ALBERT AND MARY
LASKER FOUNDATION

2006 LASKER AWARDS
for
MEDICAL RESEARCH

EMBARGOED FOR RELEASE:
For initial publication
on **Sunday, September 17, 2006**

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DISCOVERERS OF TELOMERASE AND INVENTOR OF COGNITIVE THERAPY RECEIVE LASKER AWARDS FOR MEDICAL RESEARCH

A FOUNDER OF CELL BIOLOGY AND CHAMPION OF WOMEN IN SCIENCE HONORED WITH SPECIAL ACHIEVEMENT AWARD

NEW YORK, Sunday, September 17, 2006 – The **2006 Albert Lasker Medical Research Awards** were announced today. Now celebrating its 61st anniversary, the Lasker Awards are the nation's most distinguished honor for outstanding contributions to basic and clinical medical research, as well as for special achievement in the medical research enterprise.

The **Lasker Award for Basic Medical Research** honors **Elizabeth H. Blackburn**, 57, of the University of California, San Francisco, **Carol W. Greider**, 45, of Johns Hopkins University School of Medicine, and **Jack W. Szostak**, 53, of Harvard Medical School, who **predicted and discovered telomerase**, a remarkable RNA-containing enzyme that synthesizes the ends of chromosomes, protecting them and maintaining the integrity of the genome. Their work uncovered the molecular machinery that replenishes chromosome tips, or telomeres, and laid the foundation for studies that have connected telomerase and telomeres to human cancer and age-related conditions.

The **Lasker Award for Clinical Medical Research** honors **Aaron T. Beck**, 85, Emeritus Professor of the University of Pennsylvania School of Medicine, for **developing cognitive therapy, which transformed the understanding and treatment of many psychiatric conditions**, including depression, suicidal behavior, generalized anxiety, panic attacks, and eating disorders. Cognitive therapy – whose underpinnings contradicted conventional psychiatric thinking – can reverse serious mental illnesses in two or three months of weekly sessions. Beck tested the new approach in clinical studies with a degree of rigor never before applied to any "talk therapy" and thus established a new standard for assessing the effectiveness of any type of psychotherapy.

The **Lasker Award for Special Achievement in Medical Science**, awarded bi-annually, honors **Joseph Gall**, 78, of the Carnegie Institution (Department of Embryology at Baltimore), for a **distinguished 57-year career as a founder of modern cell biology, a pioneer in the field of chromosome structure and function, and an early champion of women in science**. A bold experimentalist, he invented a technique called in situ hybridization, which enables researchers to locate a single DNA or RNA sequence inside the nucleus of cells – an achievement that has led to profound insights about the role of particular genes in embryonic development and other biological processes.

Often called "America's Nobels," the Lasker Award has been given to 71 scientists who subsequently went on to receive the **Nobel Prize**, including 20 in the last 16 years.

The Awards will be presented at a luncheon ceremony on **Friday, September 29th** at the Pierre Hotel in New York City. Harvey V. Fineberg, M.D., Ph.D. will be the keynote speaker; he is the President of the Institute of Medicine.

Dr. Joseph L. Goldstein, recipient of the 1984 Lasker Award for Basic Medical Research and the Nobel Prize in Medicine in 1985 (both with Michael Brown) for discoveries regarding cholesterol, is Chairman of the international jury of researchers that selects recipients of the Lasker Awards. He explained the significance of this year's Basic Research and Clinical Research Awards with the following comments:

"Scientists make great discoveries by pursuing curious observations, devising bold experiments, rigorously testing ideas, throwing aside conventional thought, and working with great persistence. This year's Lasker Awards honor investigators who have demonstrated these ingredients of success.

"The discovery of telomerase by the Lasker Basic Awardees is an example of pure curiosity-driven research that emerged from work on two organisms – a pond-dwelling ciliate and baker's yeast – that have no direct relevance to human disease. This basic research had no medical impact for 15 years – until the early 1990s – when scientists identified telomerase in human cells and showed that it played a crucial role in two disease-related areas: cancer and aging. Today, telomerase research is one of the hottest fields of biomedical science.

