Advances in Neurologic Diseases: MS, ALS, and Parkinson disease

Presented by: Justin C. McArthur MBBS MPH FAAN
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Disclosures

• JHU CLIA-approved Cutaneous nerve lab
• Unpaid consultant
  • Biogen, Accentia, Relevare
• Research funding ~ NIH
Objectives

– Complexities of the brain and challenges in treating neurologic disease
– Accelerating drug discovery
– New approaches for ALS, MS and PD
Neuron = nerve cell
Complexities and challenges in understanding brain disorders

- At birth, a baby’s brain contains 100 billion neurons, same as # of stars in the Milky Way
- 100 trillion synapses or connections between cells
- A single human brain has more ‘switches’ than all the computers and Internet connections on Earth (Smith, 2010).
Visualization of complexity of neuronal interactions.....Stephen Smith, Stanford U., Neuron 2010
Neurons are irreplaceable .....or are they?

- Neural stem cells exist throughout life in the brain, but stop actively generating neurons at about 2 years of age (Sanai et al., 2011).
- Adult neural stem cells have life-long activity but their numbers decline in aging and are dramatically reduced in AD (Haughey et al., 2002).
- Fetal stem cells are an abundant source of different types of brain cells, with potential application to a variety of neurological conditions.
- In animal experiments, increasing the generation of neural stem cells can increase memory performance ~ environmental stimulation, certain medications
President Obama is calling on the science community to join him in pursuing a grand challenge.

**Brain Initiative**

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES

$100 MILLION

Approximate investment to give scientists the tools they need to get a dynamic picture of the brain and better understand how we think, learn, and remember.
Why is drug discovery for brain diseases so difficult?
Drug Discovery and Development

- Average **COST** to discovery/develop a drug? $1-2 BILLION
- Average **TIME** to discover/develop a drug? 15-20 YEARS
- Average **FAILURE RATE**? 95%!
Statistics for brain drugs are even worse!

- FEWER CLINICAL SUCCESSES
  - 8.2% vs 15%

- 40% LONGER DEVELOPMENT TIMES

- NEUROLOGY TRIALS FAIL LATE IN DEVELOPMENT

Pace of CNS drug development and FDA approvals lags other drug classes

Clinical-plus-approval time for CNS drugs 35% longer vs. non-CNS drugs

- The clinical approval success rate for central nervous system (CNS) drugs from 1993 to 2004 was about one in 10, compared to one in six for all self-originated drugs.
- The Phase III-to-regulatory-submission transition rate for self-originated CNS drugs was 50% for drugs with clinical testing initiated during 2002-07.
- Clinical approval success rates for self-originated CNS drugs declined since the early 2000s.
- Since the mid-1990s, CNS drugs had relatively few priority approvals (18% vs. 46% for other drugs).
- During 1996-10, mean clinical phase time for CNS drugs, compared to non-CNS drugs, was 40% longer, while mean approval phase time was 13% longer.
A new approach at JHU: drug discovery team from Pharma recruited to JHU

- Medicinal chemistry, animal pharmacology/toxicology, drug metabolism, pharmacokinetics, assay development, business dev

- NEW JOB: To work collaboratively with faculty to translate Hopkins’ brain discoveries into clinical therapeutics
Advances in specific neurological diseases
Advances in ALS
Clinical facts about ALS

- Progressive paralysis of unknown cause, 100% lethal
- Link with frontotemporal dementia in some
- Death within 3-5 years from diagnosis
- No cure exists, and our only existing treatment prolongs life by just 3 months ~ riluzole
Epidemiological facts about ALS

- Becoming more prevalent ?: 3-5/100,000 in USA
- At any time, 30,000 individuals are affected in the U.S.
- Familial in 20% ~ C9ORF, SOD1
- Environmental triggers: smoking, toxic wastes (Gulf War), athletes + TBI, pesticides
In 2011, the most frequent cause of inherited ALS was discovered to be a large expansion of a hexanucleotide repeat in the C9ORF72 gene.

When that large repeat is copied into the messenger RNA which carries the information encoded by the gene, the mRNA aberrantly accumulates ~ and fails to mediate processing of the other RNAs.
C9orf72 Drosophila: a fly model of ALS

Zhu et al (2013) PNAS
ALS patients are not all alike
- Sporadic - may be multiple different gene mutations (e.g. C9orf72)
- Different familial forms
- Repeated clinical failure due, in part to “lumping” all patients together

Lessons from cancer therapy
- attack molecular subsets
- Maximize therapeutic success

Problems in ALS therapy development - Need to optimize and *individualize*
Individualized ALS Treatment Initiative (IATI): *Personalized ALS therapy*

*Your genes, Your neurons, Your brain.*

Designing specific solutions for *individual ALS patients*
Stem cells
When cultured, a stem cell has the ability to reproduce specialized cells (such as brain cells) for an indefinite period.

