

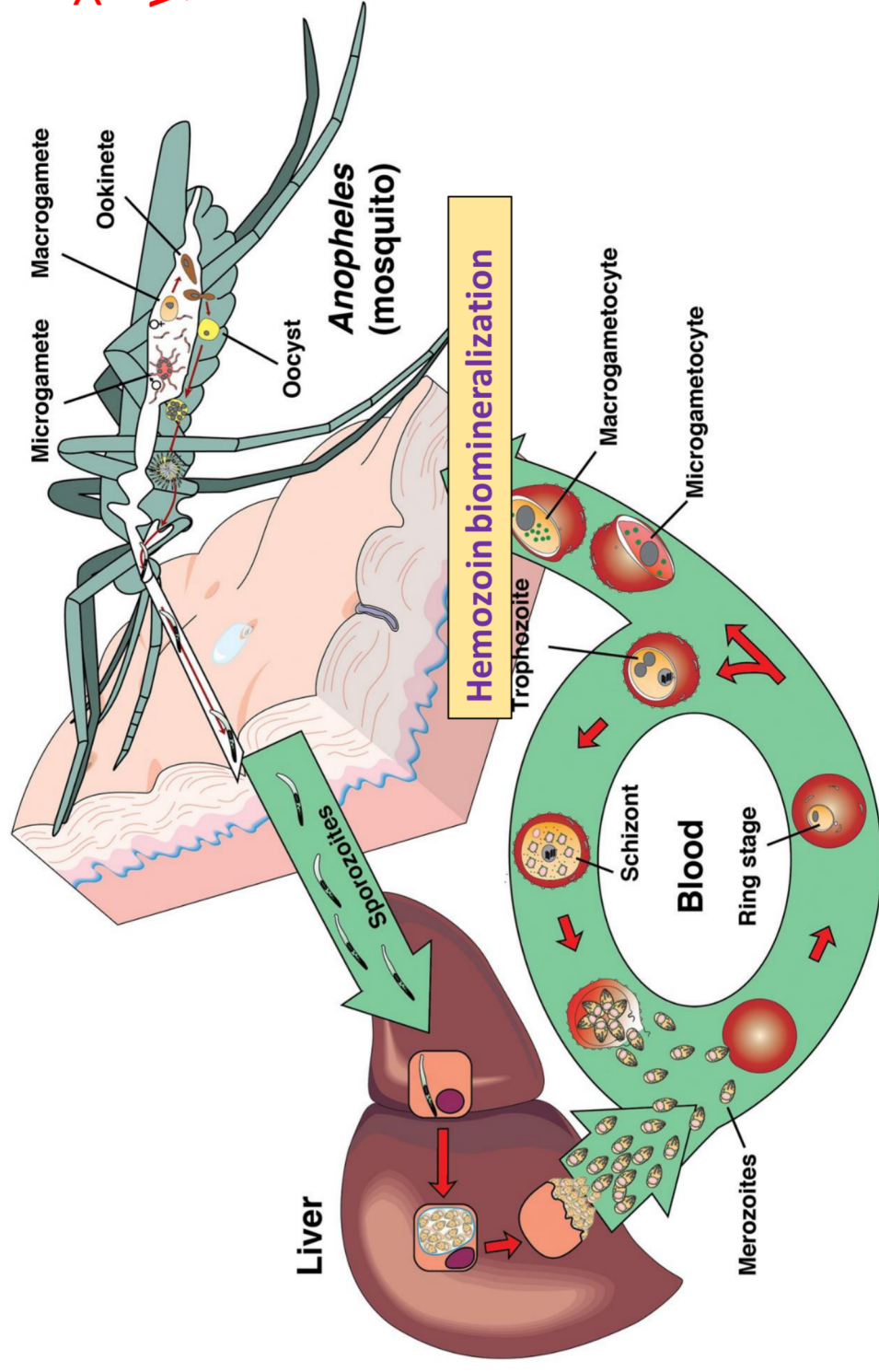


Screening FDA-approved drugs and natural compounds for hemozoin biomaterialization inhibitors in *P. falciparum*

