ORNL's unsung discovery of messenger RNA

(As published in The Oak Ridger's Historically Speaking column the week of June 7, 2021)

Carolyn Krause brings us an amazing story, yet not such a surprising one. It is a story of a research scientist at the Oak Ridge National Laboratory who 65 years ago discovered the messenger RNA (mRNA). As is sometimes the case, he did not, however, receive due credit for his discovery. Learn more in this column of Historically Speaking about Elliot (Ken) Volkin and his amazing discovery that is a key to the Covid vaccines today.

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When Karen Brunner received her first Moderna vaccination against the virus causing the COVID-19 pandemic, she told the nurse that her father co-discovered messenger RNA (mRNA), the chief ingredient in the highly successful Moderna and Pfizer-BioNTech two-shot vaccines. The nurse said, "Wow, that's pretty cool!"

In an interview with Robin Wilhoit for a recent WBIR news broadcast, Brunner said of Volkin, "He was just my dad but to my friends and family he was this giant. As soon as news about the mRNA vaccines came out, my Facebook page just blew up with comments from classmates who were so excited about this."

Her father was Elliot (Ken) Volkin, who died in 2011. He and his research partner Lazarus (Larry) Astrachan first observed and described what later came to be known as messenger RNA (ribonucleic acid) in 1956 while working in the Biology Division at Oak Ridge National Laboratory. They labeled their finding "DNA-like RNA" in their paper in the Journal of Virology.

This transitory DNA-like RNA, or mRNA, transmits genetic information from the DNA in the cell's nucleus to the protein-building ribosomes in the cell's cytoplasm, which is outside its nucleus. The ORNL researchers' discovery came three years after James Watson and Francis Crick, with the help of Rosalind Franklin, discovered in England the structure of DNA, the carrier of genetic information. The ORNL research addressed this major problem in biology: How is the hereditary information encoded in DNA used by living cells to synthesize the proteins that do the cells' work and that are needed for the structure, function and regulation of the body's tissues and organs?

If you ask Google, "Who discovered messenger RNA?", the answer you get is this: "The existence of mRNA was first suggested by Jacques Monod and François Jacob, and was subsequently discovered by Jacob, Sydney Brenner and Matthew Meselson at the California Institute of Technology in 1961." Monod and Jacob, two French researchers, won the Nobel Prize in Physiology or Medicine in 1965 "for their discoveries concerning genetic control of enzyme and virus synthesis," which included elucidation of the nature of mRNA from their observation of protein synthesis by genes of mutated bacteria in the presence of lactose.

In late 2003 I interviewed Volkin at his Oak Ridge home for an article I wrote for the ORNL Review (Vol. 37, No. 3, 2004) entitled "ORNL's Unsung Discovery." He recalled his conversation with Sydney Brenner at Cold Spring Harbor Laboratory in 1960 in New York, where Volkin conducted research on the hot topic of bacterial viruses during the summers in the late 1950s. "I can well remember sitting on the lawn at Cold Spring Harbor and telling Sydney Brenner about our experiments," Volkin told me. "I gave a presentation on our RNA research to the group there."

Early this century, former ORNL Director Alvin Weinberg wrote that the original discovery of mRNA at ORNL "has never received the acclaim it deserves," calling it "next to the original discovery of the molecular structure of DNA, probably the most important event in the history of molecular biology." Paul Berg, winner of the 1980 Nobel Prize in Chemistry, called the ORNL research an "unsung but momentous discovery of a fundamental mechanism in genetic chemistry" and a "seminal discovery [that] has never received its proper due." These quotes and subsequent quotes from Weinberg here are included in the ORNL Review article.

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When Volkin was asked later about how he felt about the French scientists being honored with a Nobel prize for work similar to what was done at ORNL, he reportedly said, "I have no hard feelings. That's the way things were." His daughter told Wilhoit: "I'll never know what was in his heart of hearts. I think he understood that that's how science works sometimes. Were it me, I probably would have felt a little cheated."

The ORNL discovery

Because DNA and RNA are organic molecules with pentose-phosphate backbones, Waldo Cohn and Volkin incorporated radioactive carbon and phosphorus into these molecules to help determine their structure using ion-exchange chromatography. That technique, first used by Cohn for separating fission products at ORNL's Graphite Reactor, was employed by him and Volkin to discover the building blocks (nucleotides) of nucleic acids in DNA and RNA. Volkin then became interested in working with bacteriophage, a virus that infects only bacteria, and Astrachan joined him in conducting experiments.

