

Cancer "Smart Bomb" Close to Launch

UCSB Researcher Discovers Way to Deliver Bigger Medicine Payload to Tumors

Tuesday, January 26, 2010

Don't talk to Erkki Ruoslahti about happy accidents or serendipity. As the Finnish-born cell biologist (whose name is pronounced "air·key roo·slot·ee") can attest from personal experience, "good luck" strikes only after years of sustained, methodical, and painstaking work. In Ruoslahti's case, that translates to more than 25 years studying the fundamental cellular biology by which cancer cells commandeer the body's otherwise healthy resources to feed malignant tumors with a fresh blood supply. Last month, Ruoslahti — now working at UCSB — co-published a research paper in the prestigious scientific journal *Cancer Cell* (along with colleagues from MIT and UC San Diego) that could prove nothing less than groundbreaking in how cancer tumors are first detected and then attacked. Thanks to the new breakthrough — which fused Ruoslahti's insights into the fundamental biology of cancer cells with nanotechnology delivery systems perfected by other scientists — the research team figured out how to get bigger payloads of cancer-fighting medicines deeper into the cancer tumors of mice than ever before.

For prospective cancer patients who might soon be facing the well-documented agonies of chemotherapy — in which all-out chemical warfare is waged on the body's cells in order to destroy the relatively few malignant ones — the implications of this research are staggering. "The more drug we have in the tumor, the bigger the effect is on the tumor," Ruoslahti explained. "But it's only the tumor that gets more drug; the normal tissues don't. That should reduce the side effects."

Or, as his longtime colleague Dr. David Cheresh from UC San Diego described it, "It's like developing a smart bomb against cancer. It's like developing a targeted missile without inflicting all the collateral damage."



Paul Wellman

Dr. Erkki Ruoslahti

In addition, Dr. Dan Greenwald of the Cancer Center of Santa Barbara stated the new research could prove invaluable in the early detection of cancer cells, when they're still too small to be tracked by traditional imaging technologies like CT scans and MRIs. But, Greenwald cautioned, it takes years to translate the basic bio-cellular research conducted by Ruoslahti (using mice) into new medicines that are both safe and effective for humans. To that end, he said, Ruoslahti is collaborating with the Cancer Center on new research, using

cast-off human tissue banked by the Cancer Center.

The lucky break for Ruoslahti came several years ago when he set out to create a new peptide chain to act as a homing device for finding and adhering to cancer tumors. (Peptides are made up of a sequence of different amino acids, the basic building blocks of protein molecules; proteins are extended chains of amino acids. The protein makeup of cancer blood vessels is slightly different than that of normal cells. For the past 25 years, Ruoslahti has sought to understand the biology of those differences so they could be exploited for medical advantage.) By adding a fourth amino acid to an already well-known combination of amino acids—a sequence that he invented 25 years ago—Ruoslahti successfully engineered a new peptide chain that, after being injected into a mouse's bloodstream, could find its way to the mouse's tumor faster and more effectively than anything seen before.

That, by itself, would have constituted a significant advance.

But Ruoslahti also noticed that his new peptide chain exhibited what he termed several "unexpected and remarkable properties." Not only did the chain function as a superior homing agent, finding and adhering to the tumor, but it also managed to penetrate the tumor as well. "It spread into the tumor in ways we had not seen before," Ruoslahti recounted. The one-two punch packed by Ruoslahti's peptide chain — described in the scientific literature as "iRGD" — is generating significant excitement in scientific circles. For the first time, scientists have isolated an agent capable of both finding the tumor and destroying it. It accomplishes the latter by functioning much like a house key, unlocking the tumor and exposing its interior to penetration by cancer-fighting drugs. (How that "key" gets in the lock is an equally complex process, one that required the injection of two nano-particle agents, each one measuring less than a thousandth the diameter of a human hair.) In the research Ruoslahti's team did with mice, they managed to inject eight to 11 times more Abraxane (a chemotherapy drug) into the mouse tumors than conventional methods. By doing this, they were able to restrict the tumors' growth.

A cliché popular among cancer researchers is that it's easy to cure cancer in mice. Mouse tumors, after all, are artificial, and the animals' anatomies significantly less complex than humans'. But Ruoslahti is already moving on to the next step, doing lab work on human tissue specimens in conjunction with the Cancer Center. He's confident that the biomechanics of his work will make the species jump from mice to humans.

In the world of bio-cellular cancer research, Ruoslahti had achieved rock-star status long before he arrived at UCSB nearly five years ago. For the previous 25 years, Ruoslahti led a team of researchers at the Burnham Institute for Medical Research in La Jolla. Ruoslahti was born, educated, and trained in Finland, which he left in 1976. "I ran into some university political problems in Finland," he explained, "and I always knew I liked California." While in La Jolla, Ruoslahti and his team created a new protein molecule that's proven invaluable in understanding the behavior of similar molecules in cancer cells. As a researcher, he was exceptionally prolific, churning out articles at an astonishing pace. A member of the National Academy of Sciences, Ruoslahti has won just about every award short of the Nobel Prize. (Last year, he was honored by the President of Finland for his scientific work.)

But after 25 years in La Jolla, Ruoslahti began itching for a change. He was drawn to the beauty of the Santa Ynez Valley and impressed with the strength of UCSB's chemistry, physics, and material science research. "They're on par with MIT or UC Berkeley," he said. And he was more than a little intrigued with the possibilities posed by the campus's burgeoning work in nanotechnology. "I told UCSB that I'd be interested," recounted Ruoslahti. "They got very interested." UCSB didn't merely hire Ruoslahti; it hired his whole team of 13 researchers, including Dr. Kazuki Sugahara and Tambet Teesalu. According to the deal, Ruoslahti and crew would be cut loose to focus exclusively on research; UCSB would provide them the lab space necessary to pursue that research, and the National Institutes of Health and the Department of Defense — along with some smaller grants and corporate pharmaceutical funding — would pay the freight for such research. With Ruoslahti happily ensconced in Santa Barbara, campus officials are working to finalize the formation of the

UCSB-Burnham Center for Nanomedicine.

In the meantime, Ruoslahti confronts a lengthy process of clinical tests and trials to demonstrate that his process works on humans, is safe, and that a proper dosage can be established. That could take anywhere from seven to 12 years. Looking back, Ruoslahti acknowledged that his research took unexpected turns and yielded unanticipated results. But those results emerged out of a lifetime of research that has built incrementally upon itself, year after year. "It is a remarkable peptide," he said. "But I wouldn't say it was serendipitous or lucky. I'd like to think we didn't stumble onto this."