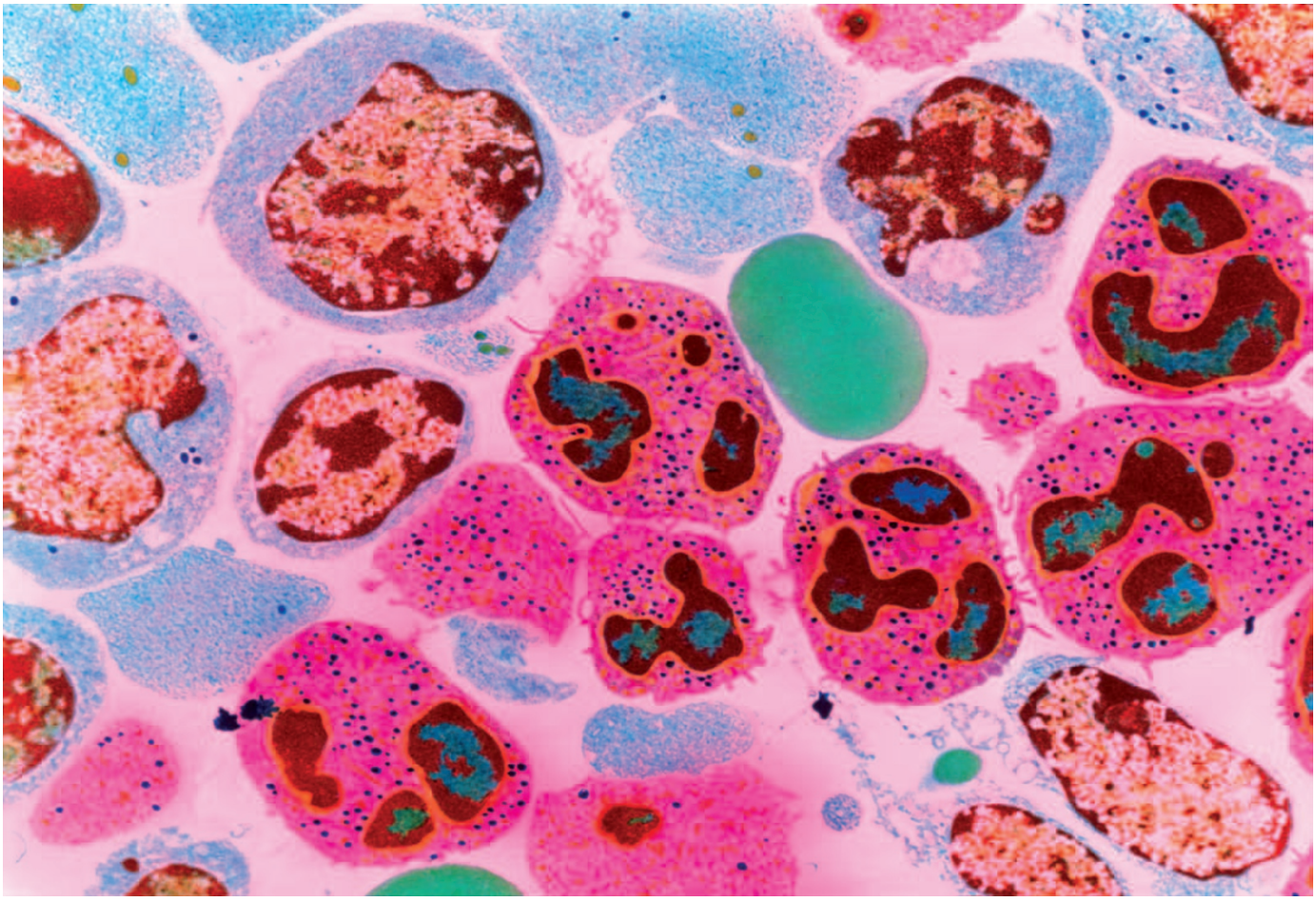

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The origins of cancer: multiple myeloma begins in white blood cells in the bone marrow.

OVERVIEW

Multiple lines of attack

Researchers are developing new weapons to fight a deadly form of blood cancer.

BY DUNCAN GRAHAM-ROWE

Multiple myeloma is a cancer of the blood that is both rare and deadly. Each year in the United States alone there are around 20,000 new cases, and just over half that number die of the disease. But in the past few years, new drugs and the availability of stem-cell therapy seem to have set multiple myeloma on a different course: the survival rate from the disease has increased faster than that of any other form of cancer. For some people, multiple myeloma is changing from an imminent death sentence to a chronic disease that can be managed for many years.

