The Center for Neural Development and Disease

(will be The Center for NeuroTherapeutics Discovery)

Handy Gelbard, Director

Professor of Neurology, Pediatrics, Microbiology & Immunology and Neuroscience

Premise: understand development of the nervous system and you will have a better chance of fixing neurodegeneration…
2nd caveat: disease-modifying strategies are likely to involve regeneration (either from endogenous or exogenous sources)

- Brief history: Centers as discrete physical entities became popular at URMC in the late 90's and the Center for Aging and Developmental Biology was started by Howard Federoff in 1999
- Investigators with diverse skill sets and interests were clustered in an open architecture environment to foster collaboration with the hope of increasing P or U level funding
- In 2007, Howard left and I took over after an external review by Jeff Macklis (Harvard) and Ted Dawson (Hopkins)
- The CNDD was "born" in 2008
- 2017 – time for the CND…

SWOT: 2008-2016

- Initial premise of CADB/CNDD was ~50% successful: two investigators (Thornton and Gelbard) achieved U and P level (respectively) funding that was renewed for multiple cycles.
- Both investigators developed strong industry ties; generated considerable IP; and one fledgling company (WavoDyne) with development compound (with backups) for which 65-70% of IND-enabling studies have been completed
- Other CNDD investigators with mixed success in investigator-initiated grants including new IP and industry ties; but in aggregate, very successful portfolio, albeit with uneven distribution between investigators
- Common ground for future efforts lies in approaches for disease-modifying therapeutic strategies with regenerative potential

Gelbard lab
Pathogenesis of HAND and other neuroinflammatory disease

- HIV-1 associated neurocognitive disorders (HAND) persist in >50%, despite effective combination antiretroviral therapy (cART)
- CNS disease persists largely because of aberrant innate immune activation and destruction of normal synaptic architecture
- Considerable overlap in signaling pathways and inflammatory mediators present in other neurodegenerative diseases

Current work

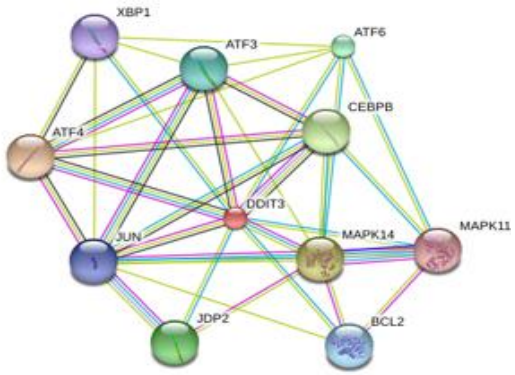
- Mechanisms related to persistent activation of CNS innate immunity
- Regeneration of synaptic architecture
- Role of autophagy in regulation of persistent/latent HIV-1 infection
- Translational – validate and extend use of “selectively non-selective” inhibition of kinase checkpoints to POCD, MS, PD, and AD
- Validate and extend to peripheral conditions such as NASH and heart failure

Future work

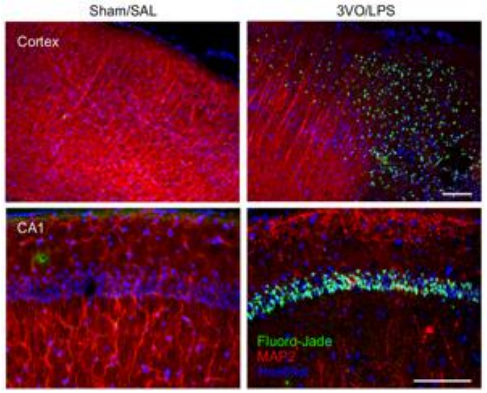
- Clinical – finish IND-enabling studies for Phase 0, 1 trials (2017-) with first-in-class “selectively non-selective” MLK3 inhibitor, URMC-099
- Find a better name for URMC-099…
- Identify disease entities for Phase 2a trials (POCD, MS and NASH likely)
- Initiate partnership(s) with NeuroNext

Halterman lab

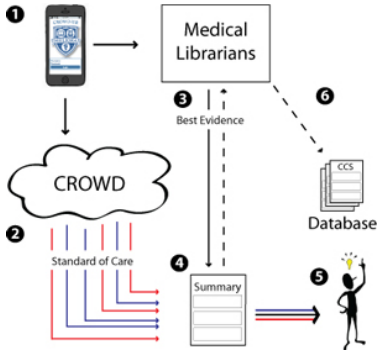
Transcription-based Therapies for Stroke



Anti-inflammatory Strategies for Post Cardiac Arrest Syndrome



Mobile Health Technology Development



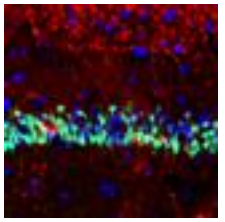
Halterman lab – UR-UPP

Onboarding

- Orientation
- Lab Safety
- Lab Meetings
- OHSP Training
- Fellowship Apps

Wet Lab

- Cell Culture
- Molecular Biology
- Animal Behavior



Dry Lab

- Bioinformatics
- Cytoscape
- Microscopy / ImageJ

Clinical

- Surveys / REDCap
- SAS
- EPIC
- Hospital Rounds

Mehta lab: work on focal ischemic stroke

Mechanistic

- Investigate molecular events that disturb blood-brain barrier integrity, leading to cerebral edema formation; Elucidate fate of ischemic neurons (survival and cell death signaling pathways)

Translational

- Develop drugs to mitigate BBB disruption in ischemia
- Boost post-ischemic endogenous pro-survival signaling

Current Work

- Define natural history / elucidate the spatiotemporal expression of members of the MASTL-alpha Ensa-PP2A regulatory module in a rat MCAo model of stroke and OGD model of cultured neurons

Next steps

- Examine protective effects of pharmacologic treatments and gene suppression in order to characterize a novel role for alpha-Ensa in post-ischemic cell fate determination and survival

Thornton lab: current work on myotonic dystrophy

Mechanistic

- What controls instability of expanded repeats?
- How does RNA gain-of-function work?

