Jacques Banchereau: On a quest for cures

Jacques Banchereau wonders why more kids don't want to grow up to be scientists. After all, what's not to like about changing lives, relieving suffering, and giving patients in need a reason to remain hopeful?

Earlier this year, Banchereau received the Dana Foundation–American Association of Immunologists (AAI) Award in Human Immunology Research for his innovative studies on treatments for maladies such as lupus, juvenile arthritis, and cancer. In collaborative efforts, he has pinpointed cytokines that underlie disease. He's found, for example, that interferon (IFN)-α drives autoimmunity in lupus (1). And in 2005, a collaborative study with Virginia Pascual revealed that interleukin (IL)-1 contributes to juvenile arthritis, and that treating arthritic children with a drug that blocks the IL-1 receptor relieved their painful symptoms (2). Two years later, Banchereau developed a new diagnostic test for juvenile arthritis using microarray approaches to measure circulating IL-1 levels before disease onset (3). He is now using human dendritic cells as vaccine vectors in hope of creating more effective treatments for cancer, HIV, and type 1 diabetes, to name just a few (4).

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Banchereau arrived at his post as head of Immunology at the Baylor Institute in 1996. Before that, he was director of the Schering-Plough Institute for Immunology Research in France, where his group discovered how to grow human dendritic cells (5). Try as I might to get him to tell me about his graduate research in the late '70s on the effects of cannabis on the immune system, Banchereau could not be shaken from his primary concern—improving lives through human immunology research.

What was your experience in biotech like?

Around the time when I began in biotech, there was a lot of excitement—a lot of hope that we would find miracle cures. In the nearly 15 years I was there, we didn't find miracle cures but we did lay groundwork. I was involved with the discovery and functional analysis of GM-CSF, IL-4, IL-5, IL-10, IL-13, and IL-17. But it's as if we were inventing the alphabet and not yet writing a book. I think that now we are ready to try to make sense out of it.

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Jacques Banchereau (right) receiving the 2009 AAI-Dana Foundation Award in Human Immunology Research from AAI President Art Weiss.

Why did you leave biotech?

One reason why I left was because I wanted to be involved with the whole process of taking a drug through clinical trials. I had been working with human cells at Schering-Plough, but I couldn't do anything in human beings. I can do this at Baylor.

Do you enjoy getting a clinical trial started?

Designing and implementing a clinical trial is painful but exciting, as the ultimate goal is to help patients. There are a lot of steps and they all need to be done properly. If you want the rainbow, you have to endure the rain.

Is it difficult to recruit people for clinical trials?

People who have terrible diseases really go for experimental therapies—often the few treatments available aren't very efficacious. If it was me, I would go for it. I'd cook up dendritic cells in my kitchen. I would do that for my family, without a doubt, as early as possible in the disease process. The [dendritic cell] vaccines don't fully work yet, but some of the responses I've seen have been phenomenal.

PERSONALIZED VACCINES

How are you using dendritic cells in therapeutic vaccines?

Dendritic cells are essential in controlling the immune system; they both launch it and put it at rest. Following in the footsteps of Ralph Steinman, we take cells from the blood—monocytes or $CD34^+$ hematopoietic progenitor cells—and we make them into dendritic cells. Then we load them with the appropriate antigens and inject them into the patient to induce an immune response. The cells can be made for melanoma, HIV, pancreatic cancer, or breast cancer. And they are adapted to the patient because they derive from the patient's own cells. We've seen some spectacular responses—but not enough of them. Now we are doing a lot of work with patients, as well as in vitro, to try to improve the outcome. Unfortunately, there is not a lot of support for this work. The NIH isn't strongly enthused, I think because people think it's too complex.

Are there particularly exciting dendritic cell vaccines in trials now?

I'm particularly excited about one in which we use dead tumor cells. This is an extension of a discovery made at

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Rockefeller University by Nina Bhardwaj years ago, using monocytes infected by influenza. Shortly thereafter we showed that dendritic cells could present the antigens of dead tumor cells. First we proved it in vitro and then we began two trials.

