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On Sources and Implications of Accelerating Innovation in Biotechnology: U.S. Opportunities and Challenges

Testimony for the U.S.-China Economic and Security Review Commission[1]
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This statement describes the development of synthetic biology and genomics within the United States and China, analyzes opportunities and challenges facing the United States and suggests how the United States might better support high-quality, advanced biotechnology research and industry development going forward.

Section I: Biotechnology Fundamentals

This section reviews sources and consequences of extraordinarily rapid change in biotechnology, with attention to:

* How advances has been enabled by a "great conjunction" of improvements in DNA sequencing and synthesis; data storage and access; pattern recognition methods; tools for redesign of organisms; and tools for gene editing; and
* How foundational advances are enabling applications including synthesis of fuel, feedstocks, scents, drugs and flavors; redesign of food crops and livestock; somatic and germline gene therapies; control of vector borne diseases; and remediation of damaged environments.

Section II: U.S. and China Policy Comparisons

This section describes how the United States, China and other major nations have supported research and industry development, with comparisons of:

* Motives for priority development of biotechnology sectors;
* Policies to develop capacity, including research funding and educational policies;
* Regulations that address privacy, security, safety and environmental concerns; and
* Policies designed to foster or limit international flows of technology.

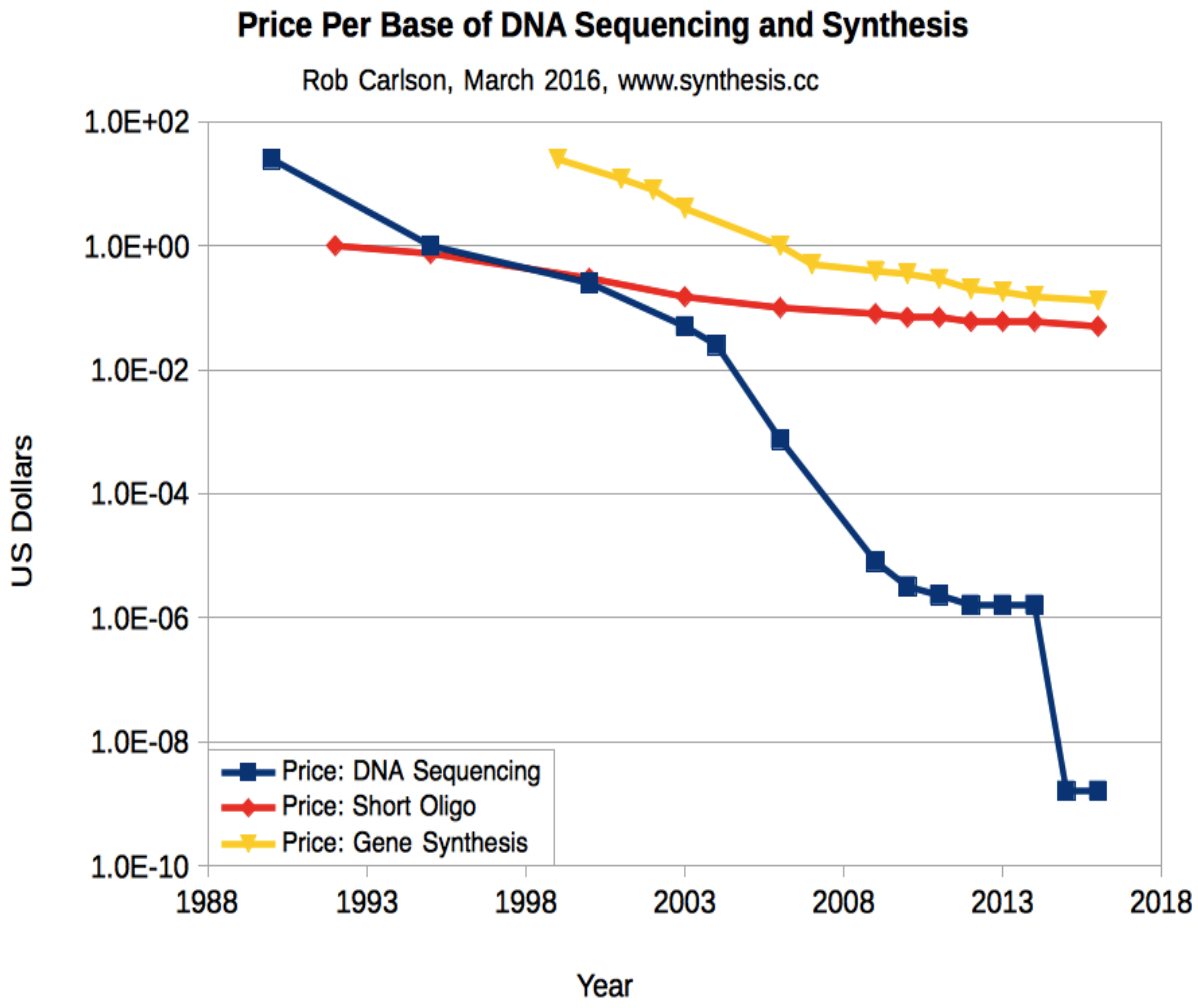
Section III: U.S. Policy Options

This section offers policy recommendations for sustaining U.S. innovation in biotechnology with regard for competitive economic interests and for common safety, health, security and environmental concerns.

[1] The author would like to express his appreciation to Samuel Weiss Evans, Michael Fischer and Edward Woll for their comments. The views expressed are the author's alone and do not represent commentators, the MIT Program on Emerging Technologies, the MIT Synthetic Biology Center, the MIT Center for Biomedical Innovation, the MIT Internet Policy Research Initiative, the MIT-Broad Institute Bio-Foundry, the International Genetically Engineered Machine Competition (iGEM), or the Engineering Biology Research Consortium (EBRC).

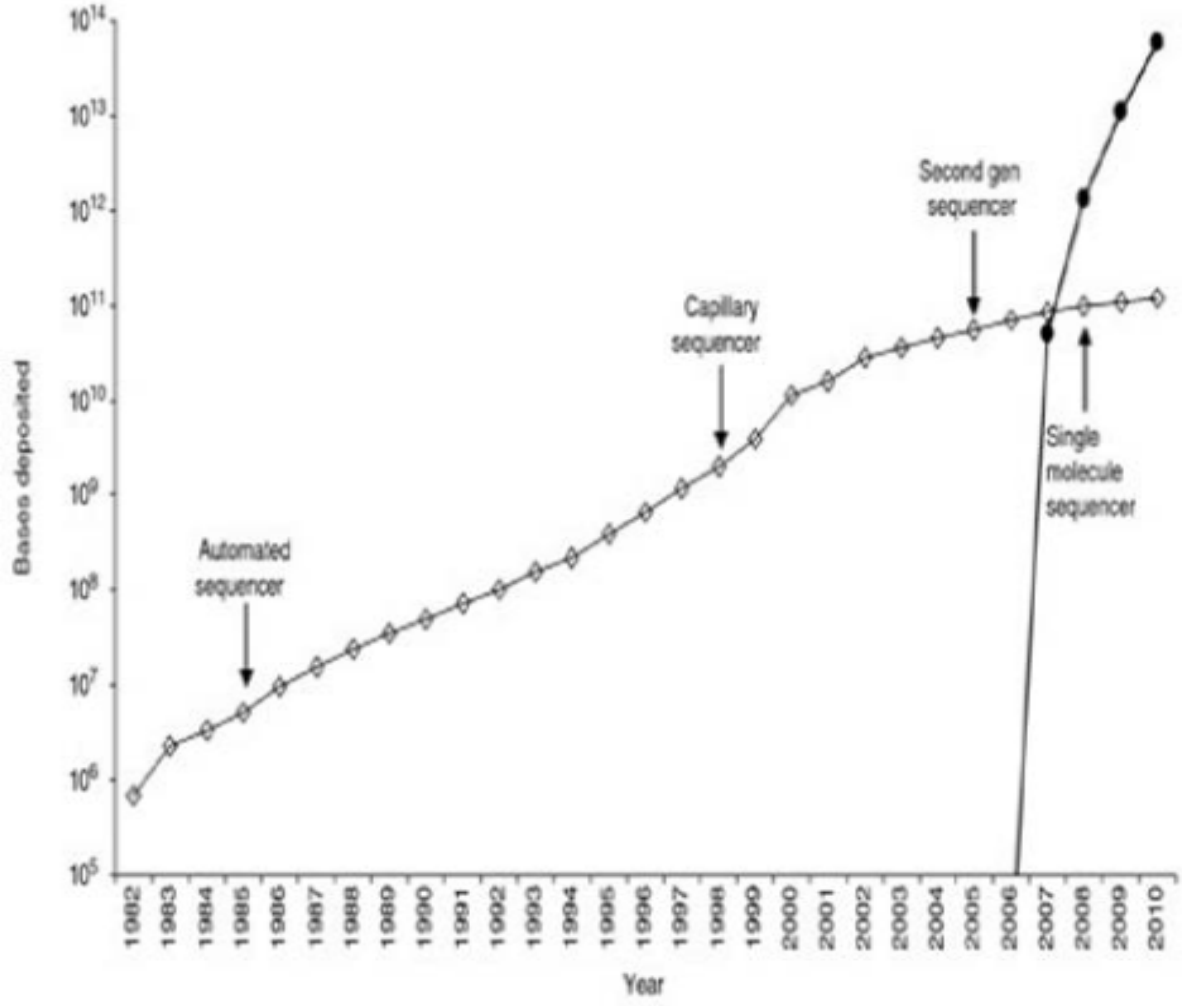
Section I: Explaining Rapid Innovation in Biotechnology

