การสัมมนา **NAC2016** 31 มีนาคม 2559 09.00-12.00 น.

อาคารศูนย์ประชุมอุทยานวิทยาศาสตร์ประเทศไทย อุทยานวิทยาศาสตร์ประเทศไทย

การค้นพบยาต้านมาลาเรีย P218: โอกาสและความท้าทายในด้านการพัฒนายาในประเทศไทย

ยงยุทธ ยุทธวงศ์

สุมาลี กำจรวงศ์ไพศาล และ ดารินทร์ คงคาสุริยะฉาย

ศูนย์พันธุวิศวกรรมและเทคโนโลยีชีวภาพแห่งชาติ

สวทช.

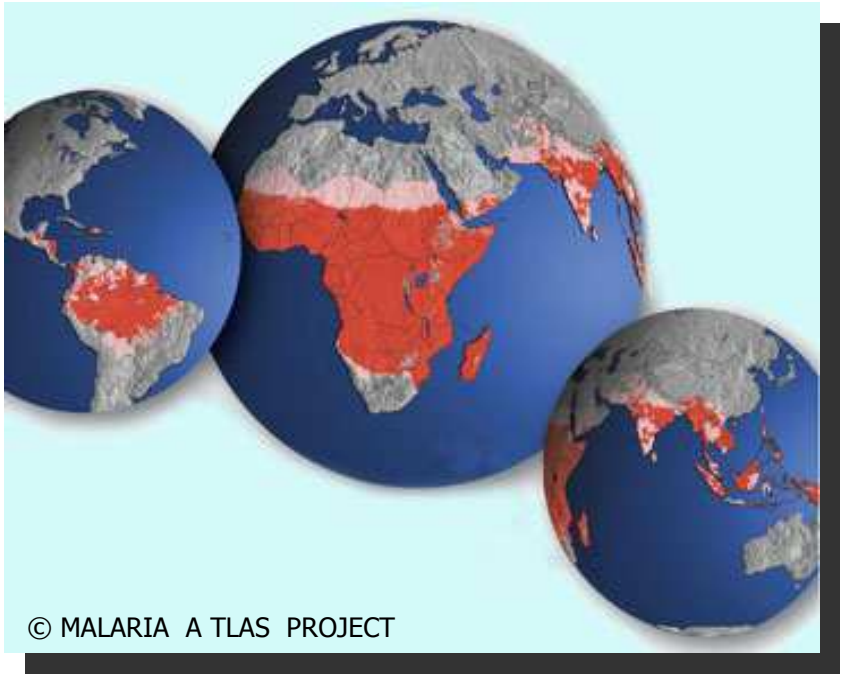
BIOTEC a member of NSTDA

สวทช NSTDA

Needs in health care for developing countries

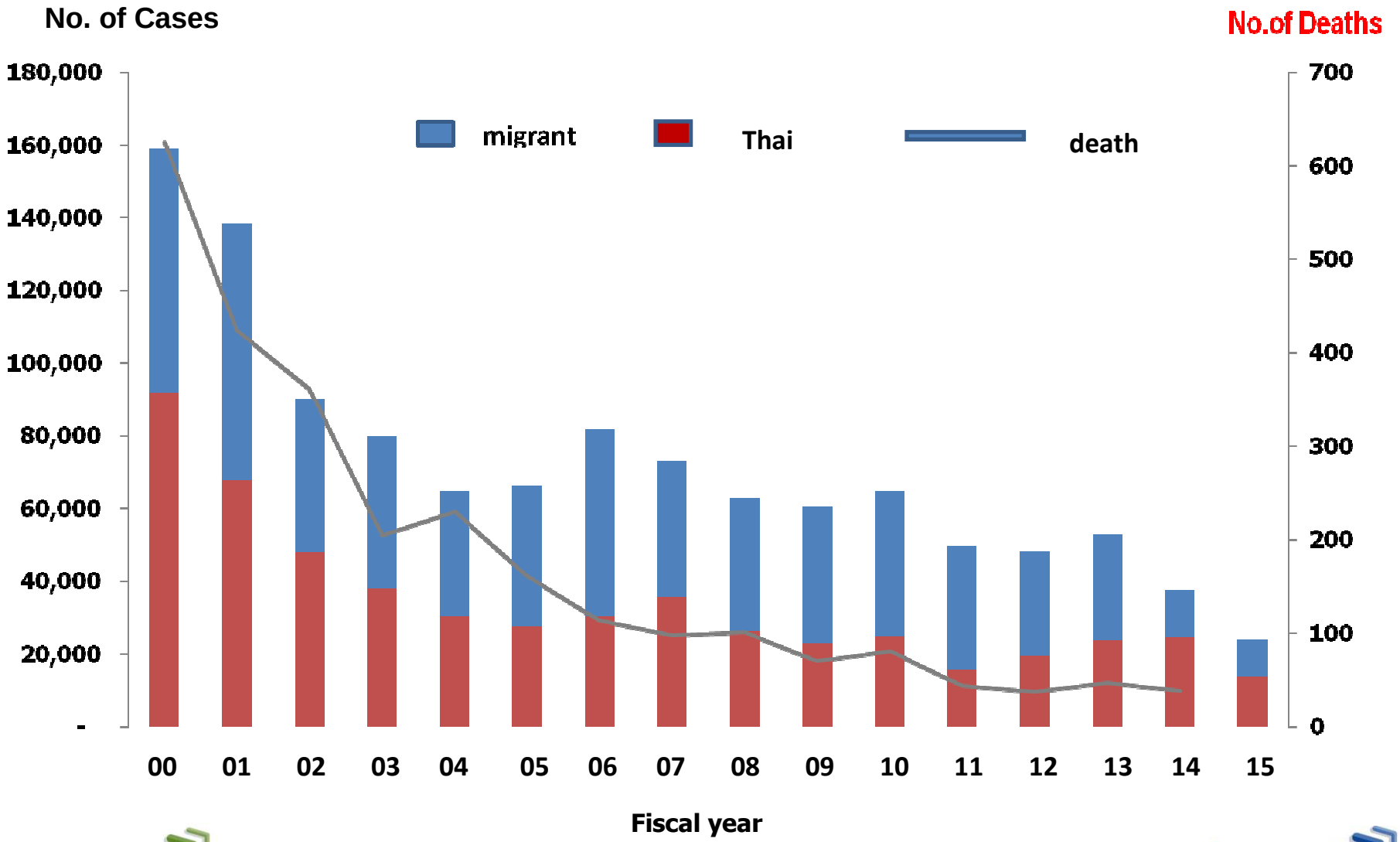
- Improving universal health care
- Care for aging and disadvantaged population
- Care for newborns, children and women
- Managing emerging and diseases of the poor (**malaria**, TB, AIDS, Dengue, etc.)
- Ability in producing medicines and health care products

BIOTEC's drug discovery program for infectious diseases of poverty – MALARIA MODEL



