# Phase I Trial of Immunotherapy with BHT-3009 Alone or Combined with Atorvastatin in Patients with Multiple Sclerosis

Recombinant DNA Advisory Committee Meeting

June 8, 2004

BAYHILL THERAPEUTICS

# BHT-3009 Treatment of Multiple Sclerosis

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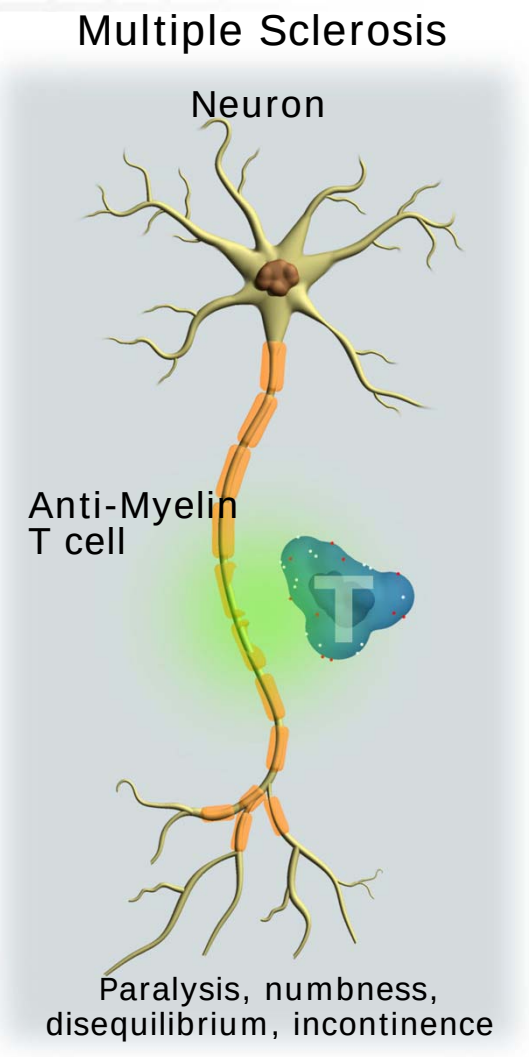
- Antigen-specific immunosuppression - Well established
  - Pre-clinical models
  - Approved product - Copaxone
  - Multiple products in clinical development
- Plasmids
  - Typically used to enhance immunity
  - Immunosuppressive in correct context
- BHT-3009
  - Strong pre-clinical rationale
  - Good safety profile
  - Phase I trial designed for careful safety monitoring

# Multiple Sclerosis (MS)

- Autoimmune disease of nervous system
- Immunological attack on the myelin sheath
- 400,000 patients in US
- Women > men
- Age < 40 years
- Clinical course
  - Relapsing remitting
  - Secondary progressive
  - Primary progressive
  - Progressive relapsing
- Lifelong progression to near total disability



# Multiple Sclerosis

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- Treatment Goal: Prevent relapses and progression of neurological disability
- Corticosteroids
  - Accelerate recovery from relapses
- Disease modifying agents
  - Interferon, Copaxone
  - Decrease relapses about 30%
  - Modest effect on disability progression
- Antigen-specific immunotherapy for MS in development

# MS Target Antigens

- Known and well characterized self antigens
  - Human immunology
  - Established animal models
- Myelin basic protein (MBP)
- Proteolipid protein (PLP)
- Myelin oligodendrocyte glycoprotein (MOG)
- Myelin associated glycoprotein (MAG)

# Trials of MBP-Specific Immunotherapy of MS

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- Copaxone
  - Random polymers of 4 amino acids derived from immunodominant epitope of myelin basic protein (MBP)
  - Decreased antigen-specific T cell response, Th2 deviation
  - Approved for treatment of MS
- MBP8289 (17 AA fragment of MBP)
  - Tolerization and decreased antibody response to MBP
  - In Phase III trial
- APL (Altered MBP83-99)
  - Decreased antigen-specific T cell response
  - In phase IIb trial (ITN-sponsored)

# MBP-specific Immunotherapy of MS: Safety

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- Worsening MS not observed with Copaxone, oral myelin, MBP8289
- APL
  - Open label single arm trial of high dose APL:
    - 2 of 8 patients had relapses
  - Randomized, double blind trial of APL:
    - 142 patients
    - 26% of placebo patients worsened
    - 18% - 23% of APL-treated patients worsened
  - Currently in 600 patient ITN sponsored Phase IIb trial
- Hypersensitivity reactions
  - Observed with Copaxone, APL (& IFNβ)
  - No IgE or anaphylaxis
  - No impact on disease activity
  - Limited relevance to plasmid-based vaccines
  - Atorvastatin
    - No increase in hypersensitivity reactions
    - Concurrent vaccination is safe

