The Convergence of Chemistry & Human Biology

Chaitan Khosla

Abstract: Over the past two decades, "chemical biology" has emerged as the term of choice to describe the interface between chemistry and biology. As its name suggests, the field draws upon chemical insights and tools to understand or engineer living things. This essay focuses on the scientific, societal, and pedagogical potential of an emerging frontier for chemical biologists: namely, the study of Homo sapiens. My goal is to highlight the opportunities and challenges presented to chemistry by human biology at a time when it costs less to sequence an individual's genome than it does to buy a car. But how does chemical biology differ from other similar-sounding fields? By first reaching a clear understanding of the scope of chemical biology, we may address more pertinent questions such as: What is the promise of the emerging interface between chemistry and human biology? Why is it important to nurture the relationship between these fields? And what are the attributes of individuals and environments that are well poised to contribute significantly to this interface?

CHAITAN KHOSLA, a Fellow of the American Academy since 2007, is Professor of Chemistry, Chemical Engineering, and (by courtesy) Biochemistry at Stanford University. He also directs Stanford ChEM-H, an institute that brings together chemists, engineers, biologists, and clinicians to understand life at a chemical level and apply that knowledge to improving human health. His work on antibiotic biosynthesis and the molecular basis for celiac disease has been published in *Science*, *Journal of the American Chemical Society*, and *Proceedings of the National Academy of Sciences*, among many others.

To someone only vaguely familiar with disciplines such as biochemistry, structural biology, molecular biology, and medicinal chemistry, the introduction of yet another related name may seem unnecessarily confusing. How does chemical biology differentiate itself from these established fields? The simple answer is that it does not. Each of the aforementioned disciplines arose when a few talented and farsighted chemists pivoted from contemporary problems in chemistry (which, as we are taught in high school, attempts to explain the properties of matter by understanding its structure and reactivity at an atomic level) to emerging challenges in biology.

Biochemistry seeks to reconstitute the essence of a biological phenomenon by placing a well-defined set of molecules in a highly controlled environment such as a test tube. Not only does biochemistry play a critical role in elucidating cell function, it also facilitates deeper insight into the chemistry of life. *Structural biology* elucidates the structures of spectacularly

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complex biological molecules and assemblies at an atomic level. To do so, it employs experimental and computational tools developed by chemists in the context of studying simpler forms of matter. The pioneers of *molecular biology* harnessed their insights into DNA structure and reactivity to transform biology from an observational science into an interventional one. Finally, *medicinal chemistry* emerged as a discipline when chemists were tasked with the goal of engineering potent drugs that modulated human physiology in a targeted manner.

In its broadest definition, chemical biology exploits a chemist's knowledge of molecular structure and reactivity, together with his or her skills in molecular design, synthesis, and analysis, to understand or engineer living organisms. In essence, this represents a return to the pioneering spirit of biochemists, structural biologists, molecular biologists, and medicinal chemists from an earlier generation. The difference today is that chemistry itself has become a far more powerful science than it was half a century ago. Our knowledge of the chemical properties of large swaths of the periodic table has grown enormously. This in turn has paved the road to cost-effective syntheses of incredibly complex molecules, some of which have become life-saving drugs. Similarly, back when antibiotics were first isolated from soil microbes, their biosynthetic origins were incomprehensible. Today, we can not only decode the chemical logic of antibiotic biosynthesis, but also engineer antibiotics ourselves. Meanwhile, chemistry's analytical methods have become so sophisticated that single molecules can be visualized with microscopes and useful information can be extracted from even the tiniest sample, such as a biopsy from a patient with an undefined illness. In this way, chemical biologists harness the evolving science of chemistry to interrogate or modify biology.

The interface between chemistry and human biology holds considerable promise for science, medicine, and society. At a fundamental level, chemistry can strengthen the foundations of human biology in a manner that is entirely analogous to its enabling role in many of biology's most notable advances in the twentieth century. Human beings are different from other living creatures (and indeed, even from each other) in many interesting ways: our brains, our diets, and our immune systems are just a few examples. Explaining these differences in the language of chemistry is a scientific frontier that has proven to have profound consequences for human health. Imagine a future where it is possible to meaningfully discuss the chemical basis of specific thoughts and emotions; or a time when our understanding of the immune system is deep enough to interpret its constantly changing responses to the effects of aging, diet, and infection on each of us. The age-old debate of nature versus nurture has taken on a new meaning with the discovery of epigenetic phenomena that can be passed on from one generation to the next. Unraveling this epigenetic code represents an exciting opportunity for chemical biologists to penetrate the mysteries of complex illnesses.

