Credit: smartboy10 / DigitalVision Vectors / Getty

A golden era of cancer clinical trials

Cancer immunotherapy is generating huge excitement, but the future may lie elsewhere, in antibody–drug conjugates, proteolysis-targeting chimeras, and liquid biopsy for early detection.

Paul Webster

Whether inside or outside their labs, cancer researchers as a whole are not known for hyperbole. But these days, their jargon is increasingly larded with talk of revolutions, renaissances and the sudden blossoming of a golden era in cancer research.

By the numbers, it is easy to see why. Since 2015, the US Food and Drug Administration (FDA) has approved more than 80 new anti-cancer drugs, or about a quarter of its total new drug approvals. Oncology clinical trial starts reached historically high levels in 2020, up 60% from 2015, and focused mostly on rare cancer indications. More than 700 companies are involved. Across the globe, an estimated 19,500 cancer clinical trials are underway, propelled in good part by a huge expansion in China, and by an increase in global spending on anti-cancer drugs, which is projected to reach US$269 billion by 2025.

Giuseppe Giaccone, Associate Director for Clinical Research at Weill–Cornell University in New York City, describes the excitement with zeal. "I've never seen the FDA approve so many drugs in such a short time, both for hematological malignancies, and now for solid tumors that never had a treatment before," he enthuses.

For lung cancer, especially, says Giaccone "it's just unbelievable what's happening. We have a new drug every month now," he says with a bemused chuckle. "And it doesn't look like it's stopping any time soon, which is good. There's a lot of investment."

Re-thinking immunotherapy

The bulk of the multi-billion-dollar action in cancer clinical trials comes from companies pursuing new niche treatments — often for so-called 'copycat drugs', says Giaccone. "They have a drug on the market that's approved for a major indication, and then they go after smaller indications," he explains. In this context, thousands of trials of relatively conventional inhibitors of the checkpoint molecule PD-1, which

harness the immune system to help restore anti-tumor immune responses, have proliferated exponentially. An estimated $100-billion has been invested in companies investigating checkpoint inhibitors, which generate over $100,000 per patient.

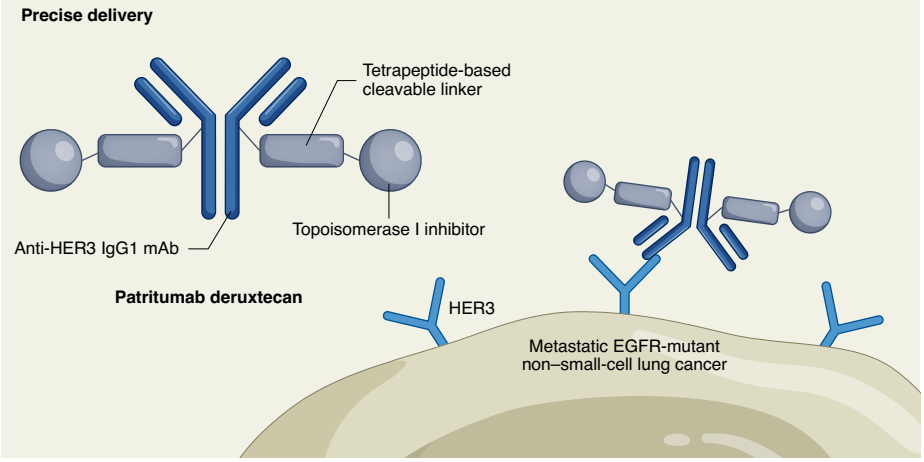
Auspiciously for novel drug development beyond immunotherapy, says Giaccone, recent advances in cancer-related genomics, genome editing, diagnostics and biomarker discoveries are energizing investigations of a number of key categories of novel therapies with an alphabet soup of names, including CAR-T, ADCs, PROTACs and bispecifics.

"We know the biology of many of the tumors so much better now," says Giaccone. "With all the genome studies that have been done, we now have a much better understanding of the potential vulnerabilities of many tumor types, as well as the potential treatment targets. And some of the new treatments work really well."

