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The Shifting Currents of Bioscience Innovation

William Hoffman

Department of Laboratory Medicine and Pathology, University of Minnesota

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Abstract

Arising from its roots in the US, biotechnology today is a global enterprise. Cutting-edge tools are transforming traditional models of drug discovery and development and diagnostic testing. They are enabling the potential for large-scale production of renewable fuels, biodegradable materials, safer industrial chemicals and food crops grown under harsh conditions. The practice of technological innovation in the industrial era – the systematic application of ideas, inventions and technology to markets, trade and social systems – is now being joined with the code of life through rapid DNA sequencing and synthesis technologies. The pace of bioscience innovation is also influenced by geographic concentration of research, entrepreneurship and investment (clusters). Policy makers are just beginning to consider and debate the implications of the new biological technologies: the promises they hold for global public health, natural resource conservation, and economic growth, and the risks they pose from their power and accessibility around the world.

Policy Implications

- Geographic expansion of bioscience research, its tools and 'users' will spur innovation and shape policy in the field.
- Innovative business models are needed to bring ideas to market in the biosciences, particularly in drug development.
- Public understanding of the new biological technologies as geo-technologies is essential for their proper governance.

Biotechnology as geo-technology: entering a game-changing era

Five hundred years ago the Columbian Exchange linked continental ecosystems together, facilitating the global dispersion of animal, plant, microbial and human genes.[1] Today the genomes of most of the major domesticated animals and plants and infectious disease pathogens in the Columbian Exchange have been fully (or nearly) sequenced (Table 1). In our Genomic Exchange era, animal, plant and microbial as well as human genetic and regulatory sequences travel around the world over high-speed data networks, a profound and disruptive advance for biotechnology.

Tools from the revolution in molecular biology developed in the 1970s and 1980s launched the biotechnology industry. Commercial use of these tools now contributes more than US$300 billion per year to the US economy alone by one estimate (Figure 1). Newer biological technologies like genomics and synthetic biology are positioned where molecular biology was in the 1970s and 1980s and are just beginning to be applied commercially. These technologies are geo-technologies, automated bioanalytical and biosynthesis instruments and systems often linked to data networks.

The DNA code of decoded organisms leads a double life: one in their cells, another outside their cells in data storage, analysis and transfer systems. Thousands of human beings including infants have been fully decoded over the past decade, with the number expected to grow exponentially as sequencing technologies grow in productivity and decline in price (Figure 2). The expected 'big data' deluge from genomics and other 'omics' poses a major data processing and analysis problem to be solved before precise, individualized medicine achieves its promise.

As digital and biological technologies continue to converge (Figure 3) and as information science and engineering move ineluctably into the domain of biology, the universe of 'users' will swell. It will encompass not only academic and corporate scientists but also entrepreneurs in startup companies, high school students in science labs and amateurs working in community labs, shops, garages and basements. That is a game-changing mode for global bioscience innovation – for diagnostics and

Table 1. Genes in transit from Columbus to global data networks: Key species of the Columbian Exchange and their genome

Types of Organism	Old World to New World	New World to Old World	Sequence reported	Base pairs (billion)*	Genes (protein encoding plus others)*
Human	*Homo sapiens*	*Homo sapiens*	2001	3.230	39,900
Domesticated animals		alpaca	2010	1.90	25,000
	cat		2007	2.460	20,300
	chicken		2004	1.070	17,500
	cow		2009	2.70	27,100
	dog		2005	2.530	24,400
		guinea pig	2012	2.720	24,300
	horse		2009	2.470	22,900
	pig		2012	2,810	26,200
	sheep		2001	2.860	24,000
		turkey	2010	1.050	16,000
Domesticated plants	apple		2010	1.870	-
	barley		2012	5.10	30,400
		cassava / manioc	2012	.420	30,700
		chile pepper	2013	3.50	37,000
		cotton (New World)	2012	.770	41,000
	grape		2007	.490	25,600
		maize / corn	2009	2.050	39,400
	oil palm		2013	1.550	34,800
		pineapple	2012	-	25,000
		potato	2011	.840	39,000
	rice		2011	.380	30,500
		rubber	2010	2.10	69,000
	sorghum		2009	.740	33,500
	soybean		2010	1.10	50,000
	wheat		2012	17.0	94–96,000
Infectious disease agents	bubonic plague (*Y. pestis*)		2001	.005	4,300
		Chagas disease (*T. cruzi*)	2005	.090	25,200
	chicken pox (*V. zoster*)		1986	.001	73
	cholera (*V. cholerae*)		2000	.004	4,000
	diphtheria (*C. diphtheriae*)		2003	.003	2,400
	leprosy (*M leprae*)		2009	.003	2,800
	malaria (*P. falciparum*)		2002	.002	5,500
	measles (measles virus)		2000	.002	6
	smallpox (Variola virus)		1996	.0002	200
		syphilis (*T. pallidum*)	2010	.001	1,100
	typhus (*R. prowazekii*)		1998	.001	900
	whooping cough (*B. pertussis*)		2011	.004	3,900
	yellow fever (Aedes flavivirus)		2009	.001	2

