DR CLIVE STANWAY, CHIEF SCIENTIST AT CANCER RESEARCH UK'S DEVELOPMENT AND COMMERCIALISATION ARM CANCER RESEARCH TECHNOLOGY, LOOKS AT THE LATEST IN MELANOMA RESEARCH

EDITED BY JENNY HONE/CLAIRE BOWIE

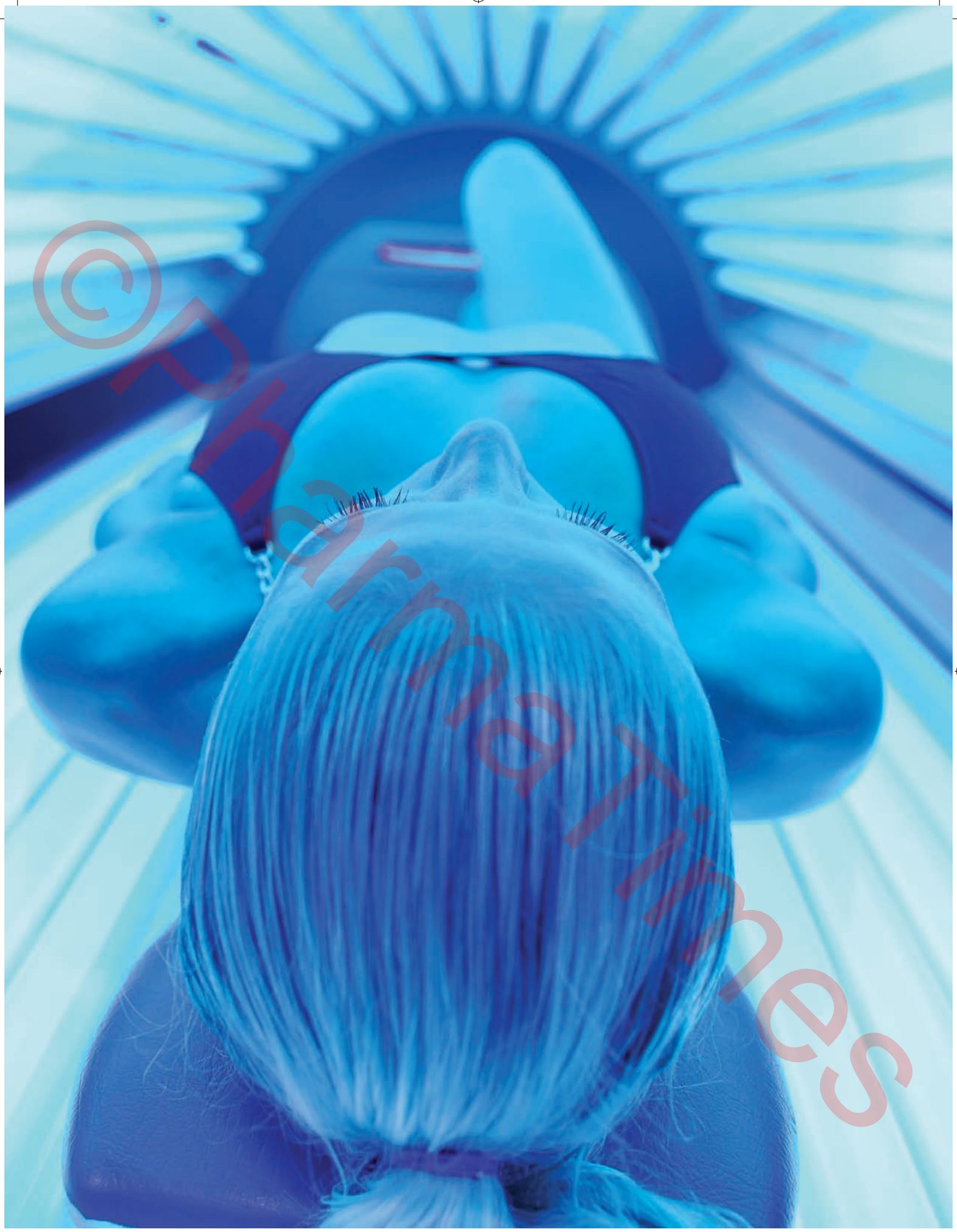
GETTING UNDER THE SKIN OF IT

Malignant melanoma is one of the fastest rising cancers in both the UK and the USA and is also by far the most deadly type of skin cancer. Although malignant melanoma accounts for a small proportion of skin cancer cases it is responsible for the majority of skin cancer deaths.

