Preclinical and Translational Models for Delirium: Recommendations for Future Research from the NIDUS Delirium Network

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Time	Section

03:10	**What we know**
	• Delirium epidemiology well-characterized
	  o Associated outcomes
	  o Multifactorial contributions
	• Pathophysiology largely unknown
	  o Complex neurobiology
	  o Largely driven by human studies
	  o Need for ID causal mechanisms: animal models

05:53	**Bridging the preclinical and clinical sciences** • Core group o Process: 4 meetings (2020-2021) with discussions and debates, Writing subgroups, Manuscript (tone: balance limitations and optimism; target audience: current investigators, new investigators, funders • Consensus group

08:09	**Key take home message**
	• No animal model perfectly recapitulates all aspects of a human condition (esp. delirium)
	  o Complex behavioral syndrome
	  o Human condition with only clinical definition
	• Animal models **FOR** (not OF) delirium
	  o Set of animal models with set of cognitive and behavioral features resembling delirium

09:11	**General principles in developing animals models for delirium** • Unlikely to experience full complexity or exhibit same characteristics • Human features not measureable or easily disentangled (inattention, disorientation, hallucinations)
09:42	**White Paper Sections** • Current knowledge • Challenges and strategies for replicating elements of human delirium in animals • Utility of fluid, neurophysiology, neuroimaging markers in animal models • Guidelines and recommendations

10:22	**Current state of knowledge**
	• Framework
	  o Underlying vulnerability
	  o Superimposed acute precipitating factors
	• Large variability
	  o Multifactorial nature
	  o Evolution from common models of human disease (e.g. APOE gene KO)

11:25	**Challenges and strategies for replicating elements of human delirium in animals**
	• Challenges:
	  o Aging (critical risk factor)
	  o Models (species, genetics, insult(s), clinical relevance)
	  o Delirium testing (when? Group vs. individual, cognitive domain?, feasibility for the model, practice, how many tests?, primary/other endpoints)
	  o Risk factors (multifactorial etiology, controls, costs)

	○ Biomarkers (timing, specificity, translation, validation) ○ Treatments (timing [pre-post], routes, efficacy, mechanisms)
31:14	**Utility of fluid, neurophysiology, neuroimaging markers in animal models** • Why animal models? ○ Advance our mechanistic understanding of delirium pathogenesis ▪ Apply experimental manipulations to test mechanistic hypotheses ▪ Determine causal mechanisms/pathways ▪ Develop targeted treatments ○ Validate clinical findings ▪ Discern association from causality ○ Extend clinical findings ▪ Link mechanisms to behavioral phenotypes, neuroanatomic abnormalities, biomarkers
35:53	**Validity frameworks** • Face validity • Construct validity • **Predictive validity** • **Target validity**
39:15	**Primary outcomes** • Behavior
40:13	**Secondary outcomes** • Electrophysiology • Biofluid markers • Tissue analysis • Imaging
41:45	**Physiology monitoring** • Animals can get sick
43:51	**Analysis focused on individual animals** • Can focus on the animal, like the focus on a patient
45:02	**Guidelines and recommendations** • General: ○ Follow PREPARE guidelines at the outset. (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence) • Choose an animal (both sexes) ○ Balance relevance and expense, where relevance= genetics, behavior, and expense = acquisition costs, housing, time, numbers and regulatory concerns • Vulnerability ○ Enhances construct validity ○ Age (18-24 mo. For rodents) ○ Frailty ○ Drugs, polypharmacy ○ Genetic manipulation ○ Include controls w/o vulnerability • Precipitant ○ Enhances construct validity ○ Anesthesia/surgery ○ Infections/LPS ○ Environmental disturbance ○ Sleep disruption ○ Include controls without precipitant

	• Physiology
	  ○ Some precipitants (e.g. anesthetics) cause severe changes in physiology, that independently may cause delirium or behavior change
	  ▪ Monitor: HR, RR, SaO2, ABGs, temp
	  ▪ Support as necessary
	  ▪ Controls without precipitant
	• Outcomes
	  ○ Mortality
	  ○ Behavioral “battery”, timing
	  ○ Pathophysiology, pathology, timing
	  ○ Biomarkers, timing
	  ○ Statistics, by individual vs. groups
	• Reporting
	  ○ ARRIVE, PREPARE guidelines
	  ○ Data deposition
	  ▪ Harvard Dataverse, AlzPed
	  ▪ NIA Biobank

51:16	**Questions and Answers**