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Techniques aim to outwit cancer's evasion tactics

From AI-enabled drug discovery to therapeutic vaccines, science is opening up fresh angles of attack against the disease. **By Michael Eisenstein**

In cancer research, lessons learnt from other diseases are proving invaluable. The success of mRNA-based COVID-19 vaccines has revitalized the pursuit of therapeutic cancer vaccines, and combination therapies are taking inspiration from antiretroviral medicines. Other approaches, such as drug discovery powered by artificial intelligence (AI)and treatments targeting the cancer-causing protein KRAS, are maturing. Here we delve into some of the most promising new techniques in the fight against cancer.

More shots at goal

With three decades of experience in computational chemistry, Gisbert Schneider recalls the previous wave of hype surrounding AI in drug discovery, which ultimately crested and broke in the late 1990s. "We realized as a community that AI promised a tad too much at the time," says Schneider, who heads the computer-assisted drug-design lab at the Swiss Federal Institute of Technology in Zurich, Switzerland.

Excitement is now surging again, but the world has changed. "I think AI is here to stay this time," says Schneider, pointing to tremendous leaps in areas such as deep learning as well as the vast repositories of biological and chemical data now at scientists' disposal to train their AI on. And, unlike the first time around, AI is propelling drugs into clinical testing.

Nimble and well-funded biotechnology companies are at the forefront of efforts to use AI for drug design. Exscientia, based in Oxford, UK, and Relay Therapeutics in Cambridge, Massachusetts, each have two clinical trials under way for cancer therapeutics, and in September 2022, Recursion Pharmaceuticals in Salt Lake City, Utah, launched a phase II trial for a colorectal cancer drug.

Large pharmaceutical companies are also embracing these capabilities. In November, for example, French health-care company Sanofi signed a deal worth up to US$1.2 billion with Hong Kong-based Insilico Medicine to develop drug candidates for multiple diseases using Insilico's proprietary PHARMA.AI platform. A 2021 multi-target drug-discovery deal with Genentech, the California-based subsidiary of Swiss multinational health-care company Roche, could earn up to US$12 billion for Recursion. These companies are also building in-house AI capabilities to help accelerate their R&D, says Insilico founder and co-chief executive, Alex Zhavoronkov.

Schneider sees early-stage discovery as the current sweet spot. AI is a powerful tool for crunching vast amounts of data to identify genes and proteins linked to specific disease states and to home in on chemical compounds that can effectively modulate those targets. Armed with generative models like those used in tools such as ChatGPT or the image-creating software DALL-E, algorithms can conjure up novel chemical architectures for drugs that fall outside existing compound libraries but are still realistic to synthesize. This means more shots at goal, even if the large majority still fail. "The great feat of AI in drug discovery is to spot unsuitable molecules early," says Schneider. "Picking the right one is tricky and will remain tricky."

Tricky does not mean impossible. Zhavoronkov's team at Insilico has built an AI-powered drug-discovery process that aims to produce leads much faster than conventional methods can achieve. The company is preparing to file for clinical testing of its lead cancer drug, an immunotherapeutic that was identified within 40 days. And in January, Insilico reported[1] that it had identified a reasonably potent drug candidate within a month that can inhibit a protein that is potentially involved in liver cancer. Notably, the structure of this target protein was not experimentally defined; instead, the company used the AI structure-prediction tool AlphaFold as a starting point.

If such drugs prevail in trials, this AI-assisted approach to early discovery could yield considerable savings in terms of time and money. But the human component of drug development remains as challenging as ever. "When it comes to predicting clinical outcomes, we're struggling with a low-data situation," says Schneider, noting the complexity of human biology at both the population and individual level. "Without enough detailed training data, it will remain difficult for algorithms to learn to identify patterns associated with the ultimate success of a drug," he says.

Considering how many drug-development

Insilico's Alex Zhavoronkov (left) and Feng Ren in the company's robotics lab, which is central to the hunt for drug candidates.

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programmes fail in efficacy testing, the development of an algorithm that can sniff out which compounds are most likely to be safe and effective in patients could change the game.

Power in numbers

For a select few people with cancer, immunotherapeutic agents known as checkpoint inhibitors can have a transformative effect, causing advanced cancers to recede or even vanish entirely. But more often, these drugs — which counter some of the mechanisms that tumours use to ward off destruction by the patient's immune system — prove insufficient on their own. Accordingly, 28 out of the 34 checkpoint inhibitor therapies approved by the US Food and Drug Administration are combinations with either conventional chemotherapy drugs or secondary immunotherapies that work in tandem with the first drug.

Mathew Garnett, a cancer biologist at the Wellcome-Sanger Institute in Hinxton, UK, says this is now the rule, rather than the exception. "Combinations are the future of oncology," says Garnett, noting that cancer treatment is following a well-trodden path in areas including antiretroviral therapy, in which multiple drugs are required to keep ever-mutating viruses such as HIV at bay.

