



# CENTER FOR AUTISM RESEARCH AND TRANSLATION

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UNIVERSITY OF CALIFORNIA, IRVINE • SCHOOL OF MEDICINE

## Why Now? The Need for Complex Research on ASD

Within the span of just two generations, Autism Spectrum Disorder (ASD), once considered a relatively rare condition, has leapt onto our radar as the fastest-growing serious developmental disability in the U.S. and an urgent national public health concern. Over the last 40 years, we have seen a *more than twentyfold increase* in ASD prevalence rates. Today, **1 in 88** children in the U.S. are on the ASD spectrum, a figure that cuts across all racial, ethnic, and socioeconomic groups.<sup>1</sup> And since boys are more likely to be affected than girls, a staggering **1 in 54 boys** live with ASD in the U.S. today.

With increased numbers and consequent costs, communities are now experiencing the impact of the disorder. While the causes of ASD are largely unknown, what is absolutely clear is that its recent upsurge demands action. The human cost of ASD – the everyday struggles of children and their families – demands a solution. This is where UC Irvine's **Center for Autism Research and Translation (CART)** is stepping up to the challenge – **because research holds the key to a solution.**

As the regional partner dedicated to developing the first transformative treatment of autism, CART has the approach, method and tools to make it happen; targeting novel compound clinical trials by 2015.

**The Approach.** The traditional model for developing treatment – finding the cause of a disorder and then addressing it – has actually become a roadblock to developing effective treatment for ASD because ASD has no

single known cause; the condition is caused by a complex combination of genetics and environmental factors, which are different for different individuals. However, recent successes in related fields have shown us that instead of trying to address “the cause,” a moving and multidimensional target, we can instead focus on the way ASD affects the biological network. This innovative approach allows us to make progress by finding key points of leverage against ASD, identifying important biomarkers and common biological pathways by which the disorder manifests and focusing treatment efforts on normalizing those pathways.

**The Method.** CART's method is to combine the deep understanding afforded to us by world-class basic science research with the practicality of real-world, results-driven objectives – to make a difference in patients' lives. In pursuit of that goal, we have facilitated unprecedented integration across disparate disciplines, from the lab bench to the bedside and back.

**The Tools.** Technology has now made it possible to transform these insights into a clinical reality. Our innovative use of high throughput biological screens and behavioral assays has already resulted in bringing potential ASD therapies to preclinical and clinical testing. Within the next three years, the combination of innovative research and high-level technology will make it possible either to design drugs or repurpose existing drugs to normalize malfunctioning pathways, setting the stage for clinical trials to effectively treat ASD.



<sup>1</sup>U.S. Centers for Disease Control and Prevention (CDC). 2012

## A World Apart – Living with Autism

What does it mean when a child faces a diagnosis of autism? Fundamentally, ASD is a complex developmental disability that affects an individual's ability to communicate and interact with others. But the answer to the question is complex – as complex as the biology behind the disorder itself – given that ASD is a “spectrum disorder” that affects individuals differently and to varying degrees. Living with ASD has been described as living in “a world apart,” where an individual's inner world is separate and disconnected from the external. For high-functioning individuals, connection to others can be difficult; when autism is severe, the disconnection is nearly complete.

Since there is no blood test that can determine if a child has ASD, in-depth interviews and observation are utilized for evaluation and diagnosis. Symptoms of ASD vary from one child to the next, but in general they fall into three areas:


- **Social impairment** – Children with ASD often appear disinterested or unaware of what's going on around them. They make little eye contact, can fail to respond to other people, do not readily share their enjoyment of toys or activities by pointing or showing things to others, and respond unusually when others show anger, distress, or affection. They may have difficulty making friends, understanding other people's feelings or social cues, and prefer to be alone.

- **Communication difficulties** – Children with ASD develop language at a delayed pace and may use language in unusual ways not associated with communication. For example, many speak only in single words or repeat certain phrases over and over, seeming unable to combine words into meaningful sentences. Even children with ASD who have relatively good language skills often have difficulties with conversation. They may display unusual or inappropriate body language, gestures, and facial expressions that do not match what they are saying.

- **Repetitive and obsessive behaviors** – Children with ASD are often obsessive in behaviors. This may include repetitive or constant body movements such as rocking or spinning. Similarly, these children may have a preoccupation with a specific topic of interest, often involving numbers or symbols like license plates and signs. Commonly, they exhibit a strong need for sameness, order, routines and may get upset by change in their activities or environment.



ASD is often thought of as a childhood disorder, since symptoms typically appear during the first three years of life, but it's a disorder that will actually affect individuals throughout their lifetimes. Behavioral therapy has come a long way and early diagnosis can make a difference but to varying degrees, autism can deprive patients and families of meaningful interaction and the joy of human-to-human connection which is so fundamental to our lives.



## The Cost of Autism

Autism Spectrum Disorder (ASD) costs over \$130 billion dollars in the United States alone each year.<sup>2</sup> This figure includes insurance costs and non-covered expenses, Medicaid waivers for autism, educational spending, housing, transportation, employment, in addition to related therapeutic services and caregiver costs. It does not take into account the growing number of individuals with ASD and the resulting pressure on our nation's health system for ASD services, the increased costs of services, and the competition for the limited funding available for services. In aggregate, the annual cost of ASD is only expected to rise, making the total cost to our society astronomical.

