

BIOTECH BRIEF

“Scanning the biotech horizon”

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RESEARCH & MEDICINE

MONSTER MICE

Physiologists were greatly surprised in the late 80's to discover the multiple functions of nitric oxide (NO). The short half-life molecule is a neurotransmitter, a cytokine mediator, is involved in inflammation and in the sexual response. NO continues to produce surprises.

Most recently, a group at Johns Hopkins reports that male mice lacking the gene for the enzyme that produces NO are unusually violent, attacking each other relentlessly and sometimes fatally. The animals also display a dramatic sexual persistence toward females, refusing to back down even when rejected by females not receptive to mating.

The mice in the Hopkins study were knockout mice generated by homologous recombination to lack the gene for nitric oxide synthase, whose gene product produces NO. The animals appear normal, and indeed are as capable as unaltered mice at several tasks that test physical skills and coordination.

At first, the researchers intended to use the NO knockout strain to study the neurotransmitter's role in brain damage caused by stroke. They did find that the animals were resistant to stroke damage. But they were puzzled when, in the mornings, they began finding one or two dead animals among each group of five male mice caged together overnight. Soon, they noticed how aggressive the animals were. Female mice did not exhibit the males' disagreeable traits.

The relevance of low levels of NO to human behavior must be determined by further studies. But studies of another brain enzyme, monoamine oxidase A, do indicate the relevance to humans of aggressive behavior in mice. Mice with deletions of the gene for this enzyme display hyperaggressive behavior, and humans with low levels of the enzyme are also hyperaggressive (Cases, O et al., *Science* 268:1763-1766 (1995); Brunner, HG et al., *Science* 262:578-580 (1993)).

Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. RJ Nelson, SH Snyder et al, *Nature* 378:383, Nov 23, 95.

Nitric oxide and bad behaviour. H Coles (News and Views), *Nature* 378:336, Nov 23, 95.

CYCLIN D AND BREAST CANCER

Pat Steeg of NCI and David Page of Vanderbilt have found that overexpression of cyclin D is associated with susceptibility to breast cancer, and is predictive of later development of invasive breast cancer.

Cyclins, which come in flavors A through E, regulate the “cyclin- dependent kinases,” the gatekeeper enzymes which control the DNA synthesis and cell division activities of cells. D-type cyclins participate directly in the phosphorylation of the retinoblastoma protein, releasing this central brake on the cell cycle and

and allowing the cell to veer into a proliferative mode.

The scientists looked at breast cancer biopsy material from three categories of patients. Cyclin D was overactive in 76% of one kind of early breast cancer, in 87% of another kind, and in 83% of late stage, invasive breast cancer. Cyclin D was overexpressed in only 18% of controls. Reported in the Dec issue of *Nature Medicine*.

In related research, Robert Weinberg of MIT and collaborators from Baylor, Harvard, and Michigan State, have created a knockout mouse strain that lacks the cyclin D1 gene. To their surprise, they found that deleting this important cog causes surprisingly little damage to the rest of the machinery. The discovery advances understanding of cancer at the molecular level, and could lead to innovations in treating breast cancer.

Even though cyclin D1 is overproduced in more than half of human breast cancer biopsies, treatment strategies have not targeted this protein because of potential damage to normal cells in other tissues. But Weinberg's new results suggest that breast cancer therapies designed to block D1 action may prevent the growth of tumor cells without harming normal tissues. Dr. Piotr Sicinski and his colleagues at the Whitehead Institute developed the mouse strain by replacing, in embryonic stem cells, the normal mouse cyclin D1 gene with a nonfunctional version. Because cyclin D1 had been thought to be a vital component of the growth machinery in all cells, the researchers had expected the mutation to be lethal. But surprisingly, a number of embryos developed to term, and the adult mice showed relatively few negative consequences: reduced body weight, mild neurological impairment and an underdeveloped retina.

But the researchers did notice a striking difference in the mutant mice when females delivered pups. The mother mice, whose breast tissue was otherwise normal, were unable to nurse after giving birth. Without cyclin D1, their mammary cells failed to undergo the rapid growth that normally occurs during preg-

nancy. They concluded that in adult female mice, the cyclin D1 molecule seems critical only for a specialized process in breast tissue: the rapid growth of mammary cells during pregnancy.

