

Development of Flubendazole as a macrofilaricide

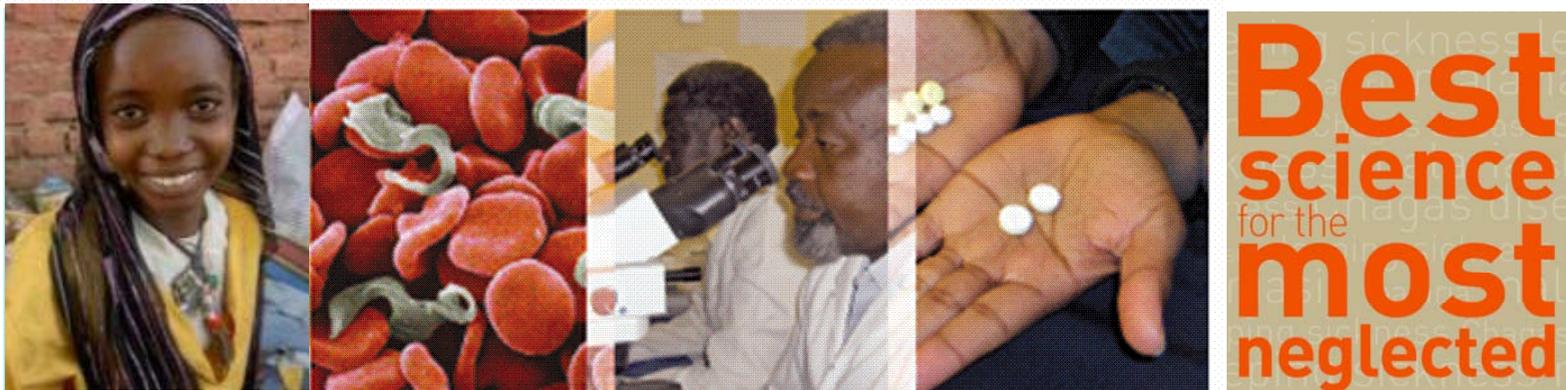


Robert Don
Discovery and Preclinical Director

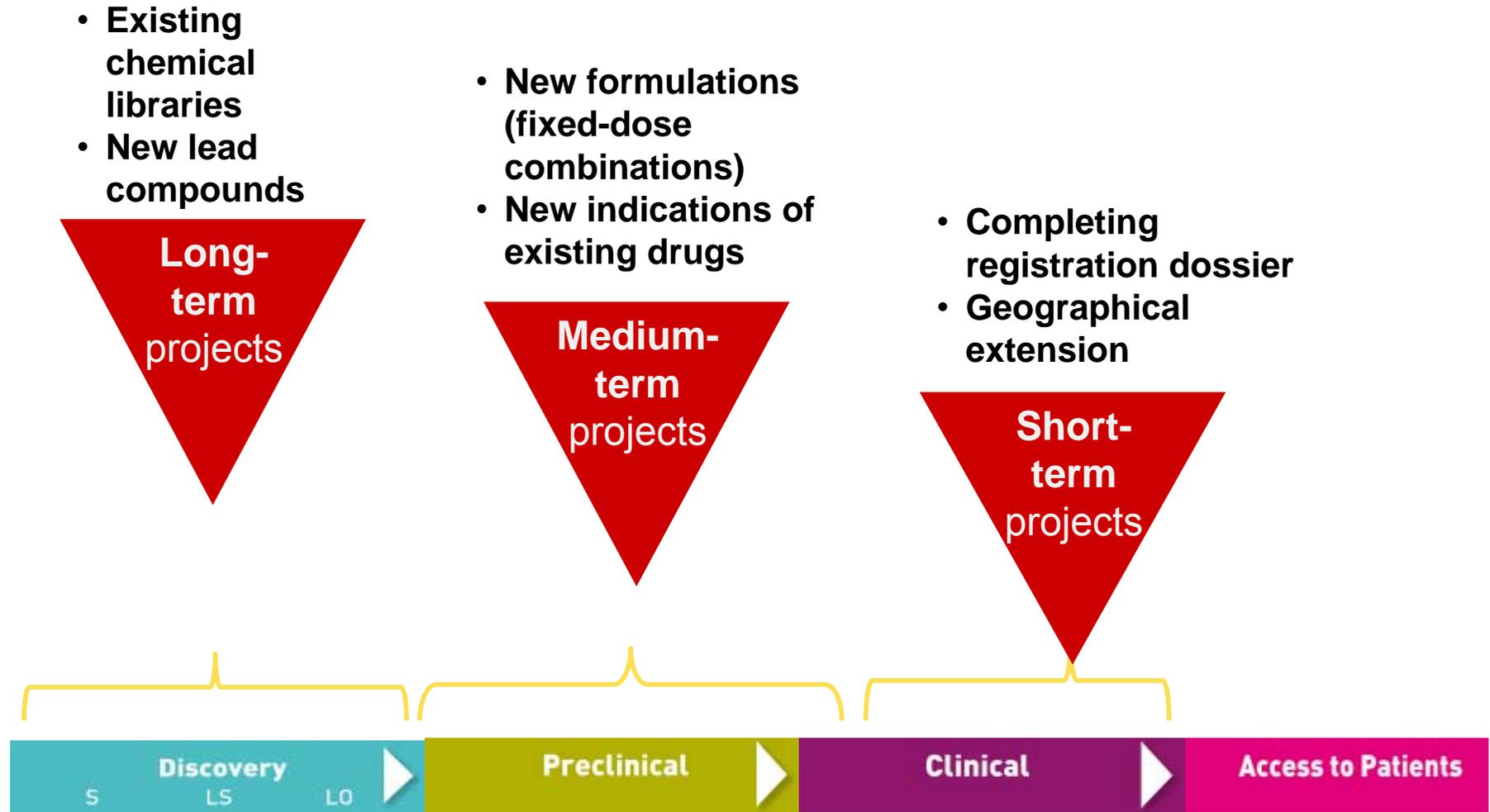
DNDi
Drugs for Neglected Diseases *initiative*

