Good afternoon.
It's still afternoon by a little bit.
So I'm Dan Colley, and it's my pleasure
to welcome you to this historic day
to kick off the lecture in the 2009 series.
Global Diseases, Voices from the Vanguard.
So Voices from the Vanguard's a
joint effort between the Center
for Tropical and Emerging Global Diseases.
And Pat Thomas, the Knight Chair in Health
and Medical Journalism in the Grady College
of Journalism and Mass Communication.
Before I move ahead, I just want to say
that there are three more in this series.
I hope you will come back for them.
And also that there's a reception
following Dr. Hoffman's talk
in Demosthenian Hall to which
you are all welcome.
Now, the purpose of this series has always been
and remains the true theme
of this inauguration day.
That is, bringing people together.
And by that, I mean for the Voices series it's intended to bring together people from across the campus here at UGA.

And especially those interested in some aspect, any aspect, of global health.

So I'm glad you're here today.

I think you're going to be glad you're here too, although I'm sorry for the delay.

But today's speaker is someone who knows all the many facets of global health from the front lines, in back corners of the world, to sophisticated research laboratories, to public health policy meetings rooms, to medical clinics on both sides of the bed pan if you will.

And modern industrial facilities.

There are not many people on this earth who has participated in more aspects of global health than today's Voices speaker, Dr. Stephen L. Hoffman.

Steve went to Penn and then Cornell for medical school.

Did his health staff training in San Diego.

Got a diploma in Tropical Medicine from London's School of Hygiene and Tropical Medicine.

And he's the recipient of many, many honors.

And has the distinction of being the most cited author on malaria from 1995 to 2005,
which happened to be a time when malaria work was expanding enormously.

He's headed major government research operations.

And founded a company against the advice of just about all his friends and colleagues, but with the support of his wife, Dr. Kim Lee Sim, and his family.

In 2006, he obtained $29.3 million to build a facility in which to pursue this grail.

The facility opened in the fall of 2007.

Now, I'm not going to tell you about that because he will and you can also read it in Esquire and Scientific American.

I will also not list Steve's many, many honors because it would take too much time and that we don't have right now.

And furthermore, Steve's not one to rest on his laurels.

He has a story to tell and I will now ask him to tell you.

I'm pleased to present Dr. Stephen Hoffman, Founder and Chief Executive of Sanaria, Inc.

A man who knows global health and who acts on his ideas.

Steve?

( Applause )
She has it upstairs.

What about a pointer?

I think he's okay.

(Inaudible).

So that doesn't help you?

No.

Dr. Hoffman: Well, I've learned how to deal with adversity and I'm.

I don't have a pointer.

I can't hit the switcher.

But it's really an honor and a pleasure to be here on this historic day.

I'm sure it was as thrilling for you as it was for me.

And I'm just really happy that there was a poet in between Barack Obama and me speaking so I didn't have to follow his act.

I'm really pleased to be here and I hope that by hearing what I have to say some of you will be excited about pursuing a career in global health.

Next slide please.

So as many of you I think know, malaria is responsible for more deaths in children
of the world than any other single infectious agent, Plasmodium falciparum, is.

Thousands of children will die today of malaria, and an estimated million in the next year.

Next slide.

So Sanaria.

Does anybody know what malaria means?

What's the word come from?

>> Bad air.

>> Dr. Hoffman: Bad air, from Italian.

So what is San-aria?

>> Good air.

>> Dr. Hoffman: Healthy air.

All right?

Is the only company in the world that's dedicated entirely to developing a malaria vaccine.

Next slide.

So. Back. There we go.

So before I go into Sanaria and what we're doing, I thought it might be useful to hear a little bit about how I got there.

So I was a second-year medical student at Cornell, and at that time,
there was no such thing as global health.

And Cornell was the only medical school in the entire country that had a required course in tropical medicine taught by a rather flamboyant professor named Ben Kean.

And every day in the second year of medical school for three weeks for four hours, it actually usually stretched for six hours, we sat in the course where Ben Kean brought in tropical medicine specialists from all over the world.

And by the end of that course, it was clear in my mind that I was going to spend my career with a white linen suit, Panama hat, bottle of rum in my pocket, a cigar, and being a tropical medicine specialist.

I wasn't quite sure how I was going to get there, but that was the idea.

So to next slide.

I got. That summer I got an NIH fellowship to study diets for malnourished children in Colombia.

And I got so enthralled with it that I withdrew from medical school and spent a year traveling around South America.

Next slide.
That was my major professor, Donna Polinar, who was a Brujo or a witch doctor in the Caqueta,

which is the upper Amazon jungle of Colombia.

And area you can't go to now because of cocaine laboratories.

Next slide.

And I really experienced tropical medicine first-hand because I got hospitalized with typhoid fever in southern Cuenca.

Southern Ecuador in a place called Cuenca for ten days.

Had amoebic dysentery three times and giardiasis three times.

And I certainly, if you can imagine, I wasn't going to call up my mother and father from southern Ecuador and say I'm in the hospital with typhoid fever.

So I kind of grinned and bear it and was in a ward where the only people in the ward had had typhoid or hepatitis.

Next slide.

So I came back from that experience energized and with the idea that I was going to spend my career in tropical medicine.

And had the vision that I would be kind of a Dr. Schweitzer in the middle of the Tropics some place and had to learn everything.
So I went into a family medicine residency at the University of California San Diego.

And then followed that with a diploma in Tropical Medicine and Hygiene at the London School of Hygiene and Tropical Medicine.

And was raring to go.

Off to the Tropics to do clinical tropical medicine and look for a job.

And I could get jobs with the universities to study the cell surface code of schistosomes or Leishmaniasis.

And I was offered a job with the CDC as an epidemiology intelligence officer and EIS Service officer.

But I really wanted to just take care of patients.

And somebody came up to me and said, you know, there's these. Why don't you join.

You know, why don't you join this guy Dave Dennis who was in Jakarta, Indonesia at the time.

And I said, you know, I think the guy's in the Navy.

And they said, no, he never wears a uniform.
Definitely not in the Navy.

[00:08:27.316] And okay, so I got in touch with him and, the next slide, I joined the Navy to see the world.

[00:08:35.896] And went off to Jakarta with my eight-month-old son,

[00:08:41.056] and you'll learn about it in a second here, and my wife.

[00:08:44.796] And started doing clinical tropical medicine.

[00:08:49.026] And primarily focusing, next slide, on typhoid fever, which was killing the most,

[00:08:55.766] you know, a lot of people in Jakarta.

