MODULAR, TARGETED POLYMERIC-PRODRUGS FOR THE TREATMENT OF INFECTIOUS DISEASES

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38APS

MALARIA: CLINICAL SETTING

ESTIMATED 249 MILLION CASES OF MALARIA AND 608,000 DEATHS IN 2022[1]

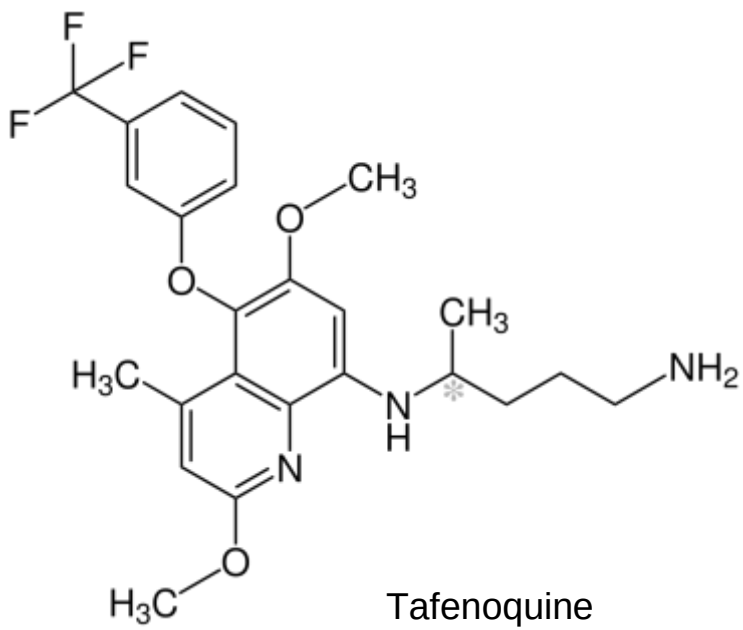
- High morbidity, mortality, & socioeconomic burden
- May cause: anemia, jaundice, organ failure, cerebral malaria, intellectual disabilities, coma, death
- *Plasmodium vivax* malaria:
  - Geographically widespread
  - Infection can result in dormant liver-stage parasites called hypnozoites

Photo courtesy of Gates Foundation

HYPNOZOITE REACTIVATION CAN CAUSE RECURRENT EPISODES OF MALARIA

STANDARD OF CARE

- Elimination of blood & liver stage parasites = ‘radical cure’
- Primaquine (PQ)- treatment for hypnozoites
  - Daily dose for 14 days → reduced patient compliance
- Tafenoquine (TQ)- FDA-approved in 2018
  - Indicated for ‘radical cure’ of P. vivax
  - Single dose therapeutically equivalent to 14 daily doses of PQ



Tafenoquine

EXTENDED HALF-LIFE AND ABILITY TO ACHIEVE RADICAL CURE WITH A SINGLE DOSE MAKE TQ A PROMISING TREATMENT IN RESOURCE-POOR SETTINGS

UNMET NEED: GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- G6PD deficiency affects 400 million people worldwide
- Common in the malaria belt
- PQ and TQ elicit hemolytic anemia in G6PD-deficient patients
- Testing needed when TQ treatment is indicated

Photo from Tori Avey

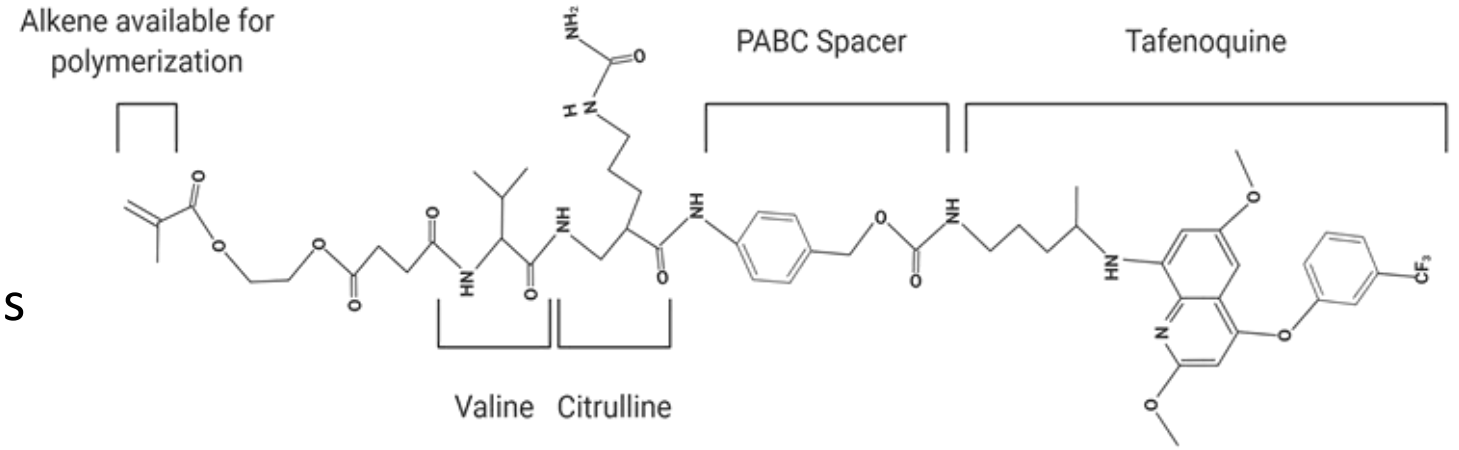
G6PD DEFICIENCY TESTING IS NOT ACCESSIBLE IN RESOURCE-POOR REGIONS WHERE MALARIA IS MOST PREVALENT

POLYMER DESIGN

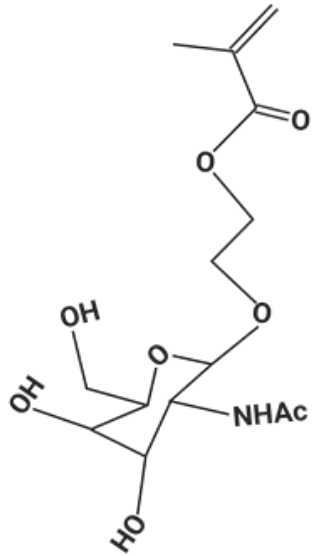
Prodrug Monomer

- Valine + citrulline + PABC spacer (VC linker) cleaved by cathepsin
- VC linker is clinically validated in ADCs
- TQ payload not bioavailable until linker is cleaved

VCTQ Monomer

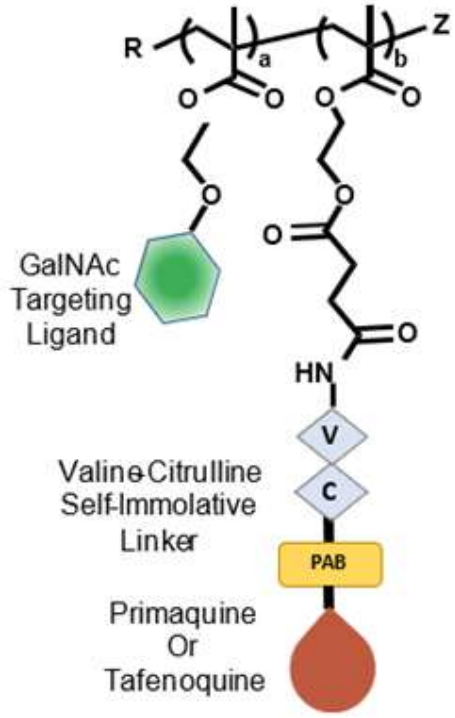


GalNAc Monomer



Targeting moiety

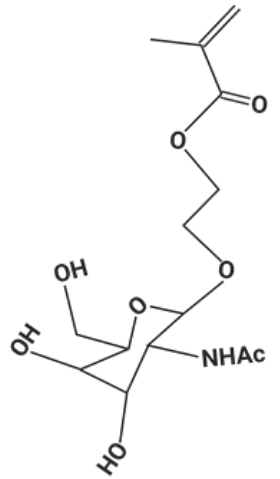
- Asialoglycoprotein receptor (ASGPR) highly expressed in hepatocytes
- GalNAc is clinically validated for liver targeting
- Increases water solubility of polymer



Srinivasan et al., J Control Release. (2020) 331:213-227

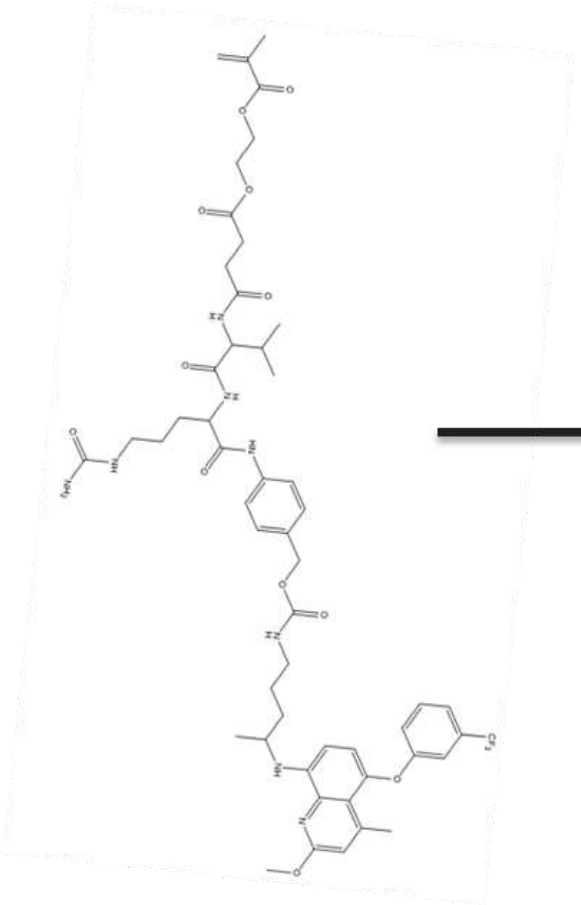
POLYMER DESIGN, CONTINUED

GalNAc monomer



+

VCTQ monomer



Synthesis via RAFT polymerization forms targeted "drugamer"

