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## DENNIS SLAMON: FROM NEW CASTLE TO NEW SCIENCE **ELI DANSKY**

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At 11:22 a.m., I'm speeding north on Westwood Blvd in a borrowed car trying to make my 11:25 a.m. appointment with Dr. Dennis Slamon. He's the man behind breast cancer wonder drug Herceptin and a fellow described in various publications as a "zealot" possessing a "murderous resolve." He is affording me the only free 40 minutes he has this month, squeezing my piddling interview between what I presume to be marathon sessions of lifesaving research. I have to get to UCLA parking lot number 9 by 11:25 to get to his office on time, and although I've nearly pounded the gas pedal into the floorboard, I'm not going to come close to making it.

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Dennis Slamon is one of the miracle workers at the center of Stand Up To Cancer. His role in the development of Herceptin is widely known and celebrated in philanthropic circles, the cancer community, scientific journals, and what he refers to as "the lay press." Robert Bazell's book *HER-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*, details Slamon's often times frustrated but ultimately triumphant journey through the maze of institutional biomedical science out onto the crest of a new wave of targeted exploration and therapy in translational cancer research.

Bazell's book, "told like a good television script," according to the New York Times Book Review, is the basis for an upcoming Lifetime movie, with Harry Connick, Jr. playing the leading man: Dennis Slamon. So even if you haven't heard the story yet, get basic cable and you'll be able to tune in at some point in the near future to get the scoop. The gist of the story of Herceptin, and in part, Dennis Slamon (POSSIBLE SPOILER ALERT), is this:

Dennis Slamon is from New Castle, PA, just West of Pittsburgh—a region known more for its propensity to produce hall-of-fame quarterbacks than world-class oncologists. But Dennis Slamon wasn't very good at football. And he drew what seemed to be the only biology teacher at his high school who wasn't a member of the football team's coaching staff.

Instead, he got a rookie. "This guy was just starting. He had a fire in his belly, was excited about the subject, and just turned me on to this whole idea of biology and

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biologic processes. And what it meant, and it's sort of secrets and the questions of life itself." By then Slamon already knew the power of medicine, learned as child when he watched as his parents' faces would flood with relief each time the doctor set foot in the Slamon home on a house call.

So it was probably a good thing that he turned out not to have a golden arm. Nothing against Dan Marino or Joe Montana, but Slamon ended up becoming a doctor and a researcher; his unwavering belief in the power of hard, objective data helped him to join the ranks of those who understood breast cancer not as one single disease but as having identifiable subtypes, various pathways. This in turn led him to help identify a genetic alteration that was part of the pathogenesis of one of the more aggressive forms of breast cancer. His belief in looking at results without pre-conceived notions led him toward the theory that antibodies might reverse or mitigate the effect of the fateful alteration and derail the disease.

It very nearly didn't happen. Skepticism ran deep, and Slamon and his closest colleagues worked hard to champion the power of the data that they produced. Eventually, relief came in the form of a cash grant from Revlon and the Entertainment Industry Foundation, with efforts spearheaded by Lilly Tartikoff and Lisa Paulsen.

By 1998, Herceptin broke through clinical trials to become one of the first gene-based therapies for cancer. It targeted the HER-2 alteration and helped to change the landscape of cancer research and treatment, transforming one of the most lethal forms of breast cancer into one of the most manageable. Future generations of women can be grateful that Dennis Slamon was a lousy football player, or he might never have jack-hammered his way from New Castle to new science and triumphed over the calcified cognoscenti regulating research.

It's a good story, made even better by the fact that it's not fiction.

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Finally I discover an entryway onto the open roof of lot number 8. It's crowded. My friend's car is a compact and I fit into the only spot available within a half-mile. And then I'm sucked into some sort of déjà vu wormhole:

I've been on this roof before. In a car belonging to the very same friend. The last time was in the summer of 2004. My friend's mother had been through several rounds of intense chemo and was in patient care for the excruciating experience of stem cell therapy in one of the buildings nearby. It was not immediately clear how much longer my friend's mom would be alive. I would drive my friend in her car so that she could spend time with her mother and have a ride back. After a while, she'd get back in the car, and we would sit for a while more. We didn't talk much. Maybe a hug. There wasn't a great deal to say.

My friend's mother was being treated by, among others, Dr. Dennis Slamon. I did not

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know Dr. Slamon or even know of him at the time. I simply drove my friend to lot number 8 and waited. Now, four years later, my friend's mother is in good health and I'm back on this roof, stuck in this car again.

It's a nice story. Stories do tend to be nice. They allow us to impose a certain degree of order on what seems like chaos.

But sometimes they are dishonest. Yes, I get to show a personal connection to this interview, but in truth I had been a third-rate, fourteenth-hand caregiver, a bench-warmer on an all-star moral support team. I was basically a chauffeur.