[00:08:57.886] And this is my colleague, Dr. Narain Penjabi, and we did this study of a new treatment for typhoid fever in which we reduced the hospital mortality of severe typhoid from 55% to 10%, and basically eliminated the mortality in the hospital.

[00:09:10.156] And that was the first study I ever did.

[00:09:14.686] It took a year-and-a-half almost living in the hospital with doing a study in which death was the primary outcome variable.

[00:09:24.726] But pretty exciting when this is when we.

[00:09:26.886] The code, we were in Jakarta, the code was broken by a CDC epidemiologist in Singapore, and sent us back the results which said it worked.

[00:09:35.286] And that's with champagne celebrating it.
And it's safe.

It's certain to say that since that day in 1982 I've never had that degree of success. It was a bad thing.

It was a great thing, but to start your career where you actually did something to save lives was rather extraordinary, and I've been trying to catch up ever since.

I then starting working on malaria.

If you're in tropical medicine or at least, you know, in that part of the world it was clear that that was really the number one problem.

And we used to go fly out to an island next to Timor called Flores.

We land on a grass landing strip.

Take a Jeep down to the coast.

And then take this kind of like African Queen Boat out to the village where we'd stay for a few weeks studying malaria.

Next slide.

And that was our research team.

I don't know if they dress that way at the University of Georgia.

But that was my staff having at the end of the day a coconut pina colada, you know.
Next slide.

[00:10:39.936] And we were studying tropical splenomegaly syndrome.

[00:10:43.006] And I'm told that from Dr. Moore that if you can figure out who

[00:10:46.206] in this slide doesn't have tropical splenomegaly syndrome you'll get an A. Next slide.

[00:10:52.626] Next. And this is another woman in the Highlands of New Guinea, which is Irian.

[00:10:58.736] It was then called Irian Jaya, now called Papua, Indonesia in West New Guinea.

[00:11:02.426] Who also had a disease called.

[00:11:05.436] It's now called hyper-reactive malarial splenomegaly.

[00:11:08.566] It's caused by chronic malaria infection, so malaria is not just a disease


[00:11:15.006] It has many other impacts pathophysiologically.

[00:11:20.096] And this woman weighed 35 kilograms and her spleen weighed 5 kilograms.

[00:11:25.436] And you can imagine if you live in a rural agrarian society and you have to drag

[00:11:30.076] that around with you, you don't do very well.

[00:11:32.076] And it eats up your red blood cells, white blood cells, and platelets and so on.

[00:11:37.936] Next slide.

[00:11:40.236] So I then wasn't doing as well with malaria as I had done with typhoid fever,
so I started interviewing witchdoctors and searching for a cure.

And this was back, that Donna Polinar in South America.

And everybody seemed to say that they had a cure.

This was a nurse in the Highlands in New Guinea.

This guy was another witch doctor.

And everybody, they all said they knew how to cure malaria, next slide, but fortunately.

Back up for a second.

So that's my son who is now a 29-year-old lawyer in Denver.

And he decided to come with me as I interviewed these guys.

What happened there?

Huh. Yeah.

There you go.
And he found a lot of different fellows.

Next slide.

And. Gees.

( Laughter)

And all of them said that they had a cure for malaria.

But he was rather precocious, so he told me to get a malaria smear on them and they were all positive.

So we abandoned that approach.

Next slide.

And I actually at that point, after spending five years in Indonesia,

came back to the United States with the idea of working on malaria.

Developing a malaria vaccine.

And I had many, you know literally hundreds of children die in my arms that I couldn't.

I mean that I treated and many of them got better, but many of them didn't.

And it was a terrific feeling of inadequacy.

And, you know, you would.

We would treat somebody, go to their bedside, think we cured them
of hypoglycemia or something like this.

[00:13:29.656]
And, you know, congratulate ourselves that we, you know,

[00:13:32.456]
that if we weren't there they would have died.

[00:13:34.516]
Two hours later the nurse said they died.

[00:13:36.856]
And it was really clear that something else needed to be done.

[00:13:41.256]
And this was at the time of the beginning of molecular biology cloning of genes and so on.

[00:13:46.066]
So I came back to the United States and began working on malaria vaccine development.

[00:13:50.086]
Next slide.

[00:13:52.216]
And spent several years, and this was kind of.

[00:13:57.156]
We all felt we were getting a Nobel Prize.

[00:13:59.266]
And in 1984, this was just before I came back, the gene encoding.

[00:14:04.876]
The circumsporozoite protein of Plasmodium falciparum had been cloned, sequenced,

[00:14:09.536]
and published in Science Magazine.

[00:14:11.926]
And there was a press conference held in Washington, which Dan probably remembers.

[00:14:17.076]
And it was clearly stated there was going to be a malaria vaccine in five years.

[00:14:21.886]
That was '84.

[00:14:22.786]
Now in '83 there had been a similar press conference in Australia at the Walter
and Eliza Hall where they had cloned some genes.

And so every kind of five years there's been another five-year window on a malaria vaccine.

But in any case, that gene was cloned and sequenced and published in June.

August of '84.

And in July of 19.

June of 1987, less than three years later, we published the first paper.

It was a yearlong study showing that a vaccine could be made with this protein.

It was safe, immunogenic, and actually protected somebody.

So there's a whole field out there called Translational Research, which aims to go from the bench to the bedside.

And 25 years ago, we were able to do that in two-and-a-half, three years.

And at this.

You know, before we got the results, because it only protected one out of six people,

we thought we were going to win the Nobel Prize right then and there.

And it helps to have that kind of vision,

but that grandiosity often doesn't really get you to the end of the day.

In any case, we started doing field studies.
This is in Kenya where I was going out to get some lymphocytes from volunteers and the.

President Obama, by the way, is from Western Kenya.

This town, Kisumu, where this plane crash was.

And he is a Luo.

And the ruling tribe in Kenya are the Kikuyu.

And in this particular plane the pilot was a Kikuyu and the co-pilot was a Luo.

And they had a fight and forgot to put the landing gear down.

And so we like.

This is how we landed about a kilometer from the.

From the terminal.

Next slide.

There was some pleasure associated with it.

That's my wife, Dr. Sim.

Next slide.

And some, you know, interesting ways of bathing out on field trips.

But in any case how did we end up, I'm going to truncate some years here,

getting from those early studies to Sanaria?
So we. In '87, or '86-'87, when we were a bit disappointed by the results,

we began testing multiple subunit vaccines based on the circumsporozoite protein

which is the major surface protein on sporozoites.

