U.S. FOOD & DRUG ADMINISTRATION

Division of Neurotoxicology

Presented by:

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Acting Division Director

U.S. Food and Drug Administration

Disclaimer: *The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy.*

Division Staff

- Government Positions (# Full Time Employees)
  - Research Scientists, Staff Fellows & Visiting Scientists: 19
  - Support Scientists: 11
  - Administrative: 1 and a separate open position
  - FDA Commissioner Fellows: 1 (term ended Oct 2018)
- ORISE Post Docs & Graduate Students: 4
- Visiting Scientists: 1

- Total = 37 staff members

Outreach

- **Collaborations**
  - NCTR Divisions: Systems Biology, Microbiology
  - FDA Regulatory Centers: CDER, CDRH, CFSAN
  - Government agencies: CDC/NIOSH, EPA, DEA, NTP, ILSI/HESI, Critical Path Institute Coalition Against Major Diseases (CAMD)

- **Global Leadership Outreach**
  - UAMS & Arkansas Children's Hospital; University of Arkansas at Fayetteville; University of Texas Health Sciences Center, San Antonio; Albert Einstein College of Medicine; University of Birmingham, UK
  - Mayo Clinic (MASK study)
  - Steering Committee of SmartTots – a collaborative effort of the FDA, the IARS and others
  - National Institute of Perinatology, Mexico
  - European Cooperation on Science and Technology (COST) - Committee for Nano4Neuro project

Division Mission (Vision)

- **Mission**

  To develop and validate quantitative biomarkers and identify biological pathways associated with the expression of neurotoxicity . . . employing fundamental research efforts in several focal areas.

- **Goals**

  To be a valued resource in advancing regulatory science research in neurotoxicology for FDA.

- **Strategies**

  Development of sophisticated imaging approaches, alternative preclinical models, and cross-species metrics of brain function to identify novel markers of neurotoxicity.

Top Three Accomplishments the Last 5 Years

- Nic-NANO US and Euro Patent
- Continued progress in pediatric-anesthetic exposure work
- Recognition of importance of microglial activation in central nervous system (CNS) vasculature damage

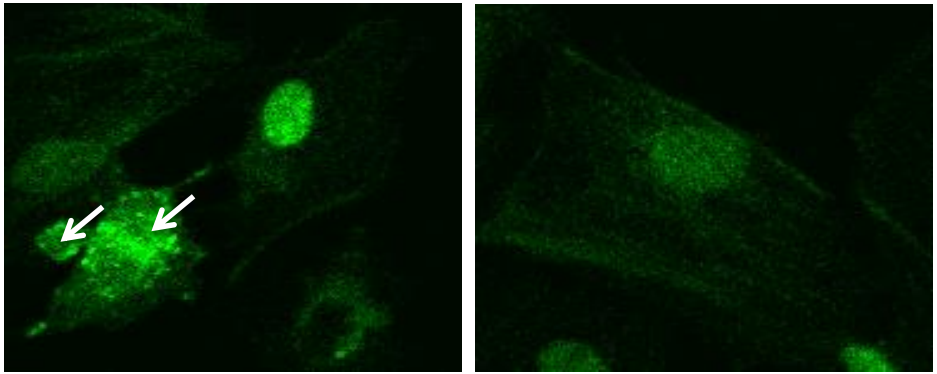
Examples of Current Projects

- Nic-NANO US and Euro Patent
- Progress in pediatric anesthetic exposure work
- Recognition of importance of microglial activation in CNS vasculature damage

Nic-NANOceria for Parkinson's Disease (PD)

PI & Inventor: Syed Imam

- 2018 – European & US patents received
- Nicotine has protective effects against PD and nanoceria have anti-oxidant properties
- The conjugate has a biodegradable coating (for sustained release) and may be administered orally
- Potential therapeutic intervention for neurodegenerative or neurological disorders



1.0 mM MPP+ | Nic 0.1/Nano 200/1.0 mM MPP+

Examples of Current Projects

- Nic-NANO US and Euro Patent
- Progress in pediatric anesthetic exposure work
- Recognition of importance of microglial activation in CNS vasculature damage

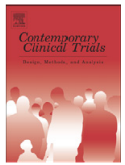
Pediatric Anesthesia – MASK Study

Contemporary Clinical Trials 41 (2015) 45–54

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Neurodevelopment of children exposed to anesthesia: Design of the Mayo Anesthesia Safety in Kids (MASK) study