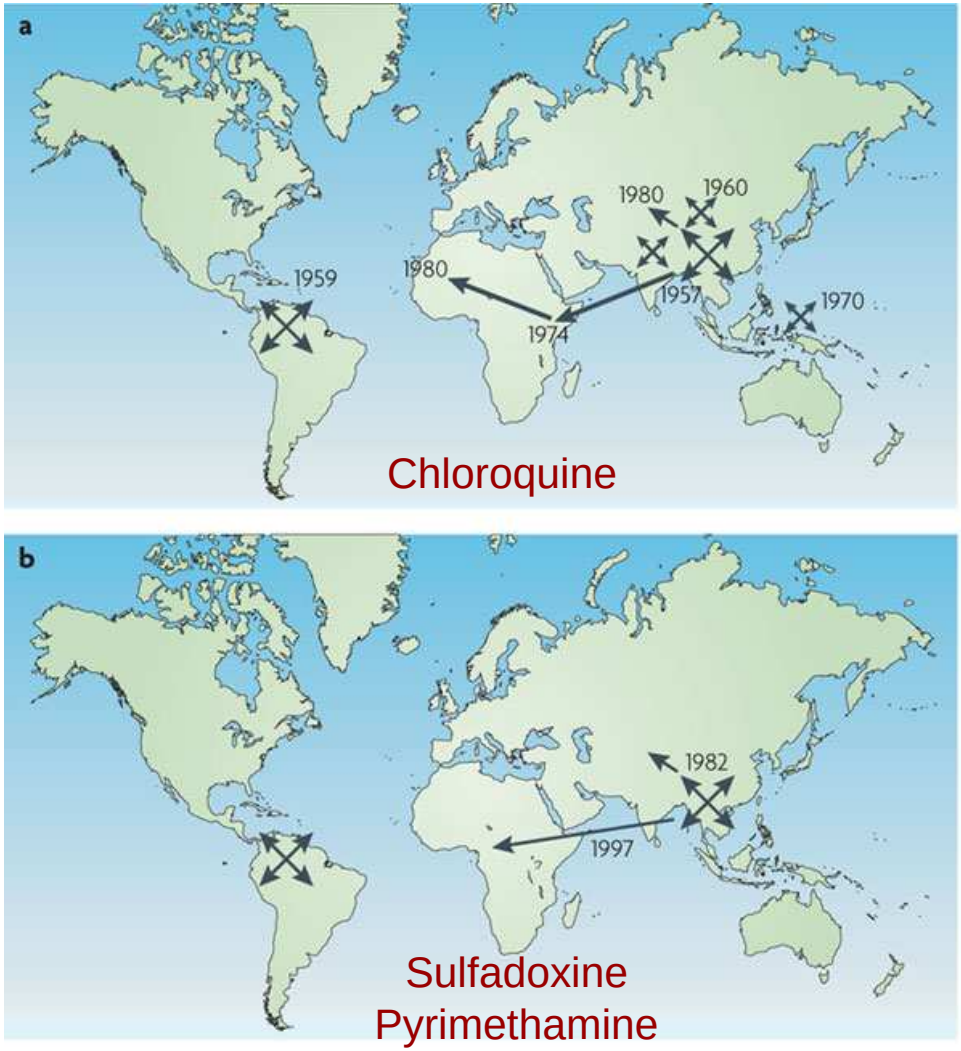
50% of world's population at risk
~214 million new malaria cases
438,000 deaths
A child dies every 2 minutes of malaria (WHO, 2015)

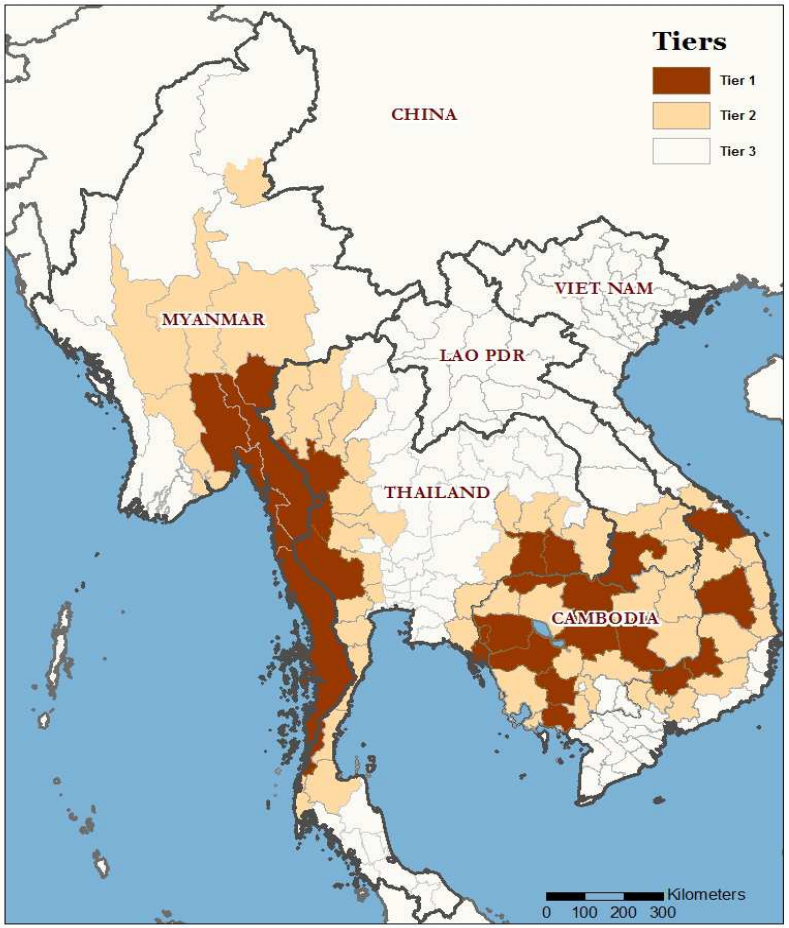
Confirmed Malaria Cases and Deaths (FY 2000-2015)



