ALZHEIMER'S DISEASE TRANSLATIONAL CENTER FOR PREDICTIVE DRUG DEVELOPMENT

OPEN SOURCE, OPEN ACCESS, OPEN OPPORTUNITY TO CURE ALZHEIMER'S DISEASE

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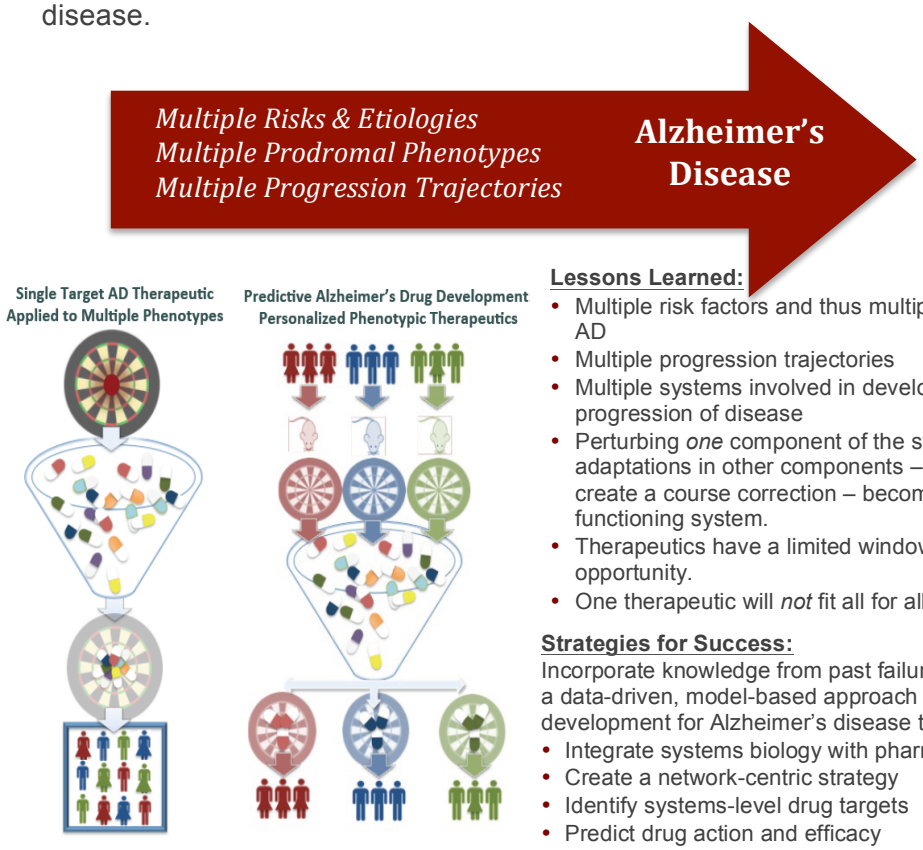
1. A NEW APPROACH TO A GROWING CRISIS

Alzheimer's disease has reached epidemic proportions both in the United States and globally. The nation and the world urgently need therapeutics to prevent, delay and treat Alzheimer's as the epidemic continues to grow with the global aging population. The devastating toll of this disease on those affected and their families is mirrored in the societal and economic impact, which will require an estimated $1.2 trillion by 2050.

Despite substantial research and development investment in Alzheimer's, effective therapeutics for the millions of patients with this debilitating disorder remains elusive. In a shift away from outmoded and ineffective "one-gene, one-receptor, one-mechanism" strategies of drug development to an interdisciplinary, multilevel systems approach, the National Institute on Aging (NIA) is soliciting Alzheimer's Disease Translational Centers for Predictive Drug Development to implement a "quantitative systems pharmacology" (QSP) approach that emphasizes big data informatics, computational modeling and integrated multi-scale analysis.

Under the leadership of Dr. Roberta Diaz Brinton, Cure Alzheimer's Disease (CURx-AD), an Alzheimer's Disease Translational Center for Predictive Drug Development, unites experts in big data, bioinformatics neuroimaging, genomics and metabolomics, systems biology, neuroscience, structural biology and drug development, predictive cellular and animal discovery models, regulatory science, health policy all united to achieve one overarching aim: development of precision therapeutics that target each stage and phenotype of Alzheimer's disease.



Lessons Learned:

- Multiple risk factors and thus multiple etiologies of AD
- Multiple progression trajectories
- Multiple systems involved in development and progression of disease
- Perturbing *one* component of the system induces adaptations in other components – does *not* create a course correction – becomes a different functioning system.
- Therapeutics have a limited window of opportunity.
- One therapeutic will *not* fit all for all patients.

Strategies for Success:

Incorporate knowledge from past failures and create a data-driven, model-based approach to therapeutic development for Alzheimer's disease to:

- Integrate systems biology with pharmacology
- Create a network-centric strategy
- Identify systems-level drug targets
- Predict drug action and efficacy
- Enable open source, open access, open opportunities

FIGURE 1: PARADIGM SHIFT from single therapeutic target applied to heterogeneous phenotypes to personalized phenotype-selective therapeutics

PUBIC PRIVATE ENTERPRISE PARTNERS

Capitalizing on the collective expertise, insights and resources of public-private partnerships is critical to achieving the goal of curing Alzheimer's.

CURx-AD industry and public institution partners will impact strategic and tactical decision making to accelerate therapeutic discovery and development.

Shared Vision

Shared Success

2. HARNESSING ENGINES OF INNOVATION

CURx-AD aims to be the preeminent center for translational Alzheimer's research, harnessing engines of innovation across multiple domains to foster innovative treatments. The center will also serve as a valuable international resource for other researchers across the public sector and in private enterprise who are contributing to the fight against this disease.

The CURx-AD team has focused on development of human capital through the recruitment of an exceptional group of investigators from multiple fields who are proven innovators at the interfaces of medical discovery and big data. Our efforts — along with those of leaders who will partner with CURx-AD in the future — will transform the field of Alzheimer's drug development.

