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**AE2BM** Association des Enseignants de Biochimie et Biologie Moléculaire des Facultés de Pharmacie

**ANTICORPS THÉRAPEUTIQUES : UNE NOUVELLE CLASSE D'HYPOLIPÉMIANTS ?**

**15 | 16** 2016  
SEPTEMBRE

Muséum national d'Histoire naturelle  
Auditorium de la Grande Galerie de l'Évolution

## LES PHARMACIENS AU MUSEUM

**Joseph SCHREVEL**




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## Evolution des deux établissements

### Museum National Histoire Naturelle

- 1635 Le Jardin royal des Plantes médicinales est créé par Guy de La Brosse
- 1718 Jardin royal des Plantes
- 1735 Académie royale des Sciences envoie une expédition scientifique dirigée par le géographe Charles Marie de la Condamine en Amérique du Sud , avec Joseph de Jussieu comme médecin-naturaliste
- 1735-37 Collecte de nombreux spécimens de quinquinas par Joseph de Jussieu et propose «la meilleure manière d' extraire le suc »
- 1737 Retour de Charles Marie de la Condamine et présentation à son nom(!) des notes de Joseph de Jussieu à l' Ecole royale des Sciences. De son côté Joseph de Jussieu restera 36 ans au Pérou et l' Equateur ramenant de nombreuses collections.
- 1753 Linné crée le genre *Cinchona* pour les quinquinas avec *C. officinalis* (boissons aromatiques) et *C. succirubra* (quinquina rouge pour la quinine)
- 1793 Décret de la Convention du 10 juin: création du Museum National Histoire Naturelle (12 chaires)
- 1994 Suppression des chaires (26)et recrutement de type universités (liste d' habilitation aussi pour le CNU 41eme section)

### Faculté de Pharmacie

- XVII ème Jardin des Apothicaires, faubourg Saint Marcel , regroupe l' Ecole de Pharmacie de Paris et la Société de Pharmacie de Paris
- 1777 déclaration royale du 25 avril avec la création du Collège de Pharmacie
- 1803 Décret du 15 vendémiaire an XII (8 octobre 1803) avec la création de l' Ecole de Pharmacie de Paris
- Nicolas Vauquelin , chimiste et pharmacien exceptionnel, Professeur au Collège de France (1801), directeur de l' Ecole de Pharmacie de Paris (1803), titulaire de chaire au Muséum (1804), Professeur de Médecine (1812) , formera de nombreux élèves dont Pelletier ,Caventou, Chevreul...
- 1820 Faculté de Pharmacie
- 1820 Isolation de la quinine par Pierre Joseph Pelletier (1795-1842) et Joseph Bienaimé Caventou (1795-1877) dans leurs ateliers. A partir de 138 tonnes d' écorce de quinquina ils en extraient 1 800 kilos de sulfate de quinine.
- 1882 Transfert avenue de l' Observatoire
- 1984 Suppression de l' Agrégation de Pharmacie

Découverte de la quinine 1620 → 1737 → 1820



Les frères de Jussieu



*Cinchona officinalis*



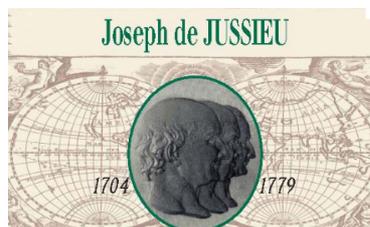
Pierre Joseph Pelletier  
1795-1842



Joseph Bienaimé Caventou  
1795-1877



1846 Joseph Dubonnet, chimiste élabore son vin de quiquina

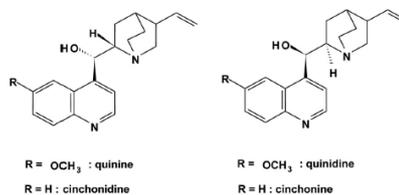


La poudre d' écorce de quinquina des indigènes a guéri un missionnaire jésuite du paludisme (1620) puis la « Poudre des jésuites » a été introduite en Europe ( Louis XIV,1649..) 1737 Description des quinquinas de la région de Loja (Equateur) par Joseph de Jussieu



Ecorce de *Cinchona officinalis*

1820 Isolation de la quinine



Structure moléculaire de quelques alcaloïdes du quinquina

2001 Synthèse totale de la quinine Stork G. et al JACS 123,3329-42

PIERRE POTIER, MÉDAILLE D'OR DU CNRS 1998

Né le 22 août 1934 à Bois-Colombes  
1957 Pharmacien  
1960 Docteur d'Etat ès-sciences physiques

CARRIÈRE

- 1971 Directeur de recherche au CNRS
- 1978 - 1984 Directeur du Programme interdisciplinaire de recherche sur les bases scientifiques du médicament (PIRMED)
- 1984 - 1989 Directeur du laboratoire mixte CNRS/Roussel-Uclaf
- 1990 - 1991 Professeur au Muséum national d'histoire naturelle, Chaire de Chimie
- 1994 - 1998 Directeur général de la Recherche et de la Technologie au Ministère de l'Éducation nationale, de l'Enseignement supérieur et de la Recherche (MENESR)
  - Co-directeur de l'Institut de chimie des substances naturelles (ICSN) à Gif-sur-Yvette (1974) et Directeur depuis 1989
  - «Visiting-Professor» à l'Université Strathclyde - Glasgow, Grande-Bretagne (1984 - 1990)
  - Docteur *Honoris Causa* de l'Université de Glasgow et de l'Université de Regensburg (1995)
  - Fondateur avec Y. Ban et co-Président de la Société franco-japonaise de chimie fine et thérapeutique et fondateur avec E. J. Corey de la Société franco-américaine de chimie
  - Membre de l'Académie des Sciences (depuis 1988)
  - Membre du Comité des applications de l'Académie des Sciences (CADAS), de l'Académie nationale de Pharmacie (1984), du Conseil d'administration de la Société française de Chimie, du Conseil d'administration de l'Institut de biologie physico-chimique (Fondation Edmond de Rothschild), du Conseil d'administration du Muséum national d'histoire naturelle, de l'Academia Europea, de l'Académie finlandaise de Science et Lettres, de l'Académie serbe des Sciences et Arts (1997), membre d'honneur de l'Académie nationale de chirurgie dentaire et membre correspondant de la Bayerische Akademie der Wissenschaften
  - Membre consultant de l'UNESCO, de l'Organisation européenne de recherche et de traitement du cancer (EORTC), du Conseil de l'Institut de cancérologie et d'immunogénétique (ICIG) et du Service des maladies sanguines et tumorales à Villejuif
  - Membre du Comité éditorial de plusieurs journaux scientifiques internationaux, du Comité de rédaction de *La Vie des Sciences*, du Comité de parrainage du Bulletin de la Société chimique de France

