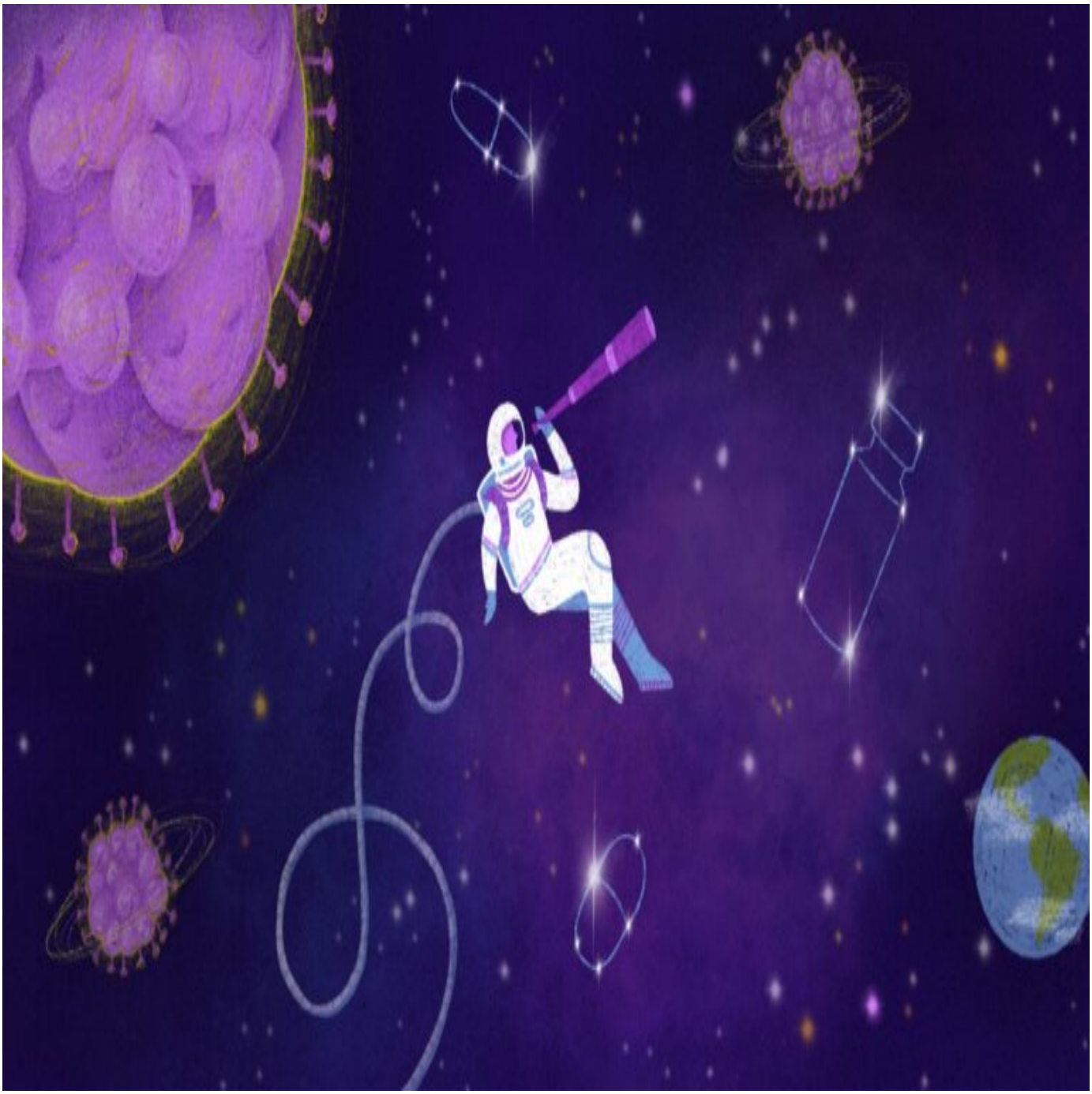
Frustrated with nature's biomarkers for cancer, biologists try making their own

- 

By Angus Chen Aug. 17, 2022



Molly Ferguson for STAT

On Target is a recurring feature from STAT that dives deep into the most promising drug targets in oncology.

The hunt for cancer cures has, to a large degree, been a hunt for

biomarkers — DNA, peptides, RNA, proteins or more — that might set tumor cells apart from healthy tissue. With the right biomarker, scientists can find cancers earlier, monitor a treatment's progress, or predict if a certain therapy will work for a given patient. The trouble is that for many cancers, the known biomarkers have been a disappointment, particularly for early cancer detection.

