July 2012

Focus on

Neurology & CNS

BIO serving as your Washington, D.C. office

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NINDS RESEARCH PROVIDES CLUES TO LATE-ONSET ALZHEIMER'S DISEASE

Researchers may have discovered a mechanism behind the largest known genetic risk factor for late-onset Alzheimer's disease. The finding suggests possible strategies for prevention as well as a potential new drug target.

A hallmark of Alzheimer's is a protein fragment called beta-amyloid, which is thought to be toxic and forms clumps within the brain. Past studies have revealed genetic risk factors for Alzheimer's disease. A gene called APOE has shown the strongest connection to the late-onset form of the disease.

APOE encodes a protein that helps regulate the levels and distribution of cholesterol and other lipids in the body. The gene exists in 3 forms. APOE2 is thought to play a protective role against both Alzheimer's & heart disease, APOE3 is believed to be neutral, and APOE4 confers a higher risk for both. Outside the brain, the APOE4 protein appears to be less effective than the other versions at clearing away cholesterol. How it contributes to Alzheimer's disease in the brain, however, has been a mystery.

A research team led by Dr. Berislav Zlokovic of USC approached the question by studying several lines of genetically engineered mice. One lacks the mouse version of the APOE gene altogether, and 3 other lines produce only human APOE2, APOE3, or APOE4. The study was funded by NINDS and NIA.

The researchers discovered that mice whose bodies made only APOE4, or no APOE at all, had a leaky blood-brain barrier. Normally, this barrier allows nutrients to pass from circulating blood into the brain while keeping harmful substances out. With the barrier compromised, harmful proteins in the blood made their way into the mice's brains. After several weeks, the researchers were able to detect a loss of small blood vessels, changes in brain function, & a loss of connections between cells.

The researchers found that APOE2 and APOE3 help control the levels of an inflammatory molecule called cyclophilin A (CypA), but APOE4 does not.Levels of CypA were raised about 5-fold in the blood vessels of mice that produce only APOE4. The excess CypA activated an enzyme called MMP-9, which destroys parts of the blood-brain barrier.

Treating the mice with the immunosuppressant drug cyclosporine A, which inhibits CypA, preserved the integrity of the blood-brain barrier and lessened damage to the brain. An inhibitor of the MMP-9 enzyme had similar effects.

These findings identify CypA as a potential new drug target for Alzheimer's disease. They also suggest that one approach to preventing Alzheimer's disease among APOE4 carriers may be to work on improving vascular health.

The connection between APOE4 & beta-amyloid remains unclear. Damage caused may make it harder to clear beta-amyloid from the brain. "Understanding the role of APOE4 in Alzheimer's disease may be one of the most important avenues to a new therapy," Zlokovic says.

For more information on this research, click here.

"Understanding the role of APOE4 in Alzheimer's disease may be one of the most important avenues to a new therapy."

NEW TECHNOLOGIES AVAILABLE FOR LICENSING FROM THE NIH TECHNOLOGY TRANSFER OFFICE

Modulators of Survival Motor Neuron Production

This technology discloses compounds that modulate the amount of Survival Motor Neuron protein (SMN). Low levels of SMN protein are associated with Spinal Muscular Atrophy (SMA), which constitutes a group of inherited diseases that cause progressive muscle degeneration leading to death. Consequently, therapeutic inventions have focused on increasing SMN protein levels. This invention discloses novel arylthiazolyl piperidines which are shown to be modulators of SMN production. This invention also discloses methods of treating SMA by administering SMN protein modulators.

