Antiparasitic drugs; malaria and the forgotten ones

Parasite - an organism that lives in or on another organism (the host) and benefits by deriving nutrients at host’s expense

Impact on humanity

Neglected Tropical Diseases (NTDs) affect more than 1 billion people. 11/18 NTDs are parasites. Impact hardest on poor, developing countries.

- decreased health
- lack of money for treatment
- economic drag
- Global society (shipping and traveling), immunosuppression, still endemic

Transmission - direct, fecal-oral, vector, predator-prey

Giardia

Malaria

trophozoites
cyst

oocysts sporozoites schizonts liver

ookinetes mosquito

merozoites blood

zygotes

gametocytes

Neglected Parasitic Infections in USA

Chagas disease - 300,000 infected
Neurocysticercosis (tapeworm) - 1,000 yearly hospitalizations
Toxocariasis - 14% population exposure
70 people blinded yearly
Toxoplasmosis - 60 million infected
Trichomoniasis - 3.7 million infected

Challenges in combating infectious parasitic disease

*parasites range from simple eukaryotes that posses bateria cellular mechanisms to multicelled "higher" organisms that share many of the same cellular processes as hosts
*parasite have evolved to evade host immune system and even evidence of coevolution (sickle cell)
*fast generation times, organism ploidy, reservoir, vectors developing resistance, natural resistance mechanisms, ability to transfer resistance
*lack of funding as most heavily affected regions tend to poorer

Baran group meeting  
October 4th, 2014 

**Antiparasitic drugs; malaria and the forgotten ones**  
Kevin M. Oberg

**Malaria "bad air" - caused by Protozoan Plasmodium**  
2012: ~207,000,000 cases with estimated 627,000 deaths

- known since ancient times (decline of Roman empire?)
- prevention and vector control most effective
- greatest genetic pressure in recent human history  

**Quinine - inhibits hemoglobin crystallization?**

![Quinine structure](image1)


1700's: isolation and structure elucidation efforts began

1907: Rabe published structure  

**Rabe (Hamburg): 1918**

![Quinotoxine synthesis](image2)

**Chem. Ber.** **1918**, *51*, 466.  

**Prelog (University of Zagreb and Zurich): 1943**


**Woodward (Harvard): 1944**

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Uskokovic (Hoffmann-La Roche, Inc.): 1970

\[
\text{OMe} \quad \xrightarrow{\text{NaOAc}} \quad \text{OMe} \quad \xrightarrow{\text{O}_2, \text{KOTBu}, \text{DMSO, tBuOH}} \quad \text{OMe}
\]

\[
\text{O} \quad \xrightarrow{\text{Ar}} \quad \text{O} \quad \xrightarrow{1. \text{LDA}, \text{DMSO}, (\text{COCl})_2, \text{NEt}_3} \quad \text{OMe}
\]

N-protected quinotoxine

1. NaBH₄
2. HF


Taylor (Princeton): 1974

synthesis of Uskokovic conjugate addition precursor using Wittig olefination


Stork (Columbia University): 2001

\[
\text{LDA, OTBDPS} \quad \xrightarrow{\text{MeO}} \quad \text{OMe} \quad \xrightarrow{1. \text{LDA}, \text{DMSO}, (\text{COCl})_2, \text{NEt}_3} \quad \text{OMe}
\]

OMe

OMe

1. MsCl
2. Δ
3. O₂, NaH, DMSO

also see; N. Burns GM; Gilbert Stork
Classics in Total Synthesis II
Baran group meeting
October 4th, 2014

Antiparasitic drugs; malaria and the forgotten ones

Jacobsen (Harvard): 2004

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

1. \(\text{H}_2, \text{Ni}\)
2. \(\text{LDA, H}_2\text{O}\)

\[
\begin{align*}
\text{OTBS} & \quad \text{TBSO} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{i} & \quad \text{Ni}
\end{align*}
\]

1. \(\text{LDA, H}_2\text{O}\)


Kobayashi (Tokyo Institute of Technology): 2004

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{Ac} & \quad \text{Ac}
\end{align*}
\]

1. \(\text{O}_3, \text{NaBH}_4\)
2. \(\text{I}_2, \text{PPh}_3, \text{im}\)
3. \(\text{BnNH}_2\)


Antiparasitic drugs; malaria and the forgotten ones

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Chloroquine (Resochin)
Andersag (Bayer): 1934

Methylene blue

Inhibits hemozoin formation: *Biochimica et Biophysica Acta* 2014, 1840, 2032.

Mefloquine: Rush-Presbyterian-St. Luke's Army Malaria Research Project

Halofantrine: SRI International contract for Walter Reed Army Institute of Research

Qinghaosu (Artemisinin)

 McKenzie: normally paired with benflumetol (slower acting)

WHO technical report series 1990, 805

Gutekunst GM Molecules of Traditional Chinese medicine 2009

Cell 2011, 146, 855.

