Leadership Focus on Advancing Cancer Research and Treatment

A Conversation Between Johannes Czernin, Caius Radu, and Antoni Ribas

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Johannes Czernin, MD, editor-in-chief of *The Journal of Nuclear Medicine*, and Caius Radu, MD, PhD, a professor of Molecular and Medical Pharmacology at the University of California Los Angeles (UCLA), talked with Antoni Ribas, MD, PhD. Dr. Ribas is a professor of Medicine, Surgery, and Molecular and Medical Pharmacology and director of the Parker Institute for Cancer Immunotherapy Center at UCLA. He is also director of the UCLA Jonsson Comprehensive Cancer Center Tumor Immunology Program. He is the president of the American Association for Cancer Research.

He earned his medical and doctoral degrees from the University of Barcelona (Spain). He completed internship and residency at the Hospital Vall d'Hebron (Barcelona) and postdoctoral fellowships in surgical oncology and a clinical fellowship in hematology/oncology at the UCLA David Geffen School of Medicine. From 2001 to 2010, Dr. Ribas was the assistant director for Clinical Programs at the UCLA Human Gene Medicine Program and led the Jonsson Cancer Center's Cell and Gene Therapy Core Facility from 2004 to 2010. He also co-led the Stand Up to Cancer Cancer Research Institute–AACR Immunotherapy Dream Team with Nobel Laureate James Allison, PhD.

His research has focused on the use of immunotherapy to treat melanoma. He led the clinical program that demonstrated the effectiveness of the immunotherapeutic pembrolizumab (Keytruda), a significant advance in treatment of melanoma and other malignancies. Recent work includes laboratory and clinical translational research in adoptive cell transfer therapy with T-cell receptor engineered lymphocytes; examining the antitumor activity of PD1-blocking antibodies; testing novel targeted therapies blocking oncogenic events in melanoma; and studying primary and acquired resistance to melanoma therapies. Dr. Ribas and his laboratory team use molecular imaging technologies to investigate the mechanisms of novel immunotherapies.

Dr. Czernin: Thank you for taking the time to talk to us. What inspired you to become a translational cancer researcher?

Dr. Ribas: I finished my clinical training as a medical oncologist in Spain in the mid-1990s. At that time, all we could do was to give chemotherapy. This worked in some patients but not in many others, and it was toxic. I did not think it was a good idea to spend the next years giving these drugs to patients without deeper knowledge. I wrote letters to various labs in the United States that pursued gene therapy and immunotherapy for cancer. My colleagues in Barcelona told me I was crazy and that this had no future. How could the immune system treat cancer? When I joined UCLA, I worked with Jim Economou, MD, PhD, who tried exactly that. I interacted with Michael Phelps, PhD, Owen Witte, MD, and Harvey Herschman, PhD, who taught me to understand the process and turn it into a therapeutic. To me, the term "translational medicine" makes a lot of sense, because if you want to treat cancer successfully you have to understand the cause and what is happening.

Antoni Ribas, MD, PhD

Dr. Radu: What was a defining moment in your career when you reached a crossroads and made a decision that brought you to where you are right now?

Dr. Ribas: After 2 years as a postdoc with Jim Economou the easy thing would have been to return to Spain. However, we were doing these interesting things, like making dendritic cells and giving them to mice where there was benefit. There was also anecdotal evidence of benefit in humans. The potential of doing something that was completely academic in a clinical trial was exciting. This helped me later to understand how things could be translated into the clinic. I decided to become a melanoma expert, understand the disease, and then apply approaches that were science based, including immunotherapy. There was a real clinical need, because radiation and chemotherapy had limited-to-no benefit in this cancer. Surgery was the only option for a cure but only for early-stage disease. It was a wide-open field where anything new that made sense could be used. That is when the BRAF mutation was discovered, and I had the benefit of seeing first-hand the work of Charles Sawyers, MD, in translating the concept of inhibiting driver mutations with drugs like Gleevec. I thought that when people made drugs targeting BRAF I wanted to be there to give them to patients. I have always focused on things that I thought had a good chance to work in patients. I have little patience for continuing with treatments that are not working. For example, when I concluded that dendritic cells were not working for the majority of patients, that was it. Even if I had grants, I would not do more experiments.

Dr. Radu: You already mentioned people with whom you interacted and by whom you were influenced. Are there other people who inspired you?

Dr. Ribas: I would go back to the names I mentioned already and would add John Glaspy, MD, my clinical mentor. These are inspirational people with whom I was lucky to be associated. Fifteen years

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ago, David Baltimore, PhD, put T-cell receptor genes into hematopoietic stem cells, and he wanted to work with someone who could do this in humans. This project also gave us the opportunity to do what Sam Gambhir, MD, PhD, had pioneered with Dr. Herschman, putting reporter genes into cells and then tracking them in people with a PET scanner. We did that and acquired these incredible images that helped us develop new therapies and understand how they work.

