THE TECHNOLOGY: HOW MRNA CANCER VACCINES WORK

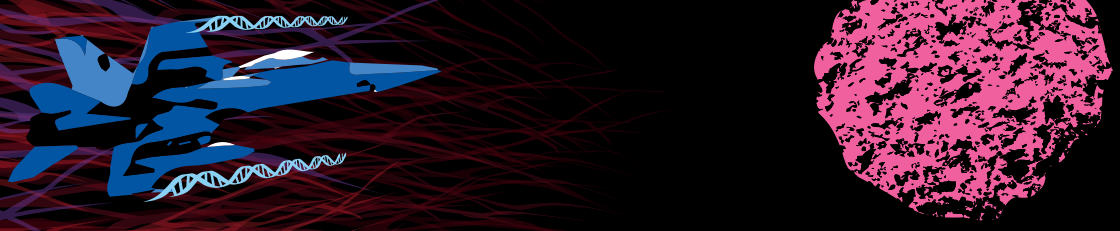
THE CHALLENGES FOR SCIENCE, SOCIETY, AND ECONOMY

THE SOLUTION FOR A FAIR AND EQUAL VACCINATION CAMPAIGN

CANCER VACCINE FAIRNESS

IMPACT 2023

AN FII INSTITUTE PUBLICATION



TUMOR NO MORE

HOW HUMANITY CAN GET RID OF CANCER

FII INSTITUTE
Future Investment Initiative Institute
Impact on Humanity

EDITORIAL

TECHNOLOGY FOR A FAIRER HEALTH SYSTEM

FULL SPEED AHEAD! We have just experienced a three-year period of acceleration in health technologies that humankind has never before seen. The ultra-rapid development of vaccines against the novel coronavirus has been the most significant contributor to the mitigation of the Covid-19 pandemic. And, it was not just more of the same in a shorter time - it was a leap into the future! The two most efficient of these new vaccines used a technology that was never before utilized in approved vaccines – mRNA technology. The first to receive approval, these vaccines continue to protect billions of people against infection and/or serious bouts of Covid-19. This is one of the best examples of the positive impact that new technologies can have on humanity, and in this report we tried to find out how the mRNA success story might continue. There's definitely more to come: the entire field of therapeutic cancer vaccination is just opening up, and mRNA technology is a very promising opponent to finally end humanity's battle against cancer. This report does a deep dive into the potential impact and challenges of cancer vaccines.

And we do more than that, because the Covid-19 pandemic has not only shown how great new health technology can be, but also how unprepared and internally focused we as humans can be. The global threat of a new virus was answered mostly by a nationalistic approach: our country first! Yes, on paper everyone agreed that a pandemic can only be over when it's over everywhere - but these programs and alliances failed to pass the inclusivity test. If mRNA vaccines now start to attack cancer, we must not only learn from the technological advancements, but also from our failures. We must use the new technology also as a tool to reach a fairer, more equitable global health system. Our driver is the third UN Sustainable Development Goal: "to ensure healthy lives and promote well-being for all at all ages."

A cancer patient in Afghanistan or Burundi is not better or worse than one in Canada or Denmark. If there is a chance for a cure, the only factors that should determine access to treatment are medical ones. Access to this lifesaving technology should neither be a question of the depth of your pockets nor the emblem of your passport. Of course, this should be the case for every lifesaving technology, but the chances of a positive outcome are higher when, as is the case with mRNA cancer vaccines, a completely new technology is implemented.

Defeating cancer with therapeutic vaccines is a challenge for humanity. At FII Institute, making an Impact on Humanity is at the core of what we do, so we want to take on that challenge as equitably and efficiently as possible. In this report, we have made a proposal for how these ambitious goals can be achieved. We see it as a step towards a world where health means wealth – and not the other way around.

Richard Attias
CEO, FII Institute

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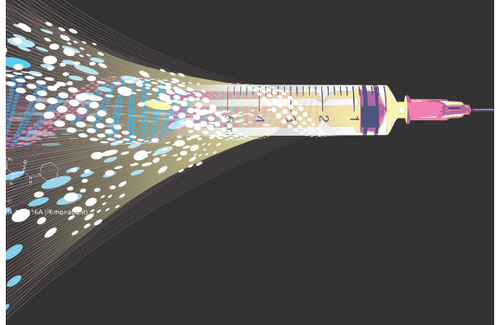

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THE TECHNOLOGY OF mRNA VACCINES AGAINST CANCER

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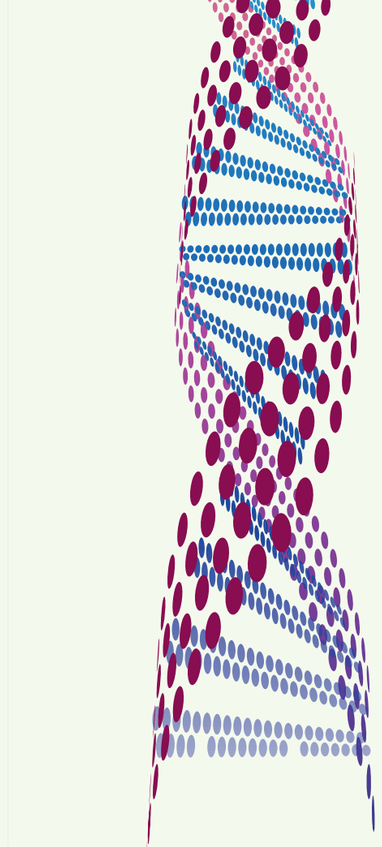

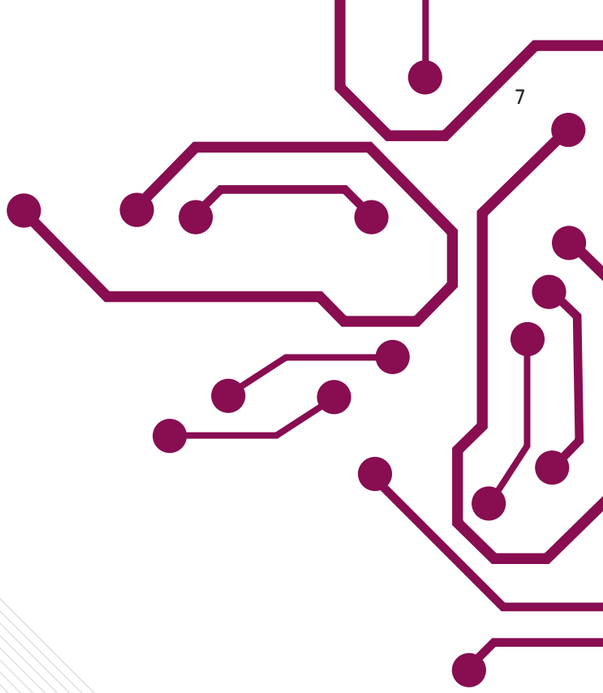

THE TECHNOLOGY
HOW CANCER VACCINES WORK

A human nightmare may soon be over, as mRNA technology promises to win the battle against cancer – by producing individual vaccines for every cancer patient. How does mRNA technology promise to do that, and when will it be able to deliver?

CANCER DIAGNOSIS HAS BEEN like a death sentence. Though improved treatments and early recognition have significantly raised survival rates, cancer is still a traumatizing and devastating (and expensive) disease causing millions of deaths per year.

Vaccination against cancer? It sounds like a long-awaited utopia. A quick shot against the scourge of humanity, which annually kills almost 10 million people around the world, and sickens almost twice as many (as of 2020), according to the International Agency for Research on Cancer.

Fundamentally, the idea is not new. As early as 1909, the German physician Paul Ehrlich suggested that the immune system fights tumor cells in the body. Decades later, researchers confirmed his observations. The idea of pushing the natural defenses to attack cancer cells in a targeted manner was obvious.

Today, there are two fundamentally different approaches to vaccination against cancer. One is preventive vaccination, which works similarly to protective vaccinations against pathogens such as viruses and bacteria. In fact, about 8% of tumors in industrialized nations are due to infections with viruses or bacteria, and the proportion is higher in the Global South. Liver cancer can be triggered by viruses, or tumors in the head and neck region. One preventive vaccination has already been highly successful for several years: vaccination against human papilloma viruses (HPV), which can trigger cervical cancer.

In addition, therapeutic vaccination against cancer is currently gaining in importance. This means that people who have already developed cancer are treated with therapeutic procedures that work on the same principle as a vaccination. The mechanism of action is the same, except the goal is not to prevent the disease, but to positively influence its course using the body's own weapons, and perhaps even to cure it.

Or, blunt and simple: With effective therapeutic vaccines, a cancer diagnosis would no longer be a death sentence – just the beginning of a temporary sickness, cured within a few weeks or months. Tumor no more.

And the most probable candidate to make this dream a reality is a substance that we have known since 1961, and that is also part of every cell in our body - and of every single cell since life on earth began some billion years ago: Messenger ribonucleic acid, in short mRNA.

A MESSENGER ENTERS THE STAGE

The Covid-19 pandemic has made this substance famous. It has helped a new technology to achieve a breakthrough that hardly anyone believed in for years: vaccines based on mRNA.

In 1961, eight years after they had discovered the double-stranded DNA, James Watson and Francis Crick also contributed to the discovery of mRNA: a single-stranded molecule of RNA that plays a central role in the process of synthesizing a protein. But ever since its discovery, mRNA was considered too unstable, too volatile, to carry any messages to any target.

Yes, mRNA served as a messenger for information within a cell, but getting information into a cell that way? In 1995, Hungarian bioscientist Katalin Kariko was demoted by her university for stubbornly working on such crazy ideas. Some years later, the German mRNA researcher and entrepreneur Ingmar Hoerr suffered a similar fate. At a conference where he presented some of his research data, a Nobel prizewinner bashed him fiercely: "This is completely shit what you're telling us here!"

And statements like "pure science fiction" were also fired at the Turkish-German scientists Özlem Türeci and Ugur Sahin when they talked about their research into mRNA as a vaccine in the first decade of the 21st century. Just three companies managed to stay afloat in that sea of skepticism: Hoerr's CureVac (founded in 2000), Sahin/Türeci's BioNTech (founded in 2008) and Derrick Rossi's Moderna (founded in 2010).

But in the years since then, the once-mocked and sidelined scientists have succeeded. They found a substance that would chemically tame the unstable messenger: fat, a substance with which we don't usually like to be associated. The mRNA researchers cleverly succeeded in packing their active ingredient into ↘

> "The best way to reach universal health coverage is to increase the capacity of all regions to manufacture the health products they need."
>
> **TEDROS ADHANOM GHEBREYESUS**
> General Director World Health Organization

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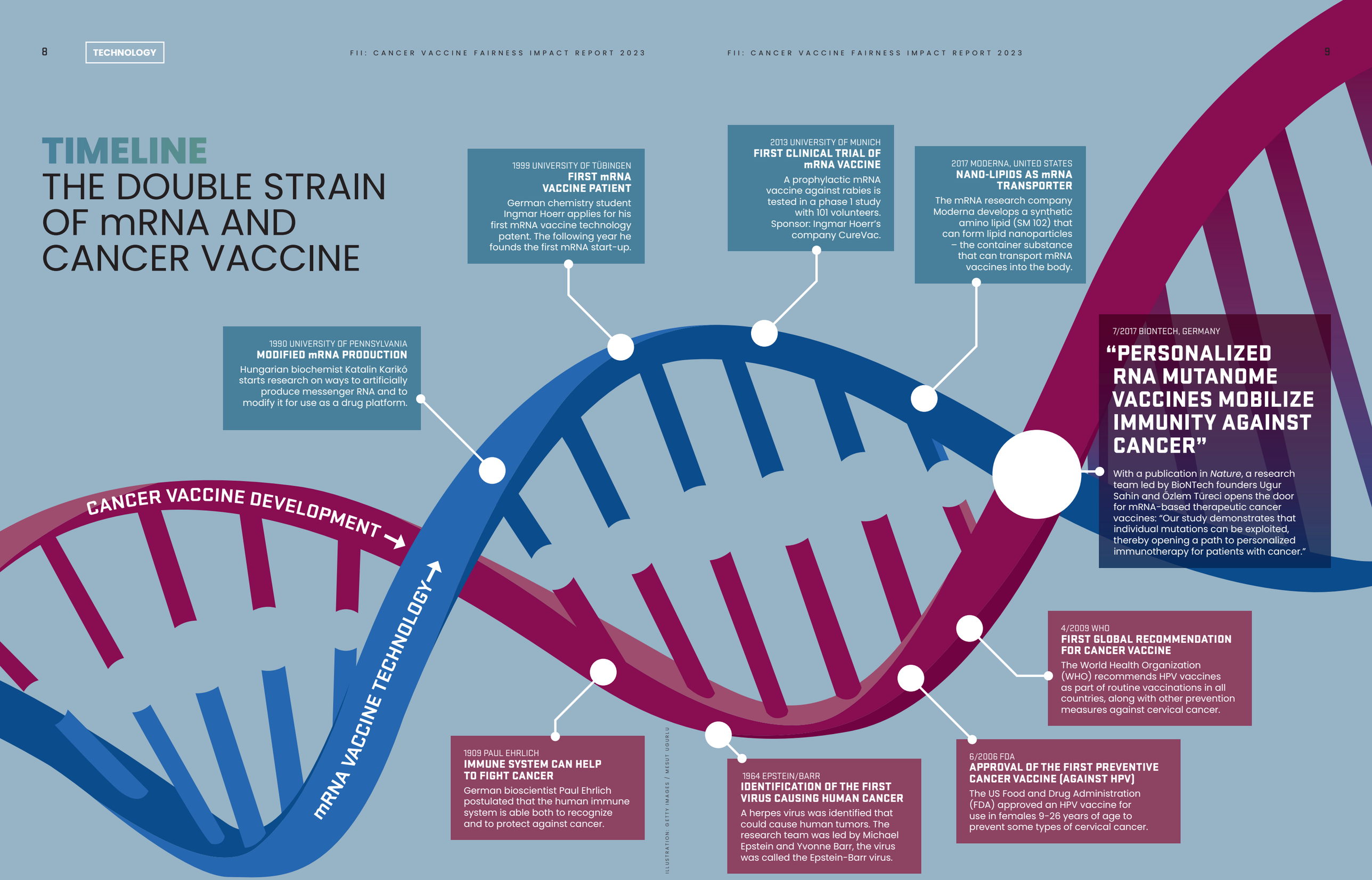
TIMELINE
THE DOUBLE STRAIN OF mRNA AND CANCER VACCINE



1990 UNIVERSITY OF PENNSYLVANIA
MODIFIED mRNA PRODUCTION
Hungarian biochemist Katalin Karikó starts research on ways to artificially produce messenger RNA and to modify it for use as a drug platform.

1999 UNIVERSITY OF TÜBINGEN
FIRST mRNA VACCINE PATIENT
German chemistry student Ingmar Hoerr applies for his first mRNA vaccine technology patent. The following year he founds the first mRNA start-up.

2013 UNIVERSITY OF MUNICH
FIRST CLINICAL TRIAL OF mRNA VACCINE
A prophylactic mRNA vaccine against rabies is tested in a phase 1 study with 101 volunteers. Sponsor: Ingmar Hoerr's company CureVac.

2017 MODERNA, UNITED STATES
NANO-LIPIDS AS mRNA TRANSPORTER
The mRNA research company Moderna develops a synthetic amino lipid (SM 102) that can form lipid nanoparticles – the container substance that can transport mRNA vaccines into the body.

7/2017 BIONTECH, GERMANY
"PERSONALIZED RNA MUTANOME VACCINES MOBILIZE IMMUNITY AGAINST CANCER"
With a publication in *Nature*, a research team led by BioNTech founders Ugur Sahin and Özlem Türeci opens the door for mRNA-based therapeutic cancer vaccines: "Our study demonstrates that individual mutations can be exploited, thereby opening a path to personalized immunotherapy for patients with cancer."

4/2009 WHO
FIRST GLOBAL RECOMMENDATION FOR CANCER VACCINE
The World Health Organization (WHO) recommends HPV vaccines as part of routine vaccinations in all countries, along with other prevention measures against cervical cancer.

6/2006 FDA
APPROVAL OF THE FIRST PREVENTIVE CANCER VACCINE (AGAINST HPV)
The US Food and Drug Administration (FDA) approved an HPV vaccine for use in females 9-26 years of age to prevent some types of cervical cancer.

1964 EPSTEIN/BARR
IDENTIFICATION OF THE FIRST VIRUS CAUSING HUMAN CANCER
A herpes virus was identified that could cause human tumors. The research team was led by Michael Epstein and Yvonne Barr, the virus was called the Epstein-Barr virus.

1909 PAUL EHRLICH
IMMUNE SYSTEM CAN HELP TO FIGHT CANCER
German bioscientist Paul Ehrlich postulated that the human immune system is able both to recognize and to protect against cancer.

ILLUSTRATION: GETTY IMAGES / MESUT UGURLU

CANCER VACCINE TECHNOLOGIES

Therapeutic vaccines are used in people who already have cancer. They are designed to stimulate the immune system in various ways to attack the tumor cells. The main forms are:

Protein/peptide-based vaccines

Patients are given as antigen an appropriate, tumor-specific protein or protein fragment. Antigen-presenting cells (APCs) are designed to take up this protein, activate matching T cells, and stimulate them to divide. The cytoxic T cells attack tumor cells carrying this antigen.

DNA- or RNA-based vaccinations

Instead of administering the finished protein to the patients themselves, they are given instructions (encoded in mRNA) on how to build that specific protein. The body then produces the protein itself and stimulates the immune system to get active and attack the protein – and with it, the cancer.

Dendritic cell therapy

Dendritic cells are part of the immune system. They can be obtained from a blood sample, multiplied in the laboratory, and given back to patients loaded with the recognition structure (the tumor antigen). This activates the T cells in the body.

Adoptive T-cell transfer (T-cell therapy)

T cells obtained from the patient's blood or tumor can be activated and multiplied outside the body by contact with antigen-presenting cells. These directly attack the tumor cells once they are returned to the patient.

CAR-T-cell therapy

Another highly innovative therapeutic vaccination option is to remove certain immune cells, known as T cells, from patients and genetically engineer them in the laboratory to match the recognition structure of the cancer cells. For this purpose, they are equipped with an artificially produced surface protein that exactly matches the respective tumor, the Chimeric Antigen Receptor (CAR). This recognizes the corresponding antigen structure on the tumor cell surface. The CAR T cells thus aligned are returned to the patient by infusion and can continue to multiply in the patient's body and fight the tumor cells.

