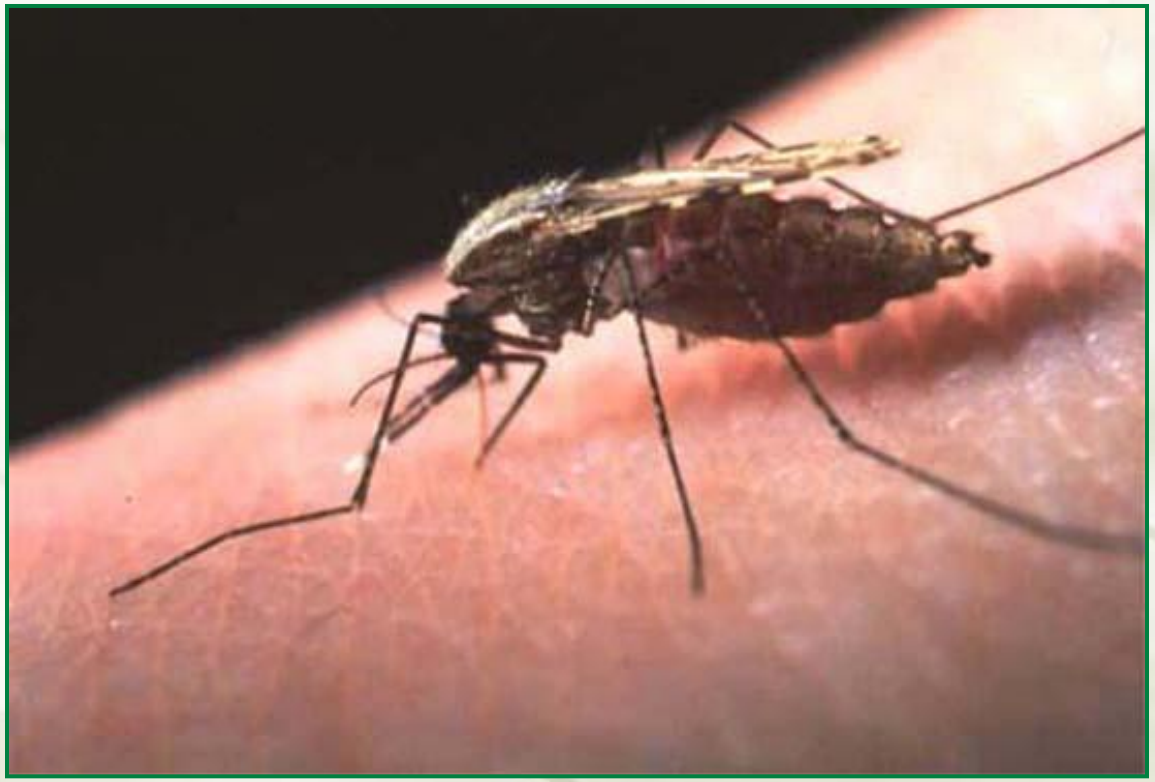
Malaria and Artemisinin: Pathways and Resistance

