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Beyond Skin Deep:

A Novel Strategy Against Melanoma

“Melanoma” is often preceded by the word “deadly,” and for good reason: Once this cancer has spread to other parts of the body, no treatment can defeat it. Now, researchers at the Albert Einstein Cancer Center have devised an ingenious therapy for melanoma, the increasingly common skin cancer that kills nearly 8,000 Americans each year.

The anti-melanoma strategy involves “piggybacking” a radiation-emitting isotope onto an antibody that seeks out melanin, the pigment that gives skin its color. Carried deep into the tumor by the blood, the antibodies target the melanin released by dying cells—a hallmark of melanoma tumors.

Once the antibodies latch onto melanin particles, their radioactive cargoes irradiate and destroy melanoma tumor cells nearby. The radiation doesn’t affect healthy, melanin-containing cells in the skin, eyes or elsewhere in the body, since melanin in these cells is tucked away in tiny compartments within the cell and therefore inaccessible to the melanin-binding antibodies.

The findings show how basic research in one area of medicine can yield unexpected benefits for an entirely different field.

“We certainly didn’t set out to find a cure for melanoma,” says Dr. Arturo Casadevall, chief of the Division of Infectious Diseases and the Selma and Dr. Jacques Mitrani Professor of Biomedical Research at Einstein. Instead, the advance emerged from his research on *Cryptococcus*, a fungus that can cause fatal infections in people with weakened immune systems.



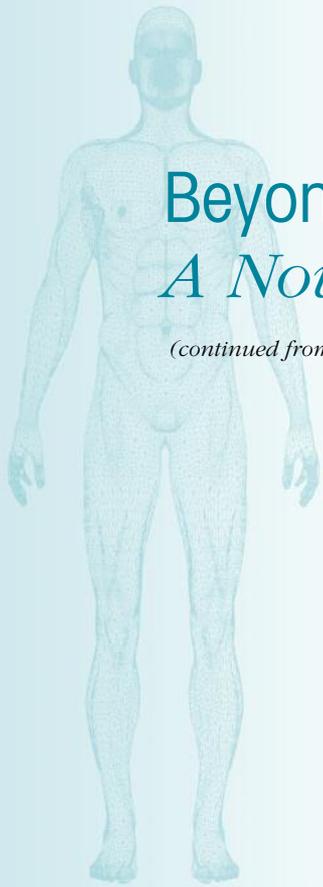
Previous studies had shown that disease-causing *Cryptococcus* strains produce melanin when grown in the laboratory. So Dr. Casadevall made antibodies to melanin to find out whether these *Cryptococcus* strains made melanin during actual infections. The antibodies revealed melanin’s presence in the tissues of infected animals, suggesting that *Cryptococcus* may owe its virulence to melanin production.

“Fungal melanin and human melanin are very similar,” says Dr. Casadevall. “After discussing my *Cryptococcus* findings with other faculty at Einstein’s Cancer Center, I realized how interesting it would be to learn whether our antibody would also bind to human melanin, and it did,” Dr. Casadevall recalls. “Aggressive melanoma tumors release copious amounts of melanin, so we knew that our melanin antibody might help against melanoma if we could somehow combine it with a therapeutic agent.”

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Beyond Skin Deep: *A Novel Strategy Against Melanoma*

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The solution—piggybacking a radioisotope onto the antibody—was suggested by Dr. Casadevall's colleague, Dr. Ekaterina Dadachova, assistant professor of nuclear medicine. Using seed money provided by the Cancer Center, Drs. Casadevall and Dadachova conducted a pilot project to test the therapy's effectiveness. The researchers first injected human melanoma cells into mice, creating melanoma tumors in the animals. Then they linked the antibody to the isotope ¹⁸⁸Rhenium and administered it intravenously to half the mice, with the remaining ones serving as untreated controls. Over the next 30 days, no deaths occurred among the treated mice, whose tumors had not grown since the day the therapy was given; by contrast, melanoma tumors grew aggressively in the control mice, all but one of which had died after 20 days.

