[MUSIC] Funding for this program is provided by Annenberg/CPB to advance excellent teaching.

[MUSIC] >> In parts of Africa, almost half of the adult population is infected with HIV. >> This is a virus that has exploited very, very successfully the inability of most women to control their own sexuality. >> Today, scientists search for a gene that could keep the virus in check and look for ways to block its infectious path.

>> Why is the existence of two distinct co-receptors important?

It turns out that they have tremendous significance for the real world biology of HIV.

>> But can HIV be stopped?

>> We can't predict the success of DNA as a vaccine approach, but I am an optimist.

I believe we will get HIV to succumb.

[MUSIC] >> In the early 1980s, there was no word for HIV or AIDS.

Young gay men in San Francisco were dying from rare cancers and pneumonias as doctors grappled with the unknown.

Today AIDS is a global epidemic with new cases spread primarily through heterosexual contact and IV drug use.

But thousands of scientists around the world are searching for answers.

They're building on the knowledge of the virus and the immune system to find new ways to treat and prevent the disease.

[MUSIC] Eric Von Muller is a real estate agent in San Francisco.

In 1984 his partner died from a rare form of pneumonia.

Soon after Eric learned he was HIV positive. >> I never expected to see the year 1985.

I certainly never expected to see the year 2000.

To be alive and see the new millennia was something that just was beyond my hope. >> Eric is a long-term non-progressor.

He's been infected with HIV for almost 20 years, but he's never developed AIDS. >> I've never experienced any symptoms, I've never taken any medications.

>> Why does Eric remain healthy?

Could something in his immune system be keeping the virus in check?

The human immune system has two lines of defense, specific immunity and non-specific immunity.

>> The non-specific, which we call innate, picks up a pattern.

So it could say it's a bacteria, so I'd better react to it.

>> At the University of California at San Fransisco, Dr. Jay Levy has dedicated his research to HIV, AIDS, and immunity. >> Specific immunity which comes later, cuz it's the non-specific that first responds, sort of gives time for this specific to arm itself.

That goes in and says, this is a herpes virus, or this is the AIDS virus or this is the pneumococcus bacteria. >> Specific immunity has two branches.

The humoral response and the cellular response.

The macrophage is often the first type of cell to face a foreign intruder. >> What it does is grinds up the microorganism into small little pieces, maybe eight or nine amino acids.

And then they get expressed on the surface of the cell.

And they then educate the specific immune system that comes in and says, I see this particular small peptide, I'm gonna respond to it.

>> Helper T lymphocytes with a surface protein called CD4 coordinate the cellular response.

When activated by an antigen Helper T-cells secrete chemical substances called cytokines.

Cytokines signal other cells including the CD8 killer T-cells to migrate towards the foreign organism.

The CD8 cells differentiate into active killer T-cells and memory T-cells.

Some of the chemical messengers from helper T-cells also stimulate the body's humoral response carried out by B cells.

B cells differentiate into plasma cells which secrete antibodies that attack free bacteria and viruses.

They also differentiate into memory B cells. >> Once they have destroyed that particular organism, there's no

more protein around so they lose interest, and what happens?

They self destruct.

You'll save a few of them, there are memory cells, so if that organism comes in again they can react very quickly.

>> With a powerful immune system fighting off disease, why can't the human body control HIV?

HIV is a sphere shaped retrovirus containing RNA and the enzyme reverse trancriptase.

The surface of the virus is covered with peg-like projections of the protein GP-120.

When HIV encounters a T-cell, the GP molecules bind with the CD4 receptor and co-receptor.

The membrane of the virus and the cell fuse and the viral core is released into the cell.

The core opens and RNA is released.

Reverse transcriptase is attached and produces a single strand of DNA followed by a second complimentary strand.

The DNA molecule enters the nucleus of the cell and is incorporated into the genome.

At first the immune system mounts a normal attack and the viral load decreases, but as the immune system battles the virus, it's helping the virus survive. >> What is the most susceptible cell to HIV?

An activated lymphocyte.

So when these activated lymphocytes come in to try to fight, the virus enters them.

So it has more cells to infect, takes advantage of the immune system. >> How have you been?

>> For 16 years Levy's been studying long term non-progressors like Eric to learn the secrets of their survival.

>> These lymph nodes, he's got very tiny ones which I like to indicate- >> Have they ever been swollen?

>> No, perfectly healthy.

This is key cuz that's the power of the immune system to control this virus.

Something that was totally unexpected when we first found the virus. >> That's right.

>> Levy's focusing his research on the protein secreted by the CD8 T-cells. >> What we found was this cell in HIV

infection doesn't necessarily kill the infected cell.