DNDi's Main Objectives

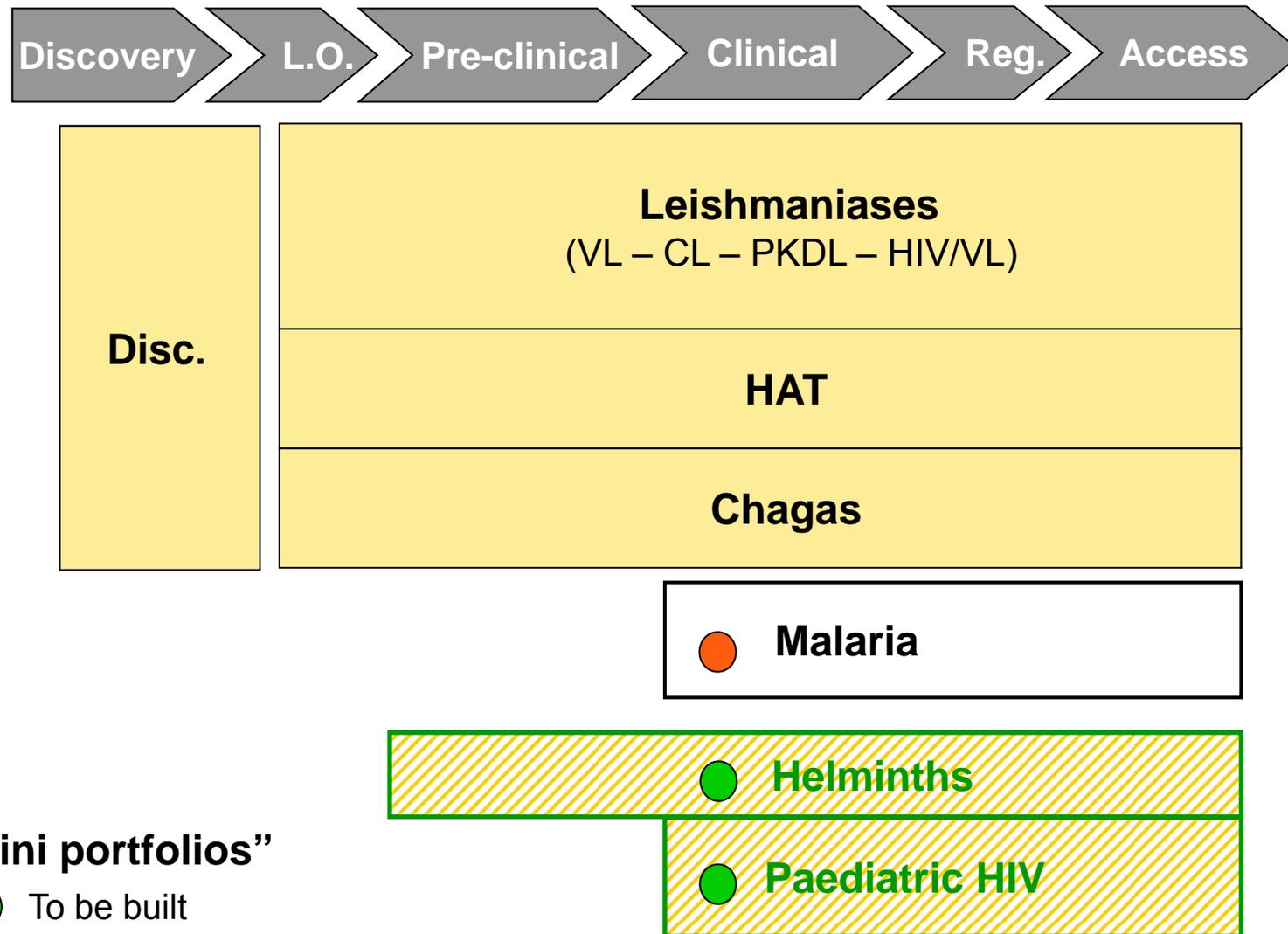
- Deliver **11-13 new treatments by 2018** for sleeping sickness, Chagas disease, leishmaniasis and malaria, and specific helminth infections and paediatric HIV
- Establish a **robust pipeline** for future needs
- Use and strengthen existing **capacity in disease-endemic countries**
- Raise awareness and advocate for increased **public responsibility**



