Interviews

In this issue, we bring forward four thoughtful interviews with key leaders, educators, and researchers in dermatology. First, David Fisher, Harvard Medical School, Boston, Massachusetts, USA, speaks on understanding how UV exposure, pigmentation, and the immune system drive cancer treatment. Next, Warren Heymann, Director, American Board of Dermatology (ABD), highlights how great dermatologists are not defined by knowledge alone, but by curiosity, empathy, and genuine care for their patients. Then, Paul Bigliardi, University of Minnesota, Minneapolis, USA, explains how dermatology outcomes also depend on recognizing drug allergies and signals that the skin reveals. Finally, Christopher Tomassian, The Dermatology Collective, Glendora, California, USA, sheds a light on how building a successful dermatology practice today means pairing strong business fundamentals with ethical, evidence-based care.

Featuring: David Fisher, Warren Heymann, Paul Bigliardiand, and Christopher Tomassian

David Fisher

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Q1 The discovery that UV exposure can trigger an endorphin response in the skin suggests a biological basis for sun-seeking behavior. What does this reveal about the evolutionary role of UV exposure, and how might this knowledge be leveraged for a new approach to skin cancer prevention?

The discovery that UV, when it hits our skin, not only induces things we've known about for a long time, like DNA damage, mutations, and the ability to induce melanin synthesis, the so-called tanning response, but also simultaneously triggers the production of endorphin, is relatively new. It was discovered and reported just over 10 years ago, and it turns out that this response, the molecular activation of endorphin synthesis, is linked molecularly to the very pathway that triggers melanin production. You cannot induce melanin, the tanning response, without making endorphin; it is part of a common precursor that involves both of these. So it is organically linked, embedded in our genomes, and it is part of evolution over presumably countless millennia.

> **UV is triggering the body's opiate-like response, producing measurable behavioral effects**

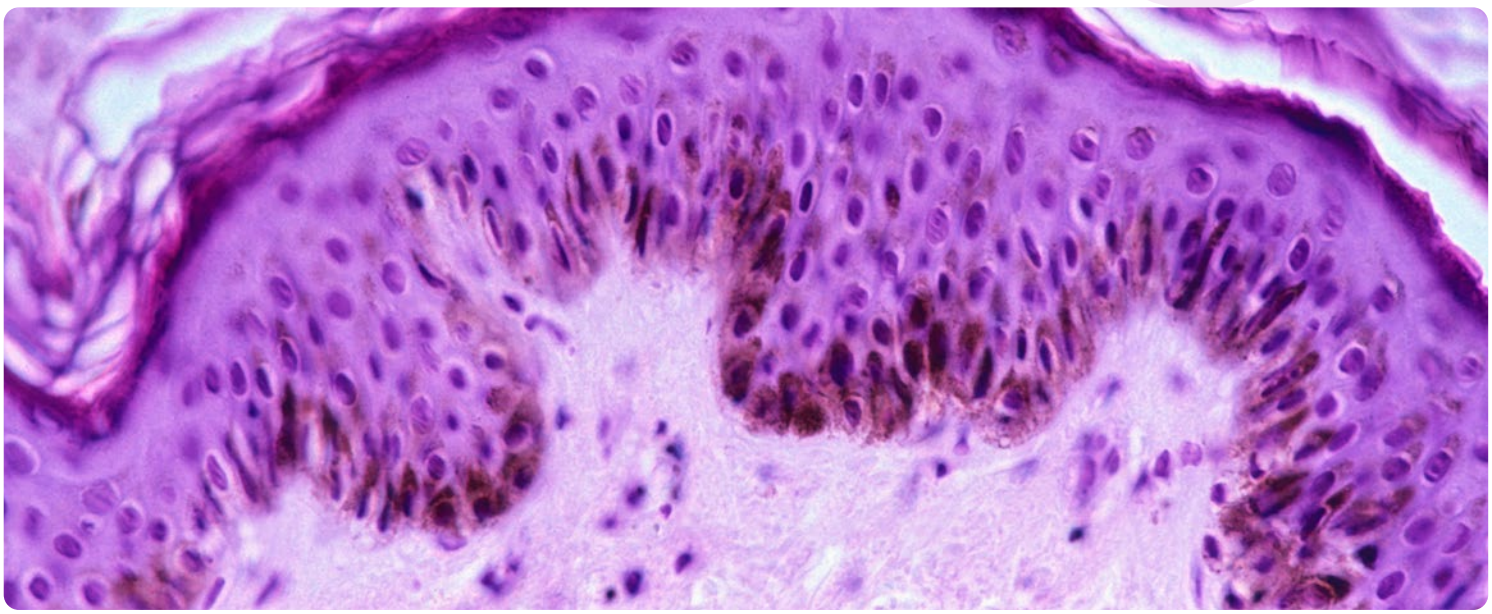
There is something extraordinarily counterintuitive about this; UV is triggering the body's opiate-like response, producing measurable behavioral effects. This has been observed in mice and identified in humans as well. There isn't a more powerful type of behavioral response than opiate responses, which can even have addictive-like consequences. But here, we see a behavioral inclination to seek UV, the most common carcinogen in our environment. How could we possibly have evolved to expose ourselves to one of the most dangerous environmental factors associated with the most common cancers in humans, skin cancers? It feels absolutely backwards.

