

# Researchers Seek to Unravel a Central Paradigm

**W**hile visiting the doctor as a child, Julian Gomez-Cambronero, Ph.D., saw blood cells through a microscope for the first time and became fascinated by the implications. “It has always intrigued me that cells are able to defend us against disease,” he says.

Today, as a professor of physiology and biophysics at Wright State and the director of the Blood Course for Year II students, he is studying the fundamental cell biology question of cell migration and the immune response at the molecular level. The goal is to better understand two classes of disease: inflammation-related tissue injury and leukemia. In March, the National Institutes of Health awarded him a four-year, \$1.4 million grant to continue this research.

“In my lab, we work with neutrophils, a type of leukocytes or white blood cells, which are part of the first-line defense of the immune system. In infection, neutrophils are ‘natural born killers.’ They patrol inside the blood vessels pretty much like a surveillance team and respond to inflammation or physical damage by releasing powerful toxic substances that destroy bacteria. This is the beginning of how a wound is healed,” he explains.

“But, the other side of the story is that the substances neutrophils are capable of producing also can destroy healthy tissue. The neutrophil, and a closely related white blood cell, the monocyte, are implicated in tissue destruction in at least 15 human inflammatory diseases, including emphysema, rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis.”

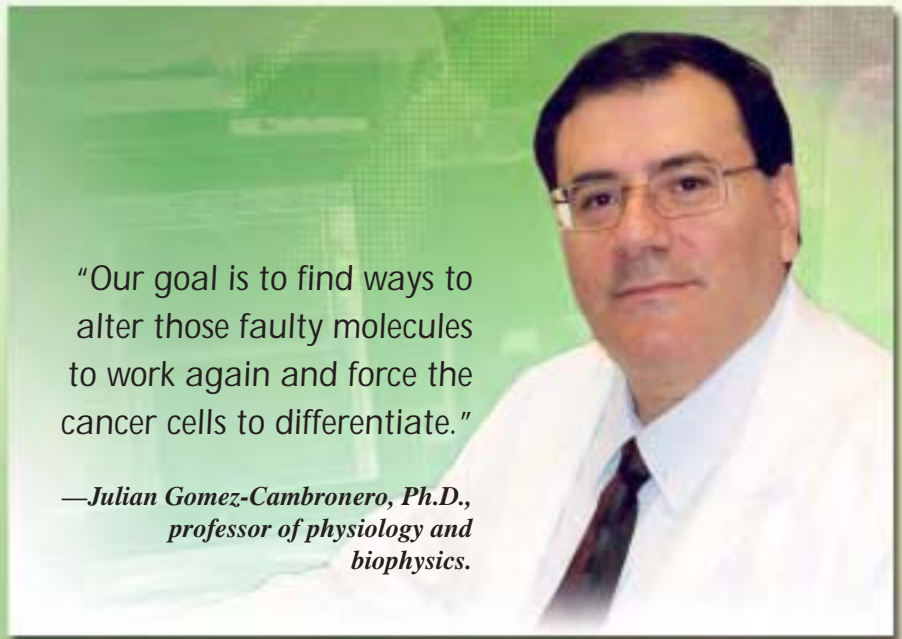
What all these diseases have in common is the first cellular reaction to trauma or pathogen invasion—the migration of white blood cells to the compromised site in response to what is essentially a chemical SOS signal produced by the injured tissue or infectious agent. These chemicals, called chemoattractants, activate a cascade of signaling reactions inside the neutrophil, “calling it to duty” at the site of inflammation.

“Understanding this process, called chemotaxis, is crucial. Our lab has discovered that a natural hormone produced inside the bone marrow in response to inflammation, GM-CSF, is a powerful leukocyte chemoattractant. We already knew that GM-CSF induces bone marrow restoration and fast recovery of blood cell counts after chemotherapy.”

Dr. Gomez-Cambronero and his team are not only interested in understanding the process of chemotaxis, they also want to attack the problem of neutrophil-inflicted damage to healthy tissue. In studying that problem, they uncovered a new mission for an immunosuppressant used clinically to prevent rejection in organ transplants: rapamycin. Derived from a fungus discovered in the soil of Easter Island, rapamycin’s action is the opposite of a chemoattractant like GM-CSF.