"You see all sorts of research groups looking at natural biomarkers," said Amin Aalipour, a resident physician at Brigham and Women's Hospital and a synthetic biology researcher. "There's limits to what we can do when you rely on what the tumor is willing to tell us."

Natural cancer biomarkers are often hard to detect, fail to last very long in the body, or are not specific enough to cancer. So, a growing field of scientists including Aalipour have started taking matters into their own hands. Rather than search for a biomarker that occurs naturally, scientists are creating completely new, synthetic biomarkers.

"Really small cancers that haven't spread, cannot be picked up on imaging, the proteins or DNA that these tumors are shedding into the blood – you just don't have that many molecules," said Gabriel Kwong, a biomedical engineer at Georgia Tech. "For cell-free tumor DNA, in a single 10 milliliter blood draw, you'd have maybe just a few molecules of cancer DNA in that blood draw." Instead of trying to search for a vanishingly small amount of a natural biomarker, Kwong decided to make his own synthetic ones.

Labs have been tinkering with synthetic biomarker designs that could

become invaluable tools in the clinic one day. Some are chemical probes that can interact with tumors, and others are even living sensors made of engineered cells. “There’s a group at Stanford where they demonstrated engineering cells that crawl into the tumor and then turn on the production of synthetic biomarker,” Kwong said. “Then some labs engineer probiotics that you find in yogurt where they can colonize tumors in the GI tract and create synthetic biomarkers.”

Then, depending on the biomarker’s design, clinicians could get a read-out in blood, urine, breath, or imaging to help diagnose or understand the patient’s tumor better. “That’s what makes a synthetic biomarker so exciting,” Kwong said. “You’re designing it at the bench and figuring out the mechanism you want to exploit to produce a signal.”

Here’s STAT’s look at synthetic biomarkers, how they might be used, and where they are in development.

The discovery

The idea for a synthetic biomarker came about “by accident” in the mid 2000s, said Sangeeta Bhatia, a biological engineer at MIT. She and two of her students, Geoff von Maltzahn and Todd Harris, were trying to create a “smart” dye that could highlight tumors in the body in an MRI. “The idea was you’d do a scan, and instead of anatomical info, you’d get tumor hotspots,” Bhatia said. “We made magnetic nanomaterials that people use as contrast agents and tried to make them smart so they would respond to the tumor microenvironment.”

Bhatia's team had connected a fluorescent peptide, the building block of a protein, to a nanoparticle. The idea was that enzymes in the tumor environment would slice off the fluorescent peptide and concentrate the dye around the tumor, highlighting the cancer on scans. "That part never really worked," Bhatia said. "But whenever we looked in tumor-bearing animals, we would see this other organ lighting up. It was the bladder."

The smart dye that Bhatia had made wasn't sticking to tumors, but rather getting into the blood, filtering through the kidneys, and showing up in the animal's urine. That made Bhatia and her lab members realize they might be able to use a version of these materials to create something like a urine test for cancer. The realization sparked a flurry of new ideas. "So that was our 'Aha!' moment, and we started to riff," Bhatia said. "We were like: this would be a cool way to monitor the body noninvasively."

Georgia Tech's Kwong joined Bhatia's lab around this time as a post-doctoral fellow, and he started to work with Bhatia to create synthetic reporters based on this principle. The first, which the two published in 2013, was a nanoparticle with 10 different chemical probes attached to it. "That can produce 10 different synthetic biomarkers you can use for cancer detection," Kwong said. "That Nature Biotech paper kickstarted the field. We used the term synthetic biomarker for the first time."

The biology

There are a couple of main approaches to creating synthetic biomarkers, Kwong said. The chemical probes that he and Bhatia's labs create use enzymes in the disease microenvironment called proteases, which slice

off the synthetic biomarkers attached to the nanoparticle. Different diseases, including cancer, tend to have different proteases, which in turn can only cut certain peptides.

That means one way to create a synthetic biomarker that can test for cancer is to attach it to another particle using a peptide "bridge" that only proteases found around tumors can cut. If the nanoparticle comes into contact with a tumor, then cancer-related enzymes should release the synthetic biomarker, allowing clinicians to search for it.

Unfortunately, tumor proteases are found not only at tumor sites, but also elsewhere including areas of tissue regeneration and other organs. "There's no single protease for cancer or any other disease," Kwong said. "There's another problem — proteases are what we call promiscuous enzymes. You can spend all this time in the lab and design a single peptide that can be cleaved by many classes of proteases."

