Jackson Laboratory Collaborative Research Center (CRC) for ME/CFS

Derya Unutmaz, MD
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
Clinical Samples

- Immune Profiling
- Metabolomics
- Microbiome Profiling

Computational Interactome
Why maintaining a balanced immune response is critically important for our health?

The Bad
- Autoimmunity
- Allergies
- Septic shock

The Good
- Clearance of infections
- Repair tissue damage

The Ugly
- Chronic inflammation
- Chronic Illness
Inappropriate immune response has terrible health cost.
Microbiome shapes the immune system

Microbes within us

Maintaining microbial equilibrium is critical for healthy immunity.

Regulatory Bacteria  Commensal Bacteria  Inflammatory Bacteria

Regulation  Inflammation

Round et al. Nature Reviews Immunology (May 2009)
Disequilibrium of microbial ecosystem causes inflammation

Dysbiosis

Pathogens

Regulation

Inflammation

Round et al. Nature Reviews Immunology (May 2009)
Diseases associated with disrupted microbiome

- Alzheimer’s
- Asthma/Allergies
- Autism
- Autoimmune diseases
- Crohn’s Disease
- Cancer
- Dental Cavities
- Mental Disorders
- Diabetes
- Eczema
- Gastric ulcers
- Hardening of the arteries
- Obesity
- Inflammatory bowel diseases
- Malnutrition
- Parkinson’s Disease

- ME/CFS?
JAX ME/CFS CRC Research Projects
Division of Labor in the Immune System

Innate immunity:
- Microbe
- Epithelial barriers
- Phagocytes
- Dendritic cells
- Complement
- NK cells

Adaptive immunity:
- B lymphocytes → Antibodies
- T lymphocytes → Effector T cells

Time after infection:
- Hours: 0, 6, 12
- Days: 1, 3, 5

Abbreviations:
- B: B lymphocytes
- T: T lymphocytes
- NK: Natural Killer cells
Functional subsets of human T cells

Naïve T cell

- Treg

Effector/Memory T cell

- Treg: Immune regulation/suppression
- TfH: Help B cells (Autoimmunity)
- Th1: Bacteria, viruses - IFNγ (Autoimmunity)
- Th2: Parasites - IL-4, IL-5 (Allergy, asthma)
- Th17: Bacteria, Fungi - IL-17, IL-22 (Autoimmunity, inflammation)
- CTL: Viruses, tumors - (Cytotoxic)
- MAIT: Intracellular bacteria, microbiome - IL-17 (Cytotoxic)
- iNKT: Bacteria, viruses, tumors? (Cytotoxic)
- gdT: Bacteria, tumors? (Cytotoxic)
Performing immune profiling using Flow Cytometry
How do we analyze the immune cell frequencies and function in human blood?
Microbiome is also personalized to each person.
Microbiome Sequencing and Culturomics

Shotgun sequence

Metagenomic reconstruction

Identification by MALDI-TOF & 16S
100 unique isolates/sample

Culturomics
Metabolome: control system of biological program

Reprogram the immune response
Computational approaches to integrate patient’s clinical phenotype with biological data

<table>
<thead>
<tr>
<th>Subhierarchy</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Severity, triggering factors, duration</td>
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<tr>
<td>Ability /response to exertion</td>
<td>Post-exertional malaise.</td>
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<tr>
<td>Sleep</td>
<td>Quantity, quality, rhythm</td>
</tr>
<tr>
<td>Pain</td>
<td>Location, migration, intensity, duration</td>
</tr>
<tr>
<td>Neurological/cognitive</td>
<td>Cognition, concentration. Perceptual and motor disturbances, nervousness</td>
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<tr>
<td>Autonomic manifestations</td>
<td>Results of autonomic function tests, R-R variability, reduced vagal modulation</td>
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<tr>
<td>Neuroendocrine manifestations</td>
<td>Cortisol, growth hormone concentration, response to endocrine testing</td>
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<tr>
<td>Immune anomalies</td>
<td>Distribution of immune cells and their functionality</td>
</tr>
<tr>
<td>History of infection</td>
<td>Infectious disease ontology</td>
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<tr>
<td>Environmental</td>
<td>Sensitivity to food, medication, odors, temperature.</td>
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<tr>
<td>Other medical history</td>
<td>Other diseases</td>
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<tr>
<td>Metabolomics, microbiota</td>
<td>Microbiome in given patient and their metabolism</td>
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Goal is to identify clinical and biomarkers that predict subgroups by dataset integration and machine-learning approaches.
“It is far more important to know which person has the disease than what disease the person has” ~ Hippocrates

Credit: The Grace Gawler Institute
Community Outreach efforts

• Organizing advocacy/patient group visits – example, MA CFIDS

• Developed JAX CRC blog to chronicle both news/advances at Jax and ME/CFS in general: https://jaxmecfs.com

• Frequent communication with patient and advocacy groups through social media and emails:
  - Active following / interaction on twitter @Derya_
  - Courtney Gunter, program manager @courtneylgunter
  - Separate community outreach program at Bateman Horne Center in Utah (Stephanie Griffin, @BatemanHorne)

• A Community Steering Committee meeting formed of patients/advocates/physicians is planned later this year.
Administrative Core Team

Program Director:
Derya Unutmaz, M.D. (Jax) – Human Immunology

Associate Program Director:
Julia Oh, Ph.D. (Jax) – Microbiome

Program manager:
Courtney Gunter, M.S. (Jax) – Data management and center project coordination and community outreach
Email: Courtney.Gunter@jax.org,
**Clinical Core and Community Outreach Team**

**Cindy Bateman, M.D.** (Bateman Horne Center) – ME/CFS clinician, lead clinical team.

**Suzanne Vernon, Ph.D.** (Bateman Horne Center) – Clinical Core Co-Lead and community manager

**Mary Dimmock**, (Connecticut), patient advocate

**Morris Papernik, M.D.** (Connecticut) Physician, ProHealth

**Carol Isaacson Barash**, Patient Advocate

**Patrick Venetucci**, Patient Advocate

**Beth Mazur**, Co-Founder, MEAction
**Immune/Microbiome Profiling Project Team**

**Peter Robinson, M.D., M.S. (Jax)** – Computational biology and Clinical Ontology

**Julia Oh, Ph.D. (Jax)** – Microbiome

**Mark Adams, Ph.D. (Jax)** – Microbial Genomics

**Derya Unutmaz, M.D. (Jax)** – Immune profiling

**Dorothy Wheatcraft, Ph.D. (Jax)** – Metabolomics

**Alison Motsinger-Reif, Ph.D. (NCSU)** – Bioinformatics and Biostatistics
Research Project Team

Julia Oh, Ph.D. (Jax) – Microbiota culturomics

Xudong Yao, Ph.D. (UCONN) – Proteomic Chemistry, bacteria metabolite identification

Derya Unutmaz, M.D. (Jax) – Human Immunology assays

Paul Robson, Ph.D. (Jax) – RNA-seq and Single Cell Biology

Duygu Ucar, Ph.D. (Jax) – Bioinformatics of transcriptomes, epigenetics
QUESTIONS ?