The chemistry–human biology interface also holds a special place in the future of drug discovery, development, and evaluation. As human beings struggle to reconcile their dreams for healthy aging with the need for cost-effective healthcare, innovative medicines are expected to be the panacea. A surprisingly large fraction of efforts to translate groundbreaking biological discoveries into patient care are bottlenecked by the lack of suitably engineered molecules or molecular assemblies. By focusing on problems where innovative molecular design, synthesis, or analysis is crucial, chemistry can accelerate the translation of advances in human biology into

clinical practice. Take, for example, the field of infectious diseases. At a time when our armamentarium of effective antibiotics has reached alarmingly low levels, our knowledge of nature's repertoire of antibiotic biosynthetic strategies is exploding. Chemical biology is poised to exploit these insights to engineer pathogen-specific therapies. Consider also the field of radiology. New chemical probes and measurement methods such as MRI (magnetic resonance imaging), PET (positron emission tomography), and ultrasound have the potential to noninvasively visualize human anatomy and physiology effortlessly and at unprecedented resolution. Equipped with an unimaginably sophisticated set of accessories and apps, the iPhone of the future may be just as important a communication tool between healthcare consumers and providers as its present-day version is between two teenagers. Chemical biologists are also opening new doors in preventive medicine. Until recently, vaccines were principally used to protect against deadly or debilitating infectious diseases. Today, synthetic vaccines are being developed against cancer and allergy. Our bodies also play host to innumerable bacterial cells (collectively referred to as the "microbiome") whose myriad health benefits remain to be understood and perhaps even engineered. Last but not least, regulatory science represents an attractive but overlooked area for applied chemical biological research. By upgrading the capacity for risk-benefit analysis at agencies such as the FDA, innovative medicines could be brought to patients who need them the most, more cheaply and quickly than is currently possible.

Perhaps the most far-reaching impact of the convergence between chemistry and human biology will be at a pedagogical level. Recent years have witnessed a gradual de-emphasizing of organic chemistry in pre-medical education. While it is difficult to envision a resurgence of interest in chemistry in mainstream medical education, dual strengths in chemistry and medicine could foster a new breed of physician-scientists who are also physical scientists. Their talent for molecular design and analysis, coupled with their passion for human biology, would allow them to play leading roles in reshaping the healthcare industry.

Several compelling examples point toward the opportunity that lies ahead at the chemistry–human biology interface. A recent report on innovation in drug discovery, development, and evaluation by the President's Council of Advisors on Science and Technology highlighted both the continuing need for innovative medicines as well as widespread concerns about their development pace and cost.[1] The report proposed doubling the current annual output of innovative new medicines as an ambitious goal. While most industry watchers will concur that seventy to eighty innovative new drugs per year would indeed represent a dramatic increase in research and development productivity, two other figures put the importance of this goal into clearer perspective. First, of the roughly 23,000 proteins encoded by the human genome (the functions of as many as half of which remain unknown), fewer than 3 percent are targeted by FDA-approved drugs. Targeting proteins in the human body is by far the most productive approach to drug design. Second, there exist at least 10,000 diseases identified by International Classification of Diseases (ICD) – including more than 6,500 "orphan conditions" (disorders, often rare, for which drug development is commercially nonviable) – which lack effective therapies. Together, these numbers suggest that, at the present pace of drug discovery and development, the road to even a moderately comprehensive arsenal of human-grade drug treatments may be a long one. More

fundamentally, in sharp contrast to biological studies on virtually every other model organism, human biology remains predominantly an observational science. Given that genetic manipulation of human beings is likely to remain severely constrained on ethical grounds, the nexus between chemistry and human biology needs to be strengthened in order for human biology to advance from its present status as a principally observational science into an interventional one.

Another argument supporting a serious re-evaluation of the chemistry–human biology interface is the current state of the pharmaceutical industry. The high cost of bringing a new drug to market (which, by some accounts, can run as high as $500 million) has forced the industry to prioritize discovery of the highest-priced medicines over new paradigms for affordable healthcare. The time is ripe for the emergence of new ideas and technologies that could spawn complementary business models and public-private partnerships to restructure the healthcare industry. The emergence of a thriving molecular biomarker industry is one example. Chemical biology could foster other analogous opportunities in the not-too-distant future. For example, innovations in molecular toxicology will be pivotal to the success of personalized medicine. Similarly, companies that harness the creativity of both chemistry and human immunology to develop fundamentally new approaches to preventive medicine will likely blaze new trails not too different from those forged by the pioneers of the Internet era.

