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Seeking Pipeline Funds, Inspire Files For Estimated $56M Offering

By Kim Coghill
Washington Editor

Inspire Pharmaceuticals Inc. said it intends to publicly offer 4 million shares of common stock to help fund its drug discovery projects and possibly to pay the cost of hiring a 60-person sales force.

Inspire, of Durham, N.C., in January filed a shelf registration statement covering $100 million in common stock, and on Friday it was declared effective. The company assumed in its prospectus an offering price of $13.99 per share, which would raise about $56 million.

Inspire's stock (NASDAQ:ISPH) fell 56 cents Tuesday to close at $13.50.

While Inspire remains in its SEC-imposed quiet period, Mary Bennett, company vice president of operations and communications, told *BioWorld Today* money raised in the

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European C21 BioInvestor Conference

European Sector Rallying Cry: Comebacks, Consolidation

By Jim Shrine
Managing Editor

MUNICH, Germany – The consolidation that biotechnology investors and observers have been clamoring for already is well under way in Europe and, for that matter, the rest of the world, one investment banker said.

"People say it's not happening, but it is happening. Consolidation is out there," said William Kridel Jr., managing director at Ferghana Partners Inc., an investment bank. "Companies are running out of money, shareholders are running out of patience and investors are running out of rope.

"It's Darwinism, and it should be."

Kridel's firm collected data showing 63 deals in 2002 that involved a European biotechnology or pharmaceutical company, subsidiary or unit as the target of a merger or

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A New AD Player Pulls Up To The Table

Hitherto Ignored, Astrocytes Are Brain Cells That Attack A-Beta In Alzheimer's Neuronal Plaques

By David N. Leff
Science Editor

Your average adult lab mouse (*Mus musculus*) weighs in at 25 grams to 30 grams. Of that payload, the murine brain tips the scales at one gram. The brain of your average adult human comes in at 1,400 grams.

But don't poor-mouth a mouse's brain. It comes equipped with a cortex, a hippocampus and other cerebral accoutrements also found in humans. But not only are human brains far weightier and more complex, their wiring diagram is far more sophisticated.

Jens Husemann, research physiologist at Columbia University College of Physicians and Surgeons, explained:

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Peptimmune Nets $41.2 Million In Series A Financing Round

By Aaron Lorenzo
Staff Writer

Peptimmune Inc. reeled in a windfall amount of venture capital funding, landing $41.2 million in its first round of financing.

The Cambridge, Mass.-based firm, spun out of Genzyme Corp. more than a year ago, features four preclinical candidates. Also located in Cambridge, Genzyme at the time of the separation provided initial capitalization for Peptimmune by purchasing $5.5 million in shares of preferred stock.

"It took us a lot longer than we thought to round up the financing because it is such a difficult environment, but I think that our technology speaks for itself," Timothy Harris, Peptimmune's vice president and chief operating officer, told *BioWorld Today*. "If we didn't have the technology,

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OTHER NEWS TO NOTE

• **3-Dimensional Pharmaceuticals Inc.**, of Yardley, Pa., said the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 expired with respect to its proposed acquisition by **Johnson & Johnson**, of New Brunswick, N.J. 3-Dimensional added that the proposed transaction is expected to close as promptly as possible after its special stockholder meeting, scheduled for March 27, subject to closing conditions.

• **Acambis plc**, of Cambridge, UK, said a Phase I trial of its smallpox vaccine, ACAM2000, reached the primary endpoint. The 100-patient, open-label trial showed that 99 percent of patients achieved the accepted indication of protective immunogenicity – the development of a pockmark on the skin. Also, 96 percent of subjects achieved a secondary endpoint – the development of a neutralizing antibody response. Under an accelerated development program, Acambis said Phase II trials of ACAM2000 are under way and further results are expected shortly. The company added that Phase III trials would begin later this year. Separately, Acambis entered an agreement with **Cangene Corp.**, of Toronto, to market the latter's vaccinia immune globulin (VIG) product in markets outside North America and Israel. The product, which is in clinical trials, is designed to treat and prevent most severe reactions that might result from a smallpox vaccine. Cangene supplies VIG under contract to the Centers for Disease Control and Prevention in Atlanta. Financial terms were not disclosed.