In the past five years, the field of synthetic biology has come of age. Tales of unrealized promise have been supplanted by partially and fully realized applications in agriculture, materials synthesis, and therapeutics, with next generation bio-remediation of contaminants, control of invasive species, and limitation of vector borne diseases on the horizon. This remarkable burst of innovation has been enabled by an unusual conjunction of several technological developments.



First, the efficiency of DNA sequencing and oligo and gene synthesis has increased dramatically. In the figure above, compiled by Rob Carlson, the vertical axis is an exponential. Reductions in the cost of sequencing, shown in the blue line, are at a rate that makes Moore's law look slow.[2]

[22] http://www.synthesis.cc/synthesis/2016/03/on_dna_and_transistors



Second, the revolution in sequencing has, in turn, fostered an explosion in the amount of genomic data deposited in data bases. In the figure above, also with an exponential vertical axis, genomic information deposited rockets upward.

Third, the revolution in applied biotechnology has also been enabled by improved access to phenotypic information and health care records that are linked to genomic information including the spread of electronic health records.

Fourth, the development of advanced computational tools has aided in inferring the effects of genetic alterations and in constructing data bases on the functions served by genetic elements and parts.

Fifth, the development of software tools to aid in the redesign of biological systems such as SGI Archetype have improved the predictability and reduced the cost of producing blueprints for biological engineering.

Finally, improved gene editing tools have greatly reduced the cost of translating blueprints into alterations of genetic material and have increased the accuracy of alterations. The development of CRISPR-Cas9 by the Doudna group at UC Berkeley and Zhang and Church groups at MIT-Harvard-Broad represents a substantial improvement over zinc fingers and talens. Further advances in gene editing tools including base editing are certain to come.

It is important to note that the revolutionary pace of change in biotechnology is the product of all of these developments, not improvements in gene editing tools alone. We can expect further acceleration in biotechnological innovation as synthetic biology comes to interface more effectively with systems biology.

These advances in fundamentals of biotechnology have enabled a broad range of applications. MIT technologists are developing nitrogen fixating non-legumes and Aquabounty has developed a variety of salmon that is more efficient in converting feed into fish. Firms have modified algae to produce low value biofuels and redesigned yeast to produce high value anti-malarial drugs, scents, and flavors. Laboratories at Stanford, University of California and Concordia have even created pathways in yeast to convert glucose into hydrocodone and morphine. The Church lab at Harvard took a large step toward xenotransplantation by using multiplex gene editing to eliminate over 60 Porcine Embedded Retro-Viruses (PERVs). Medical researchers now have over 300 somatic cell gene therapies under development and a team at Sun Yat Sen University has attempted human germline modification for a genetic blood disorder. Finally, teams in London, San Diego and MIT are developing gene drive technologies to edit the genes of plants and animals in wild populations, with the potential to contain vector borne diseases and to eradicate invasive species.

The blurring of the line between information technology and biotechnology is fundamental to most of these applications. For example, Manolis Kellis of MIT combined genomic, phenotypic and health record information and applied advanced methods from artificial intelligence to generate an hypothesis on the location of an obesity switch, then tested his proposition through gene editing, culturing cells and conducting trials on animals. Access to and analysis of information is now as critical to biological engineering as editing, splicing and synthesizing genes.[3]

[3] "FTO Obesity Variant Circuitry and Adipocyte Browning in Humans," New England Journal of Medicine 2015; 373:895-907September 3, 2015DOI: 10.1056/NEJMoa1502214
http://www.nejm.org/doi/full/10.1056/NEJMoa1502214?rss=searchAndBrowse#t=article

Section II: Comparing U.S. and Chinese Biotechnology Policies

This section describes how the United States, China and other major nations have supported research and industry development, with comparisons of:

- Motives for priority development of biotechnology sectors;
- Policies to develop capacity, including research funding and educational policies;
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- Policies designed to foster or limit international flows of tech2.