# BHT-3009:
# Designed for Immunosuppression

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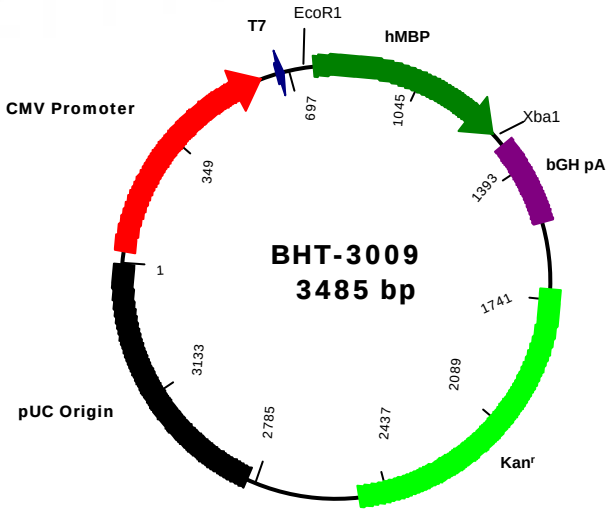
- Encodes DNA for full length hMBP
- No adjuvant
- Immunostimulatory CpG sequences reduced



# BHT-3009: Non-Clinical Studies

- Efficacy studies
  - Experimental allergic encephalomyelitis
  - Dose and schedule
- Safety
  - EAE models
  - Biodistribution
  - Cynomolgus monkey study

# EAE Model of MS

- SJL/J mice
- Well characterized model
- Relapsing & remitting course typical of MS
- Immunological mechanisms similar to human MS
- Immunodominant epitope: PLP

# BHT-DNA Treats Established EAE

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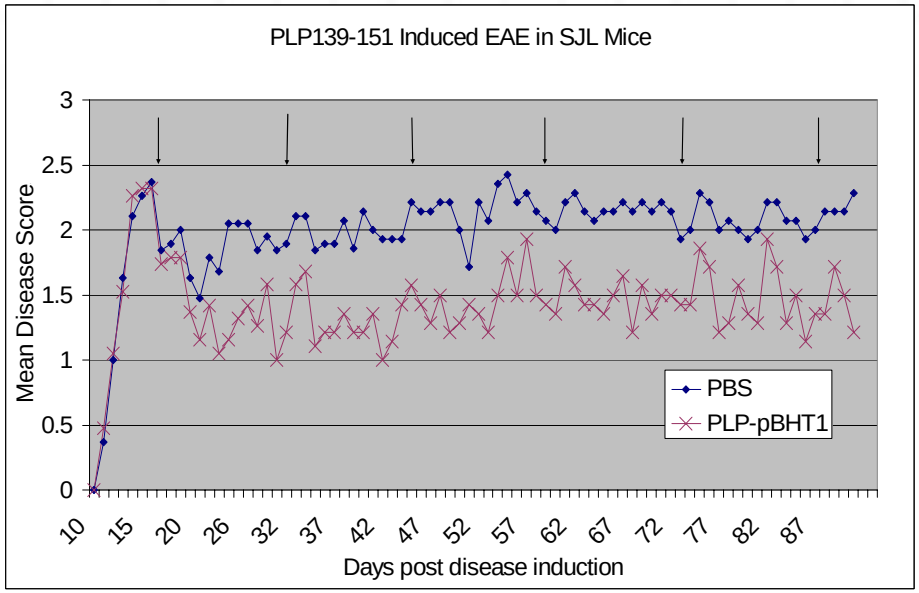
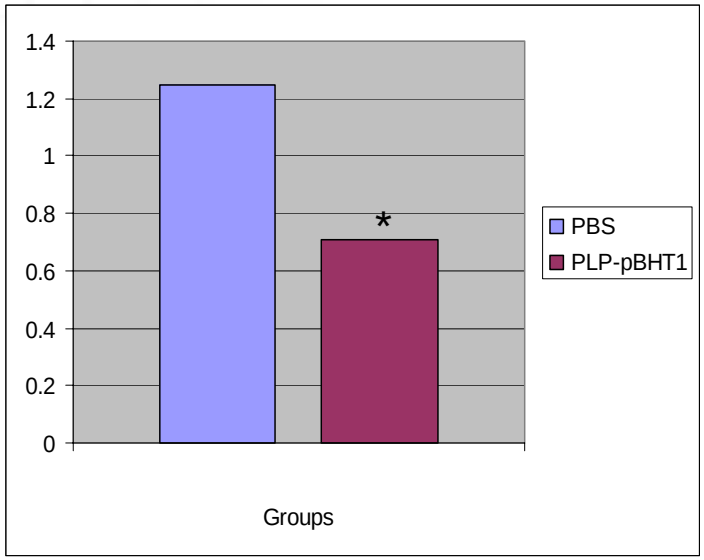
## Mean Disease Score




