Creation and revelation: two different routes to advancement in the biomedical sciences

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This past summer, two of the world's great art institutions—the Royal Academy of Arts in London and the Louvre in Paris—held exhibitions in which the highlight was the depiction of a tree. Artists have long been fascinated with trees, owing perhaps to the fact that trees are Nature's only living elements that link the Heaven, the Earth and the Underworld. The tree at the Royal Academy (a painting) and the tree at the Louvre (a sculpture) exemplify two different routes to achieving artistic greatness: one involving creation and the other involving revelation.

As in art, creation (through invention) and revelation (through discovery) are two different routes to advancement in the biomedical sciences. The 2007 Lasker Clinical Award (awarded for the invention of prosthetic cardiac valves) is an example of advancement through creation. The 2007 Lasker Basic Award (awarded for the discovery of the immune system's dendritic cells) exemplifies advancement through revelation. And the 2007 Lasker Public Service Award recognizes a life-long career devoted to both creativity and discovery.

Creating a tree at the Royal Academy of Arts

The tree at the Royal Academy of Arts is the centerpiece of a painting by the Los Angeles–based British artist David Hockney. It was shown at the Academy's annual Summer Exhibition[1], which has been in continual existence since 1769. Entitled *Bigger Trees Near Warter*, Hockney's painting is a massive mural, measuring 40 feet wide by 15 feet high (**Fig. 1**). In size, it is a close second to the largest oil painting that has ever been made: Tintoretto's *Paradiso* in the Doge's Palace in Venice. Hockney's painting depicts an ordinary English countryside in East Yorkshire that most people would pass by without a second glance. In the background of the painting, there's a small thicket of trees, and in the front there is one gigantic sycamore with its immense, complex network of spreading and intertwining branches. The painting is so enormous that it literally engulfs the viewer in a way that one feels like one is actually standing in front of a real tree.

Hockney painted *Bigger Trees Near Warter* in the outdoors in front of a live model of thicket and sycamore. His biggest hurdle in executing such a huge on-the-spot landscape was to overcome the difficulty of stepping back to view what he was doing in one part of the work in order to relate it to the rest of the painting. He solved this perspective problem by the use of an inventive tracking method that combined digital photography with computer technology. This approach allowed him to paint 50 identically sized smaller canvases that were then assembled into the final mural. Once Hockney conceived his strategy, he and one assistant completed the painting in a three-week sprint—a *tour de force* of artistic invention and creation.

Revealing a tree at the Louvre

The tree at the Louvre is a sculpture by the Italian artist Giuseppe Penone—a leading protagonist of the Arte Povera movement of conceptual art, which focuses on elements derived from nature. The Louvre invited Penone to select one of his contemporary twentieth century sculptures that would engage in a dialogue with the monumental eighteenth century French garden statuary in the glass-enclosed Cour Puget courtyard of the Richelieu wing of the Louvre.

Entitled *The 10-meter Tree,* Penone's tree is a single 10-meter timber beam that was cut in half and presented in two parts, 16.5 feet high each (**Fig. 2**). After removing the bark from the two beams, Penone used a chainsaw and a chisel to peel away the internal rings of growth. He then meticulously worked around the knots to reveal the heart and soul of the tree: the internal structure of its narrow core and its developing branches. The beams at each end were left untouched, signifying its status as a man-made object and providing natural pedestals for the two side-by-side sculptures. When juxtaposed against the voluptuous marble statuary in the Cour Puget, Penone's *The 10-meter Tree* is a work of great purity and spectacular elegance.

According to Penone[2], "the tree is an extraordinary sculpture capable of keeping within itself the memory of its growth and of its evolutionary and original form. I only reveal the form of the matter. I give back its vitality." In this sense, Penone's approach to sculpture harks back to Michelangelo's concept, according to which the sculptor does not create by adding matter to his form, but reveals the form by removing matter that is already contained in the wood or the stone. In much the same way that Michelangelo chiseled out and unveiled the statue of *David* that preexisted in his block of Carrara marble, Penone discovered and revealed *The 10-meter Tree* by taking matter away from his block of timber. This 'revelation' approach of removing matter is in striking contrast to the 'creation' approach used by Hockney, who produced his tree from scratch by adding matter to his 50 canvases.