DNDi Portfolio-Building Model



Evolution of DNDi Disease Portfolio



“Mini portfolios”

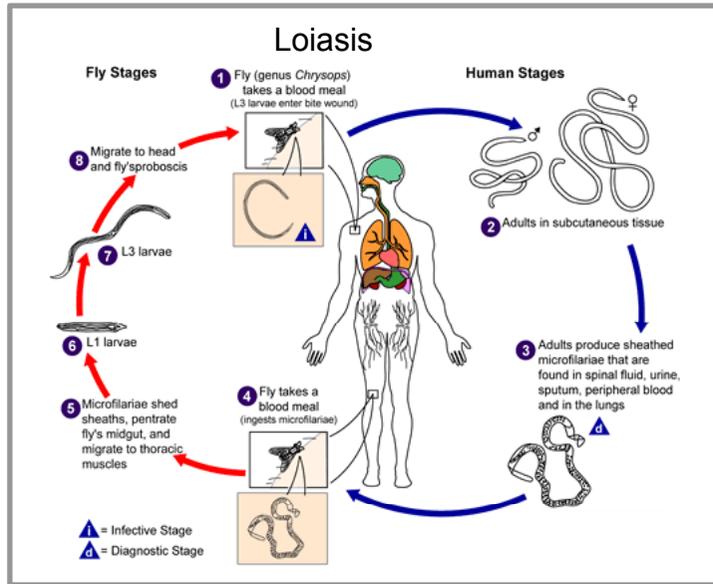
- To be built
- To complete

Flubendazole as a Macrofilaricide

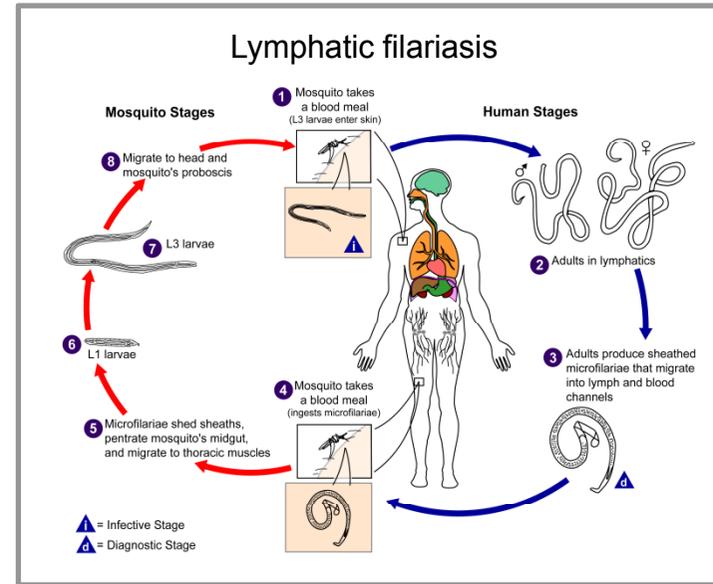
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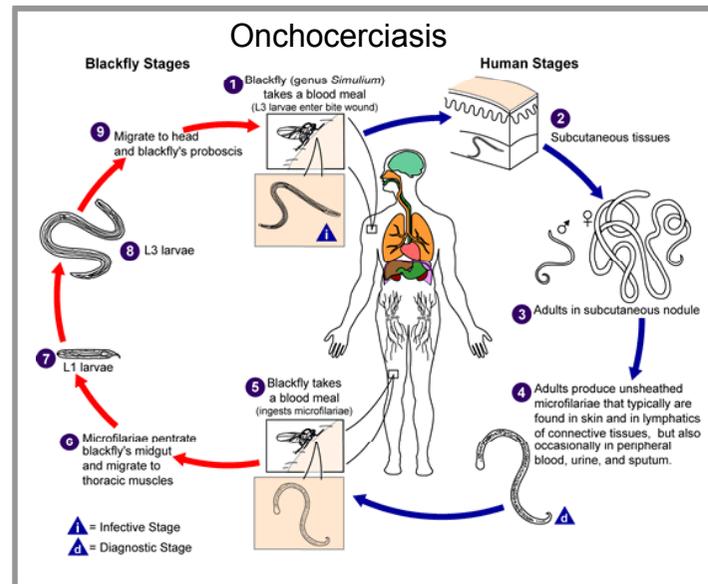
Filariasis



Loa loa



Wuchereria bancrofti
Brugia spp.



Onchocerca volvulus

Filariasis Treatment

Onchocerciasis

- Ivermectin

Lymphatic Filariasis

- Diethylcarbamazine (DEC) + Albendazole

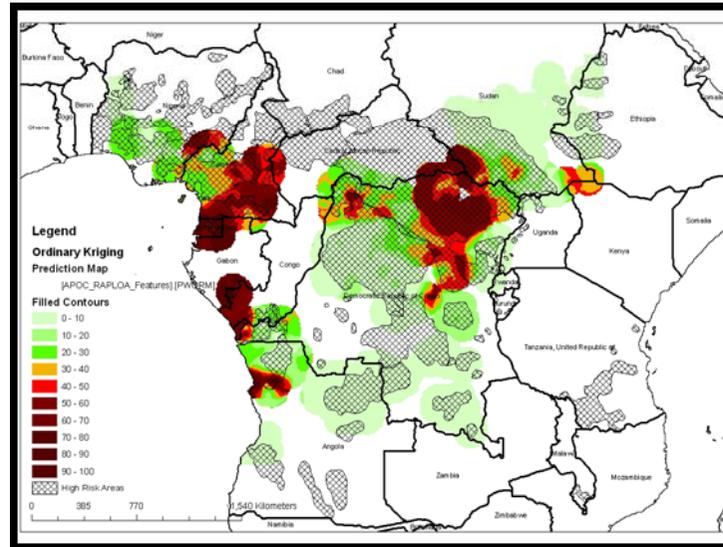
Loiasis

- Usually untreated

Limitations

- Ivermectin and DEC are microfilaricides
- Preventive chemotherapy must be maintained for long periods (up to 15 years for Oncho)
- **DEC and Ivermectin can induce encephalopathy in *Loa loa* infected patients with high microfilarial loads**
- Ivermectin is not recommended for Preventative Chemotherapy in populations coinfecting with *L. loa*

The Need



Regions of infection with *Loa loa* (coloured regions) and *Onchocerca volvulus* (Hatched areas) Source: APOC (African Program for Onchocerciasis Control)

A safe, short course macrofilaricidal drug for treatment of Onchocerciasis and Lymphatic filariasis in *Loa Loa* coendemic regions

1. Mass Drug Administration (MDA) in *Loa Loa* coendemic regions
2. As a companion or alternative to MDA programs in other regions
→ Reduction in treatment duration
3. Case management of filarial infections

Flubendazole

(LF-Onchocerciasis)

Objectives

- Short course for MDA (1 day)
 - 10-14 days p.o./i.m. for case mgt
-
- Most promising
 - Small human study reported in literature
 - “Low-hanging fruit” opportunity
 - + Explore other new drugs in animal health

