RARE DISEASES: A CALL TO ACTION

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McGill University Health Centre - Research Institute
During the past 2 years, I have/had an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation:

<table>
<thead>
<tr>
<th>Nature of relationship(s)</th>
<th>Name of for-profit or not-for-profit organization(s)</th>
<th>Description of relationship(s)</th>
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<tbody>
<tr>
<td>Any direct financial payments including receipt of honoraria</td>
<td>CSL Behring</td>
<td>Ad board</td>
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<td></td>
<td>Avir Pharma</td>
<td>Ad board</td>
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<td>Membership on advisory boards or speakers’ bureaus</td>
<td>CSL Behring</td>
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<td>Funded grants or clinical trials</td>
<td>CSL Behring</td>
<td>Clinical trial: completed</td>
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<td></td>
<td>Cidara therapeutics</td>
<td>Clinical trial: completed</td>
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<td></td>
<td>Shire (Takeda)</td>
<td>Trial site closed; no further participation</td>
</tr>
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<td></td>
<td>Vical</td>
<td>Trial closed by sponsor</td>
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<tr>
<td>Non-commercial grants:</td>
<td>CIHR; FRQS; La Fondation Grand défi Pierre Lavoie; RI-MUHC; U.S. DoD</td>
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<tr>
<td>Patents on a drug, product or device</td>
<td>N/A</td>
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<td>All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity</td>
<td>N/A</td>
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</table>
EDUCATIONAL OBJECTIVES:

• To describe what qualifies as a Rare Disease and how the characteristics of a “rare” disease impacts patients/families
• To optimize care of those affected by Rare Diseases
• To understand the value of Rare Diseases to the field of human biology and medicine
AGENDA:

• Rare Diseases: Definitions
• My path from ID into RD
• Rare Diseases at large and at MUHC
RARE DISEASES: WHAT ARE THEY?

- **Definitions:**
  - USA (Orphan Drug Act 1983): < 200,000 individuals at any given time
  - EU: < 1: 2000
  - Japan: < 1: 2500
  - Canada:...
    - Feb 2019: < 5 in 10,000 individuals
RARE DISEASES: WHAT ARE THEY?

- ~ 7000 Rare Diseases ("Health Orphans")
  - ~ 80%: Genetic
- 50% affect children
  - 30% die before age 5 years
RARE DISEASES: WHY SHOULD I CARE?

CLINICAL:
HOW TO BEST SERVE PATIENTS & PROVIDE OPTIMAL CARE

RESEARCH:
HOW TO ADVANCE THE FIELDS OF SCIENCE & MEDICINE
RARE DISEASES: WHY SHOULD I CARE? THE PATIENTS

- Rare ≠ Unimportant
- Affects: 2 – 3 million Canadians (~9%)
  - Diabetes (DM1 + DM2): 2.3 million (2017)
  - HIV: 70,000 (2016)

DID YOU MISS THEM?....

https://www150.statcan.gc.ca/n1/pub/82-625-x/2018001/article/54982-eng.htm
Challenges to the Patients

- Rare / unfamiliar disease → “Diagnostic odyssey”
- Lack of medical knowledge on these conditions
- $\alpha$1AT deficiency*: 7-8 years delay
  43% saw ≥ 3 MDs (12% saw 6-10 MDs)
- Progressive disease; Treatment ($\alpha$1AT) available
- Europe† (Crohn’s; CF; DMD; Ehlers-Danlos; Marfan’s, Prader-Willi; Tuberous Sclerosis; Fragile X): 5-30 yrs

- Complications & Futility:
  - AML → Induction → Consolidation → Conditioning/SCT
  - Inherited Bone Marrow Failure syndromes
  - 1 LRTI (pneumonia) → Antibiotics
  - Recurrent RTI (X-linked agammaglobulinemia) → Abx+++
Challenges to the Patients

- Little / No therapies available
  - 5% of Rare Diseases:

- Costs:
  - Direct: Health care costs
  - Indirect: Loss of productivity; Insurance; Psycho-social
RARE DISEASES: WHY SHOULD I CARE?

