

# UCI Center for Autism Research and Translation (UCI CART)

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Professor

Physiology & Biophysics

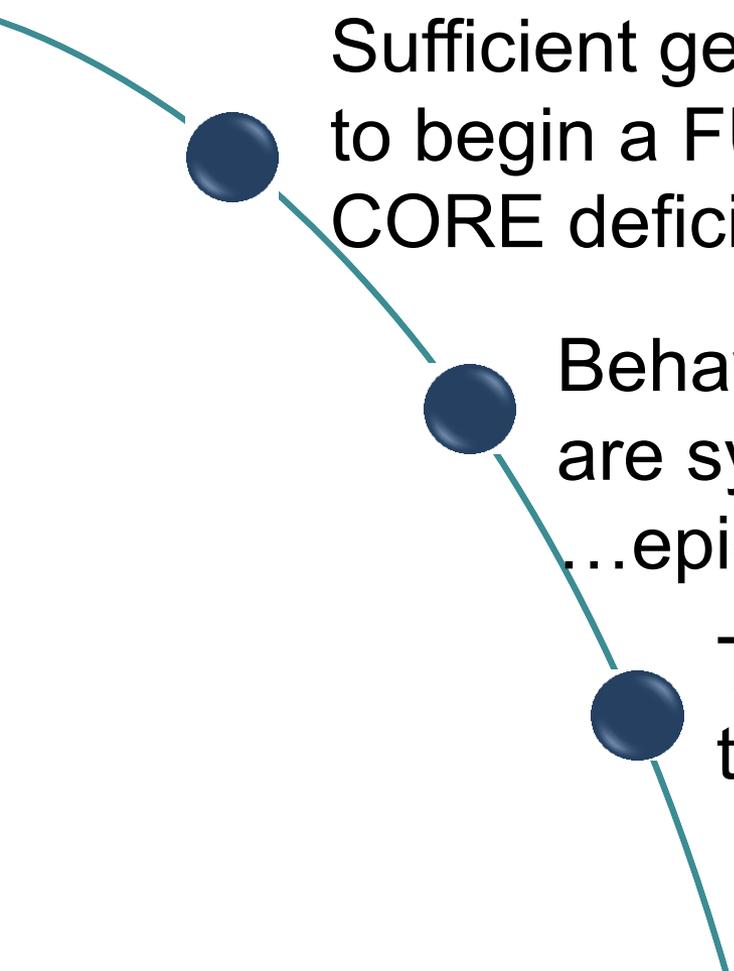
and Pediatrics, section of Human Genetics

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# We need new medicines for ASD