Stephen J. Gleich [a], Randall Flick [a], Danqing Hu [b], Michael J. Zaccariello [c], Robert C. Colligan [c], Slavica K. Katusic [d], Darrell R. Schroeder [d], Andrew Hanson [d], Shonie Buenvenida [a], Robert T. Wilder [a], Juraj Sprung [a], Robert G. Voigt [e], Merle G. Paule [f], John J. Chelonis [f], David O. Warner [a,*]

Anesthesiology, 2018

Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia

The Mayo Anesthesia Safety in Kids (MASK) Study

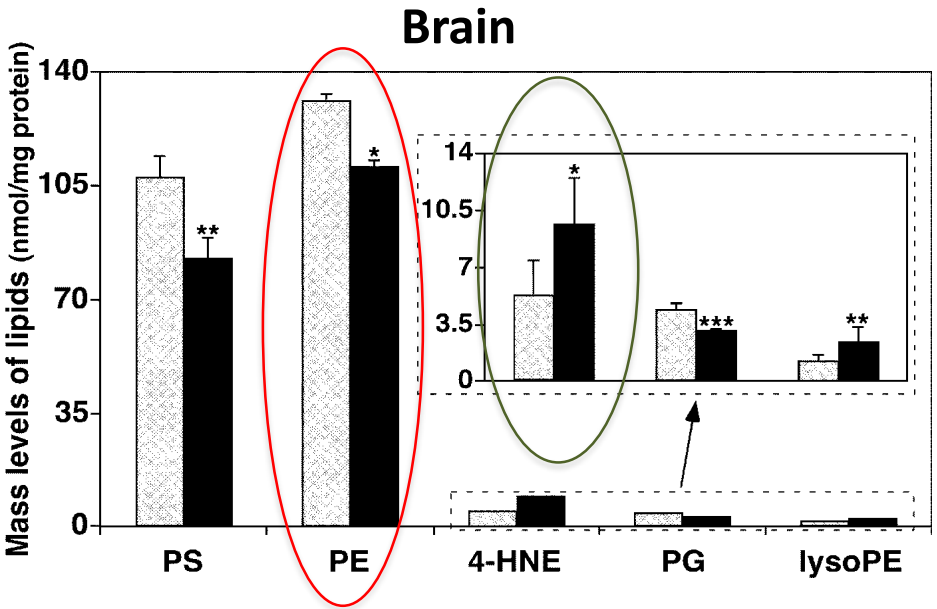
David O. Warner, M.D., Michael J. Zaccariello, Ph.D., L.P., Slavica K. Katusic, M.D., Darrell R. Schroeder, M.S., Andrew C. Hanson, B.S., Philip J. Schulte, Ph.D., Shonie L. Buenvenida, R.N., Stephen J. Gleich, M.D., Robert T. Wilder, M.D., Juraj Sprung, M.D., Danqing Hu, M.D., Robert G. Voigt, M.D., Merle G. Paule, Ph.D., John J. Chelonis, Ph.D., Randall P. Flick, M.D., M.P.H.