But the cost of autism is no less overwhelming to the individual families caring for relatives and children with ASD. Behavioral therapies for children can cost \$40,000 to \$50,000 per year, while caring for an adult with autism in a supported residential setting can cost \$50,000 to \$100,000 per year. Estimates put the lifetime costs of care for an individual with autism at \$3.2 million.

Even beyond the lifetime costs of care, the burden on families affected by autism is enormous. Parents have been known to relocate their families to states where benefits for children on the autism spectrum are better. Even today, many families are denied insurance coverage for essential treatments and services, and parents must often pay for educational and therapeutic services out of their own pockets because public schools cannot provide adequate services. Some parents must give up working to provide in-home therapies for their children, placing further economic stress on families reduced to one income.

Because ASD can be so overwhelming to a family, we as a nation have begun to bear witness to the very personal cost – parents' anxieties played out on television talk shows, chasing false hope offered by pseudo-science, desperately looking for a way to connect with their children and a cure to something inexplicable. Fortunately, we now have reason to be optimistic; ASD research is entering a new era, on the verge of being able to offer to patients and families ASD therapies that work.

### THE CURRENT STATE OF TREATMENT

*Within the lifetime of an individual with ASD, many costly medical or behavioral interventions may become necessary for the patient and the family.*

*Medical interventions are those that attempt to focus on the physical needs of the person, addressing seizures or potential genetic or biochemical deficits by medical means.*

*Behavioral treatments can include early intensive behavioral intervention by a team of professionals; these interventions may involve a child's entire family. In some early intervention programs, therapists come into the home to deliver services. Ongoing psychology services and evidence-based treatments, psychiatry services, occupational therapy, physical therapy, and nutrition, speech, and language counseling are also utilized.*

*Additionally, many families choose to pursue therapies that can include diet, nutritional and vitamin management.*

*It is important to remember that each person with autism is unique and may respond better to some treatments than others. Therefore, treatment plans are individually tailored, time consuming, and costly. All good programs share certain features such as highly trained providers, consistency, flexibility to change as the individual ages, and a multidisciplinary focus.*

## A Race for Treatment and Cure

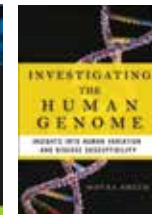
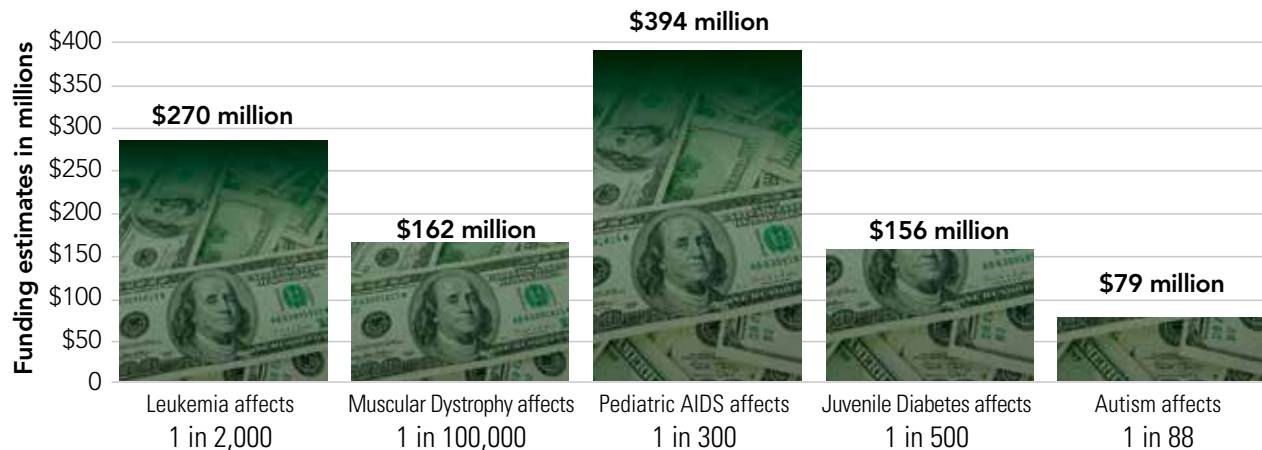
The need for ASD treatment and services is significant and growing. Estimates predict that, even if no new instances of autism occurred starting today, by 2030 the number of adults with ASD who would potentially turn to the human services delivery system for services and/or support would be 500% higher than it is today.<sup>3</sup>



**Ian Smith, PhD**  
Associate Professional  
Researcher, Neurobiology  
and Behavior; Director  
Cell Imaging Core, CART

Some of the increase in ASD prevalence is due to better and earlier detection of autism, which experts say is also critical for successful treatment. This has come about through better definition of what autism is, increased awareness about the disorder, and clearer understanding that it manifests as a spectrum – so some “high-functioning” individuals are now getting the help they need. However, a second result of this progress is a larger population identified as “at-risk” and in need of specialized support. With increased early detection capabilities, the number of children diagnosed with ASD is expected to increase dramatically.

