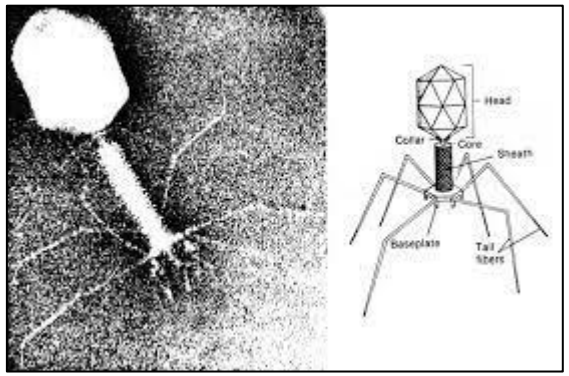
Bill Studier, the T7 System, and COVID Vaccines

John Shanklin,
Chair of Biology

Brookhaven National Laboratory

September 8, 2022



A 1983 BNL FIND IS KEY TO VACCINES

Research on obscure enzyme leads to an accidental breakthrough

BY CARL MACGOWAN
carl.macgowan@newsday.com

NEWSDAY EXCLUSIVE

STONY BROOK UNIVERSITY

F. William Studier, seen in 2004, and a team created a clone technique used in COVID-19 vaccines.

Long before anyone knew anything about COVID-19, scientists studying an obscure enzyme at Brookhaven National Laboratory stumbled upon one of the key building blocks of two vaccines that today are saving potentially millions of lives, Newsday has learned.

The discovery nearly four decades ago of the so-called T7 expression system by a Brookhaven team led by senior biophysicist F. William Studier initially was of little interest to the general public. But scientists quickly grasped it could be used to study molecules and develop cancer treatments — and pharmaceutical giants Pfizer and Moderna incorporated the process into the vaccines that so far have been used in more than 250 million injections in the United States.

And it was all an accident. Studier had no idea he would help to fight a deadly disease when he began studying a virus that infects E. coli, a bacteria known as the scourge of the agricultural industry. It was simply the kind of routine scientific research that he and others at the Upton lab conducted every day.

"He was just studying how the virus worked," said John Shanklin, chair of Brookhaven's biology department. "And he then just realized that he had, kind of, the puzzle pieces to put something together that would be uniquely useful."

Brookhaven's research is one of the reasons Moderna and Pfizer were able to manufacture their vaccines in such enormous quantities, and so much faster than what would have been possible previously, said Venki Ramakrishnan, a Nobel Prize-winning biologist with the Medical Research Council Laboratory of Molecular Biology in Cambridge, Great Britain.

Studier's 38-year-old discovery also will help those companies swiftly and efficiently develop new versions of the vaccine as the coronavirus mutates into different variants, he said.

"It's a very powerful tool," Ramakrishnan said in a telephone interview. "Of course, a lot of things went into it, but I would say the Brookhaven element is an essential component of what is needed to make this vaccine. . . . It made something possible that would not have been possible before."

Roots in gene-cloning

Pfizer and Moderna, in separate emails to Newsday, acknowledged their vaccines used the technology pioneered by the Brookhaven lab. Both companies declined to comment further.

The research leading to the T7 expression system had its roots in the 1970s gene-cloning craze, when scientists around the world were looking into copying genes of living things as small as cells and as large as sheep.

Studier had been studying bacteriophage T7, a virus that infects E. coli, since his graduate school days in the early 1960s. He continued the research at Brookhaven, where he worked with senior researcher Alan Rosenberg, the late John Dunn, graduate student Barbara Moffatt and postdoctoral fellow Parichehre Davanloo.

Their research involved studies of molecular mysteries such as messenger RNA, or mRNA, the scientific marvel that helps convert DNA into proteins.

E. coli is a common bacteria that dwells in humans, other warm-blooded animals and some foods. Some forms can cause illnesses such as diarrhea and urinary tract infections.

But E. coli has a natural enemy in T7, which kills the bacteria by infecting it and rapidly replicating its own proteins.

In an exquisite piece of scientific subterfuge, Studier realized that T7 could be tricked into copying good kinds of protein — like the kind that helps fight human diseases.

"It turned out by luck," Rosenberg said in a phone interview, "that T7 had elements that if you put them together in the right fashion, what you could do is fashion a system to [create] large amounts of messenger RNA or any protein you desired to have large amounts of."

The Brookhaven team eventually figured out how to redirect T7 toward using its powers for good instead of evil. But first they had to learn how to clone the little varmint — something that no other lab had done.

"Our group accomplished this in 1983," Studier, 84 and retired, wrote in an email from his home in Pleasanton, California. "This enabled the T7 expression system, which has been widely used for making almost any proteins. As it happens, it also enables obtaining large amounts of mRNAs for vaccines."

Studier said the result, nearly 40 years later, is enormously satisfying.

"I feel very good that our early work is helping to save so many lives," he wrote.

Shanklin said the genius of Studier's discovery was that he found he could substitute the gene of any living thing in E. coli, and then by adding components of the T7 virus, "He could trick the E. coli into essentially copying only that one protein."

The discovery revolutionized science by simplifying things that once had been laborious, Shanklin said.

