Published in final edited form as:

Pancreas. 2019 July ; 48(6): 759–779. doi:10.1097/MPA.0000000000001335.

Animal Models: Challenges and Opportunities to Determine Optimal Experimental Models of Pancreatitis and Pancreatic Cancer

Jami L. Saloman, PhD[1], **Kathryn M. Albers, PhD**[1], **Zobeida Cruz-Monserrate, PhD**[2], **Brian M. Davis, PhD**[1], **Mouad Edderkaoui, PhD**[3], **Guido Eibl, MD**[4], **Ariel Y. Epouhe, BS**[1], **Jeremy Y. Gedeon, BS**[1], **Fred S. Gorelick, MD**[5], **Paul J. Grippo, PhD**[6], **Guy E. Groblewski, PhD**[7], **Sohail Z. Husain, MD**[8], **Keane K.Y. Lai, MD**[9], **Stephen J. Pandol, MD**[4], **Aliye Uc, MD**[10], **Li Wen, MD, PhD**[8], and **David C. Whitcomb, MD, PhD**[11]

[1]Department of Neurobiology, Pittsburgh Center for Pain Research, University of Pittsburgh, Pittsburgh, PA

[2]Division of Gastroenterology, Hepatology, and Nutrition; Comprehensive Cancer Center, The Ohio State University Wexner Medical Center, Columbus, OH

[3]Basic and Translational Pancreas Research, Cedars-Sinai Medical Center, Los Angeles, CA

[4]Department of Surgery, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA

[5]Department of Internal Medicine, Section of Digestive Diseases & Department of Cell Biology Yale University School of Medicine; Veterans Affairs Connecticut Healthcare, West Haven, CT

[6]Department of Medicine, Division of Gastroenterology and Hepatology, UI Cancer Center, University of Illinois at Chicago, Chicago, IL

[7]Department of Nutritional Sciences, University of Wisconsin, Madison, WI

[8]Department of Pediatrics, Stanford University, Palo Alto, CA

[9]Department of Pathology (National Medical Center), Department of Molecular Medicine (Beckman Research Institute), and Comprehensive Cancer Center, City of Hope, Duarte, CA

[10]Stead Family Department of Pediatrics, University of Iowa, Stead Family Children's Hospital, Iowa City, IA

[11]Department of Medicine, University of Pittsburgh, Pittsburgh, PA

Abstract

Address correspondence to: Jami L. Saloman, PhD, 200 Lothrop Street, BSWTR E1457, Department of Neurobiology, Center for Pain Research, University of Pittsburgh, Pittsburgh, PA 15213 **(** jls354@pitt.edu)., Phone: 508-314-3582, Fax: 412-648-1441.
L.W. is currently with the Department of Gastroenterology, Shanghai General Hospital and Shanghai Key Laboratory of Pancreatic Disease, Institute of Pancreatic Disease, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Disclosure

A.U. is a member of the American Board of Pediatrics, Subboard of Pediatric Gastroenterology; Associate Editor of *Pancreatology*; a consultant for Cystic Fibrosis Foundation. The rest of the authors declare no conflict of interest.

At the 2018 PancreasFest meeting, experts participating in basic research met to discuss the plethora of available animal models for studying exocrine pancreatic disease. In particular, the discussion focused on the challenges currently facing the field and potential solutions. That meeting culminated in this review that describes the advantages and limitations of both common and infrequently utilized models of exocrine pancreatic disease, namely pancreatitis and exocrine pancreatic cancer. The objective is to provide a comprehensive description of the available models, but also to provide investigators with guidance in the application of these models to investigate both environmental and genetic contributions to exocrine pancreatic disease. The content covers both nongenic and genetically engineered models across multiple species (large and small). Recommendations for choosing the appropriate model as well as how to conduct and present results are presented.

Keywords

pancreatitis; pancreatic cancer; animal models

1. Introduction

Pancreatitis and pancreatic cancer are highly variable diseases with a range of etiologies and disease courses. The use of animal models in the scientific exploration of these diseases is critical. Animal models are vital tools for understanding pathophysiology and they are a key step in the drug development pipeline as well as disease biomarker discovery. In general, it has been difficult to translate findings from animal studies into meaningful changes in clinical care. During the 2018 PancreasFest conference, a working group met to discuss the challenges with animal models. The goal of this report is to emphasize issues that should be considered when performing animal studies of exocrine pancreatic disease.

Choosing the most appropriate model for a study is contingent upon the specific question being asked, what aspects of the disease are relevant as well as the time and resources one has available **(Fig. 1)**. This report introduces nongenic and genetic engineered models of pancreatitis and exocrine pancreatic cancer and identifies the key features of each model. In particular, it emphasizes the multiple factors contributing to inter-model and intra-model variability and their direct effects on the manifestation of disease.

2. Nongenic models

2.1 Pancreatitis

Pancreatitis is an umbrella diagnosis that includes sub-classifications such as acute, recurrent and chronic. It can be further characterized by the presence or absence of necrosis. Multiple non-genetic factors have been identified that increase the risk of developing pancreatitis or of more severe disease; some can be recapitulated in animals. For example, exposure to a specialized (high fat) diet, alcohol feeding, endoscopic retrograde cholangio-pancreatography (ERCP), or duct obstruction can induce pancreatitis in animals in a manner similar to clinical pancreatitis in humans (Table 1). Models have been developed based on the known biological processes contributing to pancreatitis. For instance, acute pancreatitis

(AP) involves premature activation of trypsinogen within the pancreas. Administration of supraphysiologic concentrations of the cholecystokinin analog cerulein is a popular method of inducing experimental pancreatitis. Such a “hyperstimulation” model in rodents is generally used to induce mild to moderate injury and reflects the hyperstimulation pancreatitis observed in humans following exposure to certain scorpion bites and insecticides with cholinesterase activities. There are also several chemicals that, when infused into the pancreatic duct, may mimic the effects of bile reflux and its possible role in inducing biliary pancreatitis (Table 1). The technical challenges associated with bile acid and post-ERCP induced AP have likely prevented their wide spread adoption. Another group of animal models that are less commonly used are those that mimic uncommon forms of pancreatitis such as autoimmune pancreatitis. These models use foreign serum, adoptive cell transfer, or infectious pathogens to induce disease. There are potential advantages to using nongenic models of pancreatitis, including their lower expense and, in many cases, the same method of induction can be achieved through multiple routes of administration of an agent and across both small and large animal species. Finally, the initiation of disease can often be highly synchronized across a cohort of animals.

Similar induction methods can sometimes be modified to phenocopy both acute and chronic types of pancreatitis. For example, the dosage, frequency, and route of administration of cerulein are regularly manipulated to experimentally induce both acute and chronic pancreatitis. Cerulein was first used to induce AP in rats using intravenous infusion, but it was later discovered that 6–8 hourly intraperitoneal injections also provoke mild AP whereas 12 hourly injections provoke more severe AP.[1–4] By repeating daily dosing with cerulein, one can replicate recurring episodes to develop a model of recurrent acute pancreatitis. However, many investigators use this paradigm, repeated dosing of cerulein, to generate chronic pancreatitis (CP) models. The dosing regimen is not standardized and the variability of the repeated cerulein paradigms was recently outlined by Klauss et al.[5] For example, bi-weekly sessions of 6–8 hourly injections for 6–10 weeks results in histological changes consistent with CP, but dramatic differences in fibrosis are seen in different mouse strains. Unlike clinical CP, when cerulein dosing is terminated, pancreata recover within 3–6 weeks.[6] Other groups have accelerated the repeated cerulein model and show that administering 6 hourly injections on 3 days per week for 3–4 weeks also recapitulates CP.[7] It is unclear at this time whether there are meaningful differences between the variable dosing paradigms for CP. It is also unknown whether a longer dosing schedule would generate irreversible pancreatic changes. Many laboratories currently choose the dosing paradigm based on what is most convenient for laboratory personnel; however, they have shown their chosen regimen works for their individual studies.

One step that must be taken to improve the comparability of results across studies and models is to standardize endpoints. The diagnosis and severity of pancreatitis relies heavily on pathologist-specific interpretations of histology: interstitial edema, acinar cell death (necrosis or vacuolization), parenchymal loss, hemorrhage, fat necrosis, inflammatory cell infiltrate, fat and fibrotic tissue replacement.[8] However, there are quantitative measures available for exocrine function, edema, immune responses, and endocrine function that should be employed alongside histological measures.[9–14] For example, serum enzyme levels (e.g. amylase or lipase) or intrapancreatic trypsinogen activation are standard exocrine-

related endpoints that should be included in all studies, particularly those focused on AP or early phases of CP. Furthermore, edema can be evaluated through objective comparisons of organ weight. Inflammation can be measured using a standard myeloperoxidase assay as well as pancreas-specific or systemic measures of cytokine expression. For severe or advanced disease models, measures of endocrine function such as glucose levels or glucose tolerance tests could also be informative. Though preliminary studies of stains for fibrosis are important, quantitative measures of collagen expression (collagen subtypes, hydroxproline levels) should be performed when fibrosis is an endpoint. With all AP and CP models, the time course of pancreatitis can differ among species and within strains of the same species, as well as by age or by sex in some strains of rodents. Equally important is the time point at which a particular endpoint is measured. The peak and resolution of an endpoint is likely parameter specific and more thorough investigations are ongoing. For example, in the acute cerulein model initial zymogen activation within the acinar cell begins between 15 min and 1–2 h after the first cerulein injection, but inflammatory cells mediate this at later time points.[15–18] Thus, it is particularly important to consider previous literature and conduct preliminary studies to decide on the most appropriate time points to assess your chosen parameters (e.g. 1 h, 6 h, or 24 h after the first or last cerulein injection).[19,20]

2.2 Pancreatic Cancer

Multiple chemicals have been used to model tumorigenesis (Table 2). If these carcinogens are introduced systemically tumors develop across multiple organ systems. For instance, administration through oral gavage will incite lesions throughout the gastrointestinal tract whereas intraductal instillation will restrict tumor development to the pancreas.[21–24] More recently, investigators have largely moved away from chemically induced tumor models; instead, a variety of transplantation models have gained significant favor. There are several sources for the transplants that will be discussed below. The site of the transplant in the host animal can also vary, but the most popular locations are subcutaneous or directly into the pancreas. Investigators opt for subcutaneous placement because it is easy to observe tumor growth in the absence of advanced imaging technologies as well as to perform behavioral assays. For investigators interested in metastases, tumor cells can also be implanted into the target of interest such as liver or lung. Orthotopic transplantation of pancreatic tumor cells can be used to model primary tumor growth in a synchronized manner such that an entire cohort will have similar progression of disease.

The source of pancreatic tumor cells that are transplanted is critical. There are a multitude of human pancreatic tumor cell lines available.[25–27] To perform xenografts (interspecies transplantation), nude or SCID mice must be used so the foreign cells will not be rejected. More recently, the development of the patient-derived xenograft (PDX) provided a great hope toward the development of personalized therapies since drugs could be directly tested on each individual patient’s tumor. The PDX model of pancreatic ductal adenocarcinoma (PDAC) has facilitated translational (from mouse to man) studies on pancreatic cancer. Manegold et al recently reported on “serial” subcutaneous implantations of PDX PDAC tissue into immunocompromised NOD/SCID/IL2r$\gamma^{-/-}$ (NSG) mice to study the role of CBP/β-catenin-induced pancreatic cancer cell stemness in human PDAC carcinogenesis.[28] The investigators found that the first subcutaneous implantation of human PDAC into mice

that were treated with a specific small molecule CBP/β-catenin antagonist, ICG-001, did not inhibit the growth of the xenograft. However, the ICG-001-treated tumor (which grew during the first implantation) failed to grow during the second implantation. The investigators concluded that CBP/β-catenin antagonism of pancreatic cancer cell stemness was able to prevent propagation of human PDAC. Indeed and as previously reviewed,[29] such PDX models provide a couple of key advantages because the PDAC xenografts are comprised of cells which: 1) largely retain the appropriate genetic profile even after initial selection in the mouse; 2) display a high degree of heterogeneity characteristic of PDAC at least initially; and 3) are derived from humans.

Xenograft models do have several limitations; the key one being that transplant recipients must have a compromised immune system.[30] A relatively more physiological approach is the syngeneic or allograft model in which the donor cells and recipient are of the same species. Like xenografts, either primary tumor cells or cell lines can be used for allografts. Utilizing a syngeneic approach allows a better assessment of how the intact immune system contributes to tumor growth. Previously, the Panc02 cell line was the primary cell line readily available for such syngeneic mouse models. However, the major limitation of the Panc02 cell line is the finding by Logsdon and colleagues that they do not harbor mutations in Kras or p53 which represent the most common, classical mutations in PDAC,[29] hence severely diminishing the translational relevance of such models. More recently, Kras mutant cell lines, 6606PDA and 6606l, isolated from PDAC and liver metastasis, respectively, from KrasG12D (KC) mouse[31], as well as Kras mutant and p53 mutant cell lines UN-KPC-960 and UN-KPC-961 derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice[32], have been developed and have been used in syngeneic models. Given these recently developed mouse cell lines which harbor relevant PDAC mutations as well as methods for harvesting primary tumor cells[33], the syngeneic mouse model should facilitate more in-depth assessment of how the immune system contributes to the genesis of PDAC. Overall, transplantation models are useful because they are relatively easy and quick to set up. However, most transplant models are based on the implantation of differentiated tumor cells, which could be viewed as a drawback of this approach. In patients, there is a natural progression from normal to neoplastic cells. Transplantation models lack the opportunity to study how bodily systems function together to drive the transformation of ‘normal’ cells.

2.3 Environmental Modulators

Although nongenic models have weaknesses, there are advantages to using them for the study of exocrine pancreatic diseases. Nongenic models provide an opportunity to study the impact of environmental modulators including alcohol and tobacco, major risk factors for both pancreatitis and pancreatic cancer.[34] Combining exposure to these factor(s) with the nongenic models is a useful way to examine the role of the environment in the development and progression of pancreatic disease. The most common method to introduce alcohol exposure is through the Lieber-Decarli liquid diet that allows for easy modifications of the amount of ethanol.[35] Ethanol (EtOH) administration alone does not cause a pancreatitis phenotype; however, combined with chemical (e.g. dibutyltin dichloride (DBTC), oleic acid) or diet models, it can accelerate disease and increase severity.[36–41] Furthermore, EtOH in combination with its non-oxidative metabolites, fatty acid ethyl esters or a subclinical

stimulus dose of cerulein or lipopolysaccharide is also sufficient to produce pancreatitis.[42–45] EtOH use has also been associated with development of adenocarcinoma in the dimethylbenzanthracene (DMBA) model.[46] EtOH increases multiplicity, but not incidence in the rat azaserine model, but not the hamster N-Nitrosobis(2-oxopropyl)amine (BOP) model.[47] Interestingly, dietary fat enhances carcinogenesis in both the azaserine and BOP models. Cigarette smoke has also been shown to exacerbate nongenic models of pancreatitis and pancreatic cancer.[48–50] By combing EtOH, smoke, and diet with nongenic models of exocrine pancreatic disease, investigators have been able to confirm the degree that these environmental exposures affect the risk for development or increased severity of disease.

3. Genetic Models

To study pancreatitis and pancreatic cancer, investigators have developed a plethora of genetically engineered animal models. Three key aspects for developing a genetically engineered model include choosing a method to produce the animal, choosing the genetic alteration, and choosing the gene promoter that will drive expression of that genetic alteration. In addition to the CRISPR-Cas9 technology, several classical methodologies to generate genetically engineered models are well-described.[51] There are several gene promoters that are popular for use in genetically engineered models of exocrine pancreatic disease because they are enriched in the pancreas and, when combined with a conditional technology (e.g. Cre-Loxp), are thought to restrict recombination specifically to the pancreas (Table 3). However, it is important to realize that the method and the gene targeted have implications for differing interpretations of results. Specifically, using technologies that are not inducible means that the animal will express the genetic change in all cell types that express the gene at any time throughout development, including extra pancreatic tissues. In instances where the mutation of interest is a known germ line mutation, global recombination approaches may be optimal because they mimic hereditary disease. However, this could be considered a negative when the goal is to achieve pancreas or even cell-type specific mutations. PDX1 and p48/pft1a, the two most widely used gene promoters in exocrine pancreatic disease, are expressed in multiple cell types within the pancreas and can result in multiple foci of disease.[52,53] PDX1 is also expressed in duodenum and antrum of the stomach.[54–56] Moreover, both PDX1 and p48 are expressed in various divisions of the nervous systems. Pft1a/p48 is a key regulator in the differentiation of spinal cord dorsal horn neurons, determining GABAergic versus glutamatergic cell fate.[57] PDX1 is expressed in a subset of sensory and proprioceptive neurons and regulates neuronal calcium homeostasis.[58] Neuronal PDX1 is also involved in hypothalamic control of glucose metabolism.[59,60] Thus, extra pancreatic expression and/or function of ‘pancreas specific’ genes could contribute to disease phenotype and should be considered when interpreting data.

