The heart of translation

By Gaspar Taroncher-Oldenburg, Executive Editor

After a year of publication, *SciBX* is now able to begin mapping the translational space in depth, based on the collective efforts of Nature Publishing Group and BioCentury to identify science with commercial potential and to describe the work required to complete the transition from bench to bedside.

In its first-year assessment of the scientific space, the *SciBX* team evaluated more than 16,000 peer-reviewed journal articles published in over 40 top life science journals and selected over 2,000 papers for further editorial review of their scientific and commercial merit. This effort resulted in the publication of more than 850 Distillery briefings distributed across 19 disease classes.

In terms of the translational pipeline, *SciBX* found that the largest segment of peer-reviewed science with commercial potential is being produced in the cancer space, even though the majority of disease-related deaths worldwide are from cardiovascular disease.

Indeed, cancer comprised 32% of all the translational research tracked by *SciBX* in the year, with neurology and infectious disease each following at about 15% and endocrine and cardiovascular disease coming in at 9% and 6%, respectively, among the major disease areas (see **Figure 1.1, “Peer-reviewed articles covered by *SciBX*”**).

These numbers are reflected in the industrial pipeline. “My understanding is that well over one-third of the programs in development across the entire industry are for oncology and related conditions,” noted Bruce Booth of **Atlas Venture**.

Indeed, of all clinical-stage products tracked by BioCentury, one-quarter are for cancer indications.

An analysis of the funds raised between 2006 and 2008 by private and public biotechs in different disease areas also supports this view and shows a substantial overlap with the translational science output (see **Figure 1.2, “Money raised by private and public biotechs 2006–2008”**).

In addition, the latest **NIH** funding figures for 2008 show that, in order, cancer, neurological diseases and infectious diseases constitute the three top priorities—with cardiovascular disease a distant fourth (<http://report.nih.gov/rcdc/categories/Default.aspx>; see **Figure 1.3, “NIH funding FY2008”**).

Despite these academic and private-sector priorities, the **World Health Organization** (WHO) predicts that cardiovascular disease will remain by far the top cause of mortality through 2030.¹

Indeed, WHO projects that there will be a major shift in global

disease burden over that time, as the prevalence of infectious diseases, currently the second cause of mortality in the world after cardiovascular disease, will be dramatically decreased.

Thus, according to WHO, the contributions of cancer and infectious disease will become roughly equal, and respiratory infections (primarily chronic obstructive pulmonary disease) and endocrine disease (mostly diabetes) will be more prevalent.

These five disease classes alone will account for over 50% of all mortality (see **Figure 1.4, “WHO disease burden statistics”**).

Explanations

According to Edison Liu, the prevalence of translational research in cancer may reflect the fact that “cancer is not one disease but covers all organs and is cell based. There is, therefore, a lot more territory to cover.” Liu is executive director of the **Genome Institute of Singapore**, professor of medicine at the **National University of Singapore** and director of the **Singapore Cancer Syndicate**.

Eric Topol, director of the **Scripps Translational Science Institute** (STSI) and chief academic officer of **Scripps Health**, suggested that public perceptions about cardiovascular health have changed.

By his reckoning, the mismatch between research and therapeutic need has been driven by “a general misperception that cardiovascular disease is under control; the existence of a highly active and vocal advocacy in cancer—a majority of women now believes that breast cancer is the number one cause of death among women when in fact cardiovascular disease remains the leading cause; and a flurry of negative industry news—most prominently the failure of Pfizer’s torcetrapib and the subsequent announcement that the company was backing out of its cardiovascular programs.”

Pfizer Inc. halted development of torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, in November 2007 after its Phase III **ILLUMINATE** (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) study revealed significant risks of cardiovascular events and mortality compared with what was seen with the company’s Lipitor atorvastatin.²

The pharma company announced last October that it would discontinue early-stage work in cardiovascular areas and instead focus on oncology and other diseases.³

Garrett FitzGerald, director of the **Institute for Translational Medicine and Therapeutics at University of Pennsylvania** and chair of UPenn’s Department of Pharmacology, shares the view that the public may no longer perceive the threat of cardiovascular disease.

“It was probably the success of drugs developed for cardiovascular conditions in the 1980s and 1990s itself that precipitated the change in tide for cardiovascular disease from being viewed as a public health problem to being perceived as a manageable, controllable issue,” he told *SciBX*. “This misconception has marred research and development in this area.”

Elizabeth McNally, a professor in the Department of Medicine and director of the **Institute for Cardiovascular Research at University of Chicago**, also argued that the public does not have a full understanding of cardiovascular disease.