The CURx-AD research strategy:

1. Achieving a systems-level understanding of the complex pathophysiology and phenotypes related to Alzheimer's
2. Converting human genetic data into mechanistic systems for targeted therapeutics
3. Establishing links between peripheral biochemical changes and brain function to develop blood-based biomarkers
4. Rapidly and widely sharing new data via web-based resources

We plan to address critical knowledge gaps to accelerate the discovery and delivery of safe and efficacious treatments for Alzheimer's patients at all stages of the disease. Our vision is to create a portfolio of highly effective therapeutics personalized to each patient's needs and specific to each phase and etiology of Alzheimer's.

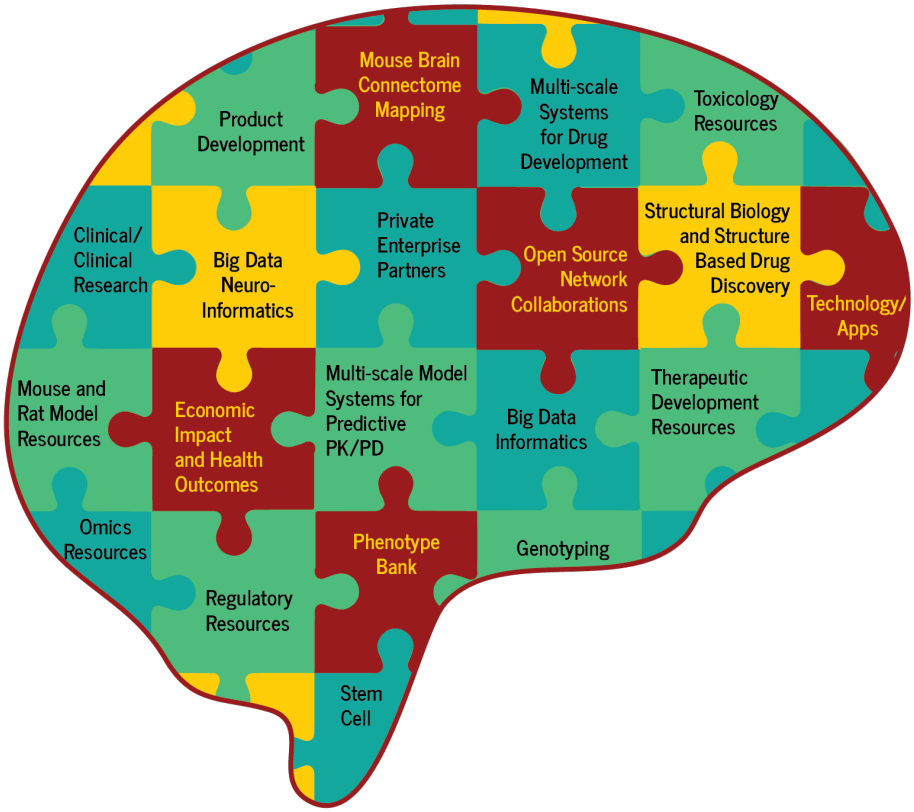


FIGURE 2: HARNESSING EXISTING ENGINES OF INNOVATION – CURx-AD areas of expertise

A. BIG DATA

SYSTEMS BIOINFORMATICS

CURx-AD will extend the reach and complexity of bioinformatics analysis, specifically targeting varied phenotypes of Alzheimer's. Channeling the full power of big data and biomedical knowledge will enable implementation of quantitative systems pharmacology and multi-scale modeling to achieve predictive, precision medicine and improve the high attrition of new chemical entities to treat Alzheimer's.

USC researchers have bolstered their expertise in this area by partnering with a world-renowned biomedical informatics and computational health sciences expert from UC San Francisco, Atul Butte, MD, PhD, and with accomplished Sage Bionetworks systems biologist and bioinformatics expert Lara Mangravite, PhD. Dr. Butte is currently leading California's statewide initiative to advance precision medicine. Dr. Mangravite leads the NIH/NIA's Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD), a public/private partnership initiative for target discovery and validation with an open source, open access informatics data platform, Synapse, available for use by the broad research community.

This team will utilize tools and bioinformatics methods to convert more than 300 billion points of molecular, clinical and epidemiological data measured by researchers and clinicians over the past decade into diagnostics and therapeutics for Alzheimer's in a platform that supports open, collaborative data analysis for clear, reproducible science.