Source: BVBD, MOPH, 2015

Hot Spots for Drug Resistant Parasites





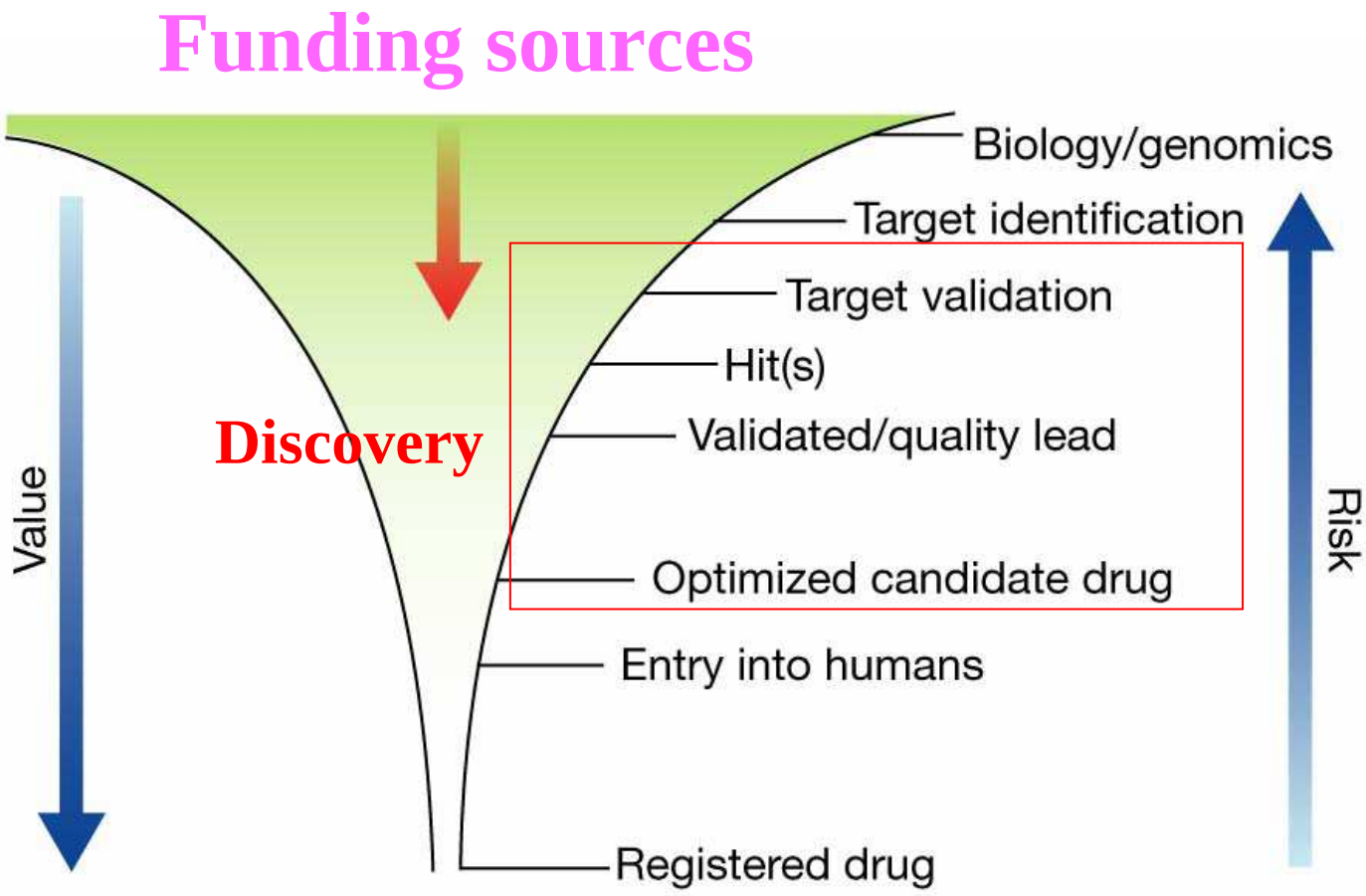
Areas with reduced efficacy using
Artemisinin Combination Therapy (ACT)

WHO 2014, Status Report on artemisinin resistance.
Dondorp AM, et al. (2010) Nature Rev Microbiol 8, 272-280.

Two major drug types

- Small molecules, molecular weight <1,000.
  - Mostly compounds from synthesis or natural products.
  - Work by binding with biological targets
- Biomolecules, molecular weight >10,000.
  - Mostly proteins from cloning
  - Work as substitutes for natural molecules (insulin, erythropoietin, etc.), boosting immune system (vaccines) or by killing pathogens, cancer cells, etc.
  - "Biotech" drugs

Discovery as part of product R&D process



Adapted from R. G. Ridley

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Prof. Lorem Ipsum
The Methodist Hospital Research Institute, USA

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Prof. Lorem Ipsum
Hebrew University of Jerusalem, Israel

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Tapping Molecular Wilderness

Yuthavong

Tapping Molecular Wilderness

Drug Development at the Interface of Chemistry, Biology, and Biodiversity

Yongyuth Yuthavong

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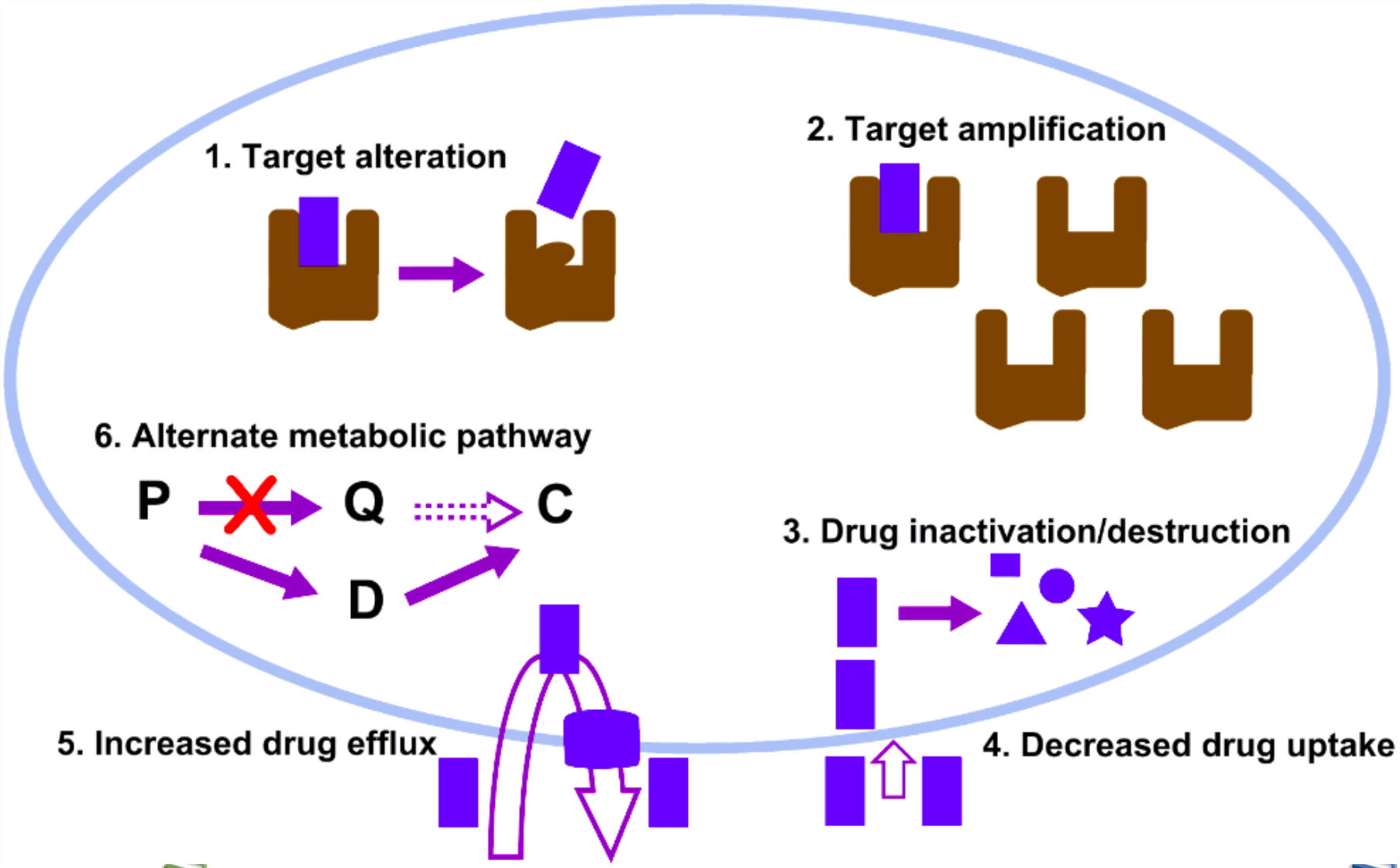
NSTDA

