Researchers at DesignMedix, led by Dr David Peyton, have successfully combined two bioactive compounds to restore the effectiveness of an anti-malarial drug neutralised by the emergence of resistant strains. Their work is paving the way for a new approach to combatting the growing problem of drug resistance.

Resistance is futile: hybrid drugs become the latest weapon in the biological arms race

What led you to look into chemical synthesis as a means of overcoming drug resistance?

The ‘gold-standard’ drug, chloroquine, had been lost, at least to its traditional use, and so we had to find another way forward. The simplest and least expensive way to salvage the best features of chloroquine was to make a ‘better chloroquine’, at least better given the current state of drug-resistance across the developing world. This meant chemical synthesis, because there is no other way to get there.

In your view, what are the main challenges facing the development of drugs for the emerging economies market?

Bridging the ‘gap’ that exists between discovery and marketing. There are resources from agencies such as the NIH for university researchers, and even funds available through programmes (for example, the SBIR or STTR mechanisms in the US) that work quite well at the early stages. But it becomes more challenging to bridge the efforts as they become more expensive and depend on resources that are not internal to universities or small businesses, such as GLP service providers. These can be unfamiliar to traditional researchers and relatively expensive, making it challenging for the usual grant mechanisms to fund fully. Then, there is the obstacle of bringing the drug through the human trials – which will require teams and financial resources that are well beyond what almost any researcher originally involved in the enterprise of drug discovery would have thought about. For malaria, there are entities that can help, but that is less true for other markets.

What makes you confident that malaria will eventually be eradicated?

That is a very large question. I am confident that malaria can be eradicated. I am confident that malaria will be eradicated just as long as sufficient resources are dedicated to the effort for as long as it takes. I also believe that this is a very serious topic, and that we should not make the mistake of making it seem easier to do this than it will be. Unless there are some unforeseen developments, the eradication effort for malaria will take decades and constant dedication. But it will be worth it. The alternative is continual evolution of resistance against each generation of newly-developed tools.

What one piece of advice would you give to someone considering creating a start-up?

Don’t do it by yourself. A scientist needs help with the ‘business side’ of the process, and everything you do takes time. Without my partners in this enterprise, I’m sure we would have not made the progress we have.

The eradication effort for malaria will take decades and constant dedication. But it will be worth it
Malaria is a devastating disease which disproportionately affects emerging economies: it is estimated to cost African nations alone $12bn a year in healthcare costs and loss of economic output. This is compounded into the perfect storm when low-cost treatments are rendered ineffective due to the evolution of resistance in parasite populations. The search for novel therapies and other control methods is ongoing, but Dr David Peyton from Portland State University (PSU) is refusing to surrender in the battle against drug resistance.

With an academic career at PSU which focussed initially on home proteins, antigen-antibody binding, and virus particle formation, Dr Peyton naturally became involved with public health. On moving to the study of medicinal chemistry, with a particular interest in malaria treatment, he came across the issue of drugs lost to evolved resistance and developed a unique approach to combat the phenomenon.

Determined that chloroquine, the safest and least expensive drug to be used against the malarial parasite, should not be lost, Dr Peyton set out to re-engineer the compound to overcome the parasite’s evolved ability to eliminate the drug. Chloroquine diffuses into the acidic digestive vacuole of the parasite during the asexual stage of its life cycle, when it is within red blood cells degrading haemoglobin for nutrition. In the acidic environment of the digestive vacuole, chloroquine undergoes protonation: because acidity is effectively the number of free protons (H+) in a solution, some molecules will accept these free protons and be converted to a hydrochloride (or base, or converted to a hydrochloride (or base, or hydrobromide, or hydroiodide) by small numbers of simple reaction steps, chloroquine can be restructured to become essentially a protonated form of chloroquine. Dr Peyton and his team hypothesised that, by linking a second proton to the chloroquine molecule. Through a small number of simple reaction steps, chloroquine can be restructured to become essentially a hybrid with imipramine, prepared as a free base, or converted to a hydrochloride (or other) salt to promote water solubility.

**A NEW WEAPON EMERGES**

From more than two hundred similar compounds (termed ‘reversed chloroquines’), DM1157 returns a tool with chloroquine’s advantages to its previous status as a low-cost and effective weapon in the fight against malaria.

**RESEARCH OBJECTIVES:**

Dr David Peyton uses pioneering techniques to restore the effectiveness of drugs. His work focusses on low-cost, safe treatments for malaria.

**FUNDING**

- NIH/NIAD
- ONAMI (Oregon Nanoscience and Microtechnologies Institute) [http://onami.us/]

**COLLABORATORS**

- Dr Michael Riscoe, Portland VA Medical Ctr and OHSU
- Dr James Kelly, Portland State
- Dr Roland Cooper, Dominican University of California
- Dr Jutta Marfurt and Dr Ric Price
- Dr Steven Burgess
- Dr Lynn Stevenson and Dr Sandra Shotwell, co-founders of DesignMedix, Inc. [http://www.designmedix.com]

**BIO**

After a PhD at UCSB in 1983, and postdocs at Weill Cornell Medical College and UCD, Dr David Peyton began his academic career at PSU, focused on home proteins, antigen-antibody binding, and virus particle formation. He then moved into medicinal chemistry to study malaria and co-founded the company DesignMedix, Inc. He also studies the toxicology of tobacco products, including e-cigarettes. His career has thus become concerned with public health.

**CONTACT**

David H. Peyton, PhD
Room 323B SB-1 (office behind lab)
Professor of Chemistry
Portland State University
Portland, OR 97207-0751
E: peytond@pdx.edu
T: +1 503 725 4872
W: [http://www.pdx.edu/profile/davidpeynton]

For more information on malaria visit: [https://www.naid.nh.gov/topics/malaria/Pages/default.aspx]