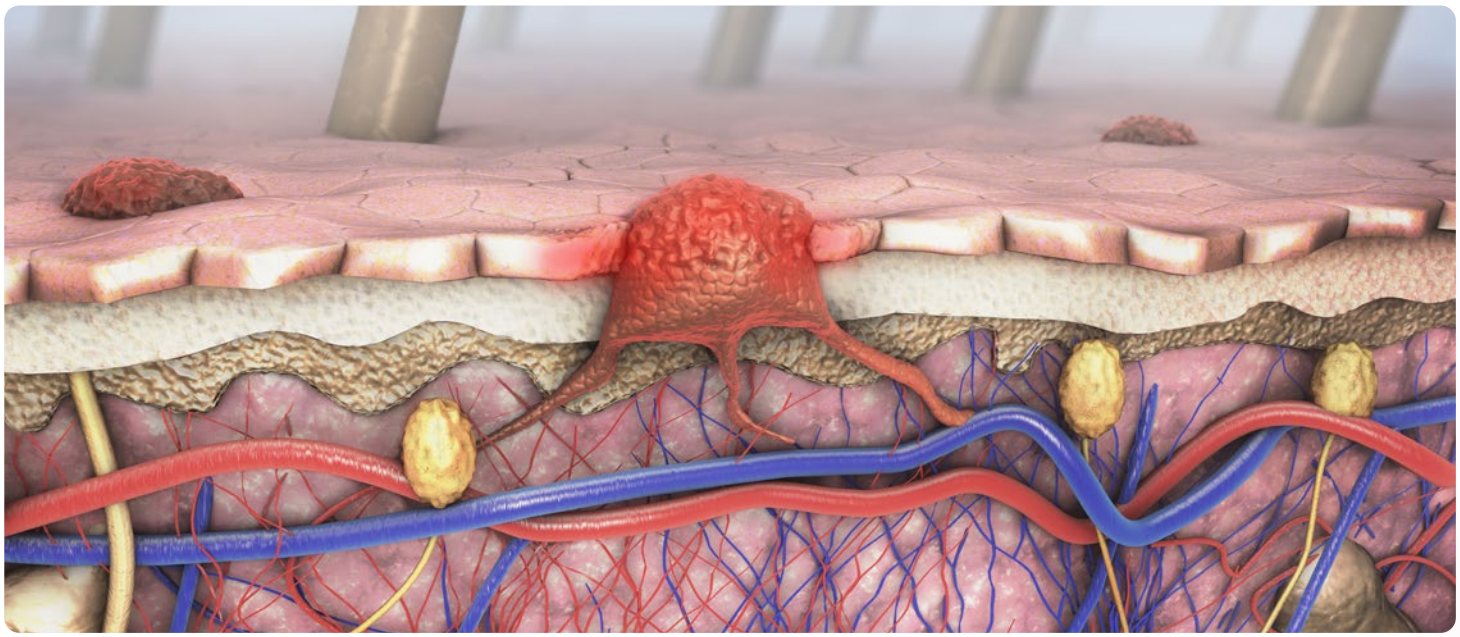
When something is so counterintuitive, an evolutionary perspective suggests it has to be true. There must be some beneficial effect that would have been selected for evolution, despite the fact that UV is so damaging to our skin and heavily implicated in skin cancer risk. Research explored this and found that UV participates in the synthesis of vitamin D in our skin. There is one carbon–carbon bond in the precursors to vitamin D that the human body, and indeed the entire animal kingdom, cannot cleave with an enzyme, but it must be cleaved to produce vitamin D; UV does this.

