Balzac's *Unknown Masterpiece*: spotting the next big thing in art and science

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There is no shortage of advice on how to become a creative writer, a creative artist or a creative scientist. Just in the last decade, hundreds of books and articles have been written on the subject, and in hundreds of TED lectures, inspired thinkers reveal their secrets for creative success. Despite this flood of contemporary advice, my favorite insight on creativity goes back over 100 years to the Irish playwright and wit Oscar Wilde, who famously proclaimed that "a writer is someone who has taught his mind to misbehave"—an assertion that can be applied to most creative individuals.

One of the virtues of a misbehaving mind is its ability to spot the next big thing— whether it be in art or in science. A great example of a famous literary figure who passed the Oscar Wilde 'misbehavior test' with flying colors is the nineteenth-century novelist Honoré de Balzac. In the 1830s, Balzac conceived the idea of writing a series of works that would describe the sweep and panorama of French society in all its splendor and squalor, from the highest aristocrats and politicians to the lowest swindlers and prostitutes. Over a 16-year period, he published a total of 91 novels and short stories, and shortly before his death in 1850 he organized his 91 works into a multivolume collection that he titled *The Human Comedy*. Balzac chose this title to contrast it with Dante's *The Divine Comedy*, which portrayed Hell, Purgatory and Heaven and had nothing to say about the realism of the earthly life that Balzac presented. *The Human Comedy* contained many astute insights into human behavior. One of the most original and popular—and a prime example of his misbehavior—was his discussion about how certain people get ahead in life through advantageous marriages rather than hard work.

Rodin's response to Balzac

Fifty years after Balzac's death, the French government commissioned Auguste Rodin to create a sculpture in memory of the writer, whose work by that time had achieved international acclaim. To capture Balzac's genius and the revolutionary nature of his work, Rodin decided to misbehave and create a revolutionary work of his own: rather than producing a realistic physical likeness of his subject, he broke with the sculptural traditions of the past and created a semiabstract figure in which only Balzac's head remains visible, with the rest of his body wrapped in the dressing gown that he wore when writing (**Fig. 1**). *Monument to Balzac*, completed in 1898, is considered the first truly modern sculpture[1].

Like Balzac's *The Human Comedy*, Rodin's *Balzac* has stood the test of time. One of the best descriptions of Rodin's sculpture is by the Belgian critic André Fontainas: "Balzac stands with his huge head thrown back, alert like a wild animal, drinking in with eyes, nostrils and lips and scenting the fever of the human comedy"[2]. Bronze casts of *Balzac* are displayed in virtually every major museum globally, and it is one of the most viewed museum sculptures in the world.

Balzac's *Unknown Masterpiece*

One of Balzac's most celebrated and intriguing stories, *The Unknown Masterpiece* (*Le Chef-d'oeuvre inconnu*), first published in 1831 and later integrated into *The Human Comedy*, deals with the subject of creativity at its most fundamental level; it tells the tale of an artist ahead of his time[3]. The story is set in seventeenth-century Paris in a studio located at 7 Rue des Grands-Augustins in the 6th arrondissement. The plot is simple. A famous aging artist, named Frenhofer, is obsessed with finishing a painting that he has been secretly working on for ten years and one that he claims will be his masterpiece—a painting that portrays a beautiful nude woman with such brilliance and artistic skill that she seems to be actually alive. When two younger painters who are great admirers of Frenhofer's work finally persuade Frenhofer to let them see the secret canvas, they are appalled and shocked. All they see is an indecipherable jumble of strange lines and paint. As they stare in horror at the work, they mock the older artist and conclude that their celebrated hero has gone mad. Realizing his failure, Frenhofer abruptly bids farewell to his two friends, burns his painting and mysteriously dies during the night. The tragedy of Frenhofer—and the brilliance of Balzac—is that the fictional artist had created the first abstract painting, inventing abstract expressionism 125 years before Jackson Pollock.

