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A scientific
community goes
after melanoma

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Through Ludwig's community approach, pieces of the melanoma puzzle are being assembled to reveal previously hidden molecular secrets of the disease.



PHOTOS

From left

Colin Goding
Oxford, UK

Donata Rimoldi
Lausanne, Switzerland

Jonathan Cebon
Melbourne, Australia

Donata Rimoldi, like most scientists, works within a neighborhood community. Her home base is with a group of Ludwig researchers at the University of Lausanne, but she also works with researchers at neighboring institutions such as the Swiss Institute of Bioinformatics, in the same city, and the University of Geneva, about 40 miles west along Lake Geneva.

As the technology needed to do cutting-edge science evolves and becomes more complicated, a community approach is sometimes the only way to accomplish major scientific objectives.

Scientists in Rimoldi's neighborhood have formed a team to dissect the genetic basis of melanoma, a deadly skin cancer which in 2008 affected almost 200,000 people worldwide, claiming more than 46,000 lives. She and her colleagues undertook a large-scale analysis of the DNA mutations found in melanoma, and showed that mutations in genes called *MAP2K1* and *MAP2K2* (mitogen-activated protein kinase) can drive growth of some tumors. The findings were published in December in *Nature Genetics*.

The project characterizes the Ludwig model for cancer research. Ludwig's scientists span the globe, converging in places like Lausanne. Ludwig researchers can set up collaborations in almost any scientific neighborhood in the world, leveraging resources and expertise that may not be available at a single institution.

"The global, collaborative aspect of the Institute distinguishes us from many other research institutes," says Bob Strausberg, who directs Ludwig's collaborative sciences program.

Where it is needed, the Ludwig Institute can provide an extra push to make projects come alive. The Institute, in this instance, provided targeted funding to support the DNA sequencing that underpins the new findings of Rimoldi and her colleagues.

Into the genome

The project began in 2008 with a conversation among genetics researchers at the University of Geneva and Rimoldi and her colleagues in Lausanne.

The Lausanne researchers had stored and cataloged hundreds of melanomas removed from patients over the previous decade. The researchers in Geneva had just installed new state-of-the-art DNA sequencing machines in their labs. Maybe the two groups could collaborate on sequencing melanoma tumors?

"All of a sudden our samples became very precious," says Rimoldi. "All the previous activity at Ludwig since the 1990s, collecting and cataloging the samples, made this project possible."

Three years later the group emerged with a comprehensive view of the mutations behind melanoma. Like other researchers before them, the group observed that most melanomas harbor mutations in a key gene, *BRAF*, which transmits molecular signals within cells.

The researchers also observed mutations in additional genes that may drive development of this cancer. These included the genes *MAP2K1* and *MAP2K2*, which operate in concert with *BRAF*. *MAP2K1* and *MAP2K2* are mutated in about 8 percent of melanomas, according to the researchers' analysis of 127 tumors. Moreover, these mutations also seem to drive cancer. For instance, cells with artificially mutated *MAP2K1* and *MAP2K2* proliferated, much like tumor cells, in a petri dish. The findings suggest that developing drugs targeting melanomas with these *MAP2K1* and *MAP2K2* mutations could help quell the disease.

Only four months before Rimoldi and her colleagues published their findings, a drug that targets the BRAF protein, called vemurafenib (marketed as Zelboraf), was approved by the US Food and Drug Administration. This drug can dramatically shrink tumors containing *BRAF* mutations, but unfortunately patients quickly become resistant to the drug and the tumor almost invariably returns. The new findings provide hope for a solution to this problem: drugs targeting the mutated *MAP2K1* and *MAP2K2* proteins might be used in combination with Zelboraf to help prevent drug resistance and re-emergence of the tumor.

“I appreciated the depths of expertise of my colleagues in areas that I was less familiar with,” says Rimoldi, whose background is in cell biology. “This project could not have come to this conclusion if we had not had all the different parts working together.”

Next steps

Rimoldi's group is currently collaborating with others in the Ludwig community as part of an initiative focused on melanoma. The initiative is led by Colin Goding in Oxford and Jonathan Cebon in Melbourne, Australia. Based on Rimoldi's initial results, this community, with Ludwig researchers in Oxford, Brussels, Melbourne, New York and Baltimore, is using advanced sequencing technologies to identify other types of drivers of melanoma. Cebon, for instance, is examining slow-growing tumor cells that are resistant to conventional treatment. These cells may help seed growth of tumors.

Through this community approach, pieces of the melanoma puzzle are being assembled to reveal previously hidden molecular secrets of the disease. The Ludwig Institute is well positioned to apply newly gained knowledge toward improved patient care, such as through clinical studies led by Cebon and Jedd Wolchok in New York (see page 18). The opportunity to perform outstanding discovery science and improve patient care throughout the world is the bond that connects researchers who are part of this initiative.

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