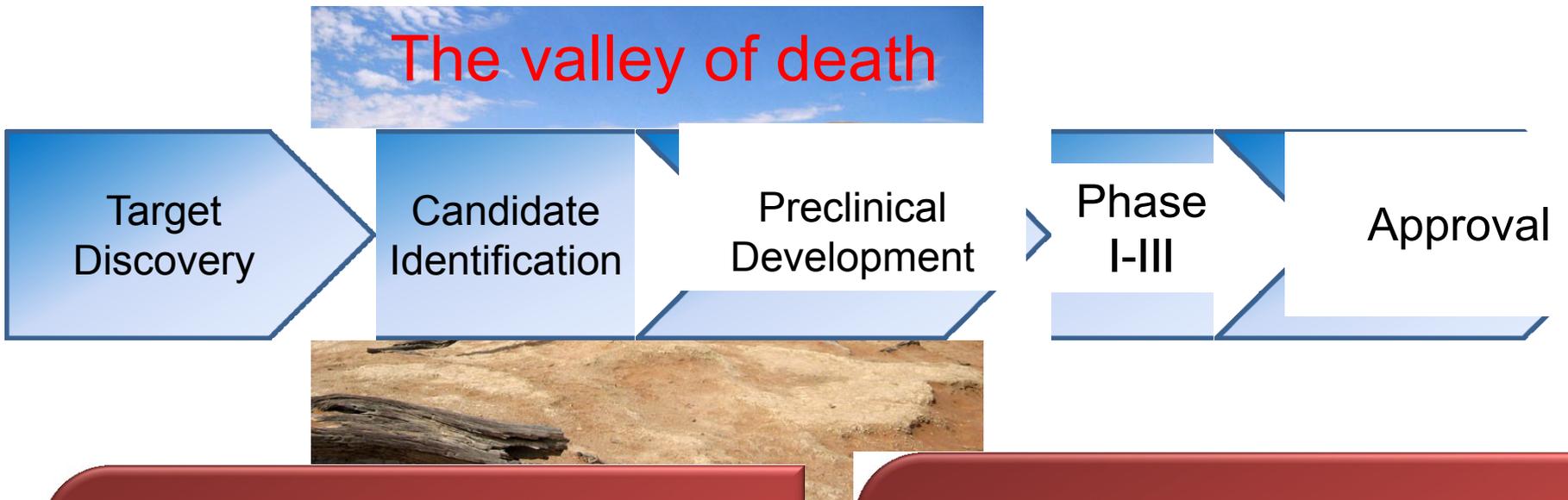


Sufficient genomic pathway information exists to begin a **FUNCTION BASED** approach to **CORE** deficits in ASD

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

There is no pharmacological therapy for **CORE** deficits in ASD

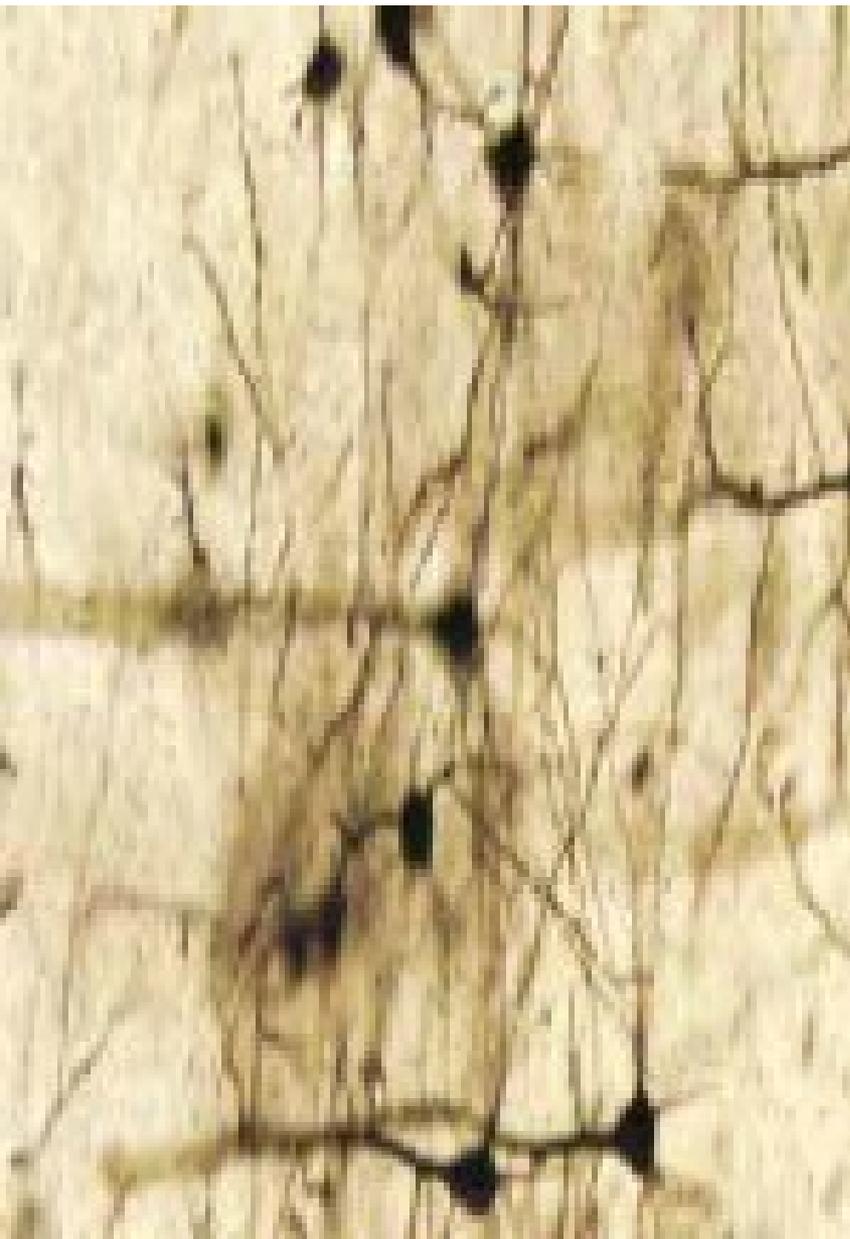
# The CART proposal



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.

