Current and Emerging Approaches in Antileishmanial Research

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Drugs for Neglected Diseases initiative

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Current Treatments

Drugs	Pentavalent Antimonials	Amphotericin B	Liposomal Amphotericin B	Miltefosine	Paromomycin sulphate
Regimen	20 mg/kg daily for 20-30 days (depends on geographic area)	1 mg/kg e.o.d. for up to 30 Days (15mg/Kg total dose)	5-20 mg/kg total dose in 4-10 doses over 10-20 days	1.5-2.5 mg daily over 28 days (India only)	15mg/kg/ for 21 days (India only)
Marketing authorisation holder	Albert David (SSG) GSK (Pentostam) Sanofi Aventis (Glucantime)	Bristol Meyers Squibb (Fungizone) Generic companies	Gilead (AmBisome®)	Paladin (Impavido)	Gland Pharma / IOWH
Administration	iv or im	iv	Iv	Oral	im
Clinical efficacy Asia Africa South America	35-95% (depending on geographic area)	> 97% all regions	> 97%; single dose: 91% Not fully established Not fully established	94-97% (India); Not established Not established	94% (India) In evaluation Assumed to be limited
Resistance	As high as 60% (Bihar, India)	Not documented	Not documented	Lab isolates	Lab isolates
Toxicity	+++ Cardiac toxicity, pancreatitis, nephrotoxicity hepatotoxicity	+++ Nephrotoxicity (in patient care needed)	+ Some nephrotoxicity	+ Gastro-intestinal (20-55% of patients, usually mild), nephrotoxicity hepatotoxicity Possible teratogenicity	+ Nephrotoxicity ototoxicity hepatotoxicity (all relatively rare)
Approximate cost of drugs per course* USD (Euros)	SSG (AD) ~$50 (37€) Glucantime (SA)~ $70 (52 €) (Based on 30 day course)	Generic price: ~ $117 (87€)	Preferential price: $280 (207€) (for 20mg/kg total dose) Commercial price: ~10x above costs	Preferential price: ~ $74 (54 €) (can be obtained at 46€ if buying >75 000 packs) Commercial price: ~ $150	~ $10 (7.3 €)
Issues	Quality control Availability Length of treatment Painful injection Toxicity Resistance in India	Need for slow iv infusion Dose-limiting nephrotoxicity Heat stability	Price Need for slow iv infusion Heat stability (Stored <25° C)	Price Possible teratogenicity Potential for resistance Patient compliance	Efficacy variable Between and within regions

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Issues with Current Treatments

- ***SSG/ antimonials:*** **SAFETY, RESISTANCE, DURATION**

Africa: registered in Sudan, Ethiopia, Kenya. Used for all above indications!
India: SSG failure in Bihar, still effective other areas

- ***AmBisome®:*** **COST, FEASIBILITY**

Africa: MSF Ethiopia field use, Dose escalation study planned
India: Phase 2 data+, combo studies done/ planned, MSF- 20mg in field setting (1000+)

- ***Ampho B:*** **SAFETY, DURATION, COST**

Africa: being replaced by Ambisome, limited use
India: Large scale use especially in private sector in Bihar (SSG failure)

- ***Paromomycin:*** **DURATION, EFFICACY?**

Africa: currently under trial, used as part 1º Rx in S Sudan by MSF
India: Registered for use, Phase 4 ongoing

- ***Miltefosine:*** **DURATION, SAFETY, COMPLIANCE**

Africa: RCT done Ethiopia, no current trials underway, 2 previously planned (no funding)
India: Registered in India, WHO roll out, In private sector, In combo studies planned

VL Target Product Profile

	Target
Target Label	VL and PKDL
Spp	All species
Distribution	All areas
Target Population	Immunocompetent and immunosuppressed
Clinical Efficacy	> 95%
Resistance	Active against resistant strains
Safety and Tolerability	No AEs requiring monitoring
Contraindications	None
Interactions	None- Compatible for combination therapy
Formulation	Oral / im depot
Stability	3 yrs in zone 4
Treatment Regimen	1/day for 10 d po/ 3 shots over 10 d
Cost	< $10 / course ($20 in 7 years)