ŒUVRES

- Plusieurs dizaines de brevets et plus de 400 publications, parmi lesquelles :
- Modification de la réaction de Polonovski. Action de l'anhydride trifluoroacétique sur un aminoxyde A. CAVE, C. KAN-FAN, J. LE MEN et P. POTIER - *Tetrahedron*, 1967, 23, 4681-4689
  - Preparation of Vinblastine, Vincristine and Leurosidine, Antitumor Alkaloids from *Catharanthus* sp. (Apocynaceae), P. MANGENEY, R. R. ANDRIAMIALISDA, N. LANGLOIS, Y. LANGLOIS and P. POTIER *J. Amer. Chem. Soc.*, 1979, 101, 2243 - 2245.
  - Chimie organique biologique - Hémi-synthèse de nouveaux analogues du taxol, étude de leur interaction avec la tubuline - V. SENILH, F. GUERITTE, D. GUENARD, M. COLIN et P. POTIER *C. R. Acad. Sc.*, 1984, 299, Série II, n°15, pp. 1039 - 1043.
  - Substances anticancéreuses d'origine végétale. Les poisons du fuseau : vincalécoblastine, leurocristine et Navelbine : Taxol et Taxotère, F. GUERITTE-VOEGELEIN, D. GUENARD et P. POTIER *C.R. Soc. Biol.*, 1992, 186, pp. 433 - 440.
  - Interactions between docetaxel (Taxotère) and *Plasmodium falciparum* infected erythrocytes, J. SCHREVEL, V. SINOÛ, P. GRELLIER, F. FRAPPIER, D. GUENARD and P. POTIER *Proc. Natl. Acad. Sci.*, 1994, 91, pp. 8472 - 8476.
  - Recherche et découverte de nouveaux médicaments anti-tumoraux : la Navelbine et le Taxotère, P. POTIER *L'actualité chimique*, 1995, janvier-février, pp. 5 - 9.

DISTINCTIONS

- Lauréat de la Faculté de Pharmacie (1954, 1955, 1956 et 1960)
- Lauréat de l'Académie nationale de Médecine (Prix Nativelle, 1960 et 1990)
- Lauréat de la Société chimique de France (Prix Le Bel, 1970 et Prix Raymond Berr, 1976)
- Prix Rosen de Cancérologie (1982)
- Prix de la Société royale de Chimie de Londres (1990)
- Médaille Hanus, Prague (1990)
- Lauréat du Prix Jeanne Loubarasse - Institut Curie (1993)
- Lauréat du Prix Gallien (1994)
- Lauréat du Prix Griffuel (1996)
- Commandeur dans l'Ordre national du Mérite
- Chevalier de la Légion d'Honneur.



PIERRE POTIER





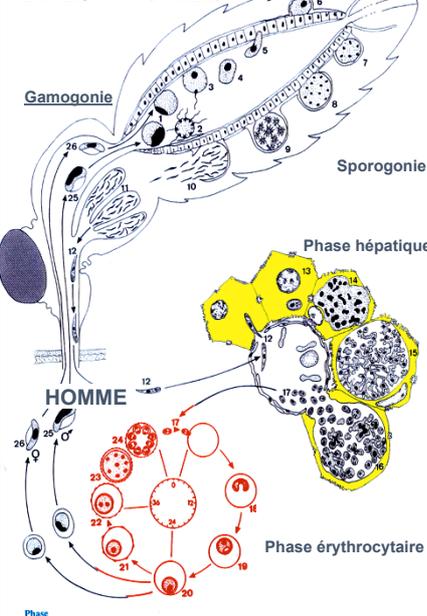
## La carrière d'enseignant de Pierre POTIER au Museum National Histoire Naturelle 1990-1991 et l'absurdité administrative



En 1990, la chaire de Professeur de Chimie (il existait encore des « chaires » à cette époque !) au Muséum National d'Histoire Naturelle devenait vacante. Je fis acte de candidature et le Conseil des Professeurs m'élut. Je commençai donc à partager mon emploi du temps entre Gif et le Muséum. Mon prédécesseur au Muséum, le Professeur D. Molho, facilita grandement mon insertion dans ce Laboratoire au passé prestigieux. Je rétablis les cours portant sur la « Chimie des corps organisés », titre de la Chaire et m'efforçais d'aider de mon mieux les chercheurs, techniciens et tout le personnel que j'avais trouvé à mon arrivée. Mais ma nomination par le Président de la République n'avait pas été immédiatement suivie de la décision administrative correspondante. Je vis ainsi arriver, de longs mois après ma nomination, la « décision » : j'étais nommé Professeur de 1<sup>re</sup> classe et cette nomination était assortie d'une indemnité compensatoire qui éveilla mon attention. En effet, je n'étais pas très au courant des grades de l'Enseignement Supérieur et j'assimilais, à tort hélas, la 1<sup>re</sup> Classe de Professeur à celle des trains.

Bref, on m'expliqua que cela n'avait rien à voir. Ainsi, au « bureau » chargé de ces affaires administratives on m'apprit que, même si j'étais (ce qui était le cas) Directeur de Recherche de classe exceptionnelle au CNRS, je ne pouvais pas être recruté comme Professeur de classe exceptionnelle au Muséum car la classe exceptionnelle n'est pas un grade de recrutement. Na ! La conséquence était que j'étais rajeuni administrativement de 17 ans ! Comme on ne pouvait pas me garantir le rajeunissement physiologique correspondant, je décidai de refuser de signer ce papier inacceptable. On me rétorqua bien que cela ne s'était jamais vu : c'est le propre même d'une invention ou d'une découverte et je connaissais ce genre de problème !

