# PANCREAS ALERTS

***Am J Physiol Gastrointest Liver Physiol 2010; Apr 22.***
*(PMID: 20413721)*

## Angiotensin II signaling through the AT1a and AT1b receptors does not have a role in the development of cerulein induced chronic pancreatitis in the mouse.

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The intraorgan renin-angiotensin system (RAS) plays an important role in the pathophysiology of a variety of diseases and has been implicated in fibrogenesis. The role of RAS in the development of chronic pancreatitis is not well established. The blockade of RAS in rat models with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor 1 (AT1) blockers (ARBs) mostly have reduced pancreatic inflammation and fibrosis with a few exceptions. At the same time, the use of ACEi and ARBs in humans is associated with a modest risk of acute pancreatitis. The aim of this study was to elucidate the effect of the AT1 signaling pathway in the development of pancreatitis using AT1a and AT1b deficient mice as well as the ARB losartan. Chronic pancreatitis was induced by repetitive cerulein administration in C57BL/6J wild type (WT) and AT1a and AT1b deficient mice (AT1a-/- and AT1b-/-) and pancreatic injury was assessed at day 10. Pancreatic weight of cerulein treated groups was significantly reduced. There was severe parenchymal atrophy and fibrosis assessed by histological examination. Fibrosis was accompanied by activation of pancreatic stellate cells (PSC) evaluated by Western blot analysis for alpha-smooth muscle actin. No differences were seen between cerulein treated WT, AT1a-/- , AT1b-/- or losartan treated WT mice with regards to morphological or molecular alterations induced by cerulein. These results demonstrate that AT1a and AT1b receptor pathways do not seem to be essential for the development of pancreatitis in the mouse model of pancreatitis induced by repetitive cerulein injury.

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***Am J Surg 2010; Apr 20.***
*(PMID: 20413104)*

## Nuclear factor kappa B-dependent gene transcription in cholecystokinin- and tumor necrosis factor-alpha-stimulated isolated acinar cells is regulated by p38 mitogen-activated protein kinase.

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Mitogen-activated protein (MAP) kinases and nuclear factor kappa B (NF-kappaB) are implicated in early stages of acute pancreatitis pathogenesis. The authors investigated the relationship between the p38 MAP kinase and NF-kappaB in isolated acinar cells. Isolated rodent acinar cells were stimulated with agonists after infection with an adenovector containing a luciferase promoter driven only by NF-kappaB and an adenovector containing the dominant negative (DN) form of p38 (empty vector in controls). Initial immunoblots confirmed that the agonist stimulated p38 activation in acinar cells was substantially attenuated by DN p38 overexpression. Stimulation of native cholecystokinin (CCK)-A receptors or tumor necrosis factor-alpha (TNF-alpha) receptors promoted a significant increase in NF-kappaB-dependent gene transcription in cells infected with the empty vector, while overexpression of DN p38 significantly abrogated NF-kappaB-dependent luciferase activity. These findings support the hypothesis that p38 is involved in the activation of proinflammatory nuclear transcription factors such as NF-kappaB in pancreatic exocrine cells.

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***Int J Clin Pract 2010; Apr 14.***
*(PMID: 20412332)*

## Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis.

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Recent case reports of acute pancreatitis in patients with type 2 diabetes (T2DM) treated with incretin-based therapies have triggered interest regarding the possibility of a mechanism-based association between pancreatitis and glucagon-like peptide-1 mimetics or dipeptidyl peptidase-4 (DPP-4) inhibitors. The objective of this review was to describe the controlled preclinical and clinical trial data regarding the incidence of pancreatitis with sitagliptin, the first DPP-4 inhibitor approved for use in patients with T2DM. Tissue samples from multiple animal species treated with sitagliptin for up to 2 years at plasma exposures substantially in excess of human exposure were evaluated to determine whether any potential gross or histomorphological changes suggestive of pancreatitis occurred. Sections were prepared by routine methods, stained with haematoxylin and eosin and examined

microscopically. A pooled analysis of 19 controlled clinical trials, comprising 10,246 patients with T2DM treated for up to 2 years, was performed using patient-level data from each study for the evaluation of clinical and laboratory adverse events. Adverse events were encoded using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 system. Incidences of adverse events were adjusted for patient exposure. Tissue samples from preclinical studies in multiple animal species did not reveal any evidence of treatment-related pancreatitis. The pooled analysis of controlled clinical trials revealed similar incidence rates of pancreatitis in patients treated with sitagliptin compared with those not treated with sitagliptin (0.08 events per 100 patient-years *vs*. 0.10 events per 100 patient-years, respectively). Preclinical and clinical trial data with sitagliptin to date do not indicate an increased risk of pancreatitis in patients with T2DM treated with sitagliptin.

