QnAs with John T. Schiller

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John T. Schiller has spent much of his career studying papillomavirus molecular biology and immunology, and he played a key role in developing virus-like particle vaccines to prevent human papillomavirus (HPV) infections. More recently, he has worked to translate his discoveries in virology into therapies for cancer and other chronic diseases. Schiller describes one such antitumor treatment in his Inaugural Article (1). Now a National Institutes of Health Distinguished Investigator and Section Chief in the Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute in Bethesda, Maryland, Schiller was elected to the National Academy of Sciences in 2020.

PNAS: How did you become interested in cancer immunotherapy?

Schiller: I'm a virologist at heart, and I think thinking from the point of virology can provide some insight into tumor immunology—and vice versa. We got interested in therapies for cancer because we found that the virus-like particles that make up the HPV prophylactic vaccine have this amazing ability to bind cancer cells specifically. So we decided that we would use them as guided missiles to attack cancers, and we developed dye-coupled virus-like particles that bind the surface of a broad spectrum of cancer cells. If you activate them with infrared light, that basically kills the cells instantaneously (2). The problem with these infrared dyes is that the light doesn't penetrate very far, so we started thinking about whether we could instead put genes for viruses that you already have immunity to, so maybe we can recruit that immunity to fight the cancer cells because the immune system will think it's a reactivation of that virus.

Immediately what came to mind was cytomegalovirus [CMV] because most people have lifelong infections, and you get reactivations and, consequently, more and more of your T cells are specific for CMV epitopes. So we've actually delivered some immunodominant mouse CMV genes into chronically infected mice using the virus-like particles. But then we thought, as a control, let's just take the same target epitopes and just inject the minimal epitopes into the tumors. They wouldn't have the specificity of binding or infecting just the tumors, but because we were injecting them in the tumors, they would mainly be collecting there. And then, the major histocompatibility complex [MHC] would be decorated with these viral peptides, and the immune system would be thinking, "man, these cells have this huge viral infection, I better go in there and kill those virus-infected cells."

PNAS: What effects did these peptides have on tumors?

Schiller: The peptides worked better than gene delivery via virus-like particles in our mouse models. It turns out that if you inject these CMV peptides into the tumors of CMV

John T. Schiller. Image credit: National Cancer Institute.

infected mice, they just basically destroy the tumors (1). Importantly, they also profoundly change the tumor microenvironment such that you now get antigen spreading to tumor neoepitopes. So you're conditioning the tumor to become essentially more immunogenic, more susceptible to the immune response. You get this combination of cytotoxicity, immune modulation, and the induction of a response to tumor neoantigens, and it's antigen-agnostic, so we don't have to know which antigens we're going to attack.

PNAS: What are the advantages of this approach?

Schiller: This approach involves recruitment of existing antiviral immunity and combines cytotoxicity and immunogenicity, and we think it can be a broadly applicable cancer treatment that can be used in low-resource settings. What I like about it is that it's just using some peptides, and you're harnessing preexisting immunity that's been in a person for a long time. For an old [person], fully 10% of

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functional CD8 and CD4 T cells will be directed to a limited number of CMV epitopes, and these T cells are fully functional. You can't get that kind of response with normal vaccines, and there are not many examples where immunity gets better as you age. So why not use that immunity that [has] been building up for years and years and recruit it to fight cancer? What's also nice is you don't have to know much about the cancer; you don't have to have any kind of tumor profiling.

Also, it's an off-the-shelf reagent, and you can take that same vial and inject it multiple times. With lots of therapies, especially biologics, you use the drugs for a while, and then you develop antibodies that prevent them from working. But with these minimal peptides, they should be too small to generate antibodies, so we think that we should be able to use them multiple times, and that's a huge advantage. The other nice thing about the technology is that making synthetic peptides using good manufacturing practices is really a pretty straightforward and well-described pathway, so we think we are going to be able to get it into the clinic relatively quickly.

PNAS: What needs to happen for this technology to be used in human cancers?

Schiller: We have to find out whether this will work in people or not and, hopefully, we will get to clinical trials before too long. The one thing that is going to have to be very carefully monitored is how much of these peptides you put in because they don't specifically stick to the tumor cells. So there is a possibility of off-target toxicity that's going to have to be carefully monitored in clinical trials.

Also, everybody has different MHCs, so, ultimately, we have to try to pick out a combination of dominant epitopes to make this into a vaccine that will work in everybody. The other really big decision is deciding what tumor do you go for first because this isn't specific for one type of tumor. At least initially we want tumors that are readily injectable, so we're thinking about targeting head and neck cancers. We haven't decided yet, but it's going to be based on a combination of ease of access and ease of monitoring what's going on, as well as the unmet need. We're really excited about this.

PNAS: How could these approaches change cancer treatment?

Schiller: I've taken up the gauntlet to try to develop cancer therapies that are simple enough to use even in low-resource settings. Almost nobody is working in that space. The trend is just to make cancer therapies more and more complicated, where you have to do all this genetic profiling of the tumors and identify specifically what the mutations are, or take out the T cells and grow them up and put them back in. All those approaches are fine and good for the few people that can afford them but, worldwide, those types of therapies aren't going to bend the curve of cancer deaths in low-resource settings. What we're hoping to do is to take these two approaches—the virus-like particles and this idea of recruiting preexisting antiviral immunity—and use them to fight cancers in low-resource settings. I hope it will inspire some smart people to try to develop other cancer therapies that are well suited for use in low-resource settings.

1. N. Çuburu et al., Harnessing anti-cytomegalovirus immunity for local immunotherapy against solid tumors. Proc. Natl. Acad. Sci. U.S.A. **119**, e2116738119 (2022).
2. R. C. Kines et al., An infrared dye-conjugated virus-like particle for the treatment of primary uveal melanoma. Mol. Cancer Ther. **17**, 565–574 (2018).