BEST SCIENCE FOR THE MOST NEGLECTED

CHALLENGES IN CUTANEOUS LEISHMANIASIS

Perspectives of treatment development and disease control

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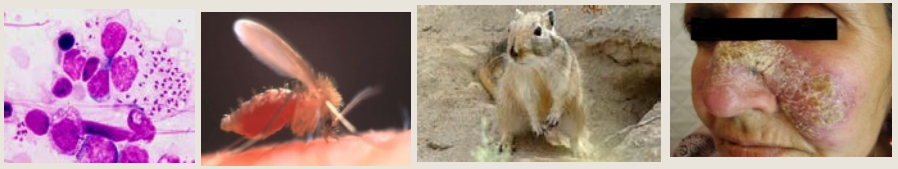
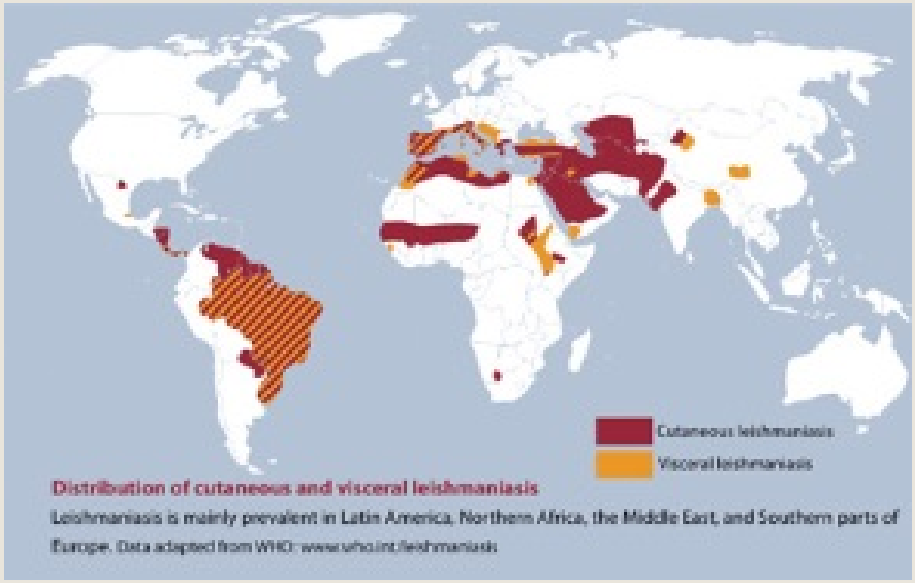
Cutaneous Leishmaniasis: Global Burden

- Leishmaniasis is endemic in **98** countries/territories with more than **350 million people at risk**.
- Leishmaniasis ranks as the leading NTD in terms of mortality and morbidity with an estimated 50,000 deaths in 2010 (Lozano et al., 2012) and 3.3 million disability adjusted life years (Murray et al., 2012).
- **0.7 to 1.3 million new CL** cases occur annually worldwide.
- Every **40 seconds** there is a new case of CL
- Eastern Mediterranean region contribute to ~60% of global CL burden
- CL is **one of the top 10** skin diseases among tourists returning from endemic countries with skin problems
- Clinical and epidemiological diversity:
- CL is a most neglected disease = **Neglected populations**



Courtesy of A. Llanos-Cuentas



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Global reported and estimated incidence of CL

	Reported CL cases/year	Countries with 5 years of data	Estimated annual CL incidence		
Americas	66,941	14/20 (70%)	187,200	to	307,800
Sub-Saharan Africa	155	5/15 (33%)	770	to	1500
East Africa	50	0/6 (0%)	35,300	to	90,500
Mediterranean	85,555	17/26 (65%)	239,500	to	393,600
Middle East to Central Asia	61,013	16/18 (89%)	226,200	to	416,400
South Asia	322	2/2 (100%)	1900	to	3500
Global total	214,036	53/87 (61%)	690,900	to	1,213,300

Alvar J, et al (2012) PLoS ONE 7(5): e35671.

