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March - April 2020

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The urgent search for a vaccine

Oncology

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We're failing our children

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COVID-19 vaccine

COVID-19 has taken the world by storm. The flu-like disease caused by the coronavirus SARS-COV-2 emerged in Wuhan, China in December and has now infected people on every continent with increasing mortality. The WHO estimates the mortality rate to be around 3.2%, so it is cause for significant concern. There is now an urgent need to develop a vaccine and treatment. In this issue we look at a number of labs that have taken up the challenge to rapidly develop a vaccine and provide some hope that we may be able to provide greater protection against this disease.

In this issue, we also report on the Pan-Cancer Analysis of Whole Genomes – a landmark global genomics project that is unveiling cancer's complexity on an unprecedented scale. By combining sequencing of the whole cancer genome with a suite of analysis tools, it is possible to highlight and describe every genetic change found in a cancer. The project will enable more personalised medicine in the future, once clinical whole genome sequencing of a patient's cancer becomes more widely adopted.

A commission of global health experts met recently under the auspices of the WHO, UNICEF and *The Lancet* and released a report calling for a radical rethink on child health. They warn that we are failing our children when it comes to protecting their health against the onslaught of ecological degradation, climate change and exploitative marketing practices. Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization, says their report serves as a wake-up call for countries to "invest in child health and development, ensure their voices are heard, protect their rights, and build a future that is fit for children".

As in each issue, in this issue you will find a wealth of health and research news.

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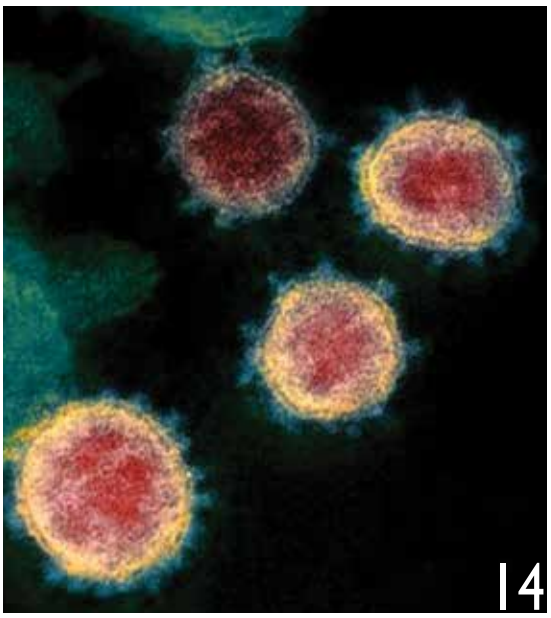

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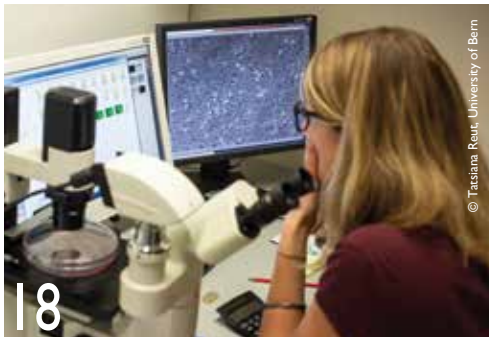

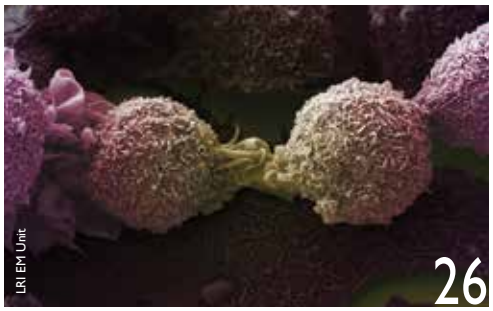

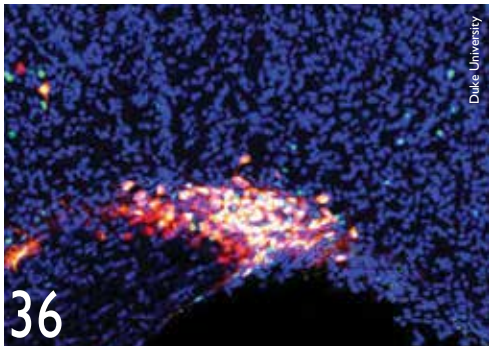

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Update from around the region

Women underestimate risk of heart disease, according to UAE survey

Many women in the UAE underestimate the significant risks posed by heart disease, believing breast cancer to be the bigger threat, according to a new survey commissioned by Cleveland Clinic Abu Dhabi.

In total, 82% of women who responded to the survey did not identify heart disease as the leading cause of death among women in the UAE. Instead, breast cancer was misidentified as the number one threat by 46% of the women surveyed – the highest proportion in the survey. Heart disease is the most frequent cause of death among women in the UAE and across the globe.

"The results of this survey are concerning. They clearly reflect the success of breast cancer awareness campaigns, with women identifying it as the greatest threat to their health. However, heart disease kills more women every year than all cancers combined. If women are unaware of their risk, they are less likely to visit a doctor for preventative care or treatment," says Dr Dima Quraini, a cardiologist at Cleveland Clinic Abu Dhabi.

Compounding the lack of overall awareness, 76% of women surveyed did not know that men and women can experience heart attacks differently. A majority also failed to identify the unique symptoms of heart attack that women can experience.

Unlike men, women are more likely to experience a 'silent heart attack' with symptoms such as shortness of breath, nausea, indigestion, neck pain and fatigue. Only 31% of women surveyed associated these symptoms with heart attack, while 58% associated them with stress.

The most common risk factors for heart disease, such as obesity, lack of exercise and smoking are generally well understood. However, the survey revealed that some of the unique factors that can increase women's risk are not well understood.

Only 17% of women understood that pregnancy can increase their risk of heart disease, a number which drops to just 8% among Arab expatriates surveyed. Early menopause has been linked to an increase in the risk of heart disease, but 67% of women over 40 who responded to the survey were not aware of this possibility.

While people are generally aware that high blood pressure increases their risk of heart disease, just 24% of female respondents knew that it increases their risk more than it would a man's.

"The bad news from this survey is that a significant proportion of women are unaware of their own risk factors. The good news is that, in 2020, we're able to do something about it. Prevention really works and can reduce a woman's chances of developing heart disease by up to 80%," concludes Dr Quraini.

Cleveland Clinic Abu Dhabi is using Heart Month in February to raise awareness of heart disease, with a particular focus on women in the UAE. The hospital recently opened a women's heart health clinic to ensure women receive comprehensive, multidisciplinary care tailored to their specific needs.

New IFC investment supports construction of healthcare facilities in Egypt and Morocco

IFC, a member of the World Bank Group, is the lead arranger for an Islamic financing package of up to US$125 million to Humania, a private healthcare company, to help expand health services and improve medical care in Morocco and Egypt.

IFC will provide Humania with a $35 million Islamic facility for its own account and is the lead arranger for the rest of the financing from the Finnish Fund for Industrial Cooperation Ltd (Finnfund), OPEC Fund for International Development, European Bank for Reconstruction and Development, and the IFC Managed Co-Lending Portfolio Program (MCPP). MCPP is an innovative syndications platform that offers institutional investors the ability to passively participate in IFC's future senior loan portfolio.

The financing will help Humania develop a network of multispecialty hospitals and healthcare assets in Egypt and Morocco. The first phase of its investment program includes three hospitals and a medical tower with nearly 600 inpatient beds and 240 outpatient clinics. The company's growth is considered key in both countries, where there are shortages of doctors and hospital beds. Egypt's healthcare sector needs $60 billion in investments by 2050 to meet rising demand for medical services, while Morocco is also facing a need to improve healthcare delivery, especially for women and young children.

"Healthcare and development are inextricably linked," said Sobhi Batterjee, Chairman of Humania. "Our partnership with IFC will allow us to provide world-class healthcare to more patients in Egypt and Morocco, and thus play a role in improving the healthcare systems and well-being of the communities in these countries."

Makarem Batterjee, President of Humania, added: "We go beyond headline numbers about supply and demand. Our focus is as much on quality of care and meeting international benchmarks, as it is about addressing supply shortage."

The investment by IFC is part of an effort to expand the role of private medical providers in the Middle East and North

Africa (MENA), where demand for health services is rising and the public sector cannot meet all needs.

"Over the coming decade, the countries of MENA will need to make substantial investments in medical care to keep their fast-growing populations healthy," said Sérgio Pimenta, IFC's Vice President for the Middle East and Africa. "Governments alone won't be able to foot the bill. The capital and expertise of the private sector can be used to make sure people in the region get the healthcare they need."

IFC is a sister organization of the World Bank and member of the World Bank Group. It is the largest global development institution focused on the private sector in emerging markets. IFC works with more than 2,000 businesses worldwide, using their capital, expertise, and influence to create markets and opportunities where they are needed most. In fiscal year 2019, IFC delivered more than $19 billion in long-term financing for developing countries, leveraging the power of the private sector to end extreme poverty and boost shared prosperity.

WHO launches regional nutrition strategy to help countries achieve nutrition-related SDGs

Malnutrition, in all its forms, is negatively impacting the health, well-being and sustainable development of people of all ages in WHO's Eastern Mediterranean Region, particularly in those countries affected by conflict in which people are experiencing high levels of food insecurity, undernutrition and micronutrient deficiencies. In the Region, nearly 20.2 million children under-5 years of age are stunted by poor nutrition, while half of adult women (50.1%) and more than two in five men (43.8%) are overweight or obese. In addition, more than 15% of children and more than half of adolescents are overweight or obese.

Noncommunicable diseases (NCDs), namely heart attacks and stroke, cancers, diabetes and lung disease, are cutting lives short. NCDs are now responsible for two thirds of deaths in the Region and unhealthy diet is a key contributor to this burden, according to the WHO.

The WHO is calling on governments to take action to improve nutrition, to reduce the burden of diet-related NCDs, and reduce undernutrition associated with conflict and political instability. In September 2015, the world agreed to eliminate all forms of malnutrition by 2030 when Member States adopted the 2030 Agenda for Sustainable Development and its related goals. Addressing malnutrition in all its forms is firmly embedded in Sustainable Development Goal (SDG) 2 – which aims to end hunger, achieve food security and improve nutrition, and promote sustainable agriculture – and SDG 3 to ensure healthy lives and promote well-being for all at all ages.

More than 600 participants from different sectors around the world attended a meeting on NCDs and mental health in Muscat, Oman, on 12 December 2019. At the meeting the WHO launched a regional nutrition strategy to help countries meet the 2030 global nutrition-related targets, achieve food security, end all forms of malnutrition and improve nutrition throughout the life course.

"With just 10 years left, countries need to leverage current momentum to improve nutrition and access to healthy diets as they continue to move through nutrition and epidemiological transitions," said Dr Ahmed Al-Mandhari, WHO Regional Director for the Eastern Mediterranean. He added that currently many countries in the region suffer from a high burden of diet-related NCDs, and some are experiencing undernutrition due to conflict and political instability.

"This strategy presents a series of recommended priority actions to address malnutrition in all its forms and accelerate progress to meet the global targets, centred around the six key areas of action of the United Nations Decade of Action on Nutrition for 2016–2025," he said.

The strategy on nutrition for the Eastern Mediterranean Region 2020-2030 aims to strengthen efforts to ensure universal access to healthy and sustainable diets and implement effective nutrition actions, in order to:

- improve nutrition throughout the life-course, including for mothers, infants, children, adolescents and older people;
- prevent undernutrition, overweight, obesity and diet-related NCDs; and
- support and protect nutrition in emergency situations.

The strategy also recommends priority actions to transform food systems, implement taxes and improve social protection to improve nutrition through adoption of an integrated, multisectoral approach.

"Transformation of food systems is critical to improving access to healthy, sustainable diets and civil society has a key role in advocating for action on nutrition, in addition to food industry actors," said Dr Al-Mandhari.

The WHO Regional Office will work closely with countries to translate the regional strategy into national action and explore ways of working in greater coordination with other key partners and United Nations agencies, such as the Food and Agriculture Organization of the United Nations, UNICEF and the World Food Programme, to ensure that nutrition occupies a prominent place in national development plans and that comprehensive, multisectoral support is provided to countries to improve nutrition across the Region. These efforts will also take into account the social, economic and environmental determinants of malnutrition and the impact on the most vulnerable populations affected by conflict and emergencies, those living in extreme poverty and marginalized and excluded groups to ensure that as nutrition improves, no one is left behind and everyone's right to adequate food and nutrition is recognized. MEH

worldwide monitor

Update from around the globe

An art installation on the campus of St. Jude Children's Research Hospital in Memphis recognizes the Pediatric Cancer Genome Project, which began in 2010.

Pediatric Cancer Genome Project marks 10 years

Ten years ago St. Jude Children's Research Hospital and Washington University School of Medicine unveiled an ambitious collaboration to identify the genetic changes that lead to some of the world's deadliest childhood cancers. The researchers proposed a three-year, $65-million project to sequence the complete normal and cancer genomes of more than 600 childhood cancer patients.

In the course of a decade the project changed cancer research, diagnosis and treatment.

"The Pediatric Cancer Genome Project has had a profound impact on the way we treat patients and on how we diagnose patients today at St. Jude. The project has also had an incredible effect on the way we think about those tumours and the avenues that we take to do research to improve our ability to treat those patients," said James R. Downing, M.D., president and chief executive officer of St. Jude. He is also the architect of the Pediatric Cancer Genome Project.

Based on the success of the first phase, St. Jude committed $30 million to extend the project in 2014. The second phase was built around two distinct efforts: a discovery project and a clinical genomics project. Through the efforts, researchers analysed cancer samples from 300 children, studying in detail a small number of different types of leukaemia, brain tumours and solid tumours. This chapter of the project also made next generation sequencing an option for every eligible St. Jude cancer patient. Findings from the Pediatric Cancer Genome Project are still being published. To date, more than 30 papers have appeared in scientific journals.

Some highlights:

- Scientists completed and analysed whole genome sequences of tumour and normal tissue from about 800 St. Jude cancer patients with 23 different types of cancer. As part of the project, scientists also sequenced the whole exome and whole transcriptome of an additional 1,200 patients.
- The team completed the sequencing goal early and under budget.
- The effort yielded ground-breaking discoveries in brain tumours, leukaemia, solid tumours and cancer of the peripheral nervous system. The findings included striking examples of genomic alterations that underscore marked differences between childhood and adult cancers.
- Clinical trials at St. Jude and the Children's Oncology Group as well as research worldwide have incorporated discoveries from the project into clinical trials. The findings have also fuelled National Cancer Institute initiatives to develop paediatric-cancer specific therapies and to provide guidance for precision medicine treatment of individual patients.
- The Pediatric Cancer Genome Project revealed that about 10% of children with cancer have germline, potentially inherited, mutations in known cancer-predisposition genes. The finding has consequences for treatment, follow-up, families and potential offspring. The findings highlight the importance of comprehensive clinical genomic sequencing as part of standard paediatric cancer care.
- St. Jude now offers comprehensive genomic testing to all eligible patients. The hospital also created the Cancer Predisposition Program to provide genetic counselling, testing and education to St. Jude patients, families and providers.
- Project data, data-visualization tools, novel analytic algorithms and biological resources have all been freely shared with the global research community. The centrepiece of that effort is St. Jude Cloud, an online data-sharing and collaboration platform.

"The legacy of this project includes how hundreds of individuals at these two institutions came together to change medicine and build a new foundation for moving forward," Downing said.

First-of-its-kind global collaboration launched to develop transformative treatment regimens for TB

A consortium of philanthropic, non-profit and private sector organisations has launched a collaboration that aims to accelerate the development of novel "pan-TB" drug regimens for the treatment of tuberculosis (TB) that are ready for phase 3 development. The regimens will be designed to have little to no drug resistance and an acceptable safety profile, and be better-tolerated, shorter in duration and simpler to use than existing options. Such regimens are intended to be a central component of efforts to address the current complexities and challenges of TB treatment.

The members of the Project to Accelerate New Treatments for Tuberculosis (PAN-TB collaboration) – Evotec, GSK, Johnson & Johnson, Otsuka Pharmaceutical, the Bill & Melinda Gates Medical Research Institute and the Bill & Melinda Gates Foundation – have committed to leveraging their unique

assets, resources and scientific expertise to advance the development of novel regimens.

"Current tools are insufficient for accelerating and sustaining global progress against TB," said Trevor Mundel, President of Global Health at the Bill & Melinda Gates Foundation. "Innovative partnerships, such as the PAN-TB collaboration, are urgently needed to develop new drugs and treatment regimens that can address TB and advance progress towards achieving global elimination TB goals."