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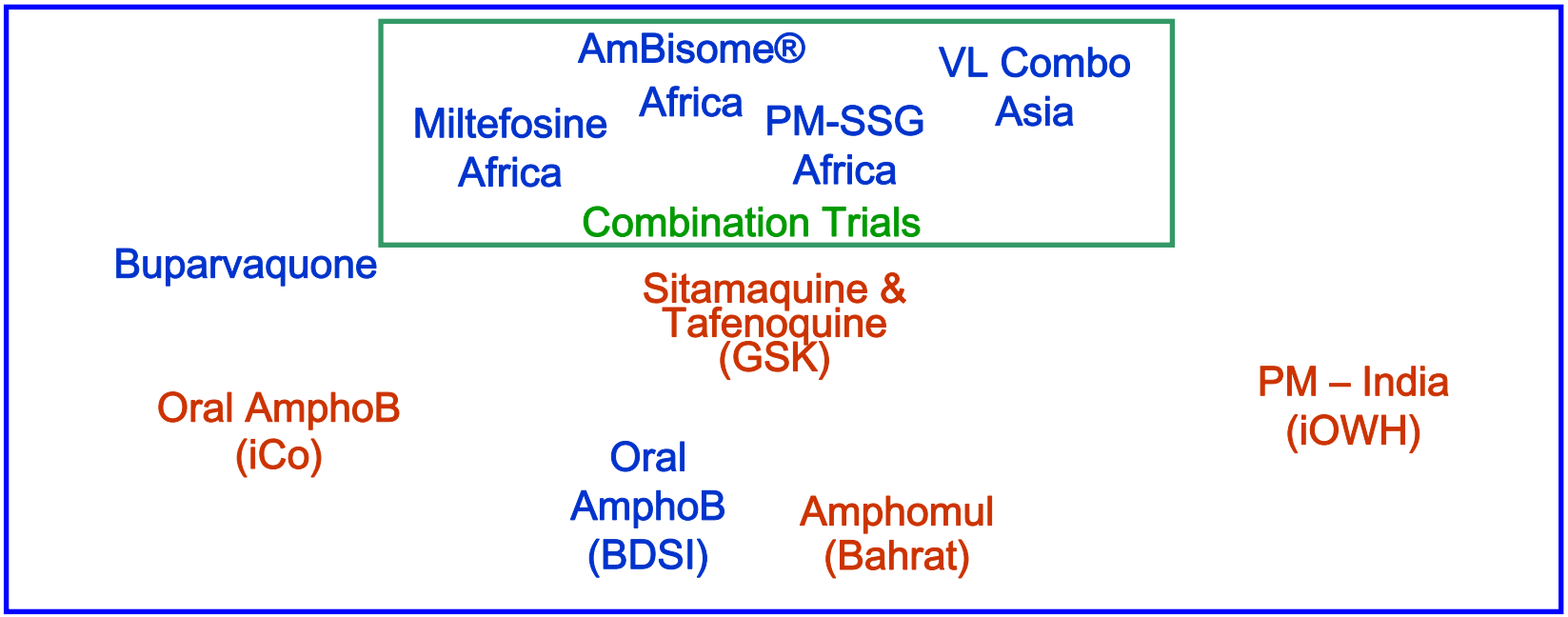
VL Preclinical and Clinical Portfolio



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DNDi Near- and Long-Term Strategy

- Ensure appropriate use of existing treatments through clinical validation of combination therapy treatments.
- Develop new formulations of existing drugs (ie. Amphotericin B)
- Identify and develop NCE

