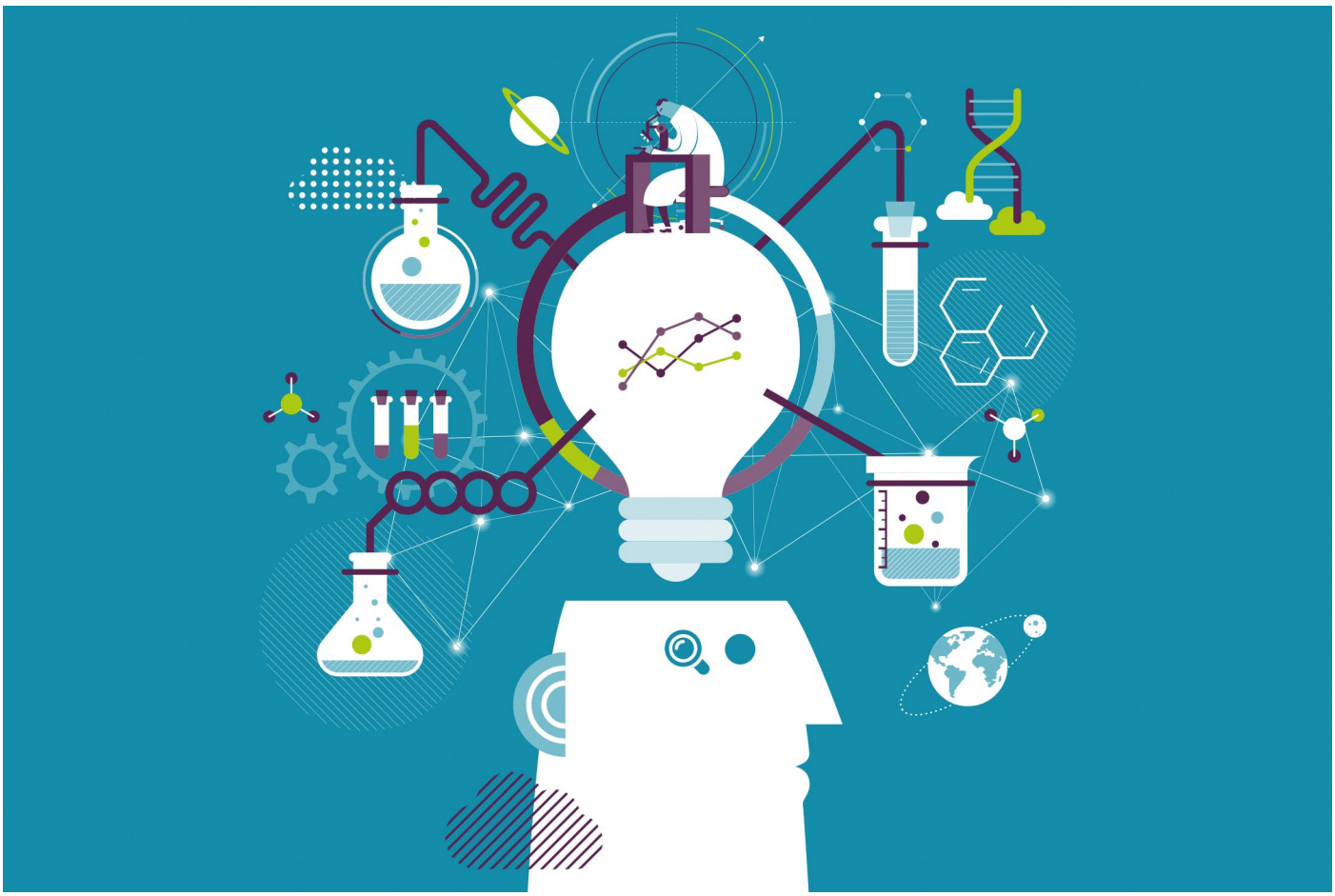


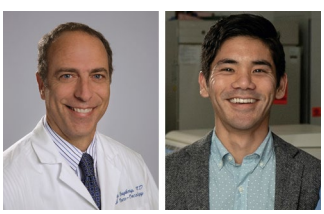
Credit: Akindo / DigitalVision Vectors / Getty

At the forefront of medical research: our cover authors share their hopes for their fields

From investigating the diversity of the vaginal microbiome to developing neuroprosthetics with sensory feedback for leg amputees, the work of the authors featured in our pages is fascinating. We asked them about their hopes for the future of medical research.

