ONCOLOGY

BLOG POSTS

QPS is committed to the support of preclinical, bioanalysis and clinical research into drug development.

QPS
CUSTOM-BUILT RESEARCH™

Table of Contents

APRIL 17, 2024

Oncology Drug Development: A Short History

Humans have practiced oncology — the study and treatment of cancer — since long before the invention of the scalpel. The history of oncology drug development is a testament to the relentless pursuit of treatments for one of humanity's most challenging diseases. Let's explore oncology drug development through the ages, from an ancient Persian queen to groundbreaking modern advancements in immunotherapy.

Exploring the History of Oncology Drug Development

Challenges with translation, record-keeping, and ancient medical misunderstandings can complicate matters for historians hoping to explore the history of medicine. However, when it comes to oncology, one thing is certain: Humanity has waged war against cancer for centuries.

Consider the case of Atossa, a Persian queen who lived around 520 BC and is often cited in early histories of cancer treatment. Historians believe that Atossa exhibited signs of a breast tumor, for which she was treated by the famed Greek healer Democedes. Long before Atossa, an ancient Egyptian man lived with signs of metastatic prostate cancer — at least, according to mummified remains evaluated via CT scans, which point to what is often considered the earliest

continued »

documented case of its kind. Fortunately, advancements in cancer treatment mean that today's oncology patients often have a far brighter outlook.

Fast Forward to Modern Oncology

While physicians may have studied cancer for centuries — even millennia — today's widely accepted cancer treatments came about relatively recently:

- **Studying cancer cells:** Physician Rudolf Virchow is known for his observations of cancer cells in the 1840s. He described them as autonomous cells derived from previous cells and also suggested that cancer cells resembled cells in the tissue from which they arose. This understanding became widely accepted by the start of the 20th century, paving the way for future cancer treatment protocols.
- **Radiotherapy to treat cancer:** In 1895, German physicist Wilhelm Conrad Röntgen became the first scientist to correctly identify the waves of radiation that we now know as X-rays. Within a year of his findings, X-rays were used to treat cancer. Fortunately, today's medical professionals know how to protect patients from the effects of radiation, targeting cancer cells while minimizing radiation's harmful effects on the rest of the body.
- **Chemotherapy:** Doctors discovered the anticancer properties of nitrogen mustard during World War II, not long after the advent of radiation drugs. From there, researchers were able to develop numerous cytotoxic drugs to target rapidly dividing cancer cells, paving the way for today's chemotherapy treatments.

Today's physicians have a host of immunotherapy options, including checkpoint inhibitors and CAR-T cell therapy, both of which build on Coley's early findings. Ultimately, oncology drug development has nowhere to go but up.

The Future of Oncology Drug Development

Innovation shines through the history of oncology drug development, and today's modern advancements are no exception. Consider, for example, recent progress in the realm of immunotherapy, which trains the immune system to recognize cancer cells as foreign, thus attacking and killing the cells. Immunotherapy is nothing new; its roots trace back to William Coley, a late nineteenth-century surgeon who observed cancer regression in a patient following a high fever induced by an infection. But today's physicians have a host of immunotherapy options, including checkpoint inhibitors and CAR-T cell therapy, both of which build on Coley's early findings. Ultimately, oncology drug development has nowhere to go but up.

MAY 24, 2023

Skin Cancer Risk Concerningly High in Millennials & Gen Xers

A recent scientific survey conducted by DermTech, Inc. identified a number of alarming trends concerning the sun exposure habits and skin health knowledge of millennials and Gen Xers. The survey's findings emphasize the need for increased education on skin cancer risks and the importance of preventative measures. To address the need for further education in these areas, DermTech, Inc. recently launched Sun Regrets, a campaign focused on educating Americans on skin health, risk factors for nonmelanoma skin cancer, and what preventative measures can be taken to reduce harm from ultraviolet (UV) radiation.

Skin Cancer Risk Factors

Repeated or prolonged exposure to UV rays, either from sunlight or from tanning beds, is a significant risk factor for skin damage and for a range of nonmelanoma skin cancers (NMSCs). UV radiation is a proven carcinogen, and prolonged or repeated exposure to UV rays damages the DNA of skin cells, leading to genetic mutations that can cause premature aging, skin damage, and both melanoma skin cancers and nonmelanoma skin cancers.

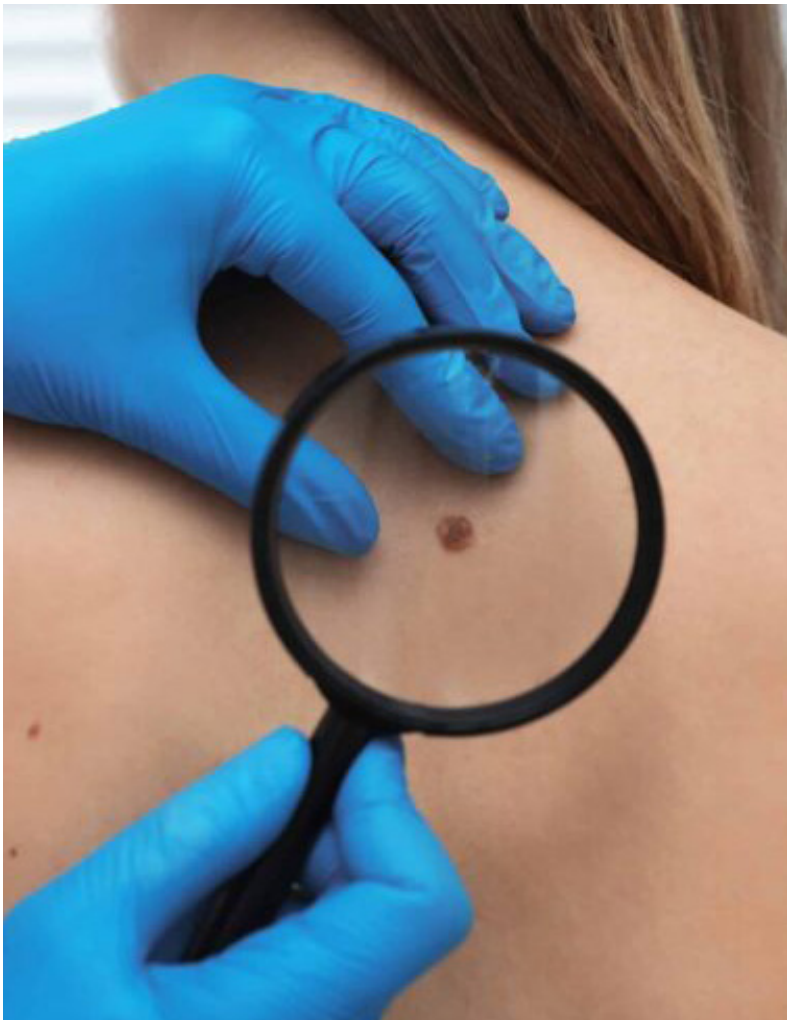
Nonmelanoma skin cancers (NMSCs), which include all cancers occurring in the skin that are not melanoma, affect 3.3 million Americans every year. And nearly 40 million Americans each year are affected by actinic keratosis (AK), a slow-forming precancerous skin growth that, left untreated, can turn into squamous cell carcinoma (SCC), one of the most common types of NMSCs. SCC, along with basal cell carcinoma (BCC) and the majority of NMSCs, are caused primarily by repeated or prolonged exposure to UV radiation from the sun or tanning beds. Taking proper precautions can help prevent skin damage and lower NMSC risk.

But despite how common and preventable many NMSCs are, a new survey has revealed that while most millennials and Gen Xers consider themselves mindful of sun exposure, most are not taking the actual steps necessary to protect against preventable NMSCs.

