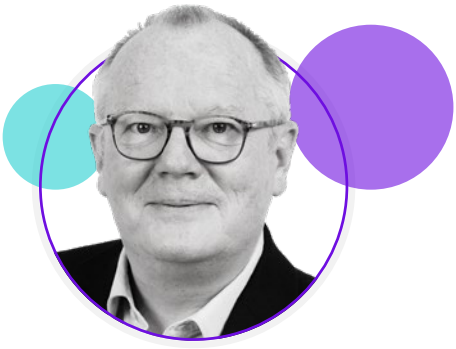
Congress Interviews

EMJ was delighted to interview both the President, Matthias Löhr, and the Vice President, Joost Drenth, of United European Gastroenterology (UEG), as they discuss the latest advancements in autoimmune pancreatitis, pancreatic cancer, and autoimmune hepatitis, as well as the future of UEG.

Featuring: Matthias Löhr and Joost Drenth



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Q1 As current President of United European Gastroenterology (UEG), what is your key goal for the future of the organisation? How are you fostering engagement and collaboration around digestive diseases in Europe and beyond?

For the organisation, we must look towards a more sustainable future for both the structures and finances of UEG. It is my goal to make the UEG fit for the future. This is a process I started when I came into office at the beginning of the year and that is ongoing, and most likely will not be finished by the time I leave office at the end of next year.

Now, for digestive diseases across and beyond Europe, we have over 30,000 virtual myUEG Associates, and they're coming from around the globe, from beyond Europe: 500 from the USA alone, 200 or so from Asia, and South America. These international collaborations and links become more and more important for the exchange of knowledge, but also for networking. We're making an effort to welcome those countries, but also to have structured contracts and collaboration agreements for the mutual benefit of both UEG, and say, the Korean, Japanese, Americans, South Americans... We had presentations from our sister society, the American Gastroenterological Association (AGA), and we had another session with our Pan-American friends, from South America. So, this is a really important part of the ongoing business.

Something else I do with my colleagues in the executive committee is to reach out to countries both within Europe, at the borders of Europe, and beyond, to tell them what UEG has in store for them, what offerings we have for members of UEG within both national societies and speciality societies, such as more chances to apply for and obtain grants, etc. Even for those outside Europe, we have lots of offers: they can become myUEG members, join consortia, post questions, ask for collaborations, e.g. for certain rare diseases.

> "It is my goal to make the UEG fit for the future"

Another thing, which I was pushing for and initiating already as vice president, is for UEG to engage with and be part of European research projects, like Horizon Europe. Where does UEG excel beside organising the world's best GI Congress? Dissemination and marketing. UEG has now engaged in two European projects where we are doing the dissemination part. But in the future, could that develop into taking over more and more responsibilities within such a European project? Those are my ideas and prospects for the future.

Q2 What originally sparked your interest in the pancreas, "the central organ"?

I was really puzzled by the fact that this is the only organ that has this endocrine-exocrine function, that produces the enzymes needed for digestion, as well as insulin, and I was interested in the interrelationship between those two parts. For my MD thesis, I started out with the endocrine pancreas, and then studied the relation to the exocrine pancreas, and, as is sometimes the case, I developed this into a career. Obviously, it has to do a lot with your environment and your mentor. I recently received the Lifetime Award from the European Pancreatic Club, where I was invited to write a small piece that reflects a little bit on that journey, and how I developed my interest in the pancreas.

Q3 Your research has significantly advanced our understanding of chronic and autoimmune pancreatitis. Can you tell us more about your work in pancreatic exocrine function and the endo-exo-axis?

Apart from the Society for Digestive and Metabolic Diseases in Germany, which is an exception, the endocrine and exocrine parts of the pancreas are treated as two different specialties, one dealing with the endocrine pancreas, as in diabetes, and the other with the exocrine pancreas, as in gastroenterology. The fascinating part is how they are really connected, and this is extremely important. Insulin is produced in the islets of Langerhans and flushed out towards the liver, but the blood passes through the exocrine pancreas; so, as a result, the highest levels of insulin are present in the pancreas. It is a prerequisite, actually, during the development of mammals, to have a pancreatic gland, because the islets need to join the exocrine pancreas to form the pancreas, and that is necessary to produce vast amounts of enzymes for digestion, particularly of proteins and fat, used to develop the brain.

