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Patient Centric Sampling in the Therapeutic Development Programs

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What is the Essence of Patient Centricity in Pharmaceutical Industry

- All clinical development aims to develop treatments for patients, so what is different about patient centricity?

- Putting the patient first in all aspects
  - Making the clinical trial experience beneficial to all participants regardless of randomization
  - Put the needs of the patient before convenience to the sponsor

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Intersection of Patient Centricity and Bioanalytical Sciences

- Ensure all biospecimens are collected for an intended purpose
  - Reduce the number of time points and total volume
  - Reduce the patient burden to provide specimens
  - Ensure quality of biospecimens to support planned analyses

- Microsampling as a tool to improve patient centricity
  - Further reduce volume per collection
  - Reduce need for phlebotomists and broaden physical location to collect
  - Develop pathway for home collection and decentralized clinical trials

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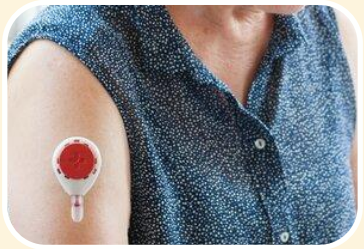
Patient-Centric Blood Collection

Capillary blood rather than venous

- Capillary blood suitable for lower volume collection
  - Standard for infants
  - Most conservative replacement is capillary serum
- Opportunities to run entirely with dried blood
  - Many advances in last decade



Tasso

TAP

BD Microtainer

Capitainer

Hemapen

Mitra

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Benefits for using microsampling

Ethical Benefits:

- Obtaining samples from infants
- Collection of samples in a closer timeframe to a clinical event
- Freeing-up blood volume to collect additional samples

Improved Patient Experience:

- Sample collection in settings more convenient to the patient
- Limiting disruption to normal life for clinical study subjects
- Less invasive than venipuncture

Direct Cost Savings:

- Ambient Temperature Sample Shipments:
- Reduced Shipping Costs

Indirect Cost Savings:

- Less Clinical Staff Needed for Blood Sample Collection
- Improved Clinical Trial Recruitment and Retention

Process Simplicity:

- Minimized On-Site Processing
- This simplification reduces labor, resources, and potential error sources.

*Spooner, 2019, DOI: 10.4155/bio-2019-0041

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