Lasker Awards and papal portraiture: turning fields upside down

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Picasso has been quoted as saying "my mother said to me, 'If you are a soldier, you will become a general. If you are a monk, you will become a Pope.' Instead, I was a painter, and I became Picasso." And, indeed, Picasso did become a Picasso. His oeuvre was extraordinary in its creativity and quantity: he produced more than 50,000 works of art, including 2,000 paintings, 1,300 sculptures, 30,000 prints and 8,000 drawings, not to mention thousands of ceramics and hundreds of tapestries and rugs.

Picasso's passion for portraiture was legendary. His subjects included virtually every living creature imaginable: wives, lovers, children, parents, himself, art dealers, artists, musicians, bathers, ballet dancers, midgets, prostitutes, soldiers, sailors, wealthy patrons, dogs, cats, sheep and roosters—but, surprisingly, no popes. At least I've never seen a Picasso picture of a pope, although, in the spirit of full disclosure, I admit that I have not looked at all 50,000 of Picasso's works.

The lack of popes in Picasso's portraiture is mystifying when one considers that Picasso was fascinated by the work of his artistic forebears. He relentlessly copied, reconfigured and transformed well-known paintings by the Old Masters. Three of the Old Masters whom he was obsessed with—Raphael, Titian and Velázquez—were themselves obsessed with painting popes. Picasso once proclaimed, "any work they can do, I can do better." He also boasted, "When I was four, I could draw like Raphael, but it has taken me a lifetime to paint like a child." But could it be that Picasso met his match with the Vatican, realizing that he could not outshine Raphael, Titian and Velázquez when it came to painting popes?

Papal portraiture has a long tradition, and the story of how it has changed over the last 500 years mirrors how changes have occurred in the biomedical sciences. In both cases, breakthroughs can be traced to the creative talents of a handful of individuals.

From Raphael to Titian

Before 1500, all papal portraits presented the pope either kneeling in prayer or in a narrative context together with his cardinals. In 1511, Raphael abruptly broke with tradition by depicting Pope Julius II in a moment of introspection: sitting alone on an armchair, ensconced in his papal regalia of crimson cap, crimson cape, white apron and the Ring of the Fisherman, a solid gold *bas relief* of Saint Peter fishing from a boat (**Fig. 1a**). Raphael's pioneering pose—the three-quarter view of the seated pope, with his eyes looking down and his forearms resting on the papal throne—defined the style of papal portraits for centuries to come. In scientific parlance, Raphael's contribution was the key breakthrough in the field of papal portraiture.

Because popes tend to be blessed with longevity, the next advance did not come until 35 years later, when Titian was summoned from Venice to Rome to paint Pope Paul III. Titian adopted Raphael's general model in terms of pose and tenor but departed from it in a radically original way. Titian used color and light to produce the luster of the velvet, the stiffness of the linen and the vigor of the flesh (**Fig. 1b**). The secret to Titian's technical innovation was his use of a bare minimum number of hues—two in this case, red and white—applied in the subtlest of gradations.

From Titian to Velázquez

One hundred years after Titian's historic portrait, the Spanish painter Velázquez journeyed to Rome, scrutinized Titian's portrait of Paul III, and requested permission to paint Pope Innocent X. Innocent X was arguably the worst of all popes; he was hot-tempered, paranoid, ruthless and unscrupulously duplicitous in taking the name of Innocent. What's remarkable about Velázquez's portrait is how he paints Innocent X in the Raphael-Titian tradition, thus satisfying his demanding client with a flattering portrait, yet at the same time conveying a hint of the pope's explosive personality and corrupt character (**Fig. 1c**).

Contrasted with the calm enthronement of Titian's Paul III, Velázquez's Innocent X looks like he is sitting on a powder keg ready to explode. Velázquez's crimson tints are so marvelously orchestrated that one critic remarked, "if the Pope were to open his tightly clinched mouth, even his saliva would be blood red." Joshua Reynolds, the influential eighteenth-century English portrait painter, thought Velázquez's Innocent X to be the finest painting he had ever seen.