Among the myriad trials underway of immune checkpoint inhibitors, Giaccone points to a multi-center lung cancer trial underway with nivolumab, which was the first checkpoint inhibitor to receive regulatory approval, in its case, for the treatment of advanced melanoma. "We're waiting to see results that could change the whole field dramatically," he says. Another major advance came with FDA approval, on 18 March 2022, of a new checkpoint inhibitor, relatlimab (Opdualag, Bristol-Myers Squibb) that works by targeting LAG-3 on T cells. Despite these successes, some have argued that immunotherapy may be on the cusp of a total rethink.

Tak Mak is a University of Toronto researcher best known for his discovery of the T cell receptor in 1984. Mak recently argued that the irregularity of tumor microvasculature imposes barriers to T cell recruitment and homing, which in turn limits the effectiveness of immunotherapy. Altered tumor characteristics, argues Mak, limit endogenous T cell migration and impinge on the efficacy of chimeric antigen receptor (CAR) T cells and adoptive cell-transfer therapies for solid tumors, Mak believes. The next chapter of immunotherapy needs to probe the complexity of immune cell–cancer cell interactions to better design more effective anti-cancer drugs, focusing on two key factors, Mak explains: "Rescuing T cell homing and dysfunction in the tumor microenvironment," and "reappropriating mononuclear phagocyte function for tumor microenvironment inflammatory remodeling."

"Cervical cancer is 95% caused by human papillomavirus. Why not give the patient a T cell directed against a piece of the human papillomavirus?" Mak asserts, citing research on patients with metastatic human papillomavirus–associated epithelial cancers, led by Christian Hinrichs of Rutgers Cancer Institute, that recently demonstrated that engineered T cells can mediate regression of common carcinomas.



Patritumab deruxtecan is an ADC that targets the human epidermal growth factor receptor (EGFR) HER3 and has recently been given an FDA Breakthrough Therapy designation in the treatment of metastatic or locally advanced non–small-cell lung cancer. IgG1, immunoglobulin G1; mAb, monoclonal antibody. Credit: Marina Spence, Nature Medicine

A newly FDA-approved therapy that also relies on T cells is tebentafusp-tebn (KIMMTRAK; Immunocore), the first bispecific immunotherapy to treat a solid tumor, and the only available treatment for metastatic uveal melanoma. Saad Usmani, chief of the myeloma service at Memorial Sloan Kettering Cancer Center, explains that "bispecific antibody constructs are engineered to have dual antigen specificity to facilitate cell-to-cell interactions between the patients' own T cells and malignant cells expressing tumor-specific antigens."

Bispecific agents like tebentafusp-tebn comprise a soluble T cell receptor fused to an immune effector molecule, such as antibody to CD3, which activates T cells to attack the tumor.

"There's really been an explosion in bispecific constructs," adds Usmani, who observes that many bispecific agents "are now making their way into early relapses in frontline treatment settings. Seeing bispecifics combined with native antibodies in the frontline setting is exciting."

Drug delivery

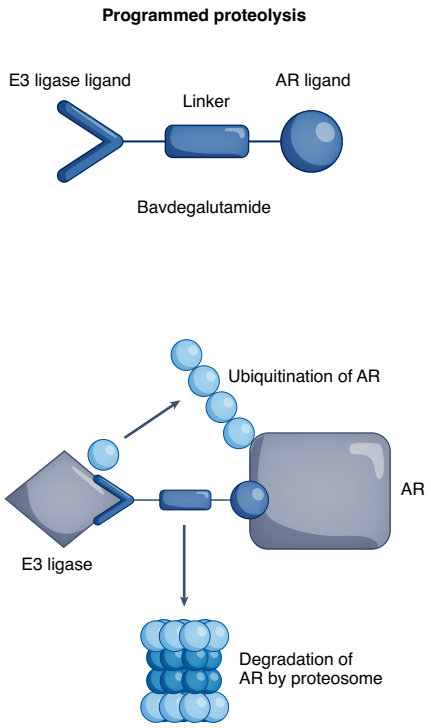
In San Antonio, Texas, Anthony Tolcher has been a principal investigator for 20 phase 1 clinical studies of FDA-approved cancer drugs, but he is now most excited by antibody–drug conjugates (ADCs), which use antibodies carrying cytotoxic payloads to attack tumor cells.

