



Grand Challenges  
African Drug Discovery  
Accelerator

## Convening Meeting 2025

Host-virus interactions in KSHV-related malignancies: evaluating the role of STIP1 as a therapeutic target

Adrienne Edkins

Supported by

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# Kaposi sarcoma associated herpesvirus (KSHV)

Human herpesvirus 8 (**HHV8**)

Enveloped DNA virus

Type 1 **carcinogen**

Three associated **malignancies**

Primary effusion lymphoma (**PEL**)

Multicentric Castleman's Disease (**MCD**)

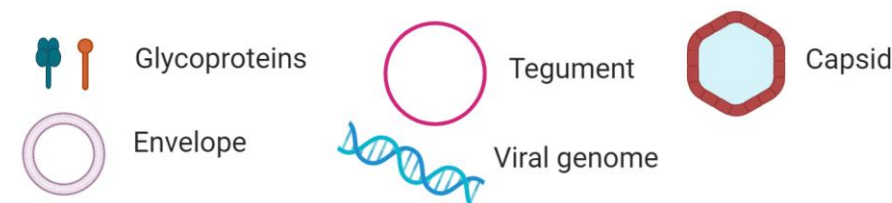
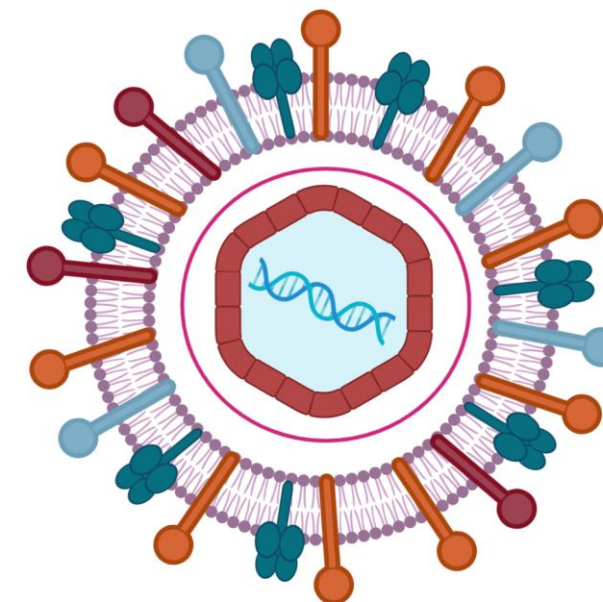
Kaposi sarcoma (**KS**)