TB causes more deaths globally than any other infectious disease, with 10 million new cases and 1.5 million deaths recorded in 2018 alone. TB is responsible for up to a third of all mortality associated with antimicrobial resistance (AMR).

Penny Heaton, M.D., CEO of the Bill & Melinda Gates Medical Research Institute, said: "The development of a regimen that can treat both drug-sensitive and drug-resistant tuberculosis could be a game changer for how the world addresses TB and growing antimicrobial resistance. The PAN-TB collaboration's unique partnership model leverages the assets and expertise of multiple partners to fill a crucial need in the tuberculosis treatment research and development pipeline."

The current regimen for drug-sensitive TB, the most common and easiest to treat form of TB, requires that patients take multiple drugs for six or more months under clinical monitoring. Patients with drug-resistant TB cannot use this regimen and face longer and more complex treatment regimens, often with significant side effects. Currently, patients must undergo additional testing to diagnose drug-resistant TB.

The PAN-TB collaboration will leverage members' collective assets, resources and scientific expertise to identify and evaluate new drug regimens with an acceptable safety profile, that have the potential to treat both drug-sensitive and drug-resistant TB, and are better-tolerated, shorter in duration and simpler to use than existing options. The collaboration will focus on advancing research through phase 2 clinical efficacy studies in order to identify promising regimens for further development.

The collaboration plans to work closely and transparently with the European Regimen Accelerator for Tuberculosis (ERA4TB), which was launched in January 2020. New molecular entities identified by ERA4TB that show promise in initial human studies could later be incorporated into the PAN-TB collaboration's later-stage, clinical research.

The regimens could help transform TB care. A shorter and safer novel regimen that can treat TB irrespective of pre-existing drug resistance and with reduced need for drug resistance testing, could provide a significant benefit to both patients and health systems.

Collaborative pre-clinical research activities have begun. Clinical trials will be announced as they are planned.

France pledges $100 million for WHO Academy

France's Minister for Europe and Foreign Affairs, Jean-Yves Le Drian, and Dr Tedros Adhanom Ghebreyesus, Director-General of WHO met 24 February at the Permanent Mission of France to the United Nations in Geneva to discuss the establishment of the WHO Academy, which will be the world's largest and most innovative lifelong learning platform in global health.

The WHO Academy aims to reach millions of people worldwide, offering high-tech learning environments at a "hub" in Lyon with "spokes" in the six WHO regions. The Academy will provide learning opportunities for leaders, educators, researchers, health workers, WHO staff and the broader public, and will deliver high quality, multilingual learning, both online and in-person, alongside a cutting-edge simulation centre for health emergencies.

The discussion follows a Declaration of Intent signed by Emmanuel Macron, President of the French Republic and Dr Tedros on 11 June 2019, and a pledge by France in the amount of US$100 million to WHO to support the creation of the WHO Academy, which will be established as an internal division within WHO.

"Technology and innovation in learning are creating exciting new opportunities to accelerate progress towards health for all in every country," said Dr Ghebreyesus. "The WHO Academy will support millions of learners to maximize health impacts with the best evidence, adult learning approaches and state-of-the-art technologies."

By propelling and strengthening digital innovations and lifelong learning opportunities around the world, the WHO Academy will play an instrumental role towards achieving WHO's triple billion goal by 2023 and the health Sustainable Development Goals: 1 billion more people will benefit from universal health coverage; 1 billion more will be better protected in health emergencies, and 1 billion more will enjoy improved health and wellbeing.

Global Heart journal goes open access

The official journal of the World Heart Federation, *Global Heart*, is now open access. As of January 2020, all issues of Global Heart can be accessed for free online <*https://globalheartjournal.com/issue/archive/*> without a subscription. Previously published issues of the journal will also become freely available under this new scheme.

Global Heart offers a platform for the dissemination of knowledge on research, developments, trends and solutions in the area of cardiovascular disease. It publishes research results, points of view and educational material on the prevention, treatment and control of cardiovascular disease, with a special focus on low resource settings.

The decision for this shift to open access publishing was made on the principle that making *Global Heart's* content freely available to the public will support a greater global exchange of knowledge, ideas and practices – one of the pillars of the World Heart Federation's mission.

"This is a big and important step for the World Heart Federation. By offering easy and unrestricted access to the articles published in *Global Heart*, we will be ensuring a faster and wider dissemination of its content, stimulating and inspiring further research in the areas which it covers," said Prof Diederick Grobbee, Editor-in-Chief, *Global Heart*. MEH

the laboratory

Medical research news from around the world

Syrian refugees

Guided self-help intervention reduces refugees' psychological distress and improves wellbeing in humanitarian crises

A recent, first-of-its-kind trial has found that multimedia guided self-help intervention can be delivered rapidly and effectively to large numbers of people in low-resource humanitarian settings by non-specialists with minimal training. It has potential application to reduce psychological stress and improve well-being among refugees in humanitarian crises and war zones.

Although longer follow-up is needed to determine the long-term effects of the intervention, the authors say that guided self-help could be a promising first-line strategy to address the vast gap in mental health support in areas where humanitarian access is difficult, such as South Sudan and Syria.

The randomised trial – a guided self-help approach that provides strategies for managing distress and coping with adversity – was shown to be is safe, and resulted in meaningful improvements in psychological distress and functioning compared to enhanced usual care over three months in 700 South Sudanese refugee women living in a settlement in Uganda. It is published in The Lancet Global Health journal.

Refugees are at greater risk of developing symptoms of common mental disorders and other forms of disabling psychological distress. Although several psychological treatments have been shown to be effective among conflict-affected populations, they tend to target single mental disorders, require a substantial clinical workforce, and reach only individuals or small groups of people at a time.

Self-Help Plus (SH+) was developed by the World Health Organization (WHO) to meet the challenges of delivering evidence-based mental health support to large numbers of people both with and without mental disorders in hard-to-reach conflict- or disaster-affected areas. SH+ is a group-based self-help intervention guided by non-specialist facilitators with minimal training. It combines a five-session pre-recorded audio course with an illustrated self-help book designed for low literacy populations and can be delivered to groups of up to 30 people.

"SH+ provides strategies for managing distress arising in the context of a range of adversities including interpersonal violence, armed conflict, and chronic poverty. The approach is based on acceptance and commitment therapy, a modern form of cognitive-behavioural therapy, that focuses on increasing psychological flexibility – primarily through mindfulness exercises – and promotes behaviours that are in line with a person's values," explains Dr Wietse Tol from Johns Hopkins Bloomberg School of Public Health and HealthRight International, USA, who co-led the research.

According to co-lead author Dr Mark van Ommeren from WHO, Switzerland: "By targeting psychological distress, regardless of whether people have mental disorders, while reducing reliance on scarce specialists and tripling the number of participants reached per session, guided self-help has enormous potential to improve reach and access to psychological support for people affected by adversity."

The study included 697 female refugees from South Sudan with at least moderate levels of psychological distress living in the Rhino Camp settlement in north-western Uganda. No psychiatric diagnosis was required to be included in the trial, but participants assessed to be at imminent risk of suicide or showing observable signs of severe mental disorder (e.g., psychosis) were excluded and offered alternative support.

Researchers randomly assigned 14 villages in the settlement to either SH+ in addition to enhanced usual care or enhanced usual care alone.

All participants completed questionnaires to assess their levels of psychological distress and to measure changes in symptoms of distress, depression and post-traumatic stress disorder (PTSD), self-reported concerns, inter-ethnic relations, feelings of anger, functional

impairment, and subjective wellbeing one week before the intervention, and one week and 3 months after the intervention had ended. On average (83%) of the women in the SH+ group participated in each session, which suggests that SH+ is acceptable to participants.

Compared to the control group, refugees in the SH+ group reported substantially greater reductions in psychological distress both immediately after the intervention and 3 months later.

At the 3-month follow-up, SH+ also led to improvements in PTSD and depression symptoms, explosive anger, functioning, and subjective well-being, and was equally beneficial among women with different trauma histories, levels of distress, and levels of exposure to gender-based violence.

Further analyses found that the vast majority of participants (84%; 582/694) rated their psychological distress as severe at the start of the study. Immediately after the intervention, women in the SH+ group were less likely to report severe levels of distress compared with the control group (110/331 [33%] vs 209/363 [48%]), and improvement in severe distress levels was maintained for 3 months (130/331 [39%] vs 174/336 [48%]).

Importantly, there were no reports of any adverse reactions related to SH+ after scrutiny by an independent data safety management board.

Despite these achievements, the study has some limitations, including that by randomising a limited number of villages, differences in unmeasured factors between the villages may have influenced the results; and the generalisability is limited to female refugees. Further adaptation and evaluation for male refugees is currently ongoing.

"Our findings indicate that SH+ offers sizeable immediate benefits, which is very promising for an intervention that has high potential for scale-up, and can be delivered in areas with limited access to care", says co-author Marx Leku from HealthRight International in Uganda.

- **doi:** 10.1016/S2214-109X(19)30504-2

Growth factor-modified stem cells help repair spinal cord injuries in rats

A recent study published in *Stem Cells Translational Medicine* is the first to illustrate the presence of oxygen-deprived clusters throughout the damaged site of a compressed spinal cord. It is also the first to show how transplanting basic growth factor with the use of a viral vector to target the oxygen-deprived sites enhances the injured spinal cord's recovery.

The study, conducted on a rat model that the study's researchers developed just for their investigation, could eventually have great implications for cellular treatment of spinal cord injury (SCI) in humans.

Every year, according to the World Health Organization, between 250,000 and 500,000 people suffer a spinal cord injury, most due to trauma from accidents. The initial blunt force damages or kills spinal nerve cells, setting in motion a cascade of secondary events that include loss of an adequate oxygen supply at the tissue level – a condition called hypoxia. The results could lead to complete paralysis, depending on the severity of the injury and where along the spinal cord it occurs.

There is currently no effective way to repair the damage. "A better understanding of the events of secondary injury would provide a target to optimize pharmacological and cellular therapies, the timing of surgery and early rehabilitation," said Jian Xiao, M.D., Ph.D. He served as senior author of this new study, conducted with his colleagues at Wenzhou Medical University in Zhejiang, China.

The team focused on the hypoxia aspect of an SCI. To begin, they established a compressive rodent model of SCI. "We then investigated the SCI using this rat model and found that areas of hypoxia were unevenly interspersed throughout the injured sites," Dr Xiao said.

Armed with this new knowledge, the team generated embryonic neural stem cells (NSCs) expressing basic fibroblast growth factor (bFGF), under the regulation of five hypoxia-responsive elements. They then used a lentiviral vector (LV-5HRE-bFGF-NSCs) to specifically target the oxygen-deprived locations. "A number of growth factors have been shown in previous studies to reduce the harmful effects of an SCI while improving neuronal survival and regeneration," Dr Xiao explained. "However, controlling the release of these factors has been a significant challenge. That's why we introduced the lentiviral vector. We suspected it might ensure the bFGF made it to the hypoxia-targeted sites."


Drew Hays

Results showed their suspicions were correct. At 60 days after SCI, the rats showed a reversal of the hypoxic microenvironment, paralleled by a decrease in cellular autophagy (a process that can lead to cell death) and reduced glial scar formation (glial scars can set up a barrier that interferes with delivering a therapy to the injured site). The team also saw an increase in axon regeneration and better locomotor function in the treated animals.

"This approach allows bFGF to target the right place at the right time and has the therapeutic potential to treat SCI via a timely improvement in the microenvironment," said Sipin Zhu, M.D., the paper's first author.

"These findings led us to propose that LV-5HRE-bFGF-NSCs might, therefore, be a good candidate to evaluate cellular SCI therapy in humans," Dr Xiao added.

"This study, focusing on spinal cord injury, shows that recovery is possible in a preclinical model," said Anthony Atala, M.D., Editor-in-Chief of *Stem Cells Translational Medicine* and director of the Wake Forest Institute for Regenerative Medicine. "The use of growth factor-modified stem cells is promising and warrants further investigation."

- **doi:** 10.1002/sctm.19-0282


Loren Joseph/Unsplash

World failing to provide for children's health

As climate and commercial threats intensify, a commission of global health experts presses for radical rethink on child health. *Middle East Health* reports.

No single country is adequately protecting children's health, their environment and their futures, finds a landmark report released February 19, 2020 by a Commission of over 40 child and adolescent health experts from around the world. The Commission – funded by the Bill & Melinda Gates Foundation – was convened by the World Health Organization (WHO), UNICEF and *The Lancet*.

The report, A Future for the World's Children?, finds that the health and future of every child and adolescent worldwide is under immediate threat from ecological degradation, climate change and exploitative marketing practices that push heavily processed fast food, sugary drinks, alcohol and tobacco at children.

"Despite improvements in child and adolescent health over the past 20 years, progress has stalled, and is set to reverse," said former Prime Minister of New Zealand and Co-Chair of the Commission, Helen Clark. "It has been estimated that around 250 million children under five years old in low- and middle-income countries are at risk of not reaching their developmental potential, based on proxy measures of stunting and poverty. But of even greater concern, every child worldwide now faces existential threats from climate change and commercial pressures.

"Countries need to overhaul their approach to child and adolescent health, to ensure that we not only look after our children today but protect the world they will inherit in the future," she added.

Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization said: "This report shows that the world's decision makers are, too often, failing today's children and youth: failing to protect their health, failing to protect their rights, and failing to protect their planet. This must be a wakeup call

for countries to invest in child health and development, ensure their voices are heard, protect their rights, and build a future that is fit for children."

Intensifying climate change

The report includes a new global index of 180 countries, comparing performance on child flourishing, including measures of child survival and well-being, such as health, education, and nutrition; sustainability, with a proxy for greenhouse gas emissions, and equity, or income gaps.

According to the report, while the poorest countries need to do more to support their children's ability to live healthy lives, excessive carbon emissions – disproportionately from wealthier countries – threaten the future of all children. If global warming exceeds 4°C by the year 2100 in line with current projections, this would lead to devastating health consequences for children, due to rising ocean levels, heatwaves, proliferation of diseases like malaria and dengue, and malnutrition.

The index shows that children in Norway, the Republic of Korea, and the Netherlands have the best chance at survival and well-being, while children in Central African Republic, Chad, Somalia, Niger and Mali face the worst odds. However, when authors took per capita CO2 emissions into account, the top countries trail behind: Norway ranked 156, the Republic of Korea 166, and the Netherlands 160. Each of the three emits 210% more CO2 per capita than their 2030 target. The United States of America (USA), Australia, and Saudi Arabia are among the ten worst emitters.

"More than 2 billion people live in countries where development is hampered by humanitarian crises, conflicts, and natural disasters, problems increasingly linked with climate change," said Minister Awa Coll-Seck from Senegal, Co-Chair of the Commission. "While some of the poorest countries have among the lowest CO2 emissions, many are exposed to the harshest impacts of a rapidly changing climate. Promoting better conditions today for children to survive and thrive nationally does not have to come at the cost of eroding children's futures globally."

The only countries on track to beat CO2 emission per capita targets by 2030, while also performing fairly (within the top 70) on child flourishing measures are: Albania, Armenia, Grenada, Jordan, Moldova, Sri Lanka, Tunisia, Uruguay and Viet Nam.

Harmful commercial marketing

The report also highlights the distinct threat posed to children from harmful marketing. Evidence suggests that children in some countries see as many as 30,000 advertisements on television alone in a single year, while youth exposure to vaping (e-cigarettes) advertisements increased by more than 250% in the USA over two years, reaching more than 24 million young people.

> Countries need to overhaul their approach to child and adolescent health, to ensure that we not only look after our children today but protect the world they will inherit in the future.

Professor Anthony Costello, one of the Commission's authors, said: "Industry self-regulation has failed. Studies in Australia, Canada, Mexico, New Zealand and the USA – among many others – have shown that self-regulation has not hampered commercial ability to advertise to children. For example, despite industry signing up to self-regulation in Australia, children and adolescent viewers were still exposed to 51 million alcohol ads during just one year of televised football, cricket and rugby. And the reality could be much worse still: we have few facts and figures about the huge expansion of social media advertising and algorithms aimed at our children."

Children's exposure to commercial marketing of junk food and sugary beverages is associated with purchase of unhealthy foods and overweight and obesity, linking predatory marketing to the alarming rise in childhood obesity. The number of obese children and adolescents increased from 11 million in 1975 to 124 million in 2016 – an 11-fold increase, with dire individual and societal costs.

