Filarial Disease Program

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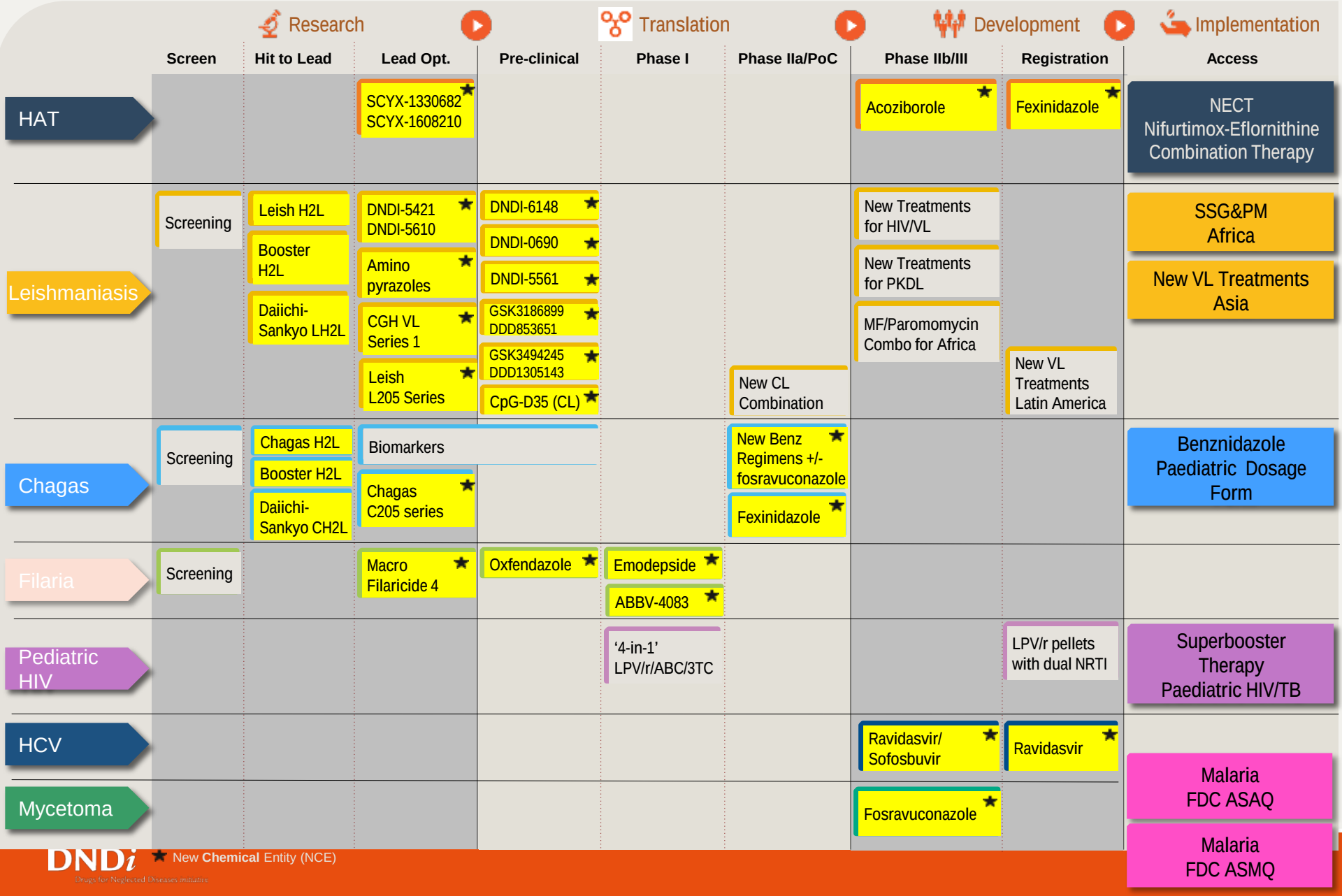
To fill the gap in R&D for neglected patients: Product Development Partnerships (PDPs)

