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Ann E. Weber, Ph.D.

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INTRODUCTION

Each year, the Pharmaceutical Research and Manufacturers of America (PhRMA) honors research scientists whose work has been of special benefit to humankind. We congratulate this year’s winners of the Discoverers Award. For the first time in the award’s 24-year history, women alone were recognized.

They represent the many Merck employees whose vision and work made this discovery possible. The award also acknowledges others who throughout history have dedicated their lives and special talents to reducing human suffering through the search for new medicines.
Preparation For The Task

Even as a very young girl in South Bend, Ind., Nancy A. Thornberry was passionate about science. She loved anything having to do with animals and the outdoors, and her parents nurtured this interest by buying her chemistry sets and dissection kits as presents.

At Muhlenberg College in Pennsylvania, she earned degrees in chemistry and biology and quickly landed a job as a biochemist at Merck. She was poised to fulfill her dream of finding a new medicine that would improve human health.

Twenty years of effort, however, only proved how incredibly hard it is to find a new medicine. She got a little taste of success when she was assigned to work on a drug to treat high blood pressure that was in its final stages of development, but, as Thornberry puts it, for some years, "I did a lot of learning about what didn’t work."

She was doing well in her career, earning promotions while contributing to projects in a number of therapeutic areas. But most pharmaceutical researchers retire without the satisfaction of discovering an important new medicine. Thornberry sometimes worried that this usual outcome could be her fate, too.

In the spring of 1999, Thornberry was provided with an opportunity to lead a group of about 30 talented biochemists and molecular biologists, and she spent most of the summer looking for new, promising...
Ann E. Weber, meanwhile, was in a different section of Merck’s research facilities in Rahway, N.J., studying a promising new drug for obesity. Weber, growing up in Oshkosh, Wis. had planned to become a medical doctor. Then, in her junior year at the University of Notre Dame, she realized two things: she loved working in the chemistry lab, and by applying chemistry to address biological programs, she could potentially help many more people. After graduating summa cum laude she earned her Ph.D. in chemistry at Harvard in 1987 and then joined Merck as a senior research chemist.

Within three years, she was assigned to a team researching a medicine for obesity—a significant health hazard that has been spreading rapidly from the developed to the developing world. It appeared her idealistic goal of helping many might actually come true.

For 10 years, at nearly every step along the way, things were going well. She grew even more excited as her group entered preclinical programs for them to work on. She became aware of some very exciting, new research about the role of a hormone called GLP-1 (glucagon-like peptide-1) in signaling the pancreas to release insulin. She was particularly interested in related studies that showed that an enzyme called DPP-4 (dipeptidyl peptidase-4) was involved in the regulation of GLP-1. This work had led to the hypothesis that DPP-4 inhibition could be a good target for the treatment of type 2 diabetes. In August that same year, she launched a program to discover a novel inhibitor of DPP-4.

“Discovering an important new medicine is the goal of every person who works in pharmaceutical research. Until it actually happens, though, there is no way to know how absolutely thrilling it is, and how incredibly and deeply satisfying it feels.”

—Nancy A. Thornberry

Weber and Thornberry thus became the first two women in Merck’s 120-year history to lead the team that discovered a new medicine. And for the first time in the Discoverers Award’s 24-year history, women alone are being honored for their special achievements of exceptional benefit to humankind.

trials and found that the compound they had created worked in animals: it slimmed down fat rats, fat dogs and fat monkeys without causing unmanageable side effects.

Then, in January 2000, data on clinical trials came back. The medicine simply did not work in humans. Weber hardly had time to register the depth of her disappointment when she was approached by Thornberry.

“We’ve got a very small but exciting program with an interesting target for type 2 diabetes we started working on last year, and we’re thinking of creating a larger team,” Thornberry told Weber. “Would you be interested in collaborating?”

As Weber was well aware, diabetes had become a global epidemic. Currently, it affects more than 285 million people worldwide—with 438 million cases predicted by 2030. Half of diagnosed patients fail to achieve adequate blood glucose control—and diabetes can lead to blindness, amputations, heart disease and nerve and kidney damage, among many other health consequences.

