{QTtext}{timescale:100}{font:Verdana}{size:20}{backColor:0,0,0}
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{plain}

[00:00:01.556]
>> Dan Colley: Good afternoon.

[00:00:02.556]
It's still afternoon by a little bit.

[00:00:06.806]
So I'm Dan Colley, and it's my pleasure
to welcome you to this historic day

[00:00:12.856]
to kick off the lecture in the 2009 series.

[00:00:17.986]
Global Diseases, Voices from the Vanguard.

[00:00:22.016]
So Voices from the Vanguard's a
joint effort between the Center

[00:00:25.216]
for Tropical and Emerging Global Diseases.

[00:00:27.526]
And Pat Thomas, the Knight Chair in Health
and Medical Journalism in the Grady College

[00:00:33.936]
of Journalism and Mass Communication.

[00:00:37.216]
Before I move ahead, I just want to say
that there are three more in this series.

[00:00:40.986]
I hope you will come back for them.

[00:00:43.216]
And also that there's a reception
following Dr. Hoffman's talk

[00:00:47.506]
in Demosthenian Hall to which
you are all welcome.

[00:00:52.166]
Now, the purpose of this series has always been

[00:00:56.176]
and remains the true theme
of this inauguration day.

[00:01:00.846]
That is, bringing people together.

[00:01:03.646]

And by that, I mean for the Voices series
it's intended to bring together people

[00:01:08.926]
from across the campus here at UGA.

[00:01:12.756]
And especially those interested in some
aspect, any aspect, of global health.

[00:01:18.626]
So I'm glad you're here today.

[00:01:19.966]
I think you're going to be glad you're
here too, although I'm sorry for the delay.

[00:01:26.436]
But today's speaker is someone who knows
all the many facets of global health

[00:01:32.986]
from the front lines, in back corners of the
world, to sophisticated research laboratories,

[00:01:40.496]
to public health policy meetings
rooms, to medical clinics

[00:01:46.546]
on both sides of the bed pan if you will.

[00:01:49.736]
And modern industrial facilities.

[00:01:53.086]
There are not many people on this earth who has
participated in more aspects of global health

[00:02:00.196]
than today's Voices speaker,
Dr. Stephen L. Hoffman.

[00:02:05.586]
Steve went to Penn and then
Cornell for medical school.

[00:02:08.756]
Did his health staff training in San Diego.

[00:02:11.476]
Got a diploma in Tropical Medicine from London's
School of Hygiene and Tropical Medicine.

[00:02:17.196]
And he's the recipient of many, many honors.

[00:02:19.716]
And has the distinction of being the most
cited author on malaria from 1995 to 2005,

[00:02:27.406]
which happened to be a time when
malaria work was expanding enormously.

[00:02:32.806]
He's headed major government
research operations.

[00:02:35.386]
And founded a company against the advice of
just about all his friends and colleagues,

[00:02:40.926]
but with the support of his wife,
Dr. Kim Lee Sim, and his family.

[00:02:45.906]
In 2006, he obtained $29.3 million to build
a facility in which to pursue this grail.

[00:02:54.106]
The facility opened in the fall of 2007.

[00:02:57.716]
Now, I'm not going to tell you about that
because he will and you can also read it

[00:03:02.546]
in Esquire and Scientific American.

[00:03:04.776]
I will also not list Steve's many, many
honors because it would take too much time

[00:03:09.776]
and that we don't have right now.

[00:03:11.826]
And furthermore, Steve's not
one to rest on his laurels.

[00:03:16.566]
He has a story to tell and I
will now ask him to tell you.

[00:03:21.066]
I'm pleased to present Dr. Stephen Hoffman,
Founder and Chief Executive of Sanaria, Inc.

[00:03:27.856]
A man who knows global health
and who acts on his ideas.

[00:03:31.996]
Steve?

[00:03:33.186]
[00:03:34.516]
( Applause )

[00:03:39.046]
>> She has it upstairs.

[00:03:41.236]
>> What about a pointer?

[00:03:44.776]
>> I think he's okay.

[00:03:47.006]
(Inaudible).

[00:03:47.156]
>> So that doesn't help you?

[00:03:48.956]
>> No.

[00:03:49.706]
>> Dr. Hoffman: Well, I've learned
how to deal with adversity and I'm.

[00:03:53.606]
I don't have a pointer.

[00:03:54.666]
I can't hit the switcher.

[00:03:56.246]
But it's really an honor and a pleasure
to be here on this historic day.

[00:04:01.126]
I'm sure it was as thrilling
for you as it was for me.

[00:04:05.396]
And I'm just really happy that there was a
poet in between Barack Obama and me speaking

[00:04:12.256]
so I didn't have to follow his act.

[00:04:17.846]
I'm really pleased to be here and I hope
that by hearing what I have to say some

[00:04:23.216]
of you will be excited about
pursuing a career in global health.

[00:04:26.856]
Next slide please.

[00:04:28.746]
So as many of you I think know, malaria
is responsible for more deaths in children

[00:04:35.026]

of the world than any other single
infectious agent, Plasmodium falciparum, is.

[00:04:39.566]
Thousands of children will die today of malaria,
and an estimated million in the next year.

[00:04:45.486]
Next slide.

[00:04:47.286]
So Sanaria.

[00:04:49.446]
Does anybody know what malaria means?

[00:04:52.556]
What's the word come from?

[00:04:53.626]
>> Bad air.

[00:04:54.866]
>> Dr. Hoffman: Bad air, from Italian.

[00:04:55.996]
So what is San-aria?

[00:04:57.176]
>> Good air.

[00:04:58.726]
>> Dr. Hoffman: Healthy air.

[00:05:00.786]
All right?

[00:05:02.126]
Is the only company in the
world that's dedicated entirely

[00:05:05.196]
to developing a malaria vaccine.

[00:05:08.846]
Next slide.

[00:05:10.246]
So. Back. There we go.

[00:05:11.926]
So before I go into Sanaria and what
we're doing, I thought it might be useful

[00:05:17.796]
to hear a little bit about how I got there.

[00:05:20.716]
So I was a second-year medical
student at Cornell, and at that time,

[00:05:25.046]
there was no such thing as global health.

[00:05:26.996]
And Cornell was the only medical school in
the entire country that had a required course

[00:05:32.156]
in tropical medicine taught by a rather
flamboyant professor named Ben Kean.

[00:05:38.076]
And every day in the second year of medical
school for three weeks for four hours,

[00:05:43.516]
and it actually usually stretched for six hours,
we sat in the course where Ben Kean brought

[00:05:48.886]
in tropical medicine specialists
from all over the world.

[00:05:52.696]
And by the end of that course, it was clear
in my mind that I was going to spend my career

[00:05:58.196]
with a white linen suit, Panama hat,
bottle of rum in my pocket, a cigar,

[00:06:02.456]
and being a tropical medicine specialist.

[00:06:04.236]
I wasn't quite sure how I was going
to get there, but that was the idea.

[00:06:08.106]
So to next slide.

[00:06:09.696]
I got. That summer I got an
NIH fellowship to study diets

[00:06:14.006]
for malnourished children in Colombia.

[00:06:17.636]
And I got so enthralled with it
that I withdrew from medical school

[00:06:22.176]
and spent a year traveling around South America.

[00:06:26.026]
Next slide.

[00:06:27.766]

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

[00:06:34.036]
which is the upper Amazon jungle of Colombia.