Myelomas are malignant plasma cells. Normally these white blood cells play an important role in the immune system, producing antibodies that help fight off infections and disease. Plasma cells are generated in the bone marrow, and when they become cancerous their unfettered growth creates lesions within the bone. The presence of more than one lesion is known as multiple myeloma.

Once formed, these lesions often crowd out healthy plasma cells, interfering with the production of other types of blood cell as well as those involved in regenerating the bone and keeping it strong. As a result, patients often have low blood counts and develop weak bones that are easily broken. Cancerous plasma cells continue to produce antibodies, but because these immunoglobulin proteins are abnormal and monoclonal (identical copies of each other), they offer no protection against infections. Instead, these so-called M proteins can damage the kidney. The main symptoms of multiple myeloma are often referred to as CRAB, for elevated calcium (caused by the destruction of bone), renal failure, anaemia and bone lesions.

Although it is the second most common form of blood cancer (after the group of diseases lumped together as non-Hodgkins lymphoma), multiple myeloma is still rare. Global incidence ranges from just 1 in 100,000 people in China to 4 in 100,000 in developed countries. The disease is more common among men than women, and is roughly twice as prevalent in African Americans as in Caucasian Americans. But by far the biggest risk factor is age — the vast majority of patients are more than 60 years old, and only 2% are younger than 40.

Until the late 1990s, life expectancy with multiple myeloma using the best available treatments, such as melphalan and prednisone, was just three to four years. But the availability of stem-cell transplants and the introduction of lenalidomide (an analogue of thalidomide marketed as Revlimid by Celgene in Summit, New Jersey) and bortezomib (a proteasome inhibitor branded

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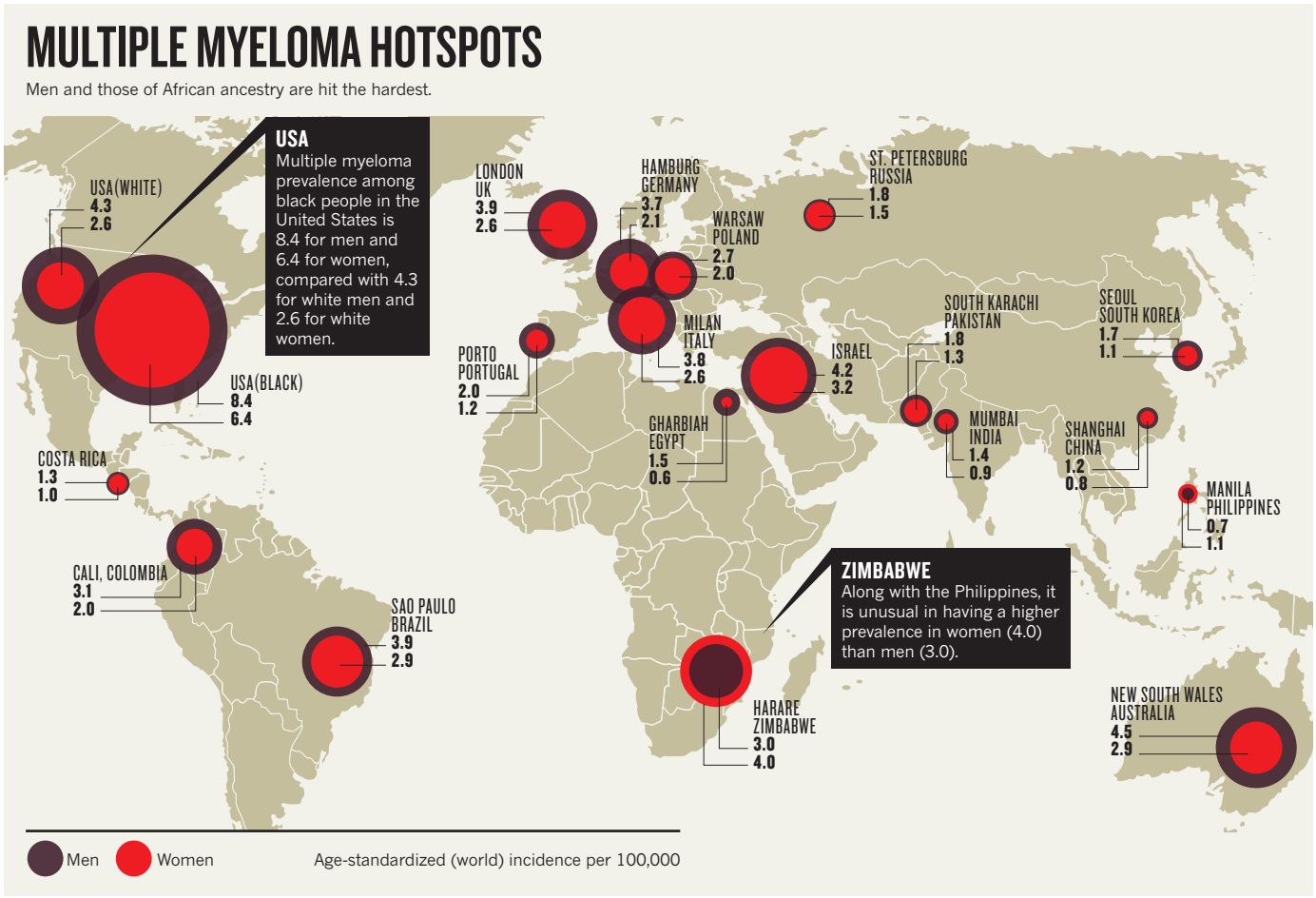