Three versions of Pope Innocent X

For the next 300 years, the field of papal iconography was bereft of innovation, both conceptually and technically. The Raphael-Titian-Velázquez model continued to hold sway over the field. Then, in 1953, the British artist Francis Bacon reinvented and reinterpreted Velázquez's portrait of Pope Innocent X in a style appropriate for twentieth-century modern art (**Fig. 2a**,**b**). Bacon subverted the pope by placing him on a throne that resembles an electric chair, cordoned off by a yellow hexagonal rail and encased in vertical lines that run up and down the painting like bars of a prison cell. Bacon dressed the pope in gaudy, blood-stained attire and distorted his face with shattered glasses and a screaming mouth.

Bacon, who detested authority figures (especially 'popeishness'), designed the screaming pope to shake people out of their traditional way of thinking and to touch them at their very core. In the world of science, this is precisely the type of work that Lasker Awards honor—work that screams out at us with new ideas and new ways of thinking.

The latest new way of thinking about papal portraiture comes from an up-and-coming young British artist named Glenn Brown, who has perfected a novel technique for rendering

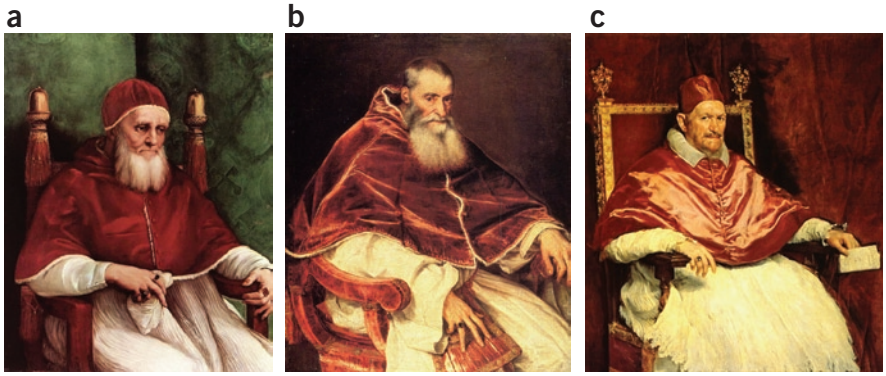

Figure 1 Papal portraiture, from Raphael to Titian to Velázquez. (**a**) Raphael, *Pope Julius II*. 1511. Oil on wood. 108 × 80.7 cm. National Gallery, London. (**b**) Titian, *Pope Paul III*. 1543. Oil on canvas. 106 × 85 cm. Museo Nazionale di Capondimonte, Naples. (**c**) Velázquez, *Pope Innocent X*. 1650. Oil on canvas. 114 × 119 cm. Palazzo Doria Pamphili, Rome.

the surface of a canvas as flat and smooth as a glossy magazine page. With this technique, Brown created a stunning painting of Pope Innocent X that appropriates elements from both Velázquez and Bacon (**Fig. 2c**). Brown's pope was exhibited for the first time last year at a retrospective of his work at the Tate Gallery in Liverpool.

Brown distorts the image of Pope Innocent X by removing his cape and cap, painting his hands gangrene green and rotating his body 180 degrees. Only the white apron and the Ring of the Fisherman are retained. In this painting, Brown literally turns the 500-year-old field of papal portraiture upside down and on its head.

When you read about the research accomplishments of this year's Lasker Basic and Clinical Award recipients, I hope you'll see how they have turned the fields of nuclear reprogramming and cancer therapeutics upside down and on their heads.

Lasker Basic Award: rethinking nuclear reprogramming

The scientific world—not to mention prize-awarding committees—loves a cut-and-dry discovery, the path of which can be traced back to a single laboratory group. This year's Albert Lasker Basic Medical Research Award is given to the two scientists whose laboratories, each singlehandedly, laid the major conceptual and methodological groundwork for nuclear reprogramming, the process that instructs specialized adult cells to form early pluripotent stem cells. Pluripotent stem cells possess the capacity to become any type of mature cell in the body and therefore have great potential for experimental and therapeutic purposes. The two honored scientists are John B. Gurdon (University of Cambridge) and Shinya Yamanaka (Kyoto University).

