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EDITORIAL

Drug delivery to the CNS

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Effective delivery of biological products to the central nervous system remains on the frontier of modern medicine. The blood–brain barrier (BBB) is an efficient and elegant system for regulating the influx and efflux of molecular entities. The selectivity of this endothelial layer is essential for maintaining a homeostatic CNS environment and protecting neuronal tissues from foreign or harmful blood born compounds. Therapeutic interventions for CNS diseases, to be effective, must contend with traversing this barrier and reaching their targets. Although there have been substantial advances in our understanding of the molecular biology of the BBB, we have yet to translate this knowledge into consistent and reliable modalities for delivering a diverse array of therapeutic biological agents.

Circumventing rather than traversing the BBB has been successfully used to deliver small molecules to the CNS for pain management, treatment of spasticity, and cancer chemotherapy. Typically, this requires the use of mechanical strategies, such as ports and pumps, to deliver drugs directly into the CSF. This approach has an inherent risk of infection, and is also limited by the physical and physiological factors governing tissue penetration and distribution. A deeper understanding of receptor-mediated transport systems and CSF dynamics is needed in order to generalize this approach to treat a broader spectrum of CNS diseases.

In July 2011, the Controlled Release Society held a workshop designed to bring together leading scientists in the fields of drug delivery, vascular biology, imaging, animal model development, and clinical research (1), with the goal of engaging in multidisciplinary discussions of the strategies needed to develop drug and biological products targeted to the CNS, from drug discovery through to clinical evaluation. The presenters were invited to participate in this special issue of *Drug Delivery and Translational Research* to capture the wealth of information and thought provoking material that was presented in this unique setting. Patricia Dickson, the workshop facilitator, describes the current state of CNS delivery and provides some insight into the challenges associated with conducting clinical trials, particularly in rare CNS diseases. William Banks provides a synopsis of the molecular interactions related to the influx/efflux modalities of the BBB and how they could be adapted to facilitate brain delivery from systemic administration. Recent work has shown that intranasal administration is a potential access point for the BBB. Leah Hanson et al. demonstrate that intranasal administration of an iron chelator reduces spatial memory loss in a mouse model of Alzheimer's disease, suggesting that this approach may be a viable, noninvasive approach for CNS delivery.

An area of intense research in CNS delivery of large molecule biologics is in the treatment of lysosomal storage diseases (LSD), a collection of ~50 different rare genetic disorders characterized by a deficiency in the activity of one of the lysosomal enzymes. In the majority of the LSDs, uncontrolled accumulation of substrate results in progressive CNS impairment and premature death. Silvia Muro provides a review of the underlying physiology of this class of diseases, and approaches to deliver protein therapeutics across the BBB. Another approach under investigation for the treatment of LSDs is the direct administration of enzyme to the CNS. Richard Pfeifer et al. provide evidence in nonhuman primates that lumbar administration is safe, well tolerated, and likely to deliver sufficient enzyme to the relevant anatomical sites within the brain.

Another major challenge in developing delivery modalities for CNS therapeutics is accurately assessing where and how much product is delivered to the targeted tissue. Immunohistochemistry, the standard method for describing biodistribution in nonclinical studies, requires a large number of animals and is not applicable in the clinical setting. Mikhail Papisov et

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al. provide two examples describing how positron emission tomography, a quantitative imaging modality, can be used to examine complex physiological transfer processes. This non-invasive technique provides strong preclinical evidence that therapeutic levels of lysosomal enzymes and bacteriophage particles can be delivered to deep brain tissues via an IT administration. Clinical evaluations are currently underway to assess the viability of IT administrations for the treatment of Hunter syndrome and Sanfilippo A disease.

I would like to personally thank all the contributing authors for making this themed issue possible. This is an important collection of work describing the challenges and strategies being investigated to effectively deliver therapeutics to the CNS. It also serves to reinforce the need for a multidisciplinary approach, from BBB transcytosis pathways, polymeric sciences, and new imaging technologies, to drive the innovation necessary to develop effective treatments for patients with devastating CNS disorders.