Note: Genomic sequencing ranges from low to high coverage and from initial drafts to well-characterized genomes based on multiple studies.

Crosby, A.W. (1973) The Columbian Exchange: Biological and Cultural Consequences of 1492. Westport, CT: Greenwood Press.

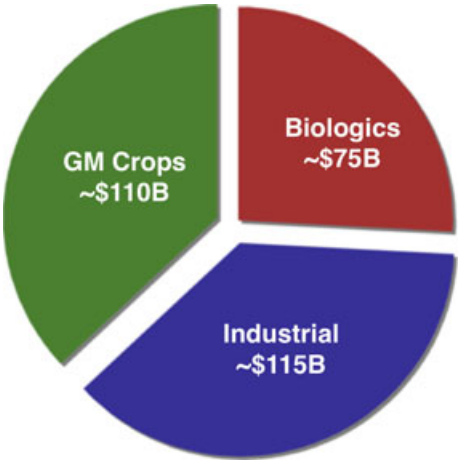
NCBI (2013) Genome Resources website, National Center for Biotechnology Information, National Institutes of Health. Available from: http://www.ncbi.nlm.nih.gov/genome [Accessed 11 April 2013].

CoGePedia (2013) Sequenced plant genomes. Available from: http://genomevolution.org/wiki/index.php/Sequenced_plant_genomes [Accessed 11 April 2013].

Plus select references concerning individual species published in peer-reviewed scientific journals and by sequencing consortia.

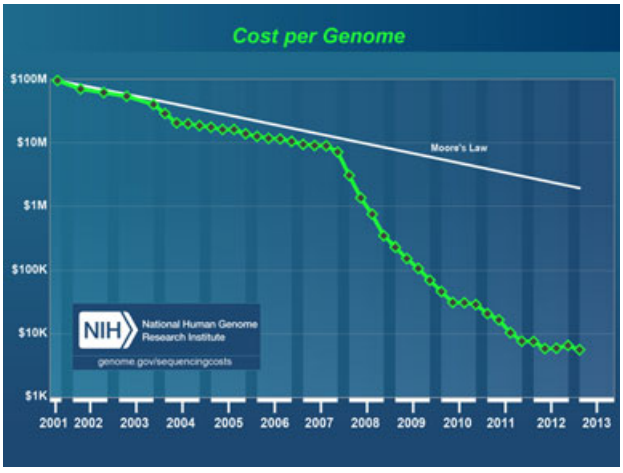
**Numbers rounded off.*

Figure 1. Breakdown of the contribution of biotechnology to the US economy.



Source: Carlson, R. (2011).

Figure 2. Cost trend of sequencing a human-sized genome and Moore's Law.



Source: : Wetterstrand (2013).

drug development, industrial and agricultural bioengineering, and public and environmental health. The convergence of biological and digital technologies, as discussed below, reframes how and where innovation in the field is done and points to some unique problems such innovations pose for global governance.

Gravitational shifts and patent cliffs

As experimentation and decoding reveal biology's complexity, that complexity will require new models for bringing ideas to market. At the same time markets themselves have entered a new dynamic. The pharmaceutical industry accounts for most of the global life sciences economic output. With an estimated 3 to 6 per cent compound annual growth rate, drug making is projected to be worth US$1.2 trillion globally by 2016 (IMS Institute, 2012). The industry's largest markets remain the US and Europe, but its fastest growing markets are 'pharmerging' countries like Brazil, China, India, Russia, Mexico, Turkey, Argentina, South Africa and Indonesia. They are where the industry is focusing its future growth.

