The Carroll A. Campbell, Jr. Neuropathology Laboratory: A Tool for Dementia Discovery in South Carolina
Roughly spherical extracellular structures that contain:

- Disrupted (dystrophic) neurites
- Reactive glia (astrocytes and microglia)
- A central Congo red-positive amyloid core
Pathology in the Hippocampus

- **Neurofibrillary tangles**
- **Granulovacuolar degeneration**
- **Hirano bodies**
Incidence & Prevalence of Neurodegenerative Diseases in the United States and South Carolina

**Prevalence:**
- **Total Americans with Alzheimer’s Disease (2015):** 5.3 Million
  - Age 65 and older: 5.1 Million
- **Prevalence by age:**
  - 65 and older: 1 in 9 people (11%)
  - 85 and older: 1 in 3 people (32%)
- **Prevalence by gender:**
  - Almost 2/3 of Americans with Alzheimer’s are women
  - Of the 5.1 million people ages 65 and older with Alzheimer’s in the US, 3.2 million are women and 1.9 million are men
- **Prevalence in South Carolina:**
  - 11.6% of individuals ≥65 have AD or another dementia
  - 44.2% of individuals ≥85 have AD or another dementia
  - African-Americans 1.68 times more likely to have AD or another dementia compared to non-Hispanic whites

**Incidence:**
- **Estimated Incidence in the US, ages 65 and older (2015):** 473,000
  - Ages 65-74: 61,000 new cases (2 per 1,000 people)
  - Ages 75-84: 172,000 new cases (13 per 1,000 people)
  - Ages 85+: 240,000 new cases (39 per 1,000 people)

Source: 2015 Alzheimer’s Disease Facts and Figures from the Alzheimer’s Association & Sg2.
The Carroll A. Campbell, Jr. Neuropathology Laboratory (Brain Bank)

- The Carroll A. Campbell, Jr. Neuropathology Laboratory, together with the Hollings Cancer Center Biorepository, form the MUSC Central Biorepository. This Biorepository also includes a component of an international Down syndrome consortium biobank and a national Neurofibromatosis and Schwannomatosis Biorepository.

- All of the cases in the Brain Bank have been examined by our neuropathologists and the diagnoses of neurodegenerative cases established following the diagnostic standards of:
  - NIA-Alzheimer’s Association Guidelines
  - Dementia with Lewy Bodies Consortium
  - Consortium for Frontotemporal Lobar Degeneration
The MUSC Biorepository

- The Brain Bank is currently located on the 3rd floor of the Walton Research Building.
- The Carroll A. Campbell, Jr. Neuropathology Laboratory, the HCC Shared Tissue Resource and the Dept. of Pathology and Laboratory Medicine Histology Core, Electron Microscopy Core and Microscopy Cores are being relocated in a new centralized facility on the 7th floor of BSB.
- MUSC has invested $1.5 million in the construction of this new facility, which is due to open in February 2019.
How The Carroll A. Campbell, Jr. Neuropathology Laboratory Serves South Carolina

- The Carroll A. Campbell, Jr. Neuropathology Laboratory benefits patients with dementia and their families by:
  - Accurately diagnosing the disease causing dementia in individual patients
  - Providing families with a written report describing the disease pathology in their loved one and answering specific questions about their disease course
  - Providing genetic testing of the autopsied patient that identifies disease variants that may put other family members at risk for dementia
Diffuse Lewy Body Disease

- Diffuse Lewy body disease is the second most common cause of dementia in the elderly
- Lewy bodies can be found from the cortex to the brainstem
- Can be found in association with Alzheimer’s type changes (Lewy body variant of Alzheimer’s disease)
Frontotemporal Lobar Degeneration (FTLD)

- FTLDs, as a group, are the third most common neurodegenerative cause of dementia in the elderly
- These patients often show a co-existing change in social conduct (disinhibition) with gradual and progressive changes in language
- FTLD is an umbrella term for several different neurodegenerative diseases that share pathology predominantly affecting the frontal and temporal lobes
Is Alzheimer’s Disease Genetic?

• Classically, about 90% of AD cases considered to be sporadic and 10% genetic

• Three different loci linked to early onset AD:
  • Amyloid precursor protein (chromosome 21)
    • Down’s syndrome (trisomy 21)
    • Point mutations in \textit{APP}
  • Presenilin-1 (chromosome 14)
  • Presenilin-2 (chromosome 1)

• Apo-E4 (chromosome 19) is a susceptibility gene that increases the chance of developing late onset Alzheimer’s disease (LOAD) in a copy number dependent fashion
## Genes Linked by the Alzheimer Disease Genetic Consortium to Late Onset AD

