Exuberant unpredictability: *sine qua non* for priceless and prizeworthy biomedical research

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Lasker Awards have been given for the past 63 years and Nobel Prizes for the past 107 years. But both of these prizes are relative newcomers to the prize-giving scene. The mother of all prizes—scientific and nonscientific—is the Gold Medal of the Royal Astronomical Society of London. This prize was first given in 1824, and it has been given continuously for the past 184 years. Einstein won it in 1926 and, in more recent times, three heroes of modern astronomy have received it: Hubble, Hoyle and Hawking.

Charles Babbage, the first prize recipient

The first recipient of the Royal Astronomical Society's Gold Medal was Charles Babbage, a brilliant and eccentric professor of mathematics at the University of Cambridge. Babbage received his medal in 1824 at age 33, the same age at which James Watson received his Nobel Prize. Babbage's prize recognized several of his accomplishments: producing the first accurate logarithmic tables, which modernized navigation by allowing precise surveys of coasts; conceiving the first actuarial tables, which led to life-insurance companies; and conceptualizing the modern postage system. Not bad, even for a 33-year-old polymathic mathematician!

Unlike many scientists who achieve success at an early age, Babbage refused to rest on his laurels. Over the next 50 years, he invented the speedometer, pioneered the art of lock picking, and relentlessly designed mathematical machines for making complex calculations and breaking codes. In 1888, he designed the first programmable computer, consisting of a memory unit, a processing unit and punch cards for giving instructions. Babbage's now-famous 'difference machine', the forerunner of the modern computer, was constructed in 1991 from his original plans with funds from the Wellcome Trust and is now on display in the Science Museum in London.

To award the first prize in history to someone with the stature of a Charles Babbage sets a high standard for all prize-giving institutions, sending the clear message that the ultimate prestige and influence of a prize is determined by how well the accomplishments of its recipients advance our understanding of the natural world and stand the test of time. This is especially worth noting as prize giving has experienced a major growth over the past 40 years. According to the standard reference book on the subject published by the Gale Research Company, a total of 2,228 prizes were given in 1969 in all fields of human endeavor. In 2007 the number had increased to 23,000, covering everything from archery to zymology (prizes in zymology are given for the best homebrewed beer). Of the 23,000 prizes given today, about 1,000 celebrate the biomedical sciences.

Awarding prizes in science and medicine not only has become a growth industry but also is a competitive business. Inasmuch as discoveries are often made by several individuals in different institutions, figuring out who did what and when they did it can become a frustrating and paralyzing exercise in ambiguity. So it is not surprising that final decisions of selection committees can sometimes elicit angry responses from the spurned scientists and snide comments from the academic community. Even in those rare situations in which there is no ambiguity in pinning down who made the key discovery, selection committees are still faced with the judgmental challenge of deciding whether discovery A is more important than discovery B or C. So, every prize has its price.

The *Prize Paintings* of Martin Kippenberger

One of the best insights into the sociology of prizes comes from the German painter and sculptor Martin Kippenberger. Kippenberger, who was born in 1953 and died prematurely from alcoholic cirrhosis in 1997, is regarded as one of the most creative artists of his generation, often referred to as the German version of Andy Warhol. One of Kippenberger's most provocative works that exemplifies his signature style of 'exuberant unpredictability' is a metal sculpture entitled *Street Lamp for Drunks* in which the lamp post is bent and curved, woozing back and forth without any human figure leaning on it (**Fig. 1**).

In 1987 and 1994, Kippenberger produced two series of paintings that exploit the double meaning of the German word '*preis*', which can be translated as 'prize' or 'price' depending on the context. In each painting, a variation of the word '*preis*' appears emblazoned in fat, dark letters across a colorful abstract grid of checks or plaids, resembling a tablecloth or drapes (**Fig. 2**).

In his 1987 series of *Preis Bilder* (*Prize Paintings*, **Fig. 2a–d**), Kippenberger titled the works to suggest awards and hierarchy: *1. Preis*, *2. Preis*, *3. Preis* (*First Prize*, *Second Prize*, *Third Prize*), and so on. Most art critics called these works the *Prize Paintings*, but a few caught the irony and called them the *Price Paintings*, raising the question as to how one distinguishes a high-priced painting from a low-priced one. Is *1. Preis* really more valuable in a financial sense than *5. Preis* or *17. Preis*?