Lasker Clinical Award: creating prosthetic heart valves

This year's Clinical Award is awarded to the two surgeons who developed the first success-

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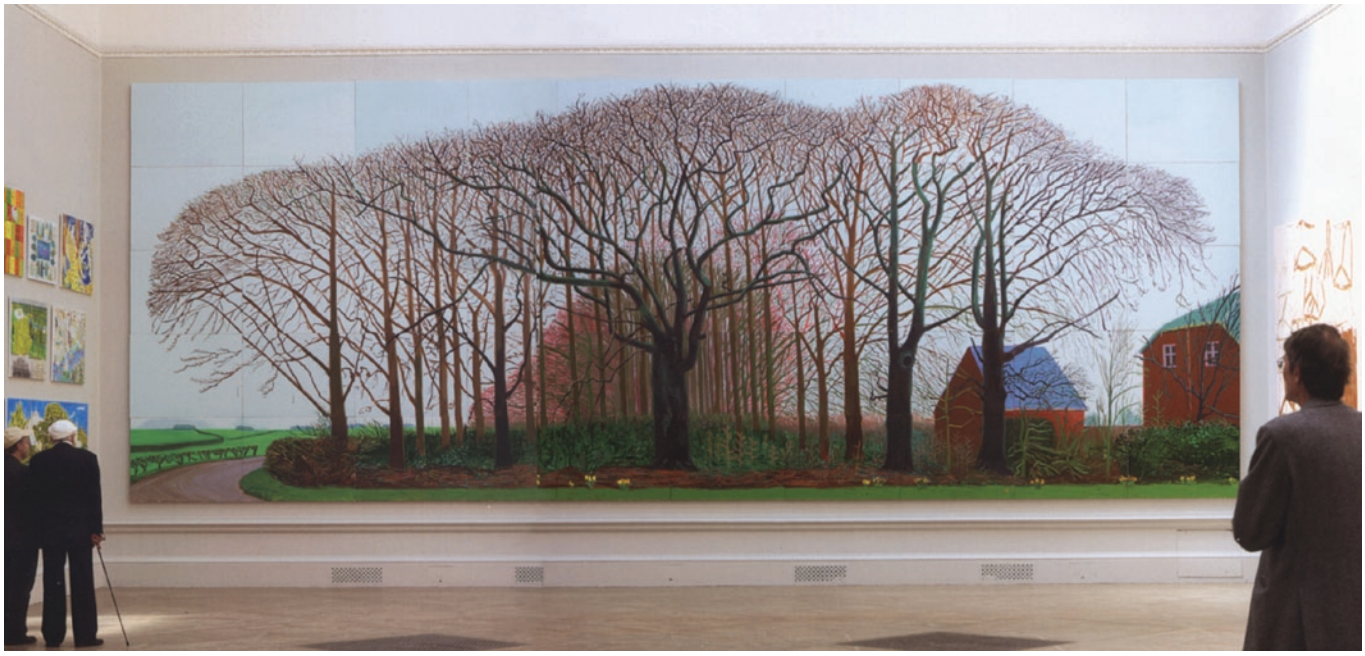

Figure 1 *Bigger Trees Near Warter*. 2007. Oil on 50 canvases, 15 × 40 feet overall. David Hockney's creation of a tree fills a whole wall in the largest gallery at London's Royal Academy of Arts. The man at the left with the walking cane is Hockney himself. The painting was on display at the Royal Academy's Summer Exhibition in London, 11 June–19 August 2007.

ful prosthetic mitral and aortic valves, which have prolonged and enhanced the lives of millions of patients with heart disease. The two honored physicians are Albert Starr (Oregon Health and Science University, Portland) and Alain Carpentier (Hôpital Européen Georges-Pompidou, Paris).

Until 1960, thousands of patients were hospitalized every year with life-threatening congestive heart failure, owing to severe abnormalities in their mitral and/or aortic valves caused by congenital defects, rheumatic fever or age-related calcification and degeneration. The first successful creation and replacement of a heart valve in patients was accomplished in 1961 as a result of a unique partnership between a 32-year-old cardiac surgeon, Albert Starr, and a 60-year-old hydraulics engineer and inveterate inventor, Lowell Edwards.

Within two years of their first meeting, Starr and Edwards designed and developed a mechanical valve, tested it in dogs and then implanted it into patients with rheumatic mitral stenosis—a *tour de force* of technical invention and creation *à la* David Hockney. The Starr-Edwards valve consisted of a silicone-rubber ball encased in a Lucite cage[3]. The original design, with minor modifications, is still widely used today for aortic and mitral replacements. Since 1962, more than 200,000 Starr-Edwards valves have been implanted worldwide, and some of the original patients who underwent valve replacement 40 years ago are still alive today.

