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p53 AND PERSONALIZED MEDICINE

As a postdoctoral researcher at the Massachusetts Institute of Technology (MIT) 30 years ago, Prof. Varda Rotter was among the first scientists to study a little-known gene called p53. "We didn't know then that it was going to turn out to be so important for cancer research," she says.

It was during those early days of her research in the laboratory of microbiologist and Nobel laureate David Baltimore that she realized, she says, "that science is one of the most exciting things one can do—you can really pursue your dreams."

Prof. Varda Rotter

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Since then, Prof. Rotter, who is head of the Weizmann Institute's Department of Molecular Cell Biology, has devoted her career to this gene, now known as the "guardian of the genome" because it protects us from developing cancer. She was one of the first to develop antibodies against p53, along with other genetic tools, laying the foundations for the study of its function.

In its normal form, p53 plays a pivotal role in protecting cells from becoming cancerous. "The p53 is a very smart gene," says Prof. Rotter. It can sense when cells have damaged DNA (from exposure to ultraviolet radiation or chemicals, for example) and signal them to either repair that damage or undergo a process of self-destruction. When p53 is mutated, however, it loses this function; as a result, cells carrying damaged DNA can go on dividing and eventually transform into tumor cells. Mutant forms of p53 are found in more than 60 percent of human tumors.

Although p53 is possibly the most studied gene ever—thousands of papers on it have been published—Prof. Rotter finds that some basic questions have still only been partially answered: What is the function of p53 in the normal cell? How does mutant p53 contribute to cancer development? She believes that if we can understand exactly how p53 works, we can find ways to use it to stop the proliferation of cancer cells. Ultimately, her goal is to come up with new kinds of therapies that she describes as "made just for you and your cancer."

She has already made progress toward this goal through her research on the possibility of tailor-made chemotherapy. Prof. Rotter and her team conducted an experiment in which they treated cancer cells with chemotherapy. Some of the cancers died, but others were very resistant to the chemo. The researchers evaluated the status of p53 in the cancers, and found that different types of mutant p53 exhibited different levels of resistance to the therapy.

Prof. Rotter thinks it may be possible, in the future, to increase the effectiveness of cancer therapy by evaluating the specific type of mutant p53 the patient is expressing and choosing a chemotherapy drug that

is suited to it. Her team is now creating a library of chemotherapy drugs targeted to various mutant forms of p53.

p53, "a very smart gene," can sense when cells have damaged DNA and signal them to either repair that damage or destroy themselves.

Since 2000, Prof. Rotter has also directed the Weizmann Institute's Women's Health Research Center, which promotes basic research on gender-related physiology and diseases and has supported studies of cancer, fertility, and osteoporosis. For example, several of the research groups have examined the buildup and breakdown of bone mass and described a number of enzymes that affect the balance of bone accumulation or loss. Understanding how bone degradation is regulated may help in developing better treatments for osteoporosis.

Prof. Rotter is optimistic that basic research will continue to lead to better cancer treatments. For her part, she will continue to search for new kinds of therapies that could compensate for the malfunction of tumor suppressor genes.

Her ongoing goals include designing genetic methods for coping with cancer and making our genes stronger—possibly through inserting better genes, strengthening existing genes, or fighting the bad genes. "When we find a way to design this kind of tailor-made therapy," she says, "I think we will solve the problem of cancer."

Prof. Varda Rotter's research is supported by the Lombroso Prize for Cancer Research; the Ridgefield Foundation; and Mr. and Mrs. Donald Schwarz, Sherman Oaks, CA. Prof. Rotter is the incumbent of the Norman and Helen Asher Chair of Cancer Research.

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