3.1 Pancreatitis

There are several genetically engineered mouse models (GEMMs) that spontaneously exhibit pancreatitis-related phenotypes (**Table 4)**. These models can be useful for questions regarding the course of idiopathic pancreatitis as well as testing pharmacological interventions. Although the majority of genetically engineered pancreatitis models are in the mouse, non-murine models are also available. The Wistar Bonn/Kobori (WBN/KOB) rat

exhibits degeneration of pancreatic parenchyma, widely distributed fibrosis, and infiltration of lymphocytes.[61] Overexpressing Sonic hedgehog or Indian hedgehog at the Ptf1a domain in zebrafish results in morphological changes in developing pancreas.[62] With age, these zebrafish show progressive pancreatic fibrosis intermingled with proliferating ductular structures and destruction of acinar structures. Our current understanding of hereditary pancreatitis has been significantly improved through the development of GEMMs. Animal models expressing mutations in trypsinogen or SPINK genes exhibit spontaneous pancreatitis or a predisposition to develop more severe disease following experimentally induced pancreatitis.[63–66] Like the combinatorial approach introduced earlier (nongenic method of induction plus exposure to environmental factors), a similar strategy is often utilized to study the role of a specific gene or signaling pathway in the development or severity of pancreatitis. In this scenario, a nongenic method of inducing pancreatitis is applied to GEMMs that do not exhibit a spontaneous disease phenotype. Investigators have successfully used this approach to implicate numerous signaling pathways in the development and severity of pancreatitis, including the complement system,[67–71] cytokine signaling,[72–77] immunoglobulins,[78,79] and, of course, protease (e.g. trypsin) pathways.[15,16,80,81] Based on the prior evidence implicating trypsin pathways, Sahin-Toth and colleagues recently created a gain of function trypsinogen mutant that effectively mimics hereditary pancreatitis.[66]

3.2 Pancreatic Cancer

The field of basic pancreatic cancer research has exploded with the development of GEMMs for pancreatic cancer. Mutations inducing a gain of function in the GTPase *Kras* occur in nearly all human pancreatic intraepithelial neoplasia (PanIN) and pancreatic ductal adenocarcinoma (PDAC).[82,83] Several basic GEMMs, described in Table 5, take advantage of oncogenic *Kras* expression combined with 'pancreas specific' promoters.[82–89] Although multiple mutations in *Kras* have been detected in PDAC patients, the most prevalent is G12D.[90–92] Thus, $Kras^{G12D}$ has become the backbone of PDAC GEMMs. The pathophysiology, histology, molecular, and clinical aspects of GEMMs that parallel the disease course of human pancreatic cancers are detailed elsewhere.[83,93–96] Briefly, GEMMs exhibit a slower disease course compared to transplant models. Lesions (e.g. PanIN or mucinous) develop followed by tumor formation, and in some cases, metastases.

Mutations in additional oncogenes such as TP53, CDKN2A, and SMAD4, occur in more than 50% of human PDAC cases.[52,83,86–89,93] The contribution of these genes to the development and progression of disease can be assessed with the complex Kras-based GEMMS described in Table 6.[97–101] Often one of the most obvious results of introducing additional pathological gene mutations is an acceleration of disease progression. The most popular complex Kras-based GEMM is the KPC model (**K**ras**P**53**C**re). KPC was originally coined to describe a GEMM in which PDX1-cre drives $Kras^{G12D}$ and $p53^{R172H}$ mutations.[102,103] Over time, however, it has been more loosely applied to GEMMs that use either PDX1-cre or p48/Pft1a-cre as well as those deleting a p53 allele ($p53^{fl/+}$).[104–107] For mice to be viable, the *Kras* mutation must be heterozygous in these models. However, it is possible to make viable mice that express different zygosities for other gene alterations. The zygosity of any additional genetic alterations incorporated into a model can directly affect the time

course of disease progression. For instance, mice expressing a single mutant p53 allele ($Kras^{G12D};p53^{(fl/+)}$) develop tumors around 16 weeks whereas dual mutant p53 alleles ($Kras^{G12D};p53^{(fl/fl)}$) develop lethal tumors by 8 weeks.[98] We encourage authors to follow this example and provide explicit descriptions of their models in every publication to avoid confusion in the field.

A key challenge with making GEMMs is the complexity of the genetics. As one moves from the basic to more complex models, there is a reduction in both cost-effectiveness and efficiency in breeding and utilizing these models (e.g. only 1 in 8 or 1 in 16 mice could have the genotype of interest). Many investigators have also opted to incorporate reporters into their models to allow for tracking of pancreatic-lineage cells as they transform, disseminate, and metastasize.[104–106,108,109] Though a creative improvement on this already valuable technology, the resulting genetic complexity presents an increased risk for unknown or unexpected side effects. Bearing in mind the caveats of complex genetic models, GEMMs are a powerful tool to aid in our investigation of PDAC.

Although the majority of current pancreatic cancer models are Kras based, there are non-Kras based models. The first transgenic mouse models of pancreatic neoplasia were generated by expressing the full-length or truncated oncogenic simian virus 40 T antigen (SV40) under the rat elastase-1 promotor.[110,111] These mice exhibit acinar dysplasia that progresses to neoplasia in adulthood. Survival is approximately 4–6 months. More recently, non-Kras based models have been developed to study the contribution of specific tumor suppressor genes to the development of PDAC. Mutations in *pten* are commonly found in several tumor types. Stanger et al developed $Pdx1\text{-}CreER^{TM};Pten^{lox/lox}$ in which *pten* is deleted from the pancreas and cre activity is confirmed through the Z/AP reporter.[112] Beginning at 3 weeks of age, mice exhibit an age-dependent phenotype with multifocal architectural changes. Acini are progressively replaced by proliferative mucin-expressing ductal structures, centroacinar cells proliferate, and ductal adenocarcinoma develops at 11 weeks. In order to parse out the contribution of the tumor suppressor genes Ink4a/Arf ($p16^{Ink4a}/p19^{Arf}$) and TP53, Bardeesy et al, examined the incidence, latency, and histological phenotype of PDAC following either hemi- or homozygous loss of p16 and p19 or p16 and p53.[113] These authors demonstrated that PDAC can develop in a non-Kras based GEMM, but also that specific tumor suppressor genotypes directly influence the phenotypes of resulting tumors.

3.3 Environmental Modulators

To explore the interactions between genetics and the environment, factors such as alcohol, diet, and tobacco can be paired with genetic models of disease. For instance, long-term ethanol feeding in the Mist1-creERT2;$XBP1^{+/-}$ model of spontaneous pancreatitis causes increased endoplasmic reticulum stress, thereby enhancing acinar cell pathology.[114] Similarly, exposure to tobacco induces flattening of ductal epithelial cells and significantly increases atrophy in the rEla1;sshIL-1β model of spontaneous pancreatitis.[76] Ethanol and smoking have also been introduced into genetic models of pancreatic cancer. Exposing KC (Pdx1-Cre; $K\text{-}Ras^{+/LSLG12D}$) mice to the Lieber-DeCarli alcohol diet in combination with cerulein results in synergistic and additive effects on PanIN formation.[104,115] Exposing KC

mice to tobacco smoke also stimulates PanIN development, fibrosis, activation of stellate cells and M2 macrophages, as well as increased expression of both stem cell and epithelial-mesenchymal transition markers.[116,117] Smoking was found to activate histone deacetylases and regulate cytokines such as interleukin-6 and interleukin-4, which promote cancer development at the early stage.[116] Smoking also activates stem cell features of pancreatic cells, through activation of PAF1 expression in KC mice.[117] The same pro-cancer effects were observed in Kras$^{+/LSLG12Vgeo}$;Elas-tTA/tetO-Cre (Ela-KRAS) mice.[118] The effect of alcohol alone on promoting PDAC is less obvious than smoking in animal models. However, the combination of alcohol with pancreatitis further promotes the progression of the disease in KC mice.[115] Analogous to the association between pancreatitis and diet, a high fat diet and obesity are associated with increased risk for pancreatic cancer. Several groups have taken of advantage of GEMMs in order to study the biological mechanisms linking obesity to pancreatic cancer. A high-fat lard-based diet in the Ela-CreERT; K-Ras$^{+/LSLG12D}$ GEMM promotes immune infiltration in addition to PanIN and PDAC development through regulating inflammation in a COX2 and lipocalin-2 dependent manner.[119,120] Similarly, a high-fat, high-calorie, corn oil-based diet given to EL-Kras and KC mice is associated with accrual of additional genetic mutations, as well as more extensive inflammation, fibrosis and neoplasia.[121,122] The incidence of cancer was particularly higher in males, which is thought to be associated with a sex-dependent localization of adipose (visceral vs. subcutaneous). Interestingly, a high calorie diet based on fish oil (menhaden) significantly delays PanIN progression.[123] Using these early stage models, including KC mice, is sometimes criticized because PDAC has not yet developed and never develops in most of these mice. However, understanding the changes in the cancer precursor cells is equally important to understanding changes in cancer cells as it will help develop a preventive strategy. Moreover, the data published in KC mice was confirmed in the *Pdx1-Cre;LSL-Kras^{G12D};Trp53$^{R172H/+}$* (KPC) mice confirming that smoking and high fat diet up-regulate tumor growth and metastasis.[118,124] It is very important to use the best model to study the effect of environmental factors on PDAC promotion; it is equally important to choose the best time to start or stop treatments as the disease progresses with different kinetics in each model.

4. Inducible Genetic models

Despite the ‘identical’ genetic background in models that use inbred strains, disease development and progression is variable across animals. Some investigators minimize this issue by utilizing inducible technologies to improve synchronization of experiments and avoid complications of expressing mutations throughout development of the animal. Many of the models described in Tables 4–6 take advantage of these inducible technologies. The most popular choice is to employ tamoxifen-dependent cre recombinase systems (e.g. CreER, CreERT, CreERT2) in which transgene expression is not induced until tamoxifen treatment. There are also models that take advantage of the tetracycline transactivator (tTA) method in which expression is triggered by the removal of doxycycline from drinking water or food.[118,125–127]

Viruses provide an alternative inducible method that allows more control over the localization of recombinant gene expression. For instance, adeno-associated virus serotype 6 (AAV6) encoding Ela-iCre infused into the pancreatic duct of calcineurin B1 (CnB1)$^{fl/fl}$

mice results in acinar cell specific loss of CnB1 gene expression.[128] In newborn pigs, ductal expression of genes can be achieved by injecting AAV9 vectors into the celiac artery, accessed via umbilical catheterization.[129] In Swiss Webster mice, intraductal infusion of lentivirus has been used to drive expression of shRNAp53, $Kras^{G12D}$ and luciferase.[130] These mice develop pathology similar to human PDAC without requiring alterations of embryonic development. They develop PanINs with increasing severity followed by tumor formation 28 weeks post-virus injection. Mice also have elevated levels of cancer markers and, in some cases, liver and lung metastases. Inducible methods have advanced the field of GEMMs by improving temporal and spatial control over these models.

Viruses also have the advantage of enabling the development of genetically engineered animal models in larger species. Viral models are becoming a popular route for developing large animal models because of their importance in drug development and improved resemblance to humans. Previously, large animal (e.g. dog, non-human primate) studies have been restricted to case reports of spontaneous disease. One type of pancreatic disease that has benefited from a viral approach is cystic fibrosis associated pancreatitis. Mutations in the *CFTR* gene lead to dysregulation of fluid transport in multiple organs, primarily lung and pancreas. Low flow of secretions leads to duct obstruction, acini destruction, severe inflammation, fibrosis, and fat replacement. With the advent of recent advances in genetics including viral-mediated gene targeting and somatic cell nuclear transfer, global manipulation of the *CFTR* gene in larger species has become possible. Two pig models, global *CFTR*-null and *CFTR*-Δ508, were generated using homologous recombination and somatic cell nuclear transfer.[131,132] Fetal and neonatal CF pigs have pancreatic lesions seen typically in humans with CF including progressive acinar cells loss, ductal plugging and fibrosis.[133,134] Although islets are morphologically normal, CF pigs demonstrate abnormal glycemic responses and decreased insulin secretion at birth.[135] A similar approach has been executed to generate *CFTR*-null ferrets.[136] CF ferrets exhibit a milder exocrine pancreatic phenotype compared to CF pigs. Newborn CF ferrets have only minor histological changes in the pancreas including dilated acini and ductules with inspissated, eosinophilic zymogen secretions, but no acinar atrophy and otherwise preserved pancreatic architecture.[137] The pancreatic disease progresses rapidly in CF ferrets after birth (>1 month) with loss of acini, inflammation, fibrosis, islet destruction/remodeling and hyperglycemia.[138,139] Another model that is worthwhile to mention is the CFTR-null zebrafish model.[140] Loss of CFTR leads to exocrine pancreatic destruction in zebrafish larva. The CFTR models are based on expression of global alterations, but viral-mediated approaches can also be used to make tissue specific manipulations. The oncopig cancer model (OCM) is a novel model in which pigs have combined $Kras^{G12D}$ and $TP53^{R167H}$ mutations under control of a cre-inducible vector.[141] Introduction of virus containing Ad-Cre directly into the pancreatic duct drives locally invasive disease that has the hallmarks of human PDAC including a dense fibroblastic stroma and acinar-to-ductal metaplasia.[142] The development of large species models creates a unique opportunity in which not only pharmacological therapies, but also novel surgical approaches, can be tested.

5. Pain

Pain is a prominent feature associated with both pancreatitis and pancreatic cancer. The role of the nervous system, neuroplasticity and neurogenic inflammation in exocrine pancreatic disease has been reviewed before.[143–146] Chronic pain, such as that associated with pancreatic disease, is often a result of sensitization of peripheral neurons. Several studies have used molecular tools to examine the expression of molecules involved in neurogenic inflammation and peripheral sensitization including growth factors, neuropeptides, and TRP channels.[147–154] A few labs have also performed functional studies (e.g. calcium imaging, electrophysiology) to directly assess sensory neuron excitability and sensitization.[148,150,155–161] Most studies, however, have focused on pain-associated behaviors (Table 7). There are two types of pain that can be assessed, experimentally evoked or ongoing pain. Experimentally evoked mechanical pain involves applying Von Frey monofilaments of increasing force to determine withdrawal thresholds. Application of radiant heat or placing the animal on a hot plate can be used to assess latency to respond to a noxious temperature. Finally, direct electrical stimulation of the pancreas evokes an abdominal muscle contraction called the visceromotor reflex (VMR). This is thought to be a model of referred pain. This technique can be used to determine the threshold to evoke a VMR or changes in the size of the VMR in controls versus animals with pancreatic disease. If the thresholds or latencies to evoke a response using any of these tests are reduced, this is interpreted as the animal experiencing pain. There are no strong models for directly measuring ongoing pain. In humans, however, ongoing pancreatic pain leads to hunching posture as well as a reduction in quality of life and spontaneous activity. Several investigators have taken advantage of this and used a variety of measures thought to indicate ongoing pain: reduced rearing, grooming, wheel running and ambulation as well as increased hunching, vocalization and catalepsy. Unfortunately, pancreatic pain related studies have been limited to rats and mice whose neural innervation, ductal structure, location, and gross anatomy is quite different from humans. Future studies need to address pain in a wider variety of animal models, including larger species, in order to improve our understanding of pain within the context of exocrine pancreatic disease.