Seroprevalence

**>40% in Africa (90%)**

20 – 30% Mediterranean

<10% Europe, Asia, USA



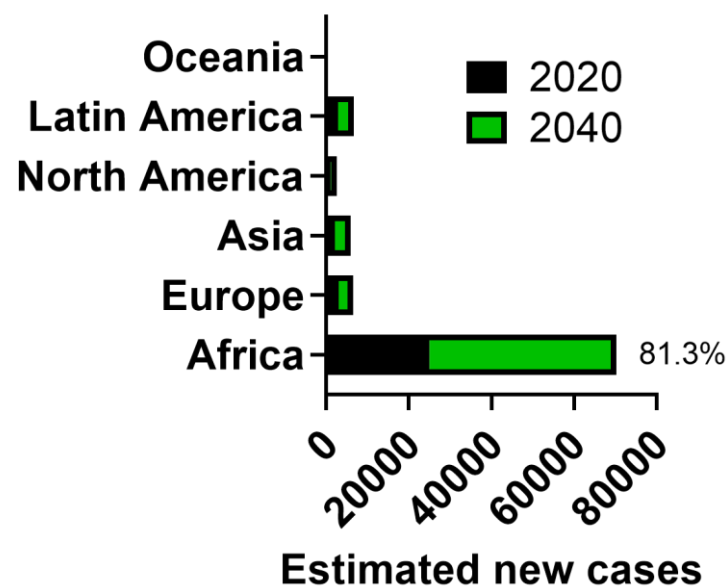
# KSHV-associated malignancies

## KS subtypes

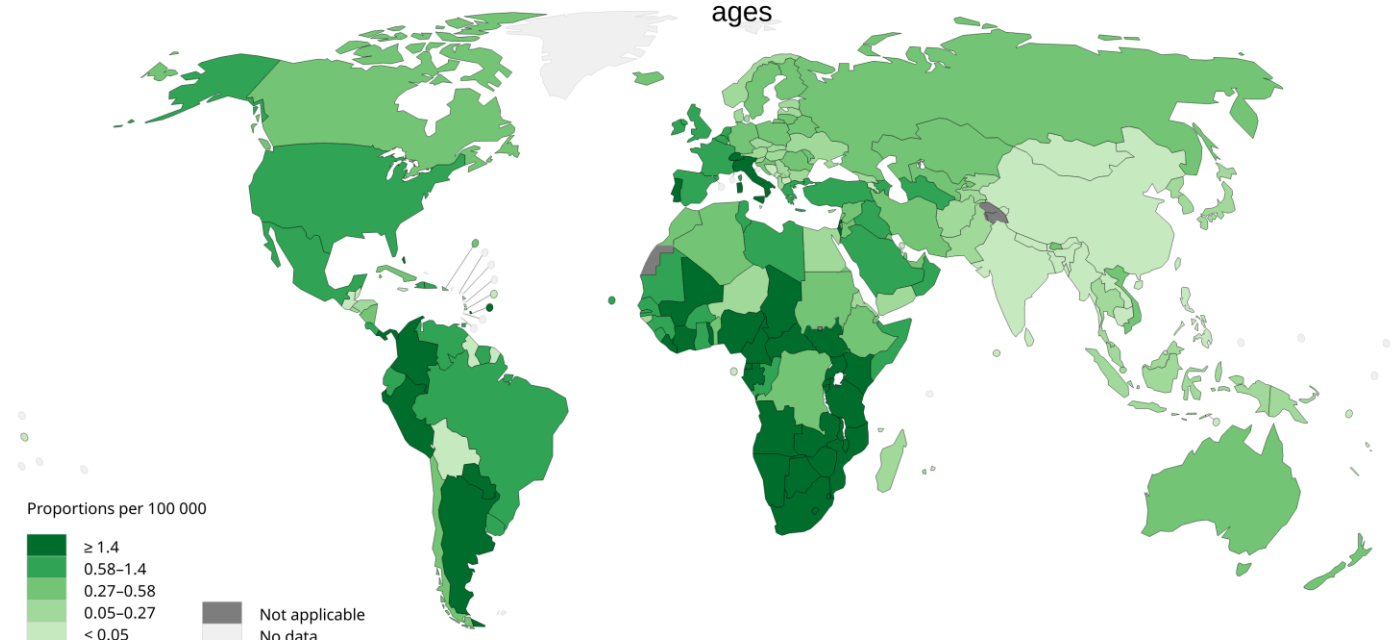
Classical  
Endemic  
Transplant-associated  
HIV-associated