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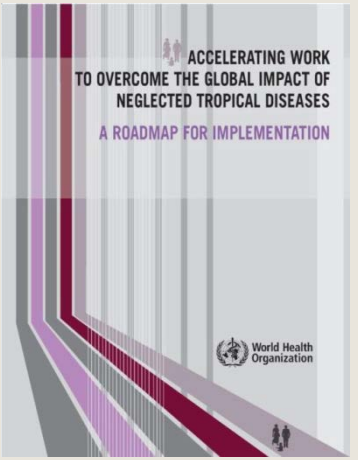
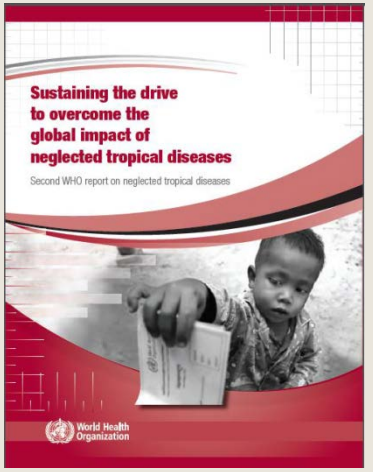
WHO Targets and milestones for Leishmaniasis control and elimination

2014	• Aim to detect and treat >90% of cases of visceral Leishmaniasis and post-kala-azar dermal Leishmaniasis in the South-East Asia Region • Complete district-level epidemiological assessment and mapping of cutaneous and visceral Leishmaniases in 50% of endemic African countries • Update treatment policy for coinfection with visceral Leishmaniasis and HIV using best available evidence • Enhance surveillance of cutaneous, mucocutaneous and visceral Leishmaniases in the Region of the Americas
2015	• Aim to detect and treat all cases of visceral Leishmaniasis and post-kala-azar dermal Leishmaniasis in the South-East Asia Region • Detect and manage >70% of cases of cutaneous Leishmaniasis in the Eastern Mediterranean Region • Detect and treat >90% of cases of cutaneous, mucocutaneous and visceral Leishmaniases in the Region of the Americas • Detect and treat >90% of cases of cutaneous and visceral Leishmaniases in all endemic countries in the European Region • Complete district-level mapping of cutaneous and visceral Leishmaniases in all endemic African countries
2016	• Detect and treat 90% of visceral Leishmaniasis cases in all endemic African countries
2017	• Aim to verify <1 case /10 000 population per year in 80% of endemic districts and subdistricts in the South-East Asia Region
2020	• Reduce the incidence of visceral Leishmaniasis to <1 case/10 000 population per year at district and subdistrict levels in the South-East Asia Region • Aim to detect and treat all cases in the African Region, Region of the Americas, the European Region and the Eastern Mediterranean Region • Detect and manage 85% of cutaneous Leishmaniasis cases in all endemic countries

Adapted from D. Argaw





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Challenges in Disease Control

- No effective vaccine is available.
- Traditional vector control methods do not appear to be effective and are often not available to or practical for at-risk populations
- No rational measures for the control of reservoir hosts are available in the New World.
- Control is unlikely to be achieved by a single intervention. A combination of case management strategies, integrated vector control and animal reservoir control if relevant, is required and should be tailored to each context.
- **The priority for control is developing and implementing improved diagnostic methods and better treatments that are more amenable to field use**

Why do we need to treat CL?

- Accelerate healing
- Minimize scarring
- Prevent complicated forms (RCL, DCL, MCL)
- Reduced transmission in ACL