6. Choosing a Model

One must consider the strengths and weaknesses implicit to each model as well as available resources and expectations regarding experiments and findings. Just as important, however, is which animal system to choose. Nongenic models can be applied to a greater variety of species, but there are a variety of potential responses. Indeed, it is important to choose the most appropriate method (+/− additional environmental factors) to induce pancreatitis and/or pancreatic cancer. For instance, the nitrosamine BOP preferentially drives pancreatic tumorigenesis in rodents, but not dogs (Table 2). There are also species differences associated with the nongenic models of pancreatitis. For example, cerulein administration to rats results in more interstitial edema and intracellular vacuolization while mice develop more acinar cell necrosis: a difference that may be explained by species-dependent roles of apoptosis and autophagy.[162,163] Mechanical models of pancreatitis have been applied across the widest range of species, from mice to non-human primates, and a diversity of responses have been reported.[164] In most species, ductal ligation and bile acid infusion evokes mild

disease; however, pigs and opossums exhibit severe disease. The variability in mechanical models is likely a consequence of the anatomical and functional differences across species.[165–167] Grossly, mouse and rabbit, for example, have diffuse pancreata scattered within the mesentery whereas dog, hamster, and pig have compact pancreata more closely resembling the retroperitoneal solid pancreas found in humans. Additionally, the ductal structure varies widely across species. Rats have a single outflow channel that may explain why rats develop fibrosis more rapidly than dogs following ductal ligation. Mice, on the other hand, have multiple ducts. This can provide an internal control within each animal if desired, but it also makes it technically challenging to execute a complete obstruction. When discussing data, it is important to consider how the anatomy of the animal may contribute to observed phenotypes.

Within a species, there are also important considerations when choosing a model (e.g. age, sex, strain, body fat). For instance, mouse strain directly impacts the severity of pancreatitis and systemic inflammation following intraductal infusion of taurocholate.[168] Serum enzymes and morphological damage are increased compared to controls in nine different strains; however, NOD/SHILT and AKR/J mice had enzyme activity significantly higher than the other strains. Further, only half of the strains exhibited elevated IL-6, a marker of inflammation. Even within substrains, differences in the severity of disease can be observed. C57BL/6J mice, for example, are more susceptible to cerulein-induced pancreatitis than their C57BL/6NHsd counterparts with regard to atrophy, morphological changes, and fibrosis.[169] Strain differences have also been reported in GEMMs. A study examining the effects of high fat diets on PDAC in the Ela- $Kras^{G12D}$ GEMM, reported that the incidence, frequency, and size of pancreatic neoplasia were significantly increased in mice on a F1 background as compared to those on the FVB background.[170] Differences are not restricted to strain, but also appear with respect to sex. Females, for instance, exhibit a much greater sensitivity to the choline-deficient ethionine-supplemented (CDE) diet because CDE induces hemorrhagic necrosis in an estrogen-dependent manner.[171,172] Another consideration is body fat status. The co-administration of interleukin-12 and interleukin-18, cytokines elevated in AP patients, drives edematous AP in wild type or lean mice.[173] However, the same doses induce necrotizing pancreatitis in both diet-induced obese mice as well as a GEMM of obesity called ob/ob mice.[173,174] Finally, age understandably plays a role in the development of disease in non-inducible genetically engineered models. However, age has also been implicated in non-genetic models. For example, in the cerulein paradigm for AP, a loss of uncoupling protein 2 aggravated the severity of disease in older but not young mice.[175]

7. Conclusion

The goal of animal models is to reproduce human disease including etiology, histopathology, pathophysiology, and therapeutic responsiveness. All of the animal models presented have both strengths and weaknesses with regard to disease phenotype. There are also considerations with respect to time and cost. The rationale for which model is chosen for a study should be clearly explained in publications. With the complex nature and variability of these models, it is essential to be overly transparent and provide explicit details regarding the design of the model used in a particular study, including which features of disease it

successfully recapitulates. Several of the models available provide an opportunity to examine the synergy between environmental and genetic contributors to disease, which would expand our understanding of the pathogenesis and progression of exocrine pancreatic diseases. However, neuroplasticity and pain are key features of both pancreatitis and pancreatic cancer. If models are going to be truly translational moving forward, they should also recapitulate alterations in the nervous system. At this time, how the nervous system is affected is unknown for most of the available models. To improve translation of basic pancreas research to clinically relevant therapies, there must be methods in place to ensure thorough interpretation of data, comparison across studies, and validation of findings. Towards that end, all future studies should incorporate objective quantitative measures to allow for these direct comparisons. Furthermore, in the event that potential therapeutics is identified, we strongly recommend simultaneous testing and/or validation by an independent laboratory at another institution. Indeed, such cross-validation should be incorporated into studies during the design phase, as potential collaborators are easily identified through the numerous pancreas associations and consortiums. Although we have made much progress, continued refinement of currently available models along with development of newer models will be important for bridging the gap between basic science and the clinic.

Funding

Hirshberg Foundation for Pancreatic Cancer Research and NIH K01DK120737 (J.L.S.), NIH R01CA177857 (B.M.D.), NIH K01AA019996 (M.E.), NIH P01CA163200 (G.E.), Veterans Administration Merit Award, NIH P01DK098108 and R01DK054021 (F.S.G.), NIH K08AA025112 (K.K.Y.L.), The National Pancreas Foundation and R01CA223204 (Z.C.M.), NIH U01DK108314 (S.J.P.), NIH U01DK108334 and R01DK118752 (A.U.), NIH U01DK108306 (D.C.W.).

REFERENCES

1. Lampel M, Kern HF. Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. Virchows Arch A Pathol Anat Histol. 1977;373:97–117. [PubMed: 139754]
2. Watanabe O, Baccino FM, Steer ML, et al. Supramaximal caerulein stimulation and ultrastructure of rat pancreatic acinar cell: early morphological changes during development of experimental pancreatitis. Am J Physiol. 1984;246:G457–G467. [PubMed: 6720895]
3. Nathan JD, Patel AA, McVey DC, et al. Capsaicin vanilloid receptor-1 mediates substance P release in experimental pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2001;281:G1322–1328. [PubMed: 11668042]
4. Kaiser AM, Saluja AK, Sengupta A, et al. Relationship between severity, necrosis, and apoptosis in five models of experimental acute pancreatitis. Am J Physiol. 1995;269:C1295–1304. [PubMed: 7491921]
5. Klauss S, Schorn S, Teller S, et al. Genetically induced vs. classical animal models of chronic pancreatitis: a critical comparison. FASEB J. 2018;32:5778–5792.
6. Neuschwander-Tetri BA, Burton FR, Presti ME, et al. Repetitive self-limited acute pancreatitis induces pancreatic fibrogenesis in the mouse. Dig Dis Sci. 2000;45:665–674. [PubMed: 10759232]
7. Xue J, Sharma V, Hsieh MH, et al. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun. 2015;6:7158. [PubMed: 25981357]
8. Zhang J, Rouse RL. Histopathology and pathogenesis of caerulein-, duct ligation-, and arginine-induced acute pancreatitis in Sprague-Dawley rats and C57BL6 mice. Histol Histopathol. 2014;29:1135–1152. [PubMed: 24585404]
9. Hoque R, Sohail M, Malik A, et al. TLR9 and the NLRP3 inflammasome link acinar cell death with inflammation in acute pancreatitis. Gastroenterology. 2011;141:358–369. [PubMed: 21439959]

10. Koopmann MC, Baumler MD, Boehler CJ, et al. Total parenteral nutrition attenuates cerulein-induced pancreatitis in rats. Pancreas. 2010;39:377–384. [PubMed: 19904225]
11. Nathan JD, Peng RY, Wang Y, et al. Primary sensory neurons: a common final pathway for inflammation in experimental pancreatitis in rats. Am J Physiol Gastrointest Liver Physiol. 2002;283:G938–946. [PubMed: 12223354]
12. Nathan JD, Romac J, Peng RY, et al. Protection against chronic pancreatitis and pancreatic fibrosis in mice overexpressing pancreatic secretory trypsin inhibitor. Pancreas. 2010;39:e24–30. [PubMed: 19904222]
13. Song R, Yu D, Park J. Changes in gene expression of tumor necrosis factor alpha and interleukin 6 in a canine model of caerulein-induced pancreatitis. Can J Vet Res. 2016;80:236–241. [PubMed: 27408338]
14. Wang Y, Kayoumu A, Lu G, et al. Experimental Models in Syrian Golden Hamster Replicate Human Acute Pancreatitis. Sci Rep. 2016;6:28014. [PubMed: 27302647]
15. Aghdassi AA, John DS, Sendler M, et al. Cathepsin D regulates cathepsin B activation and disease severity predominantly in inflammatory cells during experimental pancreatitis. J Biol Chem. 2018;293:1018–1029. [PubMed: 29229780]
16. Sendler M, Weiss FU, Golchert J, et al. Cathepsin B-Mediated Activation of Trypsinogen in Endocytosing Macrophages Increases Severity of Pancreatitis in Mice. Gastroenterology. 2018;154:704–718 e710. [PubMed: 29079517]
17. Gukovskaya AS, Gukovsky I, Algul H, et al. Autophagy, Inflammation, and Immune Dysfunction in the Pathogenesis of Pancreatitis. Gastroenterology. 2017;153:1212–1226. [PubMed: 28918190]
18. Gukovskaya AS, Vaquero E, Zaninovic V, et al. Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. Gastroenterology. 2002;122:974–984. [PubMed: 11910350]
19. Lerch MM, Gorelick FS. Models of acute and chronic pancreatitis. Gastroenterology. 2013;144:1180–1193. [PubMed: 23622127]
20. Zhan X, Wang F, Bi Y, et al. Animal models of gastrointestinal and liver diseases. Animal models of acute and chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2016;311:G343–355. [PubMed: 27418683]
21. Pour P, Gingell R, Langenbach R, et al. Carcinogenicity of N-Nitrosomethyl(2-oxopropyl)amine in Syrian Hamsters. Cancer Res. 1980;40:3585–3590. [PubMed: 7438045]
22. Pour P, Salmasi S, Runge R, et al. Carcinogenicity of N-nitrosobis(2-hydroxypropyl)amine and N-nitrosobis(2-oxopropyl)amine in MRC rats. J Natl Cancer Inst. 1979;63:181–190. [PubMed: 286828]
23. Fujii K, Hayakawa T, Kikuchi M. Tumor induction in mice administered neonatally with bis(2-oxopropyl)nitrosamine. Tohoku J Exp Med. 1994;174:361–368. [PubMed: 7732518]
24. Pour P, Althoff J, Gingell R, et al. N-Nitroso-bis(2-acetoxypropyl)amine as a Further Pancreatic Carcinogen in Syrian Golden Hamsters. Cancer Res. 1976;36:2877–2884. [PubMed: 1277198]
25. Moore PS, Sipos B, Orlandini S, et al. Genetic profile of 22 pancreatic carcinoma cell lines. Analysis of K-ras, p53, p16 and DPC4/Smad4. Virchows Arch. 2001;439:798–802. [PubMed: 11787853]
26. Sipos B, Moser S, Kalthoff H, et al. A comprehensive characterization of pancreatic ductal carcinoma cell lines: towards the establishment of an in vitro research platform. Virchows Arch. 2003;442:444–452. [PubMed: 12692724]
27. Monti P, Marchesi F, Reni M, et al. A comprehensive in vitro characterization of pancreatic ductal carcinoma cell line biological behavior and its correlation with the structural and genetic profile. Virchows Arch. 2004;445:236–247. [PubMed: 15258755]
28. Manegold P, Lai KKY, Wu Y, et al. Differentiation Therapy Targeting the β-Catenin/CBP Interaction in Pancreatic Cancer. Cancers (Basel). 2018;10.
29. Logsdon CD, Arumugam T, Ramachandran V. Animal Models of Gastrointestinal and Liver Diseases. The difficulty of animal modeling of pancreatic cancer for preclinical evaluation of therapeutics. Am J Physiol Gastrointest Liver Physiol. 2015;309:G283–291. [PubMed: 26159697]
30. Willyard C The mice with human tumours: Growing pains for a popular cancer model. Nature. 2018;560:156–157. [PubMed: 30087485]

31. Zechner D, Bürtin F, Amme J, et al. Characterization of novel carcinoma cell lines for the analysis of therapeutical strategies fighting pancreatic cancer. Cell Biosci. 2015;5:51. [PubMed: 26322225]
32. Torres MP, Rachagani S, Souchek JJ, et al. Novel pancreatic cancer cell lines derived from genetically engineered mouse models of spontaneous pancreatic adenocarcinoma: applications in diagnosis and therapy. PLoS One. 2013;8:e80580. [PubMed: 24278292]
33. Rhim AD. Creation of primary cell lines from lineage-labeled mouse models of cancer. Cold Spring Harb Protoc. 2015;2015:453–456. [PubMed: 25934932]
34. Setiawan VW, Monroe K, Lugea A, et al. Uniting Epidemiology and Experimental Disease Models for Alcohol-Related Pancreatic Disease. Alcohol Res. 2017;38:173–182. [PubMed: 28988572]
35. DeCarli LM, Lieber CS. Fatty liver in the rat after prolonged intake of ethanol with a nutritionally adequate new liquid diet. J Nutr. 1967;91:331–336. [PubMed: 6021815]
36. McIlwrath SL, Westlund KN. Pharmacological attenuation of chronic alcoholic pancreatitis induced hypersensitivity in rats. World J Gastroenterol. 2015;21:836–853. [PubMed: 25624717]
37. Vigna SR, Shahid RA, Liddle RA. Ethanol contributes to neurogenic pancreatitis by activation of TRPV1. FASEB J. 2014;28:891–896. [PubMed: 24221085]
38. Merkord J, Weber H, Jonas L, et al. The influence of ethanol on long-term effects of dibutyltin dichloride (DBTC) in pancreas and liver of rats. Hum Exp Toxicol. 1998;17:144–150. [PubMed: 9587782]
39. Weber H, Merkord J, Jonas L, et al. Oxygen radical generation and acute pancreatitis: effects of dibutyltin dichloride/ethanol and ethanol on rat pancreas. Pancreas. 1995;11:382–388. [PubMed: 8532655]
40. Zhang H, Liu B, Xu XF, et al. Pathophysiology of chronic pancreatitis induced by dibutyltin dichloride joint ethanol in mice. World J Gastroenterol. 2016;22:2960–2970. [PubMed: 26973392]
41. Huang W, Mukherjee R, Elliott V, et al. A novel model of acute alcoholic pancreatitis by concomitant administration of ethanol and fatty acid. Pancreas. 2010;39:1324.
42. Gu H, Fortunato F, Bergmann F, et al. Alcohol exacerbates LPS-induced fibrosis in subclinical acute pancreatitis. Am J Pathol. 2013;183:1508–1517. [PubMed: 24091223]
43. Pandol SJ, Periskic S, Gukovsky I, et al. Ethanol diet increases the sensitivity of rats to pancreatitis induced by cholecystokinin octapeptide. Gastroenterology. 1999;117:706–716. [PubMed: 10464148]
44. Huang W, Booth DM, Cane MC, et al. Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca2+-dependent mitochondrial dysfunction and acute pancreatitis. Gut. 2014;63:1313–1324. [PubMed: 24162590]
45. Maleth J, Balazs A, Pallagi P, et al. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. Gastroenterology. 2015;148:427–439 e416. [PubMed: 25447846]
46. Wendt LR, Osvaldt AB, Bersch VP, et al. Pancreatic intraepithelial neoplasia and ductal adenocarcinoma induced by DMBA in mice: effects of alcohol and caffeine. Acta Cir Bras. 2007;22:202–209. [PubMed: 17546293]
47. Woutersen RA, van Garderen-Hoetmer A, Bax J, et al. Modulation of dietary fat-promoted pancreatic carcinogenesis in rats and hamsters by chronic ethanol ingestion. Carcinogenesis. 1989;10:453–459. [PubMed: 2924393]
48. Alexandre M, Uduman AK, Minervini S, et al. Tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone initiates and enhances pancreatitis responses. Am J Physiol Gastrointest Liver Physiol. 2012;303:G696–704. [PubMed: 22837343]
49. Xue J, Zhao Q, Sharma V, et al. Aryl Hydrocarbon Receptor Ligands in Cigarette Smoke Induce Production of Interleukin-22 to Promote Pancreatic Fibrosis in Models of Chronic Pancreatitis. Gastroenterology. 2016;151:1206–1217. [PubMed: 27769811]
50. Bersch VP, Osvaldt AB, Edelweiss MIA, et al. Effect of Nicotine and Cigarette Smoke on an Experimental Model of Intraepithelial Lesions and Pancreatic Adenocarcinoma Induced by 7,12-Dimethylbenzanthracene in Mice. Pancreas. 2009;38:65–70. [PubMed: 18824948]
51. Ding Y, Cravero JD, Adrian K, et al. Modeling pancreatic cancer in vivo: from xenograft and carcinogen-induced systems to genetically engineered mice. Pancreas. 2010;39:283–292. [PubMed: 20335777]

