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Going MAD: Development of a “Matrix Academic Division” to Facilitate Translating Research to Personalized Medicine

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Abstract

Personalized medicine integrates an individual’s genetic and other information for the prevention or treatment of complex disorders, and translational research seeks to identify those data most important to disease processes based on observations at the bench and the bedside. To understand complex disorders such as chronic pancreatitis, inflammatory bowel disease, liver cirrhosis and other idiopathic chronic inflammatory diseases, physician-scientists must systematically collect data on relevant risks, clinical status, biomarkers, and outcomes. The author describes a “matrix academic division” (MAD), a highly effective academic program created at the University of Pittsburgh School of Medicine and the University of Pittsburgh Medical Center using translational research to rapidly develop personalized medicine for digestive diseases. MAD is designed to capture patient-specific data and biologic samples for analysis of steps in a complex process (reverse engineering), reconstructing the system conceptually and mathematically (disease modeling), and deciphering disease mechanism in individual patients to predict the effects of interventions (personalized medicine). MAD draws on the expertise of the medical school’s and medical center’s physician-scientists to translate essential disease information between the bed and the bench and to communicate with researchers from multiple domains, including epidemiology, genetics, cell biology, immunology, regenerative medicine, neuroscience, and oncology. The author illustrates this approach by describing its successful application to the reverse engineering of chronic pancreatitis.

Personalized medicine—deciphering disease mechanisms in individual patients to predict the effect of interventions—is an exciting futuristic concept for which few successful examples of systematic approaches and implementation exist. In this article, I describe a unique and highly effective academic program created at the University of Pittsburgh School of Medicine and the University of Pittsburgh Medical Center (UPMC) in the Division of Gastroenterology, Hepatology, and Nutrition to rapidly develop personalized medicine for digestive diseases. The program has required a paradigm shift away from traditional biomedical approaches that are based on the germ theory of communicable infectious diseases and scientific approaches designed to identifying a single factor responsible for a complex disease, as articulated in Koch’s postulates (stated in List 1). The need for this shift

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is predicated on the view that the current bed-to-bench-to bed process for developing effective treatments for patients with complex inflammatory diseases is comparatively inefficient, ineffective, time consuming and expensive ^{1,2}.

As an alternative to traditional statistical approaches to understand complex diseases, we have taken a reverse engineering approach to subdivide complex chronic inflammatory syndromes into scientific disciplines (where statistics are applied to test mechanistic models) and then integrate the findings into predictive disease models. Similar chronic inflammatory diseases in different organs (i.e., pancreas, intestine, liver) require similar scientific approaches, and for these types of diseases, detailed patient disease information and outcomes are organized in parallel. We approached this conceptually by aligning the names of the organ systems into rows and the names of the scientific disciplines into columns, which produces a grid. We reasoned that when phenotypic and biomarker information corresponding to each cell of a grid is collected on a patient, and the information from many patients are combined, it becomes a matrix. The advantage of the matrix is that it allows for highly organized patient information to be evaluated from multiple perspectives. This is invaluable for higher-level analysis of the interactions between genes, genes and environment, and disease modifiers linked to systemic processes instead of only the specialized cells of an organ. This level of information and organization is required for the development and implementation of personalized medicine for complex disorders.

I developed this matrix strategy in 1999 while negotiating to become division chief based on a long-term vision of personalized medicine for complex inflammatory disease, a recognition that academic physicians and scientists need specific niches for recognition and promotion, and a conviction that an academic medical center had a responsibility to solve complex medical problems. Based on the scientific strengths of the University of Pittsburgh and the patient populations served by UPMC we proposed the recruitment of a series of faculty members who had specific disease interests and scientific expertise to fill in the cells of a grid defined by seven complex digestive disorders (rows) and seven scientific disciplines (columns). Each faculty member was to serve as a “translator” for specific types of medical problems within a complex disease and recommend data elements to be collected on patients within his or her domain. Working together, groups of faculty could provide all relevant medical and scientific perspectives on complex problems, and provide more comprehensive phenotyping of each patient. Phenotypes, genotypes and biomarkers could then be integrated into personalized predictive models designed to improve outcomes at much lower cost for each individual patient.