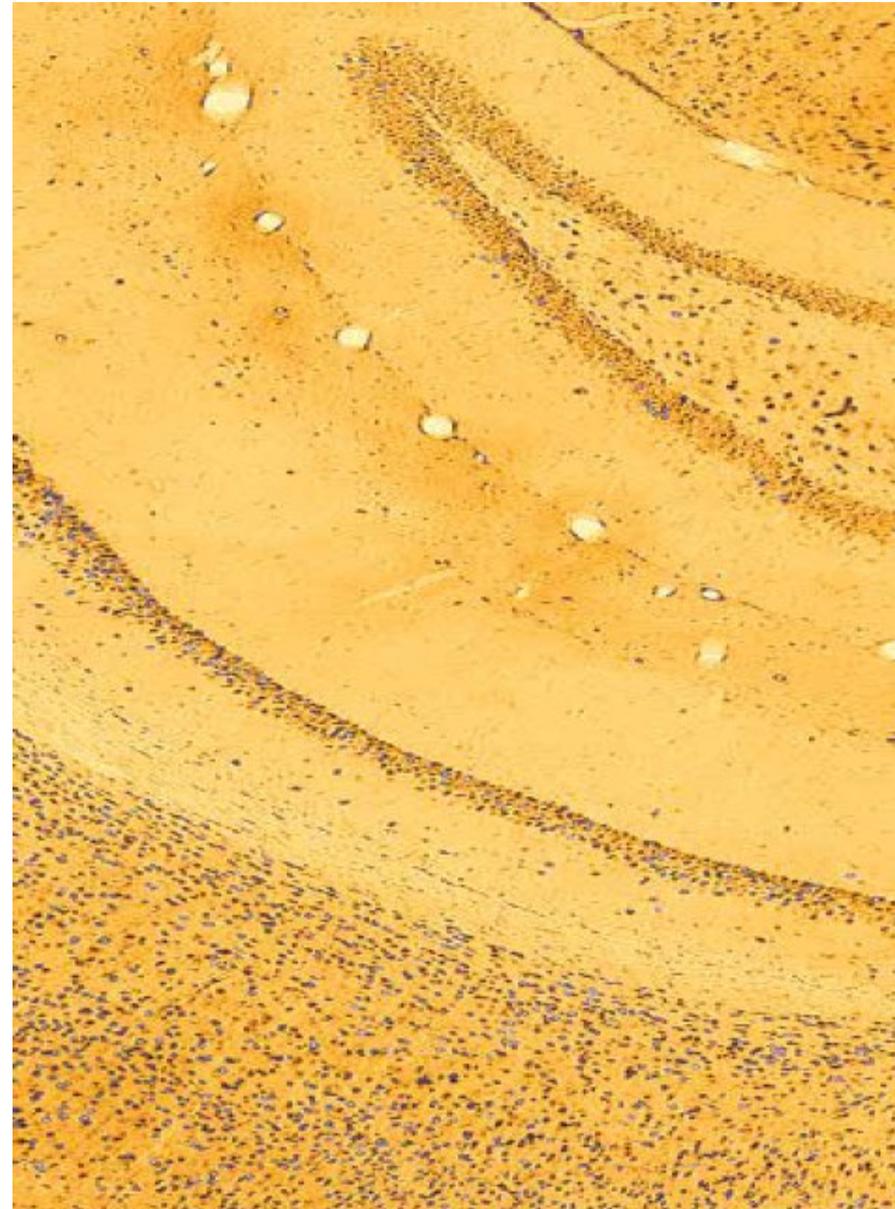
A similar drug discovery approach led to a cystic fibrosis CURE. The FDA approval-process was accelerated, which led to a bench-to-bedside timeline that's practically unheard of in pharmaceutical development.