52. Muller WJ, Sinn E, Pattengale PK, et al. Single-step induction of mammary adenocarcinoma in transgenic mice bearing the activated c-neu oncogene. Cell. 1988;54:105–115. [PubMed: 2898299]
53. Stopczynski RE, Normolle DP, Hartman DJ, et al. Neuroplastic changes occur early in the development of pancreatic ductal adenocarcinoma. Cancer Res. 2014;74:1718–1727. [PubMed: 24448244]
54. Ma J, Chen M, Wang J, et al. Pancreatic duodenal homeobox-1 (PDX1) functions as a tumor suppressor in gastric cancer. Carcinogenesis. 2008;29:1327–1333. [PubMed: 18477649]
55. Guz Y, Montminy MR, Stein R, et al. Expression of murine STF-1, a putative insulin gene transcription factor, in beta cells of pancreas, duodenal epithelium and pancreatic exocrine and endocrine progenitors during ontogeny. Development. 1995;121:11–18. [PubMed: 7867492]
56. Stoffers DA, Heller RS, Miller CP, et al. Developmental expression of the homeodomain protein IDX-1 in mice transgenic for an IDX-1 promoter/lacZ transcriptional reporter. Endocrinology. 1999;140:5374–5381. [PubMed: 10537169]
57. Glasgow SM, Henke RM, Macdonald RJ, et al. Ptf1a determines GABAergic over glutamatergic neuronal cell fate in the spinal cord dorsal horn. Development. 2005;132:5461–5469. [PubMed: 16291784]
58. Saloman JL, Davis BM. A transcription factor essential for organ differentiation is expressed in sensory neurons and regulated by nerve injury The 46th Annual Meeting of the Society for Neuroscience. San Diego, CA2016 Available at: https://www.abstractsonline.com/pp8/index.html#!/4071/presentation/21051. Accessed August 20, 2018.
59. Honig G, Liou A, Berger M, et al. Precise pattern of recombination in serotonergic and hypothalamic neurons in a Pdx1-cre transgenic mouse line. J Biomed Sci. 2010;17:82. [PubMed: 20950489]
60. Song J, Xu Y, Hu X, et al. Brain expression of Cre recombinase driven by pancreas-specific promoters. Genesis. 2010;48:628–634. [PubMed: 20824628]
61. Sakaguchi Y, Inaba M, Tsuda M, et al. The Wistar Bonn Kobori rat, a unique animal model for autoimmune pancreatitis with extrapancreatic exocrinopathy. Clin Exp Immunol. 2008;152:1–12. [PubMed: 18279444]
62. Jung IH, Jung DE, Park YN, et al. Aberrant Hedgehog ligands induce progressive pancreatic fibrosis by paracrine activation of myofibroblasts and ductular cells in transgenic zebrafish. PLoS One. 2011;6:e27941. [PubMed: 22164219]
63. Archer H, Jura N, Keller J, et al. A mouse model of hereditary pancreatitis generated by transgenic expression of R122H trypsinogen. Gastroenterology. 2006;131:1844–1855. [PubMed: 17087933]
64. Athwal T, Huang W, Mukherjee R, et al. Expression of human cationic trypsinogen (PRSS1) in murine acinar cells promotes pancreatitis and apoptotic cell death. Cell Death Dis. 2014;5:e1165. [PubMed: 24722290]
65. Gaiser S, Daniluk J, Liu Y, et al. Intracellular activation of trypsinogen in transgenic mice induces acute but not chronic pancreatitis. Gut. 2011;60:1379–1388. [PubMed: 21471572]
66. Geisz A, Sahin-Toth M. A preclinical model of chronic pancreatitis driven by trypsinogen autoactivation. Nat Commun. 2018;9:5033. [PubMed: 30487519]
67. Gerard C, Frossard JL, Bhatia M, et al. Targeted disruption of the beta-chemokine receptor CCR1 protects against pancreatitis-associated lung injury. J Clin Invest. 1997;100:2022–2027. [PubMed: 9329966]
68. Li L, Rao JN, Bass BL, et al. NF-kappaB activation and susceptibility to apoptosis after polyamine depletion in intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2001;280:G992–G1004. [PubMed: 11292609]
69. Moreno C, Nicaise C, Gustot T, et al. Chemokine receptor CCR5 deficiency exacerbates cerulein-induced acute pancreatitis in mice. Am J Physiol Gastrointest Liver Physiol. 2006;291:G1089–G1099. [PubMed: 16891300]
70. Nakamura Y, Kanai T, Saeki K, et al. CCR2 knockout exacerbates cerulein-induced chronic pancreatitis with hyperglycemia via decreased GLP-1 receptor expression and insulin secretion. Am J Physiol Gastrointest Liver Physiol. 2013;304:G700–707. [PubMed: 23449669]

71. Sendler M, Beyer G, Mahajan UM, et al. Complement Component 5 Mediates Development of Fibrosis, via Activation of Stellate Cells, in 2 Mouse Models of Chronic Pancreatitis. Gastroenterology. 2015;149:765–776.e10. [PubMed: 26001927]
72. Denham W, Yang J, Fink G, et al. Gene targeting demonstrates additive detrimental effects of interleukin 1 and tumor necrosis factor during pancreatitis. Gastroenterology. 1997;113:1741–1746. [PubMed: 9352880]
73. Oughourlian JM. [Psychosomatic reflections]. Ann Med Psychol (Paris). 1976;1:663–668. [PubMed: 970823]
74. Rajapandi T, Oliver D. Integration of SecA protein into the Escherichia coli inner membrane is regulated by its amino-terminal ATP-binding domain. Mol Microbiol. 1996;20:43–51. [PubMed: 8861203]
75. Romac JM, Shahid RA, Choi SS, et al. Pancreatic secretory trypsin inhibitor I reduces the severity of chronic pancreatitis in mice overexpressing interleukin-1beta in the pancreas. Am J Physiol Gastrointest Liver Physiol. 2012;302:G535–G541. [PubMed: 22173919]
76. Song Z, Bhagat G, Quante M, et al. Potential carcinogenic effects of cigarette smoke and Swedish moist snuff on pancreas: a study using a transgenic mouse model of chronic pancreatitis. Lab Invest. 2010;90:426–435. [PubMed: 20065943]
77. Suzuki S, Miyasaka K, Jimi A, et al. Induction of acute pancreatitis by cerulein in human IL-6 gene transgenic mice. Pancreas. 2000;21:86–92. [PubMed: 10881937]
78. Frossard JL, Saluja A, Bhagat L, et al. The role of intercellular adhesion molecule 1 and neutrophils in acute pancreatitis and pancreatitis-associated lung injury. Gastroenterology. 1999;116:694–701. [PubMed: 10029629]
79. Umans L, Serneels L, Overbergh L, et al. alpha2-macroglobulin- and murinoglobulin-1- deficient mice. A mouse model for acute pancreatitis. Am J Pathol. 1999;155:983–993. [PubMed: 10487856]
80. Jancso Z, Hegyi E, Sahin-Toth M. Chymotrypsin Reduces the Severity of Secretagogue-Induced Pancreatitis in Mice. Gastroenterology. 2018;155:1017–1021. [PubMed: 30076839]
81. Zhang Y, Zhan X, Zhang G, et al. Mutant Human PRSS1 R122H Expression in Mice Greatly Exacerbates Pancreatitis. Digestive Diseases Week; 2017; Chicago, IL. *Gastroenterology*. 2017;152 Suppl 1:S893abstract.
82. Collins MA, Bednar F, Zhang Y, et al. Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest. 2012;122:639–653. [PubMed: 22232209]
83. Tuveson DA, Hingorani SR. Ductal pancreatic cancer in humans and mice. Cold Spring Harb Symp Quant Biol. 2005;70:65–72. [PubMed: 16869739]
84. Guerra C, Barbacid M. Genetically engineered mouse models of pancreatic adenocarcinoma. Mol Oncol. 2013;7:232–247. [PubMed: 23506980]
85. Ding Y, Cravero JD, Adrian K, et al. Modeling Pancreatic Cancer In Vivo: From Xenograft and Carcinogen-Induced Systems to Genetically Engineered Mice. Pancreas. 2010;39:283–292. [PubMed: 20335777]
86. Westphalen CB, Olive KP. Genetically Engineered Mouse Models of Pancreatic Cancer. The Cancer Journal. 2012;18:502–510. [PubMed: 23187836]
87. Morris JP, Wang SC, Hebrok M. KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma. Nat Rev Cancer. 2010;10:683–695. [PubMed: 20814421]
88. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pathology of Genetically Engineered Mouse Models of Pancreatic Exocrine Cancer: Consensus Report and Recommendations. Cancer Res. 2006;66:95–106. [PubMed: 16397221]
89. Nagy A Cre recombinase: The universal reagent for genome tailoring. genesis. 2000;26:99–109. [PubMed: 10686599]
90. Rozenblum E, Schutte M, Goggins M, et al. Tumor-suppressive pathways in pancreatic carcinoma. Cancer Res. 1997;57:1731–1734. [PubMed: 9135016]
91. Hashimoto D, Arima K, Yokoyama N, et al. Heterogeneity of KRAS Mutations in Pancreatic Ductal Adenocarcinoma. Pancreas. 2016;45:1111–1114. [PubMed: 26967456]
92. The Cancer Genome Atlas Research Network. Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. Cancer Cell. 2017;32:185–203.e13. [PubMed: 28810144]

93. Lin EY, Jones JG, Li P, et al. Progression to Malignancy in the Polyoma Middle T Oncoprotein Mouse Breast Cancer Model Provides a Reliable Model for Human Diseases. Am J Pathol. 2003;163:2113–2126. [PubMed: 14578209]
94. Cardiff RD, Anver Mr, Gusterson BA, et al. The mammary pathology of genetically engineered mice: the consensus report and recommendations from the Annapolis meeting. Oncogene. 2000;19:968–988. [PubMed: 10713680]
95. Parisotto M, Metzger D. Genetically engineered mouse models of prostate cancer. Mol Oncol. 2013;7:190–205. [PubMed: 23481269]
96. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pathology of genetically engineered mouse models of pancreatic exocrine cancer: consensus report and recommendations. Cancer Res. 2006;66:95–106. [PubMed: 16397221]
97. Aguirre AJ, Bardeesy N, Sinha M, et al. Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. Genes Dev. 2003;17:3112–3126. [PubMed: 14681207]
98. Bardeesy N, Aguirre AJ, Chu GC, et al. Both p16Ink4a and the p19Arf-p53 pathway constrain progression of pancreatic adenocarcinoma in the mouse. Proc Natl Acad Sci U S A. 2006;103:5947–5952. [PubMed: 16585505]
99. Bardeesy N, Cheng K-h, Berger JH, et al. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. Genes Dev. 2006;20:3130–3146. [PubMed: 17114584]
100. Bardeesy N, Morgan J, Sinha M, et al. Obligate Roles for p16Ink4a and p19Arf-p53 in the Suppression of Murine Pancreatic Neoplasia. Mol Cell Biol. 2002;22:635–643. [PubMed: 11756558]
101. Galicia VA, He L, Dang H, et al. Expansion of Hepatic Tumor Progenitor Cells in Pten-Null Mice Requires Liver Injury and Is Reversed by Loss of AKT2. Gastroenterology. 2010;139:2170–2182. [PubMed: 20837017]
102. Hingorani SR, Petricoin EF, Maitra A, et al. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell. 2003;4:437–450. [PubMed: 14706336]
103. Bayne LJ, Beatty GL, Jhala N, et al. Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. Cancer Cell. 2012;21:822–835. [PubMed: 22698406]
104. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148:349–361. [PubMed: 22265420]
105. Saloman JL, Albers KM, Li D, et al. Ablation of sensory neurons in a genetic model of pancreatic ductal adenocarcinoma slows initiation and progression of cancer. Proc Natl Acad Sci U S A. 2016;113:3078–3083. [PubMed: 26929329]
106. Saloman JL, Singhi AD, Hartman DJ, et al. Systemic Depletion of Nerve Growth Factor Inhibits Disease Progression in a Genetically Engineered Model of Pancreatic Ductal Adenocarcinoma. Pancreas. 2018;47:856–863. [PubMed: 29975347]
107. Tuveson DA, Shaw AT, Willis NA, et al. Endogenous oncogenic K-ras(G12D) stimulates proliferation and widespread neoplastic and developmental defects. Cancer Cell. 2004;5:375–387. [PubMed: 15093544]
108. Ji B, Song J, Tsou L, et al. Robust acinar cell transgene expression of CreErT via BAC recombineering. Genesis. 2008;46:390–395. [PubMed: 18693271]
109. de Latouliere L, Manni I, Iacobini C, et al. A bioluminescent mouse model of proliferation to highlight early stages of pancreatic cancer: A suitable tool for preclinical studies. Ann Anat. 2016;207:2–8. [PubMed: 26704357]
110. Ornitz DM, Hammer RE, Messing A, et al. Pancreatic neoplasia induced by SV40 T-antigen expression in acinar cells of transgenic mice. Science. 1987;238:188–193. [PubMed: 2821617]
111. Tevethia MJ, Bonneau RH, Griffith JW, et al. A simian virus 40 large T-antigen segment containing amino acids 1 to 127 and expressed under the control of the rat elastase-1 promoter produces pancreatic acinar carcinomas in transgenic mice. J Virol. 1997;71:8157–8166. [PubMed: 9343166]

112. Stanger BZ, Stiles B, Lauwers GY, et al. Pten constrains centroacinar cell expansion and malignant transformation in the pancreas. Cancer Cell. 2005;8:185–195. [PubMed: 16169464]
113. Bardeesy N, Aguirre AJ, Chu GC, et al. Both p16(Ink4a) and the p19(Arf)-p53 pathway constrain progression of pancreatic adenocarcinoma in the mouse. Proc Natl Acad Sci U S A. 2006;103:5947–5952. [PubMed: 16585505]
114. Lugea A, Tischler D, Nguyen J, et al. Adaptive unfolded protein response attenuates alcohol-induced pancreatic damage. Gastroenterology. 2011;140:987–997. [PubMed: 21111739]
115. Xu S, Chheda C, Ouhaddi Y, et al. Characterization of Mouse Models of Early Pancreatic Lesions Induced by Alcohol and Chronic Pancreatitis. Pancreas. 2015;44:882–887. [PubMed: 26166469]
116. Edderkaoui M, Xu S, Chheda C, et al. HDAC3 mediates smoking-induced pancreatic cancer. Oncotarget. 2016;7:7747–7760. [PubMed: 26745602]
117. Nimmakayala RK, Seshacharyulu P, Lakshmanan I, et al. Cigarette Smoke Induces Stem Cell Features of Pancreatic Cancer Cells via PAF1. Gastroenterology. 2018;155:892–908.e6. [PubMed: 29864419]
118. Hermann PC, Sancho P, Cañamero M, et al. Nicotine promotes initiation and progression of KRAS-induced pancreatic cancer via Gata6-dependent dedifferentiation of acinar cells in mice. Gastroenterology. 2014;147:1119–1133.e4. [PubMed: 25127677]
119. Gomez-Chou SB, Swidnicka-Siergiejko AK, Badi N, et al. Lipocalin-2 Promotes Pancreatic Ductal Adenocarcinoma by Regulating Inflammation in the Tumor Microenvironment. Cancer Res. 2017;77:2647–2660. [PubMed: 28249896]
120. Philip B, Roland CL, Daniluk J, et al. A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. Gastroenterology. 2013;145:1449–1458. [PubMed: 23958541]
121. Chang HH, Moro A, Takakura K, et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. PLoS One. 2017;12:e0184455. [PubMed: 28886117]
122. Dawson DW, Hertzer K, Moro A, et al. High-fat, high-calorie diet promotes early pancreatic neoplasia in the conditional KrasG12D mouse model. Cancer Prev Res (Phila). 2013;6:1064–1073. [PubMed: 23943783]
123. Strouch MJ, Ding Y, Salabat MR, et al. A high omega-3 fatty acid diet mitigates murine pancreatic precancer development. J Surg Res. 2011;165:75–81. [PubMed: 19631339]
124. Okumura T, Ohuchida K, Sada M, et al. Extra-pancreatic invasion induces lipolytic and fibrotic changes in the adipose microenvironment, with released fatty acids enhancing the invasiveness of pancreatic cancer cells. Oncotarget. 2017;8:18280–18295. [PubMed: 28407685]
125. Guerra C, Schuhmacher AJ, Canamero M, et al. Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell. 2007;11:291–302. [PubMed: 17349585]
126. Aleksic T, Baumann B, Wagner M, et al. Cellular immune reaction in the pancreas is induced by constitutively active IkappaB kinase-2. Gut. 2007;56:227–236. [PubMed: 16870717]
127. Baumann B, Wagner M, Aleksic T, et al. Constitutive IKK2 activation in acinar cells is sufficient to induce pancreatitis in vivo. J Clin Invest. 2007;117:1502–1513. [PubMed: 17525799]
128. Orabi AI, Wen L, Javed TA, et al. Targeted inhibition of pancreatic acinar cell calcineurin is a novel strategy to prevent post-ERCP pancreatitis. Cell Mol Gastroenterol Hepatol. 2017;3:119–128. [PubMed: 28090570]
129. Griffin MA, Restrepo MS, Abu-El-Haija M, et al. A novel gene delivery method transduces porcine pancreatic duct epithelial cells. Gene Ther. 2014;21:123–130. [PubMed: 24257348]
130. Doiron B, DeFronzo RA. A novel experimental model for human mixed acinar-ductal pancreatic cancer. Carcinogenesis. 2018;39:180–190. [PubMed: 29106450]
131. Rogers CS, Stoltz DA, Meyerholz DK, et al. Disruption of the CFTR gene produces a model of cystic fibrosis in newborn pigs. Science. 2008;321:1837–1841. [PubMed: 18818360]
132. Ostedgaard LS, Meyerholz DK, Chen JH, et al. The DeltaF508 mutation causes CFTR misprocessing and cystic fibrosis-like disease in pigs. Sci Transl Med. 2011;3:74ra24.
133. Meyerholz DK, Stoltz DA, Pezzulo AA, et al. Pathology of gastrointestinal organs in a porcine model of cystic fibrosis. Am J Pathol. 2010;176:1377–1389. [PubMed: 20110417]