In the rest of this article, I first review modern Western medicine, using examples to illustrate why applying methods designed to identify single factors responsible for a syndrome, as in an infection, is comparatively ineffective in resolving complex disorders, where the etiology and character of the disorder require the interaction of multiple factors. I then describe a new vision of addressing complex digestive disorders, using a matrix academic division (MAD), and conclude with an example of how our institution’s MAD approach to chronic pancreatitis is leading to the successful implementation of personalized medicine.

Modern Western Medicine

The germ theory of disease

Modern Western medicine owes much of its success to adoption of the germ theory of communicable infectious diseases, first proposed in the early 1800s, and the scientific methods needed to diagnose and prove effective treatment. The underlying hypothesis is that an infectious disease is caused by single pathologic entity, such as microbes. The method to

prove that a single agent (e.g., *Bacillus anthracis*) causes a disorder (e.g., anthrax) was developed by Koch and articulated by Loeffler in the 1890s³ (see List 1). Since then, many striking advances in medicine, both in terms of diagnosis and treatment, have been seen in infectious diseases, while slow progress is also being made in diabetes, heart disease, cancer and other more complex disorders.

However, the effectiveness of Koch's method breaks down when the disease is a syndrome with multiple etiologies producing identical phenotypes, when multiple factors are required to initiate a disease (e.g., a two-hit model), and genetic and environmental factors strongly affect disease features and response to therapy. This problem distinguishes inflammation caused by germs from idiopathic inflammatory diseases; the latter results from different combinations of factors in different people that contribute to etiology, susceptibility, severity, and progression and require a new diagnostic and treatment approach. The new approach, which is the topic of this article, relies on the development and testing of disease models integrating detailed phenotypes, genetics and biomarkers to predict disease pathways and effective treatment, which is the heart of *personalized medicine*.

Translational Research in Complex Disorders

Complex inflammatory disorders appear to occur through the interaction of genetic, metabolic, and environmental factors that may not be independently pathologic but can combine and interact to initiate disease and alter disease severity, progression and complications. Furthermore, complex inflammatory disorders are not congenital but develop after an injury or some type of stressor, have organ specificity and involvement of multiple types of inflammatory cells, and variably affect the nervous system or vascular system, altering healing or tissue regeneration and increasing the risk of cancer. The mechanistic etiology of simple disorders can be resolved using standard statistics when there is an order-of-magnitude more of data than of variables. However, with the highly complex problem of idiopathic, genetic variant-associated complex diseases, there is an order-of-magnitude more of variables than of data (e.g., millions of genetic variations in the human genome and thousands of subjects). Examples of complex inflammatory disorders in the field of gastroenterology include liver cirrhosis, chronic pancreatitis, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis).

Because complex inflammatory disorders have multiple etiologies and variable outcomes, no single approach will provide all of the answers regarding their causes, nor provide a target for effective treatment. Instead, each component of the disease must be studied within an appropriate context (e.g., comparing well-matched patient subsets with and without the specific biomarker or endpoint). Thus, rather than using a global, unbiased, null-hypothesis significance test (to obtain *P* values) to identify the components of complex etiology and then build a statistical classifier model, the reverse engineering approach focuses on the components of a larger system, develops plausible models based on knowledge of biology, and uses statistics to guide the development of predictive models. One of the many advantages of the reverse engineering – predictive modeling approach is that it markedly limits the number of possible variables to be considered in each component model, and directs the selection of biomarkers to monitor disease progression and response to treatment. The mechanistic insights gained from testing the components of a complex disorder are then integrated into a more holistic overall disease model. However, model building is much more difficult than null-hypothesis significance testing and requires ongoing contributions of many different types of faculty.

The term *translation* in the context of research means different things to different people⁴. In complex inflammatory disorders, that term defines effective communication between

members of multiple clinical and scientific disciplines, as illustrated in Figure 1. In that illustration, a group of clinicians must be conversant with a group of clinical or basic scientists and pull together the complete story for each complex disorder. The basic scientists should watch for common threads across multiple organ systems identified through their conversations with the different clinical specialists. For translation to occur, there must be a translator with expert knowledge of both the disease and the science who can understand those common threads. Once that happens, the elements needed for personalized medicine can be ascertained.