A manifesto

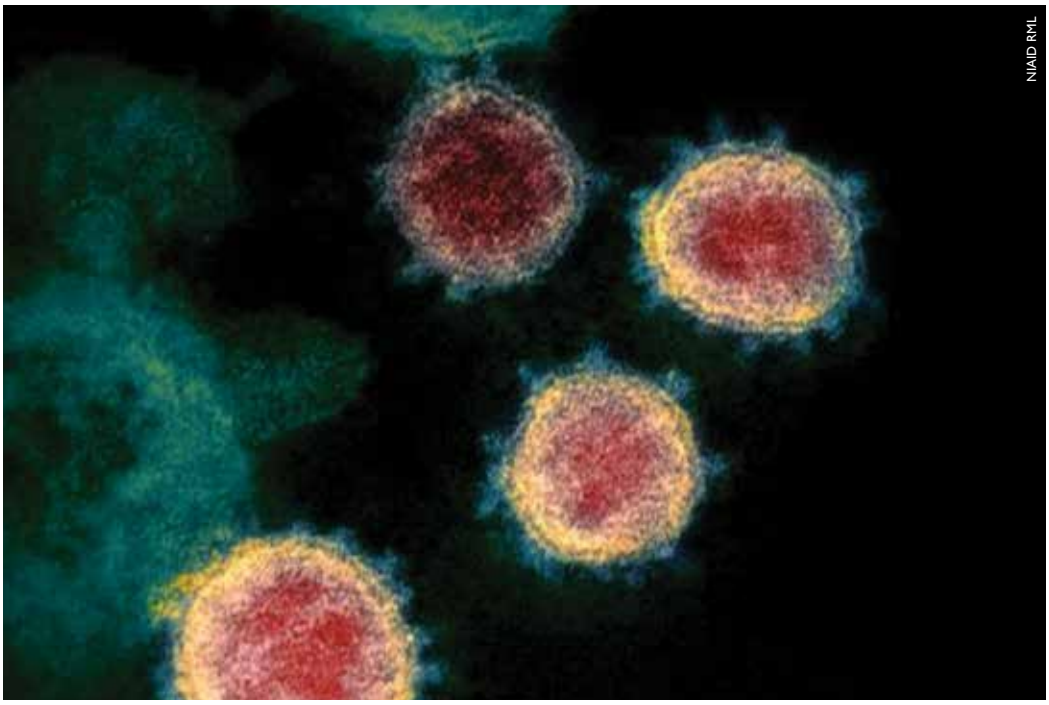
To protect children, the independent Commission authors call for a new global movement driven by and for children. Specific recommendations include:

1. Stop CO2 emissions with the utmost urgency, to ensure children have a future on this planet;
2. Place children and adolescents at the centre of our efforts to achieve sustainable development;
3. New policies and investment in all sectors to work towards child health and rights;
4. Incorporate children's voices into policy decisions;
5. Tighten national regulation of harmful commercial marketing, supported by a new Optional Protocol to the UN Convention on the Rights of the Child.

Dr Richard Horton, Editor-in-Chief of The Lancet family of journals, said: "The opportunity is great. The evidence is available. The tools are at hand. From heads-of-state to local government, from UN leaders to children themselves, this Commission calls for the birth of a new era for child and adolescent health. It will take courage and commitment to deliver. It is the supreme test of our generation."

Henrietta Fore, UNICEF Executive Director, said: "From the climate crisis to obesity and harmful commercial marketing, children around the world are having to contend with threats that were unimaginable just a few generations ago. It is time for a rethink on child health, one which places children at the top of every government's development agenda and puts their well-being above all considerations."

on the WEB A future for the world's children? A WHO-UNICEF-Lancet Commission
https://tinyurl.com/vfjjr7o



This transmission electron microscope image shows SARS-CoV-2 – formerly known as 2019-nCoV, the virus that causes COVID-19 – isolated from a patient. Virus particles are shown emerging from the surface of cells cultured in the lab. The crown-like spikes – or corona – on the outer edge of the virus particles give coronaviruses their name.

The rush to develop treatments and vaccines for COVID-19

COVID-19 disease caused by the SARS-CoV-2 virus (formerly known as 2019-nCoV) which emerged in Wuhan, China in December has captured the attention of the world since January as it continues to spread internationally with an ever-increasing death toll. SARS-CoV-2 is a coronavirus causing severe respiratory disease similar to that of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome).

Due to the rapid spread of COVID-19, we will not report on infected numbers, mortality and distribution of the disease as this will be quickly outdated by the time our readers read this. (The latest reliable continually updated info on the development of COVID-19 can be checked on the WHO website. See info box with this article.)

However, what we do report on here is the urgent development of treatments and vaccines currently underway at various research labs, which offer some promise that we may find a solution to curb the rapid spread and the rising number of deaths caused by the virus.

Remdesivir treatment

Researchers in the United States have begun – late February – a randomized, controlled clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnosed with coronavirus disease 2019 (COVID-19) at the University of Nebraska Medical Center (UNMC)

in Omaha, US. This is the first clinical trial in the United States to evaluate an experimental treatment for COVID-19.

Remdesivir was originally developed by Gilead Sciences as an Ebola vaccine, but it was not sufficiently effective. However, it has shown promise in monkeys for treating Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), which are caused by other coronaviruses. In January, a COVID-19 patient who received remdesivir on a compassionate use basis saw a substantial improvement in symptoms.

Since then, the Chinese Government has started human trials with remdesivir, the results of which are also expected soon.

Anthony S. Fauci, M.D., Director of the National Institute of Allergy and Infectious Diseases (NIAID), and a member of the U.S. Coronavirus Task Force, noted: "We urgently need a safe and effective treatment for COVID-19. Although remdesivir has been administered to some patients with COVID-19, we do not have solid data to indicate it can improve clinical outcomes. A randomized, placebo-controlled trial is the gold standard for determining if an experimental treatment can benefit patients."

The first trial participant is an American who was repatriated after being quarantined on the Diamond Princess cruise ship that docked in Yokohama, Japan and volunteered to participate in the study. The study can be adapted to evaluate additional investigative treatments and to enrol participants at other sites in the U.S. and worldwide.

Keep up to date on COVID-19

You can keep up to date with the latest developments in the spread of COVID-19 on this website:

- WHO COVID-19 Situation Reports *www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports*

There are no specific approved therapeutics for the disease. Infection can cause mild to severe respiratory illness, and symptoms can include fever, cough and shortness of breath.

- For more information, visit *ClinicalTrials.gov* and search identifier NCT04280705.

Vaccine development

Moderna's mRNA-1273

Biotech company Moderna announced February 24 that the company's experimental mRNA COVID-19 vaccine, known as mRNA-1273, is ready for human testing. Moderna is the first biotech company to take a vaccine to trial. They said an initial batch of the vaccine has been shipped to US government researchers from the National Institute of Allergy and Infectious Diseases (NIAID).

Moderna said they expect that the first clinical trials will begin late April, with around 25 healthy volunteers. Initial clinical results could be available in July or August.

Dr Fauci remarked that Moderna's development of an initial vaccine just weeks after identifying the COVID-19 genetic sequence, which was shared by researchers in China, is remarkably fast.

"Going into a phase one trial within three months of getting the sequence is unquestionably the world indoor record," he said. "Nothing has ever gone that fast."

A report on Nasdaq notes that Moderna's mRNA technology is quite promising, with mRNA vaccines hypothetically being faster and more effective than their DNA-based counterparts. This is because DNA-based vaccines need to interact with the nucleus of the cell, whereas mRNA (or messenger RNA) is found all across the cell and is much more accessible. However, given that mRNA vaccines have never been tested before on humans, it's still uncertain how well Moderna's new coronavirus vaccine will perform.

GeoVax

In late January GeoVax Labs, a US-based biotechnology company developing human immunotherapies and vaccines against infectious diseases and cancer, together with BravoVax, a vaccine developer in Wuhan, China, announced they will jointly develop a vaccine against the SARS-CoV-2 virus.

Under the collaboration, GeoVax will use its MVA-VLP vaccine platform and expertise to design and construct the vaccine candidate using genetic sequences from the ongoing coronavirus. BravoVax will provide further development, including testing and manufacturing support, as well as direct interactions with Chinese public health and regulatory authorities.

Takis and Evvivax

Two Italian biotech companies, Takis and Evvivax, announced late January their commitment to developing innovative vaccines against COVID-19.

Luigi Aurisicchio, CEO / CSO of the two companies, said: "We will immediately make available our skills gained for the development of vaccines against cancer and other infectious diseases to fight the spread of this coronavirus."

Takis and Evvivax have developed vaccines based on genetic technologies capable of inducing powerful immune responses. "Our technologies are based on genetic engineering techniques and on the use of viruses and DNA

fragments that can be used both for gene therapy and for vaccination," said Emanuele Marra, Director of the Infectious Diseases Area at Takis.

CEPI and GSK

CEPI, the Coalition for Epidemic Preparedness Innovations, and GSK on 3 February announced a new collaboration aimed at helping the global effort to develop a vaccine for the SARS-CoV-2 virus. GSK will make its established pandemic vaccine adjuvant platform technology available to enhance the development of an effective vaccine against COVID-19.

GSK is well known for the development of innovative vaccines using different adjuvant systems. An adjuvant is added to some vaccines to enhance the immune response, thereby creating a stronger and longer lasting immunity against infections than the vaccine alone. The use of an adjuvant is of particular importance in a pandemic situation since it can reduce the amount of antigen required per dose, allowing more vaccine doses to be produced and made available to more people.

CEPI will coordinate engagements between GSK and entities funded by CEPI who are interested in testing their vaccine platform with GSK's adjuvant technology to develop effective vaccines against 2019-nCoV.

Clover Biopharmaceuticals' COVID-19 S-Trimer

Clover Biopharmaceuticals, a China based global clinical-stage biotechnology company focused on developing novel and transformative biologic therapies, announced February 24 that it has entered into a research collaboration with GSK for its protein-based coronavirus vaccine candidate (COVID-19 S-Trimer). GSK will provide Clover with its pandemic adjuvant system for further evaluation of S-Trimer in preclinical studies. Having one of the largest in-house, commercial-scale cGMP biomanufacturing capabilities in China, Clover could potentially rapidly scale-up and produce large-quantities of a new coronavirus vaccine.

"The use of an adjuvant is of particular importance in a pandemic situation since it may reduce the amount of vaccine protein required per dose, allowing more vaccine doses to be produced and therefore contributing to protect more people," said Thomas Breuer, Chief Medical Officer of GSK Vaccines.

Joshua Liang, Chief Strategy Officer and Board Director at Clover, said: "Utilizing our proprietary Timer-Tag technology that has been shown to be recognized by antibodies produced by multiple previously-infected coronavirus patients, S-Trimer is being rapidly developed to support global efforts in combating this current and any future coronavirus outbreaks." MEH

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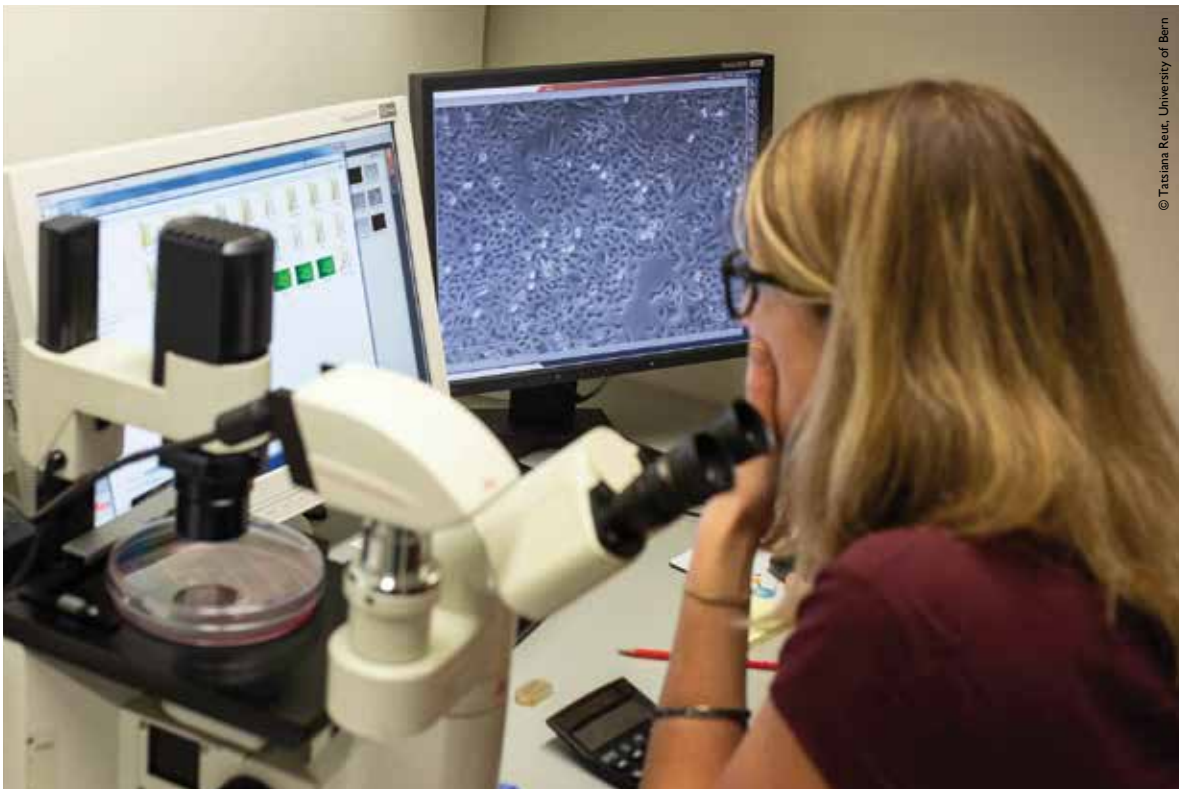


Working with cancer long noncoding RNA at Rory Johnson's GOLDLab.

Researchers develop algorithms to simplify identification of new cancer genes

It is estimated that the number of cancer cases worldwide will double by 2040. This makes the search for genes that cause cancer even more important. A team of researchers from the University of Bern and Inselspital, University Hospital Bern, has now developed algorithms that massively simplify the hunt for "cancer genes" in a poorly understood part of our genome. *Middle East Health* reports.

Cancer is caused by mutations in the genome of cells. Mutated cells grow in an uncontrolled way, adapt to new conditions and can escape the body's defence mechanisms. For this reason, researchers are increasingly focusing on the genetics of tumours. Looking at the genetic profile of these malignant cells helps us to understand how a cancer develops and what drives its spread. This also can provide clues for therapeutic targets. The hunt for mutated genes, which cause cancer – so called "driver genes", is made possible through the latest technologies for DNA sequencing.

The driver genes in tumours are identified based on their patterns of genetic mutations by means of sophisticated algorithms. Such a sensitive method must be carefully calibrated.

"Think of the weighing scale in your home, which must be adjusted from time to time to show the correct weight. In a similar way, methods to search for

Prof Dr Rory Johnson, NCCR RNA&Disease, University of Bern and Inselspital, University Hospital Bern.

driver-genes must be calibrated using 'benchmarks', that is, sets of already-known cancer genes," says Prof Dr Rory Johnson. He conducts his research at the Department for BioMedical Research of the University of Bern (DBMR) and the Inselspital, University Hospital Bern and is a member of the National Center of Competence in Research RNA & Disease. His group has assembled a dataset of genes, which significantly facilitates researchers' search for novel cancer driver genes. Their study is published in the Nature Journal *Communications Biology*.

Dark matter

The term "dark matter" of our genome refers to the over 95% of it, which does not contain instructions for building proteins. Numerous studies indicate that a part of this "dark matter", called long non-coding RNAs or "lncRNAs", play important roles in tumorigenesis and cancer progression.

If we consider DNA (deoxyribonucleic acid) to be the fixed blueprint for an organism, then RNA (ribonucleic acid) represents a "real-time" readout of that blueprint that dynamically changes in response to the needs of the cell and organism. The biological roles and molecular mechanisms of just a tiny fraction of these lncRNAs have been studied to date. ▶

New technique shows how cancer cells communicate with each other

Scientists have a developed a new technique to decipher how millions of individual cells are communicating with each other in miniature tumours grown in the lab, known as organoids, according to new research published in *Nature Methods* 14 February 2020.

This is the first time that scientists have been able to analyse many different signalling molecules at once in individual cells within replicas of patients' tumours. Understanding how cells communicate could reveal how tumours are able to evade the immune system and become resistant to treatments.

This could allow scientists to develop more effective new drugs, by revealing why tumours respond the way they do to treatments. It could also help doctors to select the best course of treatment for each individual patient, by testing treatments on a bespoke replica of a patient's tumour before prescribing them.