"Disorders of mental health are a major medical problem in the world today. As many as 20 percent of the population in the US and UK suffer from depression or a serious form of anxiety. The development of cognitive therapy by this year's Lasker Clinical Awardee is one of the most important advances – if not the most important advance – in the treatment of these diseases in the last 50 years.

"The Lasker Special Achievement Awardee is a renowned cell biologist who – among his many achievements – invented a tremendously powerful technique called in situ hybridization. This method can pinpoint a single gene among the 30,000 present in the genomes of humans and animals. Scientists now routinely use in situ hybridization to view the behavior of genes under a variety of different physiological conditions, to map genes on chromosomes, and to diagnose viral and bacterial infections."

The Lasker Awards, first presented in 1946, are administered by the Albert & Mary Lasker Foundation. The late Mary Lasker is widely recognized for her singular contribution to the growth of the National Institutes of Health and her unflagging commitment to government funding of medical research in the hope of curing devastating diseases. Her support for medical research spanned five decades, during which she was the nation's foremost citizen-activist on behalf of medical science.

Lasker Award recipients receive an honorarium ($100,000 for each Award), a citation highlighting their achievements, and an inscribed statuette of the Winged Victory of Samothrace, the Lasker Foundation's traditional symbol representing humanity's victory over disability, disease, and death.

The list of the 2006 Lasker Award recipients with their current professional and institutional affiliations is included with the full press kit. **All press materials are available** from **www.laskerfoundation.org**. Additional materials include:

- Photographs of the Awardees;
- Interviews with the Awardees;
- Information about past Awardees; and,
- Links to Web sites for additional information about the Awardees.

Full descriptions of the work of the recipients of the **2006 Lasker Awards** follow*:

- **Basic Medical Research** (pp. 5 through 8);
- **Clinical Medical Research** (pp. 9 through 13); and,
- **Special Achievement** (pp. 14 through 16).

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ALBERT LASKER AWARD FOR BASIC MEDICAL RESEARCH

For the prediction and discovery of telomerase, a remarkable RNA-containing enzyme that synthesizes the ends of chromosomes, protecting them and maintaining the integrity of the genome.

ELIZABETH H. BLACKBURN
Morris Herzstein Professor of Biology
and Physiology
Department of Biochemistry and Biophysics
University of California, San Francisco

CAROL W. GREIDER
Daniel Nathans Professor and Director
Department of Molecular Biology
and Genetics
Johns Hopkins University School of Medicine

JACK W. SZOSTAK
HHMI Investigator and
Alex Rich Distinguished Investigator
Department of Molecular Biology
Massachusetts General Hospital
and Professor of Genetics
Harvard Medical School

ALBERT LASKER AWARD FOR CLINICAL MEDICAL RESEARCH

For the development of cognitive therapy, which has transformed the understanding and treatment of many psychiatric conditions, including depression, suicidal behavior, generalized anxiety, panic attacks, and eating disorders.

AARON T. BECK
University Professor Emeritus
Department of Psychiatry
University of Pennsylvania School of Medicine

ALBERT LASKER AWARD FOR SPECIAL ACHIEVEMENT IN MEDICAL SCIENCE

For a distinguished 57-year career – as a founder of modern cell biology and the field of chromosome structure and function; bold experimentalist; inventor of in situ hybridization; and early champion of women in science.

JOSEPH G. GALL
American Cancer Society Professor of Developmental Genetics
Department of Embryology
Carnegie Institution

The Albert Lasker Award for Basic Medical Research

Presented to: Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak

For the prediction and discovery of telomerase, a remarkable RNA-containing enzyme that synthesizes the ends of chromosomes, protecting them and maintaining the integrity of the genome.

