



SYMPOSIUM



BIODIVERSITE / SUBSTANCES NATURELLES

Université des Sciences - MADAGASCAR

13-15 OCTOBRE 2009

BIOMAD 2009



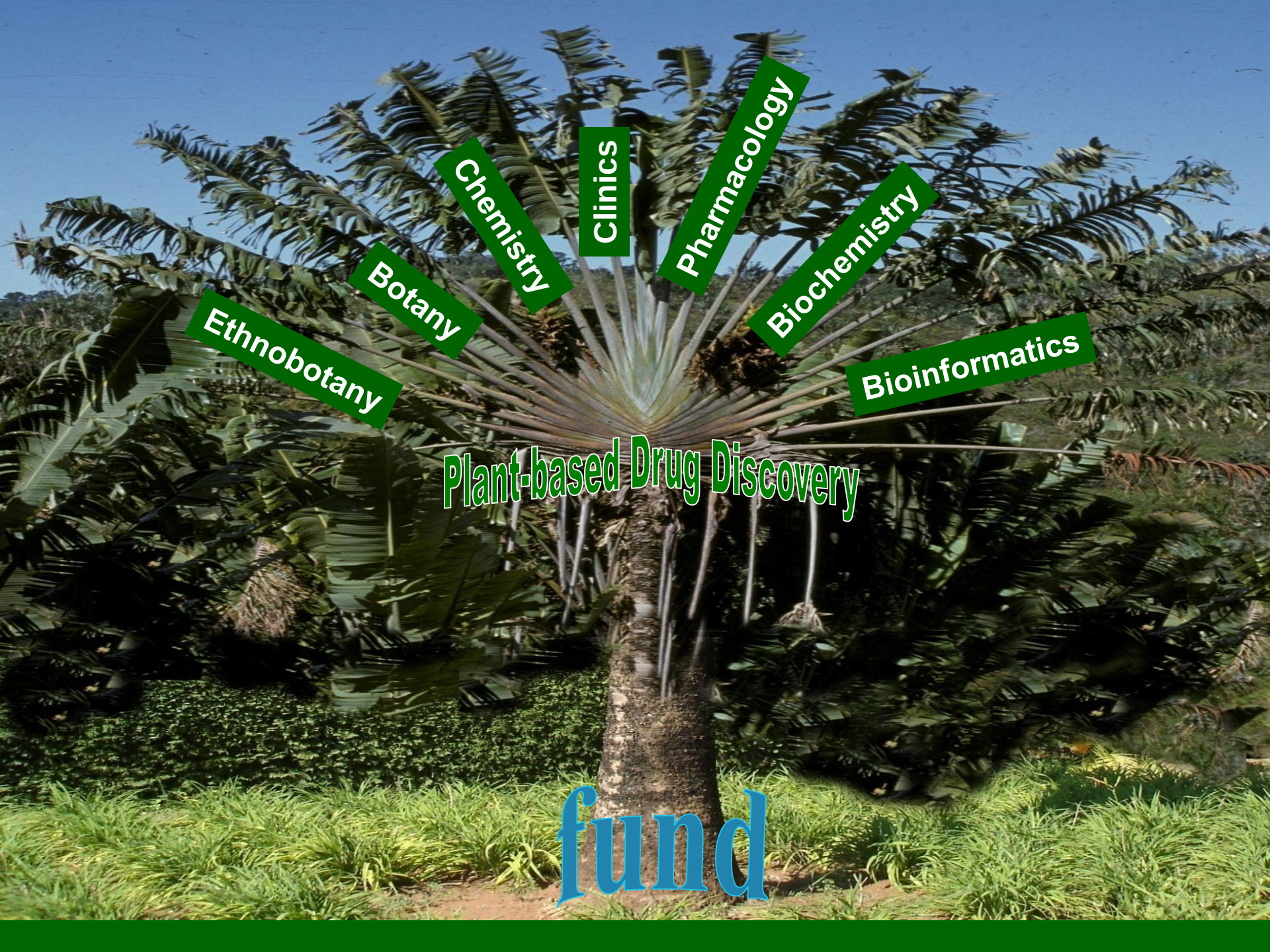
*Analyse et valorisation des substances naturelles
Chimie écologique, Chimie verte, Ecologie chimique
Législation, Brevets, Propriété intellectuelle...*

THEMIS



LESSONS LEARNED FROM PLANT-BASED DRUG DISCOVERY

Philippe Rasoanaivo



Ethnobotany

Botany

Chemistry

Clinics

Pharmacology

Biochemistry

Bioinformatics

Plant-based Drug Discovery

fund

A wide-angle photograph of a dirt road in Madagascar, lined with tall baobab trees. The trees have thick, greyish-brown trunks and sparse, leafless branches. The road is sandy and shows tire tracks. In the distance, a small cart with people is visible on the road. The sky is blue with some white clouds. Several scientific fields are labeled vertically on the trunks of the trees.

