# How to Avoid An Expensive Mistake With Avian Influenza

*or*

# Progress Towards A Universal Viral Antidote

The DM Colloquium

Philadelphia, May 11, 2006



GENOMED

# GenoMed's Mission Statement

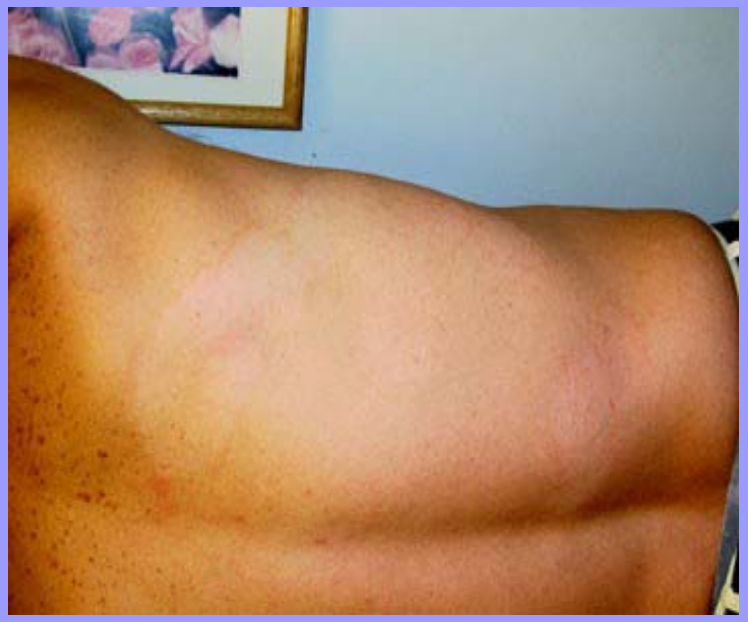
- To find the molecular basis of common diseases, and
- To use this information to improve patient outcomes as quickly and as safely as possible.

# ACE is “master” gene for chronic diseases

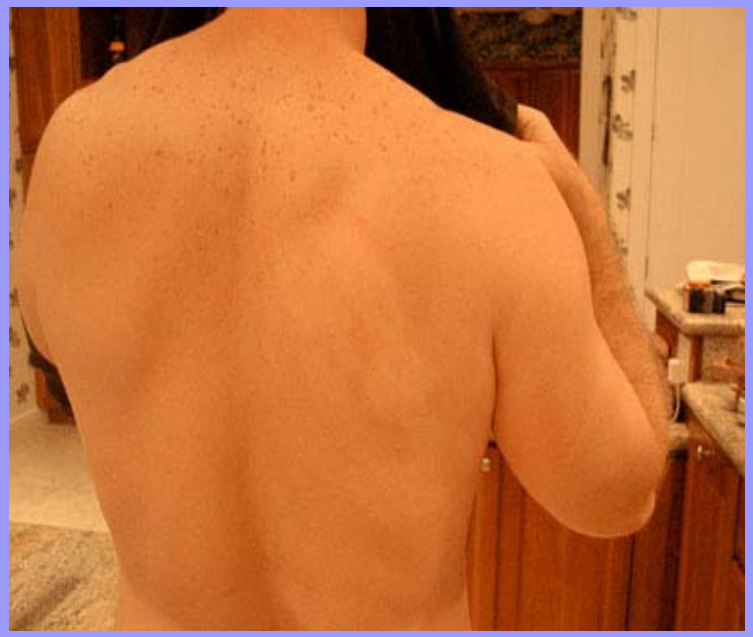
- Cardiovascular diseases
- COPD
- Cancers
- Neurodegenerative diseases, e.g. Parkinson’s
- Psychiatric diseases
- ***Autoimmune dz’s***: e.g. psoriasis

*Ref.* Moskowitz DW et al. (2002-2004)