Sihle Thabethe

Supervised by Dr C. Barnett and Prof. T.J. Egan

Life Cycle of the Parasite

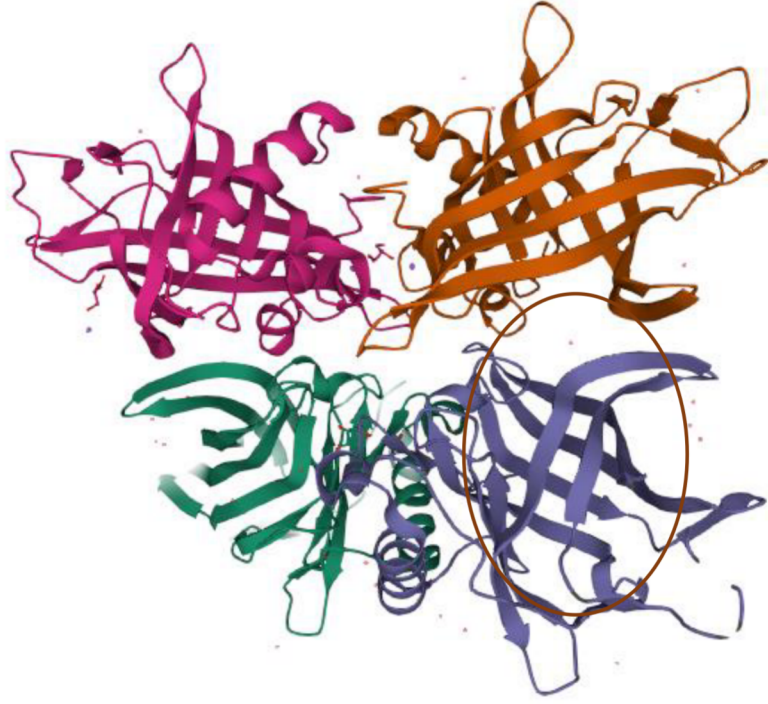


>400k deaths
yearly

Alan F. Cowman, Christopher J. Tonkin, Wai-Hong Tham, Manoj T. Duraisingh, The Molecular Basis of Erythrocyte Invasion by Malaria Parasites, Cell Host & Microbe, Volume 22, Issue 2, 2017, Pages 232-245



