

Molecular Medicine: The Future is Now

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to cancer. Molecular medicine targets some of the key genetic mutations that give rise to cancer. Using molecular technology, such as mouse knockouts, “we’re able to dissect those events and to think about ways in which we can interrupt the pathology by specific drug therapies,” Dr. Caskey explains.

Molecular Therapies for Cancer

One successful molecular therapy is the drug Herceptin from Genentech. It treats breast cancer patients with abnormally high amounts of HER2 protein (human epidermal growth factor receptor 2) in tumors. HER2 is responsible for cell growth and proliferation, an overabundance of which makes tumors grow faster.

“Herceptin will only work when the genetic diagnostic [HER2 overexpression] matches the drug,” Dr. Caskey explains. “We’re in the era of beginning to match specific diagnoses with specific therapeutics.”

Another clinically successful molecular therapy is Gleevec (Novartis Pharmaceutical Corp.), used to treat chronic myelogenous leukemia. This drug targets a genetic mutation that causes abnormally high levels of enzymatic activity of a protein called Bcr/Abl. “There is constant activity of this cancer gene in the leukemic cells. That’s what causes the cell to proliferate and for you to have leukemia.”

Gleevec efficiently inhibits this overactive enzyme. Dr. Caskey says that this drug might never have been successful using traditional drug screening methods. Since not all patients have this genetic mutation, he explains, not all patients respond to the therapy. “Had you taken that inhibitor and gone against all leukemias, you would not have found a use for it,” he says. However, by matching the molecular diagnosis, Gleevec worked for 100 percent of the patients.

Treating the Genetics of Cardiovascular Disease

“There have been several major discoveries that got us into the inroads of genes that cause atherosclerosis, such as type II hyperlipidemia,” Dr. Caskey says.

Atherosclerosis is the build-up of cholesterol in artery walls, reducing blood flow to tissues such as the heart. Type II hyperlipidemia, the presence of high levels of LDL (“bad” cholesterol), is the most common form of atherosclerosis for people within range of normal body weight. “That was the first insight into an abnormal gene that predisposed you to atherosclerosis, a major breakthrough that led to the development of new therapeutics, such as statins,” he says.

Statins treat people with or at risk of cardiovascular disease. This drug class inhibits a key enzyme responsible for making cholesterol in the body, indirectly causing reduction of LDL in the bloodstream. “If you know a patient has that defect, then a statin will delay the onset of that disease,” Dr. Caskey explains.

Translation from the Lab to the Clinic

The genetic basis of disease is now being examined through genetic analysis of patients diagnosed with the disease. “There are many causes of coronary artery disease, diabetes mellitus, type II diabetes and obesity, which have been identified by scanning patient DNA for genetic variation,” Dr. Caskey says. Current research focuses on identifying common genetic defects present in these patients, in hopes of identifying new targets for therapeutics.

The transition from scientific discovery to clinical use takes a notoriously long time. “The average is 12-15 years from the start of a development program for a new drug, to the time you finish and get an

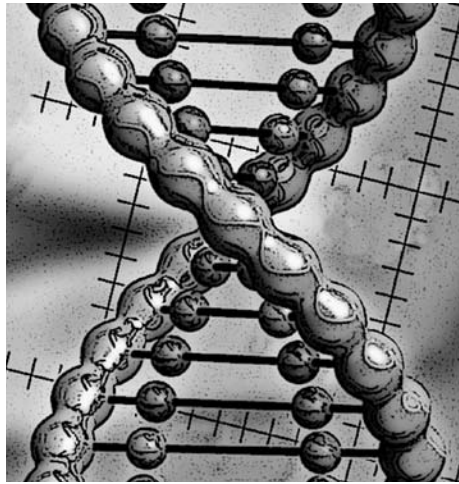


Illustration by Roy Prichard, Medical School

FDA-approved process,” Dr. Caskey says.

The discovery phase of traditional drug development is a lengthy process. Most drugs are found by a high-throughput screening technique, in which thousands of related chemicals are screened for desirable biochemical and biological properties. With molecular medicine, the therapy caters to the genetic problems underlying the disease.

But, the last thing they want to do in this institute is try to bring things out too early, Dr. Caskey explains. “My experience at Cogene (the biotechnology venture capital company he founded) was don’t bring it out too early, make sure the science is solid and you’re patent-protected. We’re trying to make the IMM a discovery and translational institute that can rapidly go from the human gene discovery to a therapeutic.”

There are two main methods by which the IMM will accomplish this task:

“One strategy is to go after small molecular weight compounds, like drugs. That’s fairly long and involved and requires a lot of technology and a lot of manpower to do that,” Dr. Caskey says.

“The second strategy is to go biologic, to either make a monoclonal antibody or to make a protein,” he explains.

“Let’s say the cause of the disease is a protein deficiency. Then supplying the protein back is the right therapeutic,” says Dr. Caskey. However, if an overactive gene causes disease, then reducing protein activity levels is the way to go to treat the disease.