## Treatment strategies

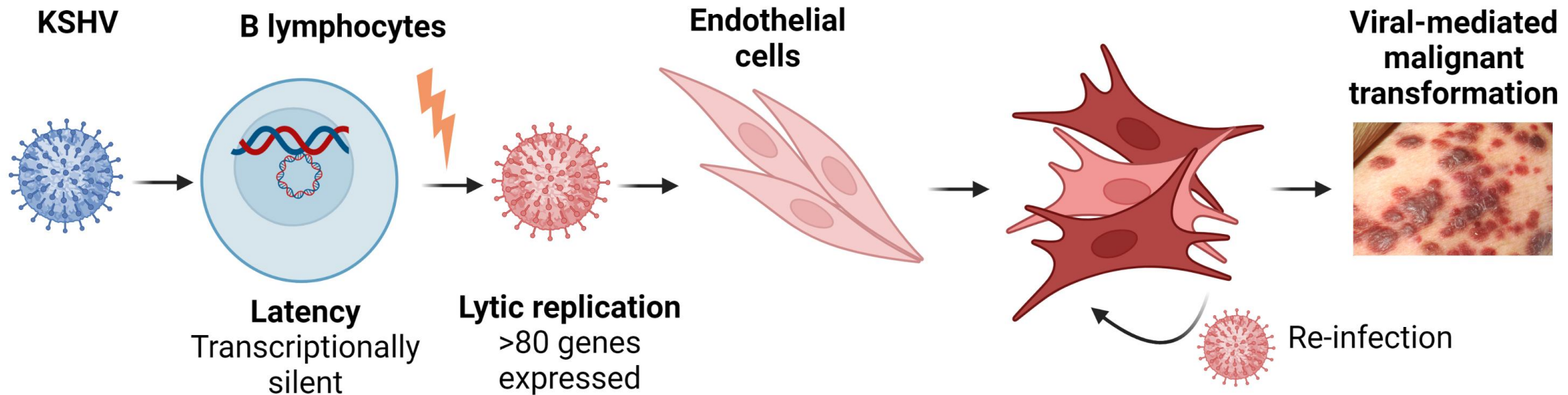
Immune reconstitution (HAART) (K-IRIS/KICS)  
Chemotherapy (e.g. Pomalidomide)  
No targeted antivirals



Estimated number of prevalent cases (5-year) as a proportion in 2020, Kaposi sarcoma, both sexes, all ages



# KSHV has a biphasic lifecycle



**Latency** and **lytic** replication required for **oncogenesis**

# Objectives

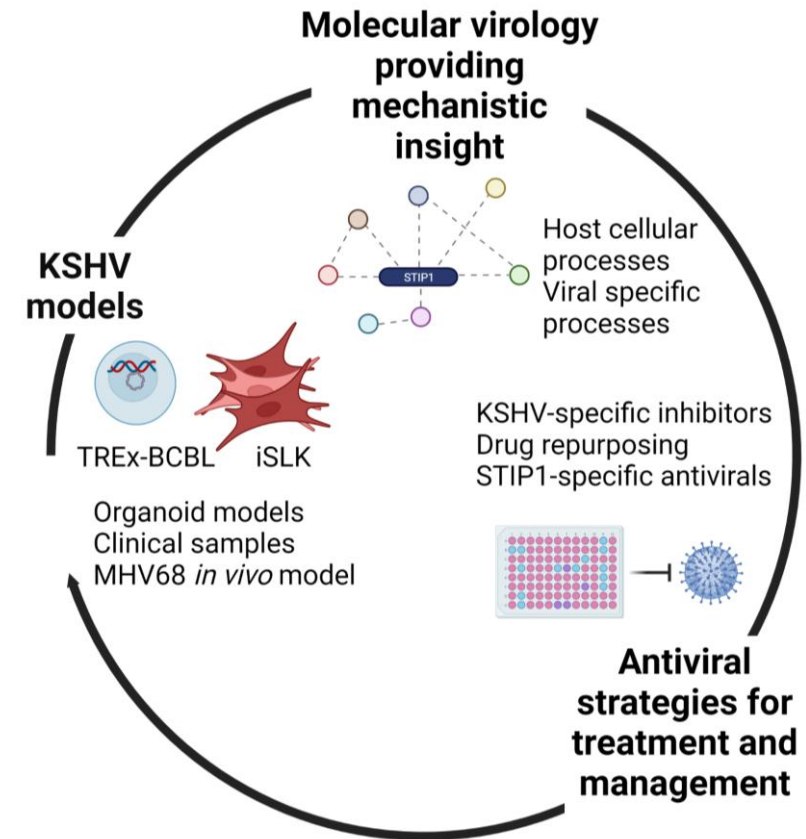
## 1. **Mechanistic** understanding of role of STIP1 in KSHV biology