Why is China seeking to develop its biotech sector? China's motives for development of biotechnologies are similar to those of the US, Europe, Japan, and India. All OECD nations and most rapidly industrializing developing countries have made development of biotechnologies a priority. Across the board, there is recognition of the increasing economic significance of biotechnology in materials fabrication, redesign of plants and animals for production of food, and development of advanced therapeutics.

China's interest in biotechnology is also driven by peculiarities of Chinese circumstance. The need for enhanced efficiency in agriculture and aquaculture is stoked by the scarcity of arable land and water. The need for cleaner fuels is stoked by world class pollution problems with rapid growth and dependency on coal and traditional biomass and by dependency on imported oil. The need for advanced methods of environmental remediation and restoration is stoked by loads imposed by traditional methods of reprocessing E waste and recycling paper and metals. Most fundamentally, advanced biotechnologies are a key element of Chinese plans to substitute high value clean sectors for low value dirty manufacturing.

China's interest in advanced biotechnology is also driven by a belief that this is an area where China can excel relative to the U.S. and Europe. As other nations commit resources to biotechnologies, China has advantages that may contribute to competitive success over the long term. Relative to the US, Chinese enjoys an advantage with respect to excellence in secondary level STEM education and the ability to direct substantial public resources to biotechnology sectoral development. Relative to Europe, China enjoys an advantage in ability to tune regulations and policies on privacy, intellectual property and environment.

How is China building its domestic capabilities in biotechnology?

Public financial resources are being used to develop industrial and educational infrastructure. The emergence of firms like BGI as the lowest cost highest volume gene sequencing firms in the world and the emergence of high quality synthetic biology educational programs in top tier and second tier Chinese universities and the headline advances by Chinese researchers in areas such as human germline modification have been fostered by strategically coherent and substantial infusions of funds. Official numbers on Chinese public funding are both hard to come by and are inherently suspect. While it is clear that Chinese public funding for development of biotechnologies is significant and has had substantial effects, we do not have a credible basis for determining whether it is commensurate with U.S. public funding via DARPA, IARPA, NIH, DoE and NSF.

Chinese biotechnology firms have been active in international mergers and acquisitions to secure ownership of key technologies. For example, back in 2012, BGI substantially enhanced its

capacity for sequencing by acquiring Complete Genomics for $120 million. [4] More recent acquisitions appear to also improve market access as well as ownership of technologies. ChemChina acquire Syngenta AG for about $43 billion. Humanwell Healthcare Group acquired Epic Pharma for $550 million. Creat Group Corp acquire Bio Products Laboratory Ltd., a maker of human blood plasma products in the U.K., for $1.2 billion. Shanghai Fosun Pharmaceutical Group Co offered to India's Gland Pharma Ltd., which is focused on injectable drugs.[5]