"It just changed everything about the way everyone did everything," he said. "It made it really simple."

WHAT TO KNOW

- **The so-called T7 expression system** was discovered by a Brookhaven team in 1983 and is a key component in the production of the coronavirus vaccine
- **In an exquisite piece of scientific subterfuge**, a senior BNL biophysicist realized that T7 could be tricked into copying good kinds of protein — like the kind that helps fight human diseases
- **BNL's 38-year-old discovery** will help Pfizer and Moderna develop new versions of the vaccine as the coronavirus mutates into different variants

Speeds vaccine production

Brookhaven officials said Studier's discovery is the most successful technology in the lab's history.

"T7 is still the go-to system for biochemists everywhere," lab officials said in a news release.

Brookhaven once held patents to the system, but they expired in 2014, lab officials said. Over the 24-year patent period, the lab was paid $70 million in royalties by hundreds of companies that used the technology.

The technique also helped to speed development of the Moderna and Pfizer vaccines by providing crucial shortcuts.

First, the technology enables swift mass production of the vaccines. Then, once injected into human arms, the mRNA in the vaccine prompts our own cells to manufacture a "spike" protein, which in turn sends our immune systems into action to fight the COVID-19 virus.

"Your cell makes the protein for you, and then you get the immunity from the protein that you made yourself," Shanklin said.

Combined with the ability to quickly alter the vaccine formula to fight COVID-19 variants, "the cumulative effect of those two things is we'll save millions of lives worldwide," Shanklin said.

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Brookhaven National Laboratory

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Newsday

Karen McNulty Walsh

Seeding tomorrow's medical discoveries

To retain a technological edge, we must inspire a love of science in the young

BY VENKI RAMAKRISHNAN

Eddie Cantor said it takes 20 years to make an overnight success, and this is certainly true of science, where a discovery can lead to revolutionary applications many years, sometimes decades or even centuries later. When Isaac Newton discovered his laws of motion, he certainly did not imagine that those very laws would be used to launch satellites 300 years later. When Michael Faraday discovered the laws of electromagnetism that make the generation of electricity possible, a British politician asked him what good it was, to which he is said to have replied, "Someday, sir, you can tax it." Even Faraday could not have imagined that 150 years later electricity would pervade almost every aspect of our lives. Even an everyday device like a smartphone is based on several Nobel Prize-winning discoveries.

If we want a society that remains at the forefront of technologies tomorrow, we have to continue to produce the scientists of tomorrow by inculcating in young people a love of science and how it works. This requires a serious commitment to science education from the earliest years. Science is not a rote collection of facts. It is a way of discovering truths about the natural world through observation and experiments, along with theories that help us interpret and understand the results. We also have to support the basic science of today, which is the seed corn for the completely unpredictable technologies of tomorrow. Trying to pick winners or focusing just on short-term applications is a guarantee of small, incremental gains rather than real, technological revolutions.

I was reminded of this by the COVID-19 vaccines, which are widely said to have been developed at unprecedented speed, available less than a year after the pandemic broke out. In fact, these vaccines were built on decades of fundamental science, including discoveries made by F. William Studier and his colleague John Dunn at Brookhaven National Laboratory. While studying how T7, a virus, attacks the bacterium E. coli, they and their colleagues figured out how to make large quantities of any RNA or protein of choice. Moderna and Pfizer, makers of today's mRNA COVID-19 vaccines, rely on Studier's approach, which uses genetic elements derived from T7 to produce the mRNA instructions for making coronavirus spike proteins. When those mRNAs are delivered to our cells, *our* cells make the corresponding spike proteins. Those spikes train our immune system to be ready to fight the real COVID-19 virus if we are exposed.

Meanwhile, Katalin Kariko at the University of Pennsylvania discovered that injected mRNA would normally be quickly destroyed because the cell senses it as coming from a virus. But unexpectedly, she discovered that it could evade the cell's response if one of the building blocks of the mRNA was synthetically modified.

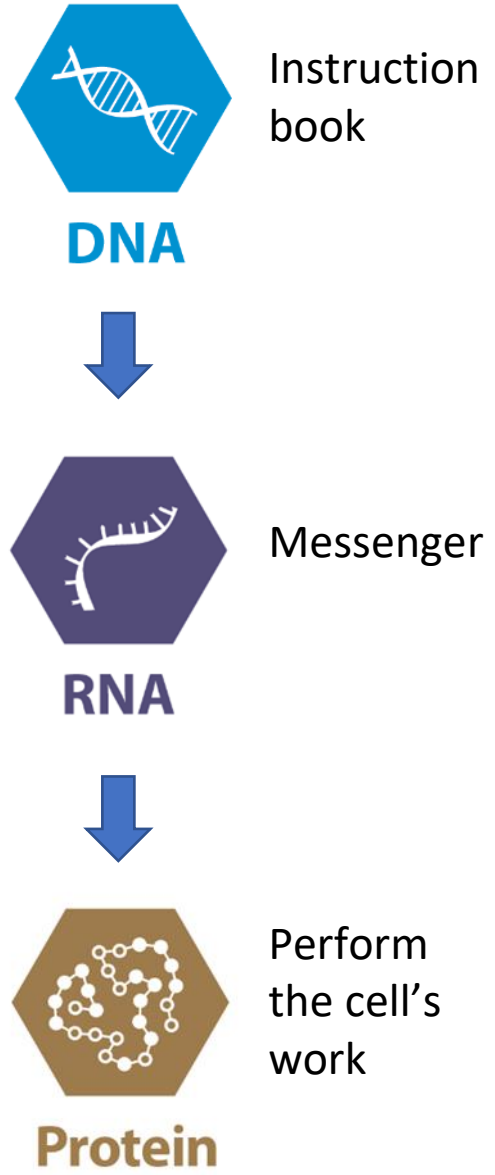
Both Studier's T7 system to produce large amounts of mRNA and Kariko's discovery of the need to modify it were essential to produce the lifesaving mRNA vaccines we have today. Today, both Pfizer and Moderna make their mRNA using Studier's T7 system while feeding it the modified building blocks based on the one that Kariko first identified. The synthetically modified mRNA is stable in the cell and allows large amounts of the COVID-19 spike protein to be made.