Picasso's response to Balzac's *Unknown Masterpiece*

The artistic crisis that Frenhofer faced in Balzac's story exerted a profound effect on Cezanne, Matisse and Picasso—all three of whom were artists of genius whose masterpiece paintings were so far ahead of their time that few of their contemporaries could recognize them as such. Picasso passionately identified with Frenhofer's failed quest for artistic perfection. In 1931, he produced 13 etchings to be included in the hundredth-anniversary reprint of Balzac's *The Unknown Masterpiece*. These etchings deal with the theme of the artist working with his model. Like Frenhofer's abstract painting, Picasso's drawings were kept a closely guarded secret, and when they first appeared in the centenary book, some of them looked like a mass of lines and smudges of ink, such as the one in **Figure 2**. The jumble of lines here was typical of Picasso's misbehaving. Did the morass of lines represent the yarn of wool in the model's hand, or was it meant to be Frenhofer's abstract painting? Today, Picasso's 13 Balzac etchings are considered landmarks in the history of engraving.

Figure 1 Auguste Rodin, *Monument to Balzac*. 1897–1898. Bronze. Height, 9 feet, 3 inches. Museum of Modern Art, New York.

Picasso was so haunted by the ghost of Balzac and by the tragedy of Frenhofer that in 1937 he moved his studio to a townhouse located at 7 Rue des Grands-Augustins, the exact same building in which *The Unknown Masterpiece* was set 100 years earlier. Soon after Picasso moved into his new studio, German warplanes bombed the Spanish Basque city of Guernica, and Picasso immediately abandoned all projects and devoted his full energy—night and day—to one large canvas, which he completed within three months. At its unveiling in 1937 at the Paris Exhibition, *Guernica*—not surprisingly—perplexed the critics. But unlike the tragic Frenhofer, the imperturbable Picasso was unfazed by the negative criticism, and he lived to see his work evolve from an unknown painting to a highly celebrated masterpiece.

Richard Hamilton's response to Balzac's *Unknown Masterpiece*

In early 2010, the National Gallery of London invited the British painter and collage artist Richard Hamilton to stage an exhibit of his most recent work. At the time, Hamilton was 88 years old and still exceptionally active and productive. The timing for the exhibit was remarkably propitious: Hamilton, like Picasso before him, had come under the spell of Balzac's short story on the search for artistic perfection, and the National Gallery's invitation would provide him a unique opportunity to bring his ideas on this work to fruition.

A brief background on Richard Hamilton will help those not familiar with his career to appreciate how he responded to *The Unknown Masterpiece*. Hamilton is one of the most influential British artists of the twentieth century. He is widely regarded as the founder of the Pop Art movement in the 1950s; his work predates that of Andy Warhol and Roy Lichtenstein by several years. One of his early iconic works was a 1956 collage titled *Just What Is It That Makes Today's Homes So Different, So Appealing?*, in which he used images cut from mass-circulation magazines. The collage depicts a contemporary Adam and Eve: a muscleman holding a giant lollipop and a nude woman on a sofa with a lampshade on her head are enjoying their living room filled with all sorts of new consumables, including a television, a vacuum cleaner and a canned ham on the coffee table.

According to the art critic John Russell, with this collage Hamilton "single-handedly laid down the terms within which Pop Art was to operate"[4]. In fact, the first time the word 'pop' ever appeared in a painting was when it was emblazoned on the lollipop at the center of Hamilton's collage.

If anyone had a misbehaving mind in the Oscar Wilde sense, it was Richard Hamilton—he was the epitome of British pluck and profound originality. Over a 60-year career, he innovated, experimented and reinvented himself, spotting the next big thing in art before any of his contemporaries. At age 80, Hamilton taught himself computer graphics. One of his most politically provocative computer-generated paintings, titled *Shock and Awe*, depicts a life-size Tony Blair dressed in a pistol-carrying cowboy costume, presiding over the invasion of Iraq.