134. Abu-El-Haija M, Ramachandran S, Meyerholz DK, et al. Pancreatic damage in fetal and newborn cystic fibrosis pigs involves the activation of inflammatory and remodeling pathways. Am J Pathol. 2012;181:499–507. [PubMed: 22683312]
135. Uc A, Olivier AK, Griffin MA, et al. Glycaemic regulation and insulin secretion are abnormal in cystic fibrosis pigs despite sparing of islet cell mass. Clin Sci (Lond). 2015;128:131–142. [PubMed: 25142104]
136. Sun X, Yan Z, Yi Y, et al. Adeno-associated virus-targeted disruption of the CFTR gene in cloned ferrets. J Clin Invest. 2008;118:1578–1583. [PubMed: 18324338]
137. Sun X, Sui H, Fisher JT, et al. Disease phenotype of a ferret CFTR-knockout model of cystic fibrosis. J Clin Invest. 2010;120:3149–3160. [PubMed: 20739752]
138. Sun X, Olivier AK, Yi Y, et al. Gastrointestinal pathology in juvenile and adult CFTR-knockout ferrets. Am J Pathol. 2014;184:1309–1322. [PubMed: 24637292]
139. Rotti PG, Xie W, Poudel A, et al. Pancreatic and Islet Remodeling in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Knockout Ferrets. Am J Pathol. 2018;188:876–890. [PubMed: 29366680]
140. Navis A, Bagnat M. Loss of cftr function leads to pancreatic destruction in larval zebrafish. Dev Biol. 2015;399:237–248. [PubMed: 25592226]
141. Schachtschneider KM, Schwind RM, Newson J, et al. The Oncopig Cancer Model: An Innovative Large Animal Translational Oncology Platform. Front Oncol. 2017;7:190. [PubMed: 28879168]
142. Principe DR, Overgaard NH, Park AJ, et al. KRAS(G12D) and TP53(R167H) Cooperate to Induce Pancreatic Ductal Adenocarcinoma in Sus scrofa Pigs. Sci Rep. 2018;8:12548. [PubMed: 30135483]
143. Saloman JL, Albers KM, Davis BM. The Role of Neurogenic Inflammation in Pancreatitis. In: Beger HG, Warshaw AL, Hruban RH, et al., eds. The Pancreas: An Integrated Textbook of Basic Science, Medicine and Surgery. 3rd Edition. Hoboken, NJ; John Wiley & Sons; 2018:173.
144. Saloman JL, Albers KM, Rhim AD, et al. Can Stopping Nerves, Stop Cancer? Trends Neurosci. 2016;39:880–889. [PubMed: 27832915]
145. Zhao JB, Liao DH, Nissen TD. Animal models of pancreatitis: can it be translated to human pain study? World J Gastroenterol. 2013;19:7222–7230. [PubMed: 24259952]
146. Vera-Portocarrero L, Westlund KN. Role of neurogenic inflammation in pancreatitis and pancreatic pain. Neurosignals. 2005;14:158–165. [PubMed: 16215298]
147. Winston JH, He ZJ, Shenoy M, et al. Molecular and behavioral changes in nociception in a novel rat model of chronic pancreatitis for the study of pain. Pain. 2005;117:214–222. [PubMed: 16098667]
148. Ceppa E, Cattaruzza F, Lyo V, et al. Transient receptor potential ion channels V4 and A1 contribute to pancreatitis pain in mice. Am J Physiol Gastrointest Liver Physiol. 2010;299:G556–G571. [PubMed: 20539005]
149. Quan-Xin F, Fan F, Xiang-Ying F, et al. Resolvin D1 reverses chronic pancreatitis-induced mechanical allodynia, phosphorylation of NMDA receptors, and cytokines expression in the thoracic spinal dorsal horn. BMC Gastroenterol. 2012;12:148. [PubMed: 23092159]
150. Schwartz ES, Christianson JA, Chen X, et al. Synergistic role of TRPV1 and TRPA1 in pancreatic pain and inflammation. Gastroenterology. 2011;140:1283–1291.e1-e2. [PubMed: 21185837]
151. Terada Y, Fujimura M, Nishimura S, et al. Contribution of TRPA1 as a downstream signal of proteinase-activated receptor-2 to pancreatic pain. J Pharmacol Sci. 2013;123:284–287. [PubMed: 24162021]
152. Hughes MS, Shenoy M, Liu L, et al. Brain-derived neurotrophic factor is upregulated in rats with chronic pancreatitis and mediates pain behavior. Pancreas. 2011;40:551–556. [PubMed: 21499209]
153. Toma H, Winston J, Micci MA, et al. Nerve growth factor expression is up-regulated in the rat model of L-arginine-induced acute pancreatitis. Gastroenterology. 2000;119:1373–1381. [PubMed: 11054396]
154. Toma H, Winston JH, Micci MA, et al. Characterization of the neurotrophic response to acute pancreatitis. Pancreas. 2002;25:31–38. [PubMed: 12131768]

155. Han L, Ma J, Duan W, et al. Pancreatic stellate cells contribute pancreatic cancer pain via activation of sHH signaling pathway. Oncotarget. 2016;7:18146–18158. [PubMed: 26934446]
156. Liu L, Zhu Y, Noe M, et al. Neuronal Transforming Growth Factor beta Signaling via SMAD3 Contributes to Pain in Animal Models of Chronic Pancreatitis. Gastroenterology. 2018;154:2252–2265.e2. [PubMed: 29505748]
157. Li C, Zhu Y, Shenoy M, et al. Anatomical and functional characterization of a duodeno-pancreatic neural reflex that can induce acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2013;304:G490–G500. [PubMed: 23306082]
158. Xu GY, Winston JH, Shenoy M, et al. Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis. Gastroenterology. 2007;133:1282–1292. [PubMed: 17698068]
159. Zhu Y, Colak T, Shenoy M, et al. Transforming growth factor beta induces sensory neuronal hyperexcitability, and contributes to pancreatic pain and hyperalgesia in rats with chronic pancreatitis. Mol Pain. 2012;8:65. [PubMed: 22963239]
160. Zhu Y, Colak T, Shenoy M, et al. Nerve growth factor modulates TRPV1 expression and function and mediates pain in chronic pancreatitis. Gastroenterology. 2011;141:370–377. [PubMed: 21473865]
161. Zhu Y, Mehta K, Li C, et al. Systemic administration of anti-NGF increases A-type potassium currents and decreases pancreatic nociceptor excitability in a rat model of chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2012;302:G176–G181. [PubMed: 22038828]
162. Mareninova OA, Sung KF, Hong P, et al. Cell death in pancreatitis: caspases protect from necrotizing pancreatitis. J Biol Chem. 2006;281:3370–3381. [PubMed: 16339139]
163. Mareninova OA, Hermann K, French SW, et al. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. J Clin Invest. 2009;119:3340–3355. [PubMed: 19805911]
164. Su KH, Cuthbertson C, Christophi C. Review of experimental animal models of acute pancreatitis. HPB (Oxford). 2006;8:264–286. [PubMed: 18333137]
165. Case RM. Is the rat pancreas an appropriate model of the human pancreas? Pancreatology. 2006;6:180–190. [PubMed: 16534243]
166. Tsuchitani M, Sato J, Kokoshima H. A comparison of the anatomical structure of the pancreas in experimental animals. J Toxicol Pathol. 2016;29:147–154. [PubMed: 27559239]
167. Dolensek J, Rupnik MS, Stozer A. Structural similarities and differences between the human and the mouse pancreas. Islets. 2015;7:e1024405. [PubMed: 26030186]
168. Seifert GJ, Sander KC, Richter S, et al. Murine genotype impacts pancreatitis severity and systemic inflammation: An experimental study. Ann Med Surg (Lond). 2017;24:8–14. [PubMed: 29062479]
169. Ulmasov B, Oshima K, Rodriguez MG, et al. Differences in the degree of cerulein-induced chronic pancreatitis in C57BL/6 mouse substrains lead to new insights in identification of potential risk factors in the development of chronic pancreatitis. Am J Pathol. 2013;183:692–708. [PubMed: 23845568]
170. Cheon EC, Strouch MJ, Barron MR, et al. Alteration of strain background and a high omega-6 fat diet induces earlier onset of pancreatic neoplasia in EL-Kras transgenic mice. Int J Cancer. 2011;128:2783–2792. [PubMed: 20725998]
171. Lombardi B, Estes LW, Longnecker DS. Acute hemorrhagic pancreatitis (massive necrosis) with fat necrosis induced in mice by DL-ethionine fed with a choline-deficient diet. Am J Pathol. 1975;79:465–480. [PubMed: 1094837]
172. Rao KN, Eagon PK, Okamura K, et al. Acute hemorrhagic pancreatic necrosis in mice. Induction in male mice treated with estradiol. Am J Pathol. 1982;109:8–14. [PubMed: 6181693]
173. Sennello JA, Fayad R, Pini M, et al. Interleukin-18, together with interleukin-12, induces severe acute pancreatitis in obese but not in nonobese leptin-deficient mice. Proc Natl Acad Sci U S A. 2008;105:8085–8090. [PubMed: 18515422]
174. Pini M, Sennello JA, Cabay RJ, et al. Effect of diet-induced obesity on acute pancreatitis induced by administration of interleukin-12 plus interleukin-18 in mice. Obesity (Silver Spring). 2010;18:476–481. [PubMed: 19696761]

175. Müller S, Kaiser H, Krüger B, et al. Age-dependent effects of UCP2 deficiency on experimental acute pancreatitis in mice. PLoS One. 2014;9:e94494. [PubMed: 24721982]
176. Vazquez-Echarri J, Baumgärtner D, Singer MV. Dose-response effects of atropine on pancreatic secretory response to intravenous cerulein in dogs. Pancreas. 1986;1:341–346. [PubMed: 3562434]
177. Hu G, Zhao Y, Tang Y, et al. Development of a novel model of hypertriglyceridemic acute pancreatitis in hamsters: protective effects of probucol. Pancreas. 2012;41:845–848. [PubMed: 22781908]
178. Lim SY, Nakamura K, Morishita K, et al. Qualitative and quantitative contrast-enhanced ultrasonographic assessment of cerulein-induced acute pancreatitis in dogs. J Vet Intern Med. 2014;28:496–503. [PubMed: 24612403]
179. Schwartz ES, La JH, Scheff NN, et al. TRPV1 and TRPA1 antagonists prevent the transition of acute to chronic inflammation and pain in chronic pancreatitis. J Neurosci. 2013;33:5603–5611. [PubMed: 23536075]
180. Niederau C, Ferrell LD, Grendell JH. Caerulein-induced acute necrotizing pancreatitis in mice: protective effects of proglumide, benzotript, and secretin. Gastroenterology. 1985;88:1192–1204. [PubMed: 2984080]
181. Sah RP, Dudeja V, Dawra RK, et al. Cerulein-induced chronic pancreatitis does not require intra-acinar activation of trypsinogen in mice. Gastroenterology. 2013;144:1076–1085.e2. [PubMed: 23354015]
182. Dawra R, Sharif R, Phillips P, et al. Development of a new mouse model of acute pancreatitis induced by administration of L-arginine. Am J Physiol Gastrointest Liver Physiol. 2007;292:G1009–G1018. [PubMed: 17170029]
183. Delaney CP, McGeeney KF, Dervan P, et al. Pancreatic atrophy: a new model using serial intra-peritoneal injections of L-arginine. Scand J Gastroenterol. 1993;28:1086–1090. [PubMed: 8303212]
184. Fredstrom SB, Jessurun J, Gallaher DD. Pancreatitis induced in rats by repetitive administration of L-arginine. Pancreas. 2009;38:344–345. [PubMed: 19307932]
185. Hegyi P, Rakonczay Z Jr, Sari R, et al. L-arginine-induced experimental pancreatitis. World J Gastroenterol. 2004;10:2003–2009. [PubMed: 15237423]
186. Varga IS, Matkovics B, Czako L, et al. Oxidative stress changes in L-arginine-induced pancreatitis in rats. Pancreas. 1997;14:355–359. [PubMed: 9163781]
187. Biczo G, Hegyi P, Dosa S, et al. The crucial role of early mitochondrial injury in L-lysine-induced acute pancreatitis. Antioxid Redox Signal. 2011;15:2669–2681. [PubMed: 21644850]
188. Biczo G, Hegyi P, Sinervirta R, et al. Characterization of polyamine homeostasis in l-ornithine-induced acute pancreatitis in rats. Pancreas. 2010;39:1047–1056. [PubMed: 20531247]
189. Sun L, Xiu M, Wang S, et al. Lipopolysaccharide enhances TGF-beta1 signalling pathway and rat pancreatic fibrosis. J Cell Mol Med. 2018;22:2346–2356. [PubMed: 29424488]
190. Clemens DL, Jerrells TR. Ethanol consumption potentiates viral pancreatitis and may inhibit pancreas regeneration: preliminary findings. Alcohol. 2004;33:183–189. [PubMed: 15596086]
191. Niederau C, Liddle RA, Ferrell LD, et al. Beneficial effects of cholecystokinin-receptor blockade and inhibition of proteolytic enzyme activity in experimental acute hemorrhagic pancreatitis in mice. Evidence for cholecystokinin as a major factor in the development of acute pancreatitis. J Clin Invest. 1986;78:1056–1063. [PubMed: 2428840]
192. Akita S, Kubota K, Kobayashi A, et al. Role of bone marrow cells in the development of pancreatic fibrosis in a rat model of pancreatitis induced by a choline-deficient/ethionine-supplemented diet. Biochem Biophys Res Commun. 2012;420:743–749. [PubMed: 22465012]
193. Rouse R, Xu L, Stewart S, et al. High fat diet and GLP-1 drugs induce pancreatic injury in mice. Toxicol Appl Pharmacol. 2014;276:104–114. [PubMed: 24534256]
194. Xu GY, Winston JH, Shenoy M, et al. Enhanced excitability and suppression of A-type K+ current of pancreas-specific afferent neurons in a rat model of chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2006;291:G424–G431. [PubMed: 16645160]