Skin Cancer Survey Findings

A new survey conducted by Onepoll on behalf of DermTech, Inc. asked 1,000 millennials and 1,000 Gen Xers questions about their sun exposure habits and skin health knowledge. While 75 percent of survey respondents claimed they were mindful of sun exposure, the survey revealed concerning information about actual behavior, knowledge, and preventative practices.

Skin Cancer Risk Concerningly High in Millenials & Gen Xers



1 in 5
Americans will develop skin cancer by the age of 70

>2
People die of skin cancer in the US every hour

>5
Lifetime sunburns doubles your risk of melanoma

5.6%
Estimated decrease of melanoma cases expected worldwide in 2023

86%
Of Melanomas can be attributed to UV radiation from the sun

99%
Survival rate when melanoma is detected early

The survey revealed significant room for improvement in skin protection practices. Despite most respondents considering themselves "mindful" of sun exposure, a mere 19 percent of respondents reported wearing sunscreen year-round. Nearly 30 percent of Gen X respondents admitted to never wearing sunscreen, and a higher percentage of women (30 percent) than men (23 percent) reported not using sunscreen at all. Survey respondents also reported failing to apply sunscreen to all areas of the body exposed to the sun, including susceptible but frequently overlooked areas like the ears, lips, scalp, and hairline.

continued »

This behavior seems likely linked to a gap in understanding about risk factors for skin cancer. Of those surveyed, only 37 percent of millennials and 45 percent of Gen Xers understood that prolonged sun exposure could cause precancerous lesions.

Equally concerning, the survey uncovered alarming data regarding tanning bed use and misconceptions. Even though tanning bed use is linked to a higher risk of skin cancer, 35 percent of survey respondents admitted to using tanning beds, and the survey found that twice as many millennials as Gen Xers falsely believed that tanning beds were safer than outdoor tanning (22 percent vs. 11 percent).

The Importance of Education and Prevention

The survey also highlighted the limited understanding of skin cancer among respondents. Of those included in the survey, only 44 percent claimed to feel knowledgeable about any type of skin cancer in general, with even lower percentages feeling knowledgeable about specific types of common NMSCs, like BCC and SCC.

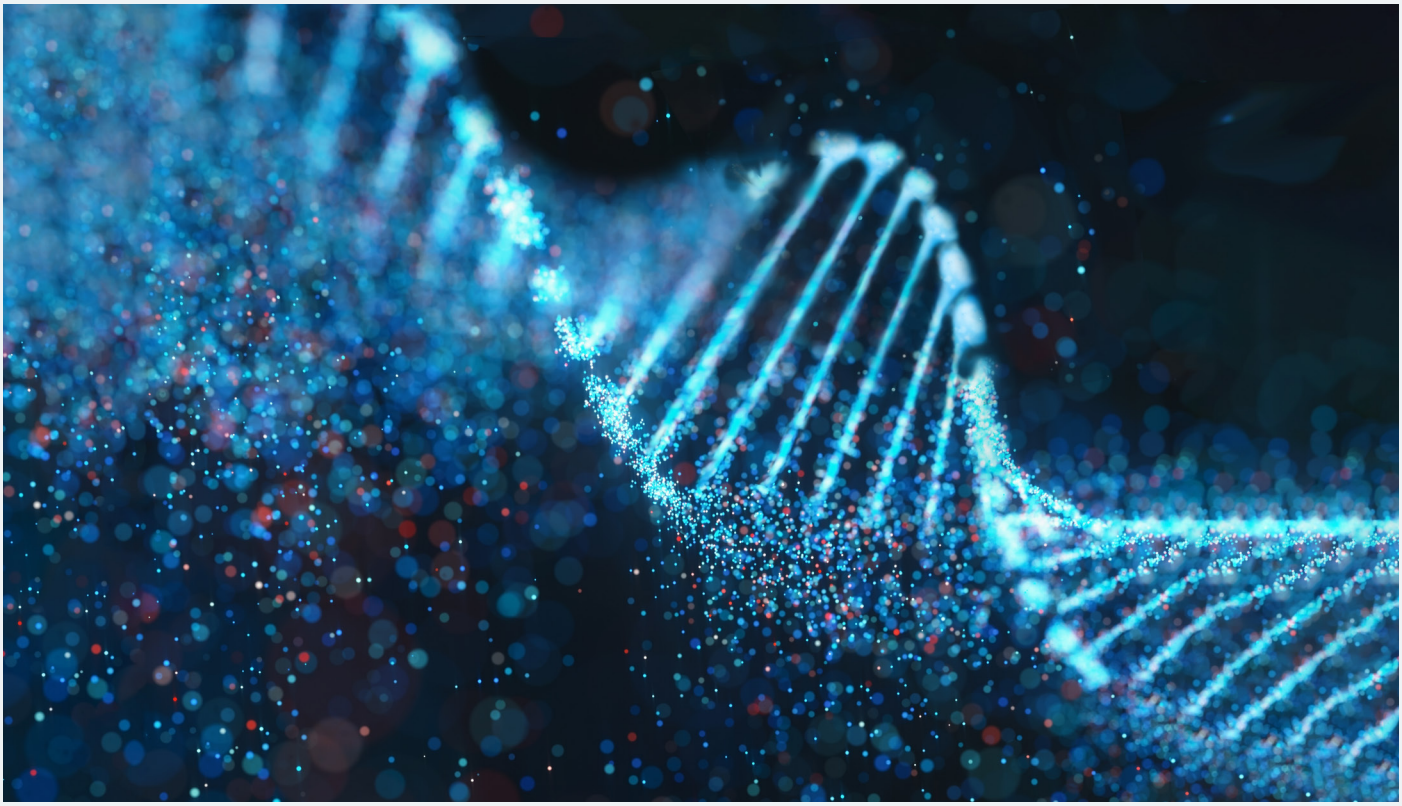
When presented with images of various skin lesions, one in three participants was unable to distinguish between different types of skin cancers and precancers. Notably, a significant proportion of respondents were unaware that slow-healing open sores could even be indicative of skin cancer.

Dr. Elizabeth K. Hale, a board-certified dermatologist and clinical associate professor at New York University Langone Medical Center, emphasized the urgent need for education regarding NMSC prevention.

“The good news,” Hale says, “is that millennials and Gen Xers are concerned about how much sun they are getting, but they still aren’t following key steps to ensure they protect their skin, such as wearing sunscreen year-round and remembering to put sunscreen on all areas that are exposed to the sun.”

Sun Regrets Campaign

To address the knowledge gaps revealed by the survey and to promote skin health awareness, DermTech, Inc. has launched its Sun Regrets campaign. This important resource aims to educate Americans about the risks of skin cancer, the factors contributing to NMSC, and the importance of preventative measures to mitigate UV damage.



Are you enjoying our blog posts?

Please visit

qps.com/blog

Whether your focus is small molecules, protein biotherapeutics, vaccines, or gene therapy, QPS provides a full range of bioanalytical solutions to support all drug development programs from discovery, through preclinical to bioanalysis, clinical development, and regulatory filing. Let's discuss how we can meet the growing demand for the development of next-generation drug therapies together.