Once Hamilton had mastered the intricacies of digital technology, he devoted his full energy, beginning in early 2010, to the National Gallery project: his homage to Balzac's *The Unknown Masterpiece*. Using computer graphics, he composed a montage consisting of four known images that he assembled digitally and refined with the use of Photoshop's Bezier's curves—nothing was painted[5].

The centerpiece of Hamilton's digital montage is a reclining nude representing Frenhofer's muse (**Fig. 3**). Hamilton created this image from a digital scan of a photograph of a nineteenth-century nude whose pose harks back to Titian's famous *Venus of Urbino* from 1538. The nude is surrounded by three famous artists—Poussin, Courbet and Titian. Titian represents Frenhofer, and Poussin and Courbet represent Frenhofer's two younger artist friends; all three were scanned digitally from reproductions of their well-known self-portraits. The three artists are absorbed in deep thought, perplexed by the mysterious sensuality of the nude in front of them. A notable feature of the montage is the empty easel that is centrally placed between Poussin and Courbet. This H-shaped easel is identical to the one that Hamilton used in his studio and may be meant to represent the specter of Hamilton himself.

The reclining nude is perfectly shaped, but she appears unreal in her glossy skin: digitally exact, but artistically artificial. Days after completing his digital montage, Hamilton died on the eve of his ninetieth birthday. His original intention was to use the digital montage as a guide for creating an authentic oil painting, which he believed would achieve Frenhofer's ideal of living purity that is missing in Hamilton's pixilated version. As fate would have it, Hamilton's 'masterpiece', like that of Frenhofer, will forever remain an unknown masterpiece—a bittersweet irony if ever there was one. The empty H-shaped easel in the digital montage now takes on an eerie meaning that the misbehaving mind of Hamilton may or may not have intended. We will never know.

Spotting the next big thing

The misbehaving minds of Balzac, Rodin, Picasso, Hamilton and Balzac's Frenhofer endowed each of them with the uncanny ability to spot the next big thing before anyone else. Spotting the next big thing is a distinguishing characteristic of scientists who win Lasker Awards and Nobel Prizes. As discussed below, this year's Lasker winners were the first to spot how the endoplasmic reticulum senses harmful unfolded proteins and corrects them (Basic Award), how the tremors of advanced Parkinson's disease can be alleviated (Clinical Award) and how certain people with early-onset breast and/or ovarian cancer owe their disease to an inherited gene, *BRCA1* (Special Achievement Award).

Basic Award: unfolding a scientific masterpiece

This year's Lasker Basic Medical Research Award is given to two scientists for their discoveries concerning the unfolded protein response (UPR)—an intracellular quality control system that detects harmful misfolded proteins in the endoplasmic reticulum (ER) and then signals the nucleus to carry out corrective measures. The two recipients are Kazutoshi Mori (Kyoto University) and