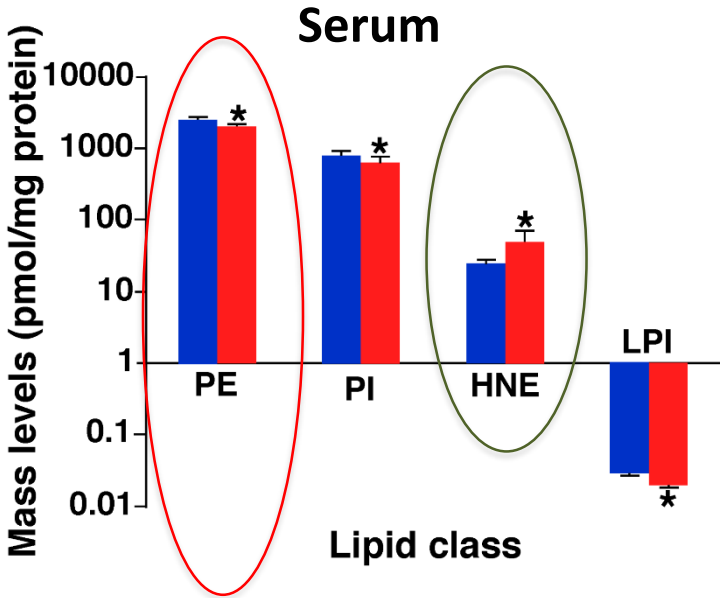
Pediatric Anesthesia – Lipid Work

Selected networks associated with lipid metabolism

DEG-Involved Network Functions Annotation	p-Value	Molecules involved
metabolism of cholesterol	1.08E-03	NPC1L1, SEC14L2, STAR
fatty acid metabolism	1.54E-03	ACACB, CADM1, MSMO1, NPC1L1, ST8SIA2, STAR
steroid metabolism	2.21E-03	MSMO1, NPC1L1, SEC14L2, STAR
concentration of lipid	3.85E-03	ACACB, AQP3, DIO2, NPC1L1, SEC14L2, STAR, VGF
concentration of cholesterol	5.19E-03	ACACB, NPC1L1, SEC14L2, STAR
concentration of triacylglycerol	5.78E-03	ACACB, AQP3, DIO2, NPC1L1
uptake of lipid	6.02E-03	NPC1L1, SEC14L2, STAR
quantity of steroid	6.30E-03	ACACB, NPC1L1, SEC14L2, STAR, VGF
synthesis of lipid	6.74E-03	ACACB, CADM1, NPC1L1, SEC14L2, ST8SIA2, STAR
metabolism of membrane lipid derivative	8.47E-03	NPC1L1, SEC14L2, ST8SIA2, STAR
synthesis of sterol	1.10E-02	NPC1L1, SEC14L2
synthesis of steroid	2.41E-02	NPC1L1, SEC14L2, STAR
transport of lipid	4.45E-02	NPC1L1, STAR

Pediatric Anesthesia – Lipid Work





PS: Phosphatidylserine; PE: Phosphatidylethanolamine
4-HNE: 4-hydroxynonenal ; PG: phosphatidylglycerol
LysoPE: Lysophosphatidylethanolamine;

PI: Phosphatidylinositol;
LPI: Lysophosphatidylinositol

Pediatric Anesthesia

- Results describe potential mechanisms of neurotoxicity and possibly implicate mitochondria as a target.
- Lipidomic signatures here may elucidate causal biochemical mechanisms underpinning cytoplasmic and mitochondrial lipid changes, and allow identification of biomarker candidates for early detection of neuronal damage.
- Disruption of membrane phospholipid integrity can cause microglia to secrete cytokines and may exacerbate inflammation.
  - Elevated cytokine levels in sevoflurane-exposed brains, suggesting an inflammatory reaction.

Examples of Current Projects

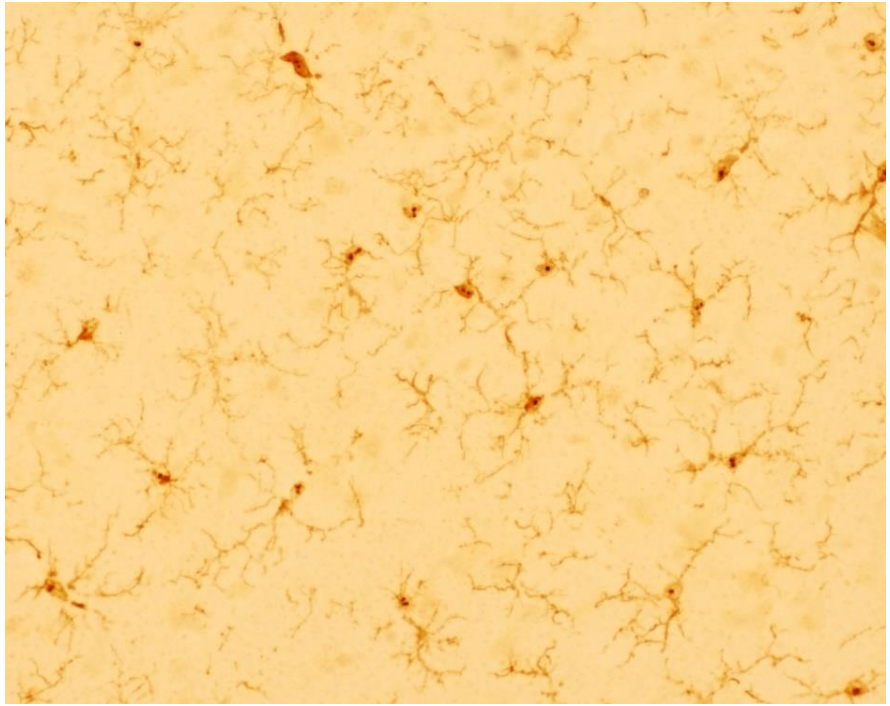
- Nic-NANO US and Euro Patent
- Pediatric anesthesia
- Recognition of importance of microglial activation in CNS vasculature damage