Dr. Czernin: Tell us a little bit about the history of chimeric T-cell receptor studies.

Dr. Ribas: The early clinical trials with engineered T cells demonstrated that if we gave enough T cells that have a receptor that recognizes a cancer antigen, we could get regressions of melanoma and synovial sarcomas. These cancers are now considered treatable. At that time, they were not treatable. In parallel, Arie Belldegrun, MD, set up a company to develop immunotherapies. I thought that redirecting T cells to a surface marker would empower T cells, for example, to treat incurable lymphoma that progressed after prior therapies. We were creating these modified T cells in our GMP facility, which helped with translation. Then we talked about commercialization, and this was the start of Kite Pharma, which became a great success story.

Dr. Czernin: What is your vision of the most appropriate and efficient industry–academia relationships? Do you have a model in mind or is it just simplifying the processes? What is the future there?

Dr. Ribas: I think molecular imaging has much to give that we have not yet realized. We do not need to image every treatment, every time. We just need to understand what the treatments do. Where does the drug go? Visualizing CD8+ T cells together with Anna Wu, PhD, using immuno-PET imaging has been among the most exciting things I have done in my career. It is a key to understanding all immunotherapy for cancer. It took her several years, and now we see the images in humans and can track T cells as they invade the tumor.

Dr. Radu: As I think back to many meetings and discussions, you have always emphasized that one must understand not only what the immune system does but also what happens in tumor cells. Sometimes we focus too much on one part or the other and lose sight of how immunotherapies impact the dynamic interplay between cancer cells and immune cells. What made you think along these lines in the first place?

Dr. Ribas: So much knowledge about how cancers grow and how they interact with their microenvironment has been generated, and we learned how one could use molecular biology to understand how cancers change and adapt to therapies. In addition, when we started seeing acquired resistance to immunotherapy, we knew we had to study cancer cells themselves. We knew we had to study what genes and which signal transduction networks had changed to allow the cancer to become resistant to immunotherapy.

"The biggest difference in the last few years has been that we no longer look at 1 gene at a time when we do an experiment; many times we look at all the genes. Every time we do something, we tend to allocate less time for the actual experiment and a lot longer for analyzing and interpreting the data."

Dr. Ribas: Our job is to develop things that work. Financial investments are needed to change medical practice and improve patients' lives. There is no way this can be done with academic grants alone. If the idea is good, people are willing to invest in it. This then becomes what we call a company. However, it is also an extension of our work. I think the academic field must embrace entrepreneurship. It is something we should not be ashamed of. Let us make things clear: we are trying to develop things that work, and someone must invest enough money to help develop that clinically. There is nothing wrong with that. We need to be open. We disclose and are honest about the goals. I think this is a process that should be celebrated, cherished, and supported as opposed to being hidden or talked down.

Dr. Czernin: Do you think that the current academic environment nationally and internationally is supportive of that concept?

Dr. Ribas: There must be checks and balances. But I do not think these interactions and collaborations should be discouraged. When there is a success, everyone jumps on it, yet you have people who frown on these relationships or talk behind others' backs. Success should mean that we develop effective therapies that help people. The NIH has always had a policy that its funds should create new knowledge. You disclose the funds that make it happen, and this becomes a patent. Then the investigator can develop the intellectual property with no strings attached. This concept has been perhaps the biggest source of new ideas and drugs that help people—more than any other funding. It has amplified and leveraged the money invested by the NIH in a logarithmic scale with benefit to many people.

Dr. Radu: Back to molecular imaging. You were one of the early adopters. What do you think about the status and future of molecular imaging? Where do you see it going?

Dr. Czernin: This leads to the question of combination therapies. What is your view of accelerating the application of rational combination therapies in cancer?

Dr. Ribas: It is rather naïve to think that in complex processes like cancer a single drug could treat a significant number of cancers successfully. We have to start somewhere, and then we need to understand how the cancers respond or escape from the treatment. We need to develop combination treatments. Cancer tries to escape in many ways. Our best options are upfront combination therapies. The cancers that are not being treated successfully with current therapies need to be tested for the effects of 3 or 4 drug combinations if this can be done safely at therapeutic levels. Our goal is to cure cancer.

Dr. Radu: I take it you don't buy into the view that one can convert the remaining most challenging types of solid tumors into some type of chronic disease that can be managed?

