A Revival For Immunity; Biotech Looks Anew at Old Ideas On Using the Body's Own Defenses

By ANDREW POLLACK

In the late 1800's a New York surgeon named William B. Coley noticed that when one of his cancer patients developed a severe bacterial infection, the cancer disappeared. Over the following decades, Dr. Coley began injecting tumors with bacteria, with some success.

But the results were inconsistent, and critics derided the work as quackery. "Coley's toxins," as they were called, faded into disuse with the advent of radiation treatments and chemotherapy.

Now, though, recent discoveries about the immune system have spurred interest in modern descendants of Coley's toxins. Big drug makers are putting money into the effort, including Pfizer and Sanofi-Aventis, which have both placed bets on a biotechnology upstart named in honor of the surgeon, the Coley Pharmaceutical Group.

In August investors snapped up six million shares of Coley Pharmaceutical at $16 each in an initial public offering. The shares sold at the high end of the expected price range, a rarity lately for a biotechnology company. Coley closed at $18.52 a share yesterday, up 15.8 percent since the offering.

The excitement centers on a class of human proteins called toll-like receptors, whose existence and crucial role in the immune system were discovered only in the last several years. The proteins act as molecular sentinels, recognizing the presence of bacteria or viruses and rousing the rest of the immune system to respond.

Coley Pharmaceutical and many other companies are now creating drugs meant to activate those sentinels, essentially fooling the body into thinking it has been infected without exposing it to real pathogens. The aim is to stimulate the immune system to fight cancer, hepatitis and other diseases.

Almost every big drug maker "is now very seriously thinking about acquiring or initiating internally a toll-like receptor effort," said Kleanthis Xanthopoulos, the chief executive of Anadys Pharmaceuticals, a publicly traded San Diego biotechnology company that develops drugs that act on the receptors.

Anadys signed a deal in June with the big pharmaceutical company Novartis to develop drugs aimed at hepatitis B and C. Anadys was to receive a $20 million upfront payment and later payments that could reach as high as $550 million if the drug comes to market and achieves certain sales goals. Only a day earlier Novartis agreed to pay Hybridon, now called Idera Pharmaceuticals, up to $136 million to collaborate in developing drugs for allergy and asthma.

And in March Pfizer agreed to pay Coley $50 million at the outset and up to $455 million later for the rights to a drug that showed some striking results in treating lung cancer and is now about to enter the final phase of clinical trials.

One drug that works through a toll-like receptor is already on the market, although it was developed before scientists recognized the role the receptor actually played. That drug, Aldara, by 3M, is used as a treatment for genital herpes, as well as for a form of skin cancer and another precancerous condition. Sales in this country last year were $211 million, according to IMS Health, a drug data and consulting firm.

In some cases drug makers, rather than activating the toll-like receptors, hope to block the receptors as a way of damping the immune system. Eisai, a Japanese company, recently reported results from a clinical trial in which a receptor blocker had modestly reduced the death rate from sepsis, an often fatal overreaction of the immune system.

Blocking toll-like receptors might also be a way to treat lupus and other autoimmune diseases, in which the body attacks its own tissues, said Douglas Golenbock, the chief of infectious diseases and immunology at the University of Massachusetts and a consultant to Idera and Eisai.

Many previous attempts to stimulate the immune system -- by using so-called cancer vaccines, for example -- have not worked. Others, like the immune-bolstering drugs interferon and interleukin-2, can cause debilitating side effects.

"The history of immune modulators is ugly," said Arthur M. Krieg, the founder and chief scientist of Coley, which is based in Wellesley, Mass. But he said that the new drugs appeared to stimulate the immune system in a more directed way.
Toll-like receptors are part of the innate immune system, which is the body's first line of defense against pathogens. The innate system's job is to keep pathogens in check for a few days until the second-line defense, the adaptive immune system, can kick in.

The adaptive immune system marshals antibodies and T cells that are highly specific for a particular pathogen. Once created, the antibodies and T cells can make quick work of the same pathogen if it appears even years later -- the reason that vaccines work and that people do not get chickenpox or measles more than once.

For many years most immunologists had paid scant attention to the innate immune system, considering it far more primitive than the adaptive system. But now scientists realize that the toll-like receptors in the innate system are necessary for activating the adaptive system.

"The adaptive immune system would not even know what hit it, without the innate immune system," said Ruslan Medzhitov, a professor of immunobiology at Yale. He is also co-founder of VaxInnate, a start-up using research in toll-like receptors in pursuit of better vaccines, including a flu shot that would work against all strains.

