Grand Challenges
African Drug Discovery Accelerator

Convening Meeting 2025

GC ADDA4Malaria:
Discovery of antimalarial lead candidates in Africa

L Birkholtz & R Amewu

Supported by

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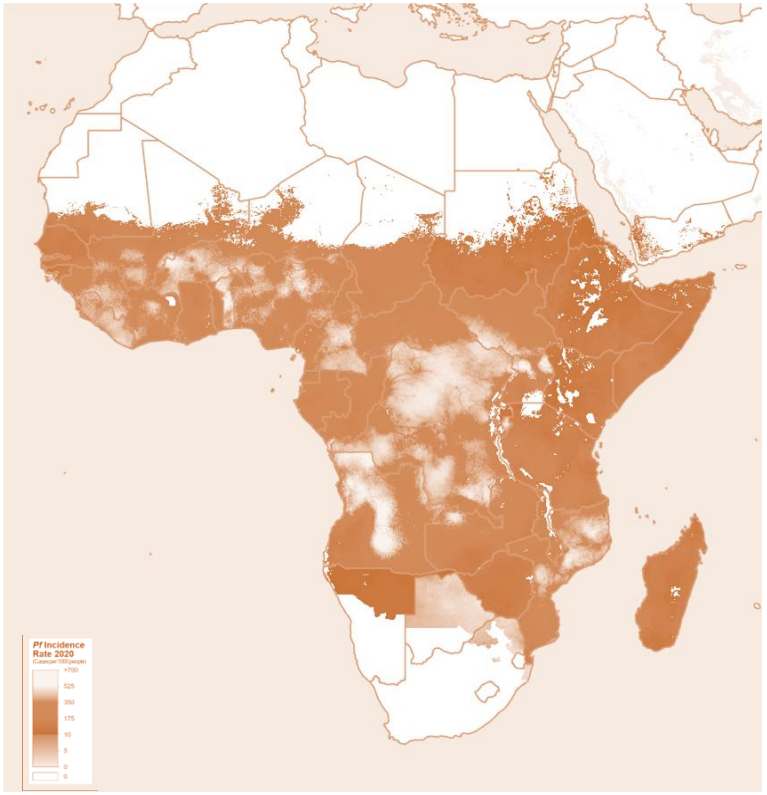
Malaria – an African challenge



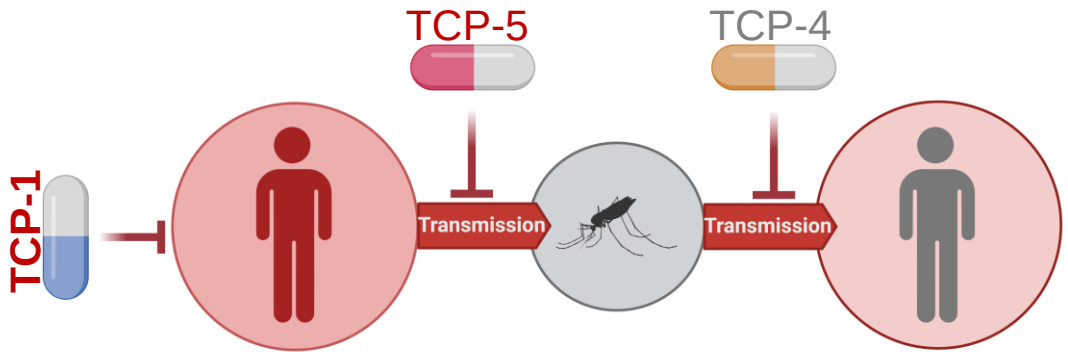
African-driven innovations against malaria

Cross-continental, consolidated effort towards deliver of antimalarial lead candidates

Antimalarial Drug Discover Flagship Project

- **Unmet medical need:**

  to deliver novel antimalarial early lead candidates, with the potential of targeting multiple life cycle stages of *Plasmodium falciparum* for malaria elimination strategies.



Primary requirement & focus:

- target the pathogenic asexual blood stages (ABS).
- therapeutic benefit (Target candidate profile, TCP1).

Additional transmission-blocking (TCP5)

- protect individuals against re-infection.
- decrease parasite prevalence.
- protect molecules with ABS activity in combination strategies by delaying the spread of resistance.

Antimalarial Drug Discover Flagship Project

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Goal:

- to deliver an integrated antimalarial drug discovery accelerator platform in Africa

AIMS:

- Integrate evidenced expertise from each partner in biology, medicinal chemistry and drug metabolism and pharmacokinetics.
- Coordinate unique strengths and capabilities across the continent through a focused project on malaria drug discovery.
- Undertake hit discovery, hit-to-lead, and later, lead optimization campaigns.

- Our vision is to deliver an early lead antimalarial candidate.