Now, this is the evolutionary, developmental part, but the important thing is, what if you no longer have insulin, as in diabetes? Then you lack this trophic effect, because insulin is a growth hormone. You lack this trophic effect primarily to the pancreatic exocrine tissue, and then obviously to the rest of the body. This endo-exo axis is really pivotal to understanding consequences in patients with diabetes, but most diabetologists have no knowledge about this. One of the things my colleagues and I do is to educate diabetologists and advocate for this kind of knowledge, so that they really look out for pancreatic exocrine insufficiency in diabetic patients, which is there. There are numerous studies that have proven that point.

Q4 What research questions still remain to be addressed?

While there's lots of circumstantial evidence that is well published and understood, we still need a very large prospective study, over many years, not just the typical 6–12 months, to recruit patients with diabetes with and without exocrine pancreatic insufficiency, and look at the outcome of giving these patients pancreatic enzymes. This is a study that is lacking, and industry is hesitant, because that's a long-term commitment and costs a lot of money.

The other thing missing is broader understanding of the exocrine pancreas, and we are in the process of publishing the third guidelines, which were actually presented during the recent UEG Week by Enrique Domínguez Muñoz, from University Hospital of Santiago de Compostela, in Spain, on exocrine pancreatic insufficiency, in the sense that you lack the digestive effect, not necessarily have less secretion by the pancreatic gland. Something we would like to convey to our colleagues in gastroenterology and beyond is that there are other conditions, such as congestive heart failure, where you could definitely develop exocrine pancreatic insufficiency.

Q5 As a key figure in the development of the first evidence-based European guidelines for chronic pancreatitis (HaPanEU), what were the biggest challenges in establishing consensus, and how do these guidelines shape clinical practice across Europe today?

The HaPanEU guidelines for the diagnosis and treatment of chronic pancreatitis were the first evidence-based guidelines that the UEG issued and approved. This is one of the things we needed, in Europe, not only for the pancreas but for other conditions. Often, for implementation of guidelines, you need to rely on national specifics, but the diagnosis around these diseases is common across European countries.

For the first time, we brought together experts not only from gastroenterology, but also oncology, endoscopy, etc. It was really a multidisciplinary, cross-sectional guideline with many working parties. For the first part, we looked into diabetes. The most interesting part is, if you do any kind of guidelines, you basically detect what is lacking in the field. That led to the latest guideline, which is now dealing with pancreatic exocrine insufficiency in all conditions, both pancreatic and non-pancreatic. The paradigm shift we introduced with the latest guidelines is that we are not defining exocrine pancreatic insufficiency as just a deficit in pancreatic secretion, that is enzyme production; we're now defining it as a lack of the effect of enzymes digesting food in the intestine. That clearly can have several kinds of aetiologies, amongst them, of course, pancreatic diseases, but also

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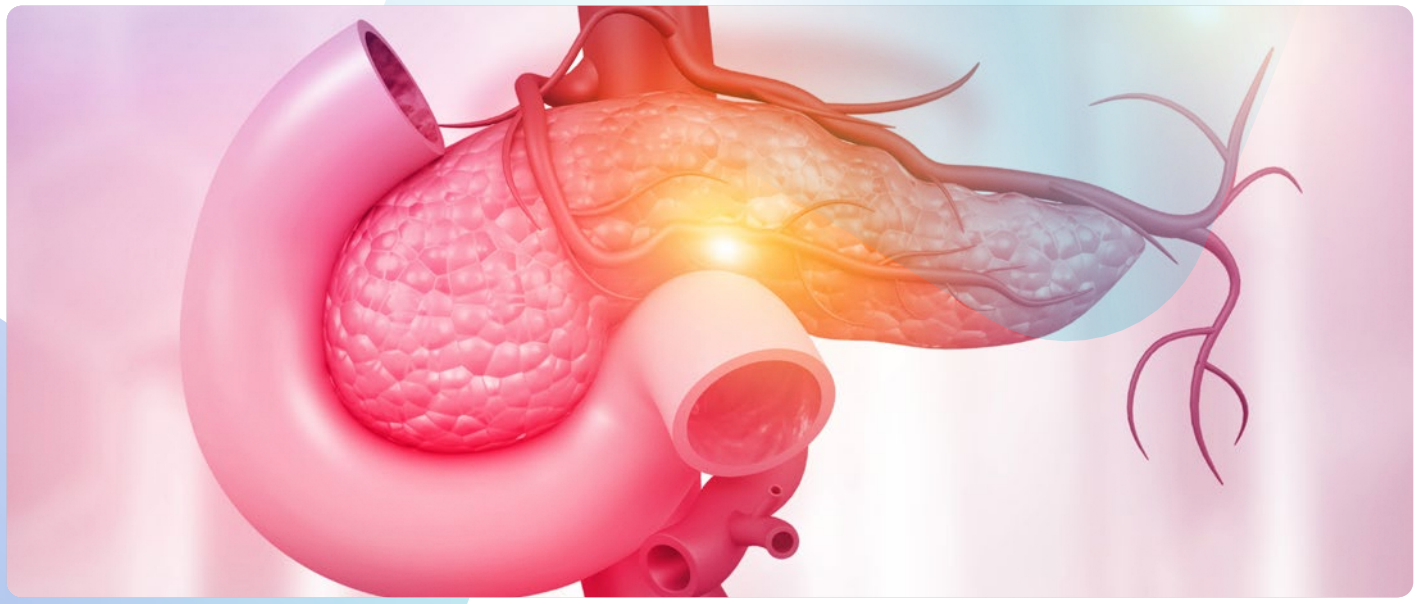