Structuring a program that can support such a matrix organization and deliver effective personalized medicine to individual patients with complex disorders has been a challenge to academic medical centers. Below, I illustrate how to structure a clinical “matrix academic division” (MAD) to facilitate translating research to personalized medicine.

Structuring a MAD for Personalized Medicine

After recognizing that unique combination of risk factors may give rise to a particular complex inflammatory disease syndrome in a specific patient, my colleagues and I at the University of Pittsburgh School of Medicine reorganized our traditional academic GI division with a clinical arm, a research arm and an educational arm to be a MAD division with the specific objective of providing the “right treatment to the right patient at the right dose at the right time”. We began with our own postulates:

1. Complex inflammatory diseases describe a multi-step process.
2. The organ or system where the disorder originates is not “normal” but, rather, has intrinsic defects in a specialized group of cells of the organ.
3. Chronic inflammatory disorders are not congenital but requires environmental stressors to become manifest.
4. Complex inflammatory disorders involve both abnormalities in specialized cells and also abnormalities in components of the immune response to injury, repair or healing. These secondary effects may be shared in different organs with chronic inflammatory processes.

Teasing out the necessary elements to solve a complex inflammatory disorder, communicating the unsolved problems to the scientists, retrieving possible mechanistic answers and applying them to clinical practice requires several critical components:

- A large patient population with diverse phenotypes and genotypes
- Immediate and continued access to experts from a wide variety of basic research disciplines
- The recruitment, training, and cooperation of dedicated physician-scientists (translators) who can link all relevant sciences to the specific syndrome and communicate with the scientists
- Biology-based disease models for organizing and testing clinical and experimental data
- Mathematical representations of general physiologic models that are then adapted to individual patients based on their individual risk, disease activity, and predicted outcome
- Sustained financial support

Fortunately, this combination of conditions exists at the University of Pittsburgh Medical Center, and we hope that our MAD division can serve as an example of a new paradigm in action.

Establishing a translational culture

A major burden of digestive diseases derives from chronic inflammatory conditions with inflammation, fibrosis, pain syndromes and inflammation-associated cancer risk. Beginning in 2000 we began restructuring the entire GI division with the ultimate goal of resolving the etiology of complex digestive disorders and their complications. Understanding the etiologies of these disorders, the risks of acquiring them, and various complications would provide the foundation for prevention and treatment.

With the assistance of an organizational development group at the University of Pittsburgh, we created an implementation plan to maximize efficiency and effectiveness as defined by clinical service opportunities, disease burden, economy of scale, and opportunities for strong collaboration in critical areas of research. In addition, the academic needs of the physician-scientist were considered and facilitated, since our expert faculty are our most valuable resource. The result was the novel MAD, as illustrated by a grid in Chart 1, for which seven centers of excellence (COEs) were created (their names are shown to the left of the chart's seven rows).

From an operations perspective, the COEs serve as a target for clinical referrals and are ideally staffed by seven or more physician-scientists (horizontal axis of the chart). Seven intersecting scientific disciplines (vertical axis) were likewise identified to focus on specific types of problems that run through multiple inflammatory diseases. The particular faculty member with expertise at the intersection of a specific clinical disorder and a specific scientific discipline has the responsibility as a translator to represent the physicians working in a COE in discussions with clinical or basic scientists of the corresponding scientific discipline within the university or elsewhere. In some cases, a scientist with a strong clinical interest and support the COE physicians functions as a translator. Such a design is powerful from an organizational standpoint because it allows each physician-scientist translator to be supported by six clinical colleagues focused on the same type of complex disease (the other six physician-scientists in a COE) and six scientific colleagues working in the same discipline (the other six scientist working in the same discipline) but focused on parallel complex diseases served by other COEs.

