INVENTION, PRODUCTION AND APPROPRIATION OF ARTEMISININ AND ACTs

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Innovation from the South

- « The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine » Nature, 2011 : identification, extraction process, isolation of active ingredients, chemical caracterisation, clinical trials on artemisinin - 1971-1974
- Scientific Awards in China in the seventies : National Invention Certificate in 1979 assigned to the Institute of Traditional Medicine
- Lasker Price Award for Tu Youyou in 2011 - China Academy of Chinese Medical Sciences ; In 2009, Zhou Yiqing got the European Patent Office's Inventors of the Year award for Coartem (Chinese chemists are « inventors » of the international patent on Artemether and Lumefantrine in 1990)

Identification, extraction, chemical structure of artemisinin : hybridizations beetween traditional medicine and biomedicine

- Involvement of several institutes of Traditional Chinese Medicine, of the Institute of chemistry and biophysics of the chinese academy of Science
- Institutes of traditional medecine employed traditional chinese practitioners, historian of traditional medecine and also chemists and pharmacologists
- Low temperature extraction method inferred from the archive of traditional pharmacopeïa (Tu Youyou)
- First derivatives developed within the Institutes of traditional medecine (Tu Touyou and Li Ying synthesized dihydroartemisinin, artemether and artesunate)

First derivatives industrialised in China

- synthesis for derivatives : artemether and artesunate in 1975
- Pharmaceutical formulations of the derivatives : Kunming Pharmaceuticals for artemether and Guilin Pharmaceuticals for artesunate
- Chinese industrialists continue nowadays to produce raw materials for the international market

First ACTs developed in China

- Therapeutical innovation by combination of molecules
- Zhou Yiking and his team developed CTAs - artemisinin and lumefantrine ; then artemether and lumefantrine (1985) : Coartem
- Li Guoqiao and his team developed artemisinin's derivatives and ACTs (dihydroartemisine + Piperaquine) : Artequick diffused in Vietnam and Cambodia

Appropriation

- Non patenting of artemisinin and of its first derivatives discovered and developed before the adoption of a patent law in China in 1985
- Artemisinin and first derivatives were freely used to invent ACTs : myriad of ACTs developed in the 1990s
- Chinese patent and international patents on artemether and Lumefantrine filed in 1990

Secrecy and Divulgation of the inventions

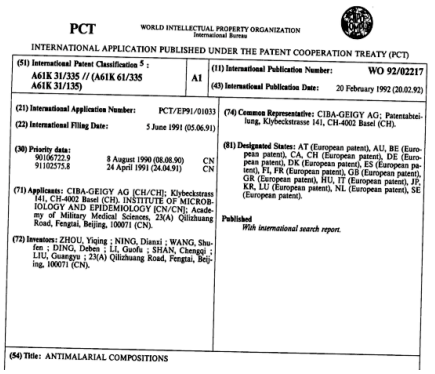
- Secrecy in the context of a military project and of the Cultural Revolution
- Divulgation through the Chinese Medical Journal in 1979 ; through the Wellcome Trust in 1980 « a present from chairman Mao » which made theses compounds known internationally ; in 1981, fourth meeting of the scientific working group on the chemotherapy of malaria (World Bank, WHO) in Beijing ; publication in Science in 1985 : An antimalarial drug from China. *Science* **1985**, *228*

Industrial agreement between Kunmings Pharmaceuticals and Rhône Poulenc Rorer 1989-1993

- Negotiations conduced through a state organisation - Citic Group
- RPR obtained form Kunmings Pharmaceuticals a licence to commercialise Paluther (injectable artemether)
- RPR took in charge the technical dossier - toxicity studies and clinical trials

Industrial agreement with Ciba Geigy (1990-1994)

- Novartis assisted their Chinese partners to redesign local production facilities, upgrade their quality assurance systems, and construct new factories to ensure compliance with GMP standards
- Co-ownership of the international patents
- Novartis acquired the rights to market the therapy outside China in 1994
- Chinese cies supply the raw material for Coartem to Novartis and Novartis produced Coartem in China and in the US



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Agreement OMS-Novartis on Coartem (2001-2011)

- Coartem added to the WHO list of essential medicines in 2001 and prequalified by WHO in 2004
- agreement signed in 2001 between Novartis and the WHO on the distribution and price of Coartem in in the public sector of endemic countries "at cost price"
- 80% of the public-sector market in 2010

ACTs and the neglected diseases movement (1999-)