Current PDP landscape working areas include:

- Vaccine R&D
- Diagnostics R&D
- R&D for new or improved treatments

DND*i* R&D Portfolio June 2018

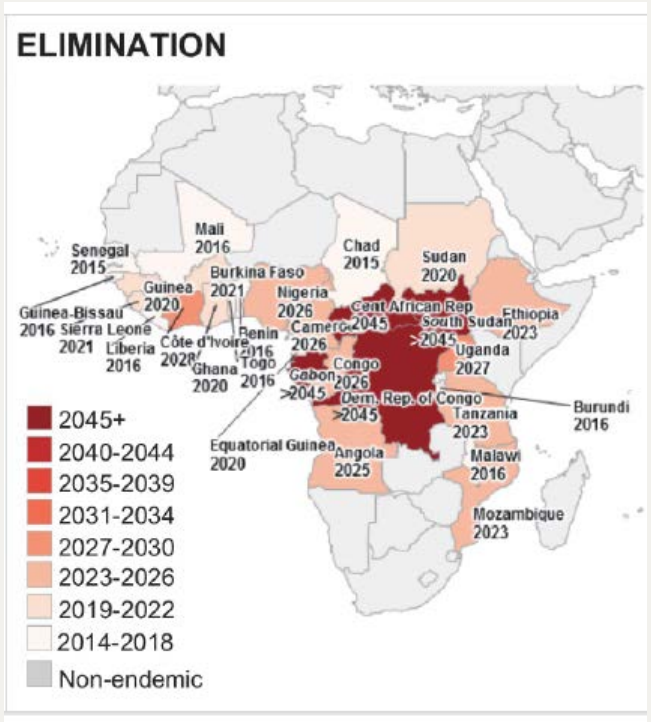
7 new treatments available and up to 16 new chemical entities in the pipeline

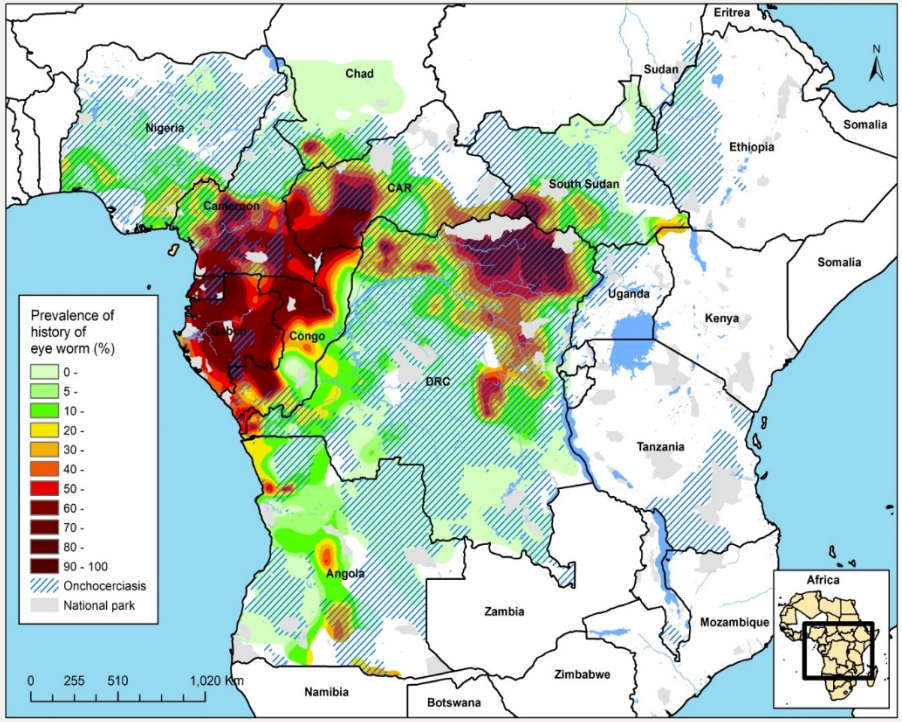


Filarial Diseases: Unmet Medical Needs

- Unmet medical needs:
  - IVM is microfilaricidal (repeated application)
  - No macrofilaricidal treatment available
  - Morbidity management
  - *Loa-loa* coinfections with risk of serious adverse events

