00:05

I want to tell you about a student of mine. A few weeks ago, she was on vacation when at 3am she got a phone call. It was her husband telling her that the city that she was in would be quarantined by 10am. She was in Wuhan, China. The epicenter of the coronavirus outbreak. By 8am she was on the road in a friend's car driving 500 miles to Shanghai Airport. The entire time, she was terrified the authorities would arrest her. She made it out on one of the last flights.

00:44

So we're all relieved that she's back home, safe in the US. But what if I told you she was in this room? What if I told you she was sitting next to you? There's no vaccine. There won't be a vaccine for at least 12 months. And this virus is mutating, so there's no guarantee that the vaccine that we produce 12 months from now will match the mutated virus. We're always playing catch-up. And this is the scenario we're in every time there's an outbreak. Our quarantines are porous, our medical responses are flat-footed.

01:29

The fundamental problem that we face in controlling these outbreaks is that viruses and other infections do two things really well: they mutate and they transmit. Our medical tools do neither of these two things. Our medical tools don't mutate or transmit. We have a fundamental mismatch between our tools, which are static, and the infections, which are dynamic. This mismatch is why we're always flat-footed. This mismatch is why we're playing catch-up. And this mismatch is universal. It's the reason that we have antibiotic-resistant infections that killed 40,000 Americans last year, and it's the reason that the flu vaccine couldn't prevent the flu from killing 60,000 Americans last year. So how do we resolve this fundamental mismatch?

02:34

I've devoted my career to studying and solving this problem. For 100 years, we've used chemicals as drugs to treat infections. Chemicals will never mutate or transmit. Similarly, our vaccines are not designed to mutate or transmit. 20 years ago, I had a radical idea to use the viruses themselves as therapies -- as building blocks for therapies. To build therapies that could mutate and transmit. Let me share with you how we've had a major breakthrough, and we're already testing these new therapies.

03:21

HIV is the most devastating pandemic of our era. 75 million infected; 33 million dead. Most of us think that HIV is a solved problem. We have truly amazing antiviral drugs: they're safe and effective, and we've spent 15 years and billions of dollars deploying these drugs around the world. So let's look at the numbers.

03:49

In 2019, 1.7 million people acquired HIV. This number only hit home for me last year when I visited this rural village outside of Durban, South Africa. I was driving along this dirt road with my 10-year-old daughter in the back seat, and walking next to us on the side of the road were girls, the same age as my daughter, barefoot. My daughter asked about why these girls are barefoot and I had to explain disparity to her, which was hard. But what really shocked me was when my colleagues, the local African scientists explained to me that these young girls the same age as my daughter --

04:37

(Breathes)

04:38

sorry -- had an 80 percent chance of acquiring HIV in their lifetime. It blew me away. How can these girls have an 80 percent risk if we have safe and effective drugs?

04:54

The reason is the fundamental mismatch. It creates barriers to controlling infectious disease, particularly in resource-limited settings. The first barrier is mutation: viruses mutate, our drugs don't. The second barrier: adherence. It's really hard to get these drugs to those who need the most. I can't even adhere to a week-long antibiotic regimen in this country. We're asking those in resource-limited settings who face enormous adversity to adhere to lifelong regimens.

05:32

And the third barrier is deployment, or access. It's super hard to get these drugs to those who need them most. Not these girls but those who engage in high-risk activities, such as commercial sex work and injection drug use. In the epidemiological parlance, these groups are called "super-spreaders." And in the 1900s, a small subset of super-spreaders drove HIV along the Trans-Africa Highway and spread the virus through the continent like this. These groups are exceptionally hard to identify, they're small, they face enormous social stigma so they don't self-identify and they're the ones we need to get to the most. All of these barriers combined created the situation we have today, where greater than 15 percent of people in Southern Africa live with HIV.

06:34

Now, conventional wisdom is: what we need to do is get more drugs to more people more effectively. I'd argue we need to solve the fundamental mismatch; we need to eliminate these barriers. If we can build therapies that mutate and transmit, we can overcome drug resistance, overcome adherence barriers, and if we do it properly, we will convert the super-spreaders from the greatest barrier to the most powerful deployment strategy that we can imagine.

