



# Global Drug Discovery for Malaria

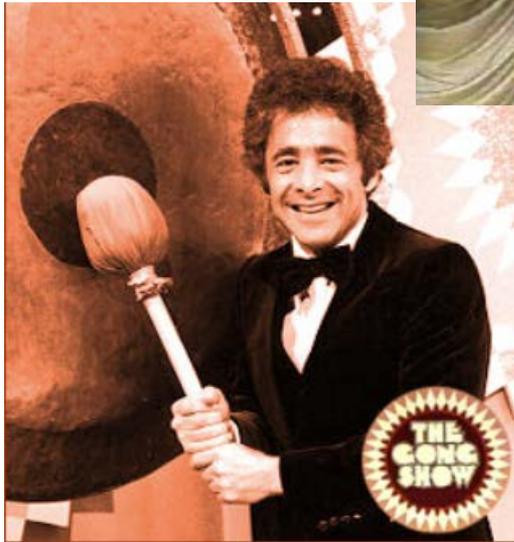
Paul Willis

Director Drug Discovery, MMV

Swiss TPH Winter Symposium, Basel December 2016

Defeating Malaria Together

**MMV**   
Medicines for Malaria Venture

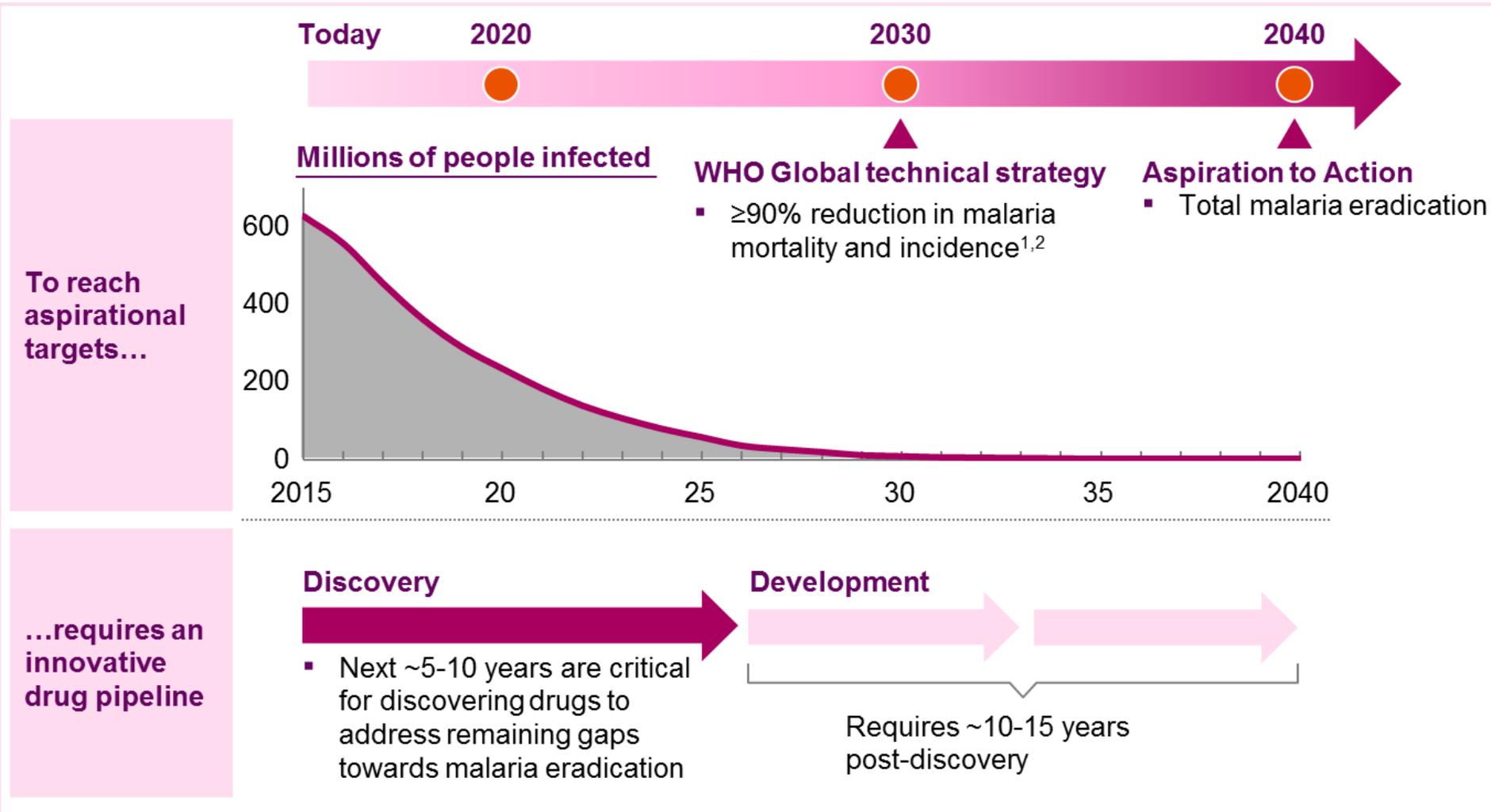


# MMV's Mission & Goal

- MMV was established in 1999
  - **MISSION:** discover, develop and deliver safe, effective and affordable antimalarial drugs
- A not-for-profit Product Development Partnership (PDP)
  - **GOAL:** cure and protect the vulnerable and help to ultimately eradicate malaria