And it is the basis of the vaccine of which there's been a lot

of publicity recently called RTSS ASO1 developed by Glaxo Smith Kline and the Walter Reed Army Institute of Research.

And what we were testing was the actual predecessor of that.

So we've actually been working on that particular protein as a vaccine since 1984, and that's 25 years.

And it's still got a ways to go.

In any case, it wasn't giving us the results that we thought we needed.

And so we began playing with other formulations of it.

We expressed it in different ways.

Made conjugates.

Gave it with multiple different adjuvants.

And we got the, cranked up
protective efficacy to about 20-25%.

[00:17:35.026] I was the director of the Navy's malaria program, and my job was to make a vaccine to prevent malaria in Marines and, and Navy Seals and so on.

[00:17:41.276] And that, for a vaccine like that, it has to be 90% efficacious or I can't go to the commandant of the Marine Corps and say I got a vaccine.

[00:17:47.416] Or I couldn't send any of, anybody in this room on a safari to Kenya or to work in the Peace Corps or to do some type of work.

[00:18:01.316] You need a vaccine that really is protective if you're going to forego a medication.

[00:18:03.866] And I came to the conclusion in 1989 that a single protein vaccine wouldn't, no matter how it was delivered, would never give that degree of protective immunity.

[00:18:15.516] And even against the same strain of parasite.

[00:18:20.156] But the fact is that we can go to Kenya today or somewhere, and one kid will be infected with ten different strains of *Plasmodium falciparum* that vary at key epitopes in that particular protein.

[00:18:28.986] So we decided to start immunizing people by the bite of irradiated infected mosquitoes.

[00:18:32.976] Now, it had been shown in the early 1970s that you actually could immunize people by the bite of irradiated infected mosquitoes,
and a few people had been protected.

And that was the foundation for the discovery of the circumsporozoite protein by Dr. Nussenzweig's group at NYU with the idea that maybe that was what the immunity was against.

And it seemed clear to me that it wasn't, except there were 5,000 genes in the genome. That it's unlikely that it was against one protein, particularly since we couldn't measure very good immune responses against that protein and people immunized with irradiated sporozoite.

So we decided to start reimmunizing people by the bite of irradiated infected mosquitoes that have these sporozoites in their salivary glands.

And to determine the mechanisms of protective immunity, the immune mechanisms. The targets of the protective immunity, meaning which pieces of the parasite.

Which means, which proteins, which epitopes on those proteins were the targets of the protection?

And then to build a subunit vaccine.

Anybody tell me what a subunit vaccine is?

What do you think sub unit means?
I mean it's part of the whole.

So that in all of us in this room have been potentially immunized with about 26 vaccines, which are on the market in the United States.

Of those, there are two recombinant protein subunit vaccines.

Anybody know what those are?

>> Hepatitis.

>> Dr. Hoffman: Hepatitis B and?

I'm sure there's some women here who got this vaccine in the last few years.

HPV, Human Papillomavirus Vaccine.

That's it.

There's only two.

We've been working on this for 25 years, and we've only managed to get two on.

All of the other vaccines come from material actually made by the infectious agent that we're trying to immunize against.

And half of those, or 16 of the 26, are actually the entire infectious agent.

And 13 of those are what we call live attenuated.

They're actually the virus or bacteria itself.
which has been rendered non-virulent by some means.

[00:21:02.186] And what we were trying to do is make a better subunit vaccine.

[00:21:08.016] This is 1989 and 1990.

[00:21:10.336] And during the next ten years, we did identify more clearly the mechanisms

[00:21:15.456] of protective immunity.

[00:21:16.906] And we were able to sequence the genome, which we started also,

[00:21:21.136] that project of Plasmodium falciparum, to get at the targets.

[00:21:25.096] And then tested all kinds of subunit vaccines.

[00:21:28.796] So the first E. coli-produced recombinant protein vaccine ever to go

[00:21:33.896] on human beings was the malaria vaccine.

[00:21:36.086] The first DNA vaccine every given to a normal human being I administered.

[00:21:41.076] It was a malaria vaccine.

[00:21:42.726] The first recombinant virus vaccine that had multiple antigens in it was a malaria vaccine.

[00:21:48.926] And by 1999, I came to the conclusion it was going to be another 20

[00:21:54.926] or 25 years before we would have such a vaccine that met the requirements

[00:22:02.496] that I thought were necessary, which was 90% protective immunity.

[00:22:06.646] And at that point, we had started the malaria
genome-sequencing project with Craig Venter

And he had announced in 1998 that despite the fact that the public sector was going
to sequence the human genome in ten years for $3 billion,
that he was going to do it in three years for $300 million.
And he kept coming to me and saying, you know, like join Celera.
We'll do this, you know.
We'll turn.
You'll turn the genome into new biologics and so on.
And I said well, I got like one more year in the Navy and I can get my retirement, so let's wait.

But in any case, around this time at 2000 I retired from the Navy and joined Celera
to be the head of biologics to turn the human genome into new immunotherapeutics for cancer.
And I guess that was because I had been so successful or unsuccessful for malaria I might
as well try something else that was easy.
Like cancer, right?
In any case, Celera was really quite an incredibly exciting place at the time.
Probably the most exciting place in
the whole world of biotechnology.

[00:23:23.266] But a year later Craig Venter had been fired by the management, and he was my best friend there.

[00:23:28.656] And in the meantime, I started analyzing the data from these ten years of immunizing people by the bite of irradiated infected mosquitoes.

[00:23:34.696] And I, to my astonishment I looked at it and I said, you know,

[00:23:37.616] I've been wasting my time for the last 10 or 15 years.

[00:23:42.756] If I had tried to make a vaccine out of sporozoites, we would have a vaccine because.

[00:23:45.886] Next slide.

[00:23:53.766] And this just shows how it's done.

[00:23:55.756] In that container there, there's 300 infected mosquitoes that had been irradiated.

[00:24:02.176] And when a volunteer has been bitten by a thousand

[00:24:06.136] of those irradiated infected mosquitoes, I'm up to 3,000 at this point.

[00:24:12.426] Next slide.

[00:24:14.386] (Inaudible) volunteer will be protected against the challenge.


[00:24:20.896] There have been 14 volunteers in the world's literature that have had that exposure.

[00:24:25.836] Thirteen of the 14, when challenged,
up to 10 weeks after their last exposure were completely protected against malaria.

In the next row down, six of those people were rechallenged within 10 weeks 15 times.

