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# Renaissance

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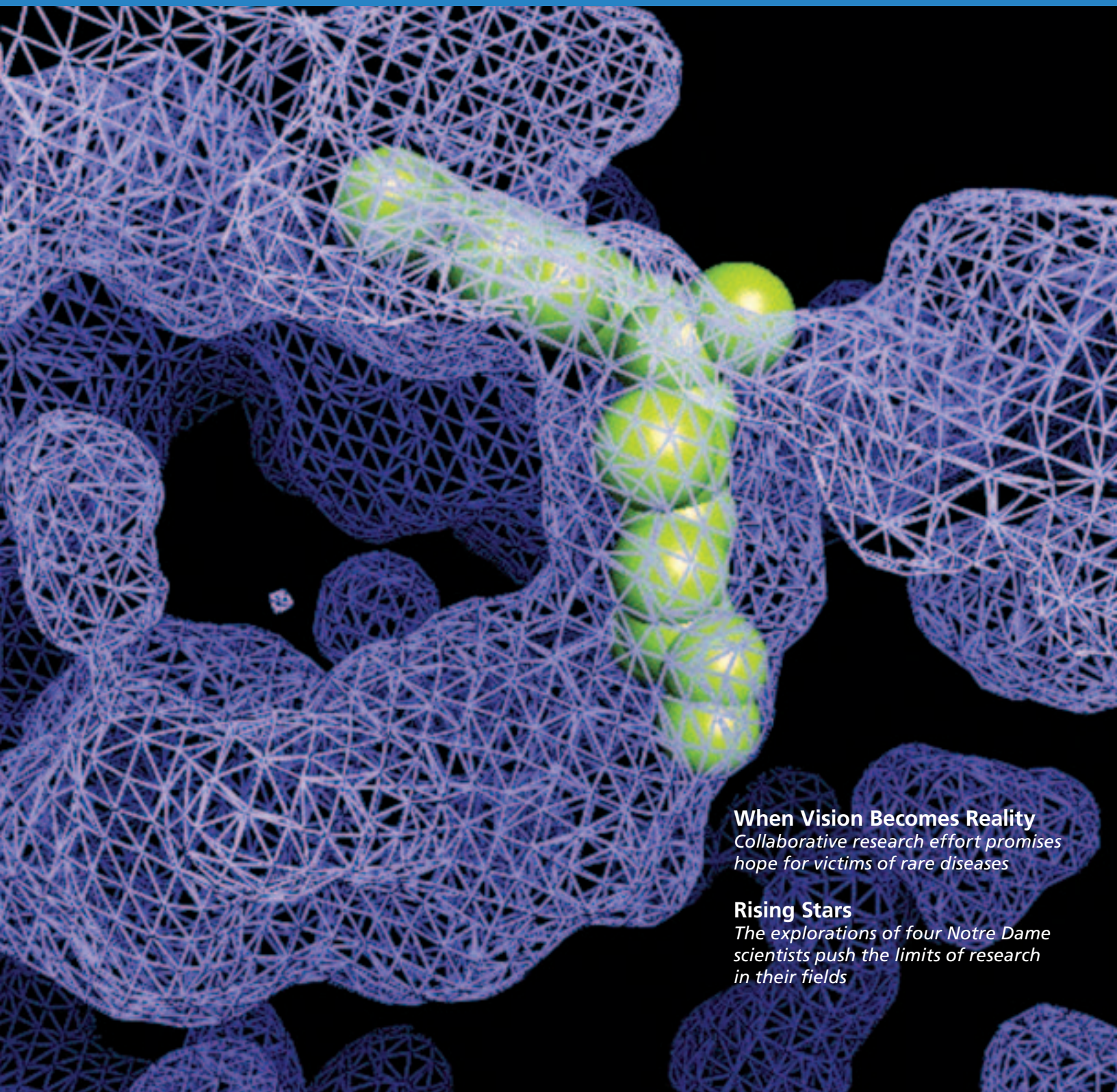

