

RESEARCH SPOTLIGHT

TRANSLATING SCIENCE TO PRACTICE

Targeting a Viral Vulnerability to Treat Disease

ACCORDING TO VIROLOGIST Dr. Robert Ricciardi, Professor and Chair of Microbiology at Penn Dental Medicine, the line between basic science and translational research is not hard and fast. You can start out pursuing a line of investigation out of pure curiosity and wonder and — with talent and hard work — find yourself with a marketable drug.

“There’s no such thing as knowledge that isn’t useful,” he says.

Dr. Ricciardi has shown this to be true in his work, which began in the realm of basic science and has since hit upon a variety of potential applications for treating viral diseases. The company he founded in 2015, ViRAZE, takes advantage of carefully crafted, interdisciplinary approaches to drug discovery. First up, ViRAZE is taking aim at molluscum contagiosum, a disease that causes skin lesions and affects millions of children and immune-compromised adults around the world. No FDA-approved therapy currently exists.

Not only would a molluscum treatment fulfill an unmet medical need, but surprisingly, could also aid in developing a back-up drug for smallpox, a closely related poxvirus. Eradicated in the population since 1980, smallpox lingers as a bioterrorism threat.

“Molluscum and smallpox replication mechanisms are so alike,” Dr. Ricciardi says, “that when you’re developing a drug aimed at targeting the molecular machinery of one virus you’re simultaneously helping to develop a drug that targets the other.”

His advancements in the arena of viral disease began with a recognition about a key molecule present in every cell of virtually every living organism and pathogen on Earth: processivity factors. Essential for DNA replication, each processivity factor acts like



Dr. Robert Ricciardi

a sliding clamp, holding the polymerase — the enzyme that performs DNA replication — onto the strand of DNA being copied. Without its processivity factor, the polymerase cannot do its job and new strands of DNA will not be made.

In the 1990s, Dr. Ricciardi and colleagues discovered a processivity factor in human herpesvirus 6, a virus that can cause a short-lasting fever and rash in very young children and is implicated in certain adult diseases.

While every organism and pathogen possesses a processivity factor, each can only work with its own individual polymerase. That single fact caused “a lightbulb to go on for me,” Dr. Ricciardi says. If he could find a molecule that would bind to and block the activity of the viral processivity factor without interfering with the human version of the protein, he might have an effective antiviral therapy on his hands.

Dr. Ricciardi’s lab has trained its sights on those potential inhibitors ever since. For years he worked on smallpox, but, because two drugs from other groups were more

advanced, one of which is now stockpiled by the United States government, the urgency for studying it had receded until recently. Because smallpox is such a devastating threat, it’s important to have two drugs available, in the event that the smallpox virus becomes resistant to the first.

A short time ago, the National Institutes of Health (NIH) and U.S. security agencies became concerned that the second smallpox drug did not gain FDA approval, leaving only one usable drug in the event of a bioterrorism attack. Dr. Ricciardi was recently contacted by the NIH, which has indicated a renewed interest in continuing work on his smallpox antivirals.

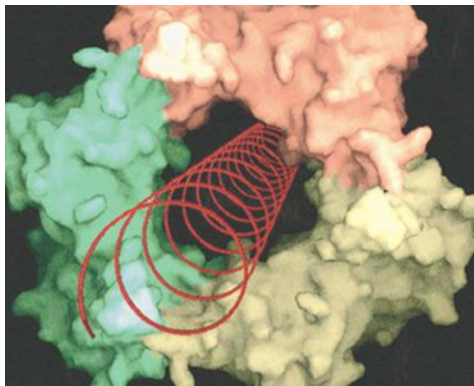
In the last several years, while working on smallpox, molluscum came to the fore. The primary reason for lack of a therapeutic for this disfiguring and sometimes painful disease that affects young children is that molluscum stubbornly resists being grown in a lab.

“I’ve gone back to papers since the 1970s where people tried to grow molluscum in tissue culture,” Ricciardi says. “It just couldn’t be done.”

Several years ago, Dr. Ricciardi teamed with physician and poxvirus expert Stuart Isaacs, an associate professor at Penn’s Perelman School of Medicine, to give it a different shot. While traditional methods didn’t succeed, they worked together with Hancheng Guan and Manunya Nuth, members of Dr. Ricciardi’s lab, to find a novel solution: a hybrid virus.

“We took the processivity factor out of molluscum and inserted it into a prototypic pox virus, called vaccinia, that is used all the time in research,” says Dr. Ricciardi. “It grows beautifully.”

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He describes that achievement not as a mere step forward but as a “quantum leap” that is on the path to drug discovery. His lab with Guan and Nuth and with the Isaacs lab began to develop antiviral molecules, targeting the molluscum-specific processivity factor, that could be tested using the hybrid system. Dr. Ricciardi’s long-standing relationship with the medicinal chemistry group at Fox Chase Chemical Diversity Center (notably CEO

Allen Reitz and Richard Scott, vice president for research) accelerated the process, as did a new approach in Dr. Ricciardi’s own lab. The approach incorporated biophysics, genetics, and computer-aided processing to identify molecules that could inhibit the activity of the molluscum processivity factor, and thus, the virus’s ability to infect human cells.

“That showed us exactly where to look,” Dr. Ricciardi says. “Combining those three things together gave us two solid leads that are moving us further and further into drug development.”

Three years ago, he worked through the Penn Center for Innovation (PCI) to spin out ViRAZE, a name intended to evoke the idea of “razing,” or destroying viruses as one would raze a building. Michael Poisel of PCI recruited business partners Rajiv Khosla, an experienced pharmaceutical and biotech executive, as the company’s CEO, and Thomas Han, a marketing expert, as

head of operations. They’ve also collaborated with Leslie Costello-Soccio, a pediatric dermatologist at the Children’s Hospital of Philadelphia, for her perspective on the clinical needs for molluscum patients.

Dr. Ricciardi is eager to make a difference for the children affected by the disease, but the molluscum therapies are only one of several directions his research into processivity factors is headed. The strategy for blocking virus’s activity via their processivity factors also has him poised to make early-stage breakthroughs in stopping another disease: ocular herpes keratitis, the most common cause of corneal blindness in the world.

“What drives me is figuring out what can this technology do?” he says. “How can I use this technology to meet unmet medical needs? That’s what we’re all about.” ■

— By Katherine Unger Baillie