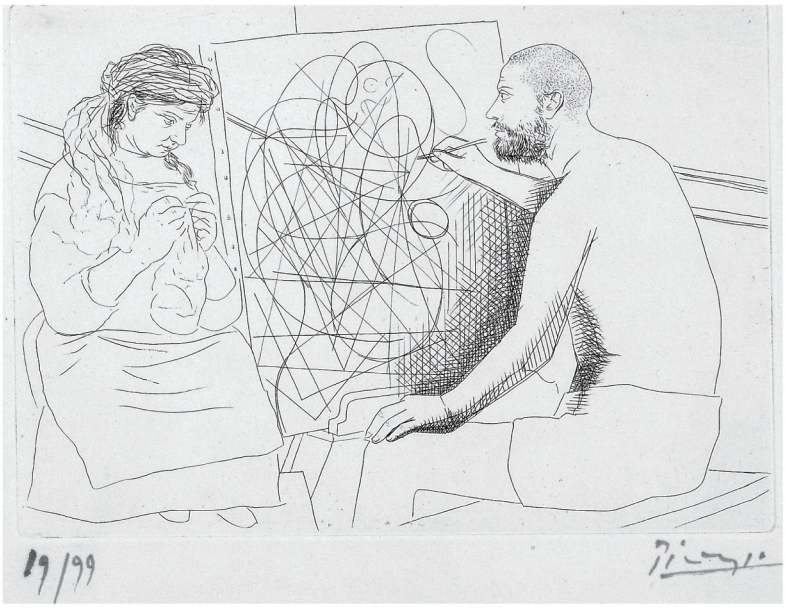

Figure 2 Pablo Picasso, *Painter and Model Knitting.* 1927. One of 13 etchings from the special centenary edition of Balzac's *The Unknown Masterpiece.* 19.5 × 21.8 cm. Exhibited at Juan March Foundation, Madrid, from October 2011 to February 2012.

Peter Walter (University of California, San Francisco (UCSF)).

Newly synthesized secretory and transmembrane proteins that are translocated into the lumen of the ER must be correctly folded and assembled to prevent their aggregation and cellular toxicity. The accumulation of aggregated unfolded proteins creates the condition of ER stress, which in turn triggers the UPR, a process that stimulates transcription of multiple genes that enhance the ER's protein-folding machinery. Genes whose transcription is enhanced by the UPR include those encoding ER chaperones (e.g., BiP and calnexin), protein-modifying enzymes (e.g., glycosyltransferases), proteins involved in expansion of the ER (e.g., lipid synthesis enzymes) and components of the ER-associated degradation (ERAD) pathway that degrade aggregated proteins.

The concept of the UPR emerged 25 years ago from research in many laboratories, notably those of Amy S. Lee (University of Southern California), Mary-Jane Gething and Joseph F. Sambrook (University of Texas Southwestern Medical Center), Linda Hendershot (University of Alabama, Birmingham) and Hugh Pelham (UK Medical Research Council Laboratory of Molecular Biology). But the central question remained unanswered: how does an essential process originating in the lumen of the ER (i.e., accumulation of unfolded proteins) signal a process in the nucleus that corrects the situation (i.e., gene transcription)?

Three parallel pathways, each mediated by a different integral ER transmembrane protein, are now known to execute the UPR. The first pathway—the Ire1 pathway—was revealed by Walter and Mori in a series of elegant genetic and biochemical studies of yeast cells beginning in the late 1980s and early 1990s. Although their work was done independently, it was remarkably complementary over a ten-year period. At the time they began their studies, Walter was a newly minted assistant professor at UCSF, and Mori was a postdoctoral fellow with Mary-Jane Gething and Joseph F. Sambrook at the University of Texas Southwestern Medical Center (he moved back to Japan in 1993 and became a professor at Kyoto University several years later).

Mori and Walter discovered that the accumulation of misfolded proteins in the ER activates a type I ER transmembrane protein called Ire1. Ire1 contains an N-terminal ER lumenal domain and a C-terminal cytoplasmic domain. The cytoplasmic domain itself contains two subdomains, one with a kinase activity and the other with an RNase activity. In the presence of ER stress, when unfolded proteins accumulate, monomeric Ire1 forms higher-order oligomers triggered by self-association of the ER lumenal domain. This oligomerization leads to autophosphorylation of Ire1's cytoplasmic domain, producing a conformational change that acts as a molecular switch to activate Ire1's RNase activity. Once fully activated, Ire1 then cleaves a specific cytosolic RNA molecule at two positions, excising an intron. The two separated RNA exons resulting from this unconventional cytosolic splicing reaction are joined together by a tRNA-like RNA ligase, generating a mature mRNA. This mRNA is now translated to produce an evolutionarily conserved gene-regulatory bZIP protein (Hac1 in yeast; XBP1 in mammals), which activates transcription of the multiple genes mediating the UPR, as described above. The mammalian version of yeast Ire1 was identified in 1998 in independent studies by David Ron (New York University Langone Medical Center) and Randal J. Kaufman (University of Michigan Medical Center).

