

Bathing suits. Check. Beach toys. Check. Sunglasses. Check. Sunscreen. Don't need it.

Soon Mom and Dad may have one less item to pack for the family trip to the beach—sunscreen. Instead, about a week before they head to Orlando, the whole family will smear on a special lotion that naturally tans their skin. But more important than the tan is the built-in UV protection. The University of Kentucky's John D'Orazio is doing the basic science work behind this revolutionary approach to stop skin cancer.

By repairing a defect in the chemical pathway that tells cells which kind of melanin (pigment) to produce, D'Orazio turned "blond" mice black. And one day the science behind this discovery may tan and protect vacation-bound families and sun-worshippers.

How did D'Orazio, a clinical pediatrician and scientist at the Markey Cancer Center, get into tanning research? "For me, the pitch was the fact that childhood sun exposure, particularly blistering sunburns, is the biggest risk factor for melanoma later in life." Melanoma is the most common cancer in young adults between ages 20 and 30, and the primary cause of cancer death in women between 25 and 30. And then, he adds, there was the curious observation that people with albinism—no pigment at all—don't get melanoma.

D'Orazio explains that pigmentation plays a big role in skin cancer. Take three groups of people, the first with dark skin (say from Africa or India), the second with fair skin (say from Ireland) and the third with albinism. "Now look at the cancer risk. There are two basic carcinoma categories. In the first category, there's basal cell carcinoma/squamous cell carcinoma—these account for over a million cases a year in the United States and don't kill you, you just get them cut out—versus the bad guy melanoma." It makes up less than 10 percent of the total cases of skin cancer, but three-quarters of the deaths.

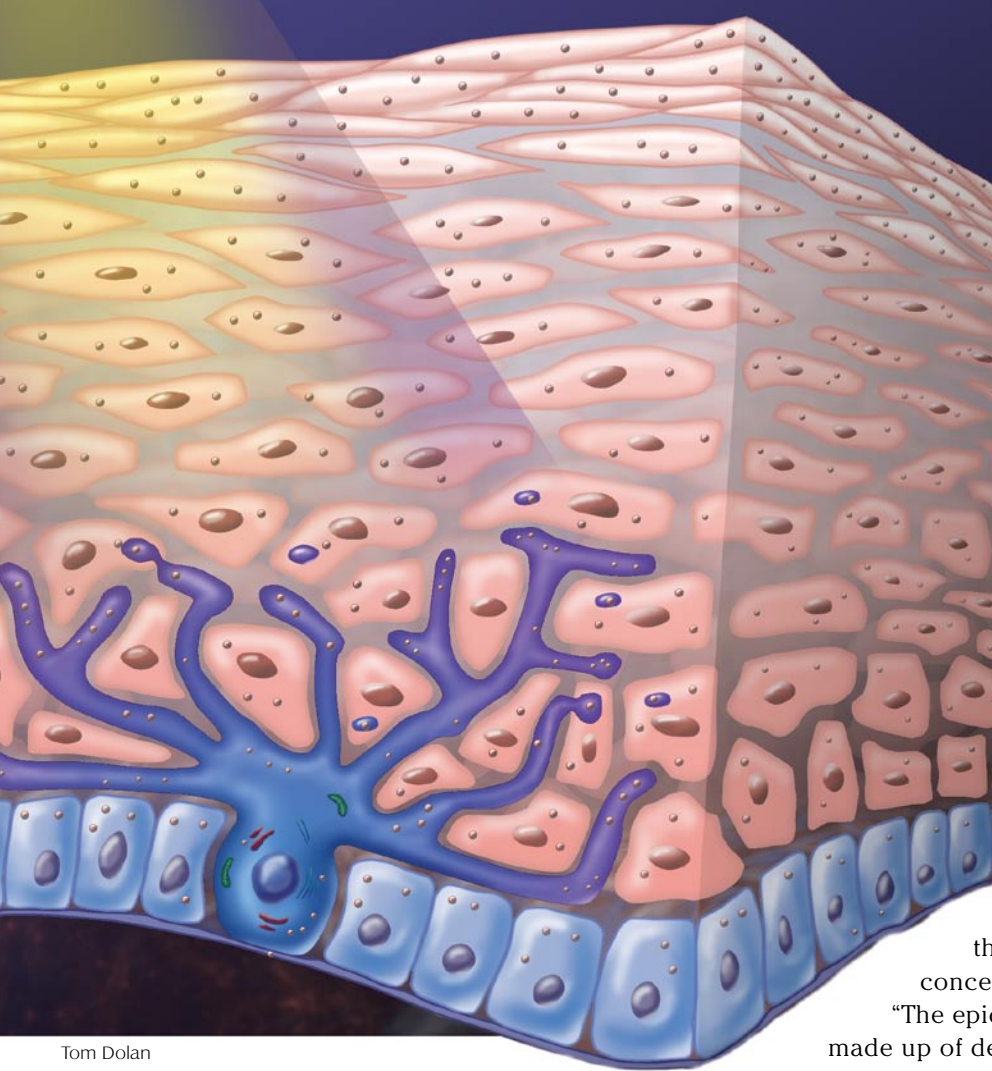
D'Orazio says, "So guess what? If you're dark skinned, you don't get either kind of cancer. If you're fair, you're at high risk for both kinds. And if you have albinism, you're at the highest risk for basal cell/squamous cell carcinoma, but you won't get melanoma."

