

National Institute on Aging

University of Southern California  
Alzheimer Disease Research Center  
(ADRC)

**Reducing Alzheimer and Vascular  
Contributions to Cognitive Impairment in  
Diverse Populations.**

# USC ADRC

1. Clarify how vascular factors contribute to cognitive impairment alone or in combination with AD.
2. Promote clinical trials and translational research in memory and aging at USC.
3. Increase recruitment and retention into UDS of minority subjects from USC's LALES (Latino) and CHES (Chinese) projects and surrounding neighborhoods.
4. Continue active participation in national initiatives, including NACC, ADCS, ADNI, and GWAS.

## Admin Core

Chui, Finch, Taylor-Munoz

Internal  
Advisory

External  
Advisory

## Data Core

Mack

## Ed Core

Gatz

## Clinical Core

Schneider

## Path Core

Miller

## Imaging Core

Singh

### Project 1

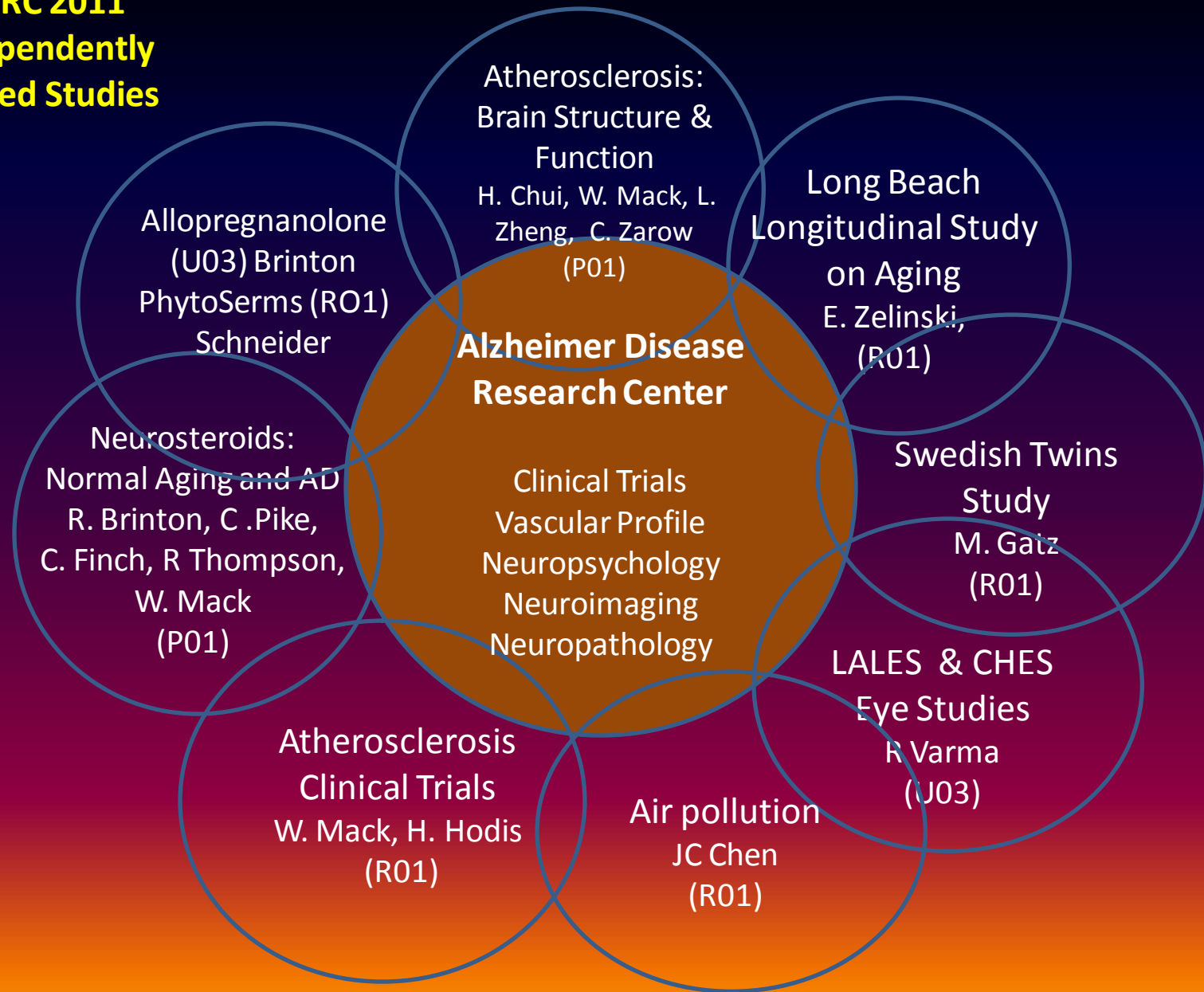
Cognitive  
Trajectories Long  
Beach  
Zelinski