[00:06:38.786]
And area you can't go to now
because of cocaine laboratories.

[00:06:42.836]
Next slide.

[00:06:44.366]
And I really experienced tropical medicine
first-hand because I got hospitalized

[00:06:48.546]
with typhoid fever in southern Cuenca.

[00:06:50.656]
Southern Ecuador in a place
called Cuenca for ten days.

[00:06:53.816]
Had amoebic dysentery three
times and giardiasis three times.

[00:06:58.476]
And I certainly, if you can imagine, I
wasn't going to call up my mother and father

[00:07:03.056]
from southern Ecuador and say I'm
in the hospital with typhoid fever.

[00:07:06.746]
So I kind of grinned and bear it and
was in a ward where the only people

[00:07:10.576]
in the ward had had typhoid or hepatitis.

[00:07:13.266]
Next slide.

[00:07:14.196]
So I came back from that experience
energized and with the idea that I was going

[00:07:19.886]
to spend my career in tropical medicine.

[00:07:23.026]
And had the vision that I would be
kind of a Dr. Schweitzer in the middle

[00:07:27.836]
of the Tropics some place
and had to learn everything.

[00:07:30.406]
So I went into a family medicine residency
at the University of California San Diego.

[00:07:36.166]
And then followed that with a diploma
in Tropical Medicine and Hygiene

[00:07:39.996]
at the London School of Hygiene
and Tropical Medicine.

[00:07:42.786]
And was raring to go.

[00:07:45.006]
Off to the Tropics to do clinical
tropical medicine and look for a job.

[00:07:49.956]
And I could get jobs with the
universities to study the cell surface code

[00:07:54.736]
of schistosomes or Leishmaniasis.

[00:07:57.106]
And I was offered a job with the CDC

[00:07:58.746]
as an epidemiology intelligence
officer and EIS Service officer.

[00:08:05.746]
But I really wanted to just
take care of patients.

[00:08:08.056]
And somebody came up to me and
said, you know, there's these.

[00:08:13.156]
Why don't you join.

[00:08:14.026]
You know, why don't you join
this guy Dave Dennis who was

[00:08:16.896]
in Jakarta, Indonesia at the time.

[00:08:19.666]
And I said, you know, I think
the guy's in the Navy.

[00:08:22.596]
And they said, no, he never wears a uniform.

[00:08:26.346]

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

[00:09:03.876]
for typhoid fever in which we reduced the
hospital mortality of severe typhoid from 55%

[00:09:10.156]
to 10%, and basically eliminated
the mortality in the hospital.

[00:09:14.686]
And that was the first study I ever did.

[00:09:17.356]
It took a year-and-a-half almost living
in the hospital with doing a study

[00:09:21.646]
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,

[00:09:32.506]
and sent us back the results
which said it worked.

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

[00:09:37.486]
And it's safe.

[00:09:38.616]
It's certain to say that since that day in
1982 I've never had that degree of success.

[00:09:46.606]
It was a bad thing.

[00:09:47.976]
It was a great thing, but to start your
career where you actually did something

[00:09:51.836]
to save lives was rather extraordinary, and
I've been trying to catch up ever since.

[00:09:57.046]
I then starting working on malaria.

[00:10:00.966]
If you're in tropical medicine or at least, you
know, in that part of the world it was clear

[00:10:04.966]
that that was really the number one problem.

[00:10:07.416]
And we used to go fly out to an
island next to Timor called Flores.

[00:10:14.516]
We land on a grass landing strip.

[00:10:17.246]
Take a Jeep down to the coast.

[00:10:18.866]
And then take this kind of like African
Queen Boat out to the village where we'd stay

[00:10:23.346]
for a few weeks studying malaria.

[00:10:25.546]
Next slide.

[00:10:27.376]
And that was our research team.

[00:10:28.996]
I don't know if they dress that
way at the University of Georgia.

[00:10:31.286]
But that was my staff having at the end of
the day a coconut pina colada, you know.

[00:10:38.336]

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

[00:11:13.196]
of children in the developing world.

[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,

[00:11:47.846]
so I started interviewing
witchdoctors and searching for a cure.

[00:11:51.546]
Next slide.

[00:11:52.936]
And this was back, that Donna
Polinar in South America.

[00:11:56.306]
And everybody seemed to say
that they had a cure.

[00:11:59.206]
Next slide.

[00:12:00.446]
This was a nurse in the Highlands in New Guinea.

[00:12:03.926]
Next slide.

[00:12:05.346]
This guy was another witch doctor.

[00:12:07.456]
And everybody, they all said they knew how
to cure malaria, next slide, but fortunately.

[00:12:12.216]
Back up for a second.

[00:12:13.806]
Back. Forward.

[00:12:14.916]
There we go.

[00:12:15.986]
So that's my son who is now a
29-year-old lawyer in Denver.

[00:12:21.566]
And he decided to come with me
as I interviewed these guys.

[00:12:25.286]
Next slide.

[00:12:26.626]
What happened there?

[00:12:29.786]
Huh. Yeah.

[00:12:32.156]
There you go.

[00:12:34.426]
And he found a lot of different fellows.

[00:12:37.426]
Next slide.

[00:12:38.666]
And. Gees.

[00:12:41.516]
( Laughter)

[00:12:45.526]
And all of them said that
they had a cure for malaria.

[00:12:48.916]
But he was rather precocious, so
he told me to get a malaria smear

[00:12:51.946]
on them and they were all positive.

[00:12:53.506]
So we abandoned that approach.

[00:12:55.736]
Next slide.

[00:12:57.096]
And I actually at that point, after
spending five years in Indonesia,

[00:13:01.456]
came back to the United States with
the idea of working on malaria.

[00:13:06.526]
Developing a malaria vaccine.

[00:13:07.846]
And I had many, you know literally hundreds
of children die in my arms that I couldn't.

[00:13:13.876]
I mean that I treated and many of them
got better, but many of them didn't.

[00:13:17.416]
And it was a terrific feeling of inadequacy.

[00:13:20.756]
And, you know, you would.

[00:13:22.896]
We would treat somebody, go to
their bedside, think we cured them

[00:13:27.106]

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

[00:14:27.306]

and Eliza Hall where they had cloned some genes.

[00:14:30.076]
And so every kind of five years there's been
another five-year window on a malaria vaccine.

[00:14:36.556]
But in any case, that gene was cloned
and sequenced and published in June.

[00:14:41.836]
August of '84.

[00:14:43.686]
And in July of 19.

[00:14:45.236]
June of 1987, less than three years
later, we published the first paper.

[00:14:50.226]
It was a yearlong study showing that a
vaccine could be made with this protein.

[00:14:56.636]
It was safe, immunogenic, and
actually protected somebody.

[00:14:59.776]
So there's a whole field out there
called Translational Research,

[00:15:04.656]
which aims to go from the bench to the bedside.

[00:15:07.606]
And 25 years ago, we were able to do
that in two-and-a-half, three years.

[00:15:11.926]
And at this.

[00:15:13.086]
You know, before we got the results, because
it only protected one out of six people,

[00:15:16.616]
we thought we were going to win the
Nobel Prize right then and there.

[00:15:20.416]
And it helps to have that kind of vision,

[00:15:22.716]
but that grandiosity often doesn't
really get you to the end of the day.

[00:15:26.876]
In any case, we started doing field studies.

[00:15:31.596]
This is in Kenya where I was going out to
get some lymphocytes from volunteers and the.

