

Advancing Clinical Trial Innovation in Pancreatic Cancer

A Conversation Between Diane Simeone, Ken Herrmann, and Johannes Czernin

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Ken Herrmann, MD, from the Universitätsklinikum Essen, and Johannes Czernin, MD, from the David Geffen School of Medicine at the University of California Los Angeles, talked with Diane M. Simeone, MD, about her career advancing clinical research in pancreatic cancer. Dr. Simeone is the Laura and Isaac Perlmutter Professor of Surgery and Pathology and director of the Pancreatic Cancer Center at New York University (NYU), where she also serves as the associate director for Translational Research. An internationally recognized pancreatic surgeon and researcher with a longstanding focus on treatment of pancreatic neoplasms, she has been the recipient of numerous National Institutes of Health (NIH) grants investigating the molecular mechanisms of pancreatic metastasis and developing novel therapeutic strategies. She has a large clinical practice taking care of patients with pancreatic neoplasms and those at elevated risk of the disease. She first discovered pancreatic cancer stem cells, identified ATDC as a novel oncogene in human cancers, and defined for the first time unique populations of cancer-associated fibroblasts in pancreatic cancer. She has been an innovator in development of therapeutic clinical trials for pancreatic cancer and is currently the principal investigator of Precision Promise, an adaptive-platform clinical trial consortium focused on next-generation trials in pancreatic cancer. She also heads the Pancreatic Early Detection Consortium (PRECEDE), an international collaboration studying a large cohort of individuals at heritable risk for pancreatic cancer. She served as chair of the scientific and medical advisory board of the Pancreatic Cancer Action Network (PanCAN) and has previously served as president of the Society of University Surgeons (SUS) and the American Pancreatic Association, as well as on the National Cancer Institute (NCI) Pancreatic Cancer Task Force. Dr. Simeone is a member of the National Academy of Medicine.

Dr. Herrmann: You are a leading pancreatic cancer surgeon and also a translational researcher. Can you give us some highlights of your career?

Dr. Simeone: My father was an economics professor. Education was always strongly emphasized in my family. But I also played basketball at Brown University, which taught me that the whole team has to perform to be able to accomplish things. My parents strongly encouraged me to go for whatever I wanted to accomplish.

Dr. Herrmann: Your university major was very different from what you are doing now.

Dr. Simeone: Yes, I majored in neuroscience, because the brain was fascinating—a black box of connections that had not been untangled. But then I went to medical school at Duke University and realized that abdominal surgery was more interesting to me. I am a hands-on person; I like the idea of fixing things, and that is what led me to surgery: I felt I could do research but also have a tangible impact on patients' lives. I was actually deterred in medical school from pursuing a career in surgery, because I was told that the lifestyle was just too hard and I wouldn't have a chance to be a mother and have balance in my life. Luckily, I was strong willed and raised in a family that taught me not to accept what somebody else put on me. I remember thinking: Who are these guys to tell me what I can or can't do? I ended up at the University of Michigan for my surgical residency. Lazar Greenfield, MD, the inventor of the Greenfield filter, was the chair of surgery. In 1988, 7 of the interns in the department were women, which was unheard of at the time. Dr. Greenfield's mantra was to take the best talent. Then I did a 2-y research fellowship with John Williams, MD, PhD, one of the pioneers in pancreatology, and Craig Logsdon, PhD. As mentors, they started me on my research path.

Dr. Czernin: What does mentorship mean to you? What is good mentorship?

Dr. Simeone: A true mentor helps the mentee to thrive and succeed. It should be about what the mentor does for the mentee, not what the mentee can do for the mentor.

Dr. Czernin: Do you have a mentoring structure? How often do you meet with your trainees or your students or postdocs?

Dr. Simeone: I see my research mentees very often, multiple times a week, and we have a weekly lab meeting. I also mentor a whole team on the clinical and clinical research side. Many are young women who want to know how to best look for their first job, negotiate, and achieve balance. I'm good at negotiating now, because I was bad at negotiating early in my career and have learned to do it successfully. When I hire people, I push the institution to give them bigger packages and more resources, because I want them to be successful.

Dr. Herrmann: Before Johannes sidetracked us, we were in Michigan. How did you get from Michigan to NYU?

