Embargoed until Oct. 18, Noon CDT
Press Room, Oct. 17–21: (312) 791-6619

Contacts: Kat Snodgrass, (202) 962-4090
Sarah Bates, (202) 962-4087

NEW RESEARCH HELPS THERAPIES GET AROUND, THROUGH BLOOD-BRAIN BARRIER

Additional studies identify new roles for barrier and the systems it separates in health and disease

CHICAGO — New findings released today show scientists are developing novel ways to bypass the blood-brain barrier (BBB), a network of blood vessels that prevents more than 95 percent of all chemicals from entering the brain from the bloodstream. The findings, presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health, could form another step toward treating brain disorders and conditions affecting the central nervous system.

While the BBB protects the brain from harmful chemicals, bacteria, and other substances, it poses a significant problem for the delivery of drugs for hard-to-treat diseases such as Alzheimer's disease and brain cancer. Researchers describe new methods for transporting drugs across the BBB as well as ways to enhance the brain's own immune response, which is separated from the body's immune system by the BBB. Additional research describes new roles for the BBB in neurodegenerative disease and the behavioral and cognitive effects of the immune system, despite its physical separation from the central nervous system.

The studies show that:

- Scientists have developed a new delivery system to shuttle drugs across the BBB by hijacking a known protein transport system. This scientific advance potentially allows researchers to develop therapies for hard-to-treat brain diseases (Jean-Paul Castaigne, MD, abstract 185.1, see attached summary).
- In preliminary reports from a clinical trial, a new drug designed to cross the BBB has helped reduce tumor growth in people with gliomas, the most common form of brain cancer (Jan Drappatz, MD, abstract 185.6, see attached summary).

Other recent research findings discussed during the meeting show that:

- Although it is separated from the central nervous system by the BBB, the immune system affects emotionality and cognition (Katherine Nautiyal, see attached speaker's summary).
- The BBB and cells in the brain that are not nerve cells may be involved in neurodegenerative diseases, including Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis. The findings may offer new avenues for future research and therapies (Berislav Zlokovic, MD, PhD, see attached speaker's summary).
- New research suggests ways to combat diseases like Alzheimer's disease by boosting the brain's immune response, which is separated from the body's immune system by the BBB (Serge Rivest, PhD, see attached speaker's summary).

"The development of novel ways to cross the blood-brain barrier has considerable potential for treating a host of debilitating and prevalent diseases and disorders," said press conference moderator John Kessler, MD, of Northwestern University, an expert in stem cell biology and regenerative neuroscience. "Scientific discoveries like those announced today lead to a better understanding of the complexities of the human brain and nervous system and highlight the importance of additional research in this area."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

– more –

Related Presentations:

Symposium: **Role of Blood-Brain Barrier and Nonneuronal Cells in Neurodegeneration**
Monday, Oct. 19, 8:30–11 a.m.

Minisymposium: **Behavioral Neuroimmunology: Linking the Immune System to Emotionality and Cognition**
Tuesday, Oct. 20, 1:30–4 p.m.

Minisymposium: **Myeloid Cells in the Brain During Health and Disease**
Wednesday, Oct. 21, 8:30–11 a.m.
# # #

Abstract 185.1 Summary

Senior author: Jean-Paul Castaigne, MD (514) 788-7800
AngioChem, Inc. jpcastaigne@angiochem.com
Montreal, Quebec

Technology Helps Drugs Cross Blood-Brain Barrier

Breaking through this blockade may aid in development of therapies for hard-to-treat brain diseases

A new delivery system may shuttle drugs across the blood-brain barrier, which prevents most chemicals in the blood from entering the brain. Currently tested in animals, the technology could one day speed the development of treatments for a variety of brain disorders, including Alzheimer's and Parkinson's diseases. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The researchers, led by Jean-Paul Castaigne, MD, at AngioChem, Inc., demonstrated that in mouse studies, the new system increased the amount of a variety of different therapeutics reaching the brain.

The new system hijacks the normal transport system that limits passage across the blood-brain barrier. Low-density lipoprotein receptor-related protein (LRP) is found throughout the blood-brain barrier. LRP normally allows only a few selected compounds into the brain. The system fuses these compounds with various therapies, offering an entry into the brain. LRP is similar to receptors in blood vessels that help transfer cholesterol out of the blood to be destroyed.

"Application of this new technology should dramatically increase the rate at which new neurological drugs can be developed," Castaigne said.