One size does not fit all

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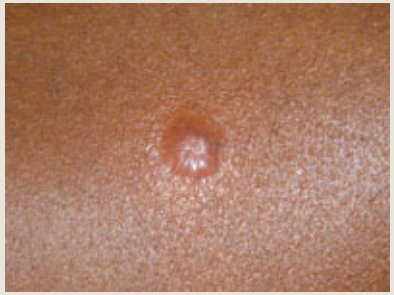
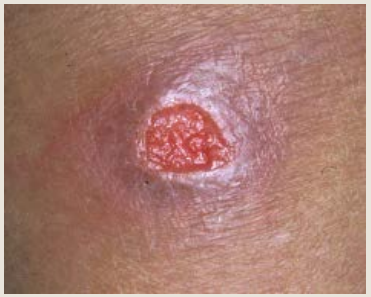
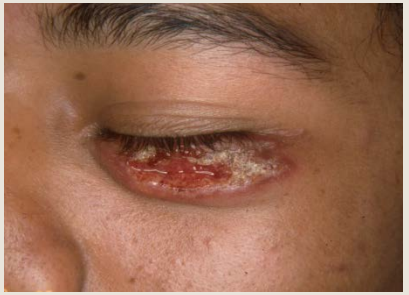
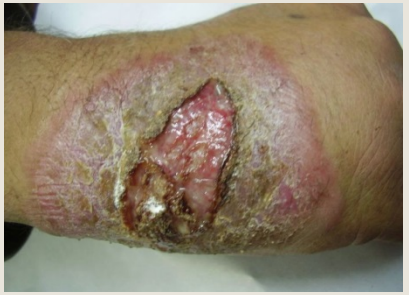
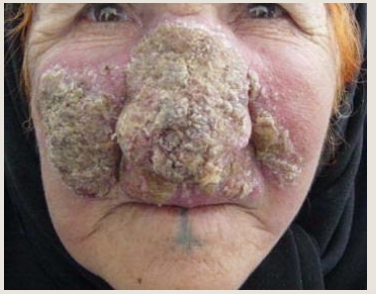
Spectrum of CL lesions and Tx. Options

Diseases Severity

No Tx | Local topical | Systemic oral | Systemic parenteral | Combinations


Multiple applications
Painful
Difficult to administrate
Cosmetic problems
1-4 small lesions

Variable efficacy
Teratogenic
GI and renal problems
Availability
Cost

Toxicity
Painful
Difficult to administrate
Low patient compliance
Efficacy is decreasing

The "gap"

Topical & oral drug, safe, effective against all forms of CL, with superior cosmetic results, at a low-cost and easy to use in rural areas.

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Adapted from M. Grogl

Considerations for the treatment of CL

1. **Clinical characteristics of the lesion(s)**
   - Number of lesions
   - Type of lesion (ulcers, nodules, plaques)
   - Lesion's size
   - Anatomical localization
   - Over infections

2. **Parasite characteristics**
   - Different species and natural history of the infecting *Leishmania* parasite
   - Parasite intrinsic variability

3. **Host Factors**
   - Age & Gender
   - Concomitant diseases
   - Host immune status
   - Patient's behaviours and perceptions

4. **Other Factors**
   - Drug availability
   - Cost
   - Travellers, displaced and refugees populations

2010 WHO Recommendations

Recommended treatment regimens for NW CL

No anti-leishmanial treatment

Local therapy, all species
15% paromomycin and 12% MBCl twice daily for 20 days (B)
Thermotherapy: 1–3 sessions with localized heat (50 °C for 30 s) (A)
Intrales antimonials: 1–5 ml per session every 3–7 days (1–5 infiltrations) (B)

Systemic
L. mexicana
ketoconazole: adult dose, 600 mg oral daily for 28 days (B)
Miltefosine: 2.5 mg/kg per day orally for 28 days (B)

L. guyanensis and *L. panamensis*
Pentamidine isethionate, IM or brief infusions of 4 mg salt/kg per dose every other day for 3 doses (C)*
Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days (C)*
Miltefosine: 2.5 mg/kg per day orally for 28 days (B)

L. braziliensis
Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days (A)
Amphotericin B deoxycholate: 0.7 mg/kg per day, by infusion, for 25–30 doses
AmBisome 2–3 mg/kg per day, by infusion, up to 20–40 mg/kg total dose (C)

L. amazonensis, L. peruviana and *L. venezuelensis*
Pentavalent antimonials: 20 mg Sb5+/kg per day for 20 days

Recommended treatment regimens for OW CL

No antileishmanial treatment

Local therapy
L. major
15% paromomycin / 12% MBCl twice daily for 20 days (A)
Intrales antimonials, 1–5 ml per session plus cryotherapy (liquid nitrogen both every 3–7 days (1–5 sessions) (A)
Thermotherapy, 1–2 sessions with localized heat (50 °C for 30 s) (A)
Intralesional antimonials or cryotherapy independently, as above (D)

