Mapping the Body's Zip Codes

Biologist Erkki Ruoslahti is renowned for his work on the homing behavior of molecules and cells. Now at UC Santa Barbara, he is studying the chemistry that guides and might destroy cancers.

The human circulatory system is a vast web of arteries, veins and capillaries through which the substances essential to life and some harmful to it flow. It's also a world of richly varied surfaces. Blood vessel walls are a tapestry of chemical markers, drawing certain molecules to certain tissue types while letting others pass. The Finnish-born Ruoslahti has been studying this complex vascular geography for most of his distinguished career. At 67, he has come to UCSB to run a new research institution and to chart a course for future cancer therapy.

The new institution is the Burnham Institute at UCSB, operated by UCSB and the La Jolla, Calif.-based Burnham Institute for Medical Research. Opened in December 2006,
its mission is to chart the markers associated with malignant tumors in hopes of using these `zip codes,' as Ruoslahti calls them, against those same cancers. Ruoslahti is a distinguished professor at Burnham, which he joined in 1979, and holds the position of adjunct distinguished professor in UCSB’s Department of Molecular, Cellular and Developmental Biology.

“We’re looking for specific features in the blood vessels and lymphatic vessels of tumors,” he says, “with the intention of then using these specific markers to enhance the delivery of drugs and diagnostic probes into the tumors.” Essentially, the object is to find the chemical address of blood vessels in cancer and send a molecule that binds specifically to the distinctive receptor protein. Attached to the molecule, there might be a chemical tracker to detect the tumor or a drug to destroy it. The research challenge is to come up with molecules such as peptides (segments of proteins) that zero in on tumor blood vessel receptors while leaving normal tissue alone.

**A Decades-Long Quest**

![Nanoparticles home in on receptors on blood vessel walls that adjoin tumors, delivering a chemical to kill or detect the tumor cells.](image)

Ruoslahti has been working toward this therapeutic target for more than 35 years. As a post-doctoral fellow at Caltech in the late 1960s, he learned of neurobiologist Roger Sperry’s research suggesting that molecules on cell surfaces precisely guided certain aspects of brain development. Ruoslahti figured that cells elsewhere in the body might also be guided by surface signals and that the spread of cancer cells throughout the body—metastasis—might be a sign of the system going awry. Returning to Finland and setting up his own lab, he worked to isolate zip-code proteins. In the early 1980s, after he had moved back to the U.S., he and his collaborators achieved a major breakthrough with the discovery of RGD, a peptide that plays a crucial role in cell attachment.

Researchers have gone on to develop RGD-based drugs to prevent blood clotting. Ruoslahti stays focused mainly on cancer, studying how tumor-specific ‘homing’ peptides that direct malignant cells during metastasis might be used instead for diagnosis and treatment. The first phase in this research is to draw the vascular map, finding out which areas on the inner surface of blood and lymph vessels, both normal and malignant, are targets for particular cancer cells. Molecules that ape the cell-attachment chemistry of the cancer cell can deliver their payload—a drug or a detection chemical such as fluorescein—to a specific type of tumor. Instead of using actual cancer cells in this process, Ruoslahti’s lab uses phages (viruses that infect bacteria)
that home in on particular types of tissue. The phages are injected into mice, extracted after they bind to the target tissue, and then reproduced in greater volume for re-injection.

Once the vascular markers of a target tissue are identified, the corresponding peptides can be isolated from the phages. These then become nanoscale delivery vehicles for drugs or other chemicals. So far, Ruoslahti says, he and his colleagues have found a number of markers that appear with any kind of cancer. More interesting, because of their therapeutic potential, are markers identified with specific types of tumors, such as breast and prostate cancer. We don’t have anything that we know is absolutely specific for a given type of cancer, he says, but we have markers that we know are limited to one of them—mostly breast cancer. He also says they have isolated markers limited to cancers from similar types of tissues—for instance, glandular tissues such as the pancreas.

The Promise of Precision

Ruoslahti says it will take some time before the homing-peptide therapies are ready for Food and Drug Administration approval. Much preclinical work needs to be done independent of the academic setting, he says, noting that it took about 15 years after his discovery of RGD for the first RGD-based drug to reach the market. But the therapeutic potential of his zip-code mapping is obvious. With a highly specific marker as its target, a drug can be delivered right to the tumor with fewer side effects. A homing peptide or other molecule that attaches to just one type of tumor would also be a precise diagnostic tool.

For Ruoslahti, bringing a new generation of cancer drugs to market would be a fitting outcome for a career that has already earned him global recognition. He has more than 400 published scientific papers and more than 100 patents to his name. As the Burnham Institute’s scientific director from 1989 to 2002, he initiated its growth to an organization with nearly 800 employees, as well as satellite centers in Florida and Santa Barbara.

What brought him to Santa Barbara? He says it was time for a change after 13 years in charge at Burnham. So he stepped down as director at the beginning of 2002. But that wasn’t enough of a change, so I decided to move somewhere. He and his life partner, the biologist Eva Engvall (herself notable for discovering ELISA, a famous immunological test), had a place picked out. Many years ago I fell in love with the Santa Ynez Valley, so we decided to move here, he said. Another attraction was that UCSB was very active in nanotechnology and materials science, and my research started gravitating in that direction. He moved to the area in September 2005 with a temporary appointment. Now he lives on some 1,000 acres overlooking the Santa Ynez Valley and works, at a much smaller scale, surveying the inner landscape of the human body.