The field of nuclear reprogramming began 45 years ago, when John Gurdon began his now classic nuclear transfer experiments in frogs. Gurdon's experiments were stimulated by the earlier work of Robert Briggs and Thomas King, who showed in 1952 that, if the nucleus of a tadpole embryo at the blastula stage is injected into an enucleated frog egg, a normal tadpole forms, yet, if nuclei from the later gastrula stage are injected, normal tadpoles do not form. Briggs and King concluded from their experiments that cell differentiation involves irreversible nuclear changes such that reprogramming of specialized adult cells to pluripotent stem cells cannot occur. Their results, however, were inconclusive, owing to technical problems such as the exact state of differentiation of the injected embryonic cells and the inability to show that the host frog eggs had been completely enucleated.

As a young independent scientist, Gurdon became obsessed with the question posed by Briggs and King—do cell differentiation and multiorgan formation in a developing animal involve the irreversible shut-off of particular genes in embryonic stem cells, or is it simply a turning off of certain genes that can subsequently be reprogrammed to their earlier, undifferentiated state? Over a ten-year period beginning in 1965, Gurdon perfected the frog nuclear transfer technique. He overcame the ambiguities in the Briggs-King experiments by injecting nuclei from adult frog cells that were fully differentiated (such as intestinal cells or keratinized skin cells from the foot pad), and by using nuclei from frogs that had been genetically marked so that he could unequivocally tell the difference between a frog derived from the differentiated nucleus and one derived from the residual genetic material in the host egg. After many attempts and many failures, Gurdon succeeded in1975 in producing healthy and sexually mature fertile frogs with functional muscle, beating hearts, well-differentiated eyes and all of the other organs. These experiments provided the first clear evidence that cell specialization does not involve irreversible inactivation in the genes required for development of an animal. In laying down this conceptual framework, Gurdon became the father of the field of nuclear reprogramming in the same sense that Raphael became the father of the field of papal portraiture.

The next major advance in nuclear reprogramming came in 1997 with the cloning of the adult sheep Dolly, which was achieved by transfer of the nuclei of breast epithelial cells from an adult sheep to enucleated sheep eggs. These experiments, carried out by Kevin Campbell and Ian Wilmut of the Roslin Institute in Edinburgh, dramatically extended Gurdon's concept from frogs to mammals and erased any lingering doubts concerning the ability of the nucleus of a specialized mature cell to direct the formation of a mature animal.

The Dolly experiment and similar work that produced monkeys, cows, dogs, mice and other animals stimulated scientists to think about using nuclear transfer to generate pluripotent human embryonic stem (ES) cells. Such an achievement, if realized, would have implications for producing patient-specific ES cells that could be used for replacement therapy of diseased cells and tissues. The application of this technique to humans, however, has been extremely limited, owing to the restricted availability of appropriate oocyte donor eggs for producing human ES cells, the low efficiency of successful nuclear transfers and the lack of any progress in identifying specific molecules from oocytes that promote the reprogramming process.

Then, in 2006, out of the blue came Shinya Yamanaka, who achieved a spectacular advance: turning adult mouse skin cells into pluripotent ES cells that have the capacity to form living mice, without the need to inject a somatic cell nucleus into an enucleated egg or to use an embryo to produce ES cells. His approach was to select 24 of the most promising genes that had been reported to confer pluripotency on somatic cells and then transfect each of them into fibroblasts, either singly or in every possible combination. After four years of intense work, Yamanaka and his postdoctoral fellow Kazutoshi Takahashi found that no one gene did the trick, but a combination of four of them—those encoding the transcription factors Oct4, Sox2, Klf4 and c-Myc—when transfected together induced fibroblasts to form pluripotent stem cells, now referred to as

induced pluripotent stem (iPS) cells. Each of the four Yamanaka factors changes the behavior of the fibroblast by turning its genes on or off to convert it to an iPS cell.