In addition to the Starr-Edwards valve, there are currently five other types of mechanical heart valves used in patients today. Mechanical valves are remarkably durable and long-lasting. Their one disadvantage is a small risk of thromboembolism, requiring that valve recipients be permanently treated with oral anticoagulants.

This drawback stimulated intense interest in developing biological valves that would overcome the complication of thromboembolism. The first such tissue valves to be implanted were aortic homographs obtained from human cadavers. These homographs solved the problem of thromboembolism, but the limited availability of healthy human cadavers precluded their widespread use.

The breakthrough in biological valves came in 1968 from the research of Alain Carpentier, a 35-year old cardiac surgeon in Paris, who pioneered the use of tissue valves obtained from pigs[4]. Pigs became the donor animal because their hearts most closely resemble those of humans. The key to Carpentier's success was his insight of treating the porcine valves with glutaraldehyde, a chemical that achieved two functions: it strengthened the valve by cross-linking cardiac tissue proteins, and it reduced the immunogenicity of the heterograft. Carpentier coined the term 'bioprosthetic valve' to denote its biological origin and its prosthetic fate.

Compared to mechanical valves, bioprosthetic valves are nonthrombogenic and therefore solve the problem of life-time anticoagulation therapy. Their one disadvantage is a shorter durability (about 15 years) versus the 30 to 40-year durability of mechanical valves.

Each year, more than 250,000 patients worldwide receive a mechanical or a bioprosthetic porcine valve. In general, younger individuals receive mechanical valves, whereas older patients receive bioprosthetic valves. Both types have benefited more than two million people over the past 45 years. Their development is a striking example of a biomedical advance achieved through the route of creation and invention.

Lasker Basic Award: revealing dendritic cells

This year's Basic Award is given to Ralph Steinman (The Rockefeller University, New York), who discovered dendritic cells—a class of immune cells that initiate and regulate the body's response to foreign antigens.

Antigen-presenting cells roam the body, sense foreign invaders such as bacteria and viruses, ingest their antigenic proteins and fragment them into short peptides. Each fragmented peptide then joins a major histocompatibility complex (MHC) molecule displayed on the surface of the antigen-presenting cell. The peptide-MHC complex is presented to naive T lymphocytes, each of which expresses a receptor molecule that enables it to recognize a different peptide-MHC combination. T cells respond to this interaction by dividing and secreting cytokines, which mobilize other

components of the immune system, including activating B cells for antibody production and activating cytotoxic T cells for killing virally infected cells and tumor cells.

At the time Steinman began his research, the prevailing dogma held that macrophages were the predominant antigen-presenting cells. Dorothy Parker, the American author celebrated for her caustic wit and brevity, famously quipped that "you can't teach an old dogma new tricks," but Steinman's work, carried out in dogged fashion over a 20-year period from 1973 to 1993, did teach the old dogs of immunology a new trick: dendritic cells, not macrophages, are the main antigen-presenting cells that teach T cells when and how to make an immune response[5].

The story began in 1970 when Steinman joined the laboratory of the late Zanvil Cohn, one of the world's preeminent cell biologists, as a postdoctoral fellow at Rockefeller University. The original goal of Steinman's project was to apply cell biological techniques to learn how antibodies were produced in the spleen, a major lymphoid organ of mice. In the course of this work, Steinman encountered a minor population of cells (about 1% of total splenic cells) that showed an unusual shape with branching tree-like projections. As these hitherto undescribed cells had several biochemical properties and cell surface markers that were distinct from those of typical macrophages, Steinman and Cohn called them 'dendritic' cells, a term derived from the Greek word for tree.

Over the next 15 years, Steinman (now in his own laboratory) systematically worked out methods for purifying dendritic cells, learned how to grow and expand them in culture and showed that pure dendritic cells are the main antigen-presenting cells that stimulate T cells to divide. In the mid 1990s, he followed up these *in vitro* studies with a series of *in vivo* experiments. In the body, dendritic cells are positioned at sites where pathogens are likely to enter: the skin and various epithelial surfaces (the airways, the gastrointestinal tract, the genital mucosa). Steinman showed that after dendritic cells capture antigens, they undergo a remarkable maturation process that involves remodeling of the actin cytoskeleton, increased antigen uptake, upregulation of MHC and costimulatory molecules and enhanced cytokine production. The maturing dendritic cells, also endowed with an increased mobility, migrate from their peripheral tissue locations to the nearest lymph nodes, where they present antigen to naive T cells.