Even with the alarming statistics and a new awareness about the condition, funding for autism research trails far behind other privately-funded endeavors, especially when rates of U.S. prevalence are compared<sup>4</sup>:



*“My work in CART is inspired by the conviction that through understanding the underlying functional changes that lead to autism, we can devise therapeutic approaches that lead to improvements, enhance abilities of children and their capacity to lead full and happy lives.”* – Moyra Smith, MD, PhD

Co-Director Genomics Core, CART, Professor Emeritus of Human Genetics and Pediatrics

While National Institutes of Health and private foundation grants will continue to play a critical role in funding autism research going forward, we at CART clearly could not have launched such an aggressive campaign without a visionary philanthropic investment and will not be able to sustain our path without ongoing support from the community.

Indeed, our efforts going forward must be highly integrative and entrepreneurial in design as we attempt to duplicate the success of the March of Dimes, a privately funded research effort that defeated another dread disease – polio, and the recent success of the Cystic Fibrosis Foundation. Using these exemplary successes as our models, we at UC Irvine have every hope of duplicating their success and to achieve nothing less than an innovative, research-based cure that has proved so elusive thus far.

<sup>3</sup>Autism Society.

<sup>4</sup>Talk About Curing Autism (TACA). 2013.

## A Unique Collaboration: Turning the Corner on Autism



*“We must stand behind world-class research. This is taking place right now at UC Irvine. Real breakthroughs must start with research that is directed toward novel treatment approaches, and the research team at UC Irvine is distinctively set up to do this. These efforts walk hand in hand with our clinical, educational and advocacy efforts.”*

– William Thompson, Chairman of the William & Nancy Thompson Family Foundation

The passion of a single family led to the collaboration of a group of key Southern California institutions that have joined together to become a catalytic force in implementing progressive research, identifying novel drug candidates, and increasing the availability and quality of services. In January 2013, two grants totaling \$14.8 million from the William & Nancy Thompson Family Foundation and the Children & Families Commission of Orange County (CFCOC) launched the Center for Autism. This center, a new hub of ASD collaboration, treatment and research in Southern California, brings together two of the leading ASD treatment and research organizations in the region; UC Irvine’s Center for Autism Research and Translation (CART) and Irvine’s Center for Autism & Neurodevelopmental Disorders (CAND). These organizations are joined by strong regional partners including Children’s Hospital of Orange County (CHOC) and Chapman University in important work that aligns with the UC Irvine Health mission: DISCOVER. TEACH. HEAL.

In addition to the incredible support offered by UC Irvine, CART’s initiatives are bolstered by ongoing National Institutes of Health grants and its faculty’s efforts. Many large pharmaceutical companies have been shutting down their brain-based research branches in recent years due to failures in translating research from mouse behavior to clinical human disease, making the work CART is pressing forward with all the more valuable. CART’s team of researchers is taking a new innovative approach to autism research, and is seeking a creative integrative method to discover novel molecules to treat those with autism. As commercial partnering opportunities emerge, they will be carefully vetted to assure they advance the mission of the Center.

### Together, the Center for Autism partners aim to:

- 1) Lead research into the discovery of novel, effective diagnostics and treatments for ASD, an integrative capability that we feel is unmatched in academia, the government or industry.
- 2) Implement state-of-the-art diagnosis and treatment for children and families with ASD.
- 3) Support education and training at all levels to meet medical, therapeutic and educational needs of such children, including community outreach and advocacy.

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

*The vision of CART is to abolish current and future burdens of autism through discovery and implementation of novel care, so that not a single child is lost to autism.*

In pursuit of this vision, we have brought together the partners and the research team who can make a difference, combining cutting-edge discovery and top-notch research methodologies with real-world clinical goals. Our team is comprised of more than 50 distinguished UC Irvine faculty members – world-class molecular geneticists, biophysicists, neurobiologists, behaviorists, pharmacologists and clinical researchers – many brought into this field because of CART and others previously engaged in the study of autism, all collaborating to develop novel, effective diagnostics and treatments for autism.

We are doing this by defining critical signaling pathways in ASD, thereby identifying key molecular biomarkers and targets for new and repurposed drugs. CART's molecular-to-clinical drug discovery platform means that comprehensive research ranges from the levels of genomic identification, to molecular composition, through generation of cellular signals and cell-to-cell communication systems, to brain function and ultimately objective clinical trials involving innovative technologies and behavioral outcomes.

The role of CART is particularly important today since major pharmaceutical houses have abandoned novel molecule discovery for neuropsychiatric disorders because their paradigm of behavioral testing for relief of symptoms proved unreliable for finding molecules that treated the human disease. In contrast, CART has developed a step-by-step set of overlapping techniques anchored to the causal genetic lesions in ASD to assure that when we reach behavioral assays we are securely anchored to the core human disease pathophysiology. Our enhanced ability to determine how and where experimental compounds act on the molecular mechanisms of the brain causing the disease is a unique strength of CART.

CART sits on the cusp of comprehending the genetic architecture of ASD, and are prepared to target this lesion much as the Cystic Fibrosis Foundation targeted the causal lesions in that disease, not merely the symptoms.

