Five young investigators tackle big questions in oncology

Early-career researchers share their priorities for cancer research, from early screening and immunotherapy to nanotechnology and counseling.

Cancer is the leading cause of death around the globe, causing more than 10 million deaths each year. Diagnostics and treatments have evolved quickly, but precision screening and accessibility remain major challenges.

Nature Medicine spoke to five early-career researchers on four continents to learn what they see as the main challenges in cancer research and which discoveries are likely to have the biggest impact on cancer treatment, diagnosis and research.

Simon Manga is a clinical consultant at the Cameroon Baptist Convention Health Services, Cameroon. **Jamie Flerlage** is a pediatric oncologist at St. Jude Children's Research Hospital in Memphis, Tennessee, USA. **Cristiane Bergerot** is a psycho-oncologist and researcher at the Brasília Cancer Centre, a private oncology center in Brasília, Brazil. **David Pinato** is a clinical senior lecturer and a consultant medical oncologist at the Department of Surgery and Cancer at Imperial College London, London, UK. **Gopinath Packirisamy** is a professor in the Department of Biosciences and Bioengineering and is head of the Centre of Nanotechnology at the Indian Institute of Technology Roorkee in Uttarakhand, India.

Simon Manga: the greatest obstacle to treatment is poverty

Simon Manga developed a deep interest in reproductive health in the early 2000s, as he saw the impact of a rising wave of human immunodeficiency virus (HIV) infections in his home country of Cameroon in West Central Africa. From 1996 to 2003, the country saw over 50,000 new HIV cases per year.

"I saw women living with HIV and suffering from a lot of different problems — from the lack of contraceptives that kept them getting pregnant to the development of sexually transmitted infections that led to cervical cancer," says Manga.

After earning his diploma in reproductive health in 2006, Manga joined the Cameroon Baptist Convention Health Services, a large faith-based healthcare organization that has several programs, from AIDS prevention and control to social services.

Simon Manga. Credit: Simon Manga

As the family-planning coordinator, he started working to prevent vertical transmission of HIV from mothers to children. "In the beginning, the program was restricted to married women," he says. But to make a real impact, Manga argued that the program should include unmarried women.

"From a practical perspective, HIV infections, cervical cancer, unwanted pregnancies and abortions are complications that would end up knocking back at our door at some point, so if we could prevent them, why not do it?" he asks. It was also a humanitarian issue, Manga argues. "We would be doing a disservice to the population if we shut the doors to those most in need. This is about the universal rights everyone should have, and we couldn't deny them," he says.

Manga also put a special focus on sex workers. "They have been abandoned and are especially vulnerable to the human papillomavirus, which causes cervical cancer. This is the right population to target if we want to create social impact," he observes.

"Cervical cancer is highly preventable, but many women, especially sex workers, still suffer from it because they can't afford to abstain from having sex for a month as part of the treatment. So it's important not only to treat them free of charge, but also help with their upkeep so they can successfully complete the treatment. It is really challenging," says Manga.

The lack of screening and early treatment for cervical cancer is a big hurdle in Cameroon and the wider African continent. Cultural issues can also affect treatment. "Some go to pastors and native doctors for prayers and potions and don't come back for re-evaluation — they just come when it's too late," says Manga. "Well-off women pay for their treatment, the poorer ones [resort] to prayers and other methods. So in the end, the greatest obstacle for treatment…is poverty."

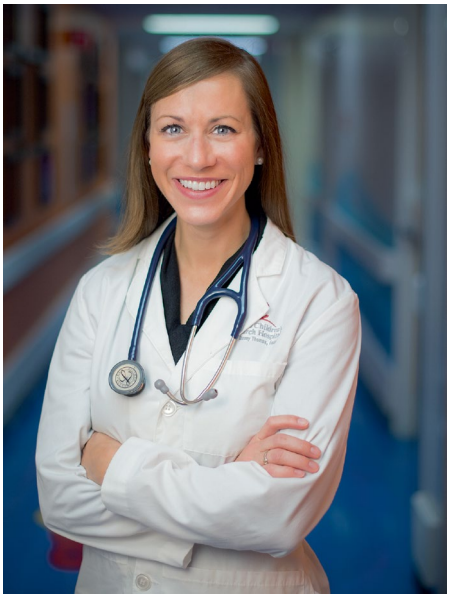
Jamie Flerlage: targeting non-responders in pediatric cancer

When Jamie Flerlage was at middle school, she had a good friend who died of leukemia. Still at a young age, she lost her grandfather to lung cancer. These experiences would help shape her career choice later on.