The **2006 Albert Lasker Award for Basic Medical Research** honors three scientists who predicted and discovered telomerase, an enzyme that replenishes the ends of chromosomes. In so doing, they unearthed a biochemical reaction that guards cells against chromosome loss and identified the molecular machinery that performs this feat. The work resolved perplexing observations about chromosome termini and explained how cells copy their DNA extremities. In the 1930s, scientists surmised that protective caps – telomeres – ensure the propagation of chromosomes during cell division and prevent them from inappropriately melding with one another. The physical nature of these structures – and how they are constructed – eluded researchers until **Elizabeth H. Blackburn**, **Carol W. Greider**, and **Jack W. Szostak** performed their groundbreaking investigations in the late 1970s and 1980s. Blackburn showed that simple repeated DNA sequences comprise chromosome ends and, with Szostak, established that these repeats stabilize chromosomes inside cells. Szostak and Blackburn predicted the existence of an enzyme that would add the sequences to chromosome termini. Greider and Blackburn then tracked down this enzyme – telomerase – and determined that each organism's telomerase contains an RNA component that serves as a template for the creature's particular telomere DNA repeat sequence. Szostak found that budding yeast unable to perform the telomerase reaction lose their telomeres – and chromosomes – over multiple generations. Eventually, the organisms stop dividing. In addition to providing insight into how chromosome ends are maintained, Blackburn, Greider, and Szostak's work laid the foundation for studies that have linked telomerase and telomeres to human cancer and age-related conditions.

The Beginning of the Ends

In the 1930s, Barbara McClintock (Lasker 1981) and Hermann Muller independently inferred that the natural termini of chromosomes display special characteristics. Unlike ends generated by DNA breakage, they don't fuse with each other. Furthermore, only chromosomal fragments containing intact ends persist when a cell duplicates. A distinct structure must seal chromosomes and confer these properties, Muller reasoned. He dubbed chromosome termini "telomeres" from the Greek "telos" for end and "meros" for part or segment. However, no one knew what made telomeres different from randomly generated ends.

A second telomere-related conundrum arose after researchers deciphered how eukaryotic cells – those with nuclei – copy DNA. The enzyme that performs this reaction should be unable to fully replenish linear DNA due to a peculiarity of its mechanism; each round of replication should generate a molecule missing a few building blocks, called nucleotides, on the DNA's end. As a result, linear chromosomes – which house genes in eukaryotes – would shorten every time a cell divides. In 1972, James Watson (Lasker 1960) speculated that organisms with linear chromosomes need a strategy to maintain chromosome tips, a theory that became known as the "end-replication problem." In parallel, Alexey Olovnikov suggested that the gradual loss of chromosome ends would lead to cellular senescence, a dormant state in which cells remain alive but can no longer divide or perform their normal functions. Although scientists discussed possible solutions to these problems, they did not have ways to test their ideas.

The Ends in Sight

In the late 1970s, Blackburn wanted to determine the sequence of DNA at the ends of a eukaryotic chromosome. Joseph Gall, then at Yale University, had found that the ciliated protozoan *Tetrahymena thermophila*, contains many DNA minichromosomes. Because the molecules are small but abundant, the number of ends relative to the rest of the DNA is large. This feature of *Tetrahymena* allowed Blackburn, working in Gall's lab as a postdoctoral fellow, to gather enough ends to sequence. Each was composed of a six-nucleotide sequence (CCCCAA) that was repeated 20-70 times. Similar sequences turned out to reside in other ciliates, but no one knew whether this odd feature appeared in distantly related organisms.

In 1980, Blackburn, by then running her own lab at the University of California, Berkeley, presented her work at the Nucleic Acids Gordon Research Conference. After her talk, she spoke with Jack Szostak, a yeast geneticist from Harvard Medical School. They decided to add the *Tetrahymena* repeats to the ends of linear DNAs and test whether the resulting DNA would persist in budding yeast. Szostak knew that non-chromosomal linear DNAs in yeast normally insert themselves into chromosomes or are destroyed by cellular enzymes, presumably because they behave as if they result from random fractures. The *Tetrahymena* sequences provided the first hope for yeast to retain such linear DNAs, The experiment worked, despite the vast evolutionary distance between budding yeast and *Tetrahymena*. The *Tetrahymena* telomeres protected the linear yeast DNA, allowing it to pass reliably from one generation to the next.

The researchers then identified short, distinctive repeats on the ends of normal yeast chromosomes and showed that this yeast telomeric sequence was tacked on to *Tetrahymena* ends that were present on linear DNA in yeast. Because yeast added its characteristic sequence to *Tetrahymena* telomeres, telomeres must not serve as templates for additional telomeric sequences. This finding and the varied number of repeats led Blackburn and Szostak to speculate that an enzyme adds telomeric sequences to chromosome ends. Such an act would replenish the genetic material predicted to be whittled away by DNA replication. This idea differed radically from other suggestions scientists had proposed to solve the end-replication problem.