Dr. Ribas: When we did not have good treatments for melanoma, people were saying, "Oh, well, let us try to get people to live 2 or 3 months longer." That changed when we started seeing that we can get these metastatic cancers to respond for years. I would not want to lower the bar to say that we will turn cancer into a chronic disease. My aim will continue to be to make metastatic cancer disappear, because we understand the vulnerabilities of the cancer and we really hit it hard. These standards have led to some people with diseases that were once a death sentence going on to live normal lives. This remains the unchanged goal.

Dr. Czernin: There is a lot of excitement about the new vaccination approaches, particularly in light of the COVID pandemic. Is there any potential translation into cancer therapies?

Dr. Ribas: Let us start with the opposite, which is the reason we had these mRNA vaccines available for COVID-19 so rapidly. They

were developed as mRNA vaccines for mutational antigens that differentiate cancer cells from normal cells to make a vaccine that would tell the immune system to target them. To do this, the developers needed a sufficiently versatile platform to move from the sequencing of the tumor to vaccinating a person in as little as 2 months. Within 2 months of having the sequence of the COVID-19 virus, 2 companies were already doing vaccine trials in humans. That's because the platform existed. The process of sequencing and making that RNA vaccine was not that different for a virus for cancer. For cancer, the problem is that it keeps growing and establishes metastases that have a whole different set of issues. We will have to see whether those vaccines are powerful enough to treat them.

Dr. Radu: In your lab, what has changed over the last decade in how people are approaching research? What would be your advice to researchers in training? What should they focus on and why?

Dr. Ribas: The biggest difference in the last few years has been that we no longer look at 1 gene at a time when we do an experiment; many times we look at all the genes. Every time we do something, we tend to allocate less time for the actual experiment and a lot longer for analyzing and interpreting the data. The number of people in my lab who are experts in bioinformatics keeps increasing, and the ones who are not admit that these skills are needed. With CRISPR screens, we are now doing experiments genome wide, which was unthinkable not that long ago. And we are learning a lot because now we can study multiple targets in a single experiment.

Dr. Radu: Are there any downsides in generating massive datasets with so many potential correlations or emerging hypotheses? What advice would you give a young scientist about dealing with and managing big data?

Dr. Ribas: The NIH grants review dogma of focusing on a system that you control completely and then interrogate only 1 thing is no longer the goal. On the other hand, fishing expeditions leading to uninterpretable data are also a bad idea. There is an approach between these, however, where you develop and incorporate new techniques that give high-throughput data but you know what you are looking for. You know why you did the experiment and then are interpreting the results based on your understanding of that biologic system.

Dr. Czernin: What are your goals as president of the AACR, and what is its current mission?

Dr. Ribas: The AACR is the oldest and largest cancer research association in the world, and it is an honor to serve as its president. The goal is to improve the life of all people with cancer. I assumed this leadership position when we were in the pandemic lockdown, when I was chair of the organizing committee of an annual meeting with close to 30,000 people registered. We converted the meeting to a virtual format at a time when there was no existing platform for large virtual meetings. We owed it to scientists who had sent their best work for oral and poster presentations. So, in an incredibly short time, the professionals at the AACR got it done and we held 2 virtual meetings. We had close to 100,000 people who attended remotely. It became the most attended medical conference ever.

Then we had the tragic deaths of George Floyd, Breonna Taylor, Ahmaud Arbery, and others. It shocked us to see that there can be so much ongoing racism in society—that our colleagues who are Black Americans struggled because they know that racism is part of their lives and that many people see them as Black before they see them as cancer researchers, clinicians, entrepreneurs, nurses, or health care workers. We had to speak up. It does not matter that some people do not agree that a cancer organization should speak up against racism. It's the right thing to do. All disparities, including health care disparities, need to be addressed. We are developing therapies that work but are very expensive. Our job is to make them available to everyone.

Dr. Radu: Can you comment on what the focus of young people who embark on a career in translational science should be?

Dr. Ribas: My father was a professor and chair of Medicine in Barcelona. He had trained in Germany and Switzerland and in the United States when he was young. He always went back to Spain because he wanted to build his department there. When I was growing up and became a physician, he taught me that it was most important to understand why things happen. When I was a full-time clinician, it was hard to focus on why things were happening. There was perhaps time to open *Harrison's Principles of Internal Medicine* to identify the best drug to use for a specific problem, but not always to completely understand the processes at work. However, we can only change and improve things when we understand why things happen. Only then can we intervene and change the outcomes.

Dr. Czernin: This is the perfect closing statement! Thank you for taking the time to talk with our readers and us.

Dr. Ribas: Thank you for the great questions and to both of you for doing this. It's an honor.