• **Agilent Technologies Inc.**, of Palo Alto, Calif., introduced an ion trap mass spectrometer that is about 10 times more sensitive than its predecessor, the company said. The Agilent 1100 Series LC/MSD Trap XCT is designed to enable improved performance for many applications such as the identification and characterization of proteins for disease research.

• **Aradigm Corp.**, of Hayward, Calif., said it closed a $15 million private placement. The company sold about 19 million shares at a negotiated price of 79 cents per share. Investors included New Enterprise Associates and Special Situations Fund, as well as members of Aradigm's senior management. The proceeds are designated to advance core development programs, reinforce working capital and enhance manufacturing and general operations. The financing was originally announced in February. (See *BioWorld Today*, Feb. 13, 2002.)

• **Basilea Pharmaceutica Ltd.**, founded in 2002 as a spin-off of **F. Hoffmann-La Roche Ltd**., of Basel, Switzerland, received fast-track designation from the FDA for its broad-spectrum cephalosporin antibiotic, BAL5788, for the treatment of complicated skin and skin structure infections (cSSSI). The company said BAL5788 has bactericidal activity toward methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*, in addition to a broad-spectrum profile toward other Gram-positive and Gram-negative pathogens. Basilea has begun a Phase II trial in patients with cSSSI.

• **Cardiome Pharma Corp.**, of Vancouver, British Columbia, began patient dosing with oxypurinol in a Phase II/III study of congestive heart failure patients. In the trial, 400 patients will receive oral oxypurinol or placebo for six months. Oxypurinol, which belongs to a class of drugs that increases the pumping action of the heart without a proportionate increase in oxygen consumption by the organ, will be administered in addition to standard medications. The study's objective is to define oxypurinol's efficacy using surrogate measures of clinical efficacy (six-minute walk test, maximum oxygen consumption and quality of life), as well as clinical outcomes (death, worsening heart failure and hospitalization).

• **DOR BioPharma Inc.**, of Lake Forest, Ill., reported the publication of the results of an intranasal version of DOR's vaccine against botulinum toxin in the journal *Infection and Immunity*. DOR is developing an oral version of the vaccine.

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OTHER NEWS TO NOTE

• **D-Pharm Ltd.**, of Rehovot, Israel, reported results from the Phase II acute stroke study with its drug candidate, DP-b99. The purpose of the trial was to determine if DP-b99 could be used in patients within a 12-hour time window following a stroke incident, and to provide pharmacokinetics and dosing information for future trials. Initial analysis of the data indicates that DP-b99 might be safely administered in that patient profile. The company said improvements were observed in clinical neurological scale scores two, seven and 30 days after the stroke.

• **Dynavax Technologies Corp.**, of Berkeley, Calif., said a single course of its anti-allergy immunotherapy, known as AIC, appears to provide protection against ragweed allergy, according to Phase II data presented at the 60th annual meeting of the American Academy of Allergy, Asthma and Immunology in Denver. AIC administration prior to the 2001 allergy season resulted in reduced allergy symptoms and other clinical markers of the allergic response through the 2002 ragweed season.

• **GeneProt Inc.**, of Geneva, promoted Bertrand Damour to CEO and elected him to its board. He had been the chief financial officer and the co-chair of the operating committee at GeneProt, which focuses on separating, identifying, characterizing, selecting and synthesizing certain human proteins for drug discovery.

• **Gilead Sciences Inc.**, of Foster City, Calif., said it received approval to market Hepsera (adefovir dipivoxil 10 mg) in the European Union. Hepsera is indicated in Europe for chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. The product received U.S. approval last fall. (See *BioWorld Today*, Sept. 24, 2002.)

• **Hybridon Inc.**, of Cambridge, Mass., reported the presentation of preclinical studies of its immunomodulatory oligonucleotides in allergic asthma models. The presentation was made at the 60th annual meeting of the American Academy of Allergy, Asthma and Immunology in Denver. The study evaluated several of Hybridon's IMO compounds containing DNA structure and containing either a natural CpG motif or synthetic CpR motif. Systemic administration of two immunomers significantly reduced conalbumin-induced airway hyper-responsiveness and eosinophil count in the studies, it said.