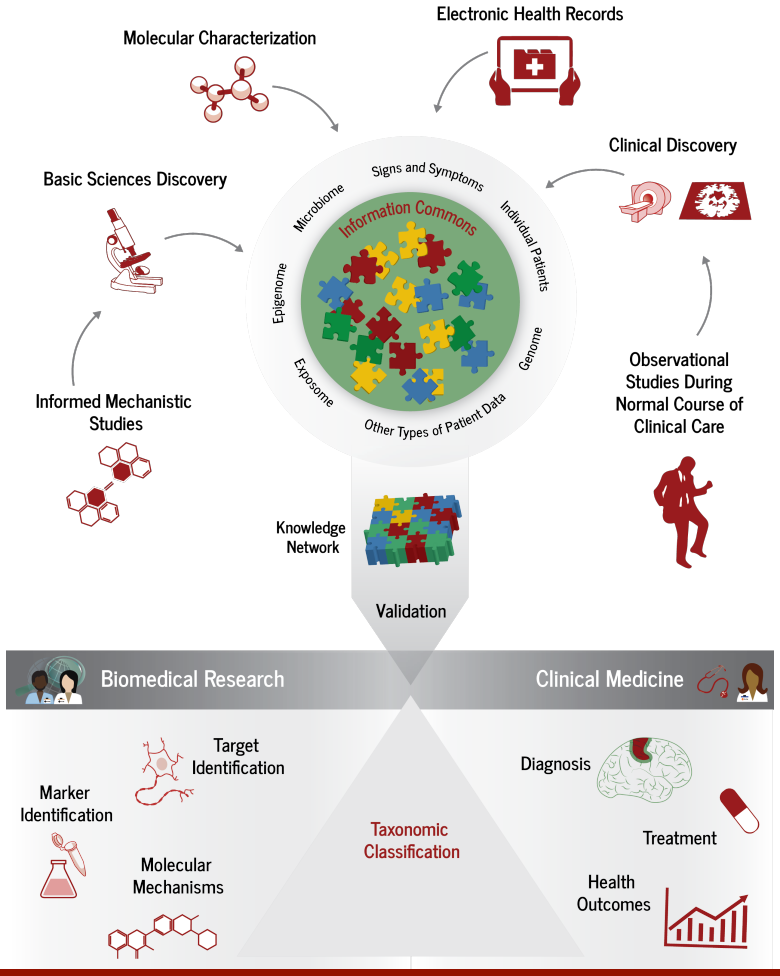


FIGURE 3: BIOMEDICAL KNOWLEDGE NETWORK to drive precision medicine

ATUL BUTTE, MD, PHD
PRECISION MEDICINE INSTITUTE FOR COMPUTATIONAL HEALTH SCIENCES, UCSF

LARA MANGRAVITE, PHD
ACCELERATING MEDICINES PARTNERSHIP (AMP-AD)
SAGE BIONETWORKS

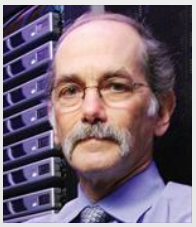
BIG DATA NEURO-INFORMATICS

CURx-AD's big data tools will enable pioneering discoveries about Alzheimer's to be mined from the vast amount of information generated by imaging science, genetic sequencing and other biomedical fields.

The USC Institute for Neuroimaging and Informatics (INI) — through its Laboratory of Neuro Imaging (LONI) — is one of the country's foremost neurological research centers. Under the direction of Arthur Toga, PhD, INI has developed the country's largest supercomputer facility devoted to neuroscience, with the capacity to analyze data from thousands of subjects with millions of data points, controlled by a graphical user interface running on any client machine, anywhere in the world. This resource makes available to our partners an unprecedented capability to examine and process data from multiple data archives.

The Enhanced Neuro Imaging Genetics through Meta Analysis (ENIGMA) Network, led by Paul Thompson, PhD, INI associate director, is a collaborative network of researchers on large-scale studies that integrate data from 70 institutions worldwide. ENIGMA has analyzed neuroimaging data from more than 12,826 subjects to tackle pressing questions of neuroscience, genetics and medicine. In addition, data from 12,171 individuals were provided by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium for replication of findings — for a total of 24,997 subjects. By meta-analyzing results from many sites, ENIGMA has detected factors affecting the brain that no individual site could find on its own and that require larger numbers of subjects than any individual neuroimaging study has ever collected.

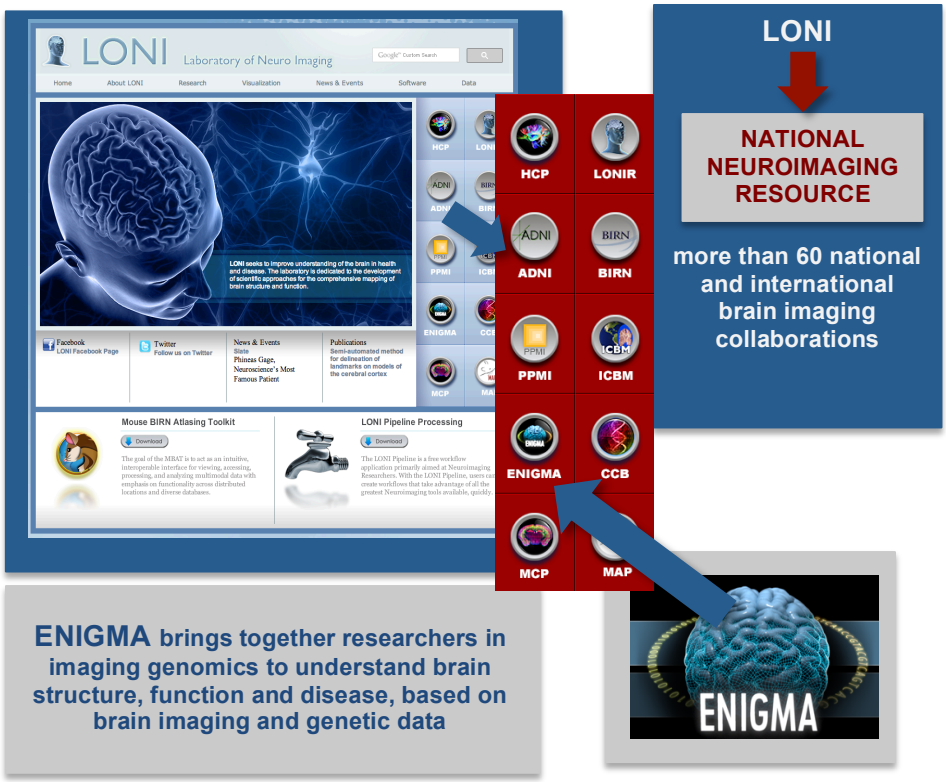
This analytic power also enables unparalleled study of ethnically and culturally diverse patient populations that may be therapeutically distinct.



ARTHUR TOGA, PHD
NEUROINFORMATICS
LABORATORY OF NEURO IMAGING (LONI)
USC

PAUL THOMPSON, PHD
NEUROINFORMATICS
ENHANCING NEURO IMAGING GENETICS THROUGH META ANALYSIS (ENIGMA)
USC

FIGURE 4: LONI AND ENIGMA



B. Structure-Based Drug Discovery and "Omics" Resources

CURx-AD is partnering with The Bridge Institute at USC, led by Ray Stevens, PhD, to develop therapeutic molecules — using a combination of chemistry, biochemistry, structural biology, cell biology and pharmacology — that will provide insight into the basis of neuronal signal transduction at the molecular level.