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***Proc Natl Acad Sci U S A. 2010; Apr 21.***
*(PMID: 20410458)*

### Bombesin functionalized gold nanoparticles show *in vitro* and *in vivo* cancer receptor specificity.

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Development of cancer receptor-specific gold nanoparticles will allow efficient targeting/optimum retention of engineered gold nanoparticles within tumors and thus provide synergistic advantages in oncology as it relates to molecular imaging and therapy. Bombesin (BBN) peptides have demonstrated high affinity toward gastrin-releasing peptide (GRP) receptors *in vivo* that are overexpressed in prostate, breast, and small-cell lung carcinoma. The authors have synthesized a library of GRP receptor-avid nanoplatforms by conjugating gold nanoparticles (AuNPs) with BBN peptides. Cellular interactions and binding affinities ($IC_{50}$) of AuNP-BBN conjugates toward GRP receptors on human prostate cancer cells have been investigated in detail. *In vivo* studies using AuNP-BBN and its radiolabeled surrogate $^{198}$AuNP-BBN, exhibiting high binding affinity ($IC_{50}$ in microgram ranges), provide unequivocal evidence that AuNP-BBN constructs are GRP-receptor-specific showing accumulation with high selectivity in GRP-receptor-rich pancreatic acne in normal mice and also in tumors in prostate-tumor-bearing, severe combined immunodeficient mice. The i.p. mode of delivery has been found to be efficient as AuNP-BBN conjugates showed reduced RES organ uptake with concomitant increase in uptake at tumor targets. The selective uptake of this new generation of GRP-receptor-specific AuNP-BBN peptide analogs has demonstrated realistic clinical potential in molecular imaging via X-ray computed tomography techniques as the contrast numbers in prostate tumor sites are severalfold higher as compared to the pretreatment group (Hounsfield unit = 150).

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***Am J Surg 2010; Apr 19.***
*(PMID: 20409526)*

### Epidermal growth factor receptor (EGFR) intron 1 polymorphism and clinical outcome in pancreatic adenocarcinoma.

**Frolov A, Liles JS, Kossenkov AV, Tzeng CW, Jhala N, Kulesza P, et *al.***

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Epidermal growth factor receptor (EGFR) intron 1 has a polymorphic region of CA repeats that is believed to be associated with increased EGFR expression, tumor aggressiveness, and worse survival in cancer patients. A large population of pancreatic adenocarcinoma patients was investigated to evaluate this polymorphism as a potential prognostic marker of clinical outcome. Deoxyribonucleic acid obtained from 50 resected pancreatic adenocarcinomas and from 85 diagnostic endoscopic ultrasound-guided fine-needle aspiration procedures corresponding to patients with unresectable tumors was included. The correlation between CA repeat length and EGFR messenger ribonucleic acid levels was also examined. Analysis of the 135 patients revealed no correlation between EGFR intron 1 CA repeat length and tumor stage. There was no difference in overall patient survival when stratified by allele length. A correlation between EGFR intron 1 length and EGFR transcript and protein levels could not be established. The length of the EGFR intron 1 CA repeats does not correlate with levels of EGFR expression and cannot be used as marker of clinical prognosis in pancreatic cancer patients.

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***Methods Mol Biol 2010; 641:347-57.***
*(PMID: 20407956)*

### Proteomic analysis of pancreatic secretory trypsin inhibitor/tumor-associated trypsin inhibitor from urine of patients with pancreatitis or prostate cancer.

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The development of proteomic methods, especially mass spectrometry, has brought new possibilities to tumor marker research. Pancreatic secretory trypsin

inhibitor (PSTI), a common known biomarker for various malignancies, occurs on genetic variants that the authors are able to detect at the protein level with proteomic techniques using immunoaffinity capture prior to liquid chromatography-mass spectrometry (LC-MS). The authors also show that PSTI can be detected in urine from cancer patients using a two-step peptide enrichment technique and LC-MS. These results show that tumor-associated peptides can be detected in urine by proteomic techniques.

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***Am J Gastroenterol 2010; Apr 20.***
*(PMID: 20407429)*

## Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm.