Ethnobotany

Bioinformatics

Clinics

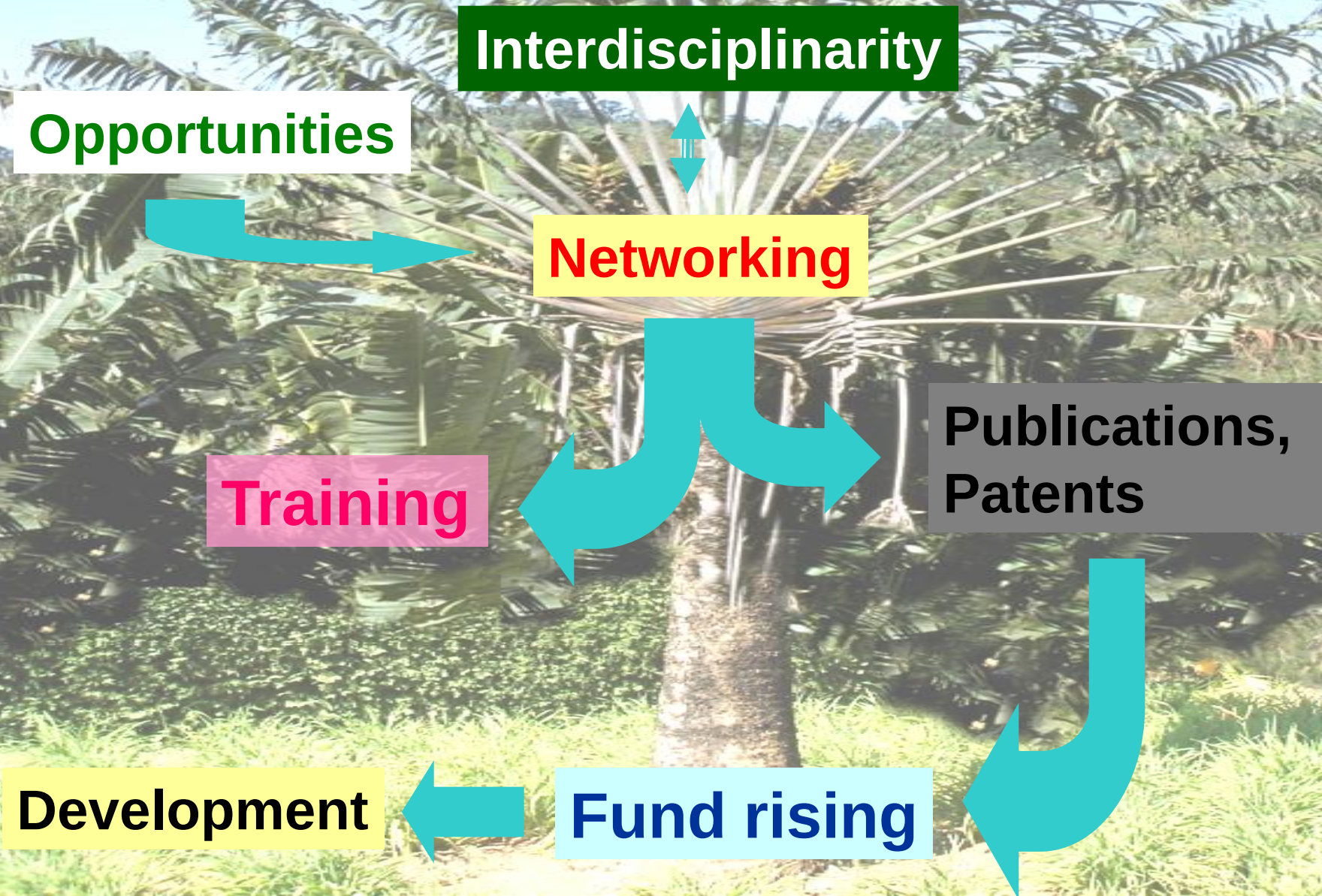
Biochemistry

Chemistry

Botany

Pharmacology

One Strategy for a successful drug discovery



Target diseases for drug discovery

At the Laboratoire de Biothérapeutique

Institut Malgache de Recherches Appliquées

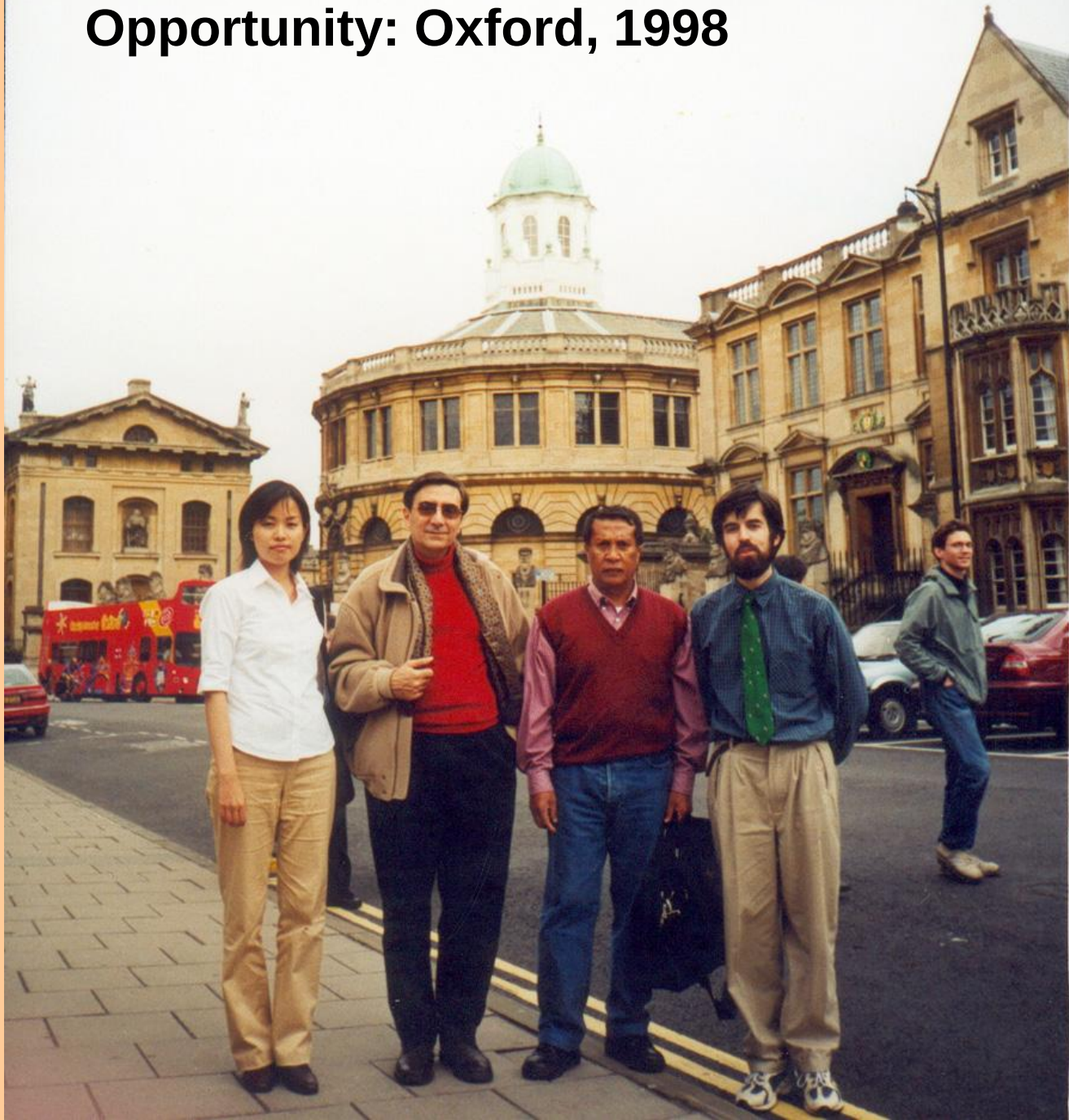
► Tropical diseases

- Malaria;
- Chikungunya.

