to treatment label and the dosing interval could be reduced to 4 weeks in patients who were losing response. Patients were evaluated during every scheduled infusion and extra visits were arranged if needed.

Results: Between 9/2015 and 7/2018, 47 patients (female = 21, UC = 31) mean age (SD) 39 ± 13.5 years and with mean disease duration (SD) 12.2 ± 8.7 years were included. Mean duration (SD) of VDZ treatment was 46.3 ± 31.3 weeks. The extent of UC was proctitis in 3, left-sided in 12, and extensive in 16 patients respectively. Among CD patients, 4 had terminal ileitis, 8 ileo-colitis and 4 had colitis. 14 of 47 (29.8%) were biologic-naïve (group A) and the 33 of 47 (70.2%) patients were anti-TNFα-exposed (group B). The most common infections which were recorded were Clostridium difficile infection (n = 5), CMV (n = 2) and upper respiratory tract infections (n = 3). These adverse events were documented in 3 patients of group A (21.4%) and 7 patients of group B (21.2%) (p = n.s.). Hospitalization was required for four of the infections that were reported and one CMV infection led to treatment discontinuation and the patient had undergone colectomy.

Discussion/Conclusion: There is no statistically significant difference in infection rates between IBD patients who have received VDZ and were either biologic-naïve or anti-TNFα-exposed.
Developing an index that predicts escalation of therapy at an outpatient appointment in patients with known ulcerative colitis (UC)

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Background: Conventional follow up for UC places demands on health services. Demand might be better managed by targeting appointments to those patients who need therapeutic decisions. The aim was to develop a model that would predict the likelihood of escalation of therapy at an appointment.

Methods: The TrueColours UC (TCUC) pilot study collected data in real time for 6 months. Appointments and treatment decisions continued independently of the study and documented in the patient’s hospital record. Escalation of therapy was defined as any increase in therapy. Each appointment (date and need for escalation of therapy) was cross-matched with the corresponding TCUC electronic record. All variables collected by TCUC (simple clinical colitis activity index (SCCAI), IBD Control-8 quality of life, IBDoc faecal calprotectin, Hb, WCC, Plt, CRP, Alb, transferrin saturation and ferritin) were retrieved. Logistic regression and backwards elimination were used to create a model. Performance and internal validation were assessed. An Escalation of Therapy Calculator was developed.

Results: 66 patients had 208 appointments, of which 62 resulted in escalation of therapy. All 10 predictors were included in the initial model. Four significant predictors were identified: SCCAI, IBD Control-8, FCal and Plt. Because blood results are rarely available before an appointment, Plt were excluded. Points were assigned to levels of SCCAI, IBD Control-8 and FCal (Figure 1) to construct a model that predicted 99% probability of therapy escalation if the total point score was ≥ 100, with a calibration intercept of 0.01 (95% CI: -0.47 to 0.48), slope 1.09 (95% CI: 0.78–1.40), and apparent c-statistic of 0.95 (95% CI: 0.91–0.97) (Figure 2).

Conclusion: Real time data collection by patients through TrueColours UC can be incorporated into a prediction score to identify patients with UC most likely to receive escalation of therapy at an outpatient appointment. If externally validated, this may help manage demand for outpatient appointments.
Figure 1: Escalation of Therapy Calculator using SCCAI, IBD Control-8 and FCal

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<th>SCCAI Points</th>
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SCCAI = Simple Clinical Colitis Activity Index, FCal = IBDoc® Faecal Calprotectin

Figure 2: Calibration plot for SCCAI, IBD Control-8 and FCal prediction model
Non-classical monocyte homing to the gut via α4β7 integrin is essential for macrophage-mediated intestinal wound healing

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Introduction: Vedolizumab, an anti-α4β7 integrin antibody, is successfully used for IBD treatment. While inhibition of α4β7-dependent gut homing of pathogenic T lymphocytes is a well characterized, the impact on gut homing of monocytes, which regulate intestinal inflammation and tissue remodelling following differentiation into macrophages, has not been investigated so far.

Methods: Gut homing integrin expression and subset composition of peripheral blood monocytes and intestinal macrophages from IBD patients and controls were analyzed by flow cytometry and immunohistochemistry, respectively. Gut homing experiments of mouse monocyte subsets with anti-α4β7 or isotype treatment was performed in vivo. In vivo latex beads assays were employed for fate-tracking of non-classical monocytes (NCM) in intestinal wound healing. Moreover, the impact of α4β7 blockade on intestinal wound healing in vivo was analyzed endoscopically and peri-lesional macrophage subsets were determined by immunohistochemistry.