07:12

This is a radical concept. It has huge potential payoff, but there's a catch. And it's serious. Before we deploy a therapy that may transmit, even if it's only in a limited population of already infected individuals, before we do this, we need to be exceptionally careful, and we need to test safety in the most rigorous ways possible. The reason I'm here today is because for the first time 20 years, we got it to work, and this is the first time I'm sharing it publicly.

07:52

(Applause and cheers)

08:01

Last two times I did this I cried, so --

08:03

(Laughter)

08:06

So in order to help you understand this breakthrough, let me take you back 20 years to 1999. I was a graduate student in Berkeley, California, studying the biophysics of HIV. For such a complex epidemic, the simplicity of this virus fascinated me. HIV, like all viruses, is just an instruction set -- malware. It hijacks a cell and converts that cell into a factory to do one thing: single-mindedly churn out more virus. All the normal functions of the cell get wiped away. HIV infects the white blood cell that keeps us healthy. This cell has already been hijacked and converted into a factory. And if we magnify, we can see the anatomy of the virus. Those squiggly red lines in the middle? That's HIV's instruction set. Its genetic material.

09:03

This genetic material directs the hijacking process, converting that cell into a factory first to make more copies of the instruction set, and then all the other components of the virus and assemble them into a particle. This is how the virus replicates. Each of these particles can go in and hijack a new cell. This is how the virus transmits. And every time a cell is hijacked, little mistakes are made in copying the genetic material. That's how the virus mutates. This ability to replicate, transmit and mutate is something that our current drugs cannot do.

09:48

So, being young and naïve and a little bit ignorant, I thought: why can't we create therapies that mutate and transmit and replicate? Here was the idea. If we can take the virus and engineer it to amputate the genetic material in blue here, this amputated instruction set can no longer hijack a cell. But this amputated instruction set can do something very special. In an already infected cell, this amputated instruction set can hijack the hijacker. It can commandeer HIV's machinery to

make more copies of itself, the amputated instruction set, and then each of these copies can steal all of HIV's other components so that the cell gets converted from a factory that produces virus to a factory that produces therapy. Hijackers. These carry no disease. This dramatically lowers HIV levels and keeps the cell healthier.

11:00

This idea consumed me for months. It was the most intense intellectual experience of my life. On every bike ride to lab, on every walk to the coffee shop, on every run in the hills above campus, the ideas, the arguments, the counterarguments, they all came so rapidly in my head, in my inner monologue, that I was physically out of breath. I thought if we can create a therapy that replicates, it would only need to be taken once. It could mutate along with the virus and possibly it could transmit between infected individuals to treat them. It was a therapy that could do all of the things that the virus could do. It solved the fundamental mismatch.

11:51

The most radical part of this concept was that the super-spreaders would also be converted from transmitting the virus to now transmitting the therapy. It was a therapy that would go viral along with the virus. This scared some people. But there's already a precedent: we already inadvertently use therapies that transmit. The vaccine that eradicated polio in the US, the oral polio vaccine, transmits between people. It's not well-known, but the fact that this vaccine transmits is part of the reason that it was chosen for the worldwide eradication effort despite its safety issues.

12:41

So the bigger problem was that these hijacker therapies didn't exist. My Berkeley advisors said to me, "Lovely idea, so sad it will never work," or, "Regulators will never allow it, drop it." But the idea wouldn't drop me.

13:05

If it ever worked, it would solve the fundamental mismatch. So we tried for years to build it. We tried every trick in the book and failed over and over again. We -- every time we thought we had a good idea, we'd spend months, sometimes years working on it only to come up empty. We once spent five years building 150,000 versions of a hijacker therapy. Every single one failed. I once asked a really bright student what he hoped to learn from me during his PhD --

13:47

(Laughter)

13:50

And he replied, "How to keep going, how to continue moving forward despite zero evidence that there's anything there."

13:58

(Laughter)

14:01

I wonder if he was trying to tell me something.