In both cases, the research was begun in pursuit of pure knowledge — and the practical applications were quite unanticipated and came decades after the original findings.

Venki Ramakrishnan is a Nobel Prize-winning biologist at the MRC Laboratory of Molecular Biology in Cambridge, England.

Biology basics: genetic and biochemical analysis

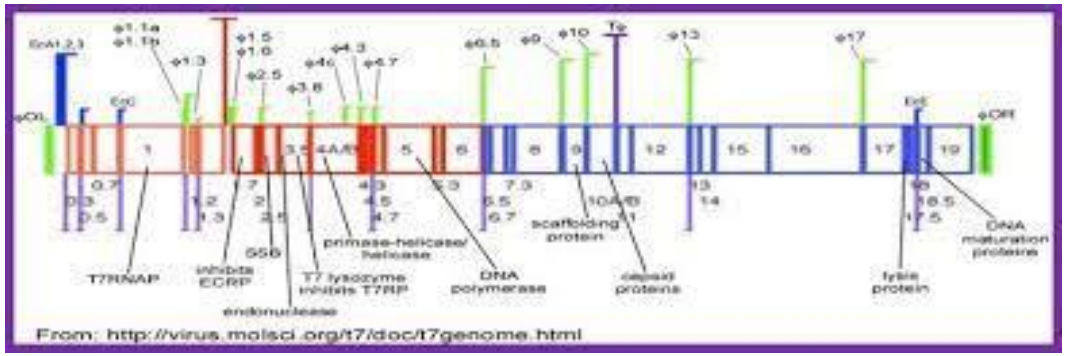
- We humans have about 25,000 genes.
- Bacteria (e.g., E. coli) have approx. 4,000 genes.
- Viruses are very simple, e.g., T7 has only 56 genes
- Viruses can't live independently; for instance, T7 virus infect E. coli cells and hijacks their cellular machinery to make new virus particles.
- New viruses fill the cells and burst them, allowing them to infect other cells.
- Studier decided to study T7 to understand a “simple” form of life.



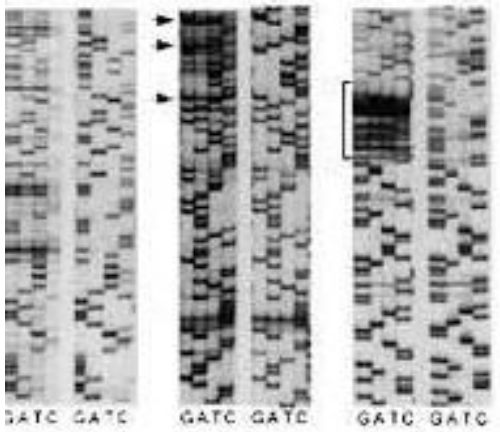
Figuring out how T7 works

- Studier's first goal was to sequence the 40,000 base pairs of its DNA genome with BNL colleague John Dunn.
- The T7 genome was amongst the first to be decoded.