There was 100% protection.

And six people were challenged as late as 42 weeks, nine-and-a-half months after their last exposure.

And five of the six were completely protected of malaria.

If you look up in the right-hand corner, you'll see 33 out of 35.

So there's been 35 challenges and total protection against malaria in 33 out of the 35 challenges, or 94%.

Now, that's as good a protective immunity as any vaccine for any indication.

If you go down on the immunizing bites, the last row there,

less than 1,000 the protection goes down.

So there's a dose response.

You need a certain level of, of the vaccine, which is not dissimilar to other vaccines.

You need a dose to get to, at which point you have protection.

Next slide.
So as I said, these are limited studies.

Thirty-five challenges in 14 people.

But the protective immunity was as good as the protective immunity of any vaccine for any indication.

Next slide.

This hadn't been.

There had been some indication of this in the literature before, so why wasn't it pursued?

Well, at the sporozoites, the immunogen were in mosquitoes and no one had ever made a vaccine in mosquitoes, or any other biologic for that matter.

And then of course, as I said, we had the discovery and,

and cloning of these major targets.

The circumsporozoite protein at the sporozoites thieves or the parasites life cycle.

The merozoite surface protein 1 at the red blood cell stage.

And so everybody had thought for the last 15 years that a subunit recombinant vaccine was imminent.

Well, the imminence gets old after a while.

And so, next slide, I decided to resign from Celera and start Sanaria in my kitchen
with my now, the son who had been with me out in the Highlands of New Guinea had graduated from college, gone off to Hawaii for a year where he was like a mate on a. First mate on a 65-foot catamaran taking people snorkeling and scuba diving.

And decided he wanted to go to law school.

He called me up and then had to take some, you know, to apply.

So he came to work with me and we started the company.

And what was the rationale?

First of all, we had an immunogen, maybe for the first time in history of vaccinology,

for a vaccine for a disease for which there wasn't a vaccine we actually knew something that worked.

We didn't have to discover it.

We didn't have to do any fancy immunology or molecular biology to find out what the target was.

It was there staring at us in the face.

The success was going to be based on bioengineering and applied entomology, parasitology and biology.

Meaning producing a vaccine in mosquitoes
and controlling all the elements of the production process.

And remember, I'd just come from this place Celera where the impossible had been achieved.

And so there was the sense that one with good people, good team,

focused effort could actually solve something.

And then I called up, I wasn't that nuts, and I called up the head of the Center for Biologics at the FDA and said, you know, I'm thinking about doing this.

Am I off my rocker here?

I mean, you know.

And the FDA became quite supportive of what we were doing.

And then I called up a fellow by the name of Maurice Hillerman,

and he was the director of the Merck Vaccine Institute.

And he is personally responsible for half the vaccines that anybody in this room has received.

There's a fantastic book written by Dr. Offit called Vaccinated, which is his biography,

which just came out, and I really would recommend that.

A tremendous guy.

And he became incredibly excited and the first member of our advisory board.
And we thought that we had a plan for paying for development and deployment in Africa because we would have the same vaccine for the entire world, and there was a potential traveler's market for this vaccine.

Next slide.

So our approach was different than all other approaches for malaria vaccine development in two fundamental ways.

One is ours was live attenuated.

And remember, the majority of vaccines that we've gotten are live attenuated.

All other approaches were subunit recombinant.

And the second was that we were aiming to prevent infection in greater than 90% of recipients.

And not because they didn't want to, but all of the other approaches were aimed at reducing the rate at which people become infected to reduce the morbidity or the illness associated and mortality.

But not to prevent infection because it was not possible to do with those approaches to vaccine development.
So we were rather grandiose, and still are, in terms of getting off the ground.

Next slide.

So why we're working on an attenuated live vaccine and not a recombinant or synthetic?

Next slide.

Because it has to do with the intended characteristics of the vaccine of getting greater than 90% protection.

Next slide.

And so this level of protection had been elicited by the immunogen, these sporozoites, but never by any subunit recombinant approach.

Nothing even close.

Next slide.

And so who would be immunized to fulfill our mission?

The primary target group is the infants in sub-Saharan Africa.

There's 25 million born annually, and a million of that 25 million eventually die of malaria, so 4%.

They all get malaria, pre-adolescent and early adolescent girls.

There's a new cohort of 7.5 to 10 million annually, and this would be to reduce fetal loss
and morbidity and mortality in the offspring associated with the low birth weights, which are associated with malaria.

How long did I say that we know this vaccine lasts for?

>> (Inaudible).

>> Nine-and-a-half to 10 months.

How long does pregnancy last for?

>> Nine months.

>> Okay. It would be a pretty. Potentially a pretty good vaccine if you could immunize before pregnancy.

Now, we don't know how long it lasts for.

I only know it lasts for at least nine-and-a-half months.

We haven't tested it beyond that, and that would be part of our vaccine-testing program.

Travelers from non-endemic countries which there's, you know, tens of millions, estimated 100 million.

And then there's many other populations in the developing world.

And as we get better at something.

Having. As we're getting better at controlling malaria.

In some places, the deaths have been
dramatically brought down, and we're thinking

[00:31:23.466] about eliminating Plasmodium
falciparum, not just controlling it.

[00:31:28.156] And that brings a whole another
strategy to the forefront which is,

[00:31:31.866] if you're going to eliminate it you have

[00:31:33.366] to eliminate transmission and
I'll get to that at the end.

[00:31:35.906] But that takes.

[00:31:36.966] You can tear up the thing about
mass administration of the vaccine,

[00:31:40.316] not just the targeted population.

[00:31:42.416] Next slide.

[00:31:44.926]

[00:31:48.776] So I should have had this in the beginning, but
I now am going to tell you about the life cycle

[00:31:54.226] of Plasmodium falciparum
or any malaria parasite.

[00:31:59.156] So if you start up there with the mosquito
biting, a female Anopheles mosquito biting

[00:32:04.826] from dusk until dawn inoculates sporozoites,
which are those little critters there

[00:32:11.496] with the little dot in the middle.

[00:32:13.486] They are uninucleate.

And they get into the liver probably within five to ten minutes, in some cases faster.

[00:32:23.476] Where during the course of about a week a uninucleate sporozoite develops

[00:32:29.016] to a mature liver-staged parasite called a schizont, which has 10,000 to 40,000 nuclei.

[00:32:36.506] Unbelievable amplification process in the liver.

[00:32:41.266] They're now called merozoites, each one of these uninucleate parasites.

