



## VA-ORD GULF WAR RESEARCH : Research Program Overview

Presented to:

National Gulf War Resource Center

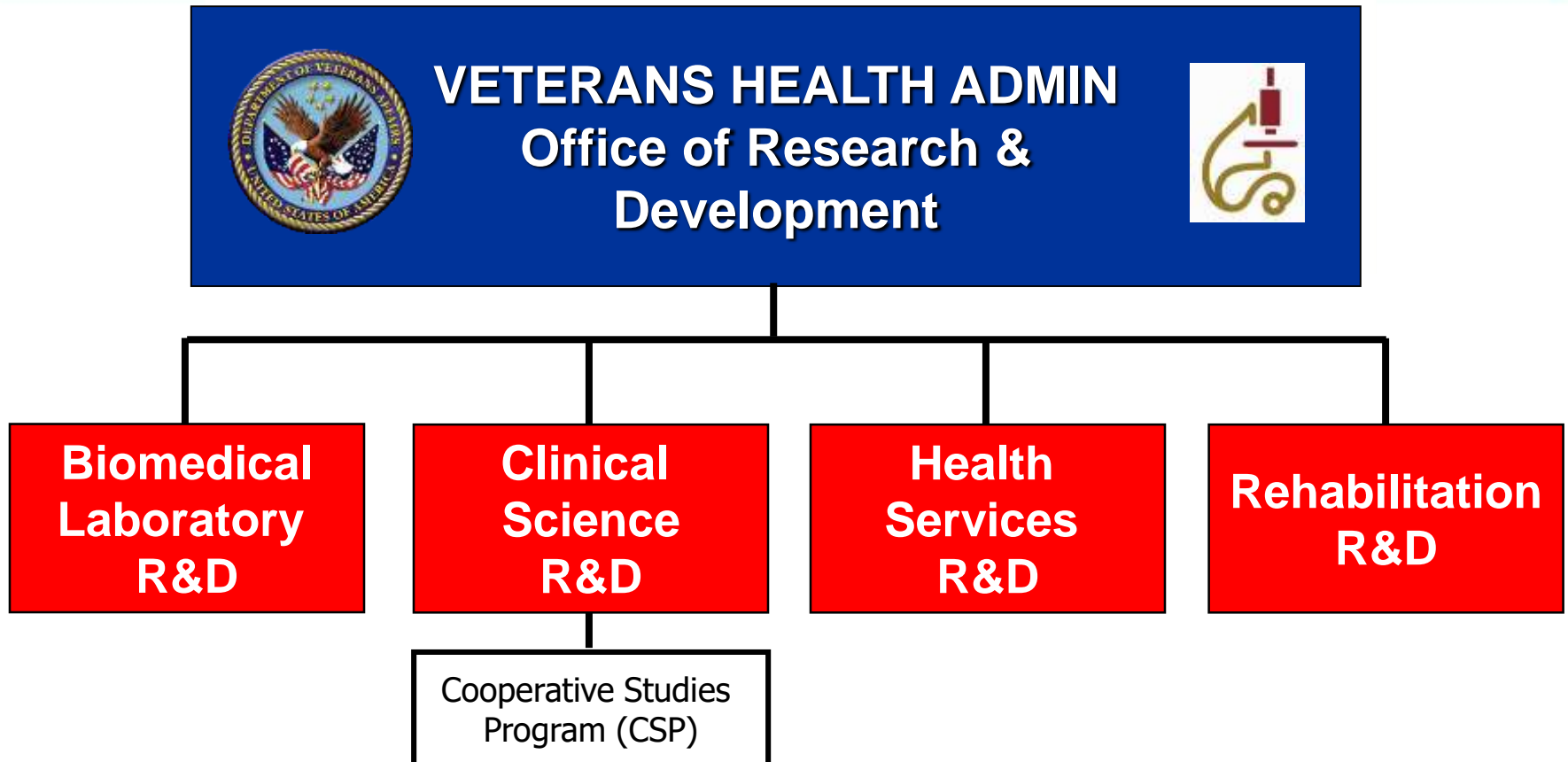
Annual Meeting & Informational Health Fair

VHA OFFICE OF RESEARCH AND DEVELOPMENT / Victor Kalasinsky, PhD

September 30, 2016

Arlington, VA

# Office of Research and Development Organizational Chart



# Gulf War Research – Requests for Applications (RFAs)

## **Biomedical Laboratory Research & Development (BLR&D):**

BX-16-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

BX-16-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

## **Clinical Science Research & Development (CSR&D):**

CX-16-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

CX-16-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

CX-16-013

Award for Research on Treatments for Gulf War Veterans' Illnesses (GWVI) – (clinical trial)