<table>
<thead>
<tr>
<th>Chr</th>
<th>Region</th>
<th># Studies</th>
<th>Supporting Studies</th>
<th>LOD scores</th>
<th>Relevant genes</th>
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<tr>
<td>1</td>
<td>1p13.3-q23.3</td>
<td>2</td>
<td>Liu et al. [2007]; Butler et al. [2009]</td>
<td>5.2</td>
<td>GSTM4, GSTM1, GSTM3, CSF1, NGF, HMGC52, PRKAB2, APH1A, CTSS, THEM5, FAM63A, CHRN8B, LMNA, FMVK, FDP5, APOA1BP, GBA, NTRK1, CRP, NCSTN</td>
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<td>2</td>
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<td>Blacker et al. [2003]; Liu et al. [2007]; Butler et al. [2009]; Kunkle et al. [2015]</td>
<td>2.1–4.0</td>
<td>F11R, USF1, FCER1G, RGS4, APOA2, RXRG, POU2F1, PRDX6, SOAT1, PTGS2, CR1</td>
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<td>3</td>
<td>3q12.3-q27.3</td>
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<td>Butler et al. [2009]; Cummings et al. [2012]; Barral et al. [2015]; Kunkle et al. [2016]</td>
<td>3.5–4.5</td>
<td>DRD3, GSK3B, TF, MME, BCHE, SLC2A2, AHS2, SLC6A3, PRKAA1</td>
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<td>4</td>
<td>5p13-p15</td>
<td>8</td>
<td>Pericak-Vance et al. [2000]; Curtis et al. [2001]; Myers et al. [2002]; Olson et al. [2002]; Blacker et al. [2003]; Lee et al. [2006]; Barral et al. [2015]; Kunkle et al. [2016];</td>
<td>1.4–2.8</td>
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<td>5</td>
<td>8p22-p21.1</td>
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<td>Lee et al. [2008]; Butler et al. [2009]</td>
<td>&gt;2.0</td>
<td>NAT1, NAT2, LPL, ADRA1A, CHRNA2, CLU, DPK5</td>
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<td>6</td>
<td>8q22.3</td>
<td>2</td>
<td>Cummings et al. [2012]; Kunkle et al. [2016]</td>
<td>0.9–3.6</td>
<td>IFT7E</td>
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<td>7</td>
<td>9p21-p22.1</td>
<td>6</td>
<td>Pericak-Vance et al. [2000]; Curtis et al. [2001]; Myers et al. [2002]; Scott et al. [2003]; Hamshire et al. [2007]; Kunkle et al. [2016]</td>
<td>&gt;1.0–4.6</td>
<td>FBP1, GOLM1, ABCA1, DFNB31, TLR4, NDUFA8, PSMB7, HSPA5, POMT1, DBH, RXRA, TRAF2, ABCA2</td>
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<tr>
<td>8</td>
<td>9q22-q34</td>
<td>9</td>
<td>Pericak-Vance et al. [2000]; Curtis et al. [2001]; Myers et al. [2002]; Olson et al. [2002]; Blacker et al. [2003]; Holmans et al. [2005]; Lee et al. [2006]; Hamshire et al. [2007]; Barral et al. [2015]</td>
<td>1.6–4.2</td>
<td>ZWINT, UBE2D1, TFAM, BICCL, ANK3, CD2C, EGR2, CTNNA3, LRRTM3, DNAJC12, SIRT1, SRSF1, SUPV3L1, TSPAN15, VPS26A, HK1, FACS, NEUROG3, SAR1A, SOLP1, P5AP, CHST3, PPP3CB, SEC24C, NDST2, CAMKK2, PLA2G4A, VCL, AP3M1, MYST4, KCNMA1</td>
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<td>9</td>
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<td>Curtis et al. [2001]; Myers et al. [2002]; Olson et al. [2002]; Blacker et al. [2003]; Holmans et al. [2005]; Hamshire et al. [2007]; Liu et al. [2007]</td>
<td>1.8–4.2</td>
<td>ZWINT, UBE2D1, TFAM, BICCL, ANK3, CD2C, EGR2, CTNNA3, LRRTM3, DNAJC12, SIRT1, SRSF1, SUPV3L1, TSPAN15, VPS26A, HK1, FACS, NEUROG3, SAR1A, SOLP1, P5AP, CHST3, PPP3CB, SEC24C, NDST2, CAMKK2, PLA2G4A, VCL, AP3M1, MYST4, KCNMA1</td>
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<td>10</td>
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<td>2</td>
<td>Barral et al. [2015]; Kunkle et al. [2016]</td>
<td>1.0–4.7</td>
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<tr>
<td>11</td>
<td>12p11-p13</td>
<td>4</td>
<td>Pericak-Vance et al. [1997]; Curtis et al. [2001]; Holmans et al. [2005]; Myers et al. [2002]</td>
<td>1.4–3.9</td>
<td>TNFRSF1A, CNAP1, GAPDH, GNB3, C1R, APOBEC1, MMP3, A2M, F2P, A2MP, OLRI, LRP5, GRIN2B, GY2S, ABCB9, PKP2P1, CTSG, NFKBIA</td>
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<td>Barral et al. [2015]; Kunkle et al. [2016]</td>
<td>2.1–3.9</td>
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<td>1.6–7.7</td>
<td>LRAP3, USF2, GADPH5, PSENEN, AKT2, TGFBI, LIPE, XRC1C, BCL3, APOE, PVHL, TOMM40, APOC1, APOE2, ERE2, CARD8, GYS2, LHB, CD33, K1H12</td>
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<tr>
<td>14</td>
<td>21q21-q22</td>
<td>4</td>
<td>Myers et al. [2002]; Olson et al. [2002]; Blacker et al. [2003]; Holmans et al. [2005]</td>
<td>1.6–4.5</td>
<td>PRSS7, NCFAM2, APP, C21orf63, C21orf55, RUNX1, DYRK1A, KCNJ6, BACE2</td>
</tr>
</tbody>
</table>

