Creative Utilization of Existing Knowledge to Harness Innovation for the Neglected

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Drugs for Neglected Diseases *initiative*

Innovation for neglected diseases

- Neglected diseases have been… neglected
- Science and technology have progressed enormously over the past few decades
- However:
  - Neglected diseases have not benefited from these scientific and technological advances
  - Virtually no new drug discovery for neglected diseases
  - Virtually no new drug development for neglected diseases
- **How to creatively harness existing knowledge to generate innovative treatments for neglected diseases**?

DND*i* Portfolio-Building Model

- New lead compounds
- Existing compounds

Long-term projects

- New uses of existing compounds
- New indications or formulations of existing drugs

Medium-term projects

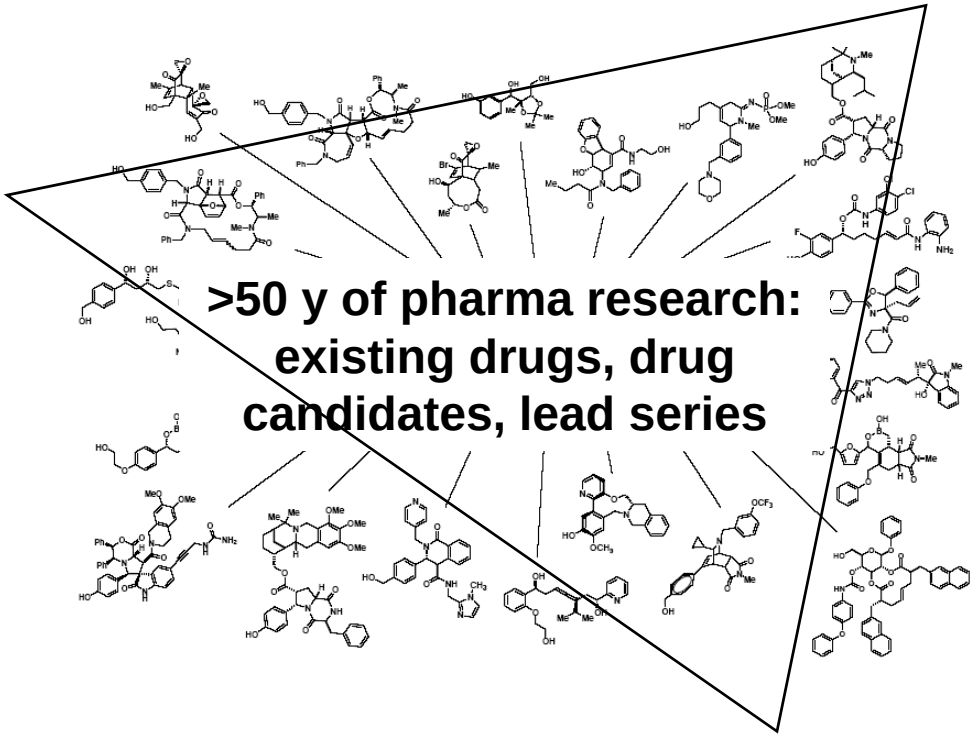
- Completing registration dossier
- Geographical extension

Short-term projects

Mining the existing knowledge base: 3 critical resources

- Existing compounds knowledge
- Disease & parasite knowledge
- People

Mining the existing knowledge base: druggable compounds

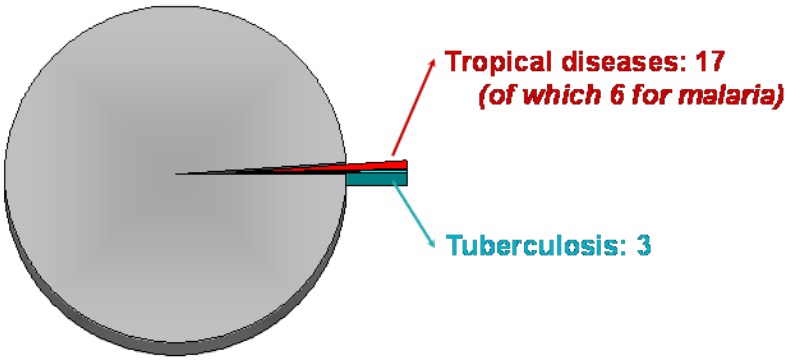


Very few have ever been assessed for activitiy against parasites causing neglected diseases