John Dunn



Genome Assembly



Sequencing Gels

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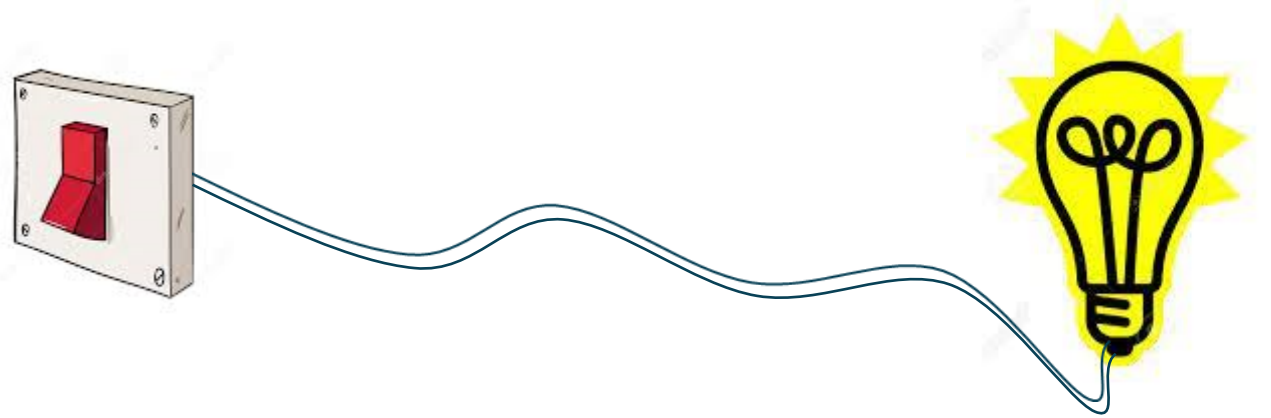
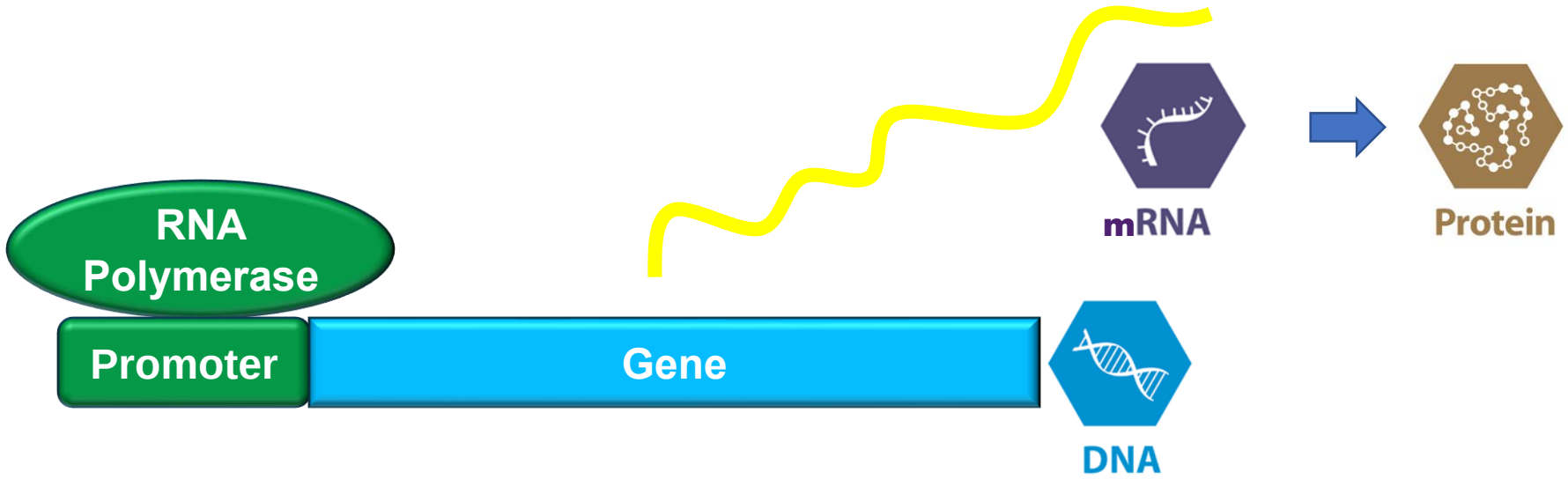
How do genes work?