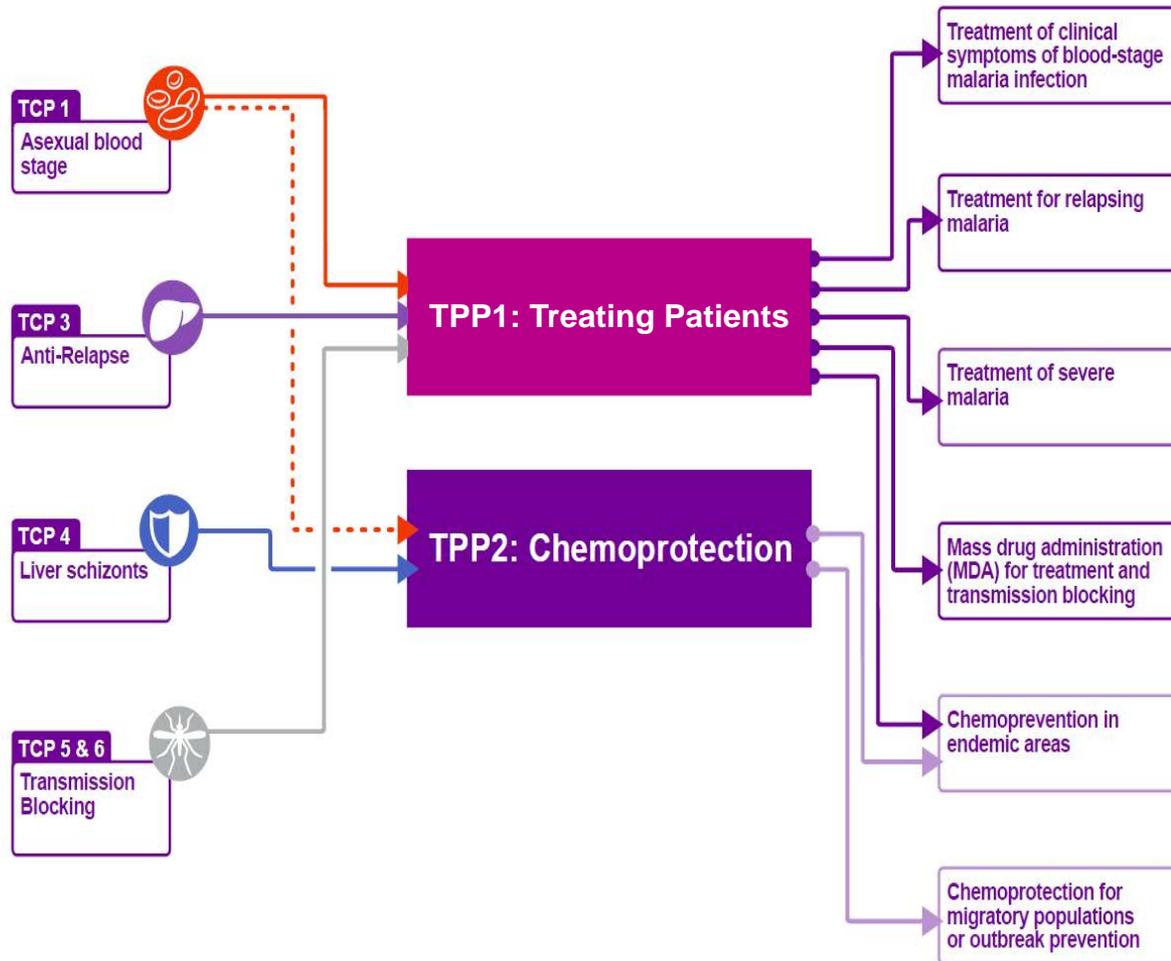
# The need for an innovative drug pipeline



<sup>1</sup> Compared to 2015

<sup>2</sup> Milestones by 2030 include eradication in  $\geq 35$  countries and prevention of re-establishment

# Agreeing the characteristics that are needed



# Agreeing definitions for candidate profiles

Burrows et al. *Malaria Journal* 2013, **12**:187  
<http://www.malariajournal.com/content/12/1/187>



**REVIEW** **Open Access**

## Designing the next generation of medicines for malaria control and eradication

Jeremy N Burrows, Rob Hooft van Huijsdijnen, Jörg J Möhrle, Claude Oeuvray and Timothy NC Wells\*

### Abstract

In the fight against malaria new medicines are an essential weapon. For the parts of the world where the current gold standard artemisinin combination therapies are active, significant improvements can still be made: for example combination medicines which allow for single dose regimens, cheaper, safer and more effective medicines, or improved stability under field conditions. For those parts of the world where the existing combinations show less than optimal activity, the priority is to have activity against emerging resistant strains, and other criteria take a secondary role. For new medicines to be optimal in malaria control they must also be able to reduce transmission and prevent relapse of dormant forms: additional constraints on a combination medicine. In the absence of a highly effective vaccine, new medicines are also needed to protect patient populations. In this paper, an outline definition of the ideal and minimally acceptable characteristics of the types of clinical candidate molecule which are needed (target candidate profiles) is suggested. In addition, the optimal and minimally acceptable characteristics of combination medicines are outlined (target product profiles). MMV presents now a suggested framework for combining the new candidates to produce the new medicines. Sustained investment over the next decade in discovery and development of new molecules is essential to enable the long-term delivery of the medicines needed to combat malaria.

**Keywords:** Malaria, Plasmodium, Anopheles, Drug discovery, Medicines, Target candidate profile, Target product profile, MMV

