

# Molecular Relay Team

RESEARCHERS DISCOVER HOW CRITICAL INFORMATION IS PASSED FROM ONE PROTEIN TO ANOTHER.

Like athletes passing batons in a relay race, protein “teams” inside cells transfer smaller proteins, called ubiquitin-like proteins, to certain other proteins to set them on track to their final destiny.

HHMI investigator Brenda A. Schulman and her colleagues at St. Jude Children’s Research Hospital have discovered new details about this process. The relay team is made up of three enzymes—E1, E2, and E3—that work in tandem to attach ubiquitin or ubiquitin-like tags to cellular proteins. The tags determine the modified proteins’ ultimate fate, such as destruction in the cell’s garbage disposal, the proteasome. Such degradation in turn can cause activation of a specific event like cell division.

The E1 enzyme selects the correct tag and forms a high-energy bond with it. Next, the activated tag is transferred to E2, which then works with E3 to ultimately hand the tag to the targeted protein. If the system gets out of sync, diseases—such as cancer and neurodegenerative disorders—may occur.

To dissect the transfer process, Schulman’s group studied the enzymatic line-up associated with the ubiquitin-like protein NEDD8, which has a relatively simple E1-E2-E3 cascade. They genetically altered the E2 enzyme to stop action, in mid-handoff, during its receipt of NEDD8 from E1. The researchers then crystallized the structures and exposed them to x-ray beams to determine their three-dimensional shapes.



To get where they need to go, certain proteins receive ubiquitin or ubiquitin-like guiding proteins from enzymatic “relay teams.”

Previous studies could not explain how the relay worked because available models showed E1 and E2 positioned with E1’s baton-carrying hand far away from E2’s baton accepting hand. Instead, says Schulman, a switch occurs as if between two novice relayers: the second turns around to face the first for the handoff.

The ubiquitin-like protein (and probably ubiquitin) not only serves as a baton, she adds, but also as a coach. “When bound to E1, it says bind to E2; when bound to E2 it says run away from E1,” says Schulman.

The group reported its results in the January 25, 2007, issue of *Nature*. They are now considering how an anchor enzyme, E3, completes the relay and adds ubiquitin or NEDD8 to the final target protein. ■ - JACQUELINE RUTTIMANN

## IN BRIEF

### SINGLE GENETIC DEFECT CAUSES EARLY HEART DISEASE

Researchers have identified a genetic mutation that causes early-onset coronary artery disease. Although the genetic defect is rare, it may offer clues about what causes the body’s metabolic machinery to malfunction in the more “garden variety” forms of heart disease.

HHMI investigator Richard P. Lifton at Yale University School of Medicine and colleagues discovered members of an Iranian family who carried a genetic mutation that caused them to die in their early fifties from coronary artery disease that resulted in heart attacks and heart failure. They also had osteoporosis. The results were published in the March 2, 2007, issue of *Science*.

Medical records and blood samples from surviving family members showed that the family members had a characteristic cluster of symptoms called metabolic syndrome. People with this syndrome have hypertension, high blood lipid levels, and diabetes, and they are at much higher risk of developing heart disease.

Detailed genetic comparison of all family members found a culprit gene called *LDL receptor-related protein 6 (LRP6)*. This

gene was previously implicated in bone development; mutation of the gene also causes problems in the Wnt signaling pathway, a key metabolic signaling pathway that is important in embryonic development and contributes to an array of normal physiological processes in adults.

The possible linkage to the Wnt pathway may become an important research target for understanding coronary heart disease, says Lifton, who added that the discovery of the *LRP6* mutation causing osteoporosis may link this disease with coronary artery disease.

### FRUIT FLY MODEL MIMICS HUMAN NEURODEGENERATIVE DISEASES

Researchers have developed a fruit fly model that replicates the genetic instability seen in a variety of neurodegenerative diseases, including spinocerebellar ataxia type 3 (SCA3) and Huntington’s disease.

In some neurodegenerative diseases, certain gene mutations cause the production of an abnormally long number of repeats of three nucleotides called triplet repeats, which encode an amino acid called glutamine, and thus leads to a protein with an abnormally long glutamine string that is toxic to cells.

The length of this glutamine string can grow or shrink as it is passed from one generation to the next—a feature called repeat instability. Expansion of repeats causes the disease to arise earlier and with greater severity in successive generations of people who carry the mutation.

Researchers have had difficulty reproducing the genetic instability of the disorders. Now, a team of scientists led by HHMI investigator Nancy Bonini at the University of Pennsylvania reported in the March 1, 2007, publication of *Science Express* that they see repeat instability in the fruit fly model of SCA3. They directed expression of the SCA-associated gene in germline cells—those associated with eggs and sperm—and saw dramatic instability from generation to generation.

They also found that a gene called *CBP*, which is involved in DNA repair pathways and has been implicated in this class of diseases, affects repeat instability. A drug that counteracts this protein in similar disease models sharply reduced repeat instability in the fruit flies. Drugs of this type are already being investigated as potential treatments for these disorders, says Bonini.