Global Malaria Portfolio

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Curing Malaria Together www.mmv.org

Medicines for Malaria Venture

MMV's Mission

- Discover, develop and deliver safe, effective and affordable antimalarials to treat and protect people most at risk of malaria
- Provide the public health community with the most appropriate tools to achieve maximum public health impact

Medicines for Malaria Venture

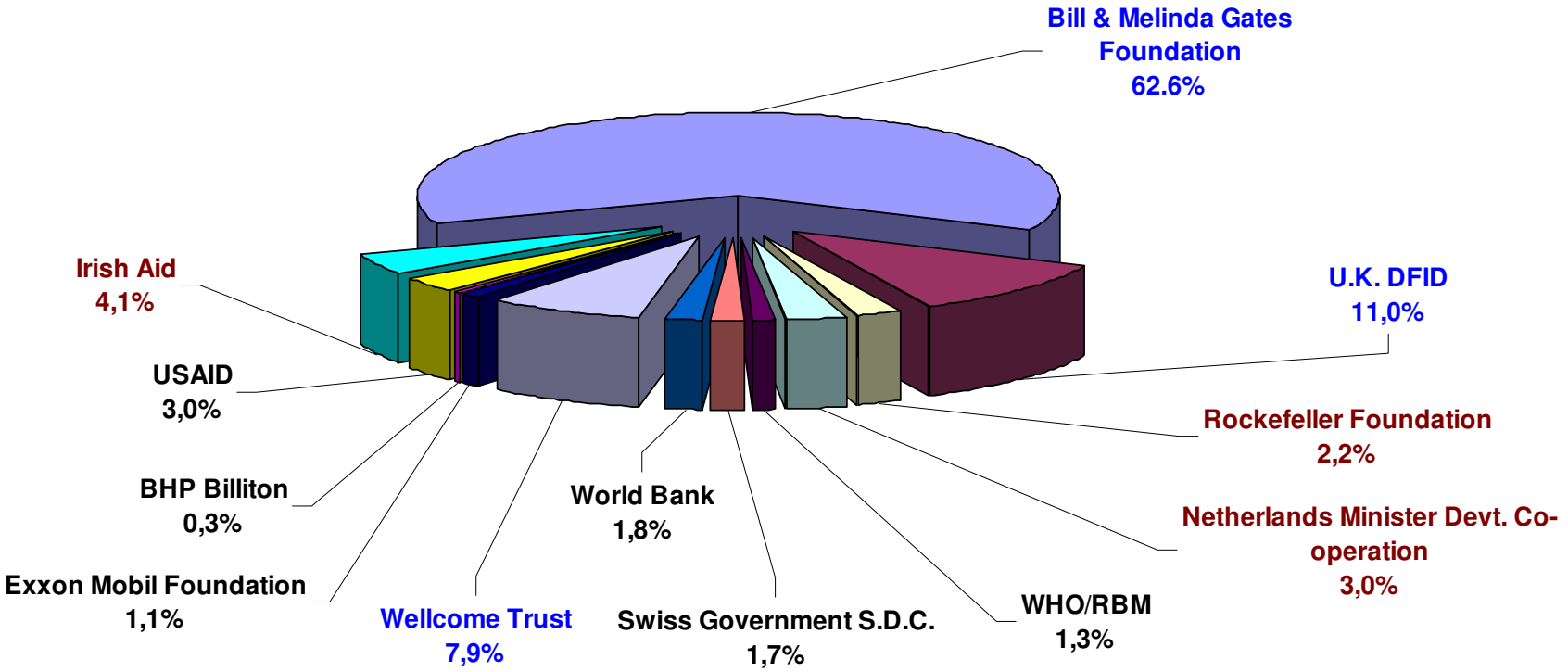
- The current portfolio of new medicines
- Developing the breadth of ACTs, understanding our exposure to resistance
- The new generation of targets – hope for the future

Medicines for Malaria Venture

MMV has a wide panel of donors

MMV - Medicines for Malaria Venture
funding from Foundation to 2010 (May 2006)

(Total Received/Pledged $263 Million)



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MMV Portfolio Non Severe Malaria March 2008