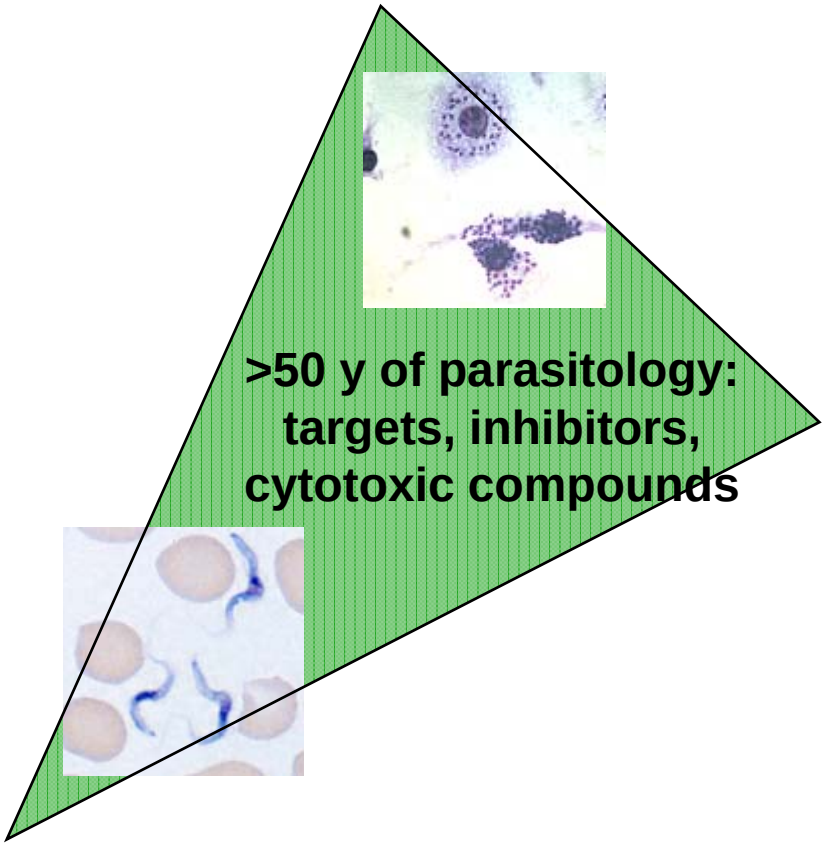
Mining the existing knowledge base: knowing how to kill the parasite

Thousands of publications
Only few new drugs:

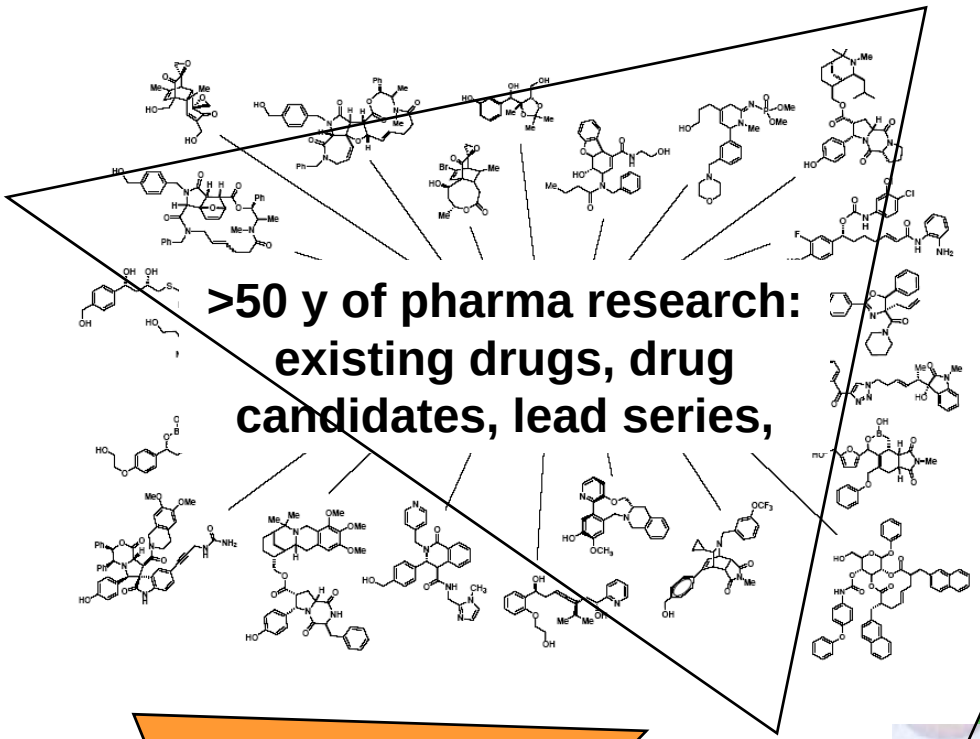
1975-2004: **1556** new chemical entities marketed