Microglial Activation

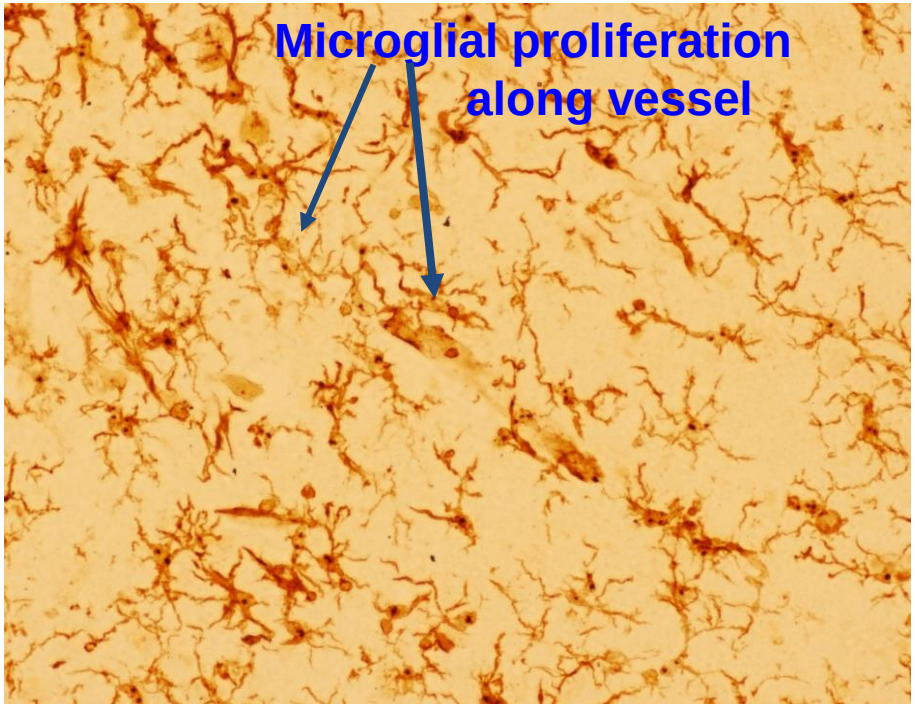
- Role of CNS vasculature in neurotoxicity
  - Chronic neuroinflammation is associated with many disorders (e.g., Alzheimer's disease [AD]) and results from activated microglia
  - For the first time, NCTR scientists have described microglia migration to the vasculature and their activation as a result of different neurotoxicities (methamphetamine treatment, thiamine deficiency, AD transgenic rats)