Facilitating communication

Within the grid, faculty translators maintain two dimensions of communication: one with the clinicians in the COE, and the other with clinical or basic scientists. In some cases, the key faculty may have primary appointments in another department, but typically have joint appointments in the Division of Gastroenterology, Hepatology and Nutrition and are integrated into MAD. Of note, there are two specialized programs with multiple faculty members sharing complementary interest within the same cell of the grid: the Center for Pain Research (CPR) with a basic science focus, and the Visceral Inflammation and Pain (VIP) center with a clinical focus. The clinical faculty translator's primary responsibility on the research side is to identify the best clinical or basic scientists to address a very specific mechanistic question. Stated in a general way, the question is "Why are we unable to predict the outcome of this subset of patients with these characteristics?" The collaborations are one-on-one and are very goal oriented.

The second dimension of communication is horizontal, which occurs in two structured formats. The physician-scientists of a COE meet in a multidisciplinary clinic on a weekly

basis with other physicians, surgeons, pathologists, and support staff. Each week, a COE sponsors one clinical case conference (a multidisciplinary conference) and a translational research conference/working group meeting to facilitate the clinical and translational research effort. This type of interaction is more of a collaborative think tank and facilitates higher-level integration.

By organizing the COEs around parallel complex inflammatory disorders, we also developed a critical mass of faculty with similar scientific interests, which justified the establishment of core research groups and core laboratories. When possible, we integrated faculty into existing basic science groups (e.g., cell biologists) or formed new ones to address a need raised by physician-scientists. For example, ten years ago, no faculty focused on visceral pain, so core discipline leaders were recruited and, in cooperation with the Departments of Neurobiology and Anesthesiology and with support of the dean, the Center for Pain Research was created.

Resources available to both clinical and basic scientists are also critical, and not just the traditional core research infrastructure and equipment. Administrative staff, data management and other costs have been paid by incorporating components into the grants that will use specific resources, by funds from philanthropy, and by seed money support from UPMC. Accurate phenotyping by dedicated physicians and the ability to create “virtual cohorts” through a robust electronic medical record system and flexible data management have been essential to our success.

Finally, our division has a monthly faculty meeting to discuss routine business, but more importantly, we continually remind the faculty of the goals, components and interactions of our MAD approach and continually celebrate remarkable advances by the faculty. Research retreats, listservs, and newsletters also facilitate communication among such a large and diverse faculty.

Using the MAD grid to generate discovery

The 7×7 part of the grid shown in Chart 1 can also be viewed as an outline for phenotyping multiple systems in a single patient. The grid of information from a single patient becomes a matrix as thousands of patients are evaluated over the same features using standardized data collection tools and biomarkers linked to each organ as viewed by a COE and each scientific discipline. The matrix then becomes a hyper-matrix as measures relevant to the 49 phenotypic components of each patient are monitored over time, with further degrees of information based on response to treatment. While the data and biospecimen management systems are beyond the scope of the current discussion, they are critical for functionality.

From a mechanistic discovery perspective, understanding all the elements of a complex disorder, which is the purpose of each COE, occurs when a series of physician-scientist translators can apply insights from their respective scientific fields in the greater disease model. Collecting the pieces of information related to normal and abnormal responses to stresses and interventions, adding detailed genetic and environmental information, organizing the data sets, and incorporating them into algorithms and predictive models constitute the role of computer scientists and biostatisticians. The proof comes from the application of the new knowledge in sequential patients with different variations of the disease.

Working Example: Pancreatitis

The Division of Gastroenterology, Hepatology and Nutrition has emerged as one of the leading groups with pancreas expertise in the world, which we believe is a direct result of

our MAD organization. Our pancreas group has published hundreds of original reports and reviews over the past decade, with some of the major advances related to the modeling of a complex inflammatory disease: chronic pancreatitis.

Chronic pancreatitis (CP) is one of the complex inflammatory diseases that challenges the germ theory. In 1896, Chiari⁵ suggested that the inflammation did not come from infection, but resulted from autodigestion of the pancreas by pancreatic digestive enzymes that became active while they were still inside the pancreas. Since then, CP has been defined by the *amount* of scarring and other complications⁶, with the assumption that the etiology was alcoholism, since no other factor could be identified. However, most alcoholics do not develop CP, and most patients with CP report little alcohol use, even under intense interrogation. In 1995, and despite years of traditional investigation, a *New England Journal of Medicine* review concluded that “chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment”⁷.