Weber knew that patients, even while they worried about having too much glucose in the blood, were at risk of having their glucose levels lowered too much using existing treatments. The condition, hypoglycemia, can cause reactions such as heart palpitations or, worse, seizures and loss of consciousness.
Weber was definitely interested.

Soon, she and Thornberry would be leading a team of scientists who would find, and in record time, the first new oral therapy for type 2 diabetes in more than a decade. The once-a-day pill named JANUVIA® (sitagliptin) is helping people control their blood sugar in 89 countries where it is approved for use.

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In The Beginning

Well before 1990, it was well known that patients with diabetes don’t produce enough of the insulin that allows their cells to use sugar that is circulating in the body’s blood. Cells are therefore deprived of energy, and the unused sugar, or glucose, thus remains in the body and causes many ill health effects over time.

But in the 1990s, scientists at different labs around the world were deepening their understanding of how the process worked. There was growing evidence that insulin was produced by the body when it was signaled to do so by gastrointestinal hormones, including one called GLP-1, or glucagon-like peptide-1. Meanwhile, parallel studies seemed to indicate that within moments of GLP-1 doing its job of stimulating insulin secretion, an enzyme called DPP-4, or dipeptidyl peptidase-4, would step in and degrade GLP-1.

By the late 1990s there was compelling evidence of both ideas—that GLP-1 signaled the release of insulin and that DPP-4 then degraded GLP-1.

Two possibilities for treating diabetes thus emerged. Perhaps GLP-1 could be injected into patients with diabetes. Alternatively, maybe more time could be allowed for naturally-occurring GLP-1 to do its job by inhibiting the enzyme DPP-4.

The team at Merck felt that inhibiting DPP-4 was the most promising approach. One attractive feature: the possibility of developing an oral therapy, which would be preferable for many patients to a medicine that had to be injected.

With the approach decided in 1999, says Thornberry, “We started the program.”
“Successful Failure”

Just about the time Weber joined the team in early 2000, Merck decided to jump-start the program by acquiring a compound from a small biotech firm that showed promise for inhibiting DPP-4. Studies of the compound began, but within several months, preclinical safety trials showed the compound wasn’t well tolerated, and it had to be abandoned.

“It was a huge disappointment, a real setback,” says Thornberry. “We didn’t know why the compound triggered toxicities. Fortunately, rather than giving up, we got the company’s support to investigate further and try to understand the mechanism of the toxicities.”

The major question was whether the side effects caused by the original compound were due to the inhibition of the DPP-4 mechanism, which was the goal, or an off-target activity. If the latter were true, then the attempt to inhibit DPP-4 might still be viable.

Rather than dropping the program, or even proceeding with the least investment possible until more was known, Merck executives agreed to pursue research on parallel tracks: the research team, led by Thornberry and Weber, worked to investigate the reason for the poor tolerability of the original in-licensed compound, and simultaneously began a medicinal chemistry effort aimed at identifying a potential drug.

The work was intense, with long hours. But it was, says Thornberry, “A labor of love. I’d be thinking about it nights and weekends and there was a big time commitment. At times it was a challenge to balance my work and my home life, but I worked hard to compartmentalize my life and be a good mom while also doing my best to bring the project forward.” Although Thornberry’s two kids were young, they seemed to understand when she would teach them about diabetes and what she was trying to do to help patients.

Weber’s team of more than 20 researchers, meanwhile, was looking for the needle in the haystack—a compound that could inhibit DPP-4 without the observed toxicities. After testing more than 800,000 compounds, two lead compounds were identified that inhibited DPP-4. Both, however, were weak, and among other things, potency would have to be increased by several orders of magnitude.

The team set to work on designing and synthesizing new molecules to systematically address the issues with the lead compounds. More than 2,000 new molecules were prepared and investigated, with nearly all of them dropping out of contention one by one. Eventually the team narrowed their search to six possible drug candidates. Then there were two, then one.