### VECTEUR : ANOPHELES



## Les molécules antipaludiques et les substances naturelles

Proc. Natl. Acad. Sci. USA  
Vol. 91, pp. 8472-8476, August 1994  
Medical Sciences

### Interactions between doctaxel (Taxotere) and Plasmodium falciparum-infected erythrocytes

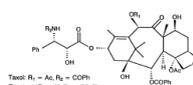
JOSEPH SCHREVEL\*, VÉRONIQUE SINOU<sup>1</sup>, PHILIPPE GRELLIER\*, FRANÇOIS FRAPPIER\*, DANIEL GUÉNARD<sup>2</sup>, AND PIERRE POTIER<sup>3</sup>

\*Laboratoire de Biologie Parasitaire et Chimiothérapie, Centre National de la Recherche Scientifique Unité de Recherche Associée 134, Muséum National d'Histoire Naturelle, 45 rue Buffon, 75231 Paris Cedex 05, France; <sup>1</sup>Laboratoire de Chimie, Centre National de la Recherche Scientifique URA 403, Muséum National d'Histoire Naturelle, 45 rue Buffon, 75231 Paris Cedex 05, France; and <sup>2</sup>Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91196 Gif-sur-Yvette, France

Communicated by Elian Blout, April 18, 1994

**ABSTRACT** Taxotere (docetaxel) inhibits *Plasmodium falciparum* erythrocytic development in vitro at nanomolar concentrations, both in chloroquine-sensitive (F32/Tanzania) and chloroquine-resistant (FCB1/Columbia, FCB3/Gambia) strains. The dose-response assays performed on asynchronous cultures during 42 hr showed clear biphasic curves with a plateau from 50 μM to 10 nM and a single sigmoid curve with a concentration inhibiting 50% of growth (IC<sub>50</sub>) of 3–6 nM observed after a 72-hr incubation. Addition of Taxotere to different stages of FCB1 revealed two types of targets: one type on ring/trophozoite-infected erythrocytes (RBCs), at the micromolar level, and another type on schizont-infected RBCs, at the nanomolar level. Pretreatment of normal RBCs with Taxotere at micromolar concentrations inhibited the merozoite invasion of erythrocytes and parasite growth. These Taxotere-RBC interactions were stable, at least for 1 day. Pulse exposures of 4 hr with Taxotere efficiently inhibit parasite development regardless of the period of the parasite's erythrocytic life cycle. However, different cellular effects were obtained depending upon periods of drug incubations. The inhibition of *P. falciparum* development by Taxotere should provide additional strategies to block parasite development.

Malaria, the major tropical disease, concerns more than 250



functions has been reported, such as the rapid decrease of tumor necrosis factor receptors and tumor necrosis factor release in macrophages exposed to taxol (1) or the inhibition of the stimulation of cell DNA synthesis by human cytomegalovirus (2). Taxol also inhibits the growth of *Trypanosoma* (3) and *Phytophthora* (4). With regard to malaria, two of us (14) have reported that Taxol has a significant inhibitory effect on *P. falciparum* growth but the cellular and molecular effects were not examined. In this report, we show that Taxotere (docetaxel), a "taxane," inhibits the *P. falciparum* in vitro development of chloroquine-sensitive and chloroquine-resistant strains, with different cell targets. At the micromolar level, Taxotere interacts with RBCs, infected with young stages and with RBCs, alone. At the nanomolar level, Taxo-

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European Journal of Medicinal Chemistry  
www.elsevier.com/locate/ejmech

### Short Communication New syntheses and potential antimalarial activities of new "retinoid-like chalcones"

Alain Villa<sup>1,\*</sup>, Benoît Villa<sup>2</sup>, Dominique Carrier<sup>3</sup>, Régis Le Gallou<sup>4</sup>, Roger Labès<sup>5</sup>, Loïc Florent<sup>6</sup>, Sébastien Chameau<sup>7</sup>, Joseph Schrevel<sup>8</sup>, Pierre Potier<sup>9</sup>

<sup>1</sup>CNRS, FR 2225, UMR de l'Université, 2008 Quimper, France; <sup>2</sup>UMR 5094, Biologie Fonctionnelle des Protéines, Muséum National d'Histoire Naturelle, 45 rue Buffon, 75231 Paris Cedex 05, France; <sup>3</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>4</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>5</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>6</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>7</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>8</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France; <sup>9</sup>IFRE 2031 CNRS, Centre de la Troisième, 97398 Gif sur Yvette, France

