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Future Horizons in Drug Discovery Research

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The current state of the pharmaceutical industry, with its lower than expected productivity as measured by FDA approvals, has been clearly documented elsewhere, as well as the corresponding effects upon limiting employment opportunities for medicinal chemists. With that context in mind, here is a long-term perspective on drug discovery research, out to 100 years in the future. Any such musings are by nature tenuous and speculative, as it is impossible to know what events will intervene that could dramatically change the very fabric of human society in the next 100 years, such as financial instabilities, conflicts, and weather-related events. On the other hand, predictions on events 100 years in the future will transcend the lifespan of all but a few of those now being born who are alive today, so there is no way to be definitively proven wrong by any who read this during my or their lifetimes.

One way to project the future 100 years of biomedical research is to consider changes that have occurred in the century prior to the present time. Up until the passage of the first Pure Food and Drug Act in 1906, it was possible to sell morphine, cocaine, or heroin without them being labeled as such. Top-selling pharmaceutical agents 100 years ago contained heavy metals such as arsenic or mercury. Salvarsan was the leading drug in 1912, an arsenic-containing drug discovered by Ehlrich and Hata in 1909 and introduced into the market by Hoechst in 1910 for the treatment of syphilis. Salvarsan was thought to contain an As=As double bond but was shown in 2005 to be a mixture of cyclic 3- and 5-membered ring As−As single bond-containing species. The design process to obtain Salvarsan involved iterative medicinal chemistry optimizing efficacy and water solubility, a forerunner to the structure−activity relationship (SAR) development campaigns of the present day.

The most successful drug of all time, and certainly of our time, is Lipitor, which is just now converted to generic status after having produced >$14 billion in sales. The discovery processes for Salvarsan and Lipitor were similar but only in the broad outlines of iterative SAR development, preclinical efficacy testing, and positive treatment outcomes in patients. The scope and scale of the two research programs are dramatically different. First, our focus now is on organic drug substances, as inorganics are generally relegated to cytotoxic anticancer drugs or contrast imaging agents. Although the time between initial preparation and commercialization of Salvarsan was ∼1.5 years, today, this transition will require 8−12 years. The much larger number of researchers, much greater cost involved, the extensive profiling required for regulatory approval, and advantages required relative to standard of care relative to an established formulary of already approved drugs have exponentially expanded and complicated the drug development process over the past century and rightfully so for the safety of patients. As Ehlrich pointed out from his own experience "the step from the laboratory to the patient's bedside...is extraordinarily arduous and fraught with danger."

The pharmaceutical industry is currently in a classic industry consolidation phase, with high levels of generic substitution and niche targets such as relating to orphan indications capturing a greater fraction of the whole. The pharmaceutical industry today can be compared with the agricultural chemical industry of ∼15 years ago, and the steel industry of the 1960s−1970s. In such cases, the margin to be achieved by value-added intellectual contributions is diminished by generic substitutions by others elsewhere competing on price with equivalent or close to equivalent perceived quality. There will continue to be a need for new drugs for indications not presently adequately treated or to provide disease modification and not just symptomatic relief and to address drug resistance or genetically engineered bioterrorism among infectious diseases. Here is a short list of predictions for what drug discovery will look like 100 years in the future.

Drug Discovery To Be Conducted Largely in the Public Sector. Where early stage drug discovery research occurs will return to the world of 1912 and Paul Ehlrich, with most basic innovation taking place in the public sector such as at universities and nonprofit research institutions. Capital intensive preclinical and clinical drug development will continue to be done by the for-profit organizations that can exploit networks of production, distribution, and marketing. This trend is obviously in full force now, as large pharmaceutical companies are reducing their early drug discovery research operations. Numerous drug discovery centers have emerged in the public sector primarily at universities, attempting ostensibly to capitalize on the funding to be achieved by licensing products externally while taking advantage of internal innovation. The tools and processes involved in drug discovery are now more of an off-the-shelf commodity-driven operation than previously. The more productive chemists in the department at the start of my career submitted ∼30 compounds per year; now, with the tools of parallel synthesis, it is common to prepare >200 compounds per year. Diversity is now more important in early library design and synthesis than fidelity in structure and purity of any particular member. Techniques such as fragment-based drug discovery in medicinal chemistry and high-content screening in pharmacology seek to produce more information while doing the same amount of work. As long as safe laboratory practices are followed, certain trained high school and undergraduate chemists can perform the work that some Ph.D.s were asked to do 10−15 years ago. Knowledge has become more of a commodity, as the Internet has allowed us to instantly create