The Means to the Ends

Blackburn, soon joined by Greider, who was then a graduate student, started seeking the hypothetical enzyme by looking for a substance that could affix telomeric repeats to chromosome ends in the test tube. Because *Tetrahymena* contained so many telomeres, the organism should provide a rich source of enzymes that act on them, they reasoned. The researchers added the contents of *Tetrahymena* cells to a mixture of radioactive nucleotides and small DNA pieces composed of the *Tetrahymena* telomere repeats, hoping to see the tagged nucleotides attach to the repeats. On Christmas Day 1984, Greider discovered that the *Tetrahymena* contents generated precisely the DNA pattern predicted for an enzyme that added the six-nucleotide repeats one building block at a time. Blackburn and Greider named the enzyme telomere terminal transferase.

Next, they wanted to figure out exactly how the telomere sequence was determined. They postulated that each organism's enzyme contained an RNA or DNA component that could serve as a template. An RNA-destroying enzyme obliterated the telomere terminal transferase activity, so Blackburn and Greider concluded that an RNA must play a crucial role. In a tour de force of biochemistry, Greider purified the enzyme, which they now called telomerase, and showed that it contained both an RNA and a protein subunit. In her own lab at Cold Spring Harbor Laboratory, she completed this work by isolating the RNA-encoding gene. It indeed carried a sequence that could specify the *Tetrahymena* telomere repeats. Furthermore, cleaving that sequence demolished telomerase activity. To prove that the internal template determines the sequence of the telomeric repeats, Blackburn altered the crucial sequence in the RNA component of telomerase; this perturbation resulted in production of telomeres that correspond to the new sequence. Later, Tom Cech (Lasker 1988) purified the protein portion of telomerase, which adds nucleotides one by one to the chromosome ends, according to instructions from the RNA component.

In the meantime, Szostak and his postdoctoral fellow Victoria Lundblad established that the inability to restore telomeres imperils the cell. They had been seeking yeast mutants that could not properly elongate telomeres. This scheme should identify genes that are crucial for telomerase function, they reasoned. Telomeres in such mutants would shrink, Szostak and Lundblad predicted, and strains harboring such defects would lose their chromosomes over many generations. At first, the yeast would grow normally, but as the genetic material disappeared, the microbes would stop dividing. The researchers found such a strain – and named the gene responsible for the defect EST1 for ever shorter telomeres. The approach subsequently led to the discovery of other proteins required for telomere stability, including telomerase's core protein. Furthermore, the finding provided the first experimental support for the end-replication problem: As predicted, the inability to replenish telomeres caused the structures to dwindle as cells reproduced. Moreover, the work implied that cells unable to solve the end-replication problem eventually senesce.

All's Well that Ends Well

The work by Blackburn, Greider, and Szostak set the stage for discoveries about the role of telomerase in human cancer and aging. Like their *Tetrahymena* and yeast counterparts, human telomeres are composed of a particular simple DNA sequence, repeated various numbers of times. Sperm and eggs manufacture telomerase, but most adult cells don't – and telomeres in most adult cells are shorter than those in sperm and eggs. Telomere attrition, at least in cells grown outside the body, leads to senescence.

Approximately 85-90 percent of human cancers reactivate telomerase (the rest maintain their telomeres through an alternative mechanism) and strong evidence suggests that the enzyme renders these cells able to proliferate uncontrollably by continually refreshing their telomeres. For example, adding the enzyme to certain human cells grown in culture dishes renders the cells immortal. Conversely, blocking its action in lab-grown cancer cells can inhibit their growth or kill them. Scientists are pursuing compounds that thwart telomerase as a potential strategy for fighting cancer. Several clinical trials of such drugs are now under way.

Along similar lines, telomere erosion during a person's lifetime could curtail cell survival, thereby promoting age-related ailments. Evidence supporting this notion comes from studies of the rare human disease dyskeratosis congenita. One form of this illness arises from genetic defects in the RNA component of telomerase. Short telomeres limit the ability of certain tissues to replace themselves. As a result, the disease generates age-like conditions: It wipes out affected individuals' bone marrow, predisposes them to a variety of human cancers, and gives them splotchy skin, ratty fingernails, and prematurely gray hair. The work on dyskeratosis congenita demonstrates that withered telomeres can accelerate physical deterioration.