Yamanaka's result was a major surprise and immediately engendered widespread skepticism. But within months of his publication, several groups had confirmed and extended his work. One striking extension was accomplished in 2008 by Rudolf Jaenisch (Whitehead Institute). Jaenisch and colleagues first generated iPS cells from a skin biopsy of a mouse with humanized sickle-cell anemia. They then proceeded to sequentially correct the hemoglobin mutation *in vitro* by gene targeting of the iPS cells, differentiate the corrected iPS cells *in vitro* into hematopoietic progenitors and transplant the differentiated hematopoietic cells into donor sickle-cell mice, rescuing the disease phenotype—a *tour de force* of genetic engineering that presages the power of the Yamanaka technology for cell replacement therapy.

In 2007, Yamanaka led the way in showing that the same four genes that work in mice can also turn human skin fibroblasts into human iPS cells, and similar results were reported shortly thereafter by James Thomson (University of Wisconsin) and George Daley (Children's Hospital Boston). Other scientists are also contributing to iPS technology, attempting to increase the efficiency of the induction system and simplify it by using chemicals to replace one or more of the Yamanaka genes.

Yamanaka literally turned the field of nuclear reprogramming upside down, in much the same way that Francis Bacon and Glenn Brown turned the field of papal portraiture on its head. The iPS cell technology has enormous potential for both basic biology and clinical medicine. For biology, iPS cells enable the identification and purification of molecules that mediate reprogramming, which ultimately should provide clues to its mechanism. For medicine, iPS cells pave the way for exploring the mechanisms underlying poorly understood disorders. Within the past year alone, four groups have generated iPS cells from individuals with various neurodegenerative diseases, as well as several mendelian and polygenic disorders. iPS cells may also provide a new form of personalized therapeutics based on cell replacement, as exemplified by the Jaenisch experiment on sickle-cell anemia.

The Gurdon and Yamanaka technologies can both generate living animals. Are the molecular and cellular mechanisms underlying these two different technologies the same or different? Answering this question will surely reveal new clues to one of the fundamental problems in biology, which is how an undifferentiated embryonic stem cell can give rise to a living animal with hundreds of different cell types and many complex organs.

Lasker Clinical Award: 'near' cure for a fatal leukemia

The clinical world—not to mention the popular press—loves a new sensational therapy that turns a fatal illness into a 'near' cure. This year's Lasker~DeBakey Clinical Medical Research Award is given to the three scientists who developed molecularly targeted treatments for chronic myeloid leukemia (CML), converting what was previously a fatal cancer into a manageable chronic condition. The three honored scientists are Brian J. Druker (Oregon Health & Science University), Nicholas B. Lydon (formerly at Novartis) and Charles L. Sawyers (Memorial Sloan-Kettering Cancer Center).

CML is a form of leukemia characterized by excessive proliferation of hematopoietic stem cells of the myeloid lineage, producing a massive 20- to 25-fold elevation of immature and mature white blood cells. The disease progresses over three to five years to an accelerated phase that culminates in blast crises and death. It occurs in about 12,000 new patients per year in the US and Europe combined and represents about 15% of all adult leukemias.

CML was the first leukemia to be described in the medical literature, in 1845, and it was the first cancer to be linked causally to a genetic abnormality—the Philadelphia chromosome. The connection between CML and the Philadelphia chromosome was made in 1960 by Peter Nowell, who originally characterized the genetic abnormality as a shortened chromosome 22. In 1973, Janet Rowley showed that the shortened chromosome 22 arises as a result of a reciprocal translocation between the long arms of chromosomes 9 and 22, called t(9:22). For their pioneering work on the genetic origin of cancer in humans, Nowell and Rowley, together with Alfred Knudson, were awarded the Lasker Clinical Medical Award in 1998.

Between 1984 and 1990, molecular biologists from the laboratories of Eli Canaani, John Groffen, Gerald Grosveld, David Baltimore and Owen Witte discovered that the t(9:22) translocation in CML fuses the *ABL1* tyrosine kinase gene (formerly known as *c-ABL*) on chromosome 9 to the *BCR* gene on chromosome 22 and that this *BCR-ABL1* fusion gene encodes a constitutively active tyrosine kinase. When introduced as a transgene into mice, the *BCR-ABL1* fusion gene produces a CML phenotype, thus establishing *BCR-ABL1* as a leukemic oncogene.