Trouiller et al., Lancet 2002, 359:2188-94;
update for 1999-2004: Chirac & Torreele, Lancet 2006 May 12; 1560-1561

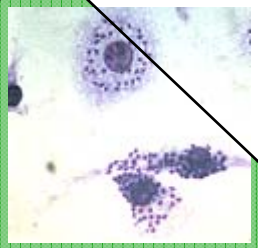


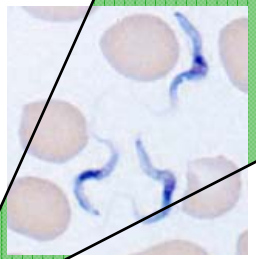
Mining the existing knowledge base: people are key



>50 y of pharma research: existing drugs, drug candidates, lead series,

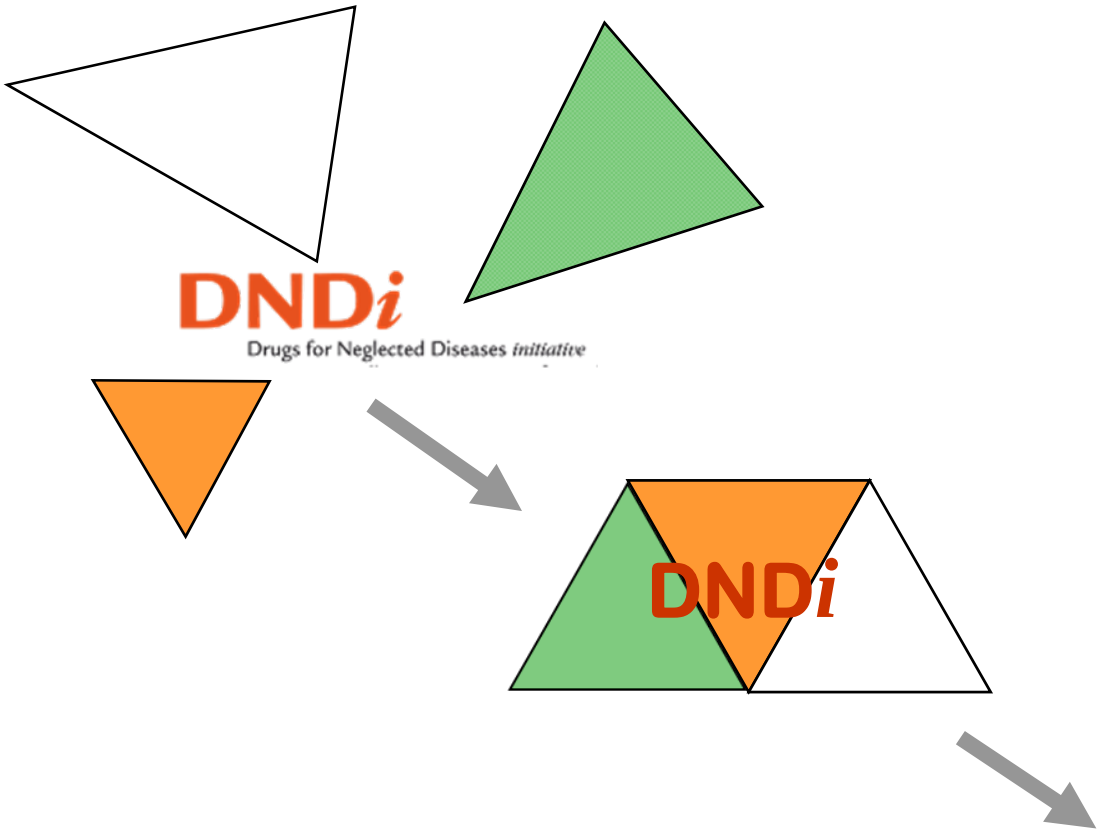
chemists, biologists, pharmacologists, toxicologists, etc committed to DNDi's goals





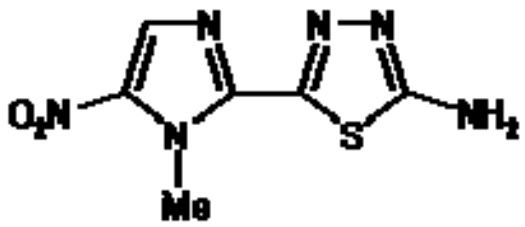
>50 y of parasitology: targets, inhibitors, cytotoxic compounds

Bringing it all together: creative harnessing of fragmented knowledge



The case of the nitroimidazoles

- Megazol:
  - Existing compound (1968) from the nitroimidazole family
  - Shown to have potent oral trypanocidal activity *in vivo*
    - Several publications in 1980s-1990s
  - But toxic (mutagenic)
- Other anti-infective drugs exist in this family: metronidazole, tinidazole, benznidazole,…



Megazol

Can we identify existing compounds with a better activity/toxicity profile?