Chr, chromosome. Bolded gene names are known GWAS signals with genome-wide statistical significance.
How The Carroll A. Campbell, Jr. Neuropathology Laboratory Serves South Carolina

- The Carroll A. Campbell, Jr. Neuropathology Laboratory benefits public health in South Carolina by:
- **Monitoring where neurodegenerative diseases occur in South Carolina and the frequency with which different types of neurodegenerative diseases occur in South Carolina**
  - Initial assessments suggest that certain Alzheimer disease mimics and Parkinson disease mimics may be more common in South Carolina than other parts of the United States
- **Monitoring for infectious diseases that produce dementia and may be a risk to public health in South Carolina**
South Carolina Neurodegenerative Inpatient Origin, FFY 14

- The majority of Neurodegenerative inpatients for the state reside in the Tertiary region.

- Overall, the % of patients in the Tri-County has grown 3% over the past 5 years.

SC Inpatient Neurodegenerative Patient Origin Trends

<table>
<thead>
<tr>
<th></th>
<th>FFY 10</th>
<th>FFY 11</th>
<th>FFY 12</th>
<th>FFY 13</th>
<th>FFY 14</th>
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<tbody>
<tr>
<td>Tertiary</td>
<td>69%</td>
<td>68%</td>
<td>67%</td>
<td>69%</td>
<td>68%</td>
</tr>
<tr>
<td>Secondary</td>
<td>22%</td>
<td>20%</td>
<td>18%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Tri-County</td>
<td>7%</td>
<td>10%</td>
<td>10%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Outside SC</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Note: Defined by the Neurodegenerative ICD-9 Codes provided.
Creutzfeldt-Jakob Disease (CJD)

- CJD presents as a rapidly progressive dementia (death in <2 years), often associated with myoclonic jerks and a “spike and wave” pattern on EEG.
- CJD is caused by prions, which are infectious agents composed of misfolded proteins. Prions aggregate in affected neurons and impair their function.
- In Great Britain, prions from infected cattle got into food and caused variant CJD. The National Prion Disease Surveillance Center monitors patients with CJD to make sure this doesn’t happen in the US.
How The Carroll A. Campbell, Jr. Neuropathology Laboratory Serves South Carolina and Beyond

• The Carroll A. Campbell, Jr. Neuropathology Laboratory supports research into the mechanisms producing dementia and the development of potential therapies by:
  
  • Conducting research into the pathologic changes that produce dementia
  
  • Collaborating with and supporting investigators at MUSC that need human biospecimens to investigate important questions in Alzheimer’s disease and other dementias.
  
  • Providing human biospecimens from patients with dementia to investigators at other institutions in South Carolina, the United States and other countries.
  
  • Establishing and participating in national and international networks that collect unique biospecimens necessary to support the work outlined above
Research that SC brain donors have enabled

- Significant contributions to research on neurodegenerative disorders (Parkinson’s, Progressive Supranuclear Palsy, Lewy Body Disease, Alzheimer’s, etc)
- The 1\textsuperscript{st} study of resolution of inflammation in Alzheimer’s Disease
- Pioneering exosome biomarker studies of Alzheimer’s Disease
- Development of novel MRI brain imaging techniques

1063 research samples shared internationally
Heart failure in Alzheimer Disease

AD brain pathology
- Healthy brain size
- Shrunken brain with Alzheimer's disease
- Dying neuron with tangles
- Plaque

Blood Brain Barrier
- Brain Aβ Amyloid
- Heart Aβ Amyloid

Amyloid

Metastatic?
Systemic?

Aβ pathology coexists in the brain and heart of AD patients. Myocardial function is compromised in AD
Abnormal accumulations of amyloid are evident in both the brain (top panels) and the heart (bottom panels) of Alzheimer’s disease patients.