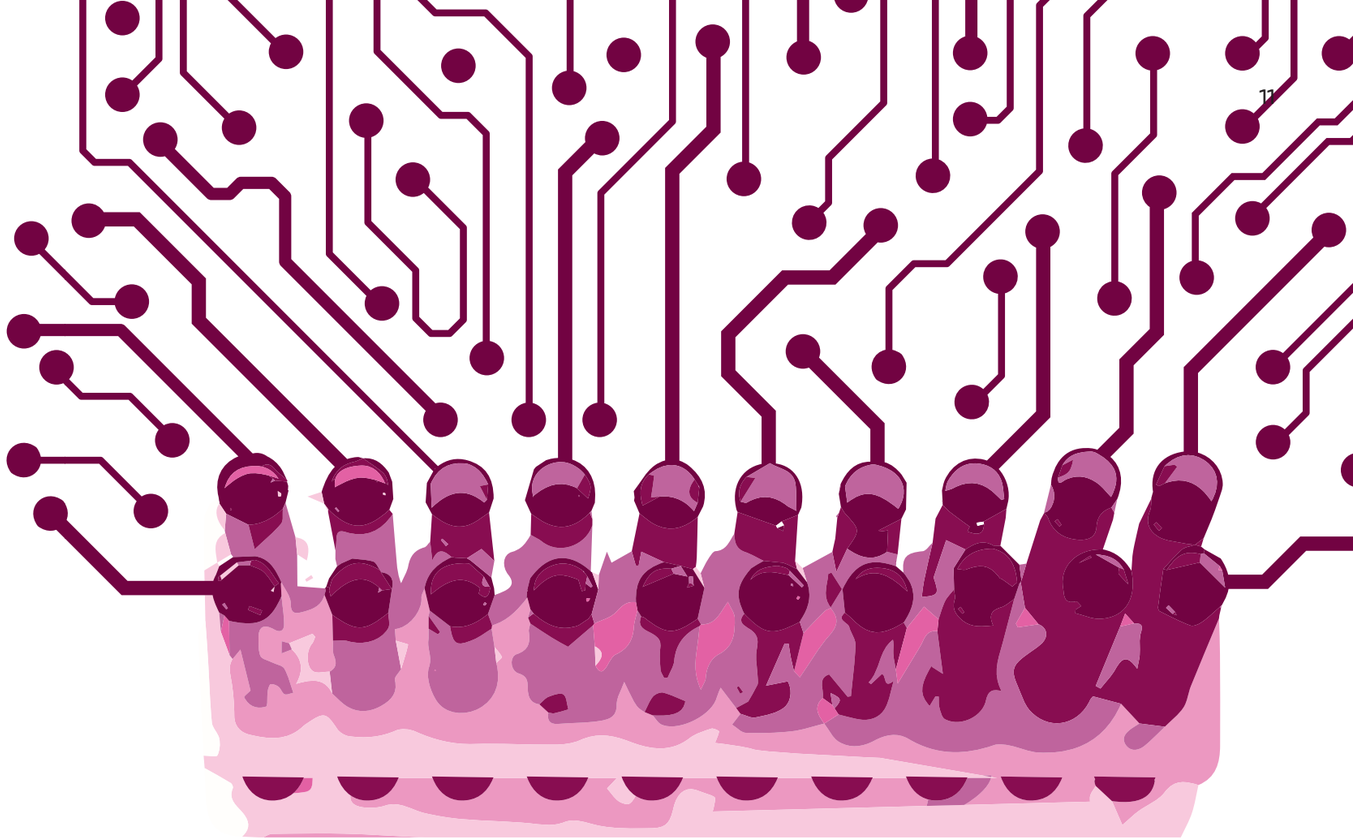


ILLUSTRATION: DANIEL HERTZBERG; ICONS: FLATICON.COM

microscopically small droplets of fat. These "lipid nanoparticles," as they're called, serve as a kind of envelope that stabilizes and protects the molecular messengers until they arrive at the target cell to unleash their message.

THE MESSAGE AS A BLUEPRINT

With the technical problem solved, the next question came up: What kind of message should the messenger carry?

During the Covid-19 pandemic, we learned (the hard way, and on fast track) that mRNA contains the blueprint to synthesize proteins. Our cells need lots of proteins to maintain their vital functions, so mRNA helps them survive. A virus also contains proteins, but different ones. So mRNA can help to kill them.

The proteins of an incoming virus are a kind of foreign language for our immune system. When it can learn just one of its words in advance, it can recognize the foreigner, the virus, as soon as it tries to enter the body. And this kind of teaching is done by mRNA vaccines: They are mainly a piece of mRNA that carries the information to build one protein specific to a virus.

In the case of the Sars-CoV2 virus that caused the Covid-19 pandemic, this one word in a foreign language is the spike protein of that virus. Today, billions of doses of mRNA vaccines have taught immune systems all over the world to be alert against the potential troublemaker: mRNA technology has finally taken off.

CANCER, THE NEXT FRONTIER

Suddenly centre-stage, mRNA technology is checked for additional uses. It's not only viruses that contain proteins, every cell does, including cancer cells. And because those cells really have no business being in our bodies in the first place, it should be possible to trigger the immune system to fight them as well. Can a technology that has proven to activate the immune system against Covid-19 also be used to activate it against cancer?

Yes, it can, according to a paper published in the July 2017 edition of the scientific magazine *Nature*: "Our study demonstrates that individual mutations can be exploited, thereby opening a path to personalized immunotherapy for patients with cancer," claimed a research team led by then little-known BioNTech-cofounder Ugur Sahin. The publication reported the results of the "first in-human application of this concept in melanoma." "This concept" was mRNA vaccination, and they were very promising results indeed: "The cumulative rate of metastatic events was highly significantly reduced after the start of vaccination, resulting in a sustained progression-free survival."

Such cancer treatments are not just possible in theory, they're already being tested. Clinical trials are currently being conducted for breast, prostate, and skin cancer, as well as for other forms of cancer (see page 26, The Challenges - Research). But there is one fundamental difference. In the case of Covid-19, mRNA can protect billions of people with one vaccine – but with cancer, it only attacks one tumor at a time.

ONE TUMOR AT A TIME

Compared to a classical vaccination, with an mRNA cancer vaccine the process is simply reversed. The structure that the immune system is supposed to recognize and attack is no longer made in the lab, but produced by the body itself. The mRNA carries the blueprints for important components of a tumor, such as proteins specific to that tumor.

"The selection of target structures is extremely important," says Niels Halama, a professor at the Translational Immunotherapy Unit of the German Cancer Research Center (DKFZ) in Heidelberg. "In order to precisely catch the tumor, they should not be present in healthy body tissue, if possible."

That's tough, but doable. In every cancer, a whole series of mutations appears inside the cancer cells. Together, the various mutations make up what is known as the tumor's "mutanome." Every tumor has its own, unique genetic fingerprint, based on the dozens or hundreds of mutations it collected during its growth. A team of researchers at the German University of Mainz led by John Castle and Sebastien Kreiter counted 563 protein mutations in one melanome.

If you can detect one specific protein of this mutanome, you can design a mRNA vaccine that targets exactly that protein – and then alerts and empowers the immune system to get rid of the cancer.

AGGRESSIVE BODY DEFENCE

Usually, the immune system should not need any empowerment at all. It is empowered to get rid of everything it doesn't like in the body. And that's a lot.

Put simply, the immune system doesn't like what it doesn't know. If something it doesn't know attempts to get into the body, it becomes aggressive. In some cases, very aggressive. It either kicks out intruders or kills them, often mobilizing whole armies to expel them.

And once something is kicked out, the immune system forms antibodies that prevent any future attack by the same ↘

bunch of intruders. This is what makes us immune. In the course of evolution, strong immune systems were rewarded. Those organisms that had more open immune systems, ones that let potential intruders into the body and gave them a chance to walk around and spread – just did not survive.

HOW TO TEACH IMMUNE SYSTEMS

But sometimes an immune system simply doesn't act fast enough - as in the case of an unknown virus. That's where a prophylactic vaccine helps by alerting the system to the potentially invading foreigner. And sometimes it doesn't act as it should – as in the case of a tumor that pretends to be just a normal part of your body. That's where a therapeutic vaccine can help by revealing to the immune system the danger that is hidden in the tumor cells.

> **"We had to study the immune system in order to be able to redirect it against cancer."**
>
> **ÖZLEM TÜRECI**
>
> Physician and bioscientist, cofounder of BioNTech SE, Mainz, Germany

No one expressed the guiding principle of vaccination more aptly than the Italian educational reformer Maria Montessori: "Help me to do it myself. Show me how. Don't do it for me. I can and want to do it myself." At the start of the 20th century, this is how Montessori described the ideal teacher-child relationship. It corresponds perfectly with the relationship between the immune system and a vaccine. While the actual vaccine has absolutely no direct effect on the virus, it helps the immune system to set up a defence against it. It gives the body's own regulatory system a kind of mugshot of the troublemaker, so they can be immediately apprehended upon entry.

Like a teacher, the vaccine gives the body the information it needs about the virus so it can develop antibodies even though it has not yet been infected. And like a sparring partner, the vaccine trains the immune system in how best to fight and win should the virus ever enter the arena. Thus, suitably trained and equipped, when the virus shows up, the body is able to defend itself or at least limit the outcome of the attack.

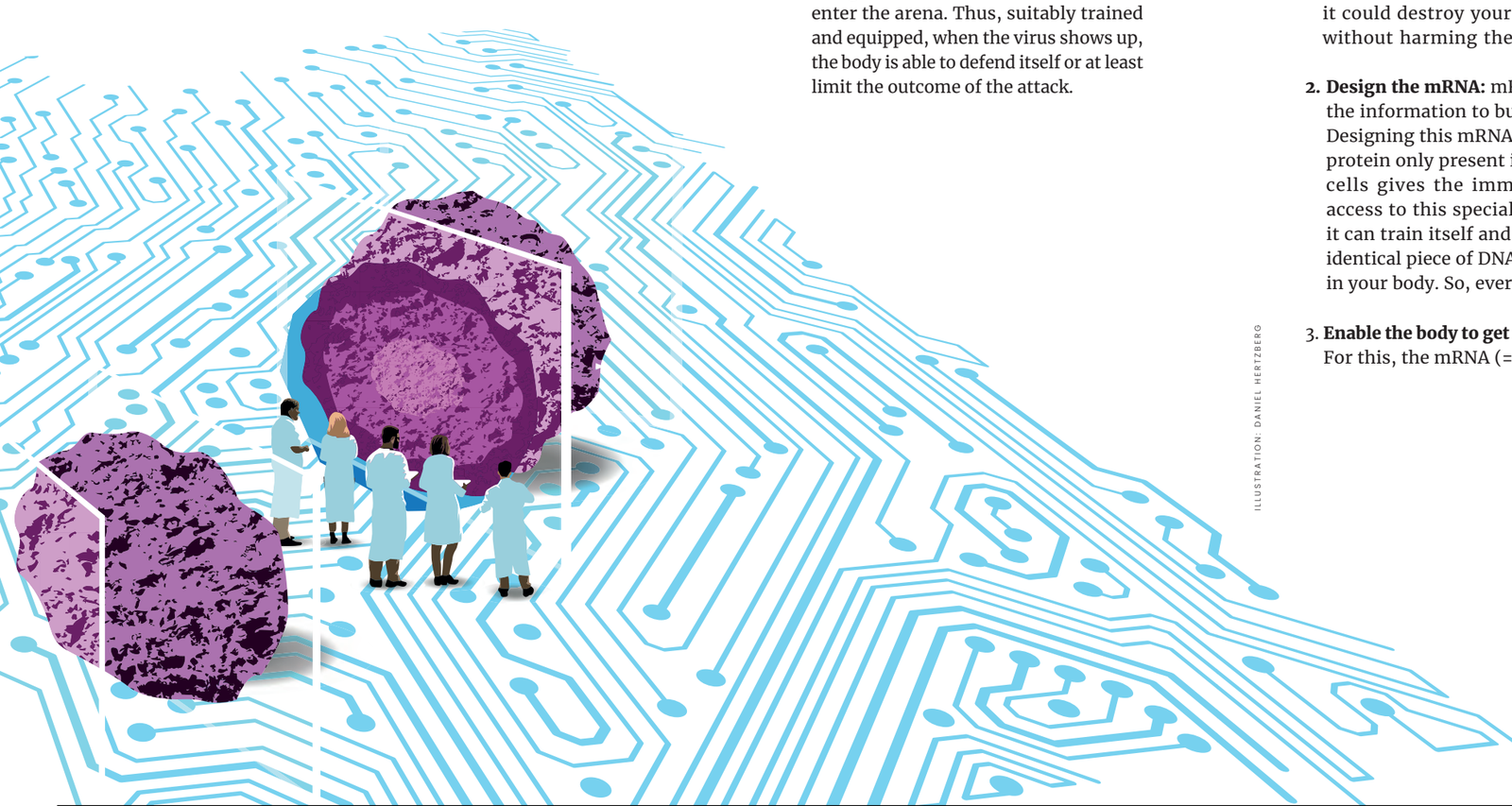


ILLUSTRATION: DANIEL HERTZBERG

BLUEPRINT AGAINST CANCER

Cancer cells are different in each cancer patient, so to attack them with mRNA technology, a different, personalized mRNA vaccine would have to be developed for each and every patient. We would have to look for a typical protein in those cancer cells, construct an mRNA strand that produces exactly that protein, and then vaccinate the respective patient with the mRNA. As with the Covid-19 vaccines, the immune system would then develop antibodies against the protein – and what combated the virus in the pandemic would then combat tumor cells in cancer.

We can sum this up in a simple three-step process.

1. **See the difference:** If your immune system could be trained to attack precisely one of the mutations of your cancer's DNA that is not present in the same part of your normal DNA, it could destroy your cancer cells without harming the rest of you.

2. **Design the mRNA:** mRNA contains the information to build proteins. Designing this mRNA for a special protein only present in the cancer cells gives the immune system access to this special mutation – it can train itself and attack every identical piece of DNA that it finds in your body. So, every cancer cell.

3. **Enable the body to get the job done:** For this, the mRNA (= the vaccine) needs to be transported the right, efficient way into the body. That transport is done by nanolipids, as we might all have heard during the Covid vaccination campaigns.

This is the basic principle of all mRNA cancer vaccines. But it doesn't work in the same way for every cancer, as some tumor types are very effective at suppressing immune reaction. That's why there are different studies for different types of cancer with different results. The most progress up to now has been made with melanomas (skin cancer).

IMMUNE CHECKPOINT INHIBITOR

This is the most successful immunotherapy against cancer so far. Immune checkpoints are mechanisms in the immune system that prevent the immune system from becoming too active and also attacking healthy tissue. At these checkpoints, immune cells exchange proteins or other signals with each other and with other cells. However, the checkpoint mechanism can also prevent tumor cells from being attacked. Antibodies directed against such checkpoints, known as checkpoint inhibitors, can lift this restraint – and the immune system is able to get going. Checkpoint inhibitors have proven to be effective against a number of cancers. They are already approved in the US, regardless of the type of cancer.

> **“For four decades, there has never been anyone who has said to me, ‘Katalin, you’re doing a good job.’”**
>
> **KATALIN KARIKO**
>
> Bioscientist since 1973, mRNA researcher since 1990, Vice President of BioNTech since 2013

ILLUSTRATION: DANIEL HERTZBERG

THREE DAYS FOR A NEW VACCINE

Developing a separate vaccine for each tumor has only been made possible by the development of very good, fast technology for decoding genetic material. As cancer usually develops quickly, speed is a key component for the development of therapeutic cancer vaccines. The faster a blueprint can be tailored to the very specific characteristics of the tumor in the individual patient, the bigger the chances of healing that patient. It can’t take decades, it can’t take years, it should be done within a few months – or better, within a few weeks.

Or even within a few days, as was proven in January 2020. To be precise: on 13 January. On Friday 10 January 2020, Zhang Yongzhen, a Chinese virologist at Fudan University in Shanghai, had put online the genome of a new virus he had received from research colleagues in Wuhan. The virus didn’t even have an official name at that time – one month later it was called SARS-CoV-2. With its genome freely accessible to anyone and everyone, researchers around the world started looking for a vaccine to combat this novel coronavirus.

Three days later, the first one got it. On Monday 13 January, an until then largely unknown US company called Moderna had already designed its vaccine and the first tests for approval were about to begin. Two weekends later, the German BioNTech followed with its own mRNA vaccine development.

Speed was important for fighting Covid-19. And it will be as important for fighting an individual cancer. Once you know which structure you’re targeting, the effort required to produce a specific mRNA for that target is fairly minor. And if you also know how tolerable and suitable the mRNA vaccine’s packaging is for the prospective patient, then nothing stands in the way of it being used. The experience that researchers and authorities have gained on similar topics with the Covid-19 mRNA vaccines can be transferred for use in the various mRNA treatments for cancer.

CANCER VACCINES AT WORK

And it’s already done in clinical studies, often in combination with other cancer therapies. BioNTech is currently working on a total of 14 immuno-oncology drugs, ranging from several mRNA-based vaccines to CAR-T cell therapies. In the journal *Nature*, BioNTech presented initial results of a study of patients with advanced-stage melanoma that were inoculated with eight mRNA vaccines containing blueprints for four common melanoma antigens. In parallel, the patients received checkpoint therapy – and tumors shrank in just over one-third of this group.