**CLINICAL:**
HOW TO BEST SERVE PATIENTS & PROVIDE OPTIMAL CARE

**RESEARCH:**
HOW TO ADVANCE THE FIELDS OF SCIENCE & MEDICINE

UNMET CLINICAL NEED
“Experiments of Nature”:

“As clinical observers, we study the experiments which Nature makes upon our fellow creatures”

- Sir William Osler
(The Army Surgeon, in Aequanimitas; 1925)

“Disease is something appertaining to the patient, and is neither an invading organism nor a poison introduced. [...] by learning how a lesion or syndrome is produced in the few cases we may gain a notion of the mode of its production in the many.”

- Sir Archibald Gerrod
(The Huxley Lecture on Diathesis; BMJ 1927)
Rare Diseases: A Real Example

- European medieval saying: “Beware the child who tastes salty, for he is betwiched and will soon die”
- 1938: Dorothy Andersen: Autopsy on child
  - R/O celiac → Noted a cystic lesion in the pancreas
  - Reviewed autopsies → “fibrocystic disease of the pancreas”
  - Living patients → presented with Failure To Thrive
  - Noted lung disease
- 1948: Paul di Sant’Agnese: CF infants
  - Admitted for heat stroke & dehydration
  - ↑ Salt in sweat
- 1959: Lewis Gibson & Robert Cooke: Sweat test
- 1989: CFTR gene cloned
- Mortality: usually by 5 yrs → avg. 52 yrs

[Cystic Fibrosis]

https://healthmatters.nyp.org/it-happened-here-dr-dorothy-h-andersen/
Rare Diseases: Relevance to Common Diseases

- 1938: Carl Muller: Xanthoma, ↑ cholesterolemia, angina pectoris
  - Familial Hypercholesterolemia (FH)
- 1950s: John Gofman: Ultracentrifugation of cholesterol
  - LDL: ↑ heart attacks; HDL: ↓ heart attacks
- 1974: Michael Brown, Joseph Goldstein:
  - FH / Mutations in LDL receptor
  - LDL → Regulated HMG CoA reductase activity
  - Among the ~30 enzymes in cholesterol synthesis, this was critical in humans → Nobel Prize
- 1970s: Akira Endo
  - Antibiotics: Studied fungal metabolites / inhibit HMG CoA reductase
  - Isolated compound from A. terreus → “LOVASTATIN”
RARE DISEASES: WHY SHOULD I CARE?

CLINICAL:
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NEW DISEASES = NEW BIOLOGY
Why is the ADULT ID guy talking to us about RARE diseases?
Why is the ID guy talking to us about RARE diseases?

- Some infections = Rare Diseases
  - Sennetsu fever; Tropical sprue; Noma

- Recurrent
- Recalcitrant
- Opportunistic w/o Imm Supp
- Unusually Severe

INBORN ERRORS of IMMUNITY (aka Primary Immunodeficiency)
Clinical Context:

- Pasteur; Koch: “Germ theory of disease”
  - Bacterium → infectious disease
- Charles Nicolle: “Infections inapparentes”
  - Bacterium → spectrum of manifestations

- Natural variability in susceptibility to developing infectious diseases
Henry Kunkel

- **Clinician (trained at Johns Hopkins)**
  - Chronic liver disease
  - SLE, RA
  - Lymphoproliferative disorders

- **Scientist (at Rockefeller)**
- Myeloma proteins are Ig
- Identified:
  - IgM
  - IgG subclasses
  - Heavy & Light chains
  - allotypes and idiotypes of Ig
  - IgM & IgD as primary membrane Ig

“Study a few patients well”
Primary Immunodeficiencies

- Inborn errors of IMMUNITY

**PHENOTYPE:**
- INFECTIONS:
  - Recurrent/Refractory; Broad
  - Single species (restricted)
- Atopy
- Auto-Inflammatory / -Immunity
- Tumors: Benign / Malignant