A Non-invasive Post-treatment Strategy for Stroke by Intranasal Delivery of Cocaine- and Amphetamine-regulated Transcript (CART)

Cocaine and amphetamine-regulated transcript (CART) is a neuropeptide known to protect against ischemic brain injury when administered before the onset of stroke in mice, both in vivo and in vitro. Utilizing a classic stroke model in rodents, middle cerebral artery occlusion (MCAo), inventors at NIDA discovered a novel post-stroke therapeutic approach involving the intranasal administration of CART. This new non-invasive treatment strategy for stroke patients is effective when initiated three days after stroke, providing a longer treatment window. Nasal delivery of CART improved behavioral recovery and reduced neurological scores in stroke animals. CART, given after stroke, modifies endogenous neural repair in stroke brain by facilitating neuroprogenitor cell proliferation and migration, enhancing reinnervation, and improving the functional recovery.

Treatment of Acute and Chronic Neurological Disorders Using GLP-1, Exendin-4 and Analogs

Glucagon-like peptide-1 (GLP-1) and related peptides, including exendin-4 and liraglutide, are incretin mimetics that enhance glucose-dependent insulin secretion following food ingestion as a regulator of glucose homeostasis. Exendin-4 and liraglutide are used clinically in the safe and effective treatment of type 2 diabetes to enhance insulin secretion and maintain a euglycemic state. These actions are primarily mediated at the level of the GLP-1 receptor in the pancreas; however, these compounds are known to enter the brain where the GLP-1 receptor also is expressed. Researchers at the NIH have discovered the novel use of GLP-1 and exendin-4 analogs in the treatment of acute and chronic neurological disorders and neurodegenerative diseases. Studies conducted in extensive cell culture and in mouse models using these analogs have demonstrated significant neurotrophic and neuroprotective actions in models of several disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, stroke, head trauma and peripheral neuropathy. These studies have now been extensively published and independently validated by other scientific groups. Furthermore, clinical studies are ongoing to evaluate the use of GLP-1 receptor agonists for the treatment of early Alzheimer's disease, Parkinson's disease and diabetic neuropathy by several groups within the US and Europe.

To learn more about these technologies and to find others available for licensing, please click here.

FDA PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

On May 14, the Peripheral and Central Nervous System Drugs Advisory Committee met to discuss new drug application (NDA) 202737 for tafamidis meglumine capsules, proposed trade name VYNDAQEL, submitted by FoldRx Pharmaceuticals, Inc. a subsidiary of Pfizer, Inc. The proposed indication is for the treatment of transthyretin (TTR) familial amyloid polyneuropathy (FAP).

FAP is caused by a mutation in the gene that codes for TTR. Patients with this mutation are clustered in Portugal, Sweden, & Japan. In the United States, the prevalence of FAP is about 2,500 patients. Currently, the treatment of choice in the United States is liver transplant, because TTR is primarily synthesized in the liver.

The sponsor's assertion is that the tafamidis-induced stabilization of TTR can successfully treat the symptoms of FAP. Toward that end, the sponsor has performed Study 005, a randomized, doubleblind, placebo controlled trial that purports to demonstrate the clinical benefit of treating patients with FAP with tafamidis. The study was 18 months in duration, and effectiveness was to be determined by statistically significant between-treatment differences at 18 months.

The materials and minutes from this meeting are available online, as well as a complete transcript. For more information, please click here.

NCATS ANNOUNCES INSTITUTIONAL CTSAs

The CTSA program was initiated by the NIH in 2006 to transform the local, regional, and national environment for clinical and translational research. Under NCATS, the goal of the CTSA program remains focused on integrated academic homes for the clinical and translational sciences that increase the quality, safety, efficiency and speed of clinical and translational research, particularly for NIH supported research.

The NCATS CTSA program supports disease- and condition-specific networks funded by other NIH Institutes and Centers, but is disease agnostic in its resources and approach. The NCATS CTSA program will include Institutional CTSA Awards, which are the subject of this FOA, and Consortial Awards and Demonstration Projects which will be the subject of future solicitations.

Institutional CTSAs are made to degree granting institutions or groups of institutions that receive significant funding from the NIH. CTSAs require institutional commitment, the status of a major scientific and administrative entity within and across an applicant and partner institution(s), and a CTSA PD(s)/PI(s) with the authority and influence necessary to successfully create an institutional home for clinical and translational research.