195. Cattaruzza F, Johnson C, Leggit A, et al. Transient receptor potential ankyrin 1 mediates chronic pancreatitis pain in mice. Am J Physiol Gastrointest Liver Physiol. 2013;304:G1002–G1012. [PubMed: 23558009]
196. Glawe C, Emmrich J, Sparmann G, et al. In vivo characterization of developing chronic pancreatitis in rats. Lab Invest. 2005;85:193–204. [PubMed: 15543202]
197. Merkord J, Weber H, Kroning G, et al. Repeated administration of a mild acute toxic dose of di-n-butyltin dichloride at intervals of 3 weeks induces severe lesions in pancreas and liver of rats. Hum Exp Toxicol. 2001;20:386–392. [PubMed: 11727788]
198. Zhao HF, Ito T, Gibo J, et al. Anti-monocyte chemoattractant protein 1 gene therapy attenuates experimental chronic pancreatitis induced by dibutyltin dichloride in rats. Gut. 2005;54:1759–1767. [PubMed: 16284287]
199. Ding SP, Li JC, Jin C. A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide. World J Gastroenterol. 2003;9:584–589. [PubMed: 12632523]
200. Imamura M, Mikami Y, Takahashi H, et al. Effect of a specific synthetic inhibitor of neutrophil elastase (ONO-5046) on the course of acute hemorrhagic pancreatitis in dogs. J Hepatobiliary Pancreat Surg. 1998;5:422–428. [PubMed: 9931392]
201. Shahid RA, Vigna SR, Layne AC, et al. Acinar Cell Production of Leukotriene B Contributes to Development of Neurogenic Pancreatitis in Mice. Cell Mol Gastroenterol Hepatol. 2015;1:75–86. [PubMed: 25729765]
202. Aho HJ, Nevalainen TJ, Aho AJ. Experimental pancreatitis in the rat. Development of pancreatic necrosis, ischemia and edema after intraductal sodium taurocholate injection. Eur Surg Res. 1983;15:28–36. [PubMed: 6840152]
203. Aho HJ, Nevalainen TJ, Lindberg RL, et al. Experimental pancreatitis in the rat. The role of phospholipase A in sodium taurocholate-induced acute haemorrhagic pancreatitis. Scand J Gastroenterol. 1980;15:1027–1031. [PubMed: 6165066]
204. Orda R, Hadas N, Orda S, et al. Experimental acute pancreatitis. Inducement by taurocholate sodium-trypsin injection into a temporarily closed duodenal loop in the rat. Arch Surg. 1980;115:327–329. [PubMed: 6153522]
205. Chikamune T, Katamoto H, Nomura K, et al. Lipoprotein profile in canine pancreatitis induced with oleic acid. J Vet Med Sci. 1998;60:413–421. [PubMed: 9592712]
206. Kitchell BE, Strombeck DR, Cullen J, et al. Clinical and pathologic changes in experimentally induced acute pancreatitis in cats. Am J Vet Res. 1986;47:1170–1173. [PubMed: 2424350]
207. Mundlos S, Adler G, Schaar M, et al. Exocrine pancreatic function in oleic acid-induced pancreatic insufficiency in rats. Pancreas. 1986;1:29–36. [PubMed: 2437560]
208. Murtaugh RJ, Jacobs RM, Sherding RG, et al. Serum pancreatic polypeptide and amylase concentrations in dogs with experimentally induced acute pancreatitis. Am J Vet Res. 1985;46:654–656. [PubMed: 2581485]
209. Tashiro M, Nakamura H, Taguchi M, et al. Oleic acid-induced pancreatitis alters expression of transforming growth factor-beta1 and extracellular matrix components in rats. Pancreas. 2003;26:197–204. [PubMed: 12604920]
210. Vollmar B, Waldner H, Schmand J, et al. Oleic acid induced pancreatitis in pigs. J Surg Res. 1991;50:196–204. [PubMed: 1990228]
211. Yamaguchi T, Nakamura H, Kihara Y, et al. Long-term overexpression of membrane type-1 matrix metalloproteinase and matrix metalloproteinase-2 in oleic acid-induced pancreatitis in rats. Pancreas. 2002;24:348–356. [PubMed: 11961487]
212. Mooren F, Hlouschek V, Finkes T, et al. Early changes in pancreatic acinar cell calcium signaling after pancreatic duct obstruction. J Biol Chem. 2003;278:9361–9369. [PubMed: 12522141]
213. Ohshio G, Saluja A, Steer ML. Effects of short-term pancreatic duct obstruction in rats. Gastroenterology. 1991;100:196–202. [PubMed: 1700960]
214. Runzi M, Saluja A, Kaiser A, et al. Biochemical and morphological changes that characterise recovery from necrotising biliary pancreatitis in the opossum. Gut. 1995;37:427–433. [PubMed: 7590443]

215. Baxter JN, Jenkins SA, Day DW, et al. Effects of somatostatin and a long-acting somatostatin analogue on the prevention and treatment of experimentally induced acute pancreatitis in the rat. Br J Surg. 1985;72:382–385. [PubMed: 2581647]
216. Boerma D, Straatsburg IH, Offerhaus GJ, et al. Experimental model of obstructive, chronic pancreatitis in pigs. Dig Surg. 2003;20:520–526. [PubMed: 14534374]
217. Chen JW, Thomas A, Woods CM, et al. Sphincter of Oddi dysfunction produces acute pancreatitis in the possum. Gut. 2000;47:539–545. [PubMed: 10986215]
218. Churg A, Richter WR. Early changes in the exocrine pancreas of the dog and rat after ligation of the pancreatic duct. A light and electron microscopic study. Am J Pathol. 1971;63:521–546. [PubMed: 5581235]
219. Isaksson G, Lundquist I, Ihse I. Effects on the exocrine and endocrine pancreas of duct occlusion with two different tissue glues in the rat. Eur Surg Res. 1983;15:136–144. [PubMed: 6345169]
220. Popper HL, Necheles H, Russell KC. Transition of pancreatic edema into pancreatic necrosis. Surg Gynecol Obstet. 1948;87:79–82. [PubMed: 18860330]
221. Simpson KW, Batt RM, McLean L, et al. Circulating concentrations of trypsin-like immunoreactivity and activities of lipase and amylase after pancreatic duct ligation in dogs. Am J Vet Res. 1989;50:629–632. [PubMed: 2471426]
222. Tanaka T, Ichiba Y, Fujii Y, et al. New canine model of chronic pancreatitis due to chronic ischemia with incomplete pancreatic duct obstruction. Digestion. 1988;41:149–155. [PubMed: 3224767]
223. Vigna SR, Shahid RA, Nathan JD, et al. Leukotriene B4 mediates inflammation via TRPV1 in duct obstruction-induced pancreatitis in rats. Pancreas. 2011;40:708–714. [PubMed: 21602738]
224. Watanabe S, Abe K, Anbo Y, et al. Changes in the mouse exocrine pancreas after pancreatic duct ligation: a qualitative and quantitative histological study. Arch Histol Cytol. 1995;58:365–374. [PubMed: 8527243]
225. Barzilai A, Ryback BJ, Medina JA, et al. The morphological changes of the pancreas in hypovolemic shock and the effect of pretreatment with steroids. Int J Pancreatol. 1987;2:23–32. [PubMed: 3681033]
226. Broe PJ, Zuidema GD, Cameron JL. The role of ischemia in acute pancreatitis: studies with an isolated perfused canine pancreas. Surgery. 1982;91:377–382. [PubMed: 6175032]
227. Hoffmann TF, Leiderer R, Waldner H, et al. Ischemia reperfusion of the pancreas: a new in vivo model for acute pancreatitis in rats. Res Exp Med (Berl). 1995;195:125–144. [PubMed: 8570908]
228. Redha F, Uhlschmid G, Ammann RW, et al. Injection of microspheres into pancreatic arteries causes acute hemorrhagic pancreatitis in the rat: a new animal model. Pancreas. 1990;5:188–193. [PubMed: 2315295]
229. Sjovall S, Holmin T, Evander A, et al. Splenic and gastro-duodenal vein occlusion--influence on the pancreatic gland and on the outcome of experimental pancreatitis. Int J Pancreatol. 1988;3:143–149. [PubMed: 2452221]
230. Dembiński A, Warzecha Z, Ceranowicz P, et al. Stimulation of sensory nerves and CGRP attenuate pancreatic damage in ischemia/reperfusion induced pancreatitis. Med Sci Monit. 2003;9:BR418–BR425. [PubMed: 14646970]
231. He ZJ, Winston JH, Yusuf TE, et al. Intraductal administration of an NK1 receptor antagonist attenuates the inflammatory response to retrograde infusion of radiological contrast in rats: implications for the pathogenesis and prevention of ERCP-induced pancreatitis. Pancreas. 2003;27:e13–e17. [PubMed: 12826913]
232. Noble MD, Romac J, Vigna SR, et al. A pH-sensitive, neurogenic pathway mediates disease severity in a model of post-ERCP pancreatitis. Gut. 2008;57:1566–1571. [PubMed: 18625695]
233. Jin S, Orabi AI, Le T, et al. Exposure to Radiocontrast Agents Induces Pancreatic Inflammation by Activation of Nuclear Factor-kappaB, Calcium Signaling, and Calcineurin. Gastroenterology. 2015;149:753–764.e11. [PubMed: 25980752]
234. Wen L, Javed TA, Yimlamai D, et al. Transient High Pressure in Pancreatic Ducts Promotes Inflammation and Alters Tight Junctions via Calcineurin Signaling in Mice. Gastroenterology. 2018;155:1250–1263.e5. [PubMed: 29928898]

235. Thal A, Brackney E. Acute hemorrhagic pancreatic necrosis produced by local Shwartzman reaction: experimental study on pancreatitis. J Am Med Assoc. 1954;155:569–574. [PubMed: 13162758]
236. Vuorinen T, Kallajoki M, Hyypia T, et al. Coxsackievirus B3-induced acute pancreatitis: analysis of histopathological and viral parameters in a mouse model. Br J Exp Pathol. 1989;70:395–403. [PubMed: 2548562]
237. Yanagawa B, Spiller OB, Proctor DG, et al. Soluble recombinant coxsackievirus and adenovirus receptor abrogates coxsackievirus b3-mediated pancreatitis and myocarditis in mice. J Infect Dis. 2004;189:1431–1439. [PubMed: 15073680]
238. Janigan DT, Nevalainen TJ, MacAulay MA, et al. Foreign serum-induced pancreatitis in mice. I. A new model of acute pancreatitis. Lab Invest. 1975;33:591–607. [PubMed: 1202281]
239. Nevalainen TJ. Pancreatic injury caused by intraductal injection of foreign serum in rat. Virchows Arch B Cell Pathol. 1978;27:89–98. [PubMed: 417460]
240. Thal A Studies on pancreatitis. II. Acute pancreatic necrosis produced experimentally by the arthus sensitization reaction. Surgery. 1955;37:911–917. [PubMed: 14373312]
241. Davidson TS, Longnecker DS, Hickey WF. An experimental model of autoimmune pancreatitis in the rat. Am J Pathol. 2005;166:729–736. [PubMed: 15743785]
242. Pour P, Althoff J, Takahashi M. Early lesions of pancreatic ductal carcinoma in the hamster model. Ame J Pathol. 1977;88:291–308.
243. Takahashi M, Hori M, Mutoh M, et al. Experimental Animal Models of Pancreatic Carcinogenesis for Prevention Studies and Their Relevance to Human Disease. Cancers. 2011;3:582–602. [PubMed: 24212630]
244. Kamano T, Azuma N, Katami A, et al. Preliminary observation on pancreatic duct adenocarcinoma induced by intraductal administration of N-ethyl-N'-nitro-N-nitrosoguanidine in dogs. Jpn J Cancer Res. 1988;79:1–4. [PubMed: 3128497]
245. Kamano T, Tamura J, Uchida T, et al. Studies by pancreatography of ductal changes induced by administration of pancreatic carcinogen in two dogs. Jpn J Clin Oncol. 1991;21:282–286. [PubMed: 1942557]
246. Birt DF, Julius AD, White LT, et al. Enhancement of pancreatic carcinogenesis in hamsters fed a high-fat diet ad libitum and at a controlled calorie intake. Cancer Res. 1989;49:5848–5851. [PubMed: 2790796]
247. Birt DF, Salmasi S, Pour PM. Enhancement of experimental pancreatic cancer in Syrian golden hamsters by dietary fat. J Natl Cancer Inst. 1981;67:1327–1332. [PubMed: 6273636]
248. Osvaldt AB, Wendt LR, Bersch VP, et al. Pancreatic intraepithelial neoplasia and ductal adenocarcinoma induced by DMBA in mice. Surgery. 2006;140:803–809. [PubMed: 17084724]
249. Z'Graggen K, Warshaw AL, Werner J, et al. Promoting effect of a high-fat/high-protein diet in DMBA-induced ductal pancreatic cancer in rats. Ann Surg. 2001;233:688–695. [PubMed: 11323507]
250. Povoski SP, Zhou W, Longnecker DS, et al. Growth of Azaserine-Induced Putative Preneoplastic Nodules in the Rat Pancreas Is Mediated Specifically by Way of Cholecystokinin-A Receptors. Ann N Y Acad Sci. 1994;713:439–441. [PubMed: 8018216]
251. Bd Roebuck, Lilja HS Curphey TJ, et al. Pathologic and biochemical effects of azaserine in inbred Wistar/Lewis rats and noninbred CD-1 mice. J Natl Cancer Inst. 1980;65:383–389. [PubMed: 6931255]
252. Roebuck BD, Baumgartner KJ, Longnecker DS. Growth of pancreatic foci and development of pancreatic cancer with a single dose of azaserine in the rat. Carcinogenesis. 1987;8:1831–1835. [PubMed: 3499996]
253. Roebuck BD, Longnecker DS, Baumgartner KJ, et al. Carcinogen-induced Lesions in the Rat Pancreas: Effects of Varying Levels of Essential Fatty Acid. Cancer Res. 1985;45:5252–5256. [PubMed: 3876880]
254. Marrache F, Tu SP, Bhagat G, et al. Overexpression of interleukin-1beta in the murine pancreas results in chronic pancreatitis. Gastroenterology. 2008;135:1277–1287. [PubMed: 18789941]
255. Iida K, Li Y, McGrath BC, et al. PERK eIF2 alpha kinase is required to regulate the viability of the exocrine pancreas in mice. BMC Cell Biol. 2007;8:38. [PubMed: 17727724]

256. Seleznik GM, Reding T, Romrig F, et al. Lymphotoxin beta receptor signaling promotes development of autoimmune pancreatitis. Gastroenterology. 2012;143:1361–1374. [PubMed: 22863765]

257. Li N, Wu X, Holzer RG, et al. Loss of acinar cell IKKalpha triggers spontaneous pancreatitis in mice. J Clin Invest. 2013;123:2231–2243. [PubMed: 23563314]

258. Cano DA, Sekine S, Hebrok M. Primary cilia deletion in pancreatic epithelial cells results in cyst formation and pancreatitis. Gastroenterology. 2006;131:1856–1869. [PubMed: 17123526]

259. Miralles F, Hebrard S, Lamotte L, et al. Conditional inactivation of the murine serum response factor in the pancreas leads to severe pancreatitis. Lab Invest. 2006;86:1020–1036. [PubMed: 16894357]

260. Diakopoulos KN, Lesina M, Wormann S, et al. Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes. Gastroenterology. 2015;148:626–638 e617. [PubMed: 25497209]

261. Hess DA, Humphrey SE, Ishibashi J, et al. Extensive pancreas regeneration following acinar-specific disruption of Xbp1 in mice. Gastroenterology. 2011;141:1463–1472. [PubMed: 21704586]

262. Lee MS, Gu D, Feng L, et al. Accumulation of extracellular matrix and developmental dysregulation in the pancreas by transgenic production of transforming growth factor-beta 1. Am J Pathol. 1995;147:42–52. [PubMed: 7604884]

263. Colby JK, Klein RD, McArthur MJ, et al. Progressive metaplastic and dysplastic changes in mouse pancreas induced by cyclooxygenase-2 overexpression. Neoplasia. 2008;10:782–796. [PubMed: 18670639]

264. Casanova L, Bravo A, Were F, et al. Tissue-specific and efficient expression of the human simple epithelial keratin 8 gene in transgenic mice. J Cell Sci. 1995;108:811–820. [PubMed: 7539440]

265. Casanova ML, Bravo A, Ramirez A, et al. Exocrine pancreatic disorders in transsgenic mice expressing human keratin 8. J Clin Invest. 1999;103:1587–1595. [PubMed: 10359568]

266. Hegyi E, Sahin-Tóth M. Human *CPA1* mutation causes digestive enzyme misfolding and chronic pancreatitis in mice. Gut. 2019;68:301–312. [PubMed: 30045879]

267. Ohmuraya M, Hirota M, Araki K, et al. Enhanced trypsin activity in pancreatic acinar cells deficient for serine protease inhibitor kazal type 3. Pancreas. 2006;33:104–106. [PubMed: 16804421]