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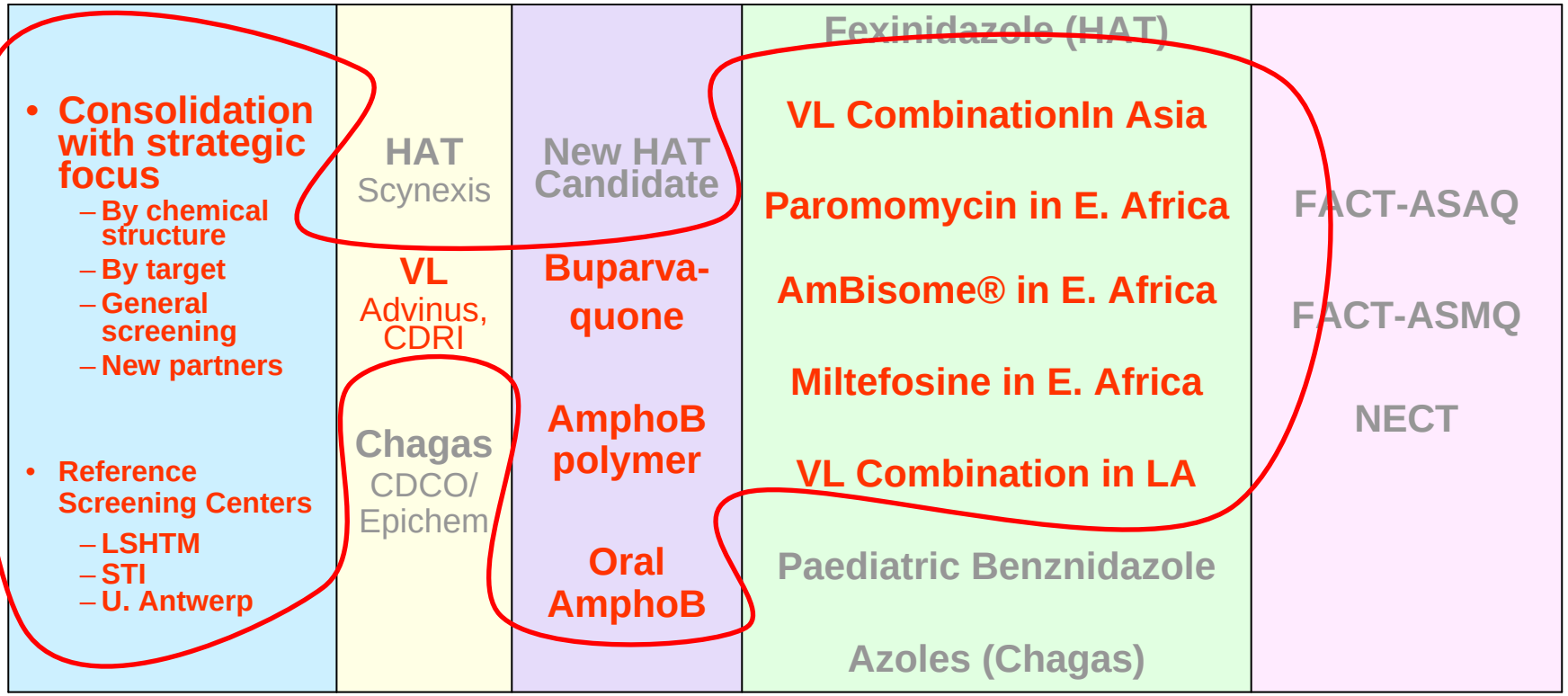
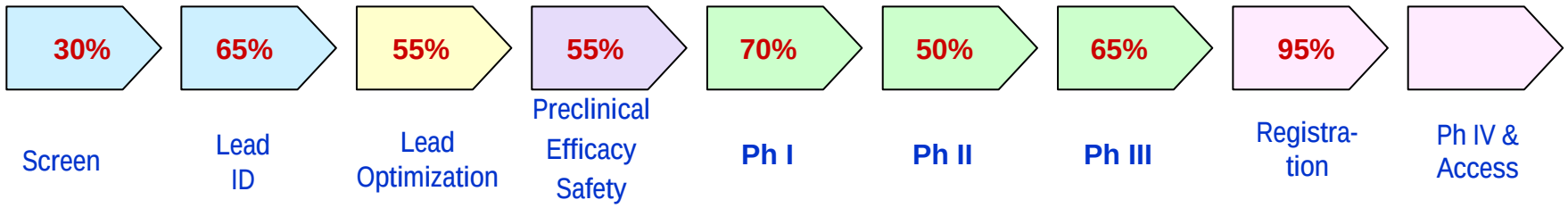
DND*i* R&D Portfolio - 2009





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DND*i* Early-Stage Discovery