[00:15:37.996]
President Obama, by the way,
is from Western Kenya.

[00:15:42.846]
This town, Kisumu, where this plane crush was.

[00:15:46.236]
And he is a Luo.

[00:15:48.106]
And the ruling tribe in Kenya are the Kikuyu.

[00:15:52.726]
And in this particular plane the pilot
was a Kikuyu and the co-pilot was a Luo.

[00:15:58.146]
And they had a fight and forgot
to put the landing gear down.

[00:16:01.096]
And so we like.

[00:16:01.746]
This is how we landed about
a kilometer from the.

[00:16:06.306]
From the terminal.

[00:16:08.326]
Next slide.

[00:16:09.876]
There was some pleasure associated with it.

[00:16:12.326]
That's my wife, Dr. Sim.

[00:16:13.726]
Next slide.

[00:16:15.596]
And some, you know, interesting
ways of bathing out on field trips.

[00:16:21.246]
Next slide.

[00:16:22.666]
But in any case how did we end up,
I'm going to truncate some years here,

[00:16:27.786]
getting from those early studies to Sanaria?

[00:16:32.796]
So we. In '87, or '86-'87, when we
were a bit disappointed by the results,

[00:16:39.826]
we began testing multiple subunit vaccines
based on the circumsporozoite protein

[00:16:45.776]
which is the major surface
protein on sporozoites.

[00:16:48.966]
And it is the basis of the
vaccine of which there's been a lot

[00:16:52.366]
of publicity recently called RTSS
ASO1 developed by Glaxo Smith Kline

[00:16:58.666]
and the Walter Reed Army Institute of Research.

[00:17:00.636]
And the furthest one along.

[00:17:02.206]
And what we were testing was
the actual predecessor of that.

[00:17:05.906]
So we've actually been working
on that particular protein

[00:17:09.436]
as a vaccine since 1984, and that's 25 years.

[00:17:14.276]
And it's still got a ways to go.

[00:17:17.036]
In any case, it wasn't giving us the
results that we thought we needed.

[00:17:21.396]
And so we began playing with
other formulations of it.

[00:17:24.056]
We expressed it in different ways.

[00:17:25.516]
Made conjugates.

[00:17:26.956]
Gave it with multiple different adjuvants.

[00:17:29.396]
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

[00:17:41.276]
to prevent malaria in Marines
and, and Navy Seals and so on.

[00:17:47.416]
And that, for a vaccine like that, it has to be
90% efficacious or I can't go to the commandant

[00:17:53.836]
of the Marine Corps and say I got a vaccine.

[00:17:56.336]
Or I couldn't send any of, anybody in
this room on a safari to Kenya or to work

[00:18:01.316]
in the Peace Corps or to do some type of work.

[00:18:03.866]
You need a vaccine that really is protective
if you're going to forego a medication.

[00:18:09.416]
And I came to the conclusion in 1989
that a single protein vaccine wouldn't,

[00:18:15.516]
no matter how it was delivered, would never
give that degree of protective immunity.

[00:18:20.156]
And even against the same strain of parasite.

[00:18:23.766]
But the fact is that we can go to Kenya today
or somewhere, and one kid will be infected

[00:18:28.986]
with ten different strains of
Plasmodium falciparum that vary

[00:18:32.976]
at key epitopes in that particular protein.

[00:18:36.886]
So we decided to start immunizing people by
the bite of irradiated infected mosquitoes.

[00:18:44.576]
Now, it had been shown in the early 1970s that
you actually could immunize people by the bite

[00:18:49.756]
of irradiated infected mosquitoes,

and a few people had been protected.

[00:18:53.586]
And that was the foundation for the
discovery of the circumsporozoite protein

[00:18:57.736]
by Dr. Nussenzweig's group at
NYU with the idea that maybe

[00:19:02.106]
that was what the immunity was against.

[00:19:04.786]
And it seemed clear to me that it wasn't,
except there were 5,000 genes in the genome.

[00:19:09.386]
That it's unlikely that it
was against one protein,

[00:19:12.606]
particularly since we couldn't measure very
good immune responses against that protein

[00:19:16.966]
and people immunized with irradiated sporozoite.

[00:19:19.066]
So we decided to start reimmunizing people
by the bite of irradiated infected mosquitoes

[00:19:25.946]
that have these sporozoites
in their salivary glands.

[00:19:28.656]
And to determine the mechanisms of
protective immunity, the immune mechanisms.

[00:19:34.796]
The targets of the protective immunity,
meaning which pieces of the parasite.

[00:19:39.316]
Which means, which proteins, which epitopes

[00:19:42.066]
on those proteins were the
targets of the protection?

[00:19:44.666]
And then to build a subunit vaccine.

[00:19:48.736]
Anybody tell me what a subunit vaccine is?

[00:19:51.786]
[00:19:54.676]
What do you think sub unit means?

[00:19:57.176]
I mean it's part of the whole.

[00:20:00.106]
So that in all of us in this room have been
potentially immunized with about 26 vaccines,

[00:20:08.986]
which are on the market in the United States.

[00:20:11.346]
Of those, there are two recombinant
protein subunit vaccines.

[00:20:17.136]
Anybody know what those are?

[00:20:18.606]
>> Hepatitis.

[00:20:19.746]
>> Dr. Hoffman: Hepatitis B and?

[00:20:22.916]
I'm sure there's some women here who
got this vaccine in the last few years.

[00:20:27.046]
HPV, Human Papillomavirus Vaccine.

[00:20:30.456]
That's it.

[00:20:31.116]
There's only two.

[00:20:32.196]
We've been working on this for 25 years,
and we've only managed to get two on.

[00:20:37.126]
All of the other vaccines come from material
actually made by the infectious agent

[00:20:42.806]
that we're trying to immunize against.

[00:20:44.566]
And half of those, or 16 of the 26, are
actually the entire infectious agent.

[00:20:50.206]
And 13 of those are what
we call live attenuated.

[00:20:53.626]
They're actually the virus or bacteria itself

[00:20:56.926]

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

[00:22:13.436]
from TIGR, The Institute for Genomic
Research, and we had become quite friendly.

[00:22:18.046]
And he had announced in 1998 that despite
the fact that the public sector was going

[00:22:25.196]
to sequence the human genome
in ten years for $3 billion,

[00:22:29.916]
that he was going to do it in
three years for $300 million.

[00:22:34.086]
And he kept coming to me and
saying, you know, like join Celera.

[00:22:38.326]
We'll do this, you know.

[00:22:39.126]
We'll turn.

[00:22:39.686]
You'll turn the genome into
new biologics and so on.

[00:22:43.066]
And I said well, I got like one more year in the
Navy and I can get my retirement, so let's wait.

[00:22:49.506]
But in any case, around this time at 2000
I retired from the Navy and joined Celera

[00:22:56.236]
to be the head of biologics to turn the human
genome into new immunotherapeutics for cancer.

[00:23:04.286]
And I guess that was because I had been so
successful or unsuccessful for malaria I might

[00:23:09.116]
as well try something else that was easy.

[00:23:12.026]
Like cancer, right?

[00:23:13.316]
In any case, Celera was really quite an
incredibly exciting place at the time.

[00:23:19.226]
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

[00:23:34.696]
by the bite of irradiated infected mosquitoes.