**When Vision Becomes Reality**
*Collaborative research effort promises hope for victims of rare diseases*

**Rising Stars**
*The explorations of four Notre Dame scientists push the limits of research in their fields*

# WHEN VISION BECOMES REALITY

**How a chance meeting between a College of Science alumnus and a Notre Dame professor led to collaborative and groundbreaking research into cures for diseases that have not received the attention of the big pharmaceutical companies.**

IT ALL CAME TOGETHER IN MAINZ, GERMANY FOR JOHANNES GUTENBERG right around 1450. The printer had invented a new kind of machine with moveable type that allowed him to print multiple copies of manuscripts in assembly-line fashion, something that had never been done before. Among the first texts to come off the world's very first copier was a large Latin Bible that would be known as the Gutenberg Bible. In time, the ideas of the Renaissance spread throughout Europe, thanks in large part to the mass-produced books that rolled off Gutenberg's machine.

L to R: Dr. Olaf Wiest (assoc. prof.), Dr. Steven Corden (postdoctoral associate), Dr. Difei Wang (postdoctoral associate), Dr. Norbert Wiech, Dr. Paul Helquist (professor), Dr. Martin Tenniswood (professor), and Mr. Jose Chaverri (technician).

IT WAS ALSO IN MAINZ, 550 YEARS LATER, that more recent events ocurred that may have long-reaching repercussions as well. In November 2001, Notre Dame chemistry professors Paul Helquist and Olaf Wiest traveled to Mainz to attend a meeting called by biochemist Norbert L. Wiech, a 1960 Notre Dame graduate and a developer of drugs to treat rare diseases. Wiech had arranged for a far-flung group of 10 researchers from the United States, Germany, Italy, and The Netherlands to assemble at the Hyatt Regency Hotel in Mainz to report the results of tests in their laboratories with novel molecules which inhibit an enzyme, histone deactylase (HDAC). These compounds were developed in a start-up pharmaceutical operation that Wiech was directing outside of Baltimore, Md.

One compound in particular, CG1521, was highlighted by several of the researchers in their presentations because of its effect on HDAC in the cell. In the mid-1990s, researchers in molecular medicine began in earnest to examine the role that HDAC plays inside a cell. They were especially curious about the way HDAC seemed to regulate

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how DNA expressed its genetic codes for the production of proteins. Histones are unique proteins that act like the spool of a fishing reel. The long double-helixed line of DNA is wrapped around these histones. But if something goes wrong and HDAC causes the DNA strands to coil too tightly around the histones, then the cell's genetic code cannot be read and proteins do not get produced.

The human body can cope with a few cells failing to produce healthy proteins. But when millions of cells cease transcriptional activity, the result is a wide range of diseases, including cancer. Researchers from around the world were focusing their attention on a new class of synthetic molecules, called HDAC inhibitors, which appeared to correct errant gene expression that was occurring in laboratory models of diseases such as cancer. With his newly developed molecule, Wiech was on the forefront of an exciting new field of science.

THE HISTORY BETWEEN WIECH, HELQUIST, AND WIEST DATES BACK TO 1999 when Wiech visited his alma mater with an offer to set up an endowment for undergraduate research in the Department of Chemistry and Biochemistry. Wiech initially met with Helquist. "My role at Notre Dame is to meet with potential benefactors who have a science interest," Helquist said. "That is how I met Norb."

Helquist recalled that after the usual pleasantries, the conversation turned to Wiech's business interests. Wiech explained his interest in finding cures for rare diseases and that his company was lacking scientists who had skills in computational and synthetic chemistry. Helquist immediately saw the possibilities that lay ahead. Helquist and Chemistry Department Chair Marvin Miller are experts in the synthesis of compounds similar in part to those being developed by Wiech and his associates. "Our interests meshed completely," he said.

Wiech returned to the Notre Dame campus with his wife Linda later that year to attend a meeting of the Notre Dame College of Science advisory council. Helquist met him for cocktails at the Morris Inn and they continued their discussions on HDAC inhibitors. "Paul and I were having a drink," Wiech recalled. "At one point while he was talking to Linda, he stopped, excused himself and grabbed a Notre Dame napkin. On the back of the napkin he drew a structure of a compound which they called ND-NAP. The structure Helquist drew that evening represented a new class of HDAC inhibitors that Helquist, Wiest, and Wiech have been studying ever since.