Why zero pigment equals zero melanoma was the driving question behind his work in David Fisher's

Fighting Cancer with a Safe Tan

by Alicia P. Gregory





Tom Dolan

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lab at the Dana-Farber Cancer Institute in Boston before D’Orazio came to UK four years ago. “David, one of the top three melanoma researchers in the world, got me interested in figuring out a way to protect kids from melanoma.” This research led to a landmark September 2006 paper in *Nature* that demonstrated an experimental lotion could protect “fair skinned” mice against UV damage. “But before we get to the mice, let’s look at your skin,” he says picking up a marker.

“Your skin is made up of layers,” D’Orazio explains, as he draws several wavy lines with small and large circles. “These big circles are keratinocytes—they make up 90 percent of skin cells. They proliferate down here at the lowest layer, and as they mature they

Melanocytes (dark blue cells) distribute pigment, a.k.a. melanin (tiny brown spheres), to the keratinocytes (peach cells). Keratinocytes make up 90 percent of skin cells, and as the keratinocytes are pushed up to the surface by new cells beneath them, the melanin gets more and more concentrated. John D’Orazio explains: “Skin rich in one type of melanin, called eumelanin, absorbs the UV light before it can get down to the danger zone where the melanocytes live.” Skin cancer happens when UV light mutates cells in the danger zone.

lose their nuclei, bind tightly to each other, and pick up melanin—pigment—from melanocytes, the only cells that produce it.” He adds that one melanocyte can interact with 30 to 50 of these keratinocytes. And as the keratinocytes are pushed up to the surface by new cells beneath them, the melanin gets more and more concentrated.

“The epidermis—the top layer of your skin—is made up of dead keratinocytes, jammed with melanin, that seal in the skin.” He draws a sun with an arrow down to the epidermis with a big “UV” next to it. “Skin rich in one type of melanin, called eumelanin, absorbs the UV light before it can get down to the danger zone where the melanocytes live.” Skin cancer happens when UV light mutates cells in the danger zone.

This eumelanin is a natural sunscreen. “I call it that because it’s not something you apply. It’s in your skin. You couldn’t get rid of it if you wanted to ... well, unless you’re Michael Jackson,” he laughs. “If you’re dark skinned you have eumelanin, and remember these folks don’t get either kind of skin cancer. If you’re blond or red haired, lots of freckles, burn easily, you have pheomelanin, and can get both kinds of cancer.”

But if you have albinism, you don’t have either of these types of melanin because your body doesn’t make the enzyme, tyrosinase, that leads to melanin production. And people with albinism are at very high risk for non-melanoma skin cancers, but they don’t get melanoma.

“UV exposure is clearly linked to melanoma, but nobody understands how,” D’Orazio adds. He and his peers across the country, however, suspect melanoma risk may be related to pheomelanin in the skin.

To get at the mechanisms behind which kind of melanin is made, D’Orazio used genetically modified mice that differed only in key genes that caused them to have eumelanin (black mice), pheomelanin (blond mice) or no melanin (albino) to study the UV responses and DNA damage in each group.

It all comes down to a signaling molecule—a chemical involved in transmitting information between cells—known as cyclic AMP (adenosine monophosphate). Cyclic AMP carries signals from the cell surface to proteins within the cell and triggers a cascade of gene and enzyme actions that produce eumelanin. When there’s a defect in this signaling process, pheomelanin is made instead.

D’Orazio found that by using a drug to bypass this defect, he could make his blond mice black. He created a lotion containing a compound called forskolin, which is made from the root of a plant called *Plectranthus barbatus* grown in the foothills of the Himalayas, used for centuries worldwide in traditional medicines, and used in labs since the 1970s. Within a couple of days of applying the lotion to the backs of these mice, he started to see the blond mice turn black. “The black skin is caused by eumelanin production, so we essentially repaired that signaling defect pharmacologically.” He found that the more you apply, the greater the UV protection, and that the protection lasts for a few weeks. “It takes a month for all your skin cells to renew, so it gradually works its way out of the skin just like a natural suntan.”

But it’s not likely that a forskolin-based lotion will end up on your drugstore shelf. “Human skin is much thicker than mouse skin. The problem is getting the drug down to the melanocytes.” He adds, if you took enough of forskolin orally to get the needed concentration, you’d probably have diarrhea. Not a vacation-friendly side effect. “We used this drug as proof-of-principle. Whether another compound that can tickle this cyclic AMP pathway in the same way ends up on the shelves will depend on whether a safe, deliverable drug can be found that works in humans.” That’s what Magen Biosciences, founded by David Fisher, is trying to do.

Along with top scientists from Harvard and MIT, D’Orazio is on the scientific advisory board of this Massachusetts-based company that is identifying and developing novel treatments for dermatological disorders. “Magen is handling the consumer product side, while we’re using our mouse model to continue to tackle the basic science questions of how UV light causes DNA damage and leads to melanoma.

“Our mouse study has implications for protection against UV light, and more cosmetically sunless tanning. We didn’t set out to get rich or put tanning salons out of business. Our goal is cancer prevention.” ■

John D’Orazio, a clinical pediatrician and scientist at the UK Markey Cancer Center, is fighting skin cancer before it starts with a lotion that optimizes skin’s natural pigment to prevent UV damage.

