Voices of biotech

***Nature Biotechnology* asks a selection of researchers about the most exciting frontier in their field and the most needed technologies for advancing knowledge and applications.**

What will be the most important areas of research in biotech over the coming years? Which technologies will be most important to advance knowledge and applications in these areas? *Nature Biotechnology* reached out to a set of investigators working in research areas representative of the journal's remit and asked them to contribute their views.

Ido Amit: A holistic, unbiased view of the interactions between various cell types in physiological and pathological processes is greatly lacking. Understanding the cross-talk between different cell types in the same niche or tissue will allow more accurate models of cells, pathways and genes involved in a process or disease. Single-cell multi-omics technologies and analytics enabling increased accuracy, throughput and sensitivity provide an extraordinary opportunity for minimally biased sampling of complete tissues, with great potential to advance biomedical research.

David Baker: Improved computational methods for *de novo* protein design will enable the development of high-activity catalysts, high-sensitivity small-molecule receptors, and non-immunogenic protein therapeutics, as well as molecular machines and motors, protein lattices for growing crystals, and protein-based computers. Computationally designed protein nanoparticles will provide the basis for targeted delivery of nucleic acids and proteins and for vaccines that integrate antigens with protein immunomodulators and small-molecule adjuvants.

Roger Barker: An exciting frontier will be the undertaking of first-in-human trials with stem cell–derived neurons or glia and the direct reprogramming of cells *in situ* in the brain for treating disease. This will require the optimization of protocols to guarantee efficient, safe and reproducible reprogramming of cells to the right phenotype.

Bonnie Berger: As biotech enters the age of massive data analytics, we gain the ability to reveal biological phenomena and personalize medicine. But large, noisy data provide new challenges of scale and precision. To enable efficient and effective analyses, we need to develop technologies that allow direct operation on compressed data by taking advantage of evolutionary constraints on their topological footprint.

Carolyn Bertozzi: Mapping the human glycome meets every definition of a 'moon shot'—impossible within the confines of present-day technology, demanding contributions from diverse scientists and engineers, and critical to our goal of improving human health. Mass spectrometry, imaging and single-molecule analytics provide certain types of molecular information, but new technologies are needed to define the glycome in all its glorious complexity.


Carolyn Bertozzi

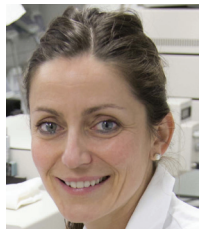
Sangeeta Bhatia: Driven by the need to speed computation, an engineering revolution has miniaturized transistors a billionfold. As clinical research and nanomedicine increasingly merge, we are beginning to understand, monitor and treat the human body via molecular conversations at the smallest scales. Continued progress will require not only convergent research in the chemical, physical and biological properties of nanomaterials but also deliberate pairing with unmet needs in medicine.


Sangeeta Bhatia


Alessandra Biffi

Alessandra Biffi: Genetic modification of hematopoietic stem cells to provide curative therapies for children with various lethal inherited diseases will grow from treating small numbers of patients into a widely available option. Crucial next steps include commercialization of these therapies together with the scale-up and optimization of currently available viral vectors and the development of feasible strategies based on gene editing.

Francesca Demichelis: We are poised to combine powerful technologies like genome-wide sequencing and gene editing to bridge research and clinical care. In the setting of precision medicine, they will likely show a synergistic effect and translate to individualized patient management. This has not been possible to date. Development of single-cell sequencing to fully and accurately map individual cell content and improved assays for non-invasive diagnostics are key elements to disentangle disease heterogeneity.


Francesca Demichelis


Andrew Doudna Cate

Jennifer Doudna

Jennifer Doudna: Exciting opportunities in genome engineering include curing human genetic disease, creating disease-resistant crops and trees, and developing fungi capable of sustainable chemical production. To advance fundamental

A full list of authors and affiliations appears at the end of the paper.

knowledge and applications of genome engineering, new technologies for delivering editing molecules into cells and tissues are needed, as well as ways of controlling DNA repair and chemical modification pathways.


Steven Dowdy

Steven F. Dowdy: Cancer is a genetic moving target that requires a therapeutic modality capable of selectively targeting all oncogenes and undergoing pharmaco-evolution to target new mutations. Although RNA interference (RNAi) therapeutics fulfill these criteria, their delivery is limited to liver. Development of anti-cancer RNAi therapeutics will require targeted delivery to malignant cells and paradigm-shifting technology to enhance endosomal escape into the cytoplasm, the rate-limiting step.