So, Kwong and Bhatia heaped multiple synthetic biomarkers onto their nanoparticles. That way, they could use machine learning to analyze what assemblages of synthetic biomarkers show up in the blood or urine of healthy and sick animals. "So, if you create a panel of 10 or 15 biomarkers, you can look at a complex mixture of synthetic biomarkers and backtrack and figure out what proteases were involved to create that signature," Kwong said.

The team was able to identify signatures that corresponded not only to cancer — but other diseases as well. "Thrombosis, liver fibrosis, hepatitis, transplant rejection — if you look at all the major diseases, a

lot of key processes are driven by proteases," Kwong said.

Other scientists, starting with the late bioengineer and oncologist Sanjiv 'Sam' Gambhir from Stanford University, have been altering living cells to create synthetic biomarkers. Gambhir's lab, where Brigham and Women's Aalipour studied, engineered immune cells known as macrophages to produce synthetic biomarkers in the presence of cancer.

"Macrophages are adept at honing in on sites of disease, cancer being one of them," Aalipour explained. "Within the tumor microenvironment and other disease microenvironments, immune cells undergo typical alterations in metabolic profile that we're aware of. So, we thought, maybe we can use that as a sensor."

When Aalipour and Gambhir's cells start undergoing the typical changes that macrophages experience in the presence of a tumor, those changes trigger an engineered genetic circuit that instructs the cell to begin producing synthetic biomarkers.

Both of these methods create biomarkers that skirt two key problems with natural biomarkers. For one, key proteins that might serve as useful biomarkers often don't last very long after they leave the tumor. "The bloodstream is full of enzymes, so that can cut up your reporter," Bhatia said. "Gabe's insight was that we can design synthetic reporters that are resistant to the body's degradation process. We don't have to use nature's building blocks. We can create analytes that fit our needs."

And scientists can create as much synthetic biomarker as they need,

making it easier to detect even when tumors are small.

The pipeline

There are still problems that researchers need to solve before synthetic biomarkers have a shot of working in the clinic, Kwong said. For one, synthetic biomarkers still need to become more specific. Enzymes that are more common in tumor environments are overrepresented in other diseases, too, like respiratory infections. The same is true for macrophage states from Aalipour and Gambhir's work — an engineered macrophage might make the same synthetic biomarkers in cancer as it would around an open wound.

"This work is certainly not ready for primetime," Aalipour said. "Specificity is one area that needs to be optimized, though we have ideas of how to do that using tricks from synthetic biology."

Synthetic biomarkers have also only been tested in humans for safety but not yet for efficacy, and scientists will need to see if what works in mice will still work in people. Finally, for cancer, current synthetic biomarkers can only tell you if a tumor exists or not, but not where in the body it is. It may not always help to know that a patient has cancer, if doctors cannot find it. "In the synthetic biomarker and the liquid biopsy world, a problem is the next step in the clinical work. This thing turns positive, and then what?" Bhatia said.

The biotech companies working to develop synthetic biomarkers include Glympse Bio, which Kwong and Bhatia co-founded, and Earli, started

by Gambhir. Bhatia noted that industry has been slow to invest in the new technology due to initial economic and regulatory barriers. “As a diagnostic, there’s a huge drive to make them inexpensive, and then you have a drug-like development cost because it’s injected. People used to say to us in 2015, like congratulations, you invented the worst of both worlds.”

Researchers are trying to solve these problems by employing more sophisticated synthetic biology, developing new synthetic biomarkers, and working on the cost. Bhatia also added that synthetic biomarkers could be regulated as devices, rather than drugs, which makes the path to approval a bit easier.

If they’re successful, synthetic biomarkers might help to usher in a new advance in precision medicine, Bhatia said. Because synthetic biomarkers are designed from scratch, scientists can potentially engineer them to be injected, inhaled, or consumed orally. In some of Kwong and Bhatia’s work, they created synthetic biomarkers that can break off a volatile organic compound that comes out in breath. Then, synthetic biomarkers can be read out in a blood draw, a urine test, or even a breathalyzer type of test.

“Imagine, in early detection for lung cancer, you can inhale a probe that produces a synthetic biomarker that comes out in the breath,” Kwong said. “Or you can design a probe and detect it on a piece of paper like a Covid test or pregnancy test.”

And if you could test for lung cancer with a breathalyzer at a doctor’s

office or quickly see if a cancer therapy is working on a urine test, the impact, Kwong imagined, would be enormous.

Previous On Target columns explored TGF-beta and immune checkpoint inhibitors.

About the Author

Angus Chen

Cancer Reporter

Angus Chen is a cancer reporter at STAT.

angus.chen@statnews.com
@angrchen

Add a Comment

Create a display name to comment

This name will appear with your comment