accurate. Adam Frankish, a computational biologist at the EBI who coordinates the manual annotation of GENCODE, says that he and his group have scanned about 100 of the protein-coding genes identified by Salzberg's team. By their assessment, only one of those seems to be a true protein-coding gene. And Pruitt's team looked at about a dozen of the Salzberg group's new protein-coding genes, but didn't find any that would meet RefSeq's criteria.

Salzberg acknowledges that the new genes on his team's list will require validation by his group and others.

Further confounding counting efforts is the imprecise and changing definition of a gene. Biologists used to see genes as sequences that code for proteins, but then it became clear that some non-coding RNA molecules have important roles in cells. Judging which are important — and should be deemed genes — is controversial, and could explain some of the discrepancies between Salzberg's count and others.

Having an accurate tally of all human genes is key for efforts to uncover links between genes and disease. Uncounted genes are often ignored, even if they contain a disease-causing mutation, Salzberg says. But hastily adding genes to the master list can pose risks, too, says Frankish. A gene that turns out to be incorrect can divert geneticists' attention away from the real problem.

Still, the inconsistencies in the number of genes from database to database are problematic for researchers, Pruitt says. "People want one answer," she adds, "but biology is complex." ■

MEDICAL RESEARCH

Silent cancer cells targeted

Researchers hunt dormant cells that break off tumours, and aim to keep them asleep.

BY HEIDI LEDFORD

After decades of designing drugs to kill rapidly dividing tumour cells, many cancer researchers are switching gears: targeting malignant cells that lie silent and scattered around the body, before they give rise to new tumours.

These cells seed the metastases responsible for about 90% of cancer deaths. They are the source of the heartbreaking cancer resurgence seen in many people whose seemingly successful initial treatment had fostered hopes that they were cured. Treatments that target proliferating tumour cells often miss these silent cells because they're not actively dividing.

Dormant cancer cells are rare, and they are difficult to sift from the trillions of normal cells in the body. For years, scientists lacked the tools to study them, says cancer researcher Julio Aguirre-Ghiso of the Icahn School of Medicine at Mount Sinai in New York City. But that is beginning to change.

From 19 to 22 June, researchers will gather in Montreal, Canada, for what Aguirre-Ghiso says is the first meeting dedicated to these sleeper cancer cells. "The mass of investigators has reached a critical number," he says. "And there is the realization that it's an important clinical need."

That demand is particularly acute in cancers — such as those in the breast, prostate and pancreas — that recur at a high rate, sometimes many years after treatment. "You remove the tumour, you irradiate, you do this, you do that," says cancer researcher Mina Bissell, of the Lawrence Berkeley National Laboratory in California. "But sooner or later the cancer metastasizes, and you say to yourself, 'Where did these things come from?'"

CELL SPOTTING

Mounting evidence suggests that dormant cells break away from a parent tumour early in its development and travel through blood vessels to new sites in the body (see *Nature Methods* **15**, 249–252; 2018). But then, after settling into other tissues or organs, such cells will effectively go to sleep, lying dormant until a trigger — as yet unknown — rouses them. Only then do they begin dividing and form a new tumour.

When cancer researchers tried to study this dormancy, they quickly ran into a problem: mouse models of cancer had been designed to generate quick-growing and highly lethal parent, or primary, tumours. Researchers studying dormancy, however, need slow-growing tumours — which have time to shed rogue cancer cells — and the ability to track those cells long after the primary tumour has been removed.

"Those sorts of animals have been very difficult to develop," says Kathy Miller, a breast-cancer specialist at Indiana University in Indianapolis. But several labs have made progress, developing models to track dormant cells in mice for more than a year.

Techniques for identifying those cells are also improving. Joshua Snyder, a cell biologist at Duke University School of Medicine in Durham, North Carolina, uses a mix of fluorescent markers to identify and trace rogue cells expressing cancer-linked genes.

"As long as those cells remain dormant, they're not killing my patient."

And at the meeting in Montreal, geneticist Jason Bielas of the Fred Hutchinson Cancer Research Center in Seattle, Washington, will present preliminary results from his efforts to barcode such cells using specific DNA sequences. The cells can then be identified using cheap DNA-detection methods at a resolution of about one in one billion cells.