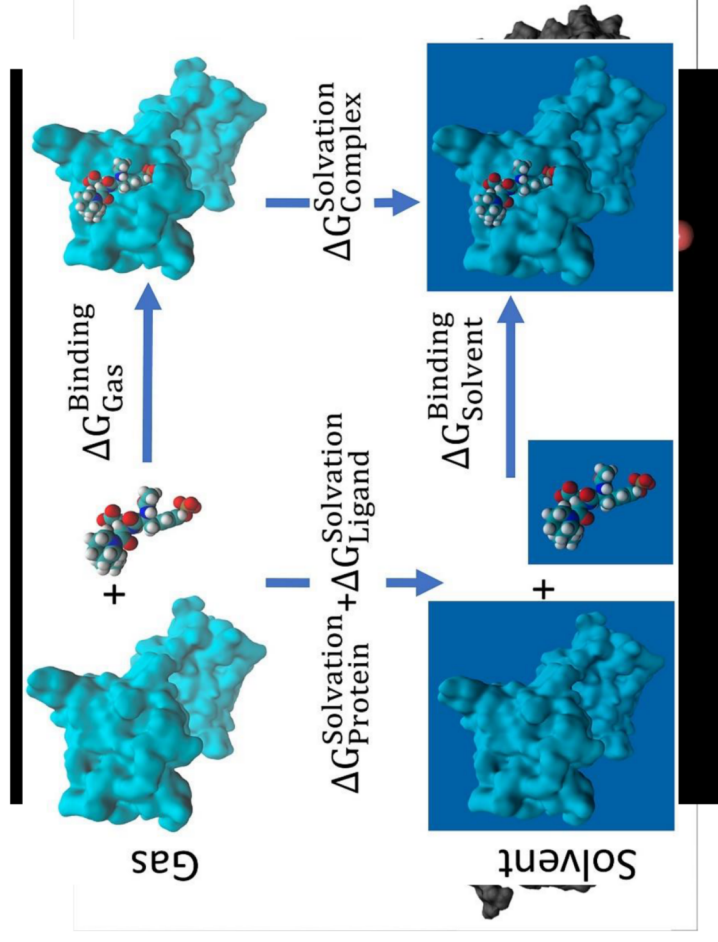
P. falciparum Lipocalin



- Proteins of the lipocalin family bind *small hydrophobic ligands*. Are involved in various physiological processes ranging from lipid transport to oxidative stress responses
- Trafficked to the digestive vacuole
- Functions involve Heme biomineralization and Relieving oxidative stress (mostly caused by ROS)
- Mutation in PfLCN shows improved antimalarial sensitivity