To learn more about the NCATS Institutional CTSA program, click here.

NCATS Institutional CTSAs

Institutional Clinical and Translational Science Award (U54)

RFA-TR-12-006

Letter of Intent Due: **December 10, 2012**

Application Due: **January 8, 2013**

NINDS FUNDING ANNOUNCEMENTS

PAR-12-183, NIA Analysis of Alzheimer's Disease Genome Sequencing Project Data (U19) – September 8, 2013

PA-09-217, The Role of Apolipoprotein E, Lipoprotein Receptors and CNS Lipid Homeostasis in Brain Aging and Alzheimer's Disease (R01) – September 8, 2012

PAR-09-263, Ancillary Studies in Clinical Trials of CNS/PNS Disorders NINDS Accelerated Awards Program (R01) – August 17, 2012

PA-09-193, Mechanisms, Measurement, and Management of Pain in Aging: from Molecular to Clinical (R01) – January 8, 2013

PA-11-014, HIV Infection of the Central Nervous System (R01) – January 8, 2014

PA-12-225, Fatigability, Activity Limitations, and Bioenergetics in Aging (R21) – September 8, 2015

PAR-12-033, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R21) – October 25, 2014

PA-11-067, Focal Cognitive Deficits in CNS Disorders (R01) – January 8, 2014

For more information or to find more funding opportunities, please click here.

PATIENT ORGANIZATION EVENTS

Alzheimer's Drug Discovery Foundation	**Child Neurology Society**	**Congress of Neurological Surgeons**
13th International Conference September 10-11, 2012 Jersey City, NJ	41st Annual Meeting October 31-November 3, 2012 Huntingdon Beach, California	2012 Annual Meeting October 6-10, 2012 Chicago, Illinois
Click here for more details.	Click here for more details.	Click here for more details.

CONGRESSIONAL HEARINGS ON BIOTECHNOLOGY

House Financial Services Committee, Subcommittee on Capital Markets
"The 10th Anniversary of the Sarbanes-Oxley Act" — July 26, 2012

At this hearing, the Capital Markets Subcommittee marked the ten-year anniversary of the Sarbanes-Oxley Act (SOX), passed in 2002. Industry representatives testified about the cost burden of SOX, especially the audit required by Section 404(b), and the impact that it can have on innovation and job creation. BIO Board Member Jeff Hatfield, CEO of Vitae Pharmaceuticals, testified about how the lack of product revenue during the biotech development process further increases the cost of the compliance burden.

House Committee on Oversight and Government Reform
"JOBS Act in Action: Overseeing Effective Implementation That Can Grow American Jobs" — June 26, 2012
"JOBS Act in Action, Part II: Overseeing Effective Implementation of the JOBS Act at the SEC" — June 28, 2012

This set of hearings focused on the implementation of the JOBS Act, which was signed into law on April 5. Witnesses and Congressmen spoke about the importance of effective implementation of the JOBS Act in order to maximize the effect its provisions will have on capital formation for growing companies. SEC Chairwoman Mary Schapiro also spoke, and gave the Committee an update on the progress the SEC is making on JOBS Act rule-making. She reported that the SEC would miss its deadline on both the Regulation D rules and the tick size study mandated by the JOBS Act (the deadline for both was July 4). She mentioned that the SEC was more optimistic about the timing of its crowdfunding rules, which are due by the end of the year.

House Committee on Energy and Commerce, Subcommittee on Health
"FDA User Fees 2012: How Innovation Helps Patients and Jobs" — April 18, 2012

At this hearing, the Health Subcommittee heard from witnesses about the importance of reauthorizing PDUFA and the impact that the FDA has on biopharmaceutical innovation and job creation. Dr. Janet Woodcock, Director of CDER at FDA, spoke about the steps FDA has taken to review and approve innovative medicines. Sara Radcliffe, EVP of Health, testified on BIO's behalf, providing the industry perspective on how important a functioning, flexible, and well-funded FDA is to the drug development process.