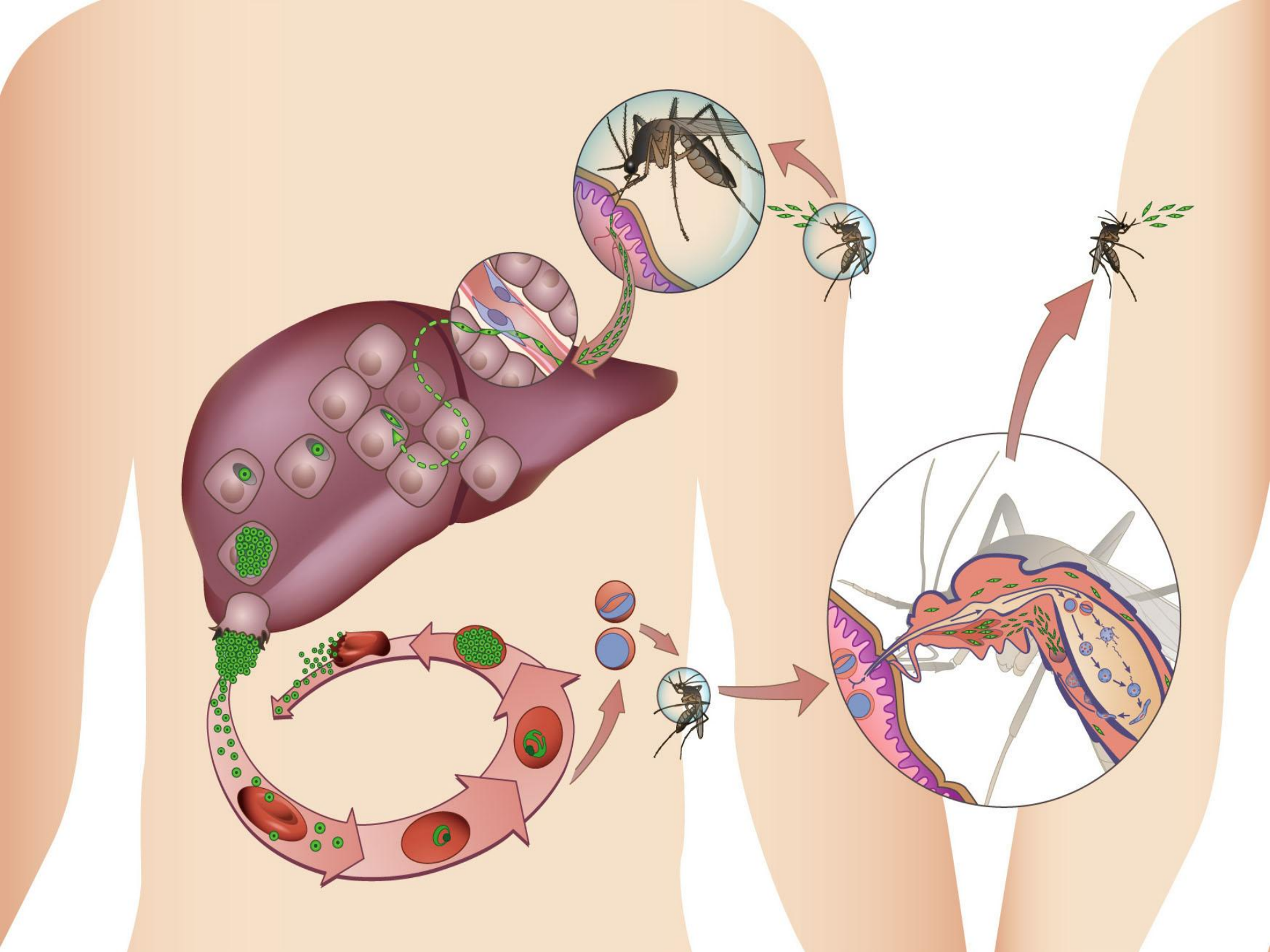


Introduction

In this paper, we aim to investigate the Artemisinin Project, one of the proof-of-concept testbeds for the Synthetic Biology Engineering Research Center (SynBERC). We will begin with a brief history of Malaria and discuss the ideas and practices surrounding anti-Malarial drugs, and the ways in which Artemsin has become an important molecule for Malarial treatment. We will examine the lived experience of having Malaria, and the and the socio-cultural and structural factors that affect malarial treatment, control, and prevention. We will discuss the global flows and forces which have come to shape the current situation of drug distribution and development,and finally come to an understanding of how the Artemsinin Project fits into this framework and they ways in which it may or may not change the face of Malaria in the world.

What is Malaria?

- Malaria is the term given to a set of systems caused by protozan parasites *P. falciparum, P. ovale, P. vivax* and *P. malariae*
- It is transmitted by infected female *Anopheles* mosquitoes



Malaria Globally

- 41% of world in endemic areas
  - Leads to evolutionary adaptations that promote partial resistance and cyclical attacks
- 1-3 million a year, primarily young die
- Resistance to first line drugs
  - Artemisinin works but is $2.40 a dose

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Symptoms

- Once infected, symptoms manifest in an individual after a 6-14 day period. These symptoms include cyclical "attacks" of fever, vomiting, sweating, anemia, and can lead to permanent cerebral damage in children.
- Severe malaria (*P. falciparum*) can cause death in a matter of hours, and has contributes to the overall 1 in 10 death rate for malaria.
- It is estimated at malarial attacks can cost an individual upwards of 5000 calories a day