Like lightbulbs, genes need to be turned on too

On signal

Switch



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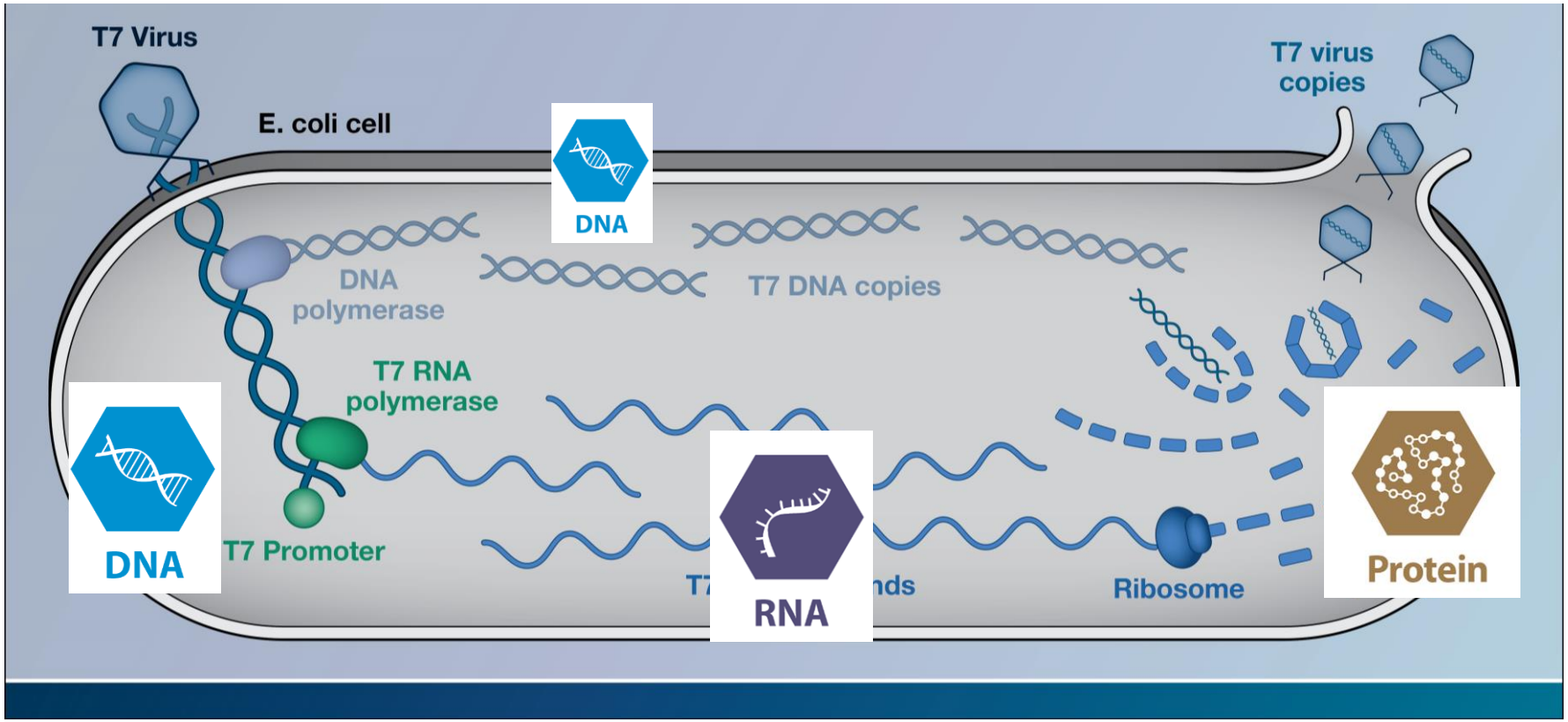
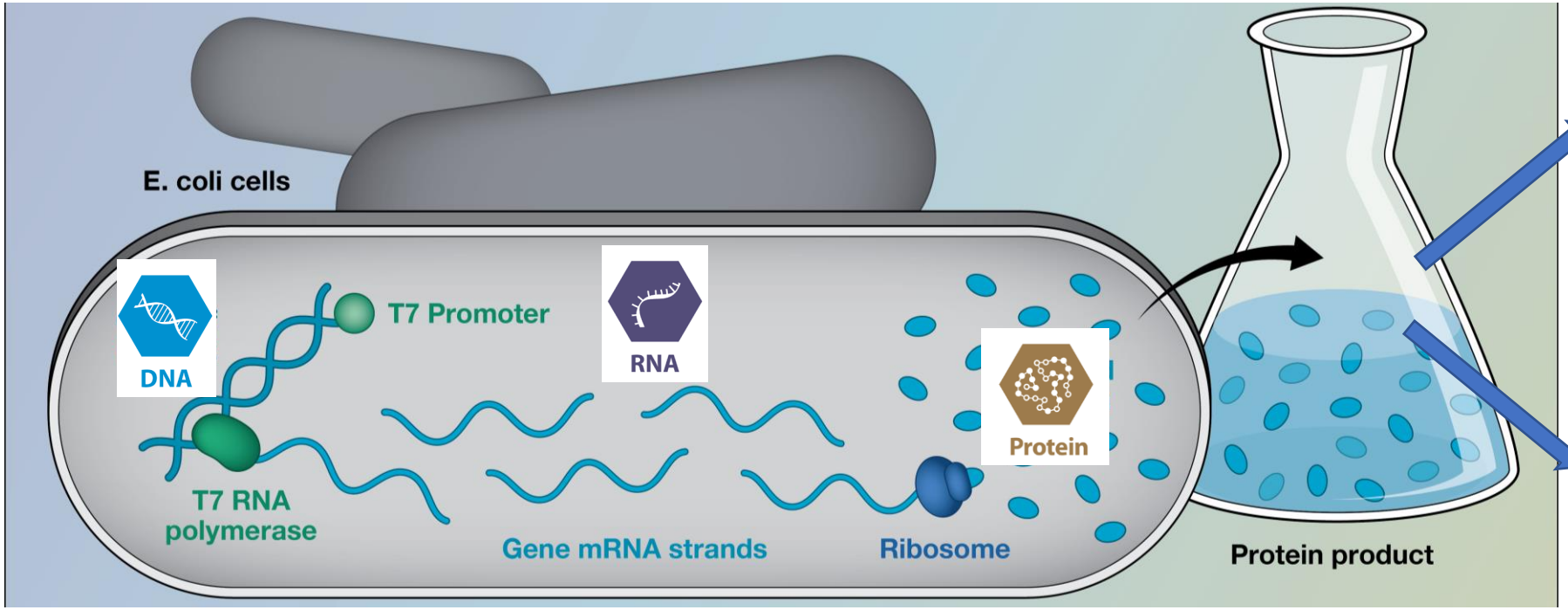
How does the T7 virus hijack E. coli?



T7 brings its RNA polymerase enzyme, which recognizes the on-switches i.e., promoters in its own DNA.