Research		Translational			Development	
Discovery	Lead Opt	Preclinical	Phase I	Phase II	Phase III	Registration
Novartis 9 projects	DHFR Thailand	Isoquine	Tafenoquine		Eurartesim	Coartem D
GSK 3 projects	DHFR NITD	MK 4815			Pyramax	
Broad/Genzyme 5 projects	Pyridones GSK	Pyridone 932121				
Others 6 projects	Macrolides GSK	OZ439				
	DHODH					
	Nat Product NITD					
	Immucillins Einstein					
	Biartemides NITD					
Likelihood to Launch (CMR)	7%	14%	27%	38%	72%	

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Global Portfolio: Non-severe malaria March 2008

2016+	2016	2014	2013	2012	2010	2008
Novartis 9 projects	DHFR Thailand	Isoquine	Tafenoquine	Fosmidomycin Clindomycin	Eurartesim	Coartem D
GSK 3 projects	DHFR NITD	MK 4815	Blue AQ	Artesunate Ferroquine	Pyramax	Mefloquine Artesunate
Broad/Genzyme 5 projects	Pyridones GSK	Pyridone 932121	AQ13 Immtech		Azithromycin chloroquine	Amodiaquine Artesunate
Others 6 projects	Macrolides GSK	Ozonides				
Others 53 projects	DHODH	SAR116242 Trioxalanes				
	Nat Product NITD					
	Immucillins Einstein					
	Biartemides NITD					
	PS22 triazine Jacobus					

MMV projects

sanofi aventis projects

Other projects

Source: iddb3 database search; MMV internal database

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Coartem Dispersible

	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q 4
Coartem D	Filing			Reg.				Launch				

- Partner: Novartis
- Key advantage: new Pediatric formulation (cherry) – tablet disperses easily
- Current Status: Phase III trial non-inferiority of crushed tablet (890 pediatric patients)
- Next Steps: Launch. Submitted to Swissmedic December 2007

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DACART (Chlorproguanil-Dapsone-Artesunate)

	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Dacart	III				Filing							

- Partners: GSK, WHO/TDR, Liverpool University
- Key advantage: once-a-day, short half-life, non-4 aminoquinoline
- Current Status: Phase III trials complete
  - Chlorproguanil-Dapsone (900) May‘07
  - Artemether-Lumefantrine (1394) June’07
- Key issue: Comparison with Artemether-Lumefantrine showed
  - Larger drop in hematocrit in G6PD- patients
  - Higher number of AE for G6PD- patients in DACART group
- Decision not to file DACART made by GSK in March 2008

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Eurartesim (DHA-Piperaquine)

	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Eurartesim	III							File				

- Partners: Sigma-Tau, Holley, Oxford University
- Key advantage: Once-a-day, prophylactic effect
- Current Status: Databases locked
  - African children (1533) vs; Artemether/ Lumefantrine
  - Asia adults (1150) vs Artesunate/ Mefloquine (still blinded)
- Next Steps: Regulatory submission to EMEA 4Q'08

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Pyramax (Pyronaridine- Artesunate)

	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Pyramax	III								Filing			

- Partner: Shin Poong, University of Iowa
- Key advantage: 3 year shelf life, pediatric formulation
- Current Status: Completing four Phase IV trials
  - Artesunate-Mefloquine
  - Artemether-Lumefantrine
  - Chloroquine (*P vivax*)
  - Paediatric
- Next Steps: Completion of Phase III and filing to EMEA (article 58)

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Global Portfolio: Non-severe malaria March 2008

Launch **2014** **2012** **2009/10** **2007/8**

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sanofi aventis projects

Other projects

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Lessons from Phase III

- MMV has eight Phase III studies completed, or completing in 2007-2008
- Lessons learned
  - Safety and efficacy have to be considered in parallel
  - ICH quality is not a luxury, but is essential for credible decisions based on data
  - Comparable endpoints result from close coordination
- MMV plays a key role ensuring the smooth interfaces

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MMV's Phase IV Objectives

- Quality data on effectiveness and safety
  - ICH quality in the evidence base for policy makers
- Addressing the gaps in the product profiles
  - Small infants (less than 5kg)
  - Pregnant and lactating mothers
  - *P. vivax* and mixed infections
  - Malnutrition status, coinfections
- New treatment paradigms in the eradication era

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MMV Partnerships
Addressing the gaps with evidence