- Forge alliance with group with complementary skill set
  - Multiple targets, broad capabilities, proven record, less management burden (U. Dundee)
- Continue to be opportunistic
  - Phasing out some one-off type of agreements as they mature,consider opportunities as the arise
- Data mining
  - STI, WRAIR
- Fill in gaps in HTS assays
  - Improvements in through-put for *T. cruzi* and *Leishmania* screens (IPK)
- Library access
  - Expand current list - pharma, ad hoc suppliers,
  - Sharing with PDPs
  - Targeted drug classes

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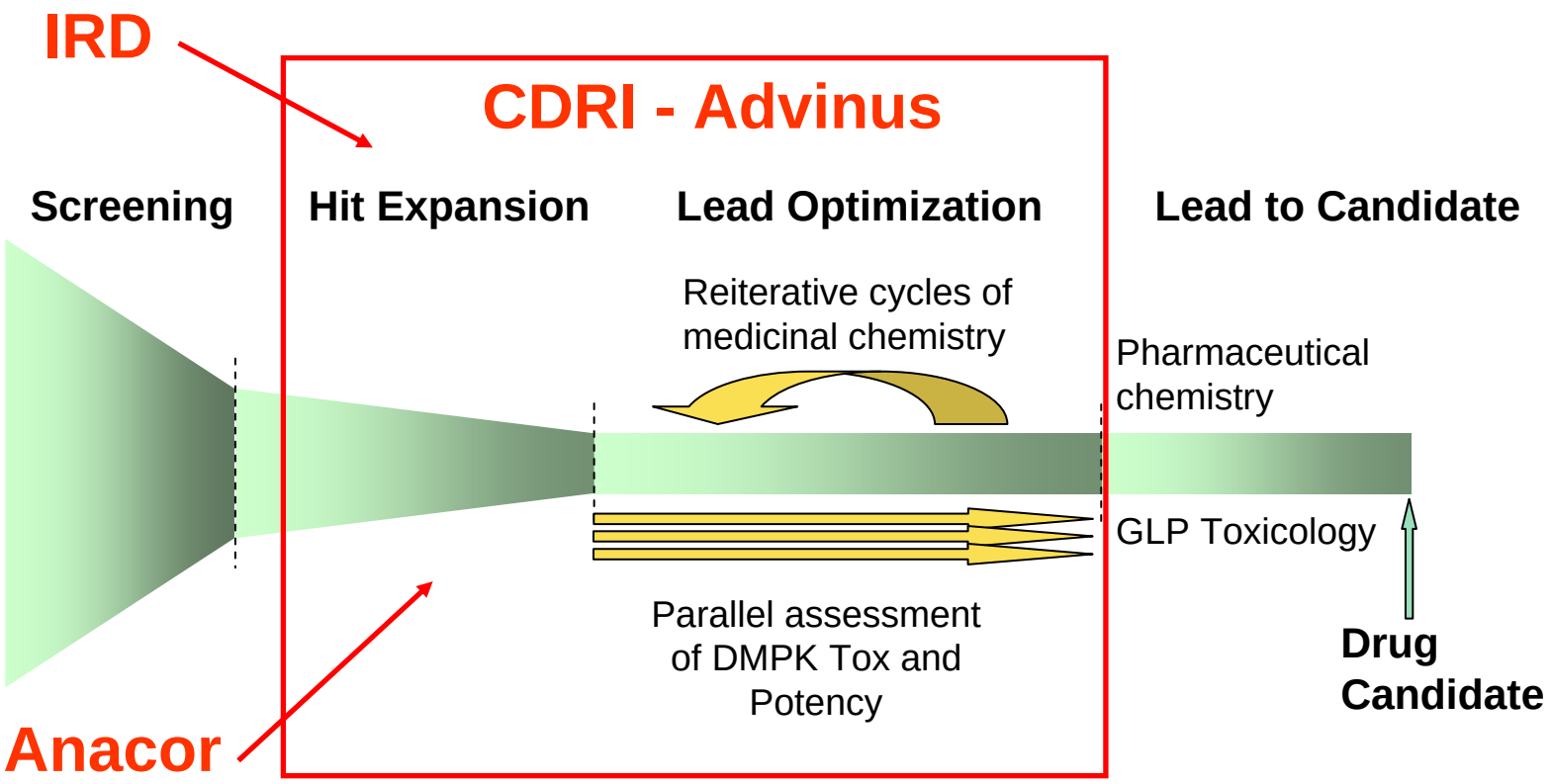
VL Lead Optimization Strategy



DNDi consortium is partially funded by the Bill & Melinda Gates Foundation.