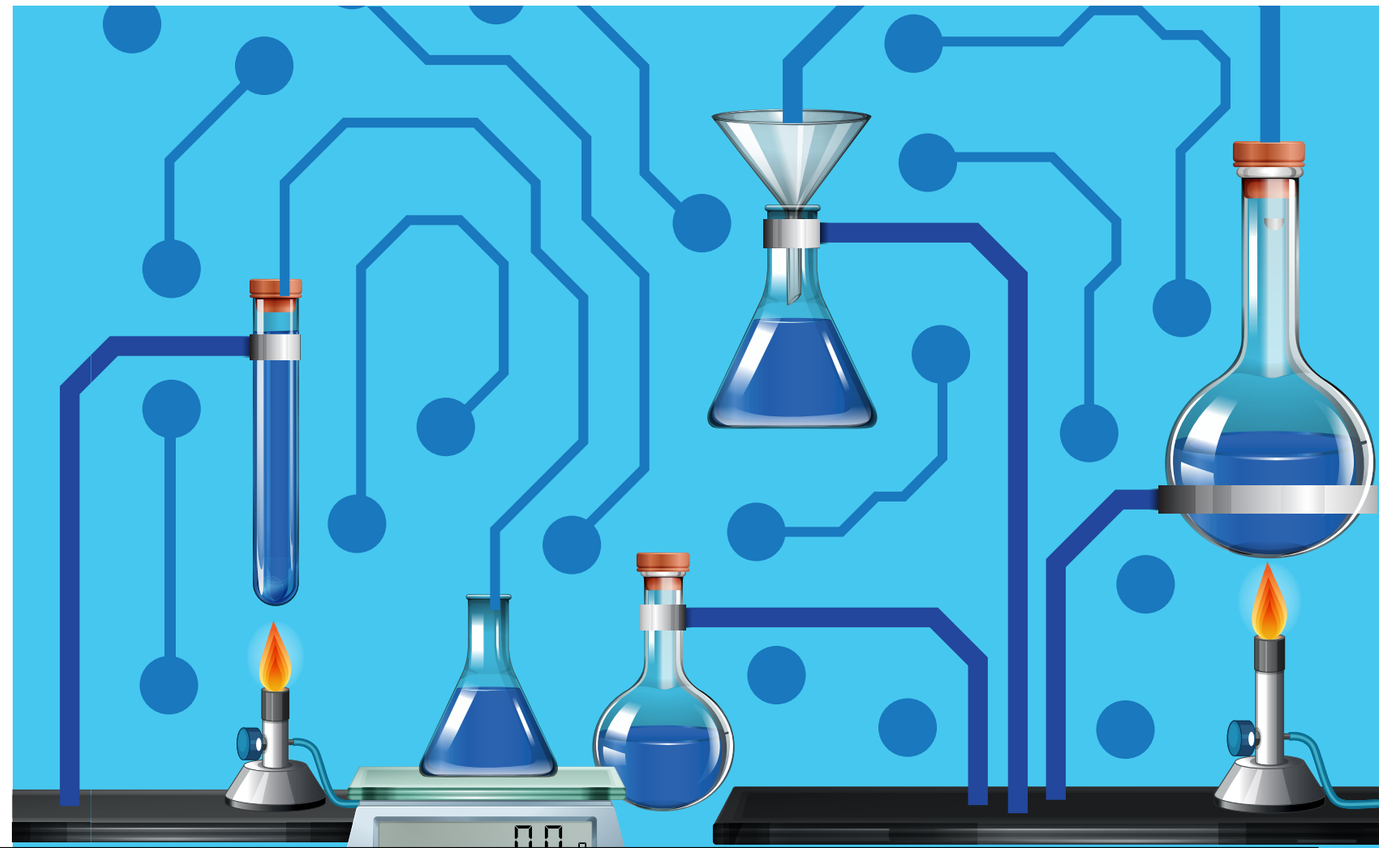
A vaccine from the Tübingen-based company Curevac, which is being tested at the Ludwig Institute for Cancer Research in the US in cooperation with the pharmaceutical company Boehringer Ingelheim, also relies on a combination of mRNA and checkpoint inhibitors in advanced lung cancer. Blueprints for six tumor proteins are first injected weekly, and later every few weeks. Results have not yet been published.

A clinical study on what’s called non-small cell lung carcinoma has already shown a significantly longer survival time for patients. It carries a large amount of a specific antigen (MUC1) on its cell surfaces and is well-suited for a vaccine. However, the effect only occurred if the patients received a chemo-radiotherapy combination in parallel with the vaccination. If this had been completed before vaccination, their survival expectancy did not change.

At the University of Heidelberg, a combination vaccination against diffuse gliomas showed good results. Diffuse gliomas are tumors that spread in the brain and are usually difficult to remove completely by surgery. The vaccine used was not an mRNA vaccine but a mutation-specific peptide vaccine. This is because, in more than 70% of patients, the tumor carries a matching gene mutation. The patients were vaccinated in addition to standard therapy; 84% of those fully vaccinated were still alive three years after treatment, while tumor growth stopped in 63%. Now the treatment set is being expanded to include immunotherapy with the checkpoint inhibitor, which is expected to further boost the immune response.

ROCKY ROAD TO HOLY GRAIL

That sounds like the discovery of the Holy Grail of cancer therapy: teaching the immune system how to get rid of a tumor. And mRNA technology seems in addition to have a huge potential beyond vaccinations (see page 18, interview). But how did a technology that was virtually unknown in the public domain at the



> **“This is just mRNA 1.0. It’s the proof of concept for a very new pharmaceutical drug class.”**
>
> **UGUR SAHIN**
>
> Physician and bioscientist, cofounder of BioNTech SE, Mainz, Germany

beginning of the decade rise within weeks to the top of medical research virtually out of nowhere? One explanation is that the new technology wasn’t really that new. As early as 1990, at the University of Pennsylvania in the US, Hungarian biochemist Katalin Karikó, 35-years-old at the time, began research on ways to artificially produce messenger RNA (mRNA), a central component of human cells, which is needed to produce proteins in the cells.

A young scientist, a new research field, new technologies – what could possibly go wrong? Well, everything. What happened to Karikó had once happened to Galileo Galilei, Edward Jenner and Ignaz Semmelweis – something still possible even after centuries of high-tech, cutting-edge research. A groundbreaking discovery made by a complete outsider is first ridiculed and then ignored by renowned experts in their field. No one was interested in Karikó’s work; not only did she not get the professorship she had hoped for, she received no state funding and had to accept a demotion to not get fired. It seemed that mRNA was an academic dead end.

It took almost a decade for the tide to turn. In 1997, standing at the faculty’s copy machine, Karikó met a comrade-in-arms, immunologist Drew Weissman. Together they developed a solution to get the mRNA into the body without the immune system rejecting it. In the same year, a research project on immunotherapy was launched at the University of Tübingen in Germany. As part of that project, chemistry student Ingmar Hoerr wrote his doctoral thesis on RNA vaccines. In 1999, he applied for his first patent on the technology, and a year later he founded the company CureVac to develop RNA vaccines.

From 2005 onwards, other researchers began entering the arena. One of them, Derrick Rossi, founded the mRNA start-up Moderna in the US in 2010. Two others, Uğur Şahin and Özlem Türeci, had already founded BioNTech in the German city of Mainz in 2008. So when Covid-19 broke out early in 2020, the whole world was caught on the wrong foot - except for these three companies. They were all on hand to catapult the former outsider’s method to the forefront of global vaccine research. As it happened, even the former near dropout Katalin Karikó was actively involved in the breakthrough involving her own idea – she has been Senior Vice President and Head of Research at BioNTech since 2013.

STILL A LONG WAY TO GO

We may still be far away from scalability of that technology. The following pages of this report provide further information about the prospects and challenges for therapeutic cancer vaccines. But we’re getting closer. It will probably take at least another five years before the first mRNA vaccine against cancer is approved. That may still be a long way off, but in the fight against cancer it’s a source of great hope in the search for a new and effective weapon.

And now is exactly the right time to start a debate about the further steps on our way to defeat cancer. Cancer is not a regional or sectoral disease. It is a disease that can attack the old and the young, the poor and the rich, the strong and the weak, the slim and the overweight – it can attack anyone, anytime.

At present, cancer is treated as your own individual disease. You can get whatever resources the medical system of your country has to offer. Bad luck, when you’ve been born in the wrong country. With a potential cure available for everyone, everywhere, cancer should be treated as a global challenge. The resources to cure your cancer should be at your disposal, no matter where it is that you come from.

During the Covid-19 pandemic, humanity failed to come up with global solidarity. Shame on us. But the technology that emerged as the best solution to overcome the pandemic of 2020/22 could now be used as a global solution for humanity’s fight against cancer. This time, we should know – and act – better.

ILLUSTRATION: DANIEL HERTZBERG

mRNA AND THE TAKE-OFF MOMENT FOR MEDICINE

Niels Halama, Professor for Translational Immunotherapy at the German Cancer Research Center (DKFZ), discusses the prospects for cancer vaccines.

Prof. Halama, let's talk about cancer vaccines and how they will change cancer therapies in the future.
This will not only be a talk about the future – the change has already started. I've been in oncology for 15 years now, and it is hard to believe how drastic the upheavals are that we just witness. First immunotherapies and now mRNA have been crucial in that. Imaging is coming, data science, everything is going to be much faster and more accurate.

You almost sound like a Silicon Valley start-up guy.
Because it's a similar situation. I think it's apt to say that medicine has entered a phase similar to the IT industry in the 1980s. Exponential growth is coming, and extreme change.

The main product that shaped the IT disruption of the 1980s was the personal computer. And with that came the demise of centralized mainframes and the rise of the individual PC on each desk. Is there something similar happening in medicine?
Exactly. Information processing is possible in a completely different way; computing power is still exploding, as are information flows and availability. That has implications for how we do medicine. Various technologies are now coming together and accelerating each other. The last time we had a situation like this was in the '80s with computer technology. Today, knowledge is generally available on the Internet, and the same could happen with medicine.

That's still data, not drugs.
That's just changing. For the first time, systems are on the market that allow people to print their own drugs at home. Click chemistry opens up the possibility of producing medicines on a small scale in one's own basement. This technology has the potential to completely turn things around for the whole industry.

Will we even be able to mix our own cancer vaccine?
Absolutely. This is no longer just a pretty fantasy for 200 years from now, but things that are coming within reach. Even for mRNA vaccines, decentralized solutions will become possible. The question of resources remains important, but it is perhaps easier to manage production locally in a decentralized way that meets demand. That could also be economically attractive, as well as more resource-efficient than what we are doing at the moment.

Maybe I would feel more comfortable if an expert like you produced my cancer vaccine than when I mix it on my own in my basement.
Absolutely. So this could lead to the emergence of new experts that can advise you – online perhaps. One of the great advantages of mRNA technology is that you don't need to develop an active ingredient of your vaccine in a laboratory or a production facility. mRNA enables your immune system to produce the active ingredients itself. And that allows for much faster and more cost-effective production adapted to the individual.

How does that work exactly?
mRNA is a kind of information transporter, like a blueprint. Thanks to very fast and exact genome decoding technologies, by sequencing the genome from the tumor and that from the healthy cells, we can compare these two genomes: What kind of mutations do the tumor cells have that distinguish them from the rest of the body cells? These differences are translated into an mRNA blueprint.

A blueprint for the production of new tumor cells?

> "It's hard to believe how drastic the upheavals are that we just witness in oncology."

NIELS HALAMA
Professor for Translational Immunotherapy at the German Cancer Research Center in Heidelberg

ILLUSTRATION: DANIEL HERTZBERG

> “The vaccine communicates the blueprint of the target structure to the immune cells.”

Of course not. A blueprint for the production of a target structure – for example to produce one distinct protein that only exists in the tumor cells. The vaccination is used as an information transporter to communicate the blueprint to the immune cells: Look out, this is the target structure that needs to be attacked.

The immune system is activated against a structure that it should already know from contact with the cancer cells. Why hasn’t this happened before?
Because the tumor cells have developed a number of very diverse mechanisms to protect themselves. The solid tumors especially – like breast cancer or colon cancer – manage to grow without the immune system being able to stop them. Some tumor cells build a kind of protective wall, some use something like a cloak of invisibility to hide from the immune system, and many other mechanisms come into play. The exciting question, which also needs to be tested in therapies, is whether vaccination alone is enough to reverse this?

And? Is it enough?
We are waiting for the results from clinical studies that can show us the way. But we have some insights from classical immunotherapy with checkpoint inhibitors. There are cancers like melanoma (skin cancer) or lung cancer that can be treated quite well with immunotherapy. A significant proportion of patients respond and we know that the tumor allows the cells of the immune system to enter the tumor microenvironment. So if you use a therapy that activates the immune system in the right way, you can kill the tumor.

With other cancers, not so much?
That’s what we’re hoping to change with vaccines, and that’s where it gets exciting. Because there are a number of diseases like pancreatic cancer or breast cancer, which cannot be treated with immunotherapy. But it seems possible that vaccination might change this situation

It seems possible? Or it really is possible?
Let me take the example of pancreatic cancer, a disease where the mechanisms to resist the attacks of the immune system are massive. But the first studies with mRNA vaccines for pancreatic cancer give us positive signals. One study at the Memorial Sloan Kettering Cancer Center in New York has been completed, and it has shown positive, unexpected results. Now discussions are ongoing to expand this approach, because there are still many answers missing.

For example?
Right now, it seems that in the case of pancreatic cancer, patients who have already had surgery may have an advantage. That needs to be better studied now. In addition, you always have to look at the combination therapies: Vaccination can be combined with other immunotherapies, such as classical checkpoint therapy, but also with classical chemotherapy, radiotherapy, or surgery. What kind of combination is best for which specific situation – that is still very much an open question.

So it’s not a magic bullet, it’s a tool in a big toolbox.
Exactly.

Why do the first results suggest that mRNA vaccines work better than expected?
An important factor seems to be that the vaccines are personalized. Before, there was just one mutation for all patients, and it didn’t work. Personalized vaccines are much more effective in activating the immune system for individual patients. That makes a decisive difference.

> “Cancer usually develops quickly, so we don’t have much time to develop a personalized therapy.”

How exactly does personalization work?
After the sample is taken, the genetic material is decoded. That takes four to eight weeks, which is incredibly fast for the technology. This speed is absolutely necessary for the personalization of mRNA cancer vaccines. Because cancer usually develops quickly, we don’t have much time to develop the personalized therapy. After decoding and comparison of healthy and tumor cells, we get to the difficult question of which kind of target structure should be selected. Which structure is best suited to be targeted immunologically? And which is useless? This selection is not an automatic process.

What obstacles still have to be overcome for this to actually get on the market?
The good news is that, through Covid, the structures of how mRNA is processed, how to package that, how it can get to the individual, have been greatly improved. Doctors and patients also have a better idea of how this works.

The willingness to participate in studies is increasing?
Absolutely. Most have had good experiences with Covid vaccination. That helps a lot, but many questions are still unanswered. It looks like we will need very different therapy patterns for each type of disease. This is a multistage process, and it will take some years before we will see which vaccine therapies are successful, and which are not.

And what about the risks of those therapies?
Tumor vaccination is a therapy that is very well tolerated, with few to almost no side effects. But it is possible this will change in combination with other therapies, as some of them weaken or even overactivate the immune system.

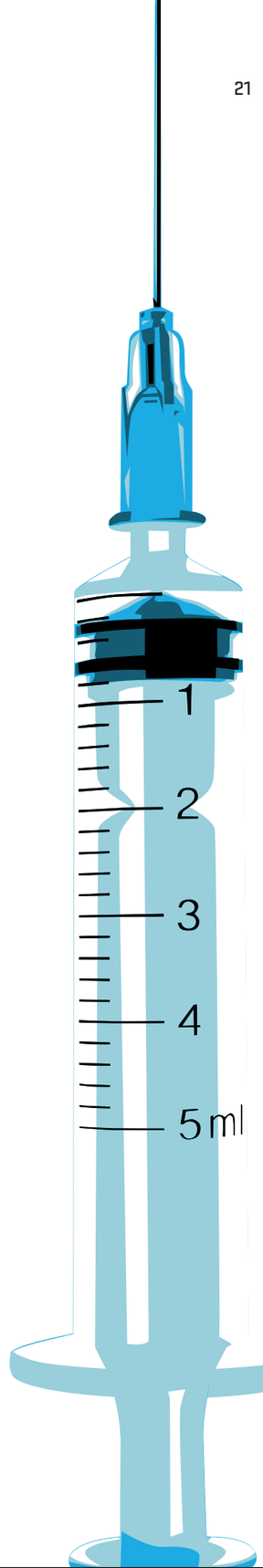


ILLUSTRATION: DANIEL HERTZBERG

This will also be considered in the admission process?
As you can imagine, for an individualized therapeutic vaccine there needs to be a completely different process. The regular way is as follows: A drug claims to have an effect, the effect is tested in different patients, and also possible side effects. In the end, the regulator grants or refuses the admission. But with a different drug for each patient this process is almost impossibly complex. So now the regulatory debate is about how much speed is acceptable – and how much risk? My perception: For the combination approaches there are few to no signals that they are riskier than other therapies. But authorities need more data.

That means more studies.
Exactly. We will get studies with clearly defined plans that treat a defined number of patients. Then we see the effects and the complications – and depending on these results, we go into the next level. Different patients, more patients, different combination of therapeutics. This way, the controllability is built into the studies. Not like the all-or-nothing approach most pharmaceutical studies have, more like a readjustment.

Those studies are mostly done at hospitals in western countries. How do you see the chances for a global rollout of cancer vaccinations? And what are the chances of a fair distribution?
I like the Biontech's idea of manufacturing production facilities so that they fit into freight containers that can be deployed wherever needed. Just four converted containers, placed on top of each other, contain everything needed to produce mRNA. These mobile production facilities can lead to global availability with rather little effort. An elegant solution – though it doesn't answer the question of patents and know-how.

> "Mobile production facilities for mRNA that fit into freight containers can lead to global availability with rather little effort."

To scale globally, you would need a lot of containers and a lot of people who could use the technology they contain.
Right now, it's just an idea, a first approach – the containers don't exist yet on a larger scale. If we want to offer personalized vaccinations globally on a mass scale, that can't be done by a single company, nor by academia. It has to be done at a completely different level.

What's the bottleneck? Funding for mRNA research?
Right now, I see less a lack of financial resources than of human resources. The expertise on mRNA technology is concentrated in a handful of companies; they have a massive technological lead. To get traction, the mRNA know-how must first be brought into the academic setting. Many people don't realize how difficult this path to mRNA technology was. For a long time, this was laughed at; it was considered useless.

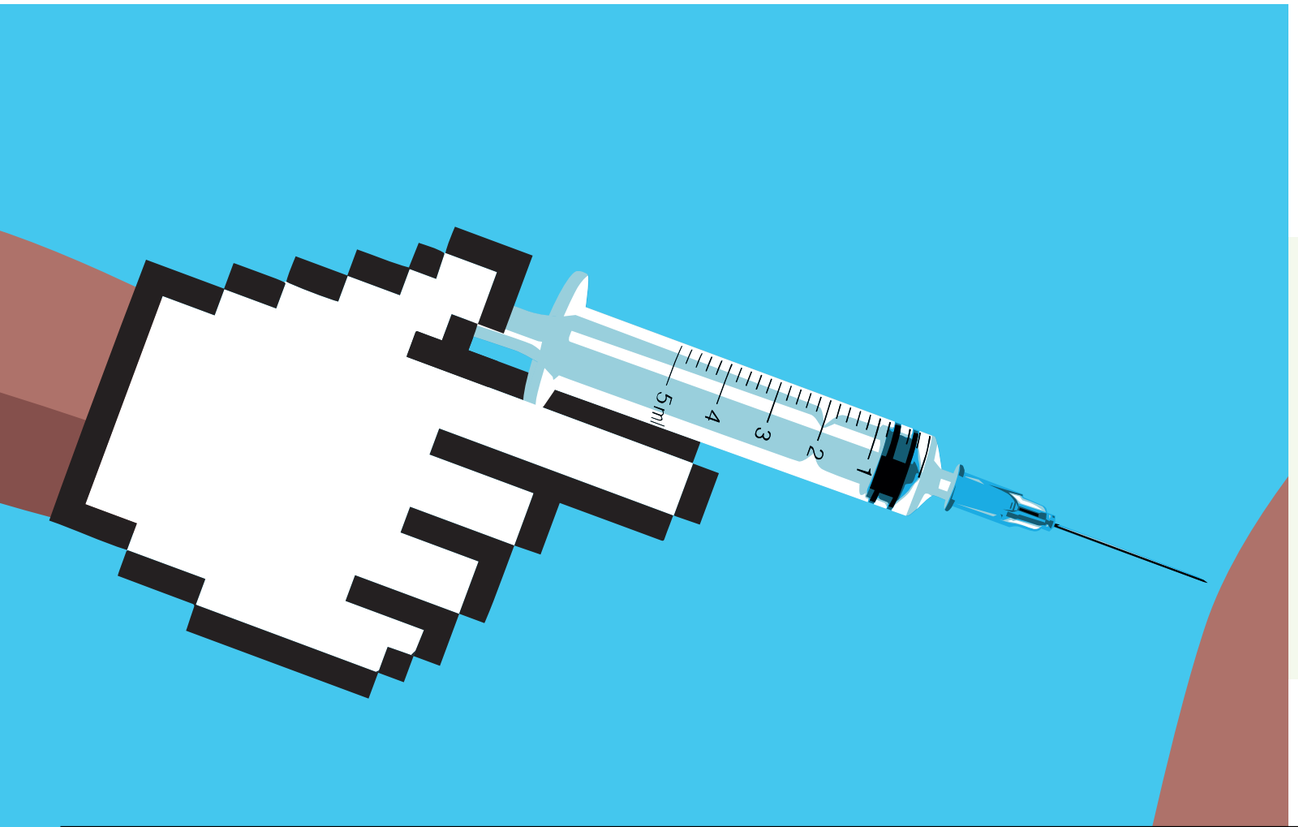


ILLUSTRATION: DANIEL HERTZBERG

> "mRNA is a tool that can be used much more broadly – vaccination is just one application. There is a huge field just opening up."