### Project 2

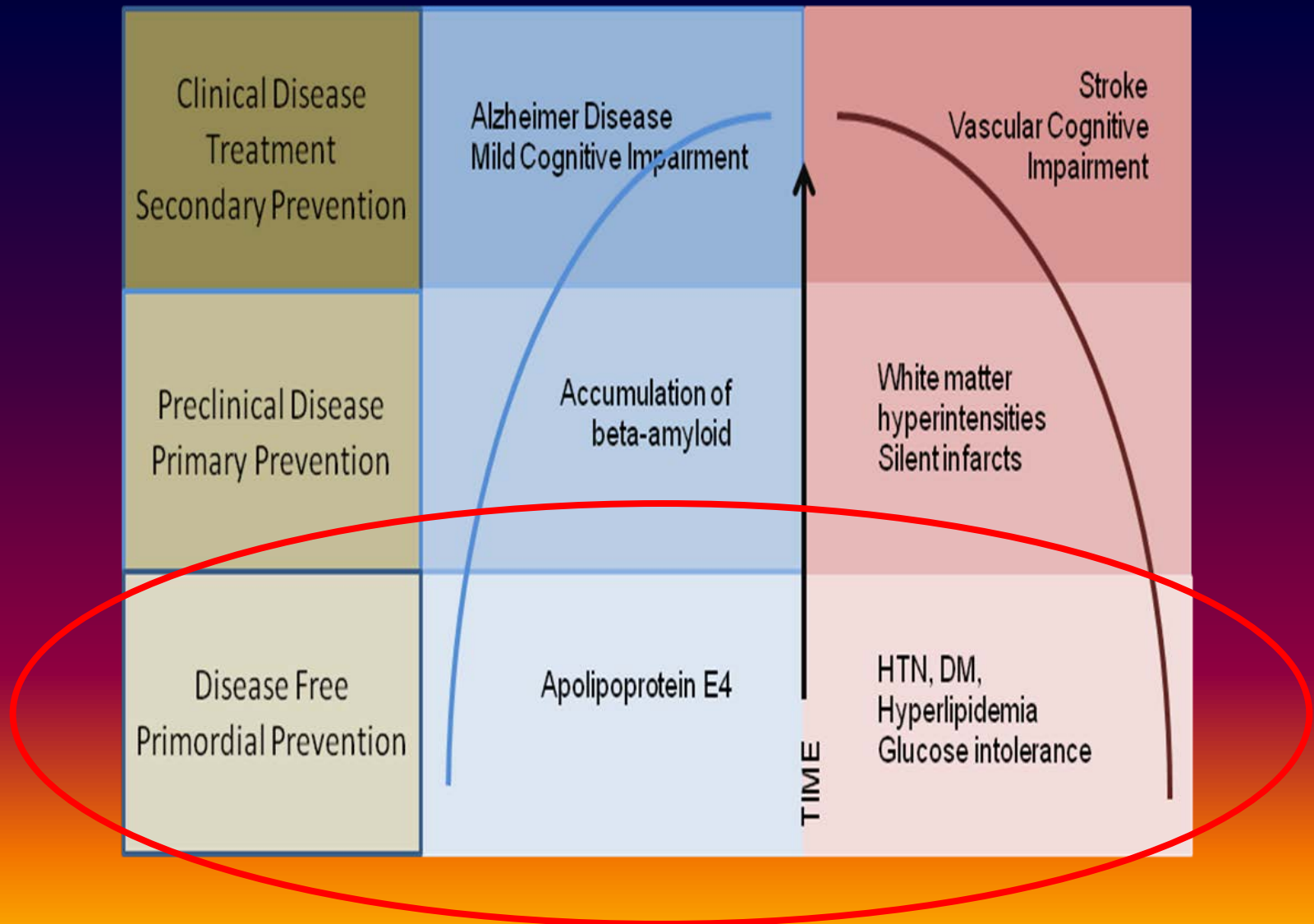
Neuro Selective  
Estrogen and  
Androgen Receptor  
Modulators  
Brinton, Pike

