



The Innovators

*Conversations
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**Interview with Dr. Alan D. Palkowitz
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Dr. Palkowitz currently has responsibility for Lilly Global Discovery Chemistry which includes research sites in Indianapolis, Spain, the United Kingdom, San Diego and China. His organization is accountable for the discovery of drug candidates targeting Cancer, Neurological, Cardiovascular and Metabolic Diseases. He has led several geography based initiatives aimed at globalization of discovery research. Dr. Palkowitz also serves on several executive oversight committees that set strategic direction for the company. Dr. Palkowitz is a co-author on numerous peer reviewed publications and is an inventor on more than fifty U.S. patents. He joined Eli Lilly in 1989. He received his B.S. from University of California at Berkeley, and his PhD in Synthetic Organic Chemistry from MIT.

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Interview conducted by Doug Berger, INNOVATE doug@innovate1st.com

Doug: Let's start by talking about how you and the researchers at Eli Lilly are framing up the challenges for the pharmaceutical industry.

Alan: Taking a high level view, I look at some of the very interesting contradictions associated with our industry right now. On the business side, we have many companies, including our own, facing major patent expirations with too few new medicines emerging from our pipelines. Consolidation of the industry through merger and acquisition is reducing the number of centers of pharmaceutical innovation. We are experiencing unprecedented pricing pressures. There are increasing regulatory and safety hurdles facing the approval of potential new medicines. Post-approval, more and more medicines are being called into question for safety issues, putting more scrutiny on the approval process itself. A question on many people's minds is, "What is it that the industry is providing?" and ultimately, "Is it going to be a good value proposition for payers and for patients?"

The other part of the contradiction is that recent decades have been a time of great scientific advancement. We know more about diseases than ever before. We're learning more about patients and the limitations of existing medicines. We also have an aging population that will live longer and create unique demands for innovative medicines.

As a company, we look at ourselves - we think about society - we are in the business of helping patients. Yet, our industry is not always trusted by patients.

A question we face is, "How does the future of drug discovery and delivering innovation to patients thrive in this climate and not become a lost casualty?"

Doug: With that in mind, where are the opportunities on which Lilly is focusing its innovation in how it goes about drug discovery and development?

Alan: I think of pharmaceutical innovation as the product of a strategy, rooted in deep scientific and medical expertise. It is also rooted in true patient need and in a business reality of what will be valued and rewarded. Our intentionality about medicine is that it dramatically improves patients' lives; that's what health care providers, payers, and patients themselves demand. If you work back from that, you have to ask yourself what's wrong with the pharma model. That really sets the stage for our current transformation.

Learning from the past, many companies were very successful by having one or multiple blockbusters that created unprecedented growth in the business, and unprecedented expectations then from investors. Success had to be replicated and growth continuously fueled. This coincided with the belief that the blockbuster approach could actually be scaled. The thinking was ... if you do more of what you did before, then you'll have greater output that will continue that pattern of unparalleled returns. There was also a belief that incrementalism for a marginally better medicine would be rewarded by payers and patients.

We found out that the opposite was true. We found that you cannot really scale the discoveries of the past by repeating similar processes again and again. We also experienced a backlash against marginal improvement over existing therapies, all of which are destined to be generic.

My personal view is that the industry went too far in taking a scientific discovery paradigm and turning it into an engineering process. Granted, technological tools and optimization of certain processes have driven out much inefficiency. However, we forgot that blockbusters didn't come from a linear process. True observations that lead to breakthroughs come from having the time to step back, ask questions and look at things in a very critical way, beyond what the technology may put in front of us. Drug discovery is hypothesis driven, with many starts and stops. In fact, predicting outcomes is very difficult. There are multiple examples of medicines that were intended for one utility and found application in another. When you have a reliance on technology and process, you can miss the things that are at the true heart of serendipity.

Doug: How are you rethinking the basics for drug discovery at Lilly?

Alan: Our bet is on innovation and the long term. We believe our challenges will not be solved by short term fixes, but leveraging our best resource, our people, to keep focused on improving outcomes for individual patients, create well defined scientific questions and broadly partner with scientists globally to bring together diverse ideas and solutions. This needs to be done in a way that reaffirms the value proposition for what we do and the trust of patients through business integrity.