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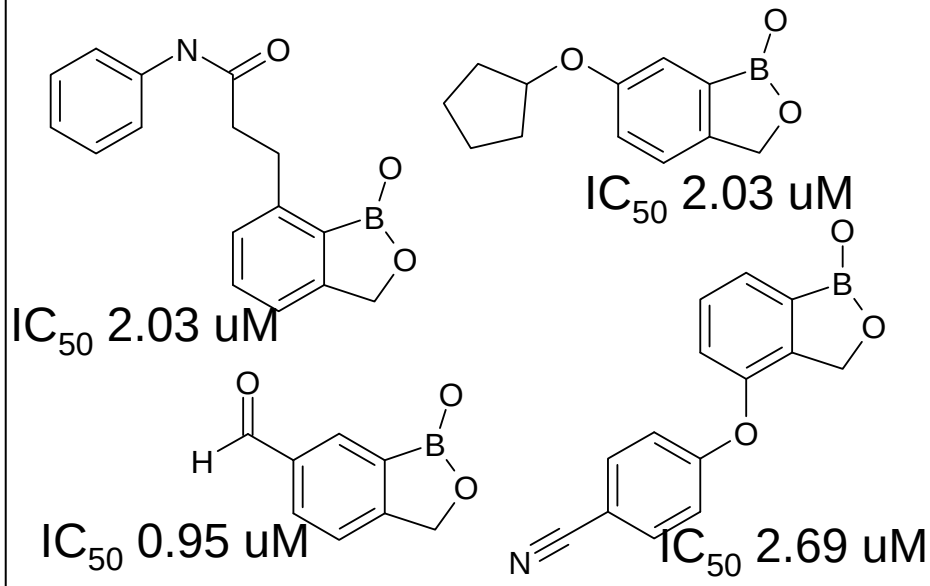
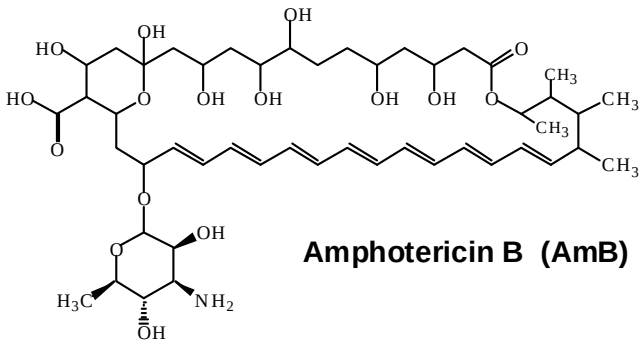
Examples of Active Scaffolds

Oxaboroles



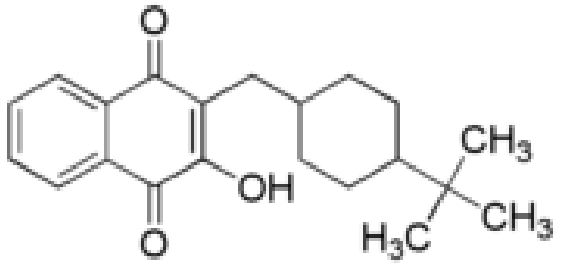
2-substituted quinolines

Amphotericin B



Amphotericin B (AmB)