14:03

(Laughter)

14:06

By 2018, things looked bad. There was no evidence that a hijacker therapy could be engineered. In fact, we had evidence that it might be impossible. It was time to face the hard truth. This solution that I'd wanted so badly, this hijacker therapy just didn't exist. For 20 years, I had been chasing a ghost.

14:38

Then one day, Elizabeth, a postdoc in my lab, came to me with this picture. It doesn't look like much. My wife thinks it looks like a pregnancy test.

14:50

(Laughter)

14:53

But this little band down here -- that was the amputated genetic material that we had been looking for for 20 years. The entire time that we had been trying to build it and failing, it had evolved by itself in a flask in the back of the lab.

15:09

(Audience) What?

15:11

(Laughter)

15:12

We finally had a foothold. And we used this to build the first hijacker. But we had no evidence that what we built was a therapy.

15:23

The first hurdle that any therapy has to clear is testing in a mouse. It can be risky. In our case, if our mice died, so did our funding, and with it, any hopes of this becoming a therapy, let alone a transformative one. After so many failures, we were all pretty skeptical but we didn't really have an alternative. We had to give it a shot; we had to try.

15:52

Amazingly, the hijacker therapy worked in a mouse, and it worked exactly as we'd predicted 20 years before. It protected the cells in a mouse from HIV. Here are the cells under a microscope. First, HIV in red infects those cells, and then the hijacker, in blue, can be activated, protects those cells and transmits to other cells. We'd finally built the hijacker after 20 years. Everyone in the lab was elated. For me, this was proof of concept. If we could do it for one virus we could do it for others.

16:35

To understand how this hijacker might impact HIV levels worldwide, we ran computer simulations. Epidemiological models. And the results were pretty amazing. If we do nothing in the hardest-hit parts of Africa, HIV prevalence will stay between 25 and 30 percent. If we manage to introduce drugs to three-quarters of the population or if we ever get the long-sought-after vaccine, we would reduce those numbers down to 20 percent. But those are best-case scenarios. If HIV evolves resistance or if people change their behaviors, these numbers could go right back up to 30 percent or even beyond. The blue is the hijacker therapy. And we've not found a way, either theoretically or experimentally, that HIV can evolve resistance to the hijacker.

17:37

The reason this hijacker works so well is the super-spreaders. If the hijacker is introduced in one place over here, the super-spreaders can pick it up and transmit it through the population. Imagine if 10 years from now, HIV is no longer a pandemic.

18:02

To get there, we have to start large-scale clinical trials in five years, which means initial human tests next year. The FDA has cleared us to start testing in HIV-positive patients who have a terminal cancer and have less than a year left to live. Volunteering for this trial is their last incredibly generous gift to the world. They're called the "Last Gift cohort." And to test in these altruistic patients next year, we have to finish our preclinical tests this year ... and I think we will.

18:43

I still meet colleagues who push back and are stridently opposed to letting us move forward with testing. They say, "What if something goes wrong? You can't unrelease it." They say, "There are ethical issues; people can't consent." Well, oral polio vaccine faced similar ethical and safety concerns. In fact, oral polio vaccine faced such an effective misinformation campaign that most people still don't know that it transmits, that it successfully eradicated polio in many countries or that this vaccine is the basis for new vaccines. When we presented this hijacker therapy idea in Africa last year, the African scientists had a different response. They said, "How can you not test this?" They said it's unethical to not test it. So even though we might fail, I think the stakes are too high not to try. If we do nothing, those girls outside of Durban will acquire HIV, and the next time that there's a new virus that emerges, we'll be in the same vulnerable position that we are today with quarantines that are porous and vaccines that we need to wait months for that may not match.

20:09

I think it's time for a new approach that's different than the static approaches of the last century. It's time for a new technology that is less reactive and more proactive. I think it's time for treatments that don't just benefit the most affluent among us but also those who face the greatest adversity. I think it's time for a new type of weapon that matches, or that solves the fundamental mismatch. I think it's time for therapies that can go viral.

20:45

Thank you very much.

20:47

(Applause)