# Psoriasis



Before ARB



4 wks after ARB

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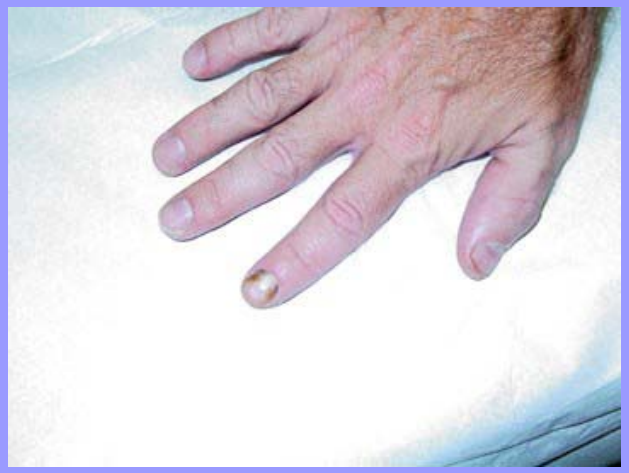
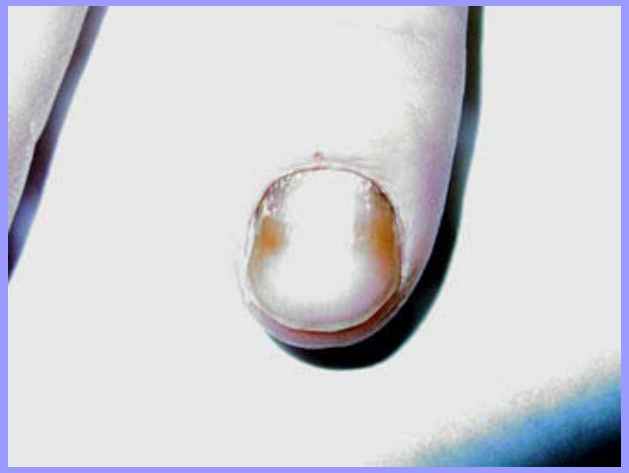
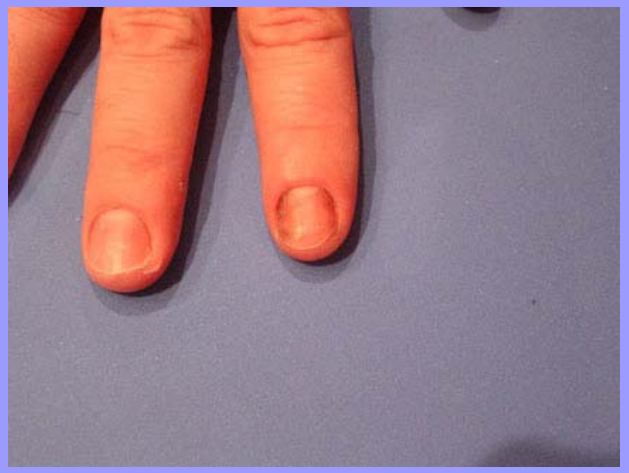
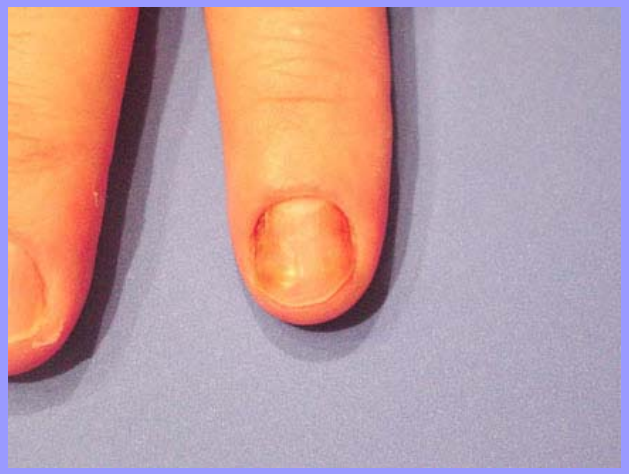
Next Generation Disease Management™