Now, as a pediatric oncologist, Flerlage's research focuses on Hodgkin lymphoma — which, unlike many cancers, has been curable for years and has had long-term survival rates above 90% for adults and children. At a multi-site consortium dedicated to pediatric Hodgkin lymphoma, Flerlage is running clinical trials with children and young people to understand why some patients do not respond to treatment.

"There is no 'one size fits all' approach in cancer. Even if we cure 98% of patients, 2% of them are still dying. Why are we losing them? This is a challenge even with the fanciest targeted therapies we have," she says.

This is also a challenge in chimeric antigen receptor T cell therapy. When directed against CD19, it works well for acute lymphoblastic leukemia, but less so for acute myeloid leukemia or Hodgkin lymphoma. "You can engineer T cells to fight off [cancer] cells that have a marker on them — and it works well



Jamie Flerlage. Credit: St. Jude Children's Research Hospital

for [acute lymphoblastic leukemia] because most of the cancer uniformly expresses that target. For [acute myeloid leukemia], the [markers] are not so strong, and they are way harder to target. In Hodgkin lymphoma, tumor cells make up only 1% to 2% of the tumor — so targeting just those cells will neglect all the background that also needs to go," Flerlage explains.

Flerlage adds that although survival rates might be high, chemo- and radiotherapies can lead to serious side effects. "How can we do it better so that patients don't have pancreatic insufficiency, or don't have osteonecrosis of their bones? How do we avoid that and cure them?"

Flerlage emphasizes that treatment is not just about the technical improvements research can bring — it is also about treating the whole patient and their family. "Anybody who has walked a cancer journey with a person knows that it takes a village to go through the treatment. It takes a village to get them to appointments, to help them when they're home, to support all those who are grieving inside during the journey. And when people die, it takes a village to get [everyone] through the journey and help them keep living."

Cristiane Bergerot: healthy minds improve cancer outcomes

Not only is cancer a burden in terms of physical health, but it also takes a toll on patients' mental health. Diagnosis and treatment often come with anxiety — and the uncertainty of whether the path will lead to remission, progression of the disease or death can be a source of dread and depression.

The psychological response to cancer fascinates Cristiane Bergerot, who works in psychosocial oncology, or 'psycho-oncology'. The field emerged in the late 1970s with the work of psychiatrist Jimmie Holland, who led the pioneering psychiatric service at the Memorial Sloan Kettering Cancer Center in New York City.

Psychiatric and psychological counseling not only extends the lives of patients but also improves quality of life during that extension, Bergerot says. "Considering normative data, our patients are reporting better quality of life than the average American without cancer," she says, based on research undertaken at the Brasília Cancer Centre (Cettro), where Bergerot works.

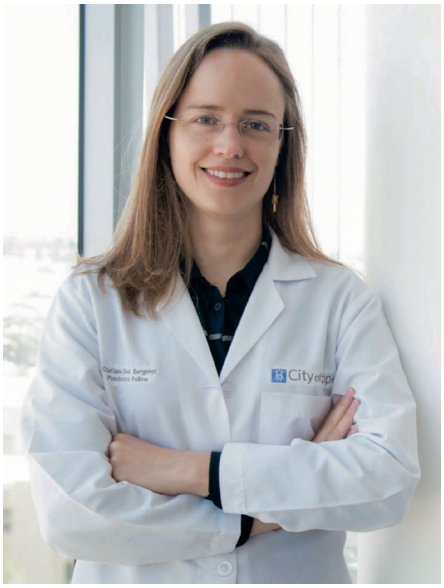
An important milestone came in 2017 with a clinical trial showing that weekly counseling sessions after chemotherapy extended the survival of patients with advanced cancer by up to five months. "It was proof that with simple actions we can improve patients' quality of life and the outcome of the treatment itself," Bergerot says.

For psycho-oncological treatments to work, doctors and care teams need to understand the patient's needs and emotional state. A precise assessment of a patient's emotional health is crucial to the development of an action plan that can best help them cope with their treatment and condition, Bergerot says.

"This is a challenge in settings where there are fewer specialized mental health professionals than the demand. This is the reality in most public hospitals in Brazil and Latin America," she says.

Technology can come in handy. "Mobile apps can reduce costs to patients and can optimize processes in terms of screening and first treatment." Metastatic renal cell carcinoma is associated with high levels of distress, so Bergerot is assessing the impact of a mindfulness app on the mental health of patients with this cancer, both in Brazil and in the United States.