In the 1994 series of *Preis Bilder* (**Fig. 2e–h**), Kippenberger turned the tables in his exuberantly unpredictable way and came up with titles that are more suggestive of price than prize: *1/2 Preis* (is it half-price or half

of a prize?), *Trostpreis* (comfortable price or consolation prize?), *Preisgünstig* (budget price or cheap prize with a small honorarium?) and *Preislos* (priceless or prize-less?).

Preislos (**Fig. 2h**) is a scathing commentary on the ridiculously high prices of the art market, where the price of a painting often has no relation to its artistic value. This priceless/prize-less metaphor applies aptly to the biomedical sciences. We are all familiar with examples of priceless research that has gone prize-less in the Nobel sense—for example, Avery's discovery that DNA is the stuff of genes, and Boyer and Cohen's development of gene cloning. And those who serve on prize selection committees are familiar with the occasional discussion where a priceless comment from a jury member can create a prize-less situation for a nominee.

Priceless and prizeworthy research

The exuberant unpredictability of Kippenberger's *Prize Paintings* is evident in the accomplishments of this year's Lasker prize winners, whose unexpected discoveries have opened new fields of basic and clinical research. Their achievements are therefore both priceless and prizeworthy—even though (with apologies to Kippenberger) there is no single German word for such double praise.

Basic Award: exuberant unpredictability at its best

This year's Lasker Basic Award recognizes the discoveries that revealed an unanticipated world of tiny RNAs that regulate gene function in plants and animals. The existence of tiny RNAs has changed the way in which scientists think about gene regulation and has thrown a monkey wrench into the strict interpretation of the central dogma of molecular biology—information in a cell flows from DNA to RNA to proteins, which then carry out all of the cell's structural, metabolic and regulatory activities. With the discovery of tiny RNAs, we now know that RNAs not only encode proteins but can also act on target mRNAs to prevent them from being translated into proteins.

The scientists who are being honored for the discovery of tiny RNAs are Victor Ambros (University of Massachusetts), Gary Ruvkun (Massachusetts General Hospital) and David Baulcombe (University of Cambridge).

In 1993, while carrying out genetic analysis of a developmental pathway in *Caenorhabditis elegans*, Ambros and Ruvkun discovered the first short, noncoding RNA and established that this tiny molecule of 22 nucleotides silences the expression of a specific protein-coding gene by base-pairing to a complementary sequence in the 3′ untranslated region of its mRNA.

Figure 1 *Laterne an Betrunkene* (*Street Lamp for Drunks*). This 1988 sculpture by Martin Kippenberger shows a light post bent and curved, woozing back and forth like an inebriated person. This sculpture exemplifies exuberant unpredictability, a characteristic of creative art and science. Steel, 280 × 40 × 40 cm. © Estate Martin Kippenberger. Galerie Gisela Capitain, Cologne, Germany.

For 6 years, this was the only example of a tiny RNA acting in this manner, and the Ambrose–Ruvkun discovery, although recognized as a sophisticated piece of genetic sleuthing, was generally considered a curiosity of worm biology. But in 1999, David Baulcombe, a botanist (then at the Sainsbury Laboratory in Norwich, UK) working on the problem of gene silencing as a mechanism that plants use to fight viruses, identified the second example of tiny, noncoding RNAs.

A year after Baulcombe's discovery, Ruvkun discovered a second tiny regulatory RNA in worms that silenced a different gene from the one he and Ambros had described earlier. This tiny RNA was broadly conserved across a wide variety of animal species, including humans—a finding that triggered an intense surge of interest in this class of tiny RNAs, now called microRNAs.

The discovery of tiny RNAs as the universal mediator molecule for RNA-directed gene silencing by Ambros, Ruvkun and Baulcombe provided the conceptual framework for understanding the biochemical basis of RNA interference (RNAi), a phenomenon described by Andrew Fire and Craig Mello in 1998. A unifying view soon emerged: long double-stranded RNAs (either produced in cells endogenously for physiological purposes or introduced exogenously as an experimental tool) are processed by ribonucleases to generate the single-stranded tiny RNAs that

silence mRNAs by promoting their degradation or inhibiting their translation.