Resolving the etiologic problem involved the study of two uncommon but striking genetic disorders that result in chronic pancreatitis. The first is hereditary pancreatitis, which targets acinar cells, and cystic fibrosis, which targets duct cells. With the cells of disease origin defined, and examples of disease mechanism illustrated, we were able to begin teasing out the influence of other genetic and environmental factors that modify disease susceptibility, severity and complications. The discovery process involved different scientific disciplines, and each was chosen based on the specific problem being studied.

Acinar cell pathophysiology in chronic pancreatitis

Our first major breakthrough came from the study of some unusual cases. In 1996, gain-of-function mutations in the cationic trypsinogen gene (*PRSSI*) were identified in a study of large families as the cause of hereditary pancreatitis⁸. This unusual form of pancreatitis begins with episodes of acute pancreatitis in childhood, CP in a subset of patients by early adulthood, and a 30-40% risk for pancreatic adenocarcinoma later in life⁸. Studies of this rare condition revealed that trypsin was a key molecule in the pathogenesis of acute pancreatitis and chronic pancreatitis^{9,10}. Evaluation of the molecular structure of trypsinogen (molecular modeling) in relation to the disease-causing genetic mutations (genetics) also linked calcium dysregulation with pancreatitis and localized the site of dysfunction to the acinar cells (cell biology). Since trypsin is primarily expressed in the pancreas, the discovery explained why this chronic inflammatory disorder was located in the pancreas (susceptibility and organ targeting). However, it did not explain disease severity, clinical course, or the likelihood of complications.

Duct cell pathophysiology in chronic pancreatitis

Cystic fibrosis is an autosomal recessive disorder caused by severe mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), which is an epithelial cell anion channel involved in fluid secretion and absorption. In the pancreas, *CFTR* is expressed in the proximal duct cells, not the acinar cells. Infants born with cystic fibrosis have abnormal sweat chloride, chronic pancreatitis, and occasionally meconium ileus, with lung disease developing later.

In 1998, two genetics groups noted an excess of heterozygous severe *CFTR* mutation in CP patients^{11,12}. While the explanation remained obscure, the CP phenotype was identical to alcoholic CP, hereditary CP, and idiopathic CP. This finding also demonstrated initiation of injury could occur in the acinar cells (*PRSSI* mutations or calcium dysregulation) or the duct (*CFTR* mutations in the duct cells or duct obstruction), and that regardless of injury location, it led to the same chronic inflammatory phenotype. Thus, the mechanism of injury

determined the organ (susceptibility), but the immune response defined the general phenotype (scarring) and determined various complications (organ dysfunction, pain, diabetes, cancer development).

Working model of CP

In 1999, we proposed the Sentinel Acute Pancreatitis Event model of CP⁹ involving a “two-hit” model in which the first (sentinel) episode of acute pancreatitis activates the immune system, while the second “hit” involves stressors that would not be sufficient to cause direct injury alone but can drive the inflammatory response toward fibrosis rather than healing^{9,10}. Potential stress factors that increased the risk of progressing to CP include alcohol use, smoking, metabolic stressors, and recurrent acute pancreatitis.

We used this conceptual framework of a mechanistic process to design the North American Pancreatitis Study 2 (NAPS2), the largest prospective, cross-sectional cohort study of recurrent acute pancreatitis and CP ever conducted in the United States (1,000 patients, 695 controls)¹³. Using broad inclusion criteria (two or more episodes of acute pancreatitis or any imaging evidence of pancreatic injury or scarring) we then classified patients according to the major known etiologic factors⁶ and family history. We quantified alcohol use and smoking throughout their lifetimes as environmental stressors. We defined specific, quantified endpoints (fibrosis, calcifications, maldigestion, pain patterns, diabetes mellitus, cancer), collected detailed data on clinical history, medication use and effectiveness, and carried out serial imaging studies as biomarkers of disease activity over time.