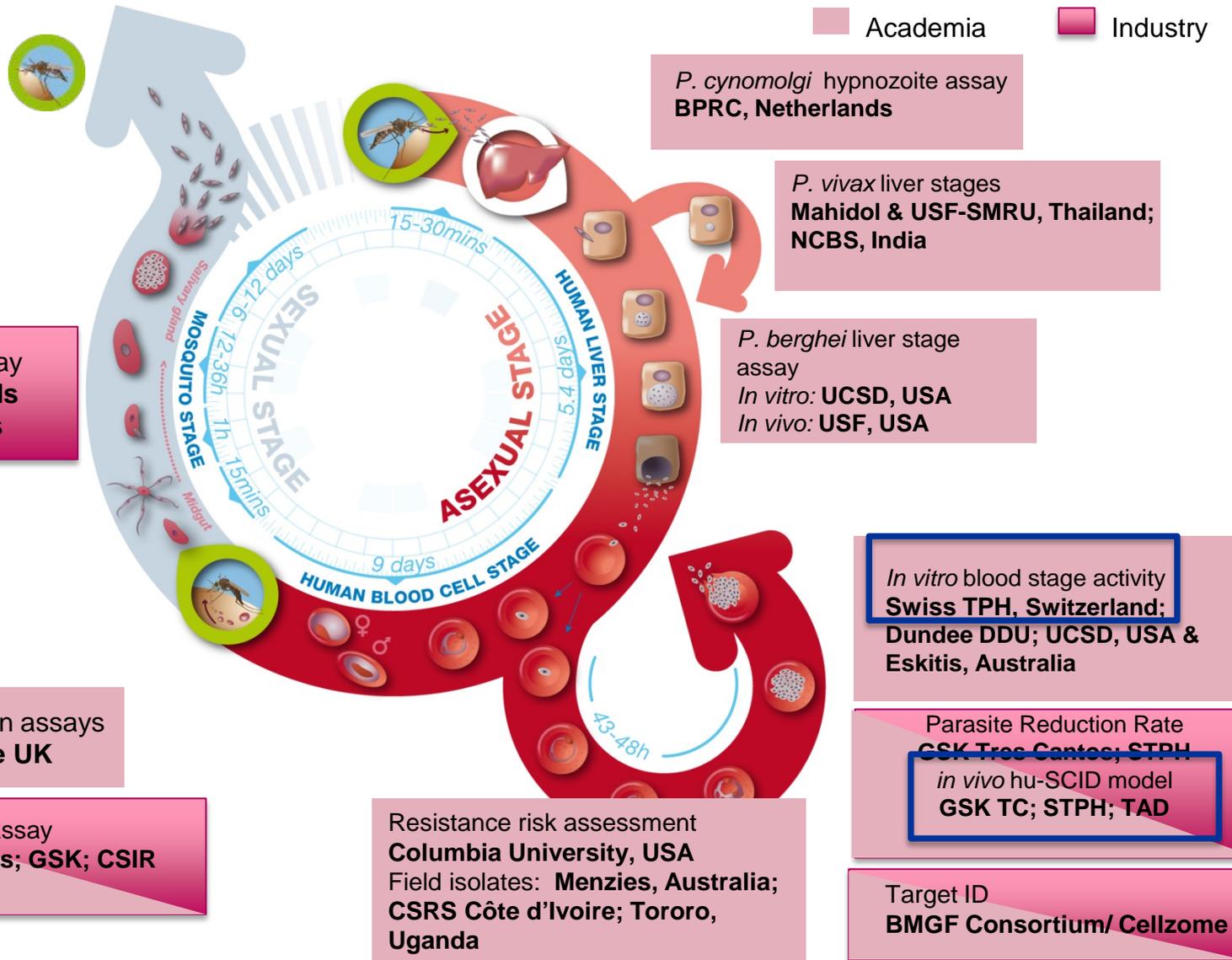
**Table 1 TCP-1**

TCP-1 criteria at human proof of concept	Minimum essential	Ideal
Dosing regimen; adult dose*	Oral, one-three doses; <1,000 mg	Oral, single dose; <100 mg
Rate of onset of action and clinical parasite reduction ratio from single dose	Immediate and rapid clearance of parasites at least as fast as chloroquine; > 6 log unit total reduction in parasites	Immediate and rapid clearance of parasites at least as fast as artesunate; > 6 log unit total reduction in parasites
Susceptibility to loss of efficacy due to acquired resistance	Low (better than atovaquone); no cross resistance with TCP-2	Very low (similar to chloroquine); no cross resistance with TCP-2. Resistance markers identified
Clinical efficacy from single dose (day 7) including patients from areas known to be drug-resistant to current first line medications	100%	
Clinical efficacy from single dose (ACPR at day 28 or more, per protocol, PCR-corrected)	>50%	>95%
Bioavailability /Food Effect - human data	>30%, <3 fold	>50%, none
Drug- drug interactions	No unmanageable risks	No interactions with other anti-malarial, anti-retroviral or TB medicines
Safety - clinical	Acceptable therapeutic ratio based on human volunteer studies between exposure at human effective dose and NOAEL, dependent on nature of toxicity	Therapeutic ratio >50 fold based on human volunteer studies between exposure at human effective dose and NOAEL; benign safety signal
G6PD (Glucose-6-phosphate dehydrogenase) deficiency status	Measured - No enhanced risk in preclinical data from relevant G6PD deficient animal models	Measured - No enhanced risk in G6PD deficient subjects
Formulation	Acceptable clinical formulation identified	
Cost of active ingredient in final medicine	Similar to current medication: ≤\$0.5 for adults, \$0.1 for infants under two years	Similar to older medications: <\$0.25 for adults, \$0.05 for infants under two years
Projected stability of final product under Zone IVb conditions (37°C 75% humidity)	≥ 6-24 months	≥1-5 years

\*As discussed in the text, should frontline therapies be lost due to reduced efficacy or tolerability then a regimen over 3 days of dosing of novel well tolerated candidates that overcome any resistance will be acceptable.

Updated version submitted to Malaria Journal (2016)