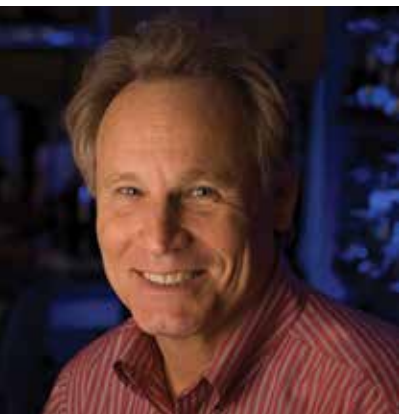
We recognize that our program is exceedingly ambitious and requires both novel technologies and unprecedented integration across disparate disciplines. CART is dedicated to beginning clinical trials of a novel compound in three years in the hope of developing the first transformative treatment of autism.

### Key Leadership



*The Director of CART is Dr. John Jay Gargus, MD, PhD, Professor, Physiology & Biophysics and Professor, Pediatrics, Human Genetics at the UC Irvine School of Medicine. Dr. Gargus, a well-published author in the field, received both his MD and PhD from Yale University. His research interests include functional genomics approaches to ion channel candidate genes in common complex polygenic disease, and the molecular pathophysiology of inborn errors in signaling, placing a heavy reliance upon function. Dr. Gargus was selected to head CART for his conceptual approach to the disease and his abilities to organize and inspire the team of researchers across the collaborative efforts of the Center.*

## CART Philosophy and Goals



***“CART provides a strong platform for our Chemistry Department research in breath gas analysis to interact with a variety of areas of autism research that wouldn’t be available otherwise.”***

– Donald Blake, PhD  
Professor, Chemistry & Earth System Science, School of Physical Sciences, Metabolomics Lead Investigator, CART

Autism research is positioned to benefit from recent discoveries in the study of cancers and certain neurological diseases such as seizures. These are complex diseases in which a dual track of causation has been recognized. In some instances, individuals have the disease on a genetic basis. Others appear to have the condition because environmental stressors (chemical, physiological, and psychological) interact to provoke the disease, but in most cases there is the interaction of both components. In ASD, researchers have recently found important genetic bases including mutations in single genes clustering in specific biological pathways, the likely final common pathway involving deficits in the signaling communication between brain cells. These defects result from malfunction of numerous processes influenced both by the genes themselves and by environmental stresses acting through these genes.

CART deploys systematic research into the mutated genes and their encoded proteins that cluster in these cellular signaling pathways of the brain to render them tractable targets for transformative drug discovery aimed at the root cause of the disease process. Just as with cancer research over the past decade, and using an approach very similar to that recently successful with cystic fibrosis, it is now possible to determine how the malfunctioning genes affect the common pathways of neuronal communication implicated in ASD. With this gene-focused pathway perspective, the CART research approach seeks to study how a number of insults from the environment can further influence the path towards ASD.

Once that is understood, it will be possible either to design drugs or to re-purpose existing drugs that should normalize those pathways, and to design and carry out high-throughput cellular screens to test for this molecular effect. The successful screen assays would thereby be rendered a “biomarker surrogate.” As such, they represent a dependable objective molecular surrogate replacing the subjective complex assay of behavioral abnormalities of the disease, and are themselves clinically useful. Furthermore, drugs that can normalize the bioassay screen on an ASD sample become promising clinical trial candidates for normalizing the brains and behaviors of those with autism.



***“With funds from CART we are establishing shared microscope facilities with the goal of mapping brain network disturbances associated with autism and, using animal models, to test if candidate therapeutics can normalize these activities.”***

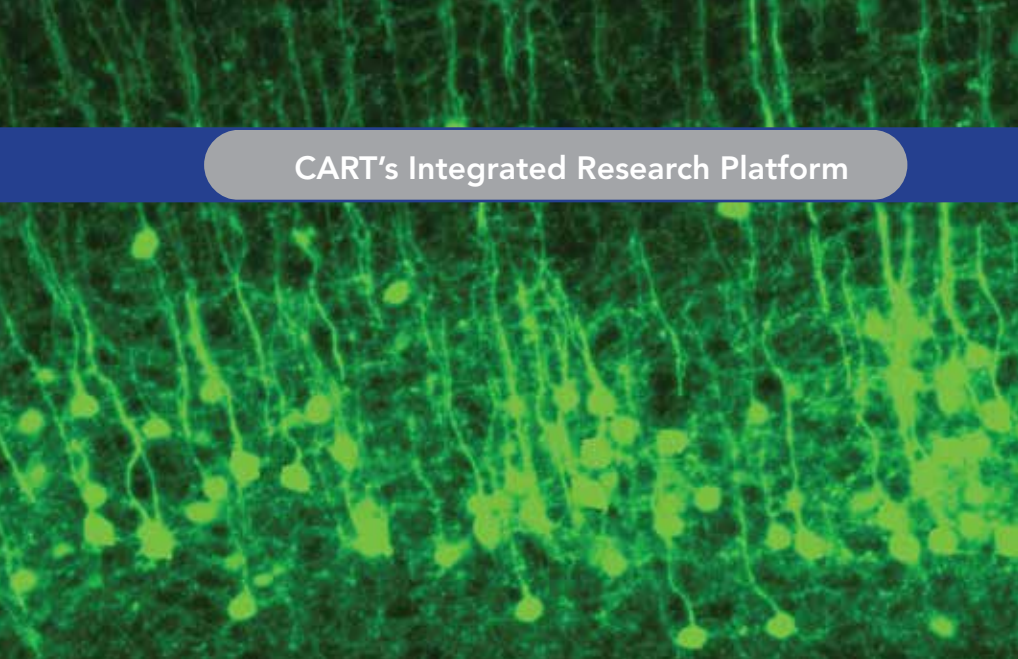
– Christine M. Gall, PhD  
Professor Anatomy & Neurobiology  
Co-Director, Synapse Core, CART