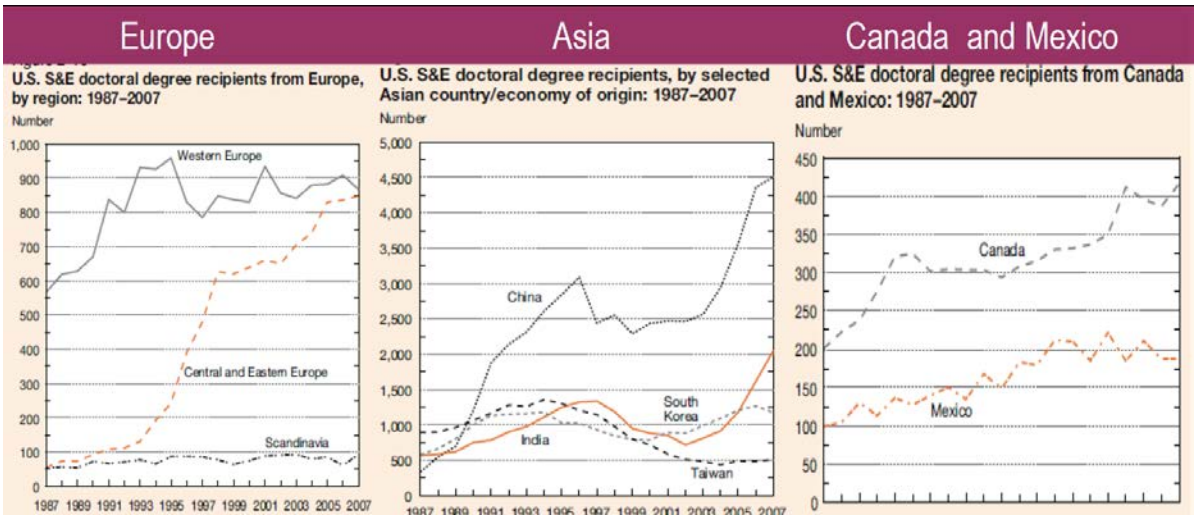
The effect of regulatory differences on development of biotechnology is complex. Chinese rules on environmental protection appear to be far less constraining than equivalent regulations in Europe, where uncontained agricultural and environmental applications of synthetic biology are effectively barred, and slightly less stringent than regulations in North America, with less clear standards for presentation of evidence on environmental effects. Chinese rules on biosecurity appear to be less stringent and explicit than U.S. equivalents, with DURC policies governing research and Australia Group guidelines on licensing and documentation governing transborder movements. Chinese rules on privacy and data utilization are unclear, but appear to be less restrictive than U.S. or European protections. On balance, it appears that Chinese firms are likely to have greater freedom to operate than their US or European counterparts, but the opacity of regulations and firm level practices precludes definitive statements on this point.

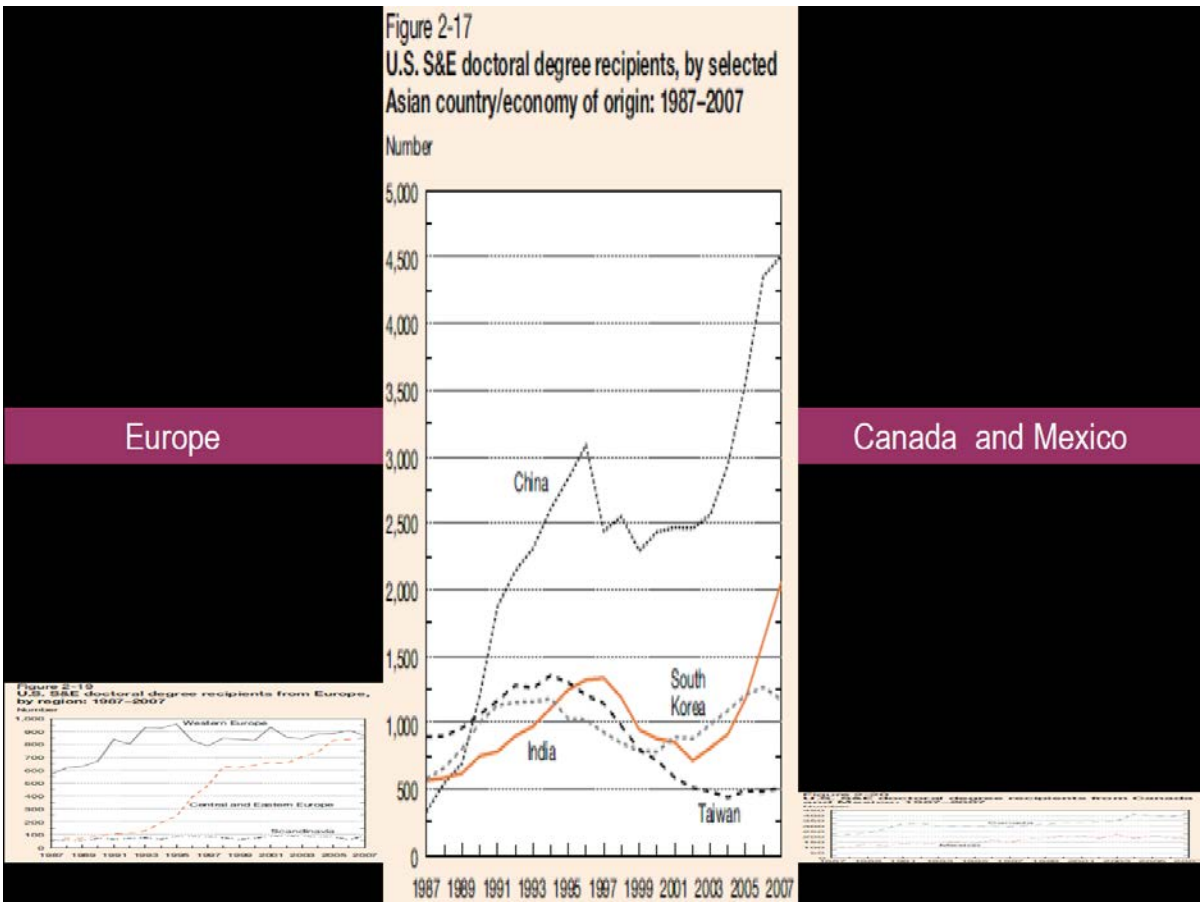
What relationships have Chinese firms, research institutes, or universities developed with U.S. universities and research institutions in biotechnology?