Malaria in History

- Malaria is possibly as old as humanity itself, and has been mentioned in records from ancient Greece to China (2700 BCE)
- A French Charles Louis Alphonse Laveran, discovered the parasites that cause malaria in 1880.
- In 1897 Ronald Ross Discovered the vector

Malaria Drug Development

- Prophylaxis vs. post-infection
  - Prophylaxis not cost effective for those in endemic areas
    - commonly used for travelers (doxycycline)
- Primaquine
  - Stateville Penitentiary Malaria Study
    - (un)ethical implications
- Choloroquine
  - Andersag in Germany with Bayer, 1934. US/UK approved 1946
- Quinine
  - first utilized in Peru from the Cinchona tree
  - chemically isolated by Pelletir and Caventou in 1820
  - artificial synthesis by Woodward in 1942

Microbial Factories

- The Artemisnin project, headed by Jay Keasling is a proof-of-concept work for SynBERC.
- The goal of the project is to synthetically create artemisnin derivatives through metabolic pathways in *Saccharomyces cerevisiae* (yeast).
- This will not only achieve the goal of creating a global supply of afforable malarial drugs, but will prove that SynBERC can take an idea and utilize parts, devices and chassis to solve a health problem.

Artemisinin

- Used in traditional Chinese Medicine
  - Isolated from *Artemisia annua* trees
- Through metabolic pathways, artemisinin produces free radicals, which destabilze and destroy the parasitic organisms while sparing red blood cells.
- Difficult to isolate, difficult to mass produce.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

What are the Scientists doing?

- Is this science as a vocation?
  - Science for sciences sake
  - Degree of commitment to the university

Mode Three?

- "In our society, we have lost even the pretence of a common culture" Snow:60
- The current equipment involved in the artemisinin project is not indicative of mode three
  - Flourishing is being hindered by a push to produce and excel.

Human Practices

- Recognizing the need for ethnography in order to better understand how people experience these problematized fields and what is actually going on
- Can artemisinin-based treatments and Synthetic Biology effectively solve the malaria problem?

Where is Ghana?

- West African country in sub-saharan Africa

History: Ghana and Outsiders

- 15th century: 1st Contact with Europeans
- 1874: Becomes a British colony
- 1957: Gains Independence

History: Ghana and Malaria

- Predates European contact
- Outsiders to Ghana experienced high mortality rates upon arrival
- Anti-malarial efforts began mainly in the colonists' self-interest

Ethnography: Methodology

- Interviewed a Germany university student named Jan
- Taught computer science in Ghana for two years to fulfill his public service requirement
- Got malaria twice

Prophylactic Drug Treatment

- Doxycyclin
- Lariam (Mefloquine)
- Malarone (Atovaquone)
- Problems: Costs, effectiveness

Symptoms and Treatment of Malaria

- Difficult to identify which mosquito
- Fever, chills, dizziness, fatigue, loss of appetite, vomiting, diarrhea
- Treatment: Lariam, artesunate (derivative of artemisinin)
- Didn't go to the hospital until later

Treatment

"The next two days were terrible! I am sure it was still because of the Lariam I took on Sunday. I was in my house, just lying in the bed. I was turning around all the time, I couldn't sleep and moreover I didn't want to fall asleep. I really thought if I would fall asleep, I would never wake up again. I thought I might die! I had nightmares, dreaming of the book I was reading at that time, *Illuminati*… I had hallucinations. When I was looking at my door I saw a picture appearing on the pattern. It was a person standing in front of a crowd of people.

Treatment

"I am not kidding. It became worse. I don't know this word – some people are saying that they have those strange experiences before they die, about the light. In Germany it's called "near-dead-experiences." I was able to leave my body and see myself lying in the bed. I am sure I was hallucinating, but while I was lying there I did not know what to believe anymore.

Treatment

"Later on, I think that was Tuesday then, I had visions. I saw some men entering the school ground, killing the watchmen and kidnapping the headmistress. I really thought it would become reality and so I left my house, feeling so dizzy and weak. I was walking towards the classrooms in order to warn the watchmen. Now it's really funny, but when I was standing on the street, I really believed it. I realized afterwards it was just because of the drugs. But I never believed in my whole life that drugs would be able to make me believe something like that!"