The technique rapidly analyses each individual cell in an organoid, looking for the presence of specific signalling molecules – messages that cells send to neighbouring cells, telling them how to behave.

Dr Chris Tape, lead researcher of the study at UCL, said: "Organoids are already revolutionising cancer research by allowing us to test whether experimental new drugs are effective on lifelike models of tumours. But crucially, this new technique helps scientists to understand why a treatment works or not, by revealing in unprecedented detail how cells are talking to each other."

In order to listen in on cancer cells, the team grew organoids in the lab. These are self-organising 3D structures made up of cancer cells alongside other types of cells, such as immune cells and connective tissue. They mimic the behaviour of cancer in the human body much more accurately than cells grown in a dish.

They then modified a complex technique called mass cytometry, which is used to detect and analyse protein molecules. The organoids were broken up into individual cells, then antibodies combined with heavy metal atoms were added. Antibodies are proteins that selectively bind to certain cancer signalling molecules. The scientists nebulised the cells, to convert them into a fine mist, and electrically charged the heavy meal atoms, so that a magnetic field could be used to separate out the different signalling molecules.

The researchers tested this technique in bowel cancer cells and were able to simultaneously detect 28 key signalling molecules, across 6 different cell types, in over 1 million cells. They found indications that the cancer cells themselves, as well as immune cells and connective tissue, had 'rewired' the normal signalling networks of bowel tissue, allowing tumours to grow unchecked.

The next steps will be to use this technique to look for ways to block the communications between cells that allow them to withstand treatment. The team also hopes to test this new technique in different types of cancer.

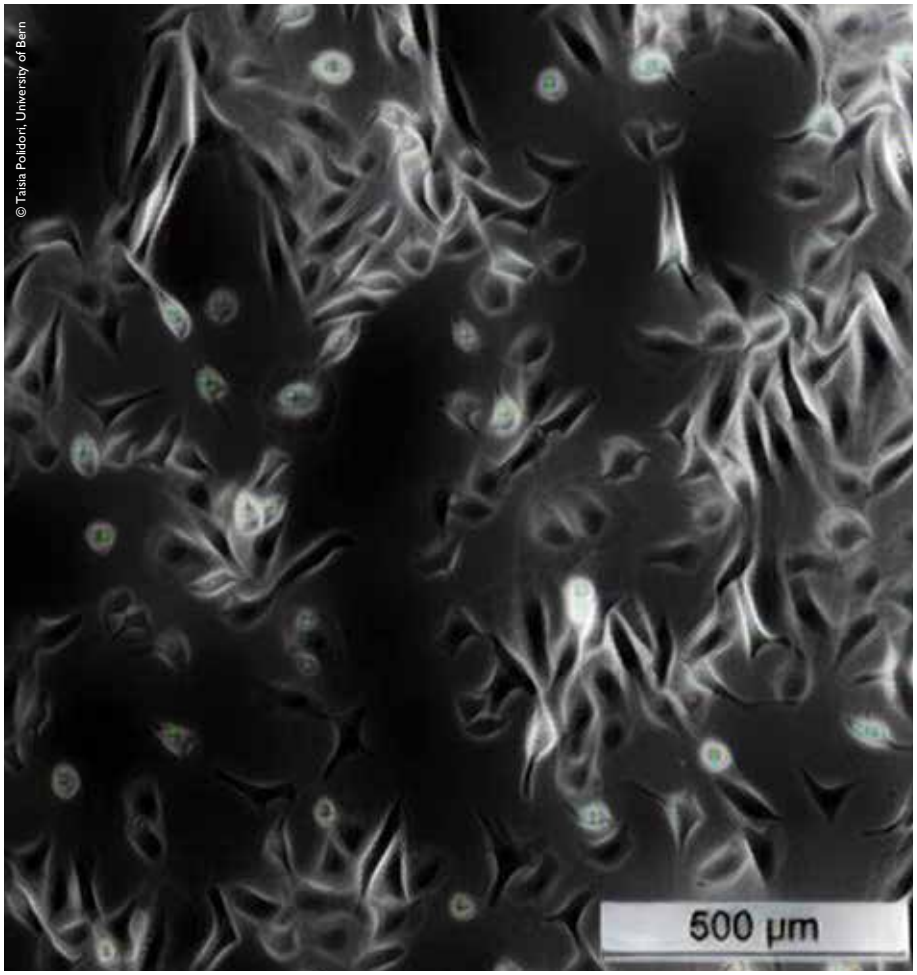
Dr Emily Armstrong, research information manager at Cancer Research UK, said: "Having a better understanding of this complex communication between cancer cells and other types of cell that make up a tumour could reveal secrets of how cancer comes back after treatment and spreads around the body.

"While this technique is in the early stages of development right now, in the future we may be able to grow replicas of individual patients' tumours, to identify early signs that a drug won't work for them so we can personalise their treatment plan. We hope this could one day help more people to survive cancer."

• doi: 10.1038/s41592-020-0737-8

”Cancer lncRNAs that provoke tumours represent an exciting new focus for the development of cancer therapies,” says Andrés Lanzos, first author of the study from the DBMR and Inselspital, University Hospital Bern, and NCCR RNA&Disease.

Cancer researchers have traditionally focused their efforts on the approximately 19,000 “classical” protein coding genes in the human genome. For these genes, a benchmark has long existed, consisting of genes known to play roles in tumorigenesis and cancer development. The team led by Prof Johnson is focused on searching for cancer lncRNAs using maps of tumour mutations from the International Cancer Genome Consortium. For this, the researchers have developed statistical methods to identify cancer lncRNAs. They wanted to calibrate the accuracy of these new methods with the help of a benchmark as is the case for classical protein-coding genes. For this purpose, the team assembled a list of 122 long-non coding RNAs that have been implicated in cancer with high confidence.



Microscopy image of a cell line used to identify long noncoding RNAs related to lung cancer.

High quality predictions

“This dataset of 122 cancer-lncRNAs has already proved an invaluable resource in many ways,” says Prof Johnson.

The team has used it to calibrate their algorithms for cancer lncRNA discovery, and it has already demonstrated that such algorithms make high quality predictions, including dozens of completely new cancer lncRNAs. Their “ExInAtor” algorithm has already been successfully used for the efforts of the International Cancer Genome Consortium, which has recently published their results in a series of papers in the journal Nature and elsewhere. This large-scale project also involved Mark Rubin, Director of the Department for BioMedical Research (DBMR) of the University of Bern and the Inselpital, University Hospital Bern.

“We are convinced that this gene dataset proves a unique resource to better understand the properties of this poorly-understood class of lncRNA genes,” explains Prof Johnson. “On the one hand this should help researchers to refine their methods for searching for cancer lncRNAs, so that we can extend the list of cancer lncRNAs, and on the other hand we hope that this enables the development of a new generation of personalized therapies for cancer patients,” he adds.

• doi: 10.1038/s42003-019-0741-7

RNA & Disease – The Role of RNA Biology in Disease Mechanisms

The NCCR «RNA & Disease – The Role of RNA Biology in Disease Mechanisms» studies a class of molecules that has long been neglected: RNA (ribonucleic acid) is pivotal for many vital processes and much more complex than initially assumed. For instance, RNA defines the conditions, in a given cell, under which a given gene is or is not activated. If any part of this process of genetic regulation breaks down or does not run smoothly, this can cause heart disease, cancer, brain disease and metabolic disorders. The NCCR brings together Swiss research groups studying different aspects of RNA biology. By researching which regulatory mechanisms are dysregulated in disease, the NCCR discovers new therapeutic targets. Leading institution is the University of Bern, with the ETH Zurich co-leading. National Centers of Compentence in Research are a research instrument of the Swiss National Science Foundation (SNSF).

- More information: *https://nccr-rna-and-disease.ch*

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Experts convene to share latest immunotherapy advances for treating hematologic malignancies

More than 150 physicians and other healthcare providers from throughout Florida, the United States and Latin America, gathered in Coconut Grove in January to attend the Inaugural Miami Cancer Institute Summit of the Americas on Immunotherapies for Hematologic Malignancies. The Summit featured experts from the Institute as well as Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, MD Anderson Cancer Center, University of Chicago, University of Pennsylvania and Florida International University, who discussed the most recent advances in the treatment of leukemia, lymphoma, multiple myeloma and stem cell transplantation by novel immunotherapies and treatment combinations.

"The caliber of our faculty was outstanding and the conference's overarching approach, incorporating all of the malignancies, rather than focusing on one disease, made it unique," said Guenther Koehne, M.D., Ph.D., course director and deputy director and chief of Stem Cell Transplantation, Hematologic Oncology and Benign Hematology at the Institute. "To be successful in attacking cancer, we cannot stay within our silos. We must take a more comprehensive view."

Dr. Koehne presented his groundbreaking work on allogeneic stem cell transplantation involving the technique he developed to manipulate donor cells in Miami Cancer Institute's Stem Cell Processing & Immunotherapy Laboratory.

In addition, Dr. Koehne is the principal investigator of a recently FDA-approved clinical trial – A Phase II Trial of CD34+ Enriched Transplants from HLA-Compatible Related or Unrelated Donors for Treatment of Patients with Hematologic Malignancies – using manipulated donor cells to treat those with acute myeloid and lymphoblastic leukemia and chronic myeloid leukemia. The study continues his work that has had promising results in diminishing the often-deadly graft-versus host disease complication of transplantation. Since allogeneic transplants began in the 1970s, survival rates have increased significantly and new techniques, like Dr. Koehne's, have made it possible for many more patients, especially elderly patients who previously would not have been considered for transplantation, to receive the treatment.

Dr. Guenther Koehne speaks at the Inaugural Miami Cancer Institute Summit of the Americas on Immunotherapies for Hematologic Malignancies.

A speaker presents at the Inaugural Miami Cancer Institute Summit of the Americas on Immunotherapies for Hematologic Malignancies

- Visit *https://cme.baptisthealth.net* for more information about accreditation or registration for next year. MEH

Miami Cancer Institute

Miami Cancer Institute brings to South Florida access to personalized clinical treatments and comprehensive support services delivered with unparalleled compassion. No other cancer program in the region has the combination of cancer-fighting expertise and advanced technology – including the first proton therapy center in South Florida, Latin America and the Caribbean, and one of the only radiation oncology program in the world with each of the newest radiation therapies in one place – to diagnose and deliver precise cancer treatments that achieve the best outcomes and improve the lives of cancer patients. The Institute offers an impressive roster of established community oncologists and renowned experts, clinical researchers and genomic scientists recruited from the nation's top cancer centers. Selected as Florida's only member of the Memorial Sloan Kettering Cancer (MSK) Alliance, Miami Cancer Institute is part of a meaningful clinical collaboration that affords patients in South Florida access to innovative treatments and ensures that the standards of care developed by their multidisciplinary disease management teams match those at MSK.

CHANGING THE FUTURE OF *CANCER CARE*

Miami Cancer Institute

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Dr. Alastair Thompson and Dr. Stacey Carter, breast surgeons at Baylor St Luke's Medical Center, at work in the OR.

Baylor St. Luke's Medical Center is the first hospital in the Southern U.S. to use non-radioactive guidance system to locate and remove tumors in patients with invasive breast cancer

Dr. Alastair Thompson and Dr. Stacey Carter, breast surgeons at Baylor St Luke's Medical Center, are the first breast surgeons in the southern United States to use the Sentimag Magnetic Localization System with both the Magseed technology and the newly FDA-approved Magtrace liquid tracer during a surgical treatment for invasive breast cancer.

The Magseed is a small metal seed the size of the tip of a pen that is used to mark and remove small tumors that are difficult for the surgeon to feel. The seed is placed directly into the center of the tumor any time before surgery under mammogram or ultrasound guidance. This enables the surgeon to accurately locate the center of the tumor and ensure it is removed in one piece while preserving as much healthy tissue. The Magseed replaces the need for a wire localization technique, which can be painful and uncomfortable for the patient.

"The Magseed technology is an incredible guidance system that takes me to a relatively small area of the breast that needs to come out while avoiding excessive tissue being removed and avoiding a mastectomy," said Thompson, who also is section chief and professor of breast surgery at Baylor College of Medicine. "Not having to have a wire placed in the breast beforehand while the patient is awake makes the experience more comfortable while giving even better technical help to me as a surgeon."

"This procedure is really transformational for the patient because it allows us to do a small day case, fine-tuned delicate surgery rather that doing a big operation," he said. "Additionally, the tumor with the seed in it and the surrounding tissue get looked at immediately by our pathologists to give an assessment while the patient is still asleep. It helps us get away from the 1 in every 3 patients across the United States that has to undergo a second operation for a re-excision."

Patients undergoing a lumpectomy often need to have their lymph nodes removed to determine whether the cancer has spread beyond the initial tumor into the lymph nodes. The Magtrace iron-oxide solution can be injected prior to a sentinel lymph node biopsy while the patient is asleep to help surgeons identify the sentinel nodes with the highest reading.

Using the system's handheld wand and base unit display, surgeons are able to find the sentinel lymph nodes for surgical removal based on the strength of the magnetic signal. The magnetic Magtrace replaces the need for the old method that typically involves the injection of a radioactive substance and a blue dye agent, which can stain the skin near the injection site and cause allergic reactions.

- For more information contact International Service at Baylor St Luke's Medical Center
Via email at *international@stlukeshealth.org*
or call +1 832 355 3350
or visit *StLukesInternational.org*
Texas Medical Center, Houston, Texas – USA MEH

Nationally Ranked

Cancer Care

BEST HOSPITALS
U.S.News & WORLD REPORT
NATIONAL CANCER
2019-20

When it comes to overcoming cancer, it's more than offering new hope through discovery. It's about providing the highest possible level of care as the clinical home for the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine, one of only three NCI-designated Comprehensive Cancer Centers in Texas. It's about giving patients access to the largest clinical genetics program in the United States. It's about giving our patients, their families, and the community more.

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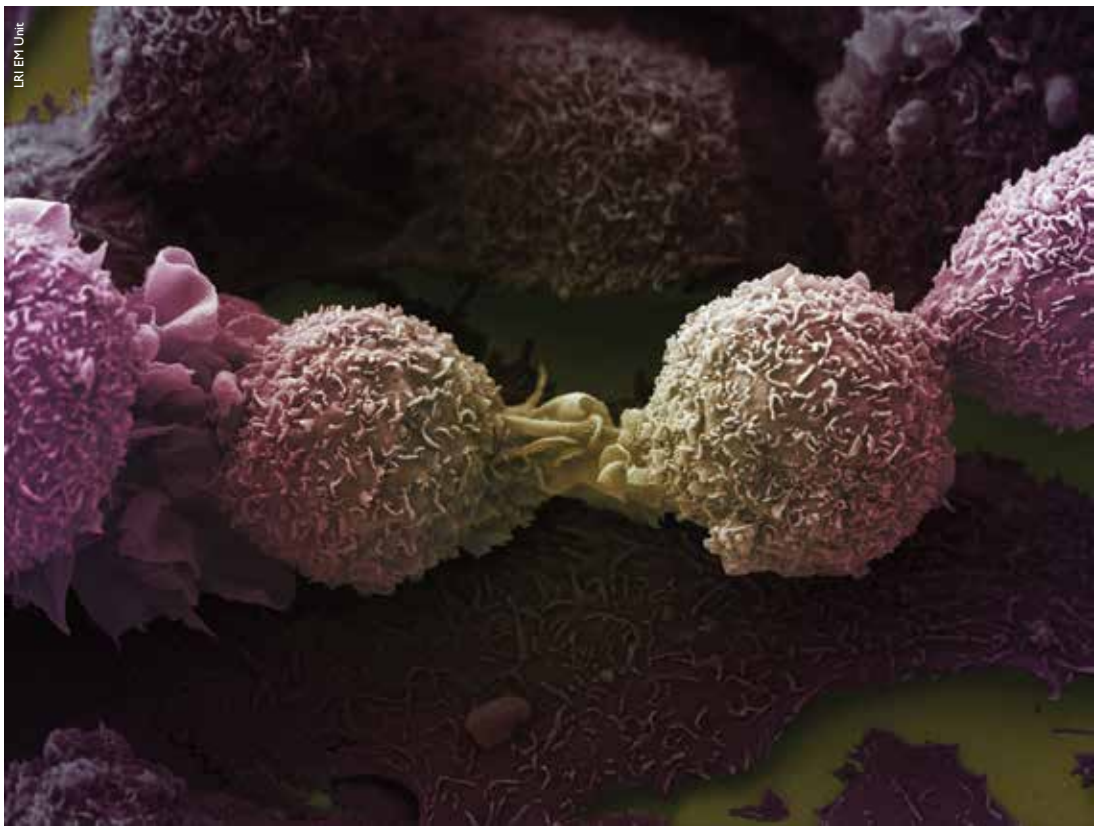
Texas Medical Center, Houston, Texas – U.S.A.