The collaboration was "on."

Wiech was interested in the use of HDAC inhibitors for the treatment of orphan diseases—that is, those diseases whose cures typically are not pursued by large pharmaceutical companies because there is no apparent financial gain in doing so. Wiech needed somebody skilled in creating computer-generated molecular models to aid in this research. Helquist knew such a man on the Notre Dame campus: Olaf Wiest.

Born in Neuwied, Germany, about 70 miles from Mainz, Wiest received his doctorate at the University of Bonn in 1993. After a stint at the University of California, Los Angeles, he came to Notre Dame in 1995 as a faculty member in organic chemistry. Some of his interests involved the computational methods needed to design new anticancer molecules for the Walther Cancer Center and for molecular electronics in the Center for Nanoscience and Technology.

Helquist wasted no time in introducing Wiech to Wiest. Shortly after this initial meeting, Wiech arranged for funds to purchase 30 computers for Wiest, who then connected them as part of a larger computer cluster to continue his computational work on his compounds in parallel. This provided the necessary computational power to proceed with the studies.

THEY MET AGAIN IN MARCH 2000 IN SAN FRANCISCO FOR THE AMERICAN CHEMICAL SOCIETY MEETING. It was at this meeting that Wiech had brought along a successful Chicago options trader, Pat Girondi, who was interested in funding promising research that would cure a rare blood disease called thalassemia that his son Rocco had developed. Wiest was becoming more than casually interested in HDAC inhibitors and he was touched by Girondi's tireless efforts to find a cure for thalassemia. "It was a time when we all really got serious," Wiest said.

But something was in store for Wiest in Mainz that November 2001 that proved important. Among the presenters was a young biologist from Amsterdam who described his findings on the effects of Wiech's HDAC inhibitor (CG1521) on adrenoleukodystrophy (ALD). Like thalassemia, ALD is a rare genetic disorder that holds no interest for the big pharmaceutical firms. Made famous in the movie "Lorenzo's Oil," ALD causes a breakdown of the myelin sheath surrounding nerve cells in the brain.

The young biologist showed how Wiech's molecule appeared to arrest the advance of ALD in his laboratory models. A hematologist from Milano, Italy also reported results that showed that these HDAC inhibitors controlled the maturation of bone marrow cells responsible for the production of hemoglobin and other elements of the blood. And a German clinician reported his observations with CG1521 and its inhibition of the growth of prostate cancer cells in the laboratory. The presentations caused something to click inside Wiest. People were dying of these so-called orphan diseases and Wiech's molecule might just offer an answer to their prayers, he thought. "As I listened to all of these presenters a picture started emerging," he recalled. "The evidence started piling up that we might really be on to something." From that point on, Wiest became a believer in Wiech's prize molecule.

BY ANY MEASURE, CG1521 SHOULDN'T WORK. Quite the opposite, it should wreak havoc within the cell's delicately balanced machinery. The cell's nucleus is where almost all DNA replication and RNA synthesis, or transcription, occur. Messenger RNA or mRNA carrying all the genetic instructions is transported out of the nucleus. Protein production machines called ribosomes carry out the instructions to arrange amino acids into an exact sequence that in turn churns out a whole array of proteins. These proteins are vital to keep us alive and healthy.

There are 11 known types of HDACs. All 11 regulate our approximately 30,000 genes in a carefully balanced minuet. Having something like CG1521 enter HDACs should be like throwing a handful of metal chaff into an electric substation. Sparks should fly, to say the least.

"Nobody really understands this at all," said Notre Dame biochemist Holly V. Goodson. "We don't know why HDAC inhibitors don't kill normal cells, and we don't understand why they seem to have the specific ability to target cancer cells and why they are so useful as therapies for diseases where the expression of a certain protein is turned up." Goodson suspects that the term histone deacetylase inhibitors may be a misnomer and that inhibiting the deacetylization of histones "may be a small fraction of their actual function. Or," she said, "Maybe it doesn't have anything to do with histones at all."

