Future vistas in alpha therapy of infectious diseases

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The need for alternative treatments of infection

Medical progress has produced large numbers of immunosuppressed individuals – cancer patients, organ transplants recipients, HIV-infected patients. There is increasing prevalence of infections with highly resistant microorganisms that are not susceptible to existing antimicrobial agents. New pathogens have emerged, many of which are not susceptible to existing therapies. There is dearth of new antibiotic classes introduced in the past decades.
Who motivates us to do this research?

**Fungal infections** - physicians (Albert Einstein College of Medicine, Massachusetts General Hospital, Rockefeller University, University of North Carolina, University of British Columbia, etc.) and veterinarians (Western College of Veterinary Medicine).

**Bacterial infections** - physicians (University of Medical Center Utrecht, The Netherlands).

**HIV** - patients.
*Cryptococcus neoformans* as a model system for development of infection RIT

*C. neoformans* is an encapsulated human pathogenic fungus. CN provides an excellent model for a chronic infection and advantages of the CN system include:

1) animal models including those for pulmonary, meningeal, and latent infection;
2) the availability of very well characterized mAbs to CN that can be developed into RIT agents;
3) well understood pathogenesis of infection and immune response.

MAb 18B7 to CN capsular polysaccharide antigen has been used in clinical trial in patients with cryptococcal meningitis. *(RA Larsen et al. Antimicrob Agents Chemotherapy. 2005; 49:952-8.)*
Mechanisms by which RIT is effective against microbes


Panel A: Radiolabeled antibody bound to shed polysaccharide kills nearby C. neoformans.

Panel B: Radiolabeled antibody kills infected cell by 'cross-fire' effect.

Antibody bound to microbial antigen expressed on surface kills cell with radiation.

Infected macrophage killed by 'cross-fire' effect.
Three foundations of successful therapy – efficacy, safety and known mechanism
Survival of A/JCr mice systemically infected with \textit{C. neoformans} cells 24 hr prior to treatment with $^{213}\text{Bi}$- or $^{188}\text{Re}$-labeled antibodies.
RIT decreases colony forming units (CFUs) in the lungs and the brains.

<table>
<thead>
<tr>
<th>Organ</th>
<th>No. of CFU’s/g tissue ($10^4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>untreated mice and treated with unlabeled 18B7, 50 $\mu$g</td>
</tr>
<tr>
<td>lungs</td>
<td>550±47</td>
</tr>
<tr>
<td>brains</td>
<td>11±5</td>
</tr>
</tbody>
</table>

RIT is more effective than Amphotericin B in mice with *C. neoformans* infection.

RIT of *C. neoformans* infection in mice is safe in regard to long-term pulmonary toxicity

a) untreated controls; b) 200 Ci $^{188}$Re-18B7; c) 200 Ci $^{213}$Bi-18B7

RIT of *C. neoformans* Spares Bystander Mammalian Cells

RIT does not create radiation-resistant mutants

\[ ^{188}\text{Re} \]

\[ ^{213}\text{Bi} \]

The levels of cytokines go down after RIT

Radioimmunotherapy of Blastomycosis in companion animals

- Soil dwelling fungus *Blastomyces dermatitidis* is endemic in Saskatchewan. Pets and humans contract the infection from the soil.
- The infection in pets is difficult and expensive to treat, many do not respond to treatment.
- In collaboration with Dr. Liz Snead from WCVM we are developing radioimmunotherapy of blastomycosis in companion animals. The data generated during the project will also help clinical translation into human patients.

![Graph showing survival percentage at different conditions](image-url)
RIT of *B. anthracis* in BALB/c mice

7.5G and 10F4 - antibodies to the protective antigen of *B. anthracis*

14FA – antibody to the lethal factor of *B. anthracis*
van Dijk B. et al., in preparation
High affinity
Ka = 0.1 nM,
3.6×10^6 binding sites per infected cell

Targeted killing
Demonstrated in vitro and in vivo killing of infected human cells. RIT reduced HIV to undetectable levels.

Low toxicity
Platelet counts and gross pathology unaffected by RIT
IT-induced killing of PBMCs derived from 15 ART-treated patients

Abbott m2000 RT-PCR detects part of the integrase region in the pol gene

Another Kind of AIDS Crisis

A striking number of HIV patients are living longer but getting older faster—showing early signs of dementia and bone weakness usually seen in the elderly.

Left: Cesar Figueroa. Age: 50 / HIV: 20 years / Has suffered from: dementia, neuropathy, depression
Right: Mike Weyand. Age: 58 / HIV: 20 years / Has suffered from: osteoporosis, lipodystrophy, memory loss.

(Photo: Marco Grob)
Mechanisms of CNS HIV Infection and Damage

- Uninfected and HIV Infected Monocytes
- Blood-Brain Barrier
- Blood
- CNS
- Macrophage infection and activation
- Astrocyte infection and activation
- Microglia infection and activation
- T Cell
- Neurons
- Demyelination, pruning, neuronal injury and loss

Cytokines:
- TNF-α, IL-1β, IL-6

Chemokines:
- CCL2

Neurotoxic Host Factors:
- NO, excitatory amino acids, Free radicals, quinolate, PAF

Neurotoxic Viral Factors:
- Tat, gp120, gp41, Nef, Vpr, Rev
RIT induced killing of HIV-infected cells in CNS

McFarren A. et al. AIDS 2016
There is enormous need for molecular imaging in infectious diseases

Figure 1 | Evaluating SIV reservoirs in monkeys. (a) Few SIV reservoirs (gray dots) can be easily reached and evaluated by biopsy (red circles). (b) SIV reservoirs can be comprehensively visualized and evaluated by immunoPET. CT, computed tomography.

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Conclusions

• Unique properties of alpha-emitters make them very attractive for treatment of infectious diseases.

• Collaborations between researchers, physicians and industry partners are needed to bring those novel therapies to patients.
Thank you!

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