The Bridge operates on the basic hypothesis that structural biology — from the molecular to the cellular to the entire human body — provides a powerful pathway to understanding precisely how biological systems function in both healthy and diseased states, as well as how to manipulate those functions to dramatically improve human health. By integrating and synthesizing such new knowledge holistically — in the sciences, engineering, medicine and the arts, at multiple size and time scales — The Bridge is assembling a virtual model of the human body that can be used to create and test new generations of therapeutics and biomarkers.

One of the world's most influential biomedical scientists, Dr. Stevens is known for his research in human cell signaling, for helping develop the area of high-throughput structural biology and for determining the structure of proteins. High-throughput structural biology fuses big data computing and automation with classical techniques to answer vital questions about cellular behavior and interactions with a speed and accuracy far beyond conventional methods. His pharmaceutical innovations include research that led to the creation of the influenza medication Tamiflu and therapeutics for multiple sclerosis and the rare but devastating disorder phenylketonuria, among other advances. He also is developing new treatments for neuromuscular diseases and autoimmune disorders.

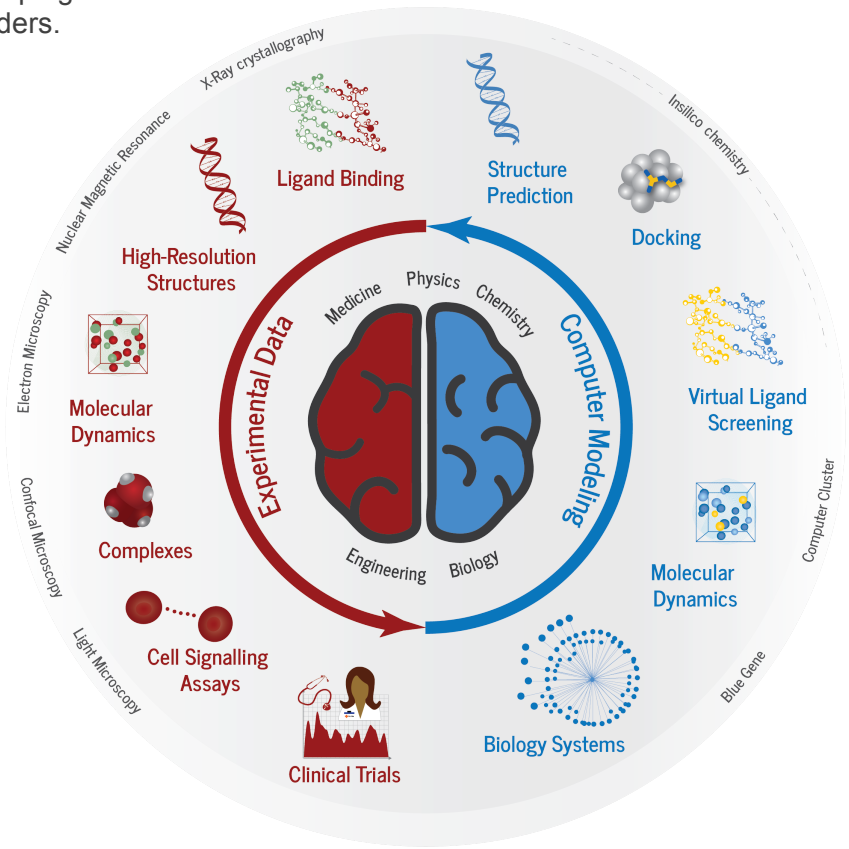


Figure 5: Structure-Based Drug Discovery at the Bridge Institute - USC

Raymond Stevens, PhD
Structure-Based Drug Discovery
The Bridge
USC

Oliver Fiehn, PhD
"Omics" Resources
West Coast Metabolomics Center
UC Davis

"OMICS" RESOURCES

The UC Davis West Coast Metabolomics Center, an NIH Regional Resource Core, led by Oliver Fiehn, PhD, integrates experimental and computational approaches to address key problems at the forefront of genomics, metabolomics, proteomics and bioinformatics. Across all cores, the Metabolomics Center serves as a national hub to conduct analyses in human, animal and cell-based samples. The Metabolomics Center provides services to biomedical, preclinical and clinical researchers through its Central Service Core Laboratories while promoting the entire field of metabolomics research through its Advanced Services laboratories. The Metabolomics Center also provides educational courses and workshops to inform biologists and clinicians about the potential and power of metabolomics for translational science.

Partnering with the UC Davis West Coast Metabolomics Center provides CURx-AD with a vast array of metabolomics resources and services. Dr. Fiehn and his team integrate experimental and computational approaches to address key problems at the forefront of metabolomics. The Metabolomics Center focuses on advancing metabolomics in breadth and depth and provides researchers with a capability to perform metabolomics studies in a collaborative manner. The Metabolomics Center offers both untargeted and targeted assays for discovery and validation studies of more than 20,000 samples annually, with more than 1,000 target molecules that can be analyzed, such as sterols, complex lipids and catecholamines, in addition to finding novel compounds that could be identified by accurate mass MS/MS. The center focuses on using this information along with genomics and proteomics data to propose novel hypotheses in the onset and progression of diseases. By quantifying the changes taking place inside cells or body fluids at specific times and under specific environmental conditions, the field offers new insights into cellular biology and an innovative path for research into and treatments of complex diseases such as Alzheimer's.

C. Systems-Pharmacology and Therapeutic Development

CURx-AD's university–industry hybrid model will leverage state-of-the-art technologies — combined with top-tier regulatory science, systems modeling and toxicology expertise within the academic sector — and will provide therapeutic targets with strong potential for Phase I and II studies to pharmaceutical industry partners. Under the leadership of Roberta Diaz Brinton, PhD, CURx-AD will partner with organizations in industry that can provide a library of compounds for screening through our in silico tools and models.