Ghanaian Perspectives

- "If you, as a white, tell them that malaria can kill them, they will just laugh."
- Everyone gets malaria – fevers are a part of life
- Causes 8% of deaths in Ghana – majority are children
- Survival in childhood helps the body produce antibodies that help resist future infections… So adults usually develop a resistance to malaria such that future infections aren't fatal (similar to the cold in America)
- Adults die only if their immune systems were already weakened

Ghanaian Language

- In many regions, the words for "fever" and "malaria" are used interchangeably
- For example, "Asra" and "Atridi" both refer to fever and malaria
- People experience many diseases with the same symptoms as malaria

Treatments

- Generally attempt self-treatment first (herbal/traditional remedies, pharmaceuticals)
- Sometimes go to the hospital if the illness is severe
- Treatments, such as artesunate, are expensive - issue of poverty
- Problem of malarial resistance to drugs

Other Problems

- HIV/AIDS
- Poverty
- Pollution
- Malnutrition
- Overpopulation

Synthetic Biology

- Synthetic Biology must anticipate and respond to the social/cultural framework in which it operates in order to effectively implement artemisinin-based drugs.
- What factors outside of specific countries are at work?

Pharmaceutical Corporation and Global Issues

- Commercialization is the ways in which pharmaceutical industries make their profit.
- Pharmaceutical companies spend more time and money on advertisement rather on research.
- When research do happen, they focus their research for lifestyle drugs which affects the developed countries(penis enlargement pills, new kinds of Advil, Viagra, and etc…).
- Very expensive medical drugs from pharmaceutical industries in first world to developing countries.

Pharmaceutical Companies and Global Issues

- The pharmaceutical companies make investments that yield the highest returns.
- Of the thousands of new compounds drug companies have brought to the market in recent years, less than 1% are for tropical disease.

"Multinational pharmaceutical companies neglect the dieseases of the tropics, not because the science is impossible but because there is, in the cold economics of the drugs companies, no market."

Isable Hilton, *A Bitter Pill For The World's Poor*

The Problems…TRIPS!!!

- Post- war policies of IMF and World Bank have cut social expenditure of the developing countries.
- When pharmaceutical companies do conduct research for the developing countries, they complain about unfair trade practices.
- Pharmaceutical industries claims that they need patent and intellectual property rights to recoup the costs of research and development.

The Problems

- The patents and intellectual property rights affect the poor countries such that:

  1) large corporation from developing countries are patenting.

  2) poorer countries that do have industrial capacity to produce generic alternatives are facing pressure not to sell them to other poor countries that do not have such capacity.

  3) Intellectual property rights restrict and allow a person or company to have exclusive control of their knowledge ad resources.

  4) creates monopoly power.

TRIPS for real?!

- WTO established Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 1994.
- TRIPS was the first intellectual property rights to be introduced to international trading system.
- TRIPS restricted and reduced the access to generic medicines.
- Created a problem in which encouraged pharmaceutical companies to put their drugs in the market with very high price.

Loosened the law

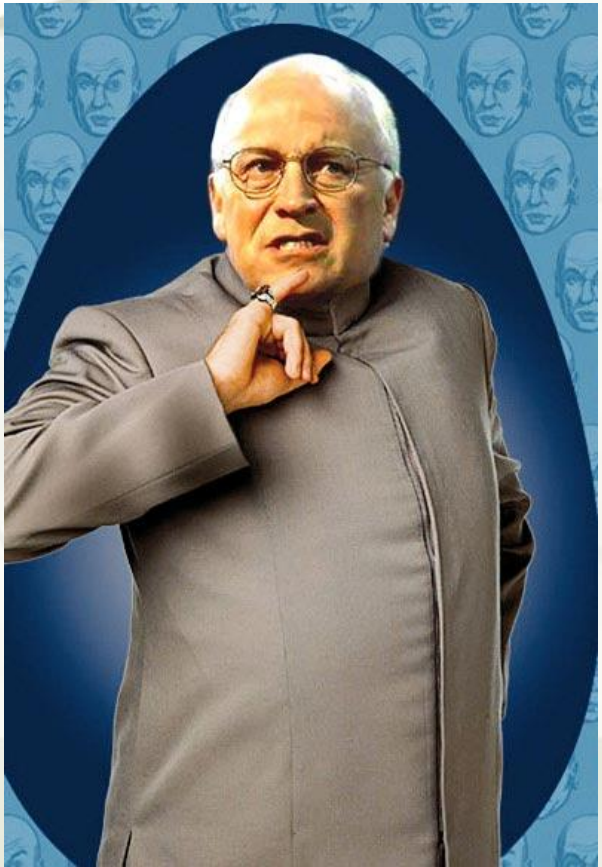
- In 2003, TRIPS agreement has loosened it's strict rules and ensure and increases access of essential drugs.
- Introduced the methods such as compulsory licensing and parallel imports.