STIP1 is a proteostasis node → may reveal alternative targets

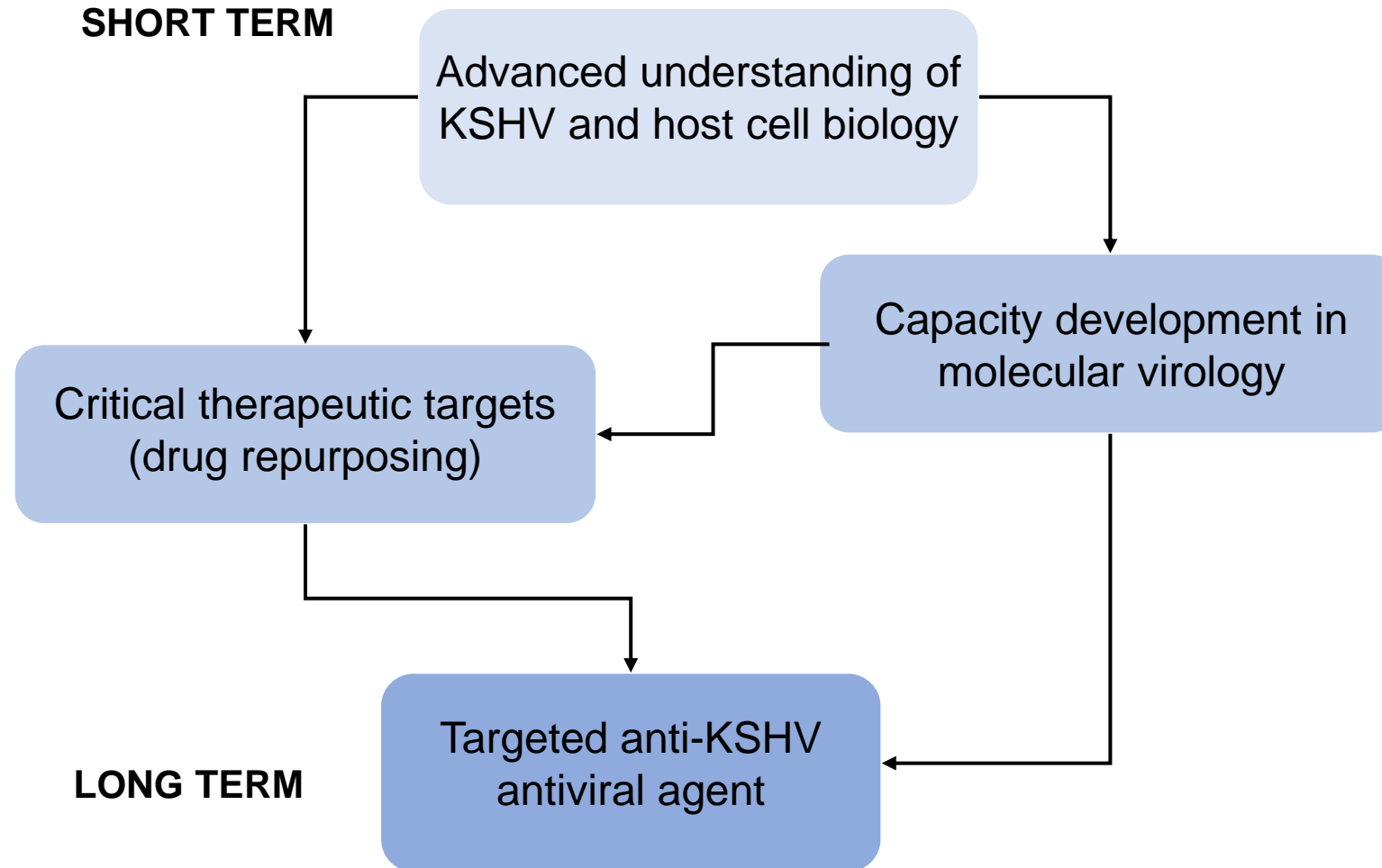
## 2. Novel STIP1-based **therapeutic strategies** for treatment and management of KS

Targeting STIP1 (undruggable)

Targeting proteins linked to STIP1 (druggable)



# Pathways to impact





# Project enabling factors

## **MRC ARL scheme**

Annual call from the **Applied Global Health** from the UK-MRC under the UKRI

## **African based PI and UK based Co-I**

Funding for 5 years

2022 – 2027

£768,000.00

Consumables

Equipment

Travel and training

Salaries (Technician; Postdoctoral Fellow)