CNS Drug Delivery: From Proof of Concept to Clinical Readiness

Day 1—Saturday, July 30, 2011		
Session/time	Topic	Presenters
8:00–8:30 a.m.	Welcome and introduction	Patti Dickson, UCLA
Session 1	Targeting delivery to the CNS part 1: CNS biology and peripheral delivery strategies	Session chair, Patti Dickson, UCLA
8:30–9:00 a.m.	Factors unique to the development of neuraxially delivered drug	Tony Yaksh, University of California, San Diego
9:00–9:30 a.m.	The blood–brain barrier: challenges and opportunities	William Banks, University of Washington
9:30–10:00 a.m.	Targeting therapeutic carriers across the blood–brain barrier	Silvia Muro, University of Maryland
10:00–10:15 a.m.	Panel discussion	Moderator: Patti Dickson
10:15–10:30 a.m.	Break	10:15–10:30 a.m.
Session 2	Targeting delivery to the CNS part 2: direct CNS administration	Session chair: Perry Calias, Shire HGT
10:30–11:00 a.m.	Intrathecal delivery of lysosomal enzymes	Tom McCauley, Shire HGT
11:00–11:30 a.m.	Nanomedicine approaches for CNS delivery of polypeptides	Alexander Kabanov, University of Nebraska
11:30–12:00 p.m.	Intranasal therapeutics (drugs, biopharmaceuticals and stem cells) bypass the blood–brain barrier to treat Alzheimer's, stroke, Parkinson's, brain tumors and other CNS disorders.	William Frey, University of Minnesota
12:00–12:15 p.m.	Panel discussions	Moderator: Perry Calias
12:15–1:15 p.m.	Lunch	12:15–1:15 p.m.
Session 3	Assessing product delivery	Moderator: David Begley, King's College, U.K.
1:15–1:45 p.m.	Strategies for CNS drug design and development	Nigel Greig, NIA
1:45–2:15 p.m.	Validation and applications of bioanalytical methods for quantitation of therapeutic enzymes in CSF and serum	Mitra Azadeh, Covance Laboratories Inc.
2:15–2:45 p.m.	Pharmacological imaging: quantitative positron emission tomography	Mikhail Papisov, MGH
2:45–3:00 p.m.	Panel discussion	Moderator: David Begley
3:00–3:15 p.m.	Break	3:00–3:15 p.m.
Session 4	Non-clinical considerations for clinical trial readiness	Session chair: David Jacobson-Kram, FDA
3:15–3:45 p.m.	Preclinical study design of centrally delivered products based on pharmacokinetics	Bob Boyd, Northern Biomedical Research
3:45–4:15 p.m.	Morphologic assessment of preclinical studies involving direct delivery to the CNS	Mark Butt, Tox Path Specialists
4:15–4:30 p.m.	Panel discussion	Moderator: David Jacobson-Kram
4:30 p.m.	Adjourn day 1	4:30 p.m.
Day 2—July 31, 2011		
Session 5	Considerations for clinical trial readiness/translational medicine part 1: biomarkers, PD measures, surrogates	Session chair: William Banks, University of Washington
8:00–8:30 a.m.	CSF biology, proteomics, and biomarkers of diseases	Reiner Haseloff, FMP, Germany
8:30–9:00 a.m.	Brain imaging to evaluate CNS drug delivery in animals and humans	Satoshi Minoshima, University of Washington
9:00–9:30 a.m.	Panel discussion	Moderator: William Banks
9:30–9:45 a.m.	Break	9:30–9:45 a.m.
Session 6	Considerations for clinical trial readiness/translational medicine part 2	Session chair: Anne Pariser, FDA
9:45–10:15 a.m.	Translational therapeutic development at NIH	Chris Austin, NHGRI, NIH, TRND
10:15–10:45 a.m.	Biomarkers in CNS therapeutics	Marc Walton, FDA
10:45–11:15 a.m.	Panel discussion	Moderator: Anne Pariser
11:15–11:30 a.m.	Closing remarks	Patti Dickson