Creative compound mining

- Extensive literature / patent review, including personal consultations with researchers (previously) active on this class of compounds
  - Personal commitment of various (ex-)researchers worldwide was critical to success
  - Tapping into brains
- Identification of multiple series of existing compounds:

Marketed drugs
Tinidazole, Satranidazole, Nitazoxanide, Nitrofurantoin

Compounds in development for other indications
PA-824, OPC-67683 (anti-TB), NLCQ-1, Doranidazole (radiosens.)

Known trypanocidal preclinical candidates
Ro-15-0216 (Roche), Fexinidazole (Hoechst)

Other molecules

Over 500 nitroimidazoles obtained and assessed as drug leads during 2005-7

Pharma

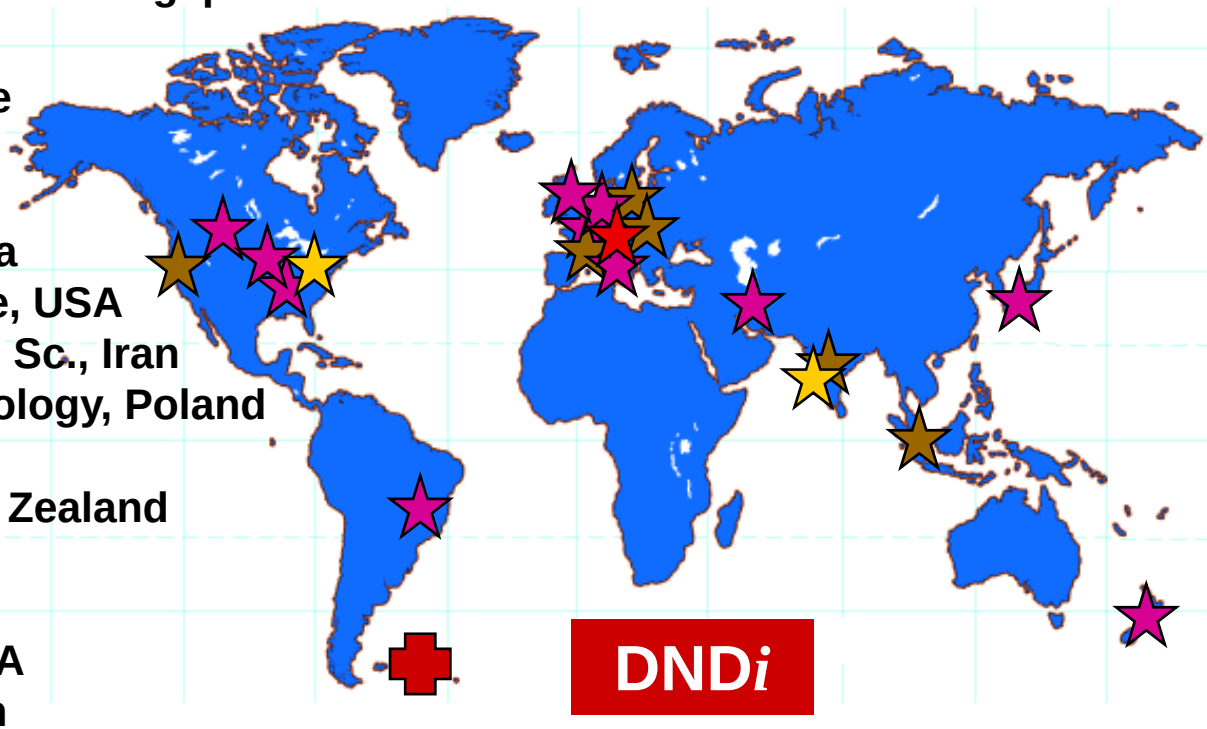
- sanofi-aventis, France - Germany
- Roche, CH
- Novartis (NITD), USA - CH -Singapore
- Alkem, India