Research questions

- What causes drug resistance?
  - *Target changes (number, binding strength), drug breakdown, drug efflux, drug inactivation etc.*
- What changes occur (at the molecular level) in the parasite enzymes/receptors that led to resistance?
  - *Are there new essential proteins in malaria to exploit as drug target?*
- Can we design new drugs that can overcome the resistance? CHEMISTRY
  - *Can we improve methods for compound screening?*
- Can we identify new drug targets to be used in rational design/random screening? BIOLOGY

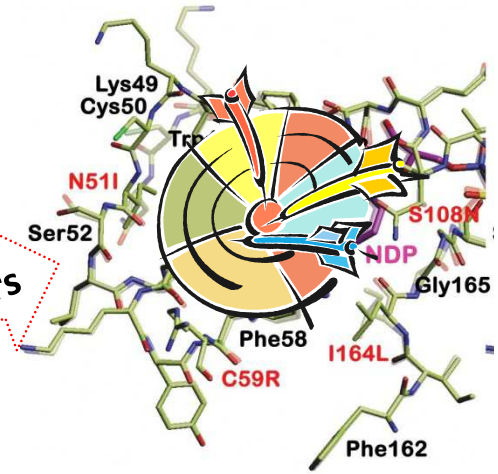
Mechanisms of drug resistance



DHFR is a moving target

Drugs must be guided arrows

Inhibitors



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Malaria Drug Discovery Research
(BIOTEC)

- ***Why DHFR?***
  - Essential for parasite survival & known target for pyrimethamine
  - Mutations in DHFR results in antifolate resistance
- ***Research interests***
  - **Rational design of anti-malaria inhibitors against *Pf*DHFR**
  - **Synthesis and screening of *Pf*DHFR inhibitors**
  - Validate new targets for development of new class of inhibitor
- ***Research** goals*
  - **To obtain lead compounds based on rational design effective against wild-type and resistant parasites**

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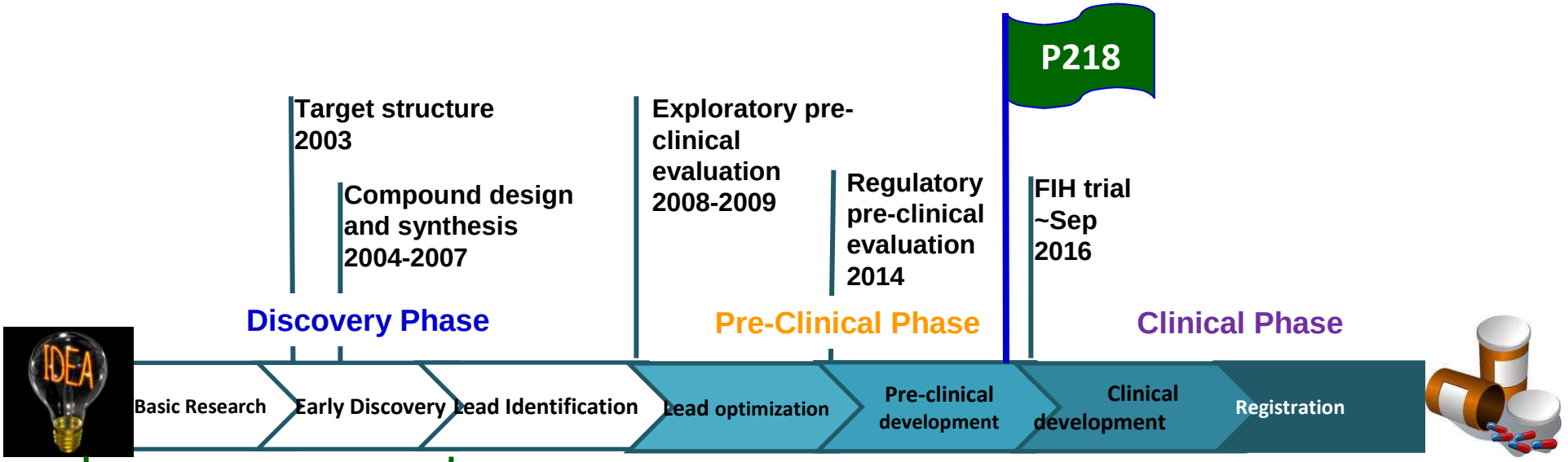
P218 development pipeline – New Compound Entity (NCE)



P218 R&D
- BIOTEC/NSTDA
- MMV
- CRO

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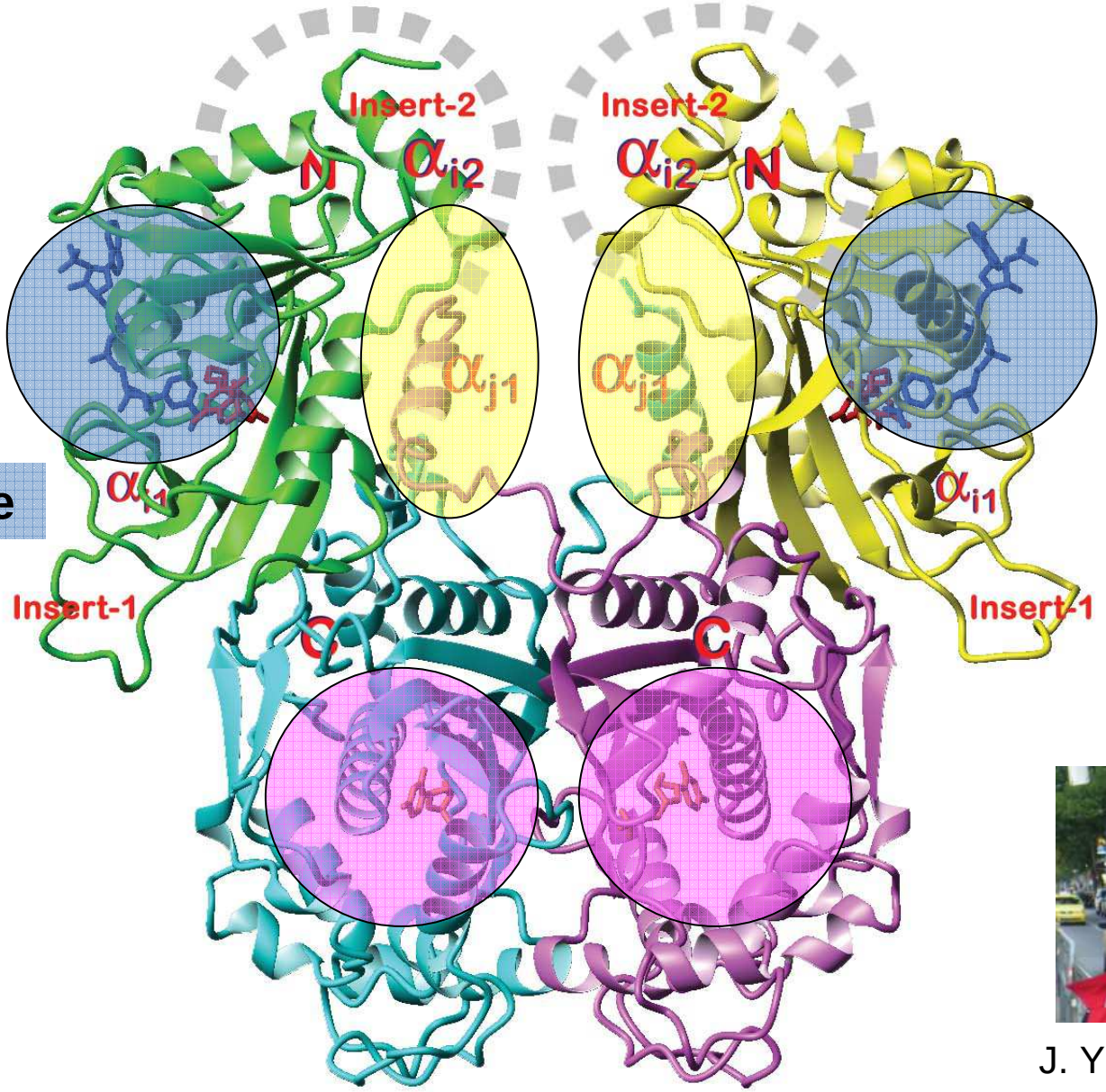
Medicines for Malaria Venture