In evolutionary terms, if you lived in low-light regions, like Scandinavia, you risked vitamin D deficiency, which could be fatal in childhood, causing rickets. Anything that enhanced the ability of light to produce vitamin D could have conferred an evolutionary advantage. This likely contributed to the evolution of lighter skin in high-latitude populations, and endorphin-mediated sun-seeking behavior may have reinforced this adaptation.

Interestingly, studies, mostly in animals, showed that vitamin D levels feedback on endorphin responses. Vitamin D-deficient animals experience stronger euphoria from endorphins, whereas animals with normal vitamin D levels do not. This forms a self-correcting loop that would have helped sustain behaviors ensuring sufficient vitamin D intake over evolutionary time.

The modern challenge is that this pathway still exists, but we no longer need UV to maintain vitamin D levels, we can get it safely from inexpensive supplements. Yet the behavioral response to sunlight remains, which continues to drive skin cancer risk. This is why, despite public health campaigns and sunscreen use, skin cancer incidence remains high.





Q2 Red hair and fair skin pigmentation are known risk factors for skin cancer. What specific molecular mechanisms, identified through your research, are responsible for this increased risk, and how can that knowledge lead to more targeted preventative measures?

There have been some very important developments in our understanding of why it is that light-skinned individuals and red-haired people are at higher risk. Red hair is one extreme example, but for light-skinned people like myself, even though my hair is not red, my skin is probably closer to a red-haired person than a darkly pigmented person. That turns out to be very important in terms of the risk of melanoma formation.

There was a study from my lab about 15 years ago that generated a lot of press. It was a disruptive observation made in the laboratory using mouse models of redheads. This was a mouse model where the exact same gene associated with the red hair phenotype in humans was engineered into mice and used as a background for studying melanoma risk. In this experiment, one of the oncogenes associated with the formation of nevi, benign moles, was crossed into the red-haired mouse background. The plan was to use UV to add additional mutations and then, if these mice developed melanomas, try to discover what those other mutations were and how melanoma gets caused on a light-skinned genetic background in a mouse model.

However, something unexpected happened. When this common oncogene, BRAF V600E, present in about two-thirds of moles, was combined with a red-haired mouse background, about half of the mice spontaneously developed melanomas over the course of 6–12 months, which is half to a full lifespan in mice, even without UV. Genetically black mice did not show this effect. This observation suggested that red-blonde pigment, called pheomelanin, has a unique chemical activity that is weakly carcinogenic. Even in the absence of UV, it produces reactive oxygen species that constantly mutate DNA in the skin.

People with red hair have an elevated risk of melanoma, which is well known, and this risk is evident even in skin that is not sun-exposed, consistent with the idea that pheomelanin itself contributes to mutations. Interestingly, albino individuals and mice that produce no pigment have a dramatically lower risk of melanoma, although they have a much higher risk of non-melanoma skin cancers, highlighting the unique role of pheomelanin.

From a prevention perspective, it is important to be careful with sun exposure. UV interacts not only with DNA but also with red-blonde pigment, amplifying reactive oxygen damage. Sun protection, clothing, and sunscreen are key.

However, traditional sunscreens, calibrated to prevent sunburn, may not provide optimal melanoma protection. SPF measures UVB

protection, which prevents burning. UVB protection is unequivocally of great importance. However UVA, which contributes to oxidative damage and photoaging, is less well filtered by most chemical sunscreen ingredients. Improving UVA protection and understanding the chemistry of pheomelanin–UV interactions is essential for more effective melanoma prevention.

Q3 Looking toward the future of melanoma therapy, what are the key milestones that you believe must be achieved to fundamentally transform how we treat the disease?

It ought to be preventable. We're not there yet in terms of prevention, and hopefully that will be coming, but for patients who have melanoma, the traditional therapy for early melanoma is surgery. You remove it, and hopefully it will never come back. Unfortunately, sometimes it does because it's a very invasive tumor, and even melanomas just thicker than 1 millimeter have, unfortunately, a significant risk of invading and metastasizing.

The treatment for metastatic melanoma has dramatically improved in recent years, and the most important component in our armamentarium has been the ability to harness the immune system through a class of drugs known as immune checkpoint inhibitors. These are antibodies that, without going into too much mechanistic detail, activate the immune system and allow it to attack the melanoma cells and kill them.