The crucial role of tiny RNAs in gene silencing is a striking example of a basic biological process that was totally unpredictable before the studies of Ambros, Ruvkun and Baulcombe. Hundreds of scientists are now working on tiny RNAs, and thousands of papers have been published on the subject in the past 15 years. The implications of this discovery for the basic biology of plants and animals, as well as for agriculture and human health, are profound. For example, we now know that the human genome encodes 500–1,000 microRNAs that regulate as many as one-third of all genes—including genes that affect embryonic development, genes that cause cancer, genes that regulate immunity and genes that govern stem-cell differentiation. This list is just the tiny tip of a large iceberg of tiny RNAs.

Clinical Award: drug discovery at its best

Atherosclerosis of the coronary arteries, which leads to heart attacks, is responsible for more than one-third of all deaths in the developed world. As many as 16 million Americans alive today have a history of coronary heart disease (CHD), and 1.2 million will have a new or recurrent heart attack this year. Over the past 100 years, four lines of evidence—experimental, genetic, epidemiological and therapeutic—have established the causal link between cholesterol-carrying low-density lipoproteins (LDL) and CHD. Building on that knowledge, scientists have successfully developed a remarkably effective class of drugs that lower LDL-cholesterol levels in blood, reducing the frequency of CHD: the statins.

This year's Lasker~DeBakey Clinical Award is given to the scientist who discovered the first statin and showed its clinical efficacy—Akira Endo, now at the Biopharm Research Laboratories in Tokyo.

As a child growing up on a farm in northern Japan, Endo became fascinated with mushrooms and molds, and as a young boy, he read several biographies of Alexander Fleming and the discovery of penicillin in a fungus. After obtaining his PhD in biochemistry in 1957, Endo joined the Sankyo Company in Tokyo as a research scientist. His main project was to identify and characterize fungal enzymes used in processing fruit juices and wines. After succeeding in this endeavor, Endo was rewarded in the late 1960s with the opportunity to work on a drug project of his own choosing. So, in 1971, he and his colleague Masao Kuroda began a search for inhibitors of cholesterol synthesis, reasoning that a decrease in cholesterol production in the body would lower cholesterol in the blood and therefore decrease CHD.

Endo's approach was to search fungal cultures for secreted natural products that, when added to a cell-free system, would inhibit synthesis of cholesterol from radiolabeled acetate. His choice of fungi as a source of a small molecule inhibitor is a prime example of exuberant unpredictability: in 1971, there was not a scintilla of experimental evidence to suggest that fungi would produce and secrete such an inhibitor.

After 2 years of negative results involving a nonstop effort at screening 6,000 different fungal strains, Endo and Kuroda discovered a strain of *Penicillium citrinum* that produced the desired inhibitory activity. They spent the next several years purifying the inhibitor, working out its structure and identifying 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase as the target enzyme. In 1976, Endo and his colleagues published their first two papers reporting the discovery and characterization of the first statin, known today as mevastatin or compactin. In the test tube, compactin inhibited HMG-CoA reductase in the low nanomolar range, and it potently inhibited the production of cholesterol in cultured cells. For historical interest, it should be pointed out that Endo's now-classic 1976 papers were not published in what is now called a 'high-profile' journal; the first one appeared in *Journal of Antibiotics* and the second one in *FEBS Letters*.

Over the next several years, Endo carried out animal studies showing that mevastatin lowered plasma cholesterol in dogs and monkeys. He then began to collaborate with Akira Yamamoto, a physician at the National Cardiovascular Centre in Osaka. Yamamoto gave oral compactin to several patients with genetic forms of hypercholesterolemia, all of whom had been poorly responsive to available cholesterol-lowering drugs. They observed a dramatic result: compactin was extremely effective in lowering plasma cholesterol. These pioneering studies were published in 1980.

By early 1978, many pharmaceutical companies, although originally skeptical about the safety of inhibiting cholesterol synthesis in the body, learned of Endo's results and jumped on the statin bandwagon, feverishly searching for new HMG-CoA reductase inhibitors. The race to the finish line was won by the Merck Sharp & Dohme Research Laboratories. Led by Alfred Alberts, Merck scientists identified in 1979 a molecule secreted by *Aspergillus terreus* that differed from compactin by one methyl group. (Endo had independently isolated the same molecule from a different organism.) Merck's molecule, lovastatin (Mevacor), in 1987 became the first statin approved for human use. Today, more than six statins (both natural products and synthetic versions) have been developed and commercialized, the most popular being atorvastatin (Lipitor) and simvastatin (Zocor).