## **Health Services Research & Development (HSR&D):**

HX-16-012

Targeted Solicitation for Service-Directed Research Award on Health Services Research on the Care of Gulf War Veterans

# Gulf War Research Strategic Plan (2013-2017)

## Eight Focus Areas

(<http://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>)

- **5.1 Symptomatic and Specific Treatments**
- **5.2 Databases and Continued Surveillance**
- **5.3 Establish an Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans**
- **5.4 Genetics, Genomics, and Systems Biology**
- **5.5 Biomarkers**
- **5.6 Animal Models**
- **5.7 Improve Coordination and Communication**
- **5.8 Translate Research Findings into Practice**

# VA-ORD Gulf War Research Funding (2007 – 2016)

Fiscal Year (FY)	VA Merit Review	UTSW Contract	FY Total
2007	\$ 7.06 M	\$ 15.00 M	\$ 22.06 M
2008	\$ 6.93 M	\$ 15.00 M	\$ 21.93 M
2009	\$ 9.63 M	\$ 6.97 M	\$ 16.60 M
2010	\$ 11.57 M	\$ 2.29 M	\$ 13.86 M
2011	\$ 5.54 M	\$ 0.03 M	\$ 5.57 M
2012	\$ 6.72 M		\$ 6.72 M
2013	\$ 7.94 M		\$ 7.94 M
2014	\$ 9.73 M		\$ 9.73 M
2015	\$ 11.63 M		\$ 11.63 M
2016*	\$ 14 M		\$ 14 M
<b>Total 2007-2016</b>	<b>\$ 90.75 M</b>	<b>\$ 39.29 M</b>	<b>\$ 130.04 M</b>

# Response Statistics for VA-ORD Gulf War Research Requests for Applications (RFAs)

	<b>Proposals Received</b>	<b>Projects Funded</b>	<b>Funds Approved</b>
<b>Spring/Fall 2011</b>	26	3	\$ 4.0 M
<b>Spring/Fall 2012</b>	32	7	\$ 11.4 M
<b>Spring/Fall 2013</b>	35	7	\$ 12.6 M
<b>Spring/Fall 2014</b>	40	5	\$ 7.5 M
<b>Spring/Fall 2015</b>	33	8	\$ 13.2 M
<b>Spring 2016</b>	12	2	\$ 1.1 M
<b>Fall 2016</b>	Sep 2016	Dec 2016	

# Gulf War Research Projects Active in 2015-2016 (slide 1 of 3)

## **Treatments/Clinical Trials**

- Impact of exercise training on pain and brain function in Gulf War Veterans (5.1)
- Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI (5.1)
- Complementary Neurosteroid Intervention in Gulf War Veterans' Illnesses (5.1)
- Cognitive Rehabilitation Therapy for Gulf War Veterans (5.1)
- Complementary and Alternative Medicine in Veterans with Gulf War Illnesses (5.1)
- RCT of Duloxetine and Pregabalin for the treatment of GWI in Veterans (5.1)
- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness (5.1)

# Gulf War Research Projects Active in 2015-2016 (slide 2 of 3)

## **Biomarkers/Mechanisms**

- Diagnostic Utility of mtDNA Content and Exercise Challenge in Vets with GWI (5.1, 5.4)
- Examination of Cognitive Fatigue in Gulf War Illness Using fMRI (5.5)
- Longitudinal assessment of Gulf War veterans with suspected Sarin exposure (5.4, 5.5)
- Multimodal Biological Assessment of Gulf War Illness (5.5)
- National Health Survey of Persian Gulf Veterans and their Families (5.2)
- Somatic hypersensitivity in Veterans with IBS (5.1)
- Vascular and Skeletal Muscle Function in Gulf War Veterans Illness (5.1, 5.4)
- Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets (5.1, 5.4)
- Genomics of Gulf War Illness in Veterans (5.4)



# Gulf War Research Projects Active in 2015-2016 (slide 3 of 3)

## Model Systems

- Central Mechanisms Modulating Visceral Sensitivity (5.4, 5.6)
- Immunoregulation of Myelin Specific T Lymphocytes (5.4, 5.6)
- Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis (5.4, 5.6)
- Sleep Neurobiology and Circuitry (5.4, 5.6)
- Prevention of Hippocampal Neurodegeneration Due to Age and Apnea (5.6)
- Epigenetic Mechanisms Relevant to the Pathogenesis of ALS (5.4, 5.6)
- Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans (5.1, 5.6)
- Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF (5.5, 5.6)
- Memory and Mood Enhancing Therapies for Gulf War Illness (5.1, 5.6)
- Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology (5.5, 5.6)
- Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk (5.6)
- Novel neurotrophic therapies in an optimized mouse model of GWVI (5.1, 5.6)
- Neuroinflammation, Oxidative Stress, and Hippocampal Defects in GWI (5.5, 5.6)
- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats (5.6)