others such as Crohn's disease, coeliac disease, gastric surgery and other intestinal surgeries, some kinds of drugs, and HIV as well. All of this is covered in these guidelines, and that is really a result of the first guidelines.

Then, of course, the important question is how these guidelines did or did not shape clinical practice in Europe. We had the idea that we should analyse the implementation of these guidelines, but the Dutch Pancreatitis Study Group just beat us by maybe 2 or 3 months. They had their paper out, and we were just finishing up on ours. The Dutch Pancreatitis Study Group did a nationwide analysis about the implementation of the HaPanEU, and we did it as one centre. Now, the bottom line here is similar: we both are not perfect, neither the Dutch nor Karolinska, and there are different levels of fulfilment of the criteria in those guidelines. Diagnosis is okay, therapy maybe not so optimal, certainly not 100%, and this is a very sobering view on what we're doing.

The good news is that, slowly, the level of adherence to guidelines improved year after year after we published our guidelines. This implementation is very important, and the evidence that is coming now is a crucial part of the guidelines themselves.

> **Poor prognosis cancers are defined by a median survival of less than 2 years, and pancreatic cancer is leading this**

Q6 You were also in charge of the UEG consensus for IgG4-related diseases. Can you summarise key points and implications for clinical practice?

IgG4-related diseases encompass pancreatitis, even immune-related autoimmune cholangitis, and for that reason, some of us were invited by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) to be part of a consensus. We learned a lot from the rheumatologists because this IgG4-related disease is a systemic rheumatological disease, in essence, which happens to have lots of manifestations in the GI tract. It was our idea to sum this up on the European level, and focus on GI diseases and obviously the pancreas.

The most important change in clinical practice that we learned from our colleagues in rheumatology is that, for second-line therapy, you no longer rely on yet another course of steroids. They switch over to biologicals quite quickly. For the time being, that was rituximab. And as a consequence of that work, another drug that already existed for some ocular disease was promoted and made available to us for a Phase III study in IgG4-related diseases, including autoimmune pancreatitis, which is going to be published very soon. So, the guidelines, number one, were very much focused on the GI tract, which I think was needed to educate our gastroenterologists about this disease in more depth; and number two, it led to a Phase III study which will bring us now the first drug ever approved and registered for IgG4-related disease. The results will be presented at the ACR meeting later this month.

Q7 Pancreatic cancer remains one of the most challenging cancers to treat. Could you tell us more about the personalised cancer medicine study you conducted in pancreatic cancer?

The driving point here is that pancreatic cancer is a terrible disease. For the time being, almost everybody who receives that diagnosis will die, and will die rather soon. The medium survival time is now less than 1 year in inoperable patients, which make up more than 80% of cases, and in operable patients, we are now reaching 2-year survival, which is good, but overall it's a very dismal prognosis.

From the UEG point of view, we have been pushing the European Commission in two ways. Number one, they opened up a category for 'poor prognosis cancers' and another for 'neglected cancers'. Poor prognosis cancers are defined by a median survival of less than 2 years, and pancreatic cancer is leading this, together with bile duct cancer and some others. The neglected cancers are not necessarily those that have the shortest life expectancy, but receive less attention and funding. There again, pancreatic cancer is number one, and ovarian cancer number two.

