Meet the Champions

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'You're Heading in the Right Direction'

An Interview with Dr. Fred Gorelick

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Abstract

In the current interview, the internationally renowned pancreatologist Fred Gorelick highlights the key importance of mentorship and gives us a hint of his experience in pancreatic research. Dr. Gorelick's discoveries on zymogen activation on the pancreatic acinar cell lead the way on the understanding of the mechanisms underlying cell damage during pancreatitis. This work opened a new field of study and has served as the foundation for subsequent work for a large number of laboratories around the world.

M.F.-Z.: What initiated you to work in pancreas research in the first place?

F.G.: I was drawn to study the pancreas as a consequence of circumstance and luck. While presenting a physiology conference on the pancreas as a GI fellow at Yale in 1977, I mentioned that the work on the pancreatic acinar cell by Jim Jamieson and George Palade led to the Nobel Prize for George Palade. After the seminar, I was informed that both Jim Jamieson and George Palade were at Yale. Soon after, I approached Jim and asked him if I could work in his laboratory to study an issue related to encephalin and acinar cell secretion. When those studies were completed in 1979, they were negative, but it was a remarkable opportunity to learn the biology of this cell. Based on studies done by Jim and Steve Freedman on calcium-dependent phosphorylation in the acinar cell and the discovery of calmodulin, we began to study calcium-dependent protein phosphorylation. Studies done with a very talented GI fellow (Jonathan Cohn, now Professor of Medicine at Duke) led to the identification of calmodulin-dependent protein kinase II in 1983 [Gorelick FS et al.: J Cell Biol 1983;97:1294–1298]. Since the levels of

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calmodulin-dependent protein kinase II are 500–1,000 times higher in the central nervous system, I shifted my studies to the brain. Working with Paul Greengard's group at Rockefeller University (1985–1987), we found that this enzyme could function as a molecular switch. Such a response was perfectly patterned to have a role in memory. Subsequent studies by others confirmed this prediction. Our laboratory's first studies on pancreatitis were performed when Steven Leach, then a Surgical Resident at Yale and now a Professor at Johns Hopkins, came to do research in our laboratory in 1989. Steve's only requirement was that his studies be clinically relevant. After discussing a list of issues that were unresolved in pancreatology, we settled on the subject of zymogen activation in acute pancreatitis. While this event had been predicted to have a role in acute pancreatitis, the site of activation had not been demonstrated. Our hypothesis was that it might occur within the pancreatic acinar cell. Steve's 1991 study was the first to demonstrate regulated protease activation of the acinar cell [Leach SD et al.: J Clin Invest 1991;87:362–366]. The work has served as the basis for subsequent work by our laboratory and others for over 15 years.

M.F.-Z.: You have pioneered the pancreas research in so many directions. At the end of the day, what has given you the most personal satisfaction?

F.G.: Three findings from our laboratory are at the forefront. The first is the work characterizing calmodulin-dependent protein kinase II in pancreas because it is relevant to many other systems. This work also gave me the confidence and knowledge base to approach other scientific issues. The second are studies on zymogen activation on the pancreatic acinar cell and of clinically relevant conditions that sensitize the cell to this activation [Leach SD et al.: J Clin Invest 1991;87:362–366]. Finally, several of our studies have promoted the notion that alcohol may cause disease, in part, by sensitizing the pancreas to injury [Katz M et al.: Am J Physiol 1996;270: G171–G175; Lu Z: Am J Physiol 2002;282:G501–G507. These studies were initiated because others had observed that alcohol could sensitize the β-adrenergic receptor to activation. While our studies are all short-term, work from several groups has shown long-term alcohol exposure may also sensitize the pancreas to injury [Clemens DL and Jerrells TR: Alcohol 2004;33:183–189; Fortunato F: Am J Physiol Gastrointest Liver Physiol 2006;290: G232–G241; Pandol SJ et al.: Gastroenterology 1999;117: 706–716]. The need for two pathologic insults (such as alcohol abuse and other factors) may help explain the infrequency of pancreatitis in alcoholics.