p value = <0.0001 (Mann-Whitney)

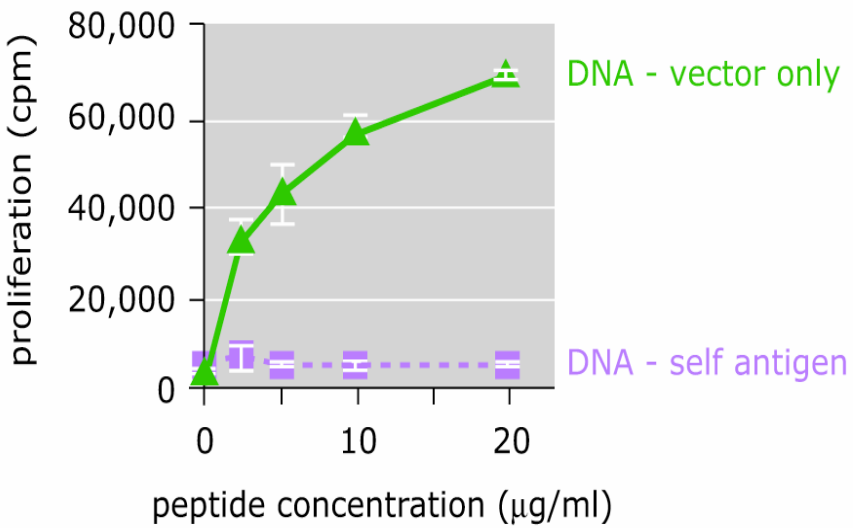
## Relapse Rate

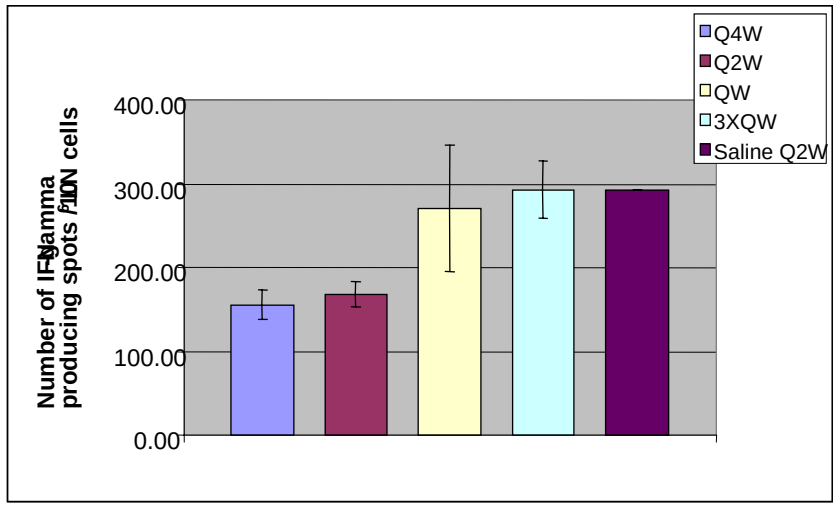



*p value = 0.04 (ANOVA-Dunnett Hsu)