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Objectives:

1. Hit validation and formal hit assessment.
   Deliverable: Validated hits with 2-3 series prioritized for H2L.
2. H2L and SAR
   Deliverable: Early lead indicated for at least 1 series, at least 1 other series with potential for early lead status identified.
3. Target ID and MoA indicators
   Deliverable: MoA indicated for 2-3 series with target ID confirmed for 1/2 series
4. Additional profiling
   Deliverable: Efficacy of lead compound against multiple *Plasmodium* species and stages indicated in field samples.
5. Identification of new chemical matter.
   Deliverable: 2-3 new series identified to be included in the project.
6. Development and capacity building.
   Deliverable: Expanding drug discovery capabilities and capacity.

Antimalarial Drug Discovery Flagship Project

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PI/co-PI

R Amewu

L Birkholtz

Chemistry

R Amewu

A Rousseau

W Nxumalo

8 researchers

Biology

L Birkholtz

L Dembele
D Ouologuem

4 researchers

DMPK

ESAC

G Liu, E McIver, J Duffy
G Basarab, I Gilbert, D Powell

External partners

Funders

Integration of evidenced expertise and capabilities biology, medicinal chemistry and drug metabolism and pharmacokinetics.

Antimalarial Drug Discovery Flagship Project

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Competitive advantages at project initiation

- Evidenced expertise across the continent.
- Prior data on 5 chemical scaffolds.
- Multiple stages targeted - ABS activity and potential transmission-blocking activity.
- Field isolates.
- Potential of additional *Plasmodium* species.
- MoA capabilities.

Screening Cascade

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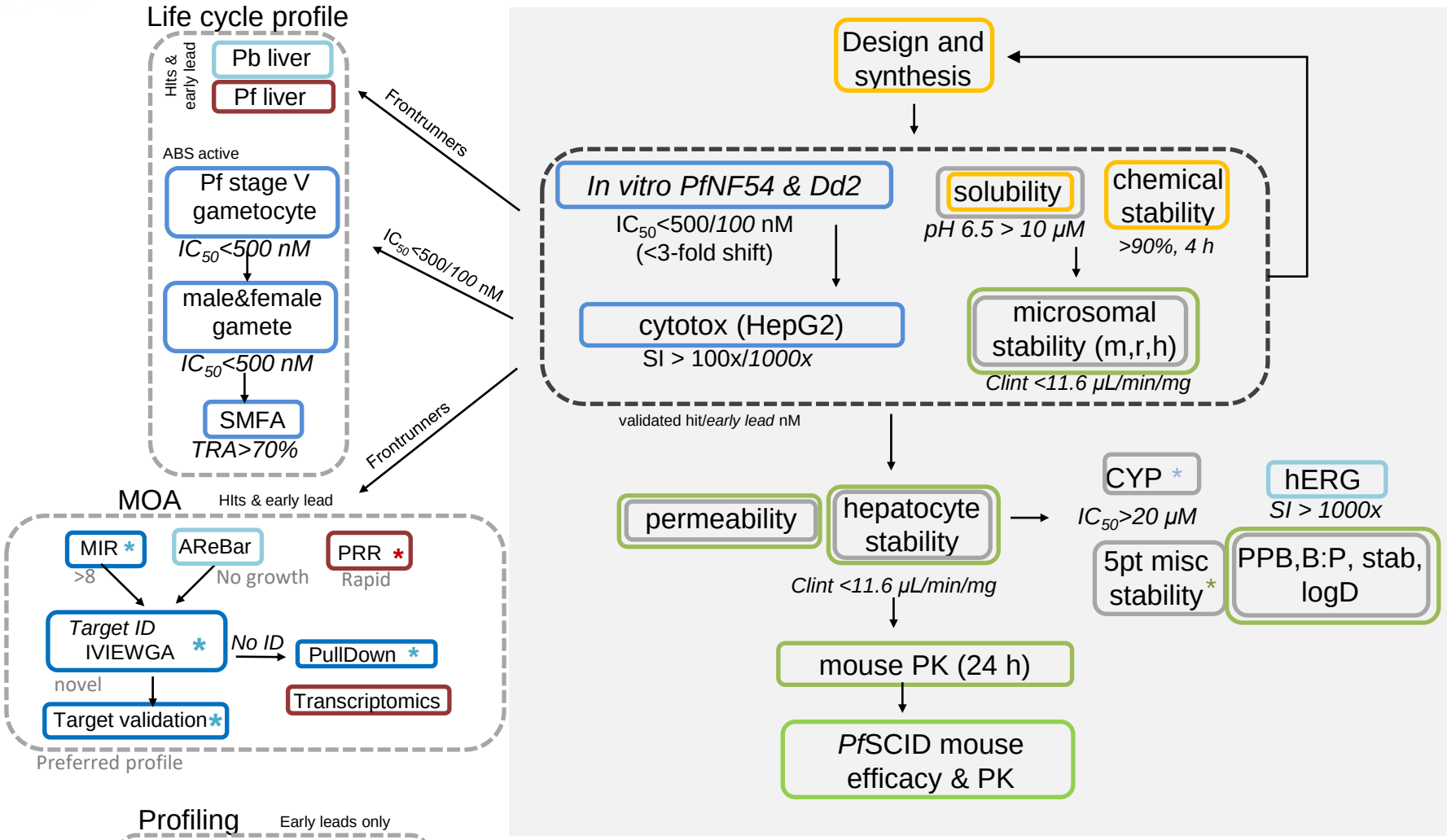