**Abstract**  
A series of "retinoid-like chalcones" and diverse derivatives related to chalcones, 6 were synthesized from a new mandelic carbon. These syntheses opened a new avenue, versatile. These new derivatives have been tested in vitro on potential antimalarial agents. The 4-hydroxy-3-methoxy-5-methyl-6-methyl-7-methyl-8-methyl-9-methyl-10-methyl-11-methyl-12-methyl-13-methyl-14-methyl-15-methyl-16-methyl-17-methyl-18-methyl-19-methyl-20-methyl-21-methyl-22-methyl-23-methyl-24-methyl-25-methyl-26-methyl-27-methyl-28-methyl-29-methyl-30-methyl-31-methyl-32-methyl-33-methyl-34-methyl-35-methyl-36-methyl-37-methyl-38-methyl-39-methyl-40-methyl-41-methyl-42-methyl-43-methyl-44-methyl-45-methyl-46-methyl-47-methyl-48-methyl-49-methyl-50-methyl-51-methyl-52-methyl-53-methyl-54-methyl-55-methyl-56-methyl-57-methyl-58-methyl-59-methyl-60-methyl-61-methyl-62-methyl-63-methyl-64-methyl-65-methyl-66-methyl-67-methyl-68-methyl-69-methyl-70-methyl-71-methyl-72-methyl-73-methyl-74-methyl-75-methyl-76-methyl-77-methyl-78-methyl-79-methyl-80-methyl-81-methyl-82-methyl-83-methyl-84-methyl-85-methyl-86-methyl-87-methyl-88-methyl-89-methyl-90-methyl-91-methyl-92-methyl-93-methyl-94-methyl-95-methyl-96-methyl-97-methyl-98-methyl-99-methyl-100-methyl-101-methyl-102-methyl-103-methyl-104-methyl-105-methyl-106-methyl-107-methyl-108-methyl-109-methyl-110-methyl-111-methyl-112-methyl-113-methyl-114-methyl-115-methyl-116-methyl-117-methyl-118-methyl-119-methyl-120-methyl-121-methyl-122-methyl-123-methyl-124-methyl-125-methyl-126-methyl-127-methyl-128-methyl-129-methyl-130-methyl-131-methyl-132-methyl-133-methyl-134-methyl-135-methyl-136-methyl-137-methyl-138-methyl-139-methyl-140-methyl-141-methyl-142-methyl-143-methyl-144-methyl-145-methyl-146-methyl-147-methyl-148-methyl-149-methyl-150-methyl-151-methyl-152-methyl-153-methyl-154-methyl-155-methyl-156-methyl-157-methyl-158-methyl-159-methyl-160-methyl-161-methyl-162-methyl-163-methyl-164-methyl-165-methyl-166-methyl-167-methyl-168-methyl-169-methyl-170-methyl-171-methyl-172-methyl-173-methyl-174-methyl-175-methyl-176-methyl-177-methyl-178-methyl-179-methyl-180-methyl-181-methyl-182-methyl-183-methyl-184-methyl-185-methyl-186-methyl-187-methyl-188-methyl-189-methyl-190-methyl-191-methyl-192-methyl-193-methyl-194-methyl-195-methyl-196-methyl-197-methyl-198-methyl-199-methyl-200-methyl-201-methyl-202-methyl-203-methyl-204-methyl-205-methyl-206-methyl-207-methyl-208-methyl-209-methyl-210-methyl-211-methyl-212-methyl-213-methyl-214-methyl-215-methyl-216-methyl-217-methyl-218-methyl-219-methyl-220-methyl-221-methyl-222-methyl-223-methyl-224-methyl-225-methyl-226-methyl-227-methyl-228-methyl-229-methyl-230-methyl-231-methyl-232-methyl-233-methyl-234-methyl-235-methyl-236-methyl-237-methyl-238-methyl-239-methyl-240-methyl-241-methyl-242-methyl-243-methyl-244-methyl-245-methyl-246-methyl-247-methyl-248-methyl-249-methyl-250-methyl-251-methyl-252-methyl-253-methyl-254-methyl-255-methyl-256-methyl-257-methyl-258-methyl-259-methyl-260-methyl-261-methyl-262-methyl-263-methyl-264-methyl-265-methyl-266-methyl-267-methyl-268-methyl-269-methyl-270-methyl-271-methyl-272-methyl-273-methyl-274-methyl-275-methyl-276-methyl-277-methyl-278-methyl-279-methyl-280-methyl-281-methyl-282-methyl-283-methyl-284-methyl-285-methyl-286-methyl-287-methyl-288-methyl-289-methyl-290-methyl-291-methyl-292-methyl-293-methyl-294-methyl-295-methyl-296-methyl-297-methyl-298-methyl-299-methyl-300-methyl-301-methyl-302-methyl-303-methyl-304-methyl-305-methyl-306-methyl-307-methyl-308-methyl-309-methyl-310-methyl-311-methyl-312-methyl-313-methyl-314-methyl-315-methyl-316-methyl-317-methyl-318-methyl-319-methyl-320-methyl-321-methyl-322-methyl-323-methyl-324-methyl-325-methyl-326-methyl-327-methyl-328-methyl-329-methyl-330-methyl-331-methyl-332-methyl-333-methyl-334-methyl-335-methyl-336-methyl-337-methyl-338-methyl-339-methyl-340-methyl-341-methyl-342-methyl-343-methyl-344-methyl-345-methyl-346-methyl-347-methyl-348-methyl-349-methyl-350-methyl-351-methyl-352-methyl-353-methyl-354-methyl-355-methyl-356-methyl-357-methyl-358-methyl-359-methyl-360-methyl-361-methyl-362-methyl-363-methyl-364-methyl-365-methyl-366-methyl-367-methyl-368-methyl-369-methyl-370-methyl-371-methyl-372-methyl-373-methyl-374-methyl-375-methyl-376-methyl-377-methyl-378-methyl-379-methyl-380-methyl-381-methyl-382-methyl-383-methyl-384-methyl-385-methyl-386-methyl-387-methyl-388-methyl-389-methyl-390-methyl-391-methyl-392-methyl-393-methyl-394-methyl-395-methyl-396-methyl-397-methyl-398-methyl-399-methyl-400-methyl-401-methyl-402-methyl-403-methyl-404-methyl-405-methyl-406-methyl-407-methyl-408-methyl-409-methyl-410-methyl-411-methyl-412-methyl-413-methyl-414-methyl-415-methyl-416-methyl-417-methyl-418-methyl-419-methyl-420-methyl-421-methyl-422-methyl-423-methyl-424-methyl-425-methyl-426-methyl-427-methyl-428-methyl-429-methyl-430-methyl-431-methyl-432-methyl-433-methyl-434-methyl-435-methyl-436-methyl-437-methyl-438-methyl-439-methyl-440-methyl-441-methyl-442-methyl-443-methyl-444-methyl-445-methyl-446-methyl-447-methyl-448-methyl-449-methyl-450-methyl-451-methyl-452-methyl-453-methyl-454-methyl-455-methyl-456-methyl-457-methyl-458-methyl-459-methyl-460-methyl-461-methyl-462-methyl-463-methyl-464-methyl-465-methyl-466-methy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## Création de l' Ecole Doctorale ED 227 du Muséum 1992-1995

Direction : J.Schrével. Conseil de l' ED : I. Florent, T.Garestier, M.Goyffon, F. Robert, M.Selo, F.Semah

L'école doctorale 227 MNHN-UPMC « Sciences de la Nature et de l'Homme : évolution et écologie » est largement transdisciplinaire. Co-acréditée Muséum national d'histoire naturelle et Université Pierre et Marie Curie (Paris 6), elle s'appuie sur 74 équipes de recherche réparties dans 25 unités de recherche des deux établissements.

### OBJECTIFS DE L'ÉCOLE DOCTORALE

Soutenir en particulier :

- la recherche naturaliste : les sciences structurales telles que la taxinomie aux échelles macroscopique, cellulaire et moléculaire, la systématique incluant la phylogénie quelle que soit la source de caractères, la morphologie, l'anatomie, la physiologie et la biochimie comparées, la paléontologie, la préhistoire, l'archéologie ;
- les approches structurales motivées par des questions ultimes tournées vers la compréhension des mécanismes, qui au Muséum spécifiquement, tirent particulièrement profit de la richesse des collections et / ou de travaux de terrain : l'étude des écosystèmes, l'étude des milieux, l'écotoxicologie, l'étude des relations entre hommes, nature et sociétés, la génomique fonctionnelle et environnementale, la morphologie fonctionnelle, la génomique comparative des populations, la chimie des substances naturelles, l'évolution du développement ;
- les recherches de type transdisciplinaire sur des « objets » permettant d'intégrer plusieurs approches (moléculaire, morphologique, environnementale...) et plusieurs niveaux d'étude spatio-temporelle, à portée générale ;
- les approches théoriques qui intègrent les résultats les plus récents, permettant de renouveler les concepts, et sur le versant de l'histoire des sciences, les approches historiques des concepts qui sont ceux des disciplines du Muséum.