**GENOTYPE:**
- MONOgenic:
  - Mendelian
  - Non-Mendelian
- OLIGOgenic

Picard et al., J Clin Imm 2018
Inborn Errors of Immunity:
### Paradigm Shift

<table>
<thead>
<tr>
<th>Primary immunodeficiencies</th>
<th>Conventional</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient and population levels</td>
<td>Rare</td>
<td><strong>Common</strong>, <strong>Sporadic</strong>, <strong>Adulthood</strong></td>
</tr>
<tr>
<td>Frequency</td>
<td>Familiar</td>
<td></td>
</tr>
<tr>
<td>Occurrence</td>
<td>Childhood</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>Spontaneously worsening</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
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</tr>
</tbody>
</table>

**Phenotype level**

- Disease-defining clinical phenotypes
  - Opportunistic infections*

**Genotype level**

- Disease-causing genes per patient
  - One (monogenic, Mendelian)

- Mode of Mendelian inheritance
  - Autosomal and X-linked recessive

- Clinical penetrance
  - Complete

- Mutations
  - Inherited from the parental genome

### More than just **Really** bad infections in **childhood**

**Can also be:** **Single** infection in **adulthood**
IEI = Molecular Medicine

- Clinical overlap:
- Genetic heterogeneity
- Genetic pleiotropy

- Molecular mechanisms:
- Autosomal Recessive
  - Bi-allelic
  - Loss-of-Function (LOF)
- Autosomal Dominant
  - Mono-allelic
  - LOF
    - Dominant-negative
    - Haploinsufficiency
    - Gain-of-Function (GOF)
- X-linked
Genetic ≠ Familial

• (-) Family History...

Could SPORADIC disease still be GENETIC?
- Consanguinity → Autosomal Recessive
- De novo / Heterozygous → Autosomal Dominant
- X-linked
- Mosaicism
- Uniparental disomy

What if we’re asking the WRONG questions, or we fail to see a link?
- Variable (incomplete) penetrance
- Variable expressivity
Genetic ≠ Pediatric

- Huntington’s disease

- Rare Diseases affect Adults:
  - Onset in childhood → Survival into adulthood
  - Onset in adulthood
    - Feature of the disease
    - Type of mutation: “Leaky”
WHO CARES?

PRECISION THERAPY:

CARD9 Deficiency:

GM-CSF


GM-CSF

Mossner et al., CID 2016

STAT1 GOF:

RUXOLITINIB

day 1
day 182

Mossner et al., CID 2016
More examples of PRECISION THERAPY:

IL1RN Deficiency

Jesus et al., Arthritis Rheum 2011

ANAKINRA (Anti-IL-1)

Severe Combined Immuno-Deficiency

Capitol Weekly, 2016
RARE DISEASES LANDSCAPE
Rare Diseases in Canada:
Rare Diseases in Canada:

- No celebrity advocates; No sensationalism
- Federal budget:
  - Development of a strategy for high-cost rare disease drugs
- 5 key areas in which support is most needed:
  - diagnosis
  - expert care
  - research
  - community support and
  - access to therapies
Rare Diseases in Québec:

• Groupe de travail québécois sur les maladies rares (2018)
  • Centre de référence suprarégionaux
  • Centre de compétence

• OptiLab: restructuring/repatriation of genetic tests (via Drs. JB Rivière and G. Rouleau)

• Patient advocacy:

• Disease-specific patient group:
  https://rqmo.org/associations-et-groupes-de-soutien/
Rare Diseases at the MUHC:

- **CRDR**: Consortium for Rare Disease Research
- **Vision**: To be a world-class clinical and translational research consortium aimed at improving the lives of people with Rare Diseases.
- **Mission**: To facilitate patient-oriented collaborative, transdisciplinary healthcare and research in Rare Diseases across the lifespan.
Rare Diseases at the MUHC: **CRDR**