268. Kruger B, Lerch MM, Tessenow W. Direct detection of premature protease activation in living pancreatic acinar cells. Lab Invest. 1998;78:763–764. [PubMed: 9645767]

269. Ohmuraya M, Hirota M, Araki M, et al. Autophagic cell death of pancreatic acinar cells in serine protease inhibitor Kazal type 3-deficient mice. Gastroenterology. 2005;129:696–705. [PubMed: 16083722]

270. Gabbi C, Kim HJ, Hultenby K, et al. Pancreatic exocrine insufficiency in LXRbeta−/− mice is associated with a reduction in aquaporin-1 expression. Proc Natl Acad Sci U S A. 2008;105:15052–15057. [PubMed: 18806227]

271. Mareninova OA, Sendler M, Malla SR, et al. Lysosome associated membrane proteins maintain pancreatic acinar cell homeostasis: LAMP-2 deficient mice develop pancreatitis. Cell Mol Gastroenterol Hepatol. 2015;1:678–694. [PubMed: 26693174]

272. Vallance BA, Hewlett BR, Snider DP, et al. T cell-mediated exocrine pancreatic damage in major histocompatibility complex class II-deficient mice. Gastroenterology. 1998;115:978–987. [PubMed: 9753501]

273. Iglesias A, Murga M, Laresgoiti U, et al. Diabetes and exocrine pancreatic insufficiency in E2F1/E2F2 double-mutant mice. J Clin Invest. 2004;113:1398–1407. [PubMed: 15146237]

274. Huang H, Liu Y, Daniluk J, et al. Activation of nuclear factor-kappaB in acinar cells increases the severity of pancreatitis in mice. Gastroenterology. 2013;144:202–210. [PubMed: 23041324]

275. Kamata K, Watanabe T, Minaga K, et al. Autoimmune Pancreatitis Mouse Model. Curr Protoc Immunol. 2018;120:15.31.1–15.31.8. [PubMed: 29512140]

276. Kanno H, Nose M, Itoh J, et al. Spontaneous development of pancreatitis in the MRL/Mp strain of mice in autoimmune mechanism. Clin Exp Immunol. 1992;89:68–73. [PubMed: 1352748]

277. Qu WM, Miyazaki T, Terada M, et al. A novel autoimmune pancreatitis model in MRL mice treated with polyinosinic:polycytidylic acid. Clin Exp Immunol. 2002;129:27–34. [PubMed: 12100019]

278. Wagner M, Greten FR, Weber CK, et al. A murine tumor progression model for pancreatic cancer recapitulating the genetic alterations of the human disease. Genes Dev. 2001;15:286–293. [PubMed: 11159909]

279. Grippo PJ, Nowlin PS, Demeure MJ, et al. Preinvasive pancreatic neoplasia of ductal phenotype induced by acinar cell targeting of mutant Kras in transgenic mice. Cancer Res. 2003;63:2016–2019. [PubMed: 12727811]

280. Carrière C, Young AL, Gunn JR, et al. Acute pancreatitis markedly accelerates pancreatic cancer progression in mice expressing oncogenic Kras. Biochem Biophys Res Commun. 2009;382:561–565. [PubMed: 19292977]

281. Carriere C, Seeley ES, Goetze T, et al. The Nestin progenitor lineage is the compartment of origin for pancreatic intraepithelial neoplasia. Proc Natl Acad Sci U S A. 2007;104:4437–4442. [PubMed: 17360542]

282. Carrière C, Young AL, Gunn JR, et al. Acute pancreatitis accelerates initiation and progression to pancreatic cancer in mice expressing oncogenic Kras in the nestin cell lineage. Plos One. 2011;6:e27725. [PubMed: 22140463]

283. De La OJ, Emerson LL, Goodman JL, et al. Notch and Kras reprogram pancreatic acinar cells to ductal intraepithelial neoplasia. Proc Natl Acad Sci U S A. 2008;105:18907–18912. [PubMed: 19028876]

284. Habbe N, Shi G, Meguid RA, et al. Spontaneous induction of murine pancreatic intraepithelial neoplasia (mPanIN) by acinar cell targeting of oncogenic Kras in adult mice. Proc Natl Acad Sci U S A. 2008;105:18913–18918. [PubMed: 19028870]

285. Gidekel Friedlander SY, Chu GC, Snyder EL, et al. Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras. Cancer Cell. 2009;16:379–389. [PubMed: 19878870]

286. Aguirre AJ, Bardeesy N, Sinha M, et al. Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. Genes Dev. 2003;17:3112–3126. [PubMed: 14681207]

287. Bardeesy N, Cheng KH, Berger JH, et al. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. Genes Dev. 2006;20:3130–3146. [PubMed: 17114584]

288. Skoulidis F, Cassidy LD, Pisupati V, et al. Germline Brca2 heterozygosity promotes Kras(G12D) -driven carcinogenesis in a murine model of familial pancreatic cancer. Cancer Cell. 2010;18:499–509. [PubMed: 21056012]

289. Morton JP, Jamieson NB, Karim SA, et al. LKB1 haploinsufficiency cooperates with Kras to promote pancreatic cancer through suppression of p21-dependent growth arrest. Gastroenterology. 2010;139:586–597, 597 e581–586. [PubMed: 20452353]

290. Hanlon L, Avila JL, Demarest RM, et al. Notch1 functions as a tumor suppressor in a model of K-ras-induced pancreatic ductal adenocarcinoma. Cancer Res. 2010;70:4280–4286. [PubMed: 20484026]

291. Perez-Mancera PA, Guerra C, Barbacid M, et al. What we have learned about pancreatic cancer from mouse models. Gastroenterology. 2012;142:1079–1092. [PubMed: 22406637]

292. Ijichi H, Chytil A, Gorska AE, et al. Inhibiting Cxcr2 disrupts tumor-stromal interactions and improves survival in a mouse model of pancreatic ductal adenocarcinoma. J Clin Invest. 2011;121:4106–4117. [PubMed: 21926469]

293. Siveke JT, Einwachter H, Sipos B, et al. Concomitant pancreatic activation of Kras(G12D) and Tgfa results in cystic papillary neoplasms reminiscent of human IPMN. Cancer Cell. 2007;12:266–279. [PubMed: 17785207]

294. Izeradjene K, Combs C, Best M, et al. Kras(G12D) and Smad4/Dpc4 haploinsufficiency cooperate to induce mucinous cystic neoplasms and invasive adenocarcinoma of the pancreas. Cancer Cell. 2007;11:229–243. [PubMed: 17349581]

295. Mazur PK, Einwachter H, Lee M, et al. Notch2 is required for progression of pancreatic intraepithelial neoplasia and development of pancreatic ductal adenocarcinoma. Proc Natl Acad Sci U S A. 2010;107:13438–13443. [PubMed: 20624967]

296. Guerra C, Collado M, Navas C, et al. Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence. Cancer Cell. 2011;19:728–739. [PubMed: 21665147]

297. Ceppa EP, Lyo V, Grady EF, et al. Serine proteases mediate inflammatory pain in acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2011;300:G1033–G1042. [PubMed: 21436316]

298. Kawabata A, Matsunami M, Tsutsumi M, et al. Suppression of pancreatitis-related allodynia/hyperalgesia by proteinase-activated receptor-2 in mice. Br J Pharmacol. 2006;148:54–60. [PubMed: 16520745]

299. Winston JH, Toma H, Shenoy M, et al. Acute pancreatitis results in referred mechanical hypersensitivity and neuropeptide up-regulation that can be suppressed by the protein kinase inhibitor k252a. J Pain. 2003;4:329–337. [PubMed: 14622690]

300. Vera-Portocarrero LP, Xie JY, Kowal J, et al. Descending facilitation from the rostral ventromedial medulla maintains visceral pain in rats with experimental pancreatitis. Gastroenterology. 2006;130:2155–2164. [PubMed: 16762636]

301. Vera-Portocarrero LP, Lu Y, Westlund KN. Nociception in persistent pancreatitis in rats: effects of morphine and neuropeptide alterations. Anesthesiology. 2003;98:474–484. [PubMed: 12552208]

302. Chen Q, Vera-Portocarrero LP, Ossipov MH, et al. Attenuation of persistent experimental pancreatitis pain by a bradykinin b2 receptor antagonist. Pancreas. 2010;39:1220–1225. [PubMed: 20531238]

303. Vardanyan M, Melemedjian OK, Price TJ, et al. Reversal of pancreatitis-induced pain by an orally available, small molecule interleukin-6 receptor antagonist. Pain. 2010;151:257–265. [PubMed: 20599324]

304. Liu L, Shenoy M, Pasricha PJ. Substance P and calcitonin gene related peptide mediate pain in chronic pancreatitis and their expression is driven by nerve growth factor. JOP. 2011;12:389–394. [PubMed: 21737902]

305. Takamido S, Kataoka Y, Tanano A, et al. Intrapancreatic axonal hyperbranching of dorsal root ganglia neurons in chronic pancreatitis model rats and its relation to pancreatic pain. Pancreas. 2006;33:268–279. [PubMed: 17003649]

306. Wang L, Xu H, Ge Y, et al. Establishment of a murine pancreatic cancer pain model and microarray analysis of painassociated genes in the spinal cord dorsal horn. Mol Med Rep. 2017;16:4429–4436. [PubMed: 28791352]

307. Liao YH, Wang J, Wei YY, et al. Histone deacetylase 2 is involved in microopioid receptor suppression in the spinal dorsal horn in a rat model of chronic pancreatitis pain. Mol Med Rep. 2018;17:2803–2810. [PubMed: 29257262]

308. Miura T, Mitsunaga S, Ikeda M, et al. Neural Invasion Spreads Macrophage-Related Allodynia via Neural Root in Pancreatic Cancer. Anesth Analg. 2018;126:1729–1738. [PubMed: 29570153]

309. Selvaraj D, Hirth M, Gandla J, et al. A mouse model for pain and neuroplastic changes associated with pancreatic ductal adenocarcinoma. Pain. 2017;158:1609–1621. [PubMed: 28715356]

310. Lindsay TH, Jonas BM, Sevcik MA, et al. Pancreatic cancer pain and its correlation with changes in tumor vasculature, macrophage infiltration, neuronal innervation, body weight and disease progression. Pain. 2005;119:233–246. [PubMed: 16298491]

311. Sevcik MA, Jonas BM, Lindsay TH, et al. Endogenous opioids inhibit early-stage pancreatic pain in a mouse model of pancreatic cancer. Gastroenterology. 2006;131:900–910. [PubMed: 16952558]

312. Demir IE, Tieftrunk E, Schorn S, et al. Activated Schwann cells in pancreatic cancer are linked to analgesia via suppression of spinal astroglia and microglia. Gut. 2016.

313. Demir IE, Kujundzic K, Pfitzinger PL, et al. Early pancreatic cancer lesions suppress pain through CXCL12-mediated chemoattraction of Schwann cells. Proc Natl Acad Sci U S A. 2017;114:E85–E94. [PubMed: 27986950]

1. What is your hypothesis? Specific Aims?
2. Within that scope, what questions are you asking?
3. Is there a particular gene or protein of interest?
4. Which cell compartment are you interested in?
5. Does this entail cell-cell or protein-protein interactions?
6. Do you have in vivo/in vitro preliminary data as a guide?
7. Are you focused on signal transductions, pathology, therapy, or combo?
8. What is your time frame? Budget?

FIGURE 1.
Questions that should be considered during study design when choosing an animal model.

TABLE 1.

Nongenic Models of Pancreatitis

Model	Examples	Type	Species	Features	References
Secretagogue	cerulein	AP RAP/CP	rat mouse hamster dog	Acute: • 5–12 hrly injections • Atrophy, fibrosis, hyperamylasemia, edema, acinar vacuolization, leukocyte infiltrate, duct distortion, pain • Simulates AP in humans that is induced by Trinidadian scorpion toxin and anti-cholinesterase insecticides RAP/Chronic: • 5–8 hrly injections, 1–3 times/wk, 3–10 wks. • fibrosis, atrophy, decreased lipase, adipose replacement, necrosis, elevated glucose, leukocyte infiltrate Routes of administration: i.v., s.c., i.p.	AP[1–4,8–11,13,14,150,176–178] RAP/CP[5–7,12,179–181]
Amino Acid	L-arginine L-lysine L-ornithine	AP CP	rat mouse hamster	Acute: • dose-dependent acinar necrosis • edema, hyperamylasemia, leukocyte infiltrate, high morbidity/mortality, including organ failure. Chronic: • long-term administration • pancreatic atrophy, fibrosis Routes or administration: i.p.	L-arginine[8,14,153,182–186] L-lysine[187] L-ornithine[188]
Cytokine	Interleukin-12 + Interleukin-18	AP	mouse	Acute: • 2 injections, 24 hr apart of interleukin-12 (150 ng) and interleukin-18 (750 ng) • 100% lethal in ob/ob (B6.V-*Lep*^{ob}/J) mice within 48 hrs after 2nd injection • Lean mice develop edematous AP whereas ob/ob mice or diet-induced obese mice develop necrotizing AP. • Obese mice show greater increase in serum amylase, lipase, and calcium, heightened acute-phase responses, and do not engage repair pathways (e.g. Reg1 and PAP). Routes or administration: i.p.	[173,174]
Diet	Lieber-DeCarli High Fat CDE	AP CP	rat mouse hamster	Lieber-DeCarli: • EtOH containing liquid diet	Lieber-DeCarli[14,35,189,190] CDE[4,171,191,192] Hih High Fat[36,177,193]

Model	Examples	Type	Species	Features	References
				• EtOH must be paired with an additional stimulus High Fat: • high fat diet combined with other stimuli (e.g. EtOH) • high fat alone induces slight increases in acinar hypertrophy, autophagy, apoptosis, necrosis, edema/inflammation, vascular injury, and duct changes CDE: • can be adjusted to achieved desired mortality rate • Constant CDE results in AP featuring severe hemorrhagic necrosis, local acinar/fat necrosis, transient atrophy, mild fibrosis; female-specific • Intermittent CDE results in CP phenotype. • Requires young female mice Routes of administration: oral	
Chemical (bile)	TNBS DBTC LPS NaTC Oleic Acids	AP CP	rat mouse hamster rabbit dog cat pig	rapid onset edematous, hemorrhagic fat/acinar necrosis, organ failure, leukocyte infiltrate, elevated lipase/amylase Routes of administration: i.v., intraductal	TNBS[161,194,195] DBTC[196–198] LPS[199,200] NaTC[14,168,201–204] Oleic acids[205–211]
Mechanical	Ligation/Obstruction Vascular/Ischemia	AP RAP/CP	rat mouse hamster rabbit dog opossum pig cat	Early phase: leukocyte infiltrate, edema, hyperamylasemia, apoptosis Late phase: atrophy, fibrosis, necrosis Invasive procedure	ligation/obstruction[4,8,212–224] vascular/ischemia[225–230]
Post-ERCP	radiocontrast hydrostatic pressure acidic saline	Post-ERCP	rat mouse	edema, increased serum amylase and markers of inflammation, neutrophil infiltration Routes of administration: intraductal infusion of radiocontrast or acidic saline; 100 mm Hg for 10 min	[128,231–234]
Infectious	E. coli Meningococci Coxsackie B	AIP	mouse rabbit goat	fatty tissue replaces acini; leukocyte infiltrate Routes of administration: i.p. or intraductal	[190,235–237]
Immune	Adoptive transfer Foreign serum	AIP	rabbit rat	necrosis, inflammation, hyperamylasemia Routes of administration: i.p. or intraductal	[238–241]

AP indicates acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; i.v., intravenous; s.c., subcutaneous; i.p., intraperitoneal; ob/ob, leptin-deficient obese mouse; CDE, choline-deficine ethionine-supplemented; TNBS, 2,4,6-trinitrobenzenesulfonic acid; DBTC, dibutyltin dichloride; LPS, lipolysaccharide; NaTC, sodium taurochlorate; mm HG, millimeters mercury; Post-ERCP, post endoscopic retrograde cholangio-pancreatography; AIP autoimmune pancreatitis

TABLE 2.