Pilot Projects

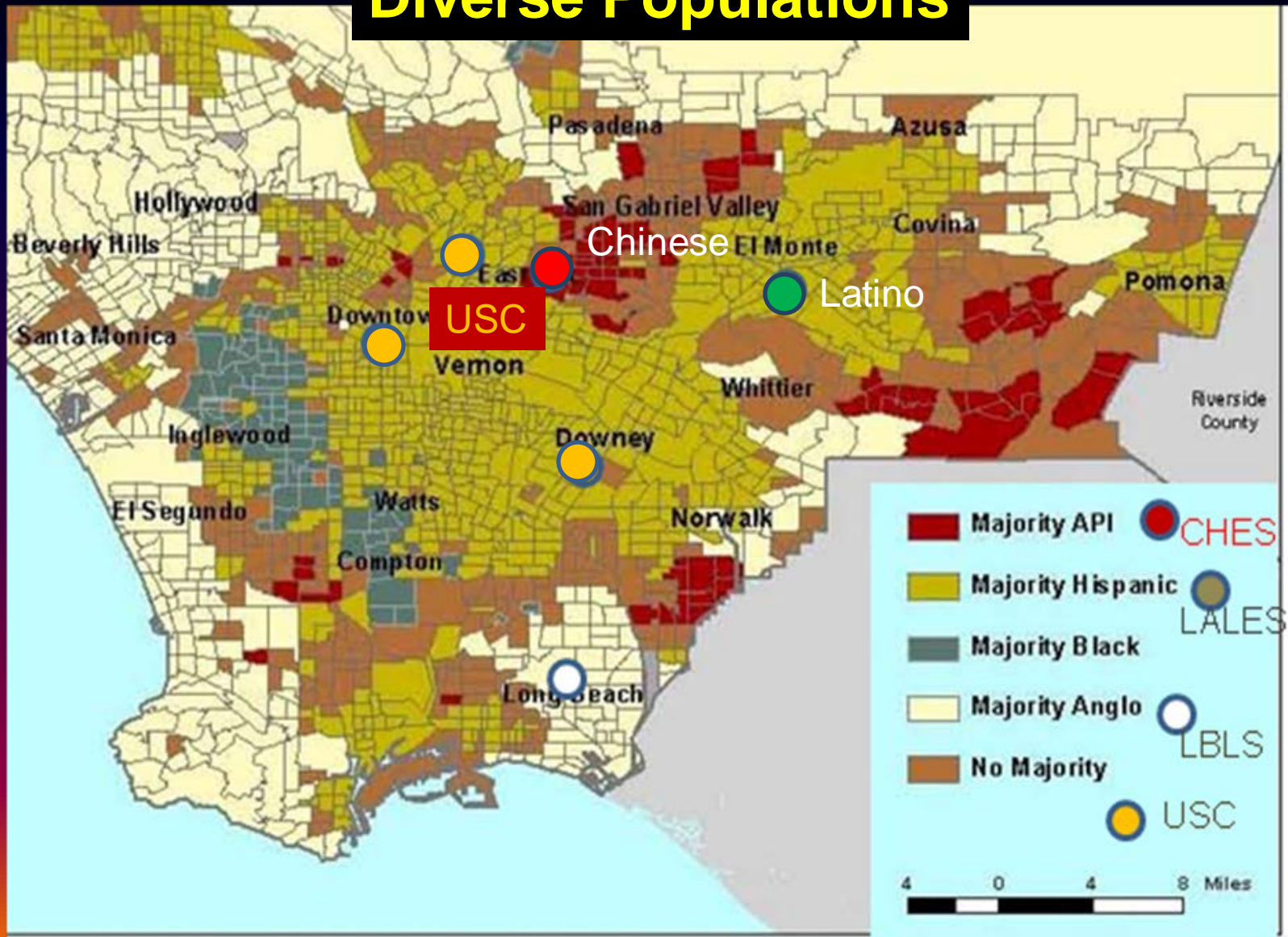
**ADRC 2011**  
**Independently**  
**Funded Studies**



# Reducing Alzheimer and vascular Contributions to cognitive impairment



# Diverse Populations



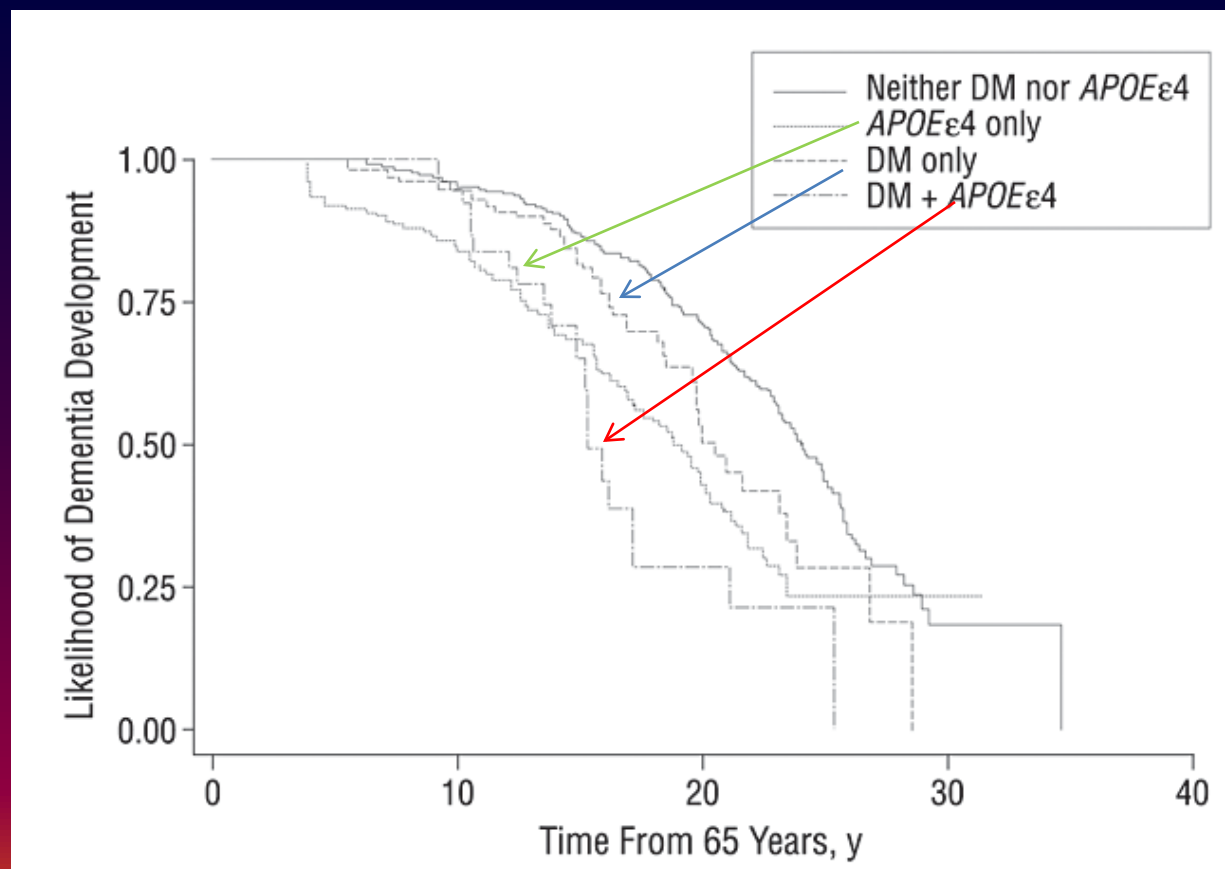
Monta and Paul Ong, UCLA Lewis Center for Regional Policy Studies