Baylor St. Luke's Medical Center

DAN L DUNCAN COMPREHENSIVE CANCER CENTER

Baylor Medicine



Electron microscopy photograph of lung cancer cells.

Protective cells could cut risk of lung cancer for ex-smokers

Protective cells in the lungs of ex-smokers could explain why quitting smoking reduces the risk of developing lung cancer. *Middle East Health* reports on new research findings published recently in *Nature*.

Cancer Research UK-funded scientists from the Wellcome Sanger Institute and University College London (UCL) have discovered that compared to current smokers, people who had stopped smoking had more genetically healthy lung cells, which have a much lower risk of developing into cancer.

The research, published in *Nature* 28 January 2020, is part of the US$26 million Mutographs of Cancer project, a Cancer Research UK Grand Challenge initiative. The project detects DNA 'signatures' that indicate the source of damage, to better understand the causes of cancer, and discover the ones we may not yet be aware of.

The study shows that quitting smoking could do much more than just stopping further damage to the lungs. Researchers believe it could also allow new, healthy cells to actively replenish the lining of our airways. This shift in proportion of healthy to damaged cells could help protect against cancer.

What is so exciting about our study is that it shows that it's never too late to quit – some of the people in our study had smoked more than 15,000 packs of cigarettes over their life, but within a few years of quitting many of the cells lining their airways showed no evidence of damage from tobacco.

These results highlight the benefits of stopping smoking completely, at any age.

Lung cancer is the most common cause of cancer death in the UK, accounting for 21% of all cancer deaths. Smoking tobacco damages DNA and hugely increases the risk of lung cancer, with around 72% of the 47,000 annual lung cancer cases in the UK caused by smoking. In the US, it is estimated that around 229,000 cases of lung cancer will be diagnosed in 2020.

Driver mutations

Damage to the DNA in cells lining the lungs creates genetic errors, and some of these are 'driver mutations', which are changes that give the cell a growth advantage. Eventually, an accumulation of these driver mutations can let the cells divide uncontrollably and become cancerous. However, when someone stops smoking, they avoid most of the subsequent risk of lung cancer.

In the first major study of the genetic effects of smoking on 'normal', non-cancerous lung cells, researchers analysed lung biopsies from 16 people including smokers, ex-smokers, people who had never smoked and children.

They sequenced the DNA of 632 individual cells from these biopsies and looked at the pattern of genetic changes in these non-cancerous lung cells.

The researchers found that despite not being cancerous, more than 9 out of every 10 lung cells in current smokers had up to 10,000 extra genetic mutations compared with non-smokers, and these mutations were caused directly by the chemicals in tobacco smoke. More than a quarter of these damaged cells had at least one cancer-driver mutation, which explains why the risk of lung cancer is so much higher in people who smoke.

Unexpected finding

Unexpectedly, in people who had stopped smoking, there was a sizable group of cells lining the airways that had escaped the genetic damage from their past smoking. Genetically, these cells were on par with those from people who had never smoked: they had much less genetic damage from smoking and would have a low risk of developing into cancer.

The researchers found that ex-smokers had four times more of these healthy cells than people who still smoked – representing up to 40% of the total lung cells in ex-smokers.

Joint senior author Dr Peter Campbell, from the Wellcome Sanger Institute, said: "People who have smoked heavily for 30, 40 or more years often say to me that it's too late to stop smoking – the damage is already done. What is so exciting about our study is that it shows that it's never too late to quit – some of the people in our study had smoked more than 15,000 packs of cigarettes over their life, but within a few years of quitting many of the cells lining their airways showed no evidence of damage from tobacco."

Dr Kate Gowers, joint first author from UCL, said: "Our study is the first time that scientists have looked in detail at the genetic effects of smoking on individual healthy lung cells. We found that even these healthy lung cells from smokers contained thousands of genetic mutations. These can be thought of as mini time-bombs waiting for the next hit that causes them to progress to cancer. Further research with larger numbers of people is needed to understand how cancer develops from these damaged lung cells."

While the study showed that these healthy lung cells could start to repair the lining of the airways in ex-smokers and help protect them against lung cancer, smoking also causes damage deeper in the lung that can lead to emphysema – chronic lung disease. This damage is not reversible, even after stopping smoking.

Professor Sam Janes, joint senior author from UCL and University College London Hospitals Trust, said: "Our study has an important public health message and shows that it really is worth quitting smoking to reduce the risk of lung cancer. Stopping smoking at any age does not just slow the accumulation of further damage, but could reawaken cells unharmed by past lifestyle choices. Further research into this process could help to understand how these cells protect against cancer, and could potentially lead to new avenues of research into anti-cancer therapeutics."

Dr Rachel Orritt, Health Information Manager at Cancer Research UK, said: "It's a really motivating idea that people who stop smoking might reap the benefits twice over - by preventing more tobacco-related damage to lung cells, and by giving their lungs the chance to balance out some of the existing damage with healthier cells. What's needed now are larger studies that look at cell changes in the same people over time to confirm these findings.

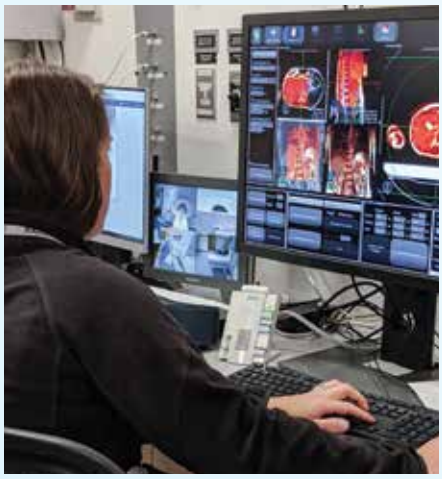
"The results add to existing evidence that, if you smoke, stopping completely is the best thing you can do for your health."

• **doi:** 10.1038/s41586-020-1961-1

Advancing Cancer Care: Greater Treatment Precision and Immunotherapy Research

Brigham and Women's Hospital and Dana-Farber Cancer Institute work in partnership to advance the research, treatment and care for all types of cancers. These world-renowned institutions work together to care for patients at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) located in Boston, Massachusetts. The following highlights two of the many ways the specialists at this center work together every day to accelerate breakthroughs and develop innovative therapies for cancer patients.

Cutting-edge Cancer Treatment



An image of the advanced MRI-RT technology.

Brigham and Women's Hospital is one of the first in the United States to offer a new state-of-the-art radiation therapy for cancer patients, known as MRI-guided radiation therapy (MRI-RT). This new therapy is part of a relentless pursuit to advance cancer care and provide the most innovative treatments for patients.

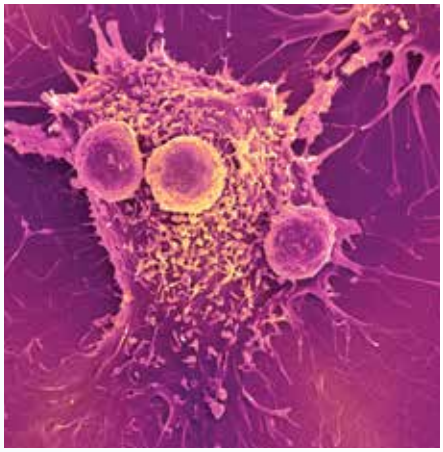
MRI-RT is a high-precision radiation treatment that targets tumors with high doses of radiation while minimizing damage to surrounding healthy tissues. This offers the greatest benefit for soft-tissue tumors, including breast, gastrointestinal, gynecological, sarcoma, prostate and head and neck tumors – and for tumors that are highly mobile (e.g., lung cancers). This revolutionary technology helps clinicians fine-tune the radiation treatment plan and personalize each treatment in ways they have never been able to do before.

"Innovations in radiation oncology are constantly occurring. Every so often there's a really transformative change in terms of what we offer patients. The MRI-guided radiation therapy technology is one of these moments of transformative change," says Daphne Haas-Kogan, MD, chair of the Department of Radiation Oncology at Brigham and Women's Hospital and Dana-Farber Cancer Institute.

Leading the Way in Immunotherapy

Immunotherapy refers to treatments that use the body's immune system to combat diseases, using it as a weapon against cancer. While the immune system can often handle very small tumors on its own, it can sometimes fail – either because a tumor grows too large, the cancer cells are too well camouflaged, or the tumor cells are able to stave off an immune system attack. The key discovery, made by Dana-Farber's Gordon Freeman, PhD, and others, was that the immune system's attack on cancer often falls short because many cancer cells display proteins, called immune checkpoint proteins, that bring the attack to a halt.

In recent years, immunotherapy has become one of the fastest growing of cancer research, fundamentally changing the way the disease is treated in many patients and setting the stage for a more extensive role in future cancer treatments. Some of the biggest inroads have occurred against leukemia and lymphoma, with treatments such as checkpoint inhibitors and CAR T-cell therapies producing long-lasting remissions in some patients.



An image of T lymphocyte cells (smaller round cells) attached to a cancer cell.

At Dana-Farber, investigators are leading clinical trials of new types of immunotherapy, ways of boosting the effectiveness of current therapies, and of novel combinations of immunotherapy drugs and other agents.

In a recent phase I clinical trial, led by Dana-Farber's John Koreth, MBBS, DPhil, investigators are testing a two-pronged approach to increasing the effectiveness of a donor stem cell transplant for patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) who have relapsed after a previous transplant.

The approach seeks to both increase the number of immune system T cells and take the shackles off the T cells' attack on tumor cells. After collecting donor T cells, technicians siphon out a subgroup known as "regulatory" T cells, which tamp down the immune system's assault on cancer, before infusing the remaining "effector" cells. To address relapse after transplant, patients will also be treated with ipilimumab, an "immune checkpoint inhibitor" that hampers cancer cells' ability to evade a T cell attack. In an earlier trial, this approach produced long-lasting remissions in some patients with AML and MDS.

A Global Leader in Cancer Care

With 12 specialized disease treatment centers, experts from DF/BWCC work together as one team to offer the most advanced treatments. Our center has a singular focus of conquering cancer and improving the way that cancer care is delivered to patients from across the world.

- For more information visit: *brighamandwomens.org/middleeasthealth* or call +1 (617) 397-5799

A Global Leader in Cancer Care

Brigham and Women's Hospital and Dana-Farber Cancer Institute, two teaching hospitals of Harvard Medical School in Boston, partner to provide multidisciplinary cancer care at Dana-Farber/Brigham and Women's Cancer Center.

We work together with you to tailor a treatment plan according to your cancer type, stage and unique situation. Our patients have access to the latest treatment options available, many of which were pioneered here.

As a destination for hundreds of patients from the Middle East, our International Patient Center offers seamless cancer care from scheduling consultations and interpreter services to coordinating your medical care and a wide range of concierge services.

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Great Ormond Street Hospital offers personalised therapy for children with cancer

Great Ormond Street Hospital for Children (GOSH) in London became one of the first hospitals in the UK to offer a new pioneering cancer therapy to paediatric patients in 2019. International patients with B-cell acute lymphoblastic leukaemia (ALL) can now receive a new personalised treatment, known as CAR-T therapy.

CAR-T therapies are specifically tailored for individual patients and work by harnessing the patient's own immune system to fight cancer. In a complex manufacturing process, immune cells are taken from a patient's blood and reprogrammed to specifically to target and kill cancer cells.

Tamim, from Saudi Arabia, was one of the first international patients at GOSH to be treated with a CAR-T therapy called Kymriah for his relapsed ALL. "I chose GOSH because Tamim's condition needed urgent treatment," explains Tamim's mum. "This treatment is only available in a limited number of countries and hospitals … the plan was to go to the United States, but we decided to come to GOSH because it would be quicker."

Dr Sara Ghorashian, Consultant Paediatric Haematologist at GOSH, explains: "Rather than being a pharmaceutical drug, this is a cellular product created by taking a patient's immune cells and then genetically-engineering them to recognise the patient's leukaemia."

When asked if she would recommend this form of treatment, Tamim's mother responded: "Of course, it was excellent. There are other forms of gene therapy available that we have tried before, and I noticed they all had some effect on Tamim. With this one, he didn't feel as affected and tired as with the other forms of gene therapy."

Dr Ghorashian says: "The CAR-T cell service at GOSH is a joint service between haematology and the bone marrow transplantation services and contributed to by consultants from each of these teams.

"We have a team of clinical nurse specialists who help coordinate a patient's care, and ward nurses. We also link in with the neurology, endocrine and intensive care departments who regularly review our patients when needed and provide specialist support. Finally, we have a team of therapists, including physiotherapists and play therapists, who support patients and their parents throughout the treatment.

"Tamim has a very resistant disease and he faced a number of complications," explains Dr Ghorashian. "He is a remarkable little boy and recently returned home."

Tamim will return to GOSH for check-ups and the family are hopeful that the treatment is successful.

ALL is a severe form of leukaemia that affects around 600 people per year, most of whom are children between the age of 2 and 5. Although the outlook for children with ALL has dramatically improved over the last decade, 10-15% of patients still do not respond to standard treatments. The new therapy has been shown to be effective in treating patients with particularly aggressive or relapsed cancers where other treatments have failed. MEH

Dr Sara Ghorashian, Consultant Paediatric Haematologist at GOSH.

Tamim, from Saudi Arabia, was one of the first international patients at GOSH to be treated with a CAR-T therapy called Kymriah.

Want to know more about Great Ormond Street Hospital (GOSH) in London?

We've been helping children overcome rare and complex conditions ever since we opened our doors in 1852. Stronger than ever, our team is made up of 300 exceptional and dedicated consultants across 60 specialties. We're a driving force in medical technology and research so we can provide much needed treatment for children across the world.

Our International and Private Patients Service supports over 5,000 children from 80 different countries every year. We have a compassionate and multi-lingual team to help all our international patients and their families feel at home.

- You can contact us on *GulfOffice@gosh.nhs.uk*
- call us +971 4 3624722
- or visit *www.gosh.ae*

Great Ormond Street Hospital for Children
International and Private Patients Service

Great Ormond Street Hospital for Children

We've been helping children overcome **rare and complex conditions** ever since we opened our doors in 1852 in London. Our expert team cares for children across 60 different specialties and sub-specialties, the largest of any UK hospital.

Our oncology and haematology departments operate as a unified cancer centre with University College Hospital London, forming the **largest paediatric and adolescent oncology centre in Europe**. We are uniquely set up to treat the **rarest and most complex forms of paediatric cancer**, with overall survival rates being comparable to the best results internationally.

We provide specialised services all under one roof for our international patients. Our International and Private Patients Service supports over 5,000 children from 80 different countries every year. We have a **compassionate and multi-lingual team** to help all our international patients and their families feel at home.

GOSH is dedicated to helping children from around the world fulfil their potential through international collaboration, education, innovation and research.

For more information or to refer a patient to Great Ormond Street Hospital for Children, please contact our Gulf Office.

Great Ormond Street Hospital for Children
International and Private Patients Service
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Landmark global genomics project unveils cancer's complexity on unprecedented scale

A global genomics project has pieced together the complex jigsaw puzzle of entire tumour genomes on an unprecedented scale – providing the most complete picture yet of how DNA mutations drive tumour cell growth. More than 1300 scientists and clinicians around the world analysed 2658 whole genomes for 38 types of cancer. The results of their analyses were released 5 February 2020 in six papers published in *Nature* and 17 in other journals.

The Pan-Cancer Analysis of Whole Genomes (PCAWG), known as the Pan-Cancer Project, is an international collaboration to identify common patterns of mutation in more than 2,600 whole cancer genomes from the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA). It builds upon the previous work of those initiatives, which predominantly concentrated on the regions of the genome that code for proteins. The research is expected to pave the way for full genome sequencing of all types of tumours which will enable a greater understanding of the causes, prevention, diagnosis and treatment of cancers.

The Pan-Cancer Project has explored the nature and consequences of DNA variations in cancer, across the entire genome, from both protein-coding genes and from areas of DNA that do not code for proteins. The Pan-Cancer Project is the most comprehensive analysis of the non-coding regions of cancer genomes performed to date.

DNA changes can be inherited (germline) or appear during a person's life (somatic), and the Pan-Cancer Project is investigating both types of these variations in DNA of cancer cells, looking at areas involved in regulating genes, sites for non-coding RNA and large-scale structural rearrangements in the genome.

Why was the ICGC/TCGA Pan-Cancer Project needed?