[00:32:46.156] And they rupture out of the liver and each one can invade a different red blood cell.

[00:32:52.486] And during the course of 48 hours, a merozoite replicates again

[00:33:00.176] and divides about 10 to 20 times.

[00:33:02.456] And so you get a mature red blood cell-staged schizont, which has perhaps 10 or 20 nuclei.

[00:33:09.496] Which means that every 48 hours in your bloodstream there's a ten-fold amplification

[00:33:15.126] of the parasite burden in your body.

[00:33:18.266] Alternatively, if you look at the bottom they can develop to gametocytes,

[00:33:22.426] which is the sexual stage, which is taken up by the mosquitoes and takes two weeks to develop

[00:33:28.286] to sporozoites in the mosquitoes.

[00:33:31.476] Now, there's no clinical symptoms or signs or pathology associated

[00:33:36.026] with the sporozoites in the circulation.

[00:33:38.566] The parasite developing within the liver.
The merozoites when they're released from the red blood cells, or those gametocytes.

It's only the cycle of invasion, development, rupture, and reinvasion of red blood cells that cause the disease we know as malaria.

So if you were going to develop a vaccine, what would you target it against?

Anybody?

>> (Inaudible).

>> Dr. Hoffman: What?

>> The pre-blood stages.

>> Dr. Hoffman: The pre what?

>> Pre-blood stages.

Good. It's called pre-erythrocytic stages.

That's when you have a chance.

There's no symptoms, signs, pathology associated with it.

Now, ideally you would like to target the sporozoite, right?

The first stage, but you have about five minutes to do the job there.

And if you get, you know, if you get 90% of them and one gets through, what happens a week later?
There's 40,000 coming out the back door of the liver.

So whereas you have a week to attack them in the liver.

And the immune responses that you would like to engender, where you can engender, is antibodies against the sporozoites because they're extracellular.

Or T cell responses against the infected hepatocyte.

So what happens with a radiation attenuated sporozoite?

The sporozoites look identical to non-irradiated sporozoites.

They wiggle on a slide the same way.

They actually invade liver cells exactly the same way.

And they start to express new proteins exactly the same way for the first three days.

After they go into hepatocyte, you can't tell the difference physically, or if by microscopy, between irradiated or non-irradiated sporozoite.

At that point the irradiated sporozoite stop.

They don't replicate.

They don't make those 10,000 nuclei.

So the parasites are metabolically active but non-replicating.
And that means that the only place they can induce an immune response against is the sporozoites to make antibodies, or the early liver stage T cells.

And we believe that the primary protective immune response is T cells against the early liver stage.

So that if you get immunized properly your body has learned how to respond, and it makes these antibodies and T cells which prevent the parasite from ever developing.

Next slide.

So all we.

Back up for a second.

So that what we had to do was figure out how are we going to in the laboratory make these sporozoites and put them in a bottle, and keep them stable and potent?

And they have to be, as I tell you, sterile.

And so that the way that we do that is, we take gametocytes, those things at the bottom, and culture them.

We grow sporozoites, mosquitoes.

They have to be sterile.

Feed them.
Allow the parasites to develop so the mosquito becomes like the bioreactor or the cell line.

And then at the end of two weeks extract the sporozoites, purify them, and put them in a bottle.

Next slide.

Easier said than done.

So we. Since we started Sanaria, we've had several phases.

First was research and development to figure out how to do this.

The second was process development where you turned it into a manufacturing process.

The third was magically manufacturer.

And the fourth, which is going to begin in April or May, is to start clinical trials.

Next slide.

Research and development.

So we had three questions when we started.

Could one administer the vaccine by a root that was applicable for a vaccine?

You can't give it by the bite of irradiated infected mosquitoes.

And all the mouse studies that had been done had been by inoculating intravenously
which is we really can't, don't do that for a vaccine.

So we did an experiment right at the beginning where we gave the sporozoite subcutaneously like many of our vaccines, and we got 100% protection in mice.

There's really no place to go after that except for the humans.

Second was could we produce adequate quantities of sporozoites?

Everybody said it's impossible.

You'll never be able to produce them.

The answer is yes, and I'll tell you about that in a second.

The third is, and this was the hardest one,

could one at a reasonable cost produce attenuated sporozoites that meet regulatory requirements to be a vaccine?

So what do you think the regulatory requirements to be a vaccine were?

>> Immunology?

>> Dr. Hoffman: What?

>> (Inaudible).

>> Dr. Hoffman: The most important one is sterile, right?
I mean you can't be injecting stuff.

And has anybody ever been in an insectory?

Like where you've grown mosquitoes with malaria in them?

It feels like you're in like the heart of darkness in Africa or something like that.

You can almost feel the fungi and the bacteria in the air and on the surfaces.

So how could we do this?

Next slide.

So we had to make a vaccine that was free.

And you can't.

If it's live, you can't sterilize it.

It has to be sterile through the whole process, which takes six weeks to produce.

And so we had to have it free of pathogens, free of mosquito material.

Adequately attenuated so it wouldn't cause malaria.

And potent, and it had to stay potent in a bottle and we had to develop the method of doing that.

Next slide.

So we did that.

It took about two years and we
figured how to do all of those things.

And then we had to move from there.

We had a group of laboratory scientists, none of whom had ever manufactured anything or had any industry experience in manufacturing, to make the vaccine.

So fortunately, Dr. Sim, my wife, had actually worked as the head of R&D at a biotech company where she had manufactured about 40 kilograms of an anti-cancer agent called Angiostatin and Endostatin under GMP that went into people intravenously.

So she became the head of vice.

She had her own company, but she became the head of manufacturing for Sanaria, and worked with our scientists, next slide, over the course of a year training them on how to do GMP, taking courses, writing the SOPs, batch records and so on.

And did 12 end-to-end practice runs during that year, each one takes six weeks so they were overlapping, to get the team in shape to actually manufacture because there was no place else you could go to do this.

Nobody had the capability, understanding or facilities to do it.
And then so they were ready to manufacture.

And so in the spring of 2007 we started to manufacture a vaccine for what's called preclinical toxicology studies.

In order to get it passed with the FDA you have to show in animals that it's safe and meets all these requirements of sterility, purity, potency, and attenuation.

Next slide.

And so when you manufacture you don't manufacture more than you need.

And we need to determine that in order to do the quality control release assays,

again which is sterility, purity, potency and safety, and attenuation, the stability studies to show the stuff would work over time.

The toxicology studies, the biodistribution studies.