[00:23:37.616]
And I, to my astonishment I
looked at it and I said, you know,

[00:23:42.756]
I've been wasting my time
for the last 10 or 15 years.

[00:23:45.886]
If I had tried to make a vaccine out of
sporozoites, we would have a vaccine because.

[00:23:52.606]
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

[00:24:17.006]
with live non-irradiated
mosquitoes with sporozoites in them.

[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,

[00:24:28.486]
up to 10 weeks after their last exposure
were completely protected against malaria.

[00:24:34.526]
In the next row down, six of those people
were rechallenged within 10 weeks 15 times.

[00:24:41.476]
There was 100% protection.

[00:24:43.616]
And six people were challenged
as late as 42 weeks,

[00:24:48.636]
nine-and-a-half months after
their last exposure.

[00:24:51.926]
And five of the six were
completely protected of malaria.

[00:24:54.716]
If you look up in the right-hand
corner, you'll see 33 out of 35.

[00:24:58.606]
So there's been 35 challenges and
total protection against malaria in 33

[00:25:04.226]
out of the 35 challenges, or 94%.

[00:25:07.376]
Now, that's as good a protective immunity
as any vaccine for any indication.

[00:25:11.856]
If you go down on the immunizing
bites, the last row there,

[00:25:15.686]
less than 1,000 the protection goes down.

[00:25:18.226]
So there's a dose response.

[00:25:19.696]
You need a certain level of, of the vaccine,
which is not dissimilar to other vaccines.

[00:25:25.326]
You need a dose to get to, at
which point you have protection.

[00:25:28.506]
Next slide.

[00:25:29.756]
So as I said, these are limited studies.

[00:25:31.716]
Thirty-five challenges in 14 people.

[00:25:33.716]
But the protective immunity was
as good as the protective immunity

[00:25:37.036]
of any vaccine for any indication.

[00:25:38.866]
Next slide.

[00:25:40.446]
This hadn't been.

[00:25:41.216]
There had been some indication of this in the
literature before, so why wasn't it pursued?

[00:25:46.846]
Well, at the sporozoites, the immunogen were in
mosquitoes and no one had ever made a vaccine

[00:25:54.626]
in mosquitoes, or any other
biologic for that matter.

[00:25:58.256]
And then of course, as I said,
we had the discovery and,

[00:26:02.346]
and cloning of these major targets.

[00:26:04.656]
The circumsporozoite protein at the
sporozoites thieves or the parasites life cycle.

[00:26:09.976]
The merozoite surface protein
1 at the red blood cell stage.

[00:26:16.536]
And so everybody had thought
for the last 15 years

[00:26:20.736]
that a subunit recombinant vaccine was imminent.

[00:26:24.836]
Well, the imminence gets old after a while.

[00:26:27.966]
And so, next slide, I decided to resign
from Celera and start Sanaria in my kitchen

[00:26:37.876]
with my now, the son who had been with me out
in the Highlands of New Guinea had graduated

[00:26:43.836]
from college, gone off to Hawaii for a year
where he was like a mate on a. First mate

[00:26:49.246]
on a 65-foot catamaran taking
people snorkeling and scuba diving.

[00:26:54.376]
And decided he wanted to go to law school.

[00:26:57.326]
He called me up and then had to
take some, you know, to apply.

[00:27:01.076]
So he came to work with me
and we started the company.

[00:27:04.866]
And what was the rationale?

[00:27:06.706]
First of all, we had an immunogen, maybe for
the first time in history of vaccinology,

[00:27:11.846]
for a vaccine for a disease for which there
wasn't a vaccine we actually knew something

[00:27:16.756]
that worked.

[00:27:17.326]
We didn't have to discover it.

[00:27:19.076]
We didn't have to do any fancy immunology

[00:27:21.926]
or molecular biology to find
out what the target was.

[00:27:24.736]
It was there staring at us in the face.

[00:27:27.456]
The success was going to
be based on bioengineering

[00:27:30.536]
and applied entomology, parasitology
and biology.

[00:27:33.696]
Meaning producing a vaccine in mosquitoes

[00:27:36.326]
and controlling all the elements
of the production process.

[00:27:39.426]
And remember, I'd just come from this place
Celera where the impossible had been achieved.

[00:27:44.506]
And so there was the sense that
one with good people, good team,

[00:27:49.126]
focused effort could actually solve something.

[00:27:52.886]
And then I called up, I wasn't that nuts, and I
called up the head of the Center for Biologics

[00:27:57.176]
at the FDA and said, you know,
I'm thinking about doing this.

[00:28:01.056]
Am I off my rocker here?

[00:28:02.486]
I mean, you know.

[00:28:03.826]
And the FDA became quite
supportive of what we were doing.

[00:28:07.316]
And then I called up a fellow by
the name of Maurice Hillerman,

[00:28:10.496]
and he was the director of
the Merck Vaccine Institute.

[00:28:13.826]
And he is personally responsible for half the
vaccines that anybody in this room has received.

[00:28:20.336]
There's a fantastic book written by Dr. Offit
called Vaccinated, which is his biography,

[00:28:27.836]
which just came out, and I
really would recommend that.

[00:28:30.046]
A tremendous guy.

[00:28:31.476]
And he became incredibly excited and
the first member of our advisory board.

[00:28:36.556]
And we thought that we had a plan for paying
for development and deployment in Africa

[00:28:41.256]
because we would have the same
vaccine for the entire world,

[00:28:43.966]
and there was a potential
traveler's market for this vaccine.

[00:28:47.076]
Next slide.

[00:28:48.746]
So our approach was different
than all other approaches

[00:28:55.776]
for malaria vaccine development
in two fundamental ways.

[00:28:59.766]
One is ours was live attenuated.

[00:29:02.986]
And remember, the majority of vaccines
that we've gotten are live attenuated.

[00:29:06.376]
All other approaches were subunit recombinant.

[00:29:09.306]
And the second was that we were
aiming to prevent infection

[00:29:14.196]
in greater than 90% of recipients.

[00:29:16.546]
And not because they didn't want to, but
all of the other approaches were aimed

[00:29:20.096]
at reducing the rate at which people
become infected to reduce the morbidity

[00:29:25.066]
or the illness associated and mortality.

[00:29:28.496]
But not to prevent infection
because it was not possible to do

[00:29:31.826]
with those approaches to vaccine development.

[00:29:34.276]

So we were rather grandiose, and still
are, in terms of getting off the ground.

[00:29:38.696]
Next slide.

[00:29:40.526]
So why we're working on an attenuated live
vaccine and not a recombinant or synthetic?

[00:29:45.476]
Next slide.

[00:29:46.946]
Because it has to do with the
intended characteristics of the vaccine

[00:29:50.536]
of getting greater than 90% protection.

[00:29:53.096]
Next slide.

[00:29:54.416]
And so this level of protection had been
elicited by the immunogen, these sporozoites,

[00:30:01.556]
but never by any subunit recombinant approach.

[00:30:04.516]
Nothing even close.

[00:30:05.766]
Next slide.

[00:30:07.146]
And so who would be immunized
to fulfill our mission?

[00:30:09.756]
The primary target group is the
infants in sub-Saharan Africa.

[00:30:14.876]
There's 25 million born annually, and a million

[00:30:18.986]
of that 25 million eventually
die of malaria, so 4%.

[00:30:22.956]
They all get malaria, pre-adolescent
and early adolescent girls.