This is the largest, most comprehensive analysis of cancer genomes to date. To understand the complex changes in the genome, a huge amount of data was needed. This was only achieved through working collaboratively and sharing data. The project analysed almost every cancer genome throughout the world that was publicly available at the start of the project.

What is the main finding from the Pan-Cancer Project?

The main point is that the cancer genome is finite and knowable, but enormously complicated. By combining sequencing of the whole cancer genome with a suite of analysis tools, it is possible to highlight and describe every genetic change found in a cancer. These include all the processes that have generated those mutations, the biochemical pathways in the cells that are affected by these genetic changes, the kinds of cells that were originally transformed from normal to cancerous, and even the order of key events during a cancer's life history.

How will this help cancer research?

The Pan-Cancer researchers have provided comprehensive insights into many aspects of cancer genomes. Previous work had documented some of these features in some tumour types, but here, on the same, large international cohort of patients across all the common tumour types, all these aspects have been analysed together. This provides a more comprehensive, more uniform map of the cancer genome than the earlier snapshots had provided.

The ICGC/TCGA Pan-Cancer project researchers have established an enormous resource for the scientific community to use, a resource that will underpin on-going development of analysis methods, provide a testing ground for new ideas about cancer development and act as a benchmark for comparison of future sequencing studies.

The Pan-Cancer data is available to the broad research community, and will help accelerate additional discoveries. Over time, these discoveries will lead to improved detection, management and treatment of cancer.

Cancer genomes are complex, and much more data, potentially in thousands to tens of thousands of patients per tumour type, are needed to fully understand them – this is why shared data and resources like the Pan-Cancer Project are so important.

The suite of analysis tools generated by the project has been also released to the scientific and clinical communities, and is free to be used and further developed – this is important because data analysis has been a major barrier to improving access to cancer genome sequencing. The raw sequencing data and downstream analytical results are also released to the community under appropriate controls to safeguard participants' privacy.

How will the Pan-Cancer Project help cancer patients?

The study will enable more personalised medicine in the future, once clinical whole

genome sequencing of a patient's cancer becomes more widely adopted. This will include accurate diagnosis of tumour type, better prediction of clinical outcome, and choice of the optimal treatment for the patient.

The Pan-Cancer researchers have developed a method to find out where cancers come from (find the 'cell of origin') in patients in whom this wasn't possible to identify using standard diagnostic techniques. This could impact diagnosis and treatment in the future.

Due to the study, researchers can now carbon-date cancers, and identify the age of tumours and the key genomic stages they pass through. This has helped identify what the earliest changes are in the evolution of many cancer types, with the potential to develop new strategies for diagnosing or intervening in tumours at earlier stages.

By looking at the 99% of the cancer genome that was previously invisible – the part that doesn't code for proteins – the study filled in gaps in our knowledge of what drives cancer. At least one causative genetic change was found in more than 95% of all cancers in the study, and many individual tumours had 5-10 or more causative mutations identified. This information will help us find better methods for diagnosis, because the causative mutations inform what type of tumour developed, and better drugs, because the causative mutations may suggest useful drug targets. A future goal, begun in the Pan-Cancer project, is to be able to identify for any given patient in clinic all of the specific mutations that drive his or her cancer.

Researchers described many new processes generating mutations in cancer genomes. These processes leave distinctive 'mutational signatures' in the genome, and these signatures can give clues as to what may have caused the cancer. For example, lifestyle exposures such as cigarette smoking and sun-bathing can cause patterns of mutation that are highly distinctive; likewise, inherited cancer disorders can lead to distinctive signatures. These signatures can be read from a patient's cancer genome, and then compared against the compendium of signatures generated in this study.

What else has the Pan-Cancer Project revealed?

- By combining data on coding and non-coding cancer-causing genetic changes, at least one mutation that caused cancer was found in virtually all (95%) of the cancers analysed, with most patients' tumours having a handful of genetic causal events identified. This suggests that we are close to the goal of cataloguing all of the biological pathways involved in cancer.
- Revealed new "roads leading to Rome" that may provide avenues for treatment. Cancers use various ways to activate pathways that lead to tumours (oncogenic pathways). The Pan-Cancer Project study has mapped out additional routes involving structure, transcription, and driver mutations in the non-coding parts of the genome for a comprehensive set of tumour types.
- There is massive complexity in how the cancer cell interprets the genome. Different genetic changes in the DNA can lead to extensive variability in the RNA transcription undertaken by the cell, which is the first level of a cell's interpretation of the genome. Many of these RNA changes are important first messages instructing the cell to behave like a cancer cell.
- The processes that generate mutations in cancer genomes are hugely diverse, with more than 80 different patterns of mutation, ranging from changes affecting single DNA letters to large-scale reorganisation of whole chromosomes.
- Many specialised regions of the genome are disrupted in cancers compared to normal cells, including DNA in mitochondria, the power-houses of cells; telomeres, which cap the ends of chromosomes; repetitive DNA sequences, which can reactivate and multiply in a tumour's genome; and virus genomes, which can insert nearby particular cancer genes.

Data resources – how people can access the data

Pan-Cancer project researchers established an enormous resource for the scientific community to use, enabling a wider and deeper exploration of the cancer genome, by making sequencing data on genomes' non-coding regions available and providing tools to examine this data. It is expected that the availability of this resource will lead to further discoveries and help researchers improve the detection, management and treatment of cancer.

The Pan-Cancer researchers have developed a method to find out where cancers come from in patients in whom this wasn't possible to identify using standard diagnostic techniques. This could impact diagnosis and treatment in the future.

- Open-tier data can be viewed on *https://dcc.icgc.org/*
- Detailed instructions for obtaining access to the controlled-tier PCAWG data can be found in the DCC PCAWG documentation pages (*https://docs.icgc.org/pcawg/data/*).
- Researchers can contact *dcc-support@icgc.org* if they have inquiries about data access.

Next steps

Further insights into cancer biology are expected to be made using the Pan-Cancer data and related software tools that have been made available to the global cancer research community.

In 2015, the ICGC, in response to the realization of the potential of genomics in healthcare, released a position "white paper" on the evolution of ICGC into more directly impacting on human health. Emanating from the ICGC for Medicine (ICGCmed) white paper is ICGC's next project which aims to Accelerate Research in Genomic Oncology (The ARGO Project), where key clinical questions and patient clinical data drive the interrogation of cancer genomes. More information can be found at: *https://icgc-argo.org/*

CAR T cell therapy and beyond

Since the first successful applications of CD19-targeting Chimeric Antigen Receptor (CAR) T-cells nearly a decade ago for adults with chronic lymphocytic leukemia and children with acute lymphoblastic leukemia, research in the field of cell therapy has soared, with several hundred clinical trials of CAR T-cells against multiple targets and other types of cell therapy approaches underway around the country. At Columbia, BMT faculty are studying the latest CAR T-cell therapies in clinical trials for aggressive lymphomas and other types of blood cancers, including **indolent lymphomas, leukemias, myeloma,** as well as developing trials for difficult-to-treat solid tumors, such as **pancreatic cancer, sarcoma, melanoma and prostate cancer**.

Ran Reshef, MD, MSc, Director, Translational Research, BMT and Cell Therapy, NewYork-Presbyterian/Columbia

While CAR T-cell therapy has had major success turning some incurable diseases into curable ones, there remains work to be done. CAR T-cells overcome one specific barrier in cancer treatment, which is target recognition, leading to dramatic responses initially but progression of cancer is still observed in some patients several months following therapy. Durable remissions, which are potential cures, range from 50 to 60 percent in patients with acute lymphoblastic leukemia and approximately 40 percent for patients with lymphoma. To address this, researchers at Columbia are in the early stages of developing approaches to increase the efficacy of existing CAR T-cells using combination therapies, for example, CAR T-cells with a checkpoint inhibitor, to help overcome barriers to treatment success, increasing response rates and durability.

Columbia researchers also are exploring additional targets beyond CD19 and surface antigens. CAR T-cells are only able to identify and find extracellular proteins. However, a considerable number of tumor antigens do not present on the cell surface and are therefore unable to be identified. The Columbia team is now exploring alternative methods that would offer a greater ability to identify and attack cells that express intracellular antigens.

Cytokine release syndrome and neurological toxicity are the two most common toxicities associated with CAR T-cells and other forms of genetically modified T-cells. The BMT program has assembled a multidisciplinary team that includes experts in intensive care and neurology and have initiated research to understand the causes of cytokine release syndrome and neurotoxicity, and how to prevent or decrease these side effects. Currently, any patient undergoing CAR T-cell therapy at Columbia is seen by a neuroimmunologist prior to admission and undergoes a neurological assessment and brain MRI to obtain baseline information against which any changes can be compared following therapy. If a patient develops a severe neurological toxicity, a neurological ICU consult is immediately available. To date, the team's experience in managing CAR T-cell side effects has been very positive, allowing the team to treat safely all types of patients, including patients with diseases that are highly refractory to standard treatments, as well as elderly individuals and those with comorbidities.

- To learn more about CAR T-Cell Therapy, please contact NewYork-Presbyterian Hospital at: +1 646-697-1122.

Interview

OKI pioneers medical printing with cutting-edge innovations

Carine Haddad, OKI's Healthcare Manager for the MEIT region, talks to *Middle East Health* about the company's latest DICOM medical printers.

The Arab Health Exhibition and Congress 2020 at the Dubai World Trade Centre saw the participation of OKI Europe Ltd, a leading global company dedicated to creating cost-effective, professional in-house printing solutions.

The company recently announced the appointment of Carine Haddad as Manager Healthcare for Middle East, India and Turkey (MEIT).

With more than 10 years' experience in sales across the Middle East, Haddad's exceptional background has helped her advance the reach of OKI's DICOM medical printers in the Levant region during the past three years she has been with the company.

She is now poised to emulate her success in the broader MEIT region.

Middle East Health spoke to Haddad and discussed her new role and the Middle East market with regard to medical printers.

Middle East Health: Can you tell us about your new role, why you were appointed to this position and what will your work entail?

Carine Haddad: I've been in the printing industry for the last six years and in my previous job my focus was on healthcare. So, I am continuing this role, especially with the orientation of our company verticals. As an office printer company, we have a range of specialty products. I am handling DICOM embedded printers, designed specifically for the healthcare sector. We are dedicated to this segment of the market. Owing to my previous experience and the company's focus on verticals, I am going to be looking after healthcare in Middle East, India and Turkey.

MEH: Can you tell us about OKI's medical printers and what sets them apart from the competition?

CH: We are the only printer company which has DICOM embedded in the printer. DICOM is a healthcare industry protocol which enables it to communicate with other medical modalities, such as X-rays, MRI, and CT. In this way our printers can directly printout of X-ray, CT and MRI images. We don't compare ourselves with other printer manufacturing companies, because we are the only ones that have DICOM embedded in our printers.

MEH: What services does OKI supply to their customers with regards to maintenance, upgrades, supply of ink and other consumables, etc.?

CH: We have partners for our office printer businesses, but for healthcare, we assign only medical dealers because they understand the healthcare environment. If you bring an office printer partner or distributor, they don't have the same knowledge as a medical vendor. Our partners are medical vendors and they are distributors at the same time. They distribute to modality vendors like GE, Siemens or directly to hospitals. So, they act like a distributor, but regarding maintenance services and supply of consumables like ink, they receive support and training from us.

MEH: How do you view the Middle East market with regard to medical printers?

CH: It's booming. Our biggest market share is in Egypt. We have established markets in Libya and Iraq. We launched in the Kingdom Saudi Arabia in September and are launching now in the UAE. We were late to the UAE because we were focussing on North Africa. We are now starting with GCC and it's looking positive.

Carrine Haddad, OKI's new Manager Healthcare for Middle East, India and Turkey

MEH: Which countries in the Middle East do you think will be your key markets and from what type of healthcare facilities do you expect most of the demand to come from?

CH: Each country is a key market, but from a different perspective. It can be a key market for DICOM or it may be a key market for ultrasound or other healthcare applications. Every country has its unique requirements. It all depends on each country's needs and demands. We can fulfil the requirements of any clinic or hospital, because in all these facilities they have medical imaging equipment, and we can take care of all their printing needs.

MEH: What challenges do you envisage?

CH: Each company has its own unique challenges. For us it's that many people in healthcare are not completely aware of the value of the printed output. They are most often completely focussed on digital. But the more you dig into the organisation, the more you see the need for physical, printed medical images. MEH

General anaesthesia hijacks sleep circuitry to knock you out

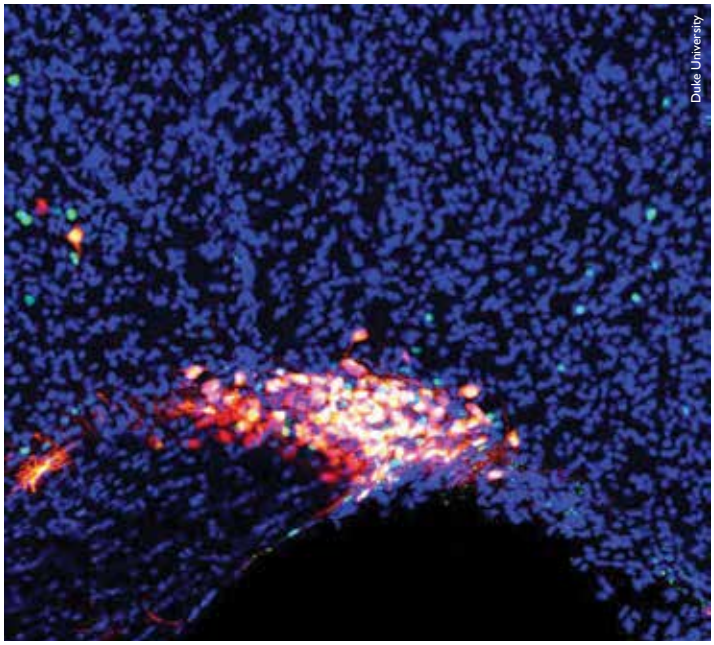
The discovery of general anaesthesia 170 years ago was a medical miracle, enabling millions of patients to undergo invasive, life-saving surgeries without pain. Yet despite decades of research, scientists still don't understand why general anaesthesia works.

Now scientists think they have discovered part of the answer. In a study published in *Neuron*, a Duke University team found that several different general anaesthesia drugs knock you out by hijacking the neural circuitry that makes you fall sleep.

The researchers traced this neural circuitry to a tiny cluster of cells at the base of the brain responsible for churning out hormones to regulate bodily functions, mood, and sleep. The finding is one of the first to suggest a role for hormones in maintaining the state of general anaesthesia, and provides valuable insights for generating newer drugs that could put people to sleep with fewer side effects.

Ever since the first patient went under general anaesthesia in 1846, scientists have been trying to figure out exactly how it works. The prevailing theory has been that many of these drugs tamp down the brain's normal activities, resulting in the inability to move or feel pain. Similar theories revolved around sleep, the sister state to general anaesthesia. However, research over the last decade has shown that sleep is a more active process than previously recognized, with entire sets of neurons clocking in to work while you catch your Z's.

Fan Wang, Ph.D., a professor of neurobiology at the Duke University School of Medicine, and Li-Feng Jiang-Xie, a graduate student in her laboratory, wondered whether the predominant view of general anaesthesia was also one-sided. "Perhaps rather than simply inhibiting neurons, anaesthetics could also activate certain neurons in the brain," said Jiang-Xie.



In a new Duke finding, general anaesthesia drugs were shown to induce unconsciousness by activating a tiny cluster of cells at the base of the brain called the supraoptic nucleus (shown in red), while the rest of the brain remains in a mostly inactive state (shown in blue).

To test their new theory, Jiang-Xie and Luping Yin, Ph.D., a postdoctoral fellow in the Wang lab, put mice under general anaesthesia with several different but commonly used drugs. Then they used molecular markers to track down the neurons that were commonly activated by the anaesthetics. They found a cluster of actively firing neurons buried in a tiny brain region called the supraoptic nucleus, which is known to have leggy projections that release large amounts of hormones like vasopressin directly into the bloodstream.

"Most of the anaesthesia-activated cells were a kind of hybrid cell that connects the nervous system and the endocrine system," said Jiang-Xie. "That took us by surprise and led us into unexplored territory for understanding the neural pathways of general anaesthesia."

Next, the researchers tapped a sophisticated technique developed in the Wang lab to turn on or off this specialized group of cells with chemicals or light. When they switched on the cells in mice, the animals stopped moving and fell into a deep slumber called slow wave sleep, typically associated with unconsciousness.

Then the research team killed off this group of cells. The mice continued to move around, unable to fall asleep.

Finally, the researchers performed similar experiments on mice under general anaesthesia. They found that artificially pre-activating the neuroendocrine cells made the mice stay under general anaesthesia for longer periods of time. Conversely, when they silenced these cells, the mice woke up from anaesthesia more easily.