Academics

- Swiss Tropical Institute
- Fiocruz, Brazil
- Glasgow Univ, UK
- Univ of Alberta, Canada
- ENH Research Institute, USA
- Tehran Univ of Medical Sc., Iran
- Silesian Univ of Technology, Poland
- LaSpienza Univ, Italy
- Univ of Auckland, New Zealand
- Univ of Dundee, UK
- Univ of Parma, Italy
- Univ of Tennessee, USA
- Tokushima Univ, Japan

other

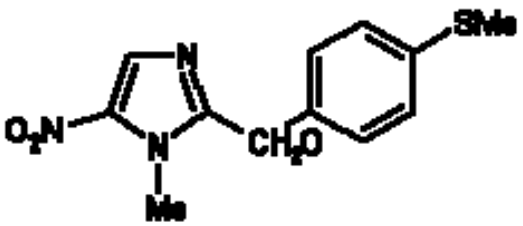
- TB Alliance
- retired pharma chemist , India



Key successes of strategy

- Identification of multiple "druggable" series
- Access to >500 compounds from >15 different sources in academia and industry
- Systematic comparative assessment:
  - Anti-parasitic activity: building on expertise at STI
  - Pharmacology, toxicology: expert consultants + CRO's
- Several promising leads and drug candidates identified and characterised for HAT, Leishmaniasis and/or Chagas disease:
  - **1 drug candidate progressed into preclinical development for HAT: fexinidazole**
  - Several back-up compounds identified for HAT
  - Several lead-compounds under assessment for Leishmaniasis and/or Chagas disease

Rediscovering fexinidazole to bring innovation to the patient



Fexinidazole

- 5-nitroimidazole (ex-Hoechst, 1970s)
- Orally active, passes BBB
- Cures mouse models of acute and chronic HAT
- Excellent safety profile in animal studies

- A promising development candidate for HAT:
  - Oral, short course, affordable
  - Useful for stage 1+2
  - Active on *T.b.gambiense* + *T.b.rhodesiense*
- **June 2008: DNDi decision to progress towards First-in-Human phase I trials (to start early 2009)**

Harnessing adequate expertise to progress fexinidazole into clinical development

DNDi project team

- **Els Torreele**: DNDi project manager
- **Michael Bray**: pharmaceutical project management consultant
- **Bernadette Bourdin**: chemistry project support & documentation
- **Guy Mazué**: toxicology, preclinical development
- **Jean-René Kiechel**: CMC, formulation, pharmacology
- **Pierre-Etienne Bost**: chemistry, preclinical development
- **David Tweats**: toxicology, in particular genetic toxicology
- **Daniela Sassella**: clinical development
- **François Chappuis**: clinical HAT expert
- Additional expert consultants:
  - **Matthias Dormeyer**: regulatory advise, IMPD
  - **Eloan Pinheiro**: formulation and manufacture
  - **Christian Burri**, **Gabriele Pohlig**: HAT clinical trials experts

Operational partners

- **Main preclinical package**
  - **Accelera** (ex Nerviano Medical Sciences), Italy: preclinical formulation, regulatory toxicology, safety pharmacology, pharmacokinetics
  - **Covance**, UK: genotoxicology
- **Disease models**
  - **STI**, Swiss Tropical Institute, Switzerland: mouse models
  - **TRC**, Trypanosomiasis Research Centre, Kenya: monkey model
- **CMC**
  - **Axyntis** (ex Orgasynth), France: chemistry, GMP-production
  - **Aptuit**, UK: clinical formulation development

Conclusion

- Creative compound mining into well-known compound classes *can* bring innovation for the patient
  - Most of the compounds were never tested
  - A wealth of untapped knowledge may be out there
- It requires major efforts:
  - Systematic mining of the (patent) literature (not only recent)
  - Personal follow up with researchers to gather unpublished knowledge
  - Access to and systematic testing of the compounds
  - Bringing the fragmented knowledge together
- This strategy allows for a significant acceleration of the development process in response to the urgent needs of long neglected patients

PANEL DISCUSSION: Experiences from Different Sectors in Critical Factors for Success

- **Cy Bacchi, PhD**

Research Professor, Pace University, USA

- **Chris Hentschel, PhD**

President & CEO, Medicines for Malaria Venture (MMV), Switzerland

- **Mel Spigelman, PhD**

Director, R&D, Global Alliance for TB Drug Development (TB Alliance)

- **Alan Magill, MD, FACP**

Director of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR), USA