



*From his birthplace in Naples to his lab at NYU Langone, this scientist continues to cross borders as he uses an interdisciplinary approach to explore the role of the cell's ubiquitin system in cell proliferation, differentiation, and death. His studies have broad implications that bridge the worlds of basic science and translational cancer biology.*

## Crossing Borders

The F-Box Family as Pandora's Box: Dr. Pagano's research explores the roles that the ubiquitin system plays and how the deregulation of this system can cause cancers. He has found that many F-box proteins have connections to cancer—for instance, a low level of one type of F-box protein is a warning that a tumor may be developing. In breast cancer, Dr. Pagano demonstrated that high levels of a different F-box protein represent a diagnostic sign that the cancer is of a highly aggressive form. Raising levels of yet another F-box protein seems to sensitize tumors to anticancer drugs. Asked if he thought much about translating his work to the bedside, Dr. Pagano replied, "All the time. We have collaborations with people at the Medical Center and with industry to explore F-box proteins as targets for cancer therapies. But, I also remind you of the words of Arthur Kornberg, the Nobel Prize-winning biochemist: 'No matter how counter-intuitive it may seem, basic research has proven over and over to be the lifeline of practical advances in medicine.'"

### **Michele Pagano, M.D.**

May Ellen and Gerald Jay Ritter Professor of Oncology;  
Professor of Pathology; Investigator, Howard Hughes Medical Institute

Now that he has been selected as a Howard Hughes Medical Institute (HHMI) Investigator—one of the highest honors that can be bestowed on a biomedical research scientist—Dr. Michele Pagano has a passport that gives him unprecedented freedom to continue his interdisciplinary investigations and “extend the boundaries of knowledge.”

His work virtually defines the HHMI criteria for creativity, innovation, and productivity. Since he joined the NYU Department of Pathology, Dr. Pagano has been working on the ubiquitin system, which is part of the cell's recycling organization. Specifically, he has focused on F-box proteins—subunits of the SCF ubiquitin ligase family of enzymes that are, as the name “ubiquitin” suggests, virtually everywhere in the cell's workings. In the past few years, his team has found that of the 69 F-box proteins identified to date, 16 play a major role in controlling cell size, proliferation, and death. Now they are working with this whole group of proteins to reveal their unknown substrates and functions.

“We opened Pandora's Box by studying this family of genes,” said Dr. Pagano. “We started with a focus on cell cycle control, but have since expanded to multiple cellular pathways—and discovered that F-box proteins are involved in controlling cell proliferation, DNA-damage checkpoints, chromosomal stability, ribosomal biogenesis, protein synthesis, apoptosis, neurogenesis, and even the setting of the body's circadian clock! Many of these pathways have been studied separately, in isolation. We are excited about opening the field to new ideas and creating fresh interactions.”