Using T7 polymerase/promoter to make any protein



- **Biochemistry of human disease**
- **Increasing crop productivity**
- **Making cancer therapeutics**
- **Other life-saving drugs**

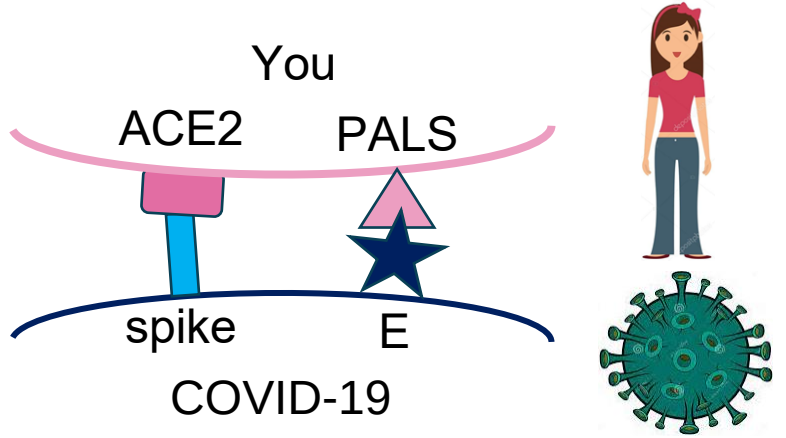
- T7 elements are so powerful, Studier used them to make an E. coli system that can churn out proteins using genes from anywhere.
- Studier's T7 system has been used in over 220,000 published studies, with about 12,000 new ones being added every year

A recent topical example…

ScienceDaily
Your source for the latest research news

How COVID-19 Wreaks Havoc on Human Lungs

New structure shows how virus envelope protein hijacks cell-junction protein and promotes viral spread. Findings could speed the design of drugs to block severe effects of COVID-19.



- BNL team used Studier's T7 system to make PALS and E proteins
- First major study from the NYS-funded cryo-Electron Microscope helped us figure out how they interact
- The team also showed that virulence depends on the E-PALS protein interaction
- Details of this interaction provided a new target for the design of drugs to prevent the interaction and block viral spread (Pfizer and others)

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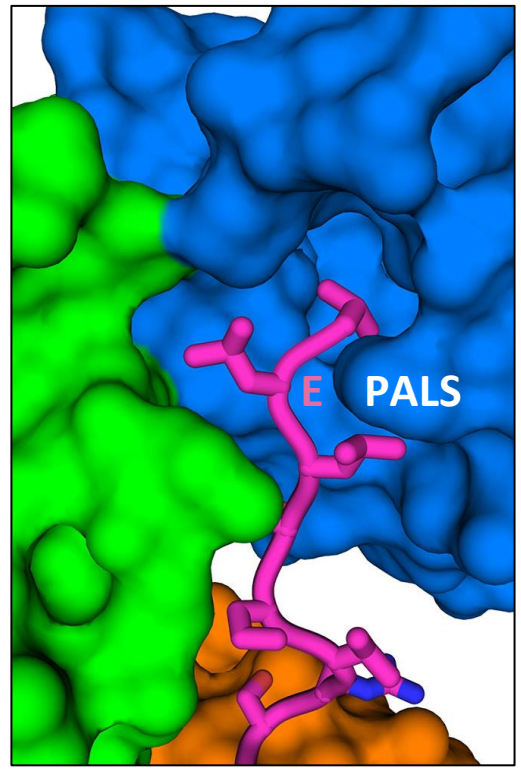