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Increasing Focus on Noncommunicable Diseases (NCDs) for the Poor. The emphasis upon new treatments for communicable diseases such as malaria, HIV, and tuberculosis has been and is admirable. Relatively effective treatments currently exist to treat AIDS, with the greatest challenge being affordability and distribution. De novo drug discovery to treat diseases that have previously been truly neglected such as trypanosomiosis are getting more attention from the WHO and elsewhere. However, the WHO has recently additionally recognized that the NCDs such as cardiovascular disease, diabetes, cancer, respiratory diseases, and neurological disorders are now also a great emerging and emerging epidemic *among the poor* (Reardon, S. A World of Chronic Disease. *Science* **2011**, *333*, 558). Of the 57 million deaths occurring worldwide in 2008, 36 million (63%) were due to NCDs, of which 80% of these occurred in low- and middle-income countries. NCDs do not thus primarily afflict the first or developed world, they are primarily diseases of the developing world and will be much more so in the future. Mortality due to NCDs is projected to increase 15−20% worldwide to the year 2020, whereas mortality due to communicable diseases is projected to decrease in absolute numbers from the present time. As children are saved from dying of malaria, they grow up to most likely suffer from a NCD requiring chronic therapeutic intervention. The WHO convened a high-level meeting to address the NCD epidemic in September, 2011, only the second such meeting to be held, with the first one associated with HIV/AIDS.

Focus on NCDs of the Elderly. More effective health care worldwide is resulting in increased life expectancies. Coupled with lower birth rates, populations of the future will have larger mean age values and numbers of elderly individuals. Chronic age-associated diseases such as Alzheimer's, diabetes, Parkinson's, macular degeneration, and ALS will increase in prevalence.

Radioprotection as a Target in Drug Discovery. Over the course of the next 100 years, release of radioactivity to large patient populations such as at Fukushima, Japan, may occur due to terrorist attacks, a full-scale or partial nuclear engagement during conflict, or by accident. There are currently four drugs with approved INDs for acute radiation syndrome (ARS), to ameliorate the effects of ionizing radiation after exposure. A prevalent molecular mechanism for radioprotection is to protect mitochondria from reactive oxygen species damage, such as by GSK-3β inhibition, a very similar therapeutic modality as for treatment of many of the neurological disorders. Radioprotective agents are also useful for the protection of normal tissue against collateral damage in radiation oncology.

Resource Disparities and Impact. We have now passed the milestone of 7 billion persons on planet earth. In spite of hunger and deprivation in parts of the world, it is remarkable that most of humanity has adequate food and shelter. The UN projects that using a "medium-fertility variant" of 2.0 children per woman, the population on earth will reach ∼10 billion by the year 2100 (*Science* **2011**, *333*, 540). A medium variant of 2.5 children per woman results in ∼15 billion persons in 2100. The resources on earth, while substantial, are limited, and over the next 100 years, we will have passed the projected midpoint of the extraction of readily available sequestered carbon sources to power our fuel-based economy. It is most likely that communities of the future will rely to a greater extent than now on local production for local consumption. The effect on drug discovery research is that cost of goods will be a greater component to drug candidate selection than before. It may not be possible to charge the equivalent of $20,000 per year for a costly treatment regimen for large patient populations, especially for the NCDs for which chronic treatment over many years is required. Under current patent law, by the year 2112, every drug whose patent was filed before 2091 will be generic. Some have suggested that the way in which new compositions are protected by monopoly-granting patents for diseases should be abandoned or modified, especially for the neglected diseases for which there is limited commercial return. Low cost chemical production coupled with efficient quality control and distribution will be the essential elements of our ability in the future to treat the large fraction of humanity that will not be able to afford more expensive treatment options. Combination therapy with cheaper complementary and alternative natural remedies may help to promote wider availability of therapeutic relief options.

Climate Change. It is well understood that the climate is warming and the oceans are rising. The apparent impact of these trends on drug discovery will be a greater prevalence of the tropical diseases such as typhus and malaria. Although this is true, as long as vector control such as for lice and mosquitos continues as a high priority, these diseases should not spread dramatically.

Personalized Medicine and New Developments Not Anticipated. Personalized medicine is expected to be more prevalent in the future, with genotypic screening to precede drug treatment. More accurate dosing should occur based upon real-time monitoring of exposure and understanding of the relative propensity for drug metabolism in any particular patient. The exploitation of new chemical scaffolds would be based on the structure elucidation of natural products yet to be identified. Atypical targets such as the protein−protein interface and nucleic acid binding transcriptional regulators will be more prevalent, as will the use of phenotypic screening and induced pluripotent stem cells in research. Protein- or gene-based approaches may gain greater acceptance. Nanotechnology as well as the use of molecular motors for tissue repair on a microscopic level could emerge as complementary to small-molecule and biologic therapy. Then, there is the "Who can possibly predict?" factor, for revolutionary new developments currently not anticipated. Science is great fun, and the "unexpected" is the driving force of new discovery.

■ SUMMARY

One can imagine a very vibrant scientific community 100 years from now using an incredible wealth of established genetic and pharmacological data on the molecular basis of disease. In the absence of the discovery of new cures, NCDs such as cancer, diabetes, and Alzheimer's disease will be prevalent throughout the world, with the greatest impact upon the poor. Low cost production and ready distribution of agents to treat all disease categories will be as important then as drugs to treat AIDs and malaria are now.

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Notes

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