Aider, en collaboration avec le délégué à la recherche et les responsables des Unités de recherche, au choix des sujets et des encadrants de thèse afin qu'ils assurent aux doctorants une « formation par la recherche » de qualité dans le cadre des objectifs prioritaires des départements. Ce travail est une des tâches principales du Conseil de l'Ecole doctorale, dans lequel siège le délégué à la recherche, ainsi qu'un certain nombre de personnalités scientifiques extérieures. Les sujets retenus sont mis au concours pour

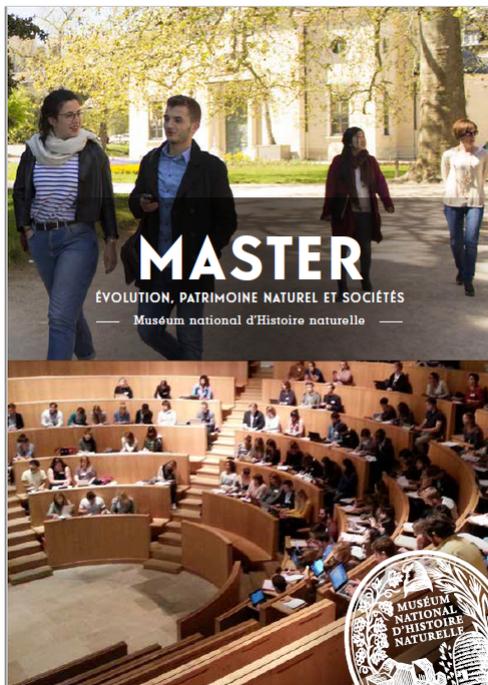
l'attribution d'allocations ministérielles de recherche selon des modalités décrites sur ce site. En outre, l'Ecole doctorale s'investit activement dans la recherche d'autres sources de financement, notamment par les régions et les instances européennes et internationales.

Assurer la formation des doctorants dans des domaines connexes de leur propre recherche, ou susceptibles de leur donner des outils et des approches nouvelles. Les modules de l'Ecole doctorale sont organisés dans ce but. Dans le cadre de la mise en place d'un Master au Muséum, et en liaison avec les équipes pédagogiques des mentions, il est envisagé de revoir le programme de ces modules afin de :

- favoriser ceux qui permettent l'acquisition d'appoints épistémologiques, conceptuels ou méthodologiques, particulièrement nécessaires dans une optique transdisciplinaire ;
- privilégier les domaines de recherche aux interfaces entre plusieurs disciplines ;
- privilégier les ateliers pratiques approfondissant les enseignements dispensés en master, et utilisant au maximum les plates-formes techniques du Muséum.

Donner aux doctorants des outils pour les aider dans leur recherche d'un emploi futur.

Veiller aux bonnes conditions d'accueil et de travail de chaque doctorant (conditions matérielles, soutien financier, soutien logistique, déroulement de la thèse), notamment par la mise en place de comités de thèse, le suivi de la charte des thèses, la sensibilisation des encadrants et directeurs d'Unité. Un conseiller doctoral veille, en compagnie du Directeur de l'école doctorale, au respect de ces bonnes conditions.



**MASTER**  
ÉVOLUTION, PATRIMOINE NATUREL ET SOCIÉTÉS  
Muséum national d'Histoire naturelle



UNE FORMATION  
ANCREE DANS LE PROJET  
GLOBAL DU MUSÉUM

À LA CROISÉE DES SCIENCES  
DE LA TERRE, DE LA VIE, DE L'HOMME  
ET DES SOCIÉTÉS, LE MUSÉUM  
SE CONSACRE À L'HISTOIRE NATURELLE  
DEPUIS PRÈS DE 4 SIÈCLES.  
L'INSTITUTION A POUR MISSION  
DE CONNAÎTRE ET COMPRENDRE  
LA DYNAMIQUE DE LA DIVERSITÉ  
NATURELLE PRÉSENTE ET PASSÉE  
POUR ANTICIPER SON AVENIR,  
CONTRIBUER DANS LE CADRE  
DU DÉVELOPPEMENT DURABLE  
À UNE GESTION RESPONSABLE,  
ET DIFFUSER LES CONNAISSANCES  
AUPRÈS DE TOUTS LES PUBLICS.

## ÉTUDIER AU MUSÉUM LE MASTER EVOLUTION, PATRIMOINE NATUREL ET SOCIÉTÉS - EPNS

### COMPÉTENCES VISÉES

Le Master forme des chercheurs, experts et professionnels dans 4 champs de compétences :

- Description et inventaire des entités naturelles et interprétation historique de celles-ci.
- Compréhension des processus du vivant, de son évolution et de sa dynamique, de l'échelle moléculaire ou génomique à celle des biotopes.
- Compréhension de l'histoire évolutive et culturelle de l'Homme, des relations passées et actuelles entre sociétés, milieux et écosystèmes.
- Diffusion des connaissances auprès de tous les publics.

### UNE MENTION DÉCLINÉE EN 6 SPÉCIALITÉS

- Écologie, Biodiversité, Évolution (**EBE**)
- Environnement : Dynamiques des Territoires et des Sociétés (**EDTS**)
- Mécanismes du Vivant et Environnement (**MVE**)
- Muséologie, Sciences, Cultures et Sociétés (**MSCS**)
- Quaternaire et Préhistoire (**QP**)
- Systématique, Évolution, Paléontologie (**SEP**)

## MVE

### Spécialité MÉCANISMES DU VIVANT ET ENVIRONNEMENT



Le but de l'enseignement dispensé dans cette spécialité est de faire découvrir aux étudiants les mécanismes régissant l'extraordinaire unité et diversité du vivant (des molécules aux écosystèmes) dans un environnement changeant, soumis à des perturbations liées aux activités humaines. Deux domaines sont essentiellement abordés : les relations environnement-santé (réponses aux toxiques, relations molécules/cibles, utilisation des substances naturelles) et le rôle des micro-organismes dans les écosystèmes. L'enseignement fait découvrir aux étudiants les mécanismes fondamentaux qui relient les structures moléculaires avec leurs fonctions via leurs modes d'action et les interactions avec leurs cibles.