# Gulf War Research Projects Selected for funding

- Models of Care for Gulf War Veterans (5.1)
- Exercise and Autonomic Dysfunction (5.1, 5.5)
- Translational Approaches to Treating Gulf War Illness (5.1, 5.8)
- Healthcare Utilization Patterns for Gulf War Era Veterans (5.1)
- Gulf War Toxicants and Neurological dysfunction (5.6)
- Integrative Medicine for Gulf War Veterans (5.1)
- Treatments for Sleep Disorders in Gulf War Veterans (5.1)
- Gastrointestinal Pain in Gulf War Veterans (5.5, 5.8)
- Aging as a Risk Factor for GWI (5.1, 5.4, 5.6)

# Recently Completed Gulf War Research Projects

- Autonomic Functions of Gulf War Veterans with Unexplained Illnesses (5.1, 5.4)
- Motor Neuron Function of Gulf War Veterans with Excessive Fatigue (5.1, 5.4, 5.5)
- Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans (5.1)
- Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP (5.1)
- Behavior of Neural Stem Cells in a Rat Model of GWS (5.6)
- Multiple Sclerosis in Gulf War Veterans (5.3)
- A Randomized Controlled Trial of a Mindfulness-Based Intervention for Gulf War Syndrome (5.1)
- Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex (5.1)
- Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease (5.4, 5.6)
- Host Defense Mechanisms in Polyaromatic Hydrocarbon Carcinogenesis (5.5, 5.6)
- MEG Synchronous Neural Interactions (SNI) in Gulf War Veterans (5.5)
- rTMS for the Treatment of Chronic Pain in GW1 Veterans (5.1)

# Research Advisory Committee on Gulf War Veterans' Illnesses San Francisco, August 8-9, 2016

- Tony Wyss-Coray, PhD; Professor of Neurology, Stanford School of Medicine
  - <https://med.stanford.edu/profiles/tony-wyss-coray>
  - “Blood Proteins as Indicators and Modifiers of Brain Function”
- Sergio E. Baranzini, PhD; Professor of Neurology, UCSF
  - <http://baranzinilab.ucsf.edu/>
  - “Microbiome: The Gut-Brain Axis, or Neuro-gastroenterology”
- Joe DeRisi, PhD; Professor of Biochemistry and Biophysics, UCSF
  - <http://profiles.ucsf.edu/joe.derisi>
  - “Pathogen Detection”
- Adam Gazzaley, MD, PhD; Professor of Neurology, Physiology, and Psychiatry, UCSF
  - <http://gazzaleylab.ucsf.edu/>
  - <http://www.nature.com/news/gaming-improves-multitasking-skills-1.13674>
  - “Neuromodulation: Video Games meet Neuroscience – The Vision of the Future of Brain Optimization”