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Successful treatment requires reliable preoperative assessment of the highly variable extension of intraductal papillary mucinous neoplasms (IPMNs). The authors aimed to determine the role of intraductal ultrasonography (IDUS) in predicting the extension of IPMN, and in selecting the method of pancreatic resection and the long-term outcome after surgery. Randomized prospective study. Forty consecutive patients who underwent IPMN resection were included in the study. Patients were randomly assigned to an IDUS group or control group, in which IDUS was not performed. Preoperative assessment by IDUS had an 85% (17 of 20) diagnostic accuracy for tumor extension of IPMN compared with 50% (10 of 20) in cases assessed by other imaging methods without IDUS (P=0.018). In 9 of 15 patients with invasive carcinoma, the tumor was located in the pancreatic head, and 11 had a main duct-type tumor. Recurrent disease was identified in 5 of 15 (33%) patients with invasive IPMN at a mean follow-up of 50 months; of them, 1 underwent preoperative IDUS and 4 were assessed by other imaging methods. None of the 25 patients with noninvasive IPMN had recurrent disease at follow-up. The overall cumulative 3-year survival rate was 79%. Preoperative IDUS was useful in determining the type of surgery and the extent of resection, especially in main-duct IPMN.

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***Am J Gastroenterol 2010; Apr 20.***
*(PMID: 20407433)*

## Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling and immunoassays identify pancreatic enzymes as a major target of the inflammatory process.

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Autoimmune pancreatitis (AIP) is thought to be an immune-mediated inflammatory process, directed against the epithelial components of the pancreas. The objective was to identify novel markers of disease and to unravel the pathogenesis of AIP. To explore key targets of the inflammatory process, the authors analyzed the expression of proteins at the RNA and protein level using genomics and proteomics, immunohistochemistry, western blot, and immuno-assay. An animal model of AIP with LP-BM5 murine leukemia virus-infected mice was studied in parallel. RNA microarrays of pancreatic tissue from 12 patients with AIP were compared with those of 8 patients with non-AIP chronic pancreatitis. Expression profiling showed 272 upregulated genes, including those encoding for immunoglobulins, chemokines and their receptors, and 86 downregulated genes, including those for pancreatic proteases such as three trypsinogen isoforms. Protein profiling showed that the expression of trypsinogens and other pancreatic enzymes was greatly reduced. Immunohistochemistry showed a near-loss of trypsin-positive acinar cells, which was also confirmed by western blotting. The serum of AIP patients contained high titers of autoantibodies against the trypsinogens PRSS1 and PRSS2 but not against PRSS3. In addition, there were autoantibodies against the trypsin inhibitor PSTI (the product of the SPINK1 gene). In the pancreas of AIP animals, the authors found similar protein patterns and a reduction in trypsinogen. These data indicate that the immune-mediated process characterizing AIP involves pancreatic acinar cells and their secretory enzymes such as trypsin isoforms. Demonstration of trypsinogen autoantibodies may be helpful for the diagnosis of AIP.

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***J Immunother 2010; Apr 8.***
*(PMID: 20386472)*

## Cancer and inflammation: promise for biologic therapy.

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Cancers often arise as the end stage of inflammation in adults, but not in children. As such there is a complex interplay between host immune cells during neoplastic development, with both an ability to promote cancer and limit or eliminate it, most often complicit with the

host. In humans, defining inflammation and the presence of inflammatory cells within or surrounding the tumor is a critical aspect of modern pathology. Groups defining staging for neoplasms are strongly encouraged to assess and incorporate measures of the presence of apoptosis, autophagy, and necrosis and also the nature and quality of the immune infiltrate. Both environmental and genetic factors enhance the risk of cigarette smoking, *Helicobacter pylori*, hepatitis B/C, human papilloma virus, solar irradiation, asbestos, pancreatitis, or other causes of chronic inflammation. Identifying suitable genetic polymorphisms in cytokines, cytokine receptors, and Toll-like receptors among other immune response genes is also seen as high value as genomic sequencing becomes less expensive. Animal models that incorporate and assess not only the genetic anlagen but also the inflammatory cells and the presence of microbial pathogens and damage-associated molecular pattern molecules are necessary. Identifying micro-RNAs involved in regulating the response to damage or injury are seen as highly promising. Although no therapeutic strategies to prevent or treat cancers based on insights into inflammatory pathways are currently approved for the common epithelial malignancies, there remains substantial interest in agents targeting COX2 or PPARgamma, ethyl pyruvate and steroids, and several novel agents on the horizon.