CAPITAL FORMATION LEGISLATION

H.R. 6161 – Fostering Innovation Act
This bill would amend the filing definitions in **SEC Rule 12b-2** to provide a more accurate picture of growing companies. Under the bill, public companies with a public float below $250 million or revenues below $100 million would be considered non-accelerated filers, providing them with **certain regulatory exemptions**, including from SOX compliance.
Sponsor: Rep. Mike Fitzpatrick (PA-8)
Status: Referred to the House Committee on Financial Services

S. 3232 – to Extend and Improve the Therapeutic Discovery Project
This bill would reauthorize the **Therapeutic Discovery Project** to cover qualifying investments made in 2011 and 2012. The bill would provide an additional $1 billion for the program and make several refinements to ensure that taxpayer dollars go to the most **deserving and innovative companies** and projects.
Sponsor: Sen. Robert Menendez (NJ)
Status: Referred to the Senate Committee on Finance

H.R. 1988 – Qualifying Therapeutic Discovery Project Tax Credit Extension Act
This bill would extend the **Therapeutic Discovery Project** through the year 2017 and fund it at **$1 billion per year**. Qualifying investments in years 2011 through 2015 would qualify for the credit or grant.
Sponsors: Rep. Susan Davis (CA-53) and Rep. Allyson Schwartz (PA-13)
Status: Referred to the House Committee on Energy and Commerce

Important Capital Formation Bills

TDP

S. 3232, Sen. Menendez

H.R. 1988, Reps. Davis & Schwartz

SOX & Rule 12b-2

H.R. 6161, Rep. Fitzpatrick

CONGRESS PASSES PDUFA REAUTHORIZATION & FDA REFORMS

On June 26, 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) and President Obama signed the bill into law on July 16. FDASIA included a reauthorization of the Prescription Drug User Fee Act (PDUFA), along with numerous reforms to the FDA that BIO believes will speed the review and approval of new medicines.

Chief among the reforms are enhancements to the Accelerated Approval process, originally proposed in Sen. Hagan's TREAT Act and Reps. Stearns's and Towns's FAST Act. These changes will expand the applicability of Accelerated Approval and give the FDA the tools it needs to expedite the development of modern, targeted, and personalized therapies for patients suffering from serious and life-threatening diseases while preserving robust standards for safety and effectiveness. The new law also includes provisions to enhance the development and review of innovative new therapies through increased transparency and scientific dialogue, advancements in regulatory science, strengthened post-market review, and increased FDA access to external expertise during the drug review process.

Further, FDASIA includes the permanent reauthorization of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act to encourage continued investment in pediatric research and help ensure that new drugs and biologics can be used safely and appropriately in pediatric patients.

For more information about FDASIA, please click here. BIO will be hosting two webinars in September to educate members about the provisions in the new law. If you are interested in attending one of these webinars, please email Charles Crain at ccrain@bio.org.

NEUROLOGY/CNS-FOCUSED LEGISLATION

H.R. 610 – Making Investments Now for Dementia (MIND) Act
This bill would authorize the Treasury Department to issue bonds to aid in the funding of Alzheimer's research. Treasury would be required to consult with NIH and HHS on the new bond program. NIH would receive the funding from sales of the **bonds to further NINDS Alzheimer's research**.
Sponsor: Rep. Michael Burgess (TX-26)
Status: Referred to the House Committee on Energy and Commerce

H.R. 1970 – National Childhood Brain Tumor Prevention Network Act
This bill would establish a **National Childhood Brain Tumor Prevention Network** to provide grants for research on the causes of and risk factors associated with childhood brain tumors.
Sponsor: Rep. Barbara Lee (CA-9)
Status: Referred to the House Committee on Energy and Commerce