NSTDA

P. Chitnumsub

DHFR active site



J. Yuvaniyama

***P. falciparum* DHFR-TS (Yuvaniyama *et al., Nature Struct. Biol.* 2003, 10, 357-365)**

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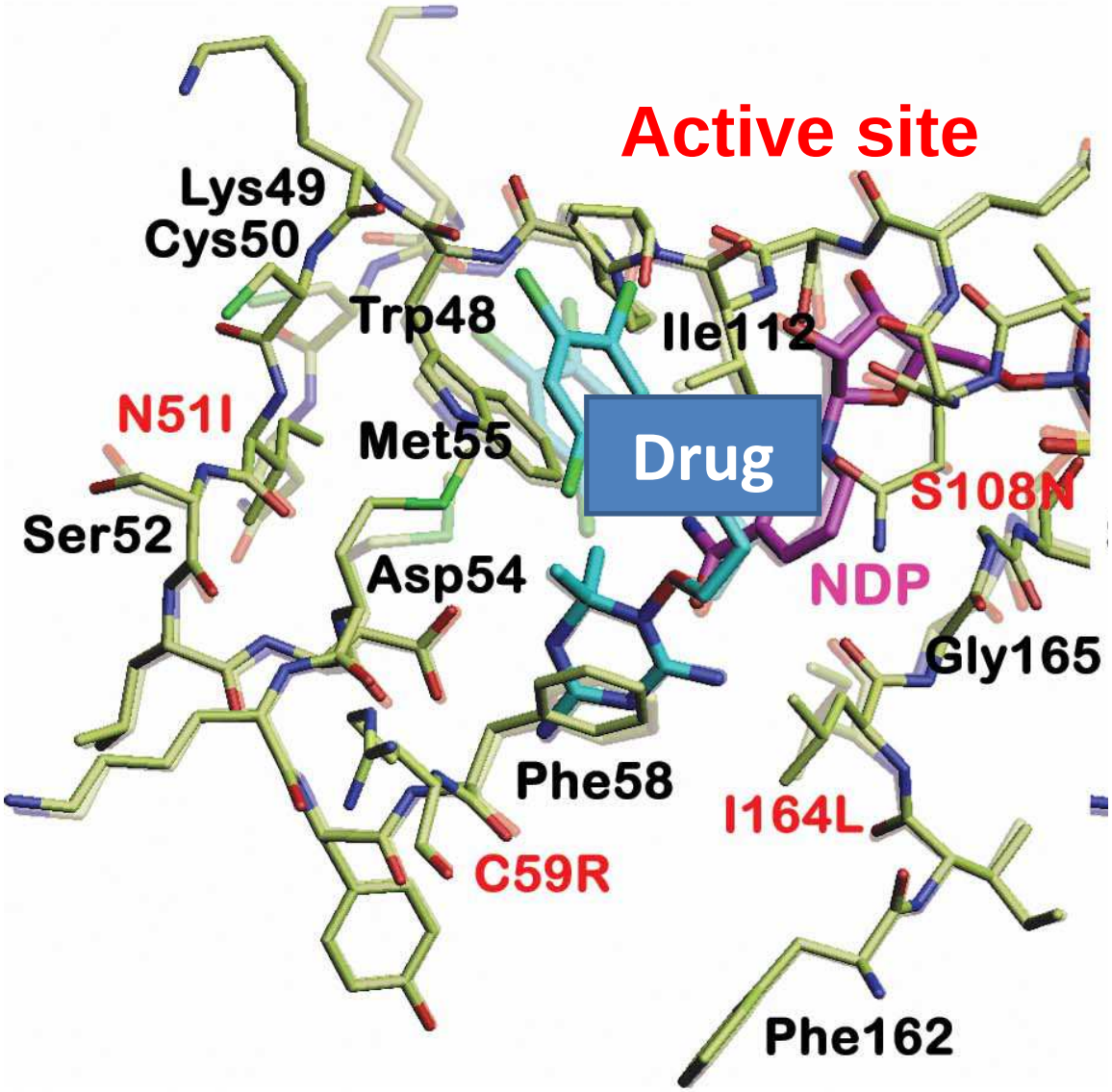

Active site
Lys49
Cys50
Trp48
Ile112
N51I
Met55
Drug
S108N
Ser52
Asp54
NDP
Gly165
Phe58
I164L
C59R
Phe162


T. Vilaivan

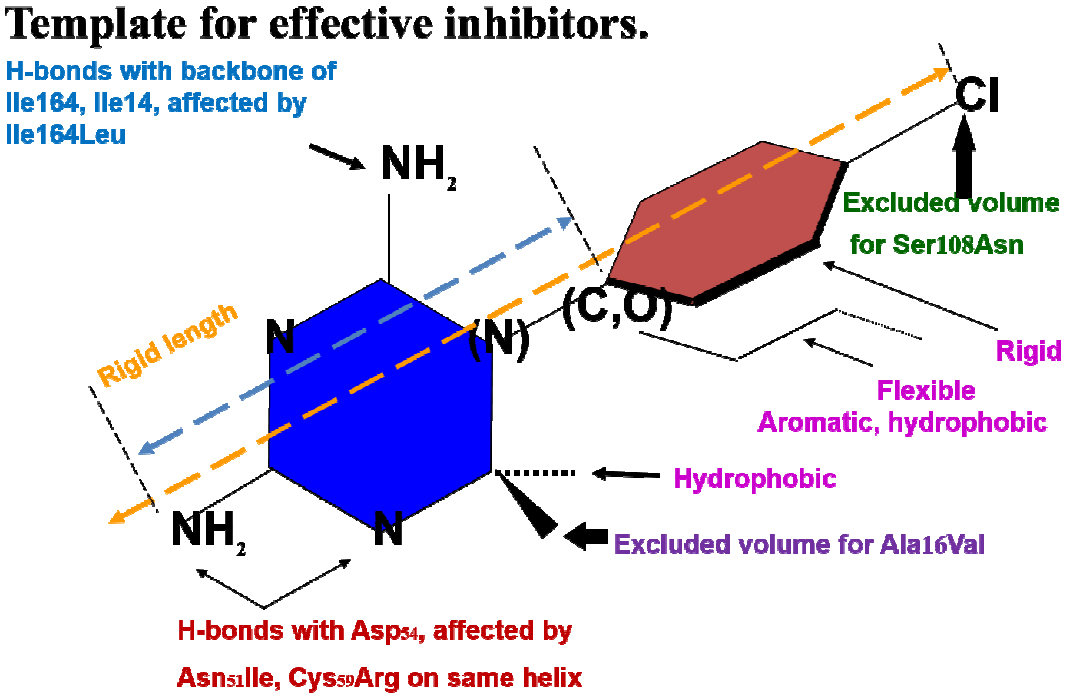

B. Tarnchompoo


C. Thongphanchang


U. Arwon

Design, synthesis and testing of DHFR inhibitors

Approximately 1000 molecules were designed, synthesized and tested for target affinity and antimalarial activity