Blackburn, Szostak, and Greider pursued basic questions of cell biology and enzymology to unveil mysteries that have huge implications for human health. The impact of their work is certain to extend long into the future.

The Albert Lasker Award for Clinical Medical Research

Presented to: Aaron T. Beck

For the development of cognitive therapy, which has transformed the understanding and treatment of many psychiatric conditions, including depression, suicidal behavior, generalized anxiety, panic attacks, and eating disorders.

The **2006 Albert Lasker Award for Clinical Medical Research** honors a scientist who transformed the understanding and treatment of a wide range of psychiatric conditions. By realizing that unrealistic negative self-perceptions foster such disturbances and then teaching patients to identify and challenge these distorted thoughts, **Aaron T. Beck** developed the theory and practice of cognitive therapy. He then subjected this strategy – which defied conventional Freudian principles – to unprecedented rigorous tests. In so doing, he demonstrated its effectiveness and established a new standard for the field of psychotherapy.

Cognitive therapy has proven as effective as medication in alleviating depression and even more effective in reducing relapse and recurrence. Beck and his trainees at the University of Pennsylvania have adapted cognitive therapy to a wide range of other psychiatric disorders. Its power derives in part from the fact that patients assume an active role in their recovery; as a result, they carry tools away from the therapist's office with which they can handle subsequent experiences that threaten their emotional well-being. In addition to conceiving cognitive therapy and showing that it works, Beck devised a number of simple yet sophisticated instruments for assessing the severity of psychiatric symptoms. These tools include the Beck Depression Inventory, Beck Cognitive Insight Scale, and Beck Suicide Intent Scale. They have helped researchers make seminal additions to our understanding of various psychiatric problems and improved suicide classification, assessment, prediction, and prevention. By discovering a previously unrecognized aspect of many mental illnesses and inventing a therapy based on his observations, Beck has made a huge impact on untold numbers of people, relieving immeasurable amounts of suffering.

Different Ways of Thinking

In 1956, Aaron T. Beck finished his training as a Freudian psychoanalyst, attracted to the field by its promise to improve people's lives. In discovering unknown continents of the mind, the ideology went, psychoanalysis offered unprecedented possibilities by helping individuals overcome the unconscious drives and desires that thwart their sense of well-being and ability to function. Many psychiatrists were skeptical about this method because its impact had not been documented scientifically. In the late 1950s, Beck decided to perform studies to establish its effectiveness. Instead of confirming the tenets of psychoanalytic theory, he showed that this approach omits a crucial root of psychological suffering.

Depression plagued the majority of Beck's patients, so he focused on that illness. According to Freud, depression arises from unconscious – and unacceptable – anger toward another person. Instead of expressing this hostility outwardly, depressed people direct it toward themselves. Psychoanalytic theory predicted that this rage manifests itself in dreams. Beck found, however, that depressed patients don't dream about anger; they dream about loss and personal inadequacy.

Perplexed at the apparent failure of the conventional theory to pass this fundamental test, Beck revised his proposal and subjected it to additional tests. Repeatedly, his observations refuted his hypotheses. Beck gradually discovered that depressed patients in their conscious lives hold the same view of themselves as that expressed in their dreams: They feel like losers.

While probing and developing these ideas, he realized that people seized by depression often have exaggerated and bleak "automatic thoughts" that trigger uncomfortable feelings. For example, self-criticism, without preceding anger, can prompt feelings of sadness or loneliness. Instead of discarding this observation that contradicted psychoanalytic theory, Beck grabbed onto it. He proposed that these internal messages foster patients' problems. The distorted view grips them, warping their self-perceptions, deflating their hopes and expectations of the future, and making suicide seem like a reasonable escape from unrelenting pain.

These realizations and ideas opened up a previously unexplored inner realm and provided the framework for the theory of cognitive therapy. As people enter depression, they filter out positive information about themselves and amplify negative information, Beck speculated. Patients view themselves as defective and helpless; their future seems hopeless and their lives seem full of insurmountable problems.