QPS
CUSTOM-BUILT RESEARCH™

MARCH 13, 2023

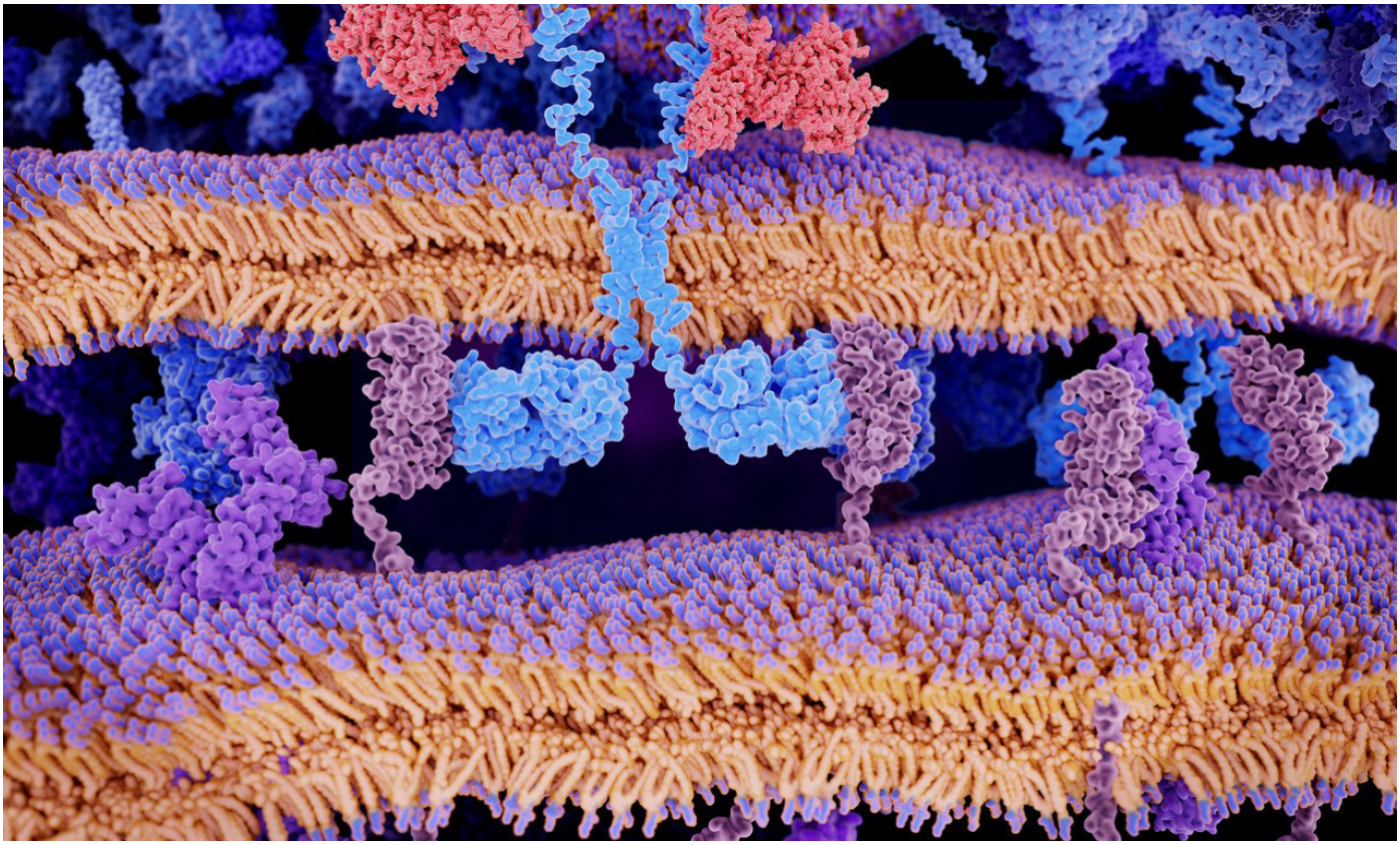
Precision Steering of CAR-T Therapies May Effectively Target More Tumor Types

Recent years have seen increased research interest in the potential of chimeric antigen receptor (CAR)-T cancer therapies. This approach uses genetic engineering to modify T cells from a person with cancer so that the cells will make CARs, proteins that can detect cancer cells and identify them as targets for killer T cells. Although such treatments have the potential to help patients achieve sustained remission, their success so far has been limited to the treatment of leukemias, lymphomas, and myelomas.

However, a pair of studies has found that "hacking" the immune cells via genetic engineering allows them to not only recognize tumor cells but also get past their defenses. The research may enable the application of CAR-T therapy to a larger number of cancer types.

Flipping the Switch

One of the studies, led by Ahmad Khalil, a synthetic biologist at Boston University, engineered CAR-T cells using a system of 11 DNA sequences. The researchers demonstrated that they could switch the T cells on and off using approved medications that interact with the genetic sequences. The T cell activities and their ability to produce a protein called IL-2, which stimulates immune responses, were thus controlled through medication.



For the second study, researchers, led by synthetic biologist Wendell Lim at the University of California, San Francisco, genetically programmed CAR-T cells to make IL-2 only when the engineered T cells encounter cancer cells. The researchers discovered that IL-2 production was most effective against tumors in mice with pancreatic cancer when it was activated via a different pathway than the one used to recognize the cancer cell.

Targeting Tumors

Both studies suggest that the technology could be harnessed to target solid tumors, which have been difficult for CAR-T drugs to attack. Tumors are more difficult for the engineered cells to enter, and they can suppress the immune response to defend themselves. "These engineered T cells overcome both roadblocks," said Andrea Schietinger, a tumor immunologist at Memorial Sloan Kettering Cancer Center in New York City. "They find their way in and then, once they're in, get the signals in the right space and at the right time to be really effective in killing the cancer cell."

The new technology and ability to switch the T cells on and off, researchers say, could make them more effective by giving them a rest period. Otherwise, the tumor-fighters can become exhausted and inactive after a prolonged period of activity.

Furthermore, the studies illustrate how CAR-T therapy research can expand to target a greater number of cancers. According to systems immunologist Grégoire Altan-Bonnet at the US National Cancer Institute, "We know a lot of the parts, now it's being able to put them together and explore," he says. "If we engineer the system well, we can really put the tumors into checkmate."

Beyond T Cells

It may be possible to apply the technology developed by Khalil and his colleagues to other cell types, such as immune cells called macrophages. This would have the advantage of making it easier to attack solid tumors. Because the system was developed to be flexible, he expects that specialists in cancer immunotherapy can modify it to meet their needs. "I hope this will capture the imagination of a lot of researchers out there," he says.

Moving forward, researchers will continue to explore the possibilities of using CAR-T therapies to treat a wider range of cancers and other diseases. With new developments and research advances, the potential for new and improved treatments is encouraging.

FEBRUARY 15, 2023

Is Stool Screening an Effective Tool for Preventing Colon Cancer?

Colonoscopies have historically been the dominant method of screening for early detection of colon cancer, the third leading cause of cancer death in the United States for both men and women. However, recent research has not only challenged the conventional wisdom on the effectiveness of colonoscopies in reducing the risk of developing and dying from colon cancer but has also pointed towards stool screening as a potentially effective alternative method of screening for colon cancer.

Stool Screening vs. Colonoscopies

The two most highly recommended methods of screening for colon cancer are the fecal immunochemical test (FIT) and colonoscopies. The U.S. Preventative Services Task Force recommends both methods with no preference given to either.

With the FIT method, a small amount of stool is collected and analyzed for the presence of blood. If blood is detected, it may indicate the presence of colon cancer or other gastrointestinal conditions. The FIT method requires only one stool sample and does not require any dietary restrictions or changes beforehand. It can be performed at home and is significantly less invasive, less time-consuming, and less expensive than other screening methods, such as colonoscopy.

A colonoscopy, on the other hand, requires that the colon be emptied using a laxative. The procedure involves inflating the colon with air or carbon dioxide and inserting a flexible tube with a tiny camera to scan the entire rectum and colon for potentially cancerous growths. One of the benefits of a colonoscopy is that during the procedure, doctors are able to remove any potentially cancerous polyps they encounter.