The finding sheds light on the observation that a majority of human breast cancer cells have higher than normal levels of cyclin D1. While normal levels of this protein are critical for normal mammary cell growth, excessive levels may lead to uncontrolled, cancerous growth. The researchers also found that the new mouse strain had a strikingly low number of retinal cells, indicating that cyclin D1 is required for the growth and development of retinal cells during embryonic development.

Collaborators in Weinberg's study included researchers from the Baylor College of Medicine in Houston, Harvard Medical School and Michigan State University, and is reported in the Aug 25 *Cell*.

CANCER AND HELICASE

Researchers from the University of Cincinnati Medical Center and the New York Blood Center have uncovered another clue in the genesis of cancer. They studied patients with Bloom's syndrome, an inherited form of dwarfism, which also carries susceptibility to infections and development of numerous cancers throughout the body. Linkage analysis of Bloom's patients' genetic material focused on an area containing a number of mutations. The locus turned out to contain the helicase gene, a protein associated with DNA replication and the cell cycle. Helicase is a DNA-binding protein that unwinds the double helix in advance of the replication engine.

The discovery is one more piece of the lethal puzzle that is cancer. Assistant Professor Joanna Groden and Joel Straughen of the University of Cincinnati Department of Molecular Genetics, and Nathan Ellis and James German of the New York Blood Center report their results in the Nov 17 *Cell*.

Source: New York Blood Center, Nov 17.

METHYLATION: A REAL TURNOFF

A preliminary study by Johns Hopkins researchers suggests that DNA methylation of the estrogen receptor gene is a risk factor for coronary artery disease in some post menopausal women.

Methylation prevents the gene from being expressed, or causes it to be expressed with lower efficiency. Reduced levels of the receptor means the tissue is less responsive to estrogen. Estrogen replacement therapy reduces heart disease risk by about 50% in post-menopausal women by improving blood flow to the heart.

The Hopkins investigators examined normal and diseased heart blood vessels and fatty deposits in the vessels in 41 men and women over age 37. They found the gene had been inactivated by methylation to a greater extent in the diseased tissue than in the healthy tissue. The results imply that the gene may be inactivated in the atrium (the heart's upper chambers) as a result of natural aging, and thereby contribute to atherosclerosis, a build-up of fatty deposits in the blood vessels to the heart.

Wendy Post, cardiology fellow at Hopkins, was lead author of the report.

Source: Hopkins Office of Communications & Public Affairs, Nov 13.

END OF THE LINE

Continuing research by Calvin Harley and colleagues at Geron Corp, in Mountain View, CA, suggests a connection between telomere length and risk of heart disease. The shorter the telomere, the older the cell. Age-related proteins are expressed in older cells, but not in young ones.

The scientists examined telomere length in endothelial cells and intimal tissue -- the primary cells and tissue separating the blood vessel wall from the blood. They found that telomere length is a reliable marker for human vascular aging. Endothelial cells lost telomeres both in vitro and in vivo as a function of replicative age. Some cellular clocks run faster than others: telomere loss was greater in arterial cells, which are more vulnerable to atherosclerosis, than in venous cells, which are less vulnerable.

It may be that the accumulation of senescent endothelial cells in the arteries contributes to atherosclerotic plaque formation and thrombosis. If so, delaying or modulating the aging of cells could be a new therapeutic route for treating or preventing heart disease. At the very least, the association between plaque formation and telomere length is a likely basis for a cardiac diagnostic.

Geron is built around the "clocking" mechanism that appears to be one of the ways cells' lives are regulated. Telomeres are structures at the ends of chromosomes that serve as a sort of turnaround area for the DNA replicative engine. It's in the nature of this machinery that a little of the telomere is lost after every replicative cycle. When the telomere is gone, that's it for the cell.

A senescent cell does not die immediately, however. It may survive for a considerable time, expressing different genes than does a young cell, leading to the production of proteins that may contribute to age-related diseases. Harley and his colleagues believe that cell senescence is a common link among age-related diseases. They propose that by controlling a cell's genetic clock they will eventually be able to induce the death of immortal cancer cells, and forestall the harmful effects of age-related diseases like osteoporosis and vascular disorders.