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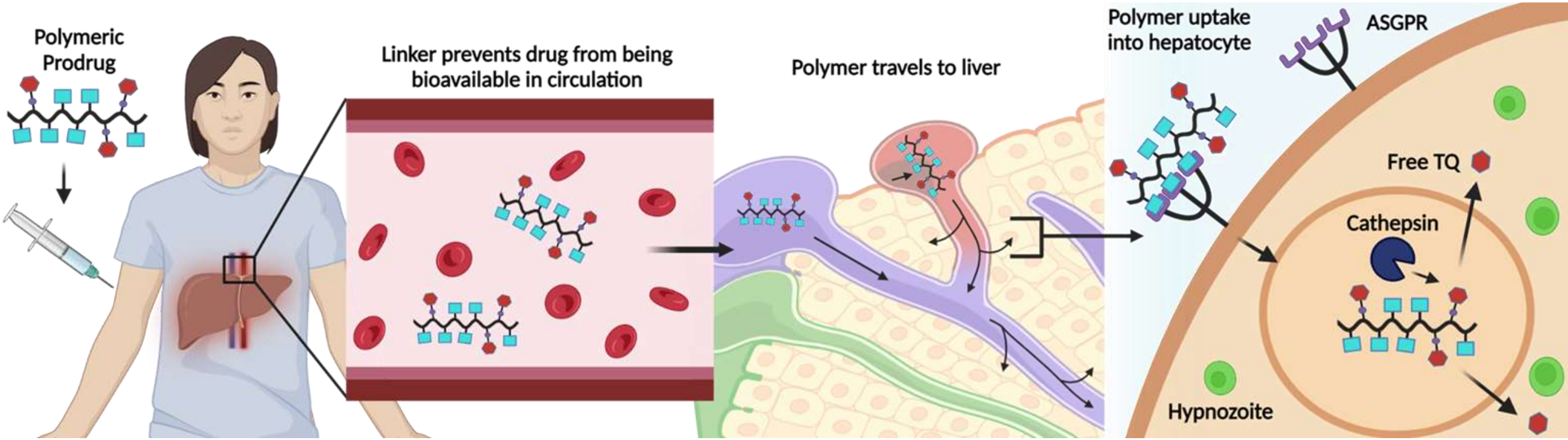
PROJECT MOTIVATIONS

- **Presence of G6PD deficiency undermines use of TQ for eradication campaigns**
- **Targeted polymeric prodrugs provide an avenue to treat hypnozoites while reducing bioavailable TQ concentrations in circulation**



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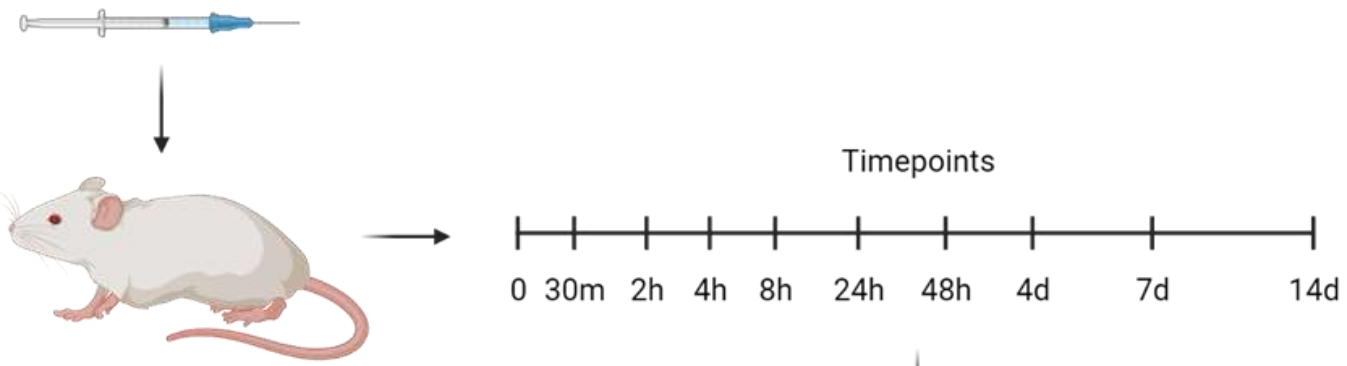
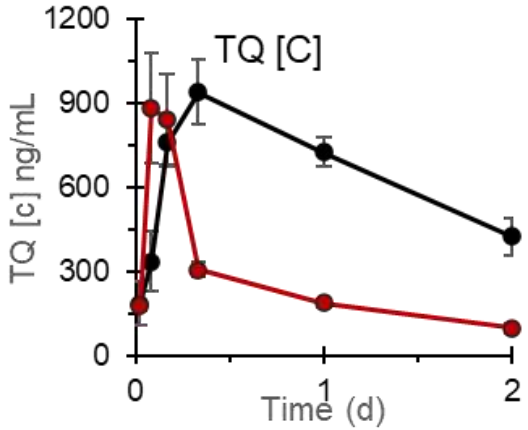
PHARMACOKINETICS OF TQ-BASED POLYMER



Liver and plasma collected

Samples processed for LCMS/MS



TQ [C] is quantified in liver and plasma

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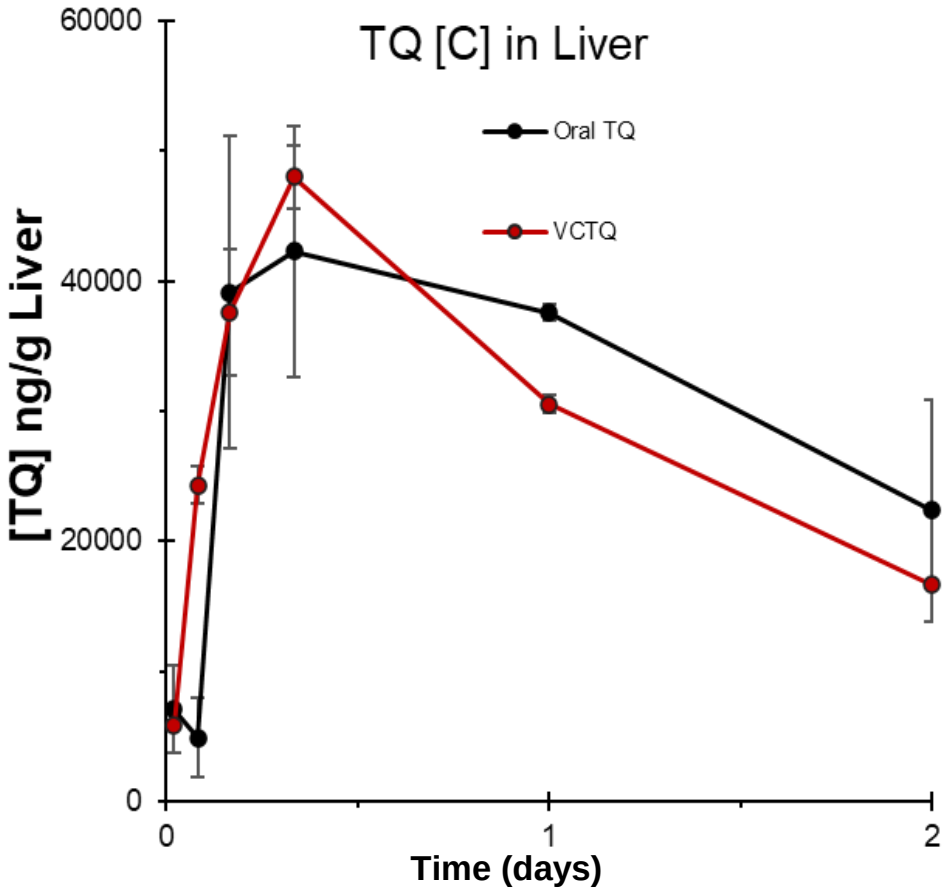
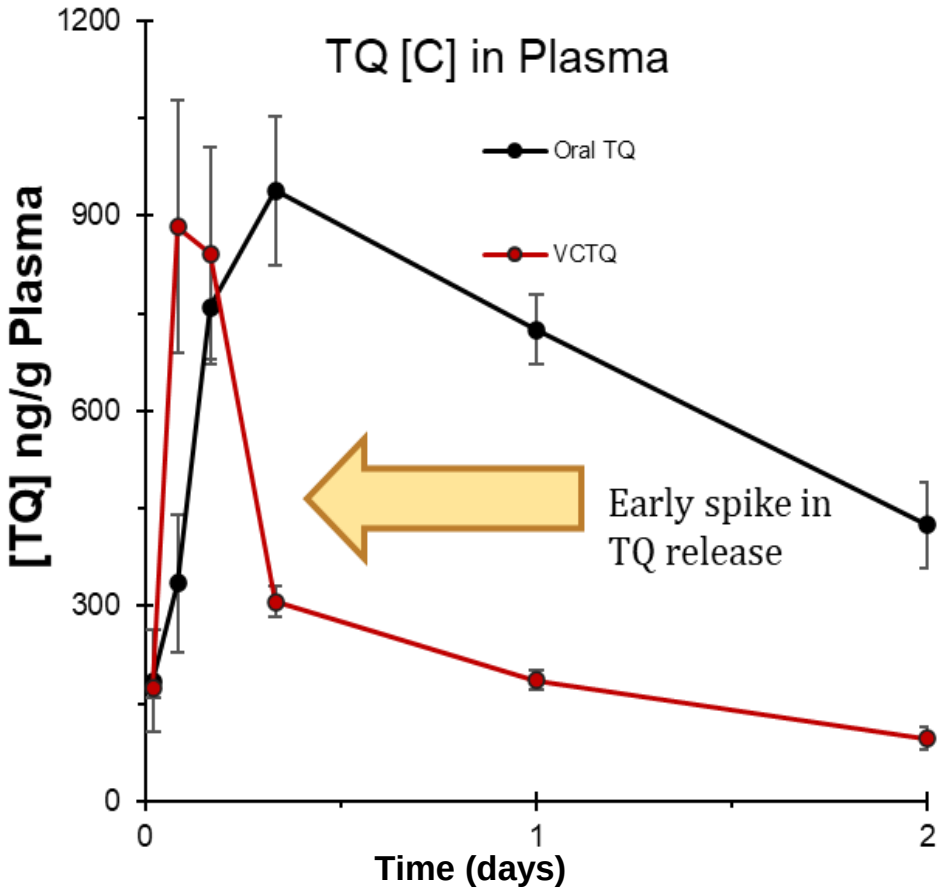
PHARMACOKINETICS OF TQ-BASED POLYMER