Meanwhile, two technological advances – genome sequencing and stem cell culture – are not only propelling the emergence of *Homo sapiens* as one of biology's most attractive targets of investigation but are also making a strong case for a closer, intellectually deeper alliance between chemistry and human biology.

The first relates to the ease of sequencing the entire genome of a human being. The National Human Genome Research Institute estimates that the present cost of sequencing an individual's genome is under $10,000; this number is expected to fall by at least an order of magnitude in the foreseeable future. It is therefore very likely that, before too long, every healthcare consumer will be able to have his or her entire genome sequenced for the price of an MRI. The question now becomes: how can one exploit this information to enhance disease management or, better yet, healthy living? Cost-effective decoding of this data may well be one of chemical biology's greatest contributions to our society since the sequencing of the genome.

Biologists have independently developed ways to produce induced pluripotent stem cells (iPSCs): cells derived from adult humans that have been genetically reprogrammed into an embryonic stem cell–like state. Notwithstanding the infancy of this technology, iPSCs have the potential to revolutionize human biology, and leading medical centers are rushing in to establish facilities for routine generation of patient-derived iPSCs. The ability to use stem cells as individualized test tubes to understand, prevent, or treat disease represents an extremely promising opportunity for chemical biology.

Although its promise is clear, the field of chemical biology has not, to date, reached its full potential. Much effort focuses on harnessing robust chemistry in conjunction with high-speed engineering platforms in order to quickly translate emerging biological knowledge into new chemical tools. This is important work from which new drugs will inevitably emerge.[2] However, the real promise of chemical biology lies in two other pursuits. At a fundamental level, chemical biology can help elucidate what causes derangement of human physiolo-

gy in the first place. There is growing consensus that complex diseases such as autism and autoimmunity are caused by genetic as well as environmental factors. If so, chemical biology may be able to shine light on the interplay between these triggers. And at the technological level, radically new molecular tool-making approaches are needed to transform knowledge of the biology of seemingly intractable diseases into practical treatments. Consider cystic fibrosis and von Gierke's disease (a glycogen storage disorder): the mutations responsible for these debilitating conditions were identified more than twenty years ago. Yet today we are no closer to translating these genetic insights into cures or even good treatments. The defective molecules in cystic fibrosis and von Gierke's disease are just two examples of scores of clinically relevant targets categorized as "undruggable" by today's drug discoverers. The human chemical biologist, on the other hand, recognizes that the reason why these genetic discoveries have fallen short is because the right kind of molecular tool has not yet been invented – but it can be done.

Several prominent academic institutions (including my own, Stanford University) have launched major initiatives at the chemistry-biology interface within the past decade. In most cases, these programs are collaborative efforts between existing chemical and biological science departments within the institution, although a few examples of cross-institutional efforts have also gained momentum. The ideal environment would bring together clinicians, scientists, and engineers, all of whom share an interest in strengthening the chemical foundations of human biology. These scholars will likely be either gifted molecular scientists or engineers who have turned their attention to important challenges in human biology, or they will be insightful biologists or physicians who can frame human biology's most fascinating mysteries in a manner that lends itself to chemical analysis or engineering. Bringing these researchers together is essential in order to encourage cross-fertilization of ideas and cultures. Environments where such collaborations occur will inevitably emerge as spectacularly powerful training grounds for a new breed of young "physician-scientist-engineers." These researchers will speak about human biology in the language of chemistry, tinker with objects on a length-scale one million times smaller than the width of a human hair, and only show deference to the laws of thermodynamics. Their talent for molecular tool-making, coupled with their passion for human biology, will allow them to evolve new industries and business models where health, not sickness, drives the bottom line.

Each fall, I find myself facing a class of around two hundred of Stanford's most accomplished undergraduates taking their first course in biochemistry. I begin my first lecture with the reminder that, up until today, my students' chemical and biological educations have been orchestrated from separate universes, but this is about to change. After all, biology is chemistry, and chemistry would be not nearly as interesting were it not for biology. Many of my students go on to become successful doctors, scientists, or engineers. I can only wonder whether any of my students will someday return to Stanford as clinician-scientist-engineers. If so, what problems will they see that none of us do? And will they see fundamentally new solutions to problems that the rest of us consider unsolvable? I look forward to that day.

ENDNOTES

1 President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation," Executive Office of the President of the United States of America, September 2012.

2 For a review of academic drug discovery operations, see Julie Frearson and Paul Wyatt, "Drug Discovery in Academia – The Third Way?" *Expert Opinion on Drug Discovery* 5 (2010): 909 – 919.