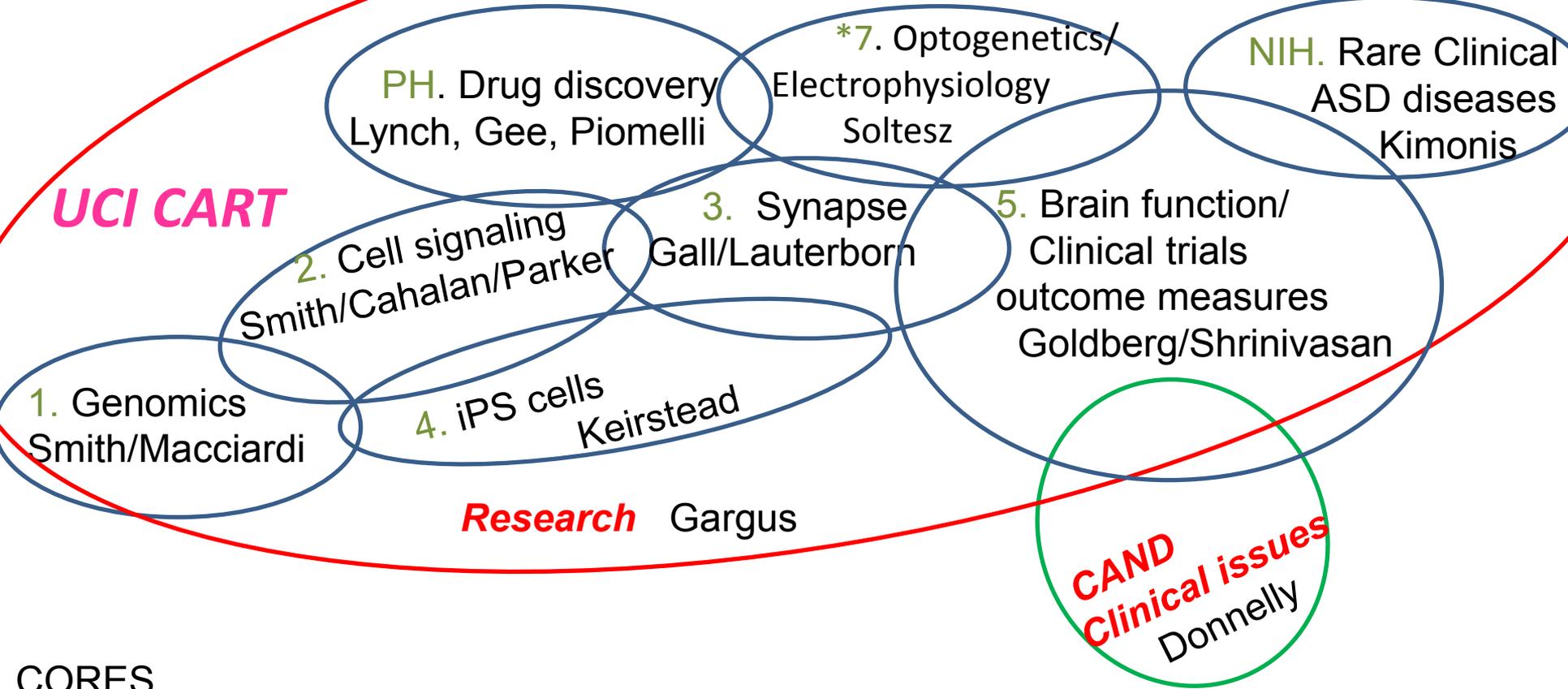
# ASD is the most highly heritable neurodevelopmental disorder

- 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

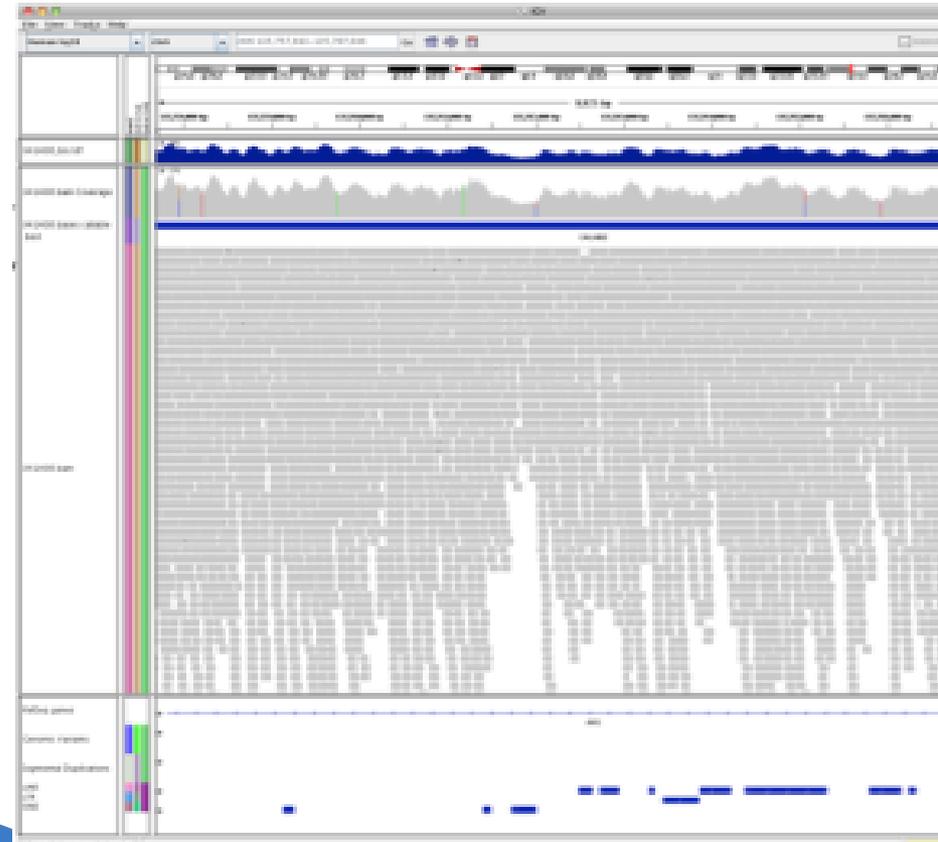
Step	Step Name	Total time	Prep. time
Step 1	Incubate small RNA	0:06	(1:20)
Step 2	Start 1' RNA Adapter ligation	0:51	(0:10)
Total time (hands-on time)		0:57	(1:30)
Step 3	Complete 2' RNA Adapter ligation	0:00	(1:20)
Step 4	Start 2' RNA Adapter ligation	0:59	(0:10)
Total time (hands-on time)		0:59	(1:30)
Step 5	Complete 3' RNA Adapter ligation	0:00	(1:20)
Step 6	Perform RT-PCR amplification	3:25	(0:31)
Total time (hands-on time)		10:01	(1:51)
Step 7	Get ready small RNA control library	4:01	(1:02)
Total time (hands-on time)		4:01	(1:02)
Workflow total time		17:44	6:53