Why that?
The biology of mRNA was well researched – we have known for a long time how it works – but it seemed to make no sense from a therapeutic point of view. These molecules have incredibly short life spans, they're used and they're gone, and they are extremely difficult to deal with. But these mRNA companies have massively improved the handling: mRNA now is better packaged and does not immediately degrade.

And the further development of mRNA technology can't be solely done by Biontech, Moderna and Curevac?
A lot is already happening in collaboration with industry partners, but there is a huge field just opening up, and we don't know yet how huge it will become. Or, rather, how many fields will emerge, because mRNA is a tool that can be used much more broadly – vaccination is only one application. We can pack quite different information into the mRNA, commands for the immune system, or even for other cells. It's like a kind of Lego kit: You can build very different things out of it to change the micro-environment. The variety of possible applications of such building blocks through mRNA technology is often overlooked in the media because it has opened up a field that did not previously exist in medicine.

So after the start-up of the cancer vaccines, you see a bunch of other start-ups coming?
In this case, we are not talking about something happening right now, but about an uncertain future. Right now mRNA is very interesting for tumor therapy, and in the future also beyond that. It is not yet possible to say how and when this will happen, but it is fair to say: It will happen!

ILLUSTRATION: DANIEL HERTZBERG

THE CHALLENGES FOR CANCER VACCINES

RESEARCH CHALLENGES
THE LONG FOREFRONT OF INNOVATION

Cancer therapy research takes time. Success is measured in the years the patients survive. Right now, dozens of cancer vaccine studies are active in hospitals all over the world. We looked into one of them.

A MORNING IN AUGUST. THE SUN is high above the Asklepios Hospital in Hamburg. Outside the door, patients sit on a bench and doze in the green of the tall deciduous trees in front of the main entrance. A strip of green paving stones points the way into the lobby. Numbers rush across the monitor by the window like at an airport terminal. A 88, please go to Admission 1, A 90 shortly, A 91 in about 6 minutes. "Waiting area" is written in German, French, Arabic, Russian, English and Italian on a coffee-brown glass panel above the upholstered waiting seats. On rubber soles, people in white and blue work clothes hurry silently through the hallway. From outside, the siren of an ambulance drifts in.

"Hi, welcome," says Dirk Arnold, opening room 1.306. Arnold heads the Department of Oncology with Hematology Section at the hospital and is Medical Director of the Asklepios Tumor Center Hamburg. With olive polo shirt, jeans, gray-silver hair, youthful laugh, he doesn't seem like a chief physician, at least not one who intimidates patients with the concentrated power of high-tech medicine. And that's an advantage, even if, as he reveals, he does put on his doctor's overall to make his professional role clear when talking to patients. "Because I have to find the right way to treat their cancer in a close, personal exchange with each patient."

Accompanying people through difficult phases in their lives. Giving them feedback through good observation, astute analysis, and a sense of their needs. Helping them to sort things out in their heads and jointly approaching solutions - that's what appealed to Arnold at his first step into medicine at a child and adolescent psychiatry. There, adolescents stumbled on their way to adulthood; in oncology, they struggle to cope with a disease extremely fraught with fear and shame.

Cancer is often associated with miserable dying. Cure hopeless. A good life with the disease hardly conceivable. "But that's generally not true," Arnold says. "Cancer is, even if incurable, often a chronic disease, like many others in internal medicine, against which much can be done now." On the on hand, tumors are usually detected much earlier – screening and diagnostics have improved. Close follow-up means that metastases cannot spread as far. On the other hand, cancer treatment is no longer limited to surgery, chemotherapy, and radiation. Immunotherapies have been added as a fourth pillar of oncology.

In the past ten years especially, these immunotherapies have made tremendous progress. Cancer cells are altered body cells. Normally, these alterations are recognized and removed by the body's immune system. If a person has cancer, this no longer works for various reasons. So immunotherapies help the immune system to detect and attack tumor cells. This is because tumor cells can evade the body's defenses in various ways, for example by putting on molecular camouflage. Modern immunotherapy attempts to switch off these evasion mechanisms in a variety of ways (see page 10, Cancer Vaccine Technologies).

> "The vaccine approach is tremendously promising."

DIRK ARNOLD

Head of Oncology Department,
Asklepios Hospital, Hamburg

A CLINICAL VACCINE STUDY

In addition, continuously improved genetic analyses over the past 20 years have revealed in detail the differences between the genetic profiles of patients with and without tumors – and, more importantly, allow insights into tumor biology. "We now know that cancer is a sum of genetic alterations of the entire body system - which we can combat with a whole bouquet of measures," Arnold says. Immunotherapies are becoming more sophisticated. The latest hope in this is called mRNA vaccination, and Dirk Arnold's oncology department is one of the first in the world to clinically test a new vaccine from research giant BioNTech against colorectal cancer.

So, vaccinating against cancer as against tetanus or measles? It's not that simple, far from it. "But the approach is tremendously promising because the whole range of the immune system is boosted," says oncologist Arnold.

Numerous studies are underway worldwide to test vaccines against a wide range of tumors, from lung cancer to melanoma. In Germany alone, according to the Paul Ehrlich Institute, 17 studies are underway – such as BioNTech's colorectal cancer study, which since early 2022 is being conducted worldwide with 200 patients at 36 European and US hospitals – including this one in Hamburg.

When BioNTech approached Arnold at Klinikum Asklepios, he immediately agreed. "Being at the forefront of innovation fascinates me," he says. His department provides BioNTech with the infrastructure it needs for such a study. The procedure is meticulously prescribed, requires extreme care in implementation and documentation, and regular quality checks by an independent monitoring body are mandatory. Arnold can show good ratings in other studies; his department has plenty of experience. A large-scale study on improved immunotherapy with checkpoint inhibitors is running in parallel.

It's 11:30 a.m. On the eighth floor of the clinic building, all rooms are occupied and the doors are open. Patients rest in wide armchairs, chemotherapy flowing into their arms from infusion bags. Others are waiting for a biopsy, an MRI or the next consultation. Here, senior physician Britta Heitmann is searching for candidates for the BioNTech study.

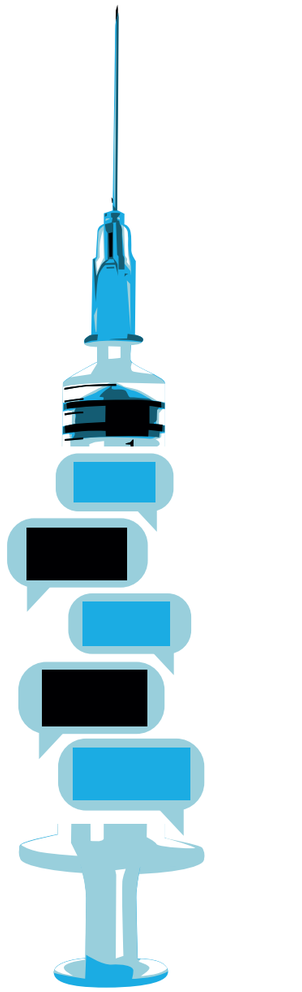
The setting of the study is narrowly defined: it aims to find out whether mRNA vaccination after surgical removal of a tumor can prevent its return – a relapse. Since the risk of relapse is not very high in most colorectal cancer patients, the vaccination is being tested in a high-risk cohort, i.e. a group at extremely high risk of relapse. This group is defined in detail. The cancer must be at a certain stage, have a certain tumor size, have already affected the lymph nodes. Crucially, tumor DNA must be detectable in the blood of each test subject, because if genetic material from the tumor is still circulating in the body, it is extremely ↘

CLINICAL STUDIES

When new pharmaceuticals or vaccines have not yet been approved by regulatory bodies, participation in clinical studies is often the only way to get the new treatment. The more promising a new therapy seems to be, the more desperate patients contact the study team and try to get onboarded.

In most cases to no avail. Each study targets a clearly defined and often narrow group of patients - e.g. certain age groups or stages of the disease in question.

Some tumors almost invite Immuno-Therapy.



TINKERING THE mRNA

However, patients with this profile are not easy to find. After an initial check of lymphatic involvement, tumor biology and size, senior physician Heitmann has identified only a handful of potential candidates. It's a task that requires a lot of tact "because usually patients feel healthy directly after an operation, the tumor is gone," says Heitmann. "Anyone who subsequently decides to do a test for tumor DNA risks bad news: a high probability of relapse. But we can at least offer them some perspective with vaccination."

After surgery, their blood is tested for tumor DNA in a set time frame. If the test is positive, tumor samples are sent to BioNTech. There, the genetic material is decoded, and from a list of many structural features, a set of individual surface characteristics of the tumor cells is filtered out – those likely to be best suited to tell the immune system that this is where it needs to attack. From this, a unique mRNA is built for each patient.

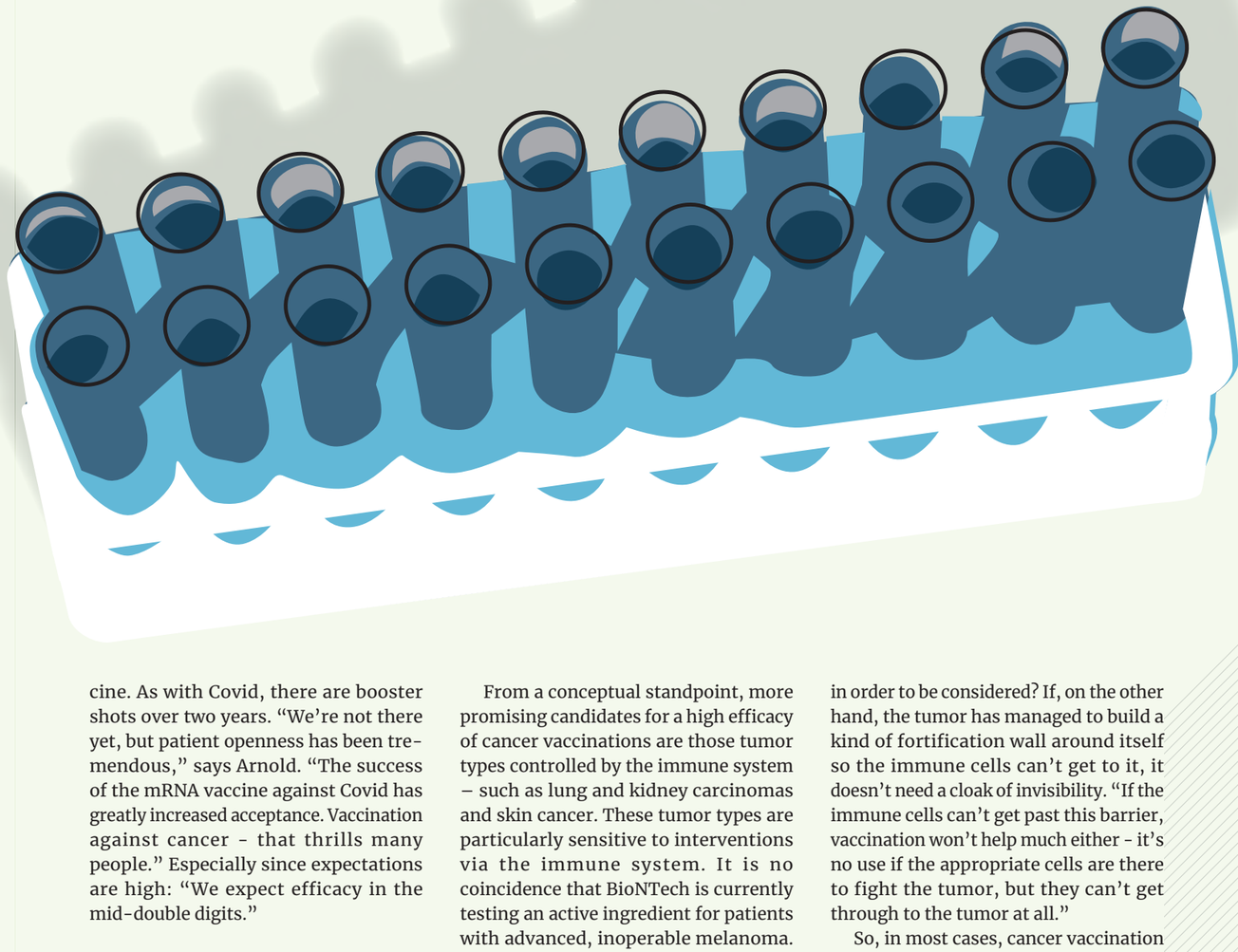
While BioNTech tinkers, patients get chemotherapy, the usual procedure for a tumor at this stage. After that, and about three to six months after surgery, Heitmann injects the customized vaccine. As with Covid, there are booster shots over two years. "We're not there yet, but patient openness has been tremendous," says Arnold. "The success of the mRNA vaccine against Covid has greatly increased acceptance. Vaccination against cancer - that thrills many people." Especially since expectations are high: "We expect efficacy in the mid-double digits."

SIDE EFFECTS

During the Covid vaccination campaigns since 2021, there have been intense debates about possible harmful side effects of the vaccine. In the field of cancer vaccines, these discussions are almost non-existent Mainly for two reasons:

1) Therapeutic vaccines are given to already sick people, so the main effect is more interesting than possible side effects.

2) All cancer therapies, especially chemo- and radiotherapy, have very heavy, high-risk side effects. The side effects of vaccines are minuscule in comparison.



ILLUSTRATIONS: DANIEL HERTZBERG

SIGNIFICANT RESULTS

"If we get significant results from a vaccine in colorectal cancer, that would be a sensation," says Niels Halama, immune therapy expert at the German Cancer Research Center. The same applies to carcinomas of the pancreas, for example, for which vaccines are currently being tested at the Memorial Sloan Kettering Center in New York. Why a sensation? Because not all cancers respond equally well to immunotherapies, and those two belong to the most challenging group. "Preliminary interim results suggest that vaccines can succeed at these cancers. An important factor is probably the personalized tailoring of the messengers, which can be used to activate the immune system with pinpoint accuracy."

From a conceptual standpoint, more promising candidates for a high efficacy of cancer vaccinations are those tumor types controlled by the immune system – such as lung and kidney carcinomas and skin cancer. These tumor types are particularly sensitive to interventions via the immune system. It is no coincidence that BioNTech is currently testing an active ingredient for patients with advanced, inoperable melanoma. The vaccines consists of a mix of four antigens typical for this specific type of skin cancer.

Whether a vaccination succeeds in stimulating the immune system to attack a tumor in a targeted manner depends on many factors, including the stage of the cancer and the patient's overall state of health. Factors of special importance for researchers are the mechanisms that the tumor uses to try to hide from the immune system. If it puts on a "cloak of invisibility" so the immune cells do not recognize it as an enemy, it is necessary to find the decisive target structures at which antigens can be directed. But which ones? They differ from patient to patient, from cancer type to cancer type. And what properties must a target structure have in order to be considered? If, on the other hand, the tumor has managed to build a kind of fortification wall around itself so the immune cells can't get to it, it doesn't need a cloak of invisibility. "If the immune cells can't get past this barrier, vaccination won't help much either - it's no use if the appropriate cells are there to fight the tumor, but they can't get through to the tumor at all."

So, in most cases, cancer vaccination will not be a miracle cure in itself, but has to be integrated into a comprehensive therapy concept. How can it be optimally combined with other methods, from surgery to chemotherapy, radiation, and other immunotherapies such as checkpoint inhibitors? When do we need which combination? What interactions occur, when, and how do they also affect the vaccinated antigens? How do I find the features that are specific enough and work precisely enough to elicit the desired immune response? Halama: "It probably takes a whole suitcase of tools from which to mix the best effective cocktail."

Such cocktails of combination therapies are already being tested in many studies worldwide. These are listed in the international database ↘

↘ ClinicalTrials.gov and cover very different types of cancer, from lung cancer to ovarian cancer to leukemias.

There will be a long way to go before the potential of mRNA is fully tapped. Not only can it be used as a vaccine, but the messenger could be piggybacked with other messages and commands for the immune system at the same time. "If, for example, the tumor builds a wall around itself so that the agent cannot penetrate, you could add to the vaccine a blueprint for how the attackers can break down the wall," says Halama. "This is then less a vaccination, but more a kind of complex program." Like a Lego kit, all sorts of things can theoretically be assembled using mRNA technology. "The diversity of possible applications is often overlooked. A huge future field has emerged there - even if we're still at the beginning in terms of concrete implementation."

