Alzheimer's and Neurological Disease Initiative
The Specter of Alzheimer’s and Neurological Diseases

- Diseases of the brain and nervous system are of great concern to many of us:
  - What can we do if we—or our loved ones—are struck by Alzheimer’s?
  - How can we protect our children and grandchildren from inheriting family tendencies toward autism, depression or Parkinson’s?
  - What can we do to halt other brain and nervous system diseases?
- Scientists at The Scripps Research Institute (TSRI) are breaking new ground in the understanding the molecular mechanisms underpinning the brain and nervous system.
- TSRI scientists aid to use these insights in developing innovative new approaches to prevention and therapy.
Alzheimer’s Disease - Stealing Memory

- More than five million Americans currently suffer from Alzheimer’s.
- One in nine people age 65 and older (11 percent) has Alzheimer’s disease; about one-third of people age 85 and older (32 percent) are afflicted.
- Alzheimer’s affects memory, language, judgment, perception and mood.
- The disease is progressive, getting worse for patients over time; patients typically live 3 to 20 years after diagnosis.
- Caring for Alzheimer’s places an emotional and financial burden on families.
- There are no effective treatments for Alzheimer’s.
- There are no early diagnostics.
Parkinson’s Disease - Robbing Independence

- More than one million Americans currently suffer from Parkinson’s.
- Parkinson’s disease plagues about one percent of people over 60 years old, as well as some younger patients.
- Symptoms of Parkinson’s disease include tremors, muscle stiffness, trouble walking, imbalance and speech problems.
- The disease is progressive, getting worse for patients over time; while life expectancy varies widely, potentially fatal late-stage complications include choking, falls and pneumonia.
- Caring for Parkinson’s patients places an emotional and financial burden on families.
- There are limited treatments for the symptoms of Parkinson’s; no treatment to prevent brain cell death exists.
- There are no early diagnostics.
Autism spectrum disorder is a group of developmental brain disorders that affects about 1 in 88 children in the United States.

Boys are about four times as likely to be affected as girls.

While ranging in character and severity, symptoms generally fall into three areas:
- Social impairment
- Communication difficulties
- Repetitive and stereotyped behaviors

While there are some educational/behavioral interventions and medications for autism-related symptoms, there is no cure.
Multiple Sclerosis – Defying Prediction

- More than 2.3 million people worldwide are affected by multiple sclerosis (MS), which is believed to be an autoimmune disease. The disease is usually diagnosed between the ages of 15 and 45. About twice as many women as men are affected.

- Symptoms, which can come and go or get progressively worse, can include overwhelming fatigue, visual disturbances, numbness, weakness, tremor, dizziness and psychiatric problems.

- The severity of MS varies widely depending on the amount of damage and the nerves affected. Severe cases can lead to blindness and paralysis.

- Medications can reduce the number of relapses and delay progression of disability; sometimes these medicines are poorly tolerated.

- No cure has yet been found.
Lou Gehrig’s Disease (ALS) – Taking Away Muscle Function

- Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig disease after the New York Yankees first baseman afflicted with the condition, destroys the nerves responsible for muscle movement.

- Approximately 5,600 people in the U.S. are diagnosed with ALS each year.

- Symptoms include muscle weakness, twitching, slurred speech and difficulty breathing and swallowing; dementia can also be involved.

- Life expectancy averages two to five years after diagnosis.

- Risk factors include genetics, age (between 40 and 75), military service and possibly smoking.

- The cause and mechanisms underlying ALS are unknown.

- No meaningful treatments are available; there is no known cure, prevention or early diagnostic.
Consensus has been growing on the need for a better understanding of the brain and nervous system.


In 2013, President Obama also announced the BRAIN Initiative—short for Brain Research through Advancing Innovative Neurotechnologies—that aims to accelerate new technologies to help researchers visualize complex neural circuits and the rapid-fire interactions of cells, laying the groundwork for new ways to treat, cure and prevent neurological disorders.

However, not enough funds have been appropriated to meet these ambitious goals; public-private partnerships are key to progress.
Federal funding for basic biomedical research has been declining in real dollars.

The research funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF) tends to be incremental. What is needed to achieve scientific breakthroughs are high-risk, high-reward endeavors.

Pharmaceutical companies rarely invest in the basic biomedical research necessary to search for diagnostics and therapies.

More than 200 completed clinical trials for Alzheimer’s have failed, as there is still too little basic information to inform the development of therapies.

Patients and families affected by many neurological diseases are desperate for better medical options.
The New Initiative at TSRI Offers a Solution

- TSRI proposes an organization that brings together varied scientific approaches to critical problems in neuroscience, funded aggressively to find breakthroughs in the shortest time feasible.

  The purpose is to find:
  - Novel therapeutic strategies.
  - Early disease diagnostics (biomarkers).
  - Effective drugs.

- This will be accomplished by assembling a critical mass of scientists, each contributing their specific expertise to an interdisciplinary approach, creating synergies and expanding the base of information needed to find solutions.
Why TSRI?