A key concept to emerge from Steinman's work is that dendritic cells mature in different ways. Depending on the molecular nature of the microbially derived structure that triggers their maturation, different dendritic cells express different gene profiles, which in turn lead them to launch different versions of T cell-activated immunity. Through the pioneering work of the late Charles Janeway, we know that this differential maturation is triggered by the interaction of different pathogens with a family of ten different Toll-like receptors and other pathogen-recognition receptors that sit on the surface of dendritic cells. The Toll-like receptors and their intracellular signaling cascades constitute the body's primary molecular sensors for foreign pathogens, ultimately governing how dendritic cells communicate with T cells.

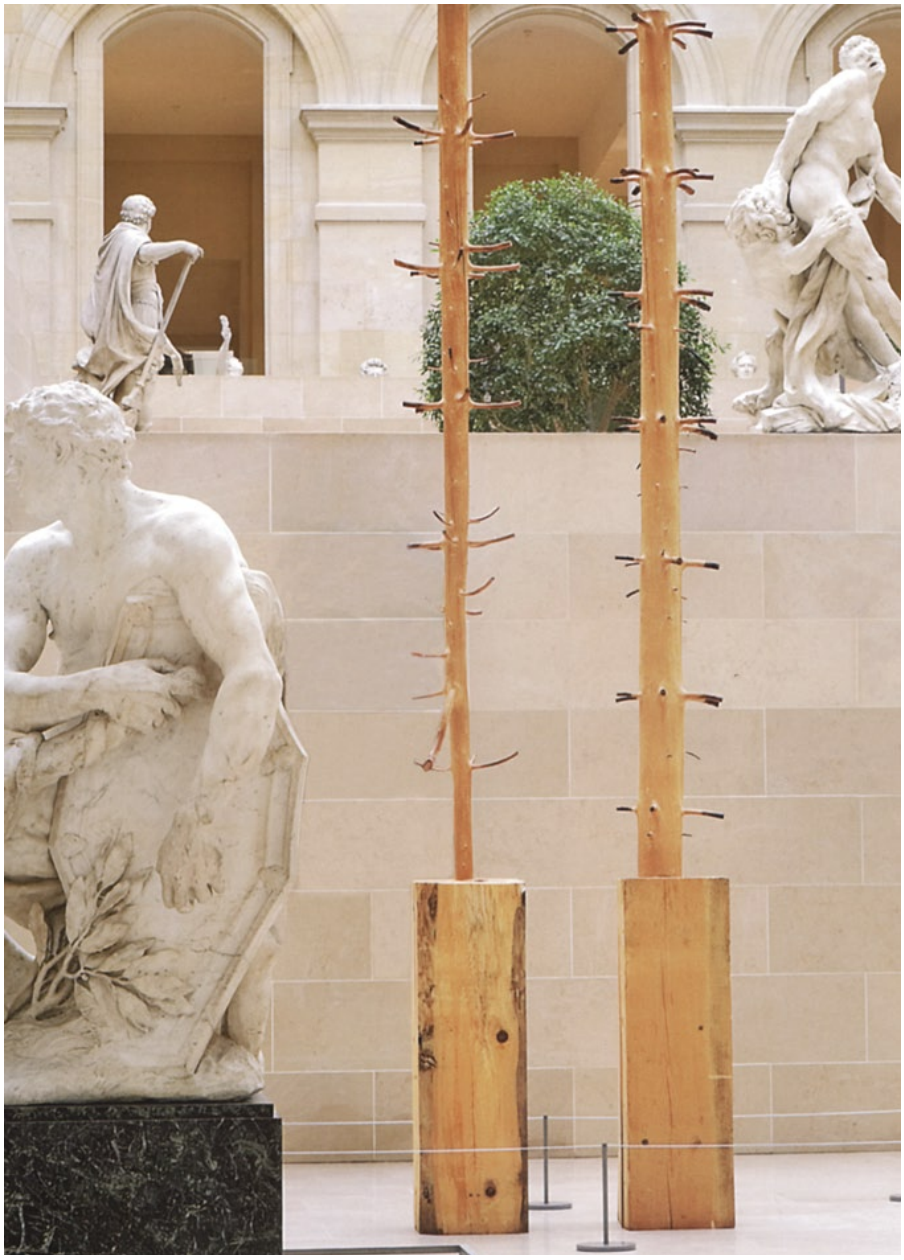

Figure 2 *The 10-meter Tree.* 1989. Wood. Tree 1, 16.5 × 1.5 × 1.6 feet; tree 2, 16.5 × 1.5 × 1.6 feet. Giuseppe Penone's revelation of a tree is shown in the Cour Puget courtyard of the Louvre, in juxtaposition with the gallery's eighteenth century French garden statuary. The sculpture was on display at the Louvre's Counterpoint III exhibition in Paris, 5 April–25 June 2007.