**Prevalence of Vascular Risk Factors  
among adults  $\geq 50$  years of age by race/ethnicity,  
Behavioral Risk Factor Surveillance System, 2001-2004**

<b>Characteristics</b>	<b>White</b>	<b>Black</b>	<b>Asian</b>	<b>Hispanic</b>
<b>N</b>	387,201	28,464	4,925	16,089
Diabetes (%)	12	<b>23.9</b>	14.2	<b>20.1</b>
Obese (%)	22.7	<b>35.8</b>	6.1	<b>27.7</b>
Hypertension (%)	44.2	<b>63.6</b>	40.3	42.5
Hypercholesterolemia(%)	<b>42.5</b>	38.7	39.6	34.8
Current smoker (%)	15.5	19.9	8	13.2
Former smoker (%)	<b>38.8</b>	30.1	22.2	30.3



**Kaplan-Meier log-rank test for equality of developing dementia,  
stratified by diabetes mellitus (DM) and the APOE  $\epsilon$ 4 allele  $X^2=64.9$  ( $P<.001$ )  
Cardiovascular Health Study (n=2,547)**



Irie, F. et al. Arch Neurol 2008;65:89-93.



# Swedish Twin Study

## Margaret Gatz

Diabetes before age 65 Is risk factor for dementia (vascular > Alzheimer).

	Subjects ( <i>n</i> )	All dementia	Alzheimer's disease	Vascular dementia
Diabetes status				
No	12,296	498; 1.00 (reference); 1.00 (reference)	236; 1.00 (reference); 1.00 (reference)	74; 1.00 (reference); 1.00 (reference)
Yes	1,396	139; 2.45 (1.97–3.03)*; 1.89 (1.51–2.38)†	56; 2.03 (1.47–2.80)*; 1.69 (1.16–2.36)†	31; 3.60 (2.33–5.57)*; 2.17 (1.36–3.47)†
Age of diabetes onset				
<65 years	643	48; 2.95 (2.14–4.08)*; 2.76 (1.97–3.87)†	16; 2.32 (1.37–3.94)*; 2.25 (1.29–3.92)†	12; 4.94 (2.61–9.35)*; 3.94 (1.90–8.15)†
≥65 years	753	91; 2.12 (1.64–2.75)*; 1.63 (1.23–2.16)†	40; 1.88 (1.29–2.74)*; 1.56 (1.05–2.32)†	19; 2.90 (1.70–4.94)*; 1.62 (0.92–2.80)†

Data are *n*; OR (95% CI) or OR (95% CI). \*Adjusted for age, sex, and education. †Adjusted for age, sex, education, stroke, heart disease, hypertension, and BMI.

# Vascular Factors

## Increase Risk of Cognitive Impairment

### Vascular Factors

- Diabetes Mellitus
- Hyperlipidemia
- Hypertension
- Atherosclerosis
- Amyloid angiopathy