Dr. Brinton, who has been recognized with the Presidential Citizens Medal, developed two novel therapeutics for prevention and treatment of Alzheimer's, from their inception at the bench to their status as NIH-sponsored clinical trials, including the first trial of a regenerative therapeutic for Alzheimer's disease. She designed, developed and directed the Center for Scientific Translation within the NIH-sponsored USC Clinical and Translational Science Institute (CTSI).

Under Dr. Brinton's leadership, USC CTSI has enabled translation of a diverse portfolio of drugs, biomarkers, stem cell therapies, and nutraceutical and medical devices, and has facilitated 20 patent filings, three startup companies, six Investigational New Drug filings and six clinical trials.

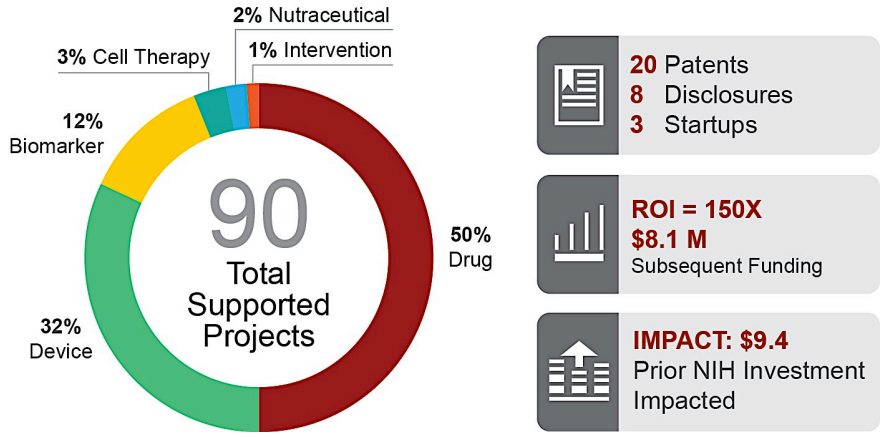


Figure 6: Diverse Portfolio of Therapeutic Strategies – Supported projects by product modality

Systems Pharmacology Modeling for Drug Discovery and Development

Pharmacokinetic (PK) modeling helps predict how the body will process a particular drug, while pharmacodynamics (PD) modeling helps predict how a drug will act on the body. A thorough understanding of the dynamics of both PK and PD is essential for the development of new therapeutic approaches to Alzheimer's disease and will provide crucial insights into how a particular drug might vary in effectiveness among different populations.

David D'Argenio PhD brings deep expertise in PK/PD modeling to predict drug outcomes across multiple drugs and populations. Dr. D'Argenio will develop and apply a framework for physiologically based disease progression modeling. This approach uses systems-physiology models of organ systems, which incorporate physiologically meaningful properties that characterize the disease process and thereby provide a rational basis for reflecting disease progression.

Systems-pharmacology models may bridge both the discovery-development and the preclinical-clinical translational barriers in drug development. CURx-AD will

Roberta Diaz Brinton, PhD
Therapeutic Discovery & Development
USC

David D'Argenio, PhD
Systems Pharmacology PK/PD
USC

Enrique Cadenas, PhD
Molecular Mechanisms in Brain Aging
USC

construct a framework for developing Systems-Pharmacology Pathway Models in Drug Discovery and Development that involve coupling existing systems-biology network models to pharmacodynamic biomarker data obtained during preclinical drug development.

MOLECULAR MECHANISMS IN BRAIN AGING

The laboratory of Enrique Cadenas, MD, PhD, focuses on the molecular mechanisms of Alzheimer's disease, quantitatively characterizing and evaluating the decline in energy metabolism associated with age-related neurodegenerative diseases by addressing the coordinated regulation of signaling and transcriptional pathways and mitochondrial function. This coordinated triad is critical in the regulation of brain glucose uptake and metabolism and has been used to assess the therapeutic potential of nutritional approaches that restore mitochondrial function and the associated signaling and transcriptional pathways as well as cognition. Dr. Cadenas collaborates extensively with international investigators focusing on modulation of nitric oxide concentration dynamics following hippocampal neuronal glutamatergic activation and hippocampal mitochondrial dysfunction in aging.

TOXICOLOGY

Kathleen Rodgers, PhD, provides CURx-AD with preclinical support and oversight of the toxicological studies essential for enabling regulatory filings for clinical trials, as well as input on the development of clinical protocols. Dr. Rodgers has extensive experience leading efforts to translate discoveries from USC laboratories into clinical trials (including three Phase I and four Phase II trials, with two Phase II trials already demonstrating positive results and moving forward). Her focus is providing translational assistance from the bench to the patient. She has consulted with companies interested in developing products that have regenerative potential and has developed recommended panels of safety studies to support clinical trials under FDA and European Union supervision. As a diplomate of the American Board of Toxicology, Dr. Rodgers has successfully guided the preclinical toxicology for seven marketed products and numerous products in clinical development.

OVERCOMING REGULATORY HURDLES

CURx-AD brings novel approaches to clinical research design as well as a wealth of expertise in navigating the regulatory paths essential to expediting patient access to new breakthrough treatments. Francis Richmond, PhD, and Eunjoo Pacifici, PharmD, PhD, of the USC International Center for Regulatory Science, have a proven track record and an innovative approach to addressing the complexities associated with industry–academia partnerships and the challenges of taking a compound from the preclinical stage through the regulatory approval process.

Together, they bring to CURx-AD unique expertise in clinical trial design and management, as well as regulation of drugs, biologics, devices and nutraceuticals. The International Center for Regulatory Science houses a research consortium with a focus on translational and regulatory research, and is affiliated with the Clinical and Translational Sciences Institute (CTSI). The International Center for Regulatory Science's consulting group provides regulatory guidance and education related to translational and regulatory questions in IND enabling strategies, global pharmaceutical markets, international medical product regulations, and research and development in emerging markets, among others.