as Velcade by Millennium Pharmaceuticals in Cambridge, Massachusetts) has since doubled life expectancy to 7–8 years. Although the response to these new drugs is positive, studies show that once patients relapse, the cancer becomes resistant to the drugs.

TAILORED TREATMENT

Multiple myeloma follows a predictable progression. It begins as a precursor condition known as monoclonal gammopathy of undetermined significance (MGUS). Characterized by an excess of M proteins, MGUS is not normally harmful to the health — people generally don't even know they have it and exhibit no symptoms of disease. But every year 1% of MGUS patients go on to develop multiple myeloma, and every case of multiple myeloma is thought to have started as MGUS. "Currently there is no good way of identifying which patients with MGUS will develop multiple myeloma," says Louise Perkins, chief scientific officer of the Multiple Myeloma Research Foundation (MMRF) in Norwalk, Connecticut.

What is now known, however, is that specific chromosomal translocations — where parts of one chromosome break off and attach to another — occur in myeloma cells. The sequencing of 38 genomes of multiple myeloma tumours earlier this year[1] led to certain genetic mutations being shown to play a major role in the pathogenesis of myelomas. These mutations alter important genetic pathways, including one known as NF-κB, which controls the transcription of DNA.

The predictive power of genetics is limited, however. There is little overlap in the genetic signatures, says Perkins, and not everyone shares the same translocations. The translocation t(4;14), for example, which when found with other genomic aberrations is an important predictor of survival, occurs in only 15% of patients, she says. Many researchers believe that multiple myeloma is best tackled by 'personalized medicine', a much-touted approach where treatments are tailored to an individual's genetic make-up. A genomic initiative is already underway, spearheaded by the MMRF in partnership with the Broad Institute in Cambridge, Massachusetts, and the Translational Genomics Research Institute in Phoenix, Arizona.

"A fair bit of high-level genetic categorization has been done," says Perkins. But one task still facing researchers, she says, is to find molecular markers that can help predict new therapeutic drugs. A central tissue bank has already been set up, and more than US$12 million has been poured into genetic profiling and 'deep' sequencing research, and to create an open portal as a resource for researchers to use. The hope is that accelerating research into this disease will ultimately lead to personalized treatment — and much better outcomes for patients. ■

HOW FAR ALONG?
Multiple myeloma has three distinct stages.

MGUS	Smouldering myeloma	Symptomatic myeloma
• Serum paraprotein <30 g l^{-1} and • Clonal plasma cells <10% on bone-marrow biopsy and • No myeloma-related organ or tissue impairment.	• Serum paraprotein >30 g l^{-1} and/or • Clonal plasma cells >10% on bone-marrow biopsy and • No myeloma-related organ or tissue impairment.	• Clonal plasma cells >10% on bone-marrow biopsy or (in any quantity) in a biopsy from other tissues • A monoclonal protein (paraprotein) in either serum or urine • Evidence of end-organ damage: hypercalcemia (corrected calcium >2.75 mmol l^{-1}); renal insufficiency; anaemia (haemoglobin <10 g dl^{-1}); bone lesions (lytic lesions or osteoporosis with compression fractures).

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1. Chapman, M. A. *et al. Nature* **471,** 467–472 (2011).