Despite the significant differences in accessibility, invasiveness, and cost, in the United States, only 11 percent of adults over the age of 50 use stool screening. Conversely, 61 percent of the same age demographic report having a colonoscopy performed in the previous decade. This difference can be attributed to a significant push toward colonoscopies from health professionals. Colonoscopies have long been considered the gold standard in early detection. But with fewer than two-thirds of adults 45 and older getting the recommended regular colon cancer screenings, the focus on colonoscopies as the preferred method of screening has a serious problem: They don't work if people don't use them.

continued »

Is Stool Screening an Effective Tool for Preventing Colon Cancer?

2nd

Second leading cause of death.

4th

Fourth most commonly diagnosed cancer.

1 in 5

Colorectal cancer patients are between 20 and 54 years old.

45

New age recommendation for routine screening (2021).

90%

Average post-surgical survival rate for localized disease.

18,000

People <50 years old and diagnosed with colon cancer (2021).

Is Stool Screening an Effective Tool for Preventing Colon Cancer? (continued)

Christopher Almario, a gastroenterologist at Cedars-Sinai in Los Angeles, puts it this way: "A lot of times people think colonoscopy is synonymous with colorectal cancer screening. But a lot of people don't want to do a colonoscopy."

Rethinking Routine Screening Methods

Almario recently published a study examining the effectiveness of stool screening as an alternative method of early colon cancer detection. In his study, he educated unscreened adults about screening methods and then asked them to choose between an annual stool test and a colonoscopy, which is recommended every 10 years. The study found that when educated on their options, the majority of unscreened adults, and 77 percent of those 50 and older, preferred stool screening over colonoscopy as their preferred screening method for colon cancer.

Almario's study raises important considerations about the potential benefits of educating the population about stool screening as an alternative to colonoscopies. While there are unique benefits to colonoscopies and potential downsides to stool screening, researchers believe there are legitimate reasons to consider alternatives to colonoscopies.

The study found that when educated on their options, the majority of unscreened adults, and 77 percent of those 50 and older, preferred stool screening over colonoscopy as their preferred screening method for colon cancer.

For one, for all of their benefits, colonoscopies are not risk-free procedures. Research shows that there are 14.6 major bleeding episodes and 3.1 colon perforations per 10,000 colonoscopies performed. Colonoscopies in the U.S. are also typically performed under sedation, which presents risks.

Recent studies have also indicated that the benefits of colonoscopies may not be quite as impressive as previously believed, with some analyses showing that colonoscopies reduced the risk of colon cancer and colon cancer death less than had previously been indicated. Researchers and scientists are clear: These studies and the risk factors of colonoscopies do not invalidate colonoscopies as a useful screening tool. Colonoscopies still have the advantage of reducing cancer incidence, which

leads to fewer surgeries, chemotherapies, immunotherapies, and other treatments. Ultimately, scientists continue to stress the importance of regular colon screenings — whether with colonoscopies, FIT tests, or sigmoidoscopies, which are procedures using a tool that only examines a small portion of the colon — for those 45 and older.

However, this new research demonstrates that it may be time to reevaluate colonoscopies' current standing as the gold standard of colon cancer screens. It also indicates that there may be a significant benefit in promoting and educating the public about alternative options that are less expensive and require less invasive tools, like stool screening, which may have more buy-in from the public. Ultimately, the goal is to increase the number of regular colon cancer screenings, which are critical in reducing colon cancer cases and fatalities.

DECEMBER 14, 2022

Attacking KRAS Proteins to Kill Cancer

Recent advancements have led to the development of new cancer therapies that target mutations in KRAS proteins, which were once considered untreatable. In 2021, the FDA approved the first KRAS-targeted cancer therapy, sotorasib (LumakrasTM). And while researchers in academia and the pharmaceutical industry continue working to develop ways to improve their approach, recent research may be offering the first glimpses of success that it may indeed be possible to drug the "undruggable" KRAS.

KRAS Proteins: The "Undruggable" Protein

KRAS proteins belong to the RAS family of proteins, which are involved in signaling cascades that regulate cell growth, differentiation, and death, and are among the most powerful drivers of cancer. Mutations in the genes encoded in RAS proteins are common in many of the most aggressive cancers, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic cancer. Approximately 25 percent of all lung tumors and 90 percent of pancreatic tumors have RAS mutations.

Significantly, because of their structure, mutations in the genes encoded KRAS proteins have historically been considered undruggable. KRAS proteins, specifically, help to facilitate not only tumor survival and proliferation but also their ability to evade treatment. And until recently, decades of research had yet to yield a drug that was effectively able to curb KRAS protein activity. The protein was considered impossible to target with treatment.

Challenges of Targeting KRAS Mutations

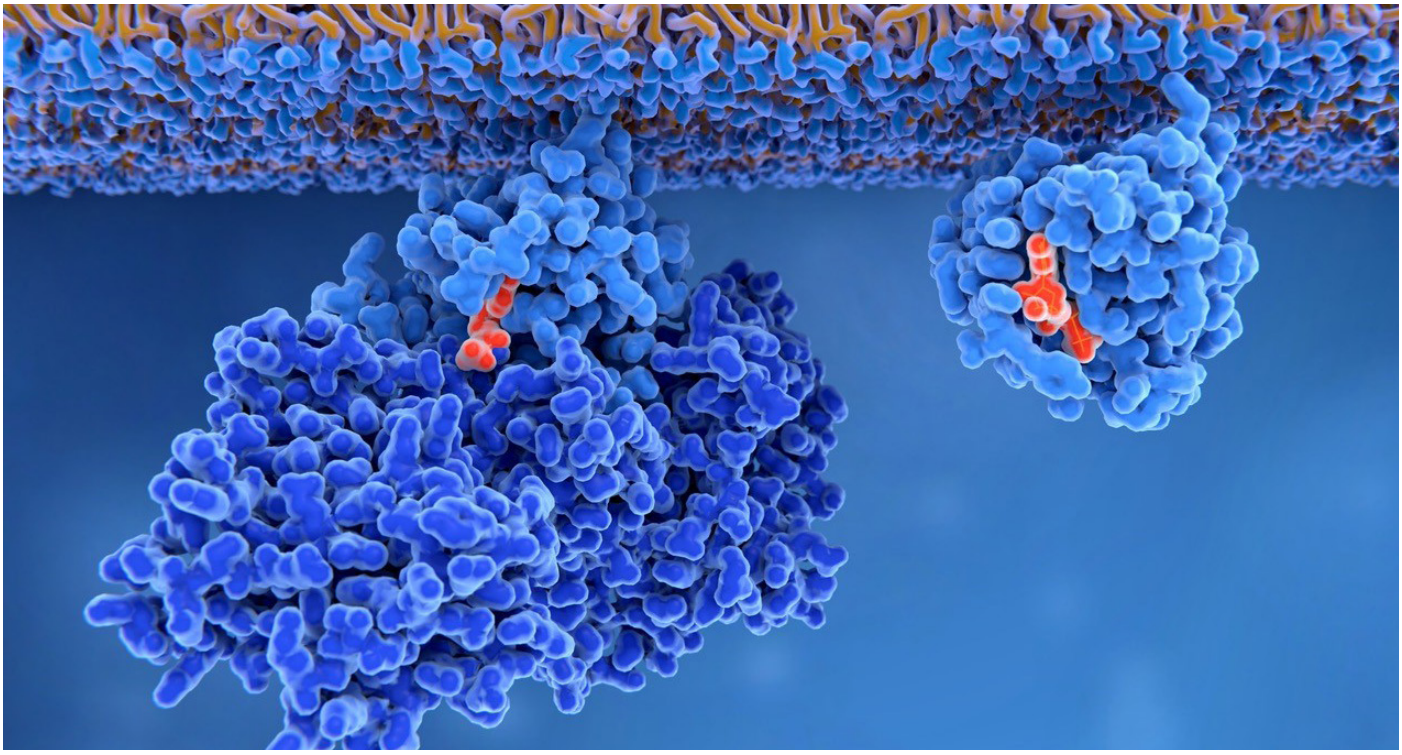
KRAS functions as a molecular switch that turns on cell growth signals. When KRAS is mutated, it is stuck in the "on" position, which results in unchecked cell growth and tumor formation. Indeed, KRAS proteins are mutated in nearly one quarter of all tumors, and often among tumors that are the most aggressive and deadly.