Parasitol Res. 2012, 111, 1.

5 step racemic synthesis = millions of saved lives

Project 523
lead investigator: Youyou Tu
China Academy of Chinese Medical Sciences

5 step racemic synthesis = millions of saved lives

Parasitol Res. 2012, 111, 1.
Antiparasitic drugs; malaria and the forgotten ones

Wei-Shan (Shanghai Institute of Organic Chemistry): 1983

(-)-citronellal

1. ZrBr₂
2. BH₃
3. BnCl
4. CrO₃

JACS 1973, 95, 6152.

GM Burns: Stork

1. Ba(OH)₂
2. (CO₂H)₂
3. Na, NH₃
4. CrO₃
5. CH₂N₂

Huaxue Xuebao 1983, 41, 574.

MeO₂C
Me

HCOOH

Qinghaosu


GM McKerrall 2011, singlet O₂

Hofheinz (Hoffmann-La Roche): 1983

(-)-isopulegol

1. HCl, MeOH
2. PCC
3. LDA, TMS

JACS 1974, 96, 3682.

GM Burns: Stork

1. Li, NH₃
2. PCC

G M Burns: StorkBnO

(-)-isopulegol

O

Bn


GM Maimone 2005 Classic Terpene

Qinghaosu

1O₂, -78 °C

MeOH

HCOOH

Qinghaosu

1O₂, 23 °C

DCM

assumed

1O₂, -78 °C

MeOH

en

[2+2]

Antiparasitic drugs; malaria and the forgotten ones

Avery (SRI International): 1987, 1992

Roth (George Mason University) and Acton (Walter Reed Army Institute of Research): 1989


GM Yuan Peroxide Chemistry (2014)

Ravindranathan (National Chemical Lab): 1990

"This work was funded by the U.S. Army. Contract number DAMD-17-85-C-5011."

Antiparasitic drugs; malaria and the forgotten ones

Liu (University of Alberta): 1993

\[ \text{(-)-}\beta\text{-pinene} \]

\[ \text{Tetrahedron Lett. 1991, 32, 2005.} \]

Constantino (Universidade de Sao Paulo): 1996

\[ \text{(-)-isopulegol} \]

\[ \text{Tetrahedron Lett. 1993, 34, 4435.} \]

Keasling (Berkeley): 2004

\[ \text{engineered} \]

\[ \text{Artemisinin} \]

\[ \text{Institute OneWorld Health Gates Fnd.} \]

Seeberger (Max-Planck Institute): 2012

\[ \text{Artemisinic acid} \]

\[ \text{Institute OneWorld Health Gates Fnd.} \]

Wei-Shan Roth/Acton process done in flow

\[ \text{Artemisinin} \]

\[ \text{Institute OneWorld Health Gates Fnd.} \]

Koichi Akibe Fnd.

Improvements; Nature 2013, 496, 528.
Antiparasitic drugs; malaria and the forgotten ones

Cook (Indiana University): 2012

1. TsNHNH2
2. nBuLi, DMF

1. (NH₄)₂MoO₄, H₂O₂
2. TsOH


Turconi and Burgard (Sonofi): 2014

1. H₂, RhL⁺
2. EtO₂CCl
3. O₂, hv, TFA

GM Yuan Peroxide Chemistry (2014)

After artemisinin resistance; the next generation?

Malaria vaccines

RTS,S vaccine (malaria protein + hepatitis B protein)


GSK with Gates Fdn.

Amphillectene

Shervi (TSRI): 2012

1. Li, lutidine
2. CuBr
3. MeMgBr


Gates Fdn.
Antiparasitic drugs; malaria and the forgotten ones

African trypanosomiasis (sleeping sickness) - caused by *Trypanosoma brucei*

1st stage

2nd stage - central nervous system has been invaded

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>melarsoprol</td>
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<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>eflornithine</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>suramin</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>trypan blue</td>
</tr>
</tbody>
</table>

Sanofi-Aventis and Bayer produce and donate all anti-HAT drugs to the WHO

- East African species - death w/in couple months
- West African species - death w/in couple years

Ehrlich had demonstrated polynaphthalene dyes to have trypanocidal activity

J. Biological Chem. 1992, 267, 150.

Toxic: 2.5-5% mortality

inhibits glycolysis? binds trypanothione? mechanism unknown...

irreversible inhibitor for ornithine decarboxylase (makes polyamines and needed for cell division)

Irreversible inhibitor for ornithine decarboxylase (makes polyamines and needed for cell division)