Before those compounds were even identified, the team of scientists now working on the project brought in clinical trial experts to begin considering a host of issues. And the team was, among other things, working to understand why the original molecule wasn’t tolerated well in preclinical studies. Thornberry got the answer in September 2001. She immediately called Weber, who was stuck in England in the aftermath of the 9/11 attacks in New York.

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Trials, But No Tribulations

There was no delay. On the day of the presentation, the teams received the decision that they should move ahead. Weber and Thornberry already had been meeting with Gary Herman and Peter Stein, medical doctors who would be involved in the clinical trials if in fact the molecule was approved for further development. Clinical supervisors Keith D. Klein and John Amatruda, both medical doctors, encouraged them to be creative, aggressive and efficient, and backed them up with resources.

In less than six months, one evening at 5:00 p.m., Weber received a call from Herman. He told her the first data had come in, but he couldn’t email it because it was brand new and hadn’t been reviewed. Weber ran to his office.

“The study showed a beautiful dose response with inhibition of DPP-4 for 24 hours,” says Weber. “I was so excited I almost worried about myself because for four days it felt like I was flying; my feet didn’t touch the ground.”

A subsequent study showed that the molecule was increasing the amount of insulin made in the pancreas and decreasing the sugar made in the liver. The clinicians had worked so closely with the research teams that they were able to move smoothly from one set of trials to the next with “no white space in between,” as Herman puts it. “We weren’t...
“Phase 2 studies take tremendous resources. They include a larger patient population and follow patients longer than Phase 1 studies,” Kaufman explained. But, given the magnitude of the unmet need in type 2 diabetes, and the promise of the molecule, Merck decided to take the financial risk and conducted the trials simultaneously, with each trial having five or six treatment arms.

The team closely monitored patient safety throughout Phase 2 but no serious issues were emerging. Both efficacy and safety were looking good. Dr. John Atmantruda, who joined Merck in 2003 and helped to supervise the clinical program, remembers his excitement when looking at safety data and seeing that patients in the study were not experiencing weight gain or hypoglycemia at a rate higher than in the placebo groups.

Phase 3 studies, which involved thousands of patients in the U.S., Canada, South America, Europe, Asia, South Africa, Australia and New Zealand, focused on a few core indications that would enable the drug to be approved as soon as was possible.

“We weren’t waiting for someone to make clinical supplies or waiting for answers to this and that. We had everything ready and were able to hit the ground running.”

“Four months into the clinical program we believed the right dose would be 100 milligrams once-a-day, and that’s what it turned out to be,” says Herman. Still, they had to be sure and two Phase 2 trials were required—one focused on different daily doses given once daily, and one focused on different doses given twice daily.

Normally, to conserve resources, those studies would be done sequentially, with one study to define the dose response and another to determine the dosing intervals. That way, if issues emerged in the first study and the project had to be abandoned, less investment would have been made in a failure.

“We next step would normally be to study several different doses and their effect on glucose levels. But the teams had worked on this issue so early, even in pre-clinical trials, they were confident they already had a good idea. Moreover, they had a biomarker that enabled them to measure DPP-4 in a patient’s blood plasma.

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—Dr. Gary Herman, M.D.

—Dr. Keith D. Kaufman, M.D.
“In many ways the stars were aligned because we had a beautiful molecule and support from senior management to really go for it. But as importantly, the collective team was magical. We had tremendous trust. Everyone was all in, and we challenged each other aggressively.”
—Dr. Gary Herman, M.D.

Hard work and creative planning also condensed the time usually taken in final stages, as data for various studies are crunched, analyses are completed and summary documents are written about everything from early studies to manufacturing.

Months were saved by planning ahead and anticipating what could be done the minute each study was completed. Separate teams took primary responsibility for individual pieces of the puzzle, while an overarching team headed by Kaufman and Amatruda focused on the big picture. And all of this work was accomplished with full attention to Merck’s extraordinarily high standards of scientific rigor.

From compound selection to filing with the U.S. Food and Drug Administration (FDA) for review took four-and-a-half years—a process that usually takes a decade.