Fortunately, however survival rates have improved in recent years largely thanks to the considerable interest within the drug development community to tackle this disease. But as the threat of this disease is increasing, it is still crucial that better treatments are made available.

Malignant melanoma develops from the pigment producing cells of the skin, known as melanocytes, which have grown out of control. The most common cause is genetic damage to the skin, which is frequently caused by UV exposure. There are also inherited forms of the disease, caused by mutations in various genes including the tumour suppressor p16.

If detected early enough surgery can lead to long term survival, and even cure. However, if the disease has spread then a patient's chances of survival are much worse. Melanoma most frequently metastasises to the liver, lung, brain, gastrointestinal tract and bone, and once established at these sites treatment options for patients become very limited. It is for these patients that new and better treatments are badly needed. ›



Malignant melanoma is now the fifth most common cancer in the UK and numbers are rising. More than 13,000 people develop the disease in the UK every year, compared with around 1,800 in 1975, and more than 75,000 are expected to be diagnosed in the USA this year.

More worryingly, the increase in incidence is accelerating. In the UK, 17 in every 100,000 people are being diagnosed with the disease every year compared with just over three per 100,000 in the mid 70s.

This dramatic rise is partly down to an explosion in package holidays dating from the late 60s and the increasing popularity of the "must-have" tan often achieved only after a damaging sunburn. Then, of course, there was the boom in sunbed use which has also helped fuel the increase in skin cancer.

Research into melanoma has made many important advances at both a genetic and pharmacological level which have greatly improved survival. A major step forward came when an early genome sequencing project, co-funded by the Wellcome Trust and Cancer Research UK, identified a high frequency alteration in the BRAF protein, which is found in approximately 60% of melanomas.

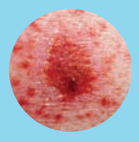
A flurry of interest

Discovering this mutation sparked a flurry of pharmaceutical interest and has resulted in several potent selective inhibitors of the mutated form of BRAF, of which the first to be approved by the US Food and Drug Administration was vemurafenib.

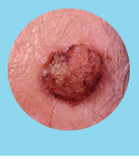
Initially, many patients responding to vemurafenib show complete sustained responses to the drug but, unfortunately, virtually all of these patients subsequently relapse within six to 12 months.

Spot the difference

There are three main types of skin cancer. Melanoma is the least common form but the most serious. The others are:



Basal cell carcinoma – a cancer of the basal cells at the bottom of the epidermis, which accounts for 75% of all skin cancers in the UK. These are slow-growing cancers that often start as a small, red, shiny spot or nodule that may bleed occasionally but almost never spread to other parts of the body.



Squamous cell carcinoma – a cancer of the keratinocytes found at the outermost layer of the skin, which accounts for about 20% of all skin cancers. Usually these cancers are slow-growing and only spread to other parts of the body if left untreated for a long time.

Moles online

- EMA advisors back GSK melanoma drug Mekinist *bit.ly/1j3tz9G*
- GSK pulls melanoma combo file in Europe *bit.ly/1kXRWtC*
- Amgen vaccine T-Vec shines again in melanoma trial *bit.ly/1fV4eV1*
- NICE says no to first-line Yervoy in advanced melanoma *bit.ly/1jerWeq*
- GSK gets US green light for melanoma combo *bit.ly/1dlTGk3*

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A patient perspective: melanoma, trials and drugs

By Imogen Cheese

Getting a melanoma diagnosis is like a thunderbolt. The uncertainty of what it is you have been diagnosed with, the growing realisation, then panic.

For me the rollercoaster of emotions only began a year ago. I was diagnosed with stage 2C melanoma. It was bad – 4.7mm, ulcerated and with a mitotic rate of 10. So bad that I should worry.

I naturally assumed there would be treatments, drugs... something? None were available on the NHS; I was told to wait until the cancer progressed.