Where do stem cells come from?
1. Stem cells can be isolated from a human embryo in early development. These are obtained with the consent of donor parents at in-vitro clinics.
2. Stem cells can be derived from fetal tissue obtained from terminated pregnancies with donor consent.
3. A normal egg cell has the nucleus removed and the cell is fused with any other body cell. These cells are not as versatile and healthy as ones obtained in the two processes above.

Human cell: Each cell's function is determined by the proteins (amino acids) it produces through DNA blueprints.
Induced pluripotent stem cells

- Obtain skin fibroblasts
- Reprogram cells to induce pluripotent stem cells
- Can become neurons, oligodendrocytes, etc
- Can serve as individualized models of disease ~ “disease in a dish”
<table>
<thead>
<tr>
<th>Undifferentiated hESCs</th>
<th>Differentiated Cell Types</th>
<th>Therapeutic Uses</th>
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</thead>
<tbody>
<tr>
<td>Human Embryonic Stem Cells (hESCs)</td>
<td>Neural Cells</td>
<td>Spinal Cord Injury</td>
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<tr>
<td></td>
<td>Cardiomyocytes</td>
<td>Heart Failure</td>
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<td></td>
<td>Islets</td>
<td>Diabetes</td>
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<td>Dendritic Cells</td>
<td>Immunotherapy</td>
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<td>Osteoblasts</td>
<td>Osteoporosis and Bone Fractures</td>
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<td>Chondrocytes</td>
<td>Osteoarthritis</td>
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<td>Hepatocytes</td>
<td>ADME Drug Testing</td>
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Geron has developed proprietary processes to convert hESCs into therapeutic cells.
Use of stem cells for ALS
Cells are capable of self-renewal and also differentiating into glia and neurons.

The exact beneficial mechanism remains unclear, but animal studies suggest that the stem cells act to protect and preserve endangered nerve synapses in the spinal cord.

Treatment appears to be safe. Efficacy outcomes too early.
Health experts warn of "stem cell tourism" dangers
Wed, Sep 1 2010

By Kate Kelland, Health and Science Correspondent

LONDON (Reuters) - Thousands of people are putting their health and life savings at risk to travel to private clinics around the world for unproven and potentially dangerous stem cell treatments, British experts said on Tuesday.

A panel of specialists highlighted individual clinics in Germany and China where so-called "stem cell tourists" go for unlicensed treatment, and said there may be up to 700 similar businesses globally offering unproven cell therapies.

Despite a lack of scientific evidence that such therapies work, patients whose lives are blighted with conditions like Parkinson's disease or childhood blindness are being lured into spending tens of thousands of dollars with little chance of success. "The patient is in danger of losing their life and health, needlessly traveling long distances away from home, friends and family, not having their condition improved, and potentially losing a large sum of money," said Chris Mason of University College London's (UCL) regenerative medicine bioprocessing unit.

The scientists cited one case of an Israeli boy who received a stem cell treatment in Russia for a spinal injury and subsequently developed multiple tumors.

In another case, they said, a 46-year-old woman was treated in Thailand for the autoimmune disease lupus. She later developed kidney failure and died from sepsis.
Resources for ALS

Create a world without ALS.
Overview of multiple sclerosis, and how we get to better treatments
So what is multiple sclerosis?.....

- An ‘autoimmune’ disease producing inflammation scattered throughout brain, spinal cord, and optic nerves
- Genetic susceptibility ~ immune response genes
- 350,000 people affected in USA, mostly 20-40 yrs old at onset
- Can produce permanent disability....but is highly variable
- Multiple varying symptoms: weakness, vision loss, sensory disturbance, fatigue, imbalance, and cognitive dysfunction
MS is highly variable in its course
Dietary Contributors to MS?

- Salt
- Polyunsaturated fatty acids
- Antioxidants
- Probiotics
- Gluten
- Milk proteins
- Other vitamins
Vitamin D and Multiple Sclerosis

Low vitamin D leads to immune activation
Through modulation of T cell antigen receptor

Vitamin D Winter: Very little if any vitamin D can be synthesized in the skin from November through February at latitudes north of 37 degrees.
# FDA Approved DMTs for MS
(in order of approval)

<table>
<thead>
<tr>
<th>DMT</th>
<th>Administration</th>
<th>Approval Date</th>
<th>Indication</th>
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<tbody>
<tr>
<td>IFNB-1b</td>
<td>250 mcg SC qod</td>
<td>1993</td>
<td>Relapsing MS, CIS</td>
</tr>
<tr>
<td>IFNB-1a</td>
<td>30 mcg IM qwk</td>
<td>1996</td>
<td>Relapsing MS, CIS</td>
</tr>
<tr>
<td>GA</td>
<td>20 mg SC qd</td>
<td>1997</td>
<td>RRMS, CIS</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/m² IV q3mths</td>
<td>2000</td>
<td>Worsening relapsing MS, SPMS</td>
</tr>
<tr>
<td>IFN-1a</td>
<td>22 and 44 mcg SC tiw</td>
<td>2002</td>
<td>Relapsing MS</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>300 mg IV q4wks</td>
<td>2004/2006</td>
<td>Relapsing MS</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.5 mg po qd</td>
<td>2010</td>
<td>Relapsing MS</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>7 and 14 mg po qd</td>
<td>2012</td>
<td>Relapsing MS</td>
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Why do we need another therapy for MS?

