Gender Differences in MS

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Bedside to Bench to Bedside: MS to EAE to MS

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EAE as a Model for MS
Bench to Bedside: Does It Work?

Based on:
- novel molecule
- cutting edge technique

Problem:
- Redundancy
- Heterogeneity
- Not physiologically important
A Different Approach

Bench to Bedside
(molecule or technique based)

Bedside to Bench to Bedside
(clinical observation based)

1. Start with a clinical observation
2. Unravel mechanism at lab bench
3. Target mechanism in a clinical trial
Clinical Observations

Pregnancy: Decreased relapses

Sex Differences: F > M susceptibility
F < M progression
Clinical Observation Late Pregnancy:

↓ Relapses by 75%

↑ Sex Hormones: Estriol, Estradiol, Progesterone, other

Estrogens

Estradiol -
“gold standard”
binds high affinity to ERα & ERβ
ERα toxicity breast and uterus

Estriol -
“weak”
ERβ > ERα
safest of the estrogens since 1980s

Spence & Voskuhl, Frontiers in Neuroendocrinology 2012
Preclinical: Estriol Treatment in EAE

four strains, both sexes, pre and post tx
spinal cord: ↓ inflammation, ↑ axons, ↑ myelin

Holmdahl, Voskuhl, Offner, Whitacre

ERα and ERβ: Direct Neuroprotective Effects in EAE
Conditional Knock Outs (CKO)

Exon 3 of ERα is floxed.

Cre-lox Recombination removes ER-α in
* neurons only (Enolase II)
* astrocytes only (GFAP)

Same strategy for ER-β

Direct Neuroprotective Effects: 
Preclinical Data

Treatment
- IFN Beta
- Copaxone
- Mitoxantrone
- Tysabri
- Fingolimod
- Teriflunomide
- BG12
- Estriol?

Direct
- Estriol?
  (ERα astrocyte)
  (ERβ oligodendrocyte)

Indirect
Decreased inflammation

J. Neuroscience 2006, PNAS 2007, Brain 2010,
Pilot Estriol Clinical Trial in MS

Clinical Data:

Oral estriol 8 mg/day for 6 months: mid-pregnancy level
10 women, single arm, crossover, monthly MRIs
Compared to 6 months Pre-Tx:
-- MRI gado lesions $\downarrow$ by 70-80%
-- $\downarrow$ TNF$\alpha$, $\uparrow$ IL5, $\uparrow$ IL10 in PBMCs
-- $\downarrow$ MMP9

Double Blinded, Placebo Controlled Multicenter Trial

Primary Outcome: Relapse Rate
Phase II (Clinical, not Surrogate)
Powered at $p = 0.1$
Treatment Duration = 24 months
“Add on” study in RRMS (no placebo only)
Copaxone (Glatiramer Acetate – GA)
n = 158
16 sites across U.S.
Site Neurologists / # randomized

University of California Los Angeles: Barbara Giesser / 27
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Estriol Trial, NIH sponsored, 16 sites, 164 patients:
Primary Outcome Measure: Relapse Rates

Phase II powered:
Reduce relapses by 1/3
24 month duration
p = 0.1

Result:
Hit Primary (24 months)
Rapid Onset (12 months)
Estrogens and Cognition

Clinical: Healthy women
Cognitive decline in E removal (ovariectomy)
Cognitive improvement with estradiol treatment

Preclinical: Healthy rats and mice
Cognitive decline in E removal (ovariectomy)
Cognitive improvement with estradiol treatment (ERβ)
Preclinical: Estriol Treatment In EAE: Hippocampus

Hippocampus: preserved CA1 volume
↓ microglia activation, ↑ synapses

Lab Invest, 2010, 2012
Preclinical Estriol Treatment in EAE: Synapses & Function

Lab Invest, 2010, 2012
Clinical: Estriol Trial: Effect on Cognition

** P < 0.05, *P < 0.10

** P < 0.05, *P < 0.10
Clinical Observation: F > M (3:1)

Bench: Female > Male: EAE in SJ L Mice

Sex Hormones
Sex Chromosomes

Lower testosterone in MS (normal = 300-900 ng/dL; MS < 500 ng/dL)

Voskuhl, Annals of Neurology 1996
F > M (3:1) - Testosterone

Bench EAE:
Castration worse / Testosterone Tx better:

LN, spleen – immunomodulation
WM: less inflammation, sparing myelin & axons

Cua & Stohlman, Bebo & Bourdette; Cuprizone: Ghandour & Schumacher, Brain, 2013
MS Pilot Testosterone Clinical Trial:

Single arm, crossover design, 10 MS men
Testosterone Levels: low to high normal

Arch. Neurol., 2007
MS Pilot Testosterone Clinical Trial: Whole Brain Atrophy

Arch. Neurol., 2007
MS Pilot Testosterone Clinical Trial:
Gray Matter Atrophy

Observation Period (P1)
[Month 0 – 6]

Transition Period (P2)
[Month 6 – 12]

Treatment Period (P3)
[Month 12 – 18]
Clinical Observation in healthy men:
Testosterone Tx improves cognition in andropause
 +/- dependence on conversion to E
Cherrier & Craft 2001-2005

Preclinical: Testosterone Tx in EAE: Hippocampal GM


Clinical Observation in MS men:
Low T - performed worse on cog testing next 2 years
Brigham & Women’s: Bove, Chitnis, MS 2014
A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER PHASE II
TRIAL TO INVESTIGATE THE EFFECTIVENESS OF TESTOSTERONE TREATMENT IN
MEN WITH MULTIPLE SCLEROSIS

PPI: Rhonda Voskuhl (UCLA)

Co-Investigators:
Ronald Swerdloff (UCLA)
Tanuja Chitnis (Brigham & Women’s)
Riley Bove (Brigham & Women’s)
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25 Clinical Sites across the United States

SUSPENDED: NOT FUNDED BY NIH
Bedside to Bench to Bedside: Clinical Observations

1. Pregnancy is protective in MS

2. Males are less likely to get MS: F>M (3:1)

3. Males: worse disability progression
Clinical Observation
Males: Worse Disability Progression

Why is there more neurodegeneration in men? Testosterone neuroprotective.

Sex chromosomes XX vs XY?
Use XX vs XY- (chromosome vs. hormone)
Use bone marrow chimeras (CNS vs immune)
4 Core Genotypes

Female gonads

- XX
- XY-

Male gonads

- XX_{Sry}
- XY_{Sry}
Determine whether there are sex chromosome effects in the CNS during EAE

Day -56: Ovariectomy

**XX Donor**

Day -49: Harvest bone marrow cells

Day -49: Inject $\sim 1.5 \times 10^7$ cells via tail vein

Days -50 & -49: 425 RADS

**XX vs. XY**
Recipient
4 weeks old

Chimera

**Bone marrow chimeras**

Group 1) XX immune, XY CNS (XX$\rightarrow$XX)
Group 2) XX immune, XX CNS (XX$\rightarrow$XY)

Proceedings of the National Academy of Sciences, PNAS, 2013
Clinical Observation: M > F Progression

XY- CNS, compared with XX, confers greater EAE disease severity

Proceedings of the National Academy of Sciences, PNAS, 2013
Clinical Observation: M > F Progression
XY- CNS, as compared to XX, have less myelin and fewer axons in spinal cord

Proceedings of the National Academy of Sciences, PNAS, 2013
Bedside to Bench to Bedside: MS to EAE to MS

1. Pregnancy decreases MS relapses
   - Estriol Tx for females
2. Males are less likely to get MS: F>M (3:1)
   - Testosterone Tx for males
3. Males worse disability progression
   - XY deleterious in CNS
Research in Sex Differences

Using EAE

1. Sex hormone effects
2. Sex chromosome effects
MS to EAE to MS

Bench to Bedside
(molecule or technique based)

Bedside to Bench to Bedside
(clinical observation based)

1. Start with a clinical observation
2. Unravel mechanism at lab bench
3. Target mechanism in a clinical trial
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MS & EAE

Most widely used for MS model
Standard Preclinical Study MS drug development
If works in EAE, may not work in MS
If does not work in EAE, even less likely to work in MS

Necessary, but Not Sufficient

Prerequisite to advance to next stage of drug development
Autoimmunity model – Neurodegenerative model

Peripheral immune activation
WM: immune cell infiltration and glial activation
WM: demyelination
WM: axonal loss
GM: synaptic loss
GM: neuronal loss
GM atrophy on in vivo MRI
WM & GM: Electrophysiology
MS & EAE

Which EAE model: Depends on the Question:

Monophasic – Relapsing – Chronic progressive

Pregnancy

Sex Differences
GENDER & MS: CLINICAL ISSUES

• What is the management of pregnant women with MS?
• What is the interaction of MS and hormones such as contraceptives and hormone replacement therapy?
• What are the effects of menopause on MS?
• What causes sexual dysfunction & how is it treated?
• What health issues should both genders address?
FAQ

• What type of birth control should I use (or not)?
• Should I take my disease modifying treatments when I am pregnant, and if not, when do I stop?
• What if I get an attack when I am pregnant?
• How will being pregnant affect my MS long term?
• Will my baby get MS?
Birth Control

• Most studies show no effect or slightly decreased risk in Oral contraceptive (OCP) users
• One study has demonstrated increased risk of developing MS in OCP users
• Barrier methods may be problematic
• Other drugs may interfere with OCPs
MS & the Menstrual Cycle