One of the many reasons why pancreatic cancer has such a bad prognosis is that the tumour is rather resistant to conventional therapy. We have learned a little about molecular profiling, but if you look at its mutational profile, pancreatic cancer does not have the most genomic alterations; this would be malignant melanoma or colorectal cancer. Mutations in pancreatic cancer are very much spread across the genome, and that is the reason why targeted

therapy, like against EGFR, which works very well in colorectal cancer, doesn't work in pancreatic cancer, at least not in such a high percentage of patients. It works in a small percentage that we call the "tail" of these Kaplan–Meier curves, and these 2–5% patients have a long-term effect from these targeted therapies. So, the idea was to perform large-scale molecular profiling, not only with two or three markers, but a whole exome, and use an AI-based software to analyse the entirety of the molecular changes in a holistic view. If the patient has wild-type KRAS, for instance, you would assume receptor blockade is working, but if you then have an activating mutation further down, it wouldn't work. The software looks at all of this and gives recommendations on what drugs can be used. We published this at the beginning of this year.

Having said this, the problem in Sweden, as in Great Britain, is that even if a drug is approved, generally speaking, that doesn't mean that you will get it for your patient because then it would be off-label use. In Germany, for instance, you can have a single request to your patient's health insurance and get that covered. In Sweden, we have to pay this out of pocket from the hospital, and apply to use a particular drug for this patient based on the molecular profile and the evidence behind it. This personal approach is valid, and as a result, Karolinska University Hospital, our comprehensive cancer centre, is now, from the hospital side, paying the molecular profiling for pancreatic cancer and other solid cancers which have not been yet treated. So that's a very good result.

> **Now, specific KRAS inhibitors for the mutations that are most prominent in pancreatic cancer, like *K12D*, are in clinical studies**

Q8 What upcoming innovations or treatments in pancreatic cancer are you most excited about?

We have just talked about individualised treatment, but I think we can look forward to two developments. One is, after decades of knowing that KRAS is the overarching driver mutation in pancreatic cancer, even of the initial malignant transformation, we now have several kinds of drugs, small inhibitors and antibodies, that address and detect mutant KRAS. Sadly, this was not developed initially for pancreatic cancer, but for colorectal cancer, and as a result, the first KRAS mutations covered were not those most prominent in pancreatic cancer. However, even in pancreatic cancer, they've worked. Now, specific KRAS inhibitors for the mutations that are most prominent in pancreatic cancer, like K12D, are in clinical studies, which is very good news. At Karolinska we are participating in these clinical studies with our Phase I unit.

The second thing, which was presented at last year's American Society of Clinical Oncology (ASCO) Meeting, is a vaccination strategy where you look at the molecular profile from the RNA, the expression of mutated genes and then proteins, to make a personal vaccine. This is basically the BioNTech mRNA approach, and they have been working on this technology already for many years. The COVID-19 vaccine was really a 'side track' to serve an obviously urgent need, but they have worked in the pancreatic cancer field for years already, and that seems to work extremely well in patients who mount a particular T cell response. They had, in an adjuvant setting, a very long disease-free survival. I think that is rather exciting, and that's why this vaccination therapy works best with the lowest tumour load, which is exactly what you have after surgery of the primary tumour.

I think the personalised medicine approach will be valid. We know by now that certain drugs, even gemcitabine, work only in a particular subtype of pancreatic cancer; this is work done by David Tuveson's group at the Sloan Kettering/Cold Spring Harbor Laboratory in New York City, USA. The knowledge for these drugs is increasing, but I think the KRAS drugs are really a breakthrough, as well as the vaccination in the adjuvant setting.

Q9 As leader of the European Educational Program for Future Pancreatologists, "Pancreas 2000", what are your key priorities for fostering the next generation of pancreatologists?

The programme was inaugurated here at Karolinska in 1999, when the pancreatologists foresaw a shortage of experts in the pancreas, both for surgery, gastroenterology, and oncology. They started this programme with a clear vision to engage young colleagues in that field. I was leading this project until last year, and now I'm still a mentor in the programme.

The first pillar of the programme is education by the best European experts in the field, through lectures, case presentations, discussions like the multidisciplinary tumour board, and conferences. When different experts discuss a patient case, you can develop a feeling of what is really important. We have also done this during UEG Week.