Chinese universities have engaged in a typical array of international exchange and outreach activities, with research partnerships with US, European and Japanese counterparts and with substantial participation in international educational collaborations. The most significant educational activity is Chinese participation in U.S. doctoral programs in biological engineering, molecular biology, systems biology, chemical engineering and computer science. To provide some sense of the scale of Chinese engagement in U.S. S&E education, consider the following figures.

[4] https://dealbook.nytimes.com/2012/09/17/chinese-company-to-acquire-dna-sequencing-firm/ and https://www.genomeweb.com/sequencing-technology/bgi-halts-revolocity-launch-cuts-complete-genomics-staff-part-strategic-shift

[5] https://www.bloomberg.com/news/articles/2016-07-05/china-inc-goes-on-a-buying-spree-for-global-health-care-assets



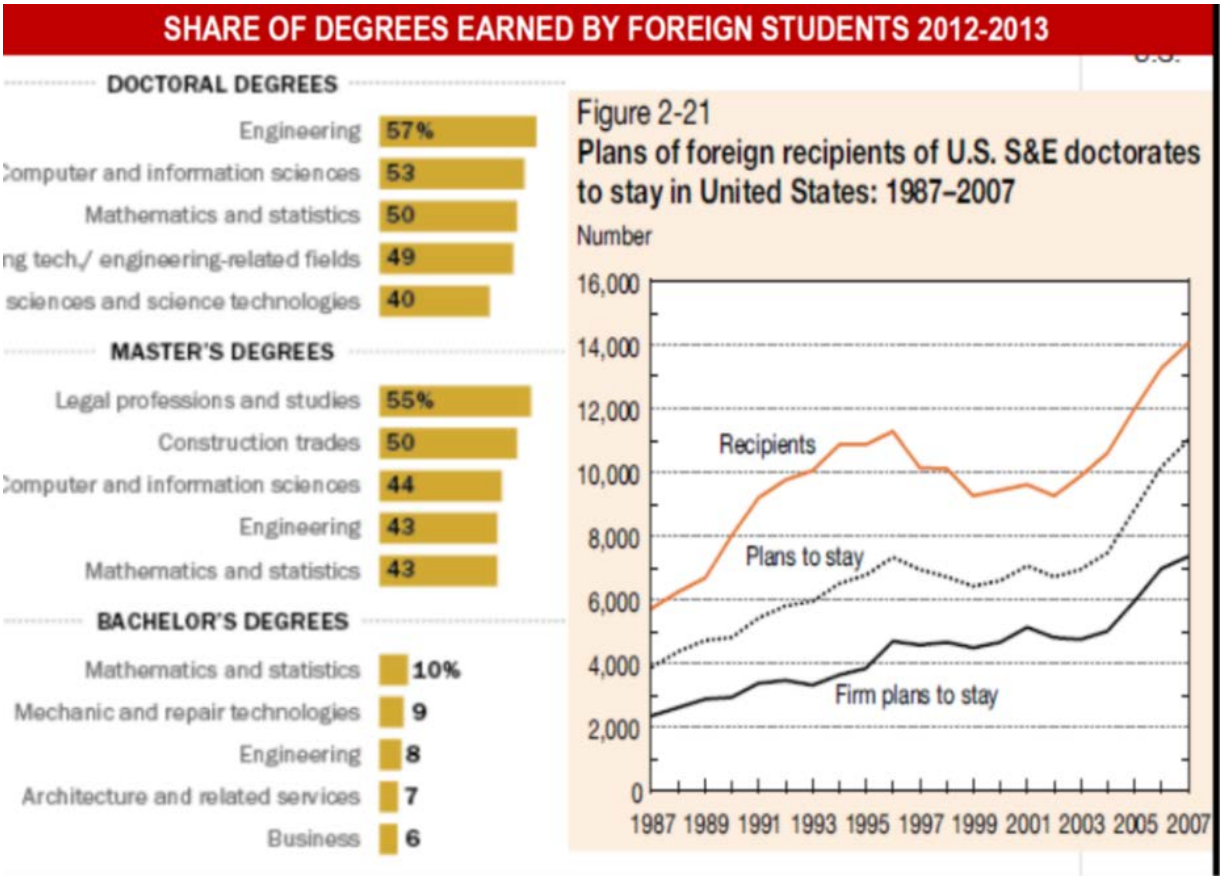


The first figure above presents international student data in S&E doctoral programs by region of origin. The second figure presents the same data rescaled on equivalent vertical axes to underscore the extent to which Chinese students are found in U.S. doctoral programs.

International collaborative activities appear to be valued highly by the government of China. One informal indicator may be found in the International Genetically Engineered Machine

Competition (iGEM), where the number teams from China increased from 30 out of 230 in 2013 to 60 out of 300 in 2016.[6] U.S. partners have structured collaborative relationships to address some risks. For example, the FBI and iGEM have cooperated in developing a biosecurity and biosafety program to reduce the risk of malicious or accidental misuse of biotechnologies. Firms and universities typically take care to protect intellectual property from appropriation, but many firms and academics have failed to take even the most basic precaution of applying for patents in China. Finally, academic researchers and scholarly journals continue to have difficulty defending themselves against fabricated research and clinical data from researchers in all settings including China. The problem of irreproducible results is not unique to the PRC.

How have these relationships benefited U.S. researchers or advancements in the field? Are there potential collaboration, research and development, exchange opportunities that should be pursued? What challenges remain?