“In many ways the stars were aligned because we had a beautiful molecule and support from senior management to really go for it,” says Herman. But as importantly, he says, the collective team was magical. “We had tremendous trust. Everyone was all in, and we challenged each other aggressively,” he says.

JANUVIA was the name given to the compound and it was approved in October 2006. Today, it is being prescribed to millions of patients with type 2 diabetes. Weber says she can’t get her head around that but takes extreme pleasure in hearing that a friend or colleague or their family member is being helped. Her father, a recently retired physician, is especially proud.

“He prescribed it for some of his patients before retiring, and even though he was not prescribing JANUVIA because of my connection to it, he always told them, ‘My daughter discovered this’, says Weber.

Thornberry has a more intimate connection—her mother takes JANUVIA. Thornberry’s mother wasn’t about to try JANUVIA just because her daughter discovered it, though. “She wanted to know how it worked and asked me lots of questions before her doctor prescribed it for her,” says Thornberry.

The discovery and development of a drug is the ultimate team effort. Thornberry and Weber, among many others at Merck, continue the battle against diabetes, looking for the next generation of medicine.

“Even with JANUVIA, there is a tremendous unmet need. Diabetes is a progressive disease, and we need to continue to work towards new therapies.”

—Nancy A. Thornberry
PREVIOUS DISCOVERERS AWARD RECIPIENTS

2010

Selzentry, antiretroviral drug in the CCR5 receptor antagonist class, Pfizer
  Anthony Wood, Ph.D.
  Elna van der Ryst, M.D., Ph.D.
  Manos Perros, Ph.D.

2009

Gardasil, vaccine to prevent cervical cancer, Merck
  Kathrin Jansen, Ph.D.
  Eliav Barr, Ph.D.
  Barry Buckland, Ph.D.

2008

Coreg, alpha-beta blocker, Smith Kline Beecham
  Eliot Ohlstein, Ph.D.
  Robert R. Ruffolo, Jr., Ph.D.
  Tian-Li Yue, Ph.D.

2007

Zyvox, first-in-class antibiotic, Upjohn
  Steven J. Brickner, Ph.D.
  Michael R. Barbachyn, Ph.D.
  Douglas K. Hutchinson, Ph.D.

2006

Zetia, cholesterol-absorption inhibitor, Schering-Plough
  Harry R. Davis, Jr., Ph.D.
  Margaret van Heek, Ph.D.
  Kevin B. Alton

2005

Prevnar, Streptococcus Pneumoniae vaccine, Wyeth
  Ronald J. Eby, Ph.D.
  Dace V. Madore, Ph.D.
  Velupillai Puvanesarajah, Ph.D.

2004

Gleevec, tyrosine kinase inhibitor anticancer medication, Novartis
  Elisabeth Buchdunger, Ph.D.
  Juerg Zimmermann, Ph.D.

2003

Mylotarg, monoclonal antibody anticancer medication, Wyeth
  George Ellestad, Ph.D.
  Philip Hamann, Ph.D.
  Janis Upeslacis, Ph.D.
2002

**Celebrex**, COX-2 inhibitor, *Pharmacia*
- Peter Isakson, Ph.D.
- Jaime Masferrer, Ph.D.
- Karen Seibert, Ph.D.
- John Talley, Ph.D.

2001

**Enbrel**, tumor necrosis factor blocking agent, *Immunex*
- Craig A. Smith, Ph.D.
- Raymond G. Goodwin, Ph.D.

2000

**Zyprexa**, atypical antipsychotic medication, *Eli Lilly*
- Jiban Chakrabarti, Ph.D.
- David Tupper, Ph.D.
- Terry Hotten, GRSC

1999

**Invirase**, protease inhibitor, *Roche*
- David Peter Clough, Ph.D.
- Ian Buchanan Duncan, Ph.D.
- Noel Roberts, Ph.D.

**Norvir**, protease inhibitor, *Abbott*
- Dale J. Kempf, Ph.D.
- Daniel W. Norbeck, Ph.D.

1998

**Zofran**, nausea and vomiting induced by cancer treatments, *SmithKline Beecham*
- Gareth J. Sanger, Ph.D.

**Kytril**, nausea and vomiting induced by cancer treatments, *Glaxo Group Research became Glaxo Wellcome*
- Michael B. Tyers, Ph.D.