RKA – Ghana, WN–SA, AR-SA

LMB -SA

LD, DO - Mali

H3D

AIBST

* = additional support at partner

DDU/MMV/malDA/CRO

Capabilities summary

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Synthesis
Analysis
Stability
Solubility
NMR
LC-MS/MS
X-ray diffraction

Synthesis
NMR
X-ray diffraction
HR-MS

Synthesis
MS
NMR

- ABS assays:
  - NF54, K1, Dd2, 7G8, W2
  - SYBR Green I (72 or 96 h)
  - pLDH (72 h)
- i-GC and m-GC assays
  - Luc reporter (48 h)
- Orthogonal tox screening
- Resistance risk
- *In vitro* resistance selections
- Rate & stage
- MoA explorations
- Target validation (cKD)

- ABS PRR assay for rate
  - Mitrotracker based
- *In vitro* resistance selections
- Field isolates western Africa
- *Ex vivo* transmission-blocking

Current status: End Y1

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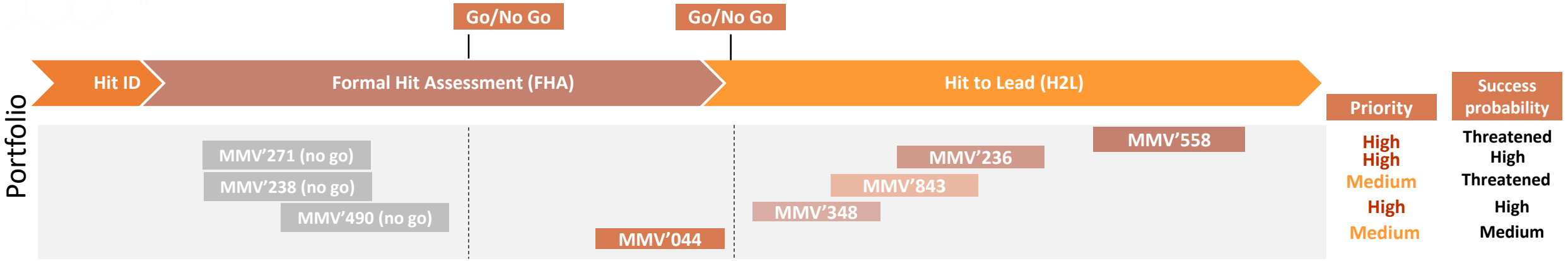
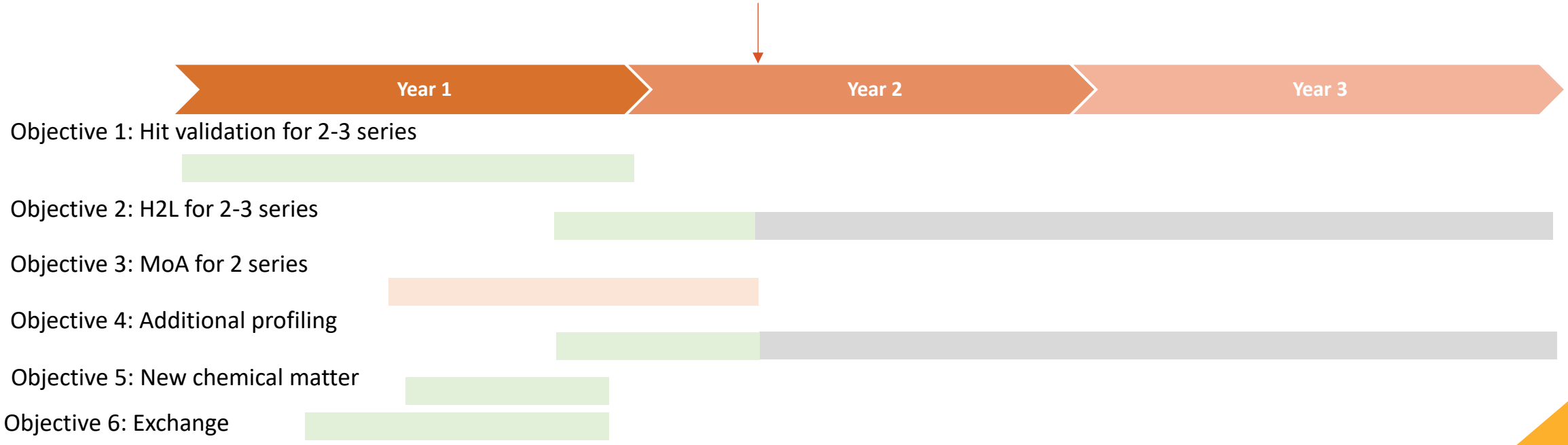