# Dr. Tony Wyss-Coray, Stanford

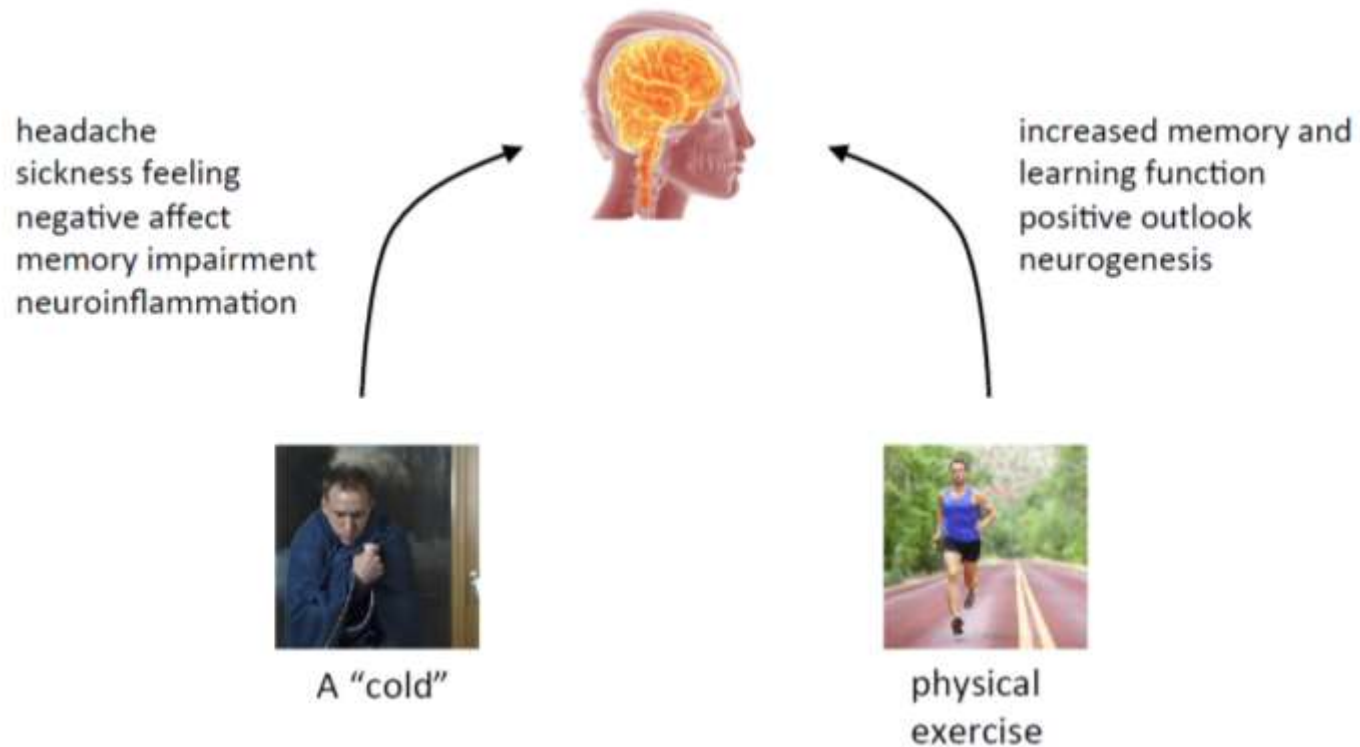
**Tony Wyss-Coray, PhD**  
**Professor of Neurology, Stanford**

## **Focus Areas**

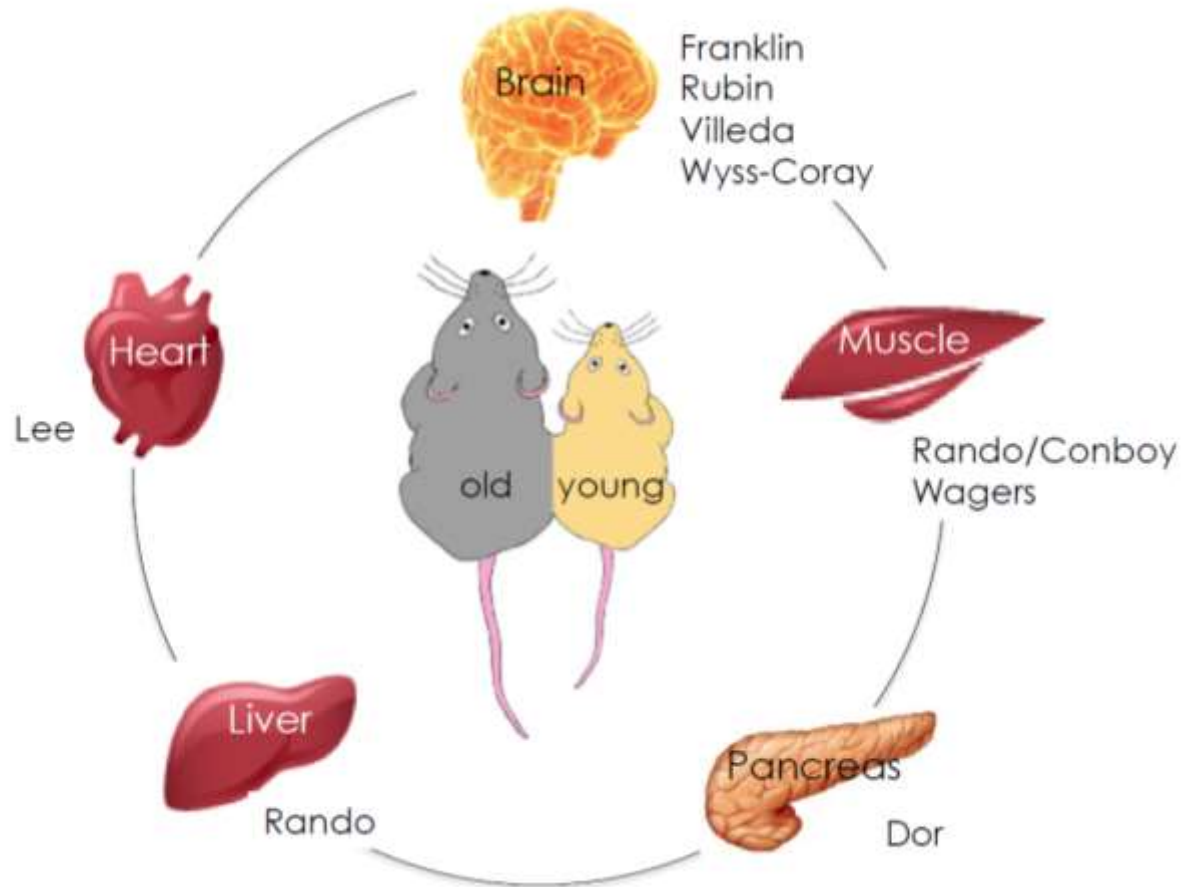
- Age-related diseases; Cognitive Aging
- Neurologic diseases
- Protein biomarkers
- Parabiosis