And to retain some we needed 228 vials of vaccine.

Next slide.

And so what you can see there is that we did four back-to-back production campaigns called 7, 8, 9, and 10 at two-week intervals,

so that's it's a six-week process overlapping by two-week intervals.

And averaged 323 vials and always
made the numbers we needed.

[00:41:36.356] And to do that we had to dissect 2,000 mosquitoes every day and vial that vaccine.

[00:41:43.796] Next slide.

[00:41:45.216] And we did a series of assays on it, all of which passed.

[00:41:49.026] Next slide.

[00:41:50.446] And then we went into repeat dose rabbit studies in which you actually give the highest dose that you're going to give to a human to rabbits.

[00:42:00.416] And you give one extra dose.

[00:42:02.286] And they passed all the, you know.

[00:42:03.976] It was safe.

[00:42:04.676] It was non-toxic.

[00:42:06.246] But we were planning in the clinical trial to give the vaccine one groups subcutaneously, and the other intradermally.

[00:42:14.386] So one in the kind of the outer layer of your skin, and one subcutaneous.

[00:42:20.206] Now, does anybody know why we thought about doing intradermal in this, you know, the outer layer of the skin?

[00:42:23.996] Anybody doing any immunology work here on T cells?

[00:42:26.246] >> Just the rabbit (inaudible).
Dr. Hoffman: What?

>> Just the rabbit sector.

Dr. Hoffman: Well, that's one thing.

So mosquitoes inoculates sporozoites in the dermis.

So we though hey, let's not try to get smarter than the mosquitoes.

Let's do that.

But also, the dermis has the highest concentration of the important dendritic cells, the antigen-presenting cells, which are important for T cell responses.

But it's really hard to give it in the dermis.

But we had a lot of fighting back and forth and controversy with the funders.

And finally, we convinced them to do two groups.

Now, this is really astonishing.

Next slide.

So we did one group of rabbits, 24 rabbits.

We gave the vaccine intradermally in males, females, and so on.

And the other we gave it subcutaneously.

The exact same vaccine, the exact same dose, the exact some dosing interval.

And the antibody responses
were 10 to 15 times higher when we gave it intradermally versus subcutaneous.

We didn't measure T cell responses. We don't do that in rabbits. But this is rather extraordinary.

If you're me sitting here, thinking about I'm going to give this vaccine, which I really don't know how to give it. No one's had any experience.

And I've already shown just changing by a few millimeters where I put it can have this dramatic effect on the immune responses, how do I know what I'm doing?

I mean. And I can't test everything, but.

So that's that result.

And then we did some biodistribution studies, next slide, and they were.

Had no unexpected results.

So we're now into, next slide, the situation where we had.

We're manufacturing this in a place that was termed in National Geographic a dismal strip mall in Rockville,
Maryland where we couldn't control the temperature.

We couldn't control what was in the air.

We had flooding.

We would, you know, freeze the place up and so on.

And our GMP. And we. And we produced perfect material.

It was sterile, pure, safe, and so on.

But the GMP, the consultants for manufacturing, said there's not a chance in the world you're going to make a vaccine in this place and give it to people even though it meets all those, you know, the testing requirements.

Next slide.

And so we were fortunate to get a large grant PATH Malaria Vaccine Initiative, with money from the Bill and Melinda Gates Foundation about $30 million.

And we were able to rent a part of this facility here.

Only about 10% so far, but we're working on getting the rest of it.

And build from scratch a custom-made manufacturing facility
because you can't go any place to manufacture in the process that we have.

[00:45:15.546] Next slide.

[00:45:16.866] And we. We.

[00:45:20.666] It was really quite remarkable.

[00:45:22.226] We finished the engineering plans for the place in April of 2007.

[00:45:26.766] And we had our grand opening in October of 2007 of world's first facility for manufacturing a live malaria vaccine.

[00:45:32.016] And there we have a bunch of dignitaries, you know.

[00:45:35.876] Other than my wife and Gina Rabinovich from the Gates Foundation, it's sort of a series of middle-aged men who are going bald, you know, cutting a ribbon there.

[00:45:38.946] But. But in any case, we opened the place up.

[00:45:53.026] Next slide.

[00:45:54.646] Ran some shakedown campaigns.

[00:45:57.656] And after.

[00:45:58.856] Well, we had to process the work, right?

[00:46:00.626] I mean we did it four times in row.

[00:46:02.586] It was they call in manufacturing robust, reproducible, consistent.

[00:46:07.456] And we moved it to a new facility.
Now, how many people here have tried to move an immunology laboratory across the hall?

All right?

And how long does it take from the assays that worked year-in year-out to work well?

You know, a lot of people said, Steve, you're. You're nuts.

I mean it's never going to work.

And I said naw, it's going to work.

We know how to do this stuff.

So we went from being the best producers of sporozoites in the world to the worst.

First, we couldn't grow the mosquitoes.

Then we started having like, you know, instead of 70,000 sporozoites for mosquitoes, it was 700, and we're going nuts.

And you can imagine waking up at 4:00 in the morning.

Now I've built this facility.

I'm spending money like water and nothing works.

And you don't know if it's the water.

Could be, you know, different water.

It could be this and that.
Fortunately, the manufacturing team solved it.

And we then moved.

Next slide.

This is the team.

Tremendously dedicated people, next slide, to what we call production campaigns 20 to 25.

Now remember, we started pieces 7, 8, 9, and 10 were the tox runs.

Eleven to 19 didn't work.

All right?

And. But then we went in and we nailed six in a row at two-week intervals,

and those were the lots of vaccine for the clinical trials.

Next slide.

And then here again we needed to make enough for the release at quality control.

Release assays, retention samples, stability assays, and the first clinical trial,

which has a 100 volunteers in it, which is huge for a first in human's clinical trial.

Next slide.

And here again we made, if you look at the bottom row, we needed about 440 vials.

We made an average of 570.

We always made what we needed.
We averaged about 70,000 sporozoites for a mosquito which is really incredibly high.

And did about 2,800 mosquitoes dissected per day.

And then we did a whole series of assays which, next slide, are listed here.

We culture the eggs, the pupae, the mosquitoes, the blood meals.

And if anything is positive it all gets thrown out.

And the team, led by Dr. Billingsley back there of the Quality Assurance team.

We turned an entomologist into a Quality Assurance specialist.

And everything essentially, you know, 99% of what we cultured was sterile.

So it's really quite remarkable.

I can't believe it.