These ideas reformulated the core problem in depression: It does not arise from unconscious drives and defenses, as psychoanalytic theory held, but from unduly negative beliefs and bias against oneself. Beck had uncovered a major cause of depression – and one that had been overlooked by the major theoretical perspectives of the time. Neither Freudian therapy nor the other major therapy of the day – behavior therapy, which posited that psychological disturbances resulted from outside forces and could best be resolved by changing the external environment – put stock in the notion that a patient's beliefs, thoughts or expectations generate distress.

By 1961, Beck had abandoned psychoanalysis. Instead, he was zeroing in on particular instances in which patients felt bad and asking what thoughts immediately preceded the uncomfortable emotion. He then coaxed patients to apply the scientific method to their beliefs, urging them to examine the evidence. A woman who felt worthless might reveal that, immediately before her mood plummeted, she had thought, "I'm a bad mother." Beck would probe further to unearth the apparent basis for this internal statement, and then ask questions such as," When siblings from other families fight with each other, does that mean their parents are doing a bad job?" "If the neighbor children went to school without their boots or forgot their lunches, would you condemn their mother?" With this approach, he prodded patients to assess the accuracy of what they were telling themselves. As they began to gain objectivity, their self-images would start to improve, and their problems would clear up. He noticed significant changes almost immediately. After 10-12 weekly sessions, patients' symptoms had usually resolved. Beck had developed a short-term therapy for depression.

By 1964, Beck had laid out the foundations of his theory and practice. These revolutionary ideas encountered resistance, but he went on to demonstrate that his new cognitive therapy altered patients' feelings and behavior quickly and in an enduring way.

Better than Drugs

In the 1970s, Beck conducted the first rigorous study of any type of "talk therapy." He pitted cognitive therapy against the best antidepressant drug at the time – imipramine – in a prospective, randomized, controlled clinical trial designed to test how effectively these two approaches ameliorated symptoms of a particular disorder: depression. In this head-to-head comparison, cognitive therapy outperformed the drug after a treatment period of up to 12 weeks. Furthermore, the benefits persisted a year later. In contrast, the effectiveness of psychoanalysis, whose normal course is years, has not been proven, as it has not been subjected to this type of randomized, controlled study. This work established cognitive therapy as a powerful clinical intervention and set a new standard for evaluating the effectiveness of any kind of psychotherapy. Numerous studies since then have reaffirmed that the approach is equal or better at combating depression than are antidepressant drugs; furthermore, it is better at preventing relapse.

Beck and his trainees spent the next three decades adapting cognitive therapy to treat additional problems – such as anxiety disorders, panic disorders, and social phobias – and testing its utility. As part of this enterprise, he developed powerful instruments with which to measure the severity of symptoms associated with various psychiatric illnesses. Prior to this work, a dearth of techniques for measuring the severity of such disturbances hampered psychiatric research.

Saving Lives

Among his major achievements, Beck has made dramatic advances in helping people with suicidal urges, in part by providing a classification and assessment scheme for predicting suicidal behavior. Beck recognized that the feeling of hopelessness is crucial for evaluating suicidal patients. He developed a "hopelessness scale" – a series of simple questions – that measure the degree to which an individual feels as if current problems are solvable. Beck and his colleagues have tracked patients for more than 30 years, and have found that this tool can indicate the likelihood of a person to commit suicide, particularly for individuals at high risk. In a study of 1958 outpatients, the test pinpointed 16 of the 17 people who killed themselves during the seven-year study; individuals who scored above a particular hopelessness rating were eleven times more likely to commit suicide in the seven years of the study than were the low scorers. Thus, the risk of hopeless patients eventually dying as a result of suicide was approximately the same as that of heavy smokers dying from lung cancer.

In 2005, Beck and his colleagues published a paper that demonstrated the effectiveness of cognitive therapy for suicidal individuals. 120 patients who were evaluated at an emergency room immediately after a suicide attempt received support and referrals from a caseworker; half of these patients underwent 10 sessions of cognitive therapy in addition. Participants in the cognitive-therapy group were almost 50% less likely than non-participants to attempt suicide during the 18-month follow-up period.