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***J Pediatr Surg 2010; 45:741-6.***
*(PMID: 20385281)*

## Recurrent pancreatitis caused by pancreatobiliary anomalies in children with annular pancreas.

**Urushihara N, Fukumoto K, Fukuzawa H, Suzuki K, Matsuoka T, Kawashima S, *et al.***

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Annular pancreas (AP) is usually associated with duodenal obstruction in neonates. Pancreatitis with AP occurs frequently in adults but is rare in children. This article describes pancreatitis in children with AP and pancreatobiliary anomalies and its surgical treatment. Six children who underwent duodenal bypass for AP subsequently developed recurrent pancreatitis. Three had trisomy 21. Duodenoduodenostomy had been performed in 5 patients and gastrojejunostomy in 1 patient for neonatal duodenal obstruction. The authors reviewed overall management, imaging, and surgical treatment in these children. All children subsequently complained of recurrent abdominal pain. Pancreatitis developed in 6 children, and magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) revealed associated pancreatobiliary anomalies such as pancreas divisum, pancreatobiliary malunion, choledochocele, and intra luminal duodenal diverticulum. In 5 cases, surgery for recurrent or chronic pancreatitis was performed. The range of follow-up was 11 to 54 months, and all children who underwent surgery had excellent results. Children with AP occasionally require reoperation for recurrent pancreatitis because of associate pancreatobiliary anomalies. Magnetic resonance cholangiopancreatography and ERCP provide excellent images of pancreatobiliary anomalies. Intraoperative cholangiopancreatography is also essential for accurate depiction of the ductal structure and selection of the appropriate surgical procedure.

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***Scand J Gastroenterol 2010; Apr 12.***
*(PMID: 20384530)*

## Pancreatic duct changes are not associated with early signs of chronic pancreatitis at magnetic resonance imaging (MRI) in patients with primary sclerosing cholangitis.

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The association between chronic pancreatitis (CP) and primary sclerosing cholangitis (PSC) has been reported previously. The aims of the present study were to evaluate the presence of early pancreatic abnormalities and duct changes, using MRCP/MRI in PSC and to evaluate possible risk factors for these changes and their clinical importance. One hundred and three patients with PSC were identified among all MRI liver/pancreas referrals in 2001-2005. MRCP was used to grade pancreatic duct changes in three groups: grade 0 (normal), grade 1 (mild) and grade 2 (severe). For detection of early MRI signs of CP, the pancreas-spleen signal intensity ratio (SIR), the arterial and early venous phase ratio (A/PV ratio) and the age-related size of the pancreas were evaluated. Pancreatic duct changes were found in 24% of the PSC patients. The pancreatic duct changes were associated with extrahepatic biliary involvement and long duration of PSC but not associated with pancreas-spleen SIR, A/PV ratio, pancreas size, previous post-ERCP or acute pancreatitis. Severe pancreatic duct changes were significantly associated to abdominal pain. Clinically significant CP was seen in one PSC patient (1%). Pancreatic duct changes are associated with extrahepatic bile duct strictures and not with the early MRI signs of CP. Therefore, pancreatic duct changes seem to be part of the spectrum of PSC and should not be defined as CP. Pancreatic duct changes are of limited clinical importance but may contribute to abdominal pain in PSC.

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***Mol Cell Biochem 2010; Apr 23.***
*(PMID: 20414703)*

## Age-related deregulation of Aire and peripheral tissue antigen genes in the thymic stroma of non-obese diabetic (NOD) mice is associated with autoimmune type 1 diabetes mellitus (DM-1).

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Gene expression of peripheral tissue antigens (PTAs) in stromal medullary thymic epithelial cells (mTECs) is a key process to the negative selection of autoreactive thymocytes. This phenomenon was termed "promiscuous gene expression" (PGE), which is partially controlled by the Aire gene. Nevertheless, reasons for the correlation of Aire and PTAs with the emergence of autoimmune diseases are largely unknown, though it may be a result of a chronological effect. Although the effect of Aire mutations in pathogenic autoimmunity is well know, it could not be a unique cause for autoimmunity. Independently of mutations, temporal deregulation of Aire expression may imbalance Aire-dependent PTAs and/or wide PGE. This deregulation may be an early warning sign for autoimmune diseases as it guarantees autoantigen representation in the thymus. To assess this hypothesis, the authors studied the expression levels of Aire, Aire-dependent (Ins2) and Aire-independent (Gad67 and Col2a1) PTAs using real-time-PCR of the thymic stromal cells of NOD mice during the development of autoimmune type 1 diabetes mellitus (DM-1). Wide PGE was studied by microarrays in which the PTA genes were identified through parallel $CD80^{+}$ mTEC 3.10 cell line expression profiling. The results show that Aire gene was down-regulated in young pre-autoimmune (pre-diabetic) NOD mice. PGE and specific PTA genes were down-regulated in adult autoimmune diabetic animals. These findings represent evidence indicating that chronological deregulation of genes important to negative selection may be associated with the development of an autoimmune disease (DM-1) in mice.

**URL:** http://www.serena.unina.it/index.php/jop/article/view/3837/4279