Flubendazole and DEC in treatment of Onchocerciasis

10 Men Flubendazole - 750mg, QWK 5 for weeks i.m.

9 Men Diethylcarbamazine - 100mg, b.i.d. for 14 days p.o.

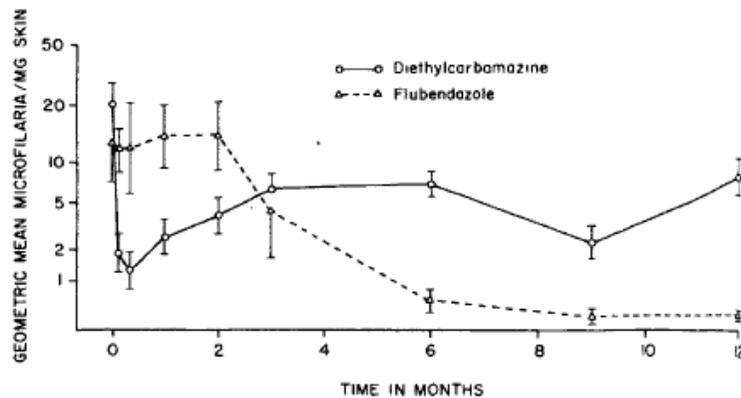


Fig. 1—Number of microfilariae per mg skin.

Error bars represent SEM. Two men in the flubendazole group who left the study at day six are excluded.

	2 MONTHS POST Rx		3 MONTHS POST Rx	
	DEC	FLUB	DEC	FLUB
DEGENERATED ADULTS	12	10	12	27
INTACT ADULTS WORMS	44	11	16	0
FEMALES WITH EMPTY UTERI	6	1	5	0
FEMALES WITH ONLY OOCYTES	8	6	14	0
REDUCTION IN DERMAL MICROFILARIAE ⁴	YES	NO	YES	NO

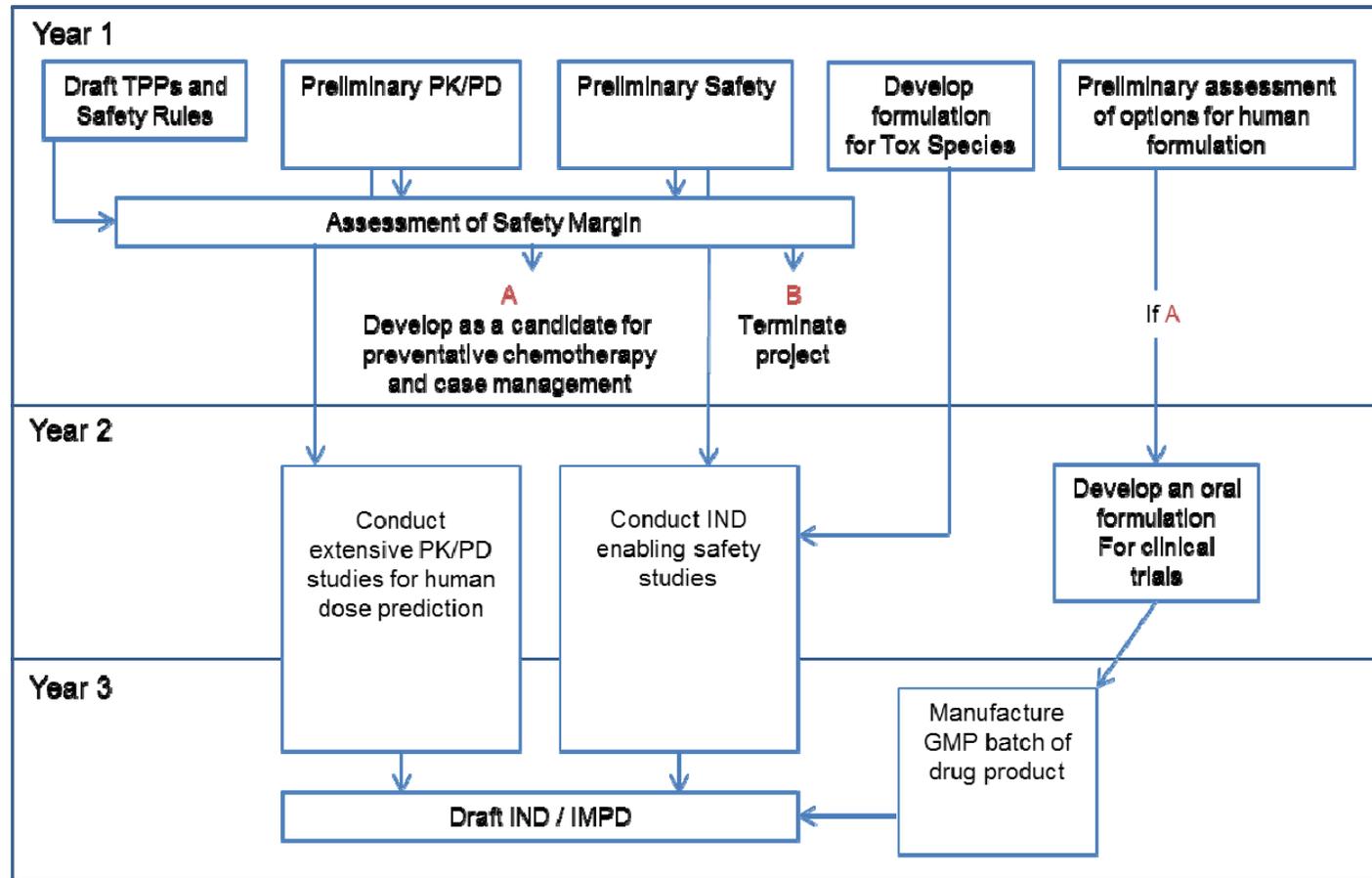
Effect of flubendazole (FLUB) and diethylcarbamazine (DEC) on adult *Onchocerca volulus* isolated from human nodules.