The severity of the diagnosis meant I was eligible for a clinical trial for Zelboraf (vemurafenib), a first-line treatment. I began two months of a battery of tests but unfortunately failed to meet the incredibly strict criteria.

My hopes were dashed. I was so willing to be on a trial – any trial, drug or placebo, because a trial gives hope. You get more than the standard three-monthly visual "glance overs" that so many melanoma patients seem to get.

I was rejected because there was too high a likelihood that the drug would cause other cancers. I didn't care – they were treatable; melanoma isn't.

There are very few drugs available and progression-free survival for many treatments is as short as four months. Not enough new solutions are coming to the table, yet there are an ever-increasing number of desperate test subjects.

Pharmaceutical companies need patients as much as patients need the drugs. The process needs to become more open, and tailored to the patient as much as to the pharma company, with more frank and open communication. This can only be of benefit to both sides.

We need more trials, we need more hope. This is the only way to save our lives.

@MelanomaBlog **www.melanomarollercoaster.co.uk**

You can find and connect with other melanoma patients like Imogen on HealthUnlocked

Nevertheless, its development brought new hope for melanoma patients when treatment options had been stagnant for decades. Prior to this, the standard of care had been dacarbazine and interferon, which was ineffective for many patients, quite toxic and offered no real survival benefit.

Vemurafenib and other BRAF inhibitors are currently in clinical development in combination with various other agents – most notably with drugs targeting the enzyme MEK – in the hope that the resulting therapy will produce more durable responses.

But its a second research front that has shown even greater benefit and promise, namely modulation of the immune system – or immunotherapy. The pathfinder drug here is ipilimumab, which alters T cell sensitivity over time. It has often been seen as a mystery why the immune system is largely unable to eradicate cancer as we know that tumour cells contain elements of 'non-self', the primary target of the immune system. But basic research, such as that funded by Cancer Research UK, has been uncovering many factors that control the immune system, including T and B cells, and it has become apparent that cancer frequently subverts these regulatory mechanisms to avoid detection.

Ipilimumab modulates the activity of one of these factors (CTLA-4) and has demonstrated significant clinical benefit in the treatment of metastatic melanoma with 15%-20% of patients showing a >

Spot on?

- Melanoma is the least common form of skin cancer but the most serious
- There are around 13,300 new cases each year in the UK, with more than 2,000 deaths
- The number of cases has doubled over 20 years and the number of people diagnosed with malignant melanoma is five times higher than it was 40 years ago
- Melanoma is the fifth most common cancer in the UK. It is also the 19th most common cancer worldwide, with rates highest in Australia and New Zealand
- The majority of malignant melanomas are caused by heavy sun-exposure in white-skinned populations
- Sunbed use is estimated to cause around 100 deaths a year from malignant melanoma in the UK
- Nine out of 10 sunbeds in the UK emit levels of radiation above recommended safety standards
- Melanomas can occur anywhere on your body, but the back, legs, arms and face are the most common locations
- Melanoma and skin cancer is the fourth most talked about cancer in public social media by UK-based healthcare professionals, with 26% of mentions occurring during the summer months of July and August 2013, according to a study by Creation Healthcare

To sunbathe or not to sunbathe?

By Katrina Megget

Staying out of the sun might make sense from a skin cancer perspective but a life behind closed doors isn't an option either because vitamin D – the sunshine vitamin – is needed for both skeletal growth and bone health. Indeed, a lack of the sun's rays has been linked to a weakened immune system and diseases such as migraines, obesity, osteoporosis and coronary artery disease, not to mention depression and the well-documented seasonal affective disorder during the winter months. More than half of British adults have insufficient levels of vitamin D, while several hundred cases of rickets in children – resulting from vitamin D deficiency – could be prevented, research suggests.

In a nutshell, up to 90% of the Vitamin D we need comes from the sun's rays, with the rest from our diet, including milk, eggs and oily fish. But diet and supplements alone are not an alternative to sunshine.