Sample Preparation



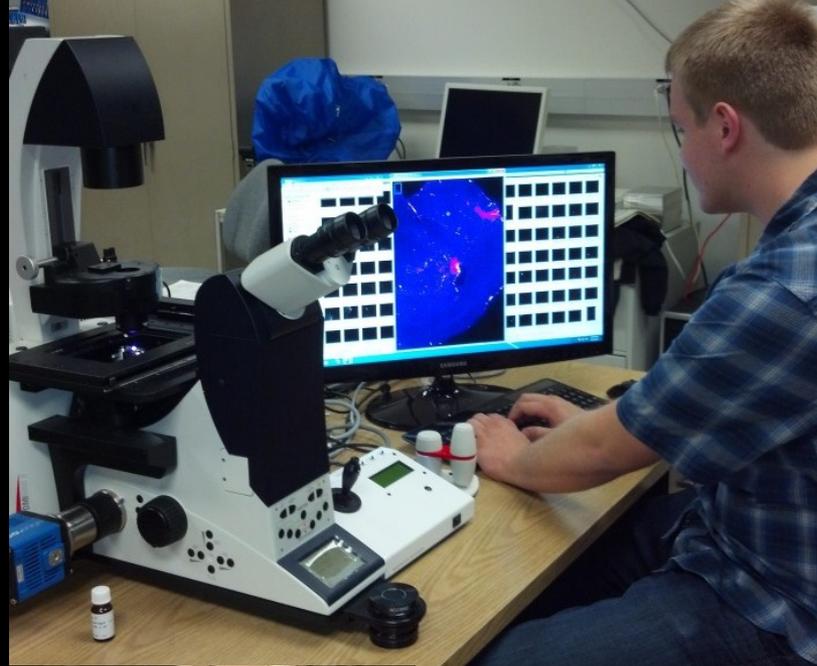
Sequencing

**SNPs, and structural variants**

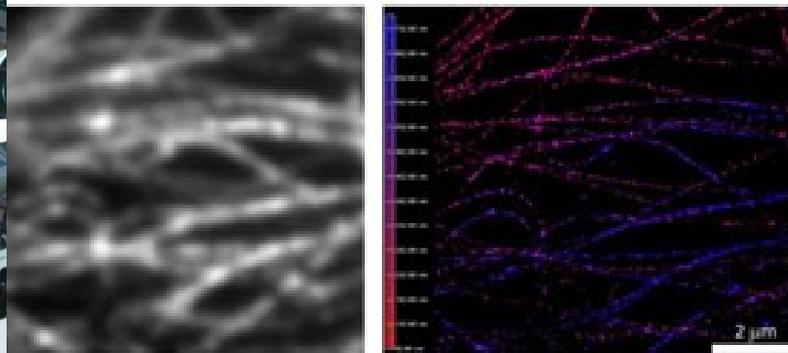


Data Analysis

# Sophisticated Microscopy



SUPER-RESOLUTION  
MICROSCOPE SYSTEM

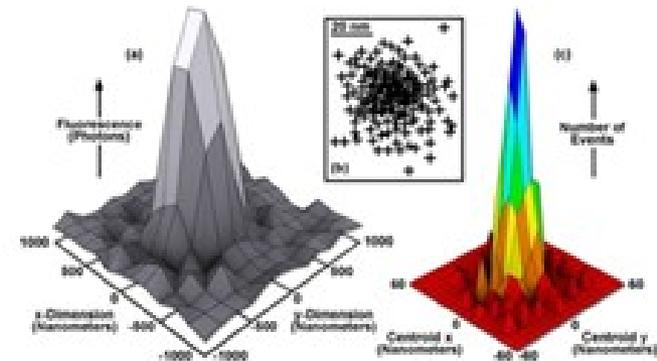


Conventional Image

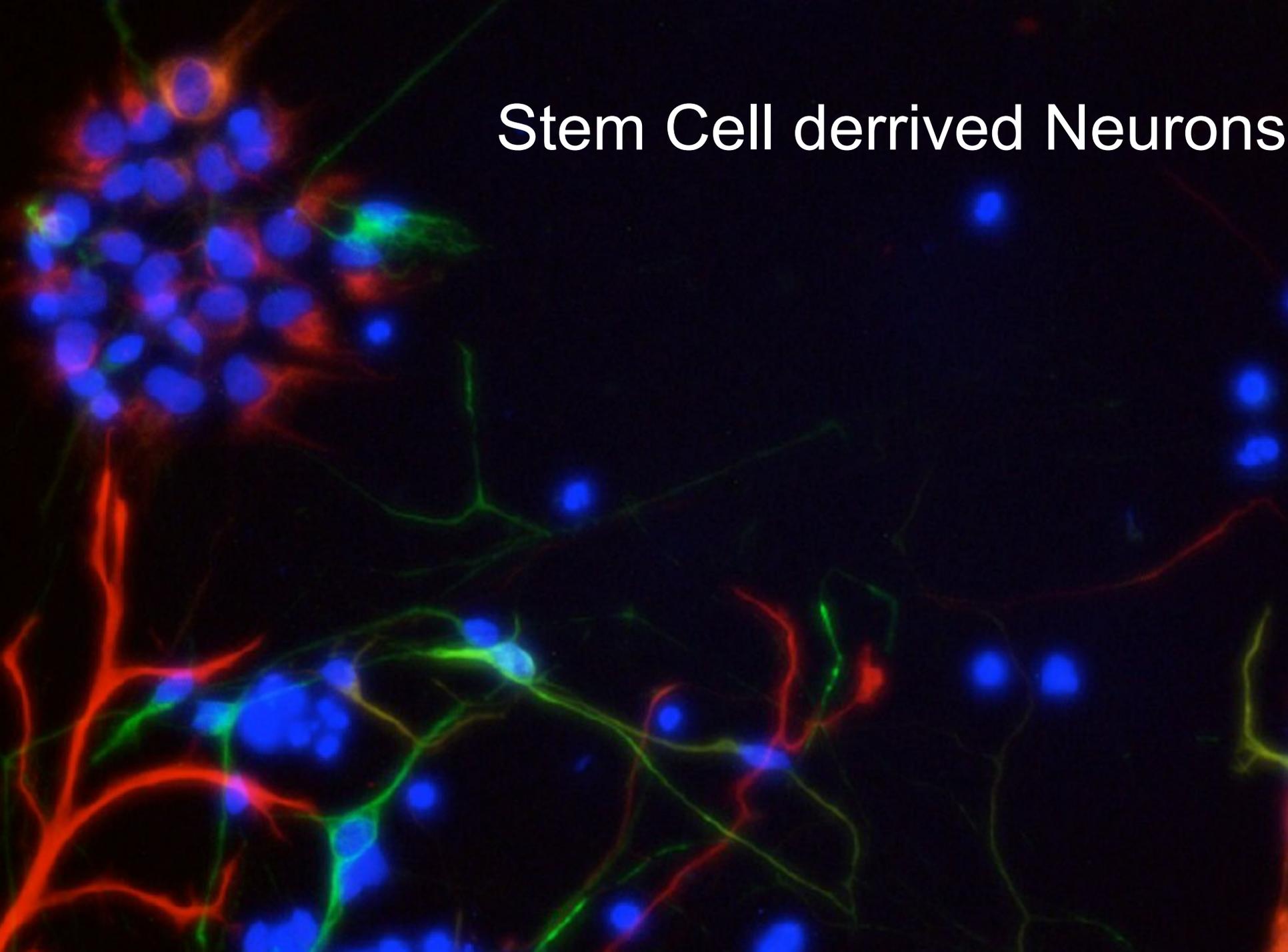