# Lifecycle assays - Preclinical

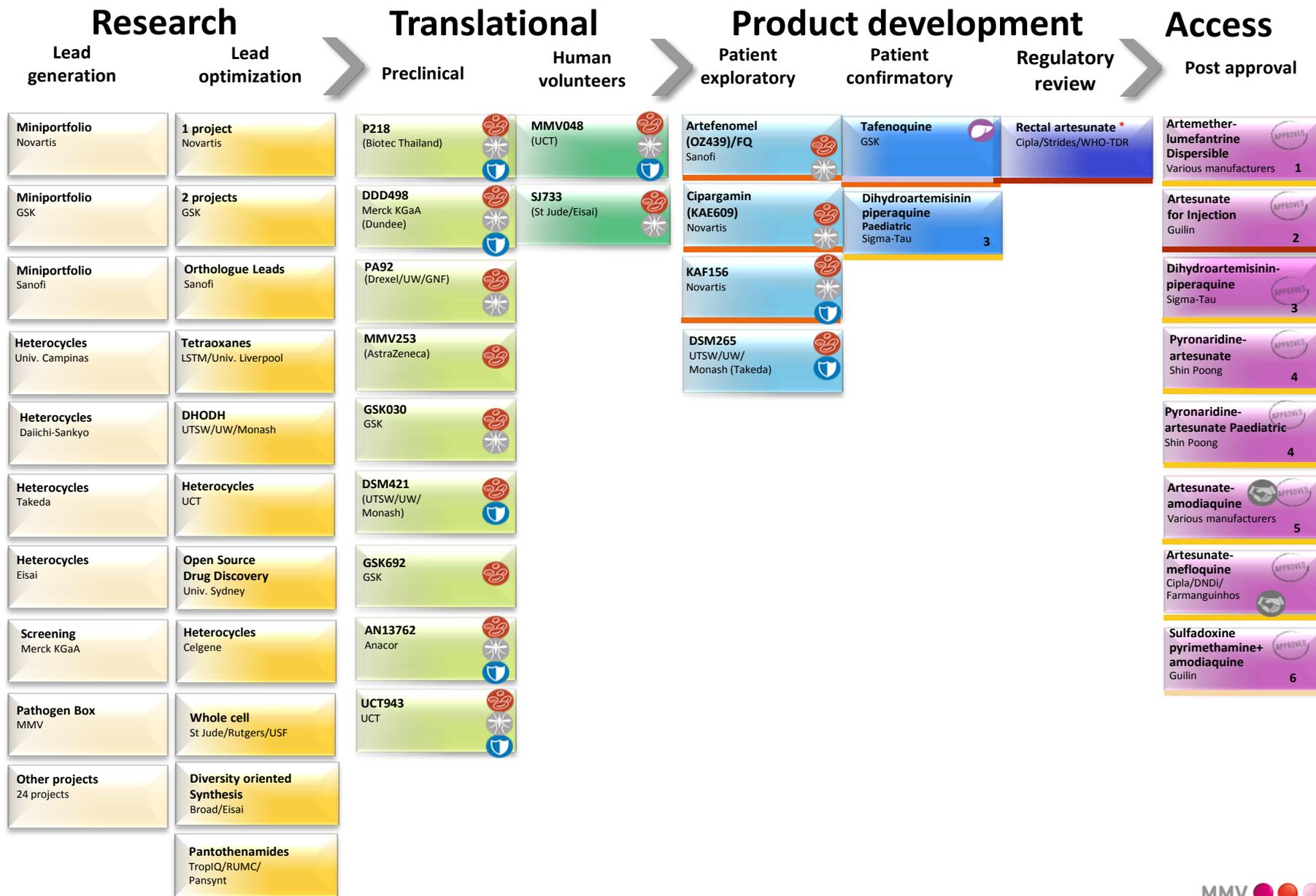


# Vivax liver stages

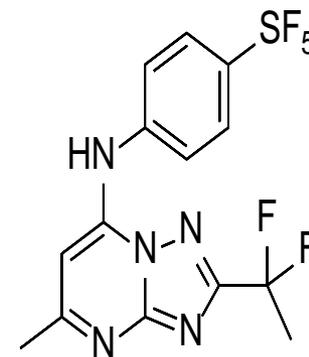
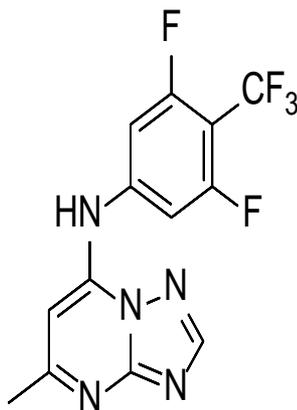
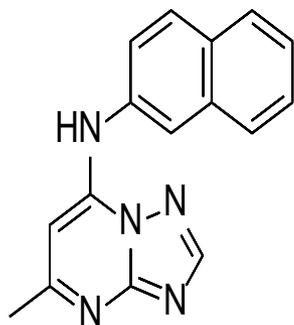
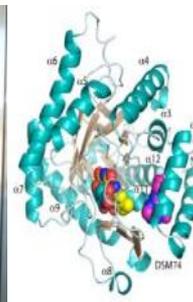
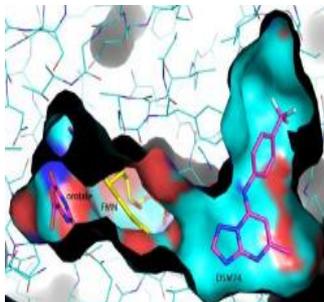


- **USF-SMRU Thailand**
  - Dennis Kyle & François Nosten
  - Use of primary cells; spatial confinement; 384 well assay
  - Compound metabolism (lower hit rate?) vs most physiological relevance
- **Mahidol University Thailand**
  - Jetsummon Sattabongkot
  - *Pv* sporozoites infecting non-metabolising HC04 liver cells in 8-96 wells
  - Working to improve throughput – 384 wells
- **NCBS/ NIMR India**
  - Logistics associated with *Pv* sporozoite hepatocyte infections in India (Varadha Sundaramurthy NCBS/ Susanta Ghosh NIMR) underway

# MMV-supported projects 2Q 2016



# Molecular Design: DHODH



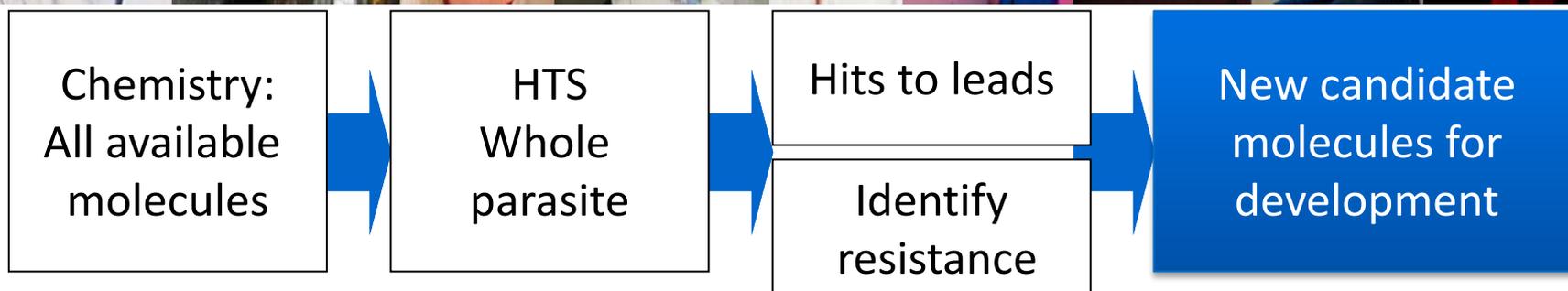
**DSM1**  
EC<sub>50</sub> 3D7 79 nM  
No oral efficacy