***“CART is dedicated to using the power of interdisciplinary research to discover innovative ways to help children and adults who have autism spectrum disorders. The synergy and creativity that come from collaborative investigations such as those under the CART umbrella are positioned to make incredible breakthroughs.”***

– Wendy A. Goldberg, PhD  
Professor & Vice Chair, Psychology & Social Behavior, Co-Director of the Clinical Trials Outcome Measures Core, CART



## CART's Integrated Research Platform

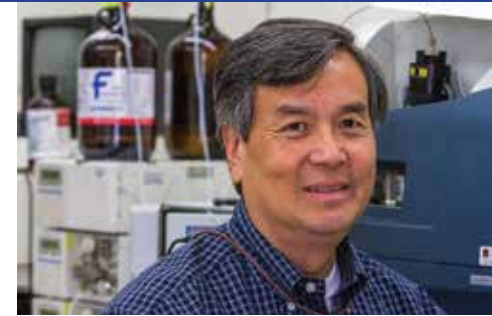


*Fluorescent cortical neurons in a genetically engineered mouse model of Fragile X syndrome is used to assess dendritic spine defects and effects of treatments. (Lauterborn and Gall)*

In order to access and explore the potential of new therapies, CART has assembled multidisciplinary expert teams to identify abnormalities and correct defects that generate the disease. CART's research teams are organized in three research orientations each contributing to the advancement of overall understanding and treatment of the disease. The Core Labs offer cutting-edge new major equipment, key biological resources and technology facilitators to provide all CART investigators the tools they need to aggressively move their science into ASD research. The Seed Grants cluster synergistic teams of researchers into specific projects that rely upon the key capabilities of the Core Labs. The Pharma leads are tested at all of the levels of complexity reflected in the Core Labs.

### **CORE LABS**

Many complex and expensive new technologies and scarce biological resources, such as model mutant or genetically-engineered cells or animals, are required to conduct state-of-the-art ASD research. Rather than having each CART investigator so burdened, a Core Lab,



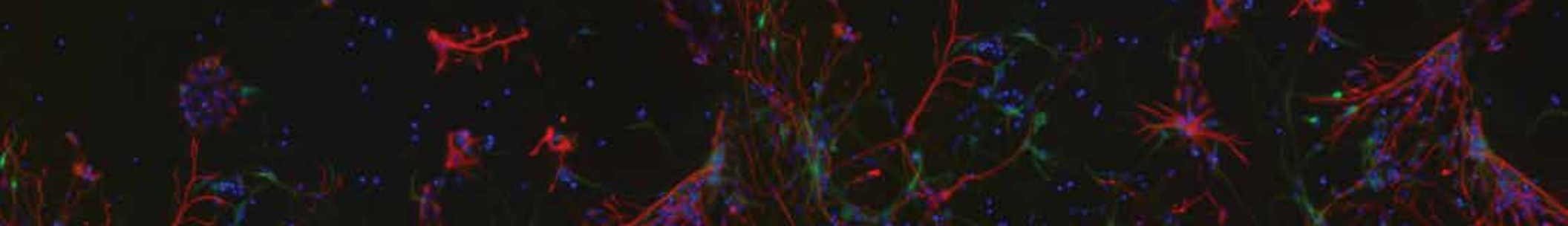
***“The more disciplines you can get under one roof, the more light bulbs you get to turn on. I think it’s great!”***

**– Kelvin W. Gee, PhD, Professor, Pharmacology,  
One of three Pharma Lead Investigators, CART**

under the direction of national leaders in the concepts and technology, houses, cares for and staffs these integrated resources. This allows all CART investigators and projects ready, user-friendly access to these sophisticated capabilities for their own work and readily allows robust addition of new dimensions of research to each project.

### **Genomics Core**

The key resources found in this core are Whole Genome Sequencing (WGS) of very well characterized ASD subjects and their families including their cell lines, serum and DNA, and a database that extends back 15 years with results from brain imaging and genetic and biochemical tests. The core also contains super-computers and analytical programs for handling vast amounts of data. Research is conducted to uncover patterns of gene dysfunction in patients by conducting an in-depth gene sequencing of all of their genomic information with state of the art techniques. The goal is to identify pertinent malfunctioning genes shared by subsets of patients who have shared database features, perhaps dissecting out subtypes of ASD.



*In the image, the green highlights mature motor neurons; red, immature; blue nuclei (more specifically the DNA) of cells. (Keirstead)*

### **Cell Signaling Core**

Research using Stochastic Optical Reconstruction Microscopy (STORM) imaging is conducted to determine cell biological consequences of malfunctioning genes. This super resolution form of microscopy on living cells achieves the resolution previously only obtained on dead tissue with an electron microscope. This technique allows single protein molecules and spreading waves of calcium signals to be followed in live, responding cells and neurons. The core also subcontracts a commercial FLIPR high-throughput screening instrument that relies upon similar fluorescent dye indicators to resolve cell signaling and screen potential drug candidates. Cell lines for key single-gene models of ASD from man and mouse are carried in this Core.