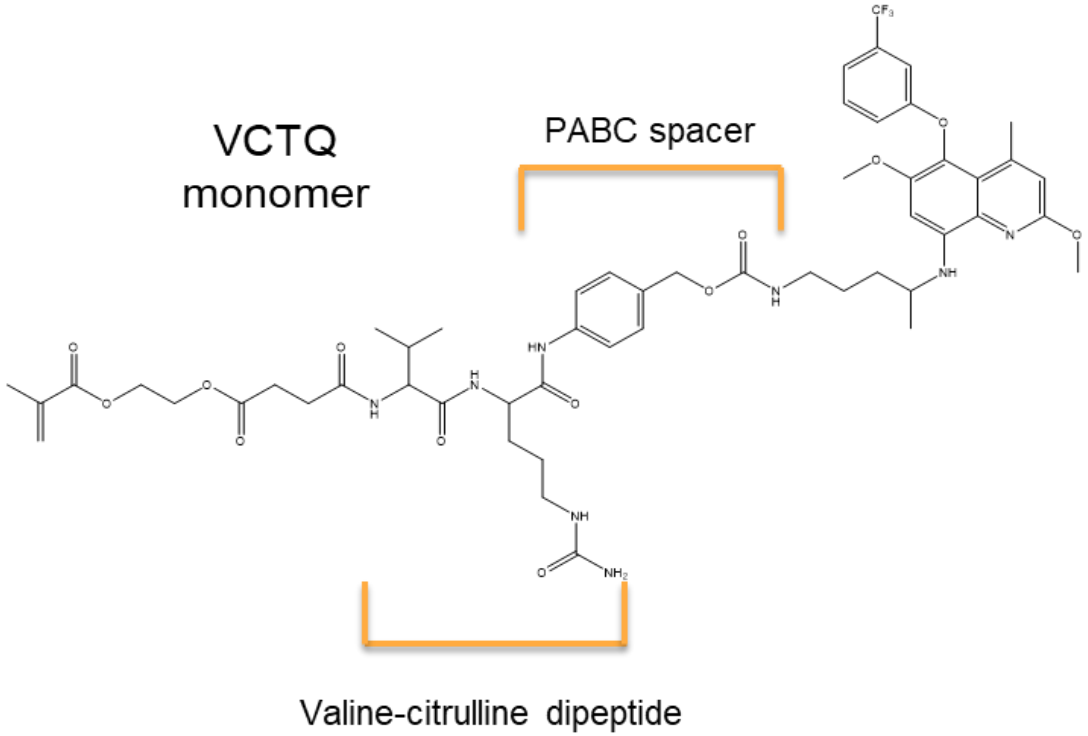


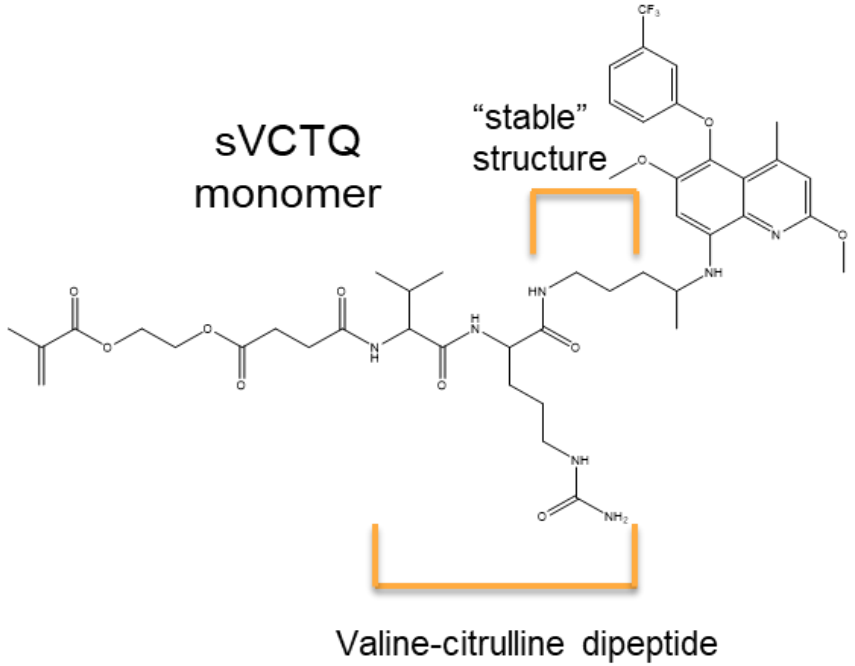


- 25mg/kg dose, IV admin vs oral

- VCTQ polymer and oral TQ had similar TQ [C] in liver
- VCTQ polymer had reduced TQ [C] in plasma
- Carboxylesterase in mouse blood → early peak of TQ in plasma