- Spanning MCH, RVH, MGH, MNI
- > 80 specialists in Rare Diseases: Clinicians, Scientists, Clinician-scientists
- > 5500 Rare Disease patients followed
CRDR:

CLINICAL:

HOW TO
BEST SERVE PATIENTS & PROVIDE OPTIMAL CARE

RESEARCH:

HOW TO ADVANCE THE FIELDS OF SCIENCE & MEDICINE
Rare Diseases at MUHC: CRDR

**CLINICAL**
- Develop information for patients, health professionals, and general public
- Facilitate efficient referrals
- Organization of diagnostic tests
- Optimize care, including
  - transition: Peds - Adults
  - access to treatments
  - assessment of families

**RESEARCH**
- Break down silos
- Cross-disciplinary research
- Consortium biology*:
  - A complementary set of laboratories or institutions, all working towards a common and well-defined goal, which could not be achieved by any one participant, either because of its magnitude or because it requires multidisciplinary input.
- Discover new diseases

*Benoit et al., Nat Rev Immunol 2012
Rare Diseases at MUHC: CRDR

- Discover new diseases = Uncover new biology
- Build cohorts
  - Once you’ve got a diagnosis, you can try and learn from other patients with that condition
- From Boundaries → To Breakthroughs
“We’ve got one of those”
DISEASE DISCOVERY: (still a) HOT TOPIC

The New England Journal of Medicine

Early-Onset Strol Associated with GATA4 mutations cause human congenital heart defects and reveal an interaction with Tbx5

Letters to Nature

ORIGIN

Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease
Rare Diseases at MUHC: CRDR

- New Biology = Innovative Therapies

**STANDARDIZED MEDICINE**

TREAT ALL PERSONS WITH A GIVEN DISEASE THE SAME WAY

PNEUMONIA = PIP/TAZO DEFICIENCY

**PERSONALIZED MEDICINE**

TREAT DISEASES BASED ON THE PERSON AFFECTED

PNEUMONIA =
- Ampicillin + Cilia stimulator
- Macrolide + Inhaled cytokine
Costs: Isn’t it just too expensive to treat these people?

![Table 1: 2007–2013 Canadian Orphan Drug Landscape and Expenditure (2014 CAD, Millions)]

<table>
<thead>
<tr>
<th>Measure</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tbody>
<tr>
<td># “Orphan only” drugs captured N = 108</td>
<td>70</td>
<td>74</td>
<td>73</td>
<td>79</td>
<td>81</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td># “Partial Orphan” drugs captured N = 39</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>30</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td># Total Orphan drugs captured N = 147</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>107</td>
<td>111</td>
<td>122</td>
<td>133</td>
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<tr>
<td>“Orphan Only” Drug Expenditure ($M)</td>
<td>537.6</td>
<td>586.7</td>
<td>649.2</td>
<td>692.6</td>
<td>729.3</td>
<td>786.8</td>
<td>868.0</td>
</tr>
<tr>
<td>“Partial Orphan” Drug Expenditure ($M)</td>
<td>72.6</td>
<td>82.5</td>
<td>94.5</td>
<td>125.5</td>
<td>151.2</td>
<td>202.8</td>
<td>232.0</td>
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<tr>
<td>Total Orphan Drug Expenditure ($M)</td>
<td>610.2</td>
<td>669.2</td>
<td>743.7</td>
<td>818.1</td>
<td>880.5</td>
<td>989.6</td>
<td>1,100.0</td>
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<tr>
<td>% “Orphan Only”/Total Orphan Expenditure</td>
<td>88.1%</td>
<td>87.7%</td>
<td>87.3%</td>
<td>84.7%</td>
<td>82.8%</td>
<td>79.5%</td>
<td>78.9%</td>
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<tr>
<td>% “Partial Orphan”/Total Orphan Expenditure</td>
<td>11.9%</td>
<td>12.3%</td>
<td>12.7%</td>
<td>15.3%</td>
<td>17.2%</td>
<td>20.5%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Total Pharmaceutical Expenditure ($M)</td>
<td>18,233.6</td>
<td>19,598.1</td>
<td>20,514.4</td>
<td>20,628.6</td>
<td>19,976.3</td>
<td>19,746.0</td>
<td>19,665.7</td>
</tr>
<tr>
<td>% Total Orphan/Total Pharmaceutical Expenditure</td>
<td>3.3%</td>
<td>3.4%</td>
<td>3.6%</td>
<td>4.0%</td>
<td>4.4%</td>
<td>5.0%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

