Thank you:

NFAR
NIMH, NINDS and NICHD
Simons Foundation
Peter Emch Family Foundation
Autism Speaks
NICHD-UMB Brain Bank
ATP/Harvard Brain Bank

Karen Pierce

Sierra

Taran
Autism in the First Years of Life

Eric Courchesne and Karen Pierce
UC San Diego
Autism Center of Excellence

Dedicated to the memory of Gail Courchesne, loving mother and gifted musician
RED FLAGS of Autism Spectrum Disorder by 12-24 Months

**Reduced social interest and affect**
- lack of warm, joyful emotional expressions
- lack of sharing emotional enjoyment or interest
- lack of response to name
- lack of showing and interacting

**Abnormal language development**
- Lack of coordination of gaze, facial expression, gesture & sound during interactions
The Prospective Study of Autism

1 Yr Well-Baby Check-Up Approach

- Fast
- Easy
- Investigates autism as it occurs in the population

Karen Pierce et al., 2011
J. Pediatrics
CSBS DP Infant-Toddler Checklist

Social Communication Composite

Expressive Speech Composite

Symbolic Composite
Dr. Robert Bjork, Dr. Michael Nelson, Dr. Cheryl Jennett
Dr. Dr. John Kafa, Dr. Douglas Wilson, Dr. Crystal De Freitas
Dr. Martin Gilboa, Dr. Patricia Juarez, Dr. George Madany,
Dr. Seven Brody, Dr. Ingrid Martinez-Andree, Dr. Irene Chang
Dr. Stephanie Powell, Dr. Adam Breslow, Dr. Patricia Pisinger
Dr. Isabel Baratta, Dr. Sheila Cason, Dr. Thomas Neglia
Dr. Stephen Balch, Dr. Randall Metsch, Dr. David Schmottlach
Dr. Sonja Brion, Dr. Anna Mendenhall, Dr. Nancy Clementino
Dr. Marshall Littman, Dr. Leslie McCormick, Dr. Sharon Sternfeld
Dr. Cara Cohen, Dr. Nicholas Tsoulos, Dr. Elena Fishman
Dr. Hilary Bowers, Dr. Albert Martinez, Dr. Genevieve Minka

Dr. Wendy Chacon, Dr. Leon Kelley, Dr. Victor Lipps, Dr. Jeffrey Selzer, Dr. Lynn Herring, Dr. Teresa O’dia, Dr. Richard Walls, Dr. Vivian Tung, Dr. Christian Archambault, Dr. Veronique James, Dr. Stuart Cohen, Dr. Nancy Shiau, Dr. Linda Smith, Dr. Tavar Henderson, Dr. Cheryl Merrall, Dr. Joseph Zumwalt, Dr. Derek Dubeye, Dr. Andrea Siano, Dr. Aida Martin, Dr. Gustafson, Dr. Rosemary Page, Dr. Maria Gollub, Dr. Jill Jones, Dr. James Moseman, Dr. Snyder Block, Dr. Lori Warner, Dr. Sheetal Ghatwani, Dr. Jorgensen, Dr. Richard Siegel, Dr. Lori Gould, Dr. Gabriela Mogrovejo, Dr. Julie Keeler, Dr. Liz Hourihan, Dr. Dania Lindenberg, Dr. Dori Mortimer, Dr. Marvin Zagula

To Date

> 40,000 babies screened!
Abnormal Brain Overgrowth in Autism by 2 to 4 Years of Age

Courchesne et al., 2001

Recent MRI Studies Also Showing Abnormal Brain Overgrowth in Autism by 2 to 4 Years of Age

Sparks et al., 2002
Carper et al. 2002
Carper & Courchesne 2005
Hazlett et al., 2005
Schumann, Courchesne 2010
Hazlett et al., 2011
Three Phases of Growth Pathology in ASD

Overgrowth

Arrested Growth

Possible Decline/Degeneration

Frontal

Temporal

Amygdala

Courchesne et al. 2001
Courchesne et al., 2003
Courchesne & Pierce 2005
Courchesne et al., 2007
RED FLAGS of Autism Spectrum Disorder by 12-24 Months

**Reduced social interest and affect**
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**Abnormal language development**

Lack of coordination of gaze, facial expression, gesture & sound during interactions
Abnormal Laterality to Language in ASD Infants & Toddlers

Eyler, Pierce and Courchesne, Brain

TYPICAL
13 to 45 months

ASD
14 to 47 months

Temporal cortex

Left - Right Difference in Mean Amplitude of Response

Effect Size (Eta²)

Age in Months

Typical
L > R

ASD
R > L
Why Do Some Infants with ASD Get Better?