The next key event in the Ire1 story occurred in 2005 when Walter, in collaboration with Robert Stroud (UCSF), solved the crystal structure of the ER lumenal domain of Ire1, providing insight into how monomeric Ire1 is initially oliogmerized and activated by misfolded proteins. The structural studies, combined with biochemical evidence, suggest that the lumenal domain forms an MHC class I–like protein-binding groove that binds unfolded proteins directly and shifts the inactive monomeric form of Ire1 to its active oligomeric state. Thus, in unstressed cells BiP binds to the lumenal domain of monomeric Ire1, stabilizing it in an inactive form. Then, when unfolded proteins accumulate, BiP dissociates from Ire1's lumenal domain, allowing the binding of unfolded proteins, which in turn leads to Ire1's oligomerization and full activation.

The second UPR pathway, called the ATF6 pathway, was discovered by Mori in 1996 in mammalian cells. Yeast cells express neither the ATF6 pathway nor the third UPR pathway (discussed below). ATF6 is a type II ER transmembrane protein containing two domains, an N-terminal lumenal domain and a C-terminal cytoplasmic domain. The activation of ATF6 by ER stress is strikingly different from that of Ire1. In the unstressed state, the BiP chaperone binds to the lumenal domain of ATF6. Under stressed conditions, the accumulation of unfolded proteins leads to dissociation of BiP from ATF6, which then allows the packaging of ATF6 into COPII-coated vesicles for transport to the Golgi apparatus. In the Golgi, ATF6 undergoes a sequential two-step cleavage by two membrane-bound proteases, S1P and S2P, resulting in the release of the cytoplasmic bZIP transcription factor domain of ATF6. The released portion of ATF6 then moves to the nucleus to activate UPR target genes, including those encoding BiP, ERAD components and XBP1. Cleaved ATF6 can activate UPR target genes either by dimerizing with itself or by forming a heterodimer with XBP1.

Subsequent to the work of Mori and Walter, in 1999 Ronald C. Wek (Indiana University School of Medicine) and David Ron independently uncovered a third UPR pathway, now called the PERK pathway. PERK is an integral transmembrane protein kinase, and its activation resembles that of Ire1. In the unstressed state, the lumenal domain of PERK interacts with BiP; but when unfolded proteins accumulate, BiP dissociates, triggering PERK dimerization, autophosphorylation and activation of its cytoplasmic kinase domain, and then phosphorylation of a translation initiation factor. This latter action abruptly attenuates protein synthesis, causing cell cycle arrest. The net result is a reduction in the flux of new proteins entering the ER, thus limiting the load of proteins to be folded.

The combined action of the three UPR pathways in mammalian cells ensures maintenance of ER homeostasis during physiological conditions of protein trafficking through the secretory system. It also allows the cells to cope with pathological situations where mutant unfolded proteins accumulate, as occurs in many inherited human diseases. For example, the most common form of hereditary α1-antitrypsin deficiency results from a mutant protein that does not fold properly and cannot be secreted from the liver into the plasma. A decrease in plasma α1-antitrypsin produces emphysema by depriving the lung of a potent inhibitor that protects the organ's elastic tissue against damage. Moreover, the misfolded mutant α1-antitrypsin that accumulates in the liver produces either severe liver damage (in individuals who apparently do not elicit an adequate UPR) or mild to no damage (in those who apparently do elicit an adequate UPR). The UPR also plays a key role in the complex pathogenesis of many other diseases, including various forms of cancer (especially multiple myeloma, where large quantities of immunoglobulins are produced and accumulate in the ER), neurodegeneration and inflammation.