The second pillar is for young colleagues to pursue a project in an interdisciplinary way. Some of them do not come from a pancreas centre, and we want to extend the network beyond the known large centres. It is amazing to see the ideas that these young colleagues, particularly those not from these centres, are coming forward with. Out of 30 participants we typically have, each provide two or three ideas, and the group of mentors then select the 15 best ones, which are then presented in person and discussed during the first meeting. Out of those 15 projects or so, we select five to six, and then the young colleagues are allocated these projects based on their interests. I always compare this to the "sorting hat" event in Harry Potter. We have been very successful in doing this. You have a group with two mentors, which then help the young colleagues develop the idea into a study protocol, get this through the institutional review board (IRB) ethics approval, and then conduct the study, collect the results, do the statistical analysis, eventually write an abstract, present it, and write the paper.

The third pillar was revolutionary at the time. In 1999–2000, Karolinska Institutet had just started a project where they would educate the leaders and give them tools to help them develop, learn about themselves, gain discussion skills, etc. At that time, this was already standard in industry, but unknown in academia, and certainly in medicine. This is still one of the pillars that the young colleagues appreciate the most.

If you look back these 25 years, 90% of participants educated in these now 11 courses have stayed in the field. The majority have obtained leading positions as departmental heads and professors. That has really fostered the entire field of pancreatology across surgery, gastroenterology, pathology, radiology, paediatrics, oncology… The priority here is to work together, and they also learn about the joy of doing that. It's rewarding. And as a result, we have founded the Young Pancreatologist Platform in Europe (YOUPPIE), which is now an alumni organisation carrying this on and giving young pancreatologists, or gastroenterologists interested in the pancreas, a chance to meet.

As I said, in a course we can only take about 30 participants, and this creates a network, which was a good starting point for the guidelines. If you want to conduct a study, you would turn to people with whom you have worked together for 2 or 3 years, right? This has created such momentum that most of the active researchers now in the field of pancreatology have been associated as mentors or participants in the Pancreas 2000 programme. It's a success story.

Finally, you learn to appreciate the challenges that those young colleagues come with: they have other ideas, other methods to communicate and learn. That is quite obvious looking back at the last 25 years or so. And they challenge you too, with a fresh attitude. This is what I like the most about being in academia.

Q10 What advice would you give to young researchers who aspire to specialise in gastroenterology?

I think two key points are most important. Number one, you really must burn for what you're doing. Once in a while, we have colleagues who just do the research and the PhD because they know this is a prerequisite to reach a senior position. This is okay, but you should really be interested in what you choose to do, in pursuing not only a profession as a gastroenterologist, but also a career in research.

Number two is that you can't do it on your own. The key element is that you need to have a mentor, a good role model. More than half of our mentors here are female; even if I think I can accommodate female young colleagues, for them to have a female role model is extremely important. So, pick the right mentor. Sometimes there is an element of serendipity to it because when you start your career, you typically don't ask these questions. You say, "they seem like a nice person... I'm a little bit interested in GI... now I've ended up with the liver or the pancreas." You don't think that much about it. Only a minority of students come to us and say that they would like to work on the pancreas. We have a stream of students coming to us to complete their research to get the points they need to pass the course, and what you have to do is show them that it's really rewarding and fun to do research.

> **MyUEG, our virtual platform, has now more than 30,000 gastroenterologists across the world. It's really the largest network in GI globally**

As a young colleague going into gastroenterology, you should identify something you're interested in when you finish medical school, or as is the case in many European countries, after finishing the "common trunk" of internal medicine before going into a subspeciality. By then you should know if gastroenterology is your "thing". Then, you should really try to find a mentor who is capable and willing to help you, has a good track record of helping young colleagues do research and finish a PhD, and someone that you have good chemistry with.

Finally, you should also look out for others in the field. MyUEG, our virtual platform, has now more than 30,000 gastroenterologists across the world. It's really the largest network in GI globally. Not only is registration free, but you can also get educational content for free, including all content from UEG Week until the end of December. Then you can join interest groups, ask questions about patients, look for colleagues in your country, even in your particular city. So, look out for others who are interested in GI, and look for the ones who are interested in a particular disease, molecule, pathway, methodology. From my own experience, we were looking for colleagues to join a retrospective analysis for some rare diseases, such as autoimmune pancreatitis, and it is really fantastic what you can do in this safe space. It's not social media such as Twitter or LinkedIn, it is really a secure space where only you, as a professional, can enter. That is a prerequisite.