The 5th Symposium on Inherited Diseases of the Pancreas took place immediately after the 37th European Pancreatic Club Meeting in Graz, Austria. The 1-day meeting was hosted at the Karl Franzens University and was attended by 100 registered participants. The aim of the symposium was to bring together not only experts for diseases of the exocrine pancreatic, but also well-known endocrinologists with an interest in the genetics of pancreatic disorders. The third group of speakers included molecular and cell biologists with a research focus on pancreatic diseases. 25 invited speakers from 8 different nations contributed to the success of the meeting. A major breakthrough reported at this meeting for the first time was the discovery of the genetic and cell biological changes underlying Johanson-Blizzard syndrome (JBS). Other highlights included progress in unraveling the molecular and cellular mechanisms that underlie the previously reported genetic changes involved in inherited pancreatic disorders.

The speakers and audience engaged in lively and sometimes controversial discussions, particularly about the pathophysiological and cellular consequences of some of the genetic changes.

The program began with the ‘Biology and biochemistry of SPINK and monitor peptide’ presented by Rolf Graf from Zurich. Ever since the N34S mutation in the SPINK-1 gene was reported to be associated with idiopathic chronic pancreatitis (ICP), the role of this endogenous trypsin inhibitor has been debated. Rolf Graf presented convincing data that SPINK-1 and monitor peptide not only inhibit trypsin in vitro but also participate in a feedback mechanism regulating trypsinogen secretion from pancreatic acinar cells. Both peptides are upregulated and induced as acute phase proteins during inflammation, cancer development and wound repair. Roger Liddle, Durham, N.C., extended our knowledge on the role of SPINK-1 in pancreatitis by engineering a transgenic mouse model. Using this model he demonstrated that SPINK-1 overexpression in the pancreas ameliorates acute, secretagogue-induced pancreatitis as well as the severity of chronic pancreatitis and long-term fibrosis. Heiko Witt, who first reported on the association between SPINK-1 mutations and idiopathic pancreatitis in 2000, presented a new concept on the role of mutated anionic trypsinogen in the development of pancreatitis. The observation that a loss of anionic trypsinogen function mutation protects against pancreatitis emphasized the critical balance between proteases and their inhibitors for the onset of the disease and the necessity to experimentally question the traditional hypothesis. Addressing the genotype/phenotype relationship, John Neoptolemos from Liverpool provided an extensive analysis of the different trypsinogen mutations. Only a minority of the various trypsinogen mutations appear to be of clinical relevance,
and the origin of the most common mutations may be explained by gene conversion, which would account for multiple founders. Even more than the previous reports, this highlighted the need for experiments that help to understand the pathophysiological contribution of trypsinogen mutations to the onset of pancreatitis.

The best answers that Miklos Sahin-Toth from Boston could provide for this question come from sophisticated in vitro experiments employing recombinant proteases into which disease-relevant mutations were introduced by site-directed mutagenesis. A controversial and critical question discussed during the symposium was whether hereditary pancreatitis is caused by an increase in active trypsin due to autoactivation, or a lack of active trypsin due to misfolding or alterations in the catalytic center.

Markus Lerch from Greifswald provided evidence for the latter by presenting experimental evidence from animal models which suggest that trypsin activity can even play a protective role in the pathogenesis of experimental pancreatitis. These experiments, however, cannot distinguish between different trypsin isoforms.

As an alternative to the trypsin activation hypothesis he pointed out that pancreatic elastase activation may have a much more profound effect on cellular injury in acute pancreatitis. One of his close collaborators, Walther Halangk from Magdeburg, showed that matters may be even more complex and that in mice five different trypsinogen isoforms of unknown function are expressed. His major finding was that in all animal strains trypsinogen-5 was absent in the pancreas of control animals, but was strongly expressed after cerulein stimulation. The appearance of trypsinogen-5 was paralleled by trypsin activity with reduced sensitivity for the soybean trypsin inhibitor, which suggests a close biochemical relationship with human mesotrypsin. This first session of the symposium confirmed that the pathophysiological role of trypsin in pancreatitis has only begun to be understood.

In the next presentation Peter Durie introduced the audience to Shwachman-Diamond syndrome (SDS). SDS is an autosomal recessive disorder with clinical features that include pancreatic exocrine insufficiency, hematological dysfunction and skeletal abnormalities. SDS is the second most common cause of exocrine pancreatic insufficiency in children, and imaging features with replacement of pancreatic tissue by fat or diffuse fatty infiltration are rather characteristic. The disease is caused by germline mutations in the SBDS gene (for the full name Shwachman-Bodian-Diamond syndrome) on chromosome 7q11 [12]. SDBS is a member of a highly conserved protein family of unknown function with putative orthologs in diverse species, including archaea and eukaryotes. The protein is most likely involved in RNA metabolism.

