

HIV, prayer, and vintage cars: Danny Douek talks shop

If a scientist is defined as a person who acquires knowledge methodologically, Douek fits the bill in every way.

After rotating through hospitals around London as a physician, Danny Douek gravitated toward a research laboratory at Hammersmith Hospital, where he earned his PhD by tackling the thymus. He continued to monitor the thymus as a postdoc at the University of Texas Southwestern Medical Center in Dallas, finding that antiretroviral therapy helps to increase thymic output in HIV-infected patients (1). Now a senior investigator at the National Institutes of Health (NIH) in Bethesda, Douek peers into the gastrointestinal tract of HIV-infected patients. The virus strikes the gut hard and fast to deplete CD4⁺ T

"The only time I use my stethoscope these days is to listen to vacuum leaks."

cells and breach one of the body's most important immunological barriers (2). More recently, Douek has been trying to halt HIV progression by taking advantage of "public" T cell responses, in which T cells from different individuals bear identical T cell receptors (3, 4).

STETHOSCOPES IN THE GARAGE

When did HIV first creep onto your radar?

I first learned about HIV around 1984 when I was in medical school at Oxford. And then as a young doctor I was looking after people with HIV infections. Usually when we saw them, they were in the hospital dying of AIDS. It was really quite tragic before the days of wonderful therapies like HAART.

Did this drive you to study HIV as a research scientist?

No, I had always wanted to be a scientist. But my clinical training did instill the sensibility that I want to make ill people better. And so after I did a PhD in immunology, I wanted to do something that translated more into the clinical arena. My PhD mentor suggested HIV.

Do you ever consider switching fields?

Yes, I find neuroscience absolutely fascinating. I find the science of aging fascinating. I find plants fascinating.

Do you honestly find plants fascinating?

Yes, I want to know about their genes, what makes them grow, why they're plants... I don't think there's anything in science that I don't find interesting. I like organic chemistry. I love quantum physics. However, I do find relativity difficult to understand.

Is it true that you have an interest in old cars too?

I used to drive a 1966 Chevy Bel Air, but that wasn't big enough so I got a lime green 1972 Buick Electra. It's the longest Buick ever built. It seats four in the front and probably five in the backseat.

When things go wrong with the car, I bring people—usually from the laboratory—around the house to have a few beers and fix things. It's fun because there's a whole diagnostic procedure in trying to work out what's wrong with the car. Actually, the only time I use my stethoscope these days is to listen to vacuum leaks.

FAITH AND VACCINES

Do you have a scientific hero?

There's a bunch of them. I think Sir Peter Medawar is one of the real greats, certainly in immunology. He had incredibly original ideas. My rabbi recently asked if scientists come up with completely original ideas. And I said, "To be honest, there are very few of those." But I think Medawar came up with some really original things. One of them being the genetic control of the immune response.

Does your rabbi often inspire you to reflect on science?

Sure. I'm a devout atheist but somewhat observant. I love going to synagogue. I relax, recharge my batteries...



Danny Douek in the kitchen.

a lot of people who go to my synagogue also work at the NIH. Some of my best ideas for experiments have come from chatting after services with other scientists.

How is it possible to be an observant atheist?

I recently heard that Jews are skewed toward atheism compared with other religions. I think it's because it's a hyper-rational religion. Some of my orthodox friends might disagree with me, but I don't think you need a belief in God to be Jewish. I think as a Jew you can go to synagogue, you can pray, you can do good things and, well, my rabbi understands me completely.

In fact, last Yom Kippur I gave a sermon on a rational argument for prayer to God for those who don't believe in God. If you go back to the Talmud, the rabbis wrote that there would be no more miracles, that God no longer played a role in the affairs of man. And so you don't need to believe in magic or miracles or anything like that in Judaism.

Do you have faith in a future HIV vaccine?
I've become more, not less, optimistic that we will be successful for two reasons. One, I think there are great people involved who have a lot of bright ideas. And second, I see more and more evidence of resistance to infection after exposure, which means that we need to work out why it's possible to be exposed and not infected.