That we can go for six weeks with mosquitoes and all this stuff and all these moving parts, and come up with a sterile product at the end.

And these are just some of the kind of tests that you do which are pretty standard.
Next. And then we went on to stability studies.

[00:49:02.186] Next slide.

[00:49:03.436] And I just say that you can see here that it's stable now.

[00:49:06.776] We. We've gone out to 30 months and it's stable, next slide,

[00:49:10.776] which is unheard of for vaccines because that's what we crowd.

[00:49:14.186] We stick. We crowd preserved this in vapor phase with liquid nitrogen

[00:49:17.816] which is a new way of doing vaccines.

[00:49:19.636] It's done for veterinary vaccines, but not yet for a human vaccine.


[00:49:24.376] And, you know, the tox lots are now out to 18 months, and we've cultured 11.7% of them

[00:49:32.526] in an outside contract sterility lab and they're all sterile.

[00:49:35.876] Next slide.

[00:49:36.946] So now, we get to what's called an IND, and Investigational New Drug application.

[00:49:41.276] We submit that hopefully to the FDA within about ten days.

[00:49:45.136] The FDA is allowed 30 days to respond to you.

[00:49:48.516] If they don't respond at the end of 30 days, you start your clinical trial.

[00:49:53.616] So the clock will be ticking in about ten days to two weeks.
And we have our first Phase 1 trial with challenge in the United States. And it's going to be run by two teams. The U.S. Military Malaria Vaccine program.

The Naval Medical Research Center. Dr. Judy Epstein and Tom Richie.

And the University of Maryland Center for Vaccine Development.

We have two teams because it's too big for one team to do this trial. They have done an incredible amount of work. Dr. Kirsten Leich and Bob Eddleman are putting together the protocols.

They've had to go through five what are called IRB's, Investigational Review Boards, committees for protection of human subjects.

because of all the organizations that are involved.

And so this kind of goes over the design of the trial, and it's called a Dose Escalation Study.
So we start with the low dose up there on the left.

[00:50:50.816] It says 7,500 sporozoites per dose.

[00:50:54.646] The next dose is 30,000 sporozoites per dose.

[00:50:58.026] And the last one is 135,000 sporozoites per dose.

[00:51:02.626] And you give the first one, and if everybody's okay after three weeks,

[00:51:06.716] you go to a safety board and they give you permission to give the 30,000 dose.

[00:51:12.426] And then you wait for several weeks.

[00:51:14.436] Bring. Put all the data together and go to the board

[00:51:18.036] and they give you permission to go to the 135,000 dose.

[00:51:21.326] There will be four doses at four-week intervals.

[00:51:24.676] And then three weeks after the last dose everybody gets challenged by the bite

[00:51:29.176] of five mosquitoes that are carrying sporozoites.

[00:51:33.336] There is a fourth group at the bottom that is not going to get challenged initially

[00:51:39.336] because the FDA asked us to observe them

[00:51:41.996] to make sure there's no break-through infections from the parasite.

[00:51:46.116] And half of the volunteers, 7 and 7, 11 and 11 and so on, will get the vaccine subcutaneously.

[00:51:53.886] And half will get in intradermally.
And this. Next slide.

And this adds up to there's the numbers of volunteers, and you can see the different groups.

It's a total of 104 because we have six infectivity controls.

Everybody.

Anybody who wants to sign up to come up for that.

You don't get the vaccine, but you get malaria.

You're guaranteed to get malaria.

So we have to have that, because how else can you determine if the vaccine works?

And we've done that now to over like 1,300 people very safely.

And people really.

It's remarkable the number of people who volunteer.

They get paid also, but they really want to be involved in this type of work.

Next slide.

Next. And this is just timeline.

Submitting the IND at the end of this month.

Starting recruitment at the end of next month.
And then the first immunizations.

[00:52:47.716] And we'll have protection data
by next October or November.

[00:52:50.886] Next slide.

[00:52:52.826] There's a whole series of antibody
and T cell studies that'll be done.

[00:52:56.806] Next slide.

[00:52:59.756] And here is something I'd like to stress.

[00:53:01.846] And so I've done, I don't
know, 30 vaccine trials.

[00:53:06.556] And I've done them with as few as 10 people
and I've done it in 20,000 people on the Island
of Sumatra with a typhoid
vaccine in the late 1980s.

[00:53:18.276] We're breaking entirely new ground here.

[00:53:20.636] We don't know anything.

[00:53:22.056] We start a study and we don't
know how many doses to give.

[00:53:25.506] We don't know the volume.

[00:53:26.736] Should you give it in 200
microliters or 500 microliters?

[00:53:29.906] Should you give it in the arm, the
leg, the rear-end, you know, the nose?

[00:53:33.726] Some people have suggested the ear.

[00:53:36.816] Should you give.

[00:53:37.286] You know, what's the interval between the doses?
What's the best way to do this?

And nobody has any idea.

And obviously the only way to test it is human beings, and we have no way of doing this many studies in human beings.

So you're always taking your best guess.

And it's scary, you know.

You invest five years.

By the time we finish the study we'll have invested almost $60 million in this.

And we're shooting in some respect in the dark.

So we're trying to minimize, but there's all kinds of issues that we're going to have to test in what we call clinical vaccinology.

Now, by the time we get done, in order to get this over the finish line,

which means a licensed vaccine, anybody have any estimate to what it would cost?

( Silence )

So what did, would, you know.

I'm sure somebody must in here demonstrated about how bad the pharmaceutical industry is and how much money they charge and so on.

It costs at least $1 billion for us to get this
finished because you have to do all this stuff.

[00:54:39.406]
And you have to do safety in thousands and thousands of people.

[00:54:43.536]
It's an extraordinarily expensive process to get it finished.

[00:54:49.086]
Next slide.

[00:54:50.376]
And so we have a clinical development plan.

[00:54:52.236]
Is how do we achieve a successful biologics license application

[00:54:55.736]
and commercialization as soon as possible?

[00:55:05.736]
And that involves, next slide, studies we'll have done with experimental challenge here

[00:55:03.916]
in the United States, because we can actually immunize and challenge.

[00:55:06.486]
Immunize and challenge.

[00:55:07.866]
Figure out some of these dosing issues.

[00:55:10.236]
Next slide.

[00:55:11.706]
As well as clinical development plan with field studies that will be done primarily in Africa,

[00:55:17.396]
but potentially in other parts of the world.

[00:55:21.216]
And which the first one will probably done in Ghana and follow immediately, you know, after.

[00:55:27.346]
After this, this first trial.

