NEW APPROACHES FOR THE MAJOR INFECTIVE DISEASES

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HIV ,TB and Malaria

- These are the major infectious diseases (killer 3).
- Major cause of death & non-productivity in SSA.
- Available treatments have been chemotherapy.
- They are expensive and prone to drug resistance.
- We are always sourcing new drugs/combinations.

The Triad of Infection

- All infectious diseases are affected by 3 factors:
  - Infectious agent (bug).
  - The host factors (most important factor).
  - The drug/s being used for treatment.
  - Interaction between the drug & the bug is presently exploited.
  - There may be need to start targeting the host immune system.

HIV and TB Co-infection

- HIV-TB is a globally common co-infection.
- Up to 80% of TB patients are also HIV-positive.
- Without treatment, HIV & TB can work as a team to shorten life of the person infected.
- Untreated latent TB & HIV infection likely result in active TB (than without HIV).
- HIV facilitates progression from latent to active TB.
- HIV infection & active TB (AIDS-defining).

Changing The Host Factors: Could They Make a Major Difference?

- HIV-1 is the number 1 infectious dx in today's world.
- Schreck & Baeurele in Germany has shown that oxidative mechanisms (peroxynitrite & hypochlorite can upregulate HIV infection).
- Van Dyke indicates has shown that a series of inexpensive antioxidants and anti-inflammatory steroids (inhibit HIV & cure FIV infection.

Antioxidants & Steroids Affect both Virus & Host

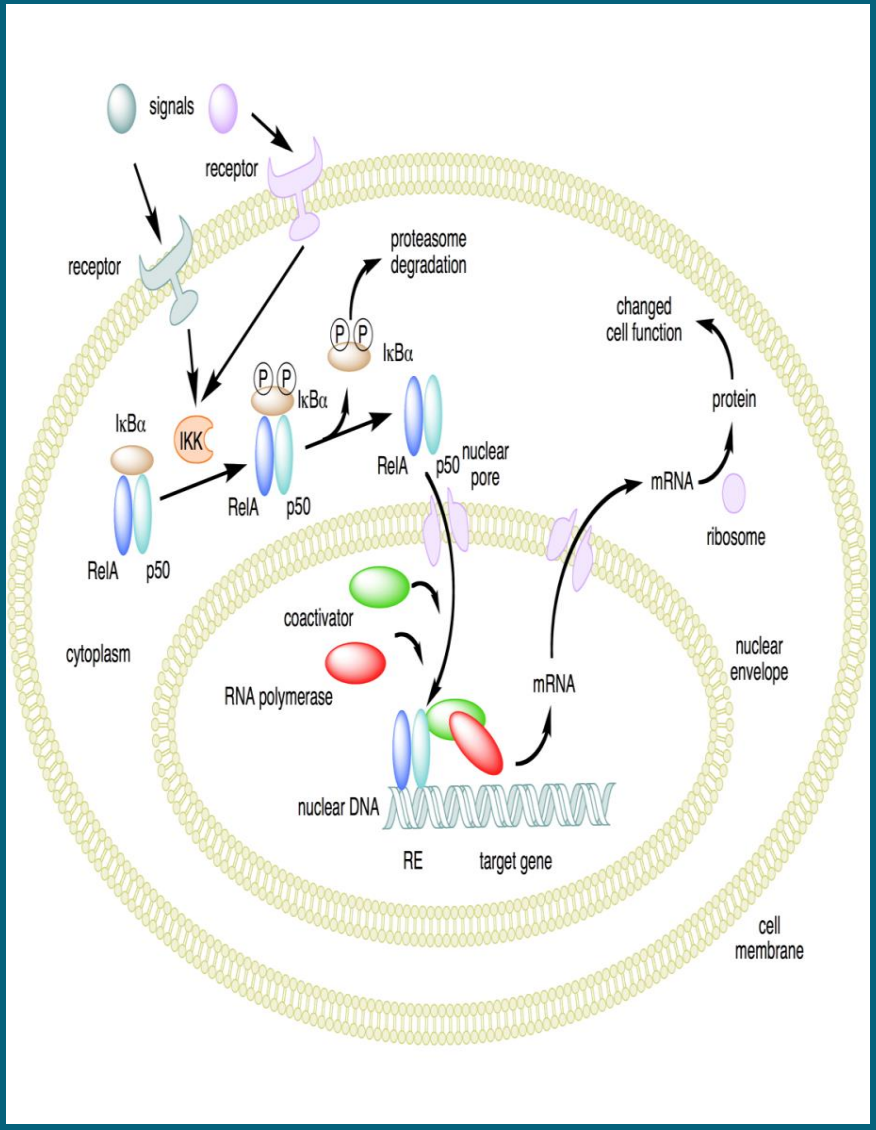
- Combination of substances was used in FIV infected cats (6) over a period of multiple months (4-5) the cats were cured from the retroviral disease. Untreated cat died.
- We found a patient with HIV for 10 years (long term survivor) who had AIDS (weak with signs of dementia).
- His physician allowed us to try our steroid/antioxidant combination and his viral load started to drop.