# Dr. Tony Wyss-Coray, Stanford

## Genes, Environment, and Aging affect Brain Health



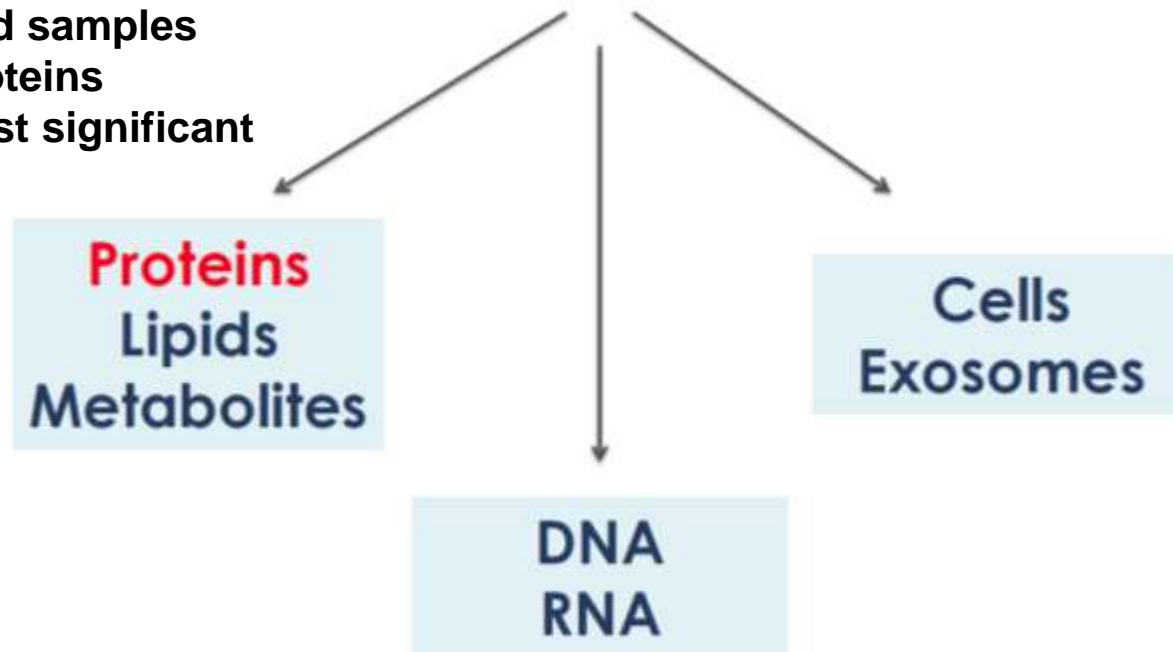
# Dr. Tony Wyss-Coray, Stanford “Parabiosis”



# Dr. Tony Wyss-Coray, Stanford

Systemic cellular and molecular changes in the periphery/blood

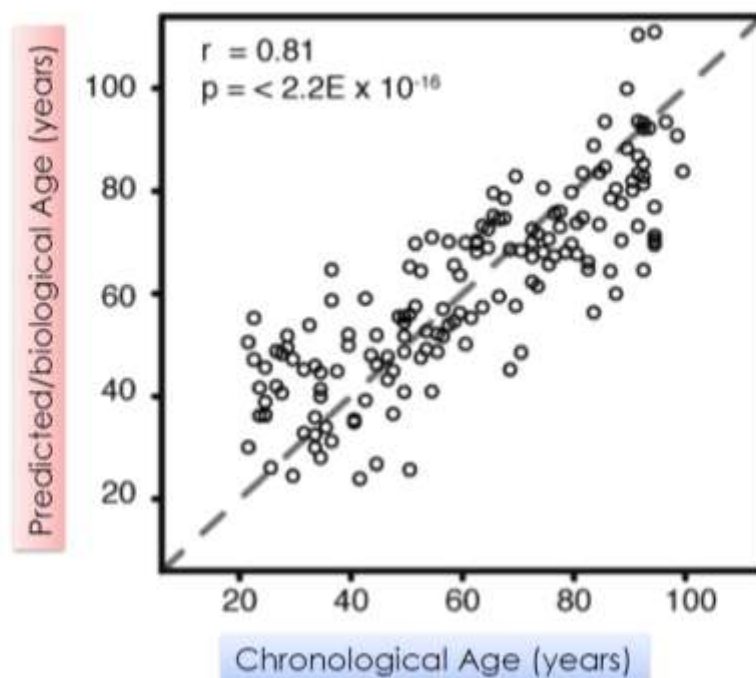
- 295 blood samples
- > 100 proteins
- 9 are most significant