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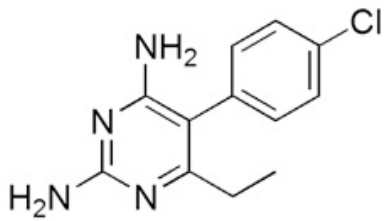
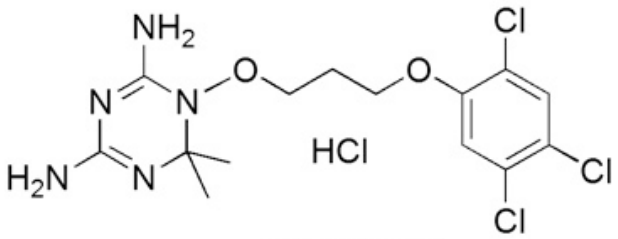
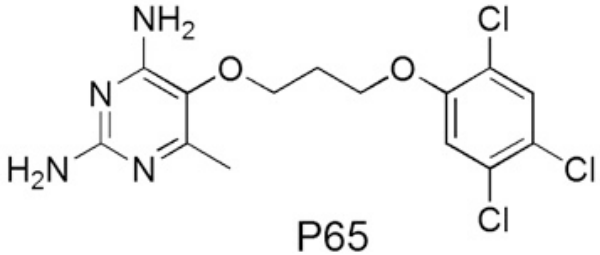
Yuthavong Y, et. al.(2012) PNAS, 109(42):16823-16828



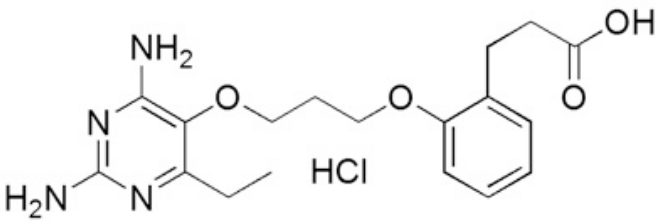
Pyrimethamine



WR99210



P65



P218

	Pyrimethamine	WR99210 *	P65 *	P218
Biological activity				
K_i quadruple mutant *P. falciparum* DHFR (nM) ± SD	385 ± 163	1.9 ± 0.8	5.59 ± 0.1	0.54 ± 0.12
IC_{50} wild-type *P. falciparum* (TM4) (nM) ± SD	58 ± 33	0.57 ± 0.1	229 ± 68	4.6 ± 1.9
IC_{50} quadruple mutant *P. falciparum* (V1/S) (nM) ± SD	>100,000	18 ± 12	3,490 ± 1,610	56 ± 20
Oral ED_{90} *P. chabaudi* (mg/kg) †	1.1	74.22	1.53	0.75

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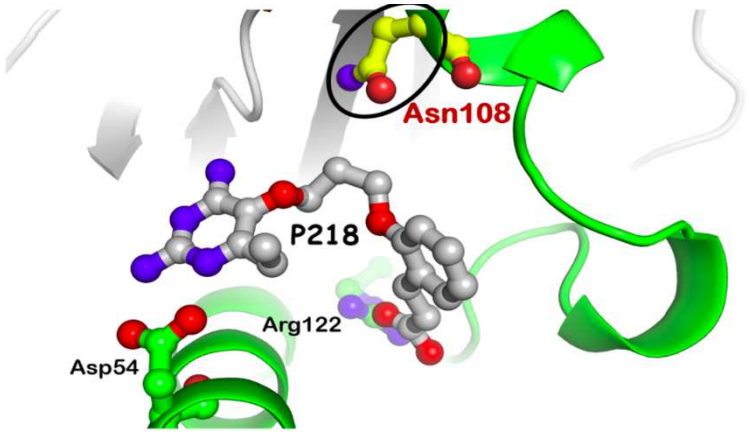
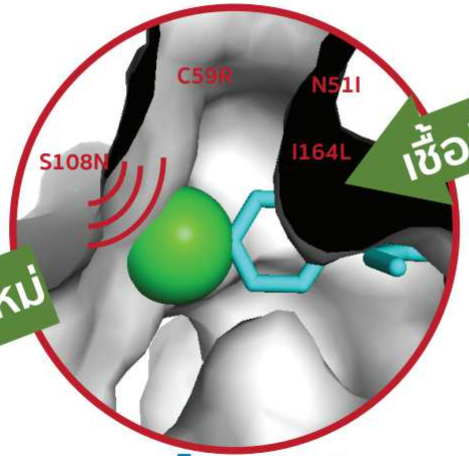
MMV Medicines for Malaria Venture

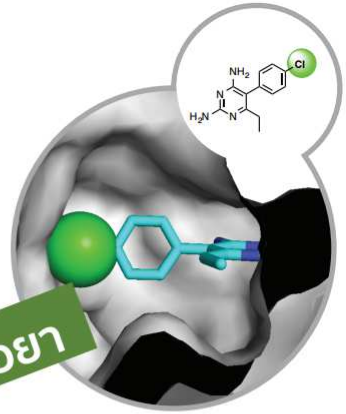
NSTDA



ออกแบบยาใหม่



เชื้อดื้อยา



ยาไพริเมทามีน
จับได้ดีในบริเวณเร่งของ
เอนไซม์ *Pf*DHFR สายพันธุ์ดั้งเดิม
(เชื้อไวต่อยาไพริเมทามีน)

ยาไพริเมทามีน
จับได้ไม่ดีในบริเวณเร่งของ
เอนไซม์ *Pf*DHFR กลายพันธุ์ 4 ตำแหน่ง
(เชื้อดื้อยาไพริเมทามีน)