**BHT-DNA reduces both disease severity and relapse rates in a treatment model**

# Inhibition of Antigen-Specific T- Cells




**Reduced Proliferation** **Reduced IFNγ Production**

*Journal of Immunology*, 1999

# BHT-3009
# Dose & Schedule

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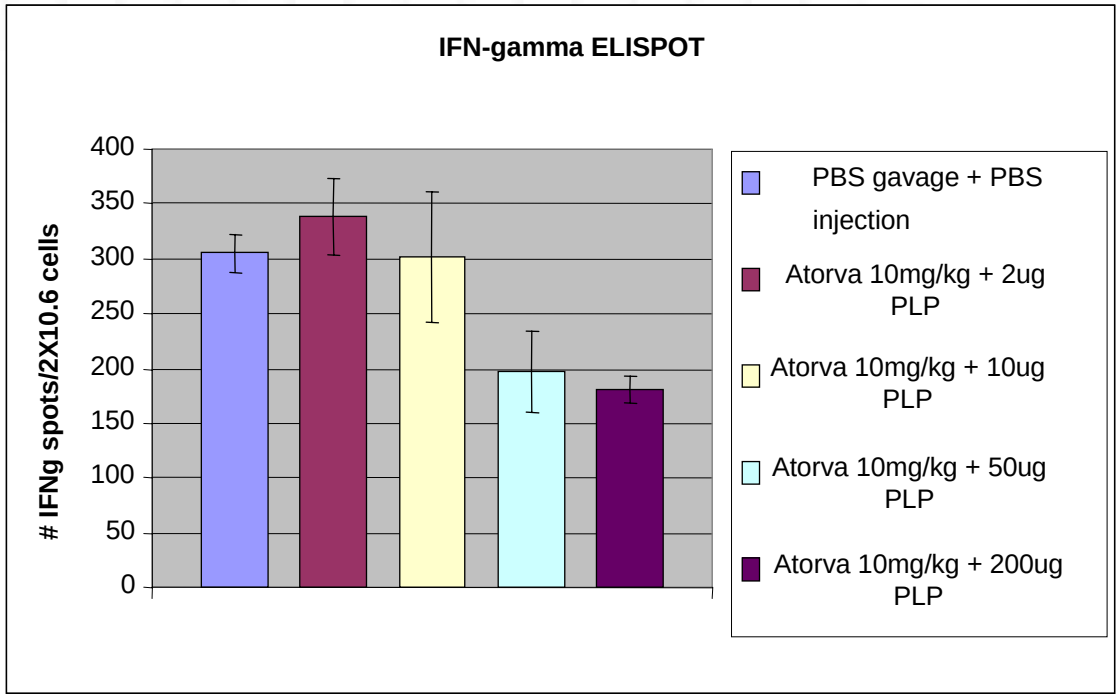
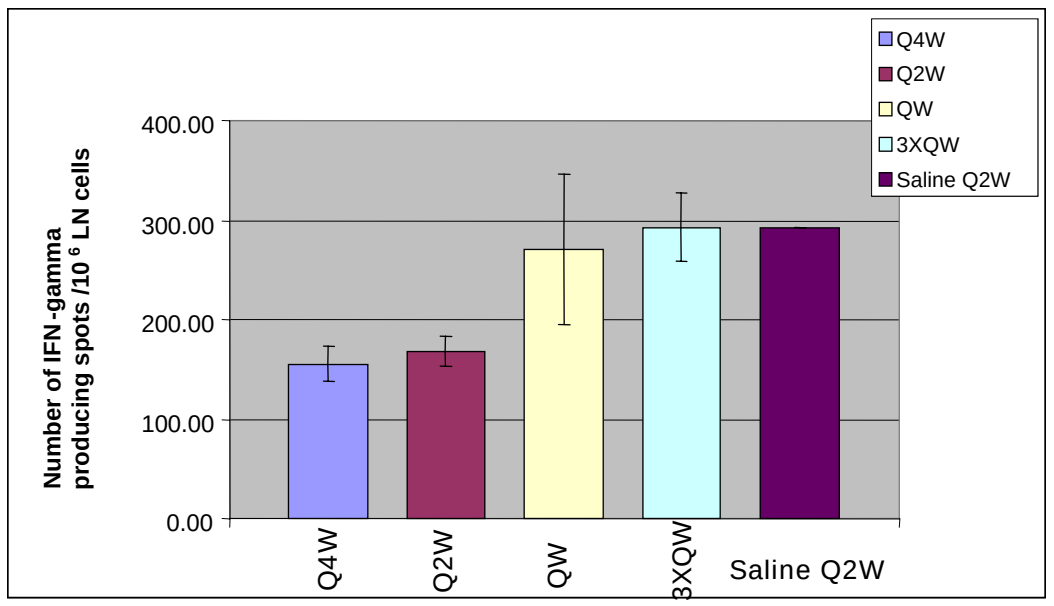
# DNA: Dose Response



# Treatment Schedule




**Every 2 to 4 week treatment decreases IFN-γ production**

# BHT-3009
# Safety - Toxicity

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# Administration of PLP-Vector to SJL/J Mice Did Not Cause or Worsen EAE