New Treatments to Target KRAS Proteins

In 2021, the FDA approved the first-ever KRAS-targeted therapy — sotorasib (Lumakras), which is currently approved to treat patients with non-small cell lung cancer (NSCLC) who have the KRAS G12C mutation. Sotorasib is a small molecule drug that works by inhibiting KRAS G12C, one of the most common KRAS mutations found in human cancers, and preventing KRAS from signaling cell growth.

Drug Limitations

While the approval of this drug was a landmark breakthrough, it does have a number of significant limitations.



Sotorasib only targets one specific KRAS protein mutation, the G12C mutation. And while the G12C mutation is the most common KRAS mutation in lung tumors, it is not the most common KRAS mutation overall. The majority of cancers with KRAS mutations occur at G12D, meaning that the majority of cancer patients with a KRAS mutation still do not have a treatment option.

Another limitation is in the drug's transient effectiveness. Research so far has shown that of those with G12C lung cancer treated with sotorasib, only about 28 percent of patients responded. In those with G12C colorectal cancer, the number was even lower: less than 10 percent. And even among those patients who did respond to treatment, the effect was not long-lasting; most patients who responded in clinical trials saw tumor growth slow for only about six months before relapsing.

Still, despite these transient effects, the research remains promising. The 28-percent response rate is nearly twice the response rate of standard chemotherapy. And the initial success in proving that the G12C mutation could be targeted has reinvigorated research into treatments targeting other KRAS protein mutations.

"The KRAS G12C story has told us that you can probably drug other undruggables if you have a phenomenal chemist," says Patricia LoRusso, an oncologist at Yale School of Medicine. "However, it's not good enough to just drug it – you have to take it one step beyond."

Currently, there are dozens of KRAS protein-inhibiting drug trials registered at clinicaltrials.gov. While the majority of these are focused on the G12C mutation, some are looking at the G12D mutation.

NOVEMBER 7, 2022

Cancer Trials Ask, What's the Gut Got to Do With It?

There are ten times more bacterial cells in your body than human cells. They live in our noses, in our guts, and everywhere in between. These microbes, our microbiota, are not mere passengers here for a ride but also interact with us in significant ways that affect our health.

This blog will briefly review what we know about health and our microbiota and look at how medical researchers are introducing changes to the gut microbiota of their patients to make cancer treatments more effective.

A Brief History

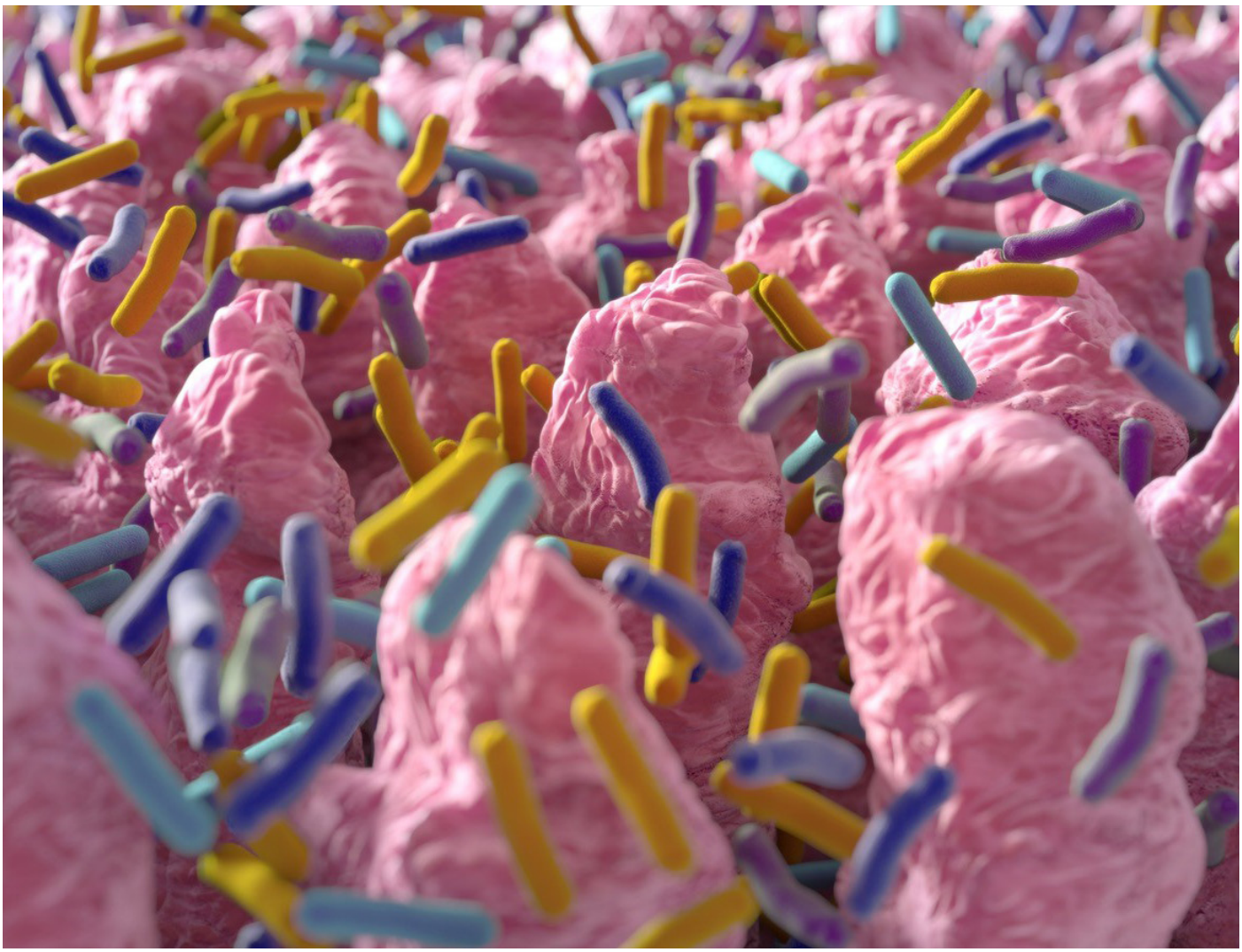
Investigation of the link between microbes and human health goes back thousands of years. The Ebers Papyrus, an Egyptian medical papyrus dating back to 1550 BCE, describes a treatment consisting of incising tumors to cause an infection to shrink tumors. Work in the intervening millennia would implicate a large set of viruses that have the potential to cause tumors. However, it wasn't until 1861 when the pioneer of microscopy, Antoine van Leeuwenhoek, looked at a stool sample using his microscope and saw "more than 1000 living" microbes that we had evidence that something else lived inside of us.

Tissier and Gasching published a paper in 1903 that is probably the first scientifically rigorous attempt to alter gut microbiota as a form of treatment. In this seminal work, the two researchers determined that a bacteria called *Bacillus acidiparalactici* could prevent milk from spoiling and was normally found in healthy infants. Tissier grew a pure culture of these "good bacteria" and gave a couple of teaspoons every day to infants who were having gut issues. He found that the gut microbiota of these infants was restored and their gut issues cleared up.