Many patients cannot pay for psychological services or live in remote areas, so apps can help reduce waiting times. The COVID-19 pandemic has sped up the adoption of telehealth. "The need for virtual assistance has forced us to depend less on physical offices. Some complementary tools can potentially help patients feel less dependent on psychotherapy and feel more independent to better deal with [cancer]," Bergerot says.



Cristiane Bergerot. Credit: City of Hope National Medical Center

David Pinato: learning from viruses to develop cancer immunotherapy

Immunotherapy is regularly heralded as a promising technique for cancer treatment, but the field still holds many unknowns. In liver cancer, immunotherapy is usually used too late, according to David Pinato.

The 5-year relative survival rate for liver cancer is just 20%, mainly because of relapses after surgery, the treatment for most early-stage cases. Patients who receive immunotherapy tend to be treated at a much later stage, when the chances of success have already decreased.

"What we're trying to do," Pinato says, "is to use immunotherapy to treat liver cancer at a very early stage, when patients would normally have the tumor removed. We want to use the therapy before surgery so that patients have increased chances of being cancer-free for life," he adds.

Pinato's team at Imperial College London is trying to determine how the immune system functions in patients with liver cancer. Because viruses such as HIV and hepatitis virus are a risk factor for a number of cancers, there could be a link between how viruses attack the human immune system and how cancer spreads — which would provide a clue to the mechanisms by which immunotherapy works.

Pinato studies links between the immunology of viral infections and cancer.

David Pinato. Credit: David Pinato

"If you have cancer and HIV, that cancer will likely grow faster. So I think the [mechanism by which] HIV impairs your immunity might be related to how cancers respond to immunotherapy," he says.

Pinato's hypothesis is that HIV dampens the response of $CD4^+$ helper T cells in a way very similar to how liver cancer does. This in turn dampens the response of cytotoxic $CD8^+$ killer T cells, which reduces the ability to fight both infections and cancer.

Intriguingly, liver cancer caused by viruses seems to respond better to immunotherapy than non-viral liver cancer does. "This could be game-changing for the developing world, where most cases of liver cancer are associated with viral infection," Pinato says.

Gopinath Packirisamy: nanotechnology can provide affordable treatments

Gopinath Packirisamy had his first contact with cancer therapy while earning his master's degree in biotechnology in the early 2000s. "Cancer gene therapy sounded like a fascinating topic and I was also very interested in molecular biology. I wanted to understand how we can use nanoparticles to improve therapeutic efficiency," he says.

"The greatest challenge in cancer is that when you give the anti-cancer drug to a patient, the drug cannot tell the difference between cancerous and healthy cells, going on to attack them all. But with a nanoparticle, you can go exactly where the target is," Gopinath says. But this targeting is a tricky thing to do. Gopinath studies two different approaches for targeting: passive and active.

In the passive approach, polymer nanoparticles about 200 nanometers in diameter attach to cancerous tissue using the abnormal blood vessels that help these nanoparticles reach the targeted tumor site. Nanoparticles, when delivered intravenously, will naturally travel into the bloodstream and cross the leaky vascular walls of cancerous tissue, entering the tumor to deliver chemotherapeutic drugs.

"These leaks in blood vessels help deliver the polymeric nanoparticles to the tumor. The other healthy vessels surrounding normal tissue do not support the transport of these nanoparticles, so they cannot be delivered to healthy tissue areas. It can only be delivered to cancerous areas."

With active targeting, the nanoparticle is attached to an antibody, peptide or tumor-targeting ligand that recognizes the cancer cell, attaching to it and delivering cytotoxic drugs. "Most breast cancer cells, for example, express folic acid receptors — so we add folic acid to the nanoparticles so that they can bind into these cancerous cells, using a lock-and-key mechanism," Gopinath explains.

Gopinath tested these approaches in vitro with breast and lung cancers, and had some positive results, as nanoparticles were more precise in reaching cancerous cells than were conventional therapies.

Gopinath Packirisamy. Credit: Indian Institute of Technology Roorkee

Another possible use for nanotechnology is nanofiber bandages, to be used after surgery. Made of biodegradable polymer that dissolves into the body, these nanofibers could surround the incision, slowly releasing chemotherapy to any remaining cancer cells. "These fibers could be made for controlled release of anti-cancer drugs if needed," Gopinath adds.

Gopinath hopes that nanotechnology can help advance precision cancer medicine and, most importantly, should be affordable in developing countries such as India. "Clinical trials are expensive in India, but I hope they will be feasible in the future."

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