• **Indevus Pharmaceuticals Inc.**, of Lexington, Mass., entered an exclusive agreement under which Shire Laboratories Inc., a subsidiary of **Shire Pharmaceuticals Group plc**, of Andover, UK, will develop extended-release formulations of trospium, a product in development for overactive bladder. The agreement includes milestone payments from Indevus to Shire, as well as royalties based on future sales of extended-release trospium. Indevus will be responsible for all development costs and commercialization. Indevus said it plans to submit to the FDA a new drug application for a twice-a-day formulation of trospium in the second quarter, contingent upon finalizing discussions with the agency.

• **InnaPhase Corp.**, of Philadelphia, said that **Biogen Inc.**, of Cambridge, Mass., signed an agreement to implement InnaPhase's Watson Laboratory Information Management System. The agreement provides Biogen with Watson licenses for its Cambridge and Research Triangle Park, N.C., facilities. The Watson product is designed to support DMPK/Bioanalytical studies in drug development while ensuring compliance with FDA guidelines.

• **Kosan Biosciences Inc.**, of Hayward, Calif., was awarded a two-year, $400,000 Phase I Small Business Innovation Research grant from the National Cancer Institute in Bethesda, Md. The company will apply its technology to develop a means of producing the polyketide laulimalide. Laulimalide, also known as fijianolide B, has demonstrated the ability to inhibit cancer cells by the same mechanism as paclitaxel and epothilones, while also exhibiting activity against paclitaxel-resistant tumors, the company said.

• **NeoRx Corp.**, of Seattle, applied to transfer its common stock listing from The Nasdaq National Market to The Nasdaq SmallCap Market. NeoRx, which said it expects to receive a decision within the next 10 days, will maintain its current National Market status pending approval. It said it meets all listing requirements of the SmallCap market, other than a minimum $1 per-share price requirement, and expects approval of the transfer given a grace period within which to satisfy the minimum bid price requirement. Its common stock will continue to trade under the symbol NERX. Separately, NeoRx named Jack Bowman executive chairman and chairman of its board. He has been the group chairman at Johnson & Johnson, of New Brunswick, N.J., with global responsibility for most of its pharmaceuticals and diagnostics businesses.

OTHER NEWS TO NOTE

• **NicOx SA**, of Sophia-Antipolis, France, clarified results from a Phase II trial of AZD3582 that failed to achieve statistical significance for its primary endpoint with respect to gastrointestinal ulcers (p=0.07). NicOx had asked for data from the trial to conduct its own analysis with outside experts following the companies' original announcement of the missed trial in February. Specifically, NicOx said that due to a lower than predicted rate of gastrointestinal ulcers in the group treated with the reference compound (14 percent vs. 20 percent to 25 percent) compared to the protocol's statistical plan, the study was underpowered to detect a statistically significant change in the primary endpoint (incidence of patients with at least one gastrointestinal ulcer of 3 mm or greater). The compound, being developed in partnership with **AstraZeneca plc**, of London, met a number of secondary endpoints, NicOx said.

• **Osiris Therapeutics Inc.**, of Baltimore, and **Boston Scientific Corp.**, of Natick, Mass., entered an alliance to develop and commercialize a therapy to treat cardiovascular disease. The alliance, which includes an equity investment by Boston Scientific in the privately held firm, initially will focus on applying mesenchymal stem cell technology to help heart attack patients. More specific financial terms were not disclosed.

• **Progen Industries Ltd.**, of Brisbane, Australia, entered a contract with **Peplin Operations Pty Ltd.**, a subsidiary of Peplin Biotech Ltd., also of Brisbane, to manufacture Peplin's anticancer compound, PEP 005, for clinical trials. Peplin and its collaborators are developing PEP 005 as a prescription topical drug for non-melanoma skin cancer.

• **Senesco Technologies Inc.**, of New Brunswick, N.J., said that inhibiting the expression of its gene, apoptosis eucaryotic initiation Factor 5A, reduced apoptosis in preclinical studies with human lamina cribrosa cells from the optic nerve head of human eyes. The lamina cribrosa is a supporting structure for the optic nerve at the point of connection with the eye. Senesco has preclinical programs testing its gene in diseased heart tissue and human cancer.