**DSM191**  
EC<sub>50</sub> 3D7 220 nM  
ED<sub>90</sub> *Pf* SCID 57 mg/kg

**DSM265**  
EC<sub>50</sub> 3D7 8 nM  
ED<sub>90</sub> *Pf* SCID 8.1 mg/kg

- Phase IIa completed December 2015

# Ask the parasite

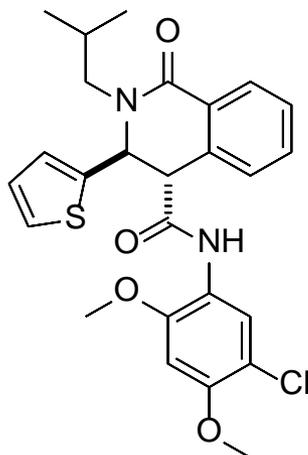


- Screened over seven million compounds: 25,000 hits
- Computational model built based on HTS data
- Fast to human trials; 12 candidates delivered
- Identifies new targets

Rottman M, *et al. Science* 2010;325:1175-80;  
Meister S, *et al. Science* 2011;334:1372-77;  
Gamo FJ, *et al. Nature* 2010;465(7296):305-10;  
Guigumde WA, *et al. Nature* 2010;465:311-15;  
Wells TNC, *et al., Science*.2010;329:1153-54

# SJ'733 – Dihydroisoquinolones

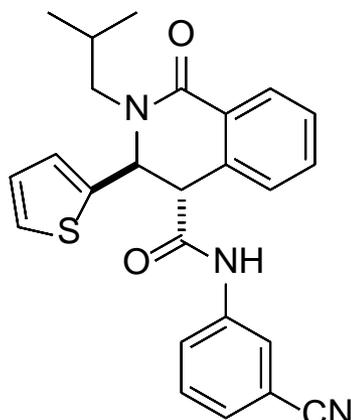
PNAS 16, 2014 (111) 50 E5455



SJ'247 "Hit"  
EC<sub>50</sub> 3D7 10nM  
*In vivo* no efficacy



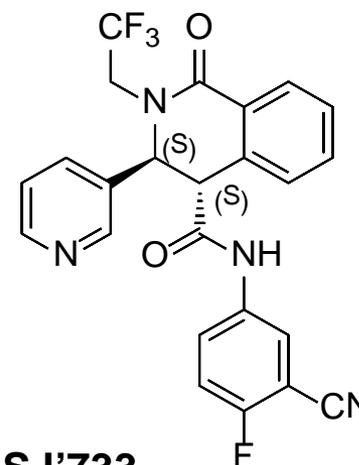
Improvement in  
Metabolic stability  
and *in vivo* efficacy



SJ'279 "Early Lead"  
EC<sub>50</sub> 3D7 50nM  
*P. Berghei* ED<sub>90</sub> <300mg/kg



Optimisation of  
aniline, metabolic  
stability, potency  
and physical  
properties



**SJ'733**  
EC<sub>50</sub> 3D7 23nM  
*P.b.* ED<sub>90</sub> 50mg/kg  
*P.f.* ED<sub>90</sub> 2mg/kg

- Excellent *in vivo* efficacy and kills gametocytes
- Inhibits *Pf* ATP4 – new chemotype
- Excellent safety profile
- Collaboration with Eisai and GHIT up to proof of concept



GHIT Fund  
Global Health Innovative Technology Fund



Australian  
National  
University



Syngene



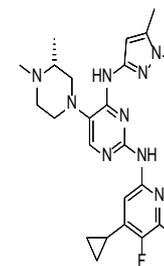
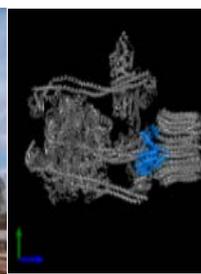
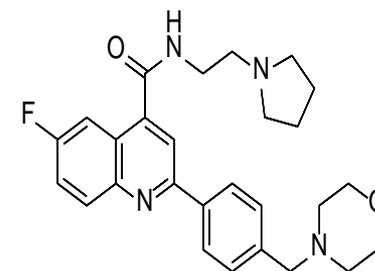
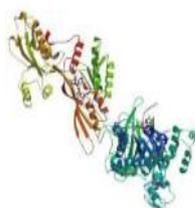
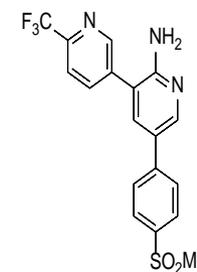
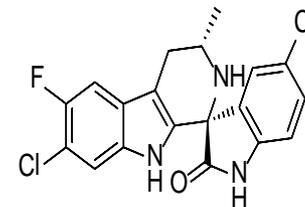
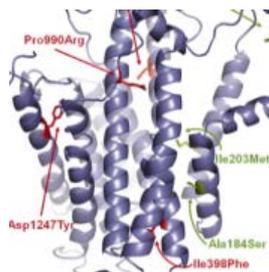
RUTGERS  
UNIVERSITY



