Life and Longevity: Crash Course History of Science #44

Crash Course: History of Science
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Last time, we asked some big questions about the future of computing and artificial intelligence.

Today, we're going to ask about the life sciences, medicine, and the brain. Like what happens when medicine shifts from treating illness to preventing it, and then to a whole new terrain: enhancing life and longevity?

What happens when life itself becomes a technology? Something increasingly cheap and fast to redesign? And why has mapping DNA been easier than mapping our brains? [Intro Music Plays] When we last left medicine, giant companies had commercialized pills that targeted specific physiological systems.

And the human genome was decoded! But the links between particular alleles, or versions of genes, and specific diseases—like cancers, immune diseases, or psychiatric disorders—remained to be proven. So in the 1990s, scientists began developing cheaper, faster, more robust genetic tests for well-known genes linked to disease.

This has given rise to a new way of associating with each other, based on shared molecules—biosociality. Nowadays, for example, many women with a family history of breast cancer get tested to see what version they have of two genes called BRCA1 and BRCA2. Communities have formed around people who have the versions of these genes that make someone much more likely to develop breast or ovarian cancer later in life.

There was a big fight over whether a private company called Myriad Genetics could patent the natural DNA tied to these genes. But the Supreme Court ruled in 2013 that they couldn't patent the natural DNA, or anything invented by evolution. Genetic testing has helped with the early diagnosis of thousands of cases of cancer.

Some medical researchers have experimented with genetic therapies. These would involve replacing a region of DNA giving rise to a disease with a doctor-designed "therapeutic gene." Basically, patients' genes get taken out, changed, and put back in. In 1990, the first genetic therapy temporarily corrected an immune system disorder.

Other trials followed. But in 1999, Jesse Gelsinger, a young man with a rare genetic liver disease, died four days after receiving a genetic therapy. This had a chilling effect on the field for years, although research continues.

Genetic therapies points toward an even bigger promise—of personalized medicine. We don't have it yet, but many companies are winning investors on the promise that we will soon. In this new regime, each patient will have care tailored to her individual genome, and more.

First, we need more basic science in human genomics and several other fields—including transcriptomics, or how regions of DNA are copied into little strands of RNA, and what effects those have. Then there's proteomics, or how proteins fold together, which affects how they work. Then there's metabolomics, or how energy moves around inside and outside of cells, through fats, sugars, and acids.

Collectively, these are called - wait for it - … omics—the total study of life at the scale smaller than the cell. But even with more information, engineering life using twentieth-century technology still meant painstakingly creating new synthetic DNA parts and proteins by hand, and testing over and over again to find the rare successful result. Plus, the vast majority of diseases are linked to many genes—so changing anything means making not one, but several stable edits.

And every edit increases the chances that something is changed elsewhere—an off-target effect. Which is potentially really bad. What was needed was a way to edit not single regions of a genome, but many regions, with less likelihood of off-target effects.

Enter the "technology of the century" and one of the most valuable suites of patents on the planet: clustered regularly inter-spaced palindromic repeats. Which just… rolls right off the tongue. Hence why everyone calls this system CRISPR.

CRISPR isn't free or one-hundred-percent perfect. But it's the most efficient way to edit genes right now, and it may revolutionize medicine and agriculture. Who "invented" CRISPR?

Our little buddies, bacteria! And archaea, bacteria's weird uncle. Many microbes use CRISPR to keep a list of viruses that can kill them by putting the bad DNA in between repeated palindromes.

It's sort of like a police directory of prior arrests: when a virus enters the microbe's cell, if it's recognized as being on the list, a CRISPR-associated protein cuts up the virus. And the system is a good editor: it reads for specific DNA sequences and only cuts these. ThoughtBubble, show us more: Spanish microbiologist Francisco Mojica first published about this system in 1993.

But back then, he saw a bunch of repeated segments of DNA with weird other DNA in between. He didn't know what it meant, and it wasn't major news. But Mojica didn't give up.

In 2003, after a long decade of clever bioinformatic work, Mojica realized that CRISPR must be an adaptive immune system— a way for microbes to protect themselves against viruses. But on its own, in nature, CRISPR didn't help humans. In fact, when Mojica submitted his discovery to the scientific journal, Nature, they rejected it!

CRISPR had to be transformed into a tool. There were lots of steps and scientists involved. First, scientists had to move beyond finding the palindromic repeats in different microbes to understanding how the whole system worked: what told the cutting protein where to cut?

How could the system be reprogrammed? Swiss microbiologist Emmanuelle Charpentier and German microbiologist Jörg Vogel figured out that a special piece of nucleic acid called a guide RNA tells the cutting Cas9 protein to cut DNA at the right place. Other scientists worked out how to move a whole system that evolved in microbes into the cells of mice and humans— a whole system of genes, tracer RNAs, and proteins.