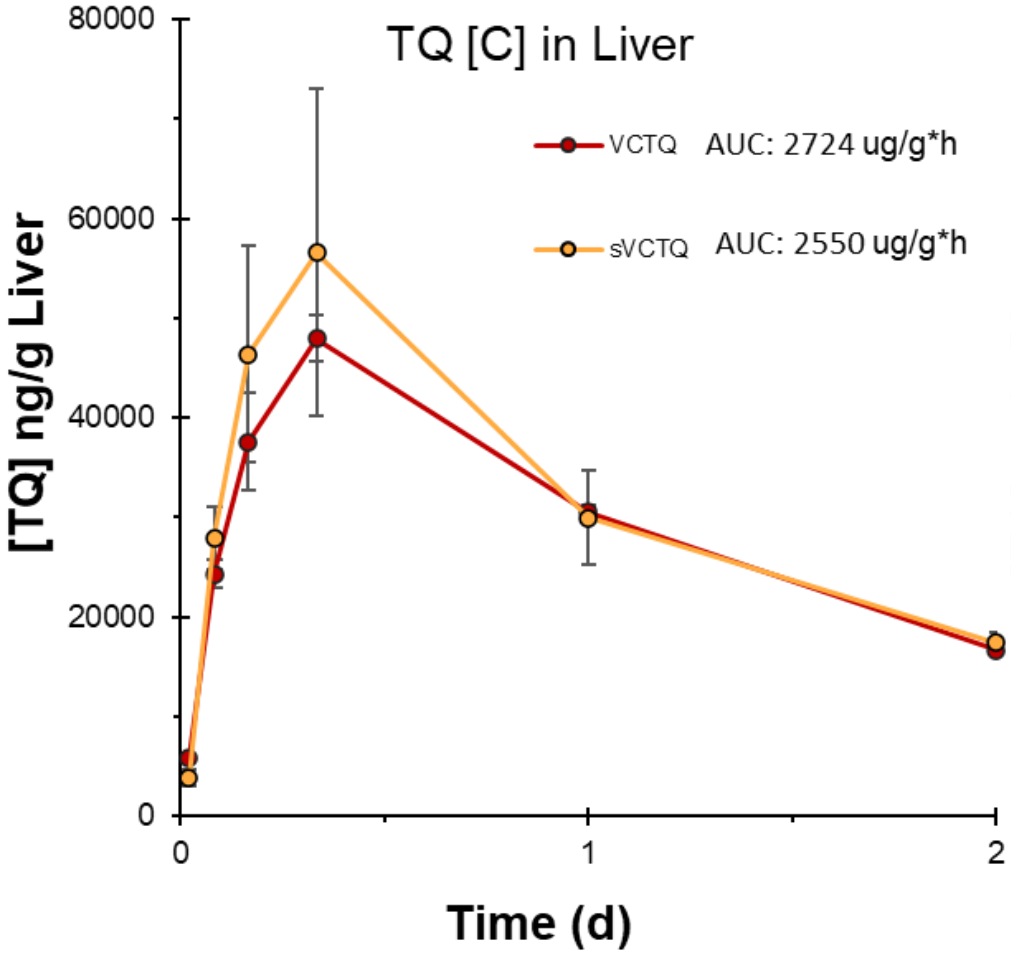
IMPROVING PK PROPERTIES OF TQ VIA LINKER MODIFICATION

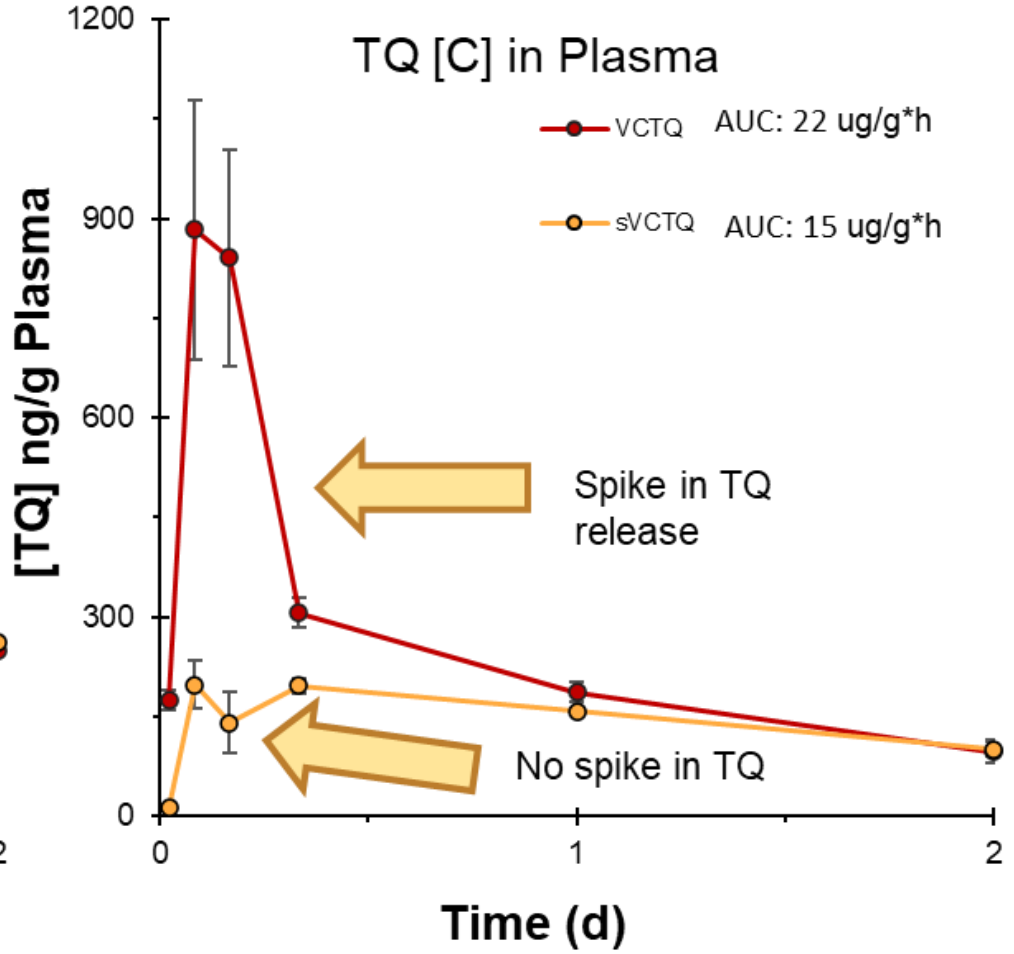




Polymers	[M]:[CTA:[I]	Monomer Conversion	Theoretical DP of Monomers	MW (Mn, g/mol)	Đ	Drug (weight %)
pVCTQ	38:1:0.13	87%	VCTQ-MA (4) GalNAc-MA (29)	14,000	1.1	14
pSVCTQ	39:1:0.14	84%	SVCTQ-MA (4) GalNAc-MA (29)	13,700	1.1	15

SVCTQ ELIMINATES BURST RELEASE IN IV ROA

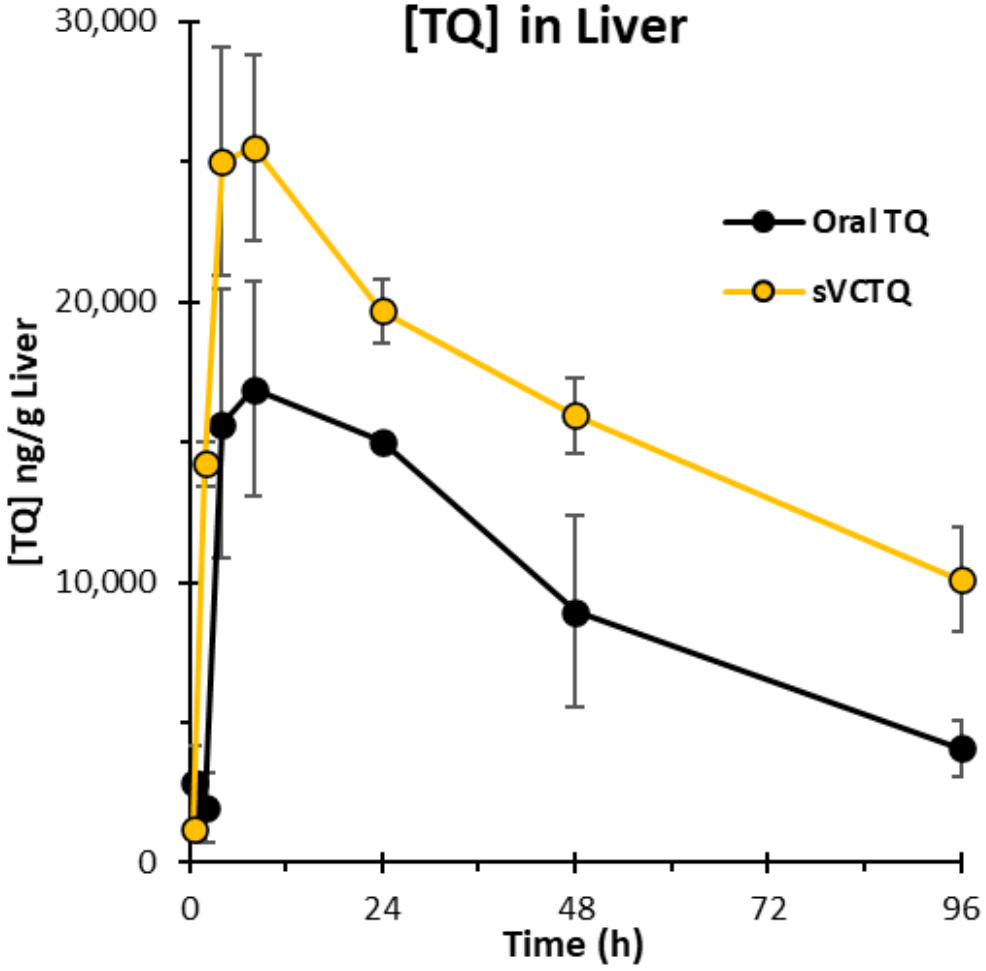


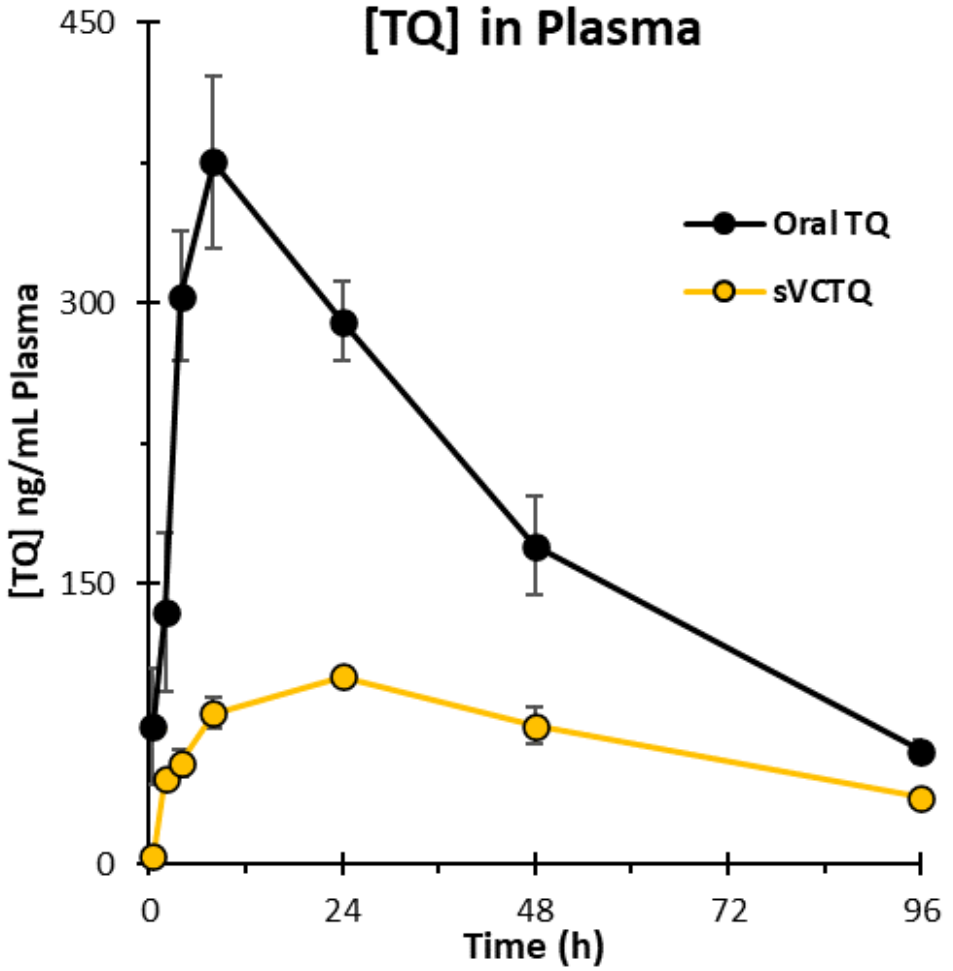


- **25mg/kg dose, IV admin**
- n=3-4

- sVCTQ polymer had no early release in plasma
- sVCTQ still resulted in high liver [c]