Similarly, many cancer drugs become less effective over time because the tumour cells develop mutations that give them resistance and activate mechanisms that allow them to grow unimpeded once more. Colorectal tumours with mutations in a protein called BRAF often respond poorly to drugs that target this protein, but in combination with agents that target a second cancer-related protein, EGFR, these drugs can extend median patient survival by more than 50%.

Finding the right combination is difficult. Tumours can evolve multiple ways to evade a given drug, and optimal complementary pairs might not be immediately obvious. Screening experiments that assess the effects of vast numbers of combinations can accelerate this process. Garnett and colleagues demonstrated such an approach in a 2022 study[2] in which they tested 2,025 drug pairs on 125 different breast, colon or pancreatic tumour cell lines. "Synergy was rare," he says, and only 5.2% of the pairs were found to be more effective

than the expected combined effect of each individual drug.

Nevertheless, one pair showed promising results in a mouse model. The study also offered valuable guidance for future searches. "Drugs that engage the control of the cell-death machinery tended to partner really well with other drugs," says Garnett, referring to the 'self-destruct' mechanism known as apoptosis, used to eliminate damaged or unwanted cells. However, the optimal pairs often varied considerably across tumour types.

There are also routes to combinatorial success beyond active synergy between drug mechanisms within a given cell. Garnett cites studies showing that pairs of drugs might effectively target completely distinct sets of malignant cells within a tumour, or wherein one drug alters the surrounding tumour microenvironment in a way that makes a second drug more effective.

"Drugs that engage the control of the cell-death machinery tended to partner really well with other drugs."

Many of these effects will only become apparent when tested on real tumours, and a 2022 publication[3] by researchers led by Oliver Jonas at Brigham and Women's Hospital in Boston, Massachusetts, and Joe Gray at the Oregon Health & Science University in Portland, has demonstrated a system that could prove helpful. They developed an implantable device that can test up to 18 drug combinations simultaneously within different regions of a single tumour in a live mouse model, capturing a more detailed and naturalistic view of the efficacy and mechanism of action for these therapies. This could streamline the vetting process to minimize the risk of testing fruitless pairs.

A targeted protein

KRAS used to be called an undruggable target, a cancer-causing protein that for decades bedevilled the efforts of scientists to develop a potent, selective protein inhibitor. But chinks are now visible in its armour. Two moderately effective anti-KRAS drugs have entered the clinic, and a growing legion of promising candidates is following close behind.

Recent estimates suggest that roughly 17% of solid tumours carry mutations in the *KRAS* gene, which encodes a key regulator of cell proliferation, including most pancreatic tumours and cases of non-small-cell lung cancer (NSCLC). Since *KRAS* was first identified as an oncogene (a mutated gene that has the potential to cause cancer) in the 1980s, researchers have been enthusiastic about the potential of developing 'inhibitor' drugs that selectively bind to and disable its mutated form, says Ravi Salgia, chair of medical oncology at City of Hope Hospital in Duarte, California. "But nothing panned out."

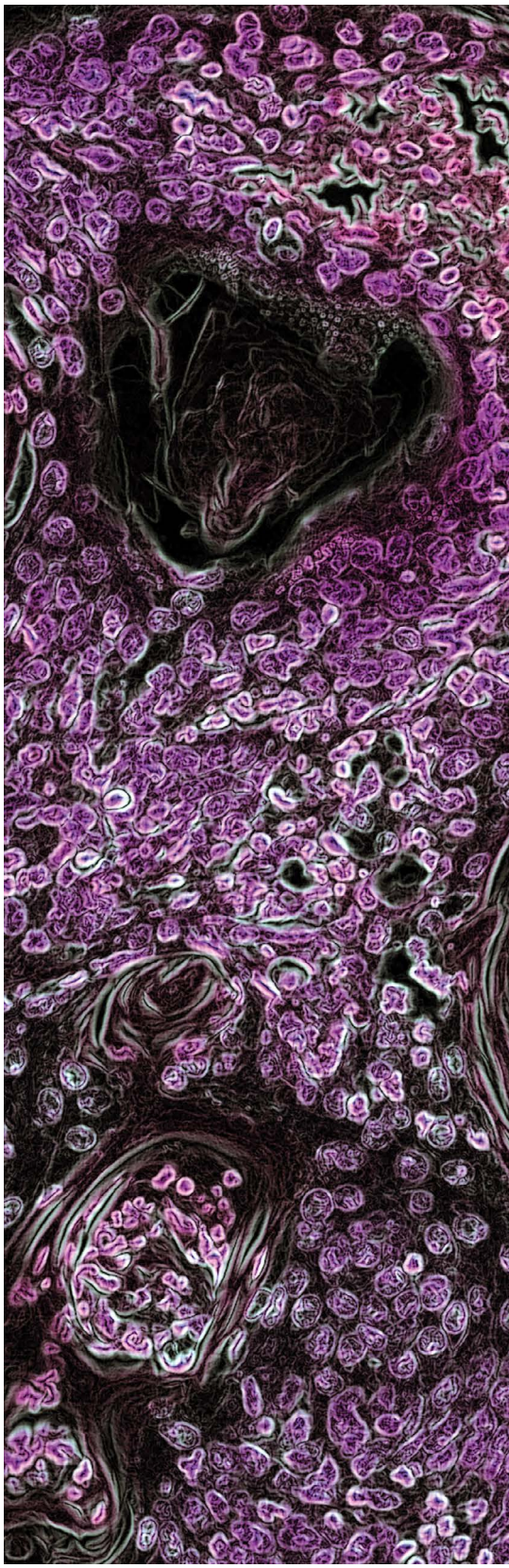
The principal challenge is that the surface of the KRAS protein is remarkably smooth, offering limited purchase for inhibitors to bind with. But a 2013 study[4] by Kevan Shokat's team at the University of California, San Francisco, demonstrated the feasibility of generating chemical compounds that irreversibly bind to KRAS proteins containing an amino-acid variant known as G12C, thereby disabling the protein. This happens to be the most common KRAS variant in NSCLC, and over the past two years, two drugs based on Shokat's approach have reached the clinic for patients with NSCLC: sotorasib, developed by American pharmaceutical giant Amgen, and adagrasib, a product of Mirati Therapeutics, a California-based biotechnology company.