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TOXICOLOGY
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FRANCES RICHMOND, PHD
INTERNATIONAL CENTER FOR REGULATORY SCIENCE
USC

EUNJOO PACIFICI, PHARMD, PHD
INTERNATIONAL CENTER FOR REGULATORY SCIENCE
USC

D. Multi-scale Computational Modeling, Biomedical Simulations and Systems Modeling

The USC Biomedical Simulations Resource (BMSR) provides CURx-AD with expertise in neural physiology, neuro-engineering and multi-scale modeling of neural systems to advance our fundamental understanding of the complex biological processes involved in Alzheimer's.

Dr. Ted Berger's team has developed a unique multi-scale model of the hippocampus. This framework links molecular, synaptic, neuron and multi-neuron dynamics and integrates a large number of complex and highly interconnected biomolecular mechanisms. The team has successfully applied their approach to the specific problem of how changes at the level of receptors or channels (whether due to pathology or functional change in response to a drug) are translated into changes in the temporal firing pattern of a single neuron, and ultimately, changes in the spatiotemporal activity of networks of neurons. Furthermore, a large-scale, multi-compartmental neuron model of the enthorhinal-dentate-CA3 component of the hippocampus has been developed, including over 1.5 million neurons modeled with 200 compartments each, with full dendritic morphologies unique for each neuron, and a total of more than 3 billion synapses. These molecular, synaptic, neuronal, and multi-neuronal representations are integrated in such a way that manipulations at any one level can be studied in terms of their functional consequences at higher levels. Such a modeling framework is highly advantageous for exploring new drugs and new drug actions.

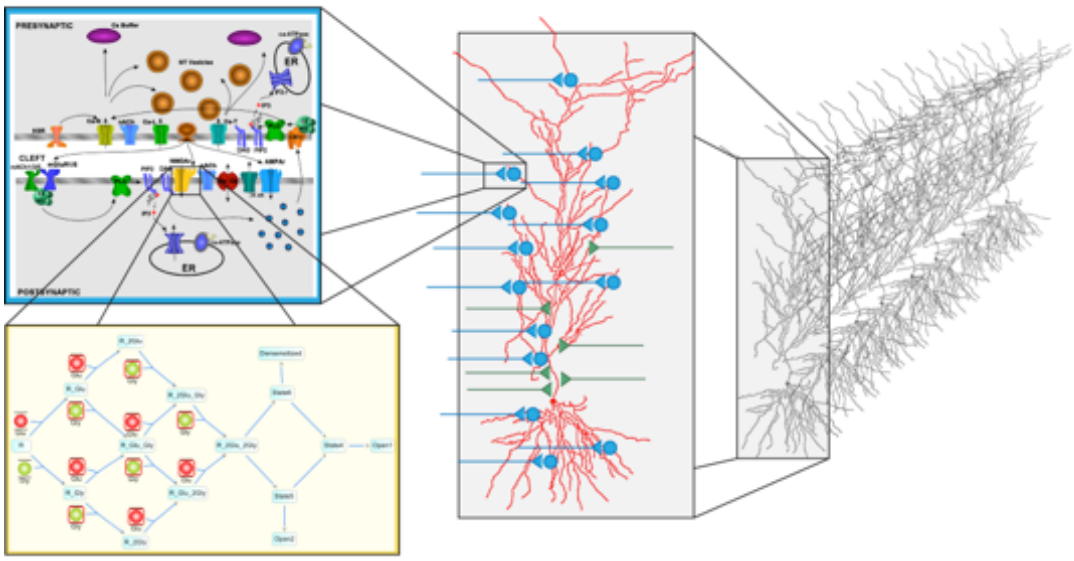


Figure 7: Levels of complexity addressed in current multi-scale model – Receptor-channel kinetics, diffusion, second-messenger pathways, etc., are represented and spatially coupled

Theodore Berger, PhD
Biomedical Simulations Resource (BMSR)
USC

Jean-Marie Boutellier, PhD
Biomedical Simulations Resource (BMSR)
USC

David D'Argenio, PhD
Biomedical Simulations Resource (BMSR)
USC

Dong Song, PhD
Biomedical Simulations Resource (BMSR)
USC

Vasilis Marmarelis, PhD
Biomedical Simulations Resource (BMSR)
USC

Over the past 30 years, systems modeling and simulation have evolved to become critical components in efforts to understand and quantify the processes of uptake, disposition and action of therapeutic drugs. Systems modeling and analysis impact all aspects of drug development including in vitro, animal and human testing, as well as drug therapy. Modeling methodologies developed for these systems-pharmacology applications confront many challenges, related in part to the severe restrictions on the number and type of measurements available from laboratory experiments and clinical trials, as well as the variability in the experiments and the complexity associated with the processes themselves. To address these challenges, Dr. D'Argenio and the BMSR team developed, distributed and supported the general-purpose software system ADAPT, used extensively by both basic and clinical researchers in industry and academia to facilitate discovery, development and rationale therapy of medicines. Between 2010-2014, more than 1,500 investigators registered downloads of ADAPT from BMSR.

The members of the CURx-AD modeling team have worked together for 28 years in the context of the NIH-supported BMSR. The BMSR is dedicated to developing new modeling methodologies, not only for use by the core research investigators, but also distributed (free of charge) to other researchers in the field. Rhenovia Pharma (Europe) and Rhenovia Pharma, Inc. (U.S.), a firm dedicated to drug development, has licensed the EONS modeling platform developed by Drs. Berger and Bouteiller. Additionally, the nonlinear input-output modeling methodologies developed by Drs. Marmarelis and Berger are currently patented and being developed for clinical use in neural prostheses; those developed exclusively by Dr. have been extended for clinical use in the context of breast cancer and Alzheimer's Disease.