NEED FOR FURTHER RESEARCH

There remain many unanswered questions, and links and interrelations are not yet well understood. The immune system is an extremely complex structure, consisting of cellular and non-cellular components that interact in many ways – and these interactions are insufficiently researched. Why exactly do all patients with the same diagnosis not respond equally well to vaccination? Are there indicators that show which defense mechanisms a tumor develops, in which patients which vaccination strategy is promising? Why do tumors shrink under vaccination and start to grow again after a while? How does therapy resistance occur? Can metastases be treated with the same antigen-based vaccines as a primary tumor? After all, they are often very different both from the primary tumor and from each other. Tumors are extremely mutable and can carry different typical characteristics at different positions in the body, so what works at one place may fail at another. And are there tumors with such a high genetic diversity among their cells that vaccination is unlikely to succeed? Though the success of cancer therapies is increasing, so is the need for more cancer research. ↘

ALL CURRENT CLINICAL STUDIES WITH THERAPEUTIC CANCER VACCINES

(clinical phase II or III, active and/or recruiting)

BRAIN CANCERS

CANCER TYPE	SPONSOR	OPENED	STATUS
Glioblastoma	Antwerp University Hospital	2015	Recruiting
Malignant neoplasms of brain	**Duke University**	**2015**	**Active, not recruiting**
Glioblastoma	Duke University	2020	Recruiting
Glioblastoma	**Duke University**	**2019**	**Recruiting**
Brain cancer, neoplasm metastasis	Guangdong 999 Brain Hospital	2016	Active, not recruiting
Recurrent glioblastoma	**Guangdong 999 Brain Hospital**	**2016**	**Active, not recruiting**
Glioblastoma	Guangdong 999 Brain Hospital	2016	Active, not recruiting
Medulloblastoma, neuroectodermal tumor	**University of Florida**	**2010**	**Active, not recruiting**
Diffuse intrinsic pontine glioma, brain stem glioma	University of Florida	2018	Recruiting
Glioblastoma, malignant glioma, astrocytoma	**Immunomic Therapeutics**	**2016**	**Recruiting**
Adult glioblastoma	University of Florida	2020	Not yet recruiting
Glioma	**Antwerp University Hospital**	**2021**	**Recruiting**

SKIN CANCERS

CANCER TYPE	SPONSOR	OPENED	STATUS
Uveal metastatic melanoma	Hasumi International Research Foundation	2020	Recruiting
Melanoma	**Memorial Sloan Kettering Cancer Center**	**2011**	**Active, not recruiting**
Uveal melanoma	University Hospital Erlangen	2014	Recruiting
Advanced melanoma	**BioNTech**	**2015**	**Active, not recruiting**
Melanoma	eTheRNA	2018	Recruiting
Melanoma	**Moderna/Merck, Sharpe & Dohme**	**2019**	**Recruiting**
Melanoma	BioNTech	2020	Not yet recruiting
Melanoma	**Genentech/BioNTech**	**2019**	**Recruiting**

SOURCES: BECK ET AL.: MRNA THERAPEUTICS IN CANCER IMMUNOTHERAPY, IN: MOLECULAR CANCER, 2021, CLINICALTRIALS.GOV, HTTPS://CLINICALTRIALS.GOV/

ILLUSTRATION: DANIEL HERTZBERG

↘ INDIVIDUALIZED THERAPY

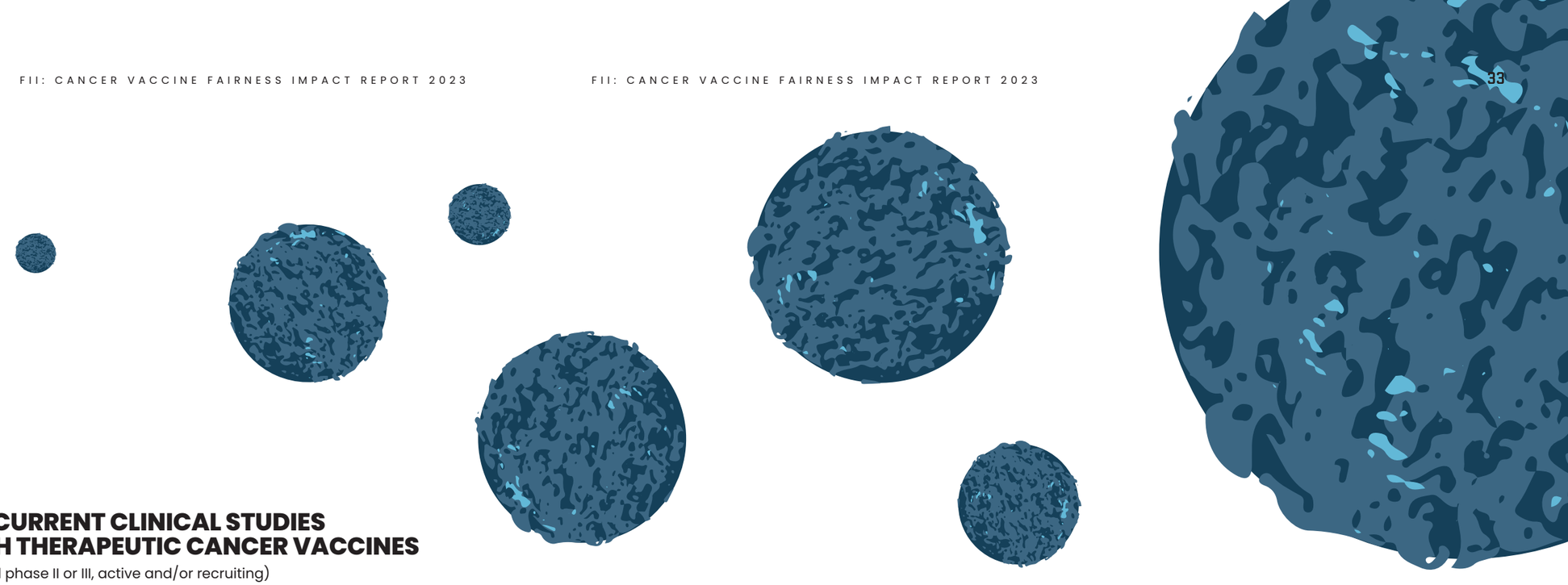
Sunlight falls into Dirk Arnold's conference room at the Asklepios Hospital in Hamburg. "We would need a lot more research funding to be able to pursue such questions. Especially in applied research, the government leaves a lot to industry. Without partnerships with companies, tumor research with studies like the ones we do here would not be possible." This obviously leads to a research focus on tumor types that offer a high probability of high financial returns. For the types that are not easy to refinance, for example because they are too rare, public funding is needed to develop treatment concepts.

Arnold is convinced that vaccinations against cancer, especially those based on mRNA, have enormous potential. Both in preventive, standardized vaccinations as against HPV infection. "Globally, there is a huge group of tumor diseases that are infection-based, like liver cancer." As well as in therapeutic vaccines, which are based on individually tailored active components. "They are certainly not a panacea, but they are a very important element in a mix of many therapies."

In May 2021, Dirk Jäger, Executive Director of the National Center for Tumor Diseases Heidelberg (NCT), emphasized at a conference just how important individual formulations are about to become. He was certain that "the future will be individualized therapy for every sick person; there will no longer be any standard therapy."

Can individualized vaccinations also be rolled out globally on a large scale? Not in the near future, Arnold says. He sees a kind of semi-individualization as the more probable scenario: "We will probably have to filter out subgroups of cancer patients with similar tumor characteristics that we treat with the same vaccine - and only diversify further if that doesn't work."

Should vaccine patents for the Global South then be released? "Ultimately, the rollout is a global health effort that must be coordinated by the global community," Arnold says. Not coincidentally, the World Health Organization has put the ↘



ALL CURRENT CLINICAL STUDIES WITH THERAPEUTIC CANCER VACCINES

(clinical phase II or III, active and/or recruiting)

OTHER CANCERS

CANCER TYPE	SPONSOR	OPENED	STATUS
Acute myeloid leukemia	Hasumi International Research Foundation	2020	Recruiting
Multiple myeloma	**Memorial Sloan Kettering Cancer Center**	**2014**	**Active, not recruiting**
Myelodysplastic syndromes, acute myeloid leukemia	University of Campinas	2016	Active, not Recruiting
Solid tumors	**BioNTech**	**2020**	**Recruiting**
Solid tumors	Genentech/BioNTech	2017	Recruiting
Solid tumors	**Moderna/Merck, Sharpe & Dohme**	**2017**	**Recruiting**
Solid tumors	National Cancer Institute / National Institutes of Health Clinical Center	2021	Recruiting
Solid tumors	**SQZ Biotechnologies**	**2022**	**Recruiting**
Malignant pleural mesothelioma	Antwerp University Hospital	2017	Recruiting
Prostate cancer	**Oslo University**	**2010**	**Active, not recruiting**
	BioNTech	2019	Recruiting
Triple-negative breast cancer	**BioNTech**	**2016**	**Active, not recruiting**
Ovarian cancer	BioNTech	2019	Recruiting
Esophageal squamous carcinoma, gastric, pancreatic and colorectal adenocarcinoma	**Changhai Hospital / Stemima Therapeutics**	**2018**	**Recruiting**
Colon cancer	Gritsone bio	2022	Recruiting
Metastatic non-small-cell lung cancer	**Ludwig Institute / Curevac / Boehringer Ingelheim**	**2017**	**Recruiting**
KRAS-mutant non-small-cell lung cancer, colorectal cancer, pancreatic adenocarcinoma	Merck, Sharpe & Dohme	2019	Recruiting

ILLUSTRATION: DANIEL HERTZBERG

SOURCES: BECK ET AL.: MRNA THERAPEUTICS IN CANCER IMMUNOTHERAPY, IN: MOLECULAR CANCER, 2021, CLINICALTRIALS.GOV, HTTPS://CLINICALTRIALS.GOV/

HIGHER CANCER BURDEN IN OLDER COUNTRIES

Death rates from cancer, measured in deaths per 100,000 persons/year

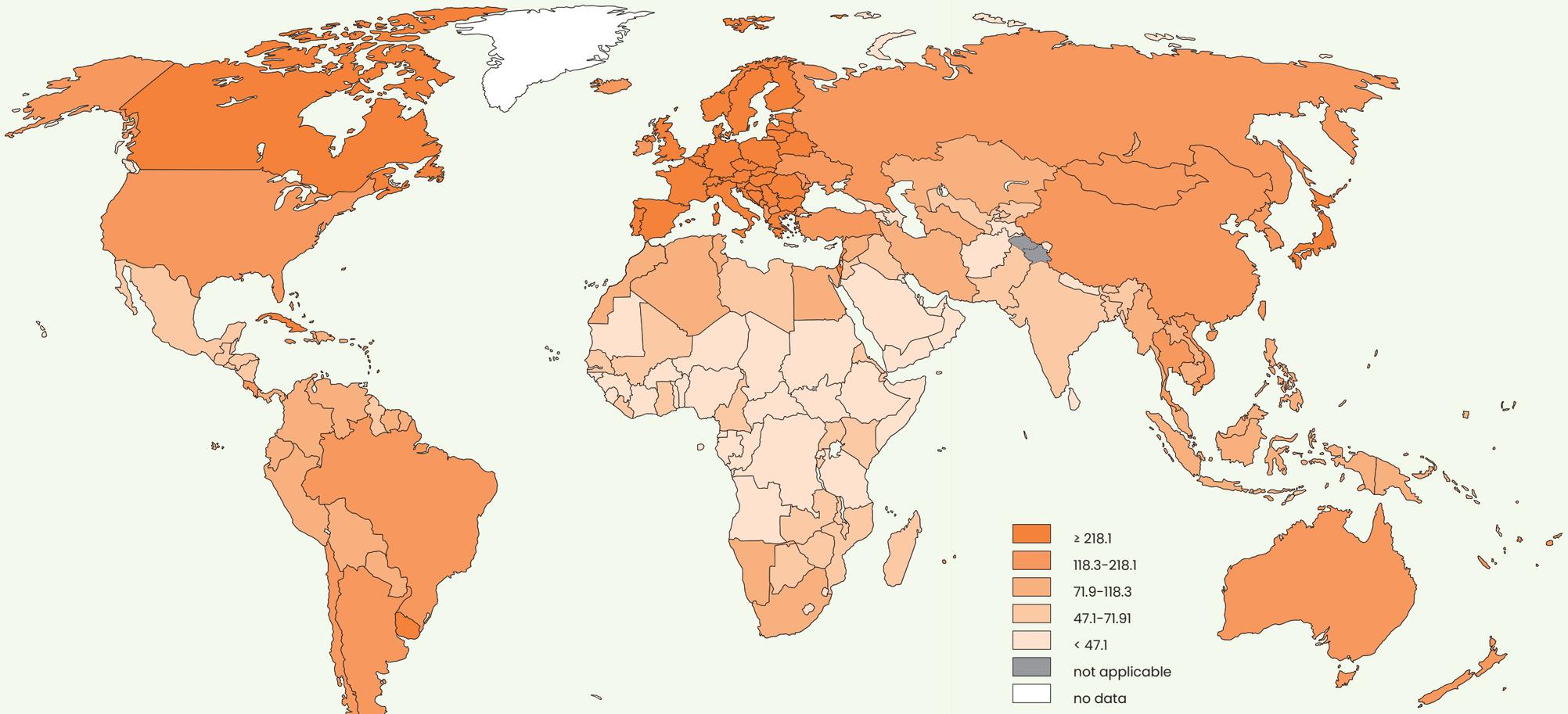


ILLUSTRATION: GETTY IMAGES

SOURCE: GLOBOCAN 2020; WORLD HEALTH ORGANIZATION

CANCER THERAPIES – MOST PROGRESS IN RICH COUNTRIES

Disease burden rates from cancer 1990–2019, measured in DALYs (Disease Adjusted Life Years) lost per 100,000 persons

INCOME GROUP	CANCER BURDEN 1990	CANCER BURDEN 2019	CHANGE IN %
WORLD	3824	3062	▼ -19.9%
HIGH INCOME	4122	3100	▼ -33.0%
UPPER MIDDLE INCOME	4263	3243	▼ -31.5%
LOWER MIDDLE INCOME	2684	2566	▼ - 4.6%
LOW INCOME	3318	2980	▼ -11.3%

↘ issue of global vaccination high on its agenda. But while the global community is far from coordinating, let alone financing, such an effort, some companies are already taking action. Arnold: "A few weeks ago, BioNTech opened its first factory in Rwanda, so maybe that's the first step toward globalizing this technology."

Dirk Arnold has to go. A pharma industry representative is waiting for research talks, and a meeting with senior physicians about building measures in the hospital is about to take place. The first results of the global colorectal cancer study will not be on the table until 2027 at the earliest. Even if enough patients with the required profile are found and treated, it will still take two or three years to evaluate the results. Ultimately, the only way to tell whether the vaccination has been successful is through observation. How many patients are still alive without relapse after three years? "Those who have survived this period have, according to most studies, a very high probability that the cancer will not come back."

It takes a lot of time to be at the forefront of innovation. Time many of today's cancer patients don't have. ■

CALL TO IMPACT

1 Diversifying sponsorship: Right now, cancer vaccine studies are mainly sponsored by three mRNA companies. A broader sponsorship base will give the research more traction.

2 Diversifying stage: mRNA vaccine studies often focus on later-stage cancers, where all other therapies have failed. Opening up to earlier-stage cancers could enhance the potential of therapeutic vaccines.

3 Diversifying scope: mRNA technology can produce more than just vaccines. A broader research scope would enlarge the mRNA toolbox.

CHALLENGES FOR SOCIETY
A BETTER GLOBALIZATION

If we really have the chance to end a human nightmare, how can we actually achieve it? Medical history offers some hints and demonstrates some obstacles.

YES, HUMANITY CAN SHOW SOLIDARITY. Not only with words, and not only for friends and family – but in real life, and on a global scale. Two examples from medical history prove it: the vaccination campaigns against smallpox and polio. Even though both campaigns started in the high-income countries of their time, they were both global issues and global successes: Smallpox was completely eradicated in every country, polio in all but two (see page 38 The War on Polio).

But medical history also offers negative examples, where politics or business – or both – stood in the way of global success. To name just three: diabetes, malaria, and Covid-19. The history of these diseases also reveals the three main obstacles to a global success for therapeutic cancer vaccines.

1. COVID OR "MY PEOPLE FIRST"

Political leaders are responsible for the fate of their people. They are not elected (or selected) to serve humanity; their duty is to serve the citizens of just one country, their own. During the Covid pandemic, that difference became palpable. Countries that could produce their own vaccine allowed its export only after national demand was satisfied. And wealthy countries bought the vaccines they needed for prices that crowded out poorer countries. The international vaccine alliance COVAX, that ought to demonstrate global solidarity,was far from succesful - more a fig leaf than a real contribution to gobal equality.

➲ TO OVERCOME NATIONAL BOUNDARIES, THE CASE FOR THE GLOBAL ISSUE HAS TO BE EXCEPTIONALLY STRONG

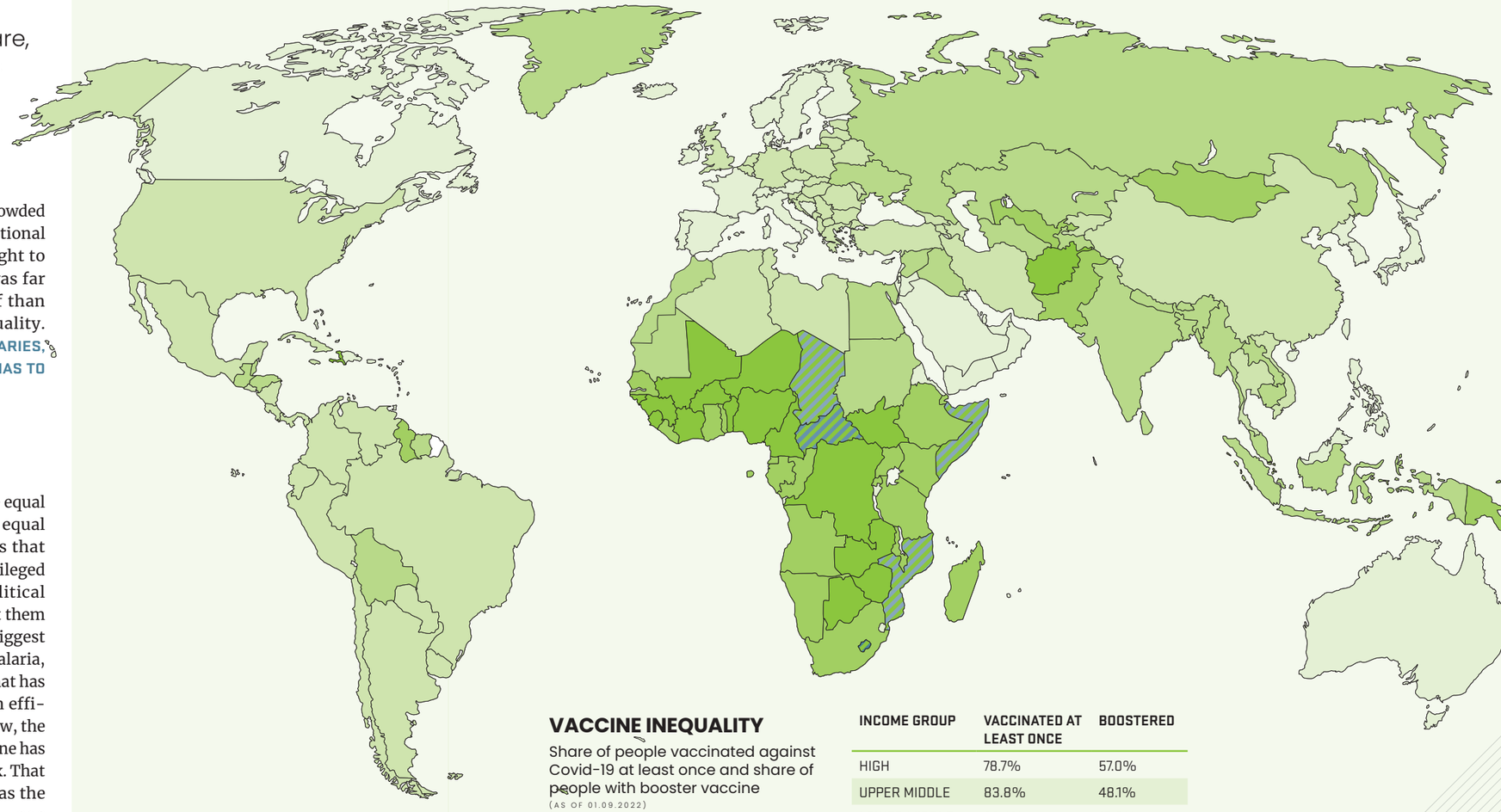
2. MALARIA OR "WHO CARES ABOUT AFRICA?"