I think the trouble with the HIV vaccine is that expectations were incredibly high, both in the community and among scientists. We have to realize that this is an iterative process. I don't think it will come in five years, but I do think it will come.

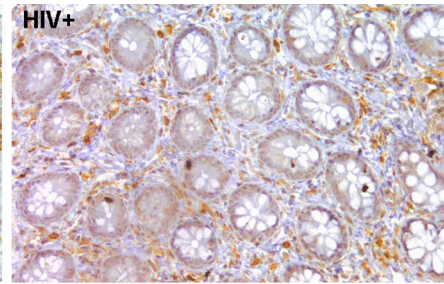
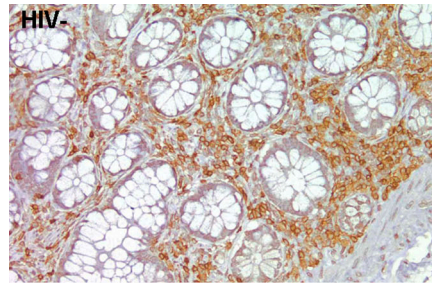
How did you feel when you heard that Merck's HIV vaccine trial was canceled?
I remember saying, "Oh, [expletive]!" I remember being upset when I heard some people saying that they could have predicted it, because I don't think one could have predicted that there would be an adverse effect. I think the outcome will be okay but it was a very troubling time, and it's still troubling because I think it really illustrated to us how difficult a vaccine will be.

I also worry that it gave T cell vaccines a bad name. But it's turning out that there were confounding factors, that it wasn't just the adenovirus vector that was the problem. For example, the circumcision data for these individuals seemed to play a big role. Still, I think it's good that everyone stopped to take a breather, because even if the effects of the vaccine were just futile, I think we should have stopped to reassess what we needed to make a vaccine.

FRONT LINES OF DEFENSE

Why do you devote so much attention to the gut?

About five years ago we looked at the gastrointestinal tract of HIV-infected individuals and we found that within the first two to three weeks of infection, the majority of all the CD4⁺ T cells in the gastrointestinal tract are depleted. The reason why that's important is that



HIV-infected intestines lose CD4⁺ T cells (brown) early on.

the gastrointestinal tract contains the majority of all the T cells in the body, so our theory is that you lose the majority of your CD4⁺ T cells in the acute phase of the infection.

Recently, we and others found that among the disappearing CD4⁺ T cells, Th17 cells are preferentially depleted, which is interesting because Th17 cells are thought to be important in the control of microbes at mucosal surfaces. In fact, we published a paper on a rare disease called Job's syndrome in which people have terrible bacterial and fungal infections. We found that they're unable to elicit Th17 cells (5). In terms of HIV, we want to understand the effect of a preferential loss of Th17 cells because that then becomes an avenue for therapeutic intervention.

What do you think of the "elite controllers" who somehow keep viral loads low?

I think they're an absolutely fascinating group of people, and if we can learn from them, we can learn about pathogenesis, therapies, and vaccines. Right now we are working with a group of elite controllers to dissect their T cell receptors and study their T cell responses.

I think these extremes are also going to tell us a lot with respect to host genetic factors that might be responsible for either a poor prognosis or for non-progression. For example, we know that most viruses use the CCR5 coreceptor to infect a CD4⁺ T cell. Individuals who have a homozygous deletion in part of CCR5, so that it's not expressed on the cell surface, can't be infected by HIV that uses CCR5. This means that

one could design a drug to block CCR5. And in fact, those drugs exist and are being administered to humans at the moment.

Does the fact that individuals like these exist indicate that we may be evolving to resist the virus?

That's a great question. Natural hosts for SIV, such as African green monkeys and sooty mangabeys, do not get AIDS although they have high viral loads. And so there are clearly host factors responsible for that nonprogressive state. I think it's critical for us to go to Africa and investigate these natural hosts to understand what makes their disease non-progressive and to see if there are any therapeutic avenues open to us.

Obviously, if a million years ago there was a pandemic in African green monkeys and the only ones who could live with the virus are the ones who survived, that's interesting from the point of evolution. But we as humans are not afforded that experiment; we have to do something now.

"We need to work out why it's possible [to HIV] and not infected."

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