Cancer cells might be vanquished by restoring a normal aging mechanism to these cells by inhibiting telomerase, an enzyme that maintains the length of telomeres, and appears to be biologically significant only in tumor and reproductive cells. In research published in the Sept. 1, 1995 *Science*, Geron cloned human telomerase RNA and used it to inhibit telomerase in cultured tumor cells. The result was gradual telomere loss and ultimately the death of nearly all of the tumor cells.

Conversely, Geron's genomics of aging program seeks to intervene in diseases of aging by reversing senescent gene expression to restore normal function in aging cells, and by extending telomere length to delay the onset of cell senescence.

Telomere length and replicative aging in human vascular tissues. E Chang, C Harley, *Proc Nat Acad Sci USA* 92(24):11190, Nov 21, 95.

CLOT BLOCKER FROM HOOK-WORM

Cardiologists are always on the lookout for blood-thinning agents that are more specific and easier to control than heparin and warfarin. A possible new candidate was reported at the American Heart Association meeting. It's a recombinant version of a small protein derived from the blood-feeding hookworm *Ancylostoma caninum*.

The so-called Nematode Anticoagulant Protein (NAP) blocks Factors Xa and VIIa, the two earliest-acting enzymes in the blood coagulation process. The substance was shown in rat and pig models to be nearly 1000-fold more potent than clinical heparin anticoagulant.

George P Vlasuk of Corvas International and his colleagues reported results of their preclinical research at the 68th meeting of the American Heart Association in San Diego, and in the October issue of *Circulation*.

Source: Corvas International (Anaheim, CA), Nov 15

PAIN-KILLER FROM SNAIL

What's wanted for severe, intractable pain is an analgesic as powerful as morphine but without the side-effects of opiates. Scientists at Neurex Corp think they have a candidate in SNX-111, a peptide based on conotoxin, from the venom of a marine snail. The substance blocks N-type, neuron specific, voltage sensitive calcium channels.

In a small trial (Ph I/II, seven patients), patients suffering with severe pain from cancer or neuropathic pain who had failed all other pain therapy, including intraspinal opiates, six of the seven responded symptomatically in the dose escalation phase, and four went into long-term treatment and were maintained on the drug essentially symptom free for periods of up to eight months. Based on these results, the company says it will initiate a controlled study with SNX-111 for the treatment of severe cancer pain in the near future. Announced at the American Pain Society Meeting in Los Angeles by W Brose, Director of the Pain Clinic at Stanford University.

Source: Neurex, Nov 13.

CANDIDATE AIDS DRUG?

Dramatic results are reported for an AZT-like drug which has apparently given a group of test animals 100% protection against SIV infection. SIV is a virus that infects monkeys, and is closely related to HIV.

The substance is a small chemical with a long name, PMPA for short. It and a related compound, PMEA, were discovered at a research institute in Belgium and licensed to Gilead Sciences, of Foster City, CA. Principal Investigator CC Tsai, a University of Washington veterinarian, participated in the study after sending out a broadside letter offering to test development stage AIDS drugs; Gilead had the drug, Tsai had the monkeys. The drug gave complete protection to the treated cohort (35 animals in treatment and control arms) during the course of the study. No toxicity data were gathered in the study, but Gilead says it hopes to begin human trials next year. PMPA was found to be significantly more effective than AZT in other, similar animal studies.

Like AZT, PMPA is a nucleotide analog chain blocker that jams reverse transcriptase, thus interfering with the replication of the viral genome. Nucleotides like PMPA can inhibit viral replication for a long time after a dose. They can remain active in virally infected cells and in uninfected or resting cells, where they can form protective reservoirs of active drug.

PMPA is structurally similar to another reverse transcriptase inhibitor, bis-POM PMEA (GS 840), which is being developed by Gilead Sciences and is in Phase I/II human studies for the potential treatment of HIV and hepatitis B infection.