IDENTIFYING INHIBITIONS

Once the silent cells are identified, new methods for determining which genes they express could help researchers to pin down the factors that induce dormancy and the triggers that can rouse sleeping cells. With that information, it might be possible to prevent the cells from waking, says Miller. "As long as those cells remain ▶

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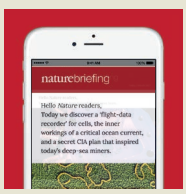

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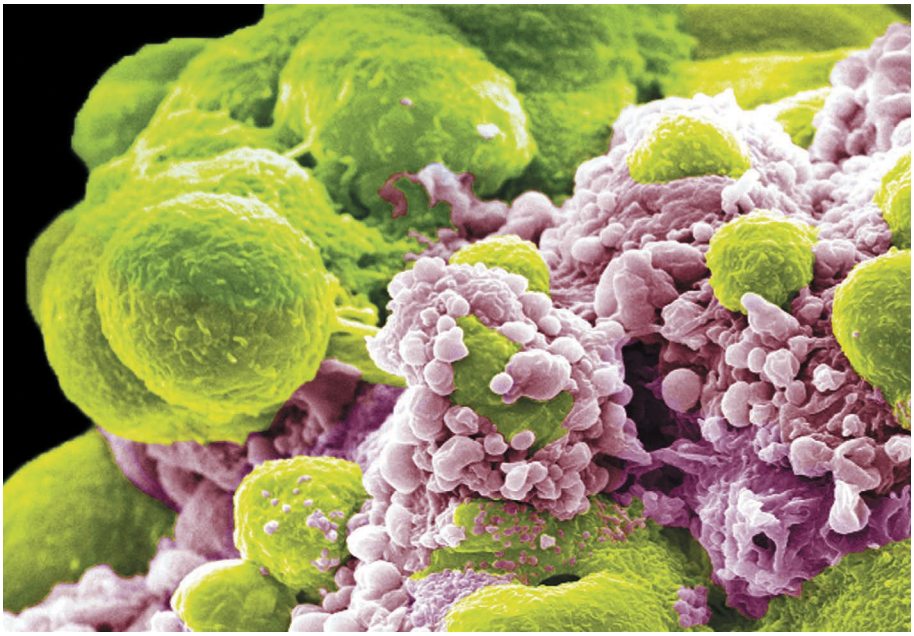

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Cancer cells (green) can splinter off of tumours and settle in other parts of the body.

dormant, they're not killing my patient."

Efforts to keep sleeper cells at bay are also under way. In 2015, Aguirre-Ghiso's laboratory reported that a combination of two approved drugs — 5-azadeoxycytidine and retinoic acid — could induce dormancy in prostate-cancer cells grown in culture, as well as in mice (M. S. Sosa *et al. Nature Commun.* **6**, 6170; 2015). Now, William Oh, an oncologist at Mount Sinai, and his colleagues are enrolling people with prostate cancer in a trial to test these findings in the clinic.

Others are looking at ways to kill the dormant cells outright. Cancer researcher Veronica Calvo-Vidal and her colleagues in Aguirre-Ghiso's lab have collaborated with pharmaceutical firm Eli Lilly of Indianapolis to characterize an inhibitor of a protein called PERK, which is expressed at unusually high levels in dormant cancer cells. Early studies in mice suggest that the inhibitor can kill the cells, and the team is now analysing gene expression in individual dormant cells to learn more about how the molecule works.

But Miller cautions that it is also important to develop ways of identifying which cancers are most likely to recur, so that physicians can select the patients who warrant such treatments. She and other oncologists who treat breast cancer already struggle to decide which patients should receive further hormone therapy to reduce the risk of recurring tumours. "We are moving closer to the day when we are able to do a much better job of identifying recurrence much earlier," she says. ■

CORRECTION

The News Feature 'Here come the waves' (*Nature* **556**, 164–168; 2018) incorrectly described Ilya Mandel as a LIGO theorist. Mandel left the LIGO collaboration in 2016.