Timothy F. Cloughesy and Aaron Y. Mochizuki

Authors of "Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma"



Credit: UCLA Jonsson Comprehensive Cancer Center

For decades, the treatment paradigm for tumors of the central nervous system has relied on maximal surgical resection followed by radiation and chemotherapy, which provides limited survival for most. In other cancers, the explosion of therapeutic options that harness one's own immune system to combat cancer—oncolytic viruses, checkpoint inhibitors, chimeric antigen receptor T cells, vaccines—are beginning to show clinical efficacy after researchers have spent years working to understand basic mechanisms. The list of cancers considered responsive to immunotherapy has not, however, so far included glioblastoma multiforme (GBM), the most common, and typically lethal, adult brain tumor. Among ongoing efforts to address this disease's seeming intractability, three recent, simultaneously published studies suggest that the timing of PD-1 blockade may be critical in promoting therapeutic efficacy. The findings are also helping researchers unfurl a map of GBM's complex immune

and genomic landscape. Immunotherapy may represent a durable, less toxic cure for brain tumors, and cancer in general, that is now within our grasp. The key to unlocking this curative potential is a deeper understanding of the complexities of the immune system's response to cancer, the changes induced by immunotherapy, and tumors' adaptability and capacity to metastasize. Cancer still remains one of the top causes of mortality in adults, yet now the tools to eliminate it may be close at hand. Let's finish the job.

Credit: Dominic Pfister

Dominik Pfister
Author of "Platelet GPIbα is a mediator and potential interventional target for NASH and subsequent liver cancer"

The field I work in, preclinical mouse models of non-alcoholic steatohepatitis (NASH)-induced hepatocellular carcinoma (HCC), has made terrific strides in unraveling the molecular mechanisms of HCC. As simple steatosis progresses to NASH, the liver undergoes tremendous changes due to chronic necroinflammation and metabolic reprogramming—laying the ground for liver dysfunction and HCC. But, unlike for many other types of tumors, this mechanistic knowledge has not led to effective therapeutic strategies for patients.

I hope to contribute to the prevention and reduction of HCC incidence by identifying efficient, low-cost and broadly effective treatment strategies for patients with NASH and NASH-induced HCC, breaking the vicious circle of chronic necroinflammation, aberrant metabolism and liver damage. For example, by studying platelets and their mechanisms of coagulation and inflammation, we begin to understand how NASH and HCC pathology progression go hand in hand with chronic imbalances in innate immune cells. Alteration of platelet-associated inflammation (e.g., through anti-platelet therapy with anti-GPIbα antibodies) could be a potential low-cost and widely accessible HCC prevention option.

To effect meaningful progress towards treatment, I hope that the field advances towards stratifying patients who have developed chronic-inflammation-triggered HCC for appropriate/personalized treatment (e.g., surgery, chemotherapy, immunotherapy). To accomplish these goals, I hope that legislative bodies, academia and industry indeed enable more efficient (e.g., through ethical approved automated screening pipelines of patient material; straightforward supportive policies of appropriate preclinical model use) and direct translational research (e.g., through closer collaborative efforts between academia and industry to use screening results for individualized therapy) for the benefit of patients in the near future.

Credit: Anca M. Pașca

Anca M. Pașca
Author of "Human 3D cellular model of hypoxic brain injury of prematurity"

In neonatal intensive care, we challenge the limits of science on a daily basis. The survival of extremely preterm infants, who fit into the palm of one hand and weigh less than a pound, has improved dramatically, but the long-term neuropsychiatric morbidities associated with preterm birth remain a substantial challenge. Gray and white matter dysmaturation, known as encephalopathy of prematurity, is common in preterm infants and predisposes them to life-long cognitive, motor and psychiatric impairments.