Further characterization of CG1521 continues in Martin Tenniswood's laboratory in Notre Dame Department of Biological Sciences. Tenniswood, a biology professor and Coleman Foundation Chair, has shown that in addition to stabilizing the acetylation of histone proteins which is necessary for the continued transcription in normal cells, CG1521 also stabilizes the acetylation of a number of other proteins in the nucleus that regulate transcription. These so-called transcription factors include

two proteins (p53 and p21) that are known to be very important in regulating cell cycle and cell survival.

p53 has been shown to be mutated or absent in nearly 50 percent of all cancers. Treatment of prostate cancer cells with CG1521 results in an increase in the level of acetylated p53, which causes the tumor cells to die.

p21 and p53 are not the only nuclear proteins that are regulated by acetylation. Tenniswood's group has demonstrated that another protein that is important in prostate cancer, the androgen receptor, is stabilized by acetylation and its level is increased after treatment with CG1521. The increased levels of the androgen receptor make the tumor cells more susceptible to standard anti-androgen therapies for prostate cancer that are currently used to treat patients with early stage prostate cancer.

The work of designing and synthesizing new HDAC inhibitors continues. In spring of 2004 the collaboration of Wiest, Helquist, and Di-Fei Wang at Notre Dame and Wiech and his colleague, Hsuan-Yin Lan-Hargest, reported in the *Journal of Medicinal Chemistry* that from computer-generated computational studies, they had discovered a hitherto unknown receptor site, or side pocket, in HDAC into which modified forms of CG1521 could dock. "By learning more about these binding sites, we can design new molecules that fit these sites and therefore will be more effective in fighting certain diseases," Helquist said. The report has caused considerable stir within the research community.

NOTRE DAME'S INVESTIGATION INTO HDAC inhibitors has drawn worldwide interest. In March 2005, Wiest will make an invited presentation to a symposium of the American Chemical Society in San Diego, California. The "big" pharmaceutical companies—all of which have a major stake in HDACs and their use in the treatment of cancer—will be there. Meanwhile, Wiech and Pat Girondi have formed a new company, Errant Gene Therapeutics, not only to develop a therapy for thalassemia, but to expand the use of HDAC inhibitors to treat other rare diseases. They are currently traveling to tell their compelling story to the world of financial investors.

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Back at Notre Dame, no less than five research laboratories have developed an interest in the role of acetylation in the cell and the transmission of gene information. It will be a long time before anyone figures out how HDACs regulate our genes and how sometimes they can cause our elaborate transcriptional system to go awry. But Wiech is optimistic that CG1521 and its future synthesized versions will lead to new therapies for the diseases—many of them considered "orphan diseases"—that are caused when this system goes haywire. Of his quest to see that future arrive, he said, "It's been one long collegial effort and for the great part it has been the spirit and intellectual curiosity of Notre Dame scientists that have led to today's excitement." For his part, Weich plans to help keep that collaboration alive so that one day his vision will become a reality that—like Gutenberg's press—will have far-reaching results. "You really do need to have other people believe in you and your concept," he said.

# A PASSIONATE PURSUIT

Pat Girondi surrounded by his three sons (left to right) Giancarlo, Francesco and Rocco.

***A father's search for a cure for a rare disease brings him to the cutting edge of science.***

Pat Girondi grew up in the Italian neighborhood of Bridgeport on the South Side of Chicago. Norbert Wiech grew up in the Windy city's Polish neighborhood. Both came from similar working class backgrounds. But the parallels fade quickly from there.

Girondi's teenaged lifestyle earned him one of those "street smart and street tough" reputations. But Girondi—survivor that he is—didn't spiral into an abyss. Rather, a string of fortunate events eventually lead him to the Chicago Board of Options Exchange.

In time, Girondi became a successful options trader despite his lack of a high school diploma. Oprah Winfrey was so impressed with Girondi's rise through the ranks that she invited him on her show.

There was little in Girondi's life that would have drawn him to Norbert Wiech. Wiech is a reserved, dignified scientist who is 25 years Girondi's senior. A 1960 graduate of Notre Dame, Wiech received his doctorate in biochemistry at Tulane University and began his professional life in the pharmaceutical industry in the late 1960s.

