The Neglected Global Diseases Initiative at UBC

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Website: https://ngdi.ubc.ca/
Twitter: @ngdiubc1

The Neglected Global Diseases Initiative at UBC

Developing Interventions for Developing Countries
How can the Poorest of the Poor Share in University Discoveries?

• Need mechanisms for **encouraging and funding** expensive research and development for Neglected Diseases.

• Must **creatively protect** early discoveries.

• **Delivery!!!!**
Mission: Developing interventions for neglected global diseases and ensuring their delivery to those in need.

www.ngdi.ubc.ca

The NGDI brings together a variety of disciplines, including bench science, biotechnology, pharmaceutical, health, social sciences, business, social policy and law.

Researchers work collaboratively to develop ways to most effectively generate affordable, life-sustaining medicines that can be brought to scale, thus reaching those most in need.
What are neglected global diseases?

Hookworm
Leprosy
Elephantitis
Sleeping Sickness
Chagas
Dengue Fever
Leishmaniasis
Soil Transmitted Helminthes

HIV/AIDS
Malaria
Tuberculosis

one in seven people worldwide is affected by a neglected tropical disease
Why are they neglected?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Amount (USD)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>KINETOPLASTIDS</td>
<td>$125,122,839</td>
<td>4.9</td>
</tr>
<tr>
<td>DIARRHOEAL DISEASES</td>
<td>$113,889,118</td>
<td>4.4</td>
</tr>
<tr>
<td>DENGUE</td>
<td>$82,013,895</td>
<td>3.2</td>
</tr>
<tr>
<td>HELMINTHS (WORMS &amp; FLUKES)</td>
<td>$51,591,638</td>
<td>2.0</td>
</tr>
<tr>
<td>BACTERIAL PNEUMONIA &amp; MENINGITIS</td>
<td>$32,517,311</td>
<td>1.3</td>
</tr>
<tr>
<td>TYPHOID &amp; PARATYPHOID FEVER</td>
<td>$9,117,212</td>
<td>0.4</td>
</tr>
<tr>
<td>LEPROSY</td>
<td>$5,619,475</td>
<td>0.2</td>
</tr>
<tr>
<td>BURUL UlCER</td>
<td>$2,412,950</td>
<td>0.1</td>
</tr>
<tr>
<td>TRACHOMA</td>
<td>$1,679,711</td>
<td>0.1</td>
</tr>
<tr>
<td>RHEUMATIC FEVER</td>
<td>$1,670,089</td>
<td>0.1</td>
</tr>
<tr>
<td>CORE FUNDING OF A MULTI-DISEASE R&amp;D ORGANIZATION</td>
<td>$110,921,673</td>
<td>4.3</td>
</tr>
<tr>
<td>PLATFORM TECHNOLOGIES</td>
<td>$9,997,189</td>
<td>0.4</td>
</tr>
<tr>
<td>UNSPECIFIED DISEASE</td>
<td>$51,619,120</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Total R&D Funding $2,560,068,749 100.0
Why are they important?

<table>
<thead>
<tr>
<th>Top 10 Causes of Death</th>
<th>Approximate Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>7,029,300</td>
</tr>
<tr>
<td>Stroke and other cerebro-vascular disease</td>
<td>5,874,200</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2,899,900</td>
</tr>
<tr>
<td>Lower Respiratory Infections</td>
<td>2,814,400</td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancers</td>
<td>1,527,100</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1,465,400</td>
</tr>
<tr>
<td>Diarrhoeal Diseases</td>
<td>1,445,800</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>1,328,500</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,281,300</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,196,000</td>
</tr>
</tbody>
</table>

Statistics from Global Burden of Disease, 2010
How has UBC responded to this?

**ACCESS**

What is "GLOBAL ACCESS" to medicines?

1/3 OF ALL PEOPLE IN THE DEVELOPING WORLD DON'T HAVE AFFORDABLE ACCESS TO MEDICINES THAT COULD SAVE THEIR LIVES.