- Modest benefit for current DMTs
- Risks associated with more aggressive DMTs
  - Natalizumab – Progressive Multifocal Leukoencephalopathy (PML)
  - Fingolimod – Macular edema, arrhythmia, human herpes virus infections
  - Mitoxantrone – Congestive heart failure, acute myelogenous leukemia
  - Rituximab and other anti-CD20s – Hypersensitivity reactions, PML?
  - Alemtuzumab – Immune thrombocytopenia, thyroid disease
- Financial cost and lifestyle burden of chronic therapies
Lemtrada™ is under review by FDA. Once a year treatment

- Humanized mAb directed against CD52 (expressed on leukocyte surface)
- Rapidly and profoundly depletes T cells, B cells, and monocytes through:
  - Antibody-dependent cell-mediated cytotoxicity
  - Complement-mediated cytotoxicity
- CD4+ cells may take ~5 years to fully recover
- Reconstituted lymphocytes appear to have regulatory properties
Tisch Medical Center: early studies showed that after injecting autologous stem cells, brain inflammation was reduced, myelin was repaired, and brain structure was improved.

Hopkins researchers developing oligodendrocyte stem cells
New techniques for imaging MS with 7T MRI and optical coherence tomography lead to earlier diagnosis and a better way to monitor therapies

Peter Calabresi, Peter van Zijl, Danny Reich, Shiv Saidha
Demonstrating tiny cortical Lesions
Diffusion Tensor Imaging shows abnormalities in white matter tracts.
Parkinson disease expertise at JHU

Zoltan Mari
Associate Professor, Interim Director, Movement Disorders Division.

Ted Dawson,
Leonard and Madlyn Abramson Professor of Neurodegenerative Diseases
Clinical features of PD
Typical gait in Parkinson disease
Parkinson disease: features

- PD affects 1m people in the USA, usually later in life with tremor, slowness of movement, gait instability, cognitive dysfunction, and rigidity.
- Loss of dopamine-producing neurons causes the disease.
- In addition to the progressive loss of dopamine neurons, PD is characterized by neurodegeneration and the accumulation of alpha-synuclein and other proteins in “Lewy bodies”.
- Mutations in at least five genes including alpha-synuclein, parkin, PINK1, DJ-1 and LRRK2 are responsible for rare familial forms of PD.
Prevalence of PD and PD-dementia (PDD) is increasing

Adapted from Dorsey et al. 2006 and Aarsland et al. 2005

Number of individuals with Parkinson disease (PD) and PD-Dementia, in millions

Year

2005 2010 2015 2020 2025 2030

PD
PDD
Utility of PET and DAT scans: improved diagnostic accuracy, especially with early symptoms
Deep brain stimulation for PD
Effects of Deep Brain Stimulation in PD

November 2, 2014
New therapeutic approaches for PD:
LRRK2 inhibitors: Ted & Valina Dawson

• The LRRK2 gene is a leading genetic cause of PD implicated in ~ 10% of inherited PD, and 4% of people without family history.
• Mutations in the gene LRRK2 may increase the rate of tagging of ribosomal proteins ~ key components of protein-making machinery inside cells.
• Gleevec® (imatinib) and other LRRK2 inhibitors are being tested in PD models.
New links between Gaucher’s disease and PD

• Mutations in the glucocerebrosidase (GBA) gene, which encodes a lysosomal enzyme deficient in Gaucher's disease, are risk factors for PD.

• 10/2014 *Neurotherapeutics*: genetically engineered mice producing too much alpha-synuclein, treated with AT2101 (developed for Gaucher disease). Motor functions improved, brain inflammation and levels of alpha-synuclein were reduced.
Using readily-available technology, we can deliver personalized care anywhere

New models of care can use telemedicine to reach people in their homes

Equipment
- Laptop
- Broadband connection
- Web cam, microphone
- Polycom encrypted software
- Total cost beyond laptop and broadband: ~$150

Resources for PD
Participation in clinical trials is a rate limiting step for drug development

Participation in clinical trials

Are not routinely informed of research opportunities …

Has your doctor ever suggested that you participate in a clinical research study?

- Yes: 7%
- No: 93%

... and foundations can help

- Create registries of patients, especially for rare conditions, willing to participate in clinical research
- Inform patients of research opportunities (e.g., MPD Foundation)
- Educate public about roles it can play in research
- Help communicate outcomes of research and their value to the public (e.g., Multiple Myeloma Research Foundation)

Source: Research!America poll data summary 2008
Take Home Messages

• The human brain is the most complex thing in the universe
• Understanding how it works and how it goes wrong is critical to treatment
• We are poised for major advances in neurologic disorders, in MS, ALS, and PD, and other disorders….but this requires a multidisciplinary team, and continuing support
Thank you.

Questions ?......