It secretes a protein, which we call CD8 antiviral factor, or CAF, that suppress the virus in the infected cell, so it cannot produce anything.

So that cell is carrying a silent gene and can function, and because it is active against all HIV strains, we're active against the monkey AIDS virus.

It's non-specific, so therefore, it has to be an innate response.

>> The lucky few, like Eric, have a strong CAF response and maintain it over time.

Those that go on to develop AIDS have lost the response.

My situation has remained unchanged.

My CD cells, my ratios have remained constant over the years and that's wonderful.

And who knows what tomorrow will bring? >> If that media ends up being toxic, we can't use it.

>> Right. >> In Levi's lab and other labs across the country, the race is on to identify the anti viral factor.

While some labs say there's more than one factor involved, Levi believes CAF is a single substance.

>> How are we gonna find it?

It's one in a million proteins produced by CD8 lymphocytes.

So we''re doing now the modern technology to find a protein.

And that's really interesting, because we couldn't have done it ten years ago. >> Using the blood of non-progressors and others, CD8 cells are grown in the lab and allowed to produce CAF. >> If we wanted to know for example if one particular patient's CD8 cells can suppress viral replication, we will culture that patient's CD8 cells with infected with CD4s.

And then measure the viral output using this asset. >> We started out with 2000 different genes and then down to 500, down to 200 and now we're down to 44. >> Once CAF is isolated, Levi says the goal is to empower the human immune system to control HIV naturally.

>> Can you give CAF to people or should you find a way in which you can tickle the CD8 cell so it makes its own CAF?

Which is the one I would expect.

So, we are trying to bring back that innate immune response to people who are infected. >> And if there is something in my immune system that is common among all the long-term non-progressors and that can be discovered and that can be used to fight this virus.

Then that would be something that would be really quite incredible.

[MUSIC] >> While some infected people like Eric stay healthy, other individuals remain HIV negative despite repeated exposure to the virus.

Researchers know that in order for HIV to enter a cell, it must bind to the CD4 receptor on the cell surface.

But is that all that's required?

>> At the Institute of Allergies and Infectious Diseases, Dr Edward Berger has been studying HIV for almost 20 years.

>> Why is the virus able to get into a human cell it has CD4 and not into a mouse cell it has CD4.

There are two simple possibilities, the one is that the mouse cell even though it has CD4 maybe it's got something else that's inhibiting a virus from getting in.

The other possibility is that maybe there is an additional thing that's required and the human cell has it and the mouse cell doesn't. >> In the early 90s, Berger and colleagues began testing the possibilities.

They constructed a hybrid cell by fusing a human cell and a mouse cell.

And put the CD4 molecule on the hybrid. >> What we found, we and other people working on this, is that the virus did get into the hybrid.

So that lead to the notion that there had to be another molecule on the human cell in addition to CD4 that was required for the virus to get in and we called that cover sector. >> But how could they identify the gene that coded for the receptor?

Using a collection or library of all the genetic material expressed by the human cell, Berger started mixing the library with mouse cells, with CD4.

Then he added only the envelope protein from the virus and measured the amount of fusion by reporter gene

activation assays.

>> Here you had no cell fusion.

>> The more co-receptor present on the cells, the more fusion occurred. >> And here even more.

>> Berger now new that the library contained a gene that coded for the mystery receptor.

[MUSIC] Further research revealed a single gene that when inserted in a mouse cell produced a surface protein that caused the cell with the HIV envelope protein and the mouse cell to fuse.

[MUSIC] >> The only function that we had for it was that it enabled the HIV virus to fuse with a cell that was expressing CD4, so we gave the protein a name, fusin.

>> At the same time Berger identified fusin, now called CXCR4.

Other researchers identified another co-receptor called CCR5.

>> Why is the existence of two distinct co-receptor is important?

It turns out that they have tremendous significance for the real world biology of HIV.

For understanding how HIV gets transmitted from one person to another, the viruses that are present during the asymptomatic phase are preferentially using CCR5.

And it's only during the transmission to the symptomatic phase that you start isolating viruses that can use CXCR4. >> But scientists know there's a mutant CCR5 gene that fails to produce a functioning receptor. >> And it turns out that one of the major explanations for why some people are not infected by HIV despite repeated exposure, is that they are carrying only the defective CCR5.

And so they're lacking the co-receptor that's required for the initial virus that takes hold in the body.

The other remarkable thing is that people that have no functional CCR5, the only medical consequence we know about it is that they are resistant to HIV. >> Because people can live without CCR5, it's become a target for new drug development. >> Really the most promising kinds of CCR5 directed therapies would be small molecular weight chemicals that bind to CCR5 in such a way that they prevent the HIV from using it as a co-receptor.

