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Oncologist, Business Leader, and Investor Arie S. Belldegrun Discusses a Career in Innovative Medical Entrepreneurship

A Conversation with Ken Herrmann and Johannes Czernin

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Ken Herrmann, MD, MBA, from the Universitätsklinikum Essen (Germany), and Johannes Czernin, MD, from the David Geffen School of Medicine at UCLA, talked with Arie Belldegrun, MD, about his career as a physician and medical entrepreneur. Belldegrun holds the Roy and Carol Doumani Chair in Urologic Oncology and is founder and director of the UCLA Institute of Urologic Oncology at the David Geffen School of Medicine there. He is also the chair of Bellco Capital and cofounder and senior managing director of Vida Ventures, a life science venture group with offices in Boston, MA, and Los Angeles, CA. He is also the executive chair and cofounder of Allogene Therapeutics, a clinical-stage biotechnology company pioneering the development of allogeneic chimeric antigen receptor T-cell (CAR-T) products for cancer and autoimmune disease.

Dr. Belldegrun has had a distinguished tenure in the life sciences, having been closely involved with the founding and advancement of several successful biopharmaceutical companies, including Cougar Biotechnology and Agensys. Abiraterone (Zytiga), developed by Cougar, is a mainstay of therapy for patients with metastatic prostate cancer. He has authored several books on oncology and more than 500 scientific articles related to urologic cancers, immunotherapies, gene therapy, and cancer vaccines. He founded Kite Pharma, a biopharmaceutical company developing immunotherapies, where he served as chair, president, and chief executive officer (CEO) until the acquisition of Kite by Gilead Sciences in October 2017. He currently serves as chair of Two River, UroGen Pharma, and Kronos Bio, as cochair of Breakthrough Properties and Symbiotic Capital, and as director at ByHeart and Ginkgo Bioworks.

Dr. Herrmann: *Arie, please tell us about your career and your personal pathway from medical school to clinician to starting and running major pharmaceutical companies.*

Dr. Belldegrun: I came to the United States in 1982 to join the residency program in surgery/urology at Harvard Medical School and the Brigham and Women's Hospital. This was a rigorous training program, spending days and nights in the operating room with a load of patient responsibilities across 3 major hospitals in the Boston area. After graduating from the program and completing my board certification, I took the advice of my department chair to enter a fellowship program at the surgery branch of the National Institutes of Health (NIH)/National Cancer Institute, under the leadership of another Brigham alum, Steven A. Rosenberg, MD, PhD. It was the best advice I ever received. I was fortunate to experience the most transformative 3 years of my early career and happened to be at the right place at the right time to be part of the birth of modern immunotherapy. I also mastered the art of translating innovative science to medicines that have the potential to change patients' lives, something I carry with me to this day.

Arie Belldegrun, MD

The principles that Rosenberg instilled in me were instrumental in establishing my own research and clinical trials at UCLA. They also gave me an understanding of the opportunities in translational medicine. Six years after joining the faculty at UCLA and after being promoted to full professor, I gradually expanded my interests to biotechnology and entrepreneurship.

Dr. Czernin: *When did your love for research actually begin?*

Dr. Belldegrun: My interest in research started during medical school at Hebrew University in Jerusalem while being involved in a project investigating the mechanism of organ graft rejection. After graduating from medical school, I decided to further my research experience by applying for a PhD program in immunology at the Weizmann Institute of Science in Israel.

Dr. Czernin: *When you joined Weizmann, did you already have an idea of why you wanted to do immunology?*

Dr. Belldegrun: From early on I was intrigued with the immune system and its ability to perform so many diverse functions—fighting inflammation, controlling cancer, inducing tolerance and rejection, autoimmunity, and more. I kept reading all that was known in those days but had no hands-on research experience. I then met Irun R. Cohen, MD, a brilliant scientist at Weizmann, who excited me with the novel experimental models he developed to study the basic mechanisms and functions of the immune system. I joined his laboratory to pursue a PhD in immunology. These were wonderful and very productive years. A decade later, on joining the UCLA faculty as an assistant professor, I finally got to establish my own independent laboratory at the UCLA Cancer Center, eager to focus my studies on kidney and prostate cancers as models for cancer immunotherapy and cancer gene therapy.

Dr. Herrmann: *What was your first entrepreneurial activity, and how did academia prepare you for this?*

Dr. Belldegrun: The first company I founded was Agensys (previously called Urogenesys), established in 1996 and dedicated to genomics, bioinformatics, and antibody drug discovery. We were successful in generating a panel of antibodies against 22 targets expressed on a variety of cancer types. One of the early targets,

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discovered in 2001, was nectin-4, resulting in the construction and development of an antibody–drug conjugate (ADC) against it, in collaboration with Seattle Genetics (Seagen). Today, the drug we generated is known as enfortumab (Padcev), acquired in 2007 by Astellas and now part of the newly acquired portfolio of Pfizer.