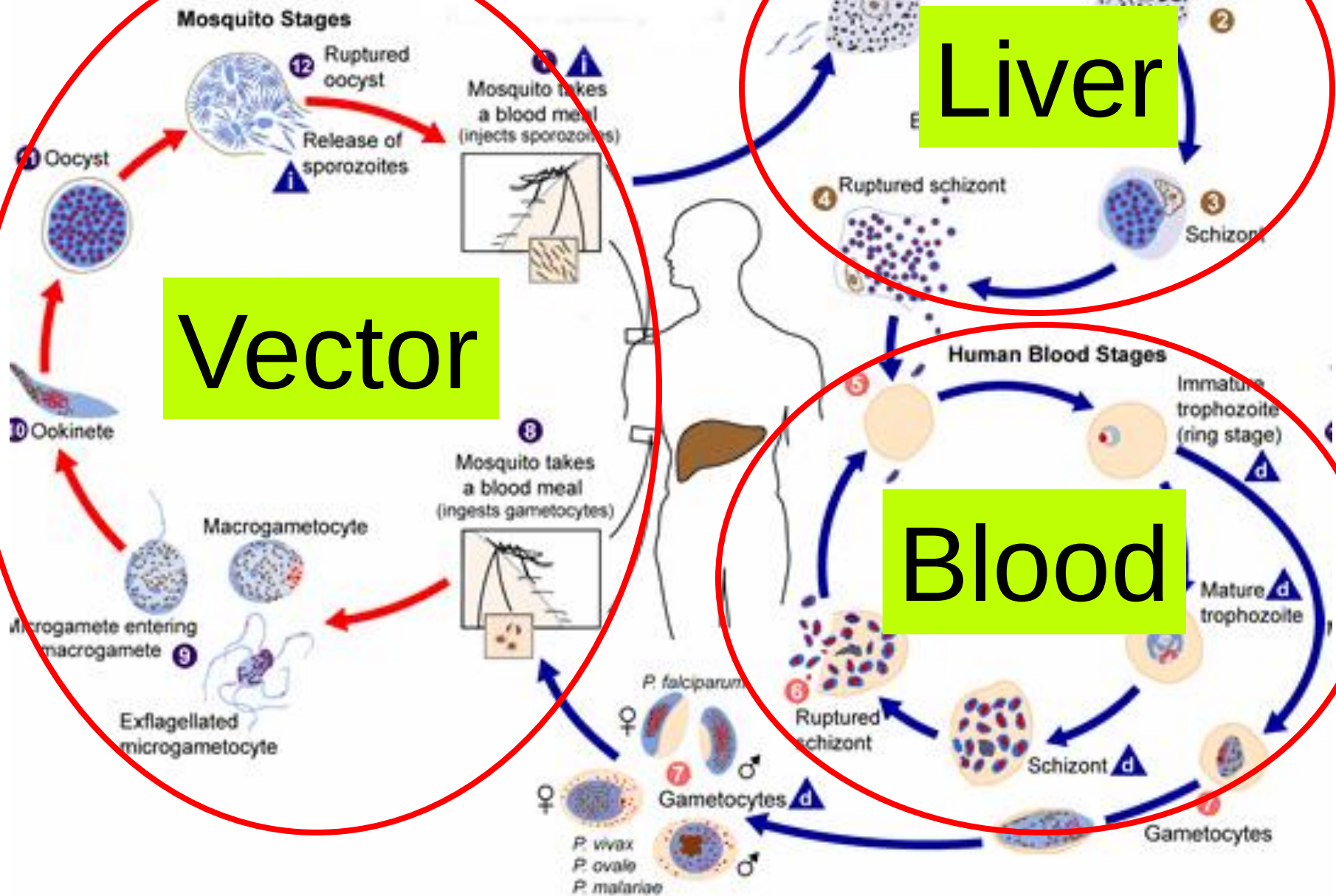
► Diseases of aging

- Memory and cognitive impairment;
- Diabetes of aging;
- Erectile and libido dysfunction.