And there is a tremendous effort going on in the pharmaceutical industry for that.

There's a real hope that this will provide another weapon against HIV.

>> Before HIV emerged, scientists thought they could control most viruses with traditional vaccines.

They had vaccines for smallpox, measles, and polio.

Traditional vaccines are generally made by two approaches.

Killed virus or live attenuated, a weakened virus that replicates enough to cause an immune response.

But HIV presents unique challenges, a live vaccine approach is dangerous because HIV could revert to a form that causes disease.

And killed virus vaccines have not worked well in preliminary testing.

>> HIV is kind of the textbook example of all the problems with making a vaccine. >> They were stable. >> At the University of Pennsylvania, Doctor's David Wiener and Jean Boyer have been working to develop a vaccine for HIV that would be as safe as a traditional kill vaccine.

But HIV's high replication and mutation rate is just one of many hurdles. >> Every time the virus goes to a single replication cycle, every time it grows, it changes a little bit.

And so within a single individual, there are many different variations of this virus.

And then as they spread to a population, there are many different variations.

And so we have to come with a vaccine that can prevent all these different variations.

It also integrates, which means antigenic materials of HIV actually is inserted into our chromosomes and so once the infection happens, the only way to get rid of that infection we believe is to destroy that cell.

And again, that would require killer T cells.

>> But how could scientists induce the desired immune response safely?

One promising approach is to use DNA as an immunogen, or vaccine.

Genes for antigenic proteins from the HIV envelope and core are engineered into a bacterial plasmid.

Other parts of the virus, like the promoter or the genetic regulatory sequences, are excluded because the virus needs them to replicate.

>> That's very important.

We also delete essential functions in something that's going to go into people, such as the protease genes have destruction in them and the reverse transcriptase genes.

And we also rearrange multiple components of the virus to make sure that it can't reshuffle itself into some novel fashion.

And we can test these in laboratory assays. >> The genetically altered plasmid is mixed in liquid and injected directly into the muscle.

DNA vaccines were first tested on mice in the early 90s. >> What we reasoned would happen was now the cell that took up this shared material would become a factory for whatever the viral protein wants that we had encoded.

And as soon it did that, the immune system would now see this cell as having a foreign protein.

And that would look to the immune system just like a virally infected cell and teach it how to make the cellular immune response's killer T cells.

But because the cell would also leak out antigen, then the B cells would see that antigen and be able to make antibodies.

And because the leaked antigen would also stimulate helper T cells, you would get basically all three components of an immune response.

The antibodies, the killer T cells, and the helper T cells that are the essence of a live, attenuated vaccine, without any of the risks of spreading infection.

>> But would DNA vaccines work?

>> We published in larger primates that we'd actually prevent HIV infection.

And in a smaller primate model, we've shown that we can impact on viral replication, lowering viral replication and protecting CD4 T cells after a viral challenge with a pathogenic virus.

[MUSIC] >> In 1999, scientists began testing DNA vaccines in people.

James Burns is HIV positive and undergoing antiviral therapy.

He volunteered in the double-blind study, testing whether the vaccine would help keep his viral load in check. >> The only things I really noticed was swelling the first day or so and a little bit of redness.

Hi, Doc, good to see you. >> Dr.

Rob Roy Macgregor administered the first vaccines. >> It had been done so much in preclinical studies that, again, I would have been willing to volunteer.

So a good general principle, if you're doing clinical research, that you have to think it's safe enough that you'd do it, too.

>> So far, DNA vaccines have worked poorly in people, but current studies continue to show promise.

>> These are the animals that were vaccinated and then challenged with our SIV, and you can see in this row and in this row, those are the animals that are controlling viral replication.

So we've been moving forward.

With each primate study we've done, we've gotten better and better responses. >> Weiner and Boyer are now investigating DNA vaccines augmented with cytokines like interleukin 12 and 15 that will help boost T-cell responses. >> We really want strong T-cell responses.

We've included the instructions for expanding T-cell immunity and shown that these work in our animal models, and now we're ready to test them with people.

And we think that this will be a magnitude jump, a ten-fold enhancement in the vaccine potency. >> Sometimes the imagination of a child can help illustrate the goals of research.

When Weiner's daughter was young, she drew a picture of her dad's vaccine. >> We asked her, what was that vaccine about?

She says, the colors are all the good things you need and none of the bad things that would hurt you.

And I think that that's really what a DNA vaccine ultimately could be like.