[00:30:27.396]
There's a new cohort of 7.5 to 10 million
annually, and this would be to reduce fetal loss

[00:30:33.926]

and morbidity and mortality in the offspring
associated with the low birth weights,

[00:30:37.826]
which are associated with malaria.

[00:30:39.526]
How long did I say that we
know this vaccine lasts for?

[00:30:42.516]
>> (Inaudible).

[00:30:44.976]
>> Nine-and-a-half to 10 months.

[00:30:46.256]
How long does pregnancy last for?

[00:30:47.656]
>> Nine months.

[00:30:49.106]
>> Okay. It would be a pretty.

[00:30:49.996]
Potentially a pretty good vaccine if
you could immunize before pregnancy.

[00:30:53.596]
Now, we don't know how long it lasts for.

[00:30:55.186]
I only know it lasts for at
least nine-and-a-half months.

[00:30:57.776]
We haven't tested it beyond that, and that
would be part of our vaccine-testing program.

[00:31:02.466]
Travelers from non-endemic
countries which there's, you know,

[00:31:06.916]
tens of millions, estimated 100 million.

[00:31:09.306]
And then there's many other
populations in the developing world.

[00:31:12.416]
And as we get better at something.

[00:31:16.256]
Having. As we're getting
better at controlling malaria.

[00:31:18.606]
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]
[00:31:46.566]
Next. Okay.

[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.

[00:32:14.846]
One nucleus.

[00:32:16.636]

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.

[00:33:42.346]
The merozoites when they're released from
the red blood cells, or those gametocytes.

[00:33:47.156]
It's only the cycle of invasion, development,
rupture, and reinvasion of red blood cells

[00:33:53.216]
that cause the disease we know as malaria.

[00:33:57.286]
So if you were going to develop a
vaccine, what would you target it against?

[00:34:02.876]
[00:34:04.016]
Anybody?

[00:34:04.296]
>> (Inaudible).

[00:34:06.056]
>> Dr. Hoffman: What?

[00:34:06.566]
>> The pre-blood stages.

[00:34:08.516]
>> Dr. Hoffman: The pre what?

[00:34:09.766]
>> Pre-blood stages.

[00:34:10.396]
>> Dr. Hoffman: Pre-blood stages.

[00:34:11.266]
Good. It's called pre-erythrocytic stages.

[00:34:14.346]
That's when you have a chance.

[00:34:15.416]
There's no symptoms, signs,
pathology associated with it.

[00:34:20.486]
Now, ideally you would like to
target the sporozoite, right?

[00:34:23.486]
The first stage, but you have about
five minutes to do the job there.

[00:34:27.706]
And if you get, you know, if you get 90% of them
and one gets through, what happens a week later?

[00:34:33.276]
There's 40,000 coming out
the back door of the liver.

[00:34:36.846]
So whereas you have a week
to attack them in the liver.

[00:34:41.906]
And the immune responses that you would
like to engender, where you can engender,

[00:34:46.906]
is antibodies against the sporozoites
because they're extracellular.

[00:34:51.216]
Or T cell responses against
the infected hepatocyte.

[00:34:54.296]
So what happens with a radiation
attenuated sporozoite?

[00:35:00.166]
The sporozoites look identical
to non-irradiated sporozoites.

[00:35:05.206]
They wiggle on a slide the same way.

[00:35:08.016]
They actually invade liver
cells exactly the same way.

[00:35:13.036]
And they start to express new proteins
exactly the same way for the first three days.

[00:35:18.286]
After they go into hepatocyte, you can't tell
the difference physically, or if by microscopy,

[00:35:24.716]
between irradiated or non-irradiated sporozoite.

[00:35:27.746]
At that point the irradiated sporozoite stop.

[00:35:31.526]
They don't replicate.

[00:35:33.116]
They don't make those 10,000 nuclei.

[00:35:37.096]
So the parasites are metabolically
active but non-replicating.

[00:35:43.566]

And that means that the only place
they can induce an immune response

[00:35:47.876]
against is the sporozoites to make
antibodies, or the early liver stage T cells.

[00:35:55.146]
And we believe that the primary
protective immune response is T cells

[00:36:00.246]
against the early liver stage.

[00:36:02.076]
So that if you get immunized properly
your body has learned how to respond,

[00:36:07.306]
and it makes these antibodies and T cells which
prevent the parasite from ever developing.

[00:36:14.046]
Next slide.

[00:36:15.446]
So all we.

[00:36:17.446]
Back up for a second.

[00:36:18.396]
So that what we had to do was
figure out how are we going

[00:36:22.796]
to in the laboratory make
these sporozoites and put them

[00:36:26.676]
in a bottle, and keep them stable and potent?

[00:36:30.376]
And they have to be, as I tell you, sterile.

[00:36:34.266]
And so that the way that we do
that is, we take gametocytes,

[00:36:37.706]
those things at the bottom, and culture them.

[00:36:39.946]
We grow sporozoites, mosquitoes.

[00:36:42.256]
They have to be sterile.

[00:36:45.046]
Feed them.

[00:36:46.146]
Allow the parasites to develop so the mosquito
becomes like the bioreactor or the cell line.

[00:36:52.606]
And then at the end of two
weeks extract the sporozoites,

[00:36:56.346]
purify them, and put them in a bottle.

[00:36:58.066]
Next slide.

[00:36:58.646]
Easier said than done.

[00:36:59.656]
So we. Since we started Sanaria,
we've had several phases.

[00:37:04.346]
First was research and development
to figure out how to do this.

[00:37:07.546]
The second was process development where
you turned it into a manufacturing process.

[00:37:12.376]
The third was magically manufacturer.

[00:37:14.686]
And the fourth, which is going to begin in
April or May, is to start clinical trials.

[00:37:19.046]
Next slide.

[00:37:21.196]
Research and development.

[00:37:22.156]
Next slide.

[00:37:23.216]
So we had three questions when we started.

[00:37:25.586]
Could one administer the vaccine by a
root that was applicable for a vaccine?

[00:37:30.266]
You can't give it by the bite of
irradiated infected mosquitoes.

[00:37:35.196]
And all the mouse studies that had been
done had been by inoculating intravenously

[00:37:39.616]
which is we really can't,
don't do that for a vaccine.

[00:37:42.896]
So we did an experiment right at the beginning
where we gave the sporozoite subcutaneously

[00:37:47.506]
like many of our vaccines, and
we got 100% protection in mice.

[00:37:51.616]
There's really no place to go
after that except for the humans.

[00:37:55.866]
Second was could we produce
adequate quantities of sporozoites?

[00:37:58.736]
Everybody said it's impossible.

[00:38:00.026]
You'll never be able to produce them.

[00:38:01.796]
The answer is yes, and I'll
tell you about that in a second.

[00:38:04.876]
The third is, and this was the hardest one,

[00:38:07.236]
could one at a reasonable cost
produce attenuated sporozoites

[00:38:10.636]
that meet regulatory requirements
to be a vaccine?

[00:38:14.276]
So what do you think the regulatory
requirements to be a vaccine were?

[00:38:17.366]
>> Immunology?

[00:38:18.866]
[00:38:20.136]
>> Dr. Hoffman: What?

[00:38:20.801]
>> (Inaudible).

[00:38:23.126]
>> Dr. Hoffman: The most
important one is sterile, right?

[00:38:24.846]
I mean you can't be injecting stuff.

[00:38:26.686]
And has anybody ever been in an insectory?