E. Predictive Cellular and Animal Model Systems

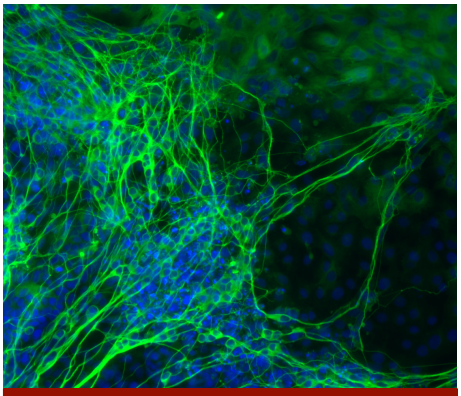


Figure 8: Human iPSC-Derived Neurons

Induced Pluripotent Cell Based Models of Human Phenotype and Genotype

Justin Ichida, PhD, of the USC Stem Cell Institute brings to CURx-AD expertise in generating induced pluripotent stem cells (iPSCs) of human phenotype and genotype from individuals with neurodegenerative disease. To enable therapeutic discovery and development, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC developed and funds a therapeutic screening facility that provides chemical screening and high-content imaging services. The Broad Center maintains a collection of some 3,000 annotated compounds including a subset of FDA-approved drugs, liquid-handling systems and state-of-the-art equipment capable of automated, high-throughput imaging. The facility specializes in performing phenotypic screens on stem cell-derived cultures. As director of this facility, Dr. Ichida is committed to enabling and expanding therapeutic development for Alzheimer's disease using iPSCs and derived neural stem cells.

Mouse and Rat Model Resources Relevant to Alzheimer's Disease

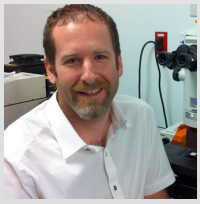
Terrence Town, PhD, of the USC Zilkha Neurogenetics Institute leads CURx-AD's program of mouse and rat model resources that are relevant to Alzheimer's disease. In 2013, the Town lab revolutionized the field of Alzheimer's disease research by generating the first rat model of the disease that manifests all of the clinico-pathological hallmarks of the human syndrome. He and his team published a study in the February 2015 issue of the peer-reviewed journal *Neuron* of their work using genetically modified, Alzheimer's-afflicted mice to show that blocking interleukin-10 activates an immune response to clear the brain of the beta-amyloid plaques that affect memory loss and brain cell damage.

Connecting the Human Connectome to Preclinical Models

Hong-Wei Dong, MD, PhD, of the USC Laboratory of Neuro Imaging (LONI) and principal investigator of the Mouse Connectome Project will lead CURx-AD's effort to link the human connectome to preclinical models. Dr. Dong offers deep expertise in mouse brain connectome mapping, neural mapping methodologies and data informatics. He is working on a comprehensive connectome map of the entorhinal cortex and hippocampus that will lay the groundwork for understanding the connecto-pathies that emerge within these brain structures in Alzheimer's disease.

This approach can be used to demonstrate how neural pathways are progressively disrupted across different stages of the disease, and to test quantitatively how therapeutic treatment can revise or prevent connectivity impairments. Further, this method provides an independent test of the validity of current and future mouse models for translatability to the human brain and has particular relevance to preclinical therapeutic development and determinants of safety and efficacy.

Justin Ichida, PhD
Stem Cell Technologies
Stem Cell Institute
USC



Terrence Town, PhD
Mouse and Rat Model Resources
Neurogenetics Institute
USC

Hong-Wei Dong, PhD
Mouse Connectome
Laboratory of Neuro Imaging (LONI)
USC

F. Clinical Analysis and Health Policy for Alzheimer's Disease

Helena Chui, MD, principal investigator of the USC Alzheimer's Disease Research Center (ADRC), ADRC clinical core director Lon Schneider, MD, and Eric Reiman, MD director of the Arizona Alzheimer's Consortium oversee clinical perspectives for CURx-AD's efforts. For the past 20 years, Dr. Chui has served as principal investigator of the Aging Brain Program Project, a multi-institutional longitudinal study to characterize interactions between vascular and Alzheimer disease, using state-of-the-art clinical-imaging-pathological correlations. Dr. Schneider is internationally recognized in clinical drug development for Alzheimer's disease and cognitive disorders, and has led numerous clinical trials for Alzheimer's therapeutics, including the paradigm shifting CATIE-AD trial. He is conducting work using trials simulations from large metadatabases to assess the effects of Alzheimer-related biomarkers and genotypes on the efficiency of targeted clinical trials to improve trials methods. Dr. Reiman directs the nation's leading model of statewide collaboration in Alzheimer's disease research, the Arizona Alzheimer's Consortium. The consortium capitalizes on its participating institutions' complementary strengths in brain imaging computer science, genomics, the basic and cognitive neurosciences and clinical and neuropathology research to promote the scientific understanding and early detection of Alzheimer's disease and find effective disease-stopping and prevention therapies.

Julie Zissimopoulos, PhD, associate director of the USC Schaeffer Center for Health Policy & Economics, leads the effort to assess the potential economic and demographic impact of interventions developed through CURx-AD.

According to research conducted by Dr. Zissimopoulos, the number of Americans 65 and older who will get Alzheimer's is expected to double between 2010 and 2050; the incidence among those 85 and older is expected to triple during that same timeframe, creating both an economic and a public health crisis. Her extensive research further suggests that medical or pharmaceutical innovations that delay the onset of the disease for five years would result in a 41 percent lower prevalence of Alzheimer's disease in 2050 among those aged 70 or more, and a reduction in societal costs of approximately 40 percent. In addition to saving and improving lives, the anticipated cost savings would be $640 billion.

Recognizing the toll Alzheimer's disease is already taking on American lives and our economy — as well as its projections for far more devastating prevalence and cost on the horizon — the National Alzheimer's Project Act was signed into law in January 2011, authorizing an historic $156 million investment in fighting the disease and the escalating crisis it is causing.