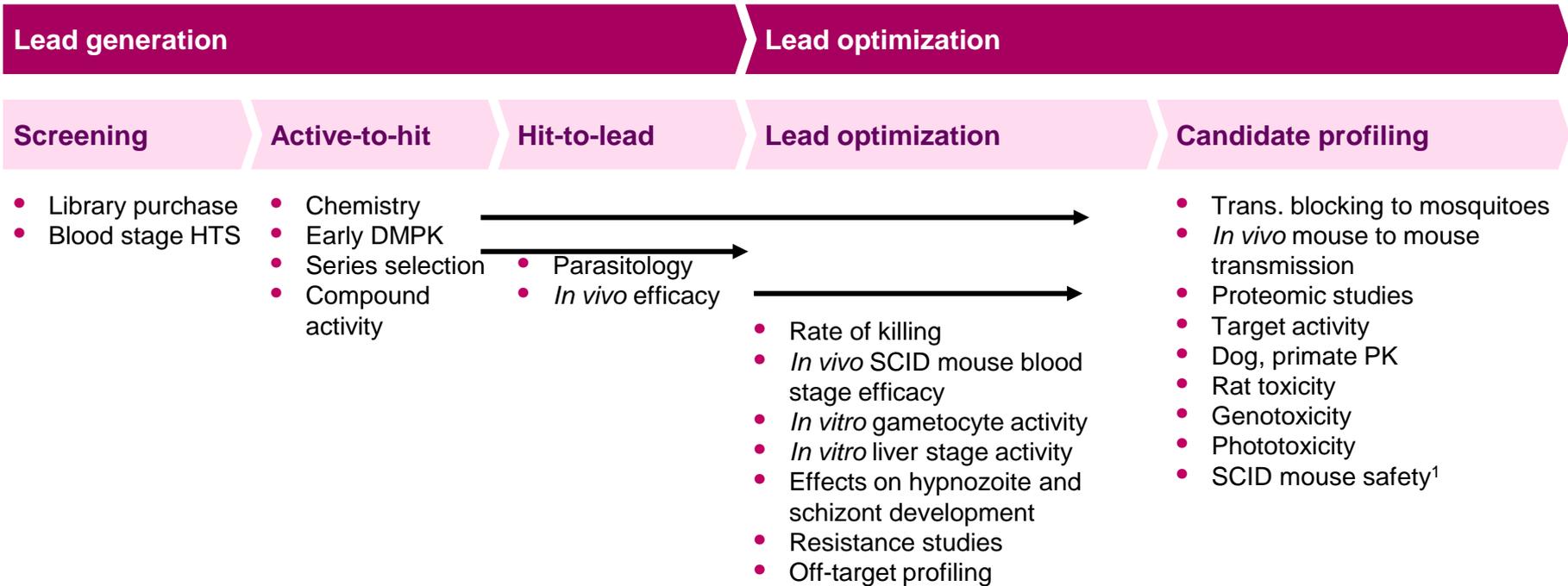
MMV Medicines for Malaria Venture



# Optimising phenotypic hits



# Partner engagement in MMV048 progression



MMV actively coordinate network of partners to draw best expertise when needed as needed



# New generation of molecular targets from phenotypic screening

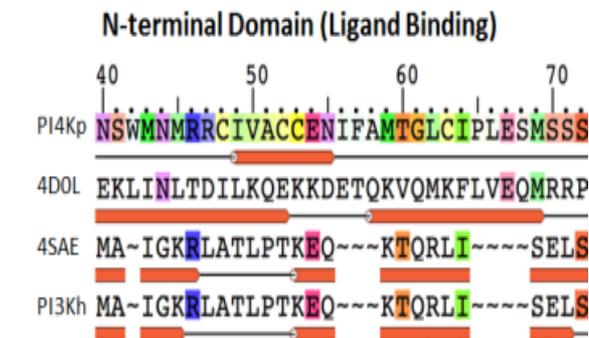
Chemotype	Biological Target	Molecules
Multiple series	ATP4	KAE609, SJ733, GSK030, PA92
Triazolo-pyrimidine	DHODH	DSM265, DSM421
Amino pyridine	PI4K	MMV048, MMV943
Quinoline amide	EF2	DDD498
Triamino-pyrimidine	V-type H+ ATPase	AZ412

Compound	Resistance gene/target (new discovery/validation in bold) 130 genomes sequenced for 24 compounds	Mechanism
MMV006767	PCMT (PF3D7_070800)-SNV	SNV
MMV007564	PCARL (PF3D7_021900) See Vegetriado et al. ACS Infectious Diseases 2016	SNV
MMV008149	cytochrome b1 (P4, P4L, P)	SNV
MMV009108	RND Transporter (PF3D7_010700)-A118T	SNV
MMV019066	serine/threonine beta subunit (PF3D7_114700)	SNV
MMV019662	RND transporter (PF3D7_010700)	SNV
MMV020746	ABC Transporter (PF3D7_021900)	SNV
MMV027634	functional dihydrofolate reductase (PF3D7_041700)	SNV
MMV029272	cellulose synthase peptidase SPAP1 (PF3D7_111670)	SNV
BRD1095	phenylalanine tRNA ligase (PF3D7_010800) Kato et al. under review	SNV
MMV019719	conserved protein (PF3D7_040400)-K216K, Acyl-CoA synthetase ACSB11 (PF3D7_020800)-F36Y	SNV
MMV011895	amino acid transporter (PF3D7_062900), PCMT (PF3D7_070800)	SNV
MMV665924	ACSB10 (PF3D7_062900), ACSB11 (PF3D7_020800)	SNV
MMV024114	PCMT (PF3D7_070800), aminopeptidase (PF3D7_040400)	SNV
MMV028038	RND transporter, pre-ribosomal assembly protein	SNV
MMV007224	PKA/Pka2 (PF3D7_020800) - 2.5x amplification in 3/3	CNV
MMV009063	PKOR1 (PF3D7_020800) - 3x amplification CNV	CNV
MMV665789	PKOR1 (PF3D7_020800) - 3x amplification CNV	CNV
MMV665882	putative transporter (PF3D7_020800), conserved protein (PF3D7_020800) - 3x amplification CNV	CNV
MMV665939	ABC Transporter (PF3D7_010700) - SNVs in 3/6, 2x amplification in 3/6	CNVs and SNVs
MMV673482	Pfk (PF3D7_020800) - SNVs in 4/6, 2.5x amplification in same gene in 1/4	CNVs and SNVs
MMV668399	Pfk domain protein (PF3D7_020800) - SNVs in 5/6, partial deletion in 1/6	CNVs and SNVs
sulfonamide glycoside	Phosphofruktokinase (PF3D7_021900)	SNV
TCMDC135051	Serine Threonine Kinase (STK) (PF3D7_010700)	SNV