### **Synapse Core**

Synapses are the connections between brain cells. Research is conducted to test which aspect of brain cell communication is affected by a given autism-related gene or environmental stressor. It uncovers a finite set of anatomical and biophysical defects in brain cell processes that are the substrata for memory and social functions affected in ASD. These defects are the candidate biomarker diagnostics of the disease and candidates to be screened for the utility of novel drugs to treat autism. Mouse strains engineered to carry key single-gene models of ASD are carried in this core.

### **Stem Cell Core**

An incredible opportunity to bridge between our mouse models of ASD, where we can study single cells but also cell-to-cell communication in brain slices that preserve the natural brain architecture, is provided by cutting-edge stem cell technology made available to all CART investigators via this core. Taking advantage of genetic engineering techniques, skin or blood cells from our genome-sequenced subjects can be first converted into stem cells (iPSC) and then differentiated into

brain neurons. This gives us an incomparable ability to cross-correlate defects identified in the mouse models with those we can see in genuine human cells from subjects with ASD on whom we have detailed phenotypes including behavior. Stem cells and iPSC-derived neurons are carried in this core from a variety of rare conditions such as Fragile X syndrome, Angelman syndrome, and tuberous sclerosis, as well as from individuals with “common” multi-gene ASD (i.e. idiopathic autism) whose genomes have been fully sequenced. These existing human cells or neurons derived from stem cell techniques, such as iPSC, can be compared with established mouse models of rare single-gene forms of ASD. Any compound that offsets the defects in neuronal communication found in all or most of these models will become a candidate for testing in young adults with autism.

### **Optogenetics Core**

This new core provides the ability to use genetically engineered signaling proteins that respond to laser light stimuli to turn on and off neuron activity in culture or inside the brain of a living model animal. This allows exquisite control over brain circuits and is an ideal way to identify key brain correlates of behavior.

### **Brain / Behavior Clinical Trials Outcomes Core**

The central focus of efforts in this Core area is to provide “whole person” research measures that are objective, reliable and valid correlates of ASD behavioral functioning. This core will grow a database of subjects with ASD who will receive key research-grade diagnostic testing, including the Autism Diagnostic Observation Schedule (ADOS) and IQ testing. They will also undergo home-based sleep studies, and sophisticated high-density electroencephalography (EEG) with prototype magnetoencephalography (MEG) as well as a sophisticated metabolomic study of their biochemical profile.

## CART Research Platforms

CART's research core offerings are bolstered by a number of seed research grants to link investigators together in groups with projects that span the capabilities of two or more Core Labs. The three Pharma lead compounds bring the entire discovery platform to life, since these are potential drugs that will be validated across all levels of complexity reflected by the overlapping Core Labs. This synthetic infrastructure in addressing the science of autism is CART's unique strength.



**Hans Keirstead, PhD**  
Professor, Anatomy & Neurobiology,  
Neurological Surgery  
Director, Stem Cell Core, CART

### PHARMACEUTICAL RESEARCH

A natural result of the interdisciplinary cooperation at CART is the discovery, development and validation of drug therapies with potential to fundamentally alter the treatment of ASD. Our research labs are focused on analyzing the root deficit of ASD at overlapping progressive levels of complexity. This entails identifying malfunctioning genes in typical ASD, understanding the molecular and cellular consequences of gene malfunction, first from the simple genetic model

ASD diseases of patients and mouse models, but then from typical ASD, and identifying possible biomarkers and drug compounds that can offset the defects in neuronal communication. Our explorations draw together broadly based holistic data across various research and clinical disciplines with the potential to ensure the awareness of environmental stressors as a dimension of the treatment of ASD. Together CART's research holds great promise for breakthroughs in drug therapy unmatched in academia or commercial pharmaceutical houses.

Thus far, four small-molecule lead compounds that show promise for the treatment of ASD are under study at CART. Two of these drugs have already been shown to be safe in people and are undergoing clinical trials for other indications. Each of these compounds is being investigated, both in vitro and in vivo, to confirm its therapeutic potential for ASD. These drugs will be screened with several sophisticated biophysical and biochemical assays, using cellular



*“CART is generating an incredibly exciting pipeline of novel research approaches to autism which inspire us to bring our expertise to bear on the challenge. The support provided by CART is making it possible for us to immediately jump in and explore new ideas.”*

– Sunil P. Gandhi, PhD, Assistant Professor, Neurobiology and Behavior and recipient of the 2013 NIH Director's New Innovator Award



*“CART offers both a concrete link to patients and families who need our research, and to colleagues who share my passion.”*

– Daniele Piomelli, PhD, Professor, Anatomy & Neurobiology and one of the three Pharma Lead Investigators, CART

models based upon the genes implicated in the disease. Each is a novel molecular scaffold known to interact at distinct cellular receptor molecules, that signal through a genetic pathway implicated in ASD. As new discoveries are made, additional compounds will be shifted into pharmaceutical research, a natural follow up and consequence to the underlying science used to pursue the care and treatment of those with ASD.

### SEED RESEARCH

CART's partnership with CAND through involvement in The Center for Autism presents a unique opportunity to have a transformational and lasting impact on autism. Currently the most important “game-changing” research occurs at the interface between traditional disciplines in science and medicine. Such creative high-risk / high-reward approaches are particularly difficult to get off the ground. In order to ensure that such research is given an optimal chance for collaborative success, CART has implemented several Seed research teams that have the advantage of being launched into a project with the help of the Core Labs and CART funding. After one year of support, the expectation is that the seed teams will develop sufficient preliminary data to give a proof-of-principle necessary to attract a nationally competitive research grant, and hence continue to sustain the project without ongoing CART funds.