In the United States, more than 30,000 people die each year from suicide, making it the eleventh leading cause of death; among people between the ages of 15 and 24, it is the third biggest killer. Worldwide, suicide is among the three leading causes of death among individuals between 15 and 44 years old. Because Beck has invented a simple tool with which to predict future suicidal behavior and a therapy that dramatically reduces attempts, his work has enormous potential for slashing those figures. Furthermore, it could tremendously benefit especially high-risk populations, such as those on college campuses.

Soothing Mental Distress Around the Globe

Cognitive therapy has become a mainstay in the practices of many mental health practitioners worldwide. The American Psychiatric Association's guidelines state that cognitive behavioral therapy (an offshoot of cognitive therapy) is one of the two best-documented psychotherapies for treating major depression. Health systems in Europe recommend it for treating a number of common psychiatric disorders. Inspired by the success of cognitive therapy in curing depression, the United Kingdom's Department of Health is launching a $6.8 million pilot program aimed at significantly increasing access to "talk" therapies. If results are favorable, the

government will expand the program and expects to save millions of dollars by helping people with mild to moderate depression get back to work and off disability benefits.

Beck's development of cognitive therapy and his discovery that it effectively treats serious mental illnesses has major public health significance. Countless individuals owe their sense of well-being – and their lives – to Beck's work.

The Albert Lasker Award for Special Achievement in Medical Science

Presented to: Joseph Gall

For a distinguished 57-year career – as a founder of modern cell biology and the field of chromosome structure and function; bold experimentalist; inventor of in situ hybridization; and early champion of women in science.

The **2006 Albert Lasker Award for Special Achievement in Medical Science** honors a seminal contributor to the field of chromosome structure and function, inventor of in situ hybridization, and long-standing champion of women in science. **Joseph G. Gall**, of the Carnegie Institution (Department of Embryology at Baltimore) ranks among the most distinguished cell biologists in the history of the discipline. Gall is widely respected for his approach to scientific problems: He is thoughtful, committed to his work, and displays a high degree of insight and integrity. He has trained many active researchers, including women, whom he welcomed into his lab before anyone was talking about excellence through diversity.

Science and nature captured Gall's interest as a child. He collected amphibians, insects, and later, tiny pond creatures. By age 14, he was peering through his own microscope to see how these organisms were built. Well before he studied zoology as a college student, he had familiarized himself with the quirks of a large number of animals and microbes. This knowledge equipped him to identify organisms that were particularly likely to lend themselves to the varied cell biological questions that he has tackled during his career.

In the 1950s, near the beginning of Gall's career, scientists were discovering the roles of DNA, RNA, and protein through studies of bacteria, single cell organisms that have no nuclei (so-called prokaryotes). At the same time, they were grappling with basic questions about how the functions of these molecules related to structures in multicellular organisms, such as humans and animals, that sequester their DNA in nuclei (eukaryotes). Few tools and techniques existed for probing these issues.

Gall was well aware of these limitations and repeatedly blazed new paths to solutions of longstanding biological conundrums. His knack for choosing the appropriate organism for studying a particular problem began during his Ph.D., when he focused on the structure of chromosomes in amphibian eggs, or oocytes. Loops extend from the axes of these exceptionally large chromosomes, creating a bristly appearance that prompted early cell biologists to name them "lampbrush" chromosomes. Their size permits observations and manipulations that are difficult or impossible with smaller chromosomes. In the early 1960s, by which time Gall was running his own lab at the University of Minnesota, scientists knew that genes were made of DNA and resided in chromosomes, but no one knew how many DNA

molecules composed a single chromosome or what held the genes together. By treating the lampbrush chromosomes with an enzyme that cuts DNA and measuring the speed at which the DNA broke, Gall gathered strong evidence to suggest that each chromosome consists of a single DNA double helix. He also showed that the loops of the lampbrush chromosomes consist of genes that are being copied into the RNAs that the egg stockpiles for use as it develops into a new individual.

Gall also used the very large amphibian oocyte nuclei to study the envelope that encases the nuclear contents. Using an electron microscope, he saw pores in this membranous pouch and demonstrated that these nuclear pores have eightfold symmetry. He thus provided the first physical characterization of the structures that we now know control the traffic of crucial molecules into and out of the nucleus.