Control – Elimination - Eradication





Elimination Scenario (beyond 2045)

Tailored interventions (1.3 billion treatments)

- Dependent on starting prevalence
- DRC, South Sudan, Central Africa,
- Conservative and optimistic models

BUT NOT BY 2030!

Major feasibility concerns (2015):

- *Loa loa* coinfection without treatment
- Political and economical situations
- Recrudescence
- Resistance

Kim et al. PloS NTD 2015

Venkeles et al. submitted

Filarial Diseases: Unmet Medical Needs

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- The aim is to:
  - deliver a short-course safe and efficacious macrofilaricidal/longterm sterilizing drug for onchocerciasis to be extended to LF

- Alternative therapy for:
  - case management / morbidity management
  - “mop-up” campaigns to contribute to elimination as public health problem
  - Test and Treat (TNT) approaches
  - Safe treatment in *Loa loa* coendemic regions

Major changes in the filarial landscape

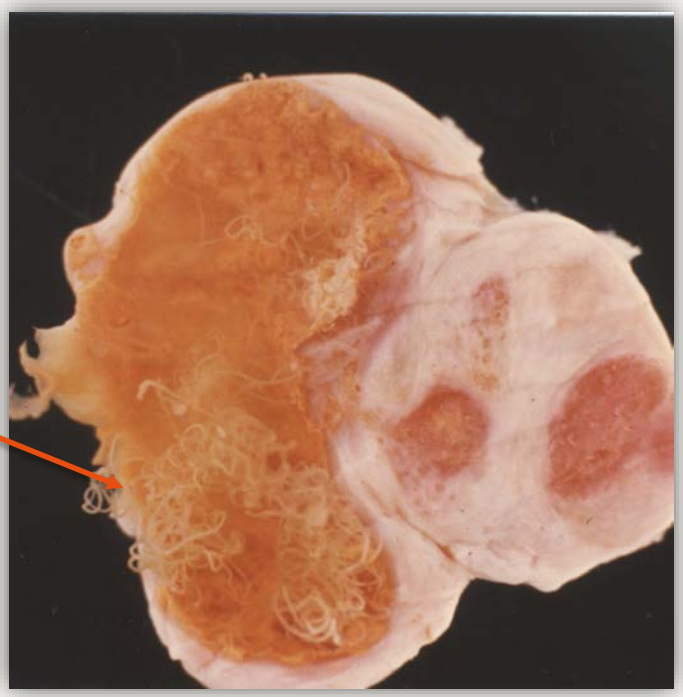
- Mass drug administration activities are increasing, but:
  - Elimination as one goal of the SDG cannot be reached with MDA
  - Tipping point expected, when test and treat becomes cheaper
  - Resistance development (clearly proven in veterinary medicine), not shown in MDA environment, as people are not followed up

- IVM/DEC/ALB (IDA) is highly effective in LF:
  - Currently investigated for onchocerciasis
  - Safety risk due to DEC?
  - Cost and logistics (treat and retreat approach)

- Moxidectin with strongly improved microfilaricidal efficacy over ivermectin, but:
  - Will be registered in the US only
  - As IVM, it is not macrofilaricidal
  - Same class as IVM, therefore high chance of (cross)resistance