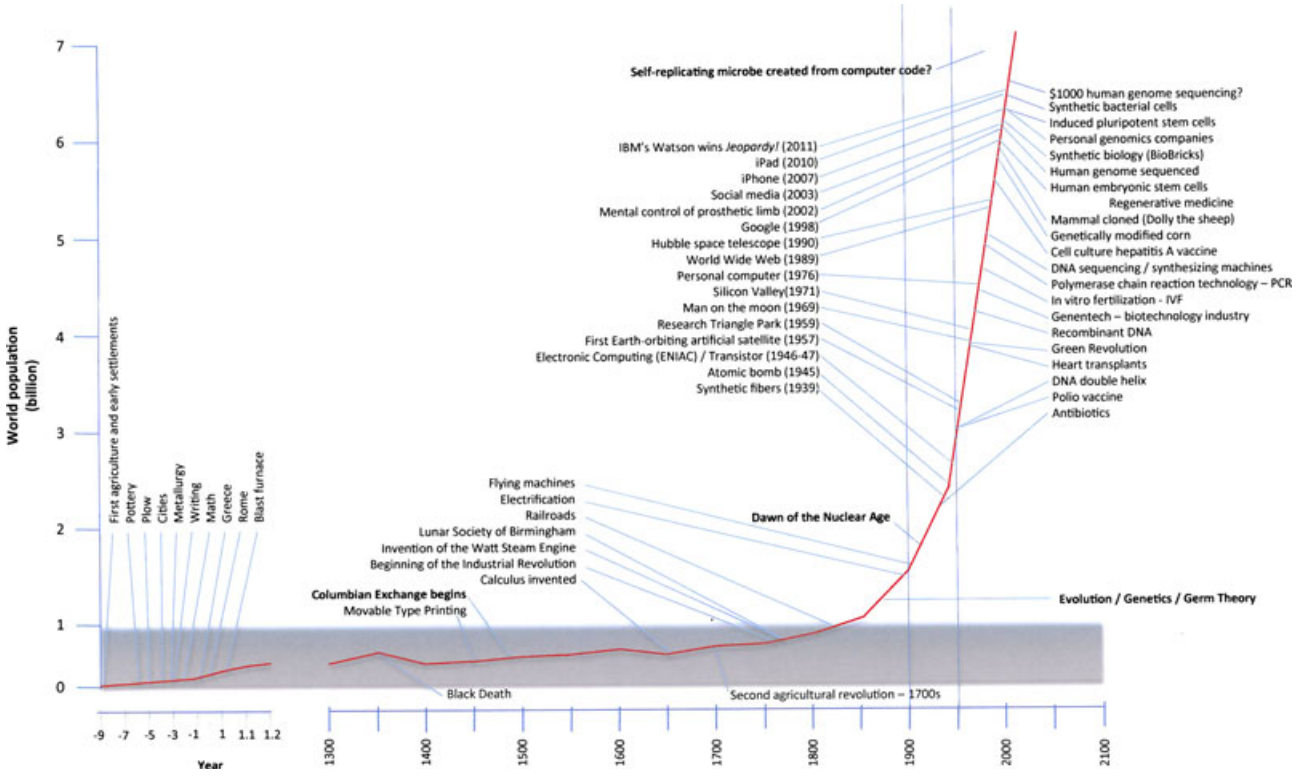
The world economy's centre of gravity has been migrating eastward for three decades, reflecting rapid growth in incomes of the vast populations of India, China and the rest of East Asia (Quah, 2011). Rapid income growth enables technological development and the drive to seek competitive advantage including through public policy. The Supreme Court of India shook the pharmaceutical world by ruling that Novartis AG's blockbuster cancer drug Glivec did not merit patent protection.[2] The ruling was yet more evidence that the traditional model of pharmaceutical innovation is no longer suited to an era of expanding overseas markets, a rapidly rising middle class in developing countries, and health cost-control pressures facing governments around the world. Problematic public policy and court rulings in fast-growing markets come on top of a decline in pharmaceutical research and development (R&D) productivity (Scannell et al., 2012) and the 'patent cliff'.[3]

Open-access organizations and systems are making inroads into traditional practices of bioscience innovation. Australia-based Cambia seeks to aerate the compact patenting terrain with knowledge-sharing tools (Patent Lens, BiOS) that foster collaboration in agricultural biotechnology and global health.[4] Precompetitive cooperation brings companies with common interests and substantial resources together to develop novel technology platforms and derive mutual advantages from them (Mullard, 2011). Enlight Biosciences, for example, is backed by Lilly, Merck, Pfizer and other drug firms in its efforts to spin out start-ups from its platform technologies. Sage Bionetworks is building a biology information commons for precompetitive drug development using open systems, incentives and standards, key features of a game-changing paradigm.

