QnAs with Joel N. Blankson

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Known as elite suppressors, some individuals infected with HIV show no symptoms and barely detectable virus levels years after initial infection, despite never having received treatment. Joel N. Blankson has spent much of his career studying elite suppressors, who represent less than 1% of people with HIV, with the hope that they may serve as models for developing new treatments. Blankson is a professor of medicine at the Johns Hopkins University School of Medicine, and his laboratory has demonstrated that elite suppressors' natural control of HIV is not due to differences or defects in the viral strains infecting them. PNAS recently spoke to Blankson about this phenomenon.

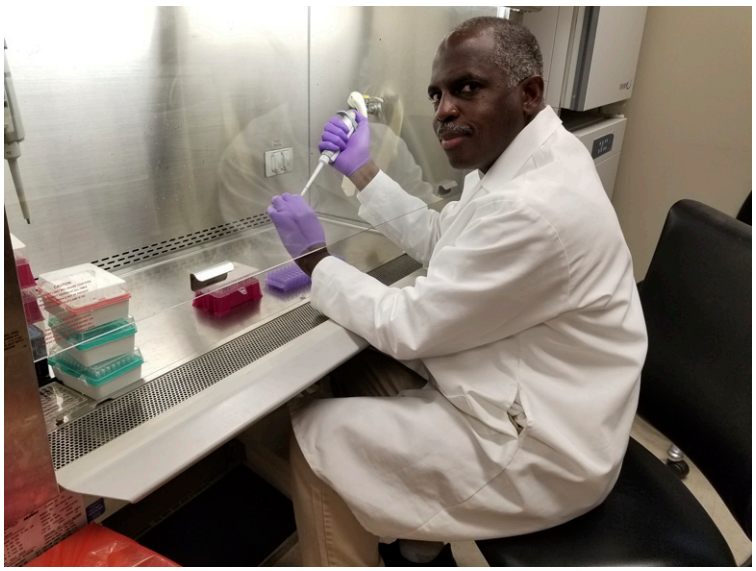
PNAS: How did you become interested in the natural control of HIV infection?

Blankson: When I was a clinical fellow, I had some clinic patients who were HIV^+ but had undetectable viral loads. And it got me thinking, "How is this possible?" The median viral load is like 30,000 in early HIV. So, for patients to be this far out, and have undetectable viral loads, I thought that it could tell us a lot about how the immune system is capable of controlling HIV.

PNAS: You have described antiretroviral therapy (ART) as a game-changer but not a cure. Can you explain how ART falls short?

Blankson: When patients go on antiretroviral therapy, their viral loads are suppressed, their $CD4^+$ T cells usually will increase, and life expectancy goes way up. But that's contingent on them being on treatment. If they stop treatment, usually within 2 to 3 weeks, their viral load will rebound back to where it was before and, therefore, it's not a cure. They have to take ART for the rest of their lives.

PNAS: You were a coauthor on a PNAS article (1) in which an intact proviral DNA assay (IPDA) was used to accurately measure the reservoir of intact, latently infected HIV proviruses in patients on ART. Can you explain how the findings from that work have informed your research?



Joel N. Blankson. Image credit: Caroline Garliss (Johns Hopkins Medical Institute, Baltimore, MD).

Blankson: Most HIV [clones] that we can amplify with a PCR are defective because reverse transcriptase is a low-fidelity enzyme, meaning it makes lots of errors. Ninety percent of what you amplify is not replication-competent. The IPDA was developed in Bob Siliciano's [laboratory] (2), and it's a high-throughput way of measuring the actual replication competency. So, in terms of elites, we did not know if the ratio of replication-competent virus to total virus, or to defective virus, was different from chronic progressor patients who are on treatment. And, by looking with the assay, it's safe to say that the ratios are pretty much the same. So, they have the same ratio of intact DNA, which is the replication-competent virus, to total DNA, which includes the defective virus (3).

PNAS: What else have you learned about how elite suppressors differ from other people with HIV infections?

Blankson: [Elite suppressors] control the virus really quickly, very early on in the disease course. In primary infection, or acute infection, most patients will have

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viral loads in the millions of copies per milliliter. Elite suppressors tend to have much lower viral loads, at the most tens of thousands, but not in the millions or tens of millions, and sometimes 100 copies [are] the most you can detect in these patients. So that's a big difference, and they're able to control the virus, obviously, without treatment. And the number of latently infected cells they have is much lower than what you see in patients who are on treatment. They have much more potent $CD8^+$ T cell responses to the virus, compared to patients who are on treatment, and we think that's what's controlling the virus [in many cases]: the T cell responses.

PNAS: Why do elite suppressors' immune systems work differently?

Blankson: There are a few major histocompatibility complex (MHC) class 1 alleles, HLA-B57 and HLA-B27, which are seen more often in elites than in chronic progressors. And one hypothesis is that these MHC molecules might be better at binding to conserved peptides that the virus cannot mutate away from easily. We think that may be it, but it doesn't answer the entire question because a lot of chronic progressors also are HLA-$B57^+$. Now, there was this nice study done by Mary Carrington (4). She took 100 HLA-$B57^+$ elites and 100 HLA-$B57^+$ chronic progressors, and she did whole-genome sequencing on each of them, and the only significant difference she found was in a natural killer cell receptor. It was statistically significant, but it didn't explain everything by any means. But it does suggest that maybe natural killer cells are also playing a role, perhaps early in infection, and that might also contribute to elite control. So, the way I think about it is: If natural killer cells are able to control viral replication early on, you develop a very strong T cell response, which can then kill infected cells; but if you don't have a good natural killer cell response or any other form of innate immunity, you develop very high viral loads and your T cells can never catch up.

PNAS: How might your findings on elite suppressors be used to develop better treatments for HIV?

Blankson: First, we have to [identify] patients during primary infection a lot more often than we do. I think very early on is where we have to act. Like I said, I think if you wait too long, the virus replicates to such an extent that it's hard for the immune system to catch up. But if we can [identify] patients in acute infection, and put them on treatment really early on, we can stop the virus from replicating, which will also limit the size of the reservoir. We think that's when the reservoir is seeded: during primary infection.

Second, how do we improve the $CD8^+$ T cell response in chronic progressors to make it look more like what we see in elites? That has been challenging. People have tried therapeutic vaccination, and it hasn't been that effective. It'll be interesting to see if mRNA vaccination might improve the responses we're seeing. And we have a study that hopefully should be published soon, showing that if you use both $CD8^+$ T cells and neutralizing antibodies together, you see an effect that's better than either alone or even better than the combination. There might be some synergy. So perhaps that's another strategy we can use.

1 F. R. Simonetti *et al.*, Intact proviral DNA assay analysis of large cohorts of people with HIV provides a benchmark for the frequency and composition of persistent proviral DNA. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 18692–18700 (2020).
2 K. M. Bruner *et al.*, A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. *Nature* **566**, 120–125 (2019).
3 A. K. Kwaa, C. C. Garliss, K. D. Ritter, G. M. Laird, J. N. Blankson, Elite suppressors have low frequencies of intact HIV-1 proviral DNA. *AIDS* **34**, 641–643 (2020).
4 M. P. Martin *et al.*, Killer cell immunoglobulin-like receptor 3DL1 variation modifies HLA-B*57 protection against HIV-1. *J. Clin. Invest.* **128**, 1903–1912 (2018).