This study also revealed a previously unexpected role of the brain's hormone-secreting cells in promoting deep sleep.

"Many people, particularly those with Alzheimer's disease, have difficulty falling to sleep, yet current medications have troublesome side effects," said Yin. "If we can find ways to manipulate this neural circuitry, perhaps by targeting hormones or small peptides, then it could lead to the development of better sleeping pills."

• **doi**: 10.1016/j.neuron.2019.03.033

Intersurgical

Intersurgical's breathing filters prevent cross contamination

The Intersurgical breathing filter, HME and HMEF range provides an effective barrier that prevents cross contamination between patients, respiratory equipment and the clinical environment.

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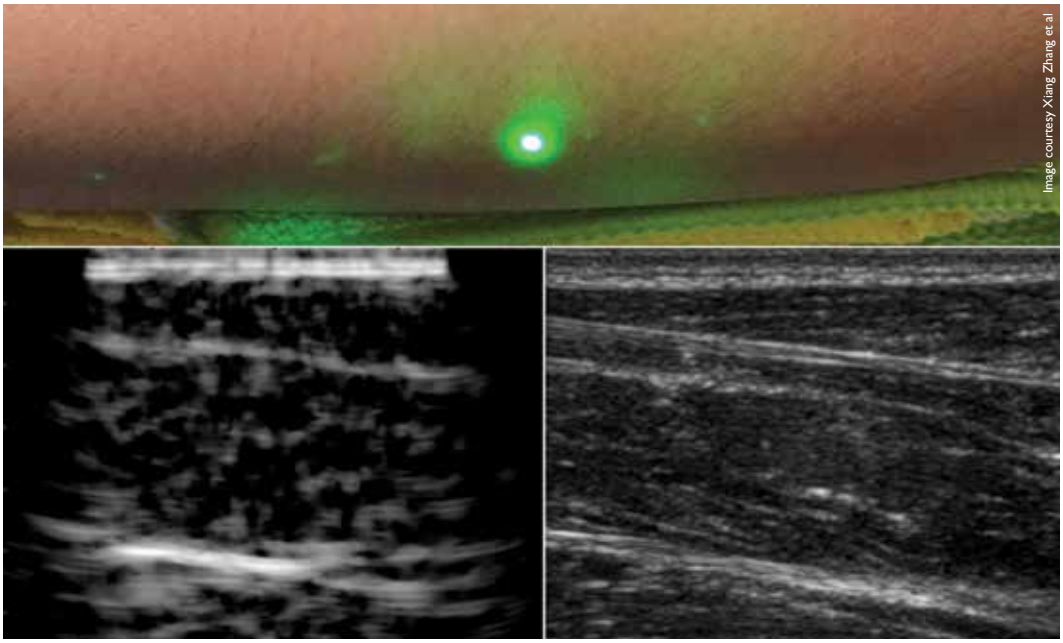


(top) Photograph of a volunteer's forearm region, imaged using laser ultrasound (LUS) and conventional ultrasound. A green tracking laser from the Laser Doppler Vibrometer is also visible. (bottom left) Reconstructed LUS image of a volunteer's forearm with multiple visible tissue layers. (bottom right) Matching conventional ultrasound image of the volunteer's forearm using a GE Logiq E9 system and a 9 MHz linear probe confirming features detected in the LUS image.

Researchers produce first non-contact laser ultrasound images of humans

Researchers have developed a new laser ultrasound technique that doesn't require contact with the body to see inside a patient. *Middle East Health* reports.

For most people, getting an ultrasound is a relatively easy procedure: As a technician gently presses a probe against a patient's skin, sound waves generated by the probe travel through the skin, bouncing off muscle, fat, and other soft tissues before reflecting back to the probe, which detects and translates the waves into an image of what lies beneath.

Conventional ultrasound doesn't expose patients to harmful radiation as X-ray and CT scanners do, and it's generally noninvasive. But it does require contact with a patient's body, and as such, may be limiting in situations where clinicians might want to image patients who don't tolerate the probe well, such as babies, burn victims, or other patients with sensitive skin. Furthermore, ultrasound probe contact induces significant image variability, which is a major challenge in modern ultrasound imaging.

Now, MIT engineers have come up with an alternative to conventional ultrasound that doesn't require contact with the body to see inside a patient. The new laser ultrasound technique leverages an eye- and skin-safe laser system to remotely image the inside of a person. When trained on a patient's skin, one laser remotely generates sound waves that bounce through the body. A second laser remotely detects the reflected waves, which researchers then translate into an image similar to conventional ultrasound.

In a paper published 20 December 2019 by Nature in the journal *Light: Science and Applications*, the team reports generating the first laser ultrasound images in humans.

The researchers scanned the forearms of several volunteers and observed common tissue features such as muscle, fat, and bone, down to about 6 centimetres below the skin. These images, comparable to conventional ultrasound, were produced using remote lasers focused on a volunteer from half a metre away.

"We're at the beginning of what we could do with laser ultrasound," says Brian W. Anthony, a principal research scientist in MIT's Department of Mechanical Engineering and Institute for Medical Engineering and Science (IMES), a senior author on the paper. "Imagine we get to a point where we can do everything ultrasound can do now, but at a distance. This gives you a whole new way of seeing organs inside the body and determining properties of deep tissue, without making contact with the patient."

Anthony's co-authors on the paper are lead author and MIT postdoc Xiang (Shawn) Zhang, recent doctoral graduate Jonathan Fincke, along with Charles Wynn, Matthew Johnson, and Robert Haupt of MIT's Lincoln Laboratory.

Yelling into a canyon – with a flashlight

In recent years, researchers have explored laser-based methods in ultrasound excitation in a field known as photoacoustics. Instead of directly sending sound waves into the body, the idea is to send in light, in the form of a pulsed laser tuned at a particular wavelength, that penetrates the skin and is absorbed by blood vessels.

The blood vessels rapidly expand and relax – instantly heated by a laser pulse then rapidly cooled by the body back to their original size – only to be struck again by another light pulse. The resulting mechanical vibrations generate sound waves that travel back up, where they can be detected by transducers placed on the skin and translated into a photoacoustic image.

While photoacoustics uses lasers to remotely probe internal structures, the technique still requires a detector in direct contact with the body in order to pick up the sound waves. What's more, light can only travel a short distance into the skin before fading away. As a result, other researchers have used photoacoustics to image blood vessels just beneath the skin, but not much deeper.

Since sound waves travel further into the body than light, Zhang, Anthony, and their colleagues looked for a way to convert a laser beam's light into sound waves at the surface of the skin, in order to image deeper in the body.

Based on their research, the team selected 1,550-nanometer lasers, a wavelength which is highly absorbed by water (and is eye- and skin-safe with a large safety margin). As skin is essentially composed of water, the team reasoned that it should efficiently absorb this light, and heat up and expand in response. As it oscillates back to its normal state, the skin itself should produce sound waves that propagate through the body.

The researchers tested this idea with a laser setup, using one pulsed laser set at 1,550 nanometers to generate sound waves, and a second continuous laser, tuned to the same wavelength, to remotely detect reflected sound waves. This second laser is a sensitive motion detector that measures vibrations on the skin surface caused by the sound waves bouncing off muscle, fat, and other tissues. Skin surface motion, generated by the reflected sound waves, causes a change in the laser's frequency, which can be measured. By mechanically scanning the lasers over the body, scientists can acquire data at different locations and generate an image of the region.

"It's like we're constantly yelling into the Grand Canyon while walking along the wall and listening at different locations," Anthony says. "That then gives you enough data to figure out the geometry of all the things inside that the waves bounced against – and the yelling is done with a flashlight."

In-home imaging

The researchers first used the new setup to image metal objects embedded in a gelatin mold roughly resembling skin's water content. They imaged the same gelatin using a commercial ultrasound probe and found both images were encouragingly similar. They moved on to image excised animal tissue – in this case, pig skin – where they found laser ultrasound could distinguish subtler features, such as the boundary between muscle, fat, and bone.

It's like we're constantly yelling into the Grand Canyon while walking along the wall and listening at different locations. That then gives you enough data to figure out the geometry of all the things inside that the waves bounced against – and the yelling is done with a flashlight.

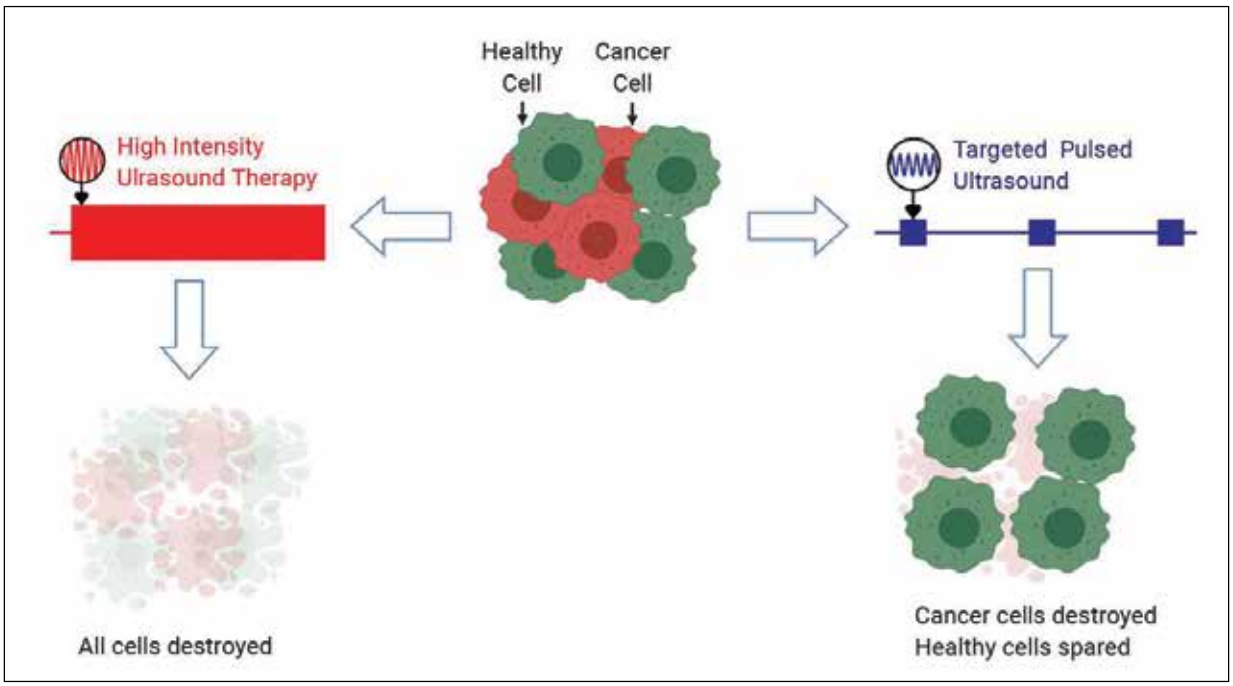
Finally, the team carried out the first laser ultrasound experiments in humans, using a protocol that was approved by the MIT Committee on the Use of Humans as Experimental Subjects. After scanning the forearms of several healthy volunteers, the researchers produced the first fully noncontact laser ultrasound images of a human. The fat, muscle, and tissue boundaries are clearly visible and comparable to images generated using commercial, contact-based ultrasound probes.

The researchers plan to improve their technique, and they are looking for ways to boost the system's performance to resolve fine features in the tissue. They are also looking to hone the detection laser's capabilities. Further down the road, they hope to miniaturize the laser setup, so that laser ultrasound might one day be deployed as a portable device.

"I can imagine a scenario where you're able to do this in the home," Anthony says. "When I get up in the morning, I can get an image of my thyroid or arteries, and can have in-home physiological imaging inside of my body. You could imagine deploying this in the ambient environment to get an understanding of your internal state."

This research was supported in part by the MIT Lincoln Laboratory Biomedical Line Program for the United States Air Force and by the U.S. Army Medical Research and Material Command's Military Operational Medicine Research Program.

- doi: 10.1038/s41377-019-0229-8



David Mittelstein

Targeted pulsed ultrasound takes advantage of the unique mechanical properties of cancer cells to destroy them while sparing healthy cells.

Ultrasound selectively damages cancer cells when tuned to correct frequencies

Doctors have used focused ultrasound to destroy tumours without invasive surgery for some time. However, the therapeutic ultrasound used in clinics today indiscriminately damages cancer and healthy cells alike.

Most forms of ultrasound-based therapies either use high-intensity beams to heat and destroy cells or special contrast agents that are injected prior to ultrasound, which can shatter nearby cells. Heat can harm healthy cells as well as cancer cells, and contrast agents only work for a minority of tumours.

Researchers at the California Institute of Technology and City of Hope Beckman Research Institute have developed a low-intensity ultrasound approach that exploits the unique physical and structural properties of tumour cells to target them and provide a more selective, safer option. By scaling down the intensity and carefully tuning the frequency to match the target cells, the group was able to break apart several types of cancer cells without harming healthy blood cells.

Their findings, reported in *Applied Physics Letters*, are a new step in the emerging field called oncotripsy, the singling out and killing of cancer cells based on their physical properties.

"This project shows that ultrasound can be used to target cancer cells based on their mechanical properties," said David Mittelstein, lead author on the paper. "This is an exciting proof of concept for a new kind of cancer therapy that doesn't require the cancer to have unique molecular markers or to be located separately from healthy cells to be targeted."

Oncotripsy

A solid mechanics lab at Caltech first developed the theory of oncotripsy, based on the idea that cells are vulnerable to ultrasound at specific frequencies – like how a trained singer can shatter a wine glass by singing a specific note.

The Caltech team found at certain frequencies, low-intensity ultrasound caused the cellular skeleton of cancer cells to break down, while nearby healthy cells were unscathed.

"Just by tuning the frequency of stimulation, we saw a dramatic difference in how cancer and healthy cells responded," Mittelstein said. "There are many questions left to investigate about the precise mechanism, but our findings are very encouraging."

The researchers hope their work will inspire others to explore oncotripsy as a treatment that could one day be used alongside chemotherapy, immunotherapy, radiation and surgery. They plan to gain a better understanding of what specifically occurs in a cell impacted by this form of ultrasound.

- **doi:** 10.1063/1.5128627. MEH

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Inclusion changes the world

Let's celebrate World Autism Awareness Day on **April 2nd** along with the launch of our initiative to integrate individuals on the spectrum into the workforce.

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SENSES
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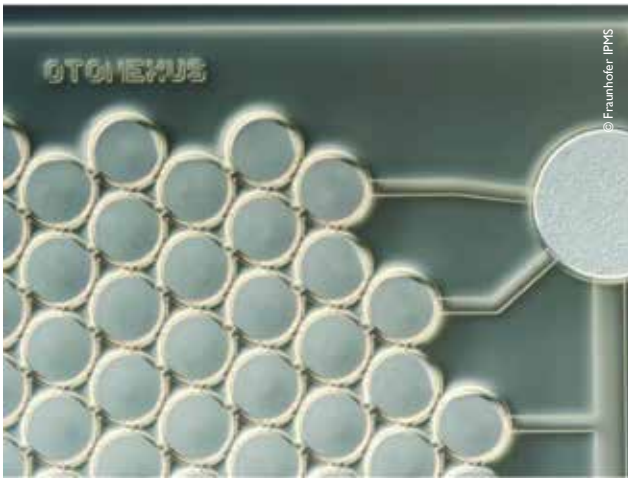
Senses

Thanks to sensor technology developed by Fraunhofer IPMS, a new device from OtoNexus Medical Technologies will significantly enhance the diagnosis of middle ear infections.



At the heart of the revolutionary otoscope from OtoNexus Medical Technologies is a unique CMUT chip from Fraunhofer IPMS based on ultrasound technology.

Diagnosing middle-ear infection

A new type of ultrasound transducer from Fraunhofer should soon be delivering a fast and reliable diagnosis of infection of the middle ear. A U.S. company and the Fraunhofer Institute for Photonic Microsystems IPMS are collaborating on the development and application of this technology. The transducer is integrated in an otoscope and helps physicians decide whether a course of antibiotics is really necessary. *Middle East Health* reports.

In cases of infection of the middle ear, particularly among infants and young children, antibiotics are often the remedy of choice. Yet the equipment used to diagnose this condition has stood still for a number of decades. As a result, doctors can only deliver a diagnosis that is subjective and unreliable. On average, diagnostic accuracy for this condition is as low as 50%, not least when it comes to distinguishing between a bacterial and viral infection. This means that lots of children are prescribed antibiotics unnecessarily. This, in turn, is feeding a growing resistance to antibiotics worldwide.