We can take out the things we don't want and put in only what we need and make them function very specifically in a relatively, hopefully cheap and easily reproducible fashion.

[MUSIC] >> Once thought a radical approach to treating disease, DNA vaccines are rapidly moving into a wide variety of clinical trials.

Scientists say that even if the vaccine was only 50% effective and lowered viral loads, it could have a significant impact on transmission rates.

But while new treatments spur optimism and hope, many parts of the world remain in the grip of a tragic epidemic.

65 million people in the world are infected with HIV, 25 million in Sub-Saharan Africa alone.

Most have no hope of getting treatment because the drugs are too expensive and the villages and towns too remote.

AIDS is killing the adults who grow the food and earn the money, leaving families with no means of support and millions of children without parents.

Laurie Garrett is a Pulitzer Prize-winning medical and science writer.

She's covered the AIDS epidemic since the early 1980s >> We can already see that AIDS is going to be the number one destabilizing factor for Africa for years and years to come.

And it already has dramatically hurt the economies of the hardest-hit countries.

We've seen the gross domestic products of these countries go backwards radically.

Life expectancy today is at World War II levels and moving backwards toward the 19th century, not forwards into the 21st.

>> The most rapidly growing epidemic of HIV is in Russia, Ukraine, and the Baltics.

It's estimated by the year 2010, up to 12% of Russians will be infected with HIV.

>> That is almost a 100% IV drug use, narcotics-driven epidemic.

Hey, that's a no-brainer.

Make sure that everybody uses clean needles.

And start building up methadone programs and drug rehab programs to get the kids off the narcotics in the first place.

Guess what?

They won't do it.

There's a greater hatred of the drug user than there is of the virus. >> In Sub-Saharan Africa, heterosexual transmission and the low status of women is at the core of the epidemic.

It is the only region of the world where more women are infected and dying of AIDS than men.

>> Number one driving force for this epidemic in Sub-Saharan Africa and increasingly in Asia is the extraordinary low power balance on the side of females.

Most women have no right of refusal of sexual intercourse.

They have no ability to dictate when, where, with whom.

Rape is so commonplace that it's only recently that it's actually thought of as a criminal activity.

And men quite commonly have well over ten women as regulars in their lives. >> Garrett says because of the social and cultural issues involved in these countries, AIDS becomes even more complicated to control. >> It's one thing to say to a drug user, here's a sterile syringe, at least don't pass your virus to any other drug user.

It's another to try and say to an entire society, change all the sexual mores that have been the cultural norm for hundreds of years and become a new kind of society.

With an entirely different sense of gender balance, of empowerment of women. >> In the country of Uganda, however, things are slowly begining to change.

That's because people are talking about AIDS and there's an aggressive educational campaign to prevent the disease.

>> There's another factor that's played a big role in Uganda, and that has been the rise of a sense of anger among the women.

And demanding accountability from their husbands, from the men they have sexual relations with, trying to teach their sons to behave differently. >> Today, scientists are recognizing the need for preventive therapies that women can control such as topical microbicides in gel or capsule form. >> The strategy that we've taken is to try to develop a very, very specific inhibitor of HIV that could be applied topically at the site of transmission.

So for heterosexual transmission, that would be in the vaginal tract.

And that's a very important development that's going on now.

And there are companies that are producing these proteins for this purpose.

And the hope is that this could be delivered in a practical way, all across the world.

>> DNA vaccines may also prove practical in the developing world.

>> DNA is fairly stable and may be able to withstand long periods without refrigeration.

And that's of course very important in tropical environments, and especially in poorer places where refrigeration might be a problem.

>> Scientists agree that public health efforts to prevent AIDS must remain the frontline defense. >> We must not lose sight of the fact that we need to prevent it through education, distribution of condoms, needle exchanges and of course a vaccine. >> Many researchers say that the AIDS epidemic is just beginning.

While drug therapy has greatly reduced the death rate in the US, many countries in the world are facing accelerating rates of infection and death.

But research is revealing new ways to fight AIDS and scientists are beginning to understand the disease not just biologically but politically, economically, and culturally.

A global view that may offer new avenues of hope.

>> You can't look at the world and see what's happening.

With 15,000 new infections every day and 8,000 deaths every day, that we can just sit back and be oblivious and not respond. >> The real hope lies with taking the younger generation on the planet today, all the teenagers on Earth, and the preteens.

And as dreadful and horrifying as it may be, getting them to actually imagine this epidemic out of the box ahead a decade, two decades.

To the point where they feel motivated not only to protect themselves but to protect their societies.

[MUSIC] >> Funding for this program is provided by Annenberg CPB to advance excellent teaching.

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