- District Level studies Effectiveness and Safety (INDEPTH)
- Strengthening the Pediatric Knowledge Base (EDCTP co-funding) <5 kg and Age/weight correlations studies
- ACTi: longitudinal studies with repeated doses
- ACT in pregnancy: extending the role of Eurartesim – through safety and efficacy in pregancy to IPTp
- ACT in Infants – safety and PK in small infants bridging to IPTi

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MMV tailoring the portfolio to address resistance

- Do our pipeline drugs work in ‘artemsisinin refractory’ patients?
  - Although pipeline has other ‘ozonide’ drugs, chemically they are very different
  - Testing all the development candidates against primary patient samples
  - Include related negative controls, blind testing
- Rapid progression to clinical proof of concept
  - How much can we afford to trust the cell biology?
- Close co-ordination with WARN

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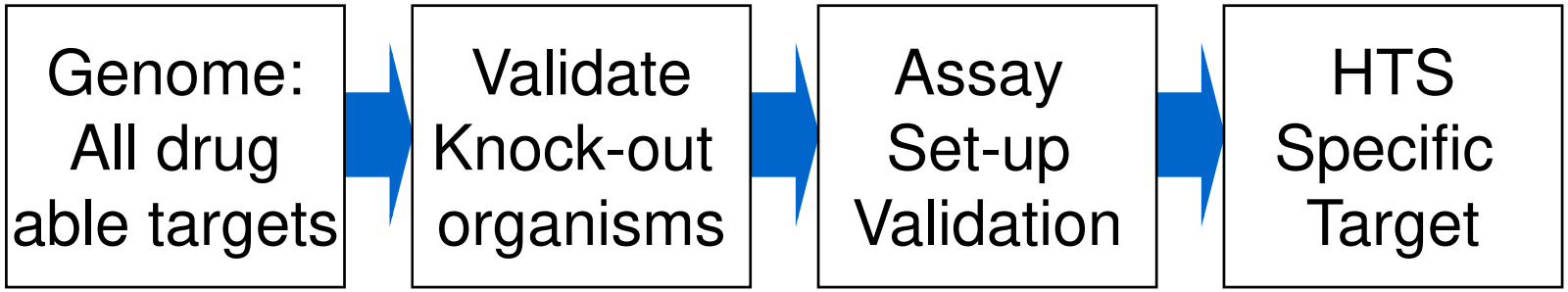
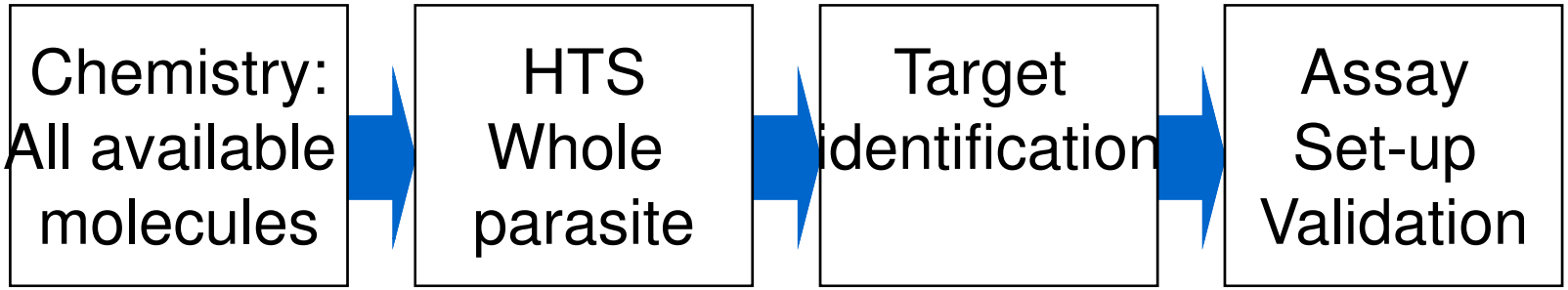
Backwards and Forwards to find Leads