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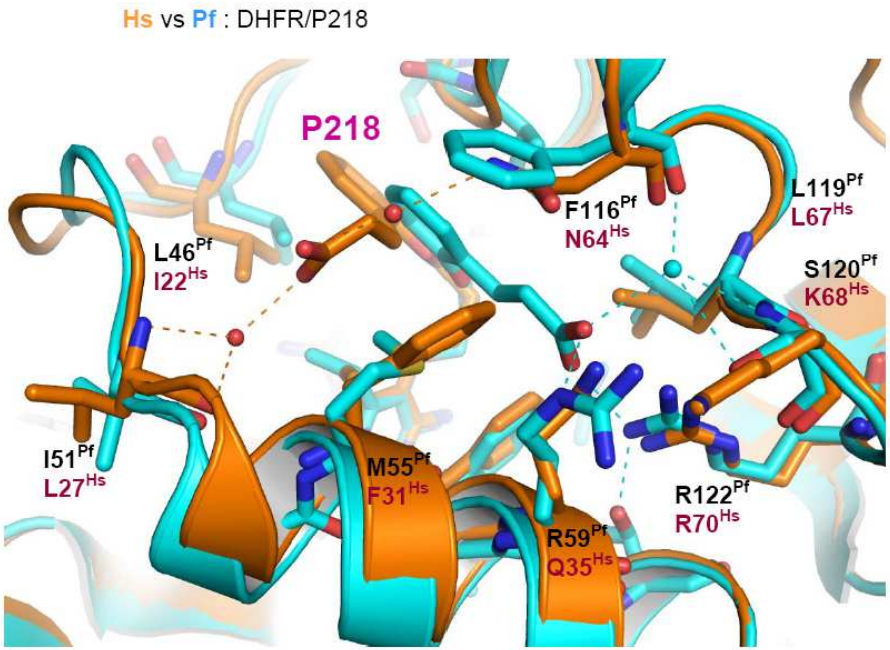
สวทช NSTDA

P. Chitnumsub

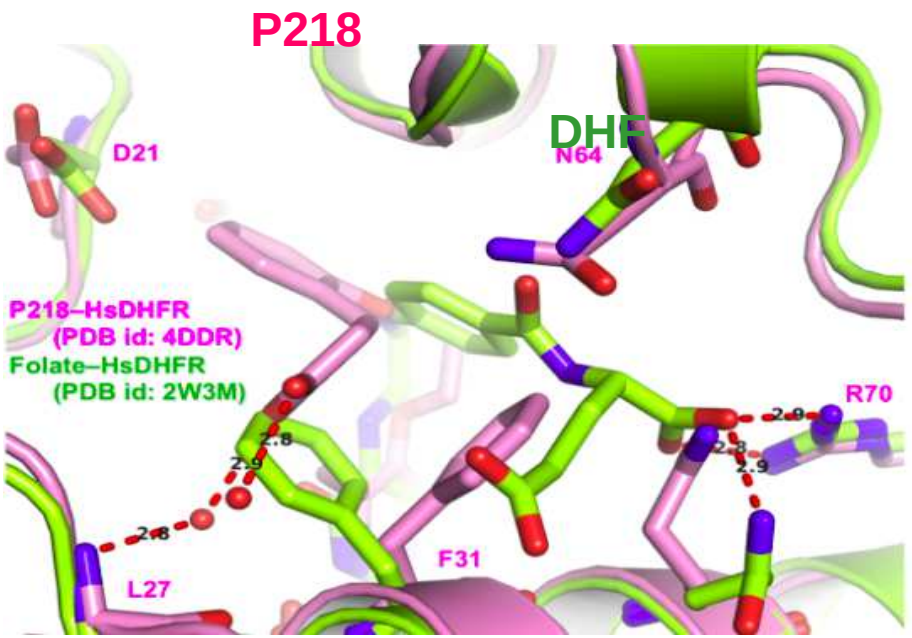
X-ray Structure of P218 in *Pf* DHFR and *Hs* DHFR

J. Vanichtanankul

Different binding conformation of P218 in *Pf* DHFR-QM and *Hs* DHFR



Pf DHFR-P218 vs *Hs* DHFR-P218



Hs DHFR-P218 vs *Hs* DHFR-DHF

(Vanichtanakul, unpublished)

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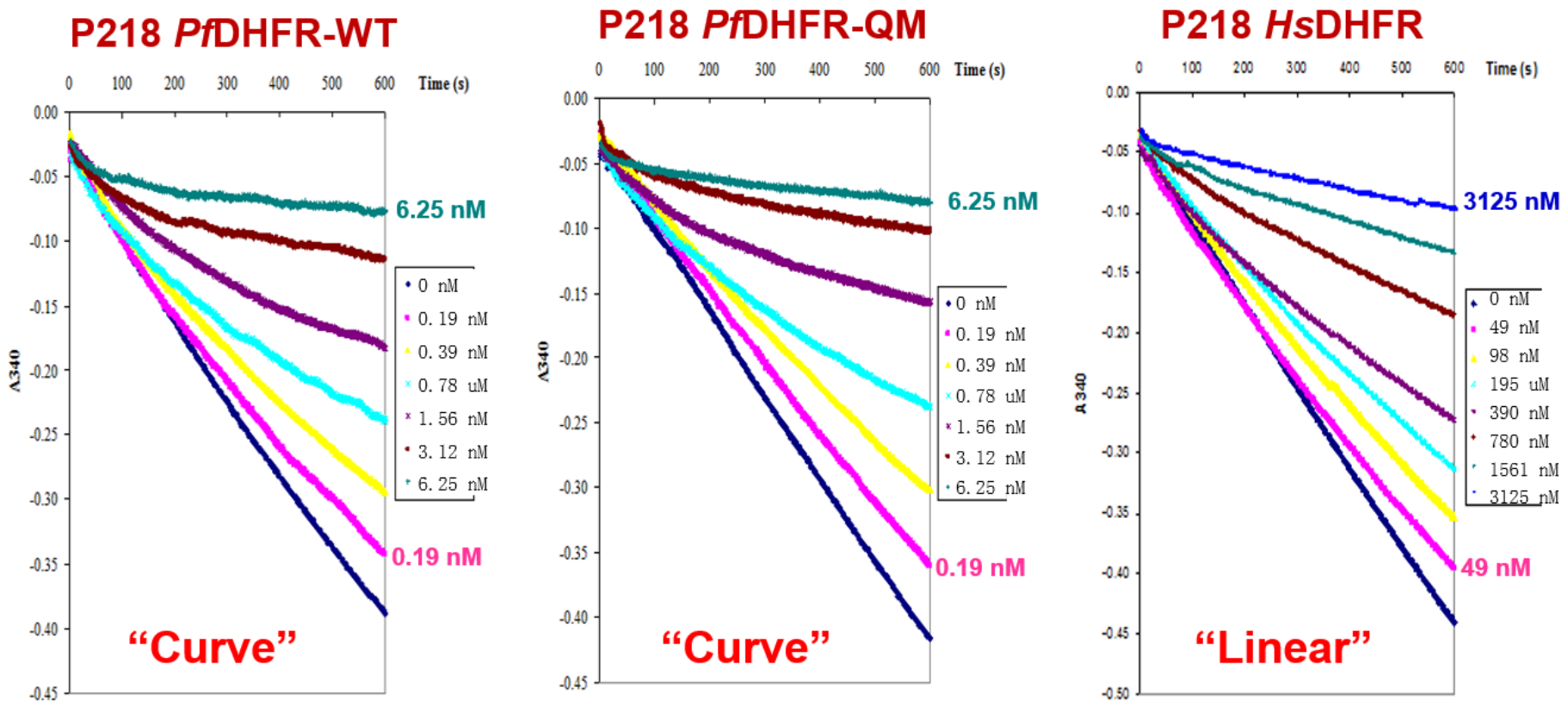
Time dependence inhibition of DHFR by P218



P218-PfDHFR = Tight binding – slow release; P218-hDHFR = competitive binding

Supannee Taweechai

Sumalee Kamchonwongpaisan

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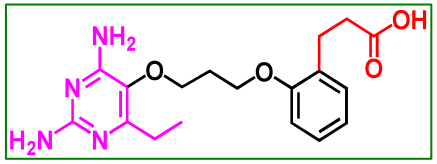
P218 selected