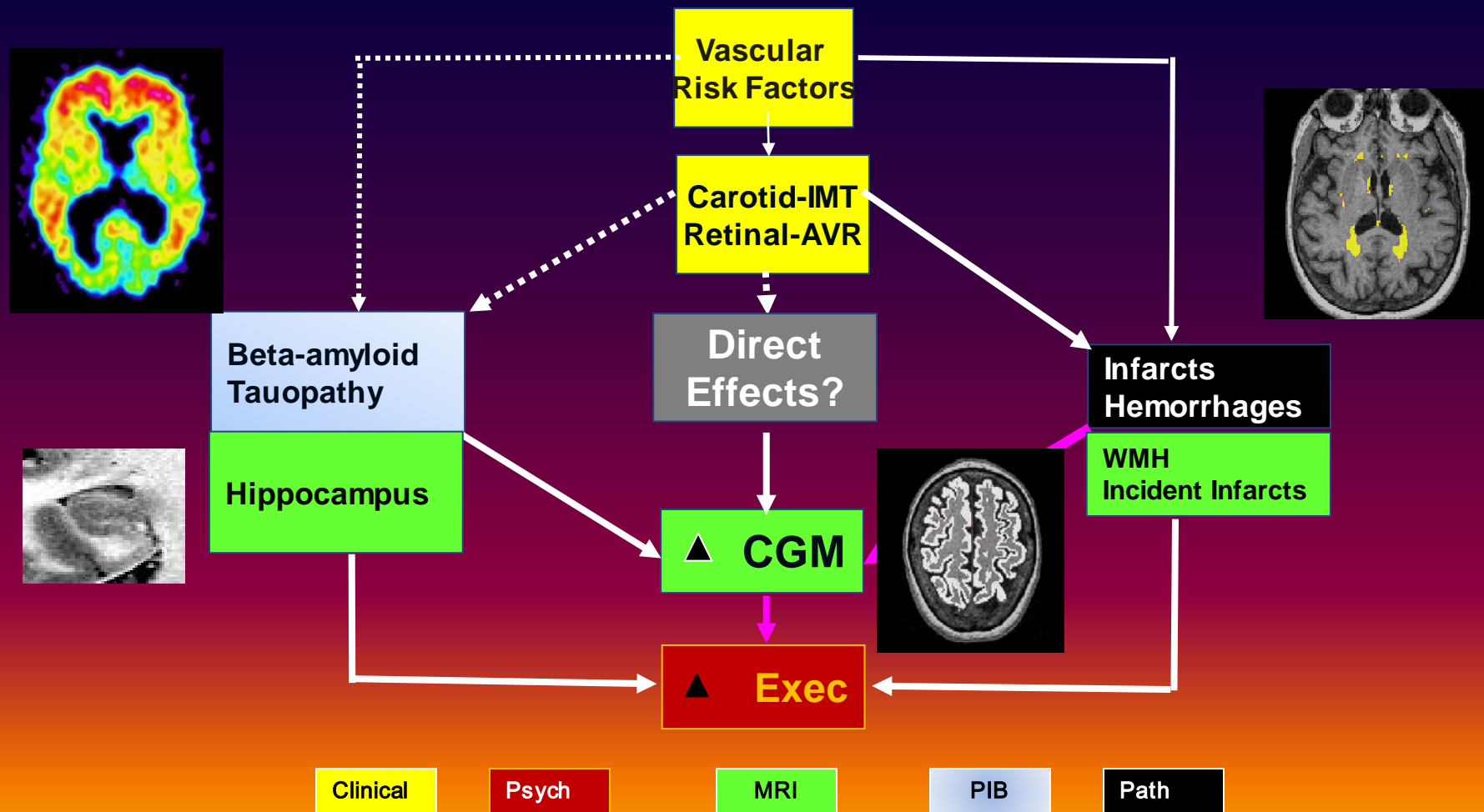
### Mechanism?

- Ischemic infarction
  - Strokes (symptomatic infarcts)
  - Microinfarcts
- Increase AD pathology?
  - Plaques and tangles
- Metabolic dysfunction?
  - Mitochondria

# USC ADRC

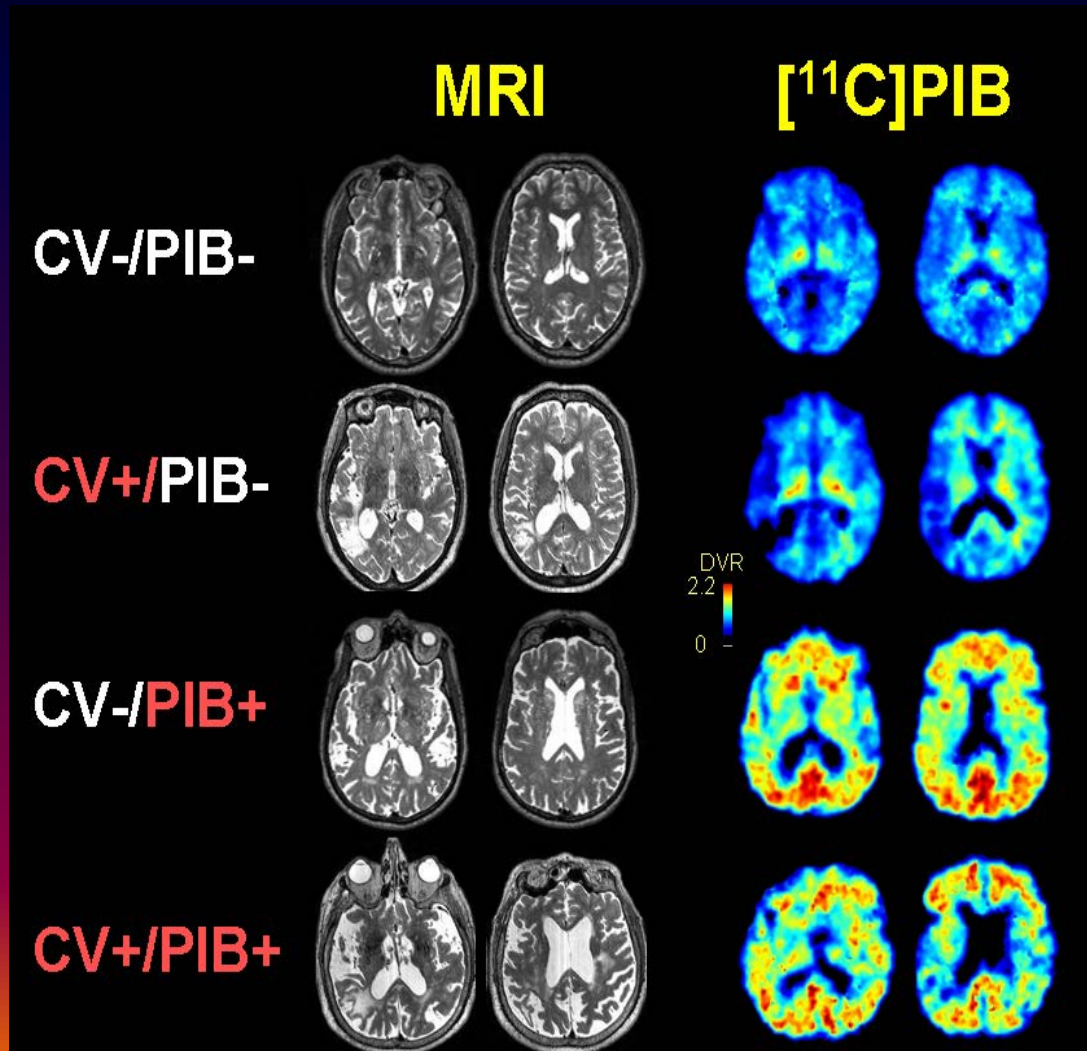
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**Program Project (Chui): The Aging Brain (USC, UCD, UCSF, UCLA, UCB)**  
**ADRC Project 1 (Zelinski): The Course of Cognitive Change in Late Life**