The next genetic disorder of the program was JBS (OMIM 243800) reported by Martin Zenker of Erlangen. JBS is an autosomal recessive multi-system disorder in humans, with abnormalities that invariably include congenital exocrine pancreatic insufficiency and often other malformations, such as nasal wing aplasia or mental retardation. Since its initial description in 1971, more than 60 cases of the syndrome have been reported in the literature. Martin Zenker reported that the genetic defect on chromosome 15q encodes an E3 ubiquitin ligase of the N-end rule pathway (UBR1). He and his collaborators further found intrauterine destructive pancreatitis as the underlying cause of exocrine pancreatic insufficiency in humans. In a murine knockout model of UBR1, known for growth retardation, stool measurements for chymotrypsin and elastase identified exocrine pancreatic insufficiency to be the cause of malnutrition. In vitro studies on pancreatic acini found impaired stimulus-secretion coupling, in the presence of normal enzyme synthesis, as the underlying mechanism. Experimental pancreatic injury in UBR1 knockouts (cerulein pancreatitis) was followed by significantly greater local and systemic inflammation than in wild-type animals. In summary, the genotype-phenotype correlation of JBS introduced proteasomal degradation as a new factor in the pathogenesis of pancreatic disorders and this may contribute to the general understanding of pancreatitis.

This session was followed by an overview on the latest results on mutations in the CFTR gene that are associated with ICP, which was given by Jonathan Cohn from Durham, N.C., and addressed in a free paper by Kaspar Truniger from Bern. Dr. Cohn concluded that 20% of patients with ICP have a CF<sup>sev</sup>/CF<sup>m-v</sup> genotype, i.e. one severe and one mild-variable mutation. This genotype increases the risk of ICP 80-fold. Unfortunately, cystic fibrosis (CF) carrier tests do not detect mild-variable mutations (CF<sup>m-v</sup>), and CF carriers (CF<sup>sev/v</sup>) do not have a high risk of ICP. Therefore most ICP patients with underlying CF mutations will not be detected by conventional screening tests.

The subsequent session was dedicated to genetic factors involved in the development of pancreatic cancer. Brian Lewis from the Massachusetts Medical School, Worcester, Mass., explained the initiating genetic lesions that determine pancreatic tumor type. He presented animal models to which he had delivered various established oncogenes by RCAS viruses targeted to specific pancreatic cell types via tva receptors regulated under cell-spe-
cific promoters like the elastase promoter or the pdx-1 promoter. On the basis of his findings he concluded that a progenitor cell is the primary target for neoplastic transformation.

Randall Brand and Detlef Bartsch spoke on ‘Genotype and phenotype of familial pancreatic cancer’. It is estimated that 5–10% of cases of pancreatic cancer are due to hereditary factors. The majority of these familial clusterings have an autosomal dominant pattern of inheritance, while other families develop pancreatic cancer associated with cancer syndromes. For most pancreatic cancer kindreds the responsible germline mutation has not been identified. The locus, 4q22–24, identified in one large American kindred as a potential locus for a disease gene, was unfortunately not confirmed by the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUPROPAC) or the Nationale Fallsammlung Familiäres Pankreaskarzinom (FaPaCa) as indicated by a LOD score of less than –2. However, this does not rule out a disease-relevant gene in that region.

Last but not least the genetics of diabetes was one of the major topics of this meeting. Affecting about 2% of the population, diabetes is one of the most common disorders in industrialized countries and the only non-infectious disease for which the WHO has recognized the status of being epidemic. Despite great efforts, Michelle Solimena from Dresden reported that only a handful of genes predisposing to type-2 diabetes have been identified so far, e.g. calpain-10, hepatocyte nuclear factor-4α, potassium inward-rectifier 6.2, peroxysome proliferator-activated receptor-γ, and insulin receptor substrate-1. However, an interesting newly identified target, calpain-pro tease-1, is part of a novel signaling pathway that directly couples the exocytosis of insulin-containing secretory granules to the regulation of gene expression and proliferation of β-cells.

Philippe Froguel, Imperial College of London, discussed the ‘Genetic basis of maturity onset diabetes mellitus of the young (MODY)’. There are several types of diabetes from the genetic point of view. Monogenic MODY is one of them and is associated with genes such as GCK, HNF1α, HNF1β, HNF4α, IPF1/Pdx1, NeuroD, and TIEG2/KLF11. It is characterized by autosomal dominant inheritance, an age of onset of <25 years, and low insulin levels. The MODY genes control insulin secretion in response to glucose. Of the MODY cases 20–60% are due to mutations in glucokinase, impairing both glucose-induced insulin secretion and hepatic glycogen synthesis.

Ton Maassen from Leiden discussed ‘Mitochondrial diabetes: genetics and pathogenesis’. The physiologic consequences of mutations in the mitochondrial DNA are related to glucose homeostasis. This imbalance results in a reduced activity of the respiratory chain, as reflected by reduced oxygen consumption. It was concluded that different gene variants that are linked to mitochondrial function affect insulin secretion but that they do not contribute to peripheral insulin resistance.

Again, this meeting has provided the latest update on the genetic basis of endocrine and exocrine pancreatic disorders. At the rapid pace with which this field moves forward and new discoveries are being made, a 2-year interval between the Inherited Diseases of the Pancreas meetings seems appropriate. The organizers and participants already look forward to the 6th meeting.