- Probability of Success = Moving to Next Stage (e.g. FHA -> H2L).



Success & key learnings to date

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- **Key success factors at project initiation**
  - Collaborative network with evidenced expertise contributed including enabling technology
    - Partners each contributed their existing expertise to the network
    - No development of new technology required
    - Contribution of prior data to allow immediate gains of project goals
    - All partners working towards a common goal

    - Prior relationships with external partners:
      - Access to external partners for expertise not available in Africa (LGenia, MMV, malDA)

Success & key learnings to date

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- **Key success factors at project initiation**
  - Legal framework for collaboration in place:
    - Bilateral agreements between UoG and each institution to allow rapid dispensing of funding
    - RCA constituted between all parties to allow data sharing freely and provide framework for collaboration
  - Key staff members appointed:
    - Programme manager (UoG) – in contact with all parties for coordination of activities
    - Staff & postdocs appointed at all sites
  - Training of early career scientists
    - Project manager to H3D (project management & drug discovery workshop)
    - 1 Chemist & 1 Biologist training at DDU

Success & key learnings to date

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- **Key success factors**
  - Leadership & guidance
    - PI, co-PI & program manager – regular monthly & ad hoc meetings
    - ESAC constituted from start
      - Members from funders and other external stakeholders
      - Strong guidance from ESAC and support from external partners
    - External guidance through malDA & MMV
    - Guidance via H3D and H3D foundation – program management and operational learnings

  - External review processes
    - 3-monthly ESAC review
    - 3-montly malDA project management team review
    - Annual ESAC review
    - Annual MMV review

Success & key learnings to date

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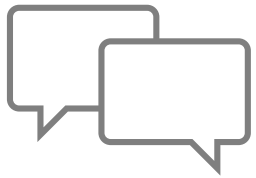
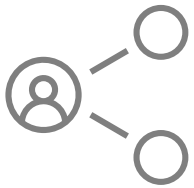
- **Key success factors**
  - Communication and networking



    - Monthly project team meetings – biology meeting & chemistry meeting
    - Monthly full team check-in meeting
      - Full biology, chemistry and DMPK team members
      - GC ADDA program management members
      - malDA program manager
      - Funders
    - 3-monthly ESAC meeting
      - All members as above + ESAC members
  - Resource sharing



    - CDD vault data sharing – training required and key people at each institution needed
    - SharePoint file sharing (managed by project manager)
    - Compound shipment between institutions coordinated via program manager, with correct SOPs for permits in place
    - Material sharing between institutions

Challenges & mitigation thereof

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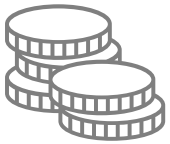
- **Timeframes:**
  - Grant awarded Oct 2023
  - Operational start at some institutions only Jan 2024
  - Funding only received at most institutions in March – June 2024
  - Reporting influenced by disconnect between grant timeframe and operational timeframe – mitigate by no-cost extension at project end.

- **Legal frameworks**
  - Takes a lot of time for a multi-institutional, multi-country framework to be agreed on and signed



- **Procurement**
  - Chemical procurement a big challenge
    - All sites report delays in delivery - each new set of compounds require new chemicals
    - MITIGATION:
      - ‘ChemiBank’ concept of archive of available chemicals at each institution for rapid sharing of materials
      - Procurement at one institution for another with courier shipment (e.g. via CombiBlocks)

Challenges & mitigation thereof

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- **Chemistry FTEs:**
  - Chemistry FTEs were underestimated per series – detrimental to rapid progress
  - MITIGATED:
    - Pivot FTEs between series – chemists were flexible and adaptable to this
    - Appointing additional FTEs from institutional funding

- **Chemical series concerns**
  - Some series showed early warning signs to success
  - MITIGATED:
    - Early no-go or hold calls on series – (on hold move to academic programs)
    - Introduction of new series to expand portfolio

- **DMPK**
  - Accessibility to assays with rapid turnaround times is needed to allow the project team to make rapid decisions on the way forward
  - Need for CRO involvement on phase 2 assays

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‘Working together to deliver early lead antimalarial candidates developed on the African continent’

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