- In a **compulsory license,** a government forces the holder of a patent, copyright, or other exclusive right to grant use to the state or others. Usually, the holder does receive some royalties, either set by law or determined through some form of arbitration.
- A **parallel import** is a non-counterfeit product imported from another country without the permission of the intellectual property owner. Parallel imports are often referred to as *grey product*, and are implicated in issues of international trade, HIV/AIDS management, and intellectual property. The practice of parallel importing occurs because companies, either the manufacturer or the distributor, set different price points for their products in different markets. Parallel importers ordinarily purchase products in one country at a price (P1) which is cheaper than the price at which they are sold in a second country (P2), import the products into the second country, and sell the products in that country at a price which is usually between P1 and P2. See arbitrage.

- Compulsory licensing and parallel importing gave opportunities for developing countries to shop around for cheaper but good quality drugs.

However…

On December 21, 2002…



Dick Cheney

- On December 21, 2002, Dick Cheney, the U.S vice-president… blocked a global deal to provide cheap drugs to poor countries, following intense lobbying of the White House by America's pharmaceutical giants.
- America's drug industry has fought tooth and nail to impose the narrowest possible interpretation of the Doha declaration, and want to restrict the deal to drugs to combat HIV/Aids, malaria, TB and a shortlist of other diseases unique to Africa.

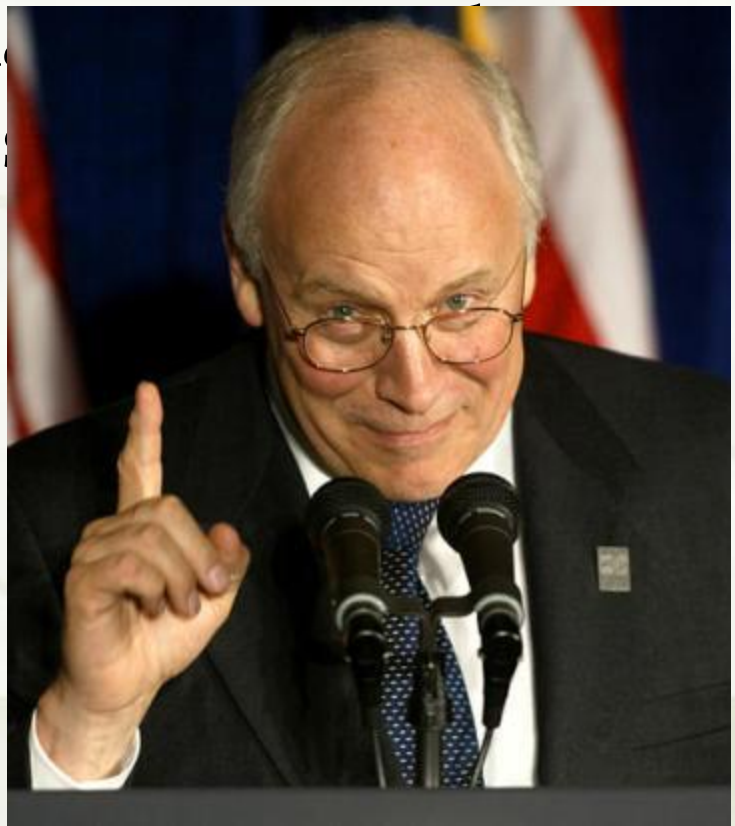
For real??

- The problem is that it only benefits America's pharmaceutical giants and other large pharmaceutical industries.
- U.S has contravened the goal of the Declaration- "access to medicines for all" by pressuring developing countries to implement "TRIPS-plus measures."

Hence…

- Once again, it made difficult for developing countries to gain access to the essential medical drugs.
- To mainstream ph
  industries, Doha i

Thanks Dick Cheney!!!