Opportunity: Oxford, 1998



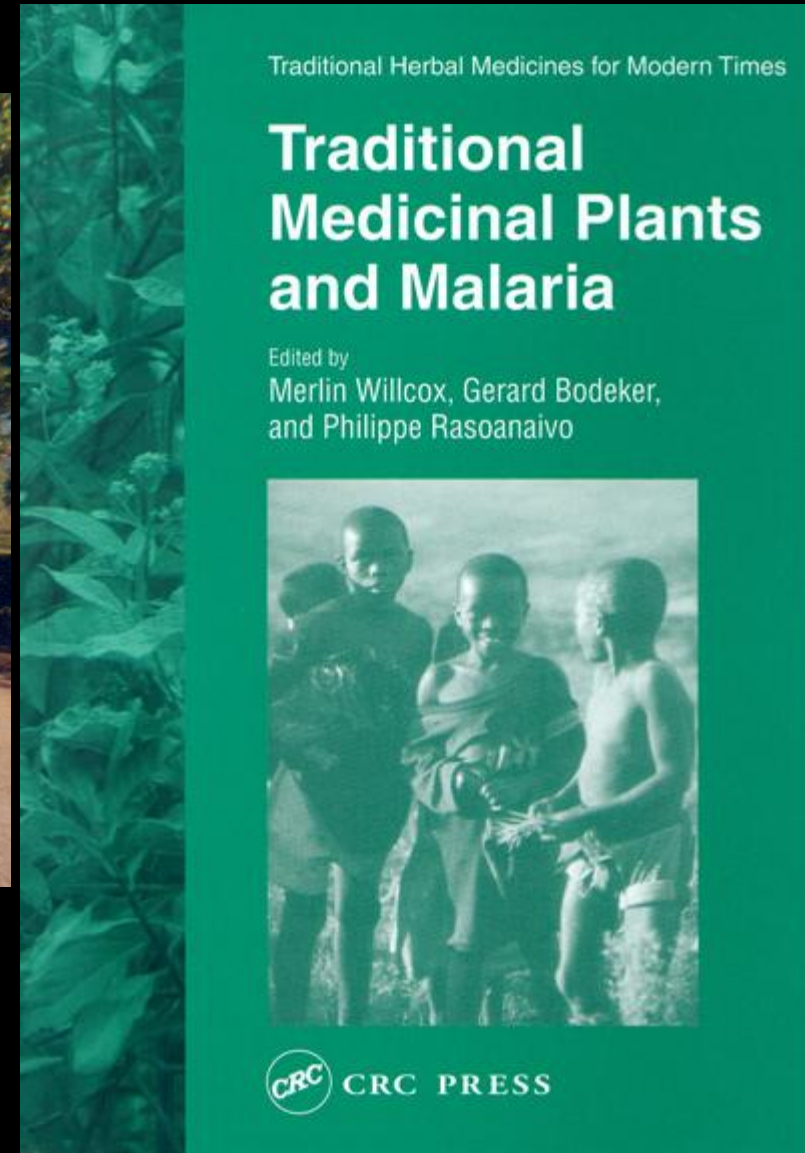
Schema of malaria life cycle



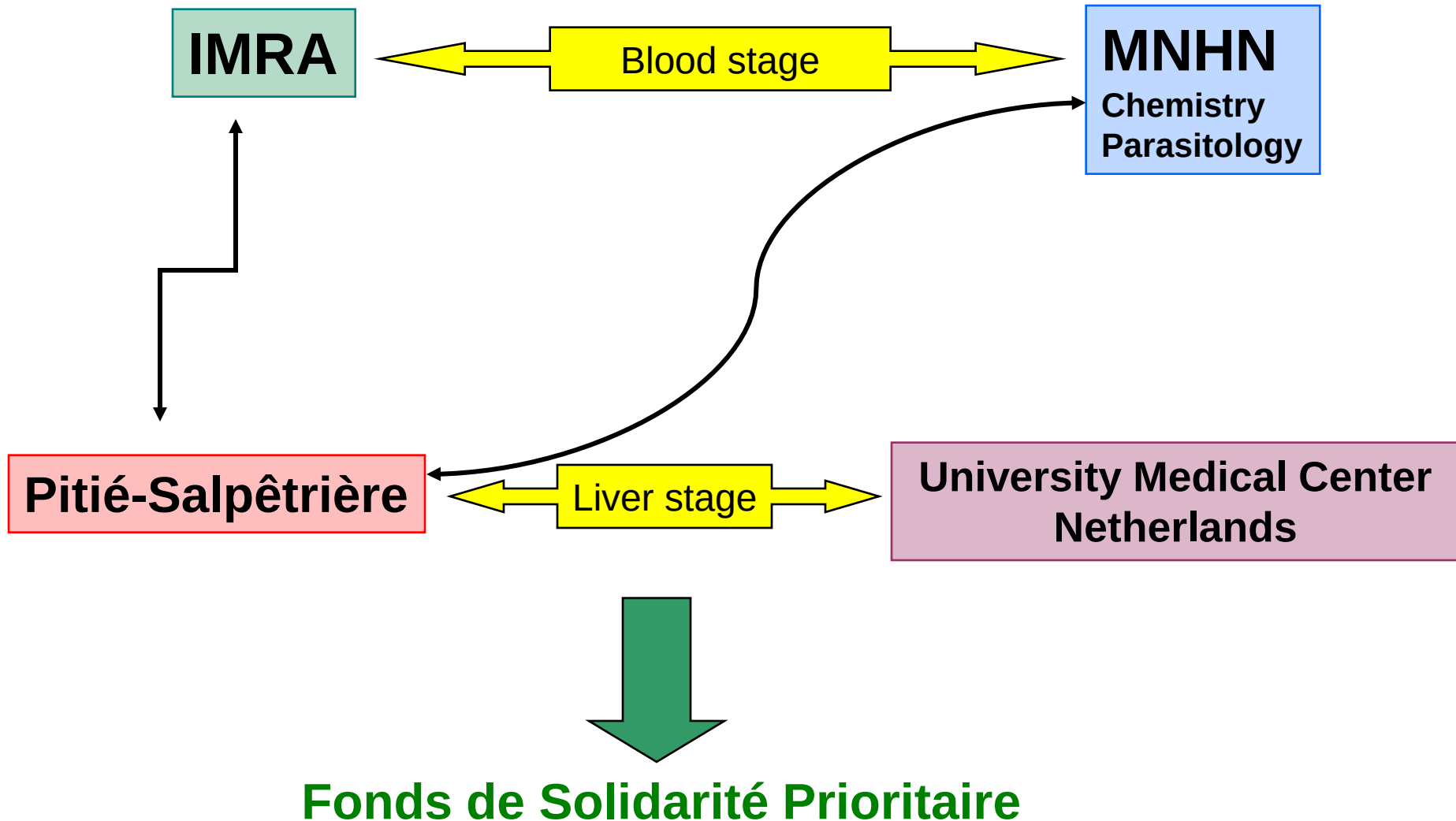
Moshi, December 1999: Birth of RITAM



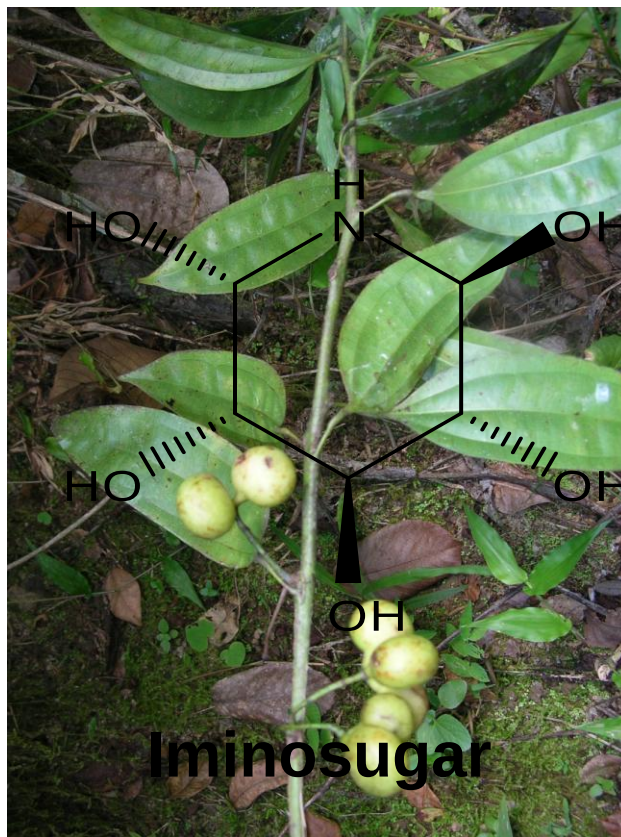
**Research Initiative on
Traditional Antimalarial Methods**



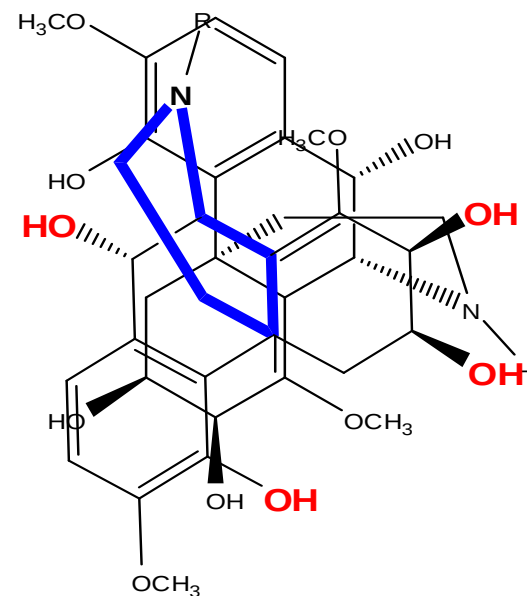
Networking; Fund rising



From traditional knowledge to patent



Strychnopsis thouarsii



Tazopsine



ANR

Obituary: the Malagasy forester Abrahama, *J. Ethnopharmacol.* 1999, 68, 1-2.

- **PCT Patent WO 2005/103009 A1, 3 November 2005.**
- M. Carraz et al. (2006) *PLoS Medicine*, 3, 2392.
- M. Carraz et al. (2008) *Bioorg. Med. Chem.* 16, 6186.



Grandes Avancées Françaises en Biologie



Pascale Cossart of the Academy of Sciences, Organiser of the “*Grandes Avancées Françaises en Biologie 2007*”, together the three young Prize winners: Christelle Durand (left), Maelle Carraz and Cécile Frolet (right).

Cultivation of *Artemisia annua*

A project which failed!

- ▶ Leadership conflicts,
- ▶ Lack of communication and transparency,
- ▶ Fear of competition,
- ▶ Useless meetings without follow-up.