• **Synsorb Biotech Inc.**, of Calgary, Alberta, said it signed a definitive agreement with an unrelated investing company that will see the former pharmaceutical research company transformed into an oil and gas enterprise. In January, Synsorb said the undisclosed company would invest up to $3 million in Synsorb, which had appointed David Tuer chairman and CEO. Completion of the financing remains subject to regulatory approvals, including Toronto Stock Exchange consent, Synsorb shareholder endorsement and other customary closing conditions. Synsorb said the investing company advised that it has completed its due diligence review with respect to Synsorb.

• **Tanox Inc.**, of Houston, said that the positive results from the TNX-901 (Hu-901) Phase II trial in patients with peanut allergy were presented at the 60th annual meeting of the American Academy of Allergy, Asthma and Immunology in Denver. The results show an increase in the amount of peanut flour required to induce a hypersensitivity reaction. The study was conducted in 84 patients with a history of immediate hypersensitivity to peanuts.

U.S. PATENT DISCLOSURES

BioCurex Inc., of Rancho Santa Margarita, Calif., was granted U.S. Patent No. 6,514,685 B1 titled "Detection of Cancer Using Antibodies to the AFP-Receptor (RECAF)." BioCurex said RECAF has been found in all cancers studied to date, including breast, lung, stomach, colorectal, ovarian and prostate cancers. The molecule has been found in 100 percent of breast cancers.

Cepheid Inc., of Sunnyvale, Calif., said the University of California's Lawrence Livermore National Laboratory received U.S. Patent No. 6,524,532. Exclusively licensed to the company, the patent covers various aspects of nucleic acid amplification technologies using sleeve-type reaction chambers such as those used in its Smart Cycler and GeneXpert instruments.

CollaGenex Pharmaceuticals Inc., of Newtown, Pa., was granted U.S. Patent No. 6,506,740 covering the first of its new IMPACS (Inhibitors of Multiple Proteases and Cytokines) compounds. Titled "4-dedimethylaminotetracycline derivatives," the patent claims a specific chemical structure and its use for a variety of diseases involving, among other things, the destruction of the body's connective tissues.

Esperion Therapeutics Inc., of Ann Arbor, Mich., was granted U.S. Patent No. 6,506,799 for its oral small-molecule program. Titled "Methods of treating cardiovascular diseases, dyslipidemia, dyslipoproteinemia, and hypertension with ether compounds," it covers methods for the use of certain small molecules to treat a variety of cardiovascular diseases.

Immtech International Inc., of Vernon Hills, Ill., was granted U.S. Patent No. 6,503,940 B2 titled "Prodrugs for Antimicrobial Amidines."

InSite Vision Inc., of Alameda, Calif., received a notice of allowance from the U.S. Patent & Trademark Office for claims covering the use of azalide antibiotic formulations to topically treat ocular infections. InSite uses azithromycin, an azalide, in ISV-401, its ocular antibiotic designed for the topical treatment of bacterial conjunctivitis.

Peptimmune

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we wouldn't have gotten the funding. We have very good programs and we have a very good intellectual property position. Unlike some other companies, we're probably a little bit more late stage than a lot of start-ups that are getting financed."

Peptimmune said its lead product, an immunotherapeutic for a skin disorder, is expected to enter clinical trials later this year. Harris said the funding, which should last several years, would be used to advance its lead product and eventually drive clinical development of other programs as well.

"The real focus of the money is going to be on the research and development side – getting these programs advanced and achieving solid milestones," he said, adding that the 14-person company expects to spend some of the funding on employee growth in scientific and regulatory positions. In the near term, though, Peptimmune remains squarely focused on its lead program.

The injectable immunotherapeutic is designed to treat pemphigus vulgaris, an autoimmune disease that causes blisters of the skin and mucous membranes. The disease affects several thousand U.S. individuals and results from an inappropriate immune response to desmoglein 3, a protein that normally holds skin cells together. Peptimmune identified a specific peptide epitope of desmoglein 3 and formulated it to induce tolerance in the patient and reduce or eliminate the immune response.