Surprising findings thus far include the discovery of a threshold amount of alcohol (≥ 60 grams of ethanol per day) that must be exceeded before CP risk increases above that for non-drinkers¹⁴; that smoking is a strong, independent risk factor for the development of CP; and that a combination of alcohol and smoking confers the greatest risk^{14,15}. Overall, alcohol abuse accounted for only about 25% of the incidence of disease, which forced us to reconsider how we look at this disease!

Insights into idiopathic CP

We quickly asked ourselves, If most cases of CP are *not* caused by alcohol, as had been assumed for decades, what is triggering the process of fibrotic injury in the pancreas? The answer is the pancreatic secretory trypsin inhibitor (gene symbol *SPINK1*), an acute-phase protein produced in the pancreatic acinar cells that is upregulated during inflammation as a feedback inhibitor of activated trypsin. In 2000, Witt et al found that in children, homozygous *SPINK1* N34S mutations were associated with pancreatitis.¹⁶ Also, we showed that heterozygous *SPINK1* mutations were associated with early-onset CP¹⁷. However, 2-3% of many populations carried the high-risk *SPINK1* haplotype¹⁷ suggesting that *SPINK1* variants acted as disease-severity modifiers in patients with recurrent trypsinogen activation within the pancreas.

We then envisioned two pathologic pathways¹⁸. One links environmental stressors to trypsin activation, followed by failed *SPINK1* feedback protection, and then immunocyte activation (macrophages and pancreatic stellate cells), to cause CP¹⁸. The other pathway involves immunocyte activation and CP independent of trypsinogen activation and *SPINK1* variants. Surprisingly, the frequency of *SPINK1* mutations was significantly lower in alcoholic CP than in idiopathic CP, indicating that following activation of the immune system, alcohol could drive inflammation and fibrosis independent of trypsin activation. This explains why the risk of alcohol, smoking and alcohol plus smoking is similar in CP and liver cirrhosis^{14,18}. On the other hand, it also indicated that idiopathic CP was often linked to recurrent trypsin activation. Separately, we developed a mathematical model of

how *CFTR* functions in pancreatic duct cells¹⁹ and predicted that mutations causing selective defects in *bicarbonate secretion* would lead to recurrent trypsin activation. We tested this hypothesis in subsets of the NAPS2 cohort and in a familial pancreatitis cohort and discovered that the common *CFTR* R75Q variant, which is not associated with cystic fibrosis, was strongly associated with CP, especially in the presence of *SPINK1* mutations²⁰. Using site-directed mutagenesis and electrophysiology in a cell system, we proved the existence of a selective defect in *CFTR* bicarbonate conductance²⁰. This defined the phenotype of a new high-risk class of *CFTR* variants (proposed Class IVb) that do not cause cystic fibrosis but do cause CP.

Our findings have launched a revolution in how chronic inflammatory diseases of the pancreas are viewed. Figure 2 summarizes the current distribution of CP etiologies in the NAPS2 cohort, with alcohol use responsible for a minority of cases. Although the observed phenotype is the same, multiple etiologies are responsible for initiating the process in the pancreas, while common factors seem to drive the process. Thus, although the disease “looks” the same in the clinic setting, different therapeutic approaches are required, depending on the etiology. Providing an appropriate prescription for each patient represents our implementation of personalized medicine.

Future Directions

To better understand complex inflammatory diseases of the pancreas, we and others are designing carefully focused clinical trials that will target subsets of patients with genetically defined risk and biomarkers of disease activity. However, as demonstrated by our faculty grid (Chart 1), there is the potential to rapidly apply discoveries in the pancreas to parallel genetically or phenotypically defined complex inflammatory syndromes in the intestines and liver. This approach will allow small but well-powered studies to be designed by minimizing subject variance and more accurately defining the biomarkers and endpoints²¹. More important, it provides a framework for rapid integration of new and complex datasets generated by next generation sequencing, molecular discoveries, and “omic” results (i.e., genomics, proteomics, metabolomics). Finally, the future will involve better design and use of electronic medical records and mechanistic mathematical models capable of integrating multiple risk factors in multiple domains over time to provide accurate predictions about the cause of the condition, the state of the condition, and the future of the condition as modeled with or without potential interventions.