The series of events leading to their eventual collaboration started when Girondi—who by 1992 was living in Italy—took a call while he was in Switzerland. It was his wife, telling him that he had to go to a hospital in Germany to take a blood exam.

"What for?" Girondi asked, somewhat annoyed.

"There's something wrong with Rocco," she replied.

Rocco, their son, was only two. But he was lethargic and pale and he wasn't gaining weight. That's how Girondi learned about a rare blood disease called thalassemia. That was the moment his world crashed in around him.

Hemoglobin is the protein in the red blood cell that carries oxygen from the lungs to the other cells of the body. Hemoglobin, itself, is composed of two smaller proteins, alpha and beta. Both must be in balance to pick up and deliver oxygen. When there is a genetically induced imbalance that alters this finely tuned composition, the oxygen-carrying ability of the hemoglobin level drops. In a nutshell, that's thalassemia, an extremely rare genetic disease.

Rocco's thalassemia had progressed to the point where he required blood transfusions and daily iron chelation.

Now 14 and an eighth grader, Rocco lives in Italy with his family. "He's a skinny little kid, about 5 feet tall and a hundred pounds," Girondi says of his son. "He looks like me, kind of. He has blond hair. He likes broads. He's respectful. He's got a lot of friends." Rocco has Girondi survival genes. He knows that the life expectancy of a thalassemia patient is 27. So he's passed the midpoint of his life.

Pat Girondi has scoured the world for people working on a cure. He learned that pharmaceutical companies are not interested in finding a cure for thalassemia. Only 2,000 people in the United States have it, and there is no money to be made on such a small number of cases. So it's an orphan disease.

As a young scientist in 1967, Norb Wiech went to work for a pharmaceutical company. His first assignment was to evaluate a treatment for a rare disorder affecting just 20,000 people. The company saw little profit in treating such a small segment of the U.S. population and decided not to invest in any more research of this disorder. "I was told that they were not interested in this kind of work," he said.

After 20 years in the big pharmaceutical industry, Wiech left to start his own small pharmaceutical services company in Baltimore. This venture led to the founding of Ucyclyd Pharma, Inc. to develop a therapy for UCD, or Urea Cycle Disorder, which is characterized by the body's inability to get rid of excess nitrogen (in the form of toxic glutamine).

It was in December 1999 when Pat Girondi heard about Norbert Wiech. "He had this drug for urea cycle, which also had some effects in thalassemic patients. I started courting him right away," Girondi recalls.

In late 2001 Girondi learned that in addition to the traditional treatment, several academic laboratories were proceeding on a biotech track and developing a gene replacement technology. Gene therapy treatment of thalassemia is a relatively low-risk procedure. A functional copy of the normal hemoglobin gene is introduced into a virus. This modified virus now becomes a vector. Bone marrow cells from the thalassemic patient are collected in the hospital and taken to the laboratory where the viral vector is added. Soon thereafter, the bone marrow cells incorporate the new genetic information and the cells are returned to the patient. Once these treated bone marrow cells are returned, the patient's own cellular machinery goes about producing normal red blood cells. The procedure holds promise not only for thalassemia but also for sickle cell anemia.

Finding a kindred spirit in Norb Wiech, Girondi proposed a partnership to bring the cure to market. They formed a company called EGT (Errant Gene Therapeutics) in 2004 to develop and commercialize a treatment for thalassemia and other orphan diseases. Their business plan projects the need to raise $7.5 million to complete the clinical trials and make the gene therapy readily available. In the U.S., the Orphan Drug Act was originally enacted in 1983 by Congress in part to attract investors to fund such high-risk research. This act offers powerful incentives to the investors in the form of tax deductions and bottom-line tax credits, explained Darren Guccione, a Chicago CPA who is helping to draft the business plan for Wiech and Girondi.

"Thalassemia has changed my life," Girondi says. "It's been a maturing experience." He finds himself on the cutting edge of modern gene replacement therapy and on the verge of finding a cure for the disease. Girondi has scripted his own ending to his saga. "I just hope the Lord sees the same end I see," he said. "I just want to say some day that my son is cured of thalassemia."