Life technologies enter the fast lane

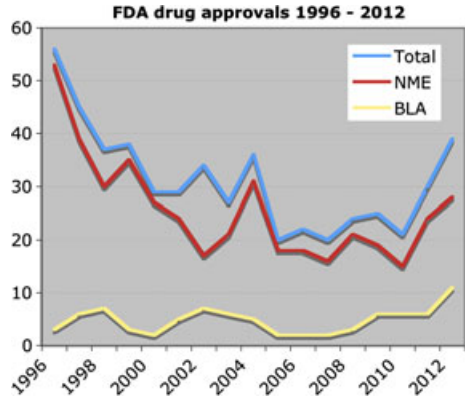
Products arising from molecular biology constitute a growing share of the global economy with each passing year as technologies evolve, markets expand and production processes are improved – the therapeutic protein production world, for example, 'is becoming flatter' (Kelley, 2009). Biopharmaceutical companies anywhere in the world now have access to a consensus-processing platform that features high cell densities and high levels of protein expression, combining to increase bioreactor production capacity and reduce costs. A US$100 billion plus global market predicted to double in several years,

Figure 3. Journey of *Homo innovaticus* since the dawn of agriculture highlighting recent advances in technology and bioscience.



Source: William Hoffman and Leo Furcht with the assistance of James Hudak, Oxford University Press, 2014. Modified from Figure 1 of Fogel (1999).

Figure 4. New molecular entities (NMEs) and biologics license applications (BLAs) approved by the US FDA.



Source: William Hoffman and Leo Furcht, Oxford University Press, 2014.

biologics now represent a quarter of recent drug approvals in the US (Figure 4).

Cutting-edge tools from genomics and bioinformatics, cellular technologies including stem cells, and synthetic biology, with assists from nanotechnology and automation, are poised to revolutionize bioscience productivity. These tools make it possible to sequence and synthesize DNA at an industrial scale, edit genes precisely, control the growth and differentiation of cells and seed them in three-dimensional (3D) constructs, and create microbial factories that produce medicines, chemicals, fuels and materials. They are transforming traditional models of drug discovery and development and diagnostic testing. The more DNA, RNA, and cellular components fall under the purview of bioengineers, the likelier we are to see large-scale production of renewable fuels, biodegradable materials, and safer industrial chemicals.

Genomics is opening a window on genetic alleles that enable food crops to adapt to a changing climate, and synthetic biology is being used to design novel environmental remediation systems. Using 3D printers puts science into the hands of people 'whether in the far corners of Africa or outer space' so that they can print drugs on demand.[5] They can be modified to print cells including stem cells, which are key to cellular differentiation and tissue repair. Digitally enabled bioprinting means on-demand tissue and organ production for surgical modelling, medical therapy, drug testing and science education.

In short, the practice of technological innovation in the industrial era – the systematic application of ideas, inventions and technology to markets, trade, and social systems

– is now being joined with the code of life, DNA, and the basic unit of life, the cell. The cell has been outfitted with transistor-like logic gates[6] that can in theory connect it to an entirely different knowledge domain – that of the US$2 trillion global electronics industry. The potent combination of genomics and 'big data' capture and analysis is making initial inroads into global health care, a multi-trillion dollar enterprise. Genomic sequencing is already a valuable tool for monitoring potentially devastating global biothreats like pandemic flu.[7] Meanwhile, mobile devices that carry applications for community health reporting, biomedical research and personal genomics have made their debut.

The persistence of place in game-changing bioscience

Ever since ancient Uruk, the first city, urbanization, concentration, and population density have gone hand in hand with innovation. The growing international dimension of scientific R&D, enabled by high-speed networks, vast databases and data mining tools, and open-source initiatives, does not mean bioscience industries are no longer so concerned about 'place'. The globalization of scientific culture has not yet 'leveled the playing field' for startups, spin offs, or expansions of existing firms.