Prevention of SIV infection in macaques by (r)-9-(2-phosphonylmethoxypropyl)adenine. CC Tsai et al, *Science* 270:1197, Nov 17, 95.

AIDS SCORECARD

American pharmaceutical research companies have 110 medicines for AIDS in development, the largest number ever, according to an annual drug industry

survey. The current survey cites 34 new drugs not present in previous surveys.

During the past 12 months, the FDA has approved two new AIDS medicines, and an advisory committee has recommended two more for approval, including the first protease inhibitor. In all, thirty drugs for AIDS and AIDS-related conditions have been approved.

Source: Pharmaceutical Manufacturer's Association (Washington, DC), Nov 20.

SLIM PILLS

The way obesity is viewed is shifting from a behavioral to a mechanistic interpretation. The latter view has been fortified with the discovery of the "ob" gene, whose activity correlates with obesity, last year by research group at Rockefeller University.

Clinics such as Biochemical Medical Care in Monsey, NY treat patients with "fen-phen," a combination of the drugs fenfluramine and phentermine. Fenfluramine boosts serotonin, the same brain chemical that Prozac enhances to elevate mood, while phentermine mimics other substances in the brain. Together the medicines suppress appetite and speed the burning of calories.

Other diet drugs in the pipeline: -- Dexfenfluramine: it boosts serotonin to suppress appetite. Clinical trials completed, awaiting FDA review. -- Sibutramine: boosts serotonin and other brain chemicals to suppress appetite and increase burning of calories. Clinical trials completed, awaiting FDA review. -- Orlistat: inhibits intestinal enzyme needed to digest fat, causing it to pass through the digestive tract without being absorbed. In Phase III (final) clinical trials. -- BTA-243: enhances activity of fat cells' "beta adrenergic receptors" to stimulate the burning of fat. In Phase II clinical trials. -- Leptin: the recombinant product of the "ob" gene; may suppress appetite and increase burning of calories. Clinical trials of this bioengineered hormone scheduled to begin in 1996.

Source: Fortune, Dec 11.

FLT3 LIGAND AND DENDRITIC CELLS

The dendritic cells of the immune system got their name because they resemble dendrite neurons, with their extraordinarily long and delicate treelike processes that branch off from the central body of the cell. They are antigen presenting cells, and play a pivotal role in the T cell-mediated immune response. They have been compared to smoke detectors, sampling the body's internal environment for foreign proteins, ie., those from bacteria, parasites, viruses, or tumor cells. Dendritic cells process these proteins and present them to T-cells, which then take appropriate action.

But because of their delicate structure and rarity (they comprise fewer than 0.1% of circulating white cells), they have, until now, been difficult to isolate and study. Immunex scientist Eugene Maraskovsky announced at the American Society for Hematology meeting in Seattle that his group has cloned a molecule, Flt3 ligand (Flt3-L), that stimulates the growth of these elusive cells of the immune system. Pre-clinical studies (in mice) generated large numbers of functional and mature dendritic cells.

One of the Hematology meeting papers reports that in mice injected daily for 10 days with Flt3-L, dendritic cells in spleen increased. Another paper reports that Flt3-L generated large numbers of dendritic cells in an ex vivo cell culture of CD34+ human bone marrow, with no loss of efficiency in the presentation of antigens.

Flt3-L will enable dendritic cells to be grown in numbers large enough that they may be thoroughly characterized. Eventually, augmenting dendritic cells could be a useful way to enhance immune response against infection or malignancy.

Source: Immunex, Inc (Seattle, WA), Nov 30.

ALZHEIMER'S AND CORTICOIDS

Responses to stress throughout the body are achieved by rapidly mobilizing glucocorticoid hormones, production of which is initiated in the hypothalamus. A binding protein holds this gland in an inactive state, but a quick release mechanism is avail-

able in the form of a release factor, corticotrophin release factor (CRF). In Alzheimer's patients, CRF is significantly decreased, occurring at levels less than 50 percent of normal in critical brain regions affected by the disease.