[00:38:29.416]
Like where you've grown mosquitoes
with malaria in them?

[00:38:31.496]
It feels like you're in like the heart of
darkness in Africa or something like that.

[00:38:35.696]
You can almost feel the fungi and the
bacteria in the air and on the surfaces.

[00:38:41.076]
So how could we do this?

[00:38:43.456]
Next slide.

[00:38:44.396]
So we had to make a vaccine that was free.

[00:38:46.536]
And you can't.

[00:38:47.496]
If it's live, you can't sterilize it.

[00:38:51.136]
It has to be sterile through the whole
process, which takes six weeks to produce.

[00:38:56.136]
And so we had to have it free of
pathogens, free of mosquito material.

[00:39:01.986]
Adequately attenuated so
it wouldn't cause malaria.

[00:39:05.506]
And potent, and it had to stay
potent in a bottle and we had

[00:39:09.156]
to develop the method of doing that.

[00:39:10.636]
Next slide.

[00:39:12.696]
So we did that.

[00:39:13.486]
It took about two years and we

figured how to do all of those things.

[00:39:17.496]
And then we had to move from there.

[00:39:19.336]
We had a group of laboratory scientists,
none of whom had ever manufactured anything

[00:39:25.176]
or had any industry experience in
manufacturing, to make the vaccine.

[00:39:31.336]
So fortunately, Dr. Sim, my wife, had actually
worked as the head of R&D at a biotech company

[00:39:38.016]
where she had manufactured about 40 kilograms
of an anti-cancer agent called Angiostatin

[00:39:44.336]
and Endostatin under GMP that
went into people intravenously.

[00:39:49.406]
So she became the head of vice.

[00:39:51.246]
She had her own company, but she became
the head of manufacturing for Sanaria,

[00:39:55.486]
and worked with our scientists, next slide,
over the course of a year training them on how

[00:40:01.076]
to do GMP, taking courses, writing
the SOPs, batch records and so on.

[00:40:06.046]
And did 12 end-to-end practice runs
during that year, each one takes six weeks

[00:40:11.866]
so they were overlapping, to get the
team in shape to actually manufacture

[00:40:16.556]
because there was no place
else you could go to do this.

[00:40:18.866]
Nobody had the capability,
understanding or facilities to do it.

[00:40:22.256]
Next slide.

[00:40:23.916]

And then so they were ready to manufacture.

[00:40:26.446]
And so in the spring of 2007 we
started to manufacture a vaccine

[00:40:33.186]
for what's called preclinical
toxicology studies.

[00:40:35.856]
In order to get it passed with the FDA
you have to show in animals that it's safe

[00:40:41.056]
and meets all these requirements of
sterility, purity, potency, and attenuation.

[00:40:46.446]
Next slide.

[00:40:47.776]
And so when you manufacture you
don't manufacture more than you need.

[00:40:53.816]
And we need to determine that in order
to do the quality control release assays,

[00:40:59.116]
again which is sterility, purity, potency and
safety, and attenuation, the stability studies

[00:41:05.376]
to show the stuff would work over time.

[00:41:08.206]
The toxicology studies, the
biodistribution studies.

[00:41:12.546]
And to retain some we needed
228 vials of vaccine.

[00:41:16.436]
Next slide.

[00:41:17.846]
And so what you can see there is that we did
four back-to-back production campaigns called 7,

[00:41:25.306]
8, 9, and 10 at two-week intervals,

[00:41:28.116]
so that's it's a six-week process
overlapping by two-week intervals.

[00:41:32.236]
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

[00:41:57.586]
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

[00:42:08.196]
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,

[00:42:23.996]
you know, the outer layer of the skin?

[00:42:26.246]
Anybody doing any immunology
work here on T cells?

[00:42:29.336]
>> Just the rabbit (inaudible).

[00:42:31.116]
>> Dr. Hoffman: What?

[00:42:31.286]
>> Just the rabbit sector.

[00:42:32.936]
>> Dr. Hoffman: Well, that's one thing.

[00:42:33.606]
So mosquitoes inoculates
sporozoites in the dermis.

[00:42:37.506]
So we though hey, let's not try to
get smarter than the mosquitoes.

[00:42:41.036]
Let's do that.

[00:42:42.106]
But also, the dermis has the highest
concentration of the important dendritic cells,

[00:42:48.926]
the antigen-presenting cells, which
are important for T cell responses.

[00:42:53.826]
But it's really hard to give it in the dermis.

[00:42:56.366]
But we had a lot of fighting back and
forth and controversy with the funders.

[00:43:00.056]
And finally, we convinced them to do two groups.

[00:43:03.636]
Now, this is really astonishing.

[00:43:05.986]
Next slide.

[00:43:07.476]
So we did one group of rabbits, 24 rabbits.

[00:43:10.376]
We gave the vaccine intradermally
in males, females, and so on.

[00:43:14.446]
And the other we gave it subcutaneously.

[00:43:16.876]
The exact same vaccine, the exact same
dose, the exact some dosing interval.

[00:43:22.866]
And the antibody responses

were 10 to 15 times higher

[00:43:27.426]
when we gave it intradermally
versus subcutaneous.

[00:43:30.506]
We didn't measure T cell responses.

[00:43:31.936]
We don't do that in rabbits.

[00:43:33.436]
But this is rather extraordinary.

[00:43:35.526]
If you're me sitting here, thinking
about I'm going to give this vaccine,

[00:43:38.676]
which I really don't know how to give it.

[00:43:40.366]
No one's had any experience.

[00:43:42.146]
And I've already shown just
changing by a few millimeters

[00:43:46.046]
where I put it can have this dramatic effect

[00:43:48.936]
on the immune responses, how
do I know what I'm doing?

[00:43:52.786]
I mean. And I can't test everything, but.

[00:43:56.936]
So that's that result.

[00:43:58.136]
And then we did some biodistribution
studies, next slide, and they were.

[00:44:02.466]
Had no unexpected results.

[00:44:03.786]
So we're now into, next slide,
the situation where we had.

[00:44:09.296]
We're manufacturing this
in a place that was termed

[00:44:12.486]
in National Geographic a
dismal strip mall in Rockville,

[00:44:16.906]
Maryland where we couldn't
control the temperature.

[00:44:19.276]
We couldn't control what was in the air.

[00:44:21.016]
We had flooding.

[00:44:22.406]
We would, you know, freeze
the place up and so on.

[00:44:25.516]
And our GMP.

[00:44:26.216]
And we. And we produced perfect material.

[00:44:29.286]
It was sterile, pure, safe, and so on.

[00:44:32.926]
But the GMP, the consultants for
manufacturing, said there's not a chance

[00:44:36.686]
in the world you're going to make
a vaccine in this place and give it

[00:44:39.956]
to people even though it meets all those,
you know, the testing requirements.

[00:44:45.206]
Next slide.

[00:44:46.856]
And so we were fortunate to get a large
grant PATH Malaria Vaccine Initiative,

[00:44:52.306]
with money from the Bill and Melinda
Gates Foundation about $30 million.

[00:44:56.216]
And we were able to rent a
part of this facility here.

[00:44:59.666]
Only about 10% so far, but we're
working on getting the rest of it.

[00:45:04.646]
And build from scratch a
custom-made manufacturing facility

[00:45:09.546]

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

[00:45:32.016]
for manufacturing a live malaria vaccine.

[00:45:35.876]
And there we have a bunch
of dignitaries, you know.