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Figure 1.

A diagram of integrated communication among physicians and scientists. The ovals (nodes) are areas where expertise is needed to translate between the complex medical disorders in an organ (rows) and the knowledge from scientific disciplines (columns) required to solve specific types of problems associated with the disorders. For such translation to occur, there must be a translator with understanding of both the disease and the science. Modeling a complex disease requires the translators to integrate their results using a higher-level model than would be required for diseases caused by a single agent.

Figure 2.

The current distribution of chronic pancreatitis etiologies in a specific patient cohort as of November 2010. Although the observed phenotype is the same, multiple etiologies are responsible for initiating the process in the pancreas, while common factors seem to drive the process. Thus, although the disease “looks” the same in the clinic setting, different therapeutic approaches are required, depending on the etiology. Providing an appropriate prescription for each patient is an implementation of personalized medicine. See the text for definitions of the various abbreviations in the figure.

List 1**Koch's Postulates***

- 1 The microorganism must be found in abundance in all organisms suffering from the disease, but not in healthy organisms.
- 2 The microorganism must be isolated from a diseased organism and grown in pure culture.
- 3 The cultured microorganism must cause disease when introduced into a healthy organism.
- 4 The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

* Koch's postulates are criteria to establish a causal relationship between a causative microbe and a disease.

Chart 1

Faculty Grid of Clinical – Basic Science Translation Activities in the Matrix Academic Division (MAD), University of Pittsburgh School of Medicine, 2011*

Center of Excellence	Epidemiology Risk factors	Genetics/Genomics	Molecular, cellular and Integrative physiology	Immunology/Transplantation	Fibrosis Tissue engineering Regenerative medicine	Neuroscience/Pain/Psychology	Cancer biology	Diagnostics & Biomarkers	Therapeutics & Outcomes
Center for Liver Diseases	physician-scientist	physician-scientist	physician-scientist	physician	scientist	<i>physician-scientist</i>	<i>scientist</i>	physician	physicians
Pancreas Center	physician-scientist	physician-scientists	physician-scientists	physician	physician-scientist	physician-scientists	physician-scientists	physician	physicians
IBD Center	physician	physician-scientists	physician-scientists	physician-scientists	physician-scientists	<i>physician-scientists</i>	physician-scientists	physician-scientists	physician
Neurogastroenterology & VIP center	TBA	<i>physician-scientists</i>	CPR [†] VIP [‡]	scientists	scientist	physician-scientists	<i>scientist</i>	physician-scientists	physician-scientists
High Risk Digestive Cancer centers	physician-scientists	physician-scientists	physician-scientists	<i>physician</i>	scientist	scientists	physician-scientists	scientists	<i>physician-scientists</i>
Center of Intestinal Health & Nutrition Support	physician	TBA	physician-scientists	<i>physician-scientists</i>	physician-scientists	scientists	physician-scientists	physician-scientists	physician-scientists
Center for Women's Digestive Health	physician	scientists	scientists	physician	NA	physician	physician	physician-scientists	TBA

* With the assistance of an organizational development group at the University of Pittsburgh, the authors and colleagues created an implementation plan to maximize efficiency and effectiveness, as defined by clinical service opportunities, disease burden, economy of scale, and opportunities for strong collaboration in critical areas of research regarding complex infectious diseases. The result was the novel MAD, for which seven centers of excellence (COEs) were created (their names are to the left of the chart's seven rows). The seven scientific disciplines involved are indicated by the titles of the first seven columns (reading left to right); applied technology areas are indicated by the titles of the eighth and ninth column. The type of faculty in each cell represents the status as of 2011. Some faculty have roles in more than one cell, and some cells have more than one expert (indicated by plural description). Italics indicate a primary appointment in another department.

[†] CPR = Center for Pain Research.

[‡] VIP = Visceral Inflammation and Pain Center.