As previously discussed, my experience as a physician/scientist at UCLA, coupled with my training at NIH under Dr. Rosenberg, served me well in founding Agensys and advancing our goal of translating innovative discovery science to medicines. Being at UCLA allowed me to interact with bright scientific leaders, such as Owen Witte, MD, James S. Economou, MD, PhD, Charles L. Sawyers, MD, and Antoni Ribas, MD, PhD, who later agreed to join me in pursuing my various entrepreneurial ventures.

Dr. Czernin: *How did you manage to organize your time between academia and the off-campus industry work?*

Dr. Belldegrun: It was a constant struggle between my activities as a physician (taking care of patients, spending time in the operating room, running an active research lab) and driving to Santa Monica, where Agensys, Cougar, or Kite were all located. It's important to note that these activities were always fully disclosed to and approved by UCLA. Their understanding of and support for my entrepreneurial ventures resulted in my continued involvement at UCLA to this day. In 2010, a year after founding Kite Pharma, I concluded that the development of CAR-T research deserved extra effort and more of my time, so I requested and was granted a 1-year sabbatical to serve as the company's chair and CEO. It was a transformative time and turned out to be essential for the success of the company and a great win for patients. Again, it was never easy, but I'm happy that it worked out—mainly because I never wanted to leave academia. It is a source of special satisfaction to see that my colleagues and venture partners, Drs. Witte, Economou, and Ribas—all involved with our companies—continue to serve as esteemed faculty members at UCLA and contribute from their vast experience in both worlds.

Dr. Herrmann: *As nuclear medicine physicians, we're interested in theranostics and what are now called radiopharmaceutical therapies. When did you first take notice of theranostics? How do you see the field, and what can we learn for the future?*

Dr. Belldegrun: My interest in theranostics, as Johannes knows, goes back almost 20 years, and I was always a believer in the space! I initiated a multidisciplinary weekly conference in genitourinary oncology at UCLA, involving medical oncology, nuclear medicine, urology, radiology, and radiation oncology. Nuclear medicine was always an integral part of the case presentations, films reviewed, and therapeutic options discussed. We all had the opportunity to be part of progress in the theranostics space. With my personal interest in kidney cancer, we even took an early look in both the lab and the clinic at carbon anhydrase IX as a nuclear imaging agent for kidney cancer and as a potential theranostic agent as well. My lab continued to search for additional agents for use as specific markers for cancer diagnosis and antibody-based therapeutic approaches, including those in the radiopharmaceutical space, similar and parallel to getting involved in the field of ADC.

Johannes, you have contributed tremendously to our appreciation of the theranostics field. I do recall our many conversations on the opportunities in the field, and we all benefited from your bright young fellows and postdocs who used to present their investigative work at Tumor Board, keeping us apprised of the new momentum in the field. It became clear to me that the key to success in the theranostics space is target identification and validation, in addition to the need for a reliable supply chain source. We even entertained between ourselves the idea of starting a company, but my increased involvement in Kite Pharma did not make it possible. Focus is the key, and that's my message for the future: believing in good science and following your own convictions, even if they are at times not popular. That was the case at Kite, where we believed in engineering the patient's own immune system to fight cancer. It was very unpopular in the beginning. By 2014, we had about 20 employees at Kite in Santa Monica. After a successful IPO, we used the majority of the proceeds to build in Los Angeles the first-ever manufacturing facility for cell therapy. It turned out to be key for our success. Today, Kite/Gilead has more than 4,000 employees globally, with sales exceeding $2.5 billion and, most important, life-changing therapy for many patients. I believe that theranostics will follow such a path very soon. It's already one of the hottest emerging technologies out there. Large pharma has clearly taken notice of the opportunity in the space. And I am so pleased to see that both of you are at the center of it all. Well deserved!

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Dr. Czernin: *Most if not all cancer therapies are combination therapies. What do you think about the need for developing combination therapies using radiopharmaceutical therapies as the backbone?*

Dr. Belldegrun: Clearly there will be a need for combination therapy. A single modality will not work in advanced and high-volume cancers. However, single-agent therapy is where one should start, to prove to the regulatory agencies the effectiveness of the agent used. Combination therapies will follow, based on rational design and following the science. I can see multiple avenues for combination therapies in this space.

Dr. Herrmann: *You mentioned the success of theranostics, as also indicated in recent acquisitions, such as that of RayzeBio by Bristol Myers Squibb for around $4 billion. Is the market perhaps a little overheated right now?*

Dr. Belldegrun: I would characterize it as a heated market but not yet overheated. Novartis was the first company to believe in the space and changed market perceptions about theranostics. Since then, a whole host of major pharma companies joined the party: Eli Lilly, Novartis, AstraZeneca, and Bristol Myers Squibb, among others. We need more innovative data to be convinced that more patients are benefiting, the field is maturing, and investment in infrastructure and supply chain are justified.