The Biome Inside Me

You may wonder how these microbes get into your gut in the first place. Where does your gut microbiota come from?

It all starts at the beginning: our gut microbiota are populated at birth. A newborn will get a different set of microbes depending on if they are born vaginally or by C-section. Different microbes thrive if the newborn is breastfed or bottle-fed. These effects continue as we grow. People tend to have a similar gut microbiota to the people they live with. Your environment and your diet have a large effect on which particular microorganisms can live inside of you.



Changing Your Gut Microbiome

Researchers have come up with multiple ways of affecting a patient's gut microbiota. One way is by changing your diet. Fermented foods, probiotics, and prebiotics have been increasingly used with positive effects to treat diseases that are heavily diet-related, such as diabetes, obesity, or inflammatory bowel disease.

A more direct approach is a procedure called fecal microbiota transplant (FMT). With FMT, feces that contain beneficial

continued »

"good" microbes are transferred into a patient. Multiple methods are available depending on where the bacteria should be placed and what the patient can tolerate. Endoscopy can be used to deliver microbes through the rectum (to reach the colon) or the nose (to reach the stomach). Enemas can be used but can take multiple applications as the transplanted feces may not reach the colon. In addition, capsules with fecal matter, so-called "poop pills," can be swallowed.

The idea of transplanting human feces has been increasingly accepted over the past five years. Despite concerns about risks like causing an infection from unidentified microbes, FMTs have displayed short- and long-term safety and are generally considered well-tolerated even in high-risk patients.

Gut Microbiota in Cancer Research

Despite the long history and growing evidence in other fields, changing the gut microbiota for cancer research has faced recent pushback.

Starting around 2010, preclinical work in mice and rats began to establish that changes to the gut microbiota can lead

The researchers analyzed stool samples from both types of patients and found that unresponsive patients had low levels of the bacterium Akkermansia muciniphila.

to different anticancer drug responses. In 2018, Bertrand Routy published his research in *Science* looking at the effect of gut microbiota on anticancer therapy. Routy's team worked with patients who were receiving a class of anticancer drugs called immune checkpoint inhibitors, or ICIs. Some of the patients responded well to ICIs, while other patients were unresponsive. The researchers analyzed stool samples from both types of patients and found that unresponsive patients had low levels of the bacterium *Akkermansia muciniphila*.

Despite promising research in humans, investigators debated in 2018 whether new clinical trials that alter the microbiome should proceed. Some people argued that more work was needed to establish exactly which microbes are beneficial and to standardize the methods used.

Clinical trials went through anyway and many of these were successful. One trial showed that dietary fiber and probiotics influenced the gut microbiome and positively affected the response to melanoma immunotherapy. Another trial found that restoring a patient's gut microbiota after chemotherapy reduced life-threatening complications, such as inflammation. Phase II studies have shown the positive effects of transferring gut microbiota between patients. These ground-breaking trials have paved the way for a new standard of care to be explored.

Next Steps

Our knowledge of gut microbes and how to best make use of them has increased significantly over the past few millennia. We're currently at a point where research has demonstrated that our gut microbiota influences cancer therapy. Today, there's been an explosion of clinical trials being conducted to translate the potential benefits of the gut microbiota into real-world advances in human health.

OCTOBER 31, 2022

Research Reveals a Fungi – Cancer Connection, with Potential Diagnostic Implications

Like bacteria, fungal microorganisms are an important part of the human microbiome and essential to human health. Scientists studying the microbiome over the past two decades have found thousands of species of microbes that live in and on the healthy body. More recently, researchers have started examining cancerous tumors to determine if they also harbor fungal life.

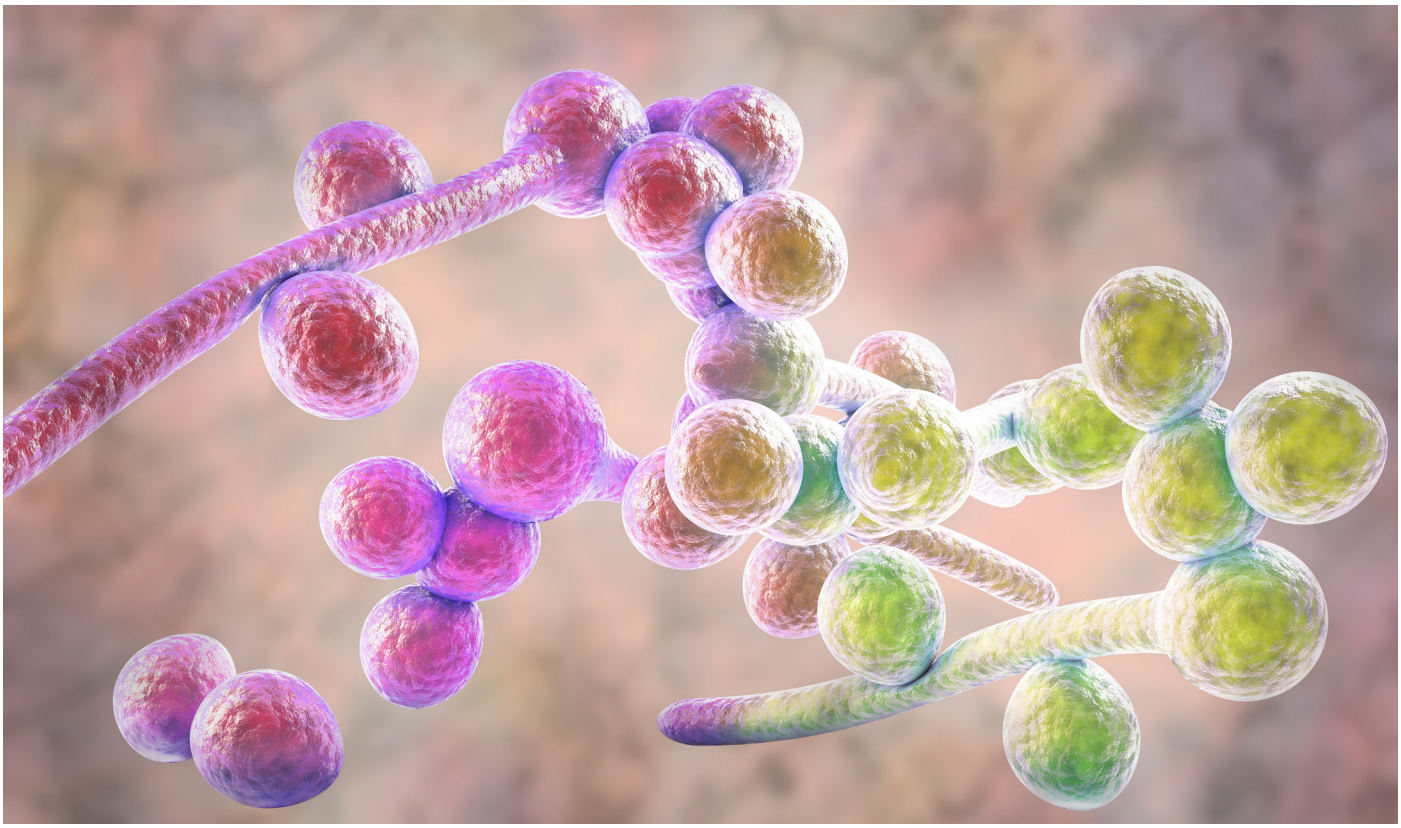
Following research published in 2020 showing that cancerous tumors contain bacteria, studies have now revealed that fungi also coexist with cancer cells. A pair of studies published in *Cell* establish a link between fungal species and certain cancers, but do not show if the fungi are directly responsible for cancer progression. Researchers say the knowledge may someday be useful in diagnosing cancer or predicting its course.