Microglial Activity

Inflammation in human AD brain

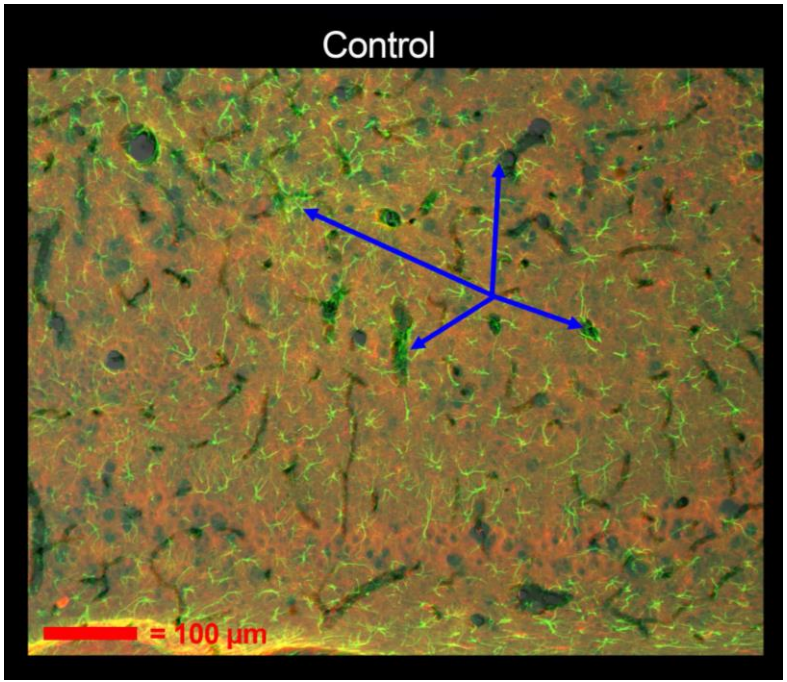


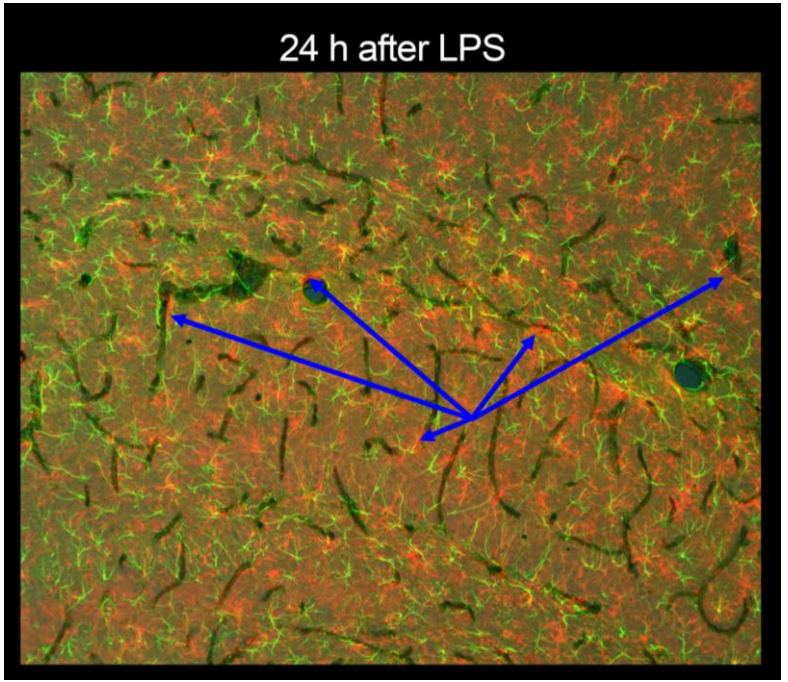
Control



Alzheimer's disease

Microglial Activity





Microglial Activity

- Vasculature degeneration may precede neurodegeneration and may occur due to blood-brain-barrier (BBB) leakage. Microglia migrate to vasculature, initially to repair BBB but if this continues, opportunistic factors enter which can permanently damage the brain.
- Those activated microglia could be distracted from their “normal” function of pruning and adjusting synaptic connections.
- **Why novel?**

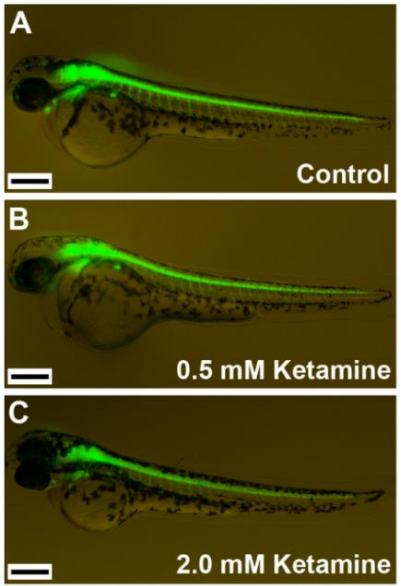
  Microglia activated before neurodegeneration occurs. This could imply novel and semi-universal mechanisms of neurotoxicity.
- **Why important?**
  - Strategies under development to temporarily open BBB for chemotherapy or other drugs to improve delivery to the brain. This could activate microglia and make BBB more difficult to open subsequent times.
  - Problems with the vasculature are not generally examined in neurotoxicological screens. This endpoint could be easily missed.

Examples of Current Projects

- Next-Generation sequencing in progress for sevoflurane-exposed monkey brain
  (Fang Liu and others)
- Neurotoxicity of ketamine use as an anti-depressant in adolescent rats *(CDER – John Talpos)*
- Developmental neurotoxicity of inorganic arsenic in rats
  (NTP – Sherry Ferguson)
- Brain-microbiome in AD rat model and AD humans (protocol under review)
  (Sumit Sarkar in collaboration with Division of Microbiology)

Future Directions

- Continue progress with zebrafish model



- Concordance with mammalian models or cells
  - Ketamine decreases ATP
  - Acetyl L-carnitine is neuroprotective
  - Ketamine's anesthetic property is enhanced with verapamil
  - Similar metabolism of ketamine
  - Ketamine regulates certain CYPs

Future Directions

- Behavioral alterations from ketamine use as an anti-depressant in adolescent rats

  (CDER – Syed Ali)

- New 4.7 T MRI for NHP work (larger bore) – installed, charged and tested and accepted
  - Two approved studies: NHP and rats

Feedback Requested

- What pressing neurotoxicological issues should we pursue?
- Are there emerging technologies we should be examining?
- How can we improve our engagement with other FDA Centers to know their needs?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