SVCTQ IMPROVES LIVER EXPOSURE IN SC ROA

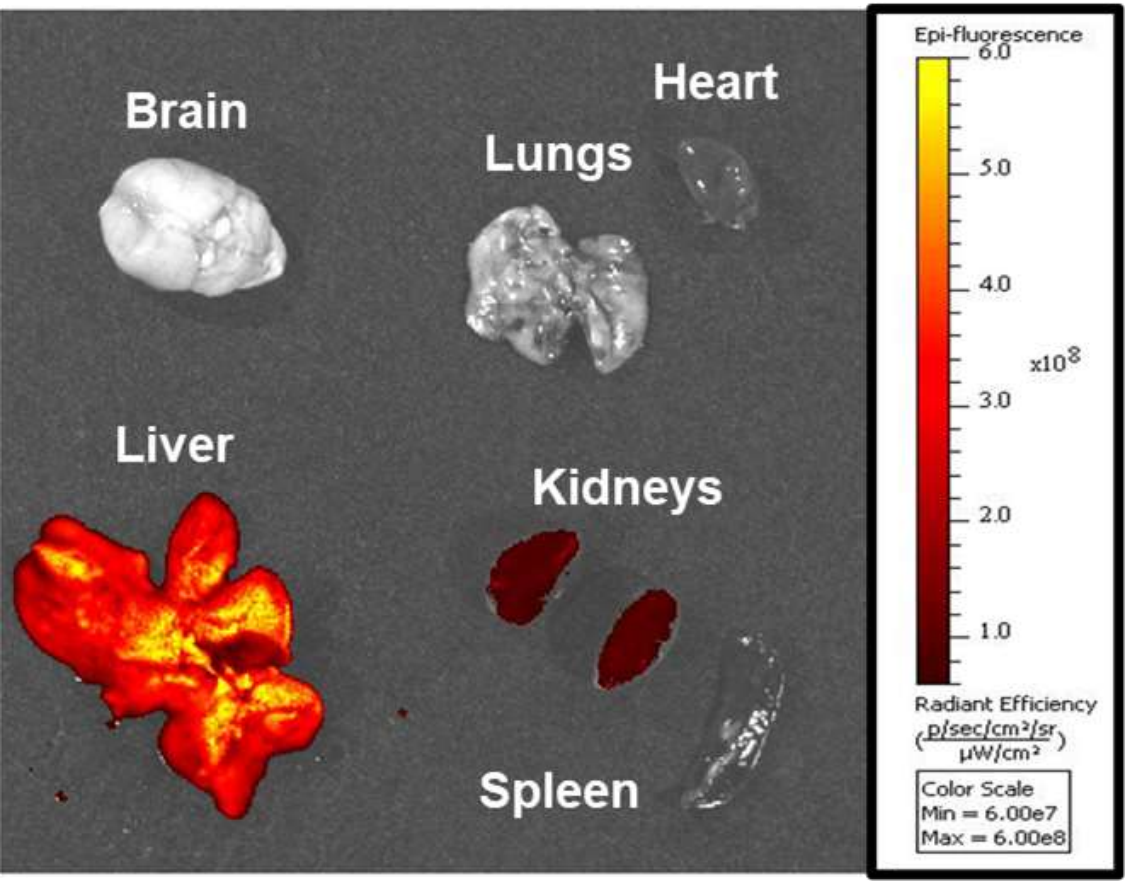




- **10mg/kg dose, SC admin**
- n=3-4

- sVCTQ resulted in high [TQ] in the liver, better TQ bioavailability
- Low TQ release in plasma

BIODISTRIBUTION AND LIVER HISTOLOGY



Tissue collected at 8h following SC 10 mg/kg dose of rhodamine-labeled sVCTQ
IVIS imaging (left) and fluorescent microscopy (right)

Liver histology: DAPI nuclei (blue), Alexa 488 Phalloidin cell membrane (green), rhodamine-labeled pSVCTQ (red)

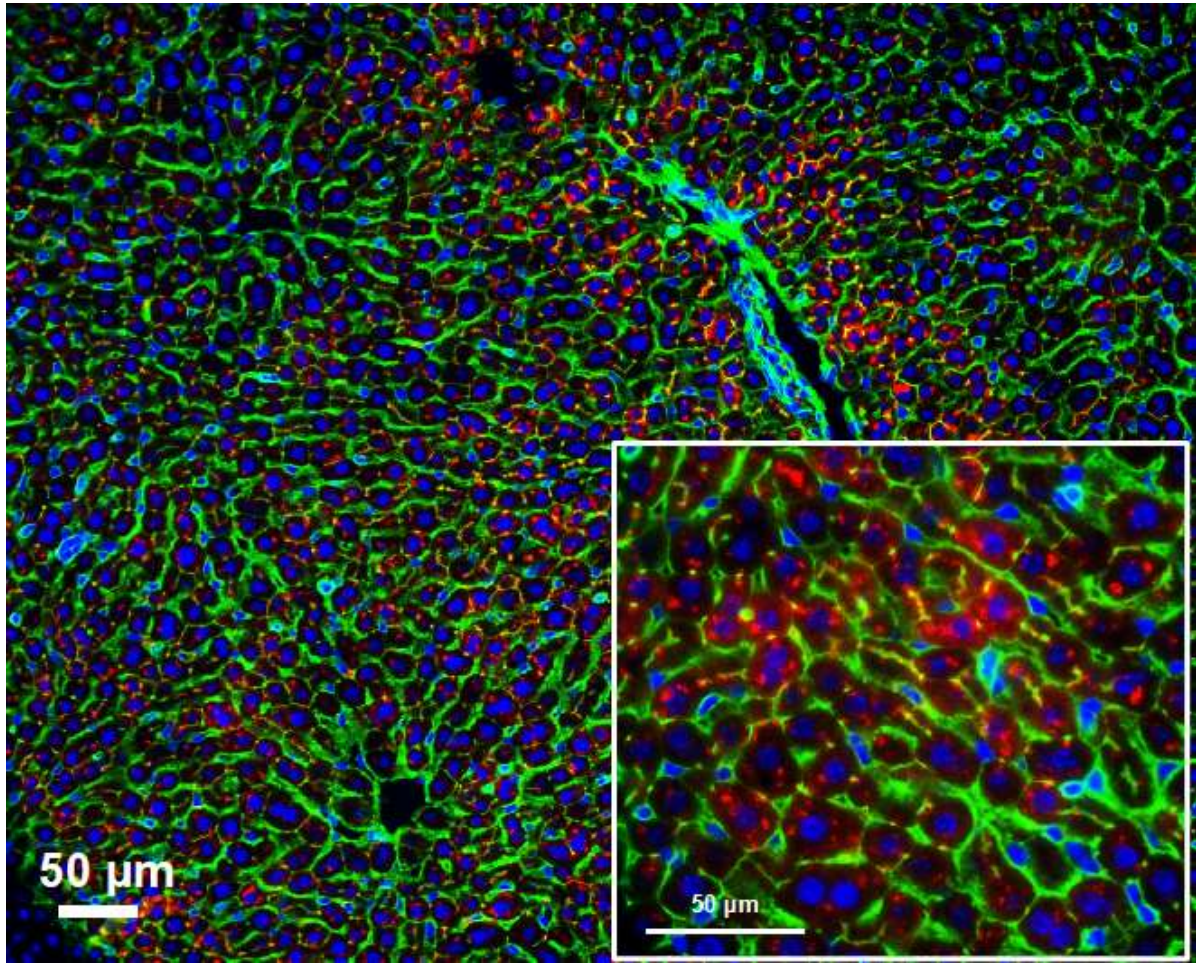


Image taken by Dr. Duy Khiet Ho

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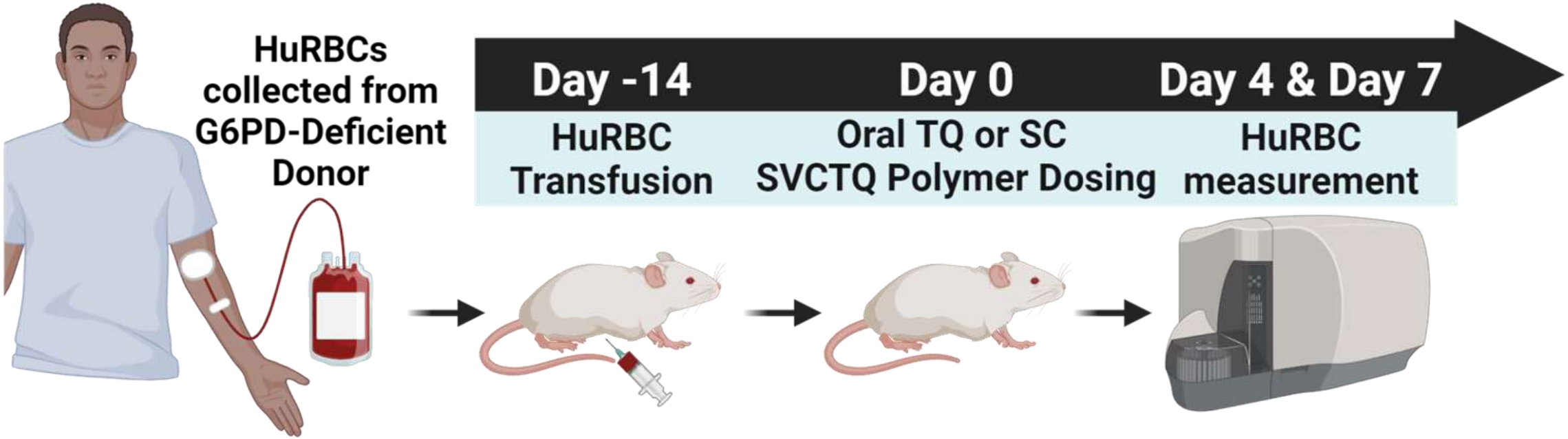
HEMOTOXICITY OF DRUGAMERS IN A HUMANIZED G6PD-DEFICIENT MOUSE MODEL