RHODES UNIVERSITY  
*Where leaders learn*



# Project background

Started in **2018: Newton Advanced Fellowship** from the Academy of Medical Sciences

Established relationship with **Prof Adrian Whitehouse** (Leeds)  
**2019: Royal Society** Resilient Futures Grant

Training, capacity development and preliminary data

**African Research Leaders (ARL) Grant**

African based PI and UK based Co-I

Applied in **2019** – not shortlisted

Applied in **2020** – shortlisted for interview, but scheme was cancelled (COVID)

Scheme reinstated in **2022** – successful at interview



# Challenges: limited capacity in KSHV

**Solution:** Money  Collaboration 

**BSL2 laboratories:** refurbished laboratory and acquired new equipment (BSL2 flow hoods, incubator)

**Cell line models:** obtained necessary permits and import logistics

**Training:** researchers visited University of Leeds and transferred skills to RSA.



Adrian Whitehouse  
Leeds University

# Challenges: Need to establish research tools

Anti-viral screening cascade

Screening methods for undruggable targets

Genetic methods for identifying repurposing targets

**Solution:**

Collaboration



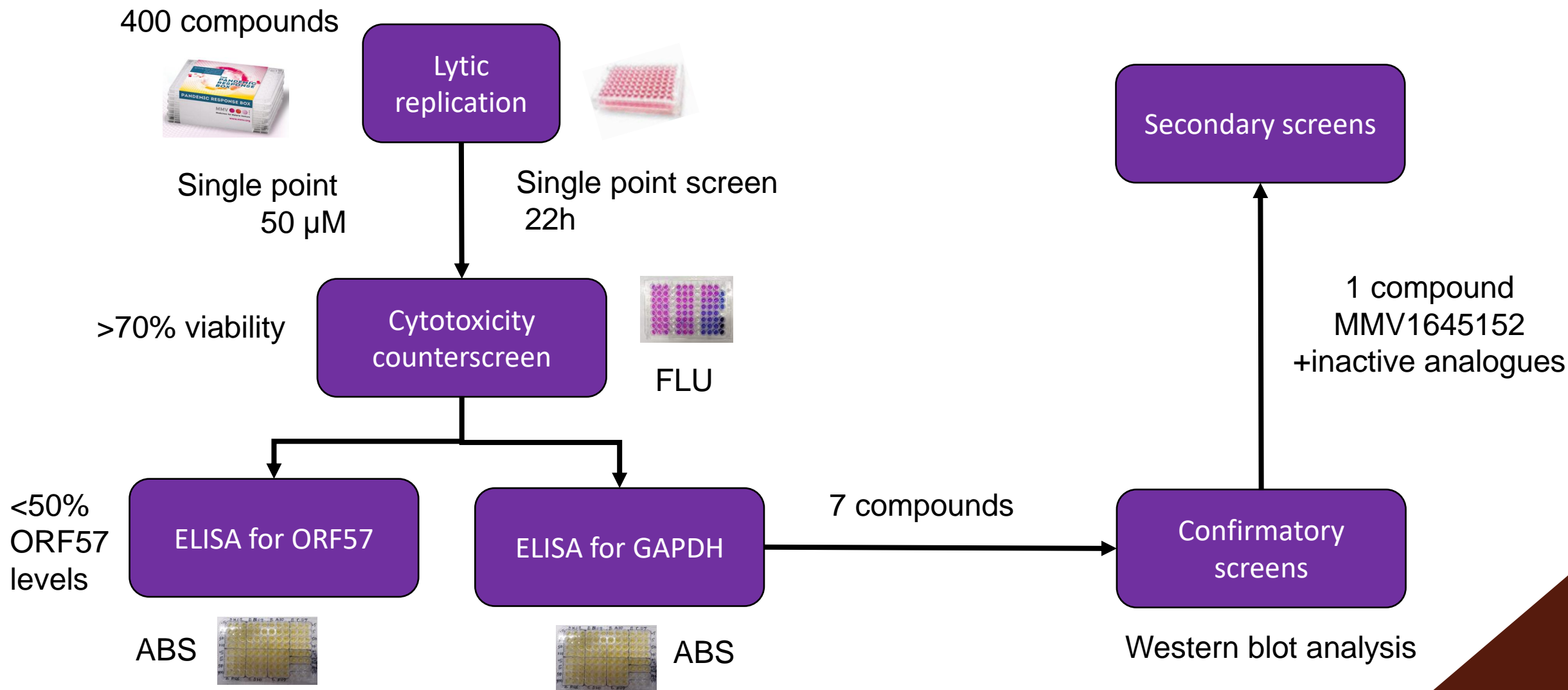
Adrian Whitehouse  
Leeds University



Clint Veale  
UCT



# Progress: Anti-viral screening cascade



# Anti-KSHV hit from Pandemic Response Box

## **MMV1645152**

Blocks KSHV lytic replication by reducing lytic gene expression culminating in reduced infectious virions

## **Next priorities**

Target/MOA identification

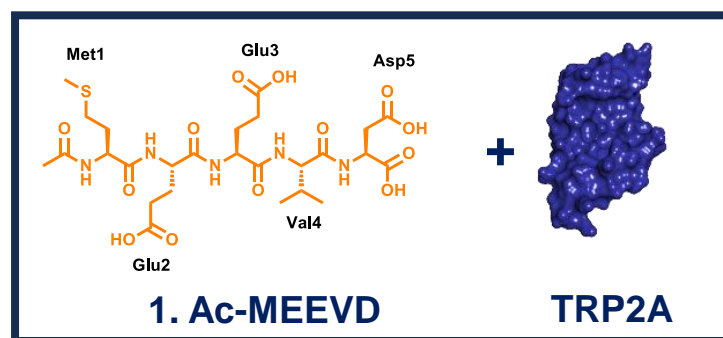
Increasing potency

PK/PD assessment

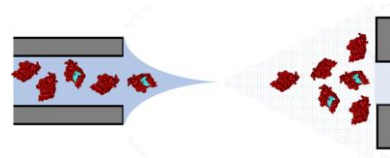
# Progress: Screening “undruggable” targets

Target lacking easily assayable **enzyme activity**

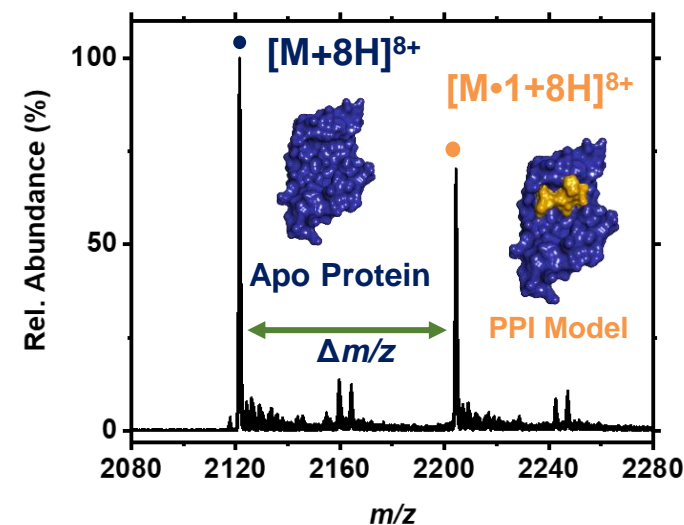
**Native mass spectrometry** to identify **Hop** binding fragments



