

Dr. Nir Hacohen

Genes on the Hunt

Nir Hacohen, PhD, investigates the role of genes in the immune system

SCONDS AFTER a virus enters the human body, the immune system mounts an offensive. Built-in sensory cells that detect the foreign organisms, like the flu virus or the bacterium that causes tuberculosis, go on a killer attack to fend off the invaders. But precisely how does the innate immune system distinguish potentially pathogenic materials – whether they are viruses, bacteria, fungi or tumors – from the healthy cells of the body before it kills them?

If that information were known, it would have vast implications for health. First, scientists could design more effective vaccines and more types of vaccines. Long ago, scientists discovered that injecting vaccines – tiny amounts of dead viral material – help our immune systems destroy some of the toughest pathogens, like polio or mumps. “Early immunologists, like (Louis) Pasteur, injected inactivated pathogens into people, called them vaccines, and saw that they worked brilliantly, so we continue doing it today,” says Nir Hacohen, PhD. The Massachusetts General Hospital researcher is investigating the inner workings of the innate immune system in a quest to learn how it senses pathogens or molecules derived from them.

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Vaccines have been the single-most effective preventive health measure science has come up with that have led directly to a longer human life span. But there is so much more work to be done on optimizing vaccines, which requires a far better understanding of immunity.”

One of the most basic implications of that knowledge, for example, might be a more effective flu vaccine that prevents all forms of the virus rather than leaving you sick in bed in February, wondering what that flu vaccine actually did for you. In addition, it would inform us about, and ultimately advance treatment for, inflammatory or autoimmune disorders like lupus or arthritis in which a patient’s immune system attacks the body’s own healthy cells.

In his research, Dr. Hacohen, assistant professor of Immunology and Inflammatory Diseases at Harvard Medical School and a senior associate member at the Broad Institute of the Massachusetts Institute of Technology, is focusing on components of pathogens – primarily DNA and RNA, which reside in pathogens and are sensed by our immune system to alert the body that a pathogen has invaded.

He’s just at the cusp of this investigation, which the National Institutes of Health (NIH) saw as so promising that it tapped him in the fall for one of its 12 New Innovator Awards. The award includes a grant of \$1.5 million over five years.

New tool of the trade

The NIH also was impressed by the tool he created to conduct this investigation. Recently, he and a team of scientists at Harvard, the Broad Institute and biotechnology industry researchers completed the compilation of an extensive “library” of 180,000 RNA molecules that can switch off genes individually. This allows Dr. Hacoheh or another user to dissect this sensing process in order to test the role of genes in fending off infectious foreign material, ultimately leading to a better understanding of the genetic underpinnings of normal biology and disease.