However, a new type of ultrasound transducer developed at the Fraunhofer Institute for Photonic Microsystems IPMS can resolve this dilemma. It employs air-coupled ultrasound to enable a precise diagnosis of infection of the middle ear, a condition also known as otitis media. The U.S. company OtoNexus Medical Technologies has developed an otoscope incorporating this technology. Their device is now undergoing clinical studies. Paediatricians and other doctors will be able to use it to examine the external auditory canal and, more particularly, the area behind the ear drum. In a matter of seconds, they will be able to tell whether there is air or fluid in the middle ear, and to characterize this fluid. This will permit them to distinguish between different stages of the illness and thereby determine the appropriate treatment.

Degree of infection

"The classic otoscope is an optical system and hasn't changed in decades," explains Dr Sandro Koch, a physicist at Fraunhofer IPMS in Dresden. "But when fitted with our ultrasound transducer, which is both a transmitter and receiver, it develops new functions."

The transducer emits ultrasonic pulses and captures the echo reflected from the eardrum. On the basis of this data, the device generates a reading that tells the doctor about the degree of infection.

The innovative transducer is designed to operate via the medium of air. It features a capacitor formed by two electrodes separated by a small air-filled gap.

"One of these electrodes is flexible," Dr Koch explains. "We use the vibrations of this electrode to transmit ultrasonic pulses. When the echo from this signal strikes a flexible membrane, the resultant vibration is converted into a detectable electrical signal."

Proprietary software developed by industry partner OtoNexus analyses the echo signal. Initial clinical studies have corroborated the accuracy of the analysis.

Mass production

The ultrasound transducer is a so called CMUT (capacitive micromachined ultrasonic transducer). It is produced on a silicon wafer by means of special microelectromechanical systems (MEMS) technology developed at Fraunhofer IPMS. The transducer has a low power consumption and can be mass-produced cheaply.

"And, unlike traditional ceramic piezo-electric ultrasound transducers, our MEMS transducer can be miniaturized," says Dr Koch. "That's a major advantage here, because it means the CMUT can be incorporated much more easily in an otoscope."

The new otoscope featuring a Fraunhofer CMUT is currently at the prototype stage with market launch anticipated within a few years.

Uses of the MEMS transducer are not restricted to medical applications. For instance, ultrasound transducers can also be incorporated in smartphones and tablets to enable gesture control or installed in vehicles to control onboard infotainment systems. They can also deliver various functions in robotics, including distance measurement. MEH

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Alzheimer's: New ultrasound technique significantly improves brain performance

In neurological diseases such as Alzheimer's disease, Parkinson's disease or Multiple Sclerosis, brain neurons are constantly being lost, resulting in memory lapses, speech disorders, mood swings and movement disorders, for example, as well as muscle tremors in the case of Parkinson's. After 6 years of development, MedUni Vienna researchers from the Department of Neurology, led by Roland Beisteiner, have developed a new method of treatment that represents a world first. Using a non-invasive ultrasound technique, it is now possible to reach all areas of the brain and activate neurons that can help to regenerate brain functions. The preliminary data, which have been prominently published on the international stage, show that this can improve brain performance.

The new method is called Transcranial Pulse Stimulation with Ultrasound (TPS) and was developed in collaboration with Swiss commercial partner Storz Medical and its project leader, Ernst Marlinghaus.

"For the first time in the world, TPS enables us to penetrate into all areas of the brain by means of an ultrasound pulse delivered directly to the skull in a non-invasive, painless procedure, during which the patient is fully conscious, and to specifically target particular areas of the brain and stimulate them," explains Beisteiner. The study was part of the inter-university cluster led by Beisteiner and Tecumseh Fitch, which is attempting to improve patients' brain functions by means of brain stimulation and is being jointly run by MedUni Vienna and the University of Vienna. Such clinical procedures must be carried out with great precision and must be tailored to the individual patient. However, the existing electromagnetic techniques such as e.g. Transcranial Magnetic Stimulation (TMS), in which magnetic fields act on the brain to stimulate or inhibit neurons, are currently incapable to provide the required clinical precision, or deep brain activation. An invasive method that is increasingly being used for serious illnesses involves placing stimulator electrodes in deep brain areas (Deep Brain Stimulation (DBS)) – associated with a lengthy operation. It is hoped that TPS could also partially replace such invasive methods in the future.

TPS: Precision medicine in the brain

The stimulating pulse emitted by the ultrasound device is between 3 and 5 mm wide and approximately 3 cm long. An accurate "map" is first of all made of the patient's brain using magnetic resonance.

Alzheimer's: New ultrasound technique significantly improves brain performance

"In the spirit of precision medicine, the area of the brain that is to be activated is very precisely targeted. These areas can be situated differently in each patient. Thanks to a navigation system, the treating neurologist can pinpoint on the screen where the pulse must be delivered and control everything very precisely," says Beisteiner.

The TPS pulse causes short-term membrane changes on the brain cells, bringing about local changes in the concentration of transmitters and other biochemical substances. This results in activation of neurons and the development of compensatory networks, which improve the affected brain function. This has been demonstrated in comprehensive laboratory studies. The result: the memory network is boosted and memory performance improves. Some patients also report a marked improvement in their mood, they find it easier to be physically active and to actively participate in conversations.

Says Beisteiner: "It is like starting up an old engine again. Those neurons that are still activatable show marked improvements after the procedure. The decline in performance is slowed down."

Apart from Alzheimer's, Parkinson's or Multiple Sclerosis, any diseases that can be improved by activating viable neurons are potential applications for TPS. At the same time, TPS offers patients an "extra chance", says Beisteiner, since all ongoing treatments with drugs and physiotherapy or occupational therapy can be continued. However, the new technique is also significant for basic neuroscientific research.

Clinical pilot study

In the clinical pilot study, published in the journal *Advanced Science*, six one-hour sessions over the course of two weeks were enough to bring about improvements in brain performance. If the results of the pilot study are confirmed, clinical neuroscientists expect a breakthrough in the treatment of brain diseases. However, before this method can be put into regular clinical use, further scientific studies are required to evaluate the results.

• **doi:** 10.1002/advs.201902583

NeuEcho innovation

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Diagnosis accessible to everyone

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Neusoft Medical's ultrasound product line, established in 1998, has 22 years of development and manufacturing experience. Neusoft Medical's ultrasound devices are proven to be of high reliability and durability. The company acquired HUMANSCAN, a well-known probe manufacturer, as the company strives to provide higher performance ultrasound for customers.

NeuEcho 10 – 4D Color Doppler Ultrasound

NeuEcho 10 is the latest ultrasound system developed by Neusoft Medical, as the company moves to make rapid imaging and diagnosis more affordable and accessible to everyone. With a deep understanding of the customer's daily requirements, NeuEcho 10 is designed to provide high quality images and a wide variety of clinical solutions that can improve diagnostic confidence across all departments, from radiology and urology to cardiovascular and obstetrics imaging.

NeuEcho 10 has a range of AI-powered tools, such as Auto EF, Auto IMT, Auto OB and Auto NT, among others. These smart-tools help doctors to be more efficient in their daily work. The user experience is also enhanced with NeuEcho 10's improved ergonomic design, such as the streamlined control panel and a wide range of available adjustments.

New products launched at Arab Health

The Neusoft Medical international team headed to Dubai to participate in the 45th Arab Health exhibition in January. As one of the leading manufacturers in the field, Neusoft Medical showcased their latest innovations including, NeuEcho 10, NeuViz Epoch 512-slice CT and NeuAngio 30C, which received much attention and praise from participants. MEH

2020 Best in KLAS Report Again Ranks UpToDate from Wolters Kluwer as Category Leader for Clinical Decision Support

Wolters Kluwer, Health, a leading global provider of trusted clinical technology and evidence-based solutions has announced that its decision support solution, UpToDate®, was ranked number one for clinical decision support (point-of-care clinical reference) in the 2020 Best in KLAS: Software and Services report.

KLAS, a research firm that specializes in monitoring and reporting the performance of healthcare vendors, found that UpToDate was the top performing point of care clinical reference tool for the second straight year.

KLAS interviews thousands of healthcare professionals and uses the responses to rate point-of-care and clinical reference tools. Evaluation questions cover several areas, including Culture, Loyalty, Operations, Product, Relationship, and Value.

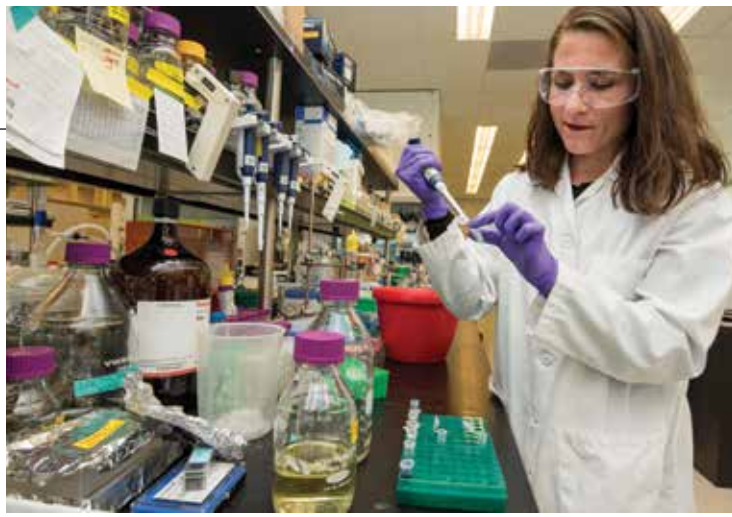
"We are committed to helping healthcare organisations deliver high quality services by providing the best available evidence to treat patients" said Alaa Darwish, Country Manager of Middle East, Turkey and Africa - Wolters Kluwer Clinical Effectiveness. "Our expert solutions help align decision making across care teams and patients, enabling more consistent and cost-effective care."

Adam Gale, President, KLAS Research, adds, "Providers and payers demand better performance, usability, and interoperability from their vendor partners every year. Best in KLAS winners set the standard of excellence in their market segment. Earning a Best in KLAS award should both excite and humble the recipients. It serves as a signal to providers that they should expect only the best from the winning vendors."

About Wolters Kluwer

Wolters Kluwer provides trusted clinical technology and evidence-based solutions that engage clinicians, patients, researchers and students with advanced clinical decision support, learning and research and clinical intelligence.

Researchers identify powerful new antibiotic using AI



Using a machine-learning algorithm, MIT researchers have identified a powerful new antibiotic compound. In laboratory tests, the drug killed many of the world's most problematic disease-causing bacteria, including some strains that are resistant to all known antibiotics. It also cleared infections in two different mouse models.

The computer model, which can screen more than a hundred million chemical compounds in a matter of days, is designed to pick out potential antibiotics that kill bacteria using different mechanisms than those of existing drugs.

"We wanted to develop a platform that would allow us to harness the power of artificial intelligence to usher in a new age of antibiotic drug discovery," says James Collins, the Termeer Professor of Medical Engineering and Science in MIT's Institute for Medical Engineering and Science (IMES) and Department of Biological Engineering. "Our approach revealed this amazing molecule which is arguably one of the more powerful antibiotics that has been discovered."

In their new study, the researchers also identified several other promising antibiotic candidates, which they plan to test further. They believe the model could also be used to design new drugs, based on what it has learned about chemical structures that enable drugs to kill bacteria.

"The machine learning model can explore, in silico, large chemical spaces that can be prohibitively expensive for traditional experimental approaches," says Regina Barzilay, the Delta Electronics Professor of Electrical Engineering and Computer Science in MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL).

Barzilay and Collins, who are faculty coleads for MIT's Abdul Latif Jameel Clinic for Machine Learning in Health, are the senior authors of the study, which appears in *Cell*. The first author of the paper is Jonathan Stokes, a postdoc at MIT and the Broad Institute of MIT and Harvard.

A new pipeline

Over the past few decades, very few new antibiotics have been developed, and most of those newly approved antibiotics are slightly different variants of existing drugs. Current methods for screening new antibiotics are often prohibitively costly, require a significant time investment, and are usually limited to a narrow spectrum of chemical diversity.

"We're facing a growing crisis around antibiotic resistance, and this situation is being generated by both an increasing number of pathogens becoming resistant to existing antibiotics, and an anaemic pipeline in the biotech and pharmaceutical industries for new antibiotics," Collins says.

To try to find completely novel compounds, he teamed up with Barzilay, Professor Tommi Jaakkola, and their students Kevin Yang, Kyle Swanson, and Wengong Jin, who have previously developed machine-learning computer models that can be trained to analyse the molecular structures of compounds and correlate them with particular traits, such as the ability to kill bacteria.

The idea of using predictive computer models for "in silico" screening is not new, but until now, these models were not sufficiently accurate to transform drug discovery. Previously, molecules were represented as vectors reflecting the presence or absence of certain chemical groups. However, the new neural networks can learn these representations automatically, mapping molecules into continuous vectors which are subsequently used to predict their properties.

In this case, the researchers designed their model to look for chemical features that make molecules effective at killing *E. coli*. To do so, they trained the model on about 2,500 molecules, including about 1,700 FDA-approved drugs and a set of 800 natural products with diverse structures and a wide range of bioactivities.

Once the model was trained, the researchers tested it on the Broad Institute's Drug Repurposing Hub, a library of about 6,000 compounds. The model picked out one molecule that was predicted to have strong antibacterial activity and had a chemical structure different from any existing antibiotics. Using a different machine-learning model, the researchers also showed that this molecule would likely have low toxicity to human cells.

This molecule, which the researchers decided to call halicin, after the fictional artificial intelligence system from "2001: A Space Odyssey," has been previously investigated as possible diabetes drug. The researchers tested it against dozens of bacterial strains isolated from patients and grown in lab dishes, and found that it was able to kill many that are resistant to treatment, including *Clostridium difficile*, *Acinetobacter baumannii*, and *Mycobacterium tuberculosis*. The drug worked against every species that they tested, with the exception of *Pseudomonas aeruginosa*, a difficult-to-treat lung pathogen.

Preliminary studies suggest that halicin kills bacteria by disrupting their ability to maintain an electrochemical gradient across their cell membranes. This gradient is necessary, among other functions, to produce ATP (molecules that cells use to store energy), so if the gradient breaks down, the cells die. This type of killing mechanism could be difficult for bacteria to develop resistance to, the researchers say.

"When you're dealing with a molecule that likely associates with membrane components, a cell can't necessarily acquire a single mutation or a couple of mutations to change the chemistry of the outer membrane. Mutations like that tend to be far more complex to acquire evolutionarily," Stokes says.

• **doi**: 10.1016/j.cell.2020.01.021

Agenda

Selected schedule of regional medical meetings, conferences and exhibitions

Event	Date / City	Contact
March 2020		
Annual Conference on Women's Health, Reproduction and Fertility	16-17 March 2020 Dubai, UAE	https://reproduction.conferenceseries.com/europe/
UAE International Conference on Antimicrobial Resistance (ICAMR)	19-20 March 2020 Dubai, UAE	http://icamr-uae.com
April 2020		
Emirates Critical Care Conference	April 2-4, 2020 Dubai, UAE	www.eccc-dubai.com
International Congress for Joint Reconstruction	April 2-4, 2020 Dubai, UAE	www.icjrmiddleeast.com
Biotechnology World Congress	April 6-7, 2020 Dubai, UAE	https://10times.com/biotechnology-world-congress
World Congress on Women's Health and Midwifery	April 6-7, 2020 Dubai, UAE	womenshealth.pulsusconference.com
Plenareno Depression Conference 2020	April 13-14, 2020 Dubai, UAE	https://depression.plenareno.com/
Plenareno Heart Congress 2020	April 13-14, 2020 Dubai, UAE	https://heart.plenareno.com/
Plenareno Pediatrics and Neonatology Conference 2020	April 13-14, 2020 Dubai, UAE	https://pediatrics.plenareno.com/
Plenareno Diabetes, Obesity and Cholesterol Metabolism Conference 2020	April 13-14, 2020 Dubai, UAE	https://metabolicdiseases.plenareno.com/
International Conference on Infectious Diseases	April 22-23, 2020 Dubai, UAE	https://researchlake.com/conferences/infectious-diseases
May 2020		
Heart & Diabetes Conference	May 11-12, 2020 Dubai, UAE	http://heartdiabetesconference.com
June 2020		
International Conference on Neurology and Cardiology	June 1-3, 2020 Dubai, UAE	www.citationsinternational.com/neurology-cardiology-2020-dubai

List your conference:
If you have upcoming conference/exhibition details which you would like to list in the agenda, please email the details to the editor: editor@MiddleEastHealthMag.com

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