Scientists associated with Neurocrine Biosciences (San Diego) have developed compounds that block the binding protein, thus raising the deficient level of CRF in an Alzheimer's brain, and allowing it to interact with its receptor on brain neurons. The compounds are peptide ligands based on selected portions of CRF from human and other species. In animal studies conducted by the team, CRF-Binding Protein blockers were shown to enhance learning and memory processes in a variety of animal models that have been used to evaluate potential treatments for dementia.

Displacement of corticotrophin-releasing factor from its binding protein as a possible treatment for Alzheimer's disease. DP Bechan, SC Heinrichs, JC Troncoso, X-J Liu, CH Kawas, N Ling, EB de Souza. *Nature* 378:284, Nov 15, 95.

VACCINE AGAINST CANCER-CAUSING VIRUS

There is no vaccine to prevent infection by the human papillomaviruses, which induce genital and oral warts, and promote cervical and oropharyngeal cancer. Researchers at Georgetown University Medical Center and MedImmune Inc (Gaithersburg, MD) have devised a systemic vaccine that completely protects against experimentally induced oral mucosal papillomas in dogs. The researchers identify the active ingredient as L1, the major capsid protein of canine oral papillomavirus, and describe a recombinant system to produce this protein in insect cells.

Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. JA Suzich, R Schlegel et al. *Proc Nat Acad Sci USA* 92:11353, Dec 5 95

FOCUS ON THE CELL CYCLE

Mitotix, the Cambridge, MA firm built around devising treatments for cancer and other diseases

based on intervening in the cell cycle, will team up with DuPont-Merck. The big conglomerate will invest up to \$55M in the small research company; existing partners will also throw another \$3M into the current development work.

The collaboration will have three principal targets: identify inhibitors of cyclin D1 and of cyclin E, and identify mimetics (analogues) of the tumor suppressor gene p16. Particular attention will be given to the molecular pathway that includes Cyclin D1 and p16. In most cancers one or more of the components of this pathway are deregulated, leading the affected cells into inappropriate modes of DNA replication and cell proliferation.

Cyclin D1 is expressed at high levels in various tumors, including breast, colon, esophageal cancers, and lymphomas. And a persuasive body of recent research indicates that in 20-50% of breast, bladder, esophageal and skin cancers p16 is missing or mutated, thus permitting uncontrolled cell growth. Cyclin E acts at a similar regulatory point in the cell cycle as does cyclin D1, but through its own biochemical pathway. Recently published research shows that elevated levels of cyclin E appear to increase the rate at which cells divide.

Mitotix holds rights to cyclin D1 and p16 from Cold Spring Harbor Laboratory, based on discoveries made by David Beach, H Hughes Medical Institute Investigator at Cold Spring and a scientific co-founder of Mitotix. The company also has rights to cyclin D1 patent applications from the Massachusetts General Hospital, and to an issued US patent covering cyclin E from the Fred Hutchinson Cancer Research Center.

The partners will also begin looking at developing anti-cancer therapeutics that act by inhibiting ubiquitin-mediated degradation of p53. Ubiquitin is a small protein present in all cells which tags proteins for destruction by proteasomes. By preventing ubiquitin tagging of p53, levels of this protein would remain higher allowing for more effective activity against tumor cells.

Source: Mitotix Inc (Cambridge, MA) and DuPont-Merck (Wilmington, DE), Dec 7.

TPA FOR STROKE

Genentech hopes to expand indications for TPA to stroke. In a 624-patient Ph III trial in which TPA was administered within three hours of the stroke event, 11% of the patients recovered with no symptoms or with only minimal function deficit. Use of TPA for strokes is based on the idea that many heart attacks and strokes (“brain attacks”) share blood clots in common.

It’s important to verify with a CT scan that the stroke is caused by a blood clot, and not by bleeding, before administering TPA for stroke.

The company will apply early next year to the FDA for approval on the basis of the trial results.

Source: New England Journal of Medicine, Dec 13.

CT AND GENE THERAPY

A phase I gene transfer technology to treat metastatic melanoma has yielded significant results in an early stage trial. The therapy is based on inserting a tissue rejection gene at the tumor site by means of injection, with the needle guided by CT imaging. The gene is the HLA-B7 antigen, a highly antigenic gene that is prominent in tissue rejection and graft versus host disease. Rationale of the therapy is to trick the immune system into launching a strong graft versus host response, as though the tumor were foreign tissue.