M.F.-Z.: Based on your experience as mentee and mentor, can you comment on the value of mentorship for the development of new investigators?

F.G.: Mentorship is absolutely critical for the success of a young investigator. While you need someone to tell you when you're heading in the correct direction, a mentor must be ready to break the bad news when your likelihood of success is low. A mentor helps the trainee focus research and clinical activities without damping the trainee's enthusiasm for knowledge. A mentor also conveys the value of communicating one's findings through both manuscripts and presentations. In this context, some of the most relevant lessons come when mentor and trainee work together writing manuscripts and developing presentations. The ability to express oneself in a clear and succinct manner is essential for scientific success but not easily learned. While rules of grant writing and responding to critiques exist, the mentor has an essential role in communicating the unwritten guidelines that can mean the difference between success and failure in securing funding. The mentor plays a central role in helping the young investigator construct documents that are based on firm and well-defended hypotheses, have an appropriate scope and evidence of feasibility and that recognize pitfalls and provide alternatives. Finally, the best mentors provide encouragement and friendship.

M.F.-Z.: What is the best advice you have received during your career? What is your advice to the young investigators that are beginning in the field of pancreas research?

F.G.: We all need approbation and confirmation that we have the right ideas and are doing work that others see as significant and valuable. While some feedback can come from funding agencies and publications, it is critical to have the input of colleagues we respect. I think the most important advice I received came from George Palade. When I showed him the first experiment by Steve Leach demonstrating regulated protease activation in the acinar cell, George responded by saying: 'Fred, I think you have something important to study.' That response affirmed my sense that we should push ahead: 15 years later, our laboratory continues to study the topic. As a consequence of this experience, I try to give young investigators an honest opinion about the potential of their work. I also suggest that young investigators think carefully about the project they select and identify an important issue that others are not studying.

M.F.-Z.: What do you think are the big questions that need to be answered in pancreatology?

F.G.: A great mystery to me is why only a subset of alcohol abusers develops pancreatitis. There must be genetic and possibly environmental factors that are responsible for this susceptibility, but they remain unclear. As discussed, the property of sensitization to injury by alcohol may be relevant to the development of disease. Important areas for future alcohol research will be the mechanisms of ethanol sensitization in the context of acute and chronic exposure. The pathologic mechanisms that link pancreatic disease and CFTR dysfunction remain unclear, as does the importance of minor mutations in causing disease. While many drugs can cause acute pancreatitis, the mechanisms remain unknown for most. Pancreatic duct stenting appears to make an important impact on the incidence of severe pancreatitis following ERCP, but we still need additional therapies to prevent this complication. Given the apparent complexity of responses that determine disease severity, it is doubtful that a single therapeutic intervention will fully prevent ERCP-induced pancreatitis. Therapies toward multiple therapeutic targets may be needed. The most daunting issues relate to pancreatic cancer – while some promising inroads have been made by understanding the molecular basis of this deadly neoplasm, much more needs to be done. The potential complexity of pancreatic cancer was underscored by the recent demonstration that breast and colon cancers host a much greater number of mutations than had been previously predicted. Similar to my notions about ERCP-induced pancreatitis, pancreatic cancer will certainly require multifaceted therapies that match its complex origins.

M.F.-Z.: What do you think is the major need that a journal like *Pancreatology* should fill?

F.G.: Investigators need a journal that provides rapid, direct and equitable evaluations. While reviewers need to be rigorous, they must also have reasonable expectations. Thus, reviewers of basic science articles should be careful not to ask for studies that have never been done in the pancreas and that are likely not feasible. Similarly, clinical studies are very difficult and virtually always imperfect. The reviewers and editors should carefully weight the value and the deficits of a submission. Shortcomings can often be handled in a discussion and with editorial comment. Finally, I believe that we need to be more open to publishing studies that are negative or in conflict with dogma.

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