As the figure above suggests, a high proportion of Chinese students who come to the US for graduate study would like to stay in the U.S. after they secure their degrees. CRISPR inventor Feng Zhang immigrated to the U.S. from China as a child. At present, the U.S. benefits from this combination of education and immigration. Over the longer term, as educational programs, standards of living and research opportunities in China improve and more students choose to return to China, this imbalance favoring U.S. interests will decline. Such was the case with

[6]http://igem.org/Team_List?year=2013 http://igem.org/Team_Wikis?year=2016

Japan, Korea and Taiwan as the proportion of students choosing to stay in the US declined as opportunities at home improved. Such will be the case with China.

How will these developments affect U.S. global competitiveness and national security?

Movement toward technological parity is likely with some effects on U.S. economic competitiveness and national security. The current preeminence of American biotechnology will decline as domestic Chinese capacity increases and as technology diffuses from the U.S. to China. The effects of these developments on U.S. competitiveness and security are complex.

The central issue is the extent to which superiority in biotechnology translates into market power and political power. This is not an area where cornering markets or forming cartels is viable. No country including China and the U.S. will be able to dominate biotechnology. The ability to do first rate biological engineering is diffusing rapidly from the U.S. to many other countries including China. This is most evident in the iGEM competition, with its exponential growth in numbers of participants and extraordinary gains in the quality of work. While some view the magnitude of technology transfer as a critical problem, the ease with which biotechnology is moving and developing in many centers suggests that this is not an area where cornering markets or forming cartels is viable. Efforts to exercise market power through collusion to extract rents, through the strategic denial of access to secure political leverage, through the control of strategic inputs into weapons systems seem likely to strengthen incentives for entry. It is difficult-to-impossible to withhold a cure for cancer, a method of producing a fuel, a drought or blight resistant strain of rice or a yeast strain that produces a pharmaceutical. Lasting advantages will be hard to obtain and harder to defend. Technological genies with the potential to address substantial environmental, economic and health problems will proliferate and cannot be captured by any one master. This is the good news.