Salgia sees these approvals as an important step. "We have some promising drugs that we can utilize," he says, but also cautions that these drugs alone are "not good enough". Data from clinical trials for these drugs suggest that 30–50% of patients with NSCLC will respond to treatment, experiencing a median period of about six months before resistance emerges and cancer progression resumes, a modest improvement on standard therapy.

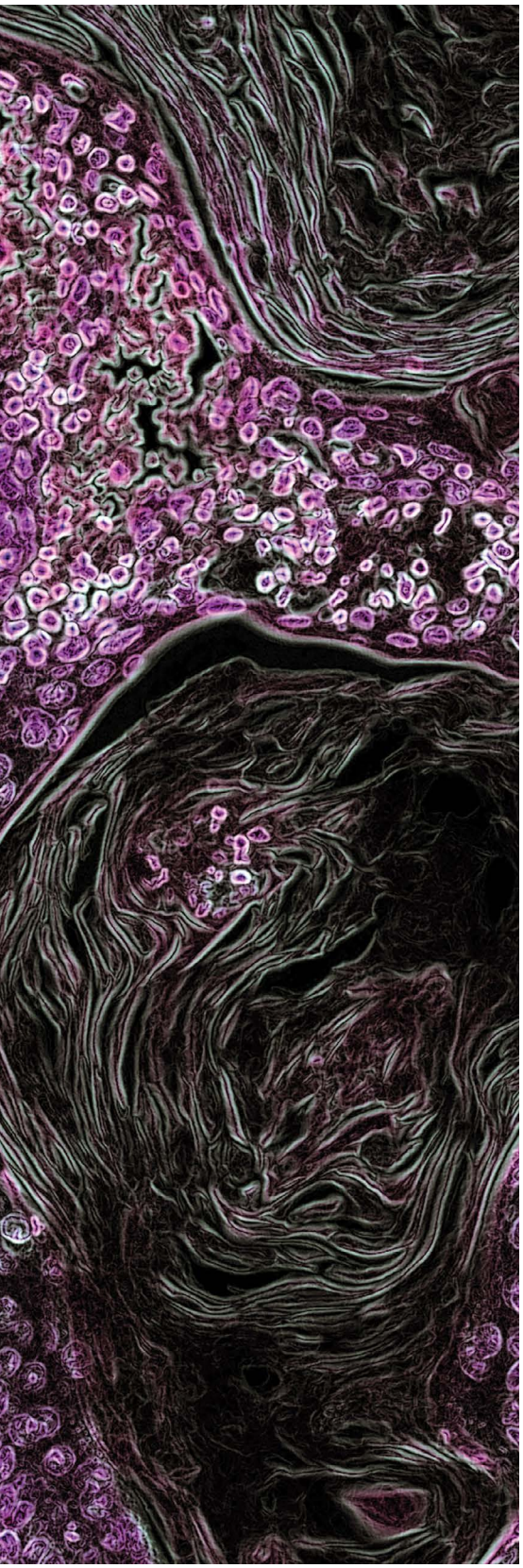
G12C is also just one of several prominent KRAS variants, and there is considerable effort under way to broaden the range of targetable variants. Mirati has developed a drug candidate called MRTX1133, which targets the most common KRAS variant in pancreatic cancer, G12D. A 2023 study[5] by University of Pennsylvania immunologists Robert Vonderheide and Ben Stanger and colleagues showed promising results in mouse models of pancreatic cancer. A clinical trial is now under way.

