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# Malaria

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## ▶ *An INTERVIEW with Dr. Stephen Hoffman*

**A** ccording to our analysis of malaria research over the past decade, the work of Dr. Stephen Hoffman ranks at #1, with 80 papers cited a total of 3,842 times. Dr. Hoffman is also a co-author on the top-ranked paper on the 10-year list: "Genome sequence of the human malaria parasite *Plasmodium falciparum*" (Gardner MJ, et al., *Nature* 419[6906]:498-511, 3 October 2002). Four other papers of his on malaria are included on the 10-year list. In [Essential Science Indicators<sup>SM</sup>](#), Dr. Hoffman's work can be found in the fields of Immunology and Microbiology. Dr. Hoffman is the founder, CEO, and Chief Scientific Officer of Sanaria, Inc. in Rockville, Maryland. In the interview below, he talks with Special Topics correspondent Gary Taubes about his highly cited work in malaria research.

**ST:** Of your five most-cited papers, three are on genomics—the malaria and mosquito sequences—and two on DNA vaccines. How did this come about?

I was doing DNA vaccine work when [Craig Ventner](#) [see also] published the sequence of influenza in the summer of 1995. That was the beginning of the genomics revolution. Two months later, he published the *Mycoplasma* genome. I saw that stuff and thought, "Geez, wouldn't it be interesting to do *Plasmodium falciparum*, the malaria parasite?"

He and I met in December of 1995 and we hit it off. We discussed it, and of course *P. falciparum* is much larger and more complicated than these bacterial genomes he had done. We estimated that we needed to do *P. falciparum* and *Plasmodium vivax*, and that it would cost \$28 million. In the end, it cost that much to do *P. falciparum* alone.

**ST:** Other than the relative size of the genome, were there other reasons this was so difficult?

Most molecular biologists working on malaria actually told us that this would not be possible, primarily because of the AT content of the genome—that's adenine and thymine. Most organisms are about half and half, or more GC than

AT, but *P. falciparum* is about 80% AT in the encoding regions. Nobody thought we'd even be able to clone the sequence to complete the job. They didn't think it was possible because we'd have so much trouble cloning large fragments of *P. falciparum* DNA. Nevertheless we went ahead with the project and it garnered a lot of interest. We quickly had an international consortium organized, which included a group at the Sanger Centre, our group at the Navy working with Venter's people at The Institute for Genomic Research, and funding from NIH, DOD, the Wellcome Trust, and the Burroughs Wellcome fund.

**ST:** Were you surprised at how quickly it came together?

Well, let me tell you one very interesting thing that happened. This was in March 1996. I got invited to go to the NIH to tell them what we were planning to do. They had just done some kind of review and I walked into talk to these project managers. I had been told that the largest grant they would give in direct expenses would be \$600,000 and it would take some time to make it happen. I gave a 20-minute presentation and they said, here's \$1 million right now. But with all that it still took us until 2002 to publish the genome.

*“The genome is going to open up entire new approaches to malaria and bring more people into malaria research, but it's not going to lead to a cure overnight.”*

**ST:** What did you learn from the genome itself?

Let me tell you first about this experience and what I learned from that, and how it got me where I am today. So we got the *falciparum* genome going and it took much longer than we hoped, primarily because it was spread out between these different labs. It would have been done much faster if it was focused just at TIGR and the Navy. I also did my DNA vaccines, and took it to the logical conclusion that they would never work. After doing this first study in humans, it was clear they wouldn't be a panacea or end-all.

I then went to work at Celera, a company with vision, courage, and a billion dollars in the bank. I was supposed to help turn genomics into proteomics and then new products, particularly immunotherapeutics for cancer. In the meanwhile, I convinced Craig Ventner that with the genome ability we had, we should sequence *Anopheles gambiae*, the malaria mosquito. This genome was 10 times larger than the malaria parasite. It took us 40 days to do it.

