

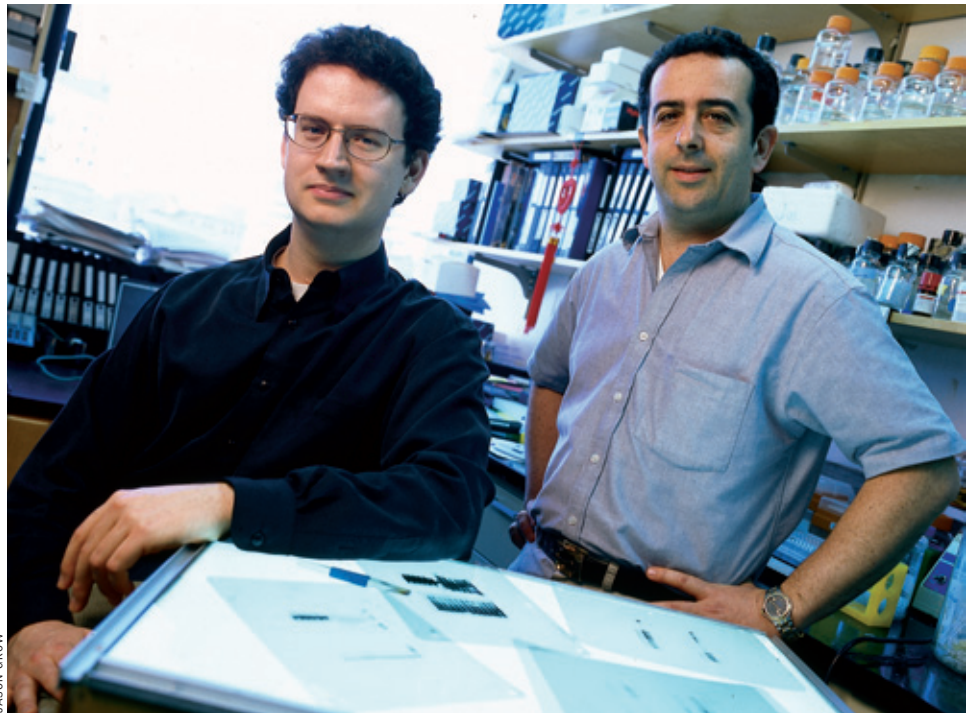
## A Chink in Melanoma's Genetic Armor

A series of recent discoveries may explain why malignant melanoma is much deadlier and harder to treat than many other cancers. The findings, published in the journal *Cell* by a team that includes several HHMI fellows and investigators, have important implications for the development of new drugs that might bring melanoma under control.

Melanoma occurs when melanocytes, which are normally stable, begin to divide. Melanocytes provide fair-skinned people with defense against sun damage. When exposed to ultraviolet (UV) rays, melanocytes manufacture melanin, giving the skin a tanned appearance. Repeated or prolonged UV exposure, however, can damage the genetic material of melanocytes, causing them to divide uncontrollably and give rise to malignant melanoma.

Melanocytes that have become malignant are notoriously difficult to kill. Statistics from the American Cancer Society bear this out: While melanomas account for only 4 percent of the 1 million new skin cancer cases diagnosed in the United States annually, they account for 80 percent of all skin cancer deaths.

What makes melanoma so tough? The key, reasoned HHMI predoctoral fellow Gaël G. McGill at Dana-Farber Cancer Institute and a team of investigators, lies in what makes melanocytes special in the first place. Over eons of evolutionary time, melanocytes developed the ability to withstand and respond to assaults such as exposure to UV radiation that would cause other types of cells to undergo genetically programmed cell death, or apoptosis. "Triggers that kill other cells don't kill melanocytes," McGill explains. "These are cells that must have evolved a



A team including Gaël McGill (left) and David Fisher (right) has found a master switch for melanoma.

particular resistance to apoptosis."

The aim of many cancer therapies is to induce apoptosis in malignant cells; it stands to reason, therefore, that cells with special resistance to apoptosis will not respond to these types of treatments. According to David E. Fisher, a former HHMI postdoc who is now an associate professor at Harvard Medical School and Dana-Farber Cancer Institute, "while a connection between pigmentation and survival is probably beneficial for normal pigment cell function, the flip side is that it may confer super survival properties and impede successful therapy" once a pigment cell becomes malignant.

Fisher, McGill and a team in Fisher's lab have devoted themselves to discovering the precise genetic processes within melanocytes that confer their resistance to cell death. The team, which includes HHMI predoc

Gabriela Motyckova and postdoc Martin Horstmann, the *Cell* paper's co-lead author, has also performed experiments suggesting novel ways of rendering malignant versions of the cells susceptible to apoptosis.