H.R. 2600 – National Pediatric Acquired Brain Injury Plan Act
This bill would require the Secretary of HHS to make a payment for each fiscal year from FY2012-FY2018 to the State Lead Center in each state for implementation of the **National Acquired Brain Injury Plan**, as developed by the International Advisory Board of the Sarah Jane Brain Foundation.
Sponsor: Rep. Lance Leonard (NJ-7)
Status: Referred to the House Committee on Energy and Commerce

H.R. 2595 – National Neurological Disease Surveillance System Act
This bill would require HHS and the CDC to enhance and expand infrastructure and activities to track the epidemiology of neurological diseases, including multiple sclerosis and Parkinson's disease, and to incorporate information obtained through such activities into a **National Neurological Diseases Surveillance System**.
Sponsor: Rep. Chris Van Hollen (MD-8)
Status: Referred to the House Committee on Energy and Commerce

H.R. 1386 – Health Outcomes, Planning, and Education (HOPE) for Alzheimer's Act
This bill would amend Medicare to ensure full coverage of comprehensive Alzheimer's disease and related dementia **diagnosis and services**.
Sponsor: Rep. Edward Markey (MD-8)
Status: Referred to the House Committee on Energy and Commerce

BIO'S EMERGING COMPANIES

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BIO Meetings and Conferences

BIO India International Conference
September 12-13, 2012
Hyderabad, India

BIO Technology Transfer Symposium
October 8, 2012
San Francisco, California

BIO Investor Forum
October 9-10, 2012
San Francisco, California

BIO China
October 24-25, 2012
Shanghai, China

BIO Europe Fall
November 11-14, 2012
Hamburg, Germany

BIO Asia International Conference
January 29-30, 2013
Tokyo, Japan

For more about BIO events, please visit bio.org.

BIO HOLDING JOBS ACT WEBINARS

This spring, Congress passed the JOBS Act with broad, bipartisan majorities. When President Obama signed the bill into law, it immediately opened up new avenues for capital formation for emerging biotech companies. From changes to the IPO process for small companies to revamped private financing models, the JOBS Act has the potential to stimulate fundraising for important R&D.

Some of the provisions of the JOBS Act took effect upon enactment, while others are awaiting rulemaking by the SEC. Two upcoming webinars sponsored by BIO will provide companies with information on the key facets of the law and offer expert analysis on how to navigate the new rules. Speakers will also give updates on the status of pending regulation and offer a Q&A session with attendees on what to expect in the upcoming months and years and how companies can best take advantage of these new opportunities.

The webinars are scheduled for **Tuesday, September 18 at 2:00 pm (EDT)** and **Wednesday, October 3 at 2:00 pm (EDT)**. The webinars are free for all BIO R&D members and BIO state affiliates. Non-member R&D companies are invited to join for $100. For more information or to register for the webinars, please email Charles Crain at ccrain@bio.org.

BIO HOLDING FDASIA WEBINARS

BIO would like to invite you to participate in our upcoming educational webinar series in September on key provisions contained in the Food and Drug Administration Safety and Innovation Act (FDASIA), which became law on July 9, 2012. These webinars will provide information on the intent and goals of the provisions in FDASIA as well as discuss implementation issues and timelines. The webinars are free for all BIO R&D members and BIO state affiliates. Non-member R&D companies are invited to join for $100.

The first webinar, *PDUFA V: Enhanced Communications and NME Reviews*, will be held on **Thursday, September 13 at 2:00 pm (EDT)**. This webinar will focus on the enhanced communications and NME provisions that were agreed to by industry, stakeholders, and FDA as part of the PDUFA technical agreement.

The second webinar, *New and Enhanced Pathways: Expanded Accelerated Approval and Breakthrough Therapies*, will be held on **Wednesday, September 26 at 2:00 pm (EDT)**. This webinar will focus on two new and enhanced pathways, Enhanced Accelerated Approval and Breakthrough Therapies, that were passed into law as part of FDASIA. For more information or to register for either webinar, please email Charles Crain at ccrain@bio.org.