# Dr. Tony Wyss-Coray, Stanford

## Prediction of “Biological Age” using top aging factors in human



# Dr. Tony Wyss-Coray, Stanford

## **Effects of “Rejuvenation” using Parabiosis**

- Increased neurogenesis
- Increased synaptic activity
- Increased plasticity-related gene expression
- Increased spine density
- Improved memory and cognition
- Reduce inflammation

## **Same Effects using Injected Plasma**

# Dr. Tony Wyss-Coray, Stanford

## Application to Alzheimer's Disease

- **Mouse Model**
- Amyloid Precursor Protein (APP) – mouse model
- Injections of “young” plasma improved learning, memory, behavior
  
- **Human Test**
- ClinicalTrials.gov - #NCT02256306
- One unit of “young” plasma per week
- Molecular tests, cognitive abilities, daily activities (from caregivers)

# Dr. Tony Wyss-Coray, Stanford

## **Plasma Studies in humans (underway or planned)**

- Alzheimer's disease
- Progressive supranuclear palsy
- Parkinson's disease
- Amyotrophic lateral sclerosis
- Depression

## Dr. Tony Wyss-Coray, Stanford Summary

- Circulatory factors from mouse or human blood can modulate aspects of brain aging and cognitive function
- Individual proteins which replicate some of these effects can be identified and used as therapeutic agents or, possibly, as biomarkers.

# Dr. Sergio Baranzini, UCSF

**Sergio E. Baranzini, PhD**  
**Professor of Neurology, UCSF**

## **Focus Areas**

- Microbiome of the gut
- Effects of microbiome on the immune system
- Applications to diseases
- Interrelation of the enteric nervous system and central nervous system

# Dr. Sergio Baranzini, UCSF

## Definitions:

- **Microbiota:** A collection of microbial communities living in a specific niche
- **Microbiome:** The collective set of genes from a given microbiota
- **Probiotic bacteria:** Live microorganisms which when administered in adequate amounts confer a health benefit on the host
- **Prebiotics:** Selectively fermented food ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confer benefits upon host health
- **Enteric Nervous System:** Mesh-like system of neurons that controls the gastrointestinal system

# Dr. Sergio Baranzini, UCSF

## **Microbiome Characteristics:**

- Composition of human gut microbiota:  $10^{13}$  –  $10^{14}$  microorganisms
- Collective microbiome is 100 to 150 times the human genome
- Microorganisms in the gut affect immune responses through the interaction of their metabolism with that of humans

## **Microbiome:**

- Varies with anatomical location of human body, but metabolic pathways remain constant
- Varies with ethnicity
- Correlates with diet



# Dr. Sergio Baranzini, UCSF

## **Examples of Research Studies**

- Microbiota and Obesity
- Microbiota and Cancer Therapy
- Normal Gut Microbiota modulates brain development and behavior
- Lactobacillus modulates emotional behavior via vagus nerve
- Microbiota and Autism
- Microbiota and Immune System

# Dr. Sergio Baranzini, UCSF

## Effect of Gut Microbiota in Autoimmune Demyelination

- Cells cultured with gut bacteria from multiple sclerosis (MS) patients show reduced immune response (58 patients)
- Experimental Autoimmune Encephalomyelitis (EAE) induces brain inflammation & demyelination in mice (model for Multiple Sclerosis)
- Mice fed MS bacteria show higher EAE scores
- DNA of individual microorganisms is being sequenced to identify those found in MS patients
- Testing MS-associated bacteria in mice
- The International MS Microbiome Study

# Dr. Joe DeRisi, UCSF

**Joseph DeRisi, PhD**

**Professor of Biochemistry and Biophysics, UCSF**

## **Focus Areas**

- Identify disease-causing microorganisms by analyzing DNA or RNA
- Small amount of DNA/RNA from microorganisms in a large amount of human DNA (“needle in a haystack”)
- Develop techniques isolate DNA/RNA from microorganisms
- Variety of specimens (blood, tissue, cerebrospinal fluid (CSF), intraocular fluid)