Buparvaquone



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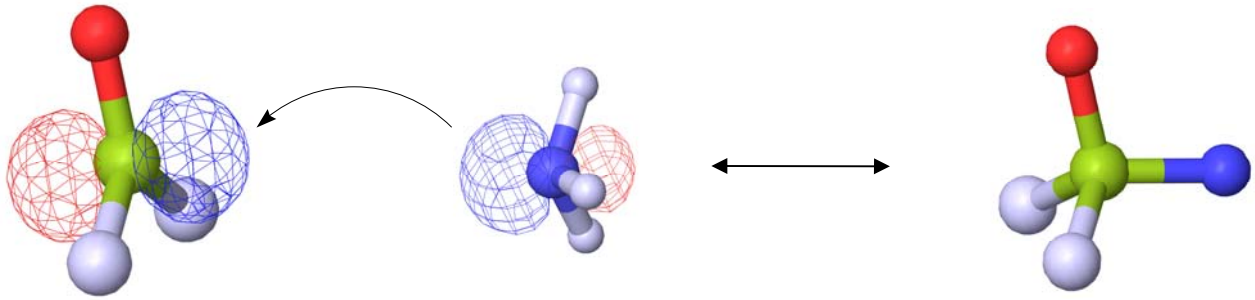
Unique Features of Boron that are Different from Carbon

Boron is normally trivalent and trigonal planar in structure
It has an empty P-orbital & can form a new bond under specific conditions
The new bond forms a tetrahedral structure
Exploiting the P-orbital reactivity allows rational drug design and creation of compounds with unique properties beyond traditional small molecule drugs



Trigonal Planar

Tetrahedral

Amphotericin B Formulations

- AmB is the most efficient treatment
- Cost, stability and route of administration are barriers for wider use
- Ongoing work to develop **cheaper** and **orally** active formulations

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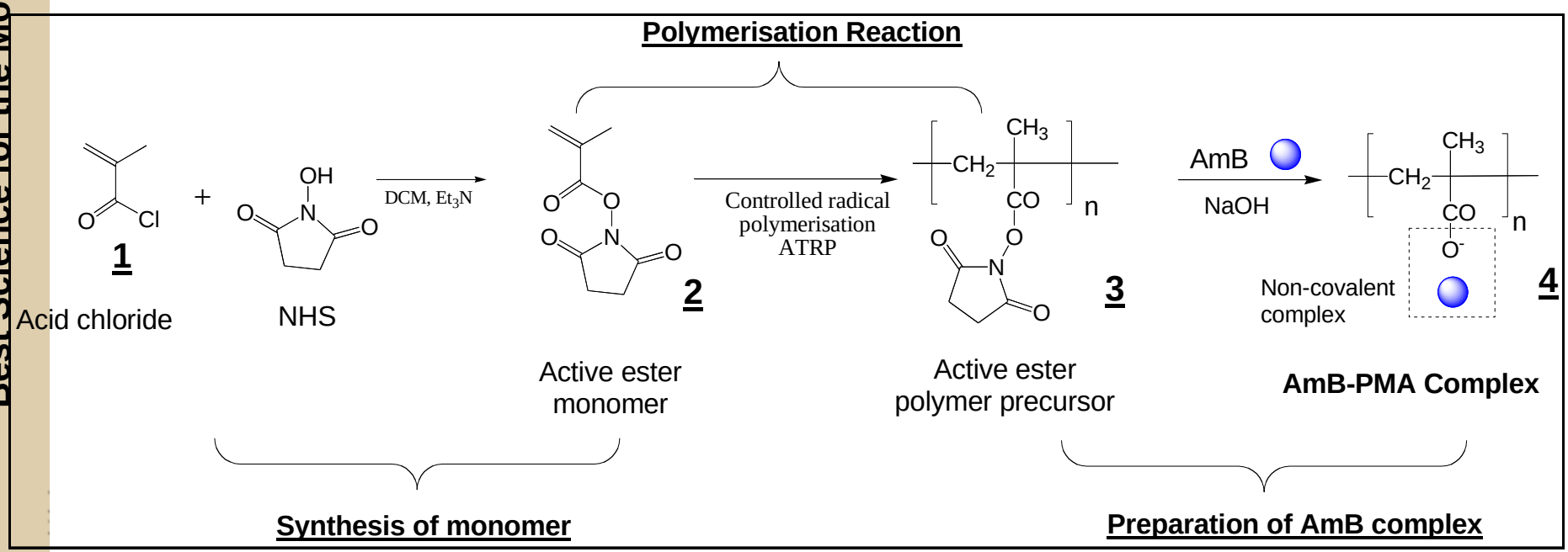
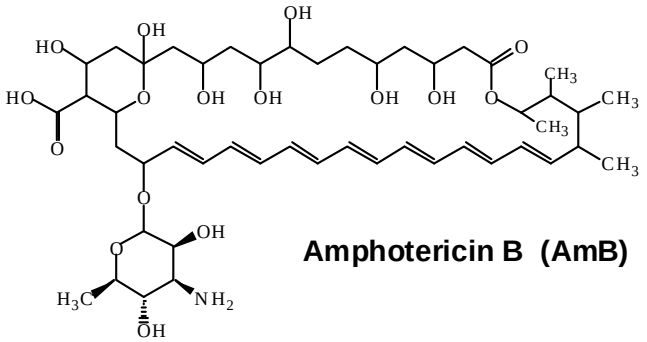
Potential cheaper iv Ampho B formulation