Clinical Award: a new Parkinson's disease

This year's Lasker~DeBakey Clinical Research Award is given to Mahlon R. DeLong (Emory University School of Medicine) and Alim-Louis Benabid (Université Joseph Fourier) for their development of deep brain stimulation, a surgical technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease. More than 100,000 patients with Parkinson's worldwide have benefited from deep brain stimulation, which involves the implantation of a medical device that sends electrical impulses to the subthalamic nuclear region of the brain.

Parkinson's disease is a chronic and progressive neurodegenerative disorder that produces, in its early stages, multiple movement abnormalities, including tremors, bradykinesia (slowness of movement), rigidity of the arms and legs and impaired balance and coordination. In the later stages, problems concerning cognition, behavior and depression may arise. Parkinson's disease affects ~1 million people in the United States and 7 million in the world with a mean age of onset of 60 years; it is the second most frequent neurodegenerative disorder after Alzheimer's disease.

The motor symptoms of Parkinson's disease result from the death of dopamine-producing neurons in the basal ganglia of the brain. Dopamine is a chemical neurotransmitter that relays messages between the basal ganglia's substantia nigra and other parts of the brain to control movements of the body. Motor symptoms occur when 60–80% of the dopamine-containing neurons are damaged. Drug treatment with orally administered L-DOPA, which is converted in the brain to dopamine, is effective during the early stages of the disease. For the last 40 years, L-DOPA has been widely used as a first-line therapy. In 1969, the late George Cotzias received a Lasker Clinical Research Award for his demonstration of the therapeutic effectiveness of L-DOPA. But after five to ten years of therapy with L-DOPA, most patients no longer respond, and their motor abnormalities become incapacitating.

In the past 15 years, deep brain stimulation has emerged as an effective therapy for many patients who either no longer respond to or suffer complications from L-DOPA treatment. The story of the development of deep brain stimulation can be told in two chapters. The first chapter began 40 years ago with Mahlon DeLong. His detailed electrical recordings revolutionized our understanding of the organization of the basal ganglia. He discovered that the basal ganglia was composed of multiple different neuronal circuits and pathways that control different motor and cognitive functions.

In 1990, DeLong experimented with a monkey model of human Parkinson's disease in which the animals are treated with a toxic chemical, MPTP, which destroys dopaminergic neurons in the substantia nigra region. This loss of dopamine causes certain neurons in the basal ganglia to fire excessively and to produce tremors in the monkeys, resembling those in humans. When DeLong created lesions in various regions of the monkeys' basal ganglia, he discovered that ablation of one particular region—the subthalamic nucleus—dramatically ameliorated the tremors.

DeLong's lesion experiments in the nonhuman primate model provided a sound rationale and a specific target for surgical intervention in patients with Parkinson's disease. However, the subthalamic nucleus was not considered a suitable target for lesioning in humans because of its tiny size and the risk of inducing bleeding.

The second chapter in the deep brain stimulation story centers on the research of Alim Benabid, who was trained both as a physicist and as a neurosurgeon. At the time that DeLong was carrying out his circuitry analysis

Figure 3 Richard Hamilton, *Balzac* (c). 2011 (printed 2012). 112 × 176 cm. Digital montage of known images. Epson inkjet on Hewlett-Packard Resolution canvas. Exhibited at National Gallery, London, from October 2012 to January 2013.

and lesion experiments in nonhuman primates, Benabid was developing new stereotactic techniques for treating patients with essential tremor. In 1987, in an operation intended to place a lesion in the thalamic nucleus ventralis intermedius (VIM) of such a patient, Benabid discovered that when he moved the electrode along the insertion pathway to the VIM, the patient's tremor stopped when the stimulus rate was increased from low frequency (1 Hz) to high frequency (100 Hz). When the stimulus was stopped, the tremor returned; when applied again, the tremor stopped; and it returned again when the stimulus was again stopped. This pivotal observation in his patient with essential tremor, together with his knowledge of DeLong's findings in the nonhuman primates with Parkinson's, led Benabid in the early 1990s to devise a bold surgical procedure: he applied bilateral, high-frequency stimulation to the subthalamic nucleus in humans with advanced Parkinson's disease. This strategy proved remarkably successful; it reduced the tremors and markedly improved the quality of life. These positive results were first reported in 1995. The benefits of deep brain stimulation typically last for about five years.