Targeted interventions to prevent or treat encephalopathy of prematurity are lacking, and progress in the field has been slow, mostly because of the evolutionary developmental limitations of commonly used animal models and the inability to access functional human brain tissue from this stage of development to study in the laboratory.

I believe that human organoids derived from stem cells mimic key features of human development in vitro and hold great promise for uncovering the cellular phenotypes and molecular mechanisms of dysmaturation in the developing human brain. These brain-region-specific organoids may reveal critical genetic predispositions, environmental insults or gene-environment interactions that contribute to developmental alterations and predispose to neuropsychiatric diseases later in life.

More importantly, I am hopeful that organoids will serve as a powerful in vitro drug-screening platform to inform clinical trials in neonates and increase the translational potential of preclinically promising pharmacotherapies.

Credit: Myrna G. Serrano

Myrna G. Serrano, Hardik I. Parikh and Gregory A. Buck
Authors of "Racioethnic diversity in the dynamics of the vaginal microbiome during pregnancy"

As recently as a decade ago, the scientific community viewed the impact of bacteria on humans only through the lens of disease. But high-throughput sequencing technologies have enabled us to see much more of the complexity of this interaction, and today we appreciate that individual microbiomes contribute to human development as healthy, immune-competent individuals and populations.

We now know that the microbiome's genome (sometimes referred to as the 'second genome') and the human genome evolved in parallel, although both the environmental and genetic contexts can influence microbiome composition. Studies indicate that the vaginal microbiome shows significant divergence across geographic, racioethnic and socioeconomic boundaries, and some of these differences have been associated with, and are possibly causes of, adverse urogenital health and adverse pregnancy outcomes.

Our expectation is that, in time, precision medicine will expand to include assessment of microbiome composition to assist clinicians in their diagnosis, prevention and treatment of disease. Thorough understanding of the composition of the vaginal microbiome in diverse groups and populations, for instance, could help clinicians more accurately predict adverse conditions for reproduction and pregnancy and identify challenges to fetal and neonate health across ethnic and socioeconomic groups.

But to achieve this level of precision in our understanding of the microbiome's effects on health and disease, large-scale studies, like the *All of Us* Research Program, with broad sampling of diverse genetic, racioethnic and socioeconomic populations are essential.

Jennifer M. Fettweis
Author of "The vaginal microbiome and preterm birth"

The NIH Human Microbiome Project has motivated new areas of scientific investigation inspired the development of novel diagnostics and therapeutics for a multitude of conditions affecting human health. I am particularly hopeful that vaginal microbiome signatures may ultimately be used clinically to predict preterm birth in pregnancy, assess risk for HIV acquisition among women and reduce the health disparities that exist for these conditions. Looking forward, teams that harmonize data

and biospecimen collection protocols across large-scale global studies will integrate data into a common framework and make it possible to compare omics signatures of disease across populations. Further, studies of the dynamic interactions of microbial consortia with the human host will provide additional mechanistic insights.

My lab also is investigating the impact of the maternal microbiome on a child's microbiome development. The vaginal microbiome has a relatively simple composition, it directly impacts reproductive outcomes, and there is preliminary evidence that vaginal delivery influences the development of the infant gut microbiome. These features make the vaginal microbiome an ideal system for discovering common features of human host–microbiome coevolution. This line of investigation may provide insights into how probiotic therapies and other interventions may possibly impact the human microbiome across generations.

Credit: Sreyan Chowdhury

Sreyan Chowdhury
Author of "Programmable bacteria induce durable tumor regression and systemic antitumor immunity"

The field of cancer immunotherapy can be traced back to the discoveries of Dr. William Coley, who, in the 1890s, demonstrated that inoculation with bacteria induced an immune reaction leading to tumor regression and long-term disease remission.

However, to date, safety risks associated with the administration of live microbes to patients with cancer, who often are immunocompromised, have meant that recent breakthroughs in cancer immunotherapy have focused on systemically administered monoclonal antibodies or engineered T cells to induce antitumor immunity.