TSRI has:

- A track record of basic discoveries translated into new therapies, including treatments for arthritis, lupus, hemophilia and cancer.
- More than 50 companies launched from TSRI discoveries.
- More than 800 patents on innovative technologies.
- 30 pharmaceuticals currently in clinical development.
- Recognition as a leader at the intersection of biology and chemistry—ranked number one in the world in chemistry, number two in microbiology (ranked by Thomson Reuters, citations per paper over a decade).
Ultimately, neurological diseases are caused by damage to nerve cells or neural networks.

Alzheimer’s, Parkinson’s and related diseases are prompted by the misfolding of specific proteins that lead them to cluster together. These microscopic fibrils or plaques are called “amyloid” and form toxic deposits that interfere with organ function.

Other mechanisms underpin other types of neurological diseases. In multiple sclerosis, for example, the protective covering around nerves is damaged, disrupting the flow of messages that travel along the nerves.

Many of the mechanisms behind neurological diseases are still a mystery.
TSRI Scientists at the Forefront

TSRI can boast of many contributions to the field, including:

- Discovering the first drug shown to slow the progression of an amyloid disease.
- Uncovering a link between prion diseases and Alzheimer's.
- Identifying a receptor in neurons that appears to control Parkinson’s damage to brain cells.
- Unveiling a surprising mechanism that controls brain formation—findings that have implications for understanding some forms of mental retardation, epilepsy, schizophrenia, autism and other diseases.
- Revealing a molecular pathway implicated in motor neuron disease.
- Developing the first of a new class of highly selective compounds that effectively suppresses the severity of MS in animal models and offering other new approaches to the disease.
- Developing compounds that reactivate the gene responsible for the inherited neurodegenerative disease Friedreich's ataxia.
## Some TSRI Researchers in the Field

For faculty bios, see [www.scripps.edu](http://www.scripps.edu)

- William Balch, PhD
- Kristin Baldwin, PhD
- Laura Bohn, PhD
- Joel Buxbaum, MD
- Jerold Chun, MD, PhD
- Benjamin Cravatt III, PhD
- Ronald Davis, PhD
- Ezros Lazzerini Denchi, PhD
- Celine DerMardirossian, PhD
- Matthew Disney, PhD
- Jane Dyson, PhD
- Sandra Encalada, PhD
- Nathalie Franc, PhD
- Michael Farzan, PhD
- Larry Gerace, PhD
- Joel Gottesfeld, PhD
- John Griffin, PhD
- Brock Grill, PhD
- Donna Gruol, PhD
- Scott Hansen, PhD
- William Ja, PhD
- Claudio Joazeiro, PhD
- Jeffery Kelly, PhD
- Theodore Kamenecka, PhD
- Shuji Kishi, PhD
- Thomas Kodadek, PhD
- Corinne Lasmezas, PhD
- Philip LoGrasso, PhD
- Jeanne Loring, PhD
- Kirill Martemyanov, PhD
- Vince Mauro, PhD
- Anton Maximov, PhD
- Mark Mayford, PhD
- Courtney Miller, PhD
- Richard Milner, PhD
- Kerri Mowen, PhD
- Ulrich Mueller, PhD
- David Nemazee, PhD
- Takanori Otomo, PhD
- Damon Page, PhD
- Michael Petrascheck, PhD
- Sathyanarayanan Puthanveettil, PhD
- Steve Reed, PhD
- Amanda Roberts, PhD
- William Roush, PhD
- Daniel Salomon, MD
- Louis Scampavia, PhD
- Supriya Srinivasan, PhD
- Srinivasa Subramaniam, PhD
- Elizabeth Thomas, PhD
- Seth Tomchik, PhD
- Peter Vanderklish, PhD
- Luke Wiseman, PhD
- Peter Wright, PhD
- Baoji Xu, PhD
- Xiang-Lei Yang, PhD
- John Yates III, PhD
- Jian Zhu, PhD
A Collaborative and Focused Effort

To find novel therapeutic strategies, early disease diagnostics and effective drugs, the initiative at TSRI will:

- Marshal an organized and focused collaborative research effort, turning the best scientific minds loose on the problem.
- Recruit talented young investigators working in the area of neurological diseases and support their initial efforts in research.
- Create a collaborative, interdisciplinary, synergistic environment that expands scientific thinking about amyloid diseases from many perspectives — including genomics, molecular studies, antibody approaches, neurosciences, stem cell work, mass spectrometry, mathematical modeling, etc.
- Evaluate initiative-funded research aggressively on an annual basis to ensure that only promising pathways are pursued.
Supporting Innovative Research

Grants

- TSRI investigators submit requests for funding for innovative, out-of-the-box research.
- Accepted projects receive funding for three years to develop new approaches that will be then competitive for National Institutes of Health (NIH) and National Science Foundation (NSF) funding to continue the work.