Knowing that the constitutive tyrosine kinase activity of BCR-ABL is responsible for its transforming activity, Brian Druker (then a postdoctoral fellow at Dana Farber Cancer Center) became obsessed with the idea that inhibiting BCR-ABL kinase would be the perfect treatment for his patients with CML. In the late 1980s, the standard therapy for CML was interferon-α together with cytarabine, which produced multiple adverse side effects and thus required discontinuation in a large number of patients. The only chance for a cure was allogeneic stem cell transplantation, but only 15% of patients were eligible, owing to age limitations or to a lack of human leukocyte antigen–matched donors.

In 1988, Druker approached Nicholas Lydon, then a research scientist at Ciba-Geigy (now Novartis), to collaborate on the identification of small-molecule inhibitors of BCR-ABL. Druker had learned that Ciba-Geigy had assembled a team of scientists, headed by Alex Matter, to develop inhibitors of various tyrosine kinases. As the biochemist of the team, Lydon had established efficient baculovirus expression systems for producing enzymatically active and highly purified tyrosine kinases—a routine procedure today, but a challenging feat two decades ago. Druker and Lydon realized

Figure 2 Three portrait versions of Pope Innocent X. (**a**) Velázquez, *Pope Innocent X.* 1650. Oil on canvas. 114 × 119 cm. Palazzo Doria Pamphili, Rome. (**b**) Francis Bacon, *Study after Velázquez's Portrait of Pope Innocent X.* 1953. Oil on canvas. 153 × 118.1 cm. Nathan Emory Coffin Collaboration, Des Moines Art Centre. (**c**) Glenn Brown, *Nausea.* 2008. Oil on panel. 155 × 120 cm. Tate Liverpool.

that even though CML was a rare cancer, it was the only one in which a single oncogene, *BCR-ABL1*, was known to be the sole cause of the malignancy.

By 1993, Lydon and two of his colleagues, cell biologist Elizabeth Buchdunger and chemist Jürg Zimmermann, had identified several promising tyrosine kinase inhibitors. The compounds were sent to Druker (by then a new faculty member in Oregon), who found that one of them, imatinib (previously called 5T1571 and now known by the trade name Gleevec), potently inhibited the growth of *BCR-ABL1*–transformed cells both in culture and when grown as tumors in mice.

Impressed with these preclinical results, Druker led the efforts to begin clinical trials in individuals with CML. In 1995, he enlisted the collaboration of Charles Sawyers (then at the University of California–Los Angeles) to help him design a strategy that would convince Novartis to move forward. Sawyers had established assays, applicable to clinical samples, for assessing the functional connections between BCR-ABL kinase and its downstream effectors—Myc, RAS and the mitogen-activated protein kinase pathway. To convince Novartis, Druker and Sawyers had several major hurdles to overcome. Arguably the biggest, from the Novartis perspective, was that Gleevec would be a drug for a small market. There was also the problem of liver toxicity in animal studies, but this was resolved with an improved oral formulation. The third hurdle was that Ciba-Geigy had just merged with Sandoz to create Novartis, and Nick Lydon, the internal Gleevec champion, had now left the company after 12 years of work on tyrosine kinase inhibitors.

The saving grace was a fortuitous one: Gleevec was not totally specific in its inhibition of BCR-ABL; it also inhibited several other tyrosine kinases, including c-KIT and the platelet-derived growth factor (PDGF) receptor tyrosine kinase. Druker and Sawyers argued that if Gleevec worked in CML, the drug could have a large market potential for other cancers that are driven by mutant c-KIT or PDGF receptors. They won their case, and Novartis moved forward. In 1998, Druker and Sawyers, together with Moshe Talpaz (The University of Texas M. D. Anderson Cancer Center), designed and initiated a phase 1–2 clinical trial in patients with who were resistant to previous interferon-α therapy. The outcome was electrifying; 53 of 54 subjects experienced complete hematological remissions within four weeks of treatment, 54% of subjects showed improved cytogenetic responses and the adverse effects were minimal. The equally impressive results of an larger phase 2 trial led the US Food and Drug Administration (FDA) to accelerate the approval process without a phase 3 trial—a record achievement for an anticancer drug. Gleevec was formally approved in the United States in June 2001. The five-year update for Gleevec in newly diagnosed patients with CML showed nearly 90% overall survival.