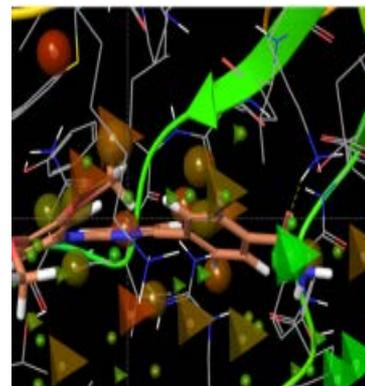
... also identifies resistance-proofed scaffolds

# New Chemotypes by calculation

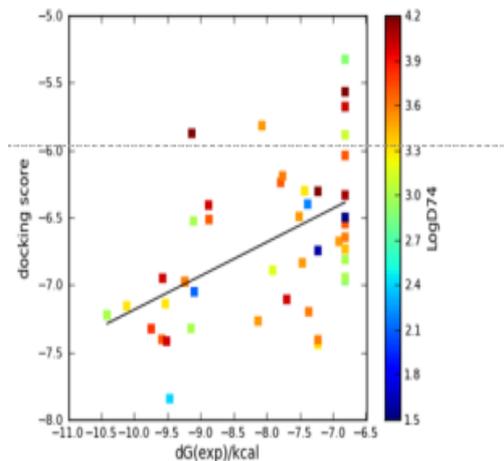
## Sequence alignments



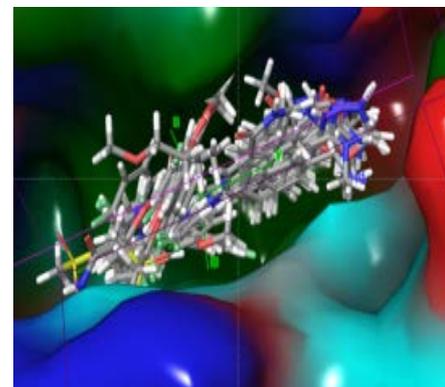
## Homology models/docking



## Validating models to drive compound design



## Prioritization of new chemistry





# Malaria Box 2011–15



- 400 compounds selected from the 20'000 original hits, confirmed blood stage actives
- Supplier information available allowing repurchase and Structure Activity Relationships
- PK data (mouse) and metabolism data available – about 30% had excellent oral bioavailability
- Supplied free to researchers, no conditions
- DFID funded 'challenge grants' to disease endemic country scientists

**250 Malaria Boxes supplied to 30 countries, > 500 assays**



# Achievements & lessons

- Several new projects in H2L with funding,
- New targets and irresistible scaffolds
- One third 'not enough for a paper' published
- Built network of like-minded scientists
- Useful training projects for medicinal chemistry
- Metabolism and PK data speeds up decisions

Cryptosporidium Chris Huston, AAC, 2014, 58, 2731

Toxoplasma gondii Fabrice Boyom, AAC, 2014, 58, 5848

Andrew Hempshill Alveolar Echinococcosis: PLoS NTD. 2016 10 4535.