Continuous HIV Treatment

- After several months treatment, his dementia subsided, he got better, his appetite returned & he started to gain weight.
- Finally after treatment for one year, he displayed undetectable HIV in his blood.
- He went to work and held 3 jobs.

Mechanisms of Antioxidant/Steroid

- Combination of antioxidants (Vit C & E) at **higher doses** oppose oxidant- stimulated replication of HIV.
- Steroids inhibit multiple nf-Kappa B sites on retroviruses.
- This prevents replication of the virus.

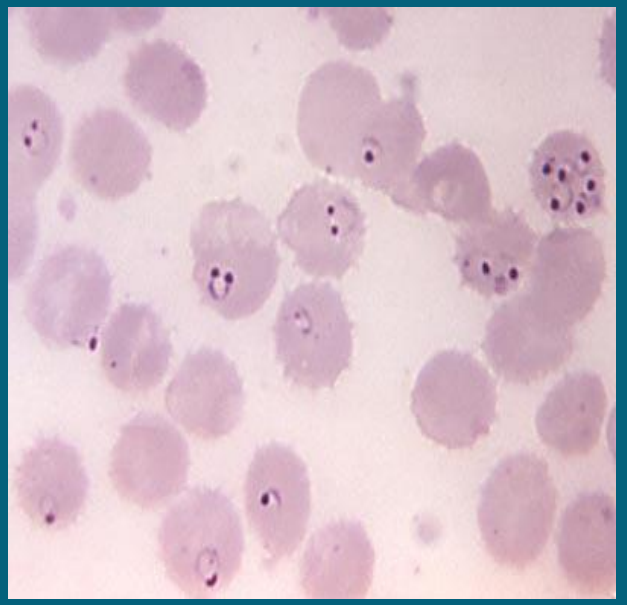


Drug Companies Not Interested

- Drug companies are not interested
- Investment costs & low potential returns from profits.
- Why? These drugs and supplements are inexpensive & the rigorous research work in humans would be too expensive to turn a profit.
- This could be a perfect solution for SSA countries.
- SSA could save precious funds to treat more people.

Malaria: The Oldest Infectious Disease

- Falciparum malaria is a major infectious diseases.
- Malaria kills millions of people /year.
- Hundreds of thousands of innocent children & pregnant women have died over the years from malaria.
- Malaria was the major cause of soldier's death in the Vietnam war.



Malaria Control Challenges

- Estimated 500m cases of malaria per year.
- Unless new strategies are deployed, the health and economic burden will worsen.
- Main obstacle to malaria control is resistance.
- Combinations therapy reduces risk of resistance.
- Combination of an artemisinin derivative & mefloquine (unrelated mode of action).
- This strategy seems the way forward (for now).

Which way with Chemotherapeutics

- Chloroquine
- Quinine
- Sulfadoxine/perimethamine
- Mefloquine
- Doxycycline
- Atovaquone
- Proguanil
- Artemisinin-Combination Therapy (ACT)
- Amodiaquine, Lumefantrine, mefloquine or Sulfadoxine/perimethamine
- Dihydroartemisinin and Piperaquine

Development of First High Throughput Antimalarial Screening System

- In 1966 Knox was assigned the task of developing a new in vitro, antimalarial screening system.
- He incubated radioactive (3H) adenosine with parasitized cells & found certain drugs inhibited the incorporation of the radioactive nucleotide into parasite nucleic acids.
- Further research showed that the parasite actually converted adenosine to the free oxidized base hypoxanthine.

Trager /Jensen falciparum culture 3H Hypoxanthine was the key label

- Knox's high throughput screening system for antimalarial drugs effectiveness using a quick DNA/RNA labeling system.
- Ye & Van Dyke used this DNA/RNA screening system to demonstrate that chloroquine resistance can be entirely overcome in vitro & in vivo by adding bisbenzylisoquinolines to chloroquine.
- Thus for the first time choroquine sensitivity can be restored!