Bilateral deep brain stimulation was approved by the US Food and Drug Administration (FDA) for essential tremor in 1997 and for Parkinson's disease in 2002. Deep brain stimulation has also received FDA approval for treatment of dystonia and obsessive-compulsive disorder and is currently being tested in multiple clinical trials involving patients with drug-resistant cases of chronic pain, major depression and Tourette's syndrome.

The implanted device used for deep brain stimulation has three components: a neurostimulator implanted subcutaneously below the clavicle or over the abdomen, an electrode implanted in the subthalamic nucleus above the spinal cord (hence the name *deep* brain stimulation) and a thin-wire extension that connects the neurostimulator to the electrode. After implantation, the device can be programmed to fine-tune the dose of stimulation required to alleviate the tremors. The batteries typically last for three to five years.

How the electrical stimulation relieves the motor symptoms of Parkinson's disease is not completely understood. One prevailing view, supported by optogenetic studies in rodent models, is that in low-dopamine states the subthalamic nucleus is hyperactive and this hyperactivity is inhibited by high-frequency stimulation.

In their independent but complementary studies carried out over the last 30 years, DeLong and Benabid have been and continue to be the undisputed leaders in temporarily halting and reversing the devastating motor abnormalities that occur in L-DOPA–resistant Parkinson's disease—an unimaginable accomplishment several decades ago. The distinguished neurobiologist Vernon B. Mountcastle (Lasker Clinical Medical Award recipient in 1983) made the following observation: "I know of no other discovery in basic neuroscience that has been applied with such success in treatment of human patients with CNS [central nervous system] disease."

Special Achievement Award: having a broad impact

The Lasker~Koshland Special Achievement Award is given to Mary-Claire King (University of Washington School of Medicine) for her bold, imaginative and diverse contributions to medical science, evolutionary biology and human rights. During her 45-year research career, she identified the first gene locus that predisposes individuals to a hereditary form of breast cancer (*BRCA1*), demonstrated the close similarity (99%) in coding-sequence genes between humans and chimpanzees and devised DNA-based strategies that reunite missing persons or their remains with their families.

As a PhD graduate student at the University of California, Berkeley in the early 1970s, King studied under the late Allan Wilson, a pioneer in the use of molecular approaches to understand human evolution. Her doctoral thesis led to a highly discussed and cited 1975 paper. Using gene and protein analysis techniques that were state of the art in the 1970s but are considered primitive by today's standards, King and Wilson showed that the protein-coding sequences in the genomes of humans and chimpanzees are nearly identical (99%)—a result that did not sit well with the traditional evolutionary theory based on fossil studies of the time. The major differences between humans and chimpanzees, according to the hypothesis advanced by King and Wilson, result from a small number of mutations affecting gene regulation and the timing of gene expression during development. This claim, controversial at the time, was validated 30 years later when the chimpanzee genome sequence was published and compared to that of humans. The King-Wilson 'regulatory theory' is now a central paradigm of human evolutionary research.

During her graduate work, King became fascinated with the genetics of complex human diseases, and when she began her independent career in 1976 as Professor of Epidemiology and Genetics at Berkeley (she moved to the University of Washington in 1995), she focused on breast cancer. The prevailing dogma was that breast cancer arose from undefined interactions between genetic and environmental mishaps, and most geneticists doubted that breast cancer could be caused by a single gene. King's initial approach in the mid-1970s was to develop mathematical models based on limited data from a scant number of families having two or more relatives affected with early-onset breast cancer (and, less often, ovarian cancer). This theoretical work soon gave way to 15 years of tenacious and fearless clinical investigation in which King and her small group of colleagues identified and interviewed 23 extended families containing 329 participating relatives, 146 of whom had breast cancer. Obtaining blood samples from the 329 participating relatives required making trips and/or contacting healthcare workers in 40 states plus Puerto Rico, Canada, Colombia and the United Kingdom.