The idea of harnessing the immune system to kill melanoma cells is over a century old, and unfortunately, did not work for most of that century. There was a breakthrough back in the 1990s and 2000s when a very specific set of molecular pathways were discovered that function as checkpoints to prevent the immune system from killing our own cells. When those checkpoints could be blocked to allow the immune system to attack the cancer cells, because cancer is our own cells, it liberated the ability of the immune system to attack melanoma cells. Between a third and a half of patients with metastatic melanoma produce major, durable remissions or complete remissions. This is a huge breakthrough. It was science-driven, based on understanding the pathways that regulate the immune system.

Why was it melanoma that benefited first? Probably because melanoma is one of the cancers with the most mutations in its genome. It has an enormous density of mutations. These mutations come largely from UV, from sunlight, because melanoma is a cancer that develops in the skin from cells exposed throughout life to UV. It turns out that when a melanoma harboring many of these mutations sets up shop wherever it metastasizes, it expresses slightly mutated genes due to these frequent UV mutations. The immune system, if lucky, may recognize some of these mutations as though they're foreign. It never saw them before.

Our immune systems are educated to avoid attacking our own cells, but these mutations produce what we call neoantigens, or UV-derived neoantigens, which are not part of our normal genome, but are clonally amplified as the tumor grows from one original cell. The immune system can look at these and say: "I never saw this before." On the other hand, if it were that simple, melanoma wouldn't exist. As soon as melanomas grew, the immune system would kill them, and we wouldn't even see them. But until recently, when these immune checkpoint inhibitors were developed, melanoma still grew and killed people.

The reason the immune system was stopped is that the tumor would fight back by telling the immune system: "I'm one of you, I'm self, you can't kill me." This is part of the tolerance mechanism. The checkpoints activated by the tumor to the immune system prevented these tumor cells from being attacked. When drugs were developed to block that tolerance mechanism, the immune system was liberated to attack and destroy the tumor. This works in about a third to half of melanoma patients. There can be simultaneous autoimmune side effects involving immune attack of separate healthy cells, in some people, as you might expect, but frequently this can be managed safely.

There is good news and frustration. The good news is that a significant fraction of patients with metastatic melanoma are cured, who otherwise would have had almost no chance of surviving for long. Even better, in recent years, these same treatments have been moved to earlier stages of the disease, such as thicker cutaneous melanomas or those spread to local lymph nodes, like under the arm or neck. These patients have a statistical risk of around 25–50% of relapse. Using immune checkpoint inhibitors in these high-risk patients shows about a 50%

reduction in relapse. This is even better because there are more patients with earlier melanoma than late melanoma. These discoveries improved outcomes by applying a rational, mechanism-based therapy first in advanced disease, and now in earlier stages.

Where does this leave us? What do we still need to overcome? The other 50% of patients who do not respond are very important. Why are they not responding? In some cases, the density of UV mutations in the tumors is not as high, so they do not make as many neoantigens, and the immune system does not recognize them as foreign. This is a problem for most human cancers, such as breast, lung, colon, etc., which generally do not respond as well to immune checkpoint inhibitors. Researchers are exploring ways to artificially inflame tumors to trick the immune system into attacking them.

For earlier melanoma, another challenge arises: some immune treatments carry rare but serious autoimmune side effects. If you have a population where 25% are at risk of relapse, offering immunotherapy reduces that risk but exposes the other 75% to potential harm. This creates a dilemma because the principle 'do no harm' applies. We need biomarkers to predict which patients are most likely to benefit, so the therapy is targeted.

Another area is targeted therapies, or drugs that go after specific mutated oncogenes driving melanoma growth. Some have impressive activity, but tumors often develop resistance. Understanding and overcoming these resistance mechanisms is crucial to make responses more durable.

Q4 Your work on giant congenital nevi involves modeling this condition in mice and developing potential topical drug treatments. Could you discuss the process of translating a laboratory finding into a viable clinical approach for a childhood condition?

Giant congenital nevi are among the most common causes of pediatric melanoma, which is a relatively uncommon but devastating disease. You can imagine a child with melanoma, and unfortunately, these are melanomas that do not arise as much from UV, and therefore do not tend to have a good response to immune checkpoint inhibitors.