Beyond that, I'd met Dennis Slamon before this interview. I knew him only to be a sweet and patient man. Resolute, to be sure, but not a scary guy. If he was a jackhammer, he was a velvet jackhammer. And whatever fears his specter might've roused were softened by the fact that he books his own appointments and is congenitally late, in this case by about an hour.

Stories are nice, but sometimes it's what happens after the end that is infinitely more complex, interesting, and important. Case in point: Slamon didn't fade to black after Herceptin hit the market. That wasn't the end of the story. And I finally got out of my friend's car to go ask him what was next.

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Eli Dansky: It seems like a hallmark of the relentlessness of good science is that you have to unlearn what the establishment believes.

Dennis Slamon: If you go with pre-conceived notions, you're as likely to get burned as you are to be successful. Everybody has pre-conceived notions based on how they were trained and what they learned. But we knew we were on new ground [with Herceptin] and went in with no pre-conceived notions and just asked, "What genes, if any, would be altered? And if they are altered, do they play a role and how would you prove that?" Setting that up as a simple paradigm and following it never let us down.

ED: So how do we get there?

DS: If you sit down with physicians and share with them the pre-clinical data and the early clinical data and keep them informed, you're able to move quickly. The objective now is to look at all the technology and the ideas we have, knowing that not all of them will work, certainly, even good ideas based in good science with good data. But you're more likely to hit oil than in a rich field. What we promise everybody we've been collaborating with, and what we need to have collaborative teams working around, is a promise to everybody that we'll be drilling in rich fields.

ED: How do you identify the rich oil fields? How do you identify the good grant proposals?

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DS: There are two schools of thought here. One is, just fund the best science and the cream will rise to the top. And there are outstanding, accomplished scientists who believe that's absolutely the way we should be proceeding. Then there's a whole separate camp which expects that you're going to do good science. But the fields are dictated by the realities of the diseases, so you want to drill where there is an absolute need and a potential for a good outcome. Now the way we're going to find our research is, we'll identify the problem and agree that we're going to commonly work on the problem. We're each going to be assigned a piece of the task, and we're responsible for that piece of the task in a real-time way - generating data, reviewing data, evaluating and deciding the next steps.

ED: What are the characteristics you'll identify for the people who are going to constitute that dream team? How do you identify the next Judah Folkman, or Dennis Slamon, for that matter?

DS: Success speaks well in and of itself, so it's nice to start with people who have a track record. That doesn't mean there aren't people out there with incredible ideas who could make a huge impact if they're brought into something like this. Identifying those people is a lot more difficult than identifying the people that have a track record. but we need to do both, and we need to do both well. The experts working in this area, in general, know all of the senior and junior people working on the problem. They're involved in the field day in and day out. They attend all the meetings. And they have a network of contacts and colleagues who tell them what's going on. So rather than information being 18 months or 24 months old, it may be 3 or 4 months old. That's getting a little closer to real time. There are plenty of successful people out there, but the big challenge is putting together the necessary puzzle pieces of expertise so that you have a picture you can look at. But I think that's eminently doable.

ED: What changes have happened for you professionally and personally since the development of Herceptin?

DS: You go from the outside to the inside pretty quickly if you're fortunate enough to be involved in a success like Herceptin. So the fact that it worked so well in metastatic disease, and ultimately in early disease, means that a lot more people believe our ideas than when we started in 1986. The problem is, we needed the help back then. not now. The drug could've been and should've been available to patients seven years before it was, and if it weren't for donor money, it would've been another five to seven years beyond that. We're talking about not having Herceptin until maybe 2008 or 2010.

ED: In 2001, on the cover of New York Magazine in an article about you, there was a quote claiming that there would be a global conquering of cancer within the next five to ten years. It doesn't sound like we're going to conquer cancer in the next two years or so. What's different now?

DS: A lot is different. First of all, I was very careful never to make a comment like that, and I was sort of shocked to see it. But that's what makes a headline. There has been

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some real progress, but not the kind that the public has come to expect based on what people have told them. There are a couple of things that are important to know. One, there won't be any silver bullet for cancer, because it isn't one disease. Even within the same organ system, it's multiple diseases, depending on what's broken. That brings us back to the hard work, which is figuring out what's broken and how to attack it. Whether we could do it in five years is saying a lot. Remember what has to happen. You have to find what's broken at the molecular level and figure out how to approach that, prove that approaching it makes an impact. Then it has to go to clinical trials. In clinical trials, now you're doing experimentation in human beings. But you have to execute those trials, and those take a long time to accrue. All we needed was 450 patients with HER-2-positive metastatic breast cancer. You'd think we could put that together in a couple of months, but it took us two years, in part because people didn't think it would work. Then there's the observation period where all the data mature. So you did your new therapeutic and you compared it to the best available standard therapeutics, and now you want to know, do the two curves diverge? The company, Genentech, predicted that the data would take four years to mature. I predicted that it would take two years. We were both wrong. In one year, the curve split apart. But still, add that twelve months on the two years it took to accrue and you're talking about three years. That's why we need teams that are equipped to do everything, with clinical people who understand how to design and execute clinical trials quickly; people who understand the right questions to ask in the laboratory; people who understand the clinical problems; and people who can recognize and critique the preclinical data. It has to work better than the way we're doing it now.