Drug targets: direct vs indirect

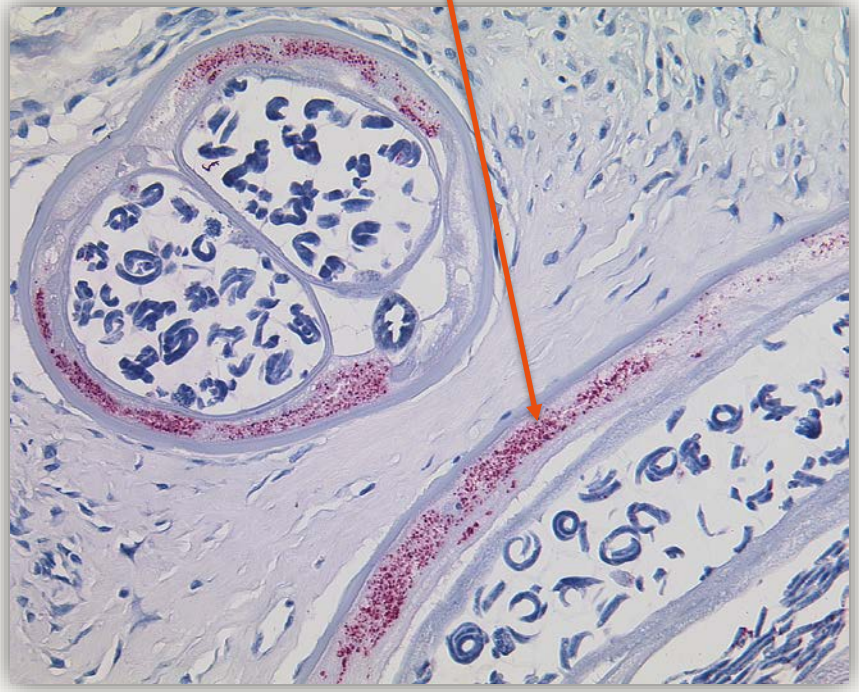
Adult worm



Onchocercoma containing male and female adult worms

Courtesy of Prof. DW Büttner

Wolbachia



Cross-section of a female *Onchocerca volvulus* worm showing *Wolbachia* (red) in the lateral hypodermal cords.

Courtesy of PD Dr. Sabine Specht

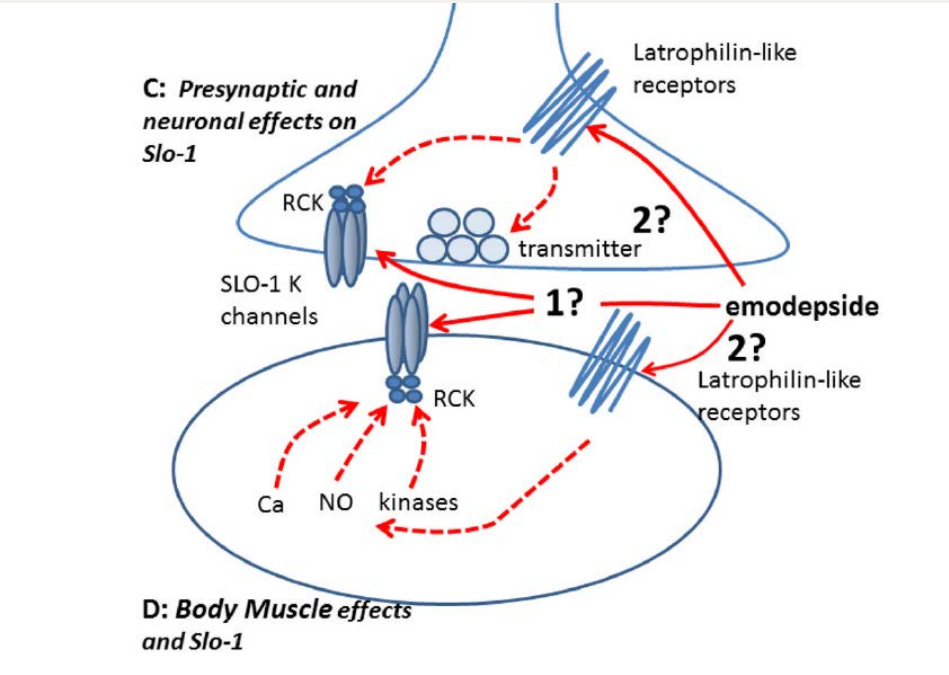
Possible mode of actions: direct vs indirect