L. tropica, *L. aethiopica** and *L. infantum**
15% paromomycin / 12% MBCl as above (D)
Intralesional antimonials plus cryotherapy, as above (D)
Thermotherapy, as above (A)
intralesional antimonials, alone, as above (B)
cryotherapy, alone, as above (C)

Systemic therapy
L. major
Fluconazole, 200 mg oral daily for 6 weeks (A)
Antimonials, 20 mg Sb5+/kg per day for 10–20 days (D)
Antimonials, 20 mg Sb5+/kg per day + pentoxyfylline, 400 mg three times a day for 10–20 days (A)

L. tropica and *L. infantum**
Antimonials, 20 mg Sb5+/kg per day for 10–20 days (D)
Antimonials, 15–20 mg Sb5+/kg per day for 15 days plus oral allopurinol 20 mg/kg for 30 days, to treat leishmaniasis recidivans caused by *L. tropica*

L. aethiopica
Antimonials 20 mg Sb5+/kg per day + paromomycin, 15 mg (11 mg base)/ kg per day IM for 60 days or longer to treat diffuse cutaneous leishmaniasis

Challenges in treatment development

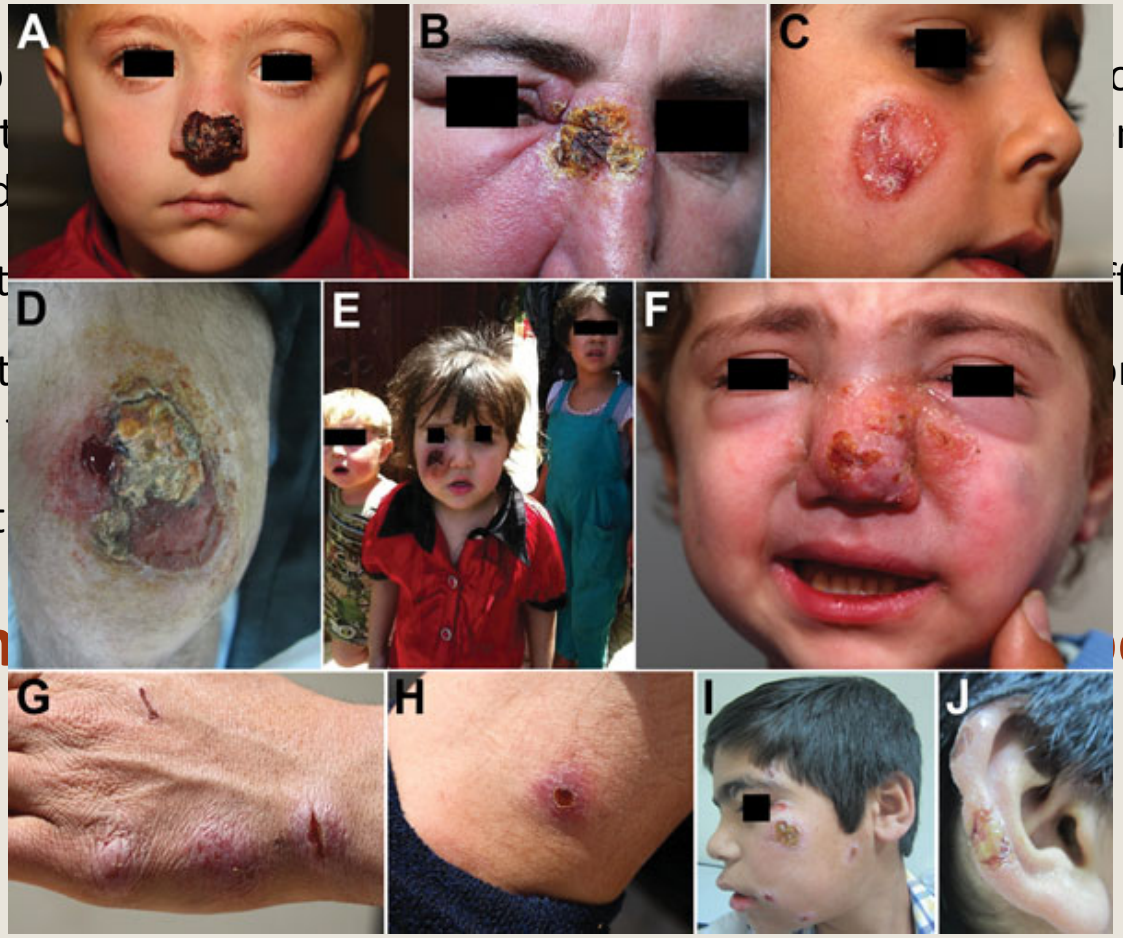
- CL is not fatal, hence very few efforts on drug screening.
- Interpretation of results from some tests, such as the *in vitro* intracellular amastigote model, is complicated given:
  - variable rate of infectivity
  - type of macrophage host cell used,
  - intrinsic susceptibility of laboratory strains and clinical isolates.
- *In vivo* experimental models for CL do not accurately reproduce the biological responses that occur in humans → not good translation of results from animal model to humans.
- Parasite and patient genetic diversity.