So, I just came from this third Johns Hopkins International Conference on malaria, and I was also at a Keystone Symposium on malaria two weeks ago, and I'm sure at least half or three-quarters of the work presented was dependent on the genomic data generated. This genome work had incredible influence on the field. It changed the way people did research, just as we predicted when we were trying to raise the money to get the *falciparum* genome sequenced. But it hasn't led to the saving of a single life from malaria, which is the focus and rationale for doing all of this.

**ST:** So you see the impact of these genome papers as decidedly mixed?

Well, on the one hand it changed the way the field does research. But to capitalize on the genome to make products to prevent one to three million deaths annually in Africa, will still take another 10-20 years. That's what everyone is saying. So having the roadmap, the genome, is not enough. That's

one thing I learned. The genome is going to open up entire new approaches to malaria and bring more people into malaria research, but it's not going to lead to a cure overnight. More importantly and more personally, it led me to where I am today because I realized from those different lines of work, all of which people said couldn't be done, that if you actually organize yourself well, get the right smart people around you, put the story together properly, you can accomplish a lot of things everybody said were impossible or impractical.

**ST:** It sounds like this experience was something of an epiphany for you?

Well, here it is: In the spring of 2002, I organized a Keystone Symposium and we had a session entitled "Malaria Vaccines, Why Is It Taking So Long?" We had everybody in the field there, and we asked, "When do you think there's going to be a malaria vaccine?" And with the exception of the group from GlaxoSmithKline, which has been pushing a form of vaccine they've been working on for 20 years, everybody said it would be 2020 or 2025 at the least, even with the genomes.

At the same time I was putting together and presenting data from 10 years of work immunizing people with radiation-attenuated whole parasites. You take the mosquito with the sporozoites, which are the stage of the parasite that the mosquito injects into humans, and you irradiate the mosquitoes and allow them to bite volunteers, and when these volunteers have been bitten by a thousand infected, irradiated mosquitoes, you find that those volunteers are actually protected against malaria.

This is an approach that was pioneered in 1967 by Ruth Nussenzweig at NYU, when she showed that she could protect mice against mouse malaria, and it was demonstrated by two groups in the early 1970s that this would work on humans. And so it was shown independently that you could protect people by this method, but it appeared to be totally impractical. But this is the lesson I learned: like sequencing the malaria genome, this was a bioengineering problem, not a scientific discovery problem.

**ST:** What made it so impractical to begin with?

At that point, we couldn't even culture the parasite, so the only way we had to make infected mosquitoes was to infect 100 people, put them on low doses of anti-malarials so they would still have the sexual stages of the parasite in them, and then feed mosquitoes on these infected volunteers. By the time we were able to produce infected mosquitoes from culture, we had the advent of the revolution in molecular biology, and we all thought we were going to win the Nobel Prize by developing a malaria vaccine based on recombinant DNA technology. But the whole field of recombinant subunit vaccines has never lived up to its promise. Maybe we just weren't smart enough. It doesn't mean it won't in the future, but right now it hasn't.

**ST:** Okay, so what made you think it was time to return to the idea of irradiating infected mosquitoes?

Well, let's go back to 2002 and Celera. We've just sequenced all these genomes, we've done great work on DNA vaccines, and the field is still saying it will take another 20 years to have a malaria vaccine. I've now put together a lot more data showing that we have a vaccine that works—an immunogen. These irradiate sporozoites. And, as I said, I realized this was a bio-engineering project not a scientific discovery project. The question is, can

we make them in a way that we can use as a vaccine, that's acceptable to the FDA and to the market from a cost-of-goods perspective? Can we make them sterile, can we make them pure, can we preserve them in a bottle so that they remain potent? Remember this is a live attenuated vaccine, not a dead vaccine. Can we ensure safety? And the last thing was, can we inject them with a needle and syringe, subcutaneously or intramuscularly? And so I left Celera and founded Sanaria in my kitchen, with the idea of doing those things. Now we have 35 employees and we've made enormous progress.

