INTERNATIONAL CONGRESS ON COMPUTERS IN BIOTECHNOLOGY

JANUARY 30-31, 1986

BALTIMORE CONVENTION CENTER, BALTIMORE MARYLAND

Chairman: Stephen R. Heller

U.S. Dept. of Agriculture, Agricultural Research Service, Beltsville, Maryland

Computers have and will continue to play a major role in the field of biotechnology, both as a support tool and as research tool. As the computer spans a vast range of activities in biotechnology, this conference will endeavor to provide timely presentations of the policy, resource, system, and applications areas which bear both on the immediate and long term activities in this fast growing, fast moving, and exciting field.

Session Topics

POLICY ISSUES – Jerrold Roschwalb, National Assoc. of State Univ. & Land Grant Colleges
This session will present the major and critical policy issues in Government support and interaction in the field. A panel discussion will follow the session. Speakers will include Dr. William Raub (NIH), Dr. Rick Weingarten (OTA), and Dr. David Kingsbury (NSF).

SYSTEMS and RESOURCES – Lewis Gevantman, National Bureau of Standards
This session will present examples of computer systems and developments related to and supporting biotechnology. Speakers will include Professor Carver Mead (CalTech), Professor David Mount (Arizona State), Richard Feldmann (NIH), Dr. Kevin Ulmer (CARB), Dr. Charlotte Hollister (BBN), and Dr. Dennis Smith (Intellicorp).

APPLICATIONS IN AGRICULTURAL BIOTECHNOLOGY – Joseph Modelevsky, International Minerals and Chemicals
Agricultural biotechnology focuses on problems ranging from the level of the gene to the plant to the farm. Computer-based tools are applied by investigators working on the whole spectrum of problems. This session will address computer applications in genetic engineering and protein design, agricultural expert systems and computer-based tools to optimize production agriculture. Speakers will include Dr. Joachim Messing (Rutgers University), Dr. Ryszard Michalski (University of Illinois), Derek Crates (Imperial Chemical Industries), Dr. James Kendrick (AGNET).

CONTRIBUTED PAPERS – Dieter Soll Yale University
Contributed papers for the poster and oral presentations are invited. Please request abstract forms from Edward Ruffing, Scherago Associates Inc. (212) 730-1050.

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cellular lysosomes where LDL is hydrolyzed and cholesterol released into the cell cytoplasm.

The freed cholesterol was shown to suppress the activity of HMG-CoA reductase, the critical and rate-limiting step of cellular cholesterol synthesis. At the same time, cholesterol-esterifying capacity mediated by the enzyme acyl-CoA–cholesterol transferase was dramatically increased. A most important function of intracellular cholesterol was further shown to be the regulation of synthesis of the LDL receptor at the transcriptional level. With low intracellular cholesterol levels, the number of LDL receptors was increased and with high cholesterol levels the opposite occurred. This mechanism allowed cells (such as those of the liver) to control their uptake of cholesterol which is essential for constructing cell membranes and for making substances such as bile acids and certain hormones that require cholesterol as building blocks.

Knowledge of the LDL receptor as worked out by Brown and Goldstein has revolutionized cholesterol and lipoprotein metabolism in emphasizing the importance of receptor binding for the regulation and particularly the catabolism of cholesterol. The relationship of the exogenous or dietary pathway of fat transport to the endogenous pathway whose regulation largely depends upon the LDL receptor in the liver has been clarified. Scientists working on lipoprotein physiology and pathology had a new paradigm, and all research in this area had to pay attention to these findings.

Receptor-Mediated Endocytosis

The process of receptor-mediated endocytosis (as demonstrated with the LDL receptor) was shown by other investigators to be the principal pathway by which cells take up different macromolecules such as insulin, epidermal and platelet-derived growth factor, transferrin, immune complexes, and others. The clustering of receptors in specialized coated pits on the cell surface followed by internalization into coated vesicles appeared to be a universal phenomenon. The mechanism of the intracellular LDL pathway now serves as a model for future elaboration of the physiologic action of the more than 20 different receptors that are involved in receptor-mediated endocytosis. The impact of Brown and Goldstein's work on cell biology therefore is enormous since receptor-mediated endocytosis plays a fundamental role in the growth, nutrition, and differentiation of all mammalian cells.