The researchers discovered that stimulation of a transcription factor called MITF upregulates the expression of the *Bcl-2* gene. In a large body of earlier work, team member Stanley J. Korsmeyer, an HHMI investigator then at Washington University in St. Louis and now at Harvard and Dana-Farber, and other scientists had demonstrated that *Bcl-2* is a potent cell-death suppressor. Fisher and others had also characterized the biochemical and functional properties of MITF, determining that it is a "master regulator" of the process by which melanocytes develop. When either MITF or *Bcl-2* are mutated or missing, black mice turn gray due to the death of melanocytes.

In collaboration with Todd R. Golub, an HHMI investigator at the Whitehead/Massachusetts Institute of Technology Center for Genome Research and Dana-Farber, the team has used DNA microarrays to demonstrate that in human tumors, the expression of the cell-death suppressor *Bcl-2* is tightly linked to MITF. These experiments reveal that the link is present in both normal melanocytes and in malignant melanoma cells. Specifically, when MITF is present, the researchers have observed a rise in the amount of BCL-2 protein and suppression of apoptosis.

The results reported in the *Cell* paper also describe attempts by McGill and his collaborators to inhibit the activity of MITF in normal and malignant cells. Blocking MITF by infecting the cells with genetically engineered adenoviruses, they succeeded in killing both healthy and cancerous melanocytes. At the same time, they demonstrated that the process works in reverse; cells in which the *Bcl-2* gene was naturally overexpressed were able to survive the researchers' attempts to induce apoptosis by blocking MITF.

Now that a link has been established between MITF and *Bcl-2*, some researchers believe that a new chapter in melanoma research—and skin biology in general—has been opened. The team's findings "really fill an important gap of knowledge," says Meenhard Herlyn, a researcher at The Wistar Institute in Philadelphia who studies the mechanisms behind the transformation of melanocytes into melanoma.

Earlier research showing that *Bcl-2* is a suppressor of cell death has already inspired drug developers to conduct clinical trials with agents that seek to shut down the gene in cancer cells. McGill points out, however, that because *Bcl-2* is expressed in every cell of the body, drugs that inhibit it could give rise to unwanted side effects. MITF, however, is present only in melanocytes and a very limited number of other cell types.

Researchers in the Fisher lab are working to find agents that block MITF or interfere with its interaction with *Bcl-2* expression. These would have potential as targeted therapies for malignant melanoma. The task, says Fisher, is to "understand where within the pathway [between MITF and *Bcl-2*] there might be drugable targets."

—CAMILLE MOJICA REY

## Baseball's Biochemist

**O**n June 4, 2002, Matthew McCarthy, a new graduate of Yale University who had majored in molecular biophysics and biochemistry, was drafted by baseball's Anaheim Angels for its farm-team system, step one for players with major-league promise. A month later, while the lefty pitcher was perfecting his curve ball in Provo, Utah, his first scientific paper was published in *The EMBO* (European Molecular Biology Organization) *Journal*.

Baseball was McCarthy's ticket to science. In 1998, the Orlando high school pitching star visited New Haven and was sold on Yale after meeting baseball coach John Stuper, who had pitched the St. Louis Cardinals to victory in game six of the 1982 World Series, enabling them to play and win game seven against the Milwaukee Brewers.

McCarthy eventually took a biochemistry course taught by HHMI investigator Joan A. Steitz. I didn't have a passion for science, or biochemistry, until I took Joan's course," McCarthy recalls. "It was the best course I took at Yale. She's top-notch as a professor and a researcher. And she was then nice enough to give me a chance in her lab." When McCarthy asked if he could perform original research in the summer of 2001, he applied for and received an HHMI summer undergraduate research fellowship. He started working in the Steitz lab immediately after the baseball season.

McCarthy studied gene expression as a function of two different entities that splice out portions of RNA so that it can get translated into the correct proteins—the U2-dependent spliceosome and the U12-dependent spliceosome. He helped show that the U12 is much less efficient than the more common U2. The guess is that U2 probably gets sent up to bat when feedback loops in the cell determine that less protein should be produced.

The third author on *The EMBO Journal* paper reporting this effort was M.D.-Ph.D. student Abhijit A. Patel. "Joan and Abhi were great," McCarthy says. "Abhi made me feel at home and took the time to explain how experiments worked. They didn't treat me as a jock or a dim undergraduate—they treated me as a fellow researcher." Then again, McCarthy earned such treatment. "Never before in 31 years of teaching at Yale have I had an undergraduate work in the lab for as



**Matthew McCarthy's baseball card lists his earned run average, strikeouts and other stats, but no mention of his published scientific paper.**

short a period as six months and truly deserve coauthorship," says Steitz.

While such praise is heartfelt, Steitz admits to having a soft spot for ballplayers. She and her husband, fellow Yale faculty member and HHMI investigator Thomas A. Steitz, are the parents of another recent Yale molecular biophysics and biochemistry graduate and pitcher, Jon, a top draft