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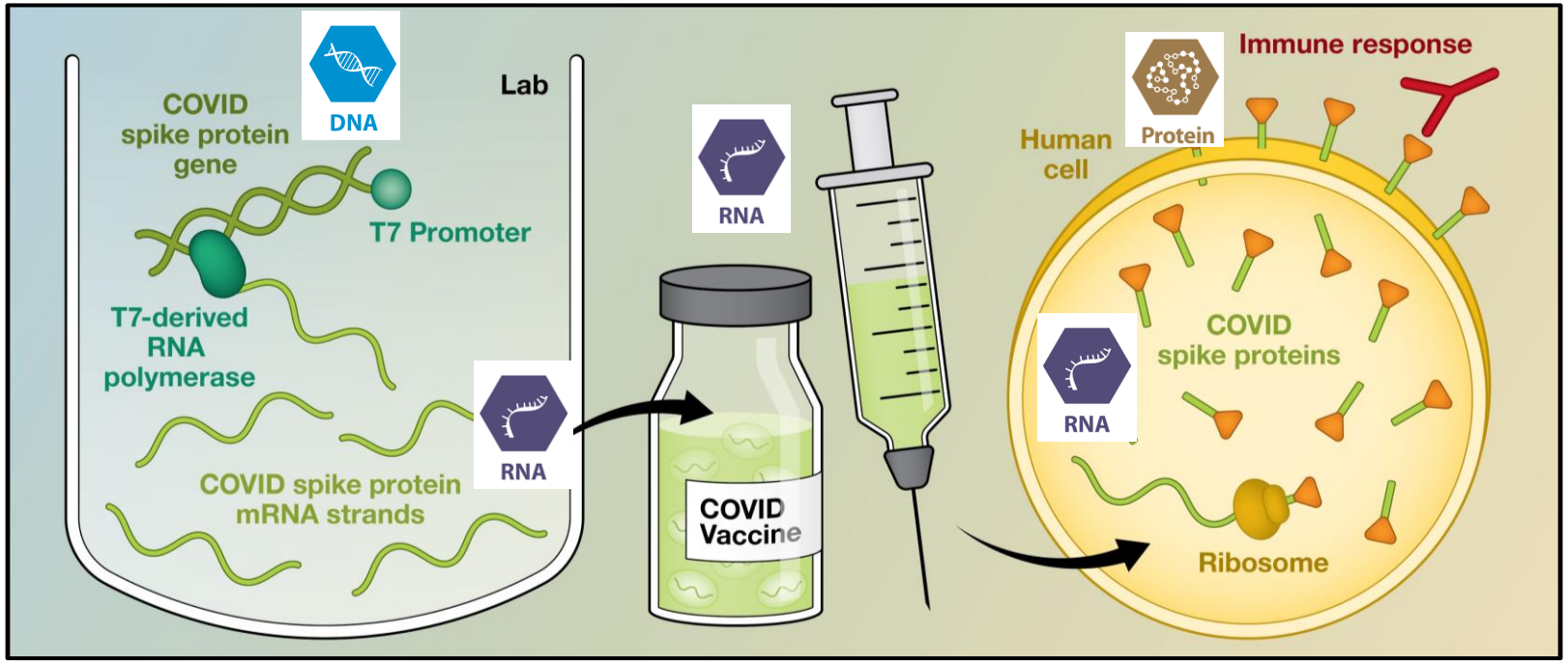
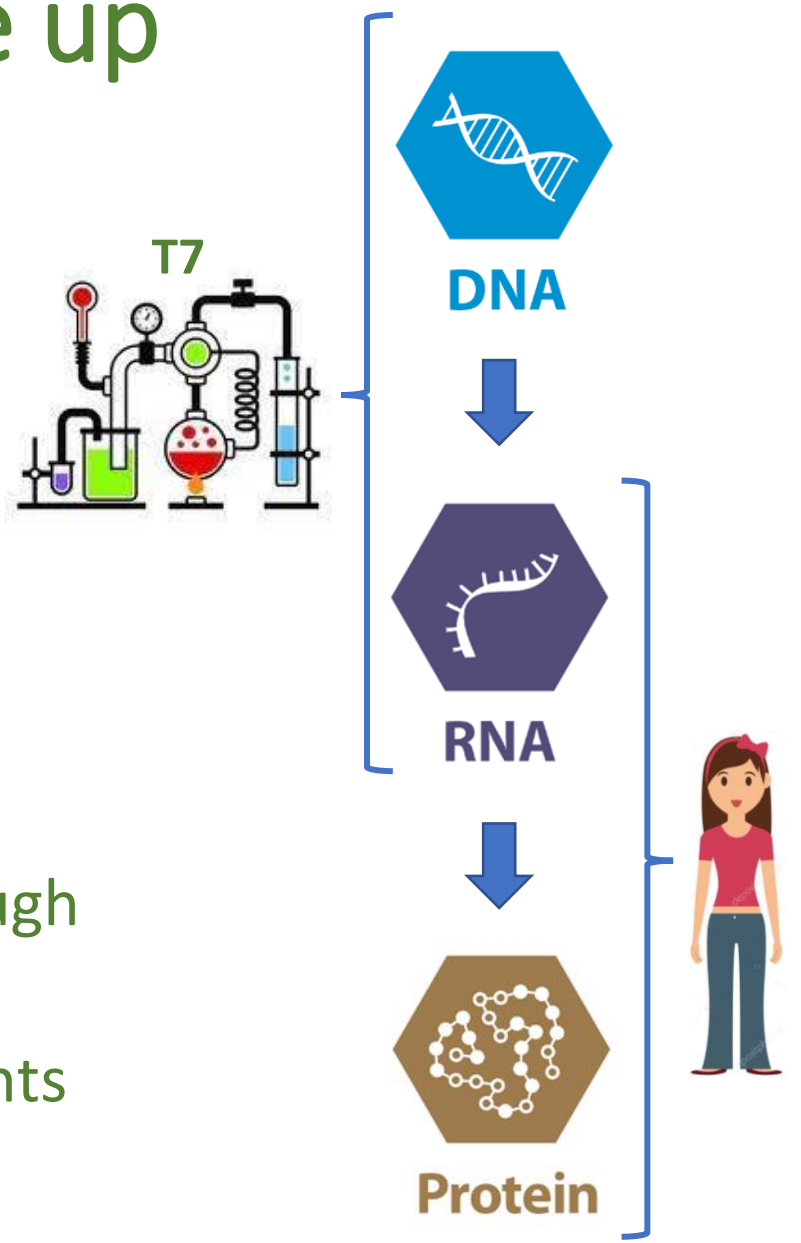
Vaccines to fight the COVID pandemic