Scientific Presentation: Sunday, Oct. 18, 8–9 a.m. South Hall A

185.1: Development Of A New Engineered Peptide Compound (Epic) Platform For The Transport Of Small And Large Therapeutics To The Cns
R. GABATHULER[1], M. DEMEULE[1], A. REGINA[1], C. CHE[1], R. BELIVEAU[2], **J.-P. CASTAIGNE**[1];
[1]Rese & Develop., AngioChem Inc, Montreal, QC, Canada; [2]Univ. of Quebec at Montreal, Montreal, QC, Canada

TECHNICAL ABSTRACT: The blood-brain barrier (BBB) is mainly formed by brain capillary endothelial cells which are closely sealed by tight junctions and express high levels of active efflux transport proteins. As a result of these restrictions, approximately 98% of small molecules and nearly 100% of large molecules, such as recombinant proteins or gene-based medicines do not cross the BBB. Overcoming the obstacle posed by the BBB is, therefore, a critical goal of CNS drug development and therapy. A new family of peptides derived from proteins that efficiently cross the BBB using low-density lipoprotein receptor related protein (LRP) has been designed and is incorporated in new therapeutics for uptake into the brain. This new engineered peptide compound platform technology (EPiC) is applicable to small and large molecules up to 150 kD in size and provides a non-invasive and flexible platform and creating new drugs which have access to the central nervous system for the treatment of CNS diseases. The lead carrier peptide (Angiopep-2) was evaluated in an in vitro model of the BBB and in vivo by in-situ brain perfusion and a non-invasive optical imaging in mice. Fluorescence associated to Cy5.5-angiopep-2 was detected very rapidly in the brain parenchyma after in-situ brain perfusion in mice. Based on these properties, we have created several new drugs. The most advanced drug ANG1005 formed by chemical conjugation of Angiopep-2 to three molecules of paclitaxel is in two phase ½ clinical trials for the treatment of primary and secondary brain tumors. Human data have confirmed the preclinical results validating the platform technology. Here, we present the application of this platform technology to neuroactive peptides, larger proteins for example mAbs and nucleic acid based agents such as siRNA. The new chemical derivatives have been synthesized using different approaches and characterized after purification by mass spectrometry. The activity of the modified compounds was measured and was unaffected by the incorporation of Angiopep-2. Furthermore, we show by mice *in-situ* brain perfusion that these new derivatives are able to cross the BBB at a higher rate than the unmodified molecules which normally do not cross the BBB efficiently. Higher brain distribution is measured for the peptides, mAbs and siRNA when modified with our peptide technology. Finally, *in vivo* studies using mice models demonstrate that these derivatives can reach therapeutic amount in the brain. By using our EPiC platform we are creating new chemical entities for small drugs, peptides and larger hydrophilic proteins with increase brain penetration agents for the treatment of CNS diseases.

Abstract 185.6 Summary

Lead author: Jan Drappatz, MD (617) 632-2166
Dana-Farber Cancer Institute jdrappatz@partners.org
Brigham and Women's Hospital
Center for Neuro-Oncology, Harvard Medical School
Boston, Mass.

New Brain Cancer Treatment Reduces Tumor Growth, Preliminary Data Shows

Early findings in clinical trial point to possible new treatment

Early findings from a clinical study show that a new drug reduced tumor growth in some people with malignant gliomas, the most common form of brain cancer. The preliminary research was presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings may one day help some of the 15,000 to 20,000 Americans diagnosed with gliomas each year, who rarely live longer than two years after diagnosis.

The researchers, led by Jan Drappatz, MD, at the Dana-Farber Cancer Institute, report stabilization of tumor growth — and in some cases reduction in tumor size — as well as reversal of neurologic deficits in people with high-grade gliomas who received the new drug, ANG1005. As of May 2009, 37 patients had been tested.

"Novel treatment options like ANG1005 are urgently needed to improve the dismal prognosis for glioma patients," Drappatz said.

ANG1005 combines a chemotherapy agent with a new drug treatment platform that is designed to create drugs and other chemicals that cross the blood-brain barrier. Brain tumors are difficult to treat in part because they are protected by the blood-brain barrier, which prevents more than 95 percent of all chemicals from entering the brain from the bloodstream.

ANG1005 is being developed and tested in the United States by AngioChem, Inc., a biotechnology company.