**INNOVATION**

What are NEGLECTED DISEASES?

ILLNESSES that MAINLY AFFECT the DEVELOPING WORLD RARELY addressed by researchers because MOST OF THE PEOPLE who suffer from them are TOO POOR TO PAY FOR NEW MEDICINES
How did we do?

1. U. OF BRITISH COLUMBIA A-
2. CASE WESTERN RESERVE B+
3. JOHNS HOPKINS U. B
4. U.C. IRVINE B
5. HARVARD U. B-
6. EMORY U. B-
7. DUKE U. C+
8. VANDERBILT U. C+
9. U. OF PENNSYLVANIA C+
10. U. OF MARYLAND BALTIMORE C+
Developing interventions for neglected global diseases and ensuring their delivery to those in need.
NGDI Model of Collaboration

**INTERVENTIONS** (Drug and Non-Drug)

- DISCOVERY
- DEVELOPMENT
- VECTOR CONTROL, TOOLS and DIAGNOSTICS

**DELIVERY** (Social Determinants & Health Equity Approach)

- SUPPLY CHAIN DYNAMICS
- HEALTH SYSTEMS RESEARCH
  - IMPLEMENTATION RESEARCH
  - OPERATIONAL RESEARCH
- POLICY WORK on AFFORDABILITY AND ADOPTION
  - Global, national, NGO & end-user levels

**ACCESS**

**BETTER HEALTH OUTCOMES**
Addressing antibiotic failure

1. Sepsis (19.7% of all deaths 2017; 9M/yr Covid)
   - Defined diagnostic CR signature; predicts severe sepsis and organ failure in ER patients Accuracy 84-92% (all-cause & Covid sepsis - 750 patients)
   - Separated ER patients into endotypes that define mechanisms & severity

2. Biofilm infections (65% of infections; multidrug resistant)
   - Peptides work against biofilm infections of all ESKAPE (MDR) bacterial pathogens in human skin organoid models (left) and animal models; synergy with antibiotics

Haney, EF, & REW Hancock. 2022 Frontiers in Drug Discovery 2:892975.
Digital Health Equity

Access • Ability • Language • Culture

1. Inclusion
2. Evidence
3. Expansion
4. Scale
5. Analysis
6. Response

First evidence that SMS communication could improve health outcomes (HIV treatment)

UBC mHealth Research
COVID-19 Pandemic Rwanda National Home-Based Care
>40,000 patients followed
18M SMS sent
NO deaths

AI, NLP Predictive Analytics

UBC Medicine

JEDI Justice Equity Diversity Inclusion

Dr. Richard Lester, MD, FRCPC

Additional use cases
• Chronic disease (NCD)
• Mental Health & Addiction
• Public Health
Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial

UBC mHealth research in global settings

Addressing severe malaria renal dysfunction & adjunctive therapy
Dr. Katherine Plewes MD DPhil FRCPCH

- Cell-free hemoglobin and oxidative stress markers correlate with renal dysfunction and are independent predictors of creatinine rise during admission and need for dialysis.

- Acetaminophen reduces creatinine in patients with elevated cell-free hemoglobin in falciparum and knowlesi malaria.

- Acetaminophen reduces risk of developing renal dysfunction in falciparum malaria.

- **PROTECTS**: Evaluating the renoprotective effect of acetaminophen in pediatric severe falciparum malaria: a randomized controlled trial.

Preventing antibiotic harm | Asthma

There is growing evidence that reducing antibiotic use in infancy may significantly reduce childhood asthma.

Both antibiotic prescribing in infancy and asthma in early childhood have gone down in British Columbia.

How can antibiotics lead to asthma?\textsuperscript{10}

Babies need antibiotics when they get a serious bacterial infection. But sometimes, we give antibiotics for things that don’t need them!

Taking antibiotics changes a baby’s gut bacteria.

Missing bacteria in the gut can cause illnesses like asthma later in childhood.