- The idea is to promote innovation for those diseases which remained largely excluded by proprietary pharmaceutical R&D ; malaria is included in neglected diseases
- In 1999, MSF organize the DND Working Group with experts from universities from Malaysia and Thailand, Fiocruz in Brazil, Harvard School of Public Health, Walter Reed Army Institute of Reasearch
- DNDI is founded in 2003

Contoversies between MSF and WHO

- MSF emphasized the WHO's reluctance to recommend the use of ACTs in Africa, in view of pressure from the USA
- WHO was very cautious about the introduction of artemisinin and ACTs in Africa regarding the price of theses news compounds comparing the prices of the treatments already used, the costs of the invention of fixed doses combinations (WHO documents in 1998 and in 2000)
- « if funding is better …. » WHO 2000

The FACT Consortium launched in 2002

- **Fixed-dose** artemisinin Combination Therapy : Pharmaceutical innovation supported and controlled by non governmental organisations
- Development of two ACTs : artesunate + amodiaquine and artesunate + mefloquine.
- This international consortium formed partnerships with organizations in the global South (Universities of Sains in Malasia and Mahidol in Thailand, the Centre for Malaria Research in Burkina Faso, the Oswaldo Cruz Foundation in Brazil) as well as the North (Universities of Bordeaux and of Oxford, small R&D firms, and then Sanofi Aventis in 2005)

FACT : Technology and methodology transfers and non patented drugs

- MSF and DNDI imposed the non patenting of the two ACTs developed : Asaq and ASMQ
- Technology and methodology - for the registration of drugs- transfers within and outside the consortium
- DNDI control the commercialization rights : agreement with Sanofi for the commercialisation of Asaq in the public and in the private sectors

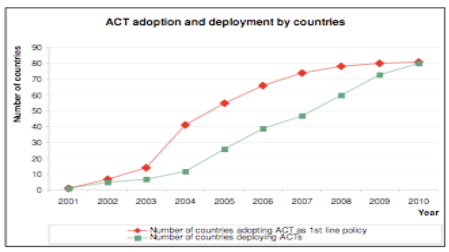
Industrialisation and production of Asaq

- Asaq is produced in Morocco in a factory with GMP standards and has been on the WHO list of essential medicines since 2011
- Generic Asaq produced by Indian firms were prequalified in 2012
- A technology transfer of Asaq is provided to the firm Zenufa (founded in RDC) in Tanzania

2005 WHO guidelines and the growing of the global market for ACTs

- The new guidelines published in 2005 by the WHO recommended the ACTs first
- WHO-UNICEF tendering process
- the WHO organized a meeting in 2006 with 43 representatives of the industry, to encourage them to develop artemisinin-based combinations and to stop their production of artemisinin in the form of monotherapies
- UNICEF Partnership with UNITAID for the ACT Scale-up Initiative (2007-2011).

ACTs adoption



the multiple roles of WHO in the development and dissemination of ACTs

- Early work of TDR - Tropical Disease Research- on ACTs
- Impact of the 2001 agreement with Novartis and of the 2005 guidelines for the adoption and deployment of ACTs/ reluctance for the deployment of costly ACTs in Africa
- Interaction with industry since 2006 to stop the production of monotherapies, to introduce Good Manufacturing Practices (GMP), and the standards that the WHO, UNICEF and the Global Fund demanded for ACTs supplied to them

Development and industrialisation of semi-synthetic artemisinin

- R&D was initiated in the 2000s to produce artemisinin synthetically or semi-synthetically, using recombinant yeasts
- The research was carried out in the form of a PPP between a non-profit organization, the Institute for One Health (IOWH), the University of Berkeley, a start up, Amyris, and Sanofi Aventis for the industrialisation
- Industrial production of semi-synthetic artemisinin started in 2013 in a Sanofi factory in Italy and is expected to grow rapidly

Economic impacts of semi-synthetic artemisinin : Stabilization or destabilization of the production and of the market ?

- If patents on this semi-synthetic artemisinin were to provide for licences without royalties in developing countries, this new industry could destabilize local farmers and production in Asia and Africa

The growing of ACTs' generics

- The production of generic ACTs is growing rapidly, especially when the API or medicines are in the public domain
- The WHO is encouraging the prequalification of generics to supply the market of foundations and international agencies. This however requires investments by generics producers in the South.
- The production of ACTs, which is increasing in Asia and especially in India and China, is also spreading in Africa (Kenya, Ghana, Tanzania, etc.), sometimes with Chinese investments (Côte d'Ivoire).

The growing of generics for Artemether/Lumefatrine