Tumors, Fungi, and Disease Outcomes

In one study, researchers at the Weizmann Institute of Science in Rehovot, Israel cataloged fungal populations in more than 17,000 tissue, blood, and plasma samples representing 35 types of cancer. Fungal DNA were present in every type of cancer studied, with different outcomes. The presence of *Malassezia globosa*, a fungus that has previously been associated with pancreatic cancer, for example, was linked to significantly reduced survival rates in breast cancer. The researchers also studied the bacteria present and found that most types of fungus had certain bacterial species that they tended to coexist with. This suggests that tumors may be non-competitive environments. In the gut, fungi and bacteria compete for shared resources rather than coexisting.

In a second study, researchers at Weill Cornell Medicine in New York City and Duke University found fungi in tumors from seven parts of the body: mouth, esophagus, stomach, colon, rectum, breasts, and lungs. Specifically, they found that gastrointestinal, lung, and breast tumors contained *Candida, Blastomyces,* and *Malassezia* fungi, respectively. Higher levels of *Candida tropicalis* and *Candida albicans* in gastrointestinal tumor cells were associated with higher gene activity that promotes inflammation, a higher rate of metastasis, and lower survival rates.

Despite these associations between fungi and disease outcomes, the research did not determine whether the fungi somehow cause these consequences or just happen to grow more easily in more advanced tumors. The researchers speculate that some microbes may disguise tumors, protecting them from the effects of the immune system or cancer drugs.



Future Research Directions

Both studies used samples from existing databases, so contamination could have happened during the collection process. Although the researchers used advanced computational methods to limit potential contamination, future research could use samples taken from a sterile environment to try to replicate the results.

Future research will also study one type of cancer at a time using cultured cells and animal models to determine if the presence of fungi among healthy cells promotes cancer development. Research could also examine how bacteria, viruses, and fungi interact to influence disease progression.

Fungal Biomarkers and Antifungal Cancer Treatment?

Finding DNA from the same fungal species in both gastrointestinal tumors and blood samples from the same patients suggests that it may be possible to detect tumors early by testing for fungal DNA. “These data are exciting because they lay the foundation for simple, inexpensive tests for Candida DNA that can more precisely delineate prognosis for gastrointestinal cancer, and augment standard tumor DNA biopsies to enable early detection of these cancers before other signs are present,” said Steven Lipkin, a study co-author and clinical geneticist at the Weill Cornell Medical Center, in a press release.

In addition, a better understanding of the fungi-cancer connection could someday allow researchers to create therapeutics that control fungal populations and limit cancer’s spread.

OCTOBER 3, 2022

Lymphatic Delivery Offers Potential Perks for Kinase Inhibitors and Other Cancer Drugs

A potential new cancer drug delivery method — through the gut's lymphatic system rather than blood vessels — could improve treatment outcomes and reduce side effects while decreasing drug resistance.

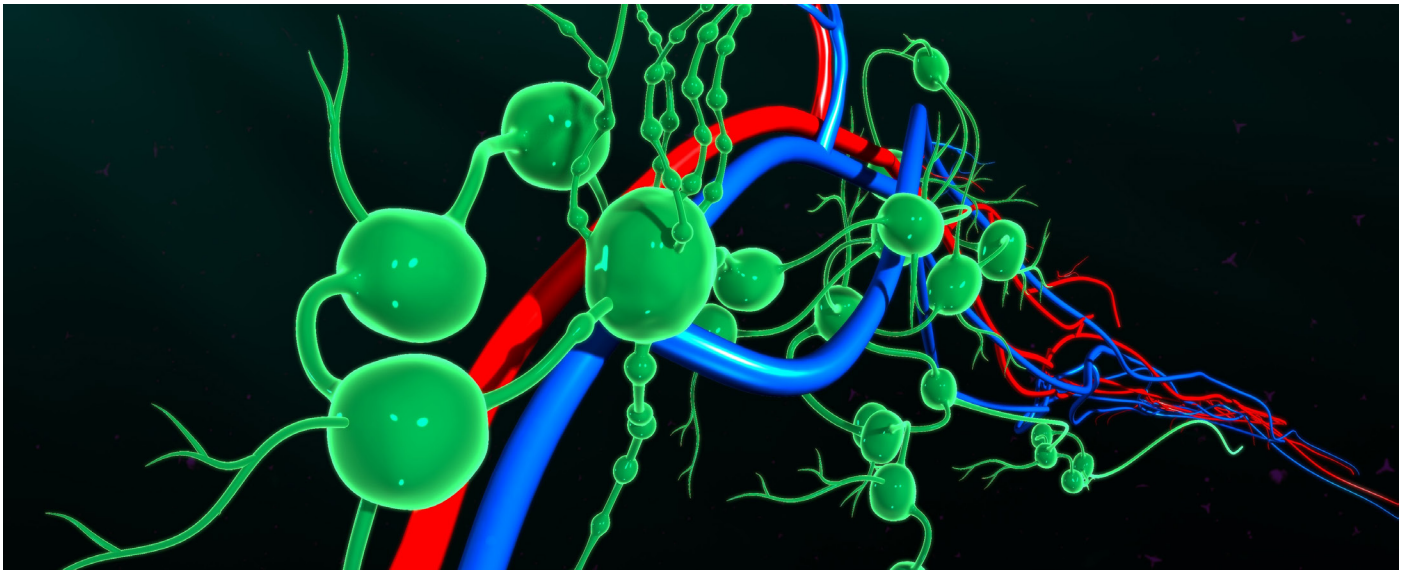
Researchers from the University of Michigan demonstrated the strategy in mice, using LP-182 – a drug designed to simultaneously inhibit phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). These kinases are intermediate signaling molecules that are part of a pathway implicated in the development of many types of cancer.

Although PI3K inhibitors have been approved to treat leukemia and lymphoma, interest has dimmed due to drug toxicity. In June, the FDA issued a warning about possible increased risk of death and serious side effects for Secura Bio's PI3K inhibitor Copiktra® (duvelisib), which earned approval in 2018 to treat relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The warning came after the company released confirmatory Phase III trial results. Recently, after reviewing data from patients followed-up after participating in clinical trials, safety concerns led the agency's Oncologic Drugs Advisory Committee to vote against use of the drug for chronic CLL and SLL previously treated with at least two therapies. In addition, Secura, Gilead, and Incyte withdrew their accelerated approvals for their PI3K inhibitors after failing to complete confirmatory trials. The FDA now requires randomized trials for PI3K inhibitors in blood cancers.

Finding the Right Balance

Combination therapy, using two or more therapeutic agents, for cancer is designed to target different cancer cell vulnerabilities. Because most oral drugs are absorbed through the blood, they first pass through the liver and can be metabolized at different rates. This can make it difficult to maintain the correct concentration of each drug in a balance that will have the intended therapeutic effect without causing side effects. It can also lead to drug resistance as the molecular pathways adapt to resist the therapy.

The Michigan researchers' new drug avoided this by first being absorbed through the lymphatic system. According to lead investigator Brian Ross, a radiology professor at the University of Michigan, the lymph nodes were "sort of like a gas can that you fill up in your car. The drug is filling up this big reservoir — it's being sequestered away from the entire body by the [lymphatic] absorption, and then slowly draining over a day into a neck vein." This slow release helps to maintain optimal drug concentrations over time and prevents the initial blast



of medicine to the system. “To my mind, it’s the world’s first kinase inhibitor that’s lymphatically absorbed,” said Ross. “It was quite astonishing, actually.”