**FADES project:
Antimalarial, toxic and fortifying plants**



FADES team



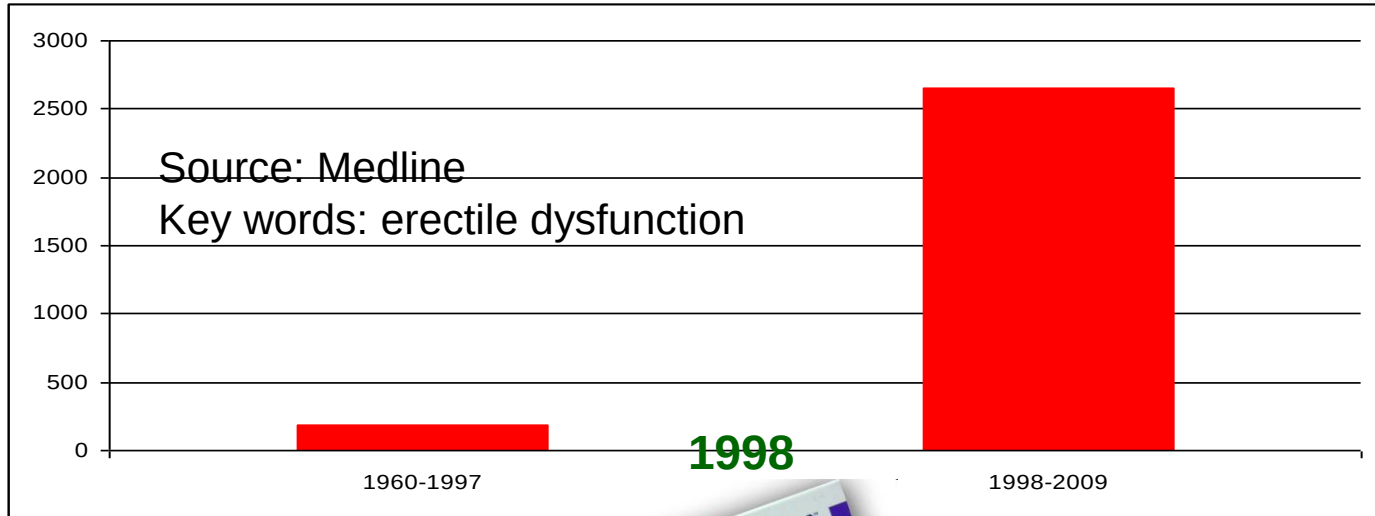
Neobeguea mahafalensis

Opportunity: Bloomfontein, South Africa, 2004

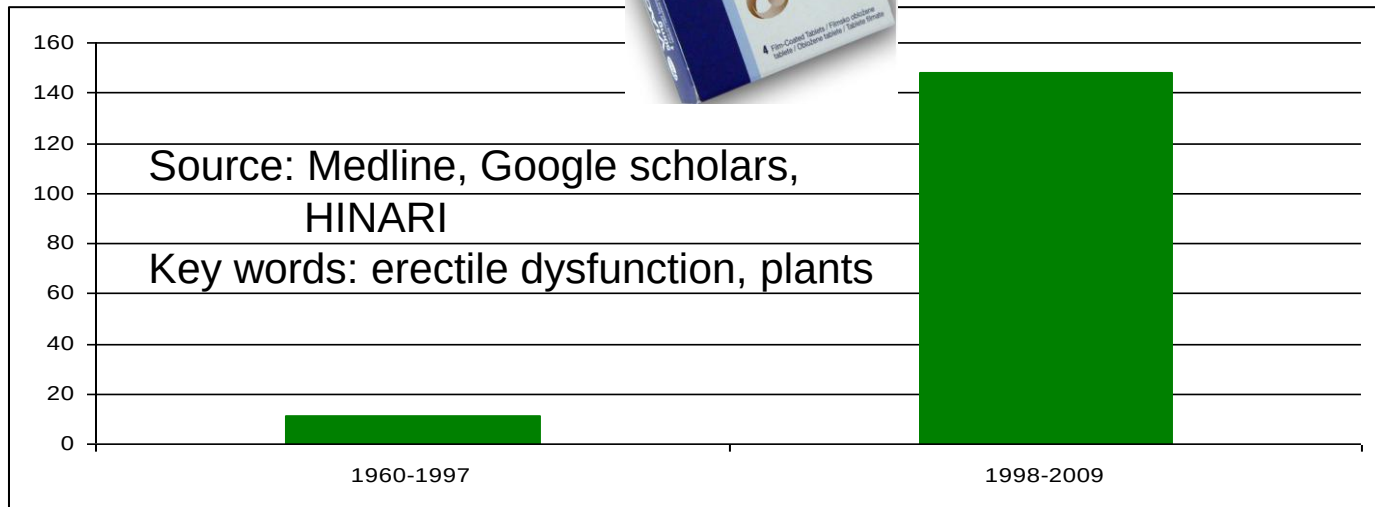


Breakthrough in ED research after 1998

Number of publications



1998



Years



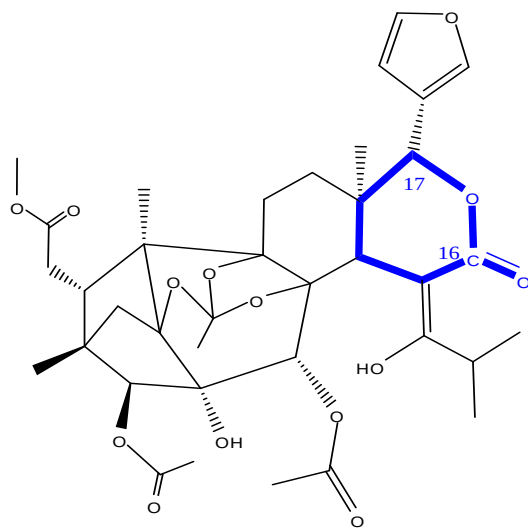
Treatment of back pains

Claimed to restore erectile function
in old men

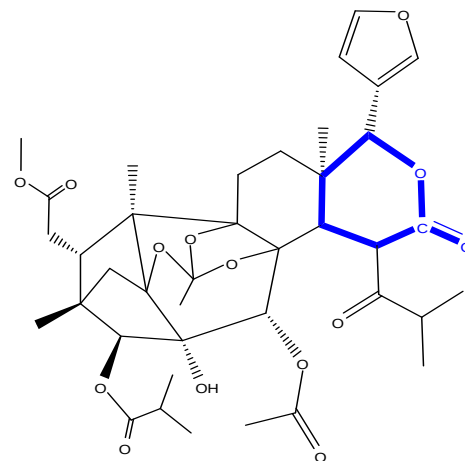
Long-lasting effects in the treatment
of erectile dysfunction



Previous work



Neobeguina



Pseudrelone

- ▶ D. A. Mulholland, D. A. H. Taylor, *Phytochemistry* **1988**, 27, 1741.
- ▶ M. Randrianarivelojosia, M. P. Kothos, D. A. Mulholland, *Phytochemistry* **1999**; 52, 1141.
- ▶ D. Naidoo, D. A. Mulholland, M. Randrianarivelojosia, P. H. Coombes, *Biochemical Systematics and Ecology* **2003**, 31, 1047.

**Karl R.
Popper**

**La logique
de la découverte
scientifique**

Payot

“Discovery consists of seeing
what everyone has seen and
thinking what nobody has thought”

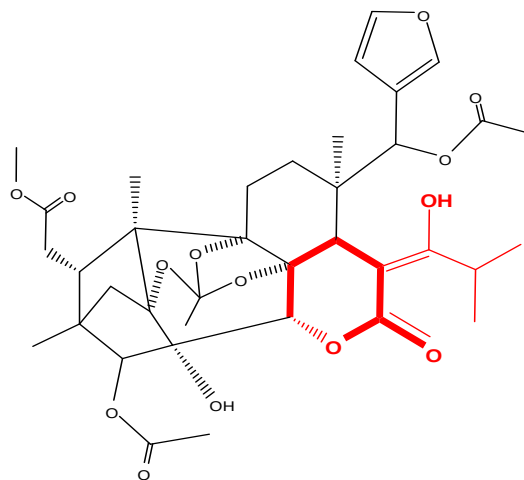
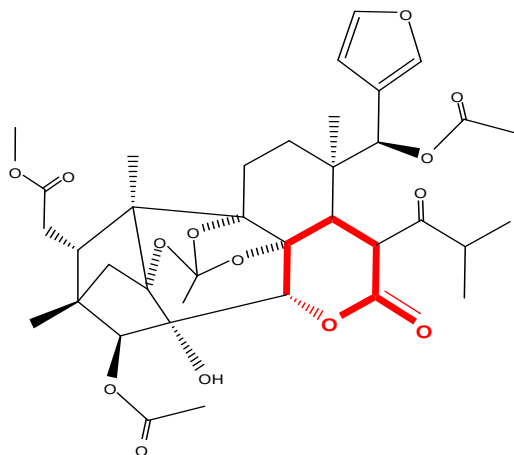
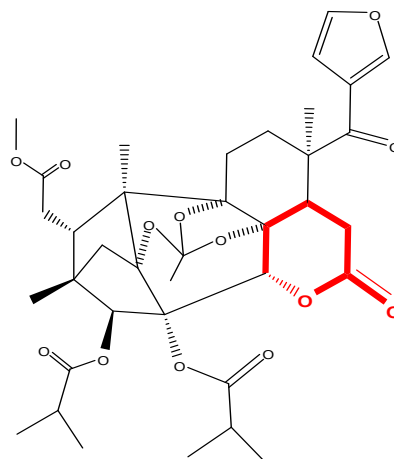
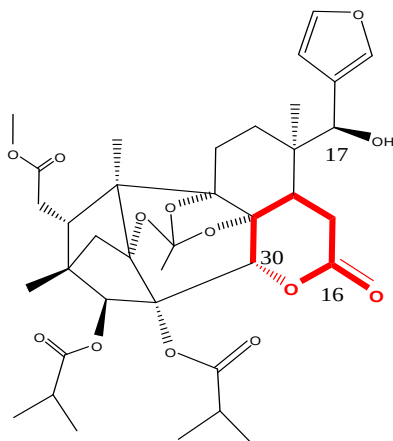
L. Pauling

« La compétition la plus intéressante n'est pas
de suivre la meute et d'essayer de grappiller
avec tout le monde. C'est avoir soi-même l'idée,
alors que les autres n'en ont pas, et puis
de faire tout ce qu'il faut pour arriver tout seul”.