According to Berg, Volkin and Astrachan "discovered that the virus 'turns off' the [bacterial] cell's machinery for making its own proteins and 'instructs' the cell's machinery to make proteins characteristic of the virus. That instruction entails making a new kind of RNA, a copy of the virus's DNA. This discovery revealed a fundamental mechanism for gene action: the coding sequences of genes are copied into short-lived RNAs that are transported out of the nucleus into the cytoplasm, where they are translated into proteins. Because such RNAs transport information from genes in the nucleus to the cytoplasm, they are designated as messenger RNAs."

In his August 2, 2003, obituary for Astrachan in the New York Times, Nicholas Wade wrote: "The Volkin-Astrachan experiment showed that there were two kinds of RNA, a long-lived type found in the ribosomes and a transitory kind whose role was unclear. They also showed that the transitory kind was made when a virus invaded bacteria and that it resembled the virus's DNA, not the bacterium's."

According to Volkin, the ORNL findings were not widely accepted by the biology community at first because they challenged prevailing theory.

Weinberg's letter

In a book review in a 2001 issue of the prestigious journal Nature, Horace Judson, a renowned historian of science, attributed the discovery of messenger RNA to François Jacob, Sydney Brenner, and Matthew Meselson. Weinberg published a letter in the November 29, 2001, issue of Nature disputing this claim.

"In fact," Weinberg wrote, "Jacob, Brenner, and Francis Crick, at an informal meeting on Good Friday 1960, suddenly 'discovered' the unique RNA found first in 1956 by Elliot Volkin and Lazarus Astrachan. Good accounts of this event can be found in "The Statue Within" by Jacob and "What Mad Pursuit" by Crick. In several publications from 1956 through 1958, Volkin and Astrachan thoroughly described the unusual properties of this RNA, which they termed DNA-like RNA. These were precisely the properties that Jacob and Jacques Monod sought to assign to the unstable intermediate (which they called X), necessary for the synthesis of galactosidase. Out of that Good Friday discussion on the lactose operon came the realization that Volkin and Astrachan's DNA-like RNA was indeed the genetic messenger, hence the messenger RNA (mRNA)."

Nicholas Wade cited Judson's history of molecular biology, "The Eighth Day of Creation," in his statement that Brenner, in a 1960 meeting in Cambridge, England, with Jacob and Crick, "realized there must be a missing ingredient that carried information from the DNA in the cell's nucleus to the ribosomes in its periphery. This ingredient, he conjectured, must be the same as the transitory form of RNA seen in the Volkin-Astrachan experiment."

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Although Weinberg acknowledged that Brenner (a 2002 Nobel Prize winner), Crick, Jacob and Monod are giants of molecular biology, he believed that Volkin and Astrachan were never appropriately recognized for their original discovery.

Volkin, who grew up near Pittsburgh, Pa., as the youngest of seven children of Lithuanian immigrants,

was honored by Pennsylvania State University, his alma mater. "Miriam and I were his escorts to Penn State when he received the Distinguished Alumni award," said Gordon Fee, former president of Lockheed Martin Energy Systems and former manager of the Y-12 National Security Complex, as well as a Penn State alumnus. After majoring in the new field of biochemistry and graduating Phi Beta Kappa from Penn State, Volkin took graduate courses at Duke University where he earned his master's and Ph.D. degrees and met his future wife Sylvia Fine Volkin, longtime food columnist for The Oak Ridger and late mother of Marcia Ann Volkin Rabinowitz (who died in 2006) and Karen Volkin Brunner.

mRNA – another Pennsylvania connection

Another mRNA discovery has a Pennsylvania connection (full disclosure—I am a Pittsburgh native, my husband is a graduate of Drexel University in Philadelphia, we both have advanced degrees from the University of Pittsburgh and his brother-in-law is a University of Pennsylvania graduate). At the University of Pennsylvania's Perelman School of Medicine, Drew Weissman, a professor of medicine, and Hungarian native Katalin Karikó, an adjunct professor at Penn and a senior vice president at BioNTech, together made discoveries that were licensed to Pfizer and Moderna, leading to the vaccines that are helping end the pandemic.

According to the Penn website, "Unmodified mRNA molecules are normally unable to slip past the body's immune system, but Weissman and Karikó's breakthrough research made key changes to the molecular structure and manufacturing of mRNA that allow the resulting modified mRNA to avoid immediate immune detection, remain active longer, and enter into target cells to efficiently instruct them to create antigens or other proteins that fight or treat disease."

The COVID-19 vaccines teach our cells to make the "spike protein" found on the novel coronavirus. As a result, our immune system learns to recognize and destroy the virus when it tries to infect us. I hope Weissman and Karikó, the woman who persisted against pushback to find therapeutic uses for mRNA, will someday win the Nobel Prize for Physiology or Medicine for their life-saving achievements.

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Thanks Carolyn, for bringing us the facts about a 65-year-old discovery that has gone essentially unrecognized yet is such a key to the success of the Covid vaccines.

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