In 2011, Charpentier met American structural biologist Jennifer Doudna, and they decided to collaborate on studying synthetic CRISPR systems, outside of microbes. Meanwhile, in Cambridge, Massachusetts, Chinese-American molecular biologist Feng Zhang and synthetic biologist George Church worked on putting CRISPR systems into mammalian cells. For example, Zhang made mouse models of human disease using CRISPR.

Within fewer than ten years, CRISPR had gone from a cool immune system for microbes to the hot new tool in biology. Thanks, ThoughtBubble. In the wake of transforming CRISPR from a microbial trick into a tool for the future of biology, Doudna and Charpentier filed patents through their universities, to work with their companies… and so did Zhang and Church, for their companies.

These biologists are academics, but they are also entrepreneurs. So, why is CRISPR such a big deal? Instead of part-by-part steps, each likely to fail, CRISPR enables a whole solution to be

programmed at once.

It's not super simple, but it's simpler than what came before. Proposed applications include precision medicine as well as a new Green Revolution: imagine staple crops edited to put their own nitrogen into the ground. Or to breathe out less water, requiring less irrigation.

Or to photosynthesize more efficiently. Or make more of the nutrients humans want. And if you can engineer an apple, you can engineer a human!

This is reprogenetics, or engineering babies—both to make them healthier and to make "designer" babies with specific traits like eye color or height. Which—yeah—eugenics never dies. But CRISPR isn't the only promising development in medicine.

Other researchers are working to understand how environmental stimuli like the foods we eat interact with genes via epigenetics, or the regulation of which genes can be expressed. Historian of science Hannah Landecker calls to rethink human health as existing in a "metabolic landscape." Another important area of research is microbiomics, or the genomics of microbes. The human gut only works because of the trillions of bacteria that live inside it.

But, just as we don't know everything about the human genome, we also don't know everything about how these microbes function, interact with each other, and interact with different foods. If scientists could understand these complex relationships better, maybe technologists could make foods that were also therapies. … Or maybe they could just remind us to eat healthy foods! With more genetic therapies and a better grasp of epigenetics and microbiomics, some scientists hope that humans will live much longer.

In fact, longevity itself is a hot topic. Finally, many life scientists are turning to one of those epistemic objects the proved remarkably stubborn for a long time: the brain. Alongside mid-twentieth century work on DNA and drugs, other researchers figured out a lot about brain surgery… But, at a basic level, the brain remained mysterious.

It's a collection of neurons, joined by little gaps called synapses. Brain signals cross the synapses through a mixture of electricity and chemicals. Thought, memory, and self are in there somewhere, and we mostly know the physical regions of the brain where they are.

Although… neuroscientist and tireless brain-mapper George Paxinos confirmed a whole new brain region, the endorestiform nucleus, only in 2018! Clearly, there's room for ongoing research. Technologies let scientists see the brain in new ways.

Invented in the 1970s, magnetic resonance imaging or MRI creates a non-invasive map of the brain. And functional MRI, or fMRI, first used in 1990, lets scientists see the blood moving around inside. But the dream for many researchers is a database: the connectome, or total map of how neurons are linked in the brain, a "wiring diagram" for a brain.

The NIH, for example, launched Human Connectome Project in 2009. To date, scientists have mapped the connectome of one animal, a worm, and are working on the mouse retina. Maybe brains are so complex that we still don't understand much about them.

But we can control them! Think about nuero-enhancement: what if there was a drug that targeted specific brain regions linked to logic problems, memory, or creativity? In fact, what if there was a drug that affected the very genes that code your brain? What if the whole world was, say, on average, five percent smarter? Finally, what if the true power of the brain came from being allowed to escape the limits of the body? A technology developed in the late 1990s called a brain–computer interface or BCI enables human brains to interact directly with computers.

BCIs can transform the lives of people suffering from paralysis, for one. What else might humans enable themselves to do by directly connecting their brains and computer systems? To conclude, let's come back to basics.

Regardless of how immediately revolutionary or still-science-fictional the various life-control technologies we've covered in this episode are, they have one thing in common: rich people will get them way before poor people. And old technologies won't go away due to new ones. Science, in the sense of a set of methods for understanding the natural world, doesn't tell us which technologies we should deploy, where, or when.

This is the realm of ethics. So even as some lucky consumers will begin to enjoy medical regimes personalized to their genomes, many people don't have access to healthcare at all. While access remains uneven, or stratified, new groups may arise based on healthcare— not genetics or other forms of biosociality.

As some epidemiologists have said: "zip code is a better predictor of health than genetic code." Next time—we'll talk about the future of the planet. It's time to tackle climate disruption, the Anthropocene, and some deep questions about what knowledge scientists should make. Crash Course History of Science is filmed in the Dr. Cheryl C. Kinney studio in Missoula, Montana and it's made with the help of all this nice people and our animation team is Thought Cafe. Crash Course is a Complexly production.

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