LDL Receptor Gene and Mutations: Structure-Function Relations

More recently, on the basis of their work with W. Schneider and in collaboration with David W. Russell, they have cloned and sequenced the LDL receptor gene, a difficult task since messenger RNA for the receptor exists only in tiny quantities. The structure of this gene proved fascinating and provides new and detailed information in molecular evolution. The LDL receptor gene turned out to be a "mosaic" built up of several exons shared with the genes of different proteins such as complement, some clotting factors, and epidermal growth factor. Here was a clear example of the evolution of a protein by the shuffling and new combination of functional units! These studies showed that the LDL receptor consisted of 839 amino acids composed of five structural domains: (i) the binding site consisting of highly characteristic repeats of cysteine-rich residues; (ii) a region homologous to the epidermal growth factor; (iii) the sugar-linked site; (iv) a membrane spanning region; (v) a tail located in the cytoplasm that mediates the clustering of the receptor in coated pits. These findings were elegant and important examples of

Michael Brown

Joseph Goldstein

relating structural information to biologic function. In this work, their analysis of the various mutations that cause familial hypercholesterolemia has been of considerable help. As in other genetic diseases, different mutational events affecting a given functional protein can impair the physiology and biochemistry of the LDL receptor and lead to defective or absent receptor function. Several classes of LDL receptor mutations that cause familial hypercholesterolemia have been categorized: (i) mutants causing defective synthesis; (ii) mutants associated with defective binding of LDL; (iii) mutants caused by defective internalization; (iv) mutants caused by defective transport of the receptor from the endoplasmic reticulum to the Golgi apparatus; and (v) failure of receptors to cluster in coated pits. At least ten different mutations have been well defined, more are likely to come, and different mutational events such as deletions, duplications, and single nucleotide base substitutions have been identified. This pioneering work opens the way for future analysis of a new class of genetic diseases caused by defects affecting other receptors. The ubiquity of receptor binding for many macromolecules suggests that such mutations should be common.

Effects on Treatment of Familial Hypercholesterolemia

What are the practical applications of this work? Persons with familial hypercholesterolemia can be treated and their cholesterol level reduced by certain oral drugs (for example, cholestyramine) that interfere with the recycling of bile acids from the intestine into the liver. This maneuver increases the number of LDL receptors on liver cells that are specified by the single normal LDL receptor gene in these persons. However, effective lowering of high cholesterol levels requires further blocking of HMG-CoA reductase which is stimulated by cholestyramine and similar drugs. New experimental drugs such as compactin and mevinolin are efficient in inhibiting HMG-CoA reductase activity. In view of many studies in human epidemiology and some clinical trials, it is almost certain that normalization of cholesterol will reduce the frequency of coronary heart disease. However, long-term investigations will be required to ensure the absence of toxicity of such drug regimens that include enzyme inhibitors.

No such manipulation with drugs would be possible with homozygous patients with familial hypercholesterolemia who lack any normal LDL receptor gene. However, the Brown-Goldstein team showed that it was possible to replace the missing normal LDL receptors by a liver transplant in a young patient. After the

transplantation, the patient's very high cholesterol was markedly reduced. Furthermore, exogenously administered LDL was shown to be removed more efficiently than before the operation. In addition, the patient's heart, which had been extensively damaged by severe coronary arteriosclerosis, was also replaced by a normal donor heart, and the patient is doing well 18 months after transplantation.

Applicability to Arteriosclerosis in General

Is our knowledge of the LDL receptor, its regulation and mutations, relevant to arteriosclerosis that is not caused by genetic LDL receptor defects? Definitive data on this important question are not yet available, but there are indications that the LDL receptor may play an important role in "garden variety" atherosclerosis. There are some suggestions that there may be alleles associated with subtle genetic structural alterations of the LDL receptor which cause variation in LDL activity. "Normal" individuals with "low capacity" LDL receptors would have higher cholesterol levels and an increased frequency of coronary heart disease since they remove cholesterol more sluggishly from their circulation. Those individuals with "high capacity" LDL receptors would have lower cholesterol levels and would be relatively protected. More important, Brown and Goldstein have suggested that the high fat, high cholesterol Western-style diet may suppress the manufacture of LDL receptors and thereby raise cholesterol to levels that cannot be adequately disposed of by the existing LDL receptors. They postulate that the human LDL receptor system evolved under evolutionary conditions of much lower fat intake and is not adapted to Western-style high fat and cholesterol diets. Cholesterol deposits, atherosclerosis, and heart attacks would follow. Animal studies in several species indicate that cholesterol feeding and a high fat intake do in fact inhibit LDL receptor synthesis. Furthermore, adding to the problem, the number of receptors may decline with aging, thus explaining the rise of cholesterol levels.