- Flu vaccines are made by amplifying the virus in eggs
- The virus is extracted, killed and its antigens purified and used as a vaccine
- The process scale-up can take up to a year
- Pfizer and Moderna used Bill's T7 system to make a new kind of COVID vaccine from spike protein mRNA instead of the virus

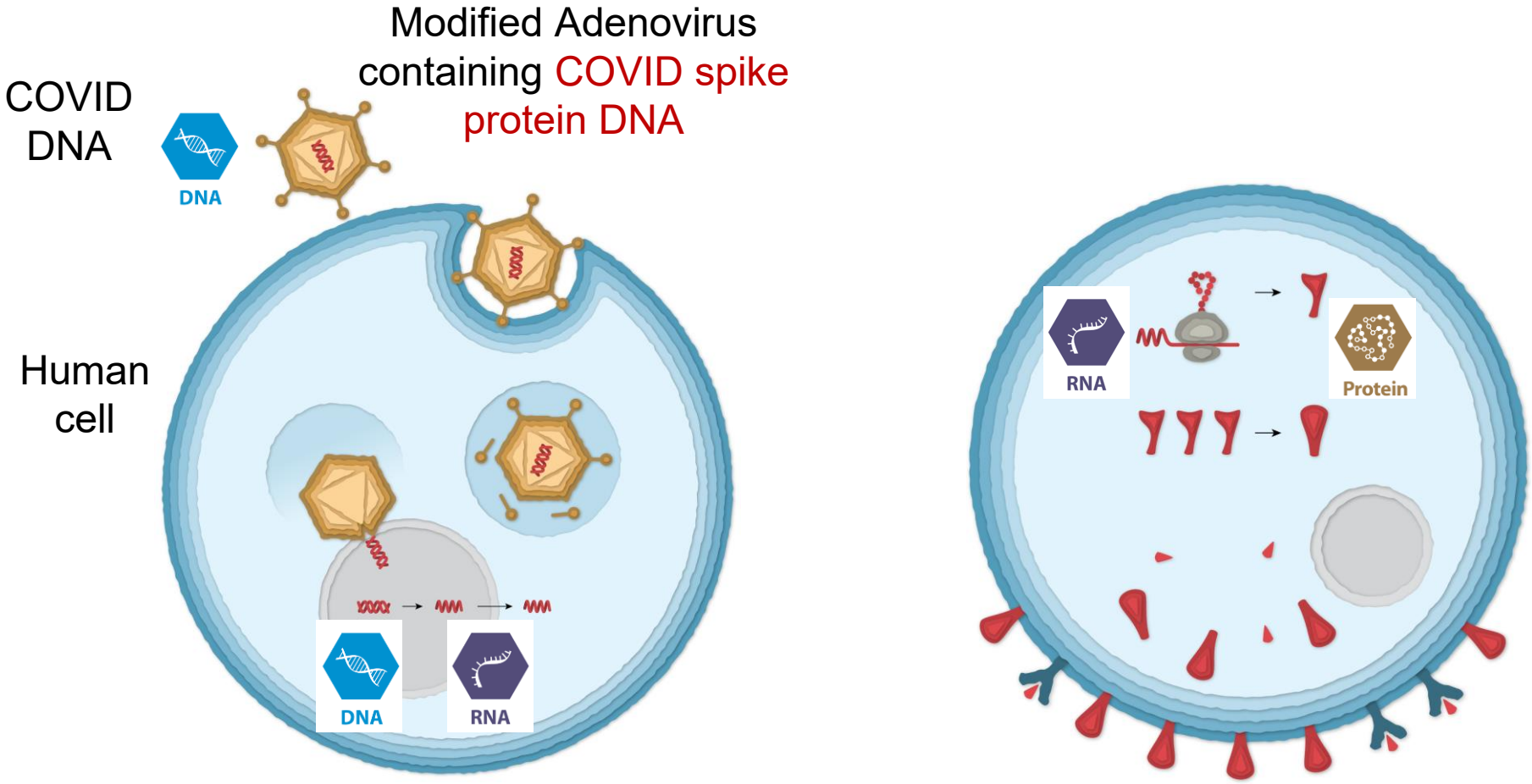
Using T7 to accelerate vaccine scale up





- Can make many kilograms of RNA in a single batch, enough to vaccinate millions of people
- Can change DNA sequence quickly to pivot to new variants
- Development in months instead of years

The J and J Vaccine is a Modified Adenovirus



Summary

Bill Studier, 2012

- In what started off as a basic science project to understand the biology and genetics of a model virus, Bill Studier made astute observations that helped him solve how to make viral RNA and proteins for study by his group at BNL
- In solving the problem of making proteins for his own studies he created a system that has powered biological advances, accelerating discoveries in biomedical research worldwide
- Application of his discoveries by Moderna and Pfizer in making the COVID-19 vaccine saved **140k deaths in the USA and over $900B in healthcare costs in first 5 months of 2020*, (global estimates are approximately 1.1M lives and 10M hospitalizations)**
- A pretty good return on investment for curiosity-driven basic science.
- **Bravo Bill!!**

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*** https://bit.ly/3jm0Eb2**