Nanotechnology and Anesthesiology

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Disclosure

I have no disclosures or conflict of interest
Learning Objectives

- Recognize the need for nanotechnology systems in neonatal and pediatric brain injury.
- Distinguish and differentiate various nanoparticle platforms with potential for diagnostic and therapeutic applications in CNS disorders.
- Design appropriate nanotherapeutics based on the underlying pathology in developmental brain injuries.
- Evaluate current nanotechnology based approaches for pediatric neuroscience applications.
The Challenge

- BBB is a major challenge for drugs and delivery vehicles
- Targeting ‘diffuse’ neuroinflammation/microglia
- Even if the vehicle is transported, can it accumulate in enough amounts to create a therapeutic effect?
- The brain injury has already occurred in utero. Can the motor deficit improve?
Overcoming barriers for delivery to the brain

1. Overcome the blood-brain barrier
2. Move within diseased brain tissue parenchyma
3. Uptake into specific disease associated cells

Neuroinflammation, mediated by microglia and astrocytes, has recently been elucidated as a major player in many brain diseases and impacts all barriers listed above.

Nanoparticles can overcome these barriers, if appropriately engineered based on disease.

Nano and Targeting

Nanoparticles: 1 to 100 nm (10^{-9} to 10^{-7} m)

Soccer Ball: ~0.1 to 1 m

Earth: ~10^{7} m

Targeting is like dropping a soccer ball in the arctic circle and asking it to land in this room!
Importance of Glial cells & Inflammation

Glial cells are more than “nerve cement”

Glial cells make up ~90% of the brain cells and more than half the volume!

Behind every neuron in a human there are 9 glia!

Microglia – ‘defense’ ministry of brain

Astrocytes – ‘Internal affairs’ ministry of the brain

Emerging idea:

Controlling glial cells
Activated glia are a therapeutic opportunity
What dictates \textit{in vivo} brain distribution and cell-specific uptake of nanoparticles in CNS disorders?

- Nanoparticle properties
- Disease etiology
- Developmental age
- Animal model
Dendrimers: ‘tree-like polymers’

- Multifunctional, nanostructured polymers (~ 5-10 nm)
- Biocompatible, and cleared intact from circulation

R Esfand, DA Tomalia - Drug Discovery Today, 2001;
Dendrimers: ‘Tree-like polymers’
In collaboration with Kannan Rangaramanujam
Co-Director, Center for Nanomedicine, Wilmer Eye Institute

- Dendrimers are well-defined, tree-like polymers made synthetically, with a size of ~ 4 – 20 nm.
- Flexible, open structure, where each component of the tree can be manipulated
- Biocompatible, can be made biodegradable
- Multifunctionality (therapy, imaging, targeting)

Strategy: use the intrinsic targeting and release properties of dendrimers as building blocks and tailor the nanodevice to the specific clinical application
Neutral PAMAM dendrimer rapidly co-localizes in activated microglia in regions affected by cerebral palsy.

No uptake in the subventricular zone (SVZ) that is predominantly comprised of neuronal progenitors.

D-OH is found in regions with BBB impairment and significant microglia activation.

Nance et al., *In preparation*
Neurodevelopmental Disorders: Magnitude of the problem

- Perinatal brain injury—a major cause of morbidity and mortality

- 1 in 303 children have cerebral palsy or 3.3 per 1,000 8-yr old children have cerebral palsy (CDC)

- Lifetime costs for an individual with cerebral palsy is about $921,000.

- Unmeasurable social and emotional costs.
Inflammation and neonatal/pediatric brain injury

- Immune dysregulation of the brain implicated in cerebral palsy

- Significant correlation between chorioamnionitis and PVL/cerebral palsy (Dammann, Wu, Yoon)

- Increased incidence of autism in patients with cerebral palsy (Kirby, 2011)

- Immune activation may be mediated by microglia in the fetal/newborn brain

- Increased presence of microglia noted in the brain of patients with PVL and autism (Haynes, 2003; Vargas)
Microglial Cells: Unique Role in the developing brain

- Resident immune cells in the brain
- Undergo dynamic changes in the developing brain
- Present in the white matter tracts in the developing brain in high density (Monier, 2007)
- Decrease in numbers and move to the cortex from the white matter tracts by 1-2 years of age (Billiards, 2006)
- Play a role in remodeling
- Activated in the presence of inflammation
But can it release the drug specifically where we want it to?

![Diagram showing reach target cells and release drug inside cells.]

- N-acetyl cysteine has anti-inflammatory and anti-oxidant effects; GSH precursor
- Has been shown to reduce infarct volume and inflammation in animal models of stroke and cerebral ischemia
- NAC conjugated to dendrimer such that it will not release in plasma but will release intracellularly in a sustained manner
- Validated in vitro

Neurobehavioral Assessment
Post-Natal Evaluation – **Day 1**

- **CP kits: PBS**
- **CP kits: Dendrimer-NAC**

**Littermates**
Significant motor function improvement:
Neurobehavioral Evaluation – **Day 5**

CP kits: PBS

CP kits: Dendrimer-NAC

Littermates
Single dose on Day 1

Patents Pending (2009/2010); Science Trans. Med (April, 2012);
Significant improvement in motor function with Dendrimer-NAC therapy

Dramatic Improvement in motor function seen by Day 5, upon Dendrimer-NAC treatment

Myelination and neuronal injury

- Associated with decrease in markers of oxidative injury
- Increase in glutathione levels
- Decrease in inflammation at day 5 of age
- Decrease in neuronal injury

Kannan S et al, SciTM 2012
Summary

- **Postnatal therapy for prenatal injury**
- **Targeted therapy can prevent or arrest fetal neuro-inflammation**
- **Platform for delivering drugs in a targeted, sustained manner for brain injury: implications in other neurodegenerative diseases**