The scope and depth of Brown and Goldstein's studies are remarkable. The creative synthesis of concepts and methods from diverse fields such as genetics, medicine, cell biology, molecular biology, biochemistry, pathology, pharmacology, electron microscopy, nuclear medicine, immunology, and surgery which they have applied in their work is distinctly unusual in this age of specialization. There are few other examples in modern biomedical research of work carried out by a small team that has been as productive and important for the biological and medical sciences.

Biographical Notes

Michael Brown was born in 1941 in New York and received his college education and his medical school training at the University of Pennsylvania where he obtained the M.D. degree in 1966. Joseph Goldstein was born in 1940 in Sumter, South Carolina; after receiving a college degree at Washington and Lee University in Virginia, he obtained his M.D. degree at the University of Texas Health Science Center in Dallas in 1966. I have been told that Joe's brilliance was recognized during his student days and prompted Dr. Donald Seldin (then and still chairman of Medicine) to offer him a future faculty job even before his graduation from medical school. Joe and Mike first met at Massachusetts General Hospital in Boston where they served for 2 years on the medical house staff. They both then went to NIH in Bethesda as clinical associates. Joe worked with Marshal Nirenberg in the Laboratory of Biochemical Genetics and Mike worked with Earl Stadtman in the Laboratory of Biochemistry. Michael Brown joined the faculty of the University of Texas Health Science Center in Dallas in 1971 while Joe Goldstein went there in 1972 after his 2-year medical genetics fellowship in Seattle. Their collaboration started immediately and led to the various discoveries. This collaboration is remarkable in that their powerful talents are complementary and make for a multiplicative rather than a merely additive effect in their work. Their effective and smooth collaboration over a period of 13 years speaks well for their easy-going personalities and is an unusual example of an extraordinary ability of two powerful independent and creative investigators to work together so well and productively for such a long time. The laboratory work at Dallas is always planned and done together, papers are written together, and outside engagements are either divided up or both share the podium consecutively for oral presentations! Brown is married with two children while Goldstein is single. Despite offers from many prestigious institutions over the years, they have remained in Dallas. Brown is the director of the Center for Genetic Disease, and Goldstein is chairman of the Department of Molecular Genetics.

Model Physician-Scientists

There has been concern in many quarters about the decline in the number of physician-scientists and its possible impact on disease-oriented research. The success of Brown and Goldstein is a shining example of the continuing viability and strength of basically oriented clinical investigators. Here are two physicians trained and certified as specialists in internal medicine who continue to function as academic physicians. Goldstein this year is president of the American Society of Clinical Investigation. In addition to their research, they both see patients, make ward rounds, and teach house staff and students in internal medicine. Yet, by acquiring training in basic sciences they were able to work out the fundamental mechanism of a disease that now serves as a model system not only for other genetic diseases but also for one of the most common scourges of advanced societies—arteriosclerosis. Brown and Goldstein show how a synthesis of medicine and the basic sciences still remains possible. The granting of the Nobel Prize to these broadly based medical scientists provides a role model for younger biomedical researchers who sometimes feel that only extreme specialization can lead to important results.

Brown and Goldstein are articulate writers and accomplished lecturers who are frequently asked to present their work and do so clearly in an exciting way. Their slides are examples of the best exposition in science and should serve as models for young scientists. In each major lecture given at one or another forum, they report new and exciting findings. They have published frequent review articles which aided many readers to understand their work and stimulated researchers in varying fields to use their concepts and methods.

Reductionist Science Vindicated

Their discoveries are also a clear vindication of the continuing success of the reductionist approach in current biomedical research. They selected a monogenic disease and dissected the structure and function of the LDL receptor by reductionist methods. Most importantly, they use these new facts to fit the various pieces and older knowledge into a more meaningful broader pattern. Some critics of biomedical science accuse modern researchers of sometimes neglecting the forest for the trees. Brown and Goldstein have shown that research on trees is first necessary to understand and manage a forest.