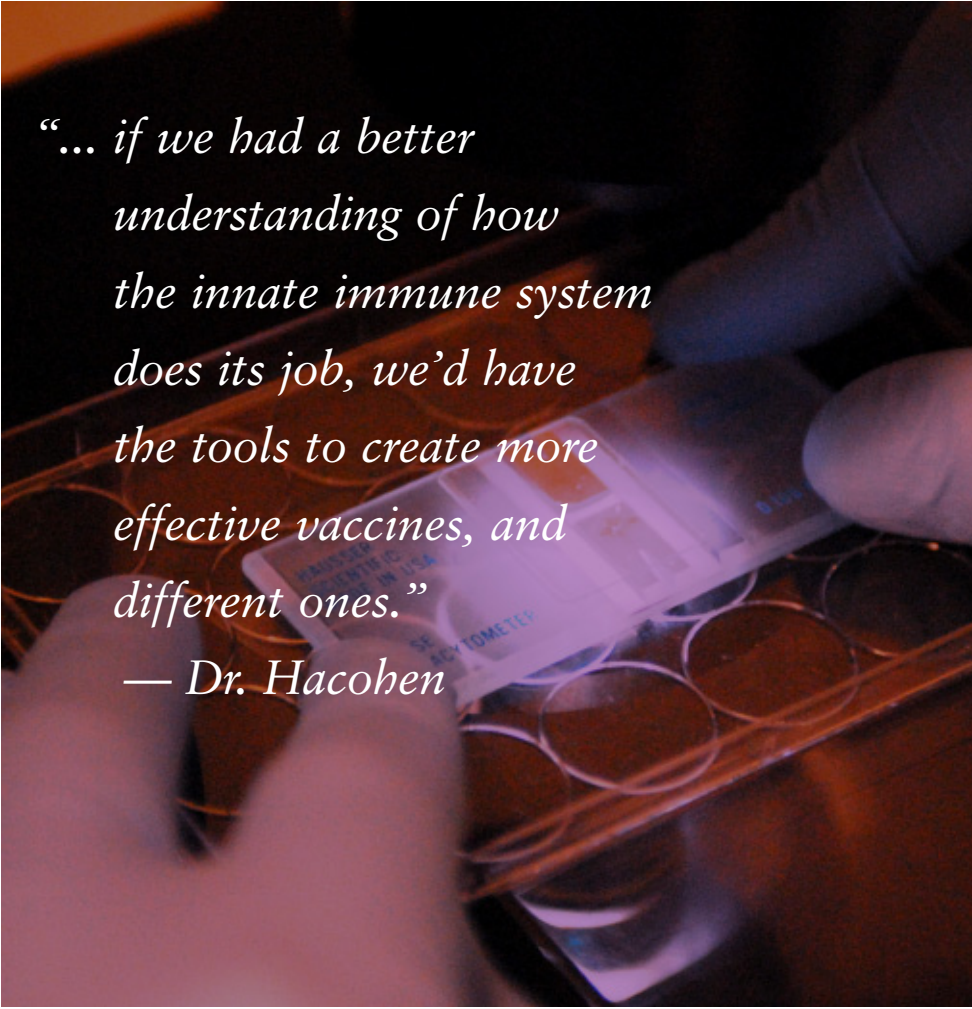
These molecules – called RNA-interference (or RNAi)-based gene inhibitors – are stored at MGH and several other sites in massive freezers cooled to 80 degrees below zero. They can be used in virtually all types of human and mouse cells for a vast array of research needs. The RNAi Consortium, as this group of scientists is known, has made the one-of-a-kind, \$18 million library available worldwide, which is enabling thousands of researchers to work towards discoveries of how genes play a role in disease.

Now Dr. Hacoheh is focused on applying the library to the study of immunology and infection. “Ultimately, what I hope to accomplish is to create a comprehensive genetic map of the innate pathogen sensory system,” he says. Another one of his long-term goals is to help refine and improve cancer vaccines that are in the works today. To date, there is only one highly effective FDA-approved cancer vaccine that prevents infection by human papillomavirus, which can lead to cervical cancer.

Dr. Hacoheh’s attention is focused on the innate immune system as opposed to the adaptive immune system, which has garnered far greater scientific attention over time. The adaptive immune system is the body’s method for preparing for long-term attacks by specific pathogens each time they are encountered, whereas the innate immune system rapidly defends the body from almost any acute infection. All mammals have both; flies, for example, only have an innate immune system. Yet the

innate system does have a unique sensing mechanism: dendritic cells, which identify pathogens and generate responses – the process that fascinates Dr. Hacoheh.

The Lupus Research Institute recently awarded Dr. Hacoheh \$100,000 in the hopes his work will lead to discoveries about why the body’s cells mistakenly attack its own healthy cells in autoimmune disorders like lupus. “We not only want to see how the immune system gets it right – when it detects and kills a pathogen – but we also want to learn how and why it gets it wrong in some people, leading to autoimmunity or inflammation,” says Dr. Hacoheh.



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This knowledge also promises to spur the creation of new and improved drugs. “Once we understand the basis for this sensing process in great molecular detail, we can use the results to guide the development of novel therapeutics to tweak the immune system in a tailored way for each infectious or autoimmune disease,” he says. “We would like to link very basic biology studies to the invention of clinically relevant therapies.” ♦ (T.M.)