More recently, advances in synthetic biology, combined with the relative ease of engineering prokaryotes, have led to renewed enthusiasm about the use of bacteria for cancer immunotherapy. For instance, we have enabled non-pathogenic *Escherichia coli* to synchronously lyse upon reaching quorum within solid tumors, leading to release of an immunotherapeutic nanobody targeted to CD47 in a localized, sustained manner in murine models. This is exciting because we are now able to re-engineer once-feared strains of bacteria into allies that may potently, yet safely, induce durable antitumor immunity in patients.

But before we can do this effectively, productive dialogue between research scientists, physicians, and regulators will be crucial to define a clinical pathway for these 'living medicines'. In the meantime, I remain inspired by Coley's pioneering work as we seek to develop engineered bacteria as safe, effective and affordable immunotherapeutics for cancer patients.

Credit: Natalia V. Bhattacharjee

Natalia V. Bhattacharjee
Author of "Mapping exclusive breastfeeding in Africa between 2000 and 2017"

"Of all the forms of inequality, injustice in health is the most shocking and inhuman." My hope for my field is that we continue to combat the injustice in health decried by Dr. Martin Luther King Jr., by developing better tools and resources to reduce inequality.

The Institute for Health Metrics and Evaluation (IHME) already helps to do this by providing publicly available tools to identify regions and communities that are most in need of healthcare support and by fostering greater collaboration between geostatisticians, public health professionals, epidemiologists and others working in the realm of global health.

But the global health community must strive to further improve equity in health. This can be done by investing in high-quality geospatial data—especially in low- and middle-income countries where information about health indicators can be scarce. Policy-makers can learn from the stories of countries that have succeeded in reducing health inequality to improve health in their own countries, and researchers can continue to develop new technologies for monitoring health indicators effectively on a global scale: for example, streaming data from health monitoring systems or crowdsourcing in real time, and developing reliable and affordable diagnostics.

The community should aspire to bridge the inequality gap by understanding patterns in the data and using the data effectively, supporting future leaders in global health and effectively communicating pressing health needs to policy makers. Additionally, global health indicators will only be able to achieve their goals or targets, thus saving and improving the lives of millions, when equal opportunities are provided, regardless of determinants such as age, gender, race and place of birth.

Credit: Alain Herzog, EPFL, Lausanne

Francesco M. Petrini
Author of "Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain"

The field of neuroprosthetics, which includes the devices I work on that interface with the peripheral nervous system (PNS), has slowly been expanding over the past ten years and is expected to accelerate. Innovative approaches have helped reduce some problems associated with impairment—for instance, reducing phantom limb pain by providing sensory feedback through PNS stimulation, thus decreasing the need for patients to take painkilling drugs with harmful side effects.

In the next decade, I envision that neuroprosthetics will allow amputees to feel touch and movement sensations from their prosthesis or to perfectly voluntarily control it, will control the release of insulin in the blood flow of diabetic patients, and will restore sensations from the numb extremities of people affected by nerve neuropathy.

At present, however, the field is experiencing issues with low transferability of technologies and a poor market for adoption by patients, which will have to be addressed. This is in part due to a dearth of attention paid to the design of clinical assessments for neuroprosthetics. Too often, investigators focus on developing the technology and limit its testing to feasibility testing, without also evaluating the crucial points of usability, patient benefits or side effects. Moreover, testing protocols are not standardized, and results often are not comparable.

In the future, I hope that researchers in neuroprosthetics will come together to decide on international standards to guide the design of clinical protocols showing benefits (or not) for patients, so as to facilitate further exploitation by industry.

Francesca Chemi and Dominic G. Rothwell
Authors of "Pulmonary venous circulating tumor cell dissemination before tumor resection and disease relapse"

Credit: Francesca Chemi and Dominic G. Rothwell

The observation that tumor cells circulate in the blood of cancer patients was first made over 150 years ago. But it is only in the past decade that technological advances in single-cell analysis and next-generation sequencing have made it possible to enumerate, isolate and characterize these circulating tumor cells (CTCs) at a molecular level, enabling several studies to demonstrate the utility of CTCs as prognostic and predictive biomarkers as well as a potential tumor surrogate.