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- Administration to naïve animals (4 biweekly injections)
  - No significant anti-PLP antibodies
  - No clinical signs of EAE
  - Histopathology: no lymphocytic infiltration of brain
  - Induction of modest levels of anti-DNA antibodies (3 of 20 mice)
- Administration of PLP-vector to animals either prior to or after induction for EAE with $PLP_{139\text{-}151}$ peptide
  - Effective for preventing and treating EAE
  - EAE-related mortality
    - 3 of 232 PLP-Vector treated mice
    - 3 of 208 control mice

# BHT-3009 Biodistribution & Expression Analyses (GLP)

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| | **Positive Tissues at Each Sacrifice Time-point** |
|---|---|
| **Biodistribution of BHT-3009 DNA:**<br>**(150 μg single dose)** | Day 3: Blood, Heart, Brain, Kidney, Inguinal LN, Iliac LN, Skin at SOA, injected muscle<br>Day 14: Brain, inguinal LN, Iliac LN, Skin at SOA<br>Day 42: Heart, skin at SOA<br>Day 70: Skin at SOA |
| **Expression of hMBP RNA**<br>**(50 μg single dose)** | Day 3: Inguinal LN<br>Day 7: Iliac LN, injected muscle<br>Day 28: Skin at SOA |
| **Expression of hMBP RNA (150 μg single dose)** | Day 3: Iliac LN, blood<br>Day 7: Iliac LN, skin at SOA, muscle<br>Day 14: Iliac LN<br>Day 28: Skin at SOA<br>Day 42: No tissues expressing hMBP |

# GLP Toxicity Study in Cynomolgus Monkeys

| | |
|---|---|
| **Species** | *Macaca fascicularis* |
| **Dose Groups** | A. Vehicle control for BHT-3009 (PBS) & atorvastatin (0.5% CMC/0.1% Tween 80)<br>B. 150 μg BHT-3009<br>C. 1500 μg BHT-3009<br>D. 1500 μg BHT-3009 + atorvastatin at 20 mg/kg/day |
| **Treatment** | ▪BHT-3009 (or PBS vehicle) administered bi-weekly (Days 1, 15, 29 and 43)<br>▪Atorvastatin (or vehicle control) administered daily on Days 1 to 49 |

# GLP Toxicity Study

- No pre-terminal mortality
- No adverse clinical observations
- Mean values for serum and hematology parameters within normal ranges
  - Trends towards a slight increase in ALT and AST in atorvastatin at 20 mg/kg/day group
- No gross or organ weight findings in terminal or recovery animals
- No histopathologic changes in either terminal or recovery animals
  - Including: cerebrum, thalamus, brain stem, cerebellum, spinal cord, sciatic nerve and bulbus oculi
- No effects on percentages of peripheral blood immune cells
- No induction of anti-dsDNA, anti-nuclear, or anti-hMBP antibodies

# Summary of Pre-clinical Data

- EAE/efficacy data support a DNA dose frequency of biweekly or monthly.
- EAE/efficacy data supports efficacy over a wide range of DNA dose levels.
- No concerning safety or toxicology issues.

# Phase I Trial of Immunotherapy with BHT-3009 Alone or Combined with Atorvastatin in Patients with Multiple Sclerosis

| | |
|---|---|
| IND Cleared | 4/04 |
| CTA (Health Canada) Cleared | 4/04 |

2 Directorates: BGTD & TPD

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# Reduced Antibody Responses