Replace the liposoamal part by polyacylic acid polymer





Amphotericin B (AmB)

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Summary of Progress

- Complexes have been made with the following features:
  - MW: from 12 kDa to 150 kDa
  - Loading: from 15% to 60%
  - Amphotericin dose: from 0.75 to 1.5 mg

- Complexes can be made directly from the polymer. No need to use the precursor polymer.

- No sign of AmB-related toxicity in mice.

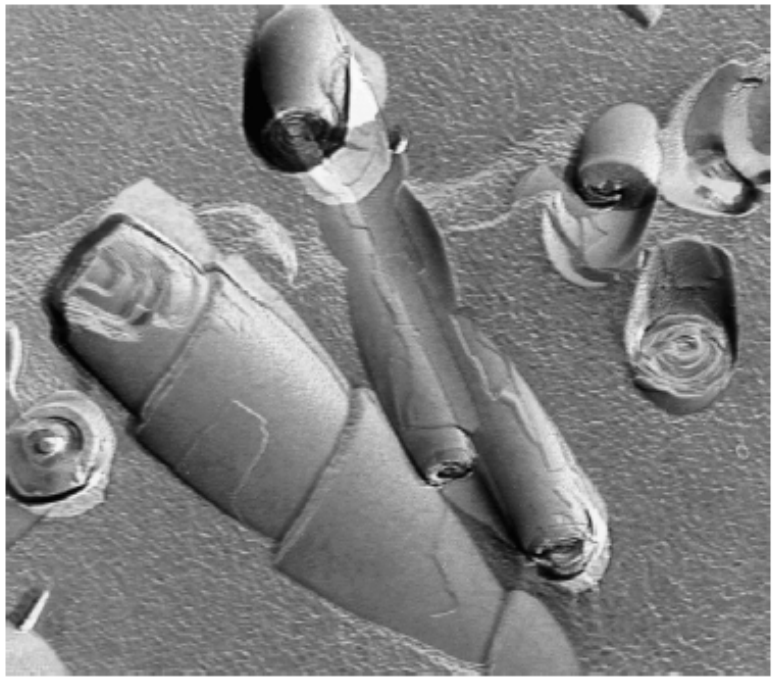
- **Issues:**

How the physicochemical properties of the complex correlates to efficacy in the *in vivo* model.

AmB Oral Formulations

- Orally active AmB formulations under development
  - Lipid-based formulation developed by iCo pharmaceuticals (pre-clinical stage)
  - "Cochleates" formulation developed by BDSI in collaboration with DNDi

BDSI Cochleates Technology



- Stable, phospholipid-calcium precipitates
- Self-assembling crystalline units
- Multilayered structure, containing little or no internal aqueous space
- Resistant to degradation in GI tract
- Increases processing and shelf-life stability
- Composed of naturally occurring materials
- Very inexpensive cost of goods and manufacturing

iCo Lipid-Based Formulation

- The laboratory of Dr. Kishor Wasan of the University of British Columbia has made significant strides toward the development of a proprietary, lipid-based AmB formulation for oral administration.
- Further development licensed to iCo Therapeutics and collaboration with CPDD.

Conclusions

- No new treatments recently made available to treat leishmaniasis
- Limited number of promising chemical series available
- International consortium built around Indian partners with international collaborations

Teams

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