Children are 2.15 times more likely to be diagnosed with asthma by age 5 if they take antibiotics before age 1.

Summary of policy instruments for prolonging effectiveness of existing antibiotics

Eswaran and Gallini, “Can Competition and Patent Policies Avert the Antibiotic Crisis?”, Canadian Public Policy, vol. 45, no. 1

• Facilitate competition, subject to:
  • Economic Breadth Requirement
  • Biological Breadth Requirement
  • “Safe harbor” on price/royalty/tax above which antitrust action would be triggered: internalize biological but not economic externality

• Set longer patent duration for narrow than broad patents to encourage firms to internalize both own- and cross-resistance.

• If profits from patent sales do not provide adequate incentives for R&D, then: supplement incentive with award that is independent of sales, e.g., Prizes, Cost-Sharing Agreements, Easing of FDA regulatory constraints.
Overall objectives:
1. Improve our basic understanding of the physiology of *M. tuberculosis*, especially those processes that are critical to pathogenesis.
2. Establish a pipeline for the development of novel inhibitors.

Why now?
1. With the emergence of XDR strains, TB is a global threat
   *novel treatment strategies are urgently required*
2. Researchers at UBC have recently discovered systems that contribute to *MTB*’s inherent resistance and unusual ability to persist in macrophages.

*Undisputed leaders in Canada and internationally recognized*
New immunomodulatory peptides show broad protection in mouse model infections.

- Survival of *P. b. ANKA* infection with peptide treatment
  - Days post-infection: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
  - % Survival: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
  - Saline 1018
  - Luminescence-tagged Citrobacter

Also protect vs. TB, *E. coli*, *Salmonella*, MRSA, VRE, *P. aeruginosa*, *IBD* Sterile inflammation, etc.

A spin off company has completed Phase I clinical trials.

These peptides developed independently for Grand Challenges Program.

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Ashwini Pathak
Brett Finlay
Bob Hancock

Centre for Microbial Diseases and Immunity Research
Prevention and Control of Dengue in Ecuador

Sustainable capacity-building and scaling-up challenges

Dr. Jerry Spiegel, SPPH / Liu Institute and Kendra Foster, ISGP PhD student

Pilots an integrated community-based approach compared to reactive insecticide-based program

- comprehensive intervention effectiveness evaluation protocol
- information system for monitoring implementation & feasibility of transforming existing vector control programs

Funded by:
Clinical Care and Training

Infectious Diseases Specialist
Tropical Medicine Clinic, Vancouver General Hospital

Visiting Physician
Gulu Regional Referral Hospital, Uganda

Infectious Diseases Consultant
Doctors without Borders, TeleMedicine

Course Director
Tropical and Geographic Medicine Course, University of British Columbia
Lobbying by strong UBC UAEM chapter and Grand Challenges funding led to consideration of new policy.

UBC first Canadian university to put forward a broad strategy to provide global access to appropriate technologies.

Provide flexibility for tailored, technology-specific strategies.

Principles versus policy; adopted by UBC in Fall 2007.

e.g. Reserved 4 of our patents with >50,000 immunomodulatory and antimicrobial peptides for the exclusive use of the Grand Challenges projects; One of these now optioned to a US company with developing country rights reserved.

http://www.uilo.ubc.ca/about/initiatives/global.html
Amphotericin B

- AmB is a BCS Class IV drug
  - Low solubility and low permeability
  - Low oral bioavailability
  - Intravenous administration
Demonstrated Efficacy

Fungal infections

Cryptococcosis

Aspergillosis

Candidiasis
Leishmaniasis: Current Disease Status

• Spectrum of disease which affects approximately 12 million people in 88 countries
  – About 2 million new cases annually
  – 75% involve cutaneous leishmaniasis, with the remainder being visceral leishmaniasis (VL)

