



#### Dissecting the Neural Circuitry of ASD with Tuberous Sclerosis as a Model

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## [Pll redacted] Story

- At 20 week *in utero* ultrasound showed "growths" in his heart
- Fetal MRI showed tubers in the brain
- Born at full term
- Started having seizures at 3 months



## [Pll redacted] Story



Today, [Pll redacted] seizures are under good control.

He has significant sleep problems.

[Pll redacted] was diagnosed with autism spectrum disorder.

#### Why is TSC a good model to study autism?

- ~ 50% of TSC patients are affected with Autism Spectrum Disorder.
- Many of the TSC patients may be diagnosed before birth or at the time of birth.
- Cellular mechanisms aberrant in TSC are beginning to be understood.
- FDA-approved specific inhibitors are available.

#### What is Tuberous Sclerosis Complex?

- Causes benign tumors in brain, eye, skin, kidneys, and heart
- Usually presents with seizures, intellectual disability, autism
- Incidence: 1:6,000-10,000
- Genes: TSC1 and TSC2

#### **TSC** is a disease of cell size...





Tapon et al., 2001



## **Cortical Tubers and Autism**

- Cortical tubers in temporal lobes necessary, but not sufficient (Bolton et al., *Brain* 2002).
- Several studies have failed to show a similar correlation, and others have implicated tubers in the cerebellum as a correlate of autism.
  - Walz et al., J Child Neurol 2002
  - Weber et al., J Autism Dev Disord 2000
  - Wang et al., J Child Neurol 2006
  - Eluvathingal et al., J Child Neurol 2006

#### Hypothesis: Miswiring of neuronal connections may contribute to the pathogenesis of TSC

## **Cerebellum in Autism and TSC**

- Most consistent finding on brain pathology in ASD: reduced Purkinje cell numbers
- 37% of newborns with isolated cerebellar hemorrhage are diagnosed with subsequent ASD (Limperopoulos et al., 2007)
- Hypermetabolism in deep cerebellar nuclei (PET imaging) in TSC patients with ASD vs No ASD (Asano et al., 2001)

#### **Autistic-like Behaviors in TSC Mice**



**Social Approach** 



Treatment with rapamycin prevents autistic-like features

Tsai et al., Nature, 2012

## Autism spectrum disorders: developmental disconnection syndromes

Daniel H Geschwind<sup>1</sup> and Pat Levitt<sup>2</sup>



# Many of the TSC patients are diagnosed pre- or neo-natally



Among fetuses or newborns with multiple cardiac tumors, the chances of having TSC is 95%.

> Tworetzky et al., Am J Cardio (2003)

### **Early Detection of Autism in TSC**

<u>Can we detect which infants with</u> <u>TSC will develop autism?</u>

- 1. Neurocognitive assessment of infants
- 2. Diffusion tensor imaging (MRI)
- 3. Neurophysiological assessment of face processing and other visual paradigms

In collaboration with Simon Warfield, Shafali Jeste and Chuck Nelson



#### **Diffusion Tensor Imaging**









TSC ASD+ 4.9 yo AFA 0.34 TSC

TSC ASD- 4.7 yo AFA 0.54

Control 5.3 yo AFA 0.53



#### **TACERN** (<u>T</u>SC <u>A</u>utism <u>C</u>enter of <u>E</u>xcellence <u>R</u>esearch <u>N</u>etwork)







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## mTOR inhibitors in TSC mouse models

- 1. Improves myelination and seizures (Meikle et al., 2008)
- 2. Prevents or stops seizures (Zeng et al., 2008)
- 3. Improves learning (Ehninger et al., 2008)
- 4. Prevents autistic-features (Tsai et al., 2012)

Randomized Phase II Trial of an mTOR inhibitor in TSC: <u>Neurocognition</u>

- 6-21 year olds with TSC, IQ>60
- Randomized placebo controlled, double blind
- 50 patients from 2 sites (Cincinnati & Boston)
- Neurocognitive testing at baseline, 3 months, 6 months
- Secondary endpoints: autism, seizures, sleep

#### **Developmental Synaptopathies Consortium (NIH)**



#### **Summary**

- TSC is a model for understanding the early biomarkers associated with ASD.
- Mutations in TSC genes affect neuronal connectivity.
- Mouse models of TSC provide insight into autisticlike behaviors and enable pre-clinical trials.
- Treatment trials in TSC may shed light on related neurodevelopmental disorders.