Dominguez-Vasquez A, Taylor HR, Greene BM, Ruvalcaba-Macias AM, Rivas-Alcala AR, Murphy RP, Beltran-Hernandez F. Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis. Lancet 1(8317), 139-43 (1983).

Flubendazole

- Toxicity,
 - Aneugenic / Teratogenic
- Formulation
 - Low solubility
 - A suspension is not bioavailable (Commercial product is used to treat intestinal infections)
 - An experimental formulation in cyclodextrin showed dramatically improved bioavailability (Potential to examine safety of orally administered drug in animals)

Flubendazole Research Plan



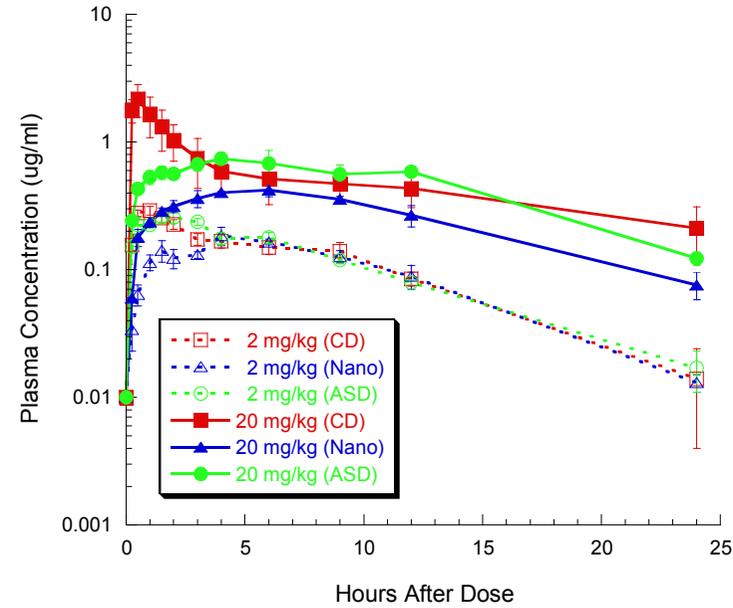
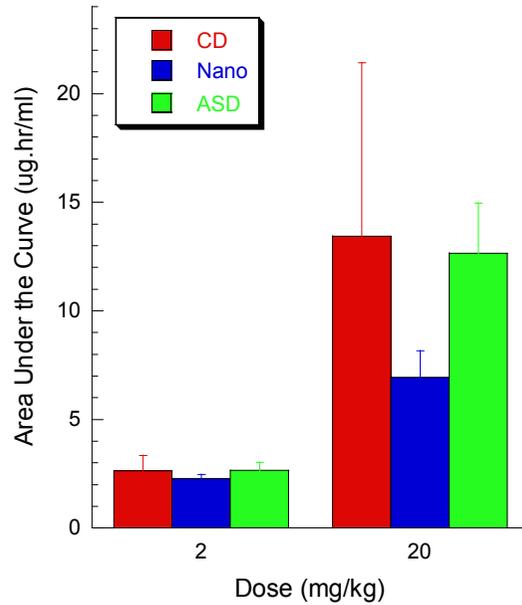
CMC