Super-resolved Image

Tubulin filaments in Cos-7 cells

Single-Molecule Localization Microscopy for Superresolution



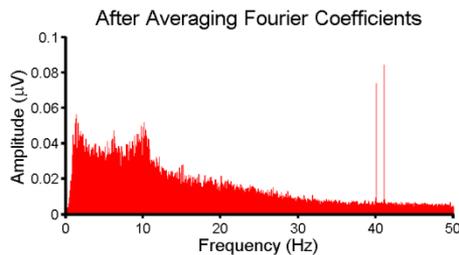
# Stem Cell derived Neurons



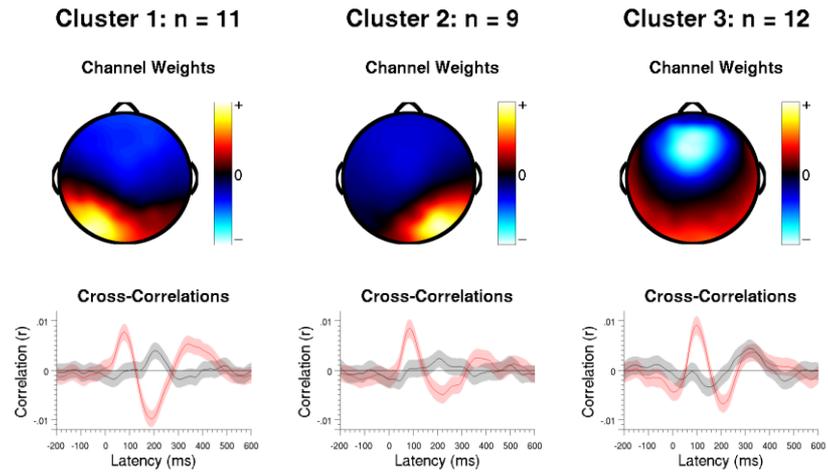
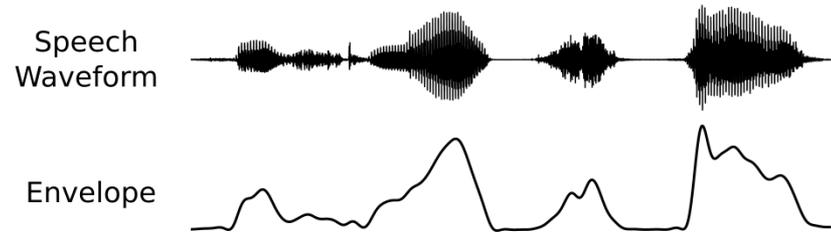