Electron microscopy

Immunohistochemistry for amyloid
The Importance of Diagnostic Biomarkers in Alzheimer Disease

- Multiple agents targeting amyloid deposits or phosphorylated tau have failed in clinical trials. This may be because:
  - Current hypotheses of AD pathogenesis are wrong
  - Interventions don’t start early enough in the course of the disease
- However, we don’t have biomarkers that identify patients in the preclinical stages of Alzheimer’s disease
- Down’s syndrome patients reproducibly develop Alzheimer’s disease
  - Together with the Barrow Neurological Institute, University of Kentucky, University of Colorado Denver, University of Denver and the Sant Pau Memory Unit in Barcelona Spain, we have established an international biobank to collect brain, blood and CSF from autopsied Down syndrome patients and blood and CSF from living Down syndrome patients
We were pioneers in the study of AD biomarkers that occur in neuronal vesicle structures called **exosomes**

Each exosome contains a snapshot of the host neuron.
Individuals with DS produce 39% more neuronal exosomes than non-DS regardless of age or clinical status.

Neuronal exosomes from individuals with DS have significantly more Alzheimer's-related biomarkers (Aβ<sub>1-42</sub>, phosphorylated Tau)
Development of Sensory Abnormalities May Also Be a Biomarker for Preclinical Alzheimer’s Disease

- Alzheimer’s patients develop problems smelling, hearing loss, visual dysfunction, problems with taste and abnormalities of locomotion.

- Our P50-supported Age-Related Hearing Loss Center is following a cohort of 2,000 aging patients and is sequencing their genomes. We are “piggy-backing” on this study to determine whether patients who showed earlier or accelerated hearing loss subsequently developed AD as well as whether specific gene variants previously linked to AD were enriched in these patients.

- The Zucker Institute for Applied Neuroscience (ZIAN) has developed a blink reflexometer and shown that patients with TBI show altered blink reflex. We will be using this instrument to see whether patients in our hearing cohort with altered blink reflexes subsequently develop AD.
Gene Doe
A Platform for Health Citizen Science

Christopher Metts, MD
Assistant Professor
Pathology and Laboratory Medicine
Biomedical Informatics Center
Medical University of South Carolina
Alzheimer’s Research

Concerned Citizens

• Periodic screening with Active Tasks and surveys
• Family and medical history
• Genetic and other lab testing and imaging
• Follow for years

Affected Citizens

• Test methods of monitoring for safety with iPhone and related technology
• Facilitate communication among family, care providers, and clinicians
• Monitor progress of disease and response to therapies
The Carroll A. Campbell, Jr. Brain Collection

- Houses a collection of ~180 human brains from patients with neurologic diseases as well as normal controls
- Information regarding brain donation can be found at: [http://pathology.musc.edu/website/research/brainbank/braindonor.html](http://pathology.musc.edu/website/research/brainbank/braindonor.html).
- Neurologic diseases represented in our collection include:
  - Alzheimer’s disease
  - Parkinson’s disease
  - Diffuse Lewy body disease
  - Multiple system atrophy
  - Argyrophilic grain disease
  - Tangle only dementia
  - Vascular dementia
  - Frontotemporal dementia
  - Amyotrophic lateral sclerosis
  - Huntington’s disease
  - Multiple sclerosis
  - Glioblastoma
  - Diffuse intrinsic pontine glioma
  - Ependymoma
Specimen Types Available from the Carroll A. Campbell, Jr. Neuropathology Laboratory

- Brains are processed using a “half-fixed, half-frozen” protocol, so that a variety of specimen types are available including:
  - Formalin-fixed, paraffin-embedded sections of brain regions typically affected by neurologic diseases
  - Formalin-fixed, cryoprotected brain tissue
  - Frozen brain tissue corresponding to regions typically affected by neurologic disease
  - Frozen slabs of brain for biochemical studies needing larger quantities of tissue
  - CSF
  - Blood
  - Eyes (globes, vitreous humor, aqueous humor)

Neurofibrillary tangles in the brain of an AD patient
Requesting Tissue from the Carroll A. Campbell, Jr. Neuropathology Laboratory

• Director: Steven L. Carroll, MD, PhD
  • 9 years working with the Neuropathology Core of the Charles F. and Joanne Knight ADRC at Washington University in St. Louis
  • 17 years as Director of the Neuropathology Core of the University of Alabama at Birmingham (UAB) ADRC
  • Research program investigating synapse loss in AD and identifying new dementia-causing genes in the UAB ADRC
  • Member of the national Alzheimer Disease Genetic Consortium

• Dr. Eric Hamlett (Brain Donation Coordinator): 843-792-7867

• To request specimens online: http://pathology.musc.edu/website/research/brainbank/brainresearch.html