Onchocerciasis only areas	Onchocerciasis + Loiasis coendemic areas
Macro- and microfilaricidal drug can be used in the total population	Microfilaricidal drug has to be used with caution ("test and not treat")

Direct acting drugs: Emodepside, Oxfendazole	Indirect-acting drugs (anti-wolbachial): TylAMac
PoC: Macrofil. (Oncho-Loa coinfected areas) Macrofil. + microfil. (Oncho only areas)* **Advantage:** Proven MoA in veterinary medicine Fast-killing, morbidity management* Potentially used for multiple nematodes **Disadvantage:** Risk of AE due to microfil. activity (Emod.) **Possible:** Combination treatments	**PoC:** Macrofil. (Oncho-Loa coinfected areas) **Advantage:** slow-killing, MoA well known, Reduction of inflammation due to removal of *Wolbachia* No side effects in loiasis infected individuals **Disadvantage:** long time to death of the adult parasite **Possible:** Combination treatments

High attrition rates: need for a variety of candidates
Pursue both approaches are valuable and build up the anti-filarial tool-kit

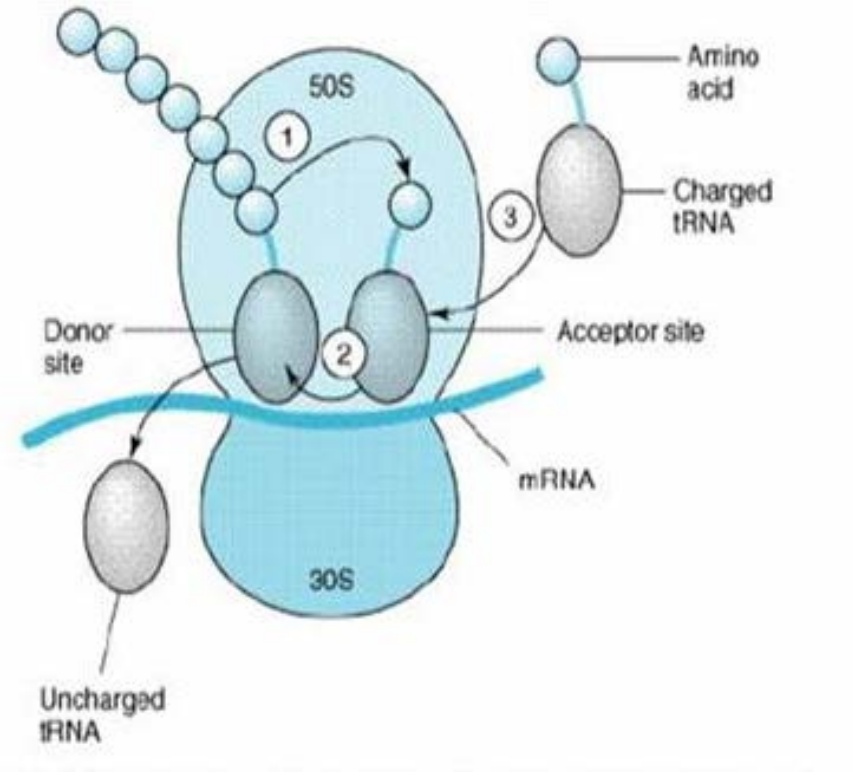
Drug targets: SLO-1 (emodepside)



SLO-1 K+ channel / big potassium channel:

- inhibition of pharyngeal pumping activity and locomotion
- slow, irreversible, concentration-dependent hyperpolarization
- Human SLO-1 is 10-100-fold less sensitive
- SLO-1 orthologues in many nematodes, correlates with spectrum of activity

Drug targets: *Wolbachia* (TylAMac)