*Arginine* from *E. coli*

Toxicol. Sci. 2012, 130, 416.
Antiparasitic drugs; malaria and the forgotten ones

American trypanosomiasis (Chagas disease) - caused by *Trypanosoma cruzi*
- Kissing bug humans
- 1st stage, mild symptoms
- 2nd stage, chronic - 10-30 years 1/3 get heart failure, enlarged esophagus/colon

Giardiasis (beaver fever) - caused by *Giardia lamblia*
- Most common parasitic infection worldwide
- 3-7% in the US, some developing countries, up to 30%
- Usually mild symptoms
- Treatment with nitroimidazoles
- Metronidazole
  www.cdc.gov

Cryptosporidiosis - caused by *Cryptosporidium*
- Treatment primarily supportive


**Biochemical Pharmacology 2010**, 79, 1736.

These drugs cure up to 80% of acute phase patients.
Cure rate drops to 5-20% for chronic patients.
Antiparasitic drugs; malaria and the forgotten ones

Toxoplasmosis (cat poop parasite) - caused by *Toxoplasma gondii*
- between 10-80% infection in different regions
- feline → rodents/livestock → humans
- acute: influenza-like, immunocompromization can lead to encephalitis or eye damage
- latent: cysts in nervous and muscle tissue
- congenital toxoplasmosis - infection of the fetus from an infected mother (worst case: miscarriage, birth defects, vision impairment)

Leishmaniasis - caused by *Leishmania*
- sandflies → humans
- cutaneous (common) - open sore on skin
- visceral - internal organs (usually spleen, liver, bone)

Pentavalent Sb introduced in the 1940's
- meglumine antimonate
- sodium stibogluconate

Paromycin, pentamidine, neomycin, sitamaquine (chloroquine derivative)

Amphotericin B
- actually an antifungal agent
- binds ergosterol in cell membrane leading to pores
- less of this sterol in mammalian, but still toxic

For syntheses, see; Classics in Total Synthesis I

www.cdc.org
Antiparasitic drugs; malaria and the forgotten ones

Amoebiasis - caused by *Entamoeba histolytica*

- can be asymptomatic
- symptoms develop over weeks - diarrhea
- can move from intestines to systemic and cause some real problems

*Act*
inhibitor

antileishmanial activity overlooked due to potential anticancer properties
oral bioavailability, but long treatment times coupled with possible teratogenicity may hinder global use

Lots of antibiotics as well

Amoebic keratitis - caused by *Acanthamoeba*

usually affects contact users


Primary amoebic meningoencephalitits - caused by *Naegleria fowleri*

free-living → human nervous system

"brain-eating amoeba"

95% fatality rate

treatment with amphotericin, miconazole, miltefosine, the kitchen sink

Fluconazole and other triazoles inhibits 14α-demethylase
(mamalian enzyme is less sensitive)

Cyst → humans

Kept to the brain

95% fatality rate


Chlorhexidine

Metronidazole resistant strains have been detected...


170 million worldwide
(inapparent infections in women up to 50% and higher in men)

Omeprazole

Only approved drug in US


Diiodohydroxyquinoline

Diloxanide furoate

Lysophosphatidylcholines

Clinical Microbiological Reviews 2004, 17, 783.
Antiparasitic drugs; malaria and the forgotten ones

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Helminths (worms) - platyhelminths (flatworms), acanthocephalins (thorny-headed worms), nematodes (roundworms)

via poor hygiene or vectors

Eggs/larva humans

Onchocerciasis (river blindness or Robles disease) - caused by *Onchocerca volvulus*

Drugs act in two ways: killing or stunning

Killers:

- Mebendazole
  - Inhibits microtubule synthesis

- Niclosamide (tapeworms)
  - Oxidative phosphorylation decoupler

Stunners:

- Praziquantel
  - Membrane disruption and paralysis

- Pyrantel pamoate
  - Depolarizing neuromuscular blocking reagent


- Omeprazole
  - Arachidonic acid metabolism inhibitor

- **Avermectins**

  - In *Nature* 1991:
    - 2004 Synthesis of imidazoles
    - 1995 Total syntheses of avermectins

  - Isolation of avermectins from Kitasato Institute (OS-3153) - *Streptomyces avermitilis* "capable of separating from worms"


**In vivo** screening: "by no means serendipitous; those who were seeking found what they sought."
Antiparasitic drugs; malaria and the forgotten ones

Streptomyces avermitilis fermentation → avermectin → avermectin

\[ \text{H}_2, (\text{PPh}_3)_3\text{RhCl} \]

Ivermectin interacts with ligand gated channels causing paralysis

Donations by Merck to WHO for eradication

Emodepside causes paralysis through excessive neurotransmitter release

Solid phase synthesis; see, Eur J Org Chem 2012, 1546.