Chemical Models of Pancreatic Cancer

Chemical	Key Features	References
Nitrosamines	• N-Nitrosobis(2-oxopropyl)amine (BOP)/N-nitroso(2-hydroxypropyl)(2-oxypropyl)amine (HPOP) – Neoplasms around 14–17 wks. – lesions develop in ducts – 50% acquire genetic mutations associated with PDAC – dietary fat enhances carcinogenesis • methyl-2-oxopropylnitrosamine (MOP) – more potent, shorter latency than BOP – 80% penetrance • N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) – Administered to canines – Results in duct dilation, hyperplasia, ductal adenocarcinoma • Species Differences – Most effective in Syrian golden hamsters – Sprague-Dawley rats more sensitive in respiratory/upper digestive tract – Wistar-MRC rats commonly develop thyroid tumors – Mice commonly have liver and lung involvement – i.p. BOP does not cause pancreatic tumors in dogs	21–23,47,242–247
DMBA	• 7,12-Dimethylbenzanthracene (DMBA) – Found in cigarette smoke, charbroiled foods, exhaust • Phenotypic PDAC – Local administration leads to PanINs and PDAC at 30–60 days • Alcohol enhances adenocarcinoma development • Nicotine promotes DMBA carcinogenesis • High fat/high protein diet promotes DMBA carcinogenesis	46,50,248,249
Azaserine	• Wistar/Lewis Rats – Atypical acini/nodules form at 4mo – Acinar cell carcinomas and adenomas at 12–18 mo.	47,250–253

Chemical	Key Features	References
	– Dietary fat enhances carcinogenesis • Outbred CD-1 mouse strain does not develop advanced lesions • Routes of administration: i.p.; s.c.	

TABLE 3.

Common Genes Used to Drive Expression in Genetic Models of Pancreatic Disease

Gene	Conditional/Inducible Expression Systems Available	Target Cell Population
PDX1	Cre CreER	Acinar Ductal Endocrine Centroacinar
Pft1a/p48	Cre CreERT	Acinar Ductal Endocrine Centroacinar
Nestin	Cre	Acinar Acinar progenitor
Elastase-1 (Ela)	$Kras^{G12D}$ Cre CreERT2 tTA	Acinar
proCPA1	CreERT2	Acinar
Mist1	Cre CreERT2	Acinar
Rip	CreERT	Insulin-expressing cells
Insulin		Islet
Neuregulin 3 (Ngn3)	Cre	Islet

Pancreas. Author manuscript; available in PMC 2020 July 01.

TABLE 4.

GEMMs With a Spontaneous Pancreatitis Phenotype

GEMM	Phenotype	References
rEla1;sshIL-1β	• Pancreatic atrophy, dilation of ducts occurred secondary to proximal fibrotic stenosis, increase acinar proliferation and apoptosis, increased expression of chemokines and cytokines • Crossing in a p53 mutation to obtain Elastase sshIL-1β*p53$^{R172H/+}$ results in the development of PanINs and lesions indicative of acinar to ductal metaplasia • Exposure to aqueous extract of cigarette smoke or Snus containing diet results in ductal epithelia flattening and proliferation, and glandular atrophy • High penetrance	76,254
rEla1;mPRSS1^{R122H} (hereditary pancreatitis)	• 7 wks-acinar damage • 12 wks-inflammatory infiltrate • 24 wks fibrosis • 40% penetrance by 1yr	63
rEla1;hPRSS1$^{R122H/N29I}$ (hereditary pancreatitis)	• Fibrosis • Pathology consistent with chronic pancreatitis (>9month) • 10% penetrance	64
PACE-try(on) Ela-creERT;ratPRSSII (hereditary pancreatitis)	• AP only, rapid caspase-3 activation, apoptosis with delayed necrosis, loss of acinar cells leads to replacement with fatty tissue. • Chronic inflammation or fibrosis does not develop.	65
Ela1-cre;PERK$^{-/-}$	• Hyperglycemic by 4 wks • Induction of ER stress response, nonapoptotic acinar cells death pronounced inflammation • Exocrine and endocrine insufficiency	255
Ela1-LTab (Ela1-LTβ)	• Model of AIP, overexpression of lymphotoxin beta • Formation of B and T cell zones (tertiary lymphoid tissues) • Systemic autoimmune response • Chronic inflammation (in pancreas)	256
PDX1-cre;IKKα−/−	• Elevated serum amylase and lipase • progressive acinar cell vacuolization and death, interstitial fibrosis, inflammation, and compensatory proliferation	257

GEMM	Phenotype	References
PDX1-cre;Kif3a$^{-/-}$	• By 2 wks. acinar to ductal metaplasia and periductal fibrosis is evident • By 12wks, acinar cells are replaced by adipose • By 6mo, pancreata composed of enlarging cysts	258
PDX1-cre;SRF−/−	• After weaning, mice develop profound morphological alterations of the exocrine pancreas, which were reminiscent of severe pancreatitis. • massive acinar injury, Nuclear Factor Kappa B activation and proinflammatory cytokine release leads to complete destruction of the exocrine pancreas and its replacement by adipose tissue	259
Pft1a-cre^{ex1}; Atg5$^{-/-}$	• Greater penetrance in male • Inflammation, necrosis, acinar-to-ductal metaplasia, acinar hypertrophy and degeneration, increased ROS, decreased glutamate metabolism, reduced autophagy, increased p62, ER and mitochondrial stress	260
Mist1-creERT2;XBP1+/−	• Activation of the unfolded protein response • Extensive apoptosis followed by recovery and regeneration of acini	114,261
hInsulin;TGFβ	• Fibrosis and inflammation	262
bK5; COX-2	• Overexpression of COX2 under the bovine K5 promotor induces CP (fibrosis and chronic inflammation) by 3 mo. • At 5–6 mo pancreatic hypertrophy • At 6–8 mo, dysplasia	263
hK8	• Overexpression of human keratin 8 • Exocrine pancreas alterations, includes dysplasia, loss of acinar architecture, redifferentiation of acinar to ductal cells, inflammation, fibrosis, and substitution of exocrine by adipose tissue, as well as increased cell proliferation and apoptosis. • Extra pancreatic epithelial changes also observed	264,265
CPA1^{N356K}	• C57Bl/6 mice harbor human p.N256K mutation in exon 7 of mouse *Cpa1* locus • At 3 mo., pancreata begin to atrophy (decrease weight) with 35–40% decrease @ 6 mo • Loss of acini (30% by 12 mo), inflammatory infiltrate, presence of pseudotubular complexes (acinar-to ductal metaplasia), widespread fibrotic changes • At 1 mo., elevated circulating amylase that is lost by 3 mo • Elevated intrapancreatic trypsin and markers of endoplasmic reticulum stress	266
SPINK3−/− (hereditary pancreatitis)	• Pancreata initially develop normally • acinar degeneration starts around E16.5	267–269

GEMM	Phenotype	References
	• Rapid onset cell death begins within days of birth • Mice die by P14.5	
D23A (hereditary pancreatitis)	• T7D23A knock-in mouse carries a heterozygous p.D23A mutation in mouse cationic trypsinogen (isoform T7) on a C57BL/6N background • Pancreata are normal for first 2–3 weeks of life, with diminution in size visible by 2 months • 4–5 weeks of age – 40% exhibit typical AP at 4–5 weeks, characterized by edema, inflammatory infiltrate (dominated by neutrophils and macrophages), and localized necrosis – >50% exhibit minimal parenchyma and widespread regeneration including fibrosis and stellate cell activation – Elevated amylase in 40% of mice • 2–12 months of age – Elevated intrapancreatic trypsin activity – Adipose replacement dominated, while inflammatory infiltrate decreased – Distorted ducts surrounded by prominent fibrosis – No calcifications and no loss of islets observed	66
LXRβ−/−	• Liver X receptor β was removed using cre-transgenic *deleter* mouse strain • Inflammation, duct dilation, fibrosis • Pancreatic exocrine insufficiency	270
LAMP2$^{-/-}$	• Begins with acinar cell vacuolization and progresses to severe damage, macrophage infiltration, and acinar cell death • Decreased amylase, increased MPO, Caspase-3	271
MHCII−/− (aged)	• At 6 mo, periductal lymphocytic infiltrate observed that progresses to selective acinar cell destruction • Significant decrease in amylase and lipase • Adoptive transfer of splenic mononuclear cells confers disease upon recipient	272
E2F1$^{-/-}$/E2F2 $^{-/-}$	• endocrine and exocrine cell dysplasia • a reduction in the number and size of acini and islets, and their replacement by ductal structures and adipose tissue. • Mutant pancreatic cells exhibit increased rates of DNA replication but also of apoptosis, resulting in severe pancreatic atrophy	273
IKK2 ^{CA} constitutively active, inducible	• CMVrtTA X tetO-IKK2-EE(IKK2) ^{CA} – Doxycycline induces constitutive IKK2 activity via S177E and S181E mutations – only minor damage, leukocyte infiltration, elevated RANTES and TNFα	126,127,274

GEMM	Phenotype	References
	• Ela1-rtTA X luciferase-$(tetO)_7$-IKK2^{CA}, Ela-creERT X LSL-IKK2 – Tamoxifen induces constitutive IKK2 activity in acinar cells – Results in edema, immune infiltration, necrosis, elevated lipase, and fibrosis – Severity increased by co-expressing p65	
MRL-Mp$^{lpr/lpr}$ (autoimmune pancreatitis, AIP)	• Express lymphoproliferative gene (lpr) • Incidence of pancreatitis is significantly greater in females, with the highest incidence (74%) in mice 34–38 weeks • spontaneous inflammatory lesions characterized by mononuclear cell infiltration, acini destruction, and replacement of parenchyma by adipose • Treating MRL-Mp mice with repeated injections of polyinosinic-polycytidylic acid drives a Type I AIP, characterized by enhanced levels of IgG4 antibodies which is associated with systemic IgG4-related disease.	275–277

TABLE 5.

Basic Kras-based GEMMs

GEMM	Lesions (Incidence %)			Observations	References
	PanIN	PDAC	MET		
Elastase-TGF-α	100	10	No	KrasG12D accelerates progression of PanIN	278
Elastase-*KRAS*^{G12D}	100 (CPN)	No	No	Acinar expression of human KRASG12D drives CPN with ductal histotype	279
Pdx1-Cre; K-Ras$^{+/LSLG12D}$ (KC model)	100	<20	Yes	Impossibility to assess cell of origin Inflammation accelerates EMT and PanIN	102,104,280
Ptf1a-Cre; K-Ras$^{+/LSLG12D}$	100	<20	Yes	Impossibility to assess cell of origin	102
Elastase-tTA; Tet-O-Cre; K-Ras$^{+/LSLG12Vgeo}$	90	10	No	Pancreatitis accelerates PanIN development	125
Nestin-Cre; K-Ras$^{+/LSLG12D}$	100	No	No	Short survival due to CNS complications. PDAC initiation & progression accelerated by AP	281,282
Elastase-tTA; Tet-O-Cre; K-Ras$^{+/LSLG12Vgeo}$ plus cerulein	100	20	No	PanIN development requires pancreatitis	125
Elastase-CreER; K-Ras$^{+/LSLG12D}$	36	NA	No	Leaky sperm. Short-term study.	283
Elastase-CreERT2; K-Ras$^{+/LSLG12D}$	63	No	No	PanIN development does not require pancreatitis	284
Mist1-CreERT2; K-Ras$^{+/LSLG12D}$	30	No	No	PanIN development does not require pancreatitis	284
Pdx1-CreER; K-Ras$^{+/LSLG12D}$	55	Rare	No	The system may target acinar and precursor cells	285
proCPA1CreERT2; K-Ras^{LSLG12D}	10	No	No	PanIN development requires pancreatitis in older mice (5–8 weeks; PanIN in 33% mice)	285
RipCreER; K-Ras$^{+/LSLG12D}$	0	No	No	Cooperation with pancreatitis	285

NA indicates not analyzed; CPN, cystic papillary neoplasms.

TABLE 6.

Complex Kras-based GEMMs

GEMM	Lesions	Metastasis	Survival, mo	References
Pdx1-Cre; K-Ras+/LSLG12D; Ink4a/Arflox/lox	PanIN and PDAC	Yes	2	286
Pdx1-Cre; K-Ras +/LSLG12D; p53R172H/+ (KPC model)	PanIN and PDAC	Yes	5	102
Pdx1-Cre; K-Ras +/LSLG12D; Ink4a/Arf−/−	PanIN and PDAC	Yes	5	287
Pdx1-Cre; K-Ras +/LSLG12D; p53lox/lox	PanIN and PDAC	No	3	287
Pdx1-Cre; K-Ras +/LSLG12D; p53lox/+; YFP	PanIN and PDAC	Yes	5	104
Pdx1-Cre; K-Ras +/LSLG12D; p53lox/lox; Ink4a/Arf−/−	PanIN and PDAC	Yes	2	287
Pdx1-Cre; K-Ras +/LSLG12D; Smad4lox/lox	IPMN and PDAC	Yes	9	287
Pdx1-Cre; K-Ras +/LSLG12D; Brca2Tr/Δ11	PanIN and PDAC	NA	NA	288
Pdx1-Cre; K-Ras +/LSLG12D; p53R270H/+; Brca2Tr/+	PanIN and PDAC	NA	<5	288
Pdx1-Cre; K-Ras +/LSLG12D; p53R270H/+; Brca2Tr/Δ11	PanIN and PDAC	Yes	2.5	288
Pdx1-Cre; K-Ras +/LSLG12D; Lkb1lox/lox	PanIN and PDAC	NA	4.5	289
Pdx1-Cre; K-Ras +/LSLG12D; Notch1lox/lox	PanIN (high grade)	No	3	290
Pdx1-Cre; K-Ras +/LSLG12D; Usp9x+/lox	PanIN and PDAC	NA	NA	291
Ptf1a(p48)-Cre; K-Ras+/LSLG12D; p53lox/+	PanIN and PDAC	Yes	5	107
Ptf1a(p48)-Cre; K-Ras+/LSLG12D; p53lox/+; tdTomato	PanIN and PDAC	Yes	5	53
Ptf1a-Cre; K-Ras+/LSLG12D; TGFβIIRlox/lox	PanIN and PDAC	Yes	2	292
Ptf1a-Cre; K-Ras+/LSLG12D; Elastase-TGF-α	PanIN, IPMN, PDAC	Yes	7	293
Ptf1a-Cre; K-Ras+/LSLG12D; Smad4lox/lox	MCN and PDAC	Yes	8	294
Ptf1a-Cre; K-Ras+/LSLG12D; Notch2lox/lox	MCN, anaplastic, PDAC	No	>12	295
Elastase-tTA; Tet-O-Cre; K-Ras+/LSLG12Vgeo; p53−/−	PanIN and PDAC	Yes	3–4	125
Elastase-tTA; Tet-O-Cre; K-Ras+/LSLG12Vgeo; p53lox/lox	PanIN and PDAC	Yes	3–4	296
Elastase-tTA; Tet-O-Cre; K-Ras+/LSLG12Vgeo; Ink4a/Arflox/lox	PanIN and PDAC	Yes	3–4	296

NA indicates not analyzed; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm

TABLE 7.

Pain Associated Behavior Analysis in Animal Models of Pancreatic Disease

Model	Species	Measure	References
Pancreatitis			
Cerulein: mild acute (6–8 injections)	Mouse Rat	Abdominal Von Frey Open Field Activity	150,151,297,298
Cerulein: severe acute (12 injections)	Mouse	Abdominal Von Frey	148
Cerulein: chronic (6 inj./2days/6wks)	Mouse	Abdominal Von Frey Open field activity	156,179
L-arginine	Rat	Abdominal Von Frey	299
DBTC (i.v.)	Rat	Abdominal Von Frey Abdominal Hargreaves Hot plate	300–303
TNBS (intraductal)	Mouse Rat	Abdominal and hind paw Von Frey Electrically-evoked visceromotor reflex Open field activity Voluntary wheel running Vocalizations Catalepsy Elevated plus maze	147,149,152,156,158,159,195,304
EtOH + HFD chronic (10 wks.) [Lieber DeCarli + high fat diet]	Rat	Abdominal Von Frey Hot plate	36
Wistar/Bonn Kobori (WBN/Kob)	Rat	Home cage activity	305
Pancreatic cancer			
Orthotopic xenograft	Mouse	Hunching Abdominal Von Frey Electrically-evoked visceromotor reflex	155,306
Subcutaneous or intraneural xenograft	Mouse Rat	Hind paw Von Frey	307,308
Orthotopic allograft	Mouse	Abdominal Von Frey Open field activity Home cage activity Voluntary wheel running	309
rEla1;SV40	Mouse	Hunching Vocalization	310,311
KC mice (p48/pft1a-cre)	Mouse	Abdominal Von Frey	312,313
KPC mice (p48/pft1a-cre)	Mouse	Hunching Open field activity	53