Note: Because of a change in the time of year of the award announcement, there was no award given in 1997.
1996

**Exosurf**, infant respiratory distress syndrome medication, *Burroughs Wellcome*
  John A. Clements, M.D.

1995

**Epogen**, erythropoiesis-stimulating agent, *Amgen*
  Fu-Kuen Lin, Ph.D.

1994

**Diflucan**, anti-fungal medication, *Pfizer*
  Ken Richardson, Ph.D.

1993

**Prozac**, selective serotonin reuptake inhibitor, *Eli Lilly*
  Brian B. Molloy, Ph.D.
  Ray W. Fuller, Ph.D.
  David T. Wong, Ph.D.

1992

**Mevacor**, statin, *Merck*
  Alfred W. Alberts
  Georg Albers-Schönberg, Ph.D.
  Arthur A. Patchett, Ph.D.

1991

**OKT 3**, immunosuppressant in organ transplants, *J&J’s Ortho Biopharmaceuticals*
  Patrick Kung, Ph.D.

**Minipress**, alpha-1 blocker, *Pfizer*
  Hans-Jürgen Hess, Ph.D.

**Ethrane & Forane**, inhalation anesthetics, *BOC Healthcare*
  Ross C. Terrell, Ph.D.

1990

**Capoten**, ACE inhibitor, *Bristol-Myers Squibb*
  David W. Cushman, Ph.D.

**Zovirax**, anti-viral drug, *Burroughs Wellcome*
  Gertrude B. Elion, D.Sc., DMS
  Howard H. Schaeffer, Ph.D.

1989

**Mectizan**, prevention of river blindness, *Merck*
  William C. Campbell, Ph.D.

**Xanax**, anti-anxiety medication, *Upjohn*
  Jackson B. Hester, Ph.D.

**Halcion**, insomnia treatment, *Upjohn*
  Jackson B. Hester, Ph.D.

**Hypertension**, vaccines, *Merck*
  Max Tischler, Ph.D.
1988

**Diuril**, chlorothiazide diuretic, *Merck*
Karl Henry Beyer, Jr., M.D., Ph.D.

**Inderal**, beta blocker, *ICI Pharmaceuticals, Smith Kline, French Welwyn Research Institute*
Sir James Black, M.D., ChB., FRCB, FRS

**Tagamet**, histamine-2 blocker, *ICI Pharmaceuticals, Smith Kline, French Welwyn Research Institute*
Sir James Black, M.D., ChB., FRCB, FRS

**Sandimmune**, immunosuppressant in organ transplant, *Sandoz*
Jean-Francois Borel, Ph.D.

**Nor-QD**, oral contraceptive, *Syntex Laboratories*
Carl Djerassi, Ph.D.

1987

**Imuran**, immunosuppressant medication, *Burroughs Wellcome*
George H. Hitchings, Ph.D.

**Zyloprim**, anti-gout medication, *Burroughs Wellcome*
George H. Hitchings, Ph.D.

**Purinethol**, anti-leukemia medication, *Burroughs Wellcome*
George H. Hitchings, Ph.D.

**Haldol**, anti-psychotic medication, *Janssen Pharmaceutica*
Paul A.J. Janssen, Ph.D.

**Cephalosporin antibiotics**, broad spectrum antibiotic, *Bristol-Myers, Merck Sharp & Dohme Research Laboratories, Eli Lilly*
Robert B. Morin, Ph.D.

**Capoten**, ACE inhibitor, *Squibb Institute for Medical Research*
Miguel A. Ondetti, Ph.D.

**Valium & Librium**, discovery of the class of psychoactive drugs called benzodiazepines, *Hoffman-La Roche*
Leo H. Sternbach, Ph.D.