Other approaches being explored include molecules that selectively mark mutant KRAS for rapid destruction by degrading enzymes responsible for cellular 'housekeeping', as well as 'pan-KRAS' drugs that can potentially act on any form of this protein. One such agent, RMC-6236, developed by California biotechnology company Revolution Medicine, is now in clinical trials.

Salgia is enthusiastic about the progress overall and the opportunities in inhibiting KRAS, but also believes a data-driven, multipronged approach will be necessary to score a decisive win. "We have a long way to go," he



Light micrograph of lung cancer cells (purple) caused by the *KRAS* oncogene.



says, "but at least these discoveries are giving us some hint of what needs to be done."

Vaccine optimism

Twenty years ago, Lisa Butterfield had a glimpse of what an effective tumour vaccine could achieve. Unlike conventional vaccines, which protect against future disease, such 'therapeutic' vaccines are administered after a cancer diagnosis. With a team led by US National Cancer Institute tumour immunologist James Economou, Butterfield and colleagues conducted a trial in which 18 participants with melanoma received a treatment designed to elicit an immune response against the tumour-associated protein MART-1. Most experienced minimal benefit, but one recipient's metastatic cancer disappeared entirely, and stayed away for years.

This programme did not produce an approved treatment, and the years that followed have yielded mostly disappointment. Only one therapeutic cancer vaccine has reached the market to date, a prostate cancer treatment known as sipuleucel-T. Nevertheless, Butterfield, who holds roles at the University of California, San Francisco, and US pharmaceutical company Merck, has remained committed to the promise of this approach. "Once you've seen what's possible, you just try to get it to work more robustly," she says.

The field has cause for optimism, with unpublished trials showing the feasibility of achieving extended remission against advanced disease, including data from a vaccine developed by Merck and Moderna, a pharmaceutical company based in Cambridge, Massachusetts, that cut risk of death or recurrence by 44% in a cohort of 157 patients with advanced melanoma.

Compared with a preventative vaccine, the therapeutic vaccine approach faces many additional challenges, because the patient's immunity is already compromised by the cancer, which uses various strategies to prevent a meaningful antitumour response. Butterfield notes that the ability to consistently elicit a strong antitumour response in meaningful numbers of patients has been a major stumbling block, but ongoing progress in other areas of cancer immunotherapy has yielded a better understanding of how to clear the immunosuppressive fog around tumours.

Researchers are also getting better at picking the best molecular targets, or antigens, on cancerous cells to generate an immune response that focuses only on the diseased cells. Some teams are going after 'shared' antigens, molecular sites that are commonly mutated in certain cancers, yielding vaccines that could be applied across a broad patient group. However, these need to be able to produce an immune response and be tumour-specific to ensure a safe and effective vaccine.

Researchers led by Inge Svane, an immunologist at Copenhagen University Hospital in Denmark, pursued a clever spin on this approach with a vaccine based on proteins that cancer cells often express to shut down host T cells. This marshals a response in the patient that attacks the tumour while also alleviating immunosuppression. In a 2021 phase I/II trial[6] for metastatic melanoma, which combined this approach with another immunotherapeutic drug, 13 out of the 30 patients who received the treatment had a complete response — meaning their cancer was no longer detectable.

"That's so high, it was difficult for me to continue to keep calm," says Svane. This vaccine programme was licensed by Danish start-up IO Biotech, which Svane co-founded, and is now undergoing phase III trials.

Considerable headway has also been made by going after 'neoantigens' — combinations of mutant proteins that are unique to a given patient. It can be labour-intensive to achieve this degree of personalization, but in-depth biopsy analysis and sophisticated algorithmic tools can accelerate the process. The Merck–Moderna vaccine is based on such an approach, incorporating dozens of antigens for each patient's vaccine. This approach also benefits from Moderna's mRNA vaccine technology.

It remains to be found whether, as with other immunotherapies, some tumours will prove too immunologically 'cold' to muster a meaningful effect from vaccination by rousing suppressed and slumbering immune cells. But there are glimmers of hope. In May, a team led by Vinod Balachandran at the Memorial Sloan-Kettering Cancer Center in New York City, showed[7] that an mRNA vaccine developed by German biotechnology company BioNTech dramatically delayed tumour progression in 8 out of 16 patients with pancreatic cancer, an immunologically cold and notoriously lethal tumour type.

Butterfield remains optimistic. "I have no reason to think that there's a tumour type that won't be susceptible," she says. "There will just be differing levels of difficulty."

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