Stanford University
Drew Endy

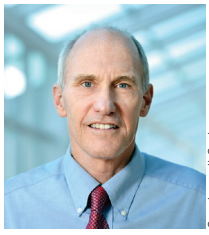
Drew Endy: Languages are systems for communicating among humans (e.g., English) or between humans and non-human systems (e.g., C++). Biotechnology is begetting a new language for scaling communication between humans and living matter, broadly defined. Over time languages tend to become free-to-use or are abandoned and go extinct. Patents are great; they expire. Languages for programming life will become free.

Moritz Helmstaedter: Neuroscience is entering the era of connectomics—exhaustive mapping of neuronal circuits at cellular resolution. Enabled by novel 3D electron microscopy and image analysis, the state-of-the-art technology is, however, still a billion times too slow for the large brains of primates and humans. In genomics, a billionfold speed gain took four decades. With sufficient acceleration, connectomics could clarify which algorithms mammalian brains employ, which diseases ensue from connectome errors, and what makes a human brain human.

Howard Junca: Our increasing ability to precisely predict, select and control the composite evolution of microbiomes toward desired functions offers a plethora of opportunities to address global sustainable development goals. The adoption of close to real-time analyses of


Howard Junca

omics surveys, novel synthetic/systems biology models and molecular engineering tools for *in situ* metagenome editing will bring closer simultaneous and refined tracking of organisms, maintenance and modulation of metabolism in complex microbial populations and finer predictions of their derived functional outputs.


Candace di Carlo
Carl June

Carl June: In the newly emerging field of cellular therapies, the most exciting frontier is the nexus between cell culture and synthetic biology. Progress in this field will rely on innovation in gene transfer technology and gene editing to deliver genetically engineered cells.


Sasha Kamb

Sasha Kamb: I think the 'bio' portion of drug discovery and development remains the biggest challenge—the lack of predictability of new medicines in patients. Although we have a broad picture of biology, we certainly lack sufficient fundamental understanding to identify disease mechanisms and interventions confidently. New technologies like ultra-high-throughput sequencing are helping to pin down at least one component of the complex dynamical system that is the human body.

Anastasia Khvorova: Despite their promise, the development of clinically relevant gene editing (CRISPR) and RNA interference (RNAi) therapies will require robust and transient delivery technology capable of targeting different tissues and cell types—the current most effective *N*-acetylgalactosamine (GalNAc) RNA conjugates solve the delivery problem for just one liver cell type. Beyond these modalities, the combination of RNA-based transcriptional modulation with nuclear oligonucleotide targeting could offer an even more powerful means of controlling up- and downregulation of gene expression.

Dae-hyeong Kim: In soft bioelectronics, minimally invasive delivery and/or skin-lamination of devices to target disease sites can solve


Dae-hyeong Kim

many unmet needs in clinical medicine. Miniaturization of high-performance sensors and actuators, modulation of their mechanical properties to match surrounding tissues, and integration of feedback therapy devices are key technologies for further advances.

Jin-Soo Kim: I am most excited about therapeutic applications of preassembled Cas9 ribonucleoproteins (RNPs) for the treatment of both genetic and nongenetic diseases. Cas9 RNPs will not be limited by host immune systems because they are degraded rapidly *in vivo* before antibodies and T cells are induced against them. Safe and efficient methods of Cas9 RNP delivery *in vivo* will be needed to harness the therapeutic potential of genome surgery.


Jin-Soo Kim

Yamuna Krishnan: Nucleic acids promise to be the molecular medium that will spawn the next breakthroughs in biomedical science. Nowhere is the frontier advancing faster than in sequencing and live imaging to understand and harness the RNA layers of gene regulation. The biggest hurdle is targeted and precise delivery of nucleic acids *in vivo*. Solve this, and we will throw open windows to new worlds.


Yamuna Krishnan


Melike Lakadamyali

Melike Lakadamyali: Understanding how the genome is organized inside the nucleus and how this organization regulates gene expression is the next frontier. Imaging technologies, especially super-resolution microscopy, will play a key role in visualizing genome organization at scales important for gene function (kilo- to megabase). In parallel, engineering tools, such as CRISPR-Cas9, will be crucial for

manipulating gene activity, as well as new methods for labeling nuclear components.

