Medical Xpress

Toward medicines that recruit the body's natural disease-fighting proteins

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Like recruiters pitching military service to a throng of people, scientists are developing drugs to recruit disease-fighting proteins present naturally in everyone's blood in medicine's war on infections, cancer and a range of other diseases. They reported on the latest advances in this new approach here today at the 244th National Meeting & Exposition of the American Chemical Society.

David Spiegel, M.D., Ph.D., who heads one of the major research teams developing "antibody-recruiting molecules" (or ARMs), said that the approach is a response to the old and seemingly impossible dream of identifying "magic bullets" for wide-ranging diseases. Antibodies are components of the immune defense system that latch onto microbes and other foreign material in the body and mark them for destruction.

"Antibodies have been wonderful drugs for autoimmune diseases and cancer," Spiegel explained. "But, like other protein-based drugs, they cannot be given in a pill, and must be injected. They can also cause life-threatening allergic or immune reactions. We are developing a work-around — antibody-recruiting medicines that can be taken orally and induce a patient's own antibodies to fight disease. They would be less expensive and easier to make. We hope it's the starting point toward entirely new approaches for treating a wide range of diseases."

Everyone has numerous antibodies circulating in the blood, each programmed by the immune system to latch onto and mark for destruction specific bacteria, viruses, allergens (like plant pollen) and

other material — termed antigens — that the body recognizes as foreign. The body makes these antibodies as people are exposed to microbes and allergens in the environment.

However, researchers don't know why people have antibodies against some structures, like the 2,4-dinitrophenyl (DNP) epitope, which is similar to ingredients found in certain pesticides and agricultural chemicals. It could be due to environmental exposures, but researchers also think the body could have made these antibodies when exposed to some other substance that resembles DNP.

Antibodies against DNP are what Spiegel's team at Yale University is using in one strategy to make the immune system target various cancers and HIV, the virus that causes AIDS.

Most of the medications in use today, from aspirin to cancer chemotherapy drugs, fall into that small-molecule category, just like ARMs.

"These ARMs don't kill HIV directly," Spiegel explained. "Instead, they just trick the body into targeting HIV for destruction by its normal immune mechanisms."

ARMs for cancer work well in laboratory mice, which are stand-ins for humans in these types of experiments, and such tests for anti-HIV ARMs are currently ongoing. Spiegel said that ARMs could also be designed to treat other conditions, such as autoimmune diseases like rheumatoid arthritis.

The team is using another approach against Staph infections. It involves tricking bacteria into the equivalent of painting a "bull's eye" on themselves, in effect inviting attack by the immune system. It represents the first time that scientists have been able to actually put small

molecules into the surface of *Staphylococcus aureus*, which is becoming more and more resistant to traditional antibiotics. Spiegel said that this method also might work on other types of bacteria, such as *Streptococcus* microbes that cause pneumonia and strep throat.

More information:

Abstract

Synthetic Immunology, the development of synthetic systems capable of modulating and/or manipulating immunological functions, represents an emerging field of research with manifold possibilities. Our laboratory's work in this area has included efforts to create low molecular-weight synthetic species, called antibody-recruiting molecules (ARMs), which are capable of enhancing antibody binding to disease-relevant cells or viruses, thus leading to immune-mediated clearance of these targets. This presentation will describe the development of ARM technologies with a particular emphasis on applications related to infectious agents, including HIV and Staph. aureus. In addition to exploring the potential therapeutic utility of ARMs and related structures, these research efforts have led to a number of unexpected scientific discoveries. Hopefully this presentation will provide insight into the many exciting research possibilities at the interface of organic chemistry, immunobiology, and infectious disease.

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