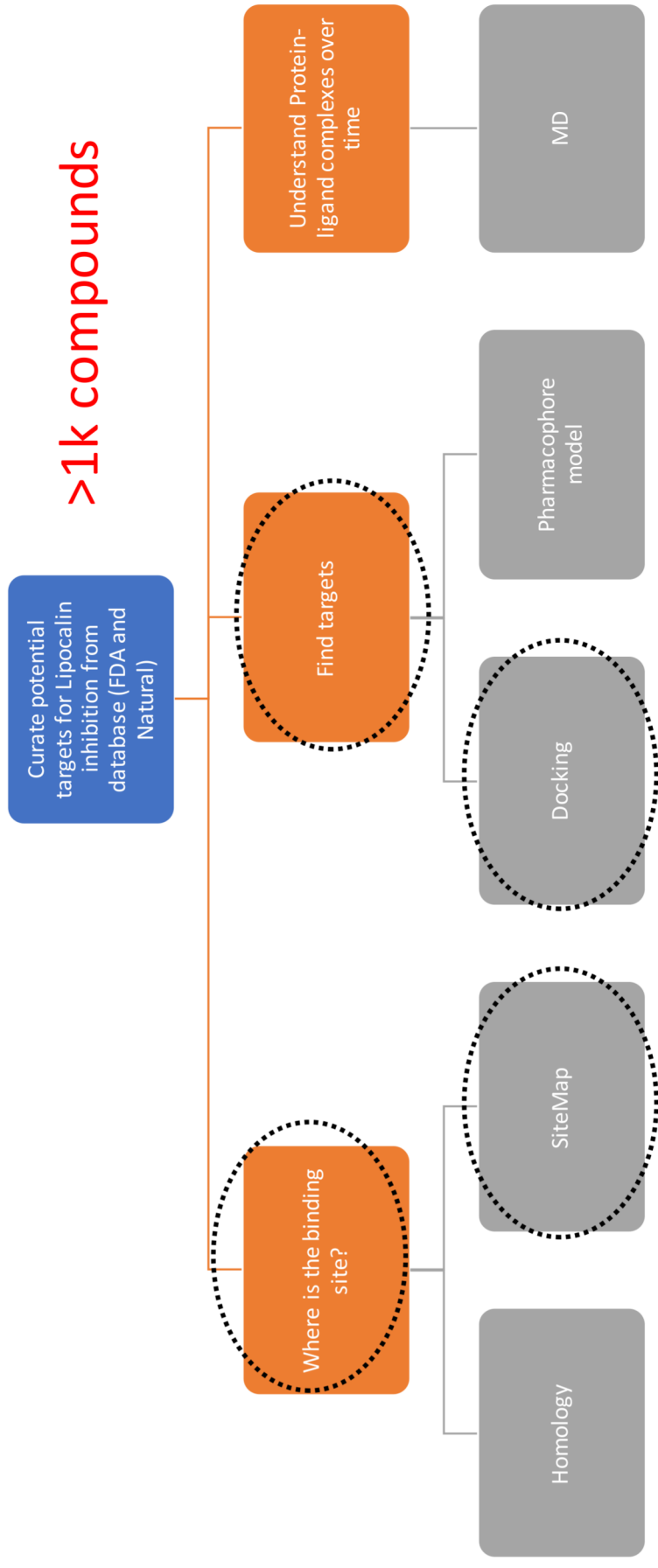
Methods



- **Molecular Docking and cheminformatics**
 - Key and lock strategy. Which molecules are likely to bind?
- **Molecular Dynamics**
 - A molecular microscope. Do molecules stay in the binding site? What happens to molecules over time?
- **Free Energy simulations**
 - MMGBSA as a scoring/ligand binding metric
 - In future: Accurate free energy calculations will require proper FEP methods



Overview



Results

Row	In	Title	Stars	Indication	red Y SD	Y Domain Score	Y Domain Alert	XP GScore	Column 1	Column 2	MMGBSA dg	ensemble receptor
103...	○	— SANC00675_minRM1.pdb	☆☆☆					-9.058			-58.09 1	
103...	○	— SANC01087_minRM1.pdb	☆☆☆					-10.135			-48.49 1	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-9.244			-48.00 1	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-9.551			-45.43 1	
103...	○	— SANC00784_minRM1.pdb	☆☆☆					-5.194			-45.20 3	
103...	○	— SANC00769_minRM1.pdb	☆☆☆					-5.246			-45.16 3	
103...	○	— SANC01083_minRM1.pdb	☆☆☆					-9.688			-43.86 1	
103...	○	— SANC00975_minRM1.pdb	☆☆☆					-8.942			-42.94 1	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-7.218			-42.73 2	
103...	○	— SANC01088_minRM1.pdb	☆☆☆					-7.540			-41.77 2	
103...	○	— SANC00762_minRM1.pdb	☆☆☆					-5.359			-41.41 3	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-5.526			-38.39 3	
103...	○	— SANC00861_minRM1.pdb	☆☆☆					-7.877			-38.04 2	
103...	○	— SANC00997_minRM1.pdb	☆☆☆					-7.639			-37.45 2	
103...	○	— SANC00845_minRM1.pdb	☆☆☆					-8.295			-37.14 2	
103...	○	— SANC00931_minRM1.pdb	☆☆☆					-5.190			-36.96 3	
103...	○	— SANC01113_minRM1.pdb	☆☆☆					-5.249			-36.56 3	
103...	○	— T3616	☆☆☆					-6.078			-34.97 2	
103...	○	— SANC01058_minRM1.pdb	☆☆☆					-5.543			-34.56 3	
103...	○	— T0725	☆☆☆					-7.670			-34.16 1	
103...	○	— SANC01085_minRM1.pdb	☆☆☆					-8.107			-34.11 2	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-9.461			-32.75 1	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-5.430			-32.58 3	
103...	○	— phasedb_WholeDrugFragment11...	☆☆☆					-7.655			-31.55 2	
103...	○	— SANC00284_minRM1.pdb	☆☆☆					-8.232			-29.87 2	
103...	○	— SANC00338_minRM1.pdb	☆☆☆					-8.926			-29.06 1	
103...	○	— T0525	☆☆☆					-4.738			-26.54 3	



Conclusions & future work

- Successfully screened over 1k cpds using VSW
- GPU, serial and serial-long jobs
- Ongoing MD
- Free energy
- Experimental work



Thank you !

I am thankful for the support from:

- ☐ University of Cape Town (UCT)
- ☐ Scientific Computing Research Unit
- ☐ Prof Egan's Heme group
- ☐ My supervisors: Dr Barnett and Prof Egan
- ☐ Leah Amod