The Artemisinin Project

Is this promise made to be broken?

The World Health Organization

&

The Bill and Melinda Gates Foundation

- 1955: power of ***Model T*** and new anti-malarials = ERADICATION through prevention and treatment.
- □□Formation of Global Malaria Strategy: held preparatory meetings to speak
- To
- □□1992: Sub-Saharan
- 1990: Real
- Now
- 2004: Recommendation of **certified ACTs** for malaria treatment.

- □□2000: Founded and since then has poured over $8 billion into solving what they have labeled as the world's most daunting problems.
- Just sitting there, waiting for Berkeley to come along?

The Artemisinin Project and Berkeley

- A story already told: In 2003, five UC Berkeley scientists discovered a way to make synthetic artemisinin.
  - Wanted to make a company around it.
- 2000: Biotech bubble popped.
  - Venture capitalists only looking to invest in drugs nearing FDA-approval.

There's been a valley of death between research coming out of academic institutions and the capital needed to fund these companies.

-John Maraganore, CEO of Alnylam Pharmaceuticals

UCB Scientists + $12 Million of iOWH grant money =…

AMYRIS BIOTECHNOLOGIES

- Love child of biotech-nonprofit marriage.
- Corporate entity with biotech jumpstart.
  - Still intends to use discoveries for profit in such areas as biofuels, vitamins, more lucrative drugs (I.e. cancer research), etc.
- Distinct advantages in this "marriage": 1)Attracts investors who receive inexpensive research due to lack of high university royalties.

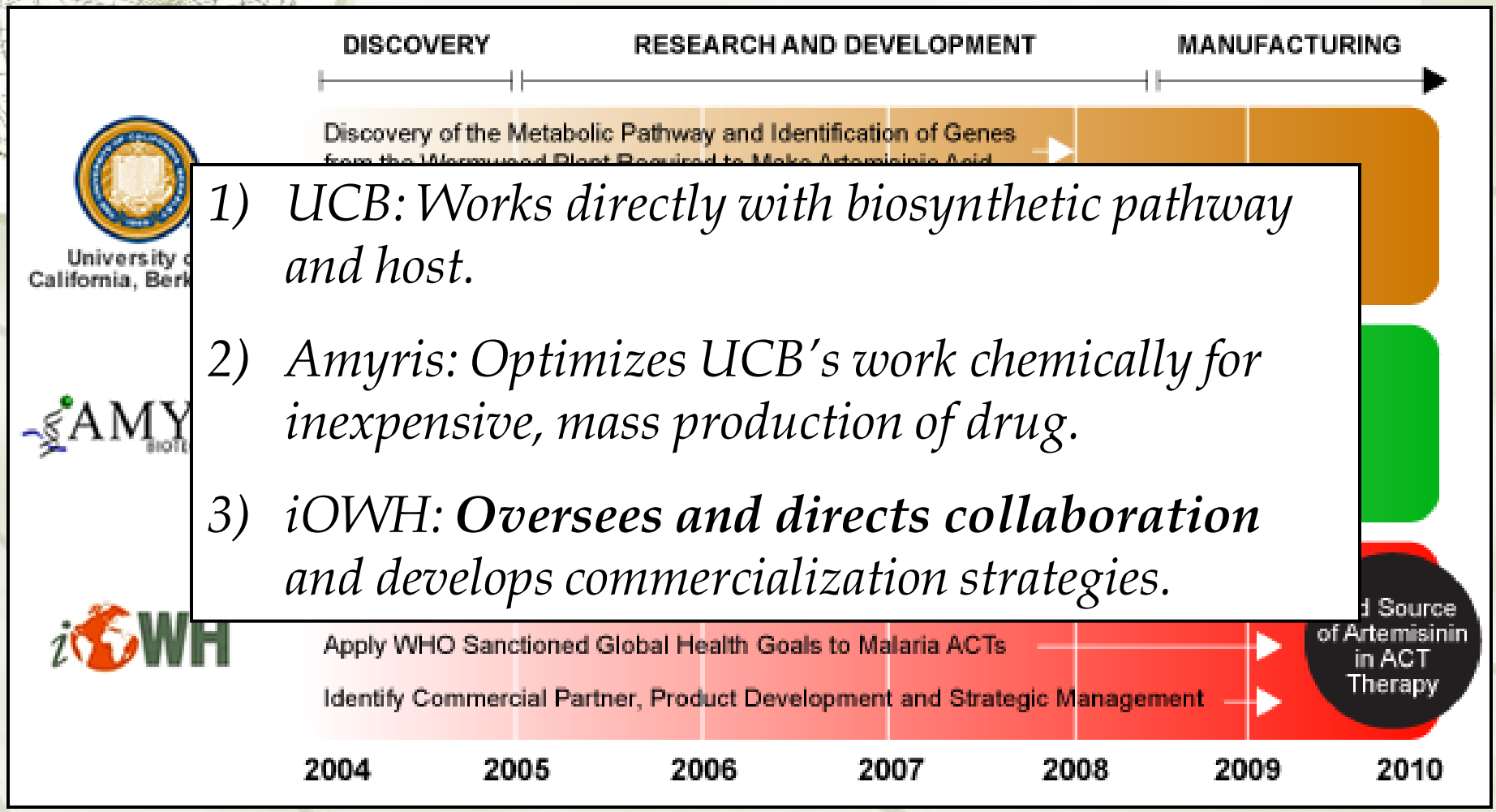
  2)Due to iOWH involvement, shareholders limited.