[00:45:38.946]
Other than my wife and Gina Rabinovich from
the Gates Foundation, it's sort of a series

[00:45:46.696]
of middle-aged men who are going bald,
you know, cutting a ribbon there.

[00:45:50.576]
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.

[00:46:09.226]
Now, how many people here have tried to move
an immunology laboratory across the hall?

[00:46:14.036]
All right?

[00:46:15.296]
And how long does it take from the assays
that worked year-in year-out to work well?

[00:46:20.726]
You know, a lot of people said, Steve, you're.

[00:46:22.316]
You're nuts.

[00:46:22.876]
I mean it's never going to work.

[00:46:24.066]
And I said naw, it's going to work.

[00:46:25.836]
We know how to do this stuff.

[00:46:27.896]
So we went from being the best producers
of sporozoites in the world to the worst.

[00:46:33.866]
First, we couldn't grow the mosquitoes.

[00:46:35.666]
Then we started having like, you know,
instead of 70,000 sporozoites for mosquitoes,

[00:46:39.536]
it was 700, and we're going nuts.

[00:46:42.576]
And you can imagine waking
up at 4:00 in the morning.

[00:46:44.536]
Now I've built this facility.

[00:46:46.226]
I'm spending money like water and nothing works.

[00:46:50.136]
And you don't know if it's the water.

[00:46:51.246]
Could be, you know, different water.

[00:46:53.086]
It could be this and that.

[00:46:54.516]

Fortunately, the manufacturing team solved it.

[00:46:58.606]
And we then moved.

[00:47:01.596]
Next slide.

[00:47:03.126]
This is the team.

[00:47:05.486]
Tremendously dedicated people, next slide, to
what we call production campaigns 20 to 25.

[00:47:12.716]
Now remember, we started pieces
7, 8, 9, and 10 were the tox runs.

[00:47:17.006]
Eleven to 19 didn't work.

[00:47:18.586]
All right?

[00:47:20.136]
And. But then we went in and we nailed
six in a row at two-week intervals,

[00:47:26.736]
and those were the lots of
vaccine for the clinical trials.

[00:47:30.916]
Next slide.

[00:47:32.606]
And then here again we needed to make
enough for the release at quality control.

[00:47:36.746]
Release assays, retention samples, stability
assays, and the first clinical trial,

[00:47:41.436]
which has a 100 volunteers in it, which is
huge for a first in human's clinical trial.

[00:47:46.036]
Next slide.

[00:47:46.936]
And here again we made, if you look at
the bottom row, we needed about 440 vials.

[00:47:51.926]
We made an average of 570.

[00:47:53.876]
We always made what we needed.

[00:47:56.176]
We averaged about 70,000 sporozoites for a
mosquito which is really incredibly high.

[00:48:01.026]
Next slide.

[00:48:01.896]
And did about 2,800 mosquitoes
dissected per day.

[00:48:07.676]
And then we did a whole series of assays
which, next slide, are listed here.

[00:48:15.346]
We culture the eggs, the pupae,
the mosquitoes, the blood meals.

[00:48:20.106]
And if anything is positive
it all gets thrown out.

[00:48:22.926]
And the team, led by Dr. Billingsley
back there of the Quality Assurance team.

[00:48:28.016]
We turned an entomologist into
a Quality Assurance specialist.

[00:48:31.666]
And everything essentially, you know,
99% of what we cultured was sterile.

[00:48:38.076]
So it's really quite remarkable.

[00:48:40.266]
I can't believe it.

[00:48:41.376]
That we can go for six weeks with mosquitoes
and all this stuff and all these moving parts,

[00:48:46.956]
and come up with a sterile product at the end.

[00:48:49.516]
Next slide.

[00:48:49.986]
And these are just some of the kind of
tests that you do which are pretty standard.

[00:48:54.986]
Next slide.

[00:48:56.786]

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.

[00:49:23.456]
Next slide.

[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.

[00:49:57.986]
Next slide.

[00:49:59.716]
And we have our first Phase 1 trial
with challenge in the United States.

[00:50:03.656]
Next slide.

[00:50:04.206]
And it's going to be run by two teams.

[00:50:08.136]
The U.S. Military Malaria Vaccine program.

[00:50:10.916]
The Naval Medical Research Center.

[00:50:12.706]
Dr. Judy Epstein and Tom Richie.

[00:50:14.716]
And the University of Maryland
Center for Vaccine Development.

[00:50:17.706]
We have two teams because it's too
big for one team to do this trial.

[00:50:21.616]
They have done an incredible amount of work.

[00:50:23.546]
Dr. Kirsten Leich and Bob Eddleman
are putting together the protocols.

[00:50:27.396]
They've had to go through five what are
called IRB's, Investigational Review Boards,

[00:50:32.736]
committees for protection of human subjects,

[00:50:35.086]
because of all the organizations
that are involved.

[00:50:37.586]
Next slide.

[00:50:39.326]
Next slide.

[00:50:40.526]
And so this kind of goes over the design of the
trial, and it's called a Dose Escalation Study.

[00:50:48.636]

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. 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.

[00:51:55.486]
And this. Next slide.

[00:51:58.296]
And this adds up to there's
the numbers of volunteers,

[00:52:00.556]
and you can see the different groups.

[00:52:02.676]
It's a total of 104 because we
have six infectivity controls.

[00:52:07.436]
Everybody.

[00:52:07.696]
Anybody who wants to sign
up to come up for that.

[00:52:10.136]
You don't get the vaccine, but you get malaria.

[00:52:13.296]
You're guaranteed to get malaria.

[00:52:15.786]
So we have to have that, because how else
can you determine if the vaccine works?

[00:52:20.576]
And we've done that now to over
like 1,300 people very safely.

[00:52:26.146]
And people really.

[00:52:28.226]
It's remarkable the number
of people who volunteer.

[00:52:30.566]
They get paid also, but they really want
to be involved in this type of work.

[00:52:35.636]
Next slide.

[00:52:38.436]
Next. And this is just timeline.

[00:52:42.026]
Submitting the IND at the end of this month.

[00:52:44.376]
Starting recruitment at the end of next month.

[00:52:46.326]

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

[00:53:13.266]
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?

[00:53:39.406]
What's the best way to do this?

[00:53:40.826]
And nobody has any idea.

[00:53:43.676]
And obviously the only way to test it
is human beings, and we have no way

[00:53:48.056]
of doing this many studies in human beings.

[00:53:50.236]
So you're always taking your best guess.

[00:53:53.256]
And it's scary, you know.

[00:53:54.316]
You invest five years.

[00:53:56.276]
By the time we finish the study we'll
have invested almost $60 million in this.

[00:54:00.966]
And we're shooting in some respect in the dark.

[00:54:05.046]
So we're trying to minimize, but there's all
kinds of issues that we're going to have to test

[00:54:09.296]
in what we call clinical vaccinology.

[00:54:11.806]
Now, by the time we get done, in order
to get this over the finish line,

[00:54:16.496]
which means a licensed vaccine, anybody
have any estimate to what it would cost?

[00:54:21.516]
( Silence )

[00:54:25.236]
So what did, would, you know.

[00:54:27.336]
I'm sure somebody must in here demonstrated
about how bad the pharmaceutical industry is

[00:54:31.606]
and how much money they charge and so on.

[00:54:33.906]
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?

[00:54:58.696]
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.