Incubate in 96 well plate



Direct Infusion n-ESI  
4 mins



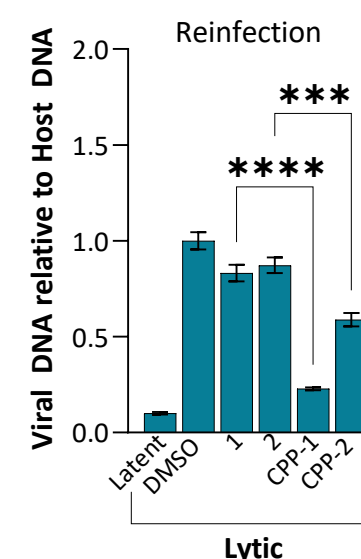
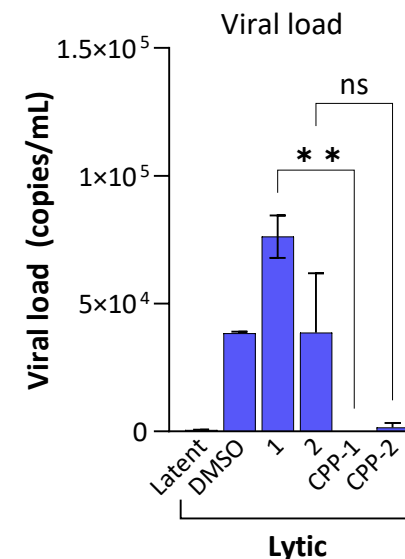
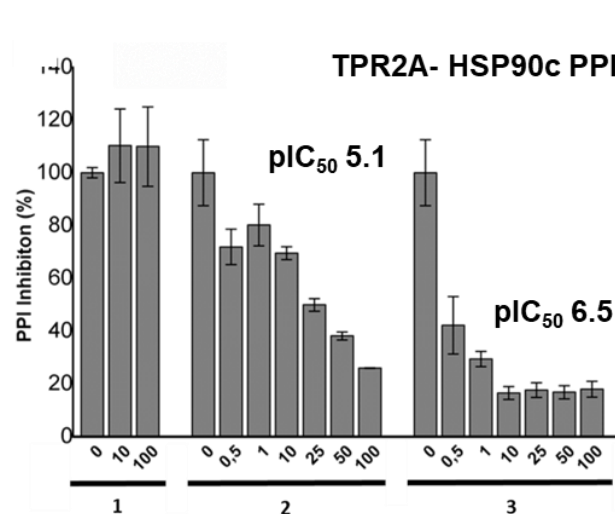
Clint Veale  
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Used a focused acidic **fragment library** – screened for Hop binders

Enrichment in **tetrazole** containing compounds

# Progress: Screening an “undruggable” target STIP1

**Proof of concept:** Blocking Hsp90-STIP1 interaction reduces KSHV lytic replication



Peptide-based  
More druggable molecule  
Identify binding site – use for rationale design



# Summary of progress

**Facilities** and **skills** for KSHV drug discovery in Africa

Identified **STIP1** as a **new host factor** for **KSHV** replication

Proof of concept for **pharmacological** targeting of **STIP1** in **KSHV** replication

**Anti-KSHV hit** compound (from MMV PRB)

Validated host **drug targets** linked to KSHV for **repurposing**

# Future directions

Financial **sustainability** beyond the ARL funding

**Hit – to – lead** optimization

Next phase of **preclinical** testing (animal models)

**Tools** that allow us to increase understanding of **viral biology** towards new **targets**

Expand **viral oncology** drug discovery in **Africa** beyond KSHV

# Acknowledgements

**Prof Adrian Whitehouse (Leeds)**  
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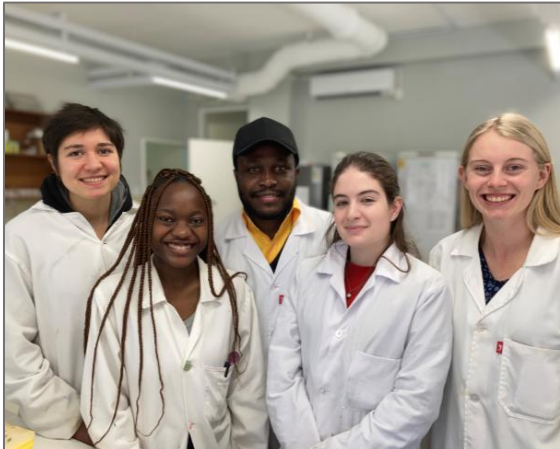
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Dr Abir Chakraborty (RU)  
Ms Jessica Watson (RU)



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Leeds University



Clint Veale UCT



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Towards affordable and effective  
therapies for viral oncology

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