- Collaboration with University of Colorado Anschutz School of Medicine
- Hemotoxic effect of drugamer on NOD/SCID mice grafted with human G6PD-deficient blood



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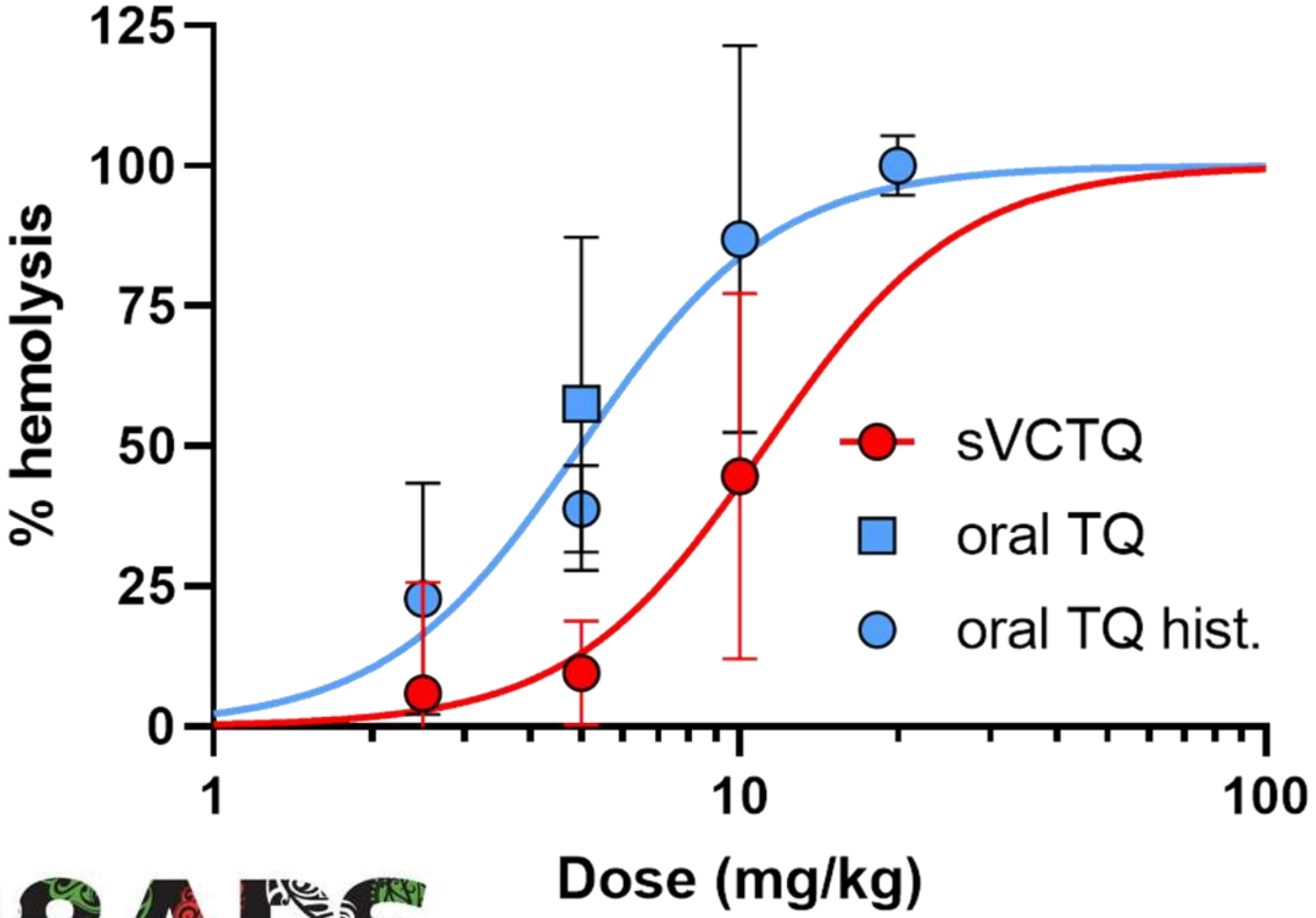
HEMOTOXICITY OF DRUGAMERS IN A HUMANIZED G6PD-DEFICIENT MOUSE MODEL

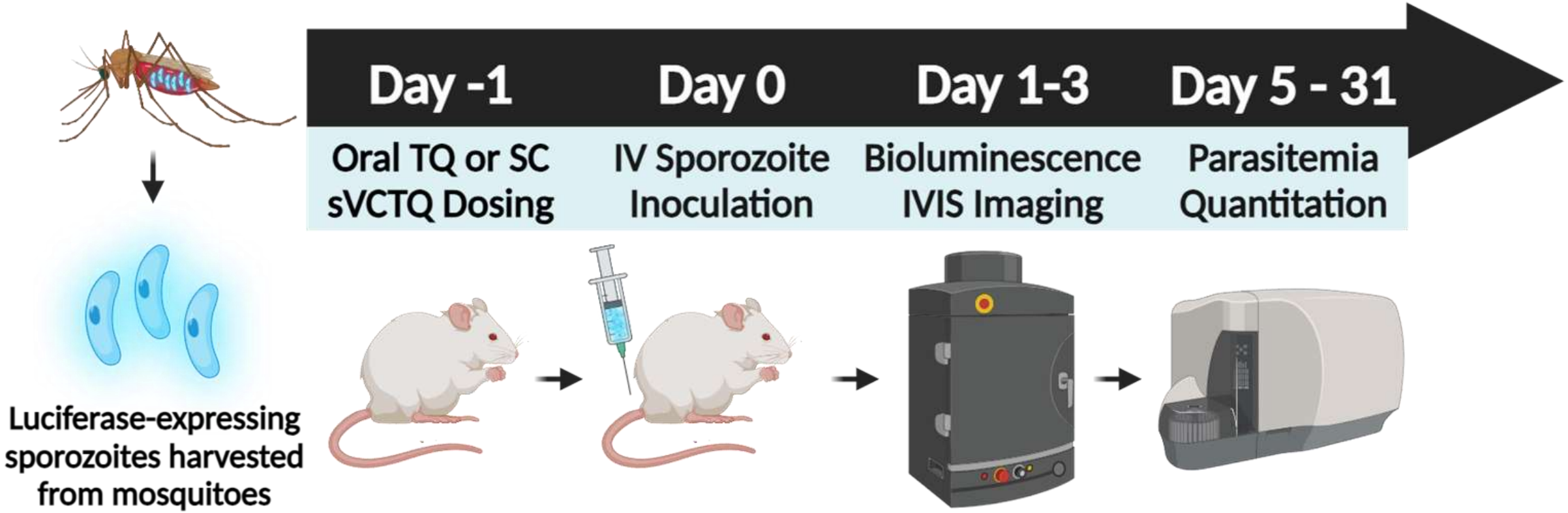


ED50 for oral TQ: 5 mg/kg

ED50 for SVCTQ: 11.2 mg/kg

EFFICACY OF DRUGAMERS IN *P. BERGHEI*-INFECTED MICE

- Collaboration with Walter Reed Army Institute of Research
- Efficacy of polymer on *P. berghei* parasites



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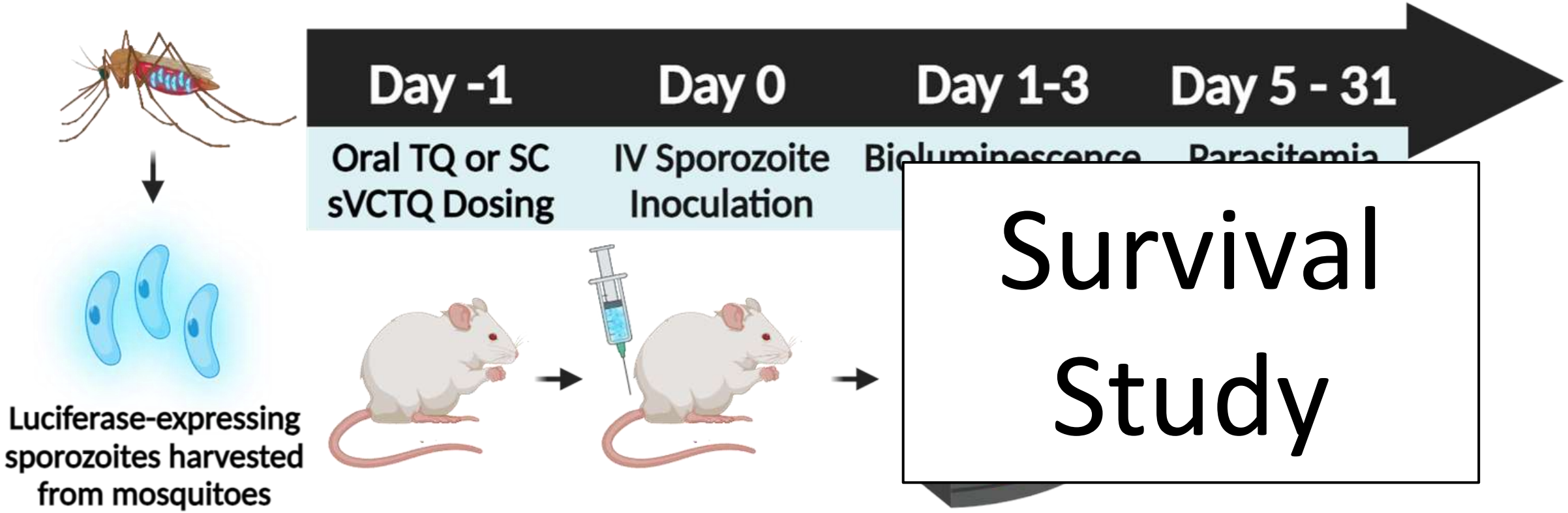
EFFICACY OF DRUGAMERS IN *P. BERGHEI*-INFECTED MICE

