

New Approaches to the Diagnosis and Treatment of Alzheimer's Disease

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Overarching Goals :
To improve the diagnosis and treatment of Alzheimer's disease.



Use state of the art technology to address important clinical problems.

Impact of Alzheimer's Disease

WHY AD?

Most prevalent form of dementia in elderly

Currently affects ~4 million people in US

By 2025 the number of AD patients in US is estimated to increase by 44%

Economics

US annual cost of care currently estimated to be \$100 billion

AD is the third most costly disease (after cardiovascular disease and cancer)

Current Diagnostic Methods

WHY AD?

Diagnosis is based on:

- Medical history
- Clinical examination
- Neuropsychological tests (can be subjective)

NINCDS-ADRDA criteria for **PROBABLE AD**:

- Dementia
- Deficits in two or more areas of cognition
- Progressive worsening of memory/cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90
- Absence of other disease that could account for symptoms

Autopsy of brain required for diagnosis of **DEFINITE AD**



Diagnosis of Definite AD: tau tangles and amyloid plaques

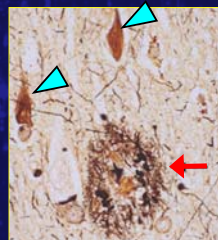
WHY AD?

Neurofibrillary tangles

- Hyperphosphorylated tau
- Intracellular

Senile plaques:

- β -amyloid deposits
- Extracellular



Taylor et al. Science 2002; 296: 1991

Probable \neq Definite

At autopsy, 10-20% of patients diagnosed with AD found to have **other** conditions and **NOT AD**

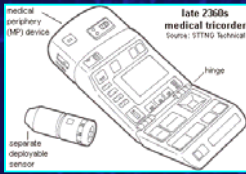
Other dementias sometimes mistaken for AD

- Vascular dementia
- Lewy body dementia
- Frontal lobe dementia
- Progressive supranuclear palsy

Thus, there is a need for better diagnosis.

Our Ideal Diagnostic Test is:
noninvasive, objective, molecular

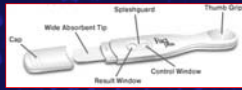
as effective as barcodes / UPC labels on packages



Medical tricorder (MP) device
 late 2300s medical tricorder
 Source: ST/NG Technical
 large
 separate deployable sensor

We would love to have a Star Trek medical tricorder, but we're not there yet


A Classic Example of a Simple, "Barcode" Diagnostic



Easy to use
 Objective, barcode readout (yes or no)
 Noninvasive
 Fast

Alzheimer's disease:
 More complex (much unknown)
 Changes occurring in brain over decades

Challenge: Definitive Diagnosis on Autopsy Is Too Late
Workaround: Premortem Sampling of Cerebrospinal Fluid (CSF)



Normal
 Different

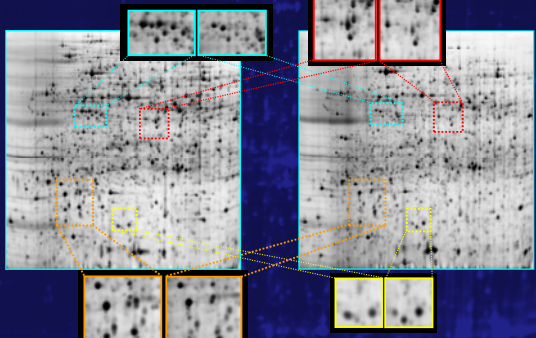
Analysis

disease specific
 disease stage (early/late)
 response to therapy

Lumbar CSF

Getting CSF is less invasive than getting brain tissue!
 CSF has ~1800 proteins which can be displayed.
 Can we identify a disease-specific 'barcodes' of protein expression?

Barcodes of Protein Expression

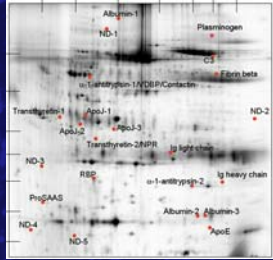


In the largest study ever, we looked for barcodes of Alzheimer's disease that would permit improved premortem diagnosis.

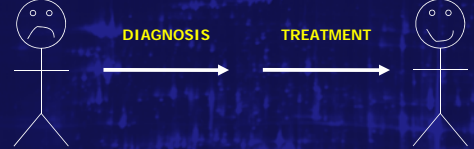
68 Subjects
 34 non-AD 34 AD

6% error rate

less invasive
 objective
 molecular



Versus 15% error rate for "clinical diagnosis" (subjective, not molecular)
 Versus 0% error rate for autopsy diagnosis (highly invasive)



DIAGNOSIS TREATMENT

We can improve diagnosis.
 Is the technology useful in assessing treatment?

Current Alzheimer's treatments don't slow the underlying disease process. Researchers are now testing an array of new therapies intended to do just that. BY ANNE UNDERWOOD

The study

Treatment Strategies

1. Antioxidants (e.g. vitamin E)
2. Anti inflammatory agents (e.g. Cox inhibitors)
3. Hormone-replacement (estrogen-replacement)
4. Cholinesterase inhibitors (e.g. donepezil) *
5. **Immunization** (to protect from amyloid deposits)

Mini-mental status examination

Immunization (to protect from amyloid plaques)

Antibodies are the molecules that protect us from bad stuff.