Infarcts on MRI for VCI

Amyloid PET for AD



*Rabinovici GC. Presented at Human Amyloid Meeting, Toronto, 2010  
Aging Brain Program Project: USC, UCD, Berkeley, UCSF, UCLA*

# Project 1: Zelinski

## The course of cognitive change in late adulthood

- The goal of this project is to combine the extensive psychometric longitudinal data obtained for up to 15 years from participants in the Long Beach Longitudinal Study (LBLE), a group of initially healthy adults,
- With vascular and brain structure measures collected at two time points three years apart to test hypotheses about vascular and AD correlates of the development of cognitive declines.

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# USC Atherosclerosis Clinical Trials

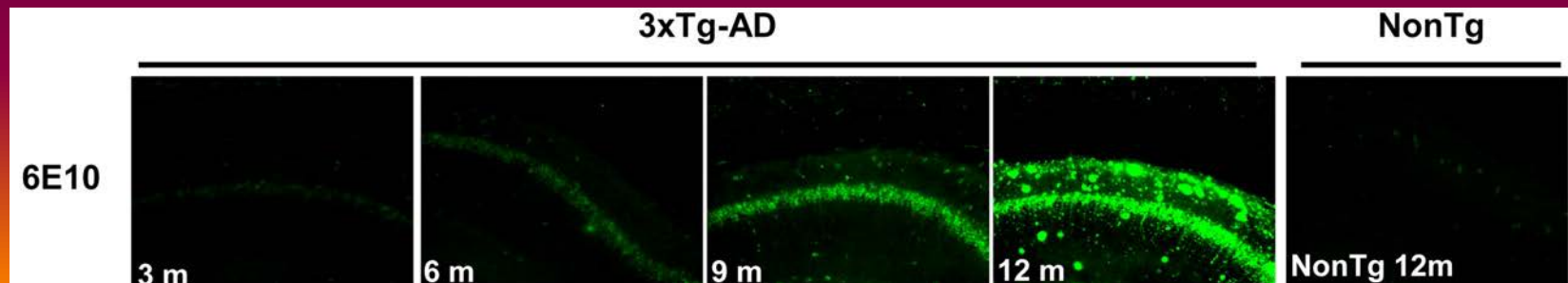
## Howard Hodis & Wendy Mack

- Estrogen in the Prevention of Atherosclerosis Trial (NIH AG-18798):
  - 43% ethnic minority, 21% Latino.
- Women's Estrogen-Progestin Lipid-Lowering Atherosclerosis Trial (NIH HL-49298):
  - 69% ethnic minority, 44% Latino.
- Troglitazone Atherosclerosis Regression Trial (Parke-Davis):
  - 89% Latino
- B-Vitamin Atherosclerosis Intervention Trial (NIH AG-17160):
  - 35% ethnic minority, 11% Latino
- Vitamin E Atherosclerosis Prevention Study (NIH AG-13860):
  - 26% ethnic minority
- Women's Isoflavone Soy Health Trial (NIH AT-001653):
  - 37% ethnic minority, 16% Latino
- Early-Late Intervention Trial of Estradiol (NIH AG-024154):
  - 32% ethnic minority, 13% Latino.