Oversight

- A scientist-director holds an endowed chair to provide administration and scientific direction.
- An internal grant committee and outside evaluators review the proposals and provide granting recommendations.
- A Scientific Advisory Board monitors the progress and research integrity of the initiative, reviews and evaluates work in progress, and issues recommendations concerning the continuation or discontinuation of projects.
The initiative will be funded by investments totaling $50 million.

Expenditure plan:

- $5 million Endowed chairs for two senior investigators (including one director)
- $5 million Upgrades to laboratories, new equipment
- $5 million Held in a 10-year term endowment to ensure resources are available to follow up on the most promising findings, for example with clinic trials

Remaining funds of $35 million to be drawn down by $3.5 million per year for 10 years:

- $500K per year for six to seven grants to exceptional postdoctoral fellows working on relevant projects
- $3 million per year to fund eight projects, chosen on the basis of merit, at $360K per year
A Lasting Contribution

Contributions totaling $50 million will support world-class talent and equipment and fund innovative research projects devoted to finding solutions to Alzheimer's and other neurological diseases. Add to that the NIH and NSF funding that is sure to result from the discoveries made at TSRI due to this initiative, and the potential for success is enormous.
Appendices
Appendix 1: Drugs Developed from TSRI Discoveries

- **Humira®** for rheumatoid arthritis, plaque psoriasis, Crohn’s disease, ulcerative colitis and other inflammatory conditions
- **Benlysta®** for lupus, a debilitating autoimmune disease
- **Leustatin®** for hairy cell leukemia, an unusual cancer of the blood
- Purification of **Factor VIII** for the bleeding disorder hemophilia
- **Vyndaqel®** for transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, progressive and fatal neurodegenerative disease
- **Surfaxin®** for infant respiratory distress syndrome, a life-threatening condition affecting pre-term infants
- **Cyramza®** for gastric and non-small cell lung cancer
- **Unituxin™** for the childhood cancer neuroblastoma
Appendix 2: Companies from TSRI Technology or Faculty

2014
- Aldabra Biosciences
- Padlock Therapeutics
- Transplant Genomics, Inc.

2013
- Blackthorn Therapeutics Inc.
- iGenomiX
- Sirenas Marine Discovery

2012
- Abide Therapeutics
- Cypher Genomics
- Vesper Biologics

2011
- RQx Pharmaceuticals

2010
- Ember Therapeutics
- Epic Science

2009
- Receptos Pharma
- Zyngenia
- Protix, Inc.

2008
- Eyecyte, Inc.
- Fate Therapeutics

2007
- Sapphire Energy
- aTyr Pharma
- Curna
- Proteostasis Therapeutics

2006
- Affinity Pharmaceuticals
- Calmune
- Viriome LLC
- Wittycell S.A.S.

2004
- Achaogen Inc.
- Motility, Inc.
- Promosome
- Rincon Pharmaceuticals (acquired by Sapphire Energy)

2003
- Ambrx Inc.
- Prion Solutions (acquired by Chiron)
- FoldRx Pharmaceuticals

2002
- NanoRX (acquired by Adaptive Therapeutics)
- CovX Research (acquired by Pfizer)
- VAXDesign (acquired by Sanofi Pasteur)

(continued)
2001
- Kalypsys
- Phenomix
- Syrxx (acquired by Takeda)

2000
- ActivX Biosciences (acquired by Kyorin)
- Neurome

1999
- Prolifaron (acquired by Alexion Pharmaceuticals)
- Optimer Pharmaceuticals
- Geneformatics (merged with Structural Bioinformatics)

1997
- Epicyte (acquired by Biolex Therapeutics)

1996
- Discovery Labs (merged with Acute Therapeutics)
- Drug Abuse Sciences
- Digital Gene Technologies (purchased by Neurome)
- Sangamo Biosciences

1995
- PharMore
- Thrombosys

1994
- Apovia AG (formerly EVAX Technologies, originally Immune Complex Corp.)

- Applied Molecular Evolution (formerly Lxsys; acquired by Lilly, Inc.)
- CombiChem (acquired by Dupont-Merck Pharmaceutical and merged with Bristol-Myers Squibb)

1993
- Ciphergen Biosystems

1992
- Sequel Therapeutics (later acquired by Cytel, which was subsequently spun-out as Epimmune)

1989
- Avanir Pharmaceuticals (formerly Lidak)
- UNASYN
- Corvas (acquired by Dendreon Corporation)

1986
- NeoMPS (formerly Multiple Peptide Systems)
- MP Biomedicals (formerly Qbiogene and Bio101)

1984
- Stratagene

1982
- Synbiotics

1981
- Quidel
### Appendix 3
Therapeutic Pipeline

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<th>MARKETED PRODUCTS</th>
<th>COMPOUND</th>
<th>THERAPEUTIC AREA</th>
<th>COMPANY</th>
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Table 9: Ambryx Products

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Table 10: Other Early Stage Products

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