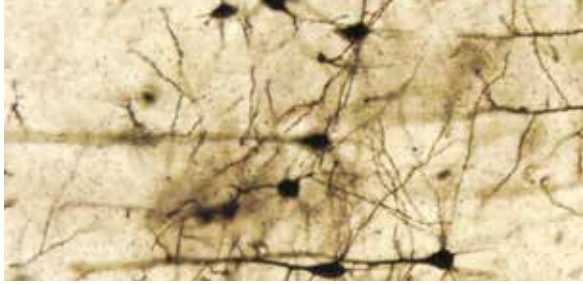
## Getting FDA-Approved Drugs to Market

It is widely believed that the next few years hold great potential for the development of a carefully targeted and more effective treatment that addresses the core defect, not just the symptoms of ASD. Pharmacological breakthroughs hold great potential to allow ASD science to move forward with promising and useful drug treatments. CART offers both the interdisciplinary resources and the depth of research expertise to develop a game-changing drug therapy. The critical CART advantage is that the pathway *causal* of core ASD deficits is being targeted, not merely its less specific downstream symptoms. However, the process to get a drug to market is at best tenuous and there are several phases that must be accomplished before approval.

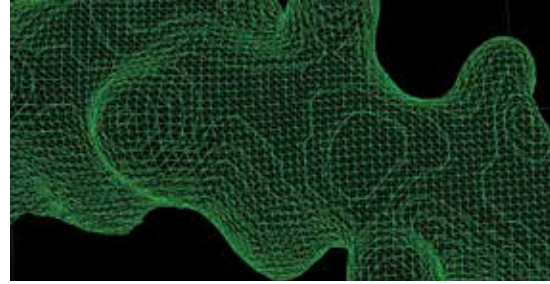
The Food and Drug Administration (FDA) is responsible for assuring that foods and cosmetics are safe and that medicines and medical devices are both safe and effective. This mission requires examining efficacy as determined from well-controlled trials, effectiveness as determined from actual use in uncontrolled settings, and safety for both prescription and over-the-counter pharmaceuticals before approving a medication for market. During the past decade alone, more than 500 new prescription drugs have been approved by the FDA, but only two compounds for ASD, and neither was novel nor more specific for ASD than targeting a symptom of the disease.<sup>5</sup>

*Mapping gene expression to visualize activated brain networks in autism models.*  
(Gall, Lynch and Lauterborn)

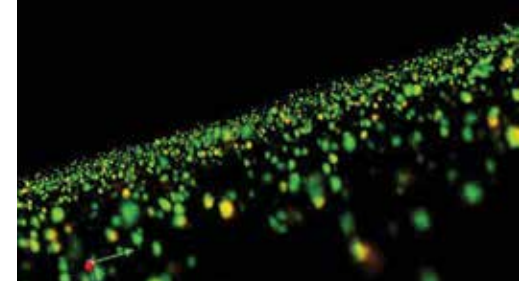
<sup>5</sup> From Idea to Market: The Drug Approval Process, Martin S. Lipsky, MD, and Lisa K. Sharp, PhD.



*Golgi staining shows the structure of cortical neurons in the Fragile X model, and can be used to reveal abnormalities in autism model mice. (Lauterborn)*



*3D reconstruction of a hippocampal dendrite; this method is used to assess effects of therapies on dendritic spines in autism model mice. (Lauterborn)*



*Photograph of synapses between neurons in the brain using procedures that allows labeling. (Gall)*

The drug development process starts with preclinical testing. For drugs that appear safe, an investigational new drug application (IND) is filed with the FDA. This step has come to be called the “Valley of Death”, since it is at this step that most drugs die. A critical goal of CART is to provide the infrastructure that allows a route across this chasm. If an IND is approved, clinical trials begin with Phase 1 studies that focus on safety and pharmacology.<sup>6</sup> Phase 2 small investigator-initiated proof of concept studies examine the effectiveness of the compound.<sup>7</sup> The value of a discovery has greatly appreciated by this point, and this is certainly as far as CART could progress without a commercial partner. Phase 3 is the very costly final step before submitting a new drug application (NDA) to the FDA.<sup>8</sup> An NDA contains all the information obtained during all phases of testing. Phase 4 studies, or post-marketing studies, are conducted after a product is approved during general use of the drug by medical practitioners.

On average, it can cost a company about \$1Billion to develop a new drug from the research lab to the patient and takes an average of 12 years.<sup>9</sup> CART, as a university institution, has a unique position in which it can partner with businesses at any point during the development phase to either work in partnership, license the intellectual property, or sell its discoveries.

Once a diagnostic test is developed, there is an opportunity for UC Irvine and CART to create an incubator partnership at which

point a technology transfer can be conducted. This incubator could then independently continue to develop the drug.