Can we learn about dendritic cell vaccines by working with mice?
You can do a lot in mice that you can't do in humans. But I think that we will only be able to cure disease by studying humans. Now, this isn't true in all immunology studies, it's just important when making vaccines. In humans there is more complexity and variability. We are limited by the type and amount of samples we can use in research and by the outbred nature of the population. Mouse studies are usually done with a single strain. Even if something works in 15 strains of mice, it still may not apply to humans.

What are some basic questions in vaccine research?
We still don't know what kinds of immune responses are good for each disease. Look at leprosy: If you make a Th1 response, you do well. But if you make a Th2 response, you're in trouble. The question is why make a Th1 response, which is beneficial, or a Th2 response, which isn't beneficial. Why do some people who get HIV survive for a long time and others die quickly? What kind of immune response protects them? And that response will probably be different from what's beneficial in TB. We have a lot of questions, and that's why we need to bring in a lot of smart young people.

What do you think of personalized medicine?
I think of dendritic cell vaccines as personalized therapeutics. And in general, I think personalized medicine is the way to go. If I have gangrene in my toe, the surgeon will not remove the whole leg, but will fix the specific problem. So I think that in the future we'll be able to assess the immune system and adapt the treatment to the patient's condition. But we'll need to know in detail what the immune system's problems are.

Are there good techniques available for assessing the human immune response?
At the moment, my colleagues and I are assessing gene expression profiles in whole blood samples. This is how we've found signatures of different diseases. Microarrays are very helpful in terms of diagnoses and prognoses. All the diseases we have tested have a different signature, so we believe that soon, patients will have their blood taken twice or four times a year and it will be put on a microarray. This technique will be the CBC of the 21st century. But we have no antigen-specific assays yet, and I'm putting a lot of effort into developing them. We are working, for example, to develop tools that assess T cell responses to antigens using a combination of different techniques, including microarrays.

HELP WANTED

You've published extensively, will you write a book?
One dream I have is to write a nice book on immune diseases that would be useful for students in the field. As for a book on my thoughts, right now I'd rather use my time for learning. Maybe when I'm retired I'll write my memoirs, but at this stage I still have energy to keep pushing the envelope of human immunology. It's our responsibility to encourage kids to enter science, to tell them that being a scientist is the most beautiful job. We need to tell them that it's exciting to find ways to cure people using your brain.

Could starting out in human immunology be risky for a young researcher who must "publish or perish"?
A young researcher must realize that human research takes longer and therefore they might not get as many publications. That's one of the problems we have. But I think this is where the system should change and reward human immunologists in a different way than mouse immunologists. Before the era of knock-in and knock-out mice, you could get [human] papers in top journals. Now it's extremely difficult because we can't address all of the questions that editors and reviewers ask. When I evaluate people, I consider conducting a clinical trial as a success. I treat it like a high-profile paper, provided that the study was done properly of course.

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What do you look for in human studies?
I like to see that the study is well conducted, explores a novel idea, and tackles a meaningful problem. I'm interested in somebody trying to solve challenging diseases, such as HIV or cancer. Studying how novel drugs influence the immune response of patients is also interesting, as are new ways of imaging, finding new diagnostic or prognostic tests, new approaches for experimental therapies… there are so many exciting studies to be done.

1. Blanco, P., et al. 2001. *Science.* 294:1540–1543.
2. Pascual, V., et al. 2005. *J. Exp. Med.* 201:1479–1486.
3. Allantaz, F., et al. 2007. *J. Exp. Med.* 204:2131–2144.
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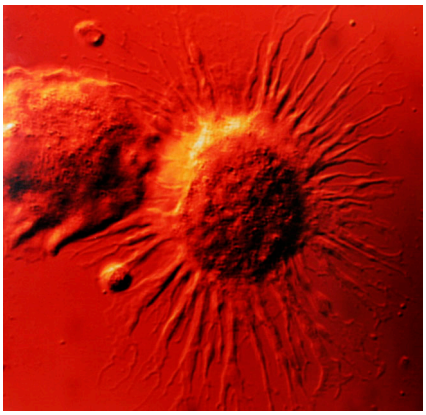
5. Caux, C., et al. 1992. *Nature.* 360:258–261.



Vaccines containing clinical dendritic cells (above) hold promise in clinical trials.