ED: So part of it is accelerating the process?

DS: Considerably accelerating the process, yes. There's often the ultimate reductionism of a question to its finest point in science, without someone backing up a little bit and saying, "How much more will learning about this pathway or the nth degree of this pathway give us?" That doesn't happen a lot in the camp that believes the best science will float to the top. Ultimate reductionism does get funded, many times. Because you know a lot about this pathway, you write your next grant proposal based on the information you have, and you keep drilling down until you drill through the well and hit dirt again. Is that going to pay off more than going out and finding a new well? We know a lot more about combination therapies than we did five years ago and eons more than we did ten years ago. All of that's exploitable now. It's just having the right people thinking about it and being incentivized to think about it. The other problem with cancer research is that in many respects, the incentives are misaligned. If you're an academic investigator you're competing with other academic investigators for grant funding and for publications, so you don't really collaborate. All science is based in some part on some collaborations, but it's not built on collaboration itself, which is what we're going to do with Stand Up to Cancer.

ED: You have a wife and two kids. You're traveling all over the world, you're curing cancer, caring for patients...how do you strike a balance?

DS: My wife and two kids would probably tell you not well, and there'd be a lot of truth

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to that. In the early days of the HER-2 story, I lived, slept, drank the science of that whole pathway. That's the kind of effort we're going to be looking for in Stand Up to Cancer. That doesn't mean you can't have somewhat of a normal life and do other things; you can and should. But we want people who are committed to fixing this problem. The public has been told for years that this effort's going to make a difference or that effort's going to make a difference. All of us involved in Stand Up to Cancer believe that this effort's going to make a difference, but we're willing to put some benchmarks on this. Will every one of our programs succeed? Of course not. But do we believe that some of them are going to succeed? Yes. And do we believe that the process will be accelerated considerably? Absolutely. So we want people who are committed, who are really going to make that effort, and we want this to be a big part of their lives. It's not simply a day job.

ED: For you, the next horizon is combination therapy.

DS: It's combination therapy, and it's how do we take the lessons we learned from the HER-2 story and apply it to other cancers? Not that it'll be the HER-2 chain or that it'll be Herceptin, but it'll be a separate gene or a separate pathway and another inhibitor of that gene or pathway. And to not make the mistakes we made in terms of the lag time of getting Herceptin to work, but actually reduce that considerably by having the right people at the table.

ED: How much did the Revlon part of development help? Is part of the slowdown in some of these areas a lack of a new infusion of funding?

DS: It's a huge part of it, and the Revlon funding, as I've said in the past, made all the difference in the world. Had we had to depend on federal funding to do this, we'd never have been able to get it done. The process by which grants are submitted, reviewed, approved and funded is incredibly long, and it reduces ideas to lowest common denominator approaches. Approaches that are innovative frequently don't get funded. They have to be vetted in a study section of a panel of twenty or twenty-five experts, all of whom have their own bias that they bring to the table, understandably. What they do is critique it: what's wrong with this, as well as what's right with it. Then they give you the critique back and probably 85% of the time say, "We don't have funding for this." So you rewrite it, take another three to six months, send it back, and then it takes another process of about twelve months to get it funded. Then you have to say what you're going to do. The monies are earmarked in different silos, and to move money out of Silo A and into Silo B if the data tell you to is like an act of Congress. You have to say at the beginning of the grant what you plan on doing over five years, and you can make a good guess, but the technology and the data may change considerably. While they say they allow for that, the reality is, they don't very easily.

ED: There are going to be certain critics who say the same thing about this. They'll ask, how can people who are outside of science dictate goals and direct study? Isn't this some sort of encroachment on the scientific process, to give lay people votes in determining what constitutes progress?

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DS: Progress is an objective thing. This isn't politics. Objective data is going to be the final arbiter of whether the approach worked. There are 4.77 billion dollars a year being spent by the National Cancer Institute on research being done in the traditional way. No one's saying disassemble that whole system. What we're saying is, here's a different model. What right do people have who are outside science? Well, they're funding the change. That gives them a lot of rights. And there are going to be objective parameters. There's going to be an advisory group of people of unchallengeable expertise who are going to be looking at what the output is of this science. They'll apply the quality assurance that the right science is getting done and that it's consistent with what the funders -- the people who are putting in their money or involved in raising money from the public -- are looking to do. And they certainly want good science that is credible and meaningful. But they want science that's likely to impact the disease, so they're going to direct the funding in that direction. We won't just fund good basic science and wait for the cream to float to the top. That isn't the right approach today.