Scientific Presentation: Sunday, Oct. 18, 9–10 a.m., South Hall A

185.6, Development of a new Engineered Peptide Compound (EPiC) for the treatment of malignant glioma
J . DRAPPATZ[1], A. BRENNER[2], S. ROSENFELD[3], D. SCHIFF[4], P. WEN[1], T. MIKKELSEN[5], M. GROVES[6], E. T. WONG[7], A. EICHLER[8], K. M. ELIAN[9], B. LAWRENCE[9], M. DEMEULE[9], J.-P. CASTAIGNE[9]; [1]Dana-Farber Cancer Inst., Boston, MA; [2]Cancer Therapy and Res. Center, UT Hlth. Sci. Ctr. San Antonio, San Antonio, TX; [3]Columbia Universtiy Med. Ctr., New York, NY; [4]Univ. of Virginia Hlth. Syst., Charlottesville, VA; [5]Henry Ford Hlth. Syst., Detroit, MI; [6]MD Anderson, Houston, TX; [7]Beth Israel Deaconess Med. Ctr., Boston, MA; [8]Massachusetts Gen. Hosp., Boston, MA; [9]Angiochem Inc., Montreal, QC, Canada

TECHNICAL ABSTRACT: Introduction: Malignant glioma (MG) is an aggressive and fatal cancer whose treatment is limited by the inability of drugs to cross the BBB. Angiochem is developing a deep and broad product pipeline of new breakthrough drugs that are uniquely capable of crossing the BBB to treat brain diseases. ANG1005, the first product created from the Engineered Peptide Compound (EPiC) platform, is a novel taxane derivative. Studies show that ANG1005 enters the brain by targeting low-density lipoprotein receptor-related protein (LRP); one of the most highly expressed receptors on the BBB, and also enters tumor cells via LRP, which is upregulated in various cancer cells including MG cells. Methods: As of 18-May-2009, 37 patients with recurrent/progressive WHO Grades III-IV MG have received ANG1005 by IV infusion at doses of 30-550 mg/m^2 once q21d without premedication. Study objectives include characterizing the safety/tolerability, identifying the MTD and obtaining preliminary PK and antitumor information in patients with MG. Drug penetration into extracted MG tumors was measured in a sub-group of patients undergoing debulking surgery following a single dose of ANG1005. Results: Dose escalation is ongoing. At doses evaluated thus far, few, if any, patients have experienced neutropenia, leucopenia, thrombocytopenia, anemia, infusion reactions, mucositis or peripheral neuropathy at a severity ≥ Grade 2 (CTCAE, v.3). Neurocognitive data show that ANG1005 does not cause CNS toxicity at these doses. Biological data show that ANG1005 does not elicit an immune response even in patients who have received multiple treatment cycles. MRI data indicate potential efficacy in tumor regression/slowing tumor progression. Pharmacokinetic data show a linear relationship between dose and bioavailability. Data from extracted tumors (n=3) showed that ANG1005 uptake was 20-40x greater than reported following an equivalent dose of paclitaxel; and ANG1005 concentration in tumor relative to blood exceeded 25%. Conclusion: Data to date demonstrate that ANG1005 has an excellent safety/tolerability profile, penetrates into tumors and shows promise as a potential treatment option for patients with recurrent/progressive MG.

Speaker's Summary

Chair: Katherine Nautiyal (212) 854-3909
Columbia University kmn2116@columbia.edu
New York, N.Y.

Mechanisms of Brain Mast Cell Modulation of Fear and Anxiety-Like Behaviors (594.5)
Minisymposium: Behavioral Neuroimmunology: Linking the Immune System to Emotionality and Cognition
Tuesday, Oct. 20, 1:30–4 p.m., Room N230

The immune and central nervous systems are traditionally thought to mediate disparate physiological functions, but in fact are interdependent. This minisymposium will highlight recent advances in the field of neuroimmunology by examining discoveries of immune system effects on emotionality and cognition from a breadth of perspectives at the molecular, behavioral and neural systems levels.

Immune challenges result in varied outcomes throughout the lifespan. From a developmental perspective, Staci Bilbo will describe the mechanisms by which early life infection alters behavioral and cognitive phenotypes in adulthood. Ruth Barrientos will discuss how hippocampal-dependent memory processes in aging rodents are especially vulnerable to disruption following an immune challenge. The immune system also modulates affect in both health and disease states. Leah Pyter will show that peripheral tumors cause dysregulation of the HPA axis and increases in production of hippocampal cytokines as well as depression and cognitive deficits. Katherine Nautiyal will describe how brain immune cells, namely mast cells, can modulate anxiety and fear behavior in the healthy animal, and also present mechanisms of these interactions. Translational aspects of neuroimmunology will also be addressed. Andrew Miller will discuss imaging data demonstrating how cytokines can alter brain circuits that modulate mood and behavior in humans. Judy Van de Water will present a neuroimmune hypothesis of mental health disorders focusing on the autoimmune etiology of autism.

Overall, these talks will argue for a causal role of immune modulation in emotionality and cognition, as well as present mechanisms by which this modulation can occur.

Speaker's Summary

Chair: Berislav Zlokovic, MD, PhD (585) 273-3132
University of Rochester berislav_zlokovic@urmc.rochester.edu
Rochester, N.Y.

