OVERTIME:
Flipping the old models on their head when every second counts

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OVERVIEW

» My Story

» Hurdles for Castleman disease and rare disease research

» Progress for Castleman disease

» Lessons Learned

» Opportunities
Castleman Disease (CD)

As common as ALS (5,000/yr)\(^2\)

MCD more deadly than lymphoma (65% 5yr survival)\(^3\)

Episodic flu-like symptoms (+CRP)

Enlarged liver/spleen

Liver dysfunction

Kidney dysfunction

Fluid accumulation

Bone Marrow failure:
- Anemia
- Thrombocytopenia
- Auto-antibodies

Siltuximab (anti-IL-6) approved for iMCD: 34% CR/PR\(^5\)

iMCD: 3X rate of cancer\(^4\)

iMCD: Etiology: unknown
Cell type: unknown
Pathway: unknown

## State of MCD Research in 2012

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<td><strong>“Four cases ever reported of HHV-8-negative MCD... One alive.”</strong></td>
<td><em>- No communication between researchers</em></td>
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<td><em>- All using different terminology systems</em></td>
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<td><strong>No understanding of the trigger, the problem cell, the cytokines involved, or the role of genetics</strong></td>
<td><strong>No consensus on diagnostic criteria</strong></td>
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<td><strong>No patient advocacy effort and $0 NIH-funded projects</strong></td>
<td><strong>Promising results with anti-IL-6</strong></td>
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<td><strong>Disease model didn’t make sense!</strong></td>
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Raise funding from patients and loved ones for research

Invite researchers to apply for funding through RFPs

Fund researcher with best proposal and requisite samples

Provide supportive resources and referrals to patients

**Hurdles in Biomedical Research**
- No overarching strategy
- Fragmented, uncoordinated
- Limited collaboration
- Few communication tools
- Misaligned incentives
- Knowledge asymmetry
“Collaborative Network” Approach

Identify, connect, and build a community for collaboration

Leverage the community to prioritize studies

Provide supportive resources and referrals to patients

Collect and share tissue samples and clinical data for research

Assemble expert team of MD, PhD, MBA students; patients; and loved ones

- **317** physician database
- **3** largest ever meetings
- **Forum with 5,304** patient/family visitors
- **14,389** website visits
- **309** patient registrants

- Established **new disease model**
- Created International Research Agenda (IRA)
- Recruited experts outside of CD

- Raising funds for IRA
- Executing IRA
- Industry-academia-CDCN partnership for global patient registry
- Establishing consensus diagnostic criteria
NEW MODEL OF PATHOGENESIS

Old Model: “Castleman Tumor”

New Model: Hyperinflammatory Disorder

IL-6

Immune Activation

Proinflammatory Hypercytokinemia

IL-6

B/T/MΦ Activation Proliferation

Untreated Inflammation

AAB by CD5+ B-Cells

Constitutional Symptoms

LAD, HGG, Plasma Cell

Vascular Proliferation

Anemia

Ascites, Edema

Renal Disease

Role in iMCD to be determined
INTERNATIONAL RESEARCH AGENDA

- **ETIOLOGY?**
- **CELL TYPE?**
- **SIGNALING PATHWAY?**
- **MECHANISM**

### AUTOIMMUNE HYPOTHESIS
- Evaluation of anti-Ro/SSA

### AUTOINFLAMMATORY HYPOTHESIS
- Whole Exome Sequencing for germline defects
- PROINFLAMMATORY CYTOKINES
  - IL-6, VEGF

### PARANEOPLASTIC HYPOTHESIS
- Proinflammatory cytokines

### VIRAL HYPOTHESIS
- Pathogen Discovery Study
  - Flow cytometry and IHC to identify signaling pathways and cells
  - Serum Proteomics Pilot to quantify cytokines

- **FLU-LIKE SYMPTOMS**
- **LIVER DYSFUNCTION**
- **CASTLEMAN-LIKE LYMPH NODE FEATURES**
- **KIDNEY DYSFUNCTION**
- **BONE MARROW DYSFUNCTION**

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**Bold:** funded

**Unbolded:** not yet funded

- **☑ Biobank**
- **☑ Patient Registry**
Welcome to Rare Disease Day at NIH!
#RDDNIH

Please silence your cell phones and pagers.

22 months!
Age of NIH-funded investigators is getting older and older...
LESSONS LEARNED

» Collaboration is essential
» Question the status quo and change the game
» Hear the clock
» We’re all jumping over the same hurdles
» It takes an army– a Castleman Warrior army!

www.CDCN.org  CDCN2  CDCN_Cure
OPPORTUNITIES

» **21st Century Cures** would help to provide an important boost for biomedical research funding
  » We must ensure that the approach is collaborative
  » We must fund studies based on consensus, merit, and impact
  » Samples and clinical data must be shared democratically

» **OPEN ACT** would promote repurposing existing drugs
  » We must centrally track and evaluate off-label therapies

» We must earmark NIH funding for young investigators
THANK YOU FROM OUR WARRIORS