VICC trial putting lung cancer therapy to the test

BY DAGNY STUART

Vanderbilt-Ingram Cancer Center (VICC) is leading a Phase 3 global trial of a cancer therapy that was initially tested and validated in a VICC research laboratory. One of the first patients treated with the therapy came to VICC after a bump on the head led to an unexpected cancer diagnosis.

That head injury may have prolonged Shawn Morgan's life. The school bus driver and swimming instructor from Sparta, Tennessee, spent several days in pain following a collision with a cabinet before family members persuaded her to visit a nearby hospital emergency room.

Tests revealed a devastating illness.

"I had all these bleeds in the brain and I was very close to death. They told my mom I had cancer, and it did not originate in the brain, it's in the lung," Morgan said.

Looking back, the mother of nine children realized that a persistent cough that lasted for months was a symptom of the lung cancer that had advanced to Stage 4. She received radiation therapy for the brain.

continued on page 4

Research sheds light on how RSV wards off potential vaccines

BY BILL SNYDER

Respiratory syncytial virus (RSV) is the major cause of life-threatening viral pneumonia in infants worldwide, yet despite repeated efforts, scientists have been unable to develop an effective vaccine against it.

"Now, a team of scientists at Vanderbilt University Medical Center (VUMC), with colleagues in California and Pennsylvania, believe they know why the virus has been so difficult to neutralize.

Reporting this week in the Proceedings of the National Academy of Sciences, they describe how competition among
Research sheds light on how RSV wards off potential vaccines...

antibodies for binding the same viral site can interfere with effective neutralization of the virus.

"Human monoclonal antibodies have proven to be a very powerful tool for studying the human immune response to viruses," said James Crowe Jr., M.D., director of the Vanderbilt Vaccine Center at VUMC, Ann Scott Carell Professor in the Vanderbilt University School of Medicine and the paper's corresponding author.

"Here they allowed us to get a snapshot of the complex fight of both beneficial and interfering antibodies competing for space on the virus," Crowe said.

The researchers focused on part of the RSV fusion (F) protein that fuses the viral particle to its target cell in the lung. This region, called antigenic site II, is the target of palivizumab (Synagis), a licensed monoclonal antibody injection that can prevent serious RSV complications in high-risk infants.

They generated a variety of human monoclonal antibodies against the F protein.

Using techniques including X-ray crystallography to visualize protein structure and mutagenesis scanning to determine protein function, they showed how antibodies capable of neutralizing the virus competed with non-neutralizing antibodies for binding at antigenic site II.

But there is a twist. When the F protein delivers its viral cargo to the "loading dock" of the target cell, it undergoes what the scientists described as a dramatic structural rearrangement, essentially pivoting like a ballet dancer into a new "pose" and revealing another, previously concealed binding site next to site II.

Non-neutralizing antibodies, which can't prevent RSV from injecting its toxic cargo into the cell, preferentially bind to the new site on the F protein, but they also cross over to site II, and thus "muscle out" neutralizing antibody.

The answer may be to design a vaccine strategy that identifies and produces neutralizing monoclonal antibodies that target only site II and not the entire F protein.

These findings may have relevance for the design of other vaccines, as the production of non-neutralizing antibodies is a common occurrence during viral infection, the researchers concluded.

Jarrod Mousa, Ph.D., a postdoctoral research fellow in Crowe's lab, was first author. Other collaborators included Vanderbilt University faculty Jens Meiler, Ph.D., and Melanie Ohi, Ph.D., and researchers at Integral Molecular Inc. in Philadelphia, the Scripps Research Institute in La Jolla, California, and Stanford University in Palo Alto, California.

The research was supported in part by National Institutes of Health grants RR026915, AI007474 and TR000445.

VICC trial putting lung cancer therapy to the test...

metastases, but doctors told her family there was no hope of survival.

Morgan's mother had other ideas and requested a second opinion at VICC, where Morgan was referred to Leora Horn, M.D., M.Sc., associate professor of Medicine and clinical director of the Vanderbilt Thoracic Group.

Horn collaborates closely with Christine Lovly, M.D., Ph.D., who operates a research laboratory at VICC. The timing of Morgan's diagnosis coincided with lung cancer research that had already been done in, selective inhibitors of a target called ALK," said Lovly, assistant professor of Medicine and Cancer Biology.

Mutations in the gene encoding anaplastic lymphoma kinase (ALK) are found in several types of cancer, including non-small cell lung cancer, lymphoma, sarcoma, and a childhood cancer called neuroblastoma.

ALK tyrosine kinase inhibitors are effective therapies for patients whose tumors ensartinib.

As a result of Lovly's preclinical drug testing, a new ALK inhibitor drug called ensartinib (or X-396) was identified. VICC led the Phase 1 and 2 clinical trials of the new drug. When Morgan arrived at VICC, Horn requested molecular testing of her tumor, which is standard of care for all non-small cell lung cancer patients.

She was hoping that her patient's young age (Morgan was 51 at the time) might point to an ALK mutation. "Many of our ALK-positive patients are younger than the average lung cancer patient and were never smokers," Horn said.

"That knock on the head was a blessing in disguise," Morgan said. "Praise God, my body just responded so well and I've done very well with it. It is a couple of pills. July 9 of this year was three years and I'm doing great. I feel very through the people at Vanderbilt."

Not all patients have the same response to therapy and it isn't clear if the Phase 3 drug trial will be successful. But Horn said these clinical trials highlight VICC's strengths as a research center.

"This is an example of our translational research and our leadership in precision medicine, including collaboration with industry," Horn explained.

Lovly said VICC's commitment to laboratory excellence is accelerating the pace of cancer drug development.

"This was rapid development of the drug, starting with..."