So place still matters, at least for the foreseeable future. Bioscience startups continue to show a strong tendency to cluster in specific regions with strong research assets and an entrepreneurial culture. The top ten innovative biotech startups in 2012, based on the series A round of venture capital funding, were US companies, most located in the traditional biotech hubs of the San Francisco, Los Angeles, and Boston-Cambridge regions, and all of them located near research universities and hospitals (Huggett, 2013). Research and clinical megacentres such as the Boston-Cambridge region in Massachusetts with its numerous research hospitals are magnets for drug and medical device entrepreneurship because they capture in one place the complex knowledge value chain (Cooke, 2007).

Technology clusters that join entrepreneurship with finance, support services, research and education tend to emerge spontaneously over time. Around the world, nations and regions have tried to seed clusters by building incubators, accelerators and science parks, typically near research facilities (Rinaldi, 2006). Because clusters are examples of complex adaptive systems that exhibit increasing returns to scale, settling on a set of criteria that defines exactly what biotech clusters are has been challenging.[8] The question of whether they actually can be successfully seeded in the biosciences may be answered by Singapore's multi-billion dollar Biopolis science park.[9] Singapore can be seen as a fulcrum for India–China cooperation in the fields of pharmaceuticals and biotechnology, a regional hub where vast pools of talent from India and China interact, taking advantage of the large markets of Southeast Asia, South Asia and China. Regional networks of emerging research economies are changing the global balance of research activity (Adams, 2012).

Venture capital (VC) investment is a key barometer of the entrepreneurial health of technology-based industries. The fact that the number of private biotech companies in the US and Europe has been basically flat (3,361 in 2007 and 3,294 in 2011) has led some to suggest that venture capital is being more evenly spread around the world (Huggett, 2012). Analysts of VC and private equity-backed investments in companies making innovative health care products in the emerging markets of Brazil, China, India, and South Africa from 2000–2012, however, found that activity is low (about US$1.7 billion in total during that period). In contrast, their governments and multinational and domestic pharmaceutical companies invest about US$14 billion in R&D in these countries annually (Chakma et al., 2013). Of the top ten destinations for venture capital and private equity invested in 2011, all involved North America, Europe, Japan or Australia with the sole exception of Singapore (Ernst & Young, 2012), probably a reflection of the city state's strong protection of intellectual property rights (Atkinson, 2013).

As the VC universe consolidates in the west, VC industries in China and India are growing (Ernst & Young, 2012). The question is whether, and if so how soon, they will turn to investing substantial sums in life sciences startup companies. A startup and scale-up culture is the foundation upon which a cluster can emerge. Another question is whether developing economies can forge public–private partnerships to spur bioscience entrepreneurship like those the Gates Foundation catalyzed in antimalarial drug development.[10]

Biomolecules and bioscenarios: Brazil, China and India

The global expansion of biomolecular manipulation and production is another game-changing development. Among the emerging economies, Brazil, China and India are well positioned in terms of resources, technologies, human capital and domestic and foreign investment to play leadership roles in different bioproduction sectors: Brazil in advanced biofuels, China in mass production aspects of biomedical research and industry, and India in biogeneric drugs.

Brazilian sugarcane is one of the highest yielding biofuel feedstocks in the world. Converting sugarcane to ethanol has become highly efficient (Eisentraut and Waldron, 2011). Sugarcane based renewable jet fuels emit a fraction of the greenhouse gases that fossil-derived jet fuels emit.[11] Through its Brazilian subsidiary, the US firm Amyris, Inc. uses an industrial synthetic biology platform of engineered yeast to convert sugarcane's

plant sugars into a renewable farnesene-based fuel for existing, unmodified diesel and jet engines. Brazilian airliners and city buses have successfully tested the fuel.

The world's largest producer of human, animal and plant DNA sequences is BGI in Shenzhen (formerly Beijing Genomics Institute). It generates an estimated 10–20 per cent of total global output from its bank of more than 150 state-of-the-art sequencing machines (Larson, 2013). It lists among its partners the pharmaceutical giant Merck in biomarker discovery for drug development and the Gates Foundation in agricultural genomics and global health. Shanghai's Fudan University is home to one of the largest animal research operations in the world. Its mouse facility houses 45,000 cages with as many as five mice per cage (Wines, 2011). The facility is the Chinese arm of the Fudan–Yale University biomedical research partnership with its mission of mapping the mouse genome using a mass production gene knockout technology.[12] If all goes as planned, each mouse gene will be assigned to performing a specific role in the mouse's body. Massive gene role assignments in mice would have major implications for human health.

