### Chronic Diseases Once Rare now Familial Disease
#### 21st Century Acquired Immune Deficiencies (AIDS)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Auto-Immune Diseases</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate*</td>
<td>Lupus</td>
<td>ME/CFS*</td>
</tr>
<tr>
<td>Breast*</td>
<td>Crohn's*</td>
<td>Gulf War Syndrome*</td>
</tr>
<tr>
<td>Multiple Myeloma*</td>
<td>Hashimoto’s Thyroiditis*</td>
<td>Autism/ASD*</td>
</tr>
<tr>
<td>Non Hodgkin’s Lymphoma*</td>
<td>Polymyositis</td>
<td>MS*</td>
</tr>
<tr>
<td>Chronic Lymphocytic</td>
<td>Sjogren’s syndrome</td>
<td>Parkinson’s*</td>
</tr>
<tr>
<td>Leukemia*</td>
<td>Bechet’s Disease*</td>
<td>ALS*</td>
</tr>
<tr>
<td>Mantle Cell Lymphoma*</td>
<td>Primary Biliary Cirrhosis*</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Hairy Cell Leukemia</td>
<td>IBD*</td>
<td>Chronic Lyme Disease*</td>
</tr>
<tr>
<td>Bladder*</td>
<td>Psoriasis, dermatitis</td>
<td>OCD</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>ADHD</td>
</tr>
<tr>
<td>Kidney*</td>
<td></td>
<td></td>
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<tr>
<td>Ovarian*</td>
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</tbody>
</table>

* RT Activity, RV sequences or proteins, antibodies to RV proteins
Acquired Immunological Susceptibility to Chronic Inflammatory diseases

Acquired immunological susceptibility:
- Environmental risk factors
- C-section
- Broad spectrum antibiotics
- Toxins from GMO food and formula

Genetic Epigenetic susceptibility

Gut dysbiosis

Cytokine Storm

Dysregulated microbiome and vaccine components, adventitious agents

Microbial toxins, casein, bovine proteins, transgenes from GMO

Stress
Language
Higher cognitive functions
Recent advance in genomic technologies have identified ~1000 nuclear genes that regulate mitochondrial function ...
The Key IS EPIGENETICS: the Expression of the gene and the Tissue Context

Retroviruses, heavy metals, genetically modified organisms, and environmental toxins: Drivers of Evolution/Devolution by way of alteration DNA Methylation/ Gene Expression
XMEM disease: a new primary immunodeficiency affecting Mg\(^{2+}\) regulation of immunity against Epstein-Barr virus

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A

XMEM Disease

Minor Features
- Sinusitis
- Otitis Media
- Streptococcal Pharyngitis
- Molluscum Contagiosum
- Varicella and Recurrent Zoster

Major Features
- EBV-positive Lymphoproliferative Disorders
- Decreased CD4/CD8 ratio
- Splenomegaly
- Neutropenia
- Thrombocytopenia
- Hemolytic Anemia
- High EBV titers

B

TCR

Mg\(^{2+}\)

MAGT1

Ca\(^{2+}\)

IP3

PLCγ1

Mg\(^{2+}\)

Endoplasmic Reticulum

T cell Activation

C

Virus Infected cell

Tumor cell

CD8 T cell

NK cell

NKG2D Ligand

MAGT1

Mg\(^{2+}\) Transporter

[Ca\(^{2+}\)]

NKG2D

(Blood. 2014;123(14):2148-2152)
In Chronic Diseases Viruses Seldom Come Alone
Synergy in Immune Dysregulation

Table 1. Mechanisms of Interactions between HIV-1 and Coinfecting Viruses

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoactivation</td>
<td>HCV, HSV-2, CMV, EBV, HTLV-2³</td>
</tr>
<tr>
<td>HIV-1 trans-activation</td>
<td>HSV-2, HTLV-1, JCV³</td>
</tr>
<tr>
<td>Abnormal production of chemokines</td>
<td>HTLV-1, HHV-6, HTLV-2, MV, GBV-C</td>
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<tr>
<td>CD4, CCR5, or CXCR4 downregulation</td>
<td>HHV-7, GBV-C</td>
</tr>
<tr>
<td>Expression of virokines and viroceptors</td>
<td>CMV, HHV-6, HHV-7</td>
</tr>
<tr>
<td>Blockage of CD4 T cell cycle</td>
<td>MV</td>
</tr>
<tr>
<td>Modulation of cytokine signaling</td>
<td>EBV, adenovirus</td>
</tr>
<tr>
<td>Inhibition of apoptosis</td>
<td>CMV, EBV</td>
</tr>
<tr>
<td>Aberrant activation of autologous complement</td>
<td>HHV-6, HHV-7</td>
</tr>
<tr>
<td>MHC downregulation</td>
<td>CMV, HHV-6, HHV-7</td>
</tr>
</tbody>
</table>

A Question of Balance

Figure 1. Host-Virus Equilibrium is Disrupted by HIV-1

War and Peace between Microbes: HIV-1 Interactions with Coinfecting Viruses: Cell Host & Microbe 6, November 19, 2009 A. Lisco, C Vanpouille, & L Margolis
Celebrex

Only certain antibiotics promote fungal overgrowth in the gut, suggesting specific commensal bacteria have the ability to prevent colonization of Candida.
New Technologies provide new opportunities for drug repurposing:
Comprehensive Sequence Analysis of Nuclear mitochondrial genes

- NGS for variants in the nuclear mitochondrial exome that contribute to neurological disorders whose symptoms resemble mitochondrial disease.

Case Reports In CFS patients Results:
- Abnormal autosomal dominant Variant was found in SCN4A gene that is likely a pathological mutation
- Pathological mutations found in two other patients also with multiple functional conditions (ME/CFS)

- Drugs targeting channelopathies (Diamox)
  - mitochondrial targets mTOR (Rapamycin)
  - apoptosis
Toxicity from Chronic Immuno-stimulation

Ponce 2008 J Immunotoxicology 5:33-41