### **Subsidy for Clinical Services**

An essential advantage of the Center for Autism is the partnership of a cutting-edge entrepreneurial research center, CART, with a broad-based large clinical diagnosis and treatment center, CAND. The patients of CAND provide the essential inspiration to the investigators for their work, and benefit from the ability to participate in the clinical trials, while the work by the CART investigators continues to offer the families of CAND hope for progress towards state-of-the-art diagnostics and treatments. One of the key benefits of this partnership within the Center for Autism is the opportunity to build clinical and research capacity and at the same time develop a shared source of income for both CART and CAND. As third parties invest in CART, either through philanthropy or to partner in the development of a drug lead or clinical trial or to license a diagnostic test or technology, a valuable portion of that investment needs to help sustain the work of CAND in support of assessment, diagnosis, care coordination, family support and education for children with ASD and other neurodevelopmental disorders. Major success in drug discovery could provide an ongoing subsidy for CAND clinical services to children and families challenged by autism and related neurodevelopmental disorders, at the same time supporting these services that are essential to the current and ongoing function of CART and that enhance its value to its supporting community.

<sup>6</sup> Phase 1 examines the pharmacologic actions and safe dosage range of a drug; how it is absorbed, distributed, metabolized, and excreted; and its duration of action.

<sup>7</sup> Phase 2 controlled studies in volunteers to assess the effectiveness of a drug. Simultaneous animal and human studies can continue to examine further the safety of the drug.

<sup>8</sup> Phase 3 testing using a greater number of volunteer patients. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and determine low-incidence adverse reactions.

<sup>9</sup> Pharmaceutical Research and Manufacturing of America.

## Supporting a Transformative Vision

The pursuit of an effective therapy for Autism Spectrum Disorder (ASD) is possible both because of the talent and focus of UC Irvine's research and clinical faculty and because of the philanthropic vision for a permanent center to support in the health and wellbeing of Orange County families who are living with autism. The time for action is now.

As a coalition of researchers from many departments, we are addressing complex issues related to ASD across discipline boundaries. Together, we have a chance to leverage our efforts and embrace new strategies. We have in our sights the first real possibility for effective patient care based in an interdisciplinary, scientific understanding of the conditions and causes of the autism spectrum disorder, not merely its symptoms. All we need is the means and the will of the community to get us there.

Beyond the science, beyond the community imperative, beyond the clinical outreach, our success can substantially address the real cost of autism on our communities, on our families, and on our children struggling to communicate with their world.



**Join us in support of this ASD research effort!**

**Together we can advance both understanding and care.**

**For more information on the CART vision and ongoing research activities, call 949-824-3484**

**or visit our website at: [www.autismresearch.uci.edu](http://www.autismresearch.uci.edu)**

## CART External Advisory Board

*Comprised of distinguished leaders in the science and autism communities, this board provides guidance to CART.*

### **Margaret Bauman, MD**

- Pediatric neurologist and research investigator who has been a pioneer in the study and treatment of autism
- Associate Professor of Neurology, Harvard Medical School
- Founding Director, LADDERS Program
- Mass General Distinguished Scholar, Lurie Family Autism Center for Children

### **Uta Francke, MD**

- Leader in the field of model mechanisms of autism such as Rett and Prader-Willi syndromes
- Past President, American Society of Human Genetics
- Senior Medical Director, 23andMe
- Professor Emeritus of Genetics and Pediatrics, Stanford University School of Medicine
- Recipient of the Allan Award

### **Gregg Mashberg, Esq**

- Partner and co-head of the Securities Litigation & Enforcement Group and former Chair of the Litigation Department of Proskauer, an international corporate law practice

### **Paul Negulescu, PhD**

- Biotech expert who led recent successful cystic fibrosis drug discovery
- Vice President of Research at Vertex

### **Jonathan Shestack**

- Co-founder, Cure Autism Now
- Member, NIH Internal Autism Coordinating Committee

### **Gabriel Vargas, MD, PhD**

- Executive Medical Director & Neuroscience Therapeutic Area Head, Early Development at Amgen

## CART Research Advisory Board

*The Director chairs the Research Advisory Board (RAB), composed of five eminent scientific leaders at UCI who have great expertise in the various elements critical to the Center. They will periodically provide the Director with objective and non-conflicted evaluations for funding and assessment of research progress.*

**Michael Cahalan, PhD**, a distinguished biophysicist and member of the National Academy of Sciences (Chair and Professor, Physiology & Biophysics, School of Medicine)

**Olivier Civelli, PhD**, a distinguished academic neuropharmacologist and prior Vice President of Roche (Chair and Professor, Pharmacology and Eric L. and Lila D. Nelson Chair in Neuropharmacology, School of Medicine; Developmental & Cell Biology, School of Biological Sciences; Pharmaceutical Sciences, College of Health Sciences)

**Marc Lerner, MD**, an expert in diagnosis, education issues and treatment and clinical trials in neurodevelopmental disorders (Professor Emeritus, Pediatrics, School of Medicine and Medical Officer, Orange County Department of Education)

**Larry Marsh, PhD**, an expert in imaging, molecular genetic mechanisms of disease and drug discovery (Professor, Developmental & Cell Biology, School of Biological Sciences; Director, Developmental Biology Center, School of Biological Sciences)

**John Weiss, MD, PhD**, an expert in excitatory neuroreceptors and plasticity and a clinical neurologist (Professor, Neurology and Anatomy & Neurobiology, School of Medicine)



CENTER FOR AUTISM RESEARCH AND TRANSLATION

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