Tuuli Lappalainen: Elucidating causal genetic effects on the molecular function of the human genome can be done *in vivo* by associating genetic variants to increasingly diverse quantitative assays, scalable to hundreds of observational population samples. Integrating this approach with experimental genome editing data *in vitro* will eventually generate a complete picture of phenotypic effects of genetic variation in the human genome.


Tuuli Lappalainen

Sharon Lewin: Understanding the risks of acquiring and transmitting infection, the natural history of disease, new diagnostics and therapeutics will be significantly advanced by large data sets, systems biology and dramatic advances in high-throughput sequencing. At the other end, single-cell analyses and imaging are critical. Advances in epigenetics and gene modulation also have huge potential in infectious diseases, especially in infections that persist indefinitely, such as in my own area of finding a cure for HIV.


Sharon Lewin

James Liao: Greenhouse gas accumulation, food shortage and the cost of drugs are likely to be the key global problems in the foreseeable future. Metabolic engineering offers the most promising tools to increase carbon dioxide fixation, convert renewable carbon to fuels, chemicals and food, and produce low-cost medication.


Nick Loman

Nick Loman: Systems that integrate portable genome sequencing and epidemiological data in real time are enabling us to track how pathogens evolve and spread, and to respond to threats like Ebola and Zika. To effectively link pathogen diagnostics and epidemiology, we need superior ways of presenting heavily contaminated clinical samples to sequencers and of sequencing pathogens at high sensitivity. Exciting possibilities include miniaturized techniques for DNA extraction and human DNA depletion and micro- or nano-fluidic 'lab-on-a-chip' solutions.


Emma Lundberg

Emma Lundberg: The field of spatial proteomics is beginning to reach a point where a holistic view of the human cell can be taken, with surprisingly many proteins not only exhibiting spatio-temporal variations at the cellular scale but also appearing multifunctional or even moonlighting. Despite the continuing frustration of unreliable antibodies, recent technological advances promise transformative improvements in how antibodies and other affinity reagents are validated and used.


Lee Lynd

Lee Lynd: A convergent set of developments make it possible to foresee systematic approaches that will allow most microbes to become genetically tractable. This would vastly broaden the reach of biotech, and in particular enable accessing phenotypes that are impractical to move from one host to another. I think that lignocellulose solubilization will likely be one such phenotype.


Cathie Martin

Cathie Martin: Information is increasing exponentially on how plant metabolites can benefit health, not only as medicines but also, more importantly, as influential dietary components. Successful applications in this area will require open-access nutritional composition information on crops and foods, such that anyone can access nutritional information and the science underpinning it, to understand how to eat healthily and improve the quality of their life.

Ira Mellman: The most exciting development over the past several years has been the rise of cancer immunotherapy. In just a few years, we have seen a paradigm shift in our understanding of how best to treat cancer patients, and a whole new field of scientific investigation has been re-invigorated. With it comes the chance for real innovation. How often does one get a chance to push back a frontier when the destination has already been validated? Courageous risks should be taken.


Ira Mellman

Atsushi Miyawaki: Biotechnologies, such as genetically encodable fluorophores, for labeling cells and biomolecules have undergone a revolution in recent decades. In the future, we may see the advent of technologies for generating and sensing electromagnetic waves that resonate with specific biomolecules and enable label-free, noninvasive imaging technologies for molecular visualization in live humans.

Christine Mummery: Disease modeling with human induced pluripotent stem cells (hiPSCs) is progressing rapidly, particularly the study of genetically corrected patient cells to identify disease targets; repurposed drugs are entering clinical trials within a year of hiPSC data being published. Key technologies include new ways of integrating biophysics and immune cells into disease models, making mature differentiated cells from hiPSCs and detecting disease phenotypes. Engineering mutations into hiPSCs will help link pathological phenotypes with genome-wide association studies.


Christine Mummery


Karen Nelson

Karen Nelson: We are in the earliest stages of understanding what the microbiome means for health and disease but tremendous developments can already be seen and advances in disease detection and treatment are on the horizon. As we move forward with a goal to elucidating mechanisms, we need to integrate host phenotype and genome information with the microbiome, treating the human system as a whole.

Jeanne Paz: Optogenetic tools have been a

major revolution in bioengineering, allowing us to manipulate firing of specific cell types in real time. This has opened the possibility of turning cells on and off or altering their firing patterns to interrogate their causality in a behavioral state (e.g., seizure or sleep). The next major breakthrough would be tools to turn on or off channels or receptors to interrogate their roles in specific conditions and cell types in real time.