P. Potier



Discovering novelty; Patenting



J.E. S. Wikberg, P. Rasoanaivo, S. A. Razafimahefa, B. Rasolondratovo.
PCT Patent WO 2008/145996 A2, 4 December 2008, **245 pages**.

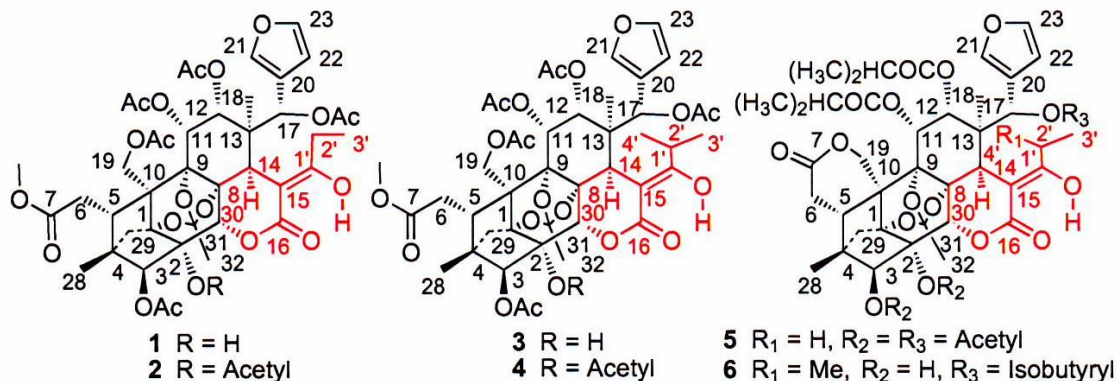
Inventors



1. Introduction

Phragmalins are a type of rings B,D-*seco* limonoids with characteristic A and B-rings of tricycle [3.3.1^{2,10}.1⁴]decane or tricycle [4.2.1^{10,30}.1⁴]decane (rearranged phragmalin), most of which exhibit insect antifeeding activity.¹ They have been discovered only from the genera of Meliaceae, such as *Chukrasia*,^{1b,2}

derivatives bearing exclusively a 1,8,9-*ortho*-acetate and C-16/17 δ -lactone ring have been reported,^{2a,7} which were suggested to be produced by acyl transfer from a C-30 ester.^{1a} In our investigation on the chemical constituents of *Chukrasia tabularis* var. *velutina*, a variety of *Chukrasia tabularis* A. Juss. growing mainly in tropical areas of Asia such as India and southern China,^{2e,8} six new C-15-acyl phragmalin derivatives, Chukvelutilides

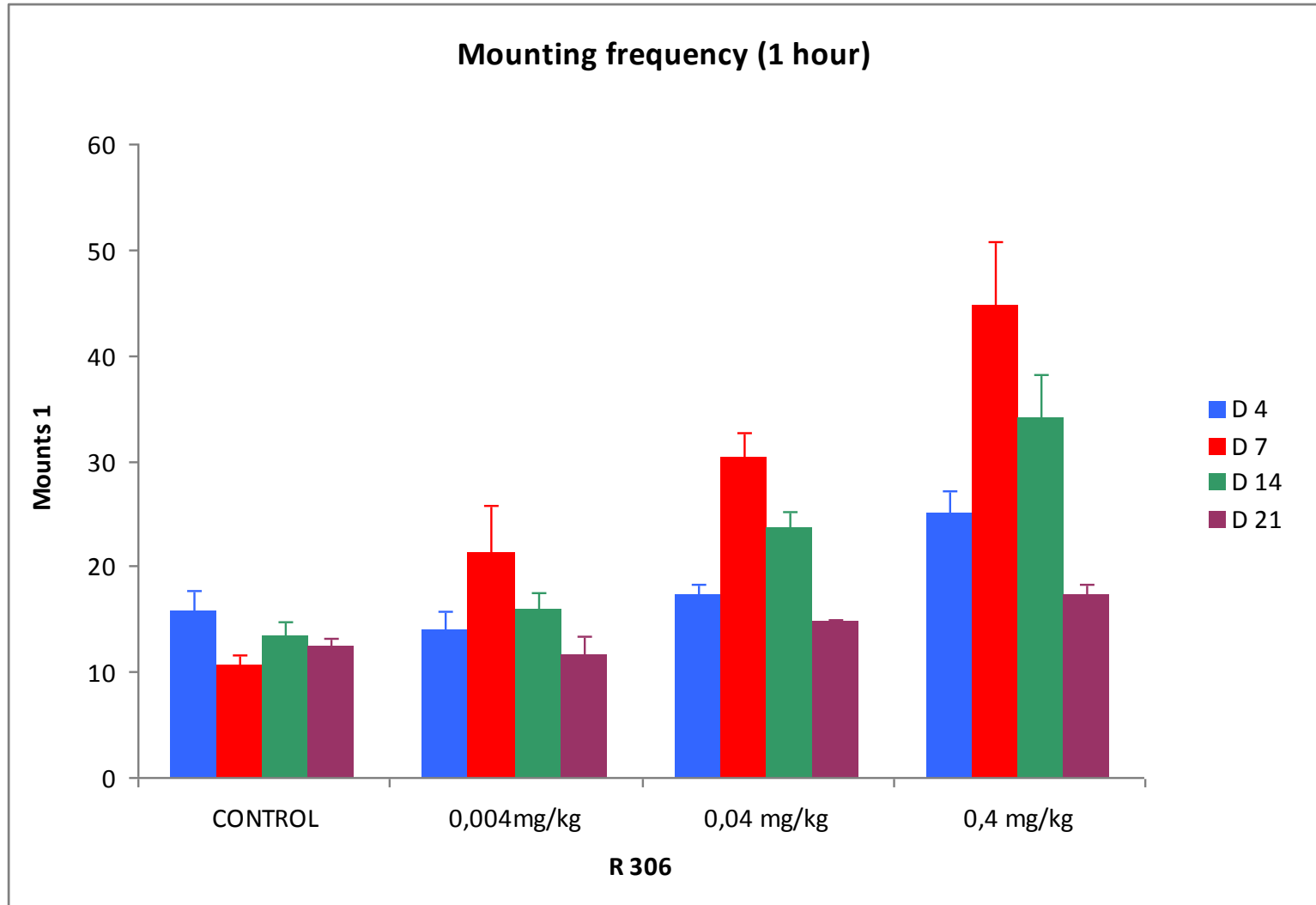


Khaya,³ *Xylocarpus*,⁴ and *Swietenia*.⁵ Most of them bear *ortho*-ester group at positions 1,8,9 or 8,9,14 or 8,9,30 or 8,9,11, and C-16/17 δ -lactone ring (ring D), which was in few cases cleaved, producing C-16/C-17 δ -lactone-*seco* compounds and C-16/C-8 γ -lactone.^{1a,2d,4b,5b,6} Among them, nineteen C-15-acyl phragmalin