ADCs consist of three conjugated elements that allow them to perform something akin to a microscopic moon landing and payload delivery directly atop a patient's tumor cells. An antibody is responsible for selective recognition of the cancer cell surface antigen, which internalizes the ADC; a drug payload is responsible for killing the cancer cell once it is released inside the cell; and a chemical linker connects the two.

After many false starts, ADCs are now entering their time in the sun, says Tolcher. "Through 20 plus years we've gone from a great idea through all sorts of defeats where the drug would fall off or not hit the right spot," he explains. "But we now have twelve approved antibody–drug conjugates, nine since 2017." Two of these drugs have achieved blockbuster status with sales of over $1 billion annually for indications that include lymphoma and breast and bladder cancer.

To put the promise of ADC research in perspective, Tolcher compares the field with immunotherapy. "We've not really had a lot of novel approvals in immunotherapy. We have lots of drugs that target PD-1 and PD-L1, but they're all the same. Whereas all of the ADC drugs approved have some degree of novelty."

Big news came on 23 December 2021, says Tolcher, when Tokyo-based Daiichi Sankyo Company was granted an FDA Breakthrough Therapy designation for patritumab deruxtecan in the treatment of metastatic or locally advanced non–small-cell lung cancer, following results from their phase 1 trial.



Bavdegalutamide is a PROTAC composed of a ligand for the androgen receptor (AR) linked to a ligand for E3 ligase, which targets the androgen receptor for proteosomal degradation. This PROTAC is being evaluated in a phase 2 trial for castration-resistant metastatic prostate cancer. Credit: Marina Spence, Nature Medicine

"We'll probably see [patritumab deruxtecan] approved for lung cancer in the next 12 months," muses Tolcher (who was not involved with the trial), "and it's probably going to work in some other indications like breast cancer and urothelial cancers," he predicts.

"There are a number of new directions that this whole field can go. Conceivably we might be able to deliver non-cytotoxic targeted therapies — things that are different from chemotherapies and that can be put on the backs of these antibodies and delivered selectively to the tumor. There's a whole lot of potential with this entire platform. We're really just starting to scratch the surface of it."

As a point of caution, Tolcher emphasizes that ADCs are non-curative by themselves. Unlike CAR T cells, for which, "quite frankly if you get the right CAR T and you've got the right tumor and all the stars align, you can eradicate a tumor," he says, with ADCs, "this is a platform that's part of the armamentarium, but it's not going to be a stand-alone cure."

At Memorial Sloan Kettering Cancer Center, Saad Usmani also sees ADC research as promising. "We're learning how to best use it and it's moving up" in importance in the hierarchy of leading cancer clinical trials arenas, he affirms.

Usmani notes that the safety profile of ADCs depends a great deal on the toxic payload used. "For certain ADC constructs, extracellular cleavage of the ADC before target cell penetration could lead to premature liberation of the toxic payload and negative effects on healthy cells," he noted, "but the use of non–cell-permeable payloads or non-cleavable linkers can reduce this concern."

Undruggable targets

New technologies mean that some cancer researchers now talk of 'drugging the undruggable'. The term 'undruggable' stems from protein structure. Although the genomic revolution has linked many specific cancers with an estimated 600 specific protein targets, as many as 400 cancer-associated proteins lack suitable binding pockets for conventional drugs. Some have broad, shallow pockets that repel small molecules; others have smooth surfaces that offer few binding sites for a small-molecule drug to adhere to and begin modulating its function. Intracellular cancer targets are intrinsically hard to target, so there are very few drugs that can successfully target scaffolding proteins, transcription factors and other non-enzymatic proteins inside the cancerous cell.

But the barriers against targeting undruggable proteins may now be falling fast, thanks in part to proteolysis-targeting chimeras (PROTACs). PROTACs rely on cellular maintenance processes that degrade intracellular proteins. Proteins are targeted for degradation by the proteasome in a process involving ubiquitin, which is transferred to the target protein by ubiquitin–protein ligases, more than 600 of which are encoded for in humans.