Dr. Czernin: *Certain risks are, of course, inherent. It is a complicated business model with many pitfalls, as history has already shown.*

Dr. Belldegrun: I agree with you, but I'm looking at what I know and have personally experienced: cell therapy. Only 10 years ago very few, if any, companies had interest in the space. Once we and others started demonstrating convincing data, the market rapidly changed. Convincing data in patients with diffuse large cell lymphoma and leukemia changed the market perception. Large pharma then followed: Novartis, Bristol Myers Squibb, Johnson & Johnson, Gilead, etc. I don't think that radiopharmaceutical therapies are more complicated or more risky. They all have challenges. It's all complicated initially, but then the next generation follows, and it gets easier and hopefully cheaper. I can see the same story here as I've seen in the evolution of cell therapy.

Dr. Herrmann: *You mentioned that targets are the key. The intellectual property associated with targets is difficult to protect. You can protect the ligand, but you cannot protect the target. This carries a certain risk. Also, a lot of the targets that are interesting for us are also interesting for ADCs. How do you see the relationship between theranostics and the ADC market?*

Dr. Belldegrun: I mentioned earlier the target nectin-4 and our ADC construct, enfortumab. Today, 20 years later, enfortumab is showing dramatic responses as first-line therapy for patients with metastatic bladder cancer when combined with a checkpoint inhibitor. There is a place for the combination therapy of the 2 modalities. Furthermore, the same target can be developed for theranostics. In fact, one of our portfolio companies at Vida Ventures, Aktis, is currently developing a differentiated theranostic approach using nectin-4. So the same target can serve both modalities. The mechanism of action for each is different, but these may even be synergistic.

The pharma world wants to deal with validated targets. I agree that this is a major bottleneck for the space, as it is also an issue for targeted immunotherapies. Once a target has been validated, it opens multiple opportunities for other approaches based on the same target to be developed.

Dr. Czernin: *We talked about the past and the present. What are you going to do in the future?*

Dr. Belldegrun: I don't know exactly, but at present I am quite busy and continue to be highly excited by the multiple opportunities in the life science space. This is the best of times to take part in the innovation and scientific revolution that is happening all around. While I am very involved in the business of science, I continue to be devoted to the academic world and contribute my best whenever I can. I am currently spending time, as cofounder and board member, on the creation of a megaproject, the California Institute of Immunology and Immunotherapy, affiliated with UCLA. It is a jewel that will transform Los Angeles into a biopharma powerhouse—nothing like it in California or anywhere else.

On the entrepreneurial side, our Bellco Capital ecosystem is currently creating new biotech startups (through Two River), investing in a host of other biotech companies (through Vida Ventures), lending money to more advanced life science companies (Symbiotic Capital), and collaboratively building life science campuses and providing state-of-the-art spaces for scientists and manufacturing (via Breakthrough Properties). We have offices now in Boston, New York, and Los Angeles, with a full team of people who are evaluating potential investments in companies in different stages: early, mid, mezzanine, pre-IPO, or IPO. We also have a Life Science and Venture Capital fellowship program for PhDs, MDs, and MD/PhDs from Harvard, MIT, Caltech, UCLA, and elsewhere who want to jump into venture immediately after earning their degrees. The fellowship program is 3–6 months, and participants commit to 20 hours per week to be with us at the venture company and be at the center of investment activities.

Dr. Herrmann: *This is a fantastic program, but it also illustrates a problem: some of the smartest people don't go into academia anymore. After the PhD, they leave, because the venture space is exciting and also has a huge financial upside. What can academia do on the other side to make sure that we don't have this brain drain to industry?*

Dr. Belldegrun: You are correct, but the world around us is constantly changing, and we must change as well. We cannot continue with the same old model. To prevent brain drain we must educate the next generation differently, provide them with knowledge about all the opportunities available, and tailor our education efforts to their talents and interests.

Scientists should also be aware today of the business of science and how they can capitalize on the amazing opportunities available to them. This will draw a better caliber of talent to engage in science and discoveries. The same goes for physicians, who should be aware of the great science and clinical drug development happening in biotech and pharma. The road I took was much longer, with many more years of training as a scientist and as a physician, but in hindsight I wouldn't do it any other way. What is engrained in me today after all these years of training is the deep commitment to help patients. The most important question I have at the back of my mind, every time that I have a business deal, is, "Is it good for the patient or not?" If it's good for the patient, and there is a clear path for clinical development, I am happy to spend more time to evaluate the opportunity. That's how I started Cougar, Kite, and several other companies.

Dr. Czernin: *Usually we ask our interviewee for advice for the next generation. What would you say?*

Dr. Belldegrun: I am blessed today that I can do what I like to do. Without academia and without the entrepreneurial spirit that I found at UCLA, this would not have been possible. Consider doing it the same way. I would not want to have done it in any other way.