Even though all human beings are equal in theory, some tend to be more equal than others in practice. Diseases that mainly hit the poor and underprivileged often lack the financial and political support to find a cure and prevent them from spreading. Take one of the biggest killers of all infectious diseases, malaria, and the painful lack of resources that has prevented the development of an efficient vaccine for decades. Right now, the first really promising malaria vaccine has been approved. Or take monkeypox. That got next to no attention as long as the disease had spread only in Africa - one outbreak to the Global North, and within days the virus became a global threat.

➲ GLOBAL INEQUALITY AS A WHOLE WON'T BE SOLVED ANY TIME SOON. BUT CANCER VACCINES WOULD BE A GOOD START FOR GLOBAL MEDICAL EQUALITY.

HIGHEST DISEASE BURDEN IN AFRICA

Global Disease Burden from all causes, measured in Disability Adjusted Life Years (DALYs) per 100,000 persons per year.

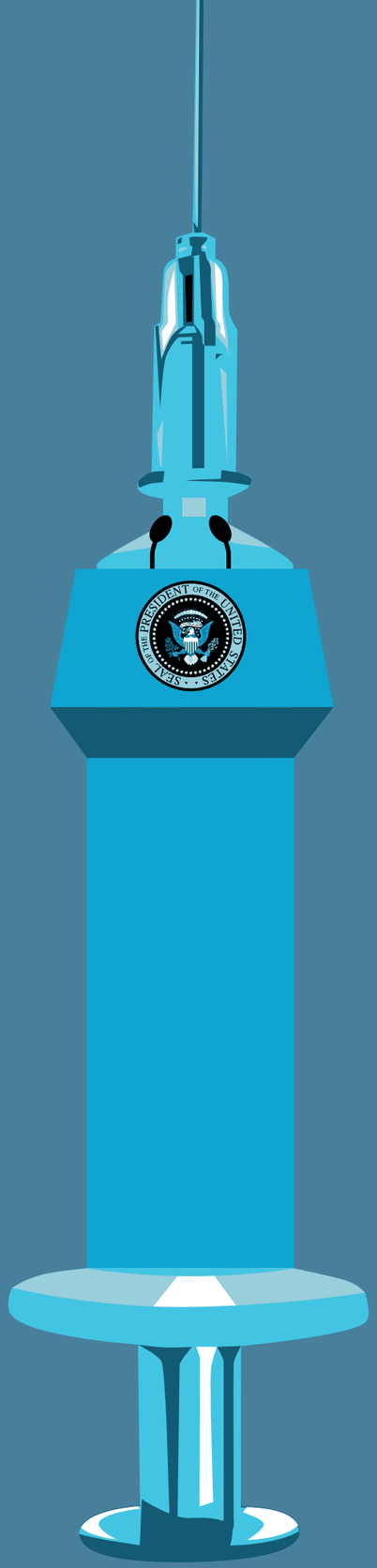


VACCINE INEQUALITY

Share of people vaccinated against Covid-19 at least once and share of people with booster vaccine
(AS OF 01.09.2022)

INCOME GROUP	VACCINATED AT LEAST ONCE	BOOSTERED
HIGH	78.7%	57.0%
UPPER MIDDLE	83.8%	48.1%
LOWER MIDDLE	63.4%	15.0%
LOW	20.9%	1.3%
WORLD	67.7%	30.6%

MAP ILLUSTRATION: GETTY IMAGES; SOURCE: IHME, GLOBAL BURDEN OF DISEASE (2019)



THE WAR ON POLIO

"The polio vaccine is safe, effective and potent." When these results of a huge US study were published on 12 April 1955, a wave of enthusiasm swept the country. Never before or since has the publication of a medical study had such an emotional effect. The US had declared the war on polio, and now there was a chance to win it. Their former World War II ally, the Soviet Union, had also developed a safe and effective polio vaccine. The Cold War competition of these superpowers helped to speed up global distribution.

In 1980, after the success with smallpox, the World Health Organization took over and set the goal of eradicating polio worldwide – with similar success. Today, there are only two countries where polio has not yet been eradicated – Afghanistan and Pakistan.

> "Americans spend more on Botox, face lifts and tummy tucks than on the scourges of polio and malaria."

VICTOR DAVIS HANSEN

Professor em. for classical history, California State University

3. DIABETES OR "DISEASE IS BUSINESS"

Frederick Banting, the Canadian scientist who discovered insulin in 1921, refused to put his name on the patent for his discovery. He felt it was unethical to profit from a discovery that would save lives. His codiscoverers sold the patent for $1 to the University of Toronto – as a present to humanity. Unfortunately, this doesn't mean that humanity today can get their insulin for free, or for a price close to production cost. Diabetes is a chronic disease, every patient needs daily injections of insulin in order to survive – so the pharma corporations try to make as much money as possible from providing diabetes patients with this lifesaving drug. The US suffers from peak absurdity here: Patents on a slightly modificated insulin formulation or on application hardware lead to prices ten times higher than elsewhere in the Global North. US diabetes patients are dying because they can't afford insulin.

Anti-cancer drugs aren't cheap anywhere. They're about the most expensive pharmaceuticals in the world – not least because people will pay an extremely high price not to die. A century after Frederick Banting, no one feels it would be unethical to profit from saving lives.

THE PRICE FOR NOT-DYING IS SOMETHING INTERNATIONAL INSTITUTIONS SHOULD NEGOTIATE WITH THE HEALTH INDUSTRY.

The "price for not-dying?" Yes, it's a very special price, and one that should definitely not be left to market forces. Because for the individual whose life is at risk, there is simply no way to make a sound and rational calculation. It's literally a decision about life or death; whatever makes you survive is of practically incalculable monetary value. That's no way to fix a price.

KID IN MALI? TYCOON IN TEXAS?

But a price has to be negotiated. Vaccine research and production need resources. Even if the patient gets his jab for free, manufacturer, physician, nurse, lab, logistics, and many others want to get paid. So pricing vaccines according to the resources spent on production and distribution seems fair.

In any case, it certainly seems more fair than a pricing based on scarcity. Supply will be scarce in the beginning, so bargaining in unregulated markets about the price of survival would produce sky-high prices and leave less wealthy patients behind.

As soon as a cancer vaccine is available in theory, the decision about who gets it in practice becomes a burning issue for global health equity. Who will be prioritized? The mother in Myanmar, the kid in Mali, the tycoon in Texas? We're still in the run-up to the first mRNA cancer vaccine approvals, so now is the time for humanity to tackle that challenge. We should establish a mechanism to guarantee that vaccines will be distributed based strictly on medical decisions.

ILLUSTRATION: DANIEL HERTZBERG

CALL TO IMPACT

1 A strong global case: The development of cancer vaccines should from the start be seen and treated as a task for humanity – not for single countries or companies.

2 A start for global medical equality: There's no reason why cancer patients in the Global South should be treated worse than those in the North. Equal care and equal distribution should be a core element of any cancer vaccine campaign.

3 A globally negotiated price: No one should be forced to bargain the price for their own survival. Global procurement can manage to keep the purchase price for vaccines close to production costs.

ECONOMIC CHALLENGES
HOW TO SCALE INDIVIDUALITY

Health industries know what it means to ramp up production for the global coverage of diseases. With cancer vaccines, the task is the same – but production and business models must be completely different.

IT SEEMS WE KNOW HOW TO SCALE. With Covid-19, it took just a few months after approval to get the first billion vaccine doses to the market. In comparison, cancer vaccines seem a minor task: 20 million cancers are detected each year – with two doses per patient this would mean 40 million doses per year for the global coverage of all cancer patients. What's the problem?

The problem is individuality. As each cancer has a different genetic fingerprint, each therapeutic vaccine has to be different. In economic terms, upscaling these mRNA vaccines will mean not mass production, but mass customization. Batch size one, but millions of them.

That's a completely different business model than the prevailing one in pharma – the "blockbuster" model. Decades of research and clinical testing one day lead to the approval of a drug, and then a huge production and distribution machine is kickstarted to get as much of the new stuff as possible to the market, in order to maximize profit in the often small time window of patent protection.

But cancer vaccines are no blockbuster. Global individualized vaccine production with batch size one will not be done in one huge factory, as no mass distribution is needed; a much more decentralized manufacturing fits better. And eradicating cancer with therapeutic vaccines will not need a dynamic, globally coordinated sales force, as you don't sell truckloads of drugs at once, but always just one vaccine dose at a time.

This may hurt today's pharma market leaders, the masters of the blockbuster business model, particularly hard. A looming structural change in a market is always daunting for the players that are best adapted to the current market. With gene-based, personalized medicine there's less need for their core competences. Individual cancer therapy can cure tens of millions of people – but with new forms of supply chain, production, distribution, and decision-making.

> "It's the proof of concept for a very new pharmaceutical drug class."
>
> **UGUR SAHIN**
>
> Co-founder BioNTech, on the Covid-19 mRNA vaccine

We are already seeing indications of how these new production and business models will look.

1. MORE LAB WORK

Numerous links along the production chain of individualized vaccines take place in a lab environment. Blood and tumor samples have to be prepared and analyzed, DNA and RNA structures have to be built and tested – and efficiency aspects mean that most of it will be best placed close to the patients. This requires the global build-up of medium-sized lab infrastructures; neither gigafactories, nor lone warriors, but a loosely knit network of up-to-date medical labs.

2. LESS PAPER WORK

Traditional drug or vaccine development requires a lot of time, research, studies, and paperwork until finally a new pharmaceutical is approved. For individualized vaccines there won't ↘

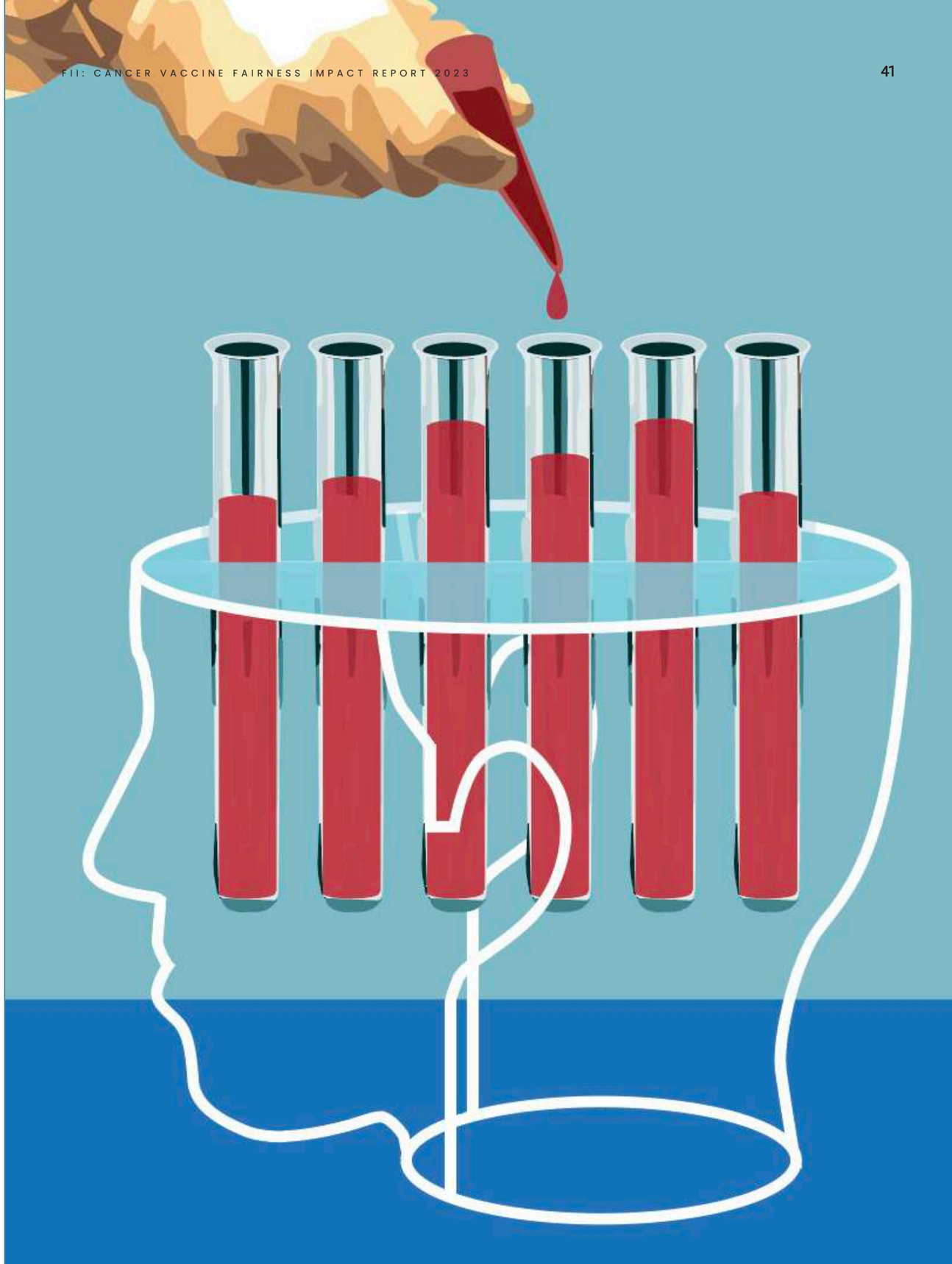


ILLUSTRATION: DANIEL HERTZBERG

WEALTH INEQUALITY

GDP per capita (in PPP) and distribution of the 50 biggest pharma corporations

SOURCES: IMF (FOR GDP), DRUG DISCOVERY TRENDS (FOR PHARMA HQS)