Pamela Peralta-Yahya

Pamela Peralta-Yahya: We have been very successful at applying directed evolution to improve proteins. Now it is time to apply directed evolution to engineer new functional cells. We need technologies to enable cellular screening at the single-cell level to reach the numbers required to obtain hits in directed-evolution experiments.


Paola Picotti

Paola Picotti: A core challenge will be to measure dynamic alterations of protein structures with high resolution on a cell-wide scale. This will provide structural markers for protein activity that can be used as powerful functional readouts for modeling biological systems and detecting pathological states. It will require automating the large-scale integration of atomic-level structural data from protein systems reconstituted *in vitro*, cell-wide structural proteomics measurements at low-resolution, and biochemical knowledge.


Kornelia Polyak

Kornelia Polyak: Single-cell manipulation and profiling are transforming our understanding of the mechanisms and importance of intratumor heterogeneity, but we still lack *in situ* profiling methods that allow the simultaneous multiparametric assessment of genetic and protein changes at the single-cell level in intact tissues. New methods are needed that would allow the quantitative (and possibly even visual) tracking of distinct cancer cell clones *in vivo*.

Kristala Prather: It's inspirational to see the many molecules being produced through the applications of metabolic engineering and synthetic biology. Advances in our ability to identify and engineer enzymes, as well as the development of novel tools for screening and metabolic regulation, will further increase the synthetic capacity of biology.


Kristala Prather


Jun Qin

Jun Qin: The most exciting frontier in proteomics would be to identify a panel of proteins, quantify 200 of them in 30 minutes from needle biopsy samples and then apply an algorithm to stratify patients into different drug response groups for precision drug treatmeants. Artificial intelligence in combination with the current most advanced proteomics technology may make this happen.


Stephen Quake

Stephen Quake: An exciting frontier is to understand the nature of cellular identity in primary tissue—how cells change identity during development, how plastic is cellular identity and how cellular identity changes in diseases like cancer. Answers to these questions will depend on technological advances in genome and transcriptome analysis of single cells.


Aviv Regev

Aviv Regev: Revolutions in single-cell omics, spatial analysis and computation suddenly put a systematic, fine-scale catalog of cell types, states and their circuits tantalizingly within reach. Spatially resolved genomics and concomitant reduction in cost coupled to systematic perturbations and new analytics on manifolds will help us build an atlas of human cells, the basic units of life.

John A. Rogers: The recent emergence of biocompatible and bioresorbable semiconductor device technologies creates many exciting new frontiers in engineering science, from the development of novel discovery tools for research in biology to the creation of advanced bio-integrated devices for clinical medicine. Improved fundamental understanding of the behavior of these systems at the biotic–abiotic interface is needed to accelerate progress.


John Rogers

Reshma Shetty: Biological engineering is entering a new era in which technical advances in synthetic biology are bearing fruit in the form of real products: perfumes from cultured fragrances, jackets from cultured spider silk, burgers from cultured meat. Rapid scaling and improvements in sequencing, synthesis and measurement technologies are going to further cement biology's place as the most important manufacturing platform this century.


Morten Sommer

Morten Sommer: The implementation of synthetic biology within industrial biotech remains in its infancy but holds great promise to transform the chemical industry, with beneficial impacts for the planet. We need to develop practical approaches for genome-wide radical refactoring and engineering of cell factories as well as portable multilayered synthetic networks for control of cell fate in industrial processes.


Molly Stevens

Molly Stevens: An exciting frontier is ultrasensitive biosensing for early disease diagnosis and to develop off-the-shelf materials for large-scale repair of complex tissues. We need more tools to help us study how cells and biomolecules interface with artificial materials at high resolution and in multimodal ways in living cells and tissues in real time.

Gustavo Stolovitzky: The analysis of complex data emerging in the life sciences is benefitting from crowdsourcing and open-science initiatives. These efforts,


Gustavo Stolovitzky

supported by cloud-enabled collaborative information technology platforms, will increasingly contribute to an objective evaluation of algorithms, leading to new biological knowledge. Leveraging the wisdom of crowds to crack the most resilient problems in biomedicine will become common practice in scientific research.

Masayo Takahashi: Exciting frontiers for the eye include the transplantation of photoreceptors, retinal prostheses and channelrhodopsin gene therapy. Gene editing will become an increasingly important technology for modifying cells in a therapeutic context. The standardization of transplantation of cells derived from hiPSCs will be accompanied by a move from autologous to allogeneic sources.