Eight patients with metastatic melanoma underwent CT, CT-guided core biopsy, and CT-guided intratumoral injection of therapeutic gene (HLA-B7 gene enclosed in a liposomal vector). Gene localization and expression and T-cell response were studied. Three of the eight patients had tumor regression in the injected nodules; none of the non-injected nodules regressed. Principal Investigator of the trial is Evan Unger, of the University of Arizona, Tucson.

Human gene therapy treatment of melanoma: CT-guided interstitial injection. Paper presented at 81st Radiological Society Meeting, Chicago, Nov 26-Dec 1, 1995

PROTEIN ENGINEERING YIELDS ONE-WAY THROMBIN

Thrombin is a protein that does a balancing act on the knife edge between clotting or uncontrolled bleeding. The protein has two opposite activities, which can be plotted as a J-curve. At low concentrations it interacts with a circulating serine protease, activated protein C, and is an anticoagulant. At higher concentrations, it interacts with the clotting factors Va and VIIIa, which in turn convert fibrinogen to fibrin, and also activates platelets, which go on to release still more thrombotic agents.

Researchers led by LLK Leung at Stanford and collaborators at Gilead Sciences (Foster City, CA) have engineered a modified thrombin they call Protein C Activator (PCA), which makes thrombin’s clotting function disappear almost totally, but which retains the protein’s normal anti-clotting activity. That the engineered protein can prevent blood clotting with decreased potential for bleeding may point to a breakthrough for treating severe heart disease.

The researchers created and evaluated 62 modified versions of thrombin, most containing a single amino acid substitution on the surface of native thrombin. Screening turned up one variant, PCA, with anti- but not pro-coagulant properties. The achievement draws on work reported in 1991 (Wu et al, PNAS 88:6675) in which the pro- and anti-coagulant activities of thrombin were dissected by site-directed mutagenesis. The method used by the researchers (“alanine scanning”) may also be extended to engineer other proteins of clinical value.

CS Gibbs, a co-author of the report, believes PCA may have applications in bypass procedures and angioplasty to treat acute coronary syndromes where safe anticoagulation is desired.

Conversion of thrombin into an anticoagulant by protein engineering. CS Gibbs, LLK Leung et al Nature 378:413, Nov 23.

HISTONE FOLD

Hopkins researchers report a basic discovery in protein structure. The “histone fold” is a structural element handed down from the beginning of biological

time. Identified in histones, the structural elements that are vital to compression and organization of DNA.

The histone fold is a specific three-dimensional arrangement of 65 amino acids. One of its important characteristics is that when its two halves are analyzed separately, one appears to be a modified duplicate of the other, perhaps produced by an ancient gene duplication event. A paper by the same authors in the July 1995 *Nucleic Acids Research*, reported on results of a computer search of all registered proteins: the structure was found in many proteins previously considered unrelated to histones, including enzymes and transcription factors.

The histone fold: a ubiquitous architectural motif utilized in DNA compaction and protein dimerization. G Arents, EN Moudrianakis, *Proc Nat Acad Sci USA* 92(24):10819, Nov 21.

COMPANY BRIEF

CANJI ABSORBED

Schering-Plough Corp has announced it will acquire the rest of Canji, Inc., the San Diego gene therapy company, that it does not already own. Canji will fit in with DNAX, a Palo Alto immunology research company previously acquired by Schering-Plough.

The acquisition is an indication of the folding in of biotech enterprise to established pharmaceutical and chemical entities, and a blurring of the boundaries that so strikingly demarcated the biotech industry in its early days.

Canji is built around developing discoveries relating to the p53 tumor suppressor and apoptosis controller gene. Value of the deal to Canji shareholders is \$54.5M, plus royalties.

Source: Schering-Plough Inc (Madison, NJ); Canji, Inc (San Diego), Dec 12. .