### DÉBOUCHÉS

Cet enseignement forme des étudiants qui pourront orienter :  
— vers la recherche fondamentale ou en Recherche & Développement,  
— vers des métiers valorisant la diversité du vivant (Biologie moléculaire et cellulaire, mécanismes d'adaptation des organismes, écologie fonctionnelle dans les environnements actuels) pour la production de molécules d'intérêt en santé humaine ou chimie durable,  
— vers des métiers, orientés vers la microbiologie de l'environnement, l'écotoxicologie, la surveillance environnementale, la dépollution, l'industrie et les agences de l'évaluation des risques.

### PARCOURS

#### Molécules et Cibles Thérapeutiques (MCT) Microbiologie-Environnement-Santé (MES)

Le parcours MCT, offre une large formation à l'interface de la chimie et la biologie. L'enseignement porte sur :  
— la variété chimique des structures moléculaires des substances naturelles en relation avec leur fonction biologique ;  
— les méthodes d'analyse de ces structures : l'utilisation des substances naturelles à des fins thérapeutiques et biotechnologiques ;  
— l'étude de cibles thérapeutiques ;  
— les mécanismes de résistance aux médicaments ;  
— la recherche de cibles thérapeutiques par les méthodes à haut débit.

Le parcours MES, vise à répondre aux demandes grandissantes des laboratoires académiques et des entreprises dans des domaines tels que la recherche fondamentale en microbiologie, la valorisation des microorganismes dans l'industrie, les écotoxicologies, l'évaluation du risque sanitaire dans l'environnement en général et dans les milieux aquatiques en particulier, le diagnostic environnemental, l'analyse de l'anthropisation des milieux. Le parcours s'appuie sur des connaissances et des compétences dispensées en écologie microbienne, en écotoxicologie, en biochimie, en biologie moléculaire, en biotransformation et en chimie.

### ORGANISATION

**M1S1** : 15 ECTS de tronc commun du Master MNHN, 15 ECTS d'enseignements propres à la spécialité MVE dont 9 ECTS mutualisés avec EBE ou SEP.

**M1S2** : 30 ECTS propres à la spécialité MVE dont 9 ECTS de stage en laboratoire (2 mois) et au moins 3 ECTS en ateliers.

**M2S3** : deux parcours possibles, MCT ou MES, 30 ECTS dont 6 ECTS mutualisés.

**M2S4** : stage en laboratoire de 5 mois pour les deux parcours, validé par 30 ECTS.

### PARTENARIATS

L'enseignement s'appuie sur la complémentarité de compétences des enseignants chercheurs du Muséum et de l'UPMC et dans le domaine de la microbiologie (incluant les microorganismes eucaryotes), de sa diversité, de son impact sur les écosystèmes (eau et sol principalement).

### RESPONSABLES

Isabelle Florent  
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## Le Magasin du Bon Dieu: les extraordinaires richesses des Substances Naturelles (Pierre Potier)

### Quelques exemples

Pomme de terre (Hauts plateaux des Andes)  
1772 Promoteur Antoine Parmentier  
(1737-1813) Pharmacien militaire  
Statue Cour de la Faculté Pharmacie de  
Paris

Les quinquinas *Cinchona* et la quinine:  
Joseph de Jussieu (1704-1779) (MNHN)  
Pierre Joseph Pelletier (1795-1842) et  
Joseph Caventou (1795-1877)  
(Faculté de Pharmacie)

Les alcaloïdes de la pervenche de Madagascar  
*Catharantus roseus*:  
Vinblastine et vincristine  
Navelbine Pierre Potier (1934-2006)  
Pharmacien ICSN AMM 1989(FR) et 1994 (USA)

Les taxanes (diterpenes en C20) de l'if  
*Taxus brevifolia* (USA) et Taxol (Paclitaxel)  
(Wani and Wall 1971 J. Am. Chem Soc 93:2325-27)  
*Taxus baccata* (Europe) et Taxotère (Docetaxel)  
Pierre Potier Pharmacien ICSN AMM 1995

Les terpènes du bois de l' Ouabaïo (Apocynaceae)  
et isolation du glycoside l' Ouabaine (Poison des flèches)  
en 1888 par Albert Arnaud (1853-1915) chimiste élève de  
Chevreul et titulaire de la chaire de Chimie (1890-1915)

Synthèse d' un analogue du Dicoumarol des  
champignons de la fermentation du fourrage le  
Pindione par Charles Mentzer (1911-1967)  
Pharmacien, titulaire de la chaire de Chimie  
(1958-1967), parrain CNRS de Pierre Potier

Les peptides des microchampignons *Trichoderma*,  
les peptaïbols et la lutte biologique contre les  
champignons phytopathogènes Bernard Bodo  
Directeur du laboratoire de Chimie (1995-2007)

Toxines et dérivés ( Serpents, Scorpions) André Menez  
(président MNHN 2006-2008), Max Goyffon ,Christiane  
Deregnacout

1894 Découverte du sérum antivenimeux  
Césaire Phisalis (1852-1906) Médecin militaire  
Gabriel Bertrand (1867-1962) Pharmacien  
Auguste Chauveau (1827-1917) Vétérinaire Chaire Muséum

Plaque commémorative du 120<sup>ème</sup> anniversaire de la découverte du sérum antivenimeux en 1894 au Museum National Histoire Naturelle Décembre 2014 . Laboratoire de Physiologie



Le Muséum et les pharmaciens depuis 1990 → une aventure qui continue

**Bisbenzylisoquinolines as Modulators of Chloroquine Resistance in *Plasmodium falciparum* and Multidrug Resistance in Tumor Cells**  
 FRANCIS FRAPPIER,<sup>1</sup>\* AKINO JOSSANG,<sup>2</sup> JACQUES SUDON,<sup>2</sup> FABRIN CALVO,<sup>2</sup> PHILIPPE RASOANAVO,<sup>2</sup> SUZANNE RATNIMAMANGA-URBERG,<sup>2</sup> HAIRO SAEZ,<sup>2</sup> JOSEPH SCHREVEL,<sup>2</sup> and PHILIPPE GUILLET<sup>2</sup>  
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 Received 1 November 1995; returned for modification 18 January 1996; accepted 20 March 1996