3 Institutions: Fusion into One Artemisinin Project

"**A unique *collaboration*** of representatives from academia, biotechnology, and the nonprofit sector is pioneering a bold approach **to make safe, effective antimalarial medicines *accessible* to people in poor countries**…Over the course of the grant, the project aims to create, optimize, scale-up, and industrialize microbial production systems **to make bulk artemisinin *available* for incorporation into ACTs**, at a low price with consistent high quality. A second source of artemisinin, in addition to plant-derived material, is needed to ensure global supply needs can be fulfilled due to current market volatility. iOWH is concurrently developing a commercialization strategy to facilitate integration of semi-synthetic artemisinin in high quality ACTs."

-The Artemisinin Project

What exactly is the Plan?



1) *UCB: Works directly with biosynthetic pathway and host.*

2) *Amyris: Optimizes UCB's work chemically for inexpensive, mass production of drug.*

3) *iOWH:* ***Oversees and directs collaboration*** *and develops commercialization strategies.*

Is this the Mode 3 SynBerc would like to see?

Collaboration: No, cooperation.

- Relay race analogy.
- Different goals fused together out of service to each other, but still with different ends.
  - Profit versus non-profit
- Phrase: "Oversees and directs Collaboration" of iOWH is problematic.

Artemisinin Project Advisory Board:

- Over ten people= All scientists.
- Called on as consultants.
- Where is thrust 4?

Kinkead Reiling of UCB/Amyris:

"Someone else has evaluated our team and technology… which will help attract future investors"… Downstream….

Some foreseeable problems on the American front…

- Vision is not fully shared/collaborative
- Keasling has patents on much of the technology being used. This is solved by royalty-free licensing to members of the Project.
- The Artemisinin Project is designing a cheap artemisinin to **sell** to pharmaceutical companies that have **already developed drugs**, **trusting** that they will lower their prices.
- Currently, Coartem of Novartis:
  - Has close ties with the iOWH and Berkeley
  - One of the only WHO sanctioned ACTs and by far the most supported.
  - Although patent is running out, will giving them new patented material lead to a monopoly?
  - Says $2.40 a pop, but many Sub-Saharan countries claim that the actual purchase cost is over $8.
  - Last year nearly 62,000 million treatments of Coartem were in Africa. It has claimed only to save 200,00 lives.

And on the Ghanaian front…

- Cultural views of malaria and prevention as detailed earlier
- Takes nearly all of the cash-flow to the Ghana Health Service to purchase ACTs
- Difficulty in distribution to the majority of the rural population
- Disenchantment of Ghanaians toward ACTs:

  Against WHO recommendation, Ghana requested to use artesunate-amodaquine instead of Coartem. WHO gave approval in 2005 and began sending shipments over. However, without the needed 6 months of training for a new drug, doctors began prescribing a cheap, locally harvested, and non-regulated version of the ACT at overly high doses. Population, like Jan, suffered mass hallucinations.
- Now, compliance of public health policy has been weakened at all levels and efforts to improve through education have not been successful.

In Conclusion…