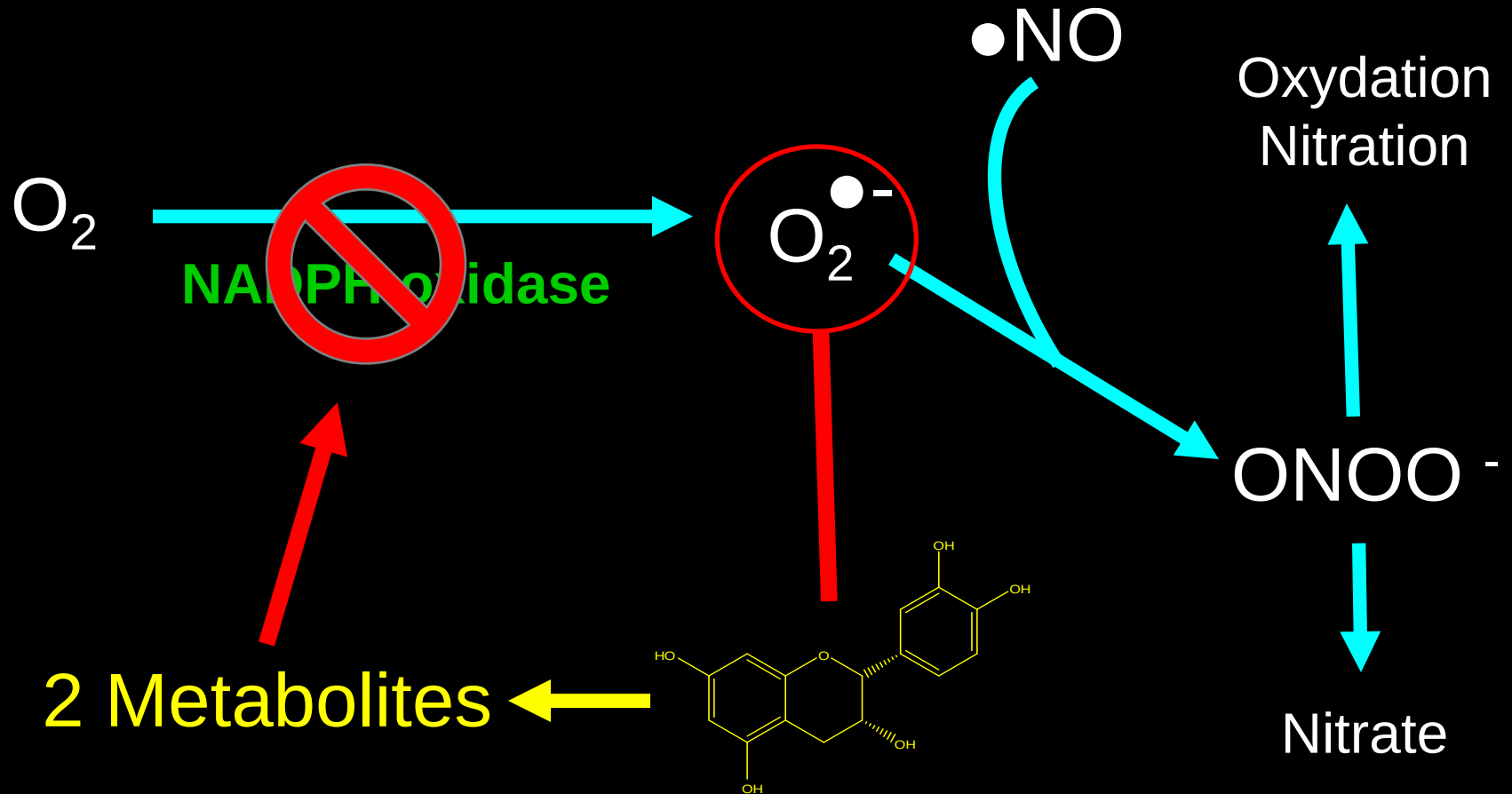
A-F (1-6), were isolated from the air-dried stem barks of this plant collected in Xishuangbanna, Yunnan Province, China. These novel compounds possess an unprecedented C-16/C-30 δ -lactone ring, a biosynthetically extended three- or four-carbon enolized acyl substituent at C-15, and 1,8,9-*ortho*-acetate group. They are the first examples of C-15-acyl phragmalins with C-16/C-30 δ -lactone ring. We report herein the isolation and structural elucidation of these compounds.

* Corresponding author. Tel.: +86 25 8539 1289; fax: +86 25 8530 1528.
E-mail address: lykong@jlonline.com (L.-Y. Kong).

Delayed and long-lasting effects of one limonoid (compilation of several tests)

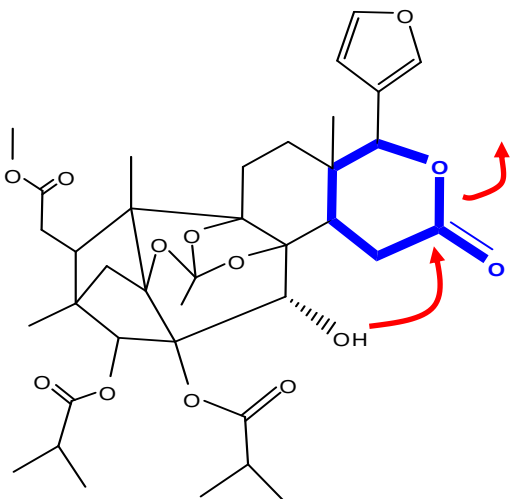


Bioactive constituents (continued): Phenolics in the acetone extract



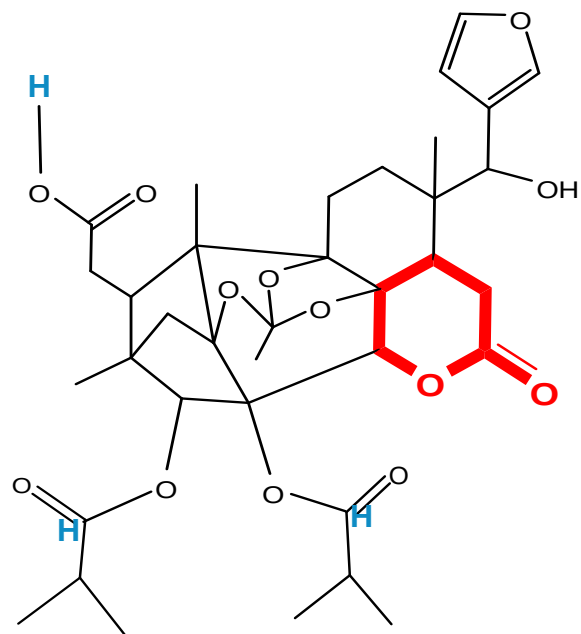
Y. Steffen et al. (2007) Epicatechin elevates NO in endothelial cells via inhibition of NADPH oxidase. *Biochem. Biophys. Res. Com.*, 359, 828-833.