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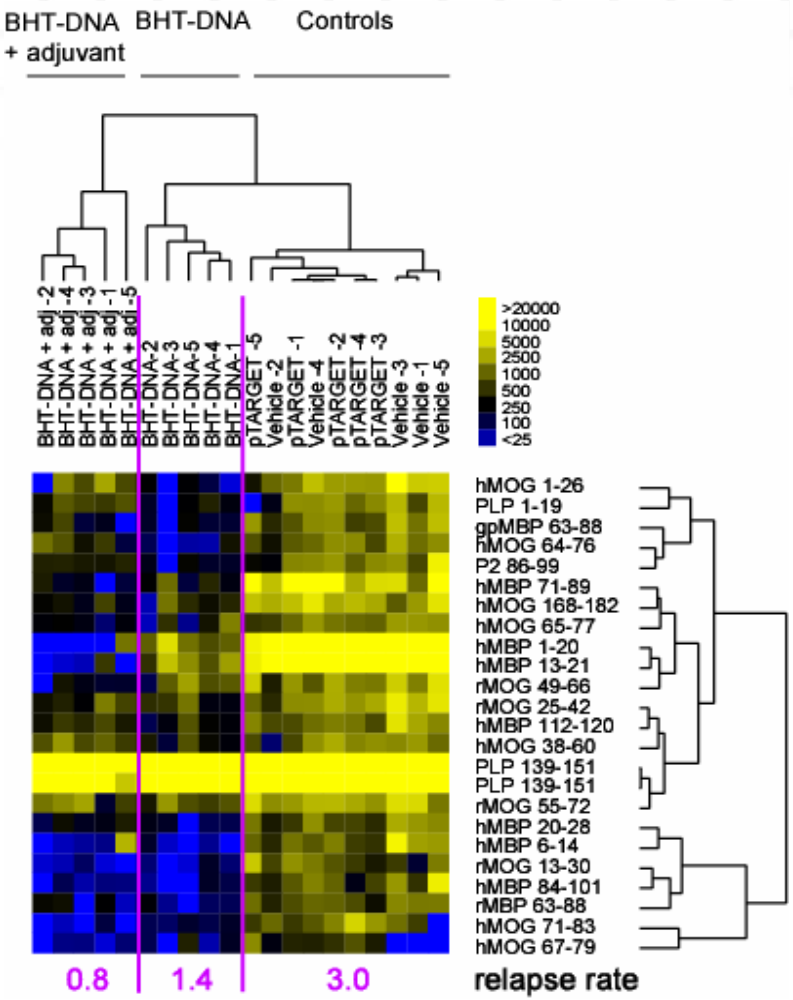


PLP, MBP, MOG & MAG plasmids

Antigens shown are statistically significant for variation of response across each group.

*(published in Nature Biotech 2003)*

# BHT-DNA Platform: Mechanism of Action (R. Steinman, et al)

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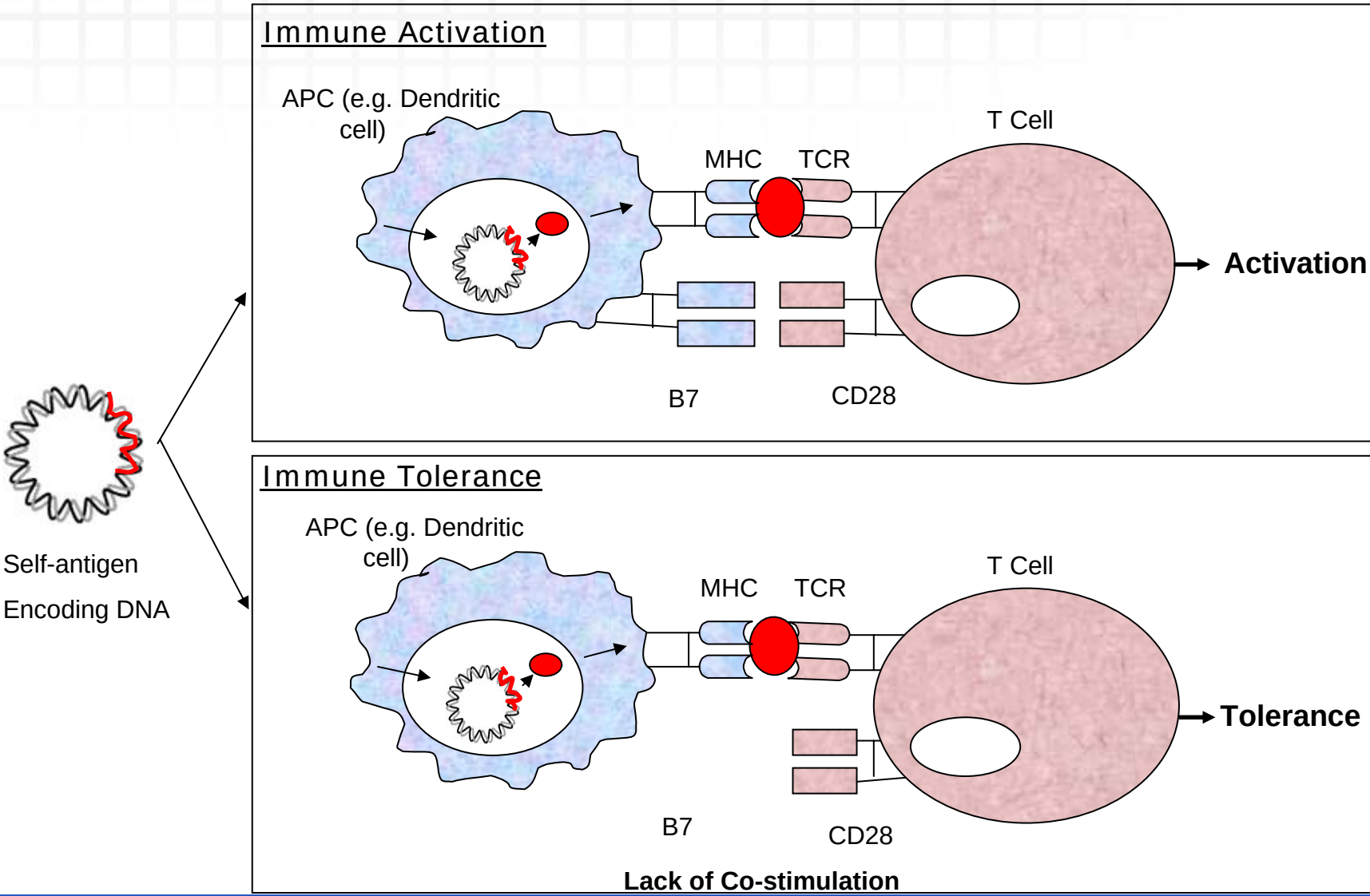
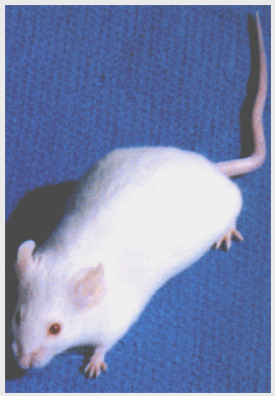
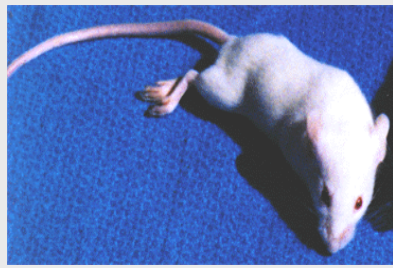


