Laskers for 2001: Knockout mice and test-tube babies

Compared with mathematics and physics, biology and medicine are mainly empirical sciences. As there are no grand unified theories to guide experiments, conceptual advances in the biomedical sciences are crucially dependent on technological innovations. Examples of such innovations that have revolutionized biology include recombinant DNA, DNA sequencing, polymerase chain reaction and monoclonal antibodies. Examples of new technologies that have revolutionized the practice of medicine include the heart–lung machine and open heart surgery, coronary angiography and coronary bypass surgery, computer-assisted tomography and positron-emission tomography, and immunosuppression and organ transplantation.

This year's Lasker Awards celebrate the development of two technologies that are comparable in inventiveness and impact to those mentioned above. The 2001 Lasker Basic Medical Research Award honors three individuals who developed a technology that allows scientists to manipulate the mouse genome with exquisite precision. With this technology, scientists can create 'designer' strains of mice in which almost any gene can be disabled or 'knocked out' and its function probed. Given that man and mouse share about 99% of their genes, these so-called 'knockout mice' provide laboratory models of human disease. The three award recipients are Mario Capecchi of the University of Utah, Martin Evans of Cardiff University in the UK and Oliver Smithies of the University of North Carolina at Chapel Hill.

Fig. 1 Katharina Fritsch, *Mann und Maus*, 1991–1992, Polyester and paint, 94½ × 51⅛ × 88½ in, © Katharina Fritsch, Courtesy of Matthew Marks Gallery, NY, NY.

Two principal developments in the 1980s made it possible for scientists to knock out specific genes in the germ line of mice. The first, pioneered by Martin Evans (then at Cambridge University), was the development of methods to culture embryonic stem cells (ES cells) derived from mouse blastocysts. Evans and his colleague Matt Kaufman showed that ES cells could be taken directly from the mouse embryo, cultured *in vitro* in a Petri dish, genetically manipulated in the dish and then mixed with cells of a normal mouse blastocyst to form an embryo. Together with Allan Bradley (a graduate student at the time) and Elizabeth Robertson (a post-doctoral fellow), Evans went on to show that genetically mutated ES cells could be transmitted through the mouse germ line, allowing the creation of mutant strains of mice. This was obviously a powerful technology, but its application was limited to only two or three genes whose mutated versions could be enriched by drug selection. A more general technology was needed.

The second development arose here. Mario Capecchi and Oliver Smithies independently devised an ingenious method of homologous recombination that allows the preplanned and precise mutation of any desired gene among the ~35,000 contained within the genome of ES cells. Combination of the Capecchi–Smithies technique of gene targeting with the Evans technique of ES cell biology led to the first knockout mice in 1989, an exceptional advance that completely changed the style of contemporary biomedical science by making it possible to study the function of almost any single gene. So far, more than 4,000 of the ~35,000 mouse genes have been knocked out, and more than 500 mouse models of human disease have been created. Knockout mice are used today by thousands of scientists, both in academia and in the pharmaceutical/biotechnology industry.

The rise of the mouse to such exalted status in biomedical research is symbolized aptly by Katharina Fritsch in her large polyester sculpture *Mann und Maus* (Figure 1). Here, a gigantic mouse (in black) sits enthroned on top of a male figure (in white) lying on a bed. The rigid division of the sculpture into black and white emphasizes the obvious importance of the mouse as the dominant animal model for human biology. Despite being dominated by the gigantic mouse, the man seems completely relaxed as he dreams of the many new advances in basic research and clinical medicine that will emerge from the new mouse technology. Curling its long tail like a question mark over the end of the duvet, the mouse wonders how long it will take for these new basic advances to be translated into clinical practice.