Removing congenital giant nevi or diagnosing melanomas and removing them very early would, of course, be the preferred approach. The problem with congenital giant nevi is that when a baby is born with these large moles over much of their body, they are very difficult to remove surgically. If you remove them surgically, you are essentially converting a giant mole into a giant scar, which will be a debility for the rest of their lives. Parents are put in an absolutely anguishing position of whether to leave it or watch very carefully, but even if they watch, the child grows up with a somewhat disfiguring, psychologically challenging condition to live with.

We wanted to study this because the oncogenes causing the growth of those nevus cells in giant congenital nevi are known in most cases, and we were able to genetically engineer models in animals. Several other research groups have been able to do this as well, creating mice born with giant congenital nevi driven by the exact same oncogene. We were able to test whether there were any drugs that might trigger regression of these lesions, avoiding the need for surgery and potentially reducing the risk of melanoma developing later.

Several years ago, we reported a study in which we used a form of immune therapy to inflame the skin and topically administer treatment to trigger infiltration by macrophages, which would gobble up and kill the nevus cells. The skin would lose hyperpigmentation after recovery. These treated mice had no melanoma formation in the treated areas, whereas untreated areas still developed melanoma, making this almost like a controlled study. It was a promising approach to developing a drug treatment.

This has not yet been studied in humans for one reason: it is highly irritating to the skin. It is a pro-inflammatory, immune-based therapy, and very itchy and annoying, although temporary. We have been deliberating whether to start treating now or try to ameliorate the itch and toxicity without losing efficacy. The risk of melanoma is significantly elevated compared to a normal child, but still only about 10%, meaning there is a 90% chance of not having melanoma. This allows time to explore anti-inflammatory approaches, adjusting dose or schedule, to make the treatment better tolerated for children, parents, and doctors.

Other groups have been testing oral drugs that do not regress lesions much but may reduce some spontaneous symptoms. The long-term effect on melanoma risk remains unclear. Fortunately, multiple research groups worldwide are working on this problem.

Although relatively uncommon, giant congenital nevi affect many children globally, and a better therapy would be a significant improvement.

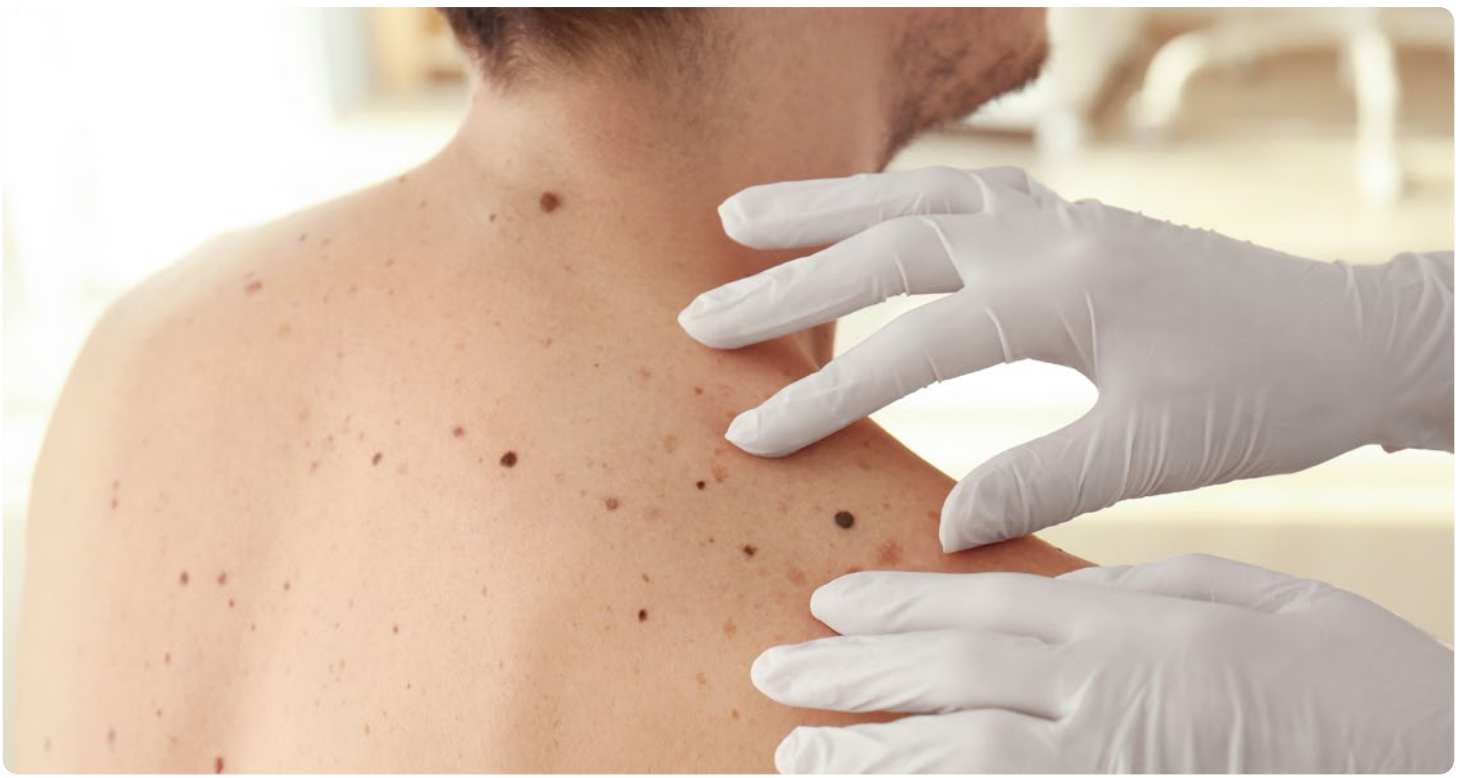
Q5 Your research has identified a direct link between the cell death pathways involved in hair graying and those that control melanocyte survival. Could you explain this intriguing connection and its therapeutic implications for both hair pigmentation and melanoma?