# EAE Model of MS



| Disease Grade | Clinical Symptoms |
|---|---|
| 0 | Healthy |
| 1 | Loss of Tail Tone |
| 2 | Hind Limb paraparesis |
| 3 | Hind Limb paralysis |
| 4 | Complete paralysis |
| 5 | Death |



# MBP-specific Immunotherapy of MS: Safety Issues

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- Hypersensitivity reactions/anaphylaxis
  - Observed with Copaxone, APL
  - Risk benefit ratio determines acceptability
  - Limited relevance to plasmid-based vaccines
- Worsening MS
  - Theoretical concern
    - Not observed in Bayhill's preclinical studies
    - Not supported by clinical data
    - Treatable with high dose steroids
  - Not observed with Copaxone, oral myelin, MBP8289
  - APL
    - Open label single arm trial:
      - 25% worsened (2 of 8 patients)
    - Randomized, double blind trial:
      - 142 patients
      - 26% of placebo patients worsened
      - 18% - 23% of APL-treated patients worsened

# Bayhill: Background

- **FOUNDERS**

- **Lawrence Steinman, M.D.**
  - Chair, Department Immunology Stanford University

- **William Robinson, M.D., Ph.D.**
  - Assistant Professor of Medicine in the Division of Immunology and Rheumatology at Stanford University

- **PJ Utz, M.D.**
  - Assistant Professor of Medicine in the Division of Rheumatology and Immunology at Stanford University

- **Hideki Garren, M.D., Ph.D.**
  - Clinical Faculty at Stanford Medical School
  - Bayhill: Director, Molecular Biology and Immunology

- **MANAGEMENT**

- **Mark Schwartz, Ph.D., CEO**
  - Calyx, Trega, Synteni, Incyte

- **Frank Valone, M.D., Clinical**
  - Dendreon, Titan

- **Hideki Garren,M.D.,Ph.D., Research**
  - Stanford, Bayhill Founder

- **Stephanie Broome,Ph.D., Regulatory**
  - PRA International, SIBIA, PowderJect