"This type of treatment, called radioimmunotherapy, was recently approved for use against non-Hodgkins lymphoma, a cancer of lymph tissue that is quite sensitive to radiation," says Dr. Dadachova. "But solid tumors such as melanomas are much more resistant to radiation and to all other

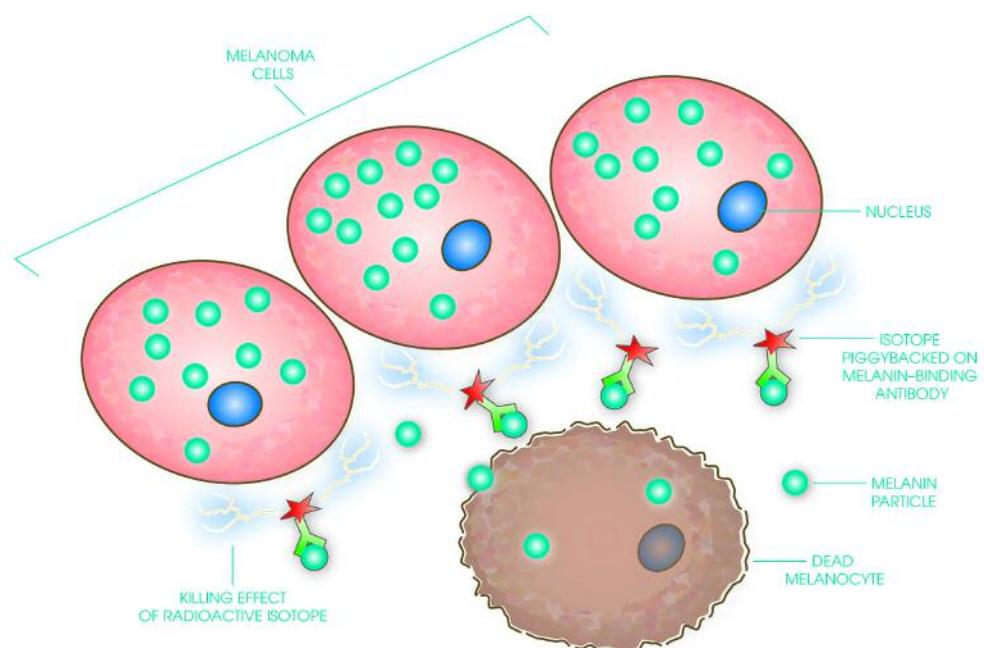
anti-cancer treatments, so our success in this study is especially gratifying."

Dr. Casadevall notes that the antibody-isotope therapy may be particularly effective against the most aggressive cases of melanoma.

"The more aggressive the tumor, the more melanin it will likely release, increasing the number of targets for the antibody," he says. "Furthermore, melanin released from tumor cells doesn't get degraded, so the therapy's effectiveness may actually increase with increasing numbers of treatment cycles as the melanin from dying tumor cells accumulates in the tissue. This is the opposite of what often occurs in cancer chemotherapy, where tumors usually develop resistance to the treatment."

The medical college has licensed the anti-melanoma technology to a pharmaceutical company, and a trial to evaluate its effectiveness in melanoma patients is scheduled to start at the end of this year.

"If our strategy is successful," says Dr. Casadevall, "it would offer a brand-new option against melanoma, a cancer for which there is essentially no treatment right now." ■



Specialized skin cells called melanocytes produce melanin particles, which protect the skin from ultraviolet light. Melanoma tumors form when melanocytes multiply uncontrollably. Within the rapidly forming melanoma, many melanocytes die off and release their melanin particles. Isotopes piggybacked onto melanin-binding antibodies are injected into the patient's bloodstream and latch onto melanin particles that are released by dead melanocytes. The isotopes emit radiation that kills off nearby melanoma tumor cells. Further treatments should make this therapy even more effective: As increasing numbers of melanoma cells are killed, more melanin targets are created for the antibody/isotope to latch onto.