In 1964, Gall moved to Yale. There he studied the RNA of ribosomes – the cell's protein-manufacturing factories. He discovered that, during egg formation, the genes encoding this RNA are duplicated multiple times in the nucleus, but outside of the chromosome. Gall thus unveiled the first example of gene amplification, a strategy by which some types of cells – such as those destined to create tumors – generate large quantities of particular DNA sequences at specified times or under certain circumstances. Furthermore, he had established that nuclear genes in eukaryotes can dwell outside of the chromosome. Similar findings were reported independently by Oscar Miller and by Donald Brown and Igor Dawid.

These observations set the stage for the development of in situ hybridization, a powerful technique that allows scientists to locate specific RNA or DNA sequences in particular regions of the cell. For years, Gall had wanted to find a way to detect individual genes within chromosomes, and he realized that he now could begin devising such a technique. The amplified ribosomal RNA genes were the key, because they provided such a large target inside the nuclei of the developing oocytes. He and Mary Lou Pardue, a graduate student in his lab, squashed cells from the ovary onto a microscope slide. Then they generated a radioactive version of the ribosomal RNA, which they spread on the slide, hoping that it would adhere to the corresponding DNA sequences. They washed away the RNA that didn't stick and placed the slide on X-ray film. The radioactive RNA exposed the film precisely where the amplified ribosomal RNA genes lay in the nuclei.

In situ hybridization quickly became one of the most widely used techniques in cell biology. It is still the standard method for mapping genes within tissues, nuclei, or chromosomes. It has proved to be an indispensable tool for pinpointing when and where particular genes turn on and off in the developing embryo, information that can hint at their physiological roles. In the 37 years since Pardue and Gall published their first paper on in situ hybridization, scientists have refined the technique. They now use different colored fluorescent molecules to adhere to multiple sequences within a single cell, thus generating an exquisitely detailed picture of genes and gene activity.

Gall then employed in situ hybridization to locate so-called satellite DNA on the mouse chromosome. He and Pardue found that this DNA, composed of repeated short sequences, lay in a particular spot that was known to lack genes. This was the first demonstration that highly repeated sequences reside at specific regions of the chromosome and it provided an explanation for the absence of genes in that region.

Gall went on to demonstrate that the protozoan Tetrahymena thermophila generates many copies of free ribosomal DNA molecules – and another example of DNA amplification independent of chromosome duplication. He and Elizabeth Blackburn used these DNA molecules to study chromosome ends, a line of inquiry that led to the discovery of telomerase (see description of the 2006 Albert Lasker Award for Basic Medical Research).

After more than five decades in the lab, most investigators would have long ago left the hands-on research to their students and postdoctoral fellows, but Gall is still at the bench. He is currently studying a structure in the nucleus, the Cajal body, which was described in 1903, but whose function is still not clear. His results suggest that these structures, which are present in all eukaryotic organisms, are assembly sites for the machinery that processes messenger RNAs, the protein templates. Although the Cajal body has been neglected for most of the century since its first identification, these new insights, pioneered by Gall, have stimulated much recent excitement in the field of nuclear structure and function.

In addition to exploring the nucleus, Gall has distinguished himself as a superb role model and mentor. Through respect, support, and the high standards that he sets in his research, he has nurtured a large number of young investigators who have gone on to achieve great success as independent researchers and leaders (see http://www.ciwemb.edu/labs/gall/index.php). In particular, he has built a strong record of training female scientists, three of whom, Mary Lou Pardue, Susan Gerbi, and Elizabeth Blackburn, served as American Society for Cell Biology presidents. Gall never made a conscious decision to promote women in science; rather, he realized before many of his peers the wisdom of accepting good students into his lab, regardless of gender.

Gall's studies on diverse problems in cell biology in many different organisms have revealed fundamental properties of chromosomes and the nucleus. He developed one of the most important techniques in cell biology. His work spans more than half a century and reflects his keen mind, focused efforts, experimental gifts, and the power of teaching by example. Gall's legacy has already permeated cell biology textbooks and will reach far into the future through the biological problems and people he has touched.