Can We Assist Host Mechanisms with Drugs to Fight Malaria more effectively?

- Macrophages are important in the host response to malaria.
- Its oxidative activity likely stems from peroxynitrite.
- Does the parasite affect the macrophages killing mechanism making it less effective? Yes!
- The macrophages has two pathways to produce NO.
  - It oxidizes L-arginine to L- citrulline and NO
  - It recycles L-citrulline to L-arginine.

Low Plasma L-Arginine Levels in Cerebral Malaria

- Lopansri *et al* demonstrated that Tanzanian children with severe cerebral malaria had low plasma L-arginine levels.
- Likely due to presence of parasitic and red cell arginase which depletes L-arginine.
- This decreased NO production greatly.
- Decreased production of NO in microglia(brain) or blood macrophages prevents parasite depletion.
- Low plasma L-arginine level is significantly associated with mortality.

Alternative Pathways for Nitric oxide Production

- Enzymatic NO synthase production of NO production can be decreased via depleted substrate.
- Direct production of NO via enzymes/ chemistry.
- Both nitrate and nitrite can generate significant amounts of NO for peroxynitrite killing purposes.
- Nitrates can be obtained from spinach, beets & seaweed by ingestion of adequate amounts.

New sources of Nitric Oxide

- Nitrate is concentrated in the salivary glands.
- It is converted in the mouth to nitrite (reduction).
- It is then reduced to NO in the acid stomach.
- Compounds are recycled over & over in the body.

Can we increase NO & assist antimalarial drug ?

- Several scientists have attempted to increase NO in malaria patients by giving l-arginine (IV & orally).
- Used various doses & found it ineffective.
- After 1 hour NO falls to minimal levels.
- The half life of l-arginine is too short and so plasma levels using these systems are ineffective.
- L-arginine & L-citrulline need to be given orally in a form that maintains more consistent levels.
- Other forms of NO production (nitrate & nitrite) are also important.

Adjunctive Therapy Starts Early

- Giving supplements in advanced cerebral malaria would likely be ineffective.
- Starting the NO producing supplements early in the disease seems the way forward.
- "A stitch in time saves nine"

TB and Supplement Treatment

- TB is the 2nd most important infectious dx globally.
- About 1/3 of the population is estimated to be infected with TB.
- People with latent infection are asymptomatic & non- infectious.
- They are potentially at risk of developing active infections.

Is L-arginine effective in Active TB?

- TB bacteria resides in macrophages
- Causes lesions in the lung.
- In active dx, the bacteria exerts a major control against the macrophagic killing (chemical suppression).
- Thus bacteria can reproduce in as well as kill macrophages.
- TB inhibits NO production via arginase destruction of l-arginine.

NO Availability is Impaired in TB

- NO bioavailability affect mycobacterial clearance.
- Severity is associated with delayed TB clearance.
- Hypoargininemia has been demonstrated in TB.

L-Arginine has proven useful In supplemental TB Treatment

- Farrazi (2015) showed that L-arginine is useful as an adjunctive therapy (1 g/day) in active TB.
- He concluded that effects were likely due to increased NO.
- Constitutional symptoms (Wt gain & reduction in CRP) were improved despite anaemia and cough.

Conclusions

- All of the three killer infectious diseases are linked to macrophage activity.
- HIV reproduction is stimulated by strong oxidants and inhibited by antioxidants.
- Anti-inflammatory steroids block the DNA transcription factor nf Kappa B.
- This blocking has a major effect on HIV & FIV replication.

Malaria and TB are Inhibited by Oxidants

- We need to be generating large & continuous amounts of peroxynitrite & other antioxidants
- The generation must be early in the disease course.
- This way the diseases can be more effectively treated with drugs.
- Accomplished by giving large and continuous amounts of substances that generate NO by different pathways.

Oxidants

- NO is a very short lived molecule (seconds).
- It must be generated continuously & at high doses using sustained release precursors.
- All three of the major NO pathways should be included so the entire body is involved.
- Some antioxidants can be used that actually transport nitric oxide (N-acetyl cysteine).

Adjunctive Therapy is the way forward against the killer 3 Infectious Diseases

- It makes economic sense to use host mechanisms to their maximal effectiveness.
- It is most likely to result in the best outcome.
- The best approach is a synergistic approach
- Way forward is to use selective chemotherapy with natural NO producing supplements

Acknowledgements

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Many thanks for your patience

I will be glad to entertain any questions you may have.