Review of formulation options

Non clinical and clinical

- Lipids: deprioritized due to low solubility
- Cyclodextrin based complexes
- Nanosuspension
- Amorphous Solid Dispersion

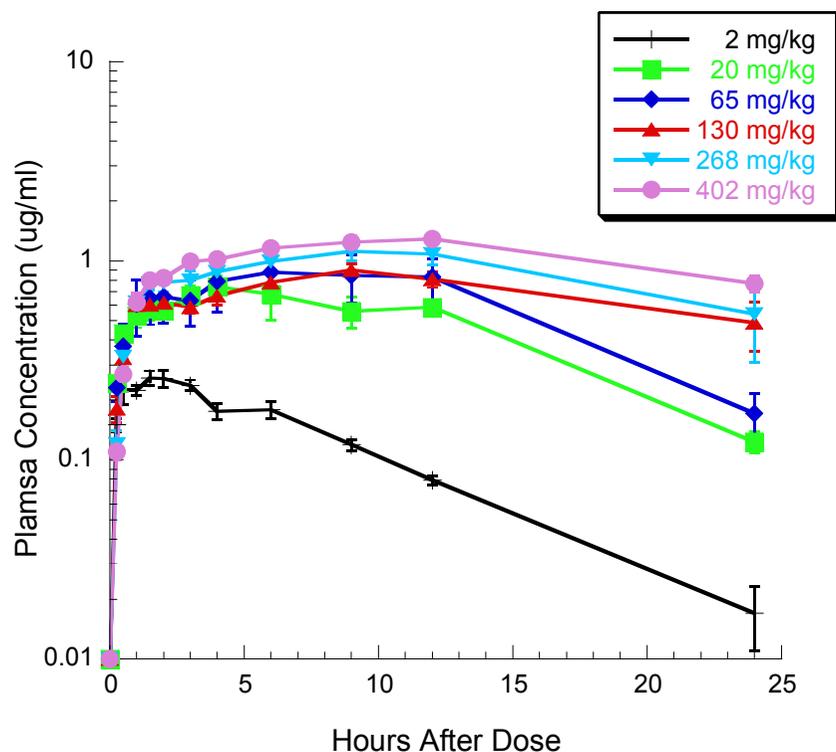
Flubendazole Research Plan



Formulation	2 mg/kg				20 mg/kg			
	$t_{1/2}^{\circ}$	C_{max}	T_{max}	AUC	$t_{1/2}$	C_{max}	T_{max}	AUC
CD (Cyclodextrin Solution)	3.5	0.29 (0.04)	0.8	2.63 (0.71)	-.-	2.19 (1.07)	0.5	13.44 (7.97)
CD (Cyclodextrin Solution) (n=2)					-.-	1.58 (0.30)	0.5	8.87 (1.18)
Nano (Nanosuspension)	4.4	0.19 (0.05)	4.7	2.28 (0.19)	7.0	0.46 (0.04)	5.0	6.94 (1.22)
ASD (Amorphous Solid Dispersion)	4.5	0.29 (0.02)	1.7	2.66 (0.36)	6.5	0.78 (0.23)	4.7	12.65 (2.31)

Data provided as Mean (SD; n=3); $^{\circ}$ harmonic mean ; $t_{1/2}$ [hr]; C_{max} [$\mu\text{g}/\text{mL}$]; T_{max} [hr]; AUC [$\mu\text{g}\cdot\text{hr}/\text{mL}$]; All formulations administered using a 10 ml/kg dose volume in non-fasted rats

