Progress and Challenges in Infectious Diseases Drug Discovery

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The sudden appearance of an epidemic typically invites panic and action. Once the crisis subsides, public attention wanes, although the threat of contagion continues, especially among the world's poor. Consider our response to severe acute respiratory syndrome, or SARS, with its more familiar germ that plagued us daily. Compare it to the dangers of smoking, or getting in a car and heading out on the road. Everyday life is precious, but when you look at the numbers, SARS just isn't as formidable a threat as we've made it out to be. Its death rate is far lower than that of AIDS or malaria, and whenever, like the one believed to cause SARS, tend to be most active in the winter and early spring.

In addition to taking the steps necessary to keep SARS at bay—watching out for new cases and isolating people who are contagious to others—we would do well to channel our energies into stemming the permanent, integrated and accountable public health system for the surveillance and prevention of the microbes that are certain to reemerge in the future. Right now, worldwide accounting of disease is incomplete at best, hampered in large measure by sketchy reporting from developing countries. These gaps slowed our containment of SARS and allowed it to spread more rapidly than reliable information. When the facts are few, it is easy for fear to fill the vacuum.

Howard Markel, professor of the history of medicine and of public health at the University of Michigan, is author of "When Germs Travel."
Challenge in 2003

• Drugs for neglected diseases
  • Old – discovered in the first half of 20\textsuperscript{th} century
  • Limited therapeutic window
  • Unknown mechanism

• Missed the revolution in drug discovery
  • Science discovery and drug discovery uncoupled
  • Technology lagged
  • Fragmented efforts
Leap-frogging into 21st Century

• Genomic revolution
  • Genetic engineering of parasites
  • Whole genome sequencing
• New Chemical Entities identified
  • Success in developing assays
  • Success in High Throughput Screening (HTS)
  • Exploration of “chemical space”
• Combining genomics and chemistry
  • New target identification
  • RNAi identification of essential pathways
• Concerted scientific effort on problem of drug and vaccine discovery
High Throughput Phenotypic Screens

Transfer compounds

384-well plate containing medium

Add parasites

Incubate at 37 °C (72 h)

Detect stained parasite DNA

Imaging-based analysis

Plate reader
Genetically engineered parasites
stage specific assays

Figure 3. Fluorescence confocal microscopy assessing GFP expression in various stages of T. cruzi pBEX/GFP.

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RNAi Strategies in Drug Discovery
Pyridoxal kinase as a drug target in the African trypanosome

Genomics as a tool in drug discovery

- Target Identification
  - Best tool in the box for Target ID
- Fitness in populations
  - Comparative growth of mutant and wild type
- Resistance creates a new molecular target
  - Potential for a new paradigm for drug combinations
The Sequencing Explosion

Cost of computing (Moore’s Law)

Cost of Sequencing

Human Genomes Sequenced

$3 billion

$1,000

Log Scale

100,000

10,000

1,000

100

10

0.1
Halofuginone – Target ID

- Incredibly potent antimalarial
- Unknown target
- Unacceptable side effects

Herman, Mazitschek et al, submitted
Resistance Selection: Intermittent + Stepwise Pressure

**Intermittent Selection**

- 10^9 Parasites For Each Independent Selection
- 10x IC_{50} for 2-8 days
- Off Drug Pressure for 7-15 days
- Parasites Tolerant of 10x IC_{50}

- Repeat Selection 2-3x

**Stepwise + Intermittent Selection**

- 10x IC_{50} for 2-8 days
- 20x IC_{50}
- 50x IC_{50}
- 200x IC_{50}
- Parasites Tolerant of 200x IC_{50}
Select-Seq

HFG Selection 2

HFG Selection 3
Can we make better combination therapies?

Combination therapy is widely used to combat resistance. Potent, but gives strong selective pressure.

Are there combinations that lead away from resistance?
Targeting drug resistant parasites

- Mutations that give rise to resistance also create new targets
  - Mutations that cause resistance to one partner are the target of the second
- Resistance mechanisms can be mutually exclusive
  - Selective pressures of the combination are offsetting
Challenges for the next decade

• New, good drugs for acute infection
  • Resistance
  • Access

• Need solutions for latent, chronic infection
  • Chagas
  • *Plasmodium vivax*
  • Others – TB, Leishmaniasis

• Address host-parasite relationship
  • Immunology
  • Metabolism and nutrition
Targeting Chronic Infections in *T. cruzi*

- Intracellular stage in mammalian host
- Most important stage of life cycle for drug development
- Little known about the biology of *T. cruzi* amastigotes or the host metabolic and cellular requirements for chronic infection
Integrated approaches to functional pathway identification in *Trypanosoma cruzi* infection.
RNAi screen identifies interconnected host metabolic pathways that support intracellular *T. cruzi* growth

Screens to candidate targets: testing the concept with host Akt

RNAi screen → Host Akt → Validation → Efficacy

A

B

C

D

siRNA: C Akt1
Akt1 
β-actin

# intracellular parasites/infected cell

C Akt1

-relative infection (% of control)

log [AktVIIIi] uM

Parasites/infected cell

WT Akt1/2−/−
Scientific Community Engagement

- Study diseases in natural setting working with endemic scientists
- Training and mutual learning with new goals
- Technology is creating the opportunity for innovation
Cures for Neglected Diseases
Imagine the possibilities