The name of the receptors comes from the German word "toll," which might be translated as "amazing" or "far out." In the mid-1980's a German scientist, Christiane Nusslein-Volhard, was mutating fruit fly genes to study the effect on embryo development, work that won her a Nobel Prize in 1995. She found one mutant embryo that struck her as so weird she gave the name "toll" to the gene that caused it.

Through the late 1990's other scientists discovered that the same toll gene also had a role in immune defense and that humans and other mammals had a whole family of similar, or toll-like, genes.

Humans have 10 known active toll-like receptors. Mainly found in certain immune system cells, the receptors sit on the surface of cells or, in some cases, inside them, and recognize particular telltale characteristics or components of pathogens.

Toll-like receptor 5, for instance, recognizes a protein in the tails that some bacteria use to swim.

The biggest focus for drug developers so far has been receptor 9, which recognizes DNA that contains a particular genetic-code sequence that is common in viruses and bacteria but not in humans. Coley's lead drug, Promune, is a short segment of DNA that contains the pathogen code pattern but has been chemically stabilized to survive longer in the body.

In a Phase 2, or midstage, clinical trial involving 112 patients with lung cancer, those who got Promune along with chemotherapy lived for a median period of 12.8 months, compared with 6.8 months for those receiving chemotherapy alone.

It was among the biggest improvements shown by any drug in that context. By the end of the year, Pfizer plans to begin testing Promune for lung cancer in Phase 3 trials, the final phase of patient testing before a drug is submitted for federal approval.

In a separate trial against the deadly skin cancer melanoma, however, Promune was not shown to be effective. And the drug does have side effects, although Coley officials and some outside experts say they have been manageable.

Coley is also working on drugs for hepatitis C and, with Sanofi-Aventis, for asthma. And it is providing its technology to vaccine companies to use as adjuvants, which are substances injected along with vaccines to strengthen the immune response.

Idera, based in Cambridge, Mass., and Dynavax Technologies, based in Berkeley, Calif., are also working on drugs to activate toll-like receptor 9. Idera's lead drug is in Phase 2 trials for kidney cancer.

Dynavax is in Phase 3 clinical trials of a treatment for ragweed allergies. It is also in the final stage of testing a hepatitis B vaccine that it says would require only two injections, instead of the three needed for the current vaccine, and would work better in older people, who have weaker immune systems.

Meanwhile, other companies, including SciClone Pharmaceuticals and GlobeImmune, are working on drugs that act at least partly through toll-like receptors.

Many uncertainties remain, though. Patent battles are under way, particularly between Coley and Dynavax, regarding drugs that work on toll-like receptor 9.

There are also concerns because stimulating different toll-like receptors, or even the same receptor with different compounds, activates the immune system in different ways. Activating just one receptor might not produce a complete immune response.

On the other hand, some animal studies suggest a risk that stimulating toll-like receptors could send the immune system into overdrive, leading to toxic shock or autoimmune diseases. Mice have been killed by immune-stimulating DNA sequences.

A concern of Wen-Ming Chu, an assistant professor at Brown University, is that the DNA-based immune-stimulating drugs can activate a gene that might help cancers resist chemotherapy.

And yet the discovery of the receptors, and the work involving them, has cheered those who still believe in William B. Coley's toxins. "This is another piece in the puzzle of the Coley discovery," said Lloyd Old, director of the Ludwig Institute for Cancer Research in New York and a pioneer in cancer immune-based therapies.
Dr. Krieg, a former professor who has done groundbreaking work in the field at the University of Iowa, started Coley in 1997. He initially named the company CpG ImmunoPharmaceuticals, with the CpG being shorthand for the DNA pattern at the heart of his work.

The company changed its name to the Coley Pharmaceutical Group in 2000, but only after receiving the blessing of Helen Coley Nauts, Dr. Coley's daughter. Ms. Nauts, who died in 2001, had preserved her father's legacy and founded the nonprofit Cancer Research Institute in New York to further the study of immune-based cancer therapy.

Coley Pharmaceutical is a donor to the institute, which in turn honored Robert L. Bratzler, Coley's chief executive, at its most recent annual dinner.

"I was struck by the fact that he had identified that immunological activity was clinically very useful," Mr. Bratzler said of Dr. Coley. "We thought it fitting to name our company after the pioneer in the field."

Correction: October 8, 2005, Saturday An article in Business Day on Wednesday about drugs that stimulate the immune system misstated the use of Aldara. It is approved to treat genital warts, not genital herpes.