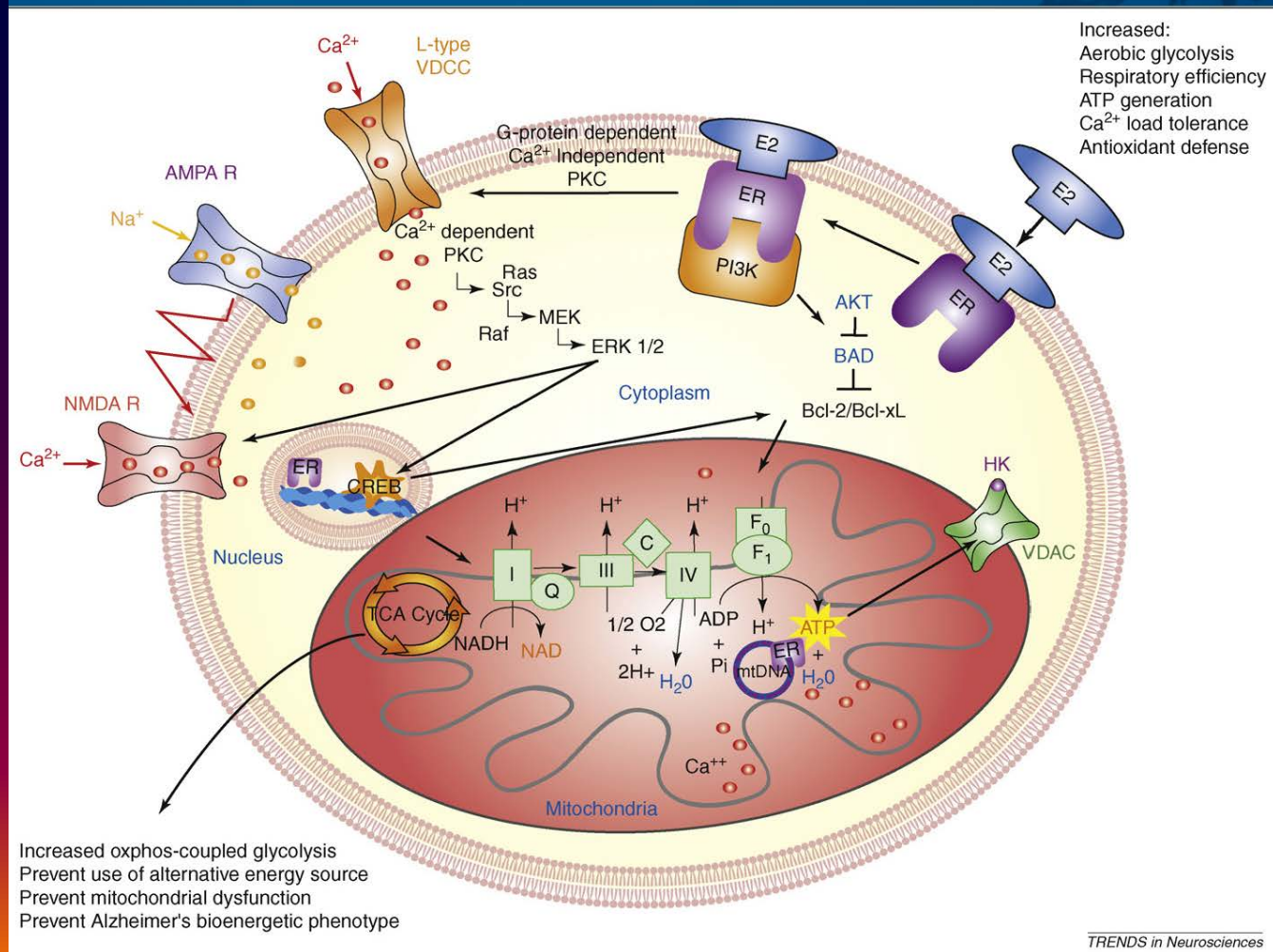
# ADRC Project 2: Brinton & Pike

## Determine the efficacy of candidate NeuroERMs and NeuroARMs to:

- ❖ Induce markers of neuroprotection, neural defense, vascular viability and to modify AD pathology development *in vitro*.
- ❖ 1) reduce levels of tau phosphorylation and A $\beta$  accumulation; 2) prevent cognitive deficits; 3) protect against vascular injury; and 4) prevent proliferation in reproductive tissues in the 3xTg-AD triple transgenic mouse model of Alzheimer's pathology.



# Estradiol-Induced Neuroprotective Signaling Pathways Converge on Mitochondria



# Estrogen Therapy Alternatives for the Brain

1997 – 2007 National Institute on Aging (2 PO1 AG14751)

Project 2 – Models of Estrogen Interactions with Alzheimer's Disease, Finch PI

2003 – 2008 National Institute of Mental Health (R01 MH67159-01A1) Estrogen-Induced Neuroprotective Mitochondrial Mechanisms Brinton, PI

