When Stuart H. Yuspa, M.D., began studying the skin in the late 1960s, scientists understood some of the basic biology of skin cancer. They knew what was required to produce and diagnose benign and malignant tumors—but not much more. “We’ve made remarkable leaps since then,” says the Co-Chief of CCR’s Laboratory of Cancer Biology and Genetics (LCBG).

No Longer Skimming the Surface of Skin Cancer

Squamous cell carcinoma (top) is a relatively aggressive skin cancer, and it shares many of the features of lethal solid tumors of the internal organs. The Yuspa laboratory’s efforts to model the biology of skin have given great insight into the genesis and treatment of this and other major skin malignancies, such as basal cell carcinoma (middle), and malignant melanoma (bottom).
What Kind of Skin Cancer?

Each type of skin cancer—melanoma, basal cell carcinoma, and squamous cell carcinoma—arises in different cells within the skin. Melanoma forms in melanocytes (skin cells that make pigment) and is the most dangerous form of skin cancer. Basal cell carcinoma forms in cells found in the hair follicles. Basal cell cancers are the most frequent human tumor in Caucasians, but they grow slowly and rarely spread to other parts of the body.

Squamous cell carcinoma, the focus of the work of Stuart Yuspa, M.D., begins in squamous cells (flat cells that arise from keratinocytes and form the surface epidermis of the skin). They are not the most frequent skin cancers, but they share many characteristics—genetically and biochemically—with highly lethal cancers that arise in internal organs like the lung, head and neck, esophagus, colon, and stomach.

The skin’s epidermis harbors the keratinocytes and melanocytes that give rise to skin cancer. The Yuspa laboratory’s efforts to model the biology of skin have given great insight into the genesis and treatment of skin cancers.
Colleagues and former students of Stuart Yuspa, M.D., unanimously point out his generosity with his ideas and time—and his love of science.

He has built a dynamic community of researchers exploring skin cancer. He sees mentoring as a happy obligation. “The only legacy that will be remembered is the people you’ve trained,” Yuspa said. “Part of my job as a scientist, mentor, and member of the NIH is to help anybody I can to succeed.”

About 36 postdocs have moved through his lab. “I couldn’t be more proud of the people who’ve trained here. They’ve been uniformly successful and most [30] have stayed in the same field,” Yuspa beamed.

“Once you go to Stu’s lab, you become part of a huge network of people from around the world who are doing top-rate science,” said Molly Kulesz-Martin, Ph.D. “We’re all excited about the skin and the science of the skin.”

And these “Yuspa graduates” open their arms to the new people who continue to come through the lab. “We share with anybody who asks. It’s a trait of Stu’s that we learned at his knee,” Kulesz-Martin continued. “I remember talking to Stu about how competitive science is and how people don’t want to share. He said, ‘I’ve always shared data. Maybe sometimes you get burned, but I always learn something new when I share.’”

The epidermis, where the keratinocytes live, is a hotbed of cell turnover, Roop explained. This outer layer of our skin replaces itself every three to four weeks in humans. “Yet many of us develop skin cancer late in life. Only the stem cells that reside for a lifetime are around to accumulate enough genetic damage to lead to cancer.”

Roop added, “Stu was also really the first to identify mutations in the Harvey ras gene [a proto-oncogene known for its connections to skin and bladder cancers] as a complete initiating event by showing that just a single Harvey ras mutant gene in a keratinocyte [that is grafted onto an animal model] would result in formation of a tumor.”

“All of us have learned so much from the work Stu started and others who’ve further developed the model,” Kulesz-Martin added.

A Physician’s Dream

“It’s everyone’s dream,” said Yuspa, “particularly if you’re a physician who’s done basic science for the last 30 years, to translate your discoveries into treatments for patients.” To do that, Yuspa’s team is focusing on two relatively new discoveries. Using a mouse model of induced skin inflammation, they are studying how inflammation influences the frequency with which skin cancers develop. In this model, skin cancer is much more frequent. The group identified a receptor that seems to be essential for tumors to develop. He hopes that it could be a novel target for preventing or treating skin cancer.

The second discovery builds on an insight made nearly 10 years ago. They have shown that inactivation of the tumor suppressor gene p53 is important for malignant...
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