Results: Human CD14+16++ NCM along with mouse CX3CR1+ NCM expressed significantly increased levels of α4β7 compared to their classical counterparts. Consistently, in vivo homing of mouse NCM in vivo was reduced by anti-α4β7 treatment. Moreover, intestinal M2-like macrophages and NCM shared a similar homing marker repertoire in humans. Tracking of NCM fate during intestinal wound healing in vivo revealed a preferential differentiation to wound healing macrophages. Furthermore, α4β7 blockade led to impaired wound closure accompanied by a decrease of peri-lesional wound healing macrophages. In vedolizumab-treated IBD patients, the proportion of NCM in the peripheral blood increased, while the amount of intestinal M2-like macrophages decreased over the course of treatment.

Discussion/Conclusion: Besides blocking lymphocyte gut homing, anti-α4β7 antibodies also inhibit non-classical monocyte homing to the gut. This might lead to a peri-lesional decrease of wound healing macrophages as well as impaired wound closure, potentially providing a potential explanation for the controversially discussed observation of increased postoperative complications in vedolizumab-treated patients.
Clinical significance of anti-Saccharomyces cerevisiae antibody in pediatric patients with Crohn’s disease

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Introduction: Antibodies against Saccharomyces cerevisiae (ASCA) occur in 60–75% of patients with Crohn’s disease (CD). Testing usually includes detecting two different classes of ASCA in the blood, IgG and IgA. Some patients have only one positive Ig class. Higher titer of ASCA is associated with higher risk for surgery in adults but data in the paediatric population are still scarce. The aim of our study was to assess the clinical significance of ASCA as a risk factor for surgery in paediatric patients with CD.

Methods: Single-centre retrospective study including children and adolescents with CD, treated in the Department of Gastroenterology and Hepatology at the University Paediatric Hospital “Prof. Ivan Mitev”, Sofia for the period March 2011–October 2018.

Results: Forty patients – 17 girls and 23 boys were included in the final analysis. The median age of the study participants was 15 years (range 7–17 years). 62.5% (25/40) had ileocolic localization (L3), 20% (8/40) had colonic (L2) and 17.5% (7/40) ileal disease (L1). Disease behavior was classified as non-stricturing and non-penetrating (B1), stricturing (B2), penetrating (B3) and stricturing and penetrating (B2B3) in 65% (26/40), 15% (6/40), 10% (4/40) and 10% (10/40), respectively. 45% (18/40) had upper gastrointestinal involvement (32.5% – L4a; 12.5% – L4b), 15% (6/40) perianal disease and 15% (6/40) growth failure (G1). 32.5% (13/40) of our patients had a complicated disease and needed a surgical intervention. 69.2% (9/13) of the patients who needed surgery were ASCA IgG and IgA positive and 77.7% (7/9) of them had ASCA > 5 times the upper limits of normal (4 patients had ASCA IgG > 100 U/l and 2 patients had ASCA IgA > 100 U/l).

Discussion/Conclusion: Paediatric patients with CD with high ASCA IgA and/or IgG titer are at increased risk for surgery.
The impact of surgical resection on bone loss in patients with Crohn’s disease

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Introduction: Bone loss is common in patients with inflammatory bowel disease (IBD). The aim of the study was to evaluate the prevalence and risk factors of bone loss in patients after surgical resection for Crohn’s disease (CD).

Methods: Cases of bone mineral density (BMD) and disease characteristics were retrieved from 155 patients with CD who had intestinal resection in a referral IBD center. BMD was measured on dual-energy X-ray absorption (DEXA). Patients were classified into normal BMD and low BMD groups based on the International Society for Clinical Densitometry. Demographic and clinical variables were evaluated with logistic regression analysis to identify potential risk factors.

Results: The DEXA of lumbar spine indicated that 45 (29.0%) CD patients had a low BMD at a median of 2.2 years after bowel resection. Body mass index (20.13 ± 2.56 vs. 18.27 ± 2.00, p < 0.001) and history of colectomy (48.2% vs. 77.8%, p = 0.001) were independently associated with the BMD of the lumbar spine. The BMD of lumbar spine showed an increase in patients with CD after small bowel resection at a median of 1.4 years and a decrease in patients after colectomy at a median of 1.1 years compared to their LS-BMD before bowel resection.