- **Martin Goldstein, J.D. Corp. Development**
  - Virologic, Roche, Genentech

# Multiple Sclerosis

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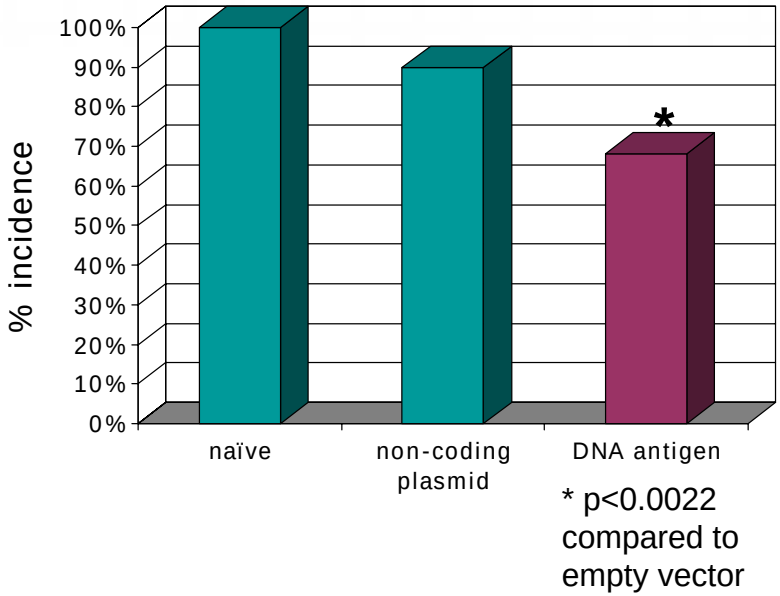
- Relapsing-remitting course
- Life-long progression to total disability
- Treatment Goal: Prevent relapses and progression of neurological disability
- Corticosteroids – relapses
- Disease modifying agents
  - Interferon
  - Copaxone
  - Mitoxantrone
- Treatment is non-specific immunosuppression
- Antigen-specific immunotherapy for MS in development

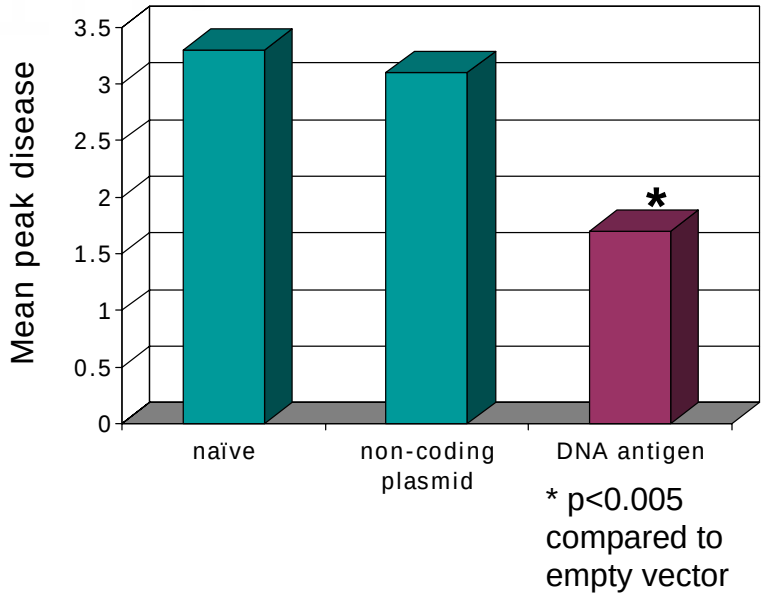
# Bayhill: Background

- Founded Spring, 2002
- Based in Palo Alto, CA
- 24 employees
- Focus on antigen-specific immunotherapy of autoimmune diseases
- Multiple technology platforms
  - Protein array
  - Plasmid DNA for immunosuppression
    - Multiple sclerosis
    - Type 1 diabetes
    - Rheumatoid arthritis

# BHT-DNA Reduces EAE Incidence




* p<0.0022 compared to empty vector




* p<0.005 compared to empty vector

**BHT-DNA reduces both disease incidence and severity in a prevention model**

*Journal of Immunology*, 1999

# BHT-DNA Schedule

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| | **Mean Disease Score (compared to each other)** | **Mean Disease Score (compared to respective control)** |
|---|---|---|
| **QW** | | P=0.22 |
| **Q2W** | Q2W injections decrease MDS by 0.25 (**p=0.01**) | **P<0.001** |
| **Q4W** | Q4W injections decrease MDS by 0.12 (**p=0.01**) | **P<0.001** |