"This is a disease for which there really is no other treatment except for chronic, high-dose steroids that have debilitating side effects over time," Harris said. "From what we have heard from patients and patient organizations, there is real strong demand for something that is new and efficacious and would allow you to sidestep some of these terrible side effects. And it's a unique opportunity – I'm not really aware of any other company that is pursuing a treatment specifically for this disease."

He likened Peptimmune's interest in the therapy to Genzyme's strategy in pursuing a treatment for another relatively rare disease – Gaucher's disease.

"There was no treatment available for that disease at the time and it was a small market that was kind of overlooked by large pharma," Harris said. "Genzyme built an extremely successful business on that, so I think in a way what we're doing is very similar to that."

Genzyme is banking on that strategy paying off again. Though the latest investment reduces its ownership interest in Peptimmune to about 10 percent, Genzyme holds a first offer right to participate in the lead product's commercialization. Genzyme originally acquired Peptimmune nearly four years ago in a deal centered on the potential pemphigus vulgaris treatment. (See *BioWorld Today*, July 28, 1999.)

Like its lead candidate, Peptimmune's other drugs are designed to selectively inhibit immune responses without compromising normal immune function. The company said each product represents a distinct therapeutic approach.

Peptimmune's cathespin S inhibitor, a small molecule designed to treat a variety of autoimmune diseases, suppresses a specific process in autoimmune and allergic diseases. Peptimmune partnered its development in a 50-50 agreement with Huddinge, Sweden-based Medivir AB prior to the beginning of its relationship with Genzyme.

The random amino acid copolymer is a peptide treatment for multiple sclerosis that works by a similar mechanism as a drug already marketed for that indication, Copaxone (glatiramer acetate for injection), which was developed by Jerusalem-based Teva Pharmaceuticals Industries Ltd.

Peptimmune's soluble MHC Class II/Ig fusion proteins are designed to deactivate disease-specific immune responses by acting as molecular decoys for disease-inducing immune cells.

Simultaneous with the financing, Peptimmune added CEO to Robert Carpenter's list of titles, which already included company president and chairman. Still the chairman of Hydra BioSciences Inc., also of Cambridge, Carpenter co-founded Waltham, Mass.-based Geltex Pharmaceuticals Inc., bought two and a half years ago by Genzyme for more than $1 billion. (See *BioWorld Today*, Sept. 12, 2000.)

He remains a director at Genzyme as well.

Peptimmune's investment was co-led by New Enterprise Associates, of Baltimore, and MPM Capital, of Boston. Additional funding came from Prism Venture Partners, of Westwood, Mass.; Vanguard Ventures, of Palo Alto, Calif.; Hunt Ventures LP, of Dallas; and Boston Medical Investors Inc., a group of which Carpenter also is president.

Four investor representatives were added to Peptimmune's board following the financing: New Enterprise's Jim Barrett, MPM's Luke Evnin, Prism's John Brooks and Vanguard's Hugh Rienhoff. ■

Conference

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acquisition. That figure compares to 14 deals in 2001 and represented about 40 percent of such mergers and acquisitions worldwide last year.

He presented the results of his research Tuesday in a panel discussion on consolidation at the third annual European C21 BioInvestor Conference being held at the Hilton Munich Park Hotel.

Thirty-five of the 63 deals involved two biotech companies. Another 13 were pharma-pharma deals, and there were13 deals in which a pharma company bought a biotech company. The final two were biotech companies purchasing pharma companies or units.

Public companies were targets in 30 of the transactions, and private firms or units were acquired in 33 of the deals. The large majority of the deals, or 52 of them, were valued at less than $200 million.

Impediments often cited as standing in the way of consolidation, such as company executive egos and inflated notions of valuations, now are being overcome simply because they have to, Kridel said.

"Companies recognize their limited positions, their impoverished positions or their compromised positions," he said. "[And] shareholders are much more restless."

Most of the deals tracked by Ferghana were across borders, and overwhelming they involved either firms in the same sector or two platform companies. The major reasons for the mergers were gaining access to cash, diversification, gaining functional expertise, gaining access to geographical markets, integration, or building size to attract institutional investors.

One tip: "Deeper beats broader," Kridel said.

Conditions Can Only Improve, Can't They?