# Sophisticated measures of Brain & Behavior for clinical trials outcomes



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



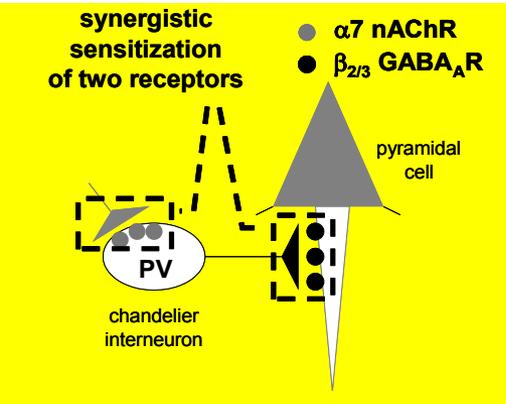
Aim 2: Characterize deficits in speech processing and audio-visual integration



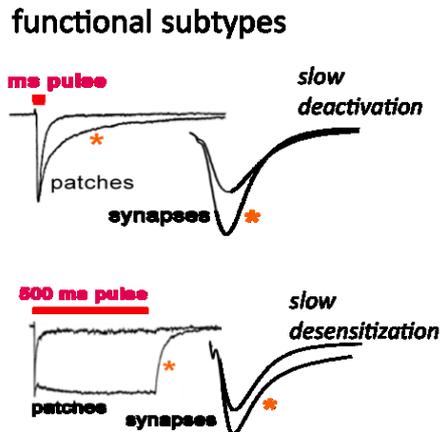
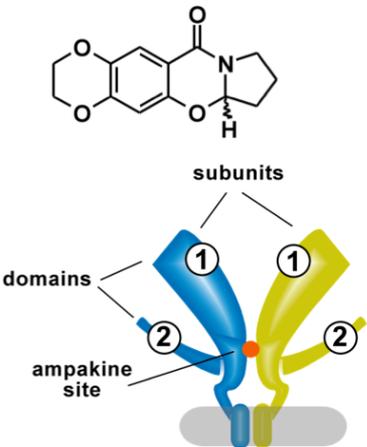
Horton et al., 2013 J Neurophysiology