Among the key goals identified by those working to implement the act include initiating research programs for translational bioinformatics and network pharmacology to support rational drug repositioning and combination therapy, launching clinical trials for novel therapeutic targets, and taking an interdisciplinary approach to developing innovative solutions to treat and prevent the disease. The team involved with CURx-AD has long been working on advances in each of these and other related areas to reduce and eventually eliminate the impact of this devastating disease on individuals, families and society.

Helena Chui, MD
Clinical Care
Alzheimer's Disease
Research Center
(ADRC USC)

Lon Schneider, MD
Clinical Care
Alzheimer's Disease
Research Center
(ADRC USC)

Eric Reiman, MD
Arizona Alzheimer's
Consortium
(University of Arizona)

Julie Zissimopoulos, PhD
Pharmaco-Economics
and Health Policy
USC

3. OPEN SOURCE, OPEN ACCESS, OPEN OPPORTUNITY

CURx-AD will leverage public–private partnerships to translate innovative research at multiple scales and steps into drug discovery and development. Integrating multi-scale, mechanistic neural systems modeling with physiologically based pharmacokinetic disease progression and pharmacological pathway models, we will provide optimal platforms for new, qualifying compounds and targets, predicting responses to single-agent and multiple drug regimens and assessing multidimensional factors controlling inter-patient variability in pharmacological responses.

The CURx-AD team brings to this project a breadth and depth of expertise in:

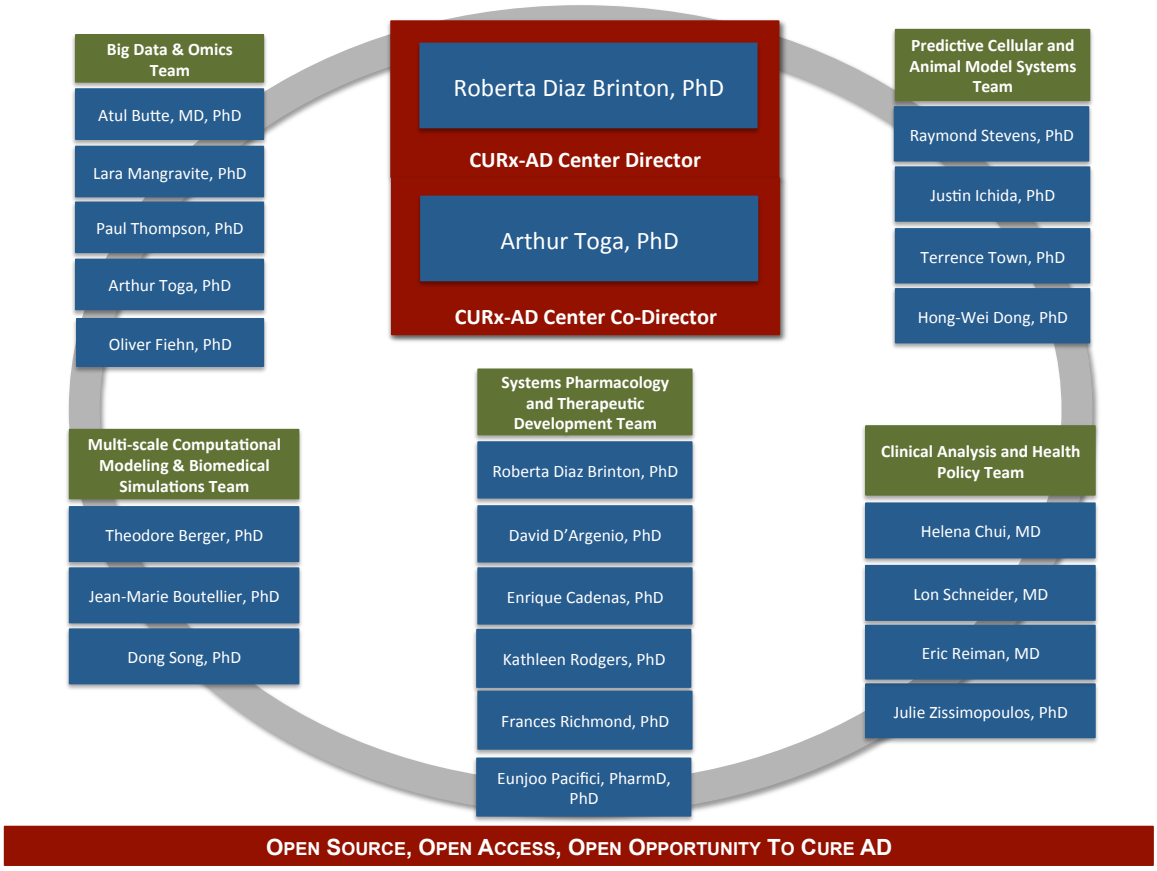
- systems biology
- neuroscience
- neuroimaging
- human induced pluripotent stem cells
- mouse and human connectome
- data analysis and visualization of the brain
- animal models for neurological diseases
- preclinical and clinical trials for drug development
- multi-scale modeling and simulations for drug development
- breadth and depth of expertise in developing and sustaining collaborative partnerships among academia and industry

The exceptional caliber of each team member is matched by their inspiring commitment to curing Alzheimer's disease.

With our coordinated team, access to big data networks and state-of-the-art tools, technologies and methods, and the ability to integrate them in an open-source platform, we have an unparalleled opportunity for innovation and solutions with the potential to produce urgently needed therapeutics.

Furthermore, the critical need for a portfolio of therapeutics that target the heterogeneity in phenotype and progression of Alzheimer's means there can be many winners in this battle — most importantly the patients and families who so desperately need them. We hope you will join us in this critical endeavor.

4. CURx-AD ORGANIZATIONAL STRUCTURE



To request further information, please email info@curxad.com or call 323.442-3355.