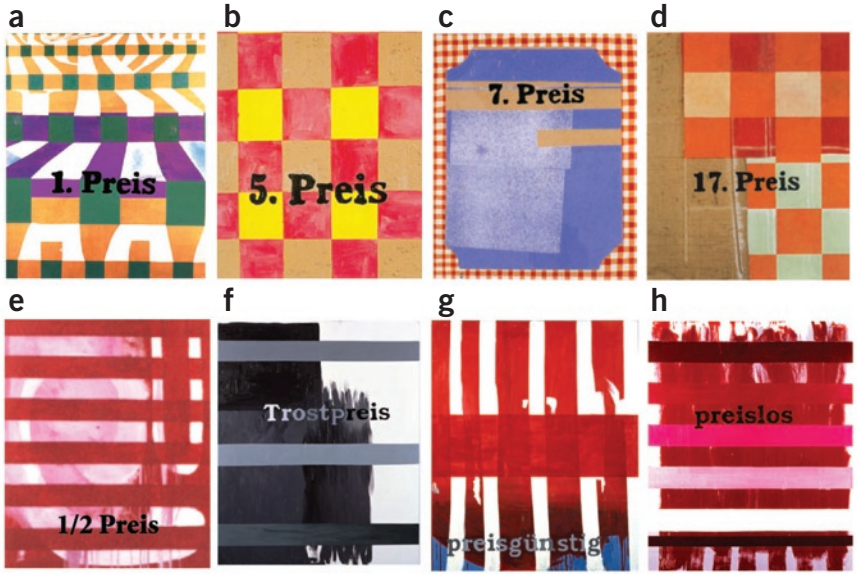

Figure 2 *Preis Bilder* (*Prize Paintings*). This montage shows eight of the paintings from Martin Kippenberger's *Preis Bilder* series of abstract paintings, in which Kippenberger exploits the double meaning of the German word '*preis*'—'prize' or 'price'. (**a**–**d**) Four of the 14 paintings from the 1987 series: *1. Preis*, *2. Preis*, *5. Preis* and *17. Preis*. Oil on canvas, 180 × 150 cm. (**e**–**h**) Four of the five paintings from the 1994 series: *1/2 Preis*, *Trostpreis*, *Preisgünstig* and *Preislos*. Oil on canvas, 120 × 100 cm. © Estate Martin Kippenberger. Galerie Gisela Capitain, Cologne, Germany.

Statins have now been tested in 14 randomized multicenter trials, involving an unprecedented number of individuals—a total of 90,056—who were followed for an average of 5 years. The results in every study have been astonishingly consistent: treatment with statins lowered plasma LDL by 25–35% and reduced the frequency of heart attacks by 25–30%. All 14 trials were carried out in individuals with an average age of 50–60 whose coronary arteries already harbored clinically silent atherosclerotic lesions. The reduction in event rate would almost certainly be even more miraculous if therapy were 10 or 15 years and if it were started at age 40 or even 30, when lesions are fewer and smaller.

A noteworthy aspect of the 14 statin trials is that no major harmful effects of lowering cholesterol, such as an increase in cancer or non-cardiovascular mortality, were observed. The remarkable safety of statins derives from their unique mechanism of action involving the body's sophisticated mechanism for cholesterol homeostasis. When a statin is ingested, the intestinally absorbed drug is routed primarily to the liver, where it binds and inhibits HMG CoA reductase, lowering cholesterol production. This decrease in hepatic cholesterol triggers a compensatory feedback loop that increases the number of LDL receptors displayed on the liver-cell surface. The increased number of LDL receptors selectively grab onto more LDL (but not HDL), remove the LDL from the blood and deliver it to lysosomes, where the LDL is digested, and its released cholesterol becomes available to the liver cell for metabolic purposes. The net effect is that the amount of cholesterol in the liver is maintained at a normal level, while the amount of LDL in blood is kept low. If all drugs worked in such a perfect way, the drug industry would be in perpetual pharmaceutical heaven.

The statins are the drugs taken at present by the largest number of patients throughout the world: an estimated 30 million people worldwide take statins, including 30% of all Medicare patients in the United States. The millions of people whose lives will be extended through statin therapy owe their good fortune to the immense contributions of Akira Endo. Without the exuberant unpredictability of Endo's hunt through 6,000 fungal extracts 35 years ago, the statins might never have been discovered.