PATENT LOG

US PATENTS, NOV 21-DEC 12, 1995

NON-TUMORIGENIC CELL LINES FOR EXPRESSION OF GENES Inventors: Barnes David W (US) Assignee: State of Oregon Pat No US 5474930 Issue Date: Dec 12, 95

MODIFIED CYCLODEXTRIN GLYCOSYLTRANSFERASES FOR PRODUCING GAMMA- CYCLODEXTRINS Inventors: Candussio Anton (DE); Schulz Georg E (DE) Assignee: Consortium fur Elektrochemische Industrie GmbH DE Assignee Code: 19872. Pat No US 5474917. Issue Date: Dec 12, 95

PROMOTION OF HIGH SPECIFICITY MOLECULAR ASSEMBLY Inventors: Pontius Brian W (US) Assignee: Stanford, Leland Jr University Trustees Assignee Code: 49136. Pat No US 5474911. Issue Date: Dec 12, 95.

THIOL LABELING OF DNA FOR ATTACHMENT TO GOLD SURFACES Inventors: Beebe Thomas P (US); Rabke-Clemmer Carol E (US) Assignee: Utah, University of Assignee Code: 88042. Pat No US 5472881. Issue Date: Dec 5, 95

ISOLATION AND CHARACTERIZATION OF THE NEMATODE HER-1 GENE AND PROTEIN PRODUCT Inventors: Perry Marc D (US); Trent Carol (US); Wood William B (US) Assignee: Colorado, University of Assignee Code: 18813. Pat No US 5472871. Issue Date: Dec 5, 95.

STABLE TRANSFORMATION OF MAIZE CELLS BY ELECTROPORATION Inventors: Anderson Paul C (US); Krzyzek Richard A (US); Laursen Cheryl R M (US) Assignee: DeKalb Genetics Corp Assignee Code: 35285. Pat No US 5472869. Issue Date: Dec 5, 95.

METHODS OF DETECTION OF TOXOPLASMA GONDII P22 GENE Inventors: De Araujo Fausto G (US); Prince Jeffrey B (US); Remington Jack S (US) Assignee: Research Inst of Palo Alto Medical Foundation. Pat No US 5472844. Issue Date: Dec 5, 95.

FAMILY OF ANTI-CARCINOEMBRYONIC ANTIGEN CHIMERIC ANTIBODIES Inventors: Gourlie Brian B (US); Kaplan Donald A (US); Mezes Peter S (US); Rixon Mark W (US); Schlom Jeffrey (US) Assignee: Dow Chemical Co The; National Institutes of Health Assignee Code: 24712 33614. Pat No US 5472693. Issue Date: Dec 5, 95.

MASPIN, A SERPIN WITH TUMOR SUPPRESSING ACTIVITY Inventors: Anisowicz Anthony (US); Sager Ruth (US); Zou Zhiqiang (US) Assignee: Dana-Farber Cancer Institute Inc Assignee Code: 11804. Pat No US 5470970. Issue Date: Nov 28, 95.

TRANSDOMINANT NEGATIVE PROTO-ONCOGENE Inventors: Verma Inder M (US); Wisdom Ronald M (US); Yen

Jong- Young J (US) Assignee: Salk Institute for Biological Studies Assignee Code: 73756. Pat No US 5470736. Issue Date: Nov 28, 95.

INSECTICIDAL PLECTOXINS FROM PLECTREURYS TRISTIS Inventors: Leisy Douglas J (US); Quistad Gary B (US); Skinner Wayne S (US) Assignee: Sandoz AG CH Assignee Code: 73920. Pat No US 5470735. Issue Date: Nov 28, 95.

METHOD OF ISOLATING RESTRICTION FRAGMENT DELETIONS IN VIBRIO CHOLERAEE, AND PRODUCTS THEREOF Inventors: Baudry-Maurelli Bernadette (US); Fasano Alessio (IT); Kaper James B (US) Assignee: University of Maryland At Baltimore. Pat No US 5470729. Issue Date: Nov 28, 95.

RETROVIRUS PACKAGING AND PRODUCER CELL LINES BASED ON GIBBON APE LEUKEMIA VIRUS Inventors: Eiden Maribeth V (US); Garcia-Martinez Jose V (US); Miller A Dusty (US); Wilson Carolyn A (US) Assignee: Hutchinson, Fred Cancer Research Center; U S of America Health & Human Services Assignee Code: 06814 14990. Pat No US 5470726. Issue Date: Nov 28, 95.