![Graph: Total Drug Spending in Canada 2007-2018]

Divino et al.  
Orphanet Journal of Rare Diseases (2016)
Balance:

The 7 Most Expensive Prescription Drugs in the World

The costs of these drugs are astronomical -- from $543,000 per year to more than $1 million per year.

Keith Speights  
(TMFFishBiz)  
Apr 18, 2017 at 6:00AM

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>2018 Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca <em>(NYSE:AZN)</em></td>
<td>Farxiga</td>
<td>$1,391 million</td>
</tr>
<tr>
<td>Johnson &amp; Johnson <em>(NYSE:JNJ)</em></td>
<td>Invokana/Invokamet</td>
<td>$881 million</td>
</tr>
<tr>
<td>Merck <em>(NYSE:MRK)</em> and Pfizer <em>(NYSE:PFE)</em></td>
<td>Steglatro</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>Eli Lilly <em>(NYSE:LLY)</em> and Boehringer Ingelheim</td>
<td>Jardiance/Synjardy/Glyxambi</td>
<td>$658 million</td>
</tr>
</tbody>
</table>

DATA SOURCE: COMPANY PRESS RELEASES. INVOKAMET CONTAINS INVOKANA PLUS GENERIC METFORMIN. SYNJARDY AND GLYXAMBI CONTAIN JARDIANE PLUS METFORMIN AND TRADJENTA, RESPECTIVELY.
KEY POINTS:

- RARE DISEASES ≠ INSIGNIFICANT
- UNMET clinical need
- We are missing them = Disservice
- Inquisitive mind: key to being a great clinician
- Research = cool biology (relevant to humans)
- Québec is mobilizing its Rare Disease initiative
  - (pssst)... this involves FUNDING
- MUHC.... Lead? Follow? Left behind?
Rare Diseases in Canada:

- 20 “orphan drugs” approved
- 2 biosimilars (Etanercept; Infliximab)
- 2 were for hepatitis C (Maviret, Vosevi)
- 1 was for anthrax (Anthrax immunoglobulin)
<table>
<thead>
<tr>
<th>Orphan Drug</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Defitelio</td>
<td>Defibrotide: hepatic veno-occlusive disease</td>
</tr>
<tr>
<td>Fibryga</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Rebinyn</td>
<td>Recombinant pegylated Factor IX</td>
</tr>
<tr>
<td>Bavencio (Avelumab)</td>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>Latruvo (Olaratumab)</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Oncospar (Peg-asparagase)</td>
<td>ALL</td>
</tr>
<tr>
<td>Protrazza (Nectiumumab)</td>
<td>NSCLC (squamous)</td>
</tr>
<tr>
<td>Rydapt (Midostaurin)</td>
<td>AML, FLT3+</td>
</tr>
<tr>
<td>Cerdelga</td>
<td>Gaucher disease type 1</td>
</tr>
<tr>
<td>Galafold</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>Haegarda</td>
<td>C1 Esterase inhibitor</td>
</tr>
<tr>
<td>Kanuma (Sebelipase alpha)</td>
<td>Lysosomal acid lipase deficiency</td>
</tr>
<tr>
<td>Procysbi</td>
<td>cystinosis</td>
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<tr>
<td>Replagal</td>
<td>Fabry disease</td>
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