The importance of dendritic cells extends beyond their ability to activate T cells and initiate an immune response to foreign antigens. Steinman also discovered that when dendritic cells process and present self-antigens, they direct the appropriate T cells to become tolerized and learn to ignore the body's own somatic cells. Many scientists are now trying to learn more about this silencing mechanism as a way to adapt dendritic cells for use in autoimmune

disease treatment, allergy and transplantation medicine.

Dendritic cells are also providing tumor biologists with a new *ex vivo* approach to develop cancer vaccines. In a typical scenario, tumor cells from a patient are isolated and incubated in culture with dendritic cells from the same patient's blood. The antigen-loaded dendritic cells are then injected back into the patient to prime their T cells, which then activate B cells (for antibodies to tumor cells) and cytotoxic T cells (for attacking the tumor cells directly). Such dendritic tumor vaccines have given positive results in animal studies and are now being tested in clinical trials in patients with melanoma, prostate cancer and other tumors.

Almost single-handedly, Steinman opened a new field of biomedical science. For 20 years, he and his team were virtually the only scientists in the world who worked on what turns out to be the essential and preeminent initial step in the regulation of the immune system that governs whether T cells are stimulated or silenced. Why were Steinman's early studies ignored, neglected and often denigrated by the immunological community? The longstanding dogma, dating back 100 years to Metchnikoff's classic studies showing that macrophages are the quintessential phagocytic cell, apparently lulled scientists into believing that macrophages were also the main antigen-presenting cell. The powerful force of this dogma made it easy for immunologists to brush aside Steinman's experiments and ideas on dendritic cells, and to view them as some type of Victorian curiosity with little or no relevance to the mainstream of immunology. Fortunately, Steinman's passionate belief in his data and his unshakable self-confidence propelled him forward despite the criticisms of his colleagues.

In analogy with Giuseppe Penone's chiseling and chipping away at a timber beam to reveal the heart and soul of a tree and discover how it forms its branches, Steinman's chiseling and chipping away on the tree-like dendritic cell revealed the heart and soul of the immune system and allowed him to discover how T cells respond to antigens.

Lasker Public Service Award: personifying creativity and discovery

The Lasker Public Service Award, selected by a special committee chaired by the late Daniel Koshland, is given biennially to honor individuals who have encouraged legislation and funds in support of medical research or who have created public health programs of major importance. The 2007 recipient of this award is Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health.

In terms of creativity, Fauci is the principal architect of the US President's Emergency Plan for AIDS Relief, signed into law on 29 May 2003. This legislation, championed by President George W. Bush after guidelines suggested to him by Fauci, provides $15 billion over a five-year period to prevent and treat HIV/AIDS in resource-poor countries. It is the largest single commitment in history for an international public health initiative.

Fauci is also noted for two other contributions to public service: his leadership role in directing the response to the US anthrax scare in 2001, wisely channeling it into good science and away from hysterical reactions in Washington and elsewhere, and his role in the US government's Defense Against Bioterrorism Program, guiding it toward solid research on infectious disease and earning the respect and approval of skeptical legislators[6].

Fauci is a true statesman of science, widely recognized as an eloquent exponent of science in an administration that does not get high marks in this arena. He is known to millions in the United States and throughout the world as the man who can explain the science behind the threat of bioterrorism. His success as a public spokesman is due to the ease with which he deploys his own quadruple threat of ability, affability, indefatigability and unflappability.

In the area of discovery, beyond his accomplishments in public service, Fauci is a card-carrying scientist whose research in immunology earned him election to the US National Academy of Sciences in 1992. He is recognized for clinical studies done early in his career (during the 1970s and 1980s) in which he developed therapies for several previously fatal inflammatory and autoimmune diseases, such as Wegener's granulomatosis and polyarteritis nodosa. For the past 25 years, he has focused on understanding how HIV destroys the body's immune defenses, leading to AIDS, and how endogenous cytokines influence disease progression.

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/.

COMPETING INTERESTS STATEMENT
The author declares no competing financial interests.

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