Allow me to go into more detail on a couple of these points. The first part of pharma reinvention is to have a focus on patients and on improving the value proposition for

patients from day one. When we now come up with a new hypothesis, we're really thinking about how the patient will benefit. At Lilly, we are making it a strategic intent to pursue tailored therapies. Instead of thinking very broadly about a disease, we are asking, "Is there a way to optimize drug discovery for a particular subset of patients that are most likely to respond?" If successful, we will be giving the right medicine to the right patient. We will not be broadly exposing patients to medicines that are ineffective, and may in fact cause them harm. To accomplish this, we not only need the tailored therapy, but diagnostic tools to identify the appropriate patients for the medicine.

There are a number of ways that this can be approached. For example, if we were developing a medicine for treatment of cancer, and we knew through our studies that one particular cell type associated with the cancer would more likely respond to a potential medicine than another, we would design a treatment based on the cancer cell type of that patient. The patient benefits and the payer's money goes to the right medication. In aggregate, you can see the potential for creating a better value proposition for each healthcare dollar.

Doug: There are things therefore, that the industry used to do late in the process to hone the match between a drug and a patient, for which you are now aiming up front. In addition, the old paradigm assumed a one size fits all match between disease and medicine, which science now understands to be false, as a disease state is not amenable to one solution.

Alan: You're exactly right. There are unique characteristics within subsets of patients. This is what we're trying to exploit in developing tailored therapies. There's an emerging discipline called translational science and medicine that compliments the traditional disciplines of drug discovery which include medicinal chemistry, disease biology, drug disposition and toxicology. At the core of this discipline, is the development of tools such as biomarkers and leveraging of clinical samples and patient genetics to allow tailored therapies to become a reality.

This leads to another change in our thinking. Right now, Lilly is at the forefront of being able to discover and develop both small molecules and large molecules such as therapeutic proteins and antibodies. We are expanding the range of molecules which can be considered as potential medicines. Having this capability will allow us to develop the best outcome for a spectrum of patients in given disease areas. This isn't new for our company, but it is something that has become more intentional in recent years with a series of strategic decisions and investments.

Doug: Let's come back to how you are redefining the role of technology in drug discovery. You were discussing that the heart of drug discovery is still a human, creative endeavor. Technology in your view isn't going to give us all of the answers, but is going to enable discovery to be more productive.

Alan: We can't lose the ability to do the critical hypothesis-driven work. We need to encourage experiments that probe the true heart of the important questions. We have to put technology in its proper place. It's the human technology that will make the difference. That's where we need to take ourselves. If we're going to do all of these great things and really improve the value proposition for patients, we have to focus on the development of scientific talent, our human capital, in addition to having key technologies available.

It is important for scientists, as they go through their careers, to always be open to reinvention. We all need to evolve our approaches in response to changes around us.

We need to be able to adapt and learn from the advancements of science and incorporate that effectively into our thinking. To do that you can never stop being a student.

Doug: You have been overturning some industry orthodoxies. Discovery is not scalable. Disease states are not a single, general condition. Move patient outcomes from late in drug development to the front end of discovery. Technology doesn't provide all of the answers. The singular importance of human creativity. What is the next aspect to introduce?

Alan: Lilly has decided to move away from being a fully integrated pharmaceutical company to becoming a fully integrated pharmaceutical network. When we look at a disease problem, we're going to bring the best ideas to the table in order to provide solutions, no longer just relying on our own history and our own scientific bias. The heart of this open approach is really finding the independent centers of creativity, diverse thought and scientific perspective that can then complement what we have internally. That really takes drug discovery to a higher plain. We are experimenting with new ways of doing collaboration and exploring new business models. Our aim is not just to create value for Lilly, but to create unique value for those with whom we are interacting.