The naturally occurring bisbenzylisoquinolines (BBIs) and two dihydro derivatives belonging to the BBIs subgroups were evaluated *in vitro* for their ability to inhibit *Plasmodium falciparum* growth and, in drug combination, to reverse the resistance to chloroquine of strain FCB1. The same alkaloids were also assessed *in vitro* for their potentiating activity against vincristine with the multidrug-resistant clone CCRF-CEM/VL8, established from lymphoblastic acute leukemia. Three of the BBIs tested had 50% inhibitory concentrations of less than 1 μM. The most potent antimalarial agent was cocaine (50% inhibitory concentration, 0.22 μM). Regarding the chloroquine-potentiating effect, langchamine exhibited the highest biological activity whereas the remaining compounds displayed either antagonistic or slight synergistic effects. Against the multidrug-resistant cancer cell line, langchamine was also by far the most active compound. Although there were clear differences between the activities of tested alkaloids, no relevant structure-activity relationship could be established. Nevertheless, langchamine appears to be a new biochemical lead able to help in the comprehension of the mechanism of both chloroquine resistance in *P. falciparum* and multidrug resistance in tumor cells.

**A 37-Kilodalton Glycoprotein of *Babesia divergens* Is a Major Component of a Protective Fraction Containing Low-Molecular-Mass Culture-Derived Exoantigens**  
 BERNARD CARCY,<sup>1</sup> ERIC FREYGOUT,<sup>1</sup> ALEXIS VALENTIN,<sup>2</sup> ANDRÉ GORENFLOT,<sup>2</sup> and JOSEPH SCHREVEL<sup>1</sup>  
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 Received 21 July 1994; returned for modification 11 October 1994; accepted 23 December 1994

The supernatants of *in vitro* cultures of *Babesia divergens* Roum 1987 in human erythrocytes, obtained by using a modified medium based on human high-density lipoproteins, were fractionated by gel filtration chromatography into four fractions, F1, F2, F3, and F4. The crude preparation as well as each fraction adsorbed with Quil-A protected gerbils from mortality due to a homologous infection challenge. Analysis of the homology region of the 18 proteomic gelbites with *B. microti* revealed major proteins with molecular masses lower than 80 kDa, whereas that a few antigens (from 80 to 17 kDa) could be important candidates for an ingested vaccine against *B. divergens* infections. As an immunodominant response was directed against the 37-kDa antigen (B47) in two different *B. divergens* strains tested, a polyclonal antibody directed against B47 was produced in a rabbit. In an immunofluorescence assay, the anti-B47 antiserum strongly labeled small internal vesicles of the macrophages and the cell surface was also labeled after fixation, whereas on live macrophages, this labeling was not observed. High-resolution gel electrophoresis demonstrated that B47 is a glycoprotein. The B47 protein can also be labeled with [<sup>125</sup>I]iodination but not with [<sup>3</sup>H]acetylation. In the *in vitro* N-ethylmaleimide phase partitioning of *B. divergens*-infected erythrocyte extracts, B47 was exclusively found into the detergent phase, indicating that the pathogen B47 protein was in the membrane fraction. In the *in vitro* separation, the glycoprotein B47 was found in a nonpathogenic form, indicating excision and/or release of the glycoprotein from the membrane.

**Structure-Activity Relationships of the Bioactive Thiazinopione Marine Natural Products Thiapolidiquinones A and B**  
 Jacques L. Harper,<sup>1</sup> Inma M. Khalil,<sup>2</sup> Lisa Shaw,<sup>3</sup> Marie-Lise Bourgois-Kondracki,<sup>1</sup> Jettie Dubois,<sup>4</sup> Alex Valentin,<sup>5</sup> David Barker,<sup>6</sup> and Brent R. Copp<sup>1\*</sup>  
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**Cytological and immunological responses to *Babesia divergens* in different hosts: ox, gerbil, and man**  
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 Accepted April 28, 1999

**Abstract.** A continuous *in vitro* culture system for *Babesia divergens* was initiated from a human isolate. It was maintained through 305 subcultures for 3 years using a low concentration of serum and low hematocrits, with no decrease in the initial virulence. This *in vitro* system by repetitive culture medium every 8–12 and to *B. divergens* isolates that were used to assess parasitemia level of 30%–40%. Different cytological aspects observed in the same isolate by optical and electron microscopy were described in parasitized ox, gerbil and human erythrocytes. The sequence of *B. divergens* antibody responses was determined in man and ox, matching the precise classification of major *B. divergens* antigens as candidates for vaccines.

have been performed using the microimmunofluorescence system (MIF) according to Levin and Ristic (1980). Low parasitemia levels (5%–10%) were obtained with bovine erythrocytes (Vignone and Torres 1982). Higher parasitemia levels were achieved by repetitive culture medium every 8–12 and to *B. divergens* isolates that were used to assess parasitemia level of 30%–40%. Different cytological aspects observed in the same isolate by optical and electron microscopy were described in parasitized ox, gerbil and human erythrocytes. The sequence of *B. divergens* antibody responses was determined in man and ox, matching the precise classification of major *B. divergens* antigens as candidates for vaccines.

**Sitamaquine as a putative antileishmanial drug candidate: from the mechanism of action to the risk of drug resistance**  
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Sitamaquine is a 6-aminopyrimidine in development for the treatment of visceral leishmaniasis by oral route, an activity being observed on the experimental murine leishmaniasis experimental models. Recent data explain how sitamaquine accumulates in *Leishmania* parasites, however its molecular targets remain to be identified. An advantage of sitamaquine is its short elimination half-life, preventing a rapid resistance emergence. The antileishmanial activity of its metabolites is not known. The selection of a sitamaquine-resistant clone of *L. donovani* in laboratory and the phase II clinical trials pointing out some adverse effects such as methemoglobinemia and hepatotoxicity are considered for a further development decision.

**Keywords:** sitamaquine, leishmaniasis, aminopyrimidine, drug action

**Synthesis of novel guttiferone A derivatives: In-vitro evaluation toward *Plasmodium falciparum*, *Trypanosoma brucei* and *Leishmania donovani***  
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**Abstract.** The current pharmacomodulation of the natural product guttiferone A, isolated from the *Symplocos glabra* tree, led to the development of a collection of novel derivatives. The most active derivatives were identified. A new molecule with anti-proliferative, cytotoxic and anti-leishmanial activities. Some compounds described below have shown potent antiparasitic activity against *Plasmodium falciparum*. In particular, compound 10 exhibited a strong activity against *P. falciparum*. The synthesis of novel guttiferone A derivatives against *Trypanosoma brucei* and *Leishmania donovani* is also reported and the activity of these natural compounds is discussed in terms of their potential as antiparasitic drug candidates.