ASD: Dose Escalation

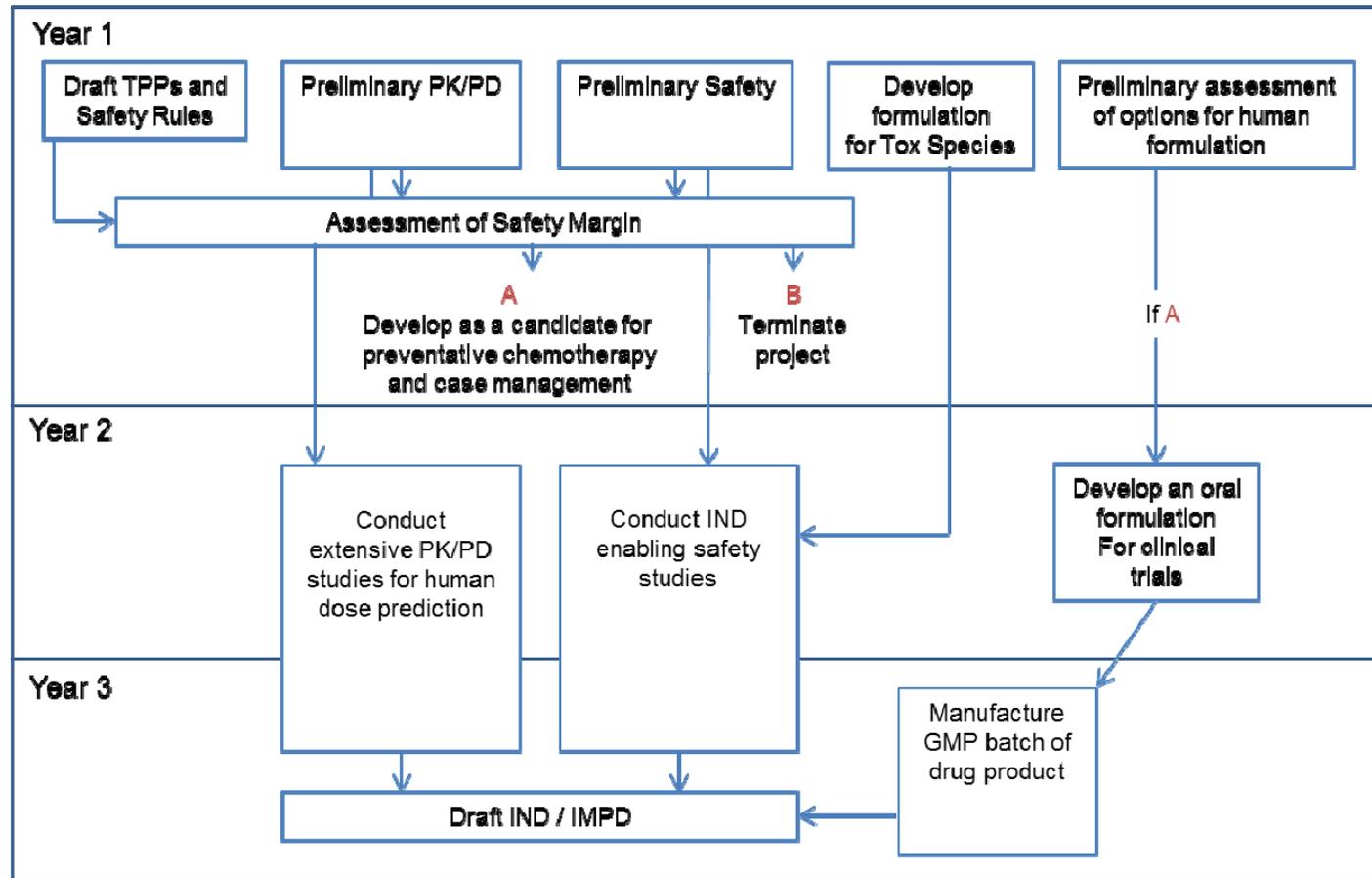


- 10 ml/kg dose: aqueous suspension
 - 20 ml/kg at 402 mg/kg
- Minimal animal to animal variability
- Increasing concentrations with increasing dose
 - Less than proportional to the dose
- Plasma concentrations maintained for >24 hr

Data provided as Mean (SD; n=3)

Flubendazole Research Plan

Next Steps



Safety

1. Flubendazole binds tubulin and blocks formation of the mitotic spindle
 - Aneugenic → Aneuploidy, Teratogenicity, embryotoxicity
 - Benzimidazoles have
 - A common mechanism of action
 - A threshold of action
 - NOAEL has been determined for Benomyl / carbendazim (Committee on mutagenicity of chemicals in food UK)
 - Determine threshold of action by dose response in an *in vitro* micronucleus assay
 - Toxicity to rat whole embryo culture
 - Preliminary reproductive toxicology (Seg 2)

Pharmacodynamics

Review of models of infection with safety experts to gain insight into therapeutic window

1. in vitro

Brugia malayi (macrofilariae and microfilariae)

2.in vivo

Brugia malayi in jirds and rats

Onchocerca ochengi in cattle