DETECTION OF MYCOBACTERIA BY MULTIPLEX NUCLEIC ACID AMPLIFICATION Inventors: Jurgensen Stewart R (US); Nadeau James G (US); Nycz Colleen M (US); Schram James L (US); Shank Daryl D (US); Spears Patricia A (US); Walker George T (US) Assignee: Becton Dickinson & Co Assignee Code: 08488. Pat No US 5470723. Issue Date: Nov 28, 95.

EQUINE HERPESVIRUS TYPE 1 GLYCOPROTEIN D NUCLEIC ACIDS Inventors: O'3 Callaghan Dennis J (US) Assignee: Research Corp Technologies Inc Assignee Code: 17457. Pat No US 5470718. Issue Date: Nov 28, 95.

GENE MAPPING BY HYBRIDIZATION TO FREE CHROMATIN Inventors: Heng Henry H Q (CA); Tsui Lap-Chee (CA) Assignee: HSC Res and Dev Ltd Partnership CA. Pat No US 5470709. Issue Date: Nov 28, 95.

PROCESS FOR THE RESCUE OF DNA AND FOR DETECTING MUTATIONS IN MARKER GENES Inventors: Gossen Jan A (NL); Vijg Jan (NL) Assignee: Nederlandse Organisatie voor toegepastwetenschappelijk onderzoek NL. Pat No US 5470706. Issue Date: Nov 28, 95.

METHODS AND COMPOSITIONS OF A POLYMER (POLOXAMER) FOR CELL REPAIR Inventors: Lee Raphael C (US) Assignee: Arch Development Corp Assignee Code: 20681. Pat No US 5470568. Issue Date: Nov 28, 95.

METHOD FOR EVALUATING IMMUNOGENICITY Inventors: Martin David W Jr (US) Assignee: Genentech Inc Assignee Code: 07579. Pat No US 5470560. Issue Date: Nov 28, 95.

RECOMBINANT DNA COMPOUNDS AND EXPRESSION VECTORS ENCODING PARA- NITROBENZYL ESTERASE ACTIVITY FROM BACILLUS Inventors: Cantwell Cathleen A (US); Hodges Roland L (US); McGilvray Derek (US); Queener Stephen W (US); Swartling James R (US); Zock Joseph M (US) Assignee: Lilly, Eli and Co Assignee Code: 49800. Pat No US 5468632. Issue Date: Nov 21, 95.

CDNA CLONE FOR HUMAN INDUCIBLE NITRIC OXIDE SYNTHASE AND PROCESS FOR PREPARING SAME Inventors: Billiar Timothy R (US); Geller David A (US); Nussler Andreas K (US); Simmons Richard L (US) Assignee: University of Pittsburg of Commonwealth System of Higher Education. Pat No US 5468630. Issue Date: Nov 21, 95.

SYSTEM TO DETECT PROTEIN-PROTEIN INTERACTIONS Inventors: Fields Stanley (US); Song Ok-Kyu (US) Assignee: New York, State University of Research Foundation of Assignee Code: 05711. Pat No US 5468614. Issue Date: Nov 21, 95.

9804 GENE AND METHODS OF USE THEREOF Inventors: Cohen Edward H (US); Landgraf Bryan E (US) Assignee: CytoMed Inc Assignee Code: 34582. Pat No US 5468612. Issue Date: Nov 21, 95.

THREE HIGHLY INFORMATIVE MICROSATELLITE REPEAT POLYMORPHIC DNA MARKERS Inventors: Merrill Carl R (US); Polymeropoulos Mihael H (US) Assignee: U S of America Health & Human Services Assignee Code: 06814. Pat No US 5468610. Issue Date: Nov 21, 95.

PRODUCTION OF INTERFERON Inventors: Revel Michel (IL); Tiollais Pierre (FR) Assignee: Yeda Research & Development Co Ltd IL Assignee Code: 93576. Pat No US 5468608. Issue Date: Nov 21, 95.

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