Elizabeth Bilsland Brugia malayi PLoS NTD 2016 10 4401

RESEARCH ARTICLE

## Open Source Drug Discovery with the Malaria Box Compound Collection for Neglected Diseases and Beyond

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Caffrey<sup>30</sup>, Gracia Camargo<sup>31</sup>, Mercedes Carrasquillo<sup>32,33</sup>, Dee Carter<sup>34</sup>, Maria Belen Casarea<sup>35</sup>, Ken Chih-Chen Cheong<sup>36</sup>, Wornath Chindaomasa<sup>37</sup>, Anthony Chubb<sup>38</sup>, Beatrice L. Colon<sup>39</sup>, Daisy D. Colón-López<sup>40</sup>, Yolanda Corbett<sup>41</sup>, Gregory J. Crowther<sup>42</sup>, Noemi Cowan<sup>43</sup>, Sarah D'Almeida<sup>44</sup>, Na Le Dang<sup>45</sup>, Michael Delves<sup>46</sup>, Joseph L. DeRitis<sup>47</sup>, Alan Y. Du<sup>48</sup>, Sandra Duffy<sup>49</sup>, Shimas Abd El-Salam El-Gayed<sup>50,51</sup>, Michael T. Ferdig<sup>52</sup>, José A. Fernández Robledo<sup>53</sup>, David A. Fidock<sup>54</sup>, Isabelle Florent<sup>55</sup>, Patrick V. T. Fokou<sup>56</sup>, Ani Galatous<sup>57</sup>, Francisco Javier Garro<sup>58</sup>, Suzanne Gokoof<sup>59</sup>, Ben Gold<sup>60</sup>, Todd Golub<sup>61</sup>, Gregory M. Goldgar<sup>62</sup>, Rajarshi Guha<sup>63</sup>, W. Armand Guimarães<sup>64</sup>, Nil Gural<sup>65</sup>, R. Kirilín Guy<sup>66</sup>, Michael A. E. Hansen<sup>67</sup>, Kirsten K. Hanson<sup>68,69</sup>, Andrew Hargrave<sup>70</sup>, Rob Hooft van Halbeek<sup>71</sup>, Yukaaki Horii<sup>72</sup>, Paul Horrocks<sup>73</sup>, Tyler B. Hughes<sup>74</sup>, Christopher Huston<sup>75</sup>, Ikuo Igarashi<sup>76</sup>, Katrin Ingram-Sieber<sup>77</sup>, Maurice A. Itoe<sup>78</sup>, Ajit Jadhav<sup>79</sup>, Amornrat Naranjantarot Jensen<sup>80</sup>, Larsen T. Jensen<sup>81</sup>, Ryoji H. Y. Jang<sup>82</sup>, Annette Kaiser<sup>83</sup>, Jennifer Keiser<sup>84</sup>, Thomas Ketas<sup>85</sup>, Sebastian Kieck<sup>86</sup>, Sunyoung Kim<sup>87</sup>, Kiaran Kirk<sup>88</sup>, Vidya P. Kumar<sup>89</sup>, Dennis E. Kyle<sup>90</sup>, Mafu Jose Lahente<sup>91</sup>, Scott Landtner<sup>92</sup>, Nathan Lee<sup>93</sup>, Sukhan Lee<sup>94</sup>, Adele M. Lehane<sup>95</sup>, Fengwei Li<sup>96</sup>, David Little<sup>97</sup>, Lijiong Liu<sup>98</sup>, Manuel Llinás<sup>99</sup>, Maria L. Loza<sup>100</sup>, Arístides Luber<sup>101</sup>, Leonardo Lucartoni<sup>102</sup>, Isabella Luceri<sup>103</sup>, Louis Maez<sup>104</sup>, Dalu Manca<sup>105</sup>, Naha R. Mansour<sup>106</sup>, Sandra March<sup>107</sup>, Sheena McGowan<sup>108</sup>, Isat Medina Vera<sup>109</sup>, Stephan Meister<sup>110</sup>, Luke Mercer<sup>111</sup>, Jordi Mestre<sup>112</sup>, Aline H. Miya<sup>113</sup>, Raj N. Mirdar<sup>114</sup>, Seunghyun Moon<sup>115</sup>, John P. Moore<sup>116</sup>, Francisca Morais Rodrigues da Costa<sup>117</sup>, Joachim Müller<sup>118</sup>, Annetta Mariana<sup>119</sup>, Stephen Nakazawa Horvitz<sup>120</sup>, Daniela Nare<sup>121</sup>, Carl Nathan<sup>122</sup>, Nathale Noraidoo<sup>123</sup>, Sujeevi Navaratna<sup>124</sup>, Kayoko K. Ojo<sup>125</sup>, Diane Odeh<sup>126</sup>, Gordana Panic<sup>127</sup>, George Papadatos<sup>128</sup>, Silvia Parapini<sup>129</sup>, Kalksh Patra<sup>130</sup>, Ngoc Pham<sup>131</sup>, Sarah Prato<sup>132</sup>, David M. Prouff<sup>133</sup>, Sally-Ann Poulson<sup>134</sup>, Anupam Pradhan<sup>135</sup>, Celis Quvedo<sup>136</sup>, Ronald J. Quinn<sup>137</sup>, Christopher A. Rice<sup>138</sup>, Mohamed Abdo Rizk<sup>139</sup>, Andrew Ruecker<sup>140</sup>, Robert St. Onge<sup>141</sup>, Rafaela Salgado Ferreira<sup>142</sup>, Joanael Santos<sup>143</sup>, Natalie G. Robinett<sup>144,145</sup>, Ulrich Schlecht<sup>146</sup>, Marjorie Schmidt<sup>147</sup>, Filipe Silva Vilas<sup>148</sup>, Francisco Silvestrin<sup>149</sup>, Robert Sinden<sup>150</sup>, Dennis A. Smith<sup>151</sup>, Thierry Soldat<sup>152</sup>, Andreas Spitzmuller<sup>153</sup>, Serge Maximilian Stamm<sup>154</sup>, David J. Sullivan<sup>155</sup>, William Sullivan<sup>156</sup>, Sundari Sureth<sup>157</sup>, Brian M. Suzuki<sup>158</sup>, Yo Suzuki<sup>159</sup>, S. Joshua Susamidas<sup>160</sup>, Donatella Taramelli<sup>161</sup>, Leve R. Y. Tchokouaha<sup>162</sup>, Anjo Theron<sup>163</sup>, David Thomas<sup>164</sup>, Kathryn F. Tonissen<sup>165</sup>, Simon Townson<sup>166</sup>, Abhai K. Tripathi<sup>167</sup>, Valentin Trofimov<sup>168</sup>, Kenneth O. Uzoaru<sup>169</sup>, Imran Ullah<sup>170</sup>, Cindy Valletta<sup>171</sup>, Edgar Vigil<sup>172</sup>, Joseph M. Vinetz<sup>173</sup>, Phat Voong Veth<sup>174</sup>, Hoan Vu<sup>175</sup>, Nao-aki Watanabe<sup>176</sup>, Kate Weatherby<sup>177</sup>, Pamela M. White<sup>178</sup>, Andrew F. Wilks<sup>179</sup>, Elizabeth A. Winzler<sup>180</sup>, Edward Wojcik<sup>181</sup>, Melanie Wroet<sup>182</sup>, Wesley Wu<sup>183</sup>, Naoko Yokoyama<sup>184</sup>, Paul H. A. Zlot<sup>185</sup>, Nade Abdi<sup>186</sup>, Benjamin Blasco<sup>187</sup>, Jeremy Burrows<sup>188</sup>, Denzil Laine<sup>189</sup>, Didier Leary<sup>190</sup>, Thomas Spangenberg<sup>191</sup>, Timothy Wells<sup>192</sup>, Paul A. Wills<sup>193</sup>



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Data Availability Statement: All relevant data are within the paper and its Supporting Information files. Much of the data also appears on [Open Access Malaria Box](https://www.malaria-box.com/).

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- 400 compounds, activity vs. neglected diseases
- Compounds selected by partnership of PDPs and disease experts
- All compounds remade and retested
- Distributed free on request
- Recipients agree to publish results
- Stimulating neglected disease drug discovery research
- Launched December 2015

Malaria  
Tuberculosis  
Chagas  
Leishmaniasis  
Lymphatic filariasis  
Onchocerciasis  
Cryptosporidiosis  
Buruli ulcer  
Human African  
Trypanosomiasis  
Schistosomiasis  
Ascaris  
Trichuris  
Hookworm

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