Technology that allows for even more sensitive detection and isolation of these rare cells from a blood sample will be needed in order to move the analysis of CTCs into routine clinical practice, where improved detection of these early disseminating tumor cells could lead to the earlier diagnosis of cancer and their molecular analysis could help toward a better understanding of metastasis. Considering their pivotal role in metastasis, could these cells even be targeted to prevent metastatic disease or cultured short-term ex vivo to test the efficacy of drugs in a patient-specific screen? Studies combining CTC enumeration, molecular profiling and ex vivo culturing are ongoing and will hopefully provide the impetus to move analysis of CTCs into routine clinical practice.

Credit: Courtesy of Dhruva Biswas

Dhruva Biswas and Nicolai J. Birkbak

Authors of "A clonal expression biomarker associates with lung cancer mortality"

Cancer is a complex, evolving disease, with a patchwork of different cells making up each individual tumor. This intratumor heterogeneity (ITH) means that, although a proportion of somatic alterations are common to every cancer cell, there is striking diversity within each individual tumor. Our broadening understanding of the patterns, fuel and sculpting forces of cancer evolution is beginning to open up avenues for more rational clinical management.

For instance, the medical community now recognizes the importance of tumor sampling bias in diagnosis, which means that you could sample two regions of the same tumor from the same patient and get two completely different results.

Strategies to address this are likely to become more commonplace in the near future. These include looking at genes that are consistently expressed across tumors and not affected by where you place the biopsy needle or by 'blending' of the tumor prior to molecular testing. As we expand our repertoire of evolutionary trajectories that are shared between patients, we envision that the link between evolution and prognosis will become better understood and will act as a predictor for risk stratification by clinicians.

Genetically unstable cancer cells can rapidly evolve resistance mutations under the selective pressure of therapy. Current approaches to mitigate this include targeting clonal mutations that are present in every cancer cell, to reduce the likelihood that a pre-existing resistant subpopulation of cancer cells will grow out. In future, it may be possible to directly target the sources of genetic instability as these are better defined: for example, the APOBEC enzyme family has been linked to subclonal mutagenesis, and inhibitors of this enzyme family are in development. Moreover, longitudinal studies, profiling the disease from diagnosis to death, may allow us to identify the 'metastatic drivers' that emerge under therapy and give rise to lethal disease.

We hope to continue working as part of a global effort at the interface of informatics and oncology, to improve understanding of cancer as an evolutionary disease and help refine its diagnosis and treatment.

Credit: Courtesy of Masoud Zamani Esteki

Masoud Zamani Esteki

Author of "In vitro fertilization does not increase the incidence of de novo copy number alterations in fetal and placental lineages"

Single-cell omics technologies and artificial intelligence (AI) are about to revolutionize our understanding of biology, including disease pathogenesis. Since the discovery of the first cell by Robert Hooke in the seventeenth century, scientists have been trying to characterize cells in different organ systems to understand their functional diversification. Until recently, analysis of bulk samples could give only an averaged readout from a population of cells. With advances in cell isolation, whole-genome and transcriptome amplification, and next-generation sequencing, the field of single-cell omics has emerged. Single-cell omics technologies provide remarkably rich information about cell-to-cell heterogeneity. Translating these observational studies into mechanisms for disease requires advanced AI-based mathematical models that integrate profiles from different molecular ('omic') layers, including (epi)genome, transcriptome, proteome and metabolome, of a single cell, and its secretome, including cell-free nucleic acids and extracellular vesicles.

My hope is that combining different molecular layers within each single cell and its secretome through AI will lead to a completely new level of understanding in health and disease. These efforts can benefit from the floods of data now being generated in international efforts, such as the Cell Atlas Project, especially if we start integrating those data with rich longitudinal phenotypes. Although this may seem far-fetched today, I believe these technologies will greatly improve the timeliness and effectiveness of prognosis and diagnosis, with treatment strategies being enriched and tailored to each individual patient. ❐

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