So where do you draw the line when it comes to getting enough sunshine? While the amount of sun time required will differ between people and time of year, scientists cited by NHS Choices believe 10-15 minutes of exposure between 11am and 3pm during the summer months should be enough. The catch is no sunscreen allowed – this is better for vitamin D production, the scientists say. However, they add, this is less than the time it takes to start going red or burn, which is the risk factor for skin cancer, though the higher the UV forecast the more pertinent it is to slop on the cream.

So pop out of the office on your lunch break – that quick walk to the deli will top your levels up in no time.

› durable complete response for periods of five to 10 years. This is a sea change in the survival prospects for these individuals and has induced a great deal of excitement and activity in the basic, clinical and pharmaceutical research arenas.

Even more questions

But this advance generates even more questions. What other regulatory factors similar to CTLA-4 may also be amenable to modulation and give clinical benefit? And why do only 15%-20% of patients respond? There is a great deal of effort being given to these and other questions by various organisations including Bristol-Myers Squibb, Merck & Co and Genentech, as well as MD Anderson Cancer Centre and Cancer Research UK.

Excitingly, there are already promising signs that benefits greater than those afforded by ipilimumab will be generated.

Better treatments will play a key role in tackling malignant melanoma, but prevention is also important. We know overexposure to UV rays from the sun or sunbeds is the main cause of malignant melanoma. This means the disease can be prevented in many cases and is why we encourage people to avoid sunburn and enjoy the sun safely. People often risk burning in their attempt to achieve a tan, but sunburn is a clear sign that your DNA has been damaged, and over time this can lead to skin cancer. It is recommended people spend some time in the shade, put on a t-shirt and apply sunscreen with at least SPF15 and good UVA protection when the sun is strong.

By charities, academic institutions and pharmaceutical companies working together we can help prevent melanoma from developing in the first place, but also have the best treatments possible for when it does. ◘

Campaign #GetNaked

By the US-based Melanoma Research Foundation

Budget

Not disclosed – but it is part of a larger programme designed to raise awareness of melanoma and includes collaborations with strategic corporate partners to offset some of the costs.

Impetus behind the campaign

The #GetNaked campaign is an educational and awareness campaign emphasising the importance of detecting melanoma early. "Despite alarming statistics, audiences are not galvanised around melanoma," the MRF says. "It's the deadliest form of skin cancer... [but]... can be survivable when it's caught early." The campaign message is simple: check your skin, know what's normal, and watch for changes.

Marketing concept

Research shows that most melanomas are caught by patients rather than doctors; that's why the major thrust of the messaging promotes self-checks or checks with a partner to evaluate hard-to-see places. To deliver this message to the broadest audience possible, the campaign focuses heavily on promotion through social media channels, with the hashtag #GetNaked.

Objectives

As well as encouraging people to be aware of their skin, to check themselves or loved ones regularly for suspicious or changing spots, and to schedule an appointment with a dermatologist, #GetNaked aims to get people tweeting and posting using MRF content.

Outcomes

To gauge the campaign's impact and reach, visits to the MRF's website (www.melanoma.org), and specifically the #GetNaked and early detection webpages, were measured, as well as social media engagement and exposure. Traffic to www.melanoma.org in the month leading up the campaign's launch on 1 May was the highest ever in the history of the MRF's website, setting a new record on the day with more than double the usual traffic. And on Facebook the number of people talking about MRF more than tripled in the week leading up to the campaign. There was an increase in website visitors ages 18-24, and of those who visited, 80% were there for the first time, meaning the campaign reached a key demographic that hadn't been accessed previously. Overall feedback has been positive and the online community says the campaign has resulted in at-home skin checks and scheduled dermatologist appointments.

Included in the campaign

The year-long campaign employs a range of media channels: hardcopy ads in high-traffic areas in major US markets, traditional media outreach, and a heavy digital media component. The MRF also put together a "soft launch" to build anticipation and prepare core constituents for social media sharing. Social media pushes will continue throughout the year, including #GetNaked and early detection blog posts, and additional digital images and early detection messages will be shared regularly with community members on Facebook, Twitter and Instagram.

Agencies

The MRF partnered with Stan Adler Associates to create provocative imagery containing the overall call to action. JPA Health Communications was brought in to develop campaign messaging, provide strategic promotional planning and to support social media activities and monitoring.