One effort that we recently initiated is PD². The intent is to tap into academic centers and small biotech startups that may have interesting molecules with potential as therapeutics. Historically, working with outside groups requires the establishment of up-front financial terms before any work is initiated. We basically had to come to the table with money in order to get started, often times before the true value of their work had been established. Interestingly, most of these groups don't have access to reliable biological assay systems or drug discovery experience and resources to evaluate their compounds in order to drive decision making. With PD², Lilly is closing this gap by providing access to a number of key assays and associated data, free of charge. These are the same assays that we developed and internally use for drug discovery. If there are interesting findings worthy of further pursuit, then we have a first right of negotiated access to the molecules or establishment of a collaboration agreement with the investigator. So, initially, our transactional currency is data - data which helps a researcher validate their hypotheses around molecules and reveal potential value. Now, we can work with that investigator to help develop their science by combining their perspective and insights with our experience. Perhaps then we will create a compound to take into clinical trials. In this way it provides a mechanism to advance discovery.

This is a very appealing and scalable proposition. We launched this initiative June 2009, and we've been overwhelmed with the positive response that we have received thus far. We currently have 109 affiliations across 17 countries, all of whom are submitting compounds that they've discovered in their laboratories. Furthermore, these investigators have their own network of collaborators that enriches our own. Through this exchange, we're aiming to have an unfiltered mechanism for ideas and molecules as a starting point for new medicines.

Doug: Open innovation is a very broad platform. How are you signaling your areas of interest to the research community?

Alan: As an example, for PD² we created a panel of assays that align with our areas of therapeutic interest including Alzheimer's, cancer, diabetes and osteoporosis. Through our website, the investigator has full knowledge of this information and our intent to welcome collaboration. What we are seeing are the ways in which investigators are

developing hypotheses and designing molecules to specifically test against those assay systems.

Doug: Venturing into a new area, I would imagine that the daily routines of the Lilly scientists and technicians are changing significantly.

Alan: Absolutely right.

Doug: I'm interested in two aspects. 1) What are the actual differences in the daily life of a scientist from a few years ago? 2) At a leadership level, what have been the few key things that Lilly has done to operationalize the paradigm shift into daily life?

Alan: You need individuals like our CEO, John Lechleiter. He began his career as a scientist at Lilly and is able to create and communicate a compelling vision that goes beyond business dimensions and speaks to the core importance of scientific innovation for our future. Our scientists are an integral part of the strategic equation and execution. They believe in the direction in which we're heading. You also have to create a mechanism for recognizing those behaviors and scientists for being pioneers. You have to set them apart as a model for your future scientists.

For many employees, the things that we're doing, especially our work with the outside world, are a significant change of life. There is a mix of laboratory work, but there is also considerable daily interaction with investigators with whom we work as part of this expanded network. It's a much more diversified type of activity versus coming into work and spending all day exclusively in the laboratory.

Doug: It's much more of a social interaction type of science.

Alan: The whole concept of time zones has created a challenge for us, as we have partnerships in different parts of the world. You have scientists who get up very early to participate in a teleconference before coming to work. When you start working in a more disaggregated, networked way however, it can create insecurity. People start thinking, "Maybe I'm not important anymore." Over time however, we have seen employees focusing on things that cannot be effectively done externally because of either available expertise or options for cost-shifting. They're adding higher and higher intrinsic value and challenging themselves to provide the greatest scientific impact to their work.

Doug: If we go back a few years when this was in its formative stages, how did you begin to populate your scientific community with these new ways of thinking and working?

Alan: If we use the PD² as a model, I really believed in and championed the idea. I knew my organization, and I went to people who I felt were of a similar mindset, had the entrepreneurial spirit and were interested in testing the boundaries of what we do. We sat down together. We drew up some concepts and ideas. Then, I was able to transfer those concepts into their hands and let their own creativity begin to further develop and put them into action. I had to be there with them, to own the challenges and actually work through problems. There is a process of validation and recognition that actually reinforces behavior. We not only looked for internal validation, but we also tested it with external individuals who would actually be potential customers and collaborators. But, you've got to make sure that as you move forward you're not going off over a cliff; that you're actually going somewhere that's going to be productive.

Once you begin to make something real, then other people begin to become a part of it, support it, and take ownership for putting a new initiative in play. When others begin to see that, you realize that you've moved into a new way of operating that can open up doors you never anticipated. You begin to see additional dimensions. You see others in the organization that come to you, look at what you've done and say, "Wow, do you realize what you're doing? You're basically putting a Lilly laboratory on potentially every street corner of the world by making this available." That process of reinforcement really gives you motivation to move forward.