Dr. Simeone: I had a wonderful academic career at Michigan. Although I did not have a tenure track position in the beginning, I fought for and got it. I met with success gradually, with my first grant in 1997 or 1998, and then built on that. In 2001 I established



Diane M. Simeone, MD

a multidisciplinary pancreas tumor clinic at a time when there were not very many multidisciplinary clinics. Only 2 people were working on pancreatic cancer at the University of Michigan. The senior surgeons would say, “Oh, it’s resectable!” This was an imprecise approach to a complex problem, so I set up a database and a tumor board. We got the radiologists to join. The point I want to make is about valuing everyone who can contribute to the team. By the time I left, we had 60 people working on pancreas cancer. We had an NCI Specialized Programs of Research Excellence grant and helped recruit people from almost every department to work on pancreas cancer. Then, Pfizer moved out of Ann Arbor, and the University of Michigan bought the Pfizer campus. It was like the Louisiana Purchase—they bought 29 buildings and 2 million square feet of space for something like \$110 million. One signature project was a translational oncology program, which I was asked to run. I arm-twisted 6 colleagues to start this with me. Within 3 y, we had about 30 faculty. The premise of the program was to leverage the entire scientific strength at the University of Michigan to tackle cancer.

Dr. Herrmann: *So how did NYU poach you?*

Dr. Simeone: After a change in leadership at Michigan, I explored other professional options. The chief scientific officer at NYU reached out and asked me to join NYU, where I could continue to work on my passion, which is pancreas cancer.

Dr. Herrmann: *One intriguing aspect of your personality is passion. And 1 example is the PRECEDE project. Can you explain what this is about?*

Dr. Simeone: We need to take the imaging that is currently being done and make sure that it is standardized and state of the art. We assembled a working group that focuses mostly on MRI and endoscopic ultrasound (EUS). The other component is to create a data cloud into which we load deidentified and longitudinal imaging data. This is supported by participating companies. I also asked experts whether we can develop more sophisticated molecular imaging tools that pick up 3-mm pancreas lesions instead of the 1.5-mm range with MRI. I do think that by having this large cohort of patients we are in a position to develop strategies for new imaging approaches that might not have been possible previously.

Dr. Czernin: *What is your key expectation for imaging. Is it high sensitivity, specificity, or both?*

Dr. Simeone: We need high sensitivity to pick up small lesions. Will this be a molecular probe or something with EUS and microbubbles? Is it going to be nanodots? I don’t know the answer. I have had this idea to issue a \$1,000,000 challenge to imagers to come to the table with their next greatest ideas, so that we can help to test them.

Dr. Herrmann: *What kind of imaging tools, in addition to MRI, do you use for screening?*

Dr. Simeone: Mostly MRI, alternating with EUS, which, of course, is somewhat more invasive. The algorithm is usually to alternate them. But I do not think that we have engaged the brain trust of the imaging community to help us solve this; this is an opportunity. If we develop a blood test that can be, for example, a first sieve for identifying someone at risk, we then need a very sensitive early-detection imaging test to locate the source.

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Dr. Simeone: It all started at Michigan. I had been working on pancreatic cancer for some time but did not know if we would be able to change survival during my career. We needed to define the problems in order to solve them. I worked with PanCAN to develop a whole new platform for drug development. We developed a new approach to clinical trials called Precision Promise, a large-scale adaptive platform. Today it involves 30 centers, with 12 new innovations never done before in clinical trials. The other component is early detection, which is the key to improved survival. We resect when tumors are very small, and then, as needed, supplement with adjuvant treatment for micrometastatic disease. About 4 y ago, I started to work on PRECEDE. The key questions focused on obstacles to early detection. We used a nonprofit group called Arbor Research and then invited others to come to the table if they agreed to share data. We now have 40 centers and have enrolled close to 3,300 patients.

Dr. Czernin: *How do you go about early detection? What are your thoughts or plans?*

Dr. Simeone: The strategy was to take a group at sufficient heritable risk of pancreatic cancer, follow them, and enable development of blood-based biomarkers, more sophisticated imaging, or better multimodal data integration. That is what the PRECEDE study is. It is a heritable risk cohort study, and we are enrolling 100–150 each month. At this pace, we will be able to enroll 10,000 patients within 5 y and then follow them for another 5 y.