[00:55:36.606]
So we've already had a site visit team that's
gone to four countries in Africa to plan

[00:55:42.946]
for the trial that comes, you know, comes
on from the Malaria Vaccine Initiative,

[00:55:46.806]
the Center for Vaccine Development,
the University of Maryland,

[00:55:50.196]
the Malaria Clinical Trial Alliance from Africa,
and the Naval Medical Research unit in Ghana.

[00:55:58.006]
Next slide.

[00:55:59.266]
And this just shows the different
places that they have gone.

[00:56:02.426]
Next slide.

[00:56:04.116]
And then the question is, how
do we get the vaccine there?

[00:56:06.346]
No one's ever delivered a vaccine in
vapor phase of liquid nitrogen before.

[00:56:10.886]
So we got a $3 million grant from
the NIH to figure out how to do that.

[00:56:15.426]
Next slide.

[00:56:17.416]
And basically Dr. Eric James from
our lab got the slide, you know.

[00:56:24.236]
Shipped it to Ghana.

[00:56:25.886]
First question is, can you get it out
of Customs in time in Ghana, right?

[00:56:29.116]
We have all had problems with that.

[00:56:31.076]
Next slide.

[00:56:32.456]

And this is picking it up
at Customs with the team

[00:56:35.936]
from the Noguchi Memorial Institute
for Medical Research in NACRA.

[00:56:39.846]
And to make a long story short, if you look
up there he shipped it from Washington.

[00:56:46.816]
It went to England then down to Ghana.

[00:56:51.166]
By another small plane out to a
smaller airport in northern Ghana.

[00:56:56.446]
And then by Jeep out to the site.

[00:56:58.756]
At each site he had to test it.

[00:57:00.926]
He had to look at the data recorders and so on.

[00:57:04.096]
And then he shipped it all the way back, and
then we tested it for viability and potency.

[00:57:09.406]
And this was just done in August and it works.

[00:57:12.826]
I mean the system works.

[00:57:13.876]
And we think that we have a very viable
way of doing this and expanding it

[00:57:17.856]
and making it practical for a vaccine.

[00:57:19.786]
Next slide.

[00:57:21.726]
So that's great.

[00:57:23.626]
We've done all this.

[00:57:24.506]
We're going to be testing this vaccine.

[00:57:25.996]
It could be, if all goes well, that by the end

[00:57:29.236]

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.

[00:57:48.056]
Or, you know, 25 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

[00:58:06.036]
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.

[00:58:26.686]
Really exciting.

[00:58:27.686]

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

[00:58:49.046]
of 2008 so we can make genetically
attenuated sporozoites.

[00:58:53.186]
The whole world is working on making mosquitoes

[00:58:56.606]
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

[00:59:28.756]
for eradication, elimination of Plasmodium
falciparum, then eradication of malaria.

[00:59:34.206]
Next slide.

[00:59:35.156]
Next. Next.

[00:59:37.726]
Next. So we can think about different phases in
this, and this is of course truncated, you know.

[00:59:44.006]
From scale-up coverage to
disease and transmission,

[00:59:46.576]
elimination there's a lot of years.

[00:59:48.626]
And. And then to final eradication.

[00:59:51.826]
If we think about the role
of vaccines in that process.

[00:59:56.126]
Next. So we have vaccines that reduce morbidity
and mortality without preventing transmission.

[01:00:01.986]
I told you that that's what everyone
else is working on, except for Sanaria.

[01:00:06.476]
And the only other vaccine that's.

[01:00:08.446]
You know, the one that's further ahead, which
is called the RTSS, doesn't prevent infection.

[01:00:13.716]
It just delays the time until you get infected

[01:00:16.096]
and thereby reduces morbidity
and hopefully mortality.

[01:00:19.926]
Those would be very useful in the first
phases of control, which is actually,

[01:00:25.606]
what we're doing now with bed nets,
spraying, good drugs and so on.

[01:00:30.126]
But, next, if we want to eliminate
then we have to have a vaccine

[01:00:36.196]

that prevents transmission either by
preventing infection, pre-erythrocytic,

[01:00:43.516]
meaning section, meaning blood stage infection.

[01:00:45.606]
Or preventing transmission to the mosquitoes.

[01:00:47.346]
And so we're actually working on both of those.

[01:00:50.516]
Our vaccine I told you about is the
pre-erythrocytic vaccine, the sporozoite.

[01:00:54.856]
But we can also produce parasites that
could be used for another type of vaccine

[01:00:59.526]
to prevent transmission in mosquitoes.

[01:01:01.606]
And these are independent mechanisms.

[01:01:03.756]
And if you combine them.

[01:01:04.976]
Suppose you had a 90% effective vaccine that
prevented the sporozoites from ever getting

[01:01:09.906]
out of the liver into the bloodstream.

[01:01:11.246]
And then you had a vaccine
that was 90% effective

[01:01:15.146]
against preventing the mosquitoes
from being infected.

[01:01:19.126]
That's 99%.

[01:01:21.056]
That by itself would eliminate malaria anywhere.

[01:01:24.106]
So it's a big challenge, but
that's what we're working on.

[01:01:27.046]
Next slide.

[01:01:28.056]
Next slide.

[01:01:30.236]
So how good is good enough?

[01:01:32.716]
You know, again, to get back to, you know,

[01:01:34.486]
I feel that good enough means
80-90-95% protective.

[01:01:38.906]
We'll just have to see.

[01:01:39.716]
I may tell a different story in
six months when we come back here

[01:01:43.346]
and get, you know, less protection.

[01:01:44.936]
We just have.

[01:01:45.906]
We just don't know.

[01:01:47.246]
Next slide.

[01:01:48.716]
We've been fortunate in working with many,
many groups throughout the world in doing this.

[01:01:53.436]
It couldn't possibly have been done just by the
people even on our team, which is now 50 people.

[01:01:58.476]
Particularly the PATH Malaria Vaccine
Initiative, protein potential LSC

[01:02:02.886]
in the U.S. military malaria vaccine program.

[01:02:05.796]
Next slide.

[01:02:07.266]
Funding has come from the NIH, the U.S. Army.

[01:02:10.866]
We even got an earmark.

[01:02:12.956]
You know those terrible things, earmarks?

[01:02:14.976]
Without an earmark scenario, a $4 million
scenario, we'd never have existed.

[01:02:20.826]
And next slide.

[01:02:23.356]
We have tremendous committees, which have
helped us gratis, so we don't pay any

[01:02:27.646]
of our advisory committees, which
are really made up of the luminaries

[01:02:31.256]
of the world and their different areas.

[01:02:33.446]
And they have all just chipped
in to, you know, to work on this.

[01:02:36.166]
It's very unusual.

[01:02:37.236]
I mean unprecedented for a company to have
all the people donating their time to help.

[01:02:42.776]
Next slide.

[01:02:44.666]
And this is the team that gets
up every single day with a dream

[01:02:49.116]
of making a malaria vaccine
that's going to prevent millions

[01:02:52.926]
of deaths in children of the world.

[01:02:55.876]
And that's the team at home.

[01:02:59.506]
That's actually in a placed called
Luang Prabang, which is Lao.

[01:03:03.786]
That's the Mekong River.

[01:03:04.926]
That was last August and so on.

[01:03:06.896]
That's the home team that
keeps me going, so thank them.

[01:03:09.606]
Thank you.

[01:03:10.516]

( Applause )

[01:03:26.560]

[01:03:27.060]