Consequences of lack of treatment development

- There are no
- Current treat
- A wide variet
- Few clinical t

o formal clinical
development
nt were repurposed
or developed
ffectiveness
r CL, but none has
been shown

CL is a m **opulations**



Saroufim M, et al Emerg Infect Dis 2014

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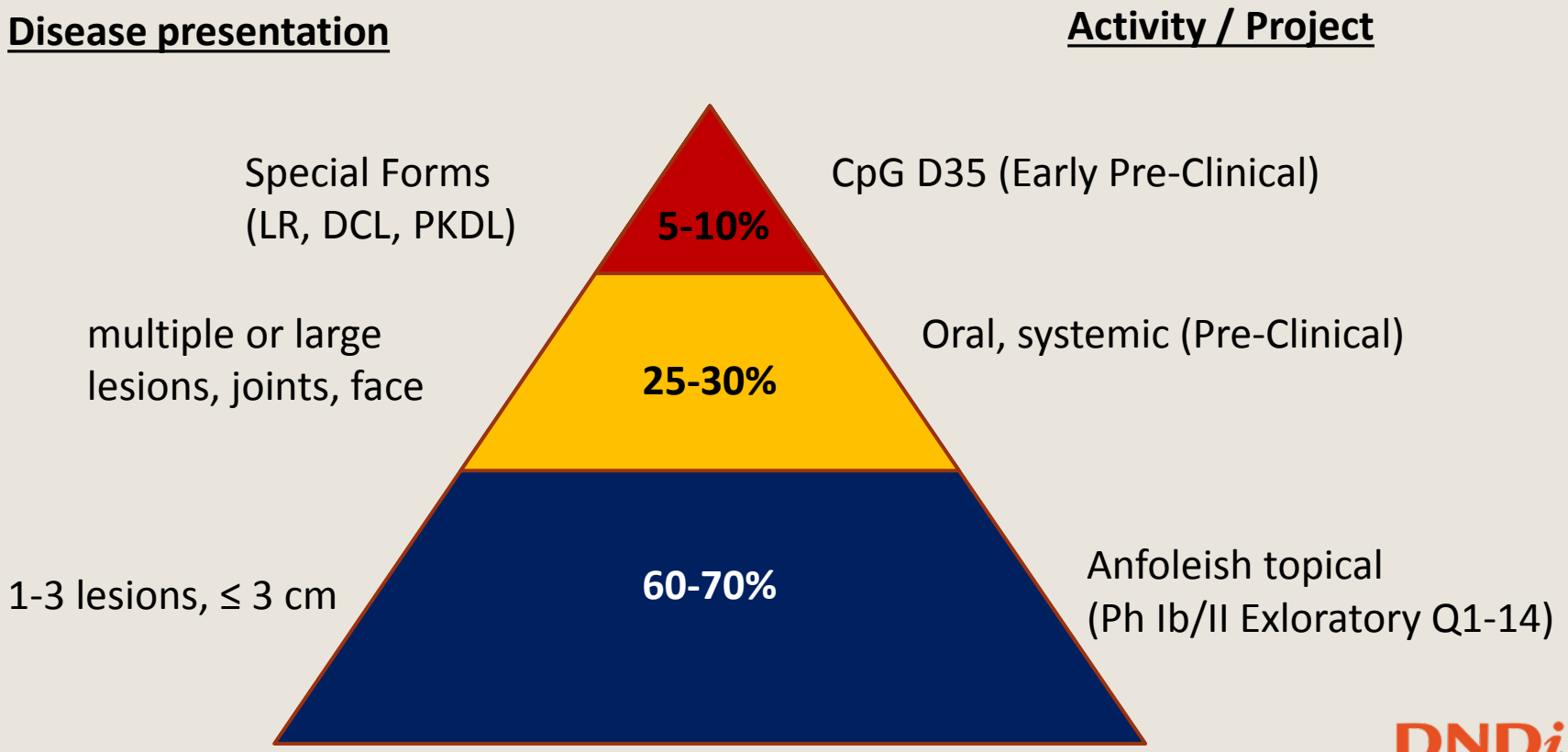
DNDi CL strategy