**ST: Where did the name Sanaria come from?**

Well, malaria means bad air. Sanaria means healthy air.

**ST: Where did you get this accumulated data on the effects of immunizing with irradiated sporozoites?**

It was in our lab book at our Navy lab. From 1989 to 1999 we had immunized 14 people, and we hadn't really put together all the data.

**ST: What was the response to your presentation at Keystone on this data?**

Well, everybody thought it was interesting and they universally dismissed the idea that this could be developed as a vaccine. Not one of the 150 people in the room thought this could possibly be done.

**ST: It's now three-and-a-half years later; what have you accomplished?**

We have solved three problems. We had to show that we can immunize with needle and syringe in clinically acceptable manner, and we've done that many times with mice. We're quite confident we can do that. We had to address the issue of the quantity of sporozoites produced. We now do mock practice production runs every Monday and Friday; we have four people dissecting mosquitoes for two hours, getting the sporozoites out of the salivary glands, and those four people produce 3,000 doses of vaccine in two hours—or what we estimate will be 3,000 doses. So we believe we have solved the quantity issue.

The biggest issue is, can we make it in a way that's acceptable to the FDA? I have been working very closely with the FDA over this whole period of time and we've developed a way of producing aseptic sporozoites and purifying sporozoites that has never been done before. We've also developed a way of stabilizing and bottling these sporozoites and assuring safety that works.

**ST: Will the dissection process have to be automated to make it efficient enough?**

Of course, there are many, many different aspects of the production process that can benefit from improved efficiency. But we believe that even for the 100 to 200 million doses of vaccine we'll want to be producing for infants in Africa, the system now in place will do extremely well. It would be great if we could automate it and improve it, but what we have in front of us is something that we know works and should be able to do the job. What we have to do now is prove the principle in humans, prove it's acceptable to the FDA from a regulatory point of view, and prove that it's safe and effective in a clinical trial.

**ST:** How many doses do you think you'll need per person to be effective?

We won't know until we do clinical trials. The estimate is that it will probably be like most vaccines, which means three doses. When children are immunized in the U.S., we do it at 2, 4, and 6 months of age. In Africa, they do it at 6, 10, and 14 weeks of age, and so we could piggy-back this vaccine on the WHO's Expanded Program for Immunization and give it at the same time as these other vaccines.

**ST:** What's the next step?

Well, we have raised about \$13 million, all in grants from the NIH, DOD, and the Gates Foundation. We need to raise another \$30 million in the next few months. We're pretty close to that. Then we'll start manufacturing for clinical trials and start trials that will address safety, immunogenicity, and protective efficacy, all in the same trial.

Within six months of giving the first shot we can challenge people with the parasite and we'll know whether it's protective or not. We'll know within 18 to 24 months of today if the vaccine meets regulatory standards, is well-tolerated and protective. At that point we have a straight path, we believe, toward getting licensed. Although we'll then have to raise roughly \$500 million to get it licensed—that's the going cost these days.

**ST:** Years ago, I wrote a story about malaria vaccines featuring your work, in which the moral was that in this business it's always a good bet to put your money on the parasite. Why do you think this is different?

Because there have been 14 people immunized by the bite of 1,000 irradiated, infected mosquitoes, and when challenged within two and a half months of the last immunization, thirteen of the fourteen were completely protected. Those people were rechallenged 35 times up to ten and a half months later, and 33 of the 35 times they still had complete protection, which means no parasites got out of the liver into the blood stream. That is protective immunity as good as you get from any vaccine. 🇺🇸

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**Dr. Stephen Hoffman's most-cited paper with 679 cites to date:**

"Genome sequence of the human malaria parasite *Plasmodium falciparum*" (Gardner MJ, *et al.*, *Nature* 419[6906]:498-511, 3 October 2002).

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