“We found that rapamycin stops neutrophils in their tracks. It inhibits cell migration without killing the cell,” he explains. “It was so exciting to see it for the first time. We reason that rapamycin could be useful in the future in those conditions where you might want to stop the activity of neutrophils, like arthritis and asthma.”

The lab has undertaken several experiments to test its theories about rapamycin’s role in chemotaxis, among them that rapamycin may work through an intracellular enzyme that regulates cell growth called p70 S6 kinase. Dr. Gomez-Cambronero will use leukemic blast cells instead of



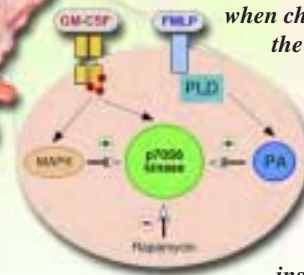
“Our goal is to find ways to alter those faulty molecules to work again and force the cancer cells to differentiate.”

—Julian Gomez-Cambronero, Ph.D.,  
professor of physiology and  
biophysics.

# in Cell Biology



*This image shows a white blood cell migrating out of a blood vessel in response to an infection. This process, an integral part of chemotaxis, starts when chemicals produced by the infection (GM-CSF and FMLP) activate an enzyme inside the blood cell (p70 S6 kinase), causing the cell to migrate to the infection site. The inset shows molecular activity inside the cell where enzymes (MAPK and PLD/PA) enhance chemotaxis while the immunosuppressant drug rapamycin inhibits it. (Illustration by Dr. Gomez-Cambronero.)*



neutrophils because they are immature and undifferentiated blood cells that are essentially immortal. Leukemic blast cells can also be induced in the lab to become neutrophil-like cells.

All this opens the window to molecular biology-based experiments. In collaboration with Patrick Dennis, Ph.D., assistant professor of biochemistry and molecular biology, and Michael Baumann, M.D., professor of medicine and chief of hematology/oncology at the Dayton VA Medical Center, they will introduce the gene for producing p70 S6 kinase into the leukemic cell, hoping to enhance its response to chemoattractants. Conversely, they will introduce mutants of the enzyme to see if chemotaxis is inhibited as it was with rapamycin.

This relates to the other major interest in Dr. Gomez-Cambronero's lab. "In trying to understand the molecular basis of acute leukemia, we ask two fundamental questions: What is the difference between the intracellular signaling in leukemic blasts and in normal leukocytes? And, is there a way to force the immature blasts to stop dividing and make them differentiate into mature neutrophils?" he says. "The lab has already identified a number of cell signaling molecules that are different in both cells. Our goal is to find ways to alter those faulty molecules to work again and force the cancer cells to differentiate."

"Over the past decade, our view of leukocytes has been revolutionized in the molecular strategies underlying complex diseases like inflammation-related tissue injury and leukemia. Several research teams are, like us, seeking to unravel the central cell biology paradigm of cell migration. The next few years are likely to see even more exciting advances in this fascinating biomedical field."

—Robin Suits

## GLOSSARY OF TERMS

**Chemotaxis:** directional migration of cells toward a chemical (chemoattractant) stimulus

**FMLP:** bacterial formyl peptide, a powerful neutrophil chemoattractant

**GM-CSF:** granulocyte-macrophage colony-stimulating factor, a hormone-like substance that stimulates blood cell growth in the bone marrow

**Leukemic blast cells:** immature, undifferentiated leukocytes found in acute leukemia that cannot perform normal physiological functions

**Leukocytes:** white blood cells (neutrophils among them) that defend us against pathogen infection

**MAPK:** mitogen activated protein kinase, an intracellular signaling enzyme important in cell growth

**p70 S6 kinase:** a signaling enzyme that modifies ribosomes during protein synthesis

**PLD:** a phospholipase that breaks down phospholipids in the cellular membrane

**PA:** a lipid product of PLD action that acts as an intracellular second messenger

**Rapamycin:** an immunosuppressant used to prevent rejection in organ transplants