MMV/BIOTEC DHFR team

- ***MMV-funded project : NSTDA/BIOTEC (Thailand), LSTMH (UK), Monash University (Australia)***
- Excellent malaria enzyme inhibition
  - Specific, tight binding with targets from both sensitive and resistant parasites.
  - Poor binding with human enzyme.
  - A subsequent slow, tighter binding found - target still inhibited even after blood level is depleted.
- Potency against blood stage, liver stage infection, and transmission stage
- Efficacy across broad range of multi-drug resistant *P. falciparum* isolates

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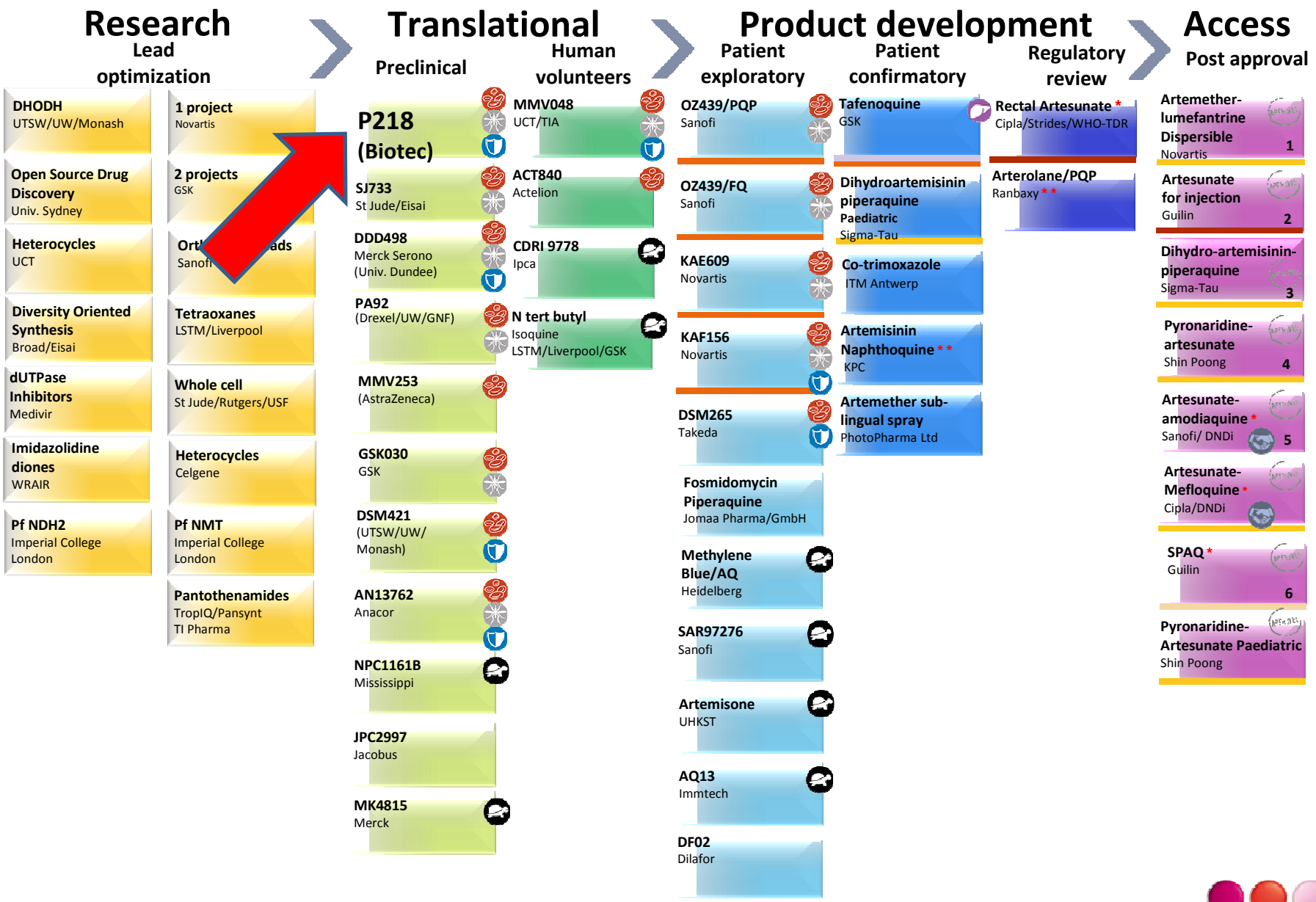
Summary of P218 properties

- PK Properties:
  - Rapid absorption and moderate half-lives (7.3 hours)
  - Good oral bioavailability across all species (30-60%)
- Preliminary toxicity
  - Negative genotoxicity and minimal cytotoxicity
  - Reversible GI toxicity in rodent and canine model
  - Rat: NOAEL at 100 mg/kg/d
- No formulation Issues expected

Global Portfolio of Antimalarial Medicines



Footnotes: Brand names 1: Coartem® Dispersible; 2: Artesun®; 3: Euratesim®; 4: Pyramax®; 5: Coarsucam™ ASAQ/Winthrop®; 6: SPAQ-CO™

Medicines for Malaria Venture

Team for drug development

- Project managers
- Discovery
- Business Dev.
- Quality / GMP
- Legal
- Chemistry
- Formulation
- Biochemistry
- ADME/PK
- Toxicology
- Clinical Pharmacology
- Medical Director
- Clinical Trials

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Medicines for Malaria Venture

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Team for drug development

Poor or not existing

Some capability

- Project managers
- Discovery
- Business Dev.
- Quality / GMP
- Legal
- Chemistry
- Formulation
- Biochemistry
- ADME/PK
- Toxicology
- Clinical Pharmacology
- Medical Director
- Clinical Trials

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Conclusion and Suggestion

- Developing countries in Asia-Pacific have potentials to develop modern pharmaceuticals, both for own use and for export markets
- However, many countries are still weak in many critical areas, such as pre-clinical stage development and coordinated clinical trials
- Co-operation among the private and public sectors across countries can help to enhance capability in pharmaceutical R&D production.

Asia-Pacific developing countries in transition

- *From* looking for help from outside
- *To* helping ourselves and helping others to help themselves
- Health care, with capability in pharmaceutical R&D and production, should be the main example

Protein-Ligand Engineering and Molecular Biology Laboratory

Back row : **Darin Kongkasuriyachai, Yongyuth Yuthavong, Uthai Arwon, Thaveechai Vachirayonstien, Pongpisid Koonyosying, Sasithorn Decharuangsilp, Bongkoch Tarnchompoo, Philip Shaw, Chairat Uthaipibull, Supannee Thaweechai, Mayurachat Poopha, Jutharat Peng-on, Yuwadee Talawanich, Ratchanu Boonyong, Jarunee Vanichtanankul, Parichat Prommana, Aiyada Aroonsri**

Front row : **Sumalee Kamchonwongpaisan, Warangkhana Songsungthong, Chayaphat Wongsombut, Roonglawan Rattanajak, Wanisa Koommuang, Nattida Suwanakitti, Tana Taechalertpaisarn, Thiprumpai Thammamongkut, Apisit Yoomuang, Navaporn Posayapisit**

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