- Collaboration with Walter Reed Army Institute of Research
- Efficacy of polymer on *Plasmodium berghei* parasites



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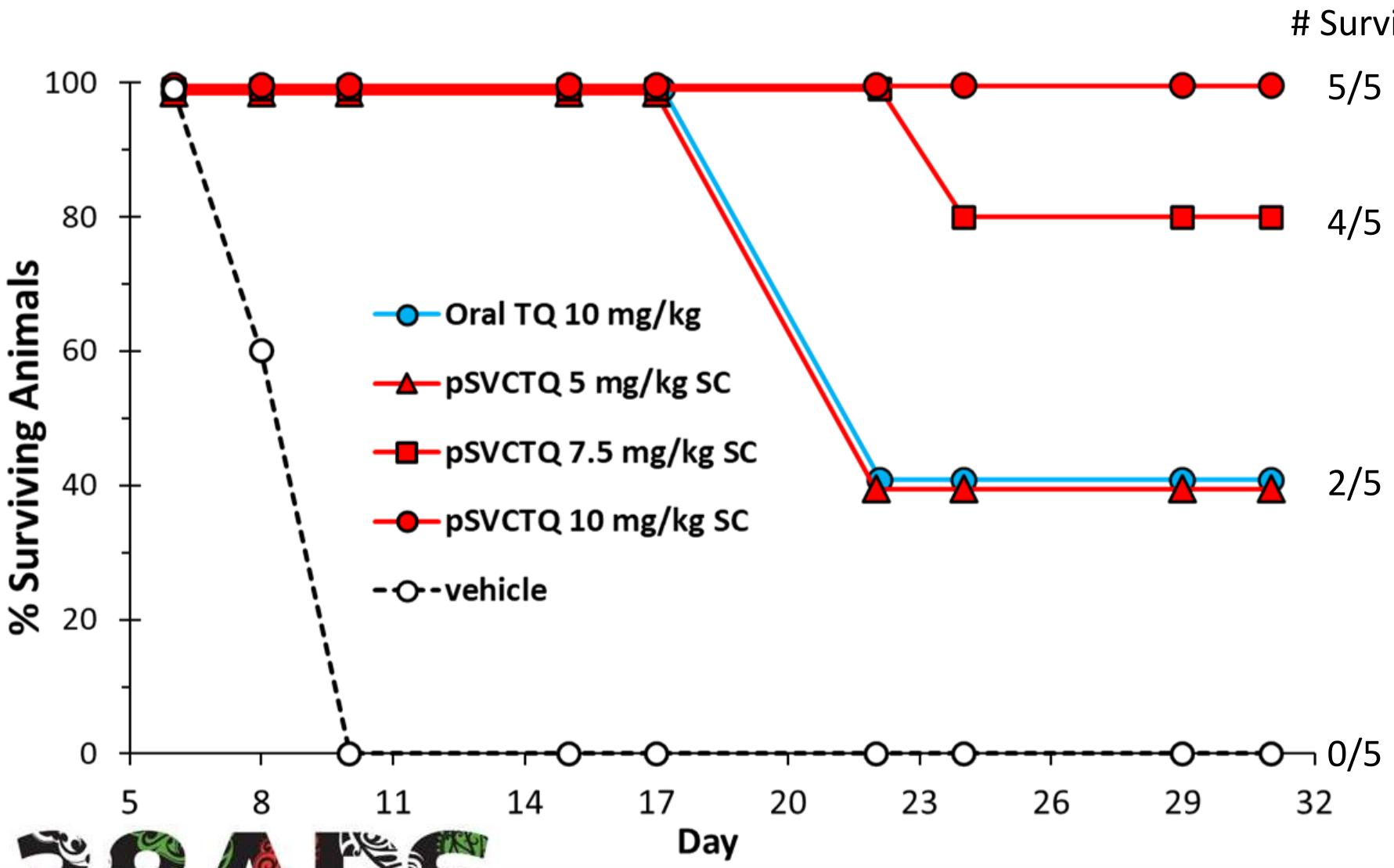

Complete causal prophylaxis at 10 mg/kg SC SVCTQ

Comparable activity at 5 mg/kg SC pSVCTQ and 10 mg/kg oral TQ

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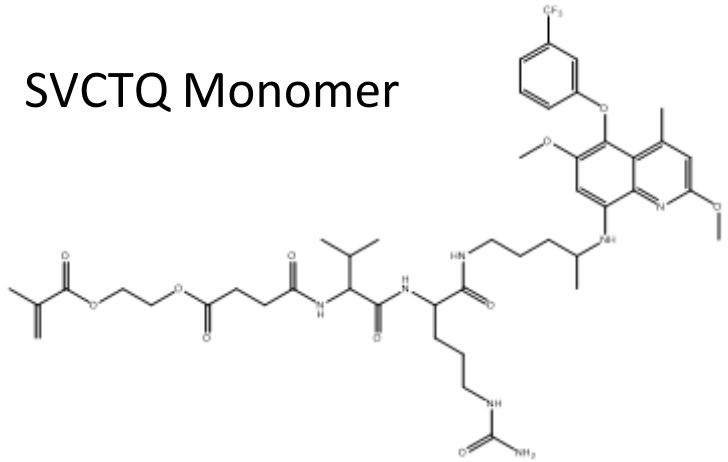
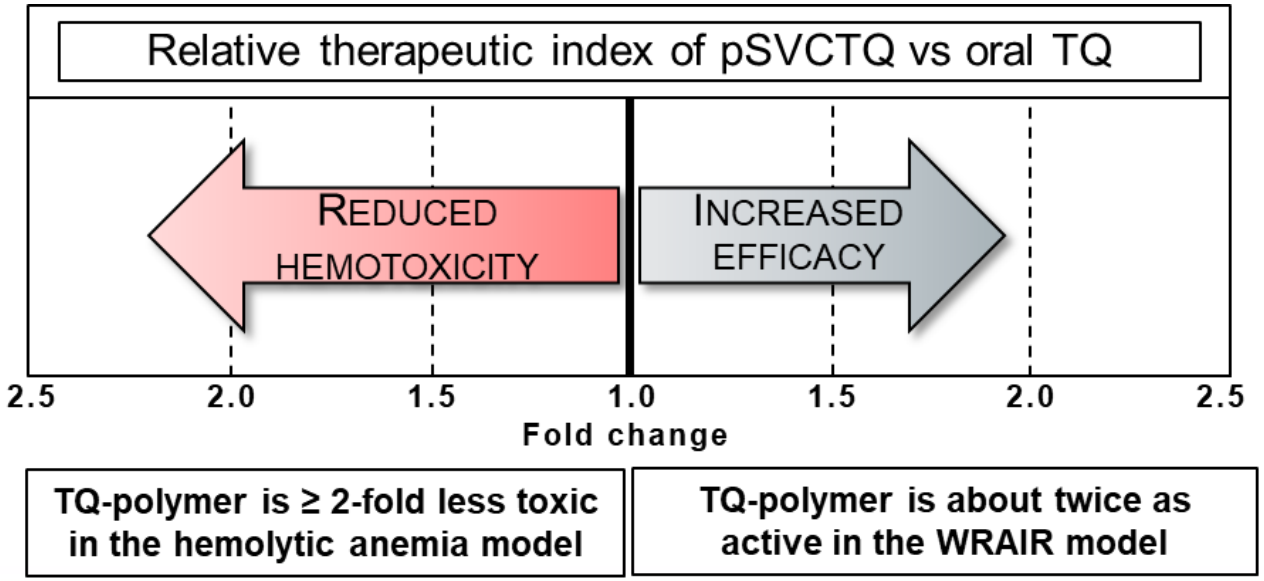
CONCLUSIONS

- ‘Stable’ VCTQ linker design:
- Produced best bioavailability in liver with reduced blood exposure
- Twice as active in WRAIR P. berghei model
- >2-fold reduction of toxicity in hemolytic anemia model
- Additional polymer designs can be used to tune drug release, reduce plasma exposure, and improve circulation of polymer