India's competitive advantage in small-molecule generic drug production appears to be carrying over to biogeneric drugs (biosimilars, follow-on biologics) despite dramatically different production processes and the difficulty of mimicking a branded biologic. Highly skilled scientists and technicians, low manufacturing costs, English proficiency, and the country's generic drug manufacturing and distribution infrastructure help position India to become a global leader in biogenerics, as do favorable public policy and court rulings. Biologic drugs worth an estimated US$80 billion in global sales are expected to go off-patent by 2015 (Virk, 2012).

Innovation, evolution and governance: navigating uncharted waters

The disruptive nature of converging technologies was highlighted when the first bacterium hosting a synthetic genome replicated successfully, an event reported by J. Craig Venter's laboratory in 2010. In that instant the worlds of digital technology and biological evolution were irrevocably bridged. In the future the programming language of the cell, nature's 3.5 billion-year-old search engine, will be used for designing, building and producing things through the directed evolution of biosynthetic pathways. Cellular components and genetic networks, integrated with computational platforms, can be imagined as the biological successors of the standardized parts of the machines that launched the Industrial Revolution and the machines that have kept it going ever since.

In their joint report on the future of global governance, the US National Intelligence Council (USNIC) and the EU's Institute for Security Studies (EUISS) identified biotechnology as one of three over-the-horizon issues that is likely to rise in importance and will demand a

Table 2. A simplified representation of global bioethical issues related to the development of biological technologies since the US Food and Drug Administration first approved a genetically modified food in 1994

Bioethical issue	Technology	At issue	Opposition	Most concerned	Ethics reference
GM crops	Molecular biology	• Environment • Human health • Food	• Greenpeace • Organic food industry	Europe India Africa	Weale, 2010
Human embryonic stem cell research	Stem cell biology	• Human dignity • Human health	• Anti-abortion groups	Germany US	Furcht and Hoffman, 2011
Engineering the bioeconomy	Synthetic biology	• Environment • Biosecurity	• ETC Group* • Friends of the Earth**	US EU UN	PCSBI, 2010 EGE, 2009
Genetic privacy	Genomics	• Human privacy	• Privacy groups	US Canada EU UN	PCSBI, 2012

*Notes: *The ETC Group (Action Group on Erosion, Technology, and Concentration) is an international organization dedicated to 'the conservation and sustainable advancement of cultural and ecological diversity and human rights.' Available from: http://www.etcgroup.org. [Accessed 1 November 2013].*
***Advocates a moratorium 'on the release and commercial use of synthetic organisms until there is a better understanding of the risks and appropriate regulations are in place'. Available from: http://www.foe.org/projects/food-and-technology/synthetic-biology [Accessed 16 October 2013].*
Source: Author

higher level of global cooperation (the others were transnational migration and resource competition in the Arctic). 'No forum currently exists for dealing comprehensively across the scientific community, industry, and governments on measures needed to diminish the risks posed by the *biotechnology revolution*' [emphasis in original] (USNIC / EUISS, 2010).

While the Organisation for Economic Cooperation and Development (OECD) invites the future 'bioeconomy',[13] the USNIC and the EUISS caution that emerging biotechnologies have the potential to alter human behaviour and association, creating profound cross-cultural ethical questions that will be politically contentious (Table 2): 'Few experts believe that current governance instruments are adequate for those challenges' (USNIC / EUISS, 2010).

The quandary was highlighted by the dispute over whether and how research on the deadly H5N1 avian flu virus should proceed after Dutch and American scientists announced that they had engineered a mutated version that can be transmitted among ferrets through the air (Herfst et al., 2012; Imai et al., 2012). More than a year of governmental, regulatory and academic wrangling ensued, some of it on the international stage. Publication of research results was delayed and researchers temporarily ceased their experiments. Then Chinese scientists succeeded in combining H5N1 with the highly contagious swine flu strain H1N1 and showed its airborne transmissibility among guinea pigs (Zhang et al., 2013).

Risks posed by biological technologies to human and environmental health, whether from unforeseen events concerning their approved use or from their deliberate misuse, are present in a menu of converging and expanding technologies (Figure 3). Among these technologies are nucleotide sequencing and biosynthesis, precise genetic editing, cellular and tissue engineering and automation of human immune system function (Hoffman, 2012), all empowered by and sometimes melding with digital technology. Increasingly they are geo-technologies that are recalibrating global innovation. Some are flowing into the plug-and-play biohacking culture.