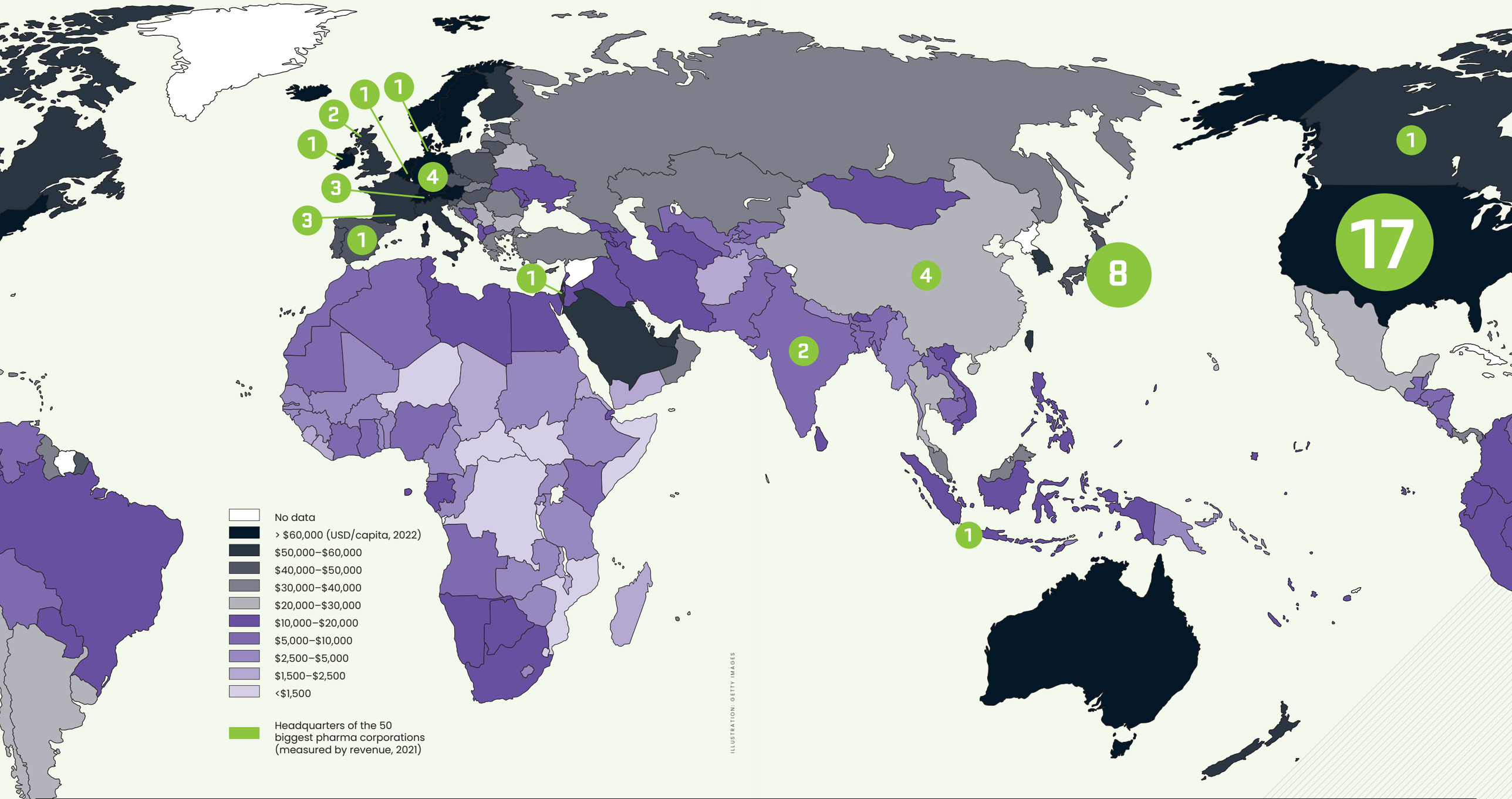


ILLUSTRATION: GETTY IMAGES

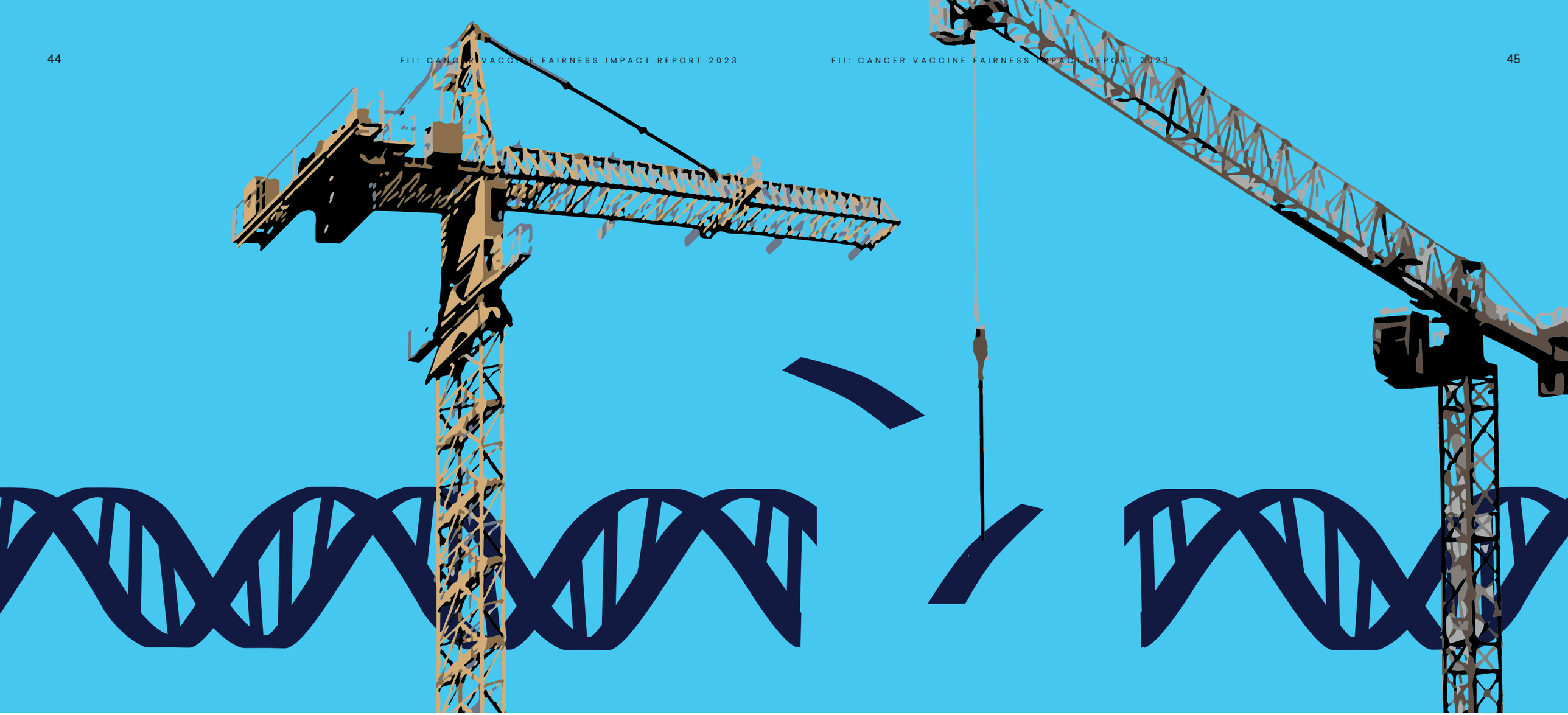


ILLUSTRATION: DANIEL HERTZBERG

↘ be 20 years of clinical studies, and they will also need much less administrative effort. The basic elements of these vaccines, such as packaging, ingredients, and carrier substance, will remain unchanged and won't have to take the same long regulatory road a second, third or hundredth time. Only one active ingredient will change from patient to patient: the individualized mRNA strain.

3. PLATFORM ECONOMY

Decentralized production chain, agile logistics, lean administration, that's not exactly how Big Pharma looks right now. These huge corporations run the risk of becoming the dinosaurs of the industry, perfectly adapted to one ecosystem, but unable to survive a harsh environmental change that leads to the emergence of a new ecosystem.

The ecosystem starting to develop around mRNA technology is a completely different economic structure that favors completely different business models: a platform economy. In its center, there's vaccine design as core competence; around it, a constantly changing float of input, output and throughput elements is evolving.

Some of these elements will be more local, some more global. Some are rooted in real life: You can't get a tumor sample without engaging with that specific patient. And some are mainly digital: you don't have to touch a cancer cell to find a target protein in its mutanome. But all of them are a threat to the incumbents of Big Pharma and Big Health.

THE GIANTS WILL SUFFER

In some industries, platform strategies have been established; media, for example (e.g. Google, Facebook), or retail (e.g. Alibaba, eBay). Former giant incumbents have suffered, such as legacy media corporations or department stores, and on the other hand, lots of small and micro competitors have successfully entered the industries. And the one who owns the platform is usually the one who gets the biggest slice of the cake.

In media and retail, the former big shots have fought the new platform ecosystems, but with meager results. We don't know yet whether the same development will occur in the health and pharma industry, but there's next to no chance that the new ecosystem will simply disappear. ■

CALL TO IMPACT

1 Science lab entrepreneurship: The decentralized lab infrastructure required should encourage local lab start-ups.

2 Ecosystemic steering: Economic policy for the vaccine sector should focus less on big shots and more on systemic relations.

3 Global platform regulation: Platform structures make sense for cancer vaccines, but regulators should prevent monopoly rents.

SOLUTIONS
FOR THE DEVELOPMENT AND ROLLOUT OF THERAPEUTIC CANCER VACCINES

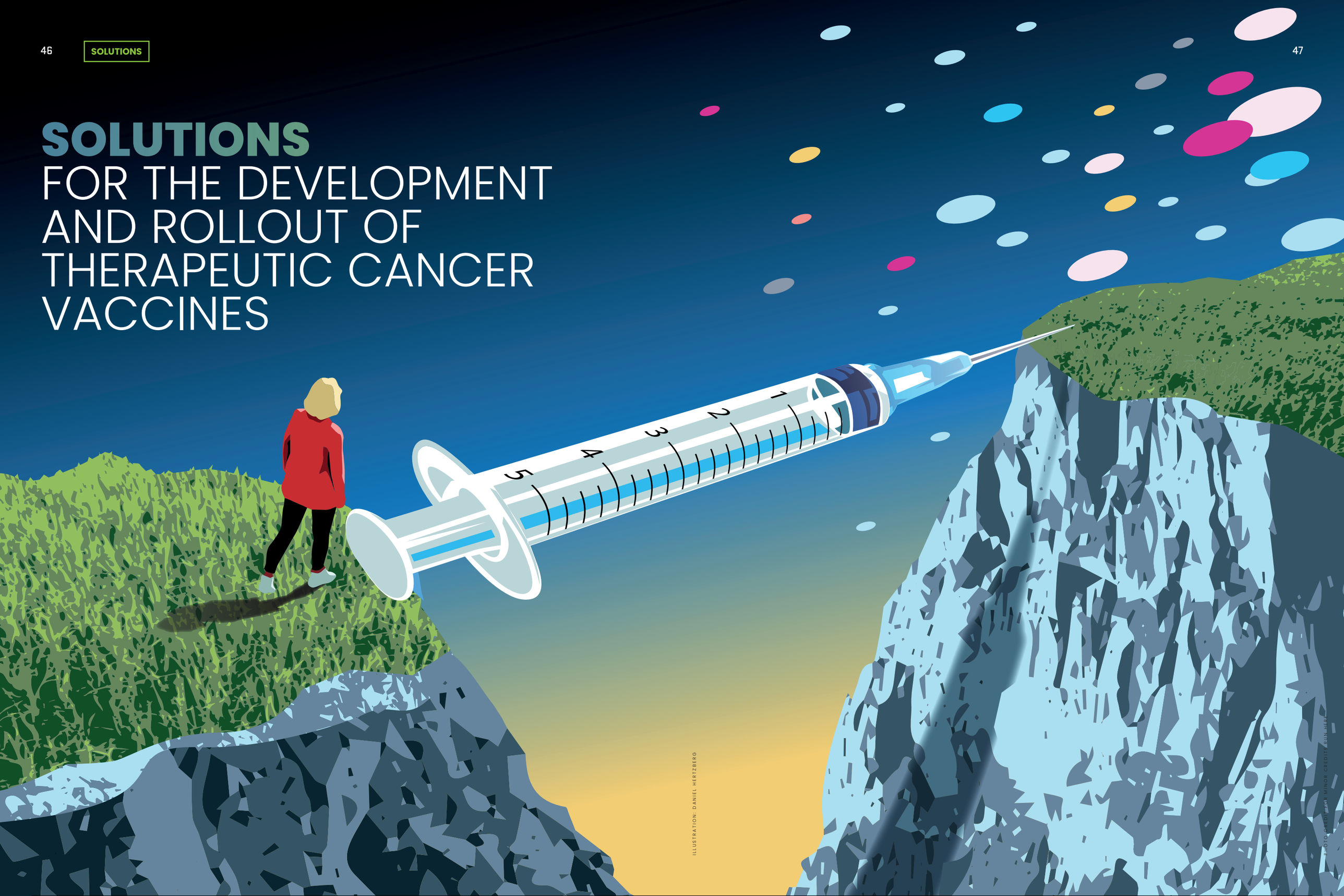


ILLUSTRATION: DANIEL HERTZBERG

PHOTO CREDIT: TOM MINOR CREDIT: TOM MINOR

VACCINE FAIRNESS
A POSTER CHILD FOR HUMAN EQUALITY

Therapeutic cancer vaccines are still a long way from a broad, global rollout. So this is exactly the right time to begin the debate about the best and fairest way to put an end to cancer - as humanity will need plenty of time to guarantee fair access for everyone in need.

THERE'S STILL A LONG JOURNEY ahead of us before therapeutic cancer vaccines are ready for a global rollout. This may be painful for the ones who need treatment right now. But it is an opportunity for humanity to build the right road for that journey. Because if we get a chance to end a nightmare, we should implement it not just any old how, but in a way that optimizes the Impact on Humanity.

Therapeutic cancer vaccines could become a poster product for human equality, as they would be able to treat (and save) everyone, without regard for origin, race, gender, social or economic status. In the moment a person gets a cancer diagnosis, it makes no difference who you are and where you come from – you have just been struck by a disease that might kill you. And you want to get rid of it as soon as possible.

The vaccine sees no differences. It can be made in precisely the same way using any cancer sample, be it from a boy in Belgium or a pensioner in Paraguay. The process of identifying the best target structure and the manufacturing of the personalized vaccine is exactly the same for everyone, and you don't need high-tech medicine or specialized staff to deliver the vaccine. It's just a jab, every nurse can do it.

Of course, there are high-tech parts of the production chain required to lead from cancer detection to vaccine delivery. These can and should be built and organized in the most efficient way to supply cancer vaccines to anyone and everyone and who needs one. And now, with at least some years until implementation, the time is right to begin the debate about the best and fairest way to put an end to cancer.

In medical emergencies – a pandemic or after a disaster – the doctors in place sometimes can't take care of everyone and everything. They have to decide who they will treat, and who has to wait, or die. For these situations, there is a globally accepted method of allocating scarce medical resources. This is triage (see box on opposite page) an assessment based strictly on medical criteria. Those with the best chances of survival through the available health measures are selected. The ones that have a good chance to survive even without assistance will have to wait, and the ones that have the worst prospects of survival even with medical assistance will be left to die.

This should not only be the way to use scarce medical resources in a disaster, but also the way to use scarce lifesaving medication. If not everyone can get a therapeutic vaccination, it should go to the ones with the best chances of survival by means of this vaccine.

If the vaccine improves your chance of survival you should get it – but only if there's enough vaccine for everyone. If not, it depends.

There's no need to define the specific medical criteria right now, especially not for a non-medical institution such as the FII Institute. What needs to be defined well before the rollout of cancer vaccines is that, in case of scarcity, the decision about who gets a vaccine and who doesn't should be based purely on medical criteria.

This doesn't happen automatically – especially not on a global scale. Prioritizing the medical decision over political or economic criteria happens almost any time a doctor is treating a patient. It happens quite often on a national basis, as could be seen in the prioritization of Covid vaccines: the elderly, the most vulnerable, and medical staff were almost everywhere among the groups given the highest priority. But rarely does it happen globally.

Building infrastructure in the best way for humanity is another thing that does not happen automatically – it could also be built in the best way for shareholders or national governments. This is what we as humanity can decide: Here we have a new, highly promising technology still in its infancy. So not the people nor the economy nor the institutions are prepared for what might evolve. In this case, the future is ours to see – and to make.

> "I will do no harm or injustice to my patients."

HIPPOCRATES (460–370 BCE)

Credited with writing the Hippocratic Oath, one of the oldest ethical standards for physicians, and still the most influential one.

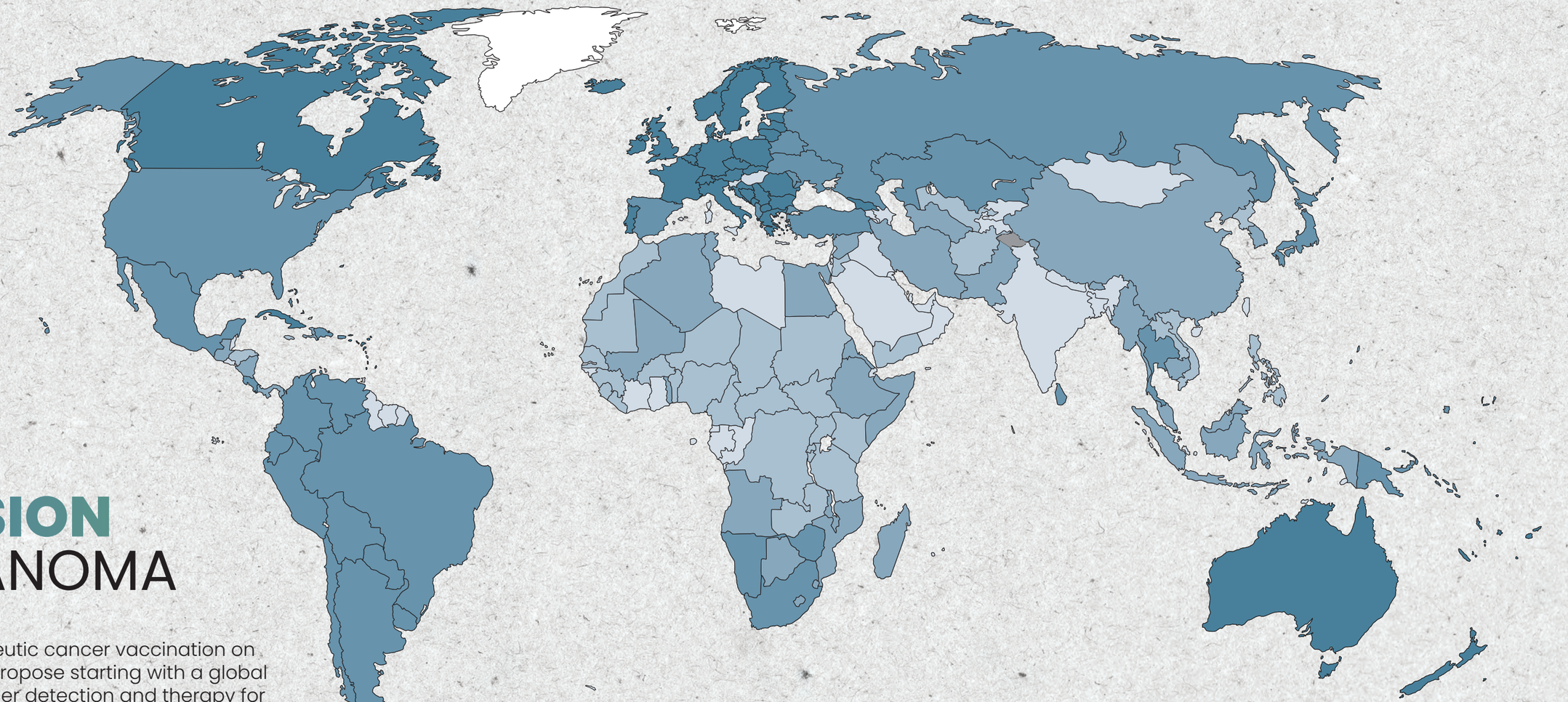
ILLUSTRATION: DANIEL HERTZBERG

TRIAGE

In medicine, the word triage means the prioritization of medical care when it can't be given to everyone for lack of resources. In its acute form it is most often required on the battlefield, during a pandemic, or after accidents with a high number of casualties.

While doctors have always had to select and prioritize medical care, standardized forms of triage began more than 200 years ago in France during the Napoleonic Wars. In the most common form of triage, the victims are divided into three categories:

Those who are likely to live, regardless of what care they receive;
Those who are unlikely to survive, even when they receive care;
Those who have a better chance of survival with immediate care.



MISSION MELANOMA

To get therapeutic cancer vaccination on the road, we propose starting with a global rollout of cancer detection and therapy for melanoma – the most lethal skin cancer.

SOME 2 TO 3 MILLION SKIN CANCERS are detected each year. This makes it one of the most frequent tumors in the world. With a death toll of about 120,000 per year, however, skin cancers are far behind the major killers such as lung cancer (2 million deaths per year), colon cancer (1 million) and breast cancer (700,000).

The main reason for that difference is that about 90% of all detected skin cancer cases belong to the much less lethal forms of nonmelanoma cancers. For melanoma, though, the actual death rate is about 25%. In any case, the earlier the treatment begins, the better the chances of survival.

A set of specific features of skin cancer make it especially well-suited to be the target for a rollout of therapeutic cancer vaccines. We will explain these features on page 50.

PHOTO: GETTY IMAGES & FOTOGRAZIA, MAP: GETTY IMAGES

SKIN CANCER MORTALITY

In deaths per 100,000 persons per year. The numbers combine **melanoma and nonmelanoma skin cancers.** Data are raw numbers, not adjusted for age difference.

- ≥ 4.3
- 1.4–4.3
- 0.81–1.4
- 0.51–-0.81
- < 0.51
- not applicable
- no data

SOURCE: GLOBOCAN 2020; WORLD HEALTH ORGANIZATION

WHY SKIN CANCER?

Six features of skin cancer make it a perfect candidate for the first global rollout of therapeutic cancer vaccines.

1. IT IS EASY TO DETECT

You don't need a hospital. You don't need a lab. For detection, you need only a picture of the suspicious tissue and someone who is experienced in checking skin alterations.

2. DETECTION IS EASY TO SCALE

The equipment needed for detection of skin cancer is available even in the remotest places on earth. It's just a phone with a camera and an online connection. The checking can be done visually in the nearest medical location, or at a central specialized hub, with or without the assistance of AI systems. Looking at pictures of altered skin tissue, deciding "yes," "no," or "need more information," doesn't take a lot of time.