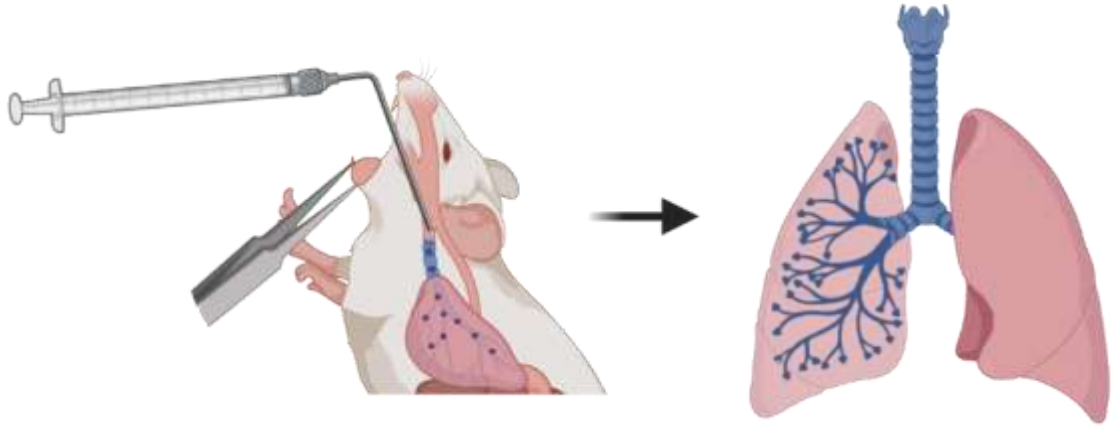
SVCTQ Monomer

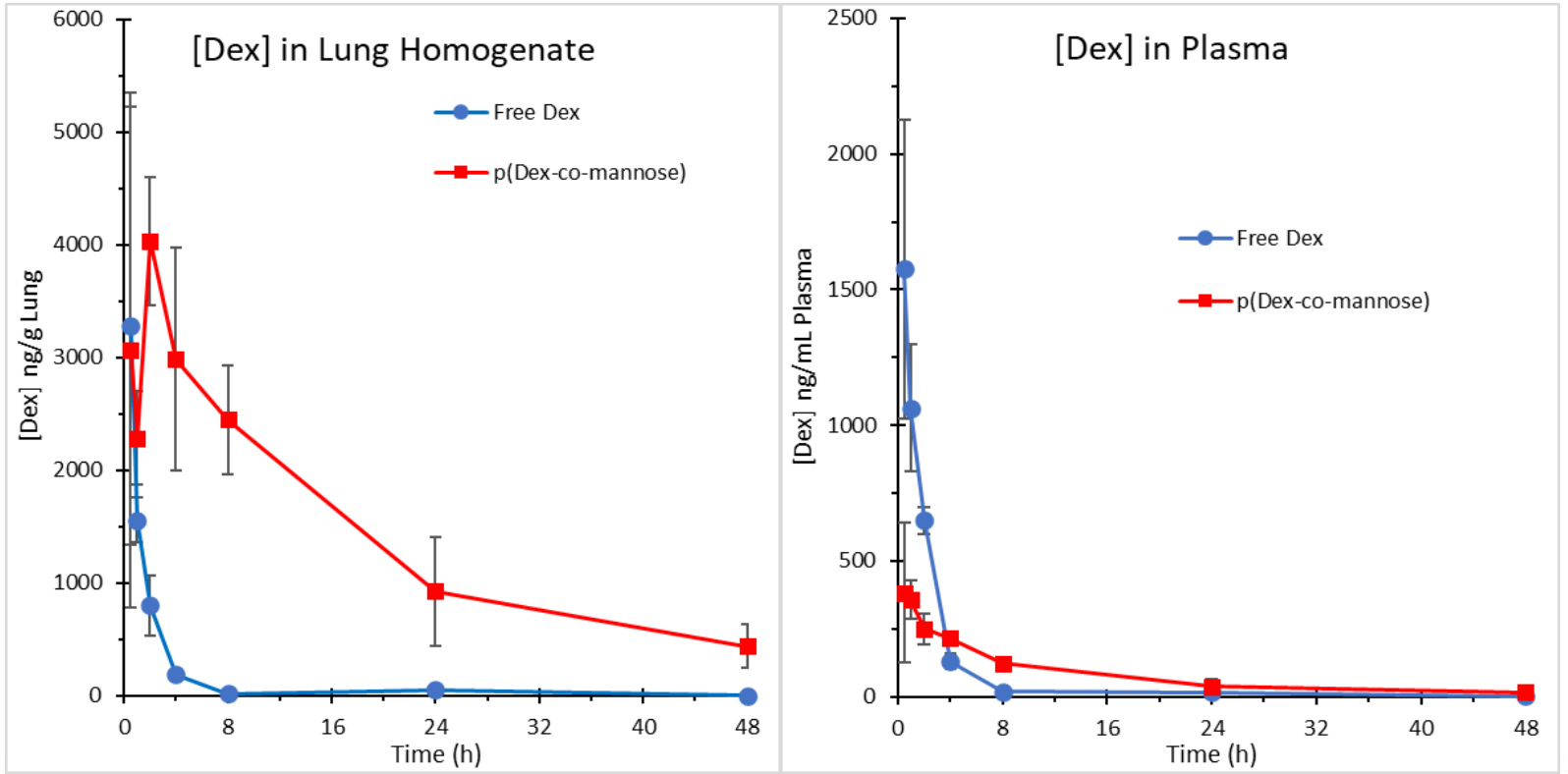




FUTURE DIRECTIONS

- Pulmonary infection applications
- Go to Dr. Patrick Stayton's talk on Tuesday at 3:55pm to hear more about drugamers!





Thank you!

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Vincent Livingston
Osvaldo Arias

Pulmonary Infection Collaboration:

Dr. Shawn Skerrett
Dr. Eoin West
Dr. Deborah Fuller
Dr. Hannah Frizzell
Guilhem Rerole

Citations:

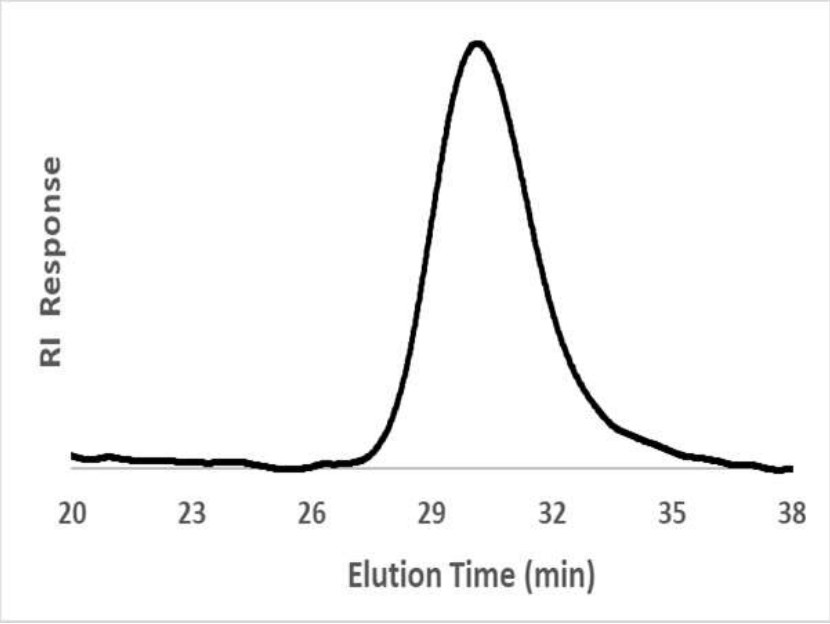
1. World Health Organization. Geneva. World Malaria Report. 2023. vol. Licence:CC BY-NC-SA 3.0 IGO.
2. S. Srinivasan, D. Roy, T. E. J. Chavas, V. Vlaskin, D. K. Ho, A. Pottenger, C. L. M. LeGuyader, M. Maktabi, P. Strauch, C. Jackson, S. M. Flaherty, H. Lin, J. Zhang, B. Pybus, Q. Li, H. E. Huber, P. A. Burke, D. Wesche, R. Rochford, P. S. Stayton, Liver-targeted polymeric prodrugs of 8-aminoquinolines for malaria radical cure. J Control Release 331, 213–227 (2020).

Backup Slides

VCTQ and SVCTQ Synthesis Information

Polymers	[M]:[CTA]:[I]	Monomer Conversion	Theoretical DP of Monomers	MW (Mn, g/mol)[a]	Đ[b]	Drug (weight %)
pVCTQ	38:1:0.13	87%	VCTQ-MA (4) GalNAc-MA (29)	14,000	1.1	14%
pSVCTQ	39:1:0.14	84%	SVCTQ-MA (4) GalNAc-MA (29)	13,700	1.1	15%

[a] Calculated by NMR spectroscopy based on monomer conversion and targeted DP; [b] determined by organic and aqueous SEC.



Representative GPC trace of p(GalNAcMA-co-SVCTQMA) in LiBr-supplemented (0.1% w/v) DMF mobile phase at a flow rate of 1 mLmin-1

SVCTQ Pharmacokinetic Summary

Drug Sample	Dose (mg/kg)	RoA	Tissue	AUC (µg/g Liver*h) or (µg/mL Plasma*h)	AUC SD%	C_{max} (µg/g Liver) or (µg/mL Plasma)	C_{max} SD%	T_{max} (hour)	Liver AUC /Plasma AUC
pVCTQ	25	IV	Liver	2725	7	48	5	8	120
			Plasma	22.62	16	0.88	22	2	
pSVCTQ	25	IV	Liver	2550	15	57	29	8	164
			Plasma	15.53	10	0.20	18	2	
pSVCTQ	10	SC	Liver	2422	13	25	13	8	252
			Plasma	9.617	8	0.10	2	24	
Parent TQ	10	OG	Liver	1404	20	17	23	8	62.8
			Plasma	22.35	14	0.38	12	8	

Anti-hypnozoite Assay