In recommending guidelines for appropriate risk governance of synthetic biology, the International Risk Governance Council sought to strike a balance between current scientific knowledge, future uncertainty and a realistic assessment of the field's potential (IRGC, 2010). Subsequently, the US Presidential Commission for the Study of Bioethical Issues called for federal oversight of the field in a way that is consistent with scientific progress, suggesting a 'prudent vigilance' standard, a regulatory middle ground. Such a standard would establish processes for assessing likely benefits, safety and security risks both before and after projects are undertaken, and mechanisms for limiting their use when necessary (PCSBI, 2010).

Conclusions

In general, there are two types of restrictions on actions involving biological technologies: upfront restrictions and limitations before any action is taken, and remediation if action taken results in physical, economic or social harm (Carlson, 2010). One of the problems of restricting user access to biological technologies is defining who legitimate practitioners are. Moreover, as noted above with respect to global bioethics, and as we see with respect to greenhouse gas emissions, countries and their governments do not perceive threats uniformly. A transnational and evolving system of rules, standards and voluntary self-reporting, as has been suggested for nanotechnology (Auplat, 2013), may be the most feasible course in the near term. Over the long term, finding broad agreement on what constitutes the appropriate use of emerging biological technologies will be one of the great challenges for 21st century global governance. The health and well-being of living systems and the environment will depend on how that challenge is met.

Notes

1. The Columbian Exchange was proposed and developed by Alfred Crosby (1973).
2. The court case is Novartis AG vs Union of India & Others, CIVIL APPEAL Nos. 2706-2716 OF 2013, 1 April 2013. The ruling was a blow to 'evergreening', the practice of making incremental improvements in drugs to extend their patent life.
3. Blockbuster drugs with a combined US$170 billion in annual sales are slated to go off-patent by 2015 (*Economist*, 2011). Some US$300 billion of drug sales are estimated to be at risk from patent expirations between 2012 and 2018. As a result, global spending on generic drugs is expected to nearly double by 2016 from US$242 billion in 2011 (Harrison, 2013).
4. For a discussion of intellectual property law, genetically modified organisms in agricultural biotechnology, open-source innovation and sustainable development, see Henry and Stiglitz (2010).
5. See Jones (2012) 'Science in Three Dimensions: The Print Revolution'. Reference is to chemist Leroy Cronin's wish to enable anyone, anywhere to make drugs on demand.
6. Bonnett et al. (2013) conclude 'Amplifying Genetic Logic Gates' observing that transcriptor-based gates 'can also likely be directly combined with other logic families to expand the power of engineered genetic computers'.
7. Since the National Institutes of Health (NIH) Influenza Genome Project was launched in 2005, some 11,000 human, avian and swine viral strains have been sequenced. Sequencing production graph available from http://gsc.jcvi.org/projects/msc/influenza/ [accessed 16 October 2013].
8. Bioscience cluster criteria proposed by Timmerman (2013) include: the number of public and private life sciences companies, NIH funding, R&D spending at public life sciences companies, the number of patents issued per capita, total life sciences employment, total venture capital dollars invested, and venture capital allocated for early stage/seed investments.
9. Biopolis hosts nearly 7,000 researchers who carry out R&D in more than 50 companies and universities and 30 public sector institutes (EDB Singapore, 2013).

10. With US$53 million from the Bill and Melinda Gates Foundation, the nonprofit OneWorld Health is partnering with academia and biotechnology and pharmaceutical companies to produce affordable supplies of the antimalaria drug artemisinin. Available from: http://www.oneworldhealth.org/malaria [Accessed 16 October 2013].
11. See Moura et al. (2012) The ICONE study was commission by the Brazilian airline Embraer, the American airline Boeing and the Inter-American Development Bank, and reviewed by the World Wildlife Fund.
12. Yale university geneticist and Fudan university alumnus Tian Xu developed the mouse gene-knockout technology and directs the partnership (Wines, 2011).
13. The OECD published *The Bioeconomy to 2030: Designing a Policy Agenda* in 2009. The book is available from www.oecd.org [accessed 16 October 2013].

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Author Information

William Hoffman has been a writer and editor in the biomedical field for more than three decades. He works closely with geneticists and bioengineers and with bioscience industries. Hoffman interacts with the research and policy communities around the world.