PhytoSERMs

Natural Source Estrogen Molecules

Nutraceutical Strategy

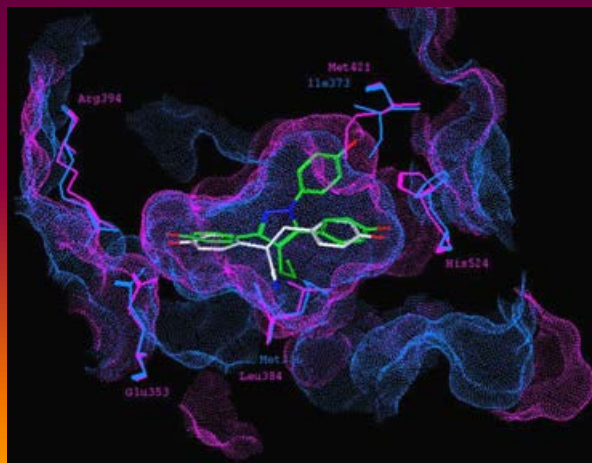
Dev 2-5 yrs

NeuroSERMs

Novel Designer Estrogen Molecules

Pharmaceutical Strategy

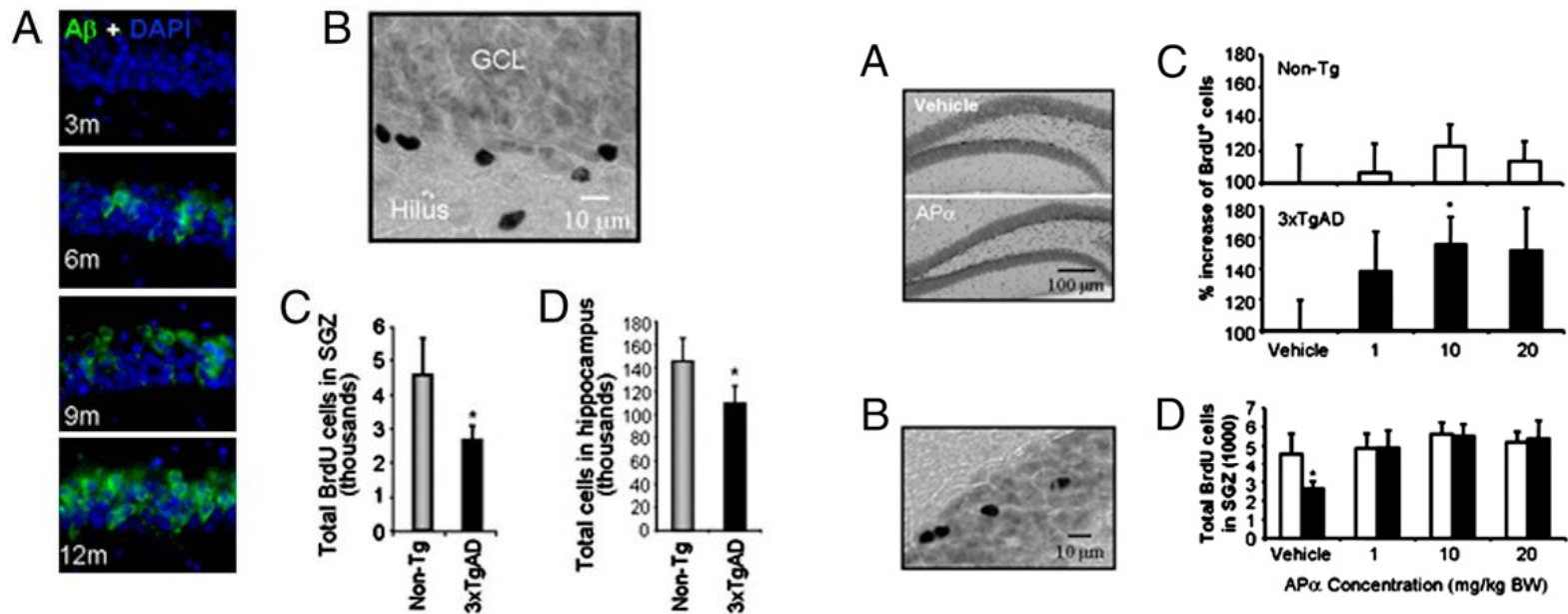
Dev 7-15 yrs



# Allopregnanolone

## Brinton & Schneider

Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease



Wang, JM et al., PNAS 2010; 107: 6498-503.

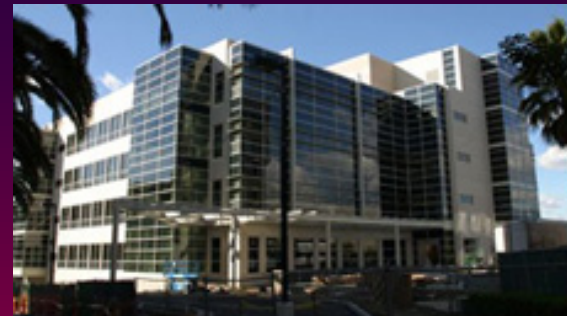


The  
University of Southern California  
Memory and Aging Center  
[www.usc.edu/adrc](http://www.usc.edu/adrc)

The  
Doctors  
of USC

Information, appointments, research participation, and referrals call:

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Los Angeles, CA  
(323) 442-7600  
[gsc@usc.edu](mailto:gsc@usc.edu)



Rancho Los Amigos National  
Rehabilitation Center  
Downey, CA  
(562) 401-8130



# Thank you!



## USC ADRC Clinical Core