• Mortality rate for VL is close to 100% in the absence of treatment

Source: WHO/TDR/Marsden
“Real World” Efficacy

2 million new cases reported every year (WHO)
Visceral leishmaniasis causes ~59,000 deaths annually
### Current Treatments of VL

<table>
<thead>
<tr>
<th></th>
<th>Liposomal amphotericin</th>
<th>Miltefosine</th>
<th>Paromomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy in VL</strong></td>
<td>~99%</td>
<td>~97%</td>
<td>~95%</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Safe</td>
<td>G-1 intolerance</td>
<td>Reversible ototoxicity 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential foetotoxicity</td>
<td>Painful injection</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Intravenous infusion</td>
<td>Oral tablet. Contraception in child-bearing age women</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td><strong>Price for 35 kg Indian VL adult</strong></td>
<td>~US $140 – 220</td>
<td>~US$ 61 – 75</td>
<td>~US$ 15</td>
</tr>
</tbody>
</table>

Wasan & Thornton 2009
Implications for Developing Countries

Parenteral administration results in:

- Loss of income
- Increased cost of administration
- Increased risk of side effects
- Decreased availability of treatment
Data Overview
Visceral Leishmania (VL)

- Mice were infected i.v. with $1 \times 10^7$ *Leishmania donovani*
- Treatment begins on Day 7 post infection
- Oral Amp B administered bid for 5 consecutive days
- Mice were sacrificed Day 14 post infection
- Livers were then weighed and impression smears prepared
- The number of *Leishmania* amastigotes per liver cell nuclei was determined microscopically
- studies performed in independent laboratory
  - part of the Consortium for Parasitic Drug Development, a Gates Foundation funded organization
Miltefosine - 3mg/kg PO, qd x 5 d
Ambisome - 2 mg/kg iv, once
iCo-009 - 10 & 20 mg/kg PO, bid x 5 d
A new oral amphotericin B formulation (iCo 009) works well vs. visceral Leishmananisis in animals

Leishman-Donovan Units (LDU)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control 40 µl PO BID</td>
<td>3273 ± 157</td>
</tr>
<tr>
<td>Oral AmpB 2.5mg/kg PO BID</td>
<td>1154 ± 568</td>
</tr>
<tr>
<td>Oral AmpB 5mg/kg PO BID</td>
<td>117 ± 54</td>
</tr>
<tr>
<td>Oral AmpB 10 mg/kg PO BID</td>
<td>24 ± 12</td>
</tr>
<tr>
<td>Ambisome IV bolus 2mg/kg</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Organism** | **Leishmania spp.**
--- | ---
**At Risk** | 350 million - Tropics and Subtropics
**Humans Infected** | 2 million
**Disease Outcome** | Visceral form (25% above) fatal
**Vaccine Prospects** | Poor - immune evasion
**Available Drugs** | Toxic, difficult to deliver
**Drug Resistance** | Documented
Oral Amphotericin B Formulation Technology

- Proprietary blend of mono- and di-glycerides (FDA GRAS approved)
- Solubilized AmpB Formulations
- Nanosuspensions/dispersions
- Affordable lipid excipients
- Ease of formulation scale-up
- Formulation Stability over 120 days
- Drug Stability at 43°C over 120 days
Advantages of Oral Amphotericin B Formulation

- Affordable
- Easy to store
- Easy to administer
- Lack of kidney toxicity
- Lack of Infusion-related side effects (i.e. fever, chills etc.)
- Lack of liver and GI toxicity
Advantages of Oral Amphotericin B Formulation

• Treating patients with drug-resistant strains (decrease hospitalization and eliminate IV AmpB Therapy)

• First available Oral Fungicidal Agent (only Fungistatic Agents, Diflucan® from Pfizer)

• Orphan Drug Designation FDA (2010)
• Positive Human Phase 1a/1b Safety Results
Advocate, Educate, Participate

Collaborate outside your discipline to expand your research

Initiate your own neglected disease research

September, 2013
NGDI-UBC Newsletter