We have been very interested in why your hair turns gray, not just because we know it is inevitable, but actually because the melanocyte, the pigment cell, which is the origin of melanoma, is a very difficult cell to kill.

If you think about it, we spend our lives under the sun, bombarded by UV. These cells accumulate mutations, but they don't die. If they died, UV would cause our skin and hair to turn white just from radiation. But melanocytes survive, somehow fending off the cell death response to all that DNA damage. There are unique survival behaviors, and we have known for many years that traditional chemotherapy drugs don't work in melanoma, as it grows right through cytotoxic chemotherapy drugs.

About 20 years ago, I became interested in understanding why melanocytes die in our hair follicles as part of the normal cycle. Hair follicles go through cycles of growth, regression, and rest. During the regression phase, melanocytes and keratinocytes undergo apoptosis or cell suicide. Keratinocytes make the hair fiber, and melanocytes make the melanin that colors the hair. At the end of each follicle cycle, which can last a few months to a few years, these cells die, and stem cells for keratinocytes and melanocytes are reawakened to form a new follicle. After growth, during which the hair is pigmented, the cells involute and die, and the cycle continues.

I wondered if understanding the efficient death of melanocytes in hair follicles could provide clues for treating melanoma. We started using hair graying as a model, where pigment cells die prematurely or stop producing pigment. In the early 2000s, the cause of hair graying was unclear. It turned out that melanocyte stem cells in the hair follicle were dying prematurely. Each hair follicle has a finite number of maybe 10–20 melanocyte stem cells. By age 20, there are fewer than at birth, and by 40 or 50, almost none remain. When there are no melanocyte stem cells in a follicle, the hair produced has no pigment and appears white. The follicle cycles are asynchronous, which is why hair looks gray first and then white over time.



More recently, in collaboration with Ya-Chieh Hsu, a stem cell biologist at Harvard University, we discovered that stress accelerates the death of melanocyte stem cells in hair follicles. This confirmed the old wives' tale that stress can turn your hair gray. In mice, various forms of stress, from social isolation to painful injections, caused subsequent hair cycles to grow hairs lacking pigment. The mechanism involves the sympathetic nervous system, which has nerve endings in the stem cell compartment of the hair follicle. It releases a neurotransmitter that causes melanocyte stem cells to differentiate prematurely, produce inappropriate melanin, and eventually die. Blocking this neurotransmitter protected against stress-associated hair graying in mice.

What does this tell us about melanoma treatment? We are not quite there yet. It shows that previously unrecognized pathways regulate life and death decisions in melanocytes. Perhaps analogous approaches could target hyper-differentiated melanoma cells to induce their demise, but this remains an open question for future research.