Figure 1.1 Peer-reviewed articles covered by SciBX **Figure 1.2 Money raised by private and public biotechs 2006–2008** **Figure 1.3 NIH funding FY08** **Figure 1.4 WHO disease burden statistics**

Figure 1. Disease statistics. Top areas of investigation by academic and industry researchers include cancer, infectious disease and neurology based on money raised by the biotech industry and the NIH's budget, whereas the World Health Organization (WHO) predicts that cardiovascular disease will remain the top cause of mortality through 2030.^A

[1.1] SciBX coverage over the last 12 months reflects the allocation of funds seen in academia and industry. Out of more than 16,000 journal articles published in over 40 top life science journals, SciBX editors selected over 2,000 papers for further editorial review based on scientific and commercial merit. This effort resulted in the publication of SciBX articles covering more than 850 peer-reviewed articles across various disease areas.

[1.2] Data on money raised includes some double-counting or triple-counting of financings as certain companies are working in more than one disease area.

[1.3] In the NIH data for fiscal year ending Sept. 30, 2008, funding allocations reflect selected general disease area classifications made by the agency. The endocrine disease area represents the combined value of NIH allocations to obesity and diabetes classifications.

[1.4] WHO's projections for change in disease burden between 2004 and 2030 for the top causes of mortality and morbidity worldwide. Data from WHO on specific indications are consolidated into eight major disease categories.

^AAll data were listed according to the rankings in [1.2].

Looking beyond coronary artery disease, she noted, heart failure is the most common hospital discharge diagnosis, and atrial fibrillation adversely affects a sizable amount of the older population.

"Research in these areas is lacking," said McNally, and this "is limiting clinical research and drug/device development."

In addition, she said, "there is congenital heart disease, stroke and hypertension—these are also areas where there is very little new to offer patients."

Indeed, FitzGerald noted, "most people in the U.S. still die of

heart disease. Increasingly, diabetes is a problem in the developing world, but most diabetics die of cardiovascular disease."

Even with this demonstrated need, he added, "most companies are running away from cardiovascular disease as they realize that they have to perform large-scale trials for approval and prefer cancer or neuroscience, where the perceived benefit:risk equation is more economically seductive."

Topol made similar comments. Even though neurological disease comes in last among the WHO's top 10 causes of mortality, the current

emphasis on funding in this area, second only to cancer, also may reflect “relative regulatory ease and strong patient advocacy like that seen in cancer,” he said.

According to Elizabeth Wilder, deputy director of NIH’s Office of Strategic Coordination, whereas the “27 institutes and centers determine specific fund distribution within their organizations, the initial allocation of funds to the individual institutes and centers is determined by congressional budget appropriations—the NIH manages these allocations but has no power to reallocate monies between institutes.”

How Congress determines the initial allocations can be shaped by interest groups, vocal constituencies and other political interests.

Moreover, said Wilder, NIH’s mission overall is “not only shaped by disease burden and associated mortality rates but also by public health burden, which includes impact on quality of life. This explains NIH’s emphasis on diseases that are not lethal but clearly affect people’s lives. Importantly, in addition to assessments of health burden, the NIH also considers scientific opportunity in particular areas when setting priorities.”

Still, cardiovascular researchers are hoping priorities shift toward cardiovascular disease.

Topol thinks NIH funding allocations should be more proportional to public health issues. Even though there is “an Alzheimer’s disease epidemic in the works, due to an overall ageing population, the funding priorities at NIH should really be in cardiovascular disease first, followed by cancer and neurological diseases in third place,” he said.

Jeffrey Towbin, professor and chief of pediatric cardiology at the **Texas Children’s Hospital**, thinks “it is necessary to emphasize cardiovascular translational science and that other non-NIH partners are needed.”

This view was echoed by the University of Chicago’s McNally. “It’s been disappointing that for the few programs that exist to fund transformative research, virtually none of it has gone to cardiovascular sciences,” she said.

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**—Elizabeth McNally,
University of Chicago**

But despite the relative dearth of translational research in cardiovascular disease, *SciBX* was able to report on new findings for about 66 targets in the space, as well as new therapeutic approaches in atherosclerosis, myocardial infarction, hypertension, thrombosis and stroke.

These included recent research suggesting that neuropeptide Y, a peptide hormone previously targeted for obesity, could be a suitable target in atherosclerosis and coronary artery disease,⁴ and a study showing that a peptide designed to disrupt interactions between two platelet-derived

chemokines may offer a new strategy to tackle atherosclerosis.⁵

Indeed, the solution to creating more cardiovascular drugs may come via the translational space.

According to Topol, boosting levels of cardiovascular research will require further “advancements in individualized medicine, which will create an opportunity for designing smaller, more targeted clinical trials that would increase the probability of their success.”

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COMPANIES AND INSTITUTIONS MENTIONED

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