Despite the triumphant success of Endo's approach to drug discovery, the major pharmaceutical companies have surprisingly and largely abandoned the screening of natural products in favor of the screening of synthetic chemical libraries. No random man-made library, no matter how large, would ever be expected to yield *de novo* an HMG-CoA reductase inhibitor with the potency and selectivity of Endo's first statin. The complex structure of mevastatin, containing seven asymmetric carbon atoms, evolved over billions of years of evolution to target the catalytic site of HMG-CoA reductase by mimicking its natural substrate (HMG-CoA). To paraphrase the second law of Leslie Orgel, the great British chemist, evolution is smarter than chemical biologists.

Special Achievement Award: microbe hunting and scientific statesmanship at their best

The Lasker~Koshland Special Achievement Award is given every other year to honor a scientist whose lifetime contribution to medical science is universally admired and respected for its creativity, importance and impact. In essence, the Special Achievement Award honors someone who exemplifies scientific statesmanship at its best.

This year's Special Achievement Award goes to Stanley Falkow of Stanford University School of Medicine. Falkow is honored for a 51-year career as one of the great microbe hunters of all time, joining the ranks of Robert Koch, Louis Pasteur, Walter Reed and Paul Erhlich—four great scientists of the late nineteenth and early twentieth centuries whose work in microbiology revolutionized medicine. Falkow is a latter-day incarnation of these classic microbe hunters.

In the early 1960s, Falkow used the then new technique of cesium chloride gradient centrifugation to physically isolate from bacteria a distinct band of DNA that comprised the genetic material responsible for antibiotic resistance. This work explained for the first time how bacteria resist antibiotics and laid the conceptual framework for all subsequent studies on the molecular basis of plasmid biology and antibiotic resistance. Drawing on this expertise, Falkow was the first, in the late 1970s, to warn the international community about the relationship between the use of antibiotics in farm animal feed and the emergence and spread of antibiotic resistance among human clinical isolates.

In the early days of the recombinant DNA era, Falkow played two key catalytic roles. First, he arranged the famous midnight meeting at a delicatessen on Waikiki Beach in Honolulu between Herbert Boyer and Stanley Cohen, a meeting that hatched the Boyer–Cohen collaboration that led to their development of recombinant DNA technology. The RSF1010 plasmid used in the classic Boyer–Cohen cloning experiments of 1973 was provided to them by Falkow. Second, by virtue of his credibility as the paramount expert in bacterial pathogenicity, Falkow played a leading role in refuting the most egregious overstatements made at the Asilomar meeting of 1975 about the dangers and pathogenic potential of cloning genes in *Escherichia coli*. The consensus that ultimately emerged, which largely reflected Falkow's influence, recommended modest restrictions on genetic engineering of the type that are still in place today.

Once the restrictions on cloning were lifted, Falkow himself became one of its first and most ardent practitioners, cloning the heat-stable enterotoxin gene of *E. coli* in 1976. This was the first bacterial virulence gene to be cloned and characterized. He and his students went on to clone and characterize most of the virulence genes of many important pathogens, including those of *Bordetella pertussis*, *Neisseria gonorrhoeae*, *Vibrio cholerae*, *Helicobacter pylori* and others. Several breakthrough experiments took place in 1985–1987, when Falkow and his team established invasion assays to study the entry of bacteria into human epithelial cells. This seminal work opened up a new field of cellular microbiology in which the focus shifted from growing bacteria in broths in the incubator to exploring new aspects of microbial pathogenesis, such as identifying the bacterial gene products that perturb the transport processes and signal transduction mechanisms of host human cells.

During his half-century career, Falkow has mentored more than 100 students and postdoctoral fellows, many of whom are now distinguished leaders in the fields of microbiology and infectious disease. Seldom has a single individual so completely dominated a field for so long and with such an incomparable battery of talents: creative scientist, bridge to clinicians, stimulating teacher, wise mentor and great citizen—all executed with an irreverent sense of humor.

Joseph L. Goldstein
Chair, Lasker Awards Jury

Lasker Award recipients receive an honorarium, a citation highlighting their achievement and an inscribed statuette of the Winged Victory of Samothrace, which is the Lasker Foundation's symbol of humankind's victory over disability, disease and death.

To read the formal remarks of speakers at the Lasker ceremony, as well as detailed information on this year's awardees, please refer to the Lasker website at http://www.laskerfoundation.org/.