The findings were recently published in *Nature Communications*. The study evaluated the effects of LP-182 on mice with myelofibrosis, a precursor to acute leukemia in which scar tissue builds up in the bone marrow. The researchers found that all mice that received the drug survived to 28 days — the planned cutoff for the study — with limited toxicity. Mice in the control group had progressive disease, “reaching humane endpoints” before 21 days. “Within the therapeutic window, we are able to maintain the on-target inhibition of two distinct pathways that are talking to one another,” said Ross in an article published on the university’s website. “This demonstrates the feasibility of delivering anti-cancer agents directly into the lymphatic system, which opens tremendous new opportunity for improving cancer therapeutic outcomes and reducing the side effects of the agents themselves,” he added.

Looking to the Future in Lymph

While Ross and his team continue to investigate how LP-182 works, they have created a new biotech firm, Lympharma, as others also work to develop cancer drugs delivered through the lymphatic system. For example, researchers from Tufts University have published a report on an mRNA cancer vaccine that is targeted to the lymph nodes and boosts T-cell response to skin cancer. Elicio Therapeutics’ Amphiphile (AMP) platform is designed to deliver peptides, proteins, and nucleic acids directly to the lymph nodes. A Phase I/II study is ongoing to evaluate Elicio’s cancer vaccine as a treatment for patients with mKRAS-driven tumors. Additionally, PureTech is developing technology to deliver drugs to the lymphatic system via an oral prodrug.

Lymphatic-delivered treatment could potentially target a broad range of cancers, including tumors, and autoimmune diseases such as lupus and multiple sclerosis. As for the drug for blood cancer Ross and his team are developing, he suggests that, optimistically, it could be in the clinic within two years.

OCTOBER 27, 2021

CRISPR and the Continuing Quest for CAR-T Safety and Durability

CAR-T is an immunotherapy that is currently used to treat blood cancers and is in clinical trials to treat other cancers as well. This treatment requires harvesting a patient's T cells from their blood, genetically modifying them to be more efficient in attacking cancer cells, growing them in the lab and then infusing them back into the patient. Because the first-generation CAR-T therapies are autologous – based on cells from the patient the therapy is intended for – these therapies are limited by the cost, time and infrastructure required to handle each person's cells. Genomic editing expands the landscape of CAR-T cell-based therapies, and CRISPR/Cas9 provides the capability of further streamlining immune cell-based therapies by enabling an off-the-shelf option.

CRISPR Therapeutics has been exploring an allogeneic CAR-T program with the potential for a large-batch "universal" therapy based on donor cells as opposed to a customized batch for an individual patient. Large-batch production would alleviate the need for health centers to maintain their own infrastructure and technology to develop patient-specific CAR-T therapies and would also be much faster and far less expensive – making it accessible for a patient population vs an individual patient.

The first batch of data from CRISPR Therapeutics' research shows 58% of the 26 large B-cell lymphoma patients who received the therapy saw their tumors shrink and that 38% had no signs of cancer whatsoever.

Safety First

The first batch of data from CRISPR Therapeutics' research shows 58% of the 26 large B-cell lymphoma patients who received the therapy saw their tumors shrink and that 38% had no signs of cancer whatsoever. This response is close to that of autologous CAR-T therapies such as Novartis's Kymriah and Gilead's Yescarta and is an early indication that off-the-shelf could be a viable option from an efficacy standpoint … but what about safety?

Autologous CAR-T therapies have been associated with cytotoxic release syndrome (CRS), a potentially fatal side effect where a patient's immune system goes into a "dangerous overdrive." In the 26 patients involved in CRISPR Therapeutics' Phase I trial, investigators saw no cases of grade three or higher CRS, and there was only one case of neurotoxicity in a patient who already had brain inflammation from a rare herpes infection. Just after this data was released, another allogeneic

CAR-T research program by Allogene Therapeutics was put on clinical hold due to a chromosomal abnormality in one of their study participants. It should be noted that the patient was responding to treatment, and the clinical significance of the abnormality is not yet known. Allogene suspects it may have been related to a gene editing enzyme that CRISPR Therapeutics doesn't use. While the safety outlook has been very positive in the early phase trials of CRISPR Therapeutics' research, there are other hurdles to consider.

Durability in Question

The clinical trials underway suggest the CRISPR/Cas9 CAR-T cell-based therapies do not have the desired staying power. Prior to the clinical hold, an Allogene trial showed that more than half of its initially responding patients relapsed within six months. That same timeframe applied for CRISPR Therapeutics, when all but three initial responders had relapsed within six months and one of these was just one month following treatment. This leads to the inevitable question – what are the implications of repeat dosing?

On the positive side, the ability to manufacture an off-the-shelf CAR-T therapy makes repeat dosing much easier. On the downside, both Allogene and CRISPR Therapeutics had mixed results when they redosed the relapsed subjects in their trials.

continued »

Of the seven subjects who had relapsed on CRISPR Therapeutics' treatment, plus an eighth who had not initially responded, there were three non-responders and five new remissions … all of whom relapsed shortly thereafter. When Allogene's five relapsed patients were redosed, all went into remission but two relapsed again.

The prospect of redosing has several issues associated with it, the least of which is the added costs of administering the therapy again. Every time a patient receives treatment, they need to undergo lymphodepletion to wipe out their immune system – something patients and doctors will likely not want to do more than once.

Will Technology Evolve to Address These Issues?

It is easy to forget that CAR-T therapies and CRISPR/Cas9 are relatively new, and there is still so much to be learned before we can assess the full potential of the technology. Just as there was no way to predict that CRISPR/Cas9 would enable allogeneic manufacturing, we can't foresee all the possible applications of CRISPR technology as it evolves.

In October, Prime Medicine announced the latest in new CRISPR technology, now being referred to as CRISPR 3.0. This will differ from its progenitor, CRISPR 2.0, which could only do base editing. With base editing researchers can repair individual DNA bases, but only in four out of the 12 possible ways: C-to-T, T-to-C, A-to-G, and G-to-A. CRISPR 3.0's prime editing, however, can make all 12 of the possible changes.

David Liu, the Harvard researcher who was instrumental in developing the CRISPR 2.0, was instrumental in showing how CRISPR 3.0 can insert, delete, or replace long stretches of DNA in any cell type and at any spot on the genome. The earlier CRISPR systems need to tether themselves to molecular anchors, which are only located in select regions of the genome.

The nicknames of CRISPR 2.0 and 3.0 may be misleading, because these are not potential replacements for older technology – they are more likely to become a collection of tools to choose from depending on the disease or condition being treated. Early-stage pipelines will likely continue to see an influx of CRISPR-based therapies, and researchers will continue to drive progress without waiting for results of those in earlier projects. We can only wait and see if these candidates all live up to their potential.

Are you enjoying our blog posts?

Please visit

qps.com/blog

Whether your focus is small molecules, protein biotherapeutics, vaccines, or gene therapy, QPS provides a full range of bioanalytical solutions to support all drug development programs from discovery, through preclinical to bioanalysis, clinical development, and regulatory filing. Let's discuss how we can meet the growing demand for the development of next-generation drug therapies together.

QPS
CUSTOM-BUILT RESEARCH™

QPS IS A GLOBAL CRO WITH LOCATIONS AROUND THE WORLD

BENEFIT FROM THE RESOURCES OF A GLOBAL CRO

Whether your focus is small molecules, protein biotherapeutics, vaccines, gene therapy or cell therapy, QPS provides a full range of preclinical, bioanalytical and clinical research services to support drug development needs from discovery to regulatory filing.

QPS
CUSTOM-BUILT RESEARCH™

TIME IS OF THE ESSENCE IN DRUG DEVELOPMENT.
CONTACT THE QPS BUSINESS DEVELOPMENT TEAM TODAY!

Email infobd@qps.com | Website www.qps.com