***Wolbachia*:**

- Inhibits binding of tRNA
- bacteriostatic
- Validated target with macrofilaricidal activity and longterm sterilizing effect

Anti-wolbachial drug: TylAMac

- Synthetic derivative of tylosin A (common veterinary macrolide antibiotic)
- Highly potent against *Wolbachia* (>200-fold more potent than doxycycline)

✓ Tox-package completed

✓ IND (Investigational New Drug) application 11/2017

✓ Phase 1 Single Ascending Dose study ongoing

Dale Kempf

Phase 1 clinical trials

- Aim:
  - Determine the maximum tolerated dose (MTD) of the new treatment
  - MTD is found by escalating the treatment dose until dose-limiting toxicity (DLT) is reached

- Design:
  - To assess the safety, tolerability, PK and PD of the drug
  - Healthy volunteers (often male)
  - Duration: 6-12 months

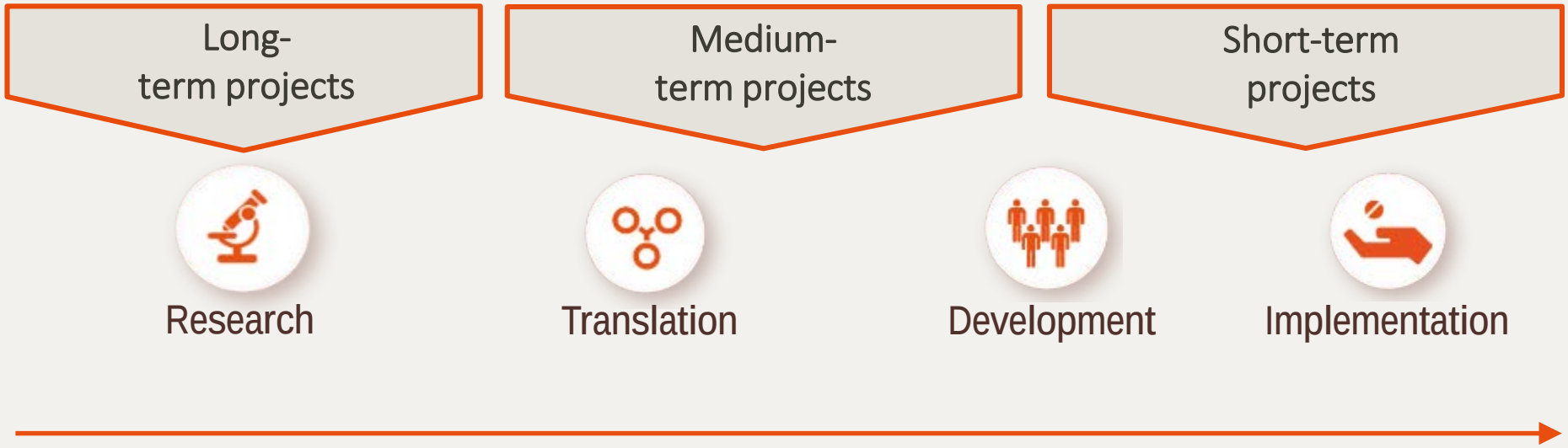
- Types of Phase 1:
  - SAD: single ascending dose
  - MAD: multiple ascending dose
  - Food Effect
  - Relative bioavailability

Find new tools for elimination and case management

Discovery programs = New Clinical Entities

New indications for existing drugs = Repurposing Strategy

Supportive Activities



Long-term

AbbVie (anti-*Wolbachia*),
Celgene (lead optimization macrofilaricide)
Filarial Clinical Trial and Research Platform

Medium-term

Repurposing of veterinary:
Emodepside (**Bayer**), oxfendazole
Based on known mode of action:
TylAMac (**AbbVie**)
Fingerprint studies

Short-term

Explore pediatric IVM
Modelling of distribution/morbidity to address the patients needs
Modelling of CT endpoints
Surrogate Biomarker

Thank you

DNDi

Drugs for Neglected Diseases *initiative*