Supply: semisynthesis

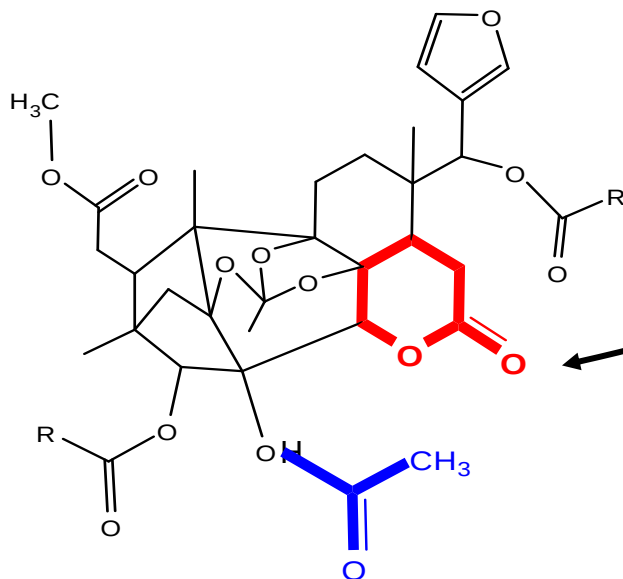


Common structure
With C-16/17 δ -lactone

Trans-esterification



Novel structure
With C-16/30 δ -lactone



Priority applications 8- 9

Metabolites from endophytic fungi & mycorrhizas



Evolving feature of networking



LaCASN, 2009

The road forward

Plant

**Standardised
extract**

**Bioactive
compounds**

Commercialisation

Dangitsyl®

“Waiting for royalties is not going to help. The timescale is too long. You have to train people, create jobs.”

Phyllis Coley

Fund rising

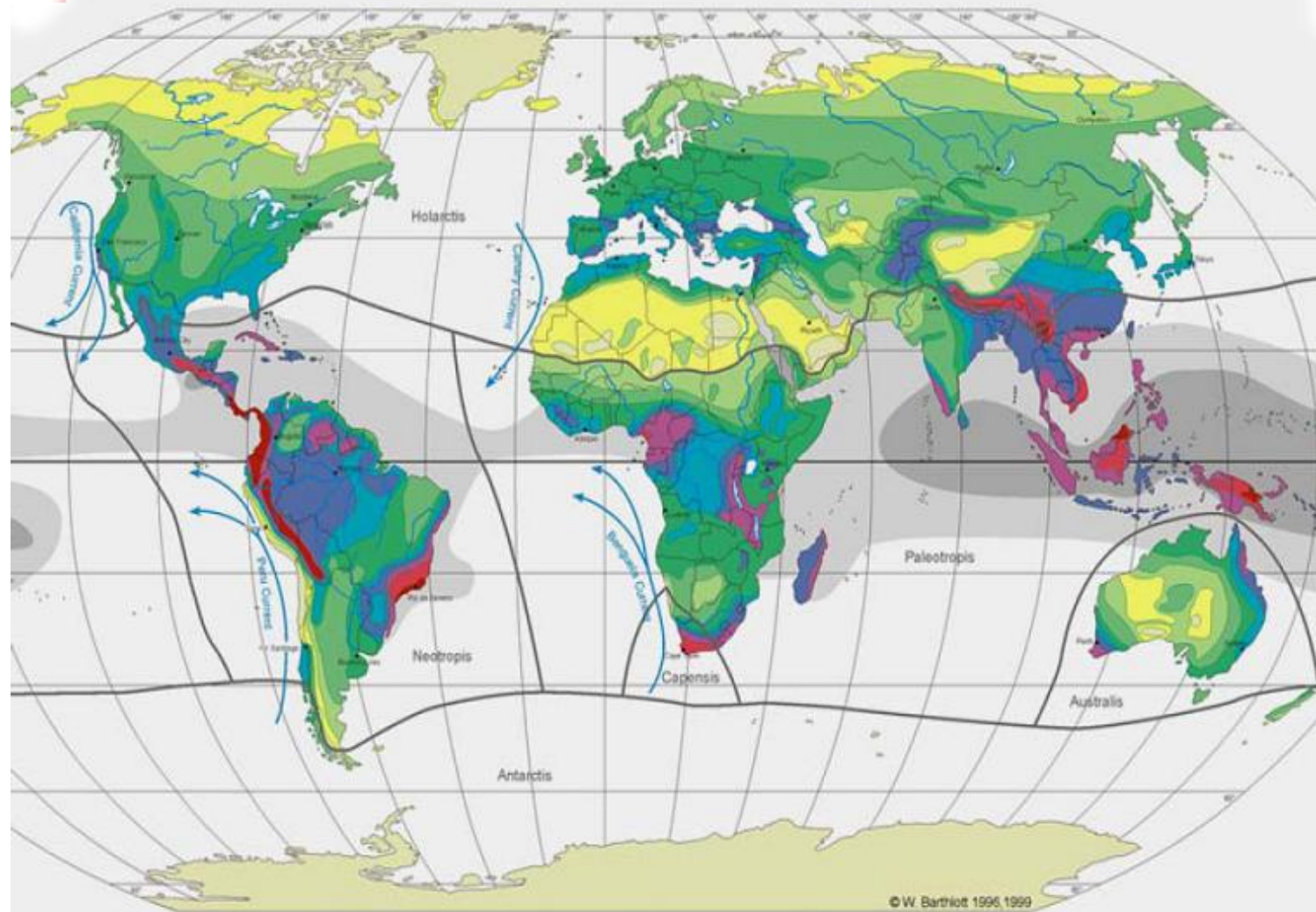
Fund raised to cover patent costs: 140.000 US\$

TWAS, IPICS projects submitted

High quality publications

Drug development

GLOBAL BIODIVERSITY: SPECIES NUMBERS OF VASCULAR PLANTS



Diversity Zones (DZ): Number of species per 10 000km²



sea surface temperature



cold currents

W Barthlott, N Biedinger, G. Braun, F. Fei
W Lauer & J. Mücke 1999
modified after
W Barthlott, W Lauer & A. Placke 1996
Department of Botany and Geography
University of Bonn
German Aerospace Research Establishment
Cartography: M. Gref
Department of Geography University of Bo

Vascular plant diversity on Earth, number of species

Bioprospecting: a tool for networking and fund rising

University of Antananarivo;
IMRA

Bioprospecting

Institut de Chimie
des Substances Naturelles

Extract library

Belgium France
**PHYTOCHIK
(CRVOI)**
Mauritius Madagascar
La Réunion

★ ★ ★ ★ ★
**AGROCOS
(EU FP7)**
★ ★

**IRNA – CHIR
(ANR)**





PHYTOCHIK consortium

La Réunion, 13 October 2009





Writing scientific projects

April 2009, Antananarivo



SUBLINE EST LA SCIENCE

ANALYSES MEDICALES



Favouring participation of young scientists in international meetings

Cape Town (South Africa), October 2008





**Favouring participation of young scientists
in international meetings
Kano (Nigeria), August 2009**

**Intellectual property rights, equitable benefit sharing,
Access to genetic resources**

**PLANTS, PEOPLE AND NATURE
Benefit Sharing in Practice**

Edited by L. Denzil Phillips

Published by: Plantaphile Ltd

Pages: 196 + 32 pages of colour inserts

Conclusion



Avoid conflicting situations

Chemistry

Pharmacology

Think positively

↑
“Pêcher dans un endroit
où il y a du poisson”

Ethno-botany
Eco-botany

Thank you for your attention