Dr. Herrmann: *Amazing strategy. What are your expectations for imaging in the next 5 to 10 y to help you accomplish your goals?*

Dr. Herrmann: *You talked about the importance of early detection for changing the outcome. Another opportunity is the development of improved therapies. What about the new drugs that come along, including KRAS inhibitors? How much can you improve 5-y survival by using these new drugs and identifying patients who would benefit?*

Dr. Simeone: That gets back to Precision Promise and setting up the platform. How do we “de-risk” bringing new therapies to pancreas cancer? We developed a pharma consortium. With the platform, cost and time to FDA approval can be cut, because it is a seamless phase II–III adaptive platform trial. You mentioned KRAS therapeutics, an area where several companies have pretty exciting new agents. With this platform, as soon as the safety studies are done, we have an accelerated testing path for a group of 30 centers around the country funded by PanCAN, the patient advocacy group that has made an investment of at least \$40 million in the platform to date.

Dr. Herrmann: *Before I switch to completely different areas, what do you think about immunotherapy and CAR-T cells in pancreatic cancer?*

Dr. Simeone: I do think now there are some interesting advances in approaches that may be quite effective in solid cancers. They just need to be tested. We are exploring that space. We know that pancreatic cancer is much more immunosuppressive than just about any other cancer. One thing we really pushed in Precision Promise was to get paired biopsies on patients before and on treatment as a critical piece that had never been done before, so that we can see

what is actually happening in the tumors. It is important to understand resistance to therapy. We are taking treatment biopsies at 8 wk for genomic and transcriptomic analyses. There are also some immune-based analyses. Of course, this is not done in isolation in humans, but in coordination with a whole preclinical research community.

Dr. Herrmann: *Let's talk about the role of women in medicine. How can we move forward to improve and support the careers of women in academia?*

Dr. Simeone: I'm disappointed that we have not seen the equity I thought we would have achieved by now. If you look at the top of every academic institution and of every co., men remain heavily dominant in leadership. We have to put women in leadership positions. I'll give you one example: When I was a member of the SUS, I was 1 of only 2 women among a group of 12–15 men. I gradually worked my way up to become president. By the time I finished being on the board and president, the board was composed equally of men and women. We had representation from minorities who had never had a seat at the table. You just have to have someone at the top who is paying attention. I give credit to Francis Collins, MD, PhD, who as NIH director announced that he would not participate in professional meetings that did not feature women in prominent speaker roles.

We need to address simple things like child care. When I was at the University of Michigan, which had thousands of employees, they had 18 slots for child care. After a positive pregnancy test, the first thing I did was put my name on the list for child care, which I never got. Better systems must be in place so that women have opportunities.

Dr. Herrmann: *Let's switch gears. We had a discussion with Declan Murphy, MBChB, a leading genitourinary surgeon at Peter MacCallum Cancer Centre. He said that he recently gave a talk on*

"Avoiding obsolescence as a cancer surgeon." How do you avoid obsolescence?

Dr. Simeone: I definitely have paid attention to that during my career. I am doing things now I never thought I would be doing, because I kept an open mind. I helped develop the largest clinical trial platform for pancreas cancer in the country and learned what I needed to learn to do this. Cancer surgeons should certainly make sure they educate themselves about precision oncology, genomics, clinical trials, and key trends in the basic sciences. The clinician/scientist is, unfortunately, a dying breed. Although we are drifting away a little from obsolescence, it is vital to sustain learning and keep an open mind. Academia must create a true continuum between basic science discovery and clinical applications. Our patients depend on us to drive change and improvement in their care, and that is what I encourage in all my colleagues, whether basic scientists or clinicians I mentor: Don't be afraid to do something big and to be ambitious, because people are counting on you to change how we care for patients.

Dr. Czernin: *Much of the academic mission is now replaced by relative value unit-driven business concepts.*

Dr. Simeone: I understand the statement "no margin, no mission," but I think we have to be true to what we're here for!

Dr. Czernin: *Maybe we should turn this around and promote the concept of "no academic mission, no margin"!*

Dr. Herrmann: *Do you have a take-home message for our young colleagues?*

Dr. Simeone: We should value everybody, every team member, who can contribute to tackling our major problems.

Dr. Czernin: *With this concise message, both Ken and I are grateful for your time and are sure that our readers will enjoy your insights.*