# Psoriasis (cont.)









Before ARB

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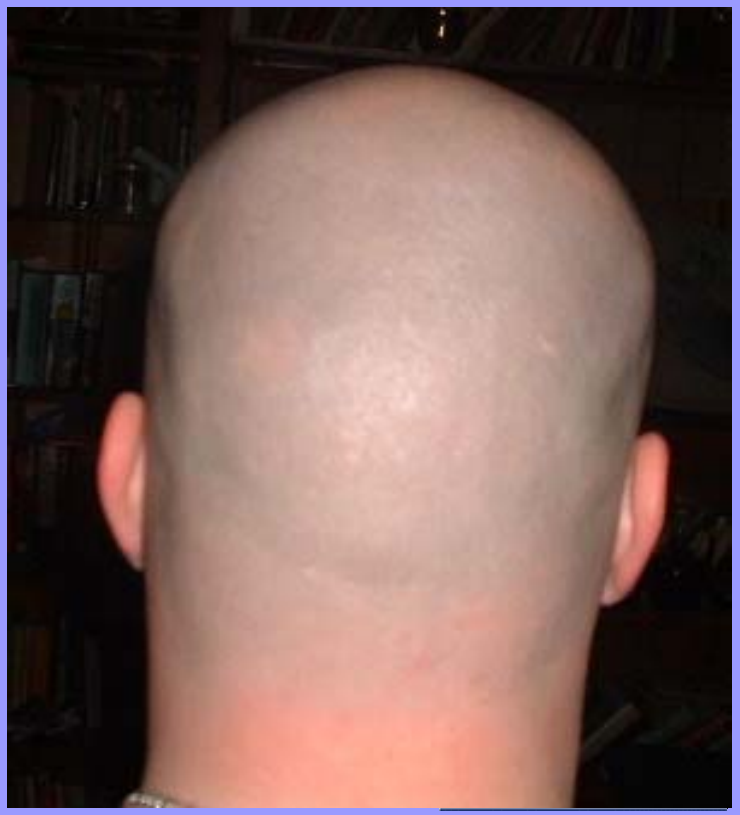
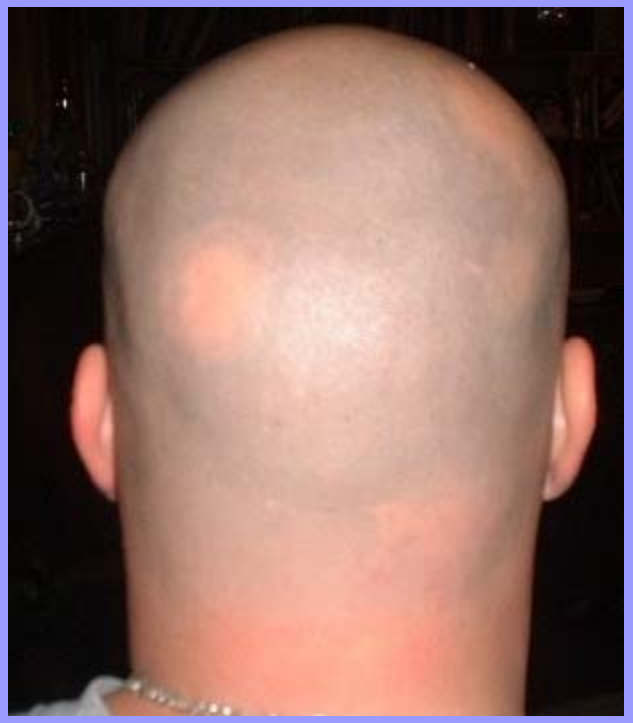
4 weeks after ARB

# Alopecia Areata

After 5 mos on ARB





Before ARB

# For immunocompetent patients, most viral diseases reflect overactivity of the innate immune response

Possible exceptions: herpesviridae (incl. CMV)

# The Innate Immune Response to Viruses: Early Response (1st wk)

- APC's:
  - Endothelial cells (viremia)
  - Pulmonary alveolar epithelial cells (inhaled virus)
  - Intestinal epithelial cells (ingested virus)
  - Salivary glands (mumps)
- Effector cells:
  - Monocyte/macrophages ("microglial" cells in CNS)

# The Innate Immune Response to Viruses: Late Responses (≥ wk 2)

- Lymphocytes
  - T cells: cytotoxic, helper, & suppressor T cells
  - B cells (IgM → IgG)

# Current Therapy

- ***Vaccines***
  - create a “memory” (l’cyte) response, incl. suppressor T cells.
- ***Antivirals***
  - ignore immunity.
  - Highly mutable viruses lead to resistance, e.g. 10% w/ Tamiflu
- ***Passive antibodies***:
  - Israeli WNV trial
  - Horse serum in pre-PCN era