In 1990, King reported the identification, by classic linkage analysis, of a gene locus at chromosomal site 17q21 that was responsible for the early-onset breast and/or ovarian cancer in the 23 families. The existence of such a putative gene (which she named *BRCA1*) triggered enormous interests in many large labs. The race was now on to isolate *BRCA1* by positional cloning, and after four years *BRCA1* was isolated and sequenced by Mark Skolnick and his colleagues at Myriad Genetics.

The approach King used in identifying *BRCA1* has become a model for detection of genes causing common complex diseases. The paradigm involves first identifying rare families in which a complex phenotype is transmitted as a Mendelian trait, then finding the responsible gene in those families and ultimately identifying mutations in the same gene in affected individuals with little or no family history. This approach has been used for discovery of genes of large effect in many common diseases and traits, including colon cancer, hyperlipidemia, coronary heart disease, hypertension, Alzheimer's disease, Parkinson's disease and age-related macular degeneration.

In the 20 years since the discovery of *BRCA1*, more than 10,000 papers on the subject have appeared in the scientific literature, and it is likely that many thousands more have appeared in the lay press. In addition to *BRCA1*, a second breast cancer gene predisposing to early-onset disease, called *BRCA2*, was mapped, identified and cloned in 1995 by a team led by Michael Stratton

and his colleagues (then at the UK Institute of Cancer Research). The abnormal proteins encoded by mutant versions of *BRCA1* and *BRCA2* fail to carry out their normal function of repairing damaged DNA, thus compromising the integrity of the genome and setting the stage for cancer.

The lifetime risk for breast cancer in females with a germline mutation in *BRCA1* or *BRCA2* is 70–80% as compared to 12% for those without mutations in either gene. The lifetime risk for ovarian cancer is 40% for individuals with a *BRCA1* mutation and 12% for those with a *BRCA2* mutation as compared to 1.4% for those without these mutations. Diagnostic screening for *BRCA1* and *BRCA2* mutations in women with a family history of breast and/or ovarian cancer is now widely available, and many women who test positive for these genes undergo prophylactic mastectomy and/or oophorectomy.

Two aspects of King's career are especially noteworthy and set her apart from other biomedical scientists. The first is the fact that even though she is a PhD without MD credentials, she nonetheless conceived and carried out virtually single-handedly one of the most outstanding examples of patient-oriented (translational) research in the last 50 years, as described above. The second relates to her pioneering work in exposing and resolving human rights abuses.

Motivated by a deep sense of social justice, King deployed genetic and genomic methods to identify orphaned children and then reunite them with their biological grandparents. During the Argentinean military dictatorship of 1975–1983, the parents of hundreds of 'lost children' were murdered, after which the children were kidnapped and illegally 'adopted' by wealthy military families. Using a variety of DNA-based assays, including the sequencing of PCR-amplified segments of mitochondrial DNA extracted from teeth, King was able to match more than 100 of the kidnapped children to their biological grandmothers or other persons who were their maternal relatives. King's genomic mitochondrial technique has also been used to identify the human remains of American soldiers, including that of an unidentified serviceman killed in the Vietnam War and entombed for 14 years in the Tomb of the Unknowns in Arlington National Cemetery.

Mary-Claire King's scientific career of 45 years began with a landmark study in human evolution, was followed with a breakthrough discovery in breast cancer genetics and has continued with genetic identification work to aid people in distressed situations. Her achievements epitomize in a special way how forward-looking genetic research can benefit humanity and society.

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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 see http://www.laskerfoundation.org/.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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