### Lipid Traffic between High Density Lipoproteins and *Plasmodium falciparum*-infected Red Blood Cells

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**Abstract.** Several intraerythrocytic growth cycles of *Plasmodium falciparum* could be achieved in vitro using a serum free medium supplemented only with a human high density lipoprotein (HDL) fraction ( $d = 1.063\text{--}1.210$ ). The parasitemia obtained was similar to that in standard culture medium containing human serum. The parasite development was incomplete with the low density lipoprotein (LDL) fraction and did not occur with the VLDL fraction. The lipid traffic from HDL to the infected erythrocytes was demonstrated by pulse labeling experiments using HDL loaded with either fluorescent NBD-phosphatidylcholine (NBD-PC) or radioactive [ $^3\text{H}$ ]palmityl-PC. At 37°C, the lipid probes rapidly accumulated in the infected cells. After incubation in HDL medium containing labeled PC, a subsequent incubation in medium with either an excess of native HDL or 20% human serum induced the disappearance of the label from the erythrocyte plasma membrane but not from the intraerythrocytic parasite. Internalization of lipids did not occur at 4°C. The

mechanism involved a unidirectional flux of lipids but no endocytosis. The absence of labeling of *P. falciparum*, with HDL, previously [ $^{125}\text{I}$ ]iodinated on their apolipoproteins AI and AII by immunofluorescence and immunoblotting, confirmed that no endocytosis of the HDL was involved. A possible pathway of lipid transport could be a membrane flux since fluorescence videomicroscopy showed numerous organelles labeled with NBD-PC moving between the erythrocyte and the parasitophorous membranes. TLC analysis showed that a partial conversion of the PC to phosphatidylethanolamine was observed in *P. falciparum*-infected red cells after pulse with [ $^3\text{H}$ ]palmityl-PC-HDL. The intensity of the lipid traffic was stage dependent with a maximum at the trophozoite and young schizont stages (38<sup>h</sup> h of the erythrocyte life cycle). We conclude that the HDL fraction appears to be a major lipid source for *Plasmodium* growth.

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### 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors Lovastatin and Simvastatin Inhibit In Vitro Development of *Plasmodium falciparum* and *Babesia divergens* in Human Erythrocytes

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The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors lovastatin and simvastatin inhibit the *in vitro* intraerythrocytic development of *Plasmodium falciparum* and *Babesia divergens*, with concentrations inhibiting parasite growth by 50% in the ranges of 10 to 20 and 5 to 10  $\mu\text{g}\cdot\text{ml}^{-1}$ , respectively. For *P. falciparum*, the 50% inhibitory concentrations were in the same range whatever the chloroquine susceptibility of the strains tested (strain F32/Tanzania [chloroquine susceptible] or FCB1/Columbia [resistant]). The stage-dependent susceptibility of *P. falciparum* to simvastatin was studied by subjecting synchronized cultures to 6-h pulses of drug throughout the 48-h erythrocyte life cycle. The most important inhibitory effects were observed between the 12th and 30th hours of the cycle, corresponding to the trophozoite stage. This period

## Les lipides et l'agent du paludisme humain *Plasmodium falciparum*

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### Bee Venom Phospholipase A<sub>2</sub> Induces Stage-specific Growth Arrest of the Intraerythrocytic *Plasmodium falciparum* via Modifications of Human Serum Components<sup>1</sup>

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Secreted phospholipases A<sub>2</sub> (sPLA<sub>2</sub>) from snake and insect venoms and from mammalian pancreas are structurally related enzymes that have been associated with several toxic, pathological, or physiological processes. We addressed the issue of whether toxic sPLA<sub>2</sub> might exert specific effects on the *Plasmodium falciparum* intraerythrocytic development. We showed that both toxic and non-toxic sPLA<sub>2</sub> are lethal to *P. falciparum* grown *in vitro*, with large discrepancies between respective IC<sub>50</sub> values; IC<sub>50</sub> values from toxic PLA<sub>2</sub>s ranged from 1.1 to 200 nM, and IC<sub>50</sub> values from non-toxic PLA<sub>2</sub>s ranged

2). From this superfamily of secreted and cytosolic enzymes, classified in 1997 into nine groups (3), the groups I, II, and III are all secreted, low molecular mass (15-18 kDa), Ca<sup>2+</sup>-dependent PLA<sub>2</sub>s (4). The pancreatic group IB is expressed at high level in the pancreas but has also been detected in various other tissues (5, 6), and apart from its role in the digestion of dietary lipids, it has been implicated in biological activities such as cell proliferation (7), cell migration (8, 9) and eicosanoid release (10). Snake and insect venoms contain a wide variety of secreted PLA<sub>2</sub>s (sPLA<sub>2</sub>s), which can be potent toxins exerting deleterious effects such as neurotoxicity, myotoxicity, cardiotoxicity,



Journal of Biological Chemistry

### In Vitro Anti-*Plasmodium falciparum* Properties of the Full Set of Human Secreted Phospholipases A<sub>2</sub>

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We have previously shown that secreted phospholipases A<sub>2</sub> (sPLA<sub>2</sub>) from animal venoms inhibit the *in vitro* development of *Plasmodium falciparum*, the agent of malaria. In addition, the inflammatory-type human group IIa (hGIIa) sPLA<sub>2</sub> circulates at high levels in the serum of malaria patients. However, the role of the different human sPLA<sub>2</sub>s in host defense against *P. falciparum* has not been investigated. We show here that 4 out of 10 human sPLA<sub>2</sub>s, namely, hGX, hGIIc, hGIII, and hGV, exhibit potent *in vitro* anti-*Plasmodium* properties with half-maximal inhibitory concentrations (IC<sub>50</sub>) of 2.9 ± 2.4, 10.7 ± 2.1, 16.5 ± 9.7, and 94.2 ± 41.9 nM, respectively. Other human sPLA<sub>2</sub>s, including hGIIa, are inactive. The inhibition is dependent on sPLA<sub>2</sub> catalytic activity and primarily due to hydrolysis of plasma lipoproteins from the parasite culture. Accordingly, purified lipoproteins from *P. falciparum* than native lipoproteins.

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