• Several self-report studies suggest that women can have peri-menstrual worsening of MS symptoms
• One study has reported that this responds to treatment with aspirin
MS and Menopause

• Very little information
• A few studies suggest worsening of MS at menopause
• Symptoms of menopause can overlap with some symptoms of MS
  - Fatigue
  - Cognitive problems
  - Bladder & sexual dysfunction
  - Mood changes
  - Sleep disturbances
MS and Pregnancy

- Effect of MS on pregnancy
- Symptom management
- Breast feeding
- Prophylaxis
Effects of MS on Pregnancy

• No effect on fertility
• No increase in miscarriage rate
• No increase in congenital malformations
• May be associated with lower birth weights
Post Partum Relapse Prevention

- Post partum likelihood of relapse related to pre-pregnancy relapse rate
- IVIG may be useful as prophylaxis
- Women at risk should resume Disease Modifying Agents (DMA) sooner
Long term effects of pregnancy

- Prospective and retrospective studies
- Follow-up 0.5-25 years
- Risk of developing MS may decrease with increasing parity
- Possible protective effect on disability
Management of Labor & Delivery

- Generally the same as for women without MS
- Epidurals not associated with increased relapse rate
- Women with severe sensory loss may require assistance during labor
- C-sections not associated with increased relapse rates
MS Symptoms Made Worse During Pregnancy

- Fatigue
- Balance/mobility
- Spasticity
- Bladder
  - Urgency, frequency
- Bowel
  - Constipation
Medication Use During Pregnancy

- Disease modifying agents not indicated during pregnancy and breast feeding
- Most drugs for symptom management not indicated during pregnancy
- Disease modifying agents need to be stopped for varying amounts of time before a planned pregnancy
Endocrine Effects of Immunomodulators

- Beta-interferon associated with menstrual irregularity and increased thyroid autoantibodies
- Alemtuzumab associated with thyroid disease
Breast Feeding

- Most studies show no effect of breast feeding on post partum relapse rate
- Some studies have reported decreased relapses with exclusive breast feeding
- Cannot breast feed and take DMA
Genetics of MS

• Risk of a child of an MS parent higher than in the general population
• Girls more at risk (5%) than boys (1%)
• About 20% of persons with MS have an affected first degree relative
Men

- Onset in men somewhat older
- Some studies report lower testosterone levels in men with MS
- More men have primary progressive MS
Sexual Dysfunction in MS

- Present in up to 80% of men, and 72% of women
- May be the first symptom
- Correlations
  - Bladder symptoms
  - Depression
  - Weakness
Symptoms of Sexual Dysfunction

- Decreased libido
- Decreased lubrication
- Decreased orgasmic capacity
- Painful intercourse
- Decreased libido
- Erectile dysfunction
- Disorders of sensation
MS Symptoms that Contribute to Sexual Dysfunction

- Pain
- Fatigue
- Spasticity
- Bladder dysfunction
- Depression
- Change in self image
- Fear of rejection
- Ability to please partner
Pharmacologic Causes of Sexual Dysfunction

- Anti-hypertensives
- Antidepressants
- Anti-seizure meds
- Anti-anxiety meds
Treatment of Sexual Dysfunction

- Hx. & PE
- Treat secondary factors
- Pharmacologic
  - ED drugs
  - Filibanserin
- Psychologic
- Devices
  - Vacuum
  - Implants/Pump
  - Vibrators
Health Maintenance

**WOMEN**
- Annual PE, LABS
- GYN, Breast exam
  - PAP smear, mammogram
- Stool guiaic, colonoscopy
- Immunizations
- DEXA scans
- Dental Health

**MEN**
- Annual PE, LABS
- Testicular/prostate exam
  - PSA
- Stool guiaic, colonoscopy
- Immunizations
- DEXA scans
- Dental Health
Summary

- Pregnancy & MS
  - Less relapses during pregnancy
  - No adverse effect on long term disability
  - Possibly protective
- Menstrual cycle & MS
  - Increase in symptoms perimenstrually
- Menopause & MS
  - Menopause symptoms and MS symptoms may overlap
- Hormone treatment & MS
  - Treatment decisions should be made on gynecologic rather than neurologic grounds
Additional Resources

- Sex Ed for Grownups – Intimacy in MS (telelearning)
- Hormones- The Basic Facts (brochure)
- MS & Pregnancy (brochure)
- MS & Pregnancy: Kara’s Story (video)
- Sex and Intimacy (video)
- Hormones, Gender and MS Part 1 & 2 (video)

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www.nationalmssociety.org/telelearning
1-800-344-4867
Q&A

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OR

the operator will assist you with asking your questions