Are There Biomarkers of Prognosis?
Overgrowth

Autistic (n=7) vs Control (n=6)
Males
Ages 2 to 16 years

79% more neurons in ASD

29% more neurons in ASD

Courchesne, Mouton, Calhoun, Arhens-Barbeau, et al 2011, JAMA
In Normal Development:
Neurogenesis in 2\textsuperscript{nd} Trimester
Followed by Apoptosis in 3\textsuperscript{rd} Trimester
Overabundance of Neurons in ASD: Possibly Due to Excess Neurogenesis and/or Failure of Apoptosis

Excess Proliferation

Reduced Apoptosis

Number of Neurons

Prenatal Life  Birth  Age  30 yrs

ASD  Control
3rd trimester apoptosis removes extra neuron: this also governs final number of neurons.

Kostovic & Judas 2010
Abnormal Patterning of Cortical Neuron Number in ASD at Ages 2 to 16 Years

% Difference in Neuron Number for Young Autism vs Control Across Different Regions, Studies, and Cases

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>% Difference</th>
<th>Number of Cases 2-16 years old (ASD, Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cerebrum*</td>
<td>36%</td>
<td>n=5, n=4</td>
</tr>
<tr>
<td>Prefrontal**</td>
<td>67%</td>
<td>n=7, n=6</td>
</tr>
<tr>
<td>DL-PFC**</td>
<td>79%</td>
<td>n=7, n=6</td>
</tr>
<tr>
<td>M-PFC**</td>
<td>29%</td>
<td>n=7, n=6</td>
</tr>
<tr>
<td>Frontoinsula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENs***</td>
<td>58%</td>
<td>n=1, n=1</td>
</tr>
<tr>
<td>VENs****</td>
<td>53%</td>
<td>n=4, n=3</td>
</tr>
<tr>
<td>Posterior Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusifrom *</td>
<td>-22%</td>
<td>n=5, n=4</td>
</tr>
<tr>
<td>B17/Occipital*</td>
<td>-11%</td>
<td>n=5, n=4</td>
</tr>
</tbody>
</table>

*Van Kooten et al 2008; **Courchesne et al 2011b; ***Kennedy et al 2007; ****Santos et al 2011

Courchesne et al., in manuscript
<table>
<thead>
<tr>
<th>Brain Region</th>
<th>% Different Neuron Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal *</td>
<td>-11%</td>
</tr>
<tr>
<td>Fusiform **</td>
<td>-13%</td>
</tr>
<tr>
<td>Occipital **</td>
<td>-4%</td>
</tr>
<tr>
<td>BA44-45 ***</td>
<td>-19.5%</td>
</tr>
</tbody>
</table>

all are averages of layers measured

*Courchesne et al 2011b

** van Kooten et al 2008 online data

***Hof et al, work in progress
79% more DL-PFC neurons

What is the Cause of Excess Cells?

What are the Resulting Cortical Defects?

Gene Expression and CNV analyses

Anatomic Microstructure
Laminar-markers and autism-relevant candidate genes in dorsolateral prefrontal cortex

Allen Institute (Ed Lein) and UCSD (Rich Stoner and Eric Courchesne)
79% more DL-PFC neurons

What is the Cause of Excess Cells?

What are the Resulting Cortical Defects?

Gene Expression and CNV analyses

Anatomic Microstructure
Abnormal Frontal Cortex Gene Expression at Young Ages (2 to 14 years) in Autism

102 differentially expressed genes

Dysregulation of Pathways Governing Cell Numbers and Functional Integrity

- Neurogenesis
- Cell cycle regulation
- DNA damage responses
- Apoptosis and survival

Cell differentiation

Immune/Neuroinflammation

Abnormal Down-Regulation of Several Cortical Patterning Genes

- FGF1, HOXD1, NDE1, NODAL, PCSK6

Chow, Pramparo et al., PLoS Genetics, March 2012
Examples of near distance microglia-neuron interaction in subjects with autism. 

A. **Process encirclement of a neighboring neuron in the young subject with autism** (BTB-4029) that demonstrated the most markedly increased spatial clustering relative to randomness.

B. **Processes encircling a neighboring neuron in an adolescent subject with autism** (UMB-4899) that demonstrated markedly increased local clustering relative to randomness.

C. **Processes encircling a neuron at a substantial distance from the microglial soma** in UMB-4899.