But the good news on economic effects is the bad news on security effects. If diffusion of relevant skills, technologies and data is a hallmark of emerging biotechnologies, then it will be difficult to check the potential for malevolent or unintentional misuse of advanced biotechnologies by nations, groups or individuals. Potential misuses include the modification of existing pathogens to increase virulence, with H5N1 gain-of-function adjustments as a possible model for other diseases; circumvention of materials controls through synthesis of a listed pathogen; production of controlled substances; and novel threats that I do not wish to discuss in an open hearing. Because advanced biotechnologies cannot be stuffed back in the bottle and will diffuse, addressing potential security risks is a wicked difficult problem.[7]

[7] "What rough beast? Synthetic biology, uncertainty, and the future of biosecurity" Gautam Mukunda, Kenneth A. Oye and Scott C. Mohr Politics and the Life Sciences Vol. 28, No. 2 (September 2009), pp. 2-26 https://www.jstor.org/stable/40587998?seq=1#page_scan_tab_contents; "0n Regulating Gene Drives" KA Oye, K Esvelt et al, Science 08 Aug 2014: Vol. 345, Issue 6197, pp. 626-628 DOI: 10.1126/science.1254287http://science.sciencemag.org/content/345/6197/626; "On Regulating Home Brew Opiates" KA Oye, C Lawson, T Bubela, Nature 18 May 2015 http://www.nature.com/news/drugs-regulate-home-brew-opiates-1.17563

Section III: U.S. Policy Options

The U.S. current enjoys significant advantages relative to China in terms of clusters of innovation, the openness of U.S. educational and research systems, and continuing utilization of talents of international students. The options offered below include policies that the U.S. should take to strengthen these advantages and wrong actions that the U.S. should avoid to avoid weakening these advantages.

A. Do – Recommended Policies

A1. Enhance data access and sharing while protecting privacy: At present, U.S. development of advanced therapeutics is impeded by limits on effective access to genomic, phenotypic and health care records and by the side effects of privacy protections on ability to curate data. The U.S. should consider adopting an "opt out" system modelled on Finland to enable more effective utilization and curation of data for purposes of medical research.[8] Considerations should be given to international pooling of data to enhance medical research.

A2. Address Security Commons Problems: The U.S. should expand current activities and initiatives directed at strengthening international norms and conventions that prohibit malicious misuse of biotechnologies, including the US Department of State Biosecurity Engagement Program, expand the institutional capacity of the UN Biological Weapons Convention, enlarge FBI programs with iGEM, and strengthen the Australia Group Guidelines with explicit attention to drawing China into the Australia Group.

A3. Address Environmental Commons Problems: The U.S. should expand current activities and initiatives directed at generating early information on potential environmental benefits and risks and fostering national actions and international agreements to mitigate risks.

A4. Address Pharmaceutical Licensing Problems: To improve management of safety and efficacy over the life cycle of drugs and to improve competition in smaller-and-smaller treatment groups, the U.S. should move toward adaptive pathways in pharmaceuticals licensing, based on FDA experience with Breakthrough Product Designation and accelerated approval and with Health Canada and European Medicines Agency experience with adaptive licensing pilots.

A5. Expand Research Funding for Fundamental Research: DARPA, IARPA, NIH, DOE and NSF funding for applications of synthetic biology should continue with expansion of funding for the development of fundamental tools and methods and for work to assess environmental, security and safety risks. This should include strengthening and expanding the USDA-FDA-EPA BRAG program.

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[8] "The next frontier: Fostering innovation by improving health data access and utilization," KA Oye et al, Clinical Pharmacology and Therapeutics, 10 September 2015 http://onlinelibrary.wiley.com/doi/10.1002/cpt.191/abstract.

A6. Implement Reforms of Coordinated Framework on Biotechnology: In 2016, the White House OSTP completed an evaluation of the Coordinated Framework on Biotechnology, with active engagement of industry, academia, regulators and civil society. Ongoing interagency consultations on unresolved matters should be continued.

B. Don't – Avoid these Policies

B1. Resist the impulse to extend DURC guidelines and to expand the scope of classification. Moving sensitive research behind closed doors would have the effect of limiting free and full evaluation of claims on benefits and risks of genomic research and would stoke concern over possible state led activities in tension with obligations under the UN Biological Weapons Convention.

B2. Resist the temptation to strengthen or weaken IPR protections. The current intellectual property rights system is of necessity an imperfect response to the complex tradeoff across creating incentives for investment through private ownership vs facilitating synergism through sharing. Both are requisites of innovation. Major adjustments to the IPR system are likely to increase ambiguity and uncertainty to the detriment of both private investment and synergistic sharing.

B3. Resist the temptation to limit the number of international students entering U.S. doctoral programs, to extend "deemed exports" and to cut visas for graduating students in a manner that would reduce the appeal of the U.S. academic-industrial complex to student immigrants. The current system has produced an extraordinary burst of innovation that has strengthened the U.S. economy.

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