# Dr. Joe DeRisi, UCSF

## **Examples of Microorganisms Detected/Diagnosed:**

- Herpes Simplex 1 (HSV-1)
- Rubella virus
- West Nile virus (renal transplant)
- Malaria (*Plasmodium falciparum*)
- Amoeba (*Balamuthia mandrillaris*)
- Fungus (*Cryptococcus neoformans*)
- Tapeworm (*Taenia solium*)
- Protozoan (*Toxoplasma gondii*)

# Dr. Adam Gazzaley, UCSF

**Adam Gazzaley, MD, PhD**

**Professor of Neurology, Physiology, and Psychiatry, UCSF**

## **Focus Areas**

- Enhance cognitive abilities in healthy patients or those with neurological diseases
- Educational – help young minds develop
- Improve how the brain functions
- Improve neuroplasticity (the brain's ability to modify itself)

# Dr. Adam Gazzaley, UCSF

## **Treating Neurological Problems:**

- Targeted
- Personalized
- Multimodal
- Closed-loop

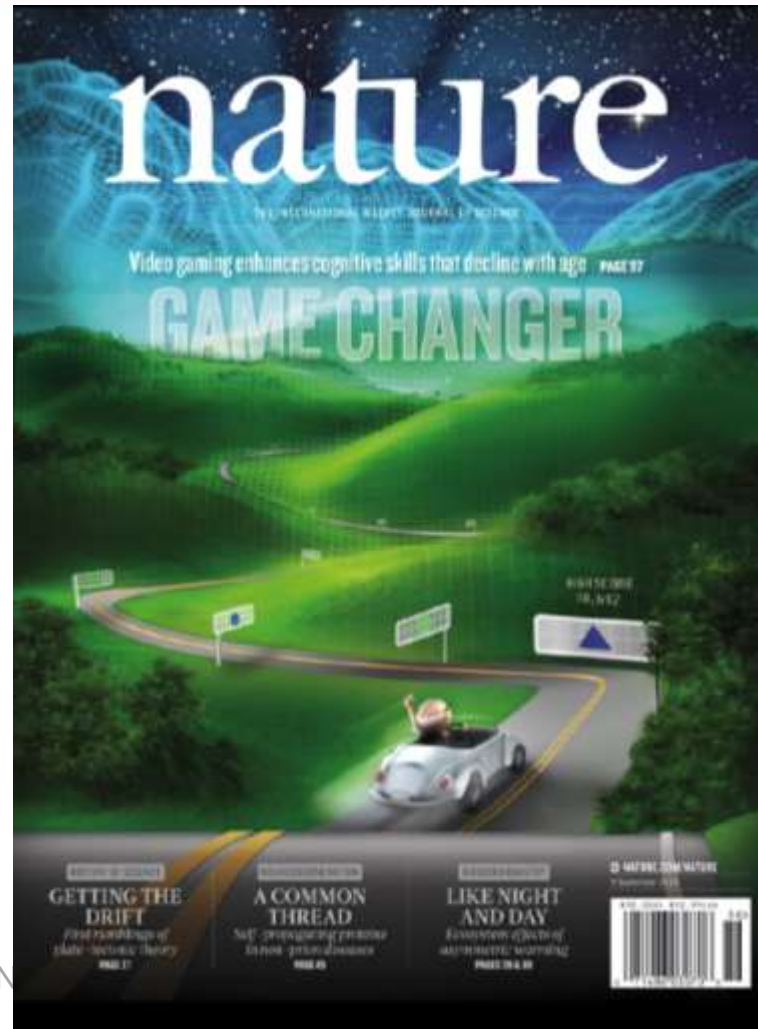
## **Using Consumer-Level Information Technology:**

- Virtual Reality
- Augmented Reality
- Wearable Physiological Devices
- 3-D Video Games Engines
- Artificial Intelligence
- Motion Capture