3. IT IS EASY TO CURE

About 2 million nonmelanoma cancers are detected each year. Their lethality ratio of about 2.5% can be further reduced if the cancer is detected in earlier stages. The same holds true for the melanoma type of skin cancer, which is ten times more lethal.

4. IT OFTEN NEEDN'T BE FOUGHT WITH VACCINES

In fact, for the majority of cases that are still in the early stages and localized, it's usually sufficient to just cut out the altered tissue.

5. IT CAN EASILY BE TREATED WITH MRNA VACCINES

Melanoma don't hide. They are as visible for the immune system as they are visible on the skin. Clinical tests up to now have shown a high effectiveness of mRNA vaccines in the treatment of skin cancer.

6. IT MAINLY OCCURS IN REGIONS WITH WELL-EQUIPPED HEALTHCARE SYSTEMS

Most skin cancer victims have fair skin. This makes it, looked at realistically, easier to convince the rich countries to enter into a system of global solidarity – so this is not only a test-run for cancer vaccines, but also for the fairness of the Global North.

In every individual case, there is also a journey: starting with the detection of an individual cancer and hopefully ending with its elimination. There are different steps at different times and places, some of them need a medical decision (like a triage), some need other decisions (like logistics or money), and some just need someone doing the job.

This leads to a **roadmap for skin cancer vaccination (see pages 52–53).**

THE SKIN TYPE EFFECT

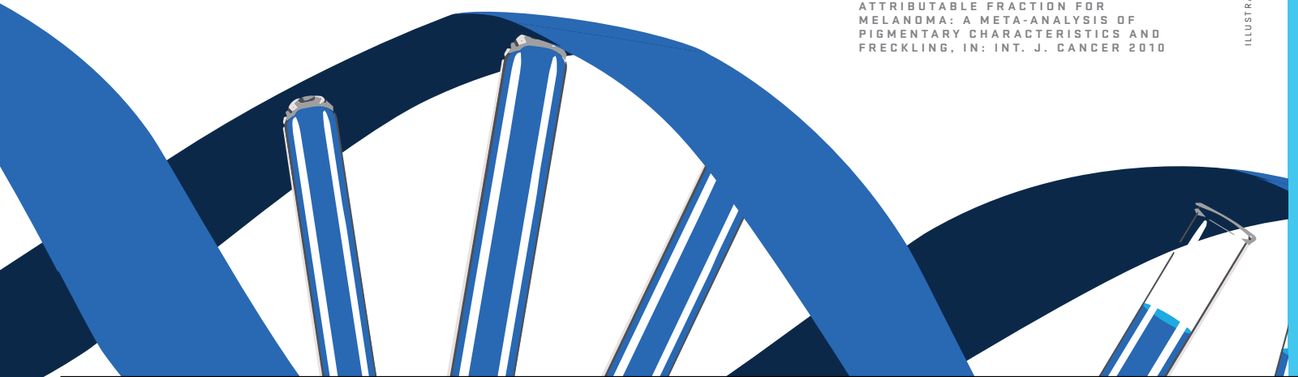
Share of people vaccinated against Relative Melanoma Risk for different skin types (Risk for Olive Brown skin type = 100):

SKIN TYPE	RELATIVE RISK
I PALE	227
II FAIR	199
III LIGHT BROWN	135
IV OLIVE BROWN	100

For Skin Types V (Brown) and VI (Black) the Relative melanoma Risk is lower, though not quantified in studies.

SOURCE: C. OLSEN, H. CARROLL, D. WHITEMAN: ESTIMATING THE ATTRIBUTABLE FRACTION FOR MELANOMA: A META-ANALYSIS OF PIGMENTARY CHARACTERISTICS AND FRECKLING, IN: INT. J. CANCER 2010

ILLUSTRATION: DANIEL HERTZBERG



ROADMAP FOR SKIN CANCER VACCINATION

FOR EVERY PATIENT

CANCER DETECTION

How?
Visual check of altered tissue

Who?
Doctor, Specialist, AI

What to do?
Build-up of telemedicine systems in remote rural regions

CANCER DIAGNOSIS

How?
Type and stage of cancer

Who?
Doctor/medical institution

What to do?
Allocation of financial resources to allow treatment for everyone

THERAPY ASSESSMENT

How?
Surgery?
Chemotherapy?
Radiotherapy?
Immunotherapy?
Vaccination? Or a combination?

Who?
Doctor/medical institution

What to do?
Instruction and training of medical staff to enable reliable assessment

THERAPY DECISION

How?
Based on predicted effects and risks of each assessed therapy

Who?
Doctor and patient

What to do?
Creation of simple, understandable explanations to enable informed decisions to allow treatment for everyone

If for any given patient in the world the best therapy would be a cancer vaccine, the patient should be able to get it.

→ Organizing this is a challenge for humanity

FOR EVERY PATIENT TO BE VACCINATED

TAKING BLOOD AND TUMOR SAMPLE

How?
Extraction of tumor cells and of healthy cells (usually blood)

Who?
Local doctor/nurse

PREPARATION OF TUMOR CELLS

How?
Fine tissue sections from the tumor sample to investigate its molecular make-up

Who?
Regional lab

What to do?
Creation or strengthening of regional lab infrastructure

ANALYSIS AND COMPARISON OF CELLS

How?
Sequencing of both genomes, determining the genetic modifications

Who?
Specialized lab

What to do?
Upscaling of genome-sequencing facilities

PRIORITIZATION AND SELECTION OF MUTATIONS

How?
Software-based shortlist of the most promising mutations to target, human-based final selection

Who?
Lab, specialist or vaccine producer

What to do?
Streamlining of selection process

DESIGN AND MANUFACTURING OF VACCINE

How?
Defining the lead structure for the therapy and manufacturing the individualized therapy

Who?
Vaccine manufacturer

What to do?
Decentralization of manufacturing facilities, restructuring from mass production to mass customization

These steps are the ones that will need massive investment for scaling-up. The price should be the same for every patient and should be paid via a scheme of international solidarity.

→ Organizing this is a challenge for humanity

TRANSFER TO VACCINATOR

How?
Release of the quality-controlled vaccine, ready for treatment

Who?
Specialized logistics

What to do?
Build-up of cooling chain, where needed

VACCINATION

How?
Vaccine is administered to the specific patient

Who?
Doctor or hospital

CHECK FOR IMMUNE RESPONSE

How?
Patient is controlled for effect on the tumor and for potential side effects

Who?
Doctor or hospital

VACCINATION AND BEYOND

If scaling-up is not fast enough, there should be established an internationally accepted process to make the decision about who will be served, and who not (as e.g. for organ trans-plants). This should be a purely medical decision.

→ Challenge for health community

ICONS: FLATICON.COM

THE BOTTLENECKS FOR THE IMPLEMENTATION OF CANCER VACCINES

Beyond the medical issues, these are the main obstacles humanity has to overcome.

SCALING-UP

MAKING VACCINES ACCESSIBLE FOR EVERYONE WHO NEEDS THEM

As with every new technology, broad and fast implementation needs scaling of production and distribution. But to achieve a fair accessibility for everyone who can be saved by cancer vaccines, size and speed alone are not enough: production and distribution capacities have to be expanded in all regions across the globe.

ANTITRUST POLICY

PREVENTING COMPETITORS FROM OBSTRUCTING THE ROLLOUT

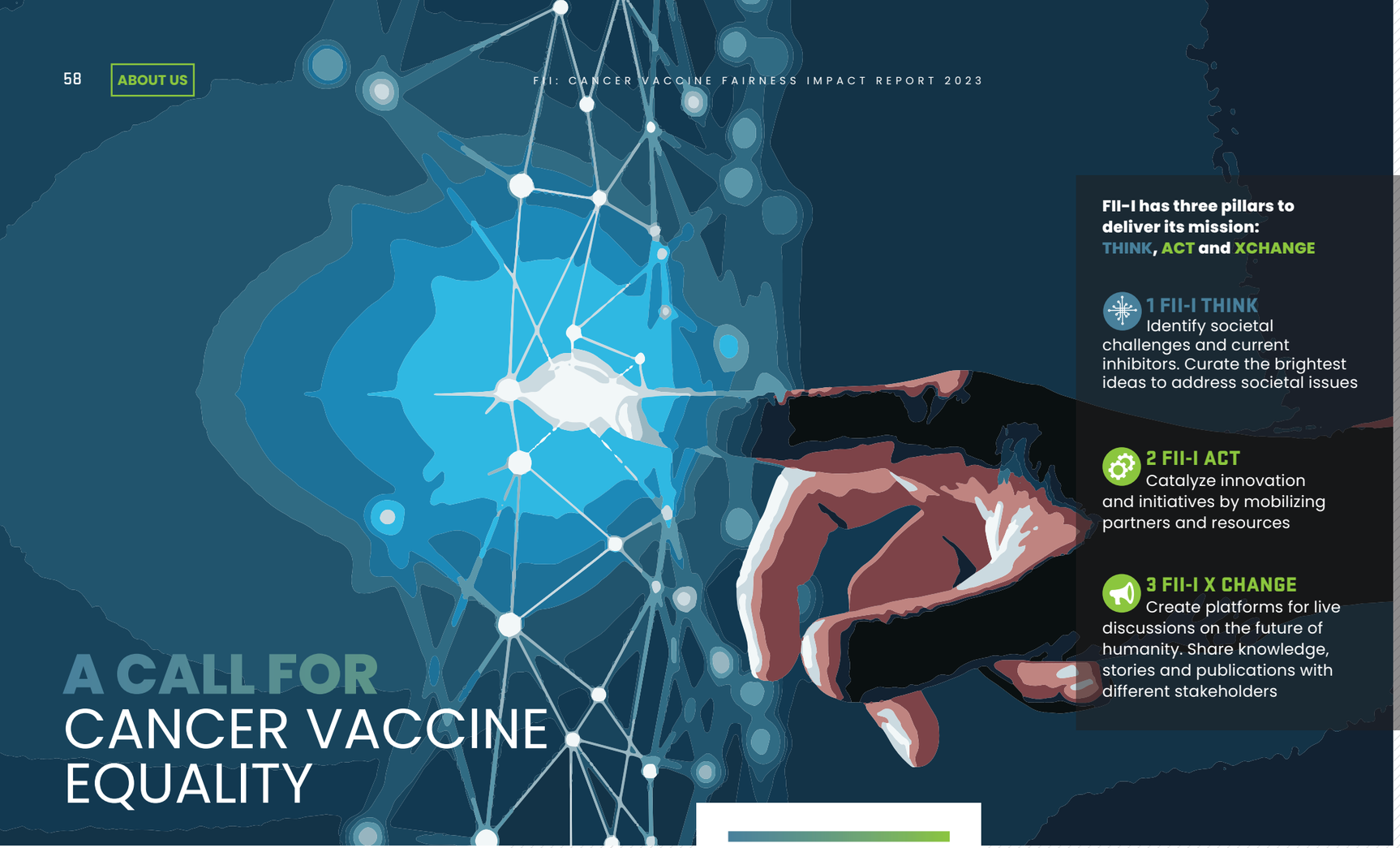
A success of cancer vaccines can not only save lives, but also money – if the vaccine replaces radiation or chemotherapies. A boon for humanity, but a threat to a multi-billion dollar industry. That may lead to obstruction and delay tactics. Preventing such foul play needs political rigor and a clear focus on the best possible Impact on Humanity.

COMMUNICATION

GETTING THE MESSAGE OUT TO THE LOCAL DECISION-MAKERS

In this case, the decision-makers are the patients and the local medical staff. They have to know how to detect the cancer, that they are part of the global effort to fight this specific disease, and that they have a good chance to win that fight through vaccination. This requires accessible and inclusive information, as well as training.

ILLUSTRATION: DANIEL HERTZBERG, FLATICON.COM(3)



A CALL FOR CANCER VACCINE EQUALITY

FII-I has three pillars to deliver its mission: THINK, ACT and XCHANGE

1 FII-I THINK
Identify societal challenges and current inhibitors. Curate the brightest ideas to address societal issues

2 FII-I ACT
Catalyze innovation and initiatives by mobilizing partners and resources

3 FII-I X CHANGE
Create platforms for live discussions on the future of humanity. Share knowledge, stories and publications with different stakeholders

WE'RE FAR AHEAD OF THE CURVE. That's how we like it. The mRNA technology has only just begun to disrupt the health industries, but this is exactly the right time to ask how this revolution can have the maximum Impact on Humanity.

The mRNA technology promises to win the battle against cancer – by producing individual vaccines for every cancer patient. In this report, we have looked into the research, the encouraging and the disappointing results, and into the challenges for seociety and economy. Eradicating cancer can not only become a blessing for humanity, but also a chance to get closer to global health equality. The mother in Kenia, the kid in Mali, the tycoon in Texas – they all can, and shall, have the same chance to get cured from a once diagnosed cancer.

That does not happen automatically. But it can happen, when we reach the window of opportunity to lay the foundation for maximizing the impact of Cancer vaccines. That's why this report also proposes to start with a global roll-out for cancer detection and therapeutic mRNA vaccination against the most lethal skin cancer – we call it "Mission Melanoma".

ABOUT THE FII INSTITUTE

THE FUTURE INVESTMENT INITIATIVE (FII) INSTITUTE is a new global nonprofit foundation with an investment arm and one agenda: Impact on Humanity. Global, inclusive and committed to Environmental, Social and Governance (ESG) principles, we foster great minds from around the world and turn ideas into real-world solutions in five critical areas: Artificial Intelligence (AI) and Robotics, Education, Healthcare and Sustainability. We are in the right place at the right time: when decision-makers, investors and an engaged generation of youth come together in aspiration, energized and ready for change.

We harness that energy into three pillars: **THINK, XCHANGE, ACT.**

- Our **THINK** pillar empowers the world's brightest minds to identify technological solutions to the most pressing issues facing humanity.
- Our **XCHANGE** pillar builds inclusive platforms for international dialogue, knowledge sharing and partnership.
- Our **ACT** pillar curates and invests directly in the technologies of the future to secure sustainable real-world solutions.

Join us to own, co-create and actualize a brighter, more sustainable future for humanity. ■

THE FII INSTITUTE

is guided in all it does by a strong purpose, vision and mission.

PURPOSE
"Enabling a brighter future for humanity"

VISION
"Empowering the world's brightest minds to shape a brighter future for ALL, and with ALL"

MISSION
"Curating and enabling ideas to impact humanity sustainably"

PHOTO: ADOBE STOCK, FII INSTITUTE

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Overview of key sources used for this report

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The Vaccination Booklet for Everyone
German Edition
Arabic Edition

COMPANIES

Biontech
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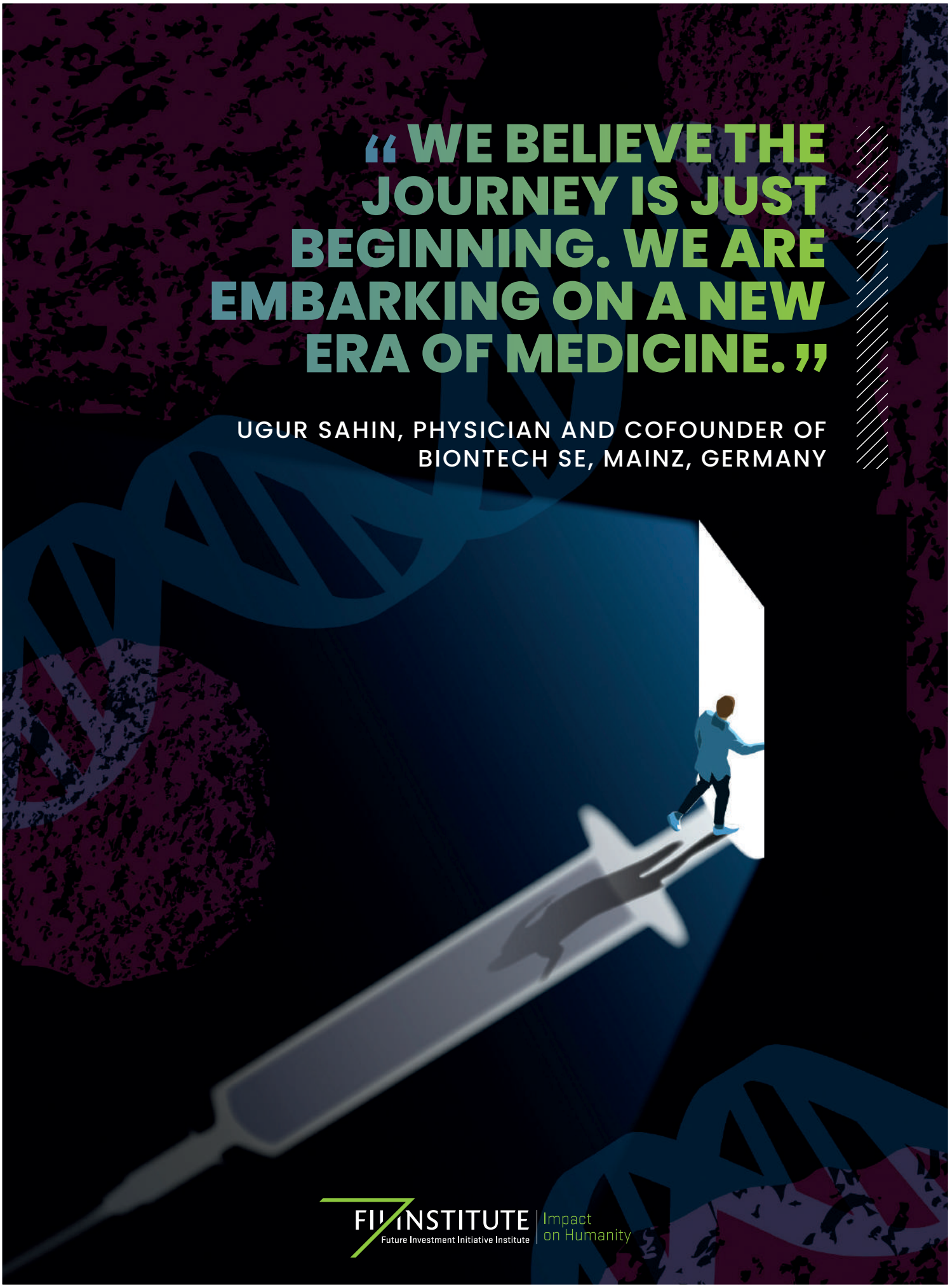
“WE BELIEVE THE JOURNEY IS JUST BEGINNING. WE ARE EMBARKING ON A NEW ERA OF MEDICINE.”
UGUR SAHIN, PHYSICIAN AND COFOUNDER OF BIONTECH SE, MAINZ, GERMANY
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