Other Honors and Achievements

In view of their remarkable achievements, the granting of the Nobel Prize came as the natural culmination of a series of scientific honors and prizes. They had been awarded many different scientific prizes including the Heinrich Weiland Prize, the Pfizer Award, the Passano Award, the Lounsbery Award, the Gairdner Award, the New York Academy of Sciences Award, the Lita Annenberg Hazen Award, the V. D. Mattia award, the distinguished research award of the Association of American Medical Colleges, the research achievement award of the American Heart Association, the Louisa Gross Horvitz Award, the 3-M Life Sciences Award (FASEB), the William Allan Award of the American Society of Human Genetics, and most recently the Lasker award. Both were elected to the National Academy of Sciences in 1980. They have been asked to give many prestigious lectures, were given honorary doctorates (University of Chicago and Rensselaer Polytechnic Institute), and belong to many review committees and editorial boards. Brown is a member of the Board of Scientific Advisers of the James Coffin Clinical Fund and is a senior consultant to the Lucille P. Markey Trust. Goldstein is a member of the Scientific Advisory Board of the Howard Hughes Medical Institute and a nonresident fellow of the Salk Institute. The Nobel Prize therefore came as no surprise to observers of the never-ending stream of Brown and Goldstein's important discoveries. The only question was its timing. Considering their past record, the scientific community is eagerly awaiting their future work.

Background and Mass Extinctions: The Alternation of Macroevolutionary Regimes

DAVID JABLONSKI

Comparison of evolutionary patterns among Late Cretaceous marine bivalves and gastropods during times of normal, background levels of extinction and during the end-Cretaceous mass extinction indicates that mass extinctions are neither an intensification of background patterns nor an entirely random culling of the biota. During background times, traits such as planktotrophic larval development, broad geographic range of constituent species, and high species richness enhanced survivorship of species and genera. In contrast, during the end-Cretaceous and other mass extinctions these factors were ineffectual, but broad geographic deployment of an entire lineage, regardless of the ranges of its constituent species, enhanced survivorship. Large-scale evolutionary patterns are evidently shaped by the alternation of these two macroevolutionary regimes, with rare but important mass extinctions driving shifts in the composition of the biota that have little relation to success during the background regime. Lineages or adaptations can be lost during mass extinctions for reasons unrelated to their survival values for organisms or species during background times, and long-term success would require the chance occurrence within a single lineage of sets of traits conducive to survivorship under both regimes.

THE PAST FEW YEARS HAVE SEEN A BURGEONING OF DATA and hypotheses on mass extinctions (*1, 2*). Most of this work has focused on evidence for or against extraterrestrial impacts as forcing mechanisms, particularly at the Cretaceous-Tertiary boundary, and the evolutionary role of this and other mass extinction events has been relatively neglected. A comparison of extinction patterns among bivalves and gastropods of the Gulf and Atlantic Coastal Plain region over the last 16 million years (m.y.) of the Cretaceous Period with those across the mass extinction boundary, corroborated from the literature on other taxa and extinction events, indicates that mass extinctions are not simply intensifications of processes operating during background times. Current evolutionary theory is formulated almost exclusively in terms of pattern and process during background times (*3, 4*), but if mass and background extinctions are qualitatively as well as quantitatively different in their effects, the alternation of background and mass extinction regimes shapes large-scale evolutionary patterns in the history of life.

Background extinction. For the shallow-water, bottom-dwelling marine organisms that constitute much of the fossil record, three factors affecting survivorship of species and higher taxa during times of normal background extinction are mode of larval development, geographic range (which for some groups is closely tied to larval mode), and the number of species within a taxonomic group (species richness). Each factor will be tested in turn for its effects on background and mass extinction in Late Cretaceous mollusks of the Gulf and Atlantic Coastal Plain of North America (*5*).

Speciation and extinction rates should be relatively high in species having nonplanktotrophic development because characteristically low rates of larval dispersal will be unable to maintain genetic continuity among disjunct populations; isolated populations will tend to become extinct or diverge into new species. Both rates should be lower in planktotrophs, with greater larval dispersal suppressing divergence of populations and imparting colonizing ability and broad geographic ranges that enhance species' ability to survive local extinctions (*6–10*). These predictions were verified in the fossil record for marine gastropods, in which the earliest parts of the shell preserve a record of larval development. In late Cretaceous

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