# Neuroracer (Dr. Gazzaley, UCSF)

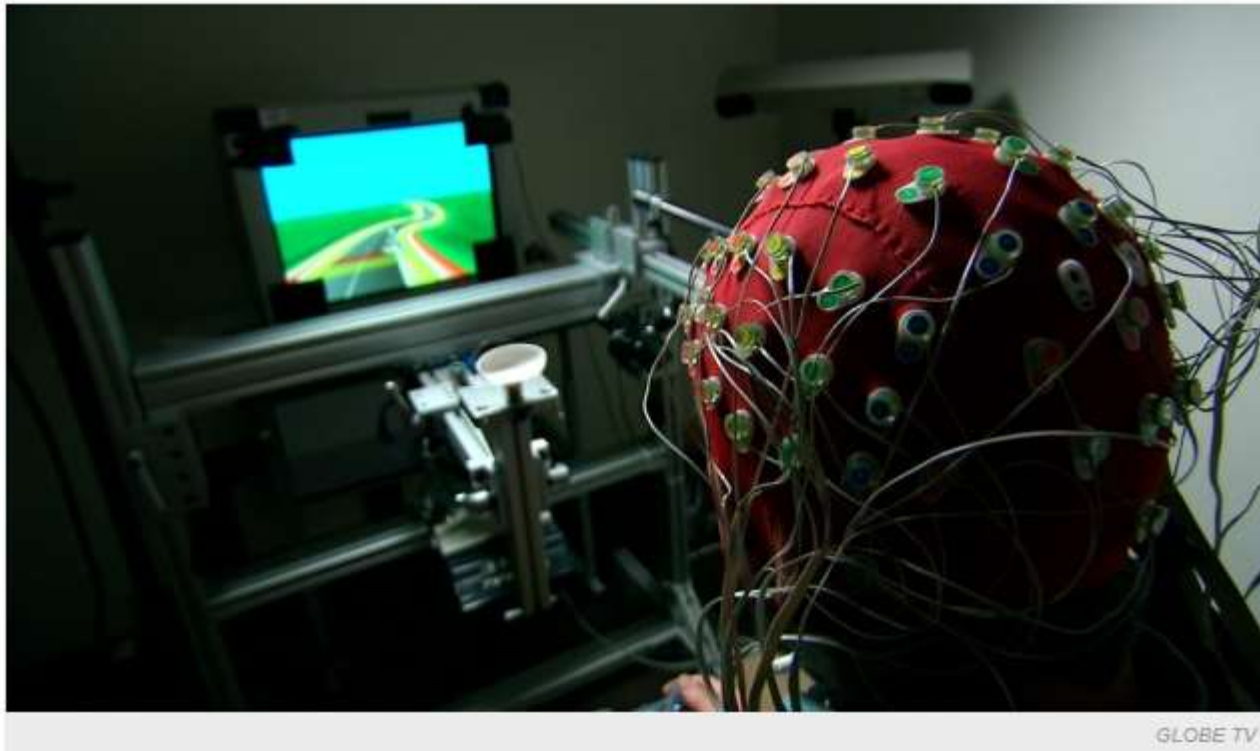


Nature, Sep 5, 2013  
Vol. 501, No. 7465, p. 18





# Neuroracer (Dr. Gazzaley, UCSF) EEG



Nature, 2013 (Sep 5); 501(7465):18

<http://www.nature.com/news/gaming-improves-multitasking-skills-1.13674>

# Dr. Adam Gazzaley, UCSF

## **Couple the Video Games with:**

- EEG (electroencephalogram) topology plots
- MRI (magnetic resonance imaging)
- Cognitive testing
- Blood tests  
(inflammatory markers, hormones, proteins, etc.)

# Video Games (Dr. Gazzaley, UCSF)

- **New Video Games**

- **Meditrain** - Concentrated meditation with feedback to learn how to control internal distractions
- **Rhythmicity** - Using the rhythm of music to help the rhythms of the brain to improve cognitive function
- **Virtual Attention** - Learning to focus and broaden one's attention over space and time
- **Body-Brain Trainer** - Combines cognitive and physical feedback to modify the game to keep your heart rate in an optimum range

- **Enhance the Effects of Video Games**

- Neuromodulation
- Neurofeedback

## Research Over the Next Ten Years (Dr. Gazzaley, UCSF)

- **PTSD – (in conjunction with VA)**
- **Traumatic Brain Injury**
- **Alzheimer's Disease**
- **Parkinson's Disease**
- **Multiple Sclerosis**
- **Attention Deficit Disorder**
- **Anxiety Disorder**
- **Schizophrenia**
- **Depression**
- **Addiction**
- **Autism**

# Websites of Interest

## Gulf War Research

- <http://clinicaltrials.gov> Information on current and past clinical treatment trials
- <http://projectreporter.nih.gov/> Current and previously funded research projects
- <http://www.ncbi.nlm.nih.gov/pubmed> Published results of research studies
- <http://www.publichealth.va.gov/> VA's Post-Deployment Health Service website
- <http://www.research.va.gov/> VA's Office of Research and Development
- <http://www.research.va.gov/pubs/docs/GWRResearch-StrategicPlan.pdf>
- [http://www.research.va.gov/programs/tissue\\_banking/gwvib/default.cfm](http://www.research.va.gov/programs/tissue_banking/gwvib/default.cfm)
- <http://www.research.va.gov/programs/csp/585/default.cfm>
- <http://www.va.gov/rac-gwvi/> Research Advisory Committee on Gulf War Veterans' Illnesses

# Gulf War Research Activities

**QUESTIONS?**