Translational

- Develop drugs that mitigate RNA toxicity or stabilize repeats

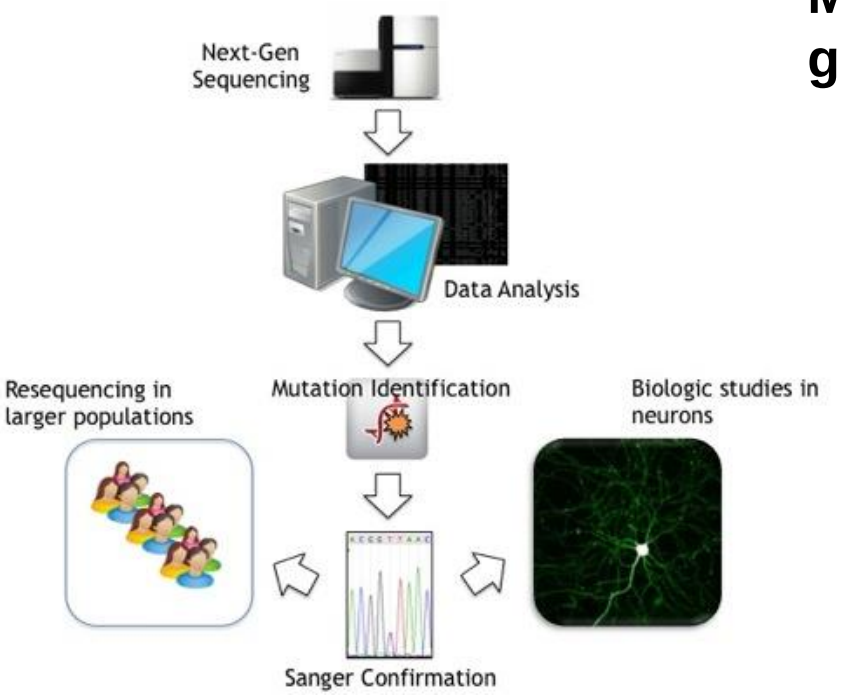
Clinical

- Phase I trial of antisense drug
- Validate biomarkers of therapeutic response
- Define natural history
- Select endpoints for clinical trials

New work pertinent to this forum

- Develop mouse model of CNS involvement
  - When CTG repeat expansion is large it causes intellectual disability or autism
  - New resource needed: targeted integration of large repeat at mouse locus
- Examine reversibility of CNS symptoms (antisense and small molecule drugs)

Paciorkowski lab



Massively parallel sequencing for gene discovery in individuals with:

- Autism
- Epilepsy
- Intellectual disability
- Movement disorders

Whole genome sequencing
Exome sequencing
Targeted ultra-deep sequencing

Development of novel bioinformatics tools

REPORT *Am J Hum Gen, 2014*

De Novo Mutations in the Beta-Tubulin Gene *TUBB2A* Cause Simplified Gyral Patterning and Infantile-Onset Epilepsy

Thomas D. Cushion,[1,10] Alex R. Paciorkowski,[2,3,4,10] Daniela T. Pilz,[5,6] Jonathan G.L. Mullins,[1] Laurie E. Seltzer,[2] Robert W. Marion,[7] Emily Tuttle,[4] Dalia Ghoneim,[4] Susan L. Christian,[8] Seo-Kyung Chung,[1,6] Mark I. Rees,[1,6,11,*] and William B. Dobyns[8,9,11,*]

REPORT *Am J Hum Gen, 2015*

De Novo Mutations in *SIK1* Cause a Spectrum of Developmental Epilepsies

Jeanne Hansen,[1] Chelsi Snow,[2] Emily Tuttle,[1] Dalia H. Ghoneim,[1] Chun-Song Yang,[2] Adam Spencer,[2] Sonya A. Gunter,[3] Christopher D. Smyser,[4] Christina A. Gurnett,[4] Marwan Shinawi,[5] William B. Dobyns,[6,7] James Wheless,[8] Marc W. Halterman,[1,9] Laura A. Jansen,[3] Bryce M. Paschal,[2,10] and Alex R. Paciorkowski[1,9,11,*]

Portman Lab

Sex differences in neural circuit development, function, and plasticity: insights from *C. elegans*

- Sex differences provide a powerful handle on mechanisms that regulate neural circuit development and function.
- Our current work aims to use sex differences to identify the neural and genetic underpinnings of behavioral plasticity in a simple* model.

  *actually, exceedingly complex
- This work helps build a framework that informs our understanding of numerous neurological and neuropsychiatric conditions — with particular significance for those that exhibit sex bias in incidence and/or severity

Portman Lab

Sex differences in neural circuit development, function, and plasticity: insights from *C. elegans*

Current work:

- **Behavioral choice:** Sex-specific tuning of chemosensory repertoire guides behavioral prioritization.
- **Circuit plasticity:** Developmental stage and feeding state dynamically regulate sensory function.
- **Development:** Genetic sex regulates precursor proliferation, cell fate, and functional modulation in the nervous system.