UCI Center for Autism Research and Translation (UCI CART)

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We need new medicines for ASD

Sufficient genomic pathway information exists to begin a FUNCTION BASED approach to CORE deficits in ASD

Behavioral therapies are important, but are symptom-directed & not sufficient ...epidemic increase continues unabated

There is no pharmacological therapy for CORE deficits in ASD
The CART proposal

The valley of death

Target Discovery
Candidate Identification
Preclinical Development
Phase I-III
Approval

- Speed up the drug discovery process in ASD through a public-private partnership catalyzed by CART
- Keep the partnership sustainable by spinning off commercial opportunities (start-ups, licensing)
Concept of UCI CART

- Center for Autism Research and Translation (UCI CART) is a unique public-private partnership seeded by generous philanthropic support from the William & Nancy Thompson Family Foundation for Autism.
- ... to carry out a comprehensive research and translation effort to develop novel, effective diagnostics and treatments for autism.
- Our goal is to abolish current and future cases of autism through discovery, translation and implementation.
- With the escalating costs of autism care, and fewer Medicare and MediCal funds to cover them, new drug treatments are the ONLY effective approach to stem this tide.
UCI CART is *distinctive* from other autism research centers

- Real breakthroughs must start with research that is *directed* toward novel treatment approaches, and the CART research team is distinctively organized to do this.
- World-class research has been taking place at UC Irvine in Genomics and the Neurosciences.
- CART takes existing UCI Science that wasn’t autism-related, re-directs it and tunes it...... to immediately apply to studies key to autism.

CART has launched an innovative drug discovery effort uniting multidisciplinary campus scientists in a common purpose: to develop an effective pharmaceutical therapy for the core deficits of autism, not symptoms.
UCI CART speeds up discovery and lowers the barrier between great research and great impact to society.

- It is now clear that autism has a genetic basis, and targeting the cellular functions disrupted by the mutations, from multiple approaches, presents the best approach to a novel therapeutic.

- By determining the mechanisms by which malfunctioning genes affect the common pathways linked to autism, it will be possible to design or repurpose existing drugs to normalize those functions.

- CART is **NOW** supporting three separate ongoing drug discovery efforts by UC Irvine neuroscientists on UC Irvine patented compounds that target pathways implicated in ASD.

- While not originally created for autism, these three novel compounds, through the lens of genetics, can be recognized to target biological machinery implicated by the mutations found in ASD.

- Because these compounds have **ALREADY** been found effective in rodent models of ASD, and some have already been found safe for people, they’re much closer to reaching early-stage testing in human patients.

- A similar drug discovery approach led to a cystic fibrosis **CURE**. The FDA approval-process was accelerated, which led to a bench-to-bedside timeline that’s practically unheard of in pharmaceutical development.
ASD is the most highly heritable neurodevelopmental disorder

- Shows a High Heritability
  - Genes involved

- Inheritance pattern...complex
  - Many “at risk” (susceptibility) gene variants (mutations) work together
  - Identical twins are MUCH MORE alike than fraternal twins or sibs
  - BUT identical twins can be DISCORDANT

- SO there is ALSO a SIGNIFICANT “non-gene” component
  - “Environment”
Key Milestones to Cure Autism

• Define PATHOGENESIS
  ...how disease arises
  – Best start is genes.... not just statistically associated...
    ....but with roles proven with functional analysis
  – Functional genes are target to screen for environment

• Genes give TARGETS for DIAGNOSTIC TESTS

• Genes give TARGETS for DRUG DISCOVERY

• Genes give MODEL ORGANISMS for DRUG discovery and ENVIRONMENTAL impact

• TRANSLATE into CLINICAL INVESTIGATIONS model and drug/environment effects
CORES
1-Genomic…whole genome sequence, computers, ASD pt database w/ DNA/cells/arrays
2-Cell signal…super-resolution STORM signaling, monogenic ASD model cell lines
3-Synapse…deconvolution microscopy, behavioral assays, monogenic murine lines
4- iPSC….rare diseases iPS and neurons & produce genuine WGSed ASD iPS/neurons
5-Brain clinical trials outcomes….fancy & portable EEGs, sleep study, ASD phenotyping
7- Electrophysiology & Optogenetics….fancy control of channel activity in cells & animals

PHARMA
Lynch….ampakines
Gee…”duallys”….combination 15q located GABA/α7
Piomelli….endocannabinoids

* = year 2 funding
NextGen DNA Sequencing

Sample Preparation

Sequencing

SNPs, and structural variants

Data Analysis
Stem Cell derived Neurons
Sophisticated measures of Brain & Behavior for clinical trials outcomes

Aim 1: Characterize Sensory deficits in responses to simple amplitude modulated sounds: (1) tones (2) noise (3) speech

Aim 2: Characterize deficits in speech processing and audio-visual integration

Horton et al., 2013 J Neurophysiology
Deficit in Regulation of Endocannabinoids

Endocannabinoid System as a Therapeutic Target for Autism

Targeting $\alpha_7$ nACh and GABA$_A$ receptors simultaneously ASD

Pharma lead compounds

Endocannabinoid System as a Therapeutic Target for Autism

Ampakine Rescue Synaptic Plasticity In ASD
Functional infrastructure is in place to drive discoveries for Autism,

but there is a gap between the basic science research entrepreneurial philanthropy launched

and the final stages of drug research

and this would be an important gap State support could help close
• The State is in a powerful position to be the *amplifier effect* for current research

• In fact, it already has served as the catalyst to innovation 10 years ago when it funded four multidisciplinary research institutes established to accelerate discovery and innovation. QB3 was one.

• California Institute for Quantitative Biosciences (known as QB3) is a joint venture between the three University of California campuses at Berkeley, San Francisco, and Santa Cruz. QB3 and its partners have helped launch 60 new bioscience companies. There is no SoCal equivalent.
• QB3 State and government initiated funding
  Fostering entrepreneurial spirit
  Fantastically successful incubator program
  Science, startups, jobs, products, economic return
  Renewed interest and new investment by big pharma
  (Pfizer Alliance ($50M - http://qb3.org/industry-partnerships/Pfizer)

• California Institute for Biomedical Research (Calibr)
  New non-profit devoted to working with academic investigators on drug discovery
  Collaborations with UCSD, Scripps, Salk
  (Merck---$90M funding - http://www.calibr.org)

• California Institute for Regenerative Medicine (CIRM)
  State funding $3 billion for stem cell research
  Outcomes: jobs, science, startups, more jobs, clinical trials, treatments and cures