Fuchou Tang: Developing and optimizing new single-cell functional genomic sequencing technologies, especially single-cell multiple omics sequencing technologies, is the most exciting frontier for the stem cell field. We need new technologies that can repeatedly measure the exome of a single cell several times. This will profoundly increase detection accuracy and offer authentic validation of the identified features in the same single cell.


Sarah Teichmann

Sarah Teichmann: Single-cell genomics will shine a high-resolution microscope on the transcriptomes and lineages of cells, both within organisms and in contexts such as iPSC-derived cells. The next 2–5 years will see a tsunami of data from single-cell genomics technologies, which need to be coupled to good cell-capture and imaging techniques.

Maria-Elena Torres-Padilla: One key chicken-and-egg question is whether chromatin organization is instructive for cell plasticity or rather a cause of it. A second major challenge is to decipher the molecular mechanisms behind epigenetic inheritance in single cells and the features of chromatin that are truly epigenetic (i.e., perpetuate functional information). Together with advances


M.-E. Torres-Padilla

in molecular biology, biophysics and computational methods, single-cell approaches to unravel quantitative molecular relationships will be key to progress in the field.


Leena Tripathi

Leena Tripathi: To meet future food demands, we need to exploit modern technologies for improving agriculture. Biotech, along with other conventional technologies, can be applied to enhance production of staple crops, leading to improved food security, income and well-being of resource-poor people. Transgenic technology has great potential to improve agriculture, particularly in Africa, where the green revolution has had little influence.

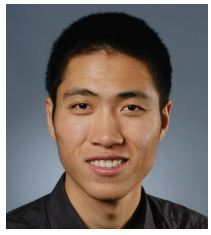

Praveen Vemula

Praveen Vemula: A holy grail in organ transplantation is prevention of rejection episodes in transplanted solid organs and vascularized composite allografts, without completely shutting down the host immune system. Addressing this problem will require not only biomaterial-based local delivery of immunosuppressants in response to inflammation but also delineation of biomarkers that differentiate infection-induced and donor-induced immune activation.


Greg Verdine

Greg Verdine: We are at the earliest stages of a revolutionary expansion in molecular forms of drugs that will redefine what medicines can do. These new therapeutic modalities will drug intractable intracellular targets, effect gains-of-function, and home selectively to target tissues via endocytic transport—and they will save and improve millions of lives worldwide. The greatest technical challenge that must be overcome is to measure drug concentrations in real time in all tissues in a minimally invasive manner at the cellular level.

Frank Vollmer: Achievement of real time, label-free detection of single molecules in solution is of ultimate importance for the development of fast and accurate biomedical assays and understanding the fundamental behavior of enzymes and other biomolecular machines. To this end, I foresee groundbreaking advancements of optical 'whispering-gallery mode' biosensors, enabling the readout of complex structural dynamics and kinetic fingerprints of single biomolecules.


Jun Wang

Jun Wang: In the upcoming years, we will see the convergence of biotech and information technology, based on big data and artificial intelligence (AI). Sequencing and other omics technologies along with biosensors are facilitating the digitization of individuals while the Internet then connects the digital 'us' in real time. AI is essential in interpreting these big data with millions of samples and will eventually transform health management and disease control in the manner of personalized healthcare, nutrition and medical care.


Jackie Ying

Jackie Y. Ying: The future of biotech lies in the large-scale culture of stem cells, primary cells and cancer cells for drug screening, in vitro toxicology, cell therapy, tissue engineering and regenerative medicine. This will require the development of new materials as synthetic cell-culture substrates and new assays for the rapid monitoring of cellular performance (e.g., cell viability, metabolism and stemness) in bioreactors.

Feng Zhang: Being able to modify the genome and to modulate gene expression precisely has enormous potential for advancing our understanding of biology, treatment of diseases and development of important agricultural products. The efficiency of making precise genetic changes needs to be increased. We need to advance our understanding of DNA damage and repair processes and to explore and harness the diversity of DNA-acting molecular mechanisms in nature.

Tian Zhang: We need to develop efficient bioprocesses to convert inexpensive substrates harmful for the environment, such as CO2, into useful chemicals. A promising strategy to achieve this objective is the design of hybrid systems that combine the extraordinary capacity of inorganic devices to collect renewable energy with the metabolic plasticity of living cells.

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