# GenoMed's Approach

- Tone down the immune response
- Ignore the virus
- Convert every patient into an asymptomatic shedder of virus
- Only for immunocompetent pts. (the general population)
- Should work for ~all viruses
  - Not herpes, CMV, ?EEE

# Macrophage is Key Player in Viral Diseases

- Symptoms (fever, myalgias, arthralgias, cachexia, fatigue, headache) can all be ascribed to a single MΦ cytokine, TNF-α
- Macrophage Permeability Factor (MPF) increases leakiness of blood vessels→ ↑ICP → severe HA (WNV), pulm. edema (avian flu)
- Macrophage Migration Inhibitory

Factor (MIF), a chemotactin, induces accumulation of macrophages

# A II is an early activator of macrophages

- Macrophages express ACE (CD143) upon activation
- Angiotensin II (via PKC) induces expression of above cytokines (TNF-α, MPF, MMIF) + IL-8, etc.
- A II stimulates MΦ proliferation
- AT1R's stimulate; AT2R's inhibit & promote apoptosis

# Examples

- WNV neuropathology @ 1-2 wks: perivascular cuffing by microglial cells, very little viral antigen present in CNS in 4 of 5 pts. Ref. B. Samson, Ann NY Acad Sci 2001.
- SARS autopsy results: sheets of monocytes filling alveoli; little virus seen. Ref. NEJM articles 4/2003.

Similar picture for all other viruses besides Herpesviruses/CMV

# Inhaled Viruses: Pathophysiology

- Virus binds to alveolar epithelial cell (type 2 pneumocyte), replicates, and is presented to alveolar macrophage
- Alveolar macrophage recruits add'l MΦ's
- Alveolar epithelial cell commits apoptosis, helped by A II made by activated alveolar MΦ's

# Viral Pneumonia: Clinical Picture

- Result: airspace filled by monocyte/MΦ's, necrotic debris (alveolar epithelial cells)
- "White-out" on CXR
- Widening A-a $O_2$ gradient w/ inability to ventilate (ARDS-like picture)
- Exs: SARS, RSV, avian influenza, human influenza, hantavirus, monkey pox

# Viral Encephalitis: Pathophysiology

- Virus homes to CNS arteriolar endothelial cells, proliferates therein, & is presented to circulating monocytes
- Circulating monocytes become activated, express plasma membrane ACE, generate local A II, which induces MPF, MIF, etc.
- MΦ's-"microglia"-surround neurons
- Neurons commit apoptosis
- Paralysis results

# Viral Encephalitis

- Hallmark of pathology: Inflammatory cells (microglia) without virus

- Exs.: WNV, polio, rabies, St. Louis Equine Encephalitis, Eastern Equine Encephalitis, Japanese Encephalitis, Tick-borne Encephalitis, etc.

# Hemorrhagic Fevers: Pathophysiology

- Virus homes to endothelial cells throughout vascular tree, & rapidly proliferates
- Endothelial cells apoptose/necrose
- Circulating monocyte/MΦ's are activated strongly with thrombosis (A II-mediated)
- DIC picture results
- Exs.: Ebola, Dengue, CCHF

[cf. sickle cell crisis]

# WNV Results:

## 19 – 3

since 2003

# Next Steps

- Test this approach for as many viral diseases as soon as possible
  - Mumps; WNV, EEE, hantavirus; influenza, common cold, RSV (but CDC won't collaborate)
  - Avian influenza (but WHO won't collaborate)
  - Viral bioterrorist threats: Ebola, Dengue, etc.—epidemics already exist

# Advantages of This Approach

- ARBs and ACEI's are safe, inexpensive, & already available in every drug store on earth
- No viral resistance
- Immediately applicable world-wide
  - GMED's "use" patent good only in US

# Problems w/ This Approach

- Shrinks antiviral market to only immunosuppressed patients
  - WHO and Roche?
  - Gilead and US Government?
- Eliminates need for vaccines
- Paradigm shift for virology:
  - host, not virus, is major problem
  - the opposite of interferon

**For any questions, please contact:**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