If there's gloom in the industry, there is not yet a sense of doom in most corners. The feeling is that there will be some sort of upswing, products will emerge, investors will make money. Someday the corner will be turned.

One upside: From the venture capitalist perspective, fundamentals are extremely strong, said Mark Wegter, general partner at LSP Services Deutschland GmbH in Munich. Also, the number of companies in Europe increased to 1,775 from 975 between 1997 and 2001, he said.

Alexandra Goll, a partner at Techno Venture Management GmbH in Munich, put the number of European companies at 1,879 and the revenue they generate at €15.3 billion. Still, however, indices are down more than 50 percent from their heights, initial public offering markets are closed and the ratio of product failures to successes is not good.

Tim Wilson, a biotech veteran who has worked on both sides of the Atlantic, said it's been worse in the U.S. before (1994), but perhaps never this bad in Europe. But he likened it to someone who drank bottles of vodka one evening and vowed, while suffering in bed the next day, never to do it again. But eventually he will – and eventually people will gravitate back to biotech investing.

"We think when prices are down you buy, and when prices are up you sell," said Wilson, principal, life science investments at Atlas Venture in London. There are some decent companies out there in mid-stage development that are running low on cash, he said, which "as an investor, that's attractive."

The conference continues through today. ■

Inspire

Continued from Page 1

offering will be used to "aggressively develop the rhinitis program" and to "continue to fund important discovery programs leading to new investigational drug applications."

She added that the company has an option to co-promote the products Restasis and diquafosol. Assuming both reach the market and Inspire picks up the option, she said Inspire "would be looking to build a specialty 60-rep sales force in the fourth quarter of this year."

Restasis, due to be launched in April, is Allergan Inc.'s dry-eye product cleared in December for marketing. In June 2001, Inspire and Allergan entered a deal for Restasis and Inspire's diquafosol tetrasodium (INS365), which also is a dry-eye product. Bennett said Inspire would receive royalties on Restasis worldwide, excluding larger Asian markets. (See *BioWorld Today*, June 28, 2001.)

Meanwhile, Inspire expects to submit a new drug application for INS365 mid-year. The product is an eye drop administered four times daily in patients who suffer from chronic dry eye, a condition involving abnormalities and deficiencies in the tear film. (See *BioWorld Today*, Oct. 31, 2002.)

Inspire also is working on INS37217 Intranasal for the treatment of upper respiratory disorders. The company completed one Phase I/II trial and two Phase II studies on the product, and recently completed enrollment in a Phase III study in perennial allergic rhinitis. (Allergic rhinitis is a condition that results from exposure to allergens, either at specific times of the year or year-round.) INS37217 also is being studied in cystic fibrosis and as a treatment for retinal disease.

In total, Inspire has five product candidates, all of which are P2Y2 receptor agonists.

For the year ended Dec. 31, 2002, Inspire had $31.1 million in cash and investments, Bennett said. Inspire said in its prospectus it would have about 29.9 million shares outstanding following the offer.

Revenues decreased in 2002 to $4.9 million from $7.3 million for the year. The company reported a net loss of $24.7 million, or 96 cents per common share for 2002, compared to $23.1 million, or 90 cents per common share in 2001.

Deutsch Bank Securities, of New York, is acting as book-running manager for the offering, with U.S. Bancorp Piper Jaffray, of Minneapolis, acting as co-lead manager. The underwriters have an option on 600,000 shares to cover any overallotments. ■

Astrocytes

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"Both species, human and mouse, make APP, the amyloid precursor protein, from which is cleaved Amyloid-beta (A-beta) – a shorter fragment of the longer APP. This A-beta in humans is three amino acids different from the mouse A-beta. Human A-beta tends to aggregate; mouse A-beta does not. Therefore, in aged humans you will find those plaques in Alzheimer's disease; in aged mice, no A-beta deposits.

"There are transgenic mice that do develop A-beta plaques," Husemann continued, "but they are genetically engineered. The mice with the human APP developed plaques, and the researchers injected human synthetic A-beta, a protein that led to production of antibodies. These then attacked and dissolved those plaques."

This made it possible in recent years to recruit those fuzzy-minded rodents as animal models for human Alzheimer's disease.