The 2001 Lasker Clinical Medical Research Award honors Robert Edwards of Cambridge University in the UK for developing *in vitro* fertilization (IVF), a technology that has revolutionized the treatment of human infertility. A considerable and common medical problem, infertility affects one in six couples throughout the world. In developing IVF, Edwards had to overcome formidable technical problems. He had to learn how to induce ovulation in women, how to collect their eggs from the ovary, how to incubate them *in vitro* in a test tube with sperm so that fertilization would occur, and how to implant the fertilized embryos into the mother's uterus in such a way that a normal baby would be born. These problems were solved through a fruitful 20-year collaboration with Patrick Steptoe, a surgeon who practiced gynecology full time in a small hospital in Oldham, UK. Even though Steptoe had no links to an academic institution, he became one of the world's leading experts in abdominal laparoscopy, a 'keyhole' surgical technique that allowed him

to obtain eggs from the ovaries of women. This procedure was essential to the successful development of IVF.

Ten years after Edwards and Steptoe began their collaboration and after many unsuccessful attempts at IVF, Louise Joy Brown, the first 'test-tube' baby, was born 25 July 1978. A new field of clinical medicine, now called assisted reproduction, was also born on 25 July 1978. Since the birth of Louise Brown 23 years ago, nearly one million healthy babies have been born to infertile parents. In addition to IVF, the research of Edwards and Steptoe paved the way for four other new areas of clinical investigation: preimplantation diagnosis of genetic diseases, cryo-preservation of human embryos, intracytoplasmic sperm injection for treatment of male infertility and, most recently, human embryonic stem cell research for cell therapy of common disorders, such as Parkinson disease and Type 1 diabetes. The birth of Louise Brown also led to the new field of reproductive bioethics and law, which is especially timely given the current controversy surrounding human embryonic stem cell research.

Patrick Steptoe, Edwards' long-term clinical collaborator, died in 1988 at age 75, one week before he was to be knighted at Buckingham Palace by Queen Elizabeth II. Were Steptoe alive today, he would have undoubtedly shared in this Lasker Award with Robert Edwards.

Most advances in clinical medicine are just that—an advance—but a precious few are revolutionary. The way we know IVF was truly revolutionary is that in its early days Edwards and Steptoe were viciously attacked by the 'Holy Trinity': the Pope, the press and prominent Nobel Laureates. This millennial year, the UK issued four stamps to celebrate the most noteworthy British advances in clinical medicine over the last 1,000 years. Those honored were Edward Jenner, for vaccination against smallpox (1796), Florence Nightingale, for founding the field of nursing (1890), Alexander Fleming, for discovering penicillin (1928), and Robert Edwards, for developing IVF (1978). If one picture is worth 1,000 words, one's picture on a millennial stamp should be worth 1,000 Lasker Awards!

JOSEPH L. GOLDSTEIN
Chair, Lasker Awards Jury

Lasker Award recipients receive an honorarium, a citation highlighting their achievements 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 web site at www.laskerfoundation.org.

An inspiring leadership toward improving global health

Conventional wisdom suggests that it may take as long as 30 years from the 'eureka' of a basic medical research discovery to the availability of salutary treatment for a crippling disease or life-threatening illness, and then it may take yet another 30 years or more to create the right public health infrastructures that will make it possible to deliver this effective treatment to a living human being who can experience its health benefits. The 2001 Mary Woodard Lasker Award for Public Service honors an individual whose inventive concepts and dedication to saving lives and to alleviating human suffering from disease, over a lifetime of work, were not deterred by the political and social obstacles that often stand in the way of bringing medical treatments and cures to countless numbers of people, many of whom are living in remote parts of the world. The award recipient is William H. Foege, former Director of both the Centers for Disease Control and the Carter Center.

Dr. Foege is honored for his exceptional leadership in the fight to eradicate smallpox from the world, and for his continuing battle to eliminate other major diseases including polio, guinea worm disease, measles, AIDS and 'river blindness'. His imaginative thinking and physical courage have been among his leadership qualities that made his campaign to bring the fruits of medical research to the people of the world, a dream of Mary Lasker, for whom this award is named. Dr. Foege is now a professor at Emory University and a senior advisor to the Melinda and Bill Gates Foundation.

DANIEL E. KOSHLAND JR
Chairman, Lasker Public Service Award Selection Committee