# Pharma lead compounds

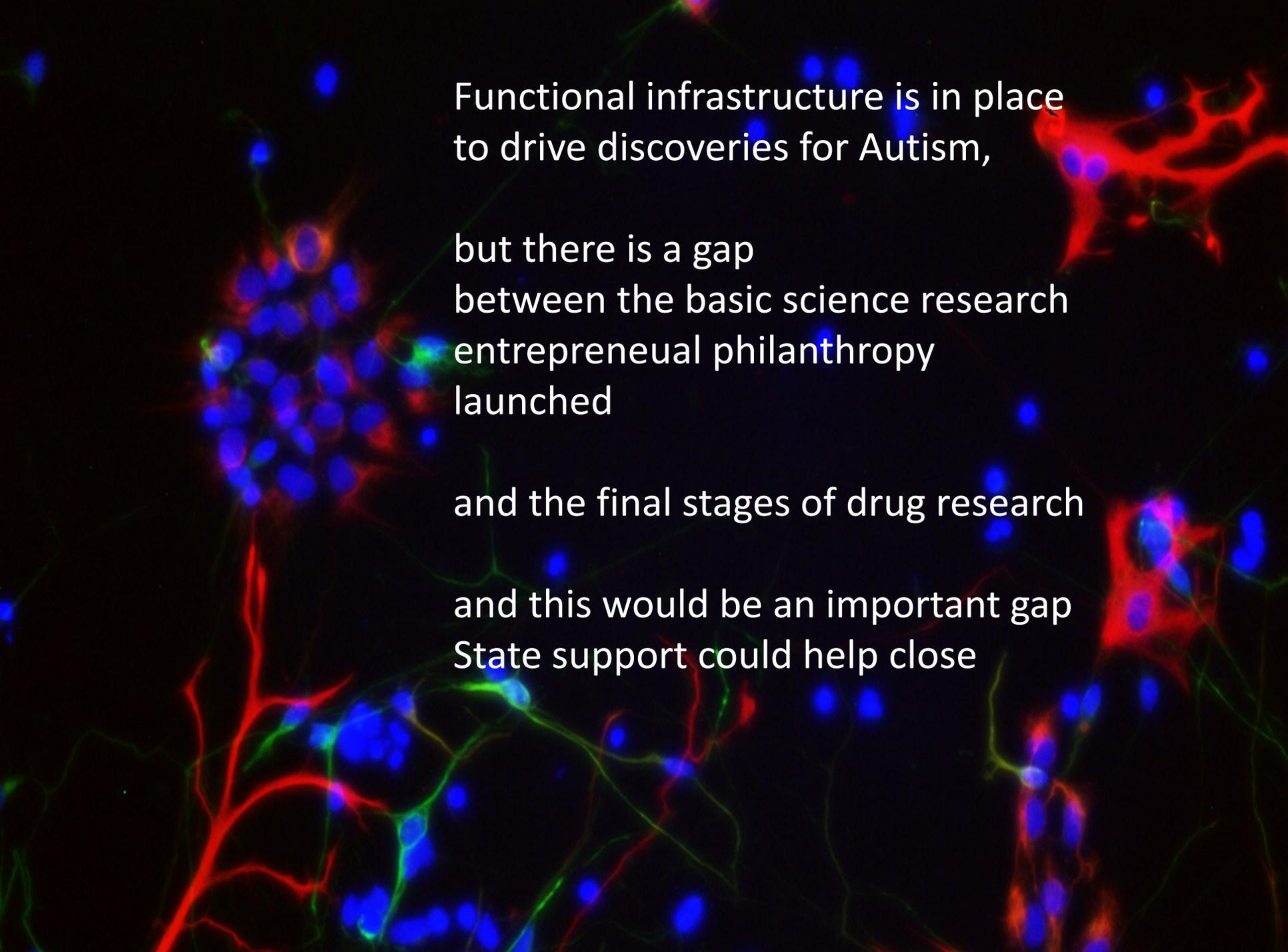
Targeting  $\alpha 7$  nACh and GABA<sub>A</sub> receptors simultaneously ASD



## 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