Research at the IMM will follow a clear time line for discovery and development of therapeutics with the potential to be used in the clinic. “The strategy we’re taking right now is to take the human gene discoveries, translate those into mouse models, and develop therapeutics — either a protein or a monoclonal antibody, which we do in-house, or develop a new chemical,” Dr. Caskey says.

He feels the two avenues of therapeutic development will be more time-efficient than the long, expensive path to traditional drug development. In addition, this new breed of therapeutics may circumvent standard problems of drug toxicity. “These therapeutics are fast and very specific. They’re not prone to off-target toxic effects,” Dr. Caskey explains.

Along with IMM co-director Ferid Murad, M.D., Ph.D., and deputy director Irma Gigli, M.D., Dr. Caskey has helped set the main focus areas for IMM research.

He says he’s extremely excited by the research taking place in the immunology group in the area of asthma and inflammatory disease. “The discoveries that have come out of that program are leading us in the directions of new therapeutics,” Dr. Caskey says. “The cardiovascular and immunology research programs are right at the surface of breaking through into the clinical.”

Research at the IMM also focuses on neurological disorders — Alzheimer’s and affective disorders: schizophrenia, manic-

depression, depression and autism.

“There are a number of testing systems available in the mouse based on learning or on the way they respond to their environment, that are said to be associated with behavioral and affective disorders in humans,” Dr. Caskey says.

New Developments in Molecular Therapeutics

One of the first new molecular therapies he predicts will hit the clinic is an HIV vaccine. Dr. Caskey also sees advances to come by combining devices with therapeutics. “In terms of a novel idea, until recently, no one ever thought about putting a gadget with a drug. It’s also being worked on for hip or shoulder replacement, where the drug is part of the replacement that stimulates bone,” he explains.

Aptamers, a new breed of therapeutics, have recently come onto the scene, and he is excited about their potential. “Aptamers are a totally new structure of drugs. They are short nucleic acid sequences that have the ability to bind to

a protein and inhibit or stimulate the protein. That’s a revolutionary idea,” Dr. Caskey says.

Macugen, from OSI Eyetech Pharmaceuticals Inc. and Pfizer, is the first aptamer to be approved for wet age-related macular degeneration. This disease develops with age and is characterized by increasing distortion in the center of vision, such as blurs or wavy lines.

He also sees advances in nanotechnology in the near future. “Nanotechnology will probably provide new strategies for imaging. We’re going to be able to image diseased tissues much more precisely than we can today,” Dr. Caskey says, “which may change drug delivery.” The drug may be delivered specifically to diseased tissue as opposed to how it is currently delivered, by exposing the whole body to a drug.

“Molecular medicine is exciting — the rate of discovery is fast, it’s high and our ability to take that information into the clinic is very swift,” Dr. Caskey says, “Molecular medicine is a reality.” ★

UT Scientists Develop Promising Human Stem Cell Differentiation Process

By Rob Cahill, *Institutional Advancement*

Molecular scientists at The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) have developed a new procedure for the differentiation of human embryonic stem cells, with which they have created the first transplantable source of lung epithelial cells.

The process, created in the laboratory of Rick A. Wetsel, Ph.D., a professor of molecular medicine at the IMM, is described in a recent edition of the *Proceedings of the National Academy of Sciences*. Research scientist Dachun Wang, M.D., is lead author of the article, “A pure population of lung alveolar epithelial type II cells derived from human embryonic stem cells.”

“We have developed a reliable molecular procedure which facilitates, via genetic selection, the differentiation of human embryonic stem cells into an essentially pure population of lung epithelial cells,” said Wetsel, noting the procedure also can be used to create other types of highly specialized cells.

Scientists at the IMM used the in vitro method to create lung epithelial cells known as alveolar epithelial type II. The cells were derived from a human embryonic stem cell line approved by the National Institutes of Health (NIH).

James T. Willerson, M.D., president of the UT Health Science Center at Houston, said, “I believe this is an important development

by the Wetsel laboratory at the IMM. I look forward to seeing its translational impact.”

Alveolar epithelial type II cells are called “the stem cells of the lungs” because of their versatility and many important functions. They produce proteins including surfactant that inflates lungs. They also make other cells lining the inner lung. “They regulate lung fluids and oxygen levels and can potentially be used for regenerative lung repair,” Wetsel said.

Hereditary lung disorders most likely to benefit from transplantation of alveolar epithelial type II cells include respiratory distress syndrome of the newborn, alpha-1 related emphysema and cystic fibrosis, Wetsel believes. “All three of these diseases are caused by single gene defects and therefore have been logical candidates for gene therapy,” Wetsel said.

Transplantable alveolar epithelial type II cells may also one day be helpful in the treatment of other lung diseases including asthma and chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the United States, Wetsel said. COPD claimed the lives of 122,283 Americans in 2003.

Still years away from their use in regenerative medicine, Wetsel said the next step involves research trials with mice.

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