PROTACs recruit and bind a protein of interest while also recruiting a ubiquitin ligase. This heterobifunctional binding triggers degradation of the target protein while the PROTAC itself is recycled to target again.

Despite reporting of the first fully synthetic PROTAC in 2001, the first clinical proof of concept came in 2020, with separate trials of PROTACs directed against the estrogen receptor or the androgen receptor, both important cancer targets; these PROTACs are in phase 2 trials. Bavdegalutamide (ARV-110; Arvinas), which targets the androgen receptor, has shown early signs of clinical efficacy for the treatment of metastatic castration-resistant prostate cancer, according to a press release from the company. This trial is being watched closely, says Yue Xiong, Chief Scientific Officer at Cullgen, in San Diego.

Safety concerns about PROTACs are an issue because of their intense potency, acknowledges Xiong. Complete depletion of a protein target with a PROTAC might be detrimental if the protein is essential for normal cell function; many PROTACs are not completely selective and can degrade proteins other than their desired targets. Nonetheless, Xiong sees "tremendous opportunities" for PROTAC development, noting that the vast majority of E3 ligases have not been explored. This presents enormous opportunities for the development of PROTACs that target oncoproteins with tissue, tumor and subcellular selectivity.

"The key attraction of PROTACs is that they act catalytically, they can target virtually any protein, and this technology opens the door for drug delivery," Xiong says. "Put all that together, and you can see the future."

Early detection

Developing new anti-cancer treatments is undoubtedly important, but early detection has an arguably greater potential to save lives. Jacqui Shaw, co-director of the Leicester Precision Medicine Institute at the University of Leicester, points to a set of "mission-critical" ongoing clinical trials into the vast potential utility of liquid biopsy tests.

By analyzing blood and urine samples for circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA), Shaw explains, liquid biopsies can detect cancer quickly and early. Once the DNA is sampled, tumor mutations must be detected, usually by PCR testing, whole-exome or whole-genome sequencing, or "cancer personalized profiling by deep sequencing."

As well as liquid biopsy for diagnosis, these tests, Shaw emphasizes, are becoming an important aid in cancer prognosis, in the selection of targeted therapies, and in the measurement of treatment efficacy over varying time periods. But liquid biopsy has some unresolved problems.

Intriguingly, tumoral and tumor microenvironment–associated cells release two types of DNA into the extracellular space: DNA that has cancer-driver mutations, and non-cancer DNA. Because these non-cancer fragments also feed the cfDNA pool, and their contributions to the cfDNA pool fluctuate between cancer stages, and because it has been reported that normal (non-cancerous) cells can harbor tumor-related mutations, the false-positive rate of liquid biopsy analyses is a major concern, says Shaw.

Nevertheless, the field of liquid biopsy is expanding and diversifying rapidly, says Shaw. The ECLIPSE trial, staged by California-based Guardant Health, incorporates somatic genomic variant detection, epigenomic analysis and a bioinformatics classifier with which to filter non-tumor variants. In a pilot study of this test, known as 'LUNAR', ctDNA detection in patients with early-stage colorectal cancer had 94% specificity, and incorporation of epigenomic analysis significantly enhanced ctDNA detection, according to Guardant Health.

Another study, from Washington University School of Medicine in St. Louis, demonstrated that a liquid biopsy of blood or urine helped gauge the effectiveness of therapy for colorectal cancer that had spread beyond the original tumor.

Giaccone is enthusiastic about liquid biopsy research. "We're now seeing exquisite sensitivity that raises the possibility we may be able to diagnose cancer, where you can't see [clinical signs], by just a blood test," Giaccone enthuses. "[Liquid biopsy] could theoretically revolutionize the whole field. Right now we're screening for breast, lung, colon cancers. But, theoretically, you could have just one blood test for everything."

Liquid biopsy, adds Giaccone, "will open up the field to better know which patients should receive adjunct treatment. But even more, it will probably allow early detection. And that's the holy grail of oncology." ❐

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