Discussion/Conclusion: Low BMD was common in CD patients after surgical treatment. A low BMI and history of (hemi)colectomy were significant clinical risk factors for low BMD in CD patients.
Persistent fever – Rare presentation of anti-TNF-induced systemic reaction in patient with severe Crohn’s disease

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Introduction: Anti-TNF drugs are usually well-tolerated, however, there have been reports of many potentially serious adverse effects (Katz J, Frank M. 2012). Crohn’s disease (CD) patients who are treated with anti-TNF are at risk for developing infections, malignancies, infusion reactions and hypersensitivity etc. (Connor V. 2011). The side effects seen in children, adolescents are similar to those seen in adults (Hirsch J, et al. 2016).

Methods: This is a prospective observational review of a 19-year-old patient with fibrostenotic CD (A1L2B2,3). Patient presented from 1 year and 3 months old with growth retardation, later in childhood age patient diagnosed with decreased weight, reduced appetite, anaemia. At 14 years old patient treated with mesalazine and azathioprine.

Results: From January 2014 treatment with adalimumab (SQ) was started in a dosage 80 mg – 40 mg – further 20 mg every 2 weeks. From May 2014 patient presented with febrile fever. All infectious causes were excluded. A medication-induced late side effect was determined to be the most likely explanation of his fever. Adalimumab was discontinued and oral prednisolone 1 mg/kg/day was started. In July 2015, due to high activity of disease (CDAI = 350), patient treatment was initiated with infliximab (Remsima®) 5 mg/kg. After few months, in February 2016, patient presented with febrile fever again. Endoscopical and radiological improvement of CD was observed and dosage of infliximab was stepped up to 10 mg/kg. Still the febrile temperature was present, infliximab was discontinued in October 2016. At 2017 MRI was performed were perianal transspincteric fistula was diagnosed. At 14th of August 2018 patient started treatment with IL-12/23 monoclonal antibody – ustekinumab. His clinical and laboratory tests showed the decreasing activity of CD (CDAI = 104). No febrile temperature is present any more.

Conclusion: Case report presented a medication-induced fever due to anti-TNF therapy and a successful treatment outcome with IL-12/23 monoclonal antibody.
Serum catestatin levels and arterial stiffness parameters in patients with Crohn’s disease

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Introduction: Catestatin is endogenous functional protein that acts as an inhibitor of catecholamine secretion. Studies implicate its role in pathophysiology of cardiovascular disorders and various metabolic alterations. Furthermore, recent studies conducted on experimental colitis models suggest upregulation of catestatin in those conditions, and its possible role in attenuating inflammation process. To our best knowledge, there are no published studies that investigated catestatin in Crohn’s disease (CD) patients. Therefore, aim of this study was to determine catestatin levels and its connection with arterial stiffness parameters in patients with CD.

Methods: This study enrolled 40 patients with diagnosed CD and 40 controls matched in age, gender and anthropometric measurements. Serum catestatin level was determined with ELISA kit (Phoenix Pharmaceuticals, Phoenix, USA), while arterial stiffness measurement was performed with SphygmoCor device (AtCor Medical, Inc., Sydney, Australia).

Results: CD group had significantly higher serum catestatin levels in comparison with controls (10.7 ± 7.8 vs. 6.3 ± 3.4 ng/ml, p = 0.004). Additionally, CD patients had higher pulse wave velocity (PWV) (7.6 ± 2.0 vs. 6.3 ± 1.4 m/s, p = 0.001) and central augmentation index (Aix) (17.3 ± 14.8 vs. 10.2 ± 12.9%, p = 0.026). Furthermore, serum catestatin significantly correlated with PWV (r = 0.262, p = 0.019) and Aix (r = 0.311, p = 0.005). Multiple linear regression showed that catestatin remained in significant association with PWV after adjustment for age, sex and BMI (β = 0.980, SE = 0.4, p = 0.019). Finally, multiple logistic regression analysis adjusted for age, sex and BMI revealed that catestatin (OR = 1.123, 95% CI: 1.013–1.243, p = 0.026) and PWV (OR = 1.706, 95% CI: 1.205–2.415, p = 0.003) were independent and significant predictors of positive CD status.

Discussion/Conclusion: The results of this study show that patients with CD have higher serum catestatin levels when compared to healthy controls. Furthermore, catestatin may have a role in arterial stiffness in these patients. Further studies are needed to clarify the importance of these findings.
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