Symposium**: Role of Blood-Brain Barrier and Nonneuronal Cells in Neurodegeneration**
Monday, Oct. 19, 8:30–11 a.m., Room S100B

This symposium will integrate current knowledge on the role of blood-brain barrier (BBB) and non-neuronal cells in major human neurodegenerative disorders including Alzheimer's disease (AD), multiple sclerosis (MS), neuroinflammatory disease and amytrophic lateral sclerosis (ALS). The symposium will highlight new cellular and molecular mechanisms of CNS vascular dysfunction, BBB immune responses, and microglial and astrcoytes roles in regulating risk for different forms of neurodegeneration and non-cell autonomous killing of neurons.

The role of BBB receptors RAGE and LRP, endothelial MEOX-2 homeobox gene and vascular smooth muscle cells myocardin-SRF pathway in controlling brain amyloid β-peptide (Aβ) accumulation, neuroinflammation and blood flow reductions leading to neurodegeneration in AD, and the role of BBB breakdown in ALS, will be discussed.

The BBB restricts leukocyte trafficking. How lymphocyte-derived cytokines IL-1b and IL-17 regulate the localization and migration of antigen-specific lymphocytes across the BBB during MS and neuroinflammatory disease via chemoattractant molecules and their receptors CXCL12, CXCR4 and CXCR7 will be described.

Modulating the interactions of Aβ with its cellular receptors is a potential therapeutic strategy for AD. We have identified a novel microglial receptor complex that mediates the interactions of these cells with Aβ. In this presentation we will discuss the role of this receptor complex in the pathogenesis of AD in mouse models.

An inherited form of ALS is caused by dominant mutations in superoxide dismutase 1 (SOD-1). SOD-1 mutant damage within motor neurons initiates disease onset, but SOD-1 mutant damage within astrocytes and microglia sharply accelerates disease progression and non-cell autonomous killing of motor neurons.

Speaker's Summary

Speaker: Serge Rivest, PhD (418) 654-2296
Centre Hospitalier de l'Universite Laval serge.rivest@crchul.ulaval.ca
Quebec City, Quebec

Bone Marrow-Derived Microglia as a Cure for Brain Injuries and Diseases (693.6)
Minisymposium**:** Myeloid Cells in the Brain During Health and Disease
Wednesday, Oct. 21, 9:55–10:15 a.m., Room S401

Microglia are the immune cells of the central nervous system (CNS). They patrol the brain environment with their ramifications and they respond quickly in presence of pathogens and brain damages. We found that bone marrow stem cells (BMSCs) have the ability to populate the CNS and differentiate into microglia in regions afflicted by neurodegeneration or neurological insults. Of great interest is the fact that these cells are associated with amyloid plaques and they are able to prevent the formation or eliminate the presence of amyloid deposits in mice that develop the major hallmark of Alzheimer's Disease (AD). AD is a neurodegenerative disorder that represents the most important cause of dementia in humans. Extracellular deposits of beta-amyloid peptides (Aβ), often termed senile plaques, and formation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein are the two principal hallmarks of this disease. Aβ aggregates are known to induce synaptic dysfunction and thus, are linked with learning and memory deficits both in human and in mouse models of AD, making Aβ deposits a target for prevention or treatment against this disorder.

It is therefore possible that stimulating the haematopoietic system may be a new therapeutic approach for the treatment of Alzheimer's disease. In this regard, low macrophage colony-stimulating factor (M-CSF) levels were recently found in patients with presymptomatic Alzheimer's disease or mild cognitive impairment, which together with low levels of other haematopoietic cytokines predicted the rapid development of the disease toward a dementia state 2 to 6 years later. Exposure of mouse microglia to M-CSF in vitro enables the acidification of their lysosomes and subsequently, the degradation of internalized Aβ. Treatment of transgenic mice that spontaneously develop Alzheimer's disease with M-CSF on a weekly basis prior to the appearance of learning and memory deficits prevented cognitive loss. The treatment also increased the number of microglia in the parenchyma and greatly decreased Aβ levels in the brain. In addition, M-CSF treatment resulted in the stabilization of the cognitive decline state in transgenic mice that already had Aβ-meditated pathology.

BMSCs would be an ideal alternative to other cells employed in gene therapy, including neural or embryonic stem cells and fibroblasts, because of their natural capacity to populate the adult nervous system and to adapt to inflammatory conditions. In addition, the self-donation of bone marrow would present the advantage of being safe, widely applicable and ethically acceptable. Since toxic and secreted proteins are frequently the cause of many brain diseases, such a cellular therapy may prove to be quite effective for the treatment of many neurodegenerative diseases and CNS injuries.

The Canadian Institutes in Health Research (CIHR) supports this research.