Classical 'Forward' approach



Reverse approach



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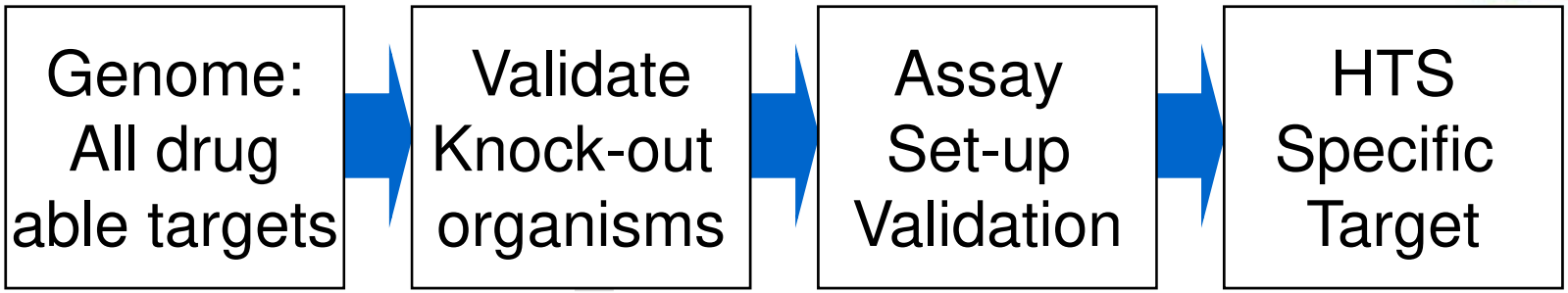
Forward approach – build from Genomics



- **Key Success Factor**: we have all the genomes, great expectations
- **Advantage**: rapid prediction of drugable targets
- **Disadvantage**: validation is not always possible

- **Next step**: Chemical validation using reference sets

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Reverse approach – built on biology

Chemistry: All available molecules → HTS Whole parasite → Target identification → Assay Set-up Validation

- **Key Success Factor:** Automation of biology, image processing and storage
- **Advantage:** Data - over 4.1m compounds in ’06 – ‘07, > 10’000 positives
- **Disadvantage:** finding the target – it may not even be a protein

- Next Steps: Expand to new biology and chemistries

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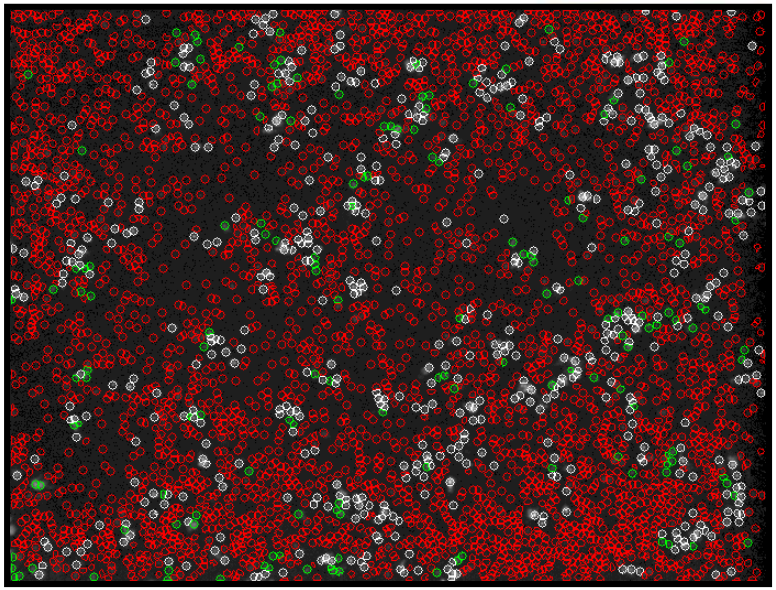
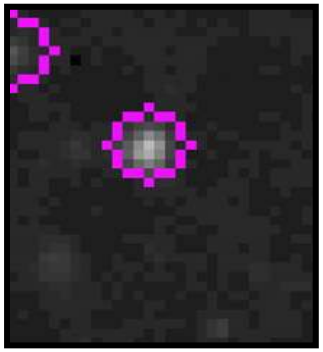
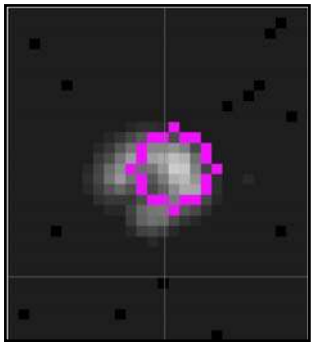
Parasite biology: high content screening goes beyond life and death

- Biology in 1536 well plates
  - Image the parasite growing inside erythrocytes
  - Eliminate false positives
  - Biology: distinguishes different stages







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