When a person's brain begins to falter late in life, Alzheimer's disease (AD) is the best-known form of dementia. At post mortem, the AD brain displays clumps of Amyloid-beta, cluttering up the neurons of memory and cognition. These senile plaques are not found in the brains of aging mice. Seeing its main chance, Dublin, Ireland-based Elan Corp. plc immunized naïve mice with A-beta protein and injected the resulting antibodies into other rodents, thus rendering their brains resistant to the formation of neuronal plaques. Then researchers moved from preclinical experiments to clinical, and vaccinated some 360 mild to moderate AD patients with the human 42-amino-acid A-beta peptide. That Phase IIa controlled human trial didn't last long.

Abrupt Ending To Putative Human AD Vaccine

Husemann picks up the debacle story. "The failure of the Elan clinical trial," he recalled, "occurred because participants suffered from swelling of the brain and encephalitis – complications that led to halting the trial. Two years ago, Elan and others used a mouse model for AD, immunizing the animal with A-beta peptide, and elicited an immune response. What they found was that the accumulation and deposition of A-beta was significantly reduced in those amyloid-immunized mice. This suggested that an immune response in A-beta leads to clearance of the peptide from the brain.

"Then Elan in South San Francisco tried the same thing in humans," Husemann continued. "After going through all the preclinical work in animals, they immunized humans with the A-beta peptide. That failed because 15 of the patients enrolled in that clinical trial developed those severe side effects. That was about half a year ago. So they had to stop that clinical trial. The way we saw this work was that antibodies to A-beta protein seemed to bind to the plaque, and the microglia – other brain cells – had an option to attack the plaque and remove it from the brain. It didn't work in humans."

Husemann is senior author of an article in *Nature Medicine*, released online March 3, 2003. It bears the title: "Adult mouse astrocytes degrade amyloid-β in vitro and in situ." He cited three major findings in the paper.

"The first one was that we identified astrocytes as a brain cell that can bind to, internalize and degrade A-beta – at least in vitro. The degradation in the dish," Husemann recounted, "is as follows. We coated glass slides with amyloid protein, seeded the astrocytes on top and incubated that structure for a day. We found that around the astrocytes, the amyloid was removed from the glass, but reappeared inside the cell, which suggested internalization. And after another day of incubation, even that internalized A-beta was gone – totally eliminated from the dish. We went one step further and took brain sections from transgenic mice that developed amyloid plaques in their brain.

"We sliced those brains very thinly, seeded our adult astrocytes on top and incubated them, again for a day. Then we measured the A-beta content in those brain sections – before, with or without astrocyte treatment. Those cells were capable of removing the amyloid protein present in sections from transgenic mice that have A-beta plaques in their brain. So we now have another cell we can work with: stimulate it, activate it and find out by which mechanism these astrocytes remove or clear A-beta.

"Second, we asked why can't exogenous astrocytes, the most abundant cells in the brain, deal with A-beta? There is something wrong with astrocytes in AD patients. They're made in our brains in every nucleated cell, day in and day out, but it does not accumulate in a healthy person. For some reason, in patients with AD, this protein accumulates. So we're asking: Is there something wrong with the astrocytes so they cannot clear the A-beta anymore, which leads to accumulation, and maybe to AD? That pile-up of A-beta actually causes neuronal cell death, resulting dementia, perhaps AD and eventual death."

Neonatal, Adult Cells Side By Side

"Thirdly," Husemann continued, "most neurobiology research is being done with cells from neonatal rats and mice. The neonatal brain is very easy to digest in culture and the cells you want – neurons or astrocytes – are fairly easy to generate. In our paper, we did some side-by-side comparisons – comparing astrocytes generated from adult mouse brains with their neonatal counterparts. We found significant functional differences there.

"We did the degradation on the slides with either adult or neonatal astrocytes. And we found that adult astrocytes were capable of removing the A-beta, but neonatal ones were not. Most of the research today is done with neonatal cells. We did not; we used adult cells. Now we have to figure out which is the better cell to use. Which represents the astrocyte in vivo, in the living brain, better than neonatal cells or adult cells in culture?

"What we are working on right now," Husemann concluded, "is how can we stimulate astrocytes, and possibly microglial cells, to enter the plaque and remove the A-beta protein from the brain?" ■