[00:55:29.496]
And hopefully it'll start in next, you know, late fall or January.

[00:55:34.756]
Next slide.
So we've already had a site visit team that's gone to four countries in Africa to plan for the trial that comes, you know, comes on from the Malaria Vaccine Initiative, the Center for Vaccine Development, the University of Maryland, the Malaria Clinical Trial Alliance from Africa, and the Naval Medical Research unit in Ghana.

Next slide.

And this just shows the different places that they have gone.

Next slide.

And then the question is, how do we get the vaccine there?

No one's ever delivered a vaccine in vapor phase of liquid nitrogen before.

So we got a $3 million grant from the NIH to figure out how to do that.

Next slide.

And basically Dr. Eric James from our lab got the slide, you know.

Shipped it to Ghana.

First question is, can you get it out of Customs in time in Ghana, right?

We have all had problems with that.

Next slide.
And this is picking it up at Customs with the team from the Noguchi Memorial Institute for Medical Research in NACRA.

And to make a long story short, if you look up there he shipped it from Washington. It went to England then down to Ghana. By another small plane out to a smaller airport in northern Ghana. And then by Jeep out to the site. At each site he had to test it. He had to look at the data recorders and so on. And then he shipped it all the way back, and then we tested it for viability and potency. And this was just done in August and it works. I mean the system works. And we think that we have a very viable way of doing this and expanding it and making it practical for a vaccine.

Next slide.

So that's great. We've done all this. We're going to be testing this vaccine. It could be, if all goes well, that by the end
of this year we'll have really strong data about how effective it is.

[00:57:33.346] But how do we go from producing my 550 vials and so on?

[00:57:38.496] I hope each vial will have five doses of vaccine in it.

[00:57:41.536] We can't know what the dose is until we test it.

[00:57:44.276] To producing enough to immunize 100 million children.


[00:57:49.686] We have to go back to the laboratory now.

[00:57:54.556] Increase the efficiency of production.

[00:57:56.776] Figure out how to scale it up.

[00:57:59.316] Figure out if you have to do something called validation, which is incredibly expensive.

[00:58:02.946] But you have to be able to show that you could take five operators and they all can do the same thing reproducibly because your manufacturing process is so good.

[00:58:12.926] And then we have to design a facility to build it in and it won't be for that.

[00:58:18.006] For the, you know, 100 million doses a year.

[00:58:20.326] It'll probably be for 10 million first.

[00:58:22.536] And so a tremendous amount of work that's going to have to go on.

Next slide.

[00:58:29.166]
And then we're trying to optimize the whole process, so we're now.

[00:58:33.746]
Right now we attenuate the parasites by radiation.

[00:58:37.926]
Alternatively we could attenuate them by genetic deletion so we can knock out particular genes.

[00:58:43.816]
And we actually published on that with our collaborators from Nijmegen earlier at the end of 2008 so we can make genetically attenuated sporozoites.

[00:58:53.186]
The whole world is working on making mosquitoes that don't support malaria's transmission or dengue transmission.

[00:59:02.366]
We have a grant from the NIH to make mosquitoes that make more parasites, as you know,

[00:59:07.066]
by genetically altering the parasites.

[00:59:08.816]
And then we're working on extraction formulation and so on and so forth.

[00:59:13.066]
The logistics, how we give it.

[00:59:14.926]
How do we give the vaccine best?

[00:59:16.986]
Next slide.

[00:59:18.026]
So in closing, let me just say that if we think about malaria vaccines in a transition

[00:59:24.176]
from scale-up to its now the gauntlet's been thrown down by Bill and Melinda Gates to go for eradication, elimination of Plasmodium falciparum, then eradication of malaria.
Next slide.

Next. Next.

Next. So we can think about different phases in this, and this is of course truncated, you know.

From scale-up coverage to disease and transmission,

elimination there's a lot of years.

And. And then to final eradication.

If we think about the role of vaccines in that process.

Next. So we have vaccines that reduce morbidity and mortality without preventing transmission.

I told you that that's what everyone else is working on, except for Sanaria.

And the only other vaccine that's.

You know, the one that's further ahead, which is called the RTSS, doesn't prevent infection.

It just delays the time until you get infected and thereby reduces morbidity and hopefully mortality.

Those would be very useful in the first phases of control, which is actually,

what we're doing now with bed nets, spraying, good drugs and so on.

But, next, if we want to eliminate then we have to have a vaccine
that prevents transmission either by preventing infection, pre-erythrocytic,

meaning section, meaning blood stage infection.

Or preventing transmission to the mosquitoes.

And so we're actually working on both of those.

Our vaccine I told you about is the pre-erythrocytic vaccine, the sporozoite.

But we can also produce parasites that could be used for another type of vaccine to prevent transmission in mosquitoes.

And these are independent mechanisms.

And if you combine them.

Suppose you had a 90% effective vaccine that prevented the sporozoites from ever getting out of the liver into the bloodstream.

And then you had a vaccine that was 90% effective against preventing the mosquitoes from being infected.

That's 99%.

That by itself would eliminate malaria anywhere.

So it's a big challenge, but that's what we're working on.

Next slide.

Next slide.
So how good is good enough?

You know, again, to get back to, you know,

I feel that good enough means 80-90-95% protective.

We'll just have to see.

I may tell a different story in six months when we come back here and get, you know, less protection.

We just have.

We just don't know.

Next slide.

We've been fortunate in working with many, many groups throughout the world in doing this.

It couldn't possibly have been done just by the people even on our team, which is now 50 people.

Particularly the PATH Malaria Vaccine Initiative, protein potential LSC

in the U.S. military malaria vaccine program.

Next slide.

Funding has come from the NIH, the U.S. Army.

We even got an earmark.

You know those terrible things, earmarks?

Without an earmark scenario, a $4 million scenario, we'd never have existed.
And next slide.

We have tremendous committees, which have helped us gratis, so we don't pay any

of our advisory committees, which are really made up of the luminaries

of the world and their different areas.

And they have all just chipped in to, you know, to work on this.

It's very unusual.

I mean unprecedented for a company to have all the people donating their time to help.

Next slide.

And this is the team that gets up every single day with a dream

of making a malaria vaccine that's going to prevent millions

of deaths in children of the world.

And that's the team at home.

That's actually in a place called Luang Prabang, which is Lao.

That's the Mekong River.

That was last August and so on.

That's the home team that keeps me going, so thank them.

Thank you.
( Applause )

[01:03:26.560]

[01:03:27.060]