Objective: To achieve short, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL, mainly caused by *L. tropica* and *L. braziliensis.*



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Current developments

Topical

- WR 279,396 (paromomycin and gentamicin)
- Anfotericin B 3% (Anfoleish)
- Meglumine Antimonate Ointment
- Liposomal formulations

Systemic

- Fexinidazole
- Edelfosine (D121)

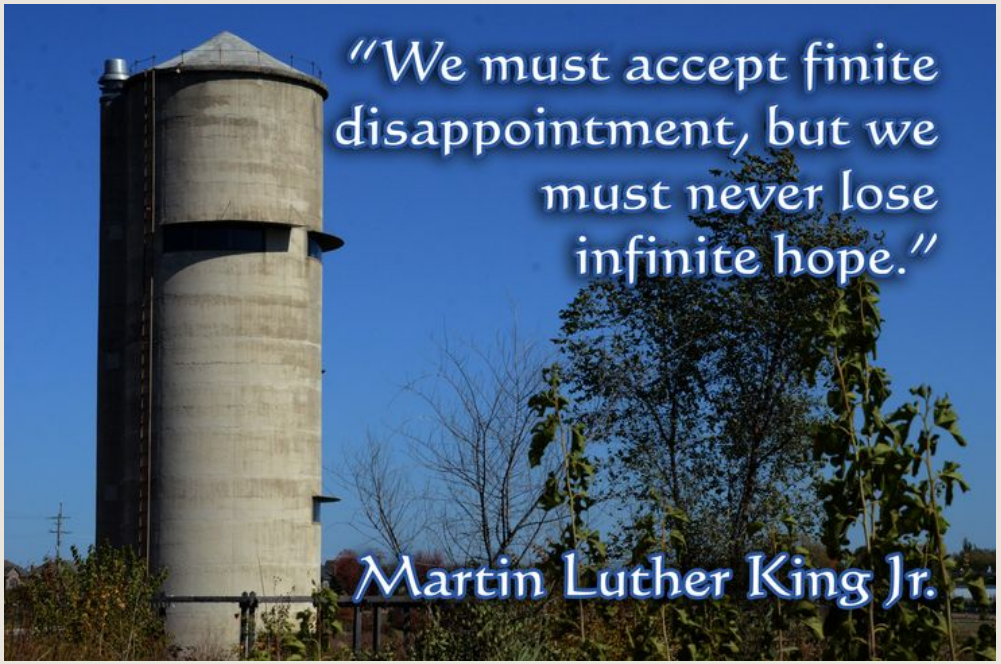
Combinations

- Pentoxifylline + SAG
- Nitric Oxide Releasing Patch + SAG
- CpG D35 + Antiparasitic drug

Summary

- Treatment of CL is not a simple task
- Treatment has long depended on antiquated drugs that would be considered far too toxic for introduction under modern registration systems.
- Even though progress has been made for VL treatment, for CL it seems that what is currently available will probably represent almost the entire therapeutic arsenal for the coming years.
- Although basic research will continue the current challenge is to make better use of what is already available.

THANK YOU



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