As predicted by Druker and Sawyers, Gleevec's promiscuous action in inhibiting c-KIT and the PDFG receptor proved extremely useful in treating patients with malignancies driven by these two oncogenes. The most striking example occurs in individuals with gastrointestinal stromal tumors, who harbor activating mutations in c-KIT. Gleevec is also effective in other hematopoietic diseases arising from translocations that constitutively activate the PDGF receptor, including hypereosinophilic syndrome, chronic eosinophilic leukemia and a subset of patients with chronic myelomonocytic leukemia. In a remarkable irony, Gleevec is now one of Novartis's two best-selling drugs.

Each year, about 5% of Gleevec-treated patients with CML develop resistance to the drug, but this is where Sawyers' expertise in assessing BCR-ABL kinase activity has paid off handsomely. Using clinical samples from individuals with CML who no longer responded to Gleevec, Sawyers identified a series of point mutations in the kinase domain of BCR-ABL that, he believed, were the probable cause of the resistance. Although each resistant patient had only one mutation, more than 50 different resistance mutations have now been identified. The mutations are scattered all over the kinase domain, with several localized to the drug's binding site. A key insight came from the crystal structure of the BCR-ABL kinase, obtained by John Kuriyan (University of California–Berkeley), which showed that the kinase exists in two conformations: 'on' (active) and 'off' (inactive). The enzyme's optimal shape for binding to Gleevec turned out, surprisingly, to be the 'off' conformation; Gleevec inhibits the kinase by blocking its ability to cycle from the 'off' to the 'on' conformation. In collaborative studies with Kuriyan, Sawyers found that all of the *BCR-ABL1* mutations in Gleevec-resistant patients (except for the several binding-site mutations) jam the enzyme into the 'on' conformation, preventing the drug from inhibiting the enzyme.

These structural insights led Sawyers to collaborate with scientists at Bristol-Myers Squibb, who had identified a dual ABL-SRC kinase inhibitor known as dasatinib (Sprycel). Sawyers suspected that Sprycel, on the basis of its kinetic properties, would bind to the 'on' conformation of resistant BCR-ABL kinases and then block enzyme activity. His suspicion turned out to be correct, leading him, together with Moshe Talpaz, to design and spearhead a phase 1 clinical trial of dasatinib in Gleevec-resistant CML patients. To paraphrase Yogi Berra, "it was Gleevec *déjà vu* all over again." The results were so striking—every subject responded except for the one predicted not to respond—and the toxicity was so negligible that the FDA granted approval for Sprycel in 2006, just five years after Sawyers' discovery of the first Gleevec-resistant mutations. Sawyers' work provides compelling evidence that these mutations in *BCR-ABL1* are in fact the primary cause of the drug resistance, ruling out other mechanisms such as increased elimination of the drug or its inactivation by other proteins.

Gleevec has unquestionably transformed the treatment of people with CML in much the same way that insulin transformed the treatment of people with type 1 diabetes. The discoveries of Druker, Lydon and Sawyers illustrate a number of 'firsts' in cancer therapeutics and drug development: the first targeted cancer therapy involving a small molecule (a tyrosine kinase inhibitor) directed at the root cause of the disease; the first reversal of a fatal cancer by the oral ingestion of one or two pills each day; the first example of a cancer therapy in which resistance to the first drug pointed the way to the rapid development of a new, second-line drug that is equally effective; the first example of two drugs that were developed through partnerships involving academic and pharmaceutical scientists from beginning (identification of target) to end (FDA approval); and the first example in which a drug originally developed for a rare disease turned out to become one of the best-selling drugs in the world today.

Druker, Lydon and Sawyers have literally turned the field of cancer therapeutics upside down and completely around, transcending the Old Masters—the one thing that Picasso never did.

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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 refer to the Lasker website at http://www.laskerfoundation.org/.