ED: So SU2C supports a different sort of accountability than the NCI?

DS: It's a different sort of accountability in the sense that the money's being put up front and reviewed on the back end in terms of progress.

ED: We keep talking about curing cancer, curing cancer. What does curing cancer really mean?

DS: If we turn cancer into a chronic disease that's manageable, have we cured it? No, not any more than you "cure" hypertension. You treat hypertension, and if you successfully treat hypertension the patient may die, but they're going to die of something other than hypertension or the diseases related to hypertension. Does that constitute a cure? It constitutes an appropriate control of the disease so that it isn't what's life-ending. This sounds like dancing around the question, but it's not. Cancer is a real consequence of who and what we are biologically and what has to happen inside cells every time they divide. Can we make the perfect cell that will never make a mistake? Possibly, but we don't have the technology right now. Even when we do it in the laboratory in the best experimental setting, mistakes get made in the copy of genetic material. If you think about the number of cell divisions that need to occur in a human being's life, it's astronomical. A mistake only has to be made in one of those cells in the right gene and you're off to the races. So cancer is a consequence of being alive. Now the issue is, let's make it not a life-ending disease.

ED: So that's why the funding, the research, is still so important.

DS: Exactly. It's critically important. And there are things that we're going to learn from the research about how to prevent certain alterations. But to say that we're going to have a preventive strategy that means you'll never have cancer would be lying to the public.

ED: So what will be happening in five or ten years?

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DS: Five or ten years? I'd be disappointed if we didn't have really meaningful results in three years. There are diseases for which, today, the best available standard therapy is horrific in terms of outcomes. Pancreas cancer, ovarian cancer, lung cancer, some forms of prostate cancer, gastric cancer, some forms of colorectal cancer. We can do a lot better with those diseases than we currently do, and that's just to name a handful. If we are successful, if we raise enough funds to launch a series of "dream teams" as part of the Stand Up to Cancer initiative, and each of the teams approaches this in a Manhattan-Project-like approach where you have the right people sitting at the table, thinking together, the right kind of teams will make an impact. And there will be incredible cross-fertilization between teams. There will be real communication and real interaction about findings from Team A and how they might apply to Team B. Now, it's a new approach. I believe it's a very logical approach. I believe it's an approach that will work. The proof of the pudding is in the tasting. Let's get it launched and see what happens in twenty-four and thirty-six months in terms of the outcome and the output of what these teams will be. And everyone's going to be looking at it. It isn't going to slip under the radar screen, because there will be enough people saying, "You said there was going to be something different. Where's the beef?"

ED: So it's not five to ten years to curing cancer, it's five to ten years to having discernable impact.

DS: In five to ten years I think for sure we're going to have a discernable impact. Otherwise we'll have failed.

ED: So if and when this does work to a tangible degree, do you think that organizations like the NCI will take note? Do you think that this is a game changer? That people will understand that this as a model that should be applied elsewhere?

DS: Yes. I certainly think so, and I hope so. That doesn't mean that the NCI approach is ever going to go away. Nor should it go away. The idea of funding the best science and hoping that the cream will float to the top is not a bad idea. But putting all your eggs in that basket is probably a bad idea. When we proposed Stand Up to Cancer and the approach we're taking, not everybody was enthusiastic about it. There were many people from the orthodox scientific community who said you can't use this approach, it'll never pass the smell test, and my answer was, what passes the smell test is what works. And what the public wants, I believe, is what works. How we get there, as long as we do everything right scientifically, is less relevant to the public and more relative to the scientific bureaucracy. So I absolutely believe that this approach will work and that some federal money will get allocated to this kind of approach. Foundations and donor money are already being used this way, in large part, so they know something, obviously, that other people don't. And I can only go back to my own experience, my own story. If we hadn't had Revlon, the Entertainment Industry Foundation, Lilly Tartikoff and the Los Angeles community get behind us, I can assure you with a great deal of certainty that we'd never have been able to accomplish what we accomplished, and certainly not in the time we accomplished it. And that's what we want to do in Stand Up to Cancer.

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Eli Dansky, Editor of SU2C Magazine, was born and raised in and around Philly and graduated with a B.A. in Creative Writing from The New School in NYC. He lives and writes in Venice, CA.

\*\*\*\*\* [www.standup2cancer.org/magazine](http://www.standup2cancer.org/magazine)