1. Activate immune system response by exposing to flu proteins.
2. Make antibodies against flu proteins.
3. Antibodies confer protection from flu virus.

activate by exposure, make antibodies, confer protection

Previous Efforts to protect against amyloid deposits (Elan and Wyeth)

Phase I:
anti-amyloid response in AD patients
positive response in daily living activities

Phase II:
trial stopped: encephalitis (brain inflammation)
autopsies indicated fewer plaques than expected

Right idea, wrong method ?

Active Immunization	➔	Passive Immunization
<p>activate immune system by administering β-amyloid protein/peptide</p> <ol style="list-style-type: none"> 1. <u>Activate</u> immune system response. 2. Make <u>antibodies</u> against flu proteins. 3. Antibodies confer <u>protection</u> from flu virus. 		<p>inject β-amyloid antibodies</p> <ol style="list-style-type: none"> 1. Deliver <u>antibodies</u> against flu proteins. 2. Antibodies confer <u>protection</u> from flu virus.

Antibodies against cancer proteins are blockbuster biotechnology drugs and used to treat cancer.

What is IVIg ?

IVIg is a pooled human antibody preparation obtained from the blood of several thousand donors :

Contains >90% of all relevant antibodies.

Currently approved to treat :

- Immune deficiency disorders
- Idiopathic thrombocytic purpura (ITP)
- Kawasaki's Syndrome
- Lymphocytic Leukemia

Is this mixture of antibodies useful to treat AD ?
Does it contain anti-amyloid antibodies ?

Why IVIg as an immunotherapy for AD?

We all make our own anti-amyloid antibodies.

AD patients have decreased amounts of free anti-amyloid antibodies in blood. (Hyman 2002, Weksler 2003)

IVIg contains anti-amyloid antibodies and infusion increases the amount of them in the blood. (Dodel 2003)

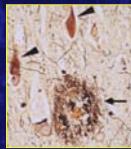
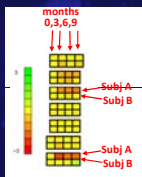
More than 2 decades of clinical experience with IVIg
 –can reduce the time and risks of testing IVIg for AD.

So Where Does Proteomics Come Into This?

The FDA wants molecular level evidence that the therapy is doing what it is supposed to be doing.

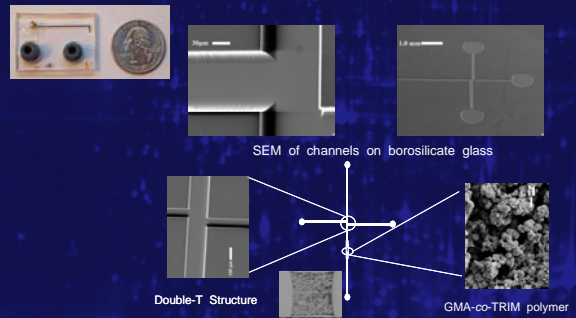
Clinical outcomes alone are not good enough.

IVIg Leads to Changes in Amyloid Clearance Plaques Going Away



Proteomic fingerprints consistent with plaque clearance.

In parallel: develop technology to make widely available



Background : joined UD /DBI 9/07

Professional Background:

Assistant through Full Professor at Cornell.
 Samuel C. and Nancy M. Fleming Chair Professor.
 Graduate Fields: Biomed Engg, Chem Engg, Genomics, Computational Biology.

Related Experience from last institution:

Oversight council for Tech Transfer Office.
 Start-up companies.
 Responsible for Cornell Presidential Life Science Grad Fellowships.
 Facilitated construction of \$150M Weill Hall for life science research.
 Worked closely with Development Office.
 Engineering College Strategic Planning Council.
 Responsibility for Ithaca-Med partnership (IT, grants, donors, IP, etc.).

Director, Cornell Biotechnology Institute and
 Director, New York State Center for Life Science Enterprise

Research themes:

Alzheimer's disease, protein secretion and translation, proteomics.

Center for Life Science Enterprise at Cornell (administered by Cornell Biotechnology Institute)

Center for Advanced Technology supported by NYS.

Director is primary liaison with state officials on matters related to support of certain programs at Cornell.

\$1M per year from state. Other related programs.

Job creation/retention (model based on establishment of start-up companies).

Entrepreneurial workshops to develop business plans.

Creation of first on campus business incubator (part of Weill Hall) with \$25M from state.

Return on NYS investment (industrial matching gifts, federal funds, etc.).

Track patents and licenses for funded technologies.

NYS workforce development activities.

Cornell Biotechnology Institute
(est. 1983)

~78 staff (~17 direct reports)

Administer NYS CAT.

Administer an on campus grants program (12-18 projects per year) for faculty working closely with industry.

Work closely with Deans / Chairs to recruit and retain life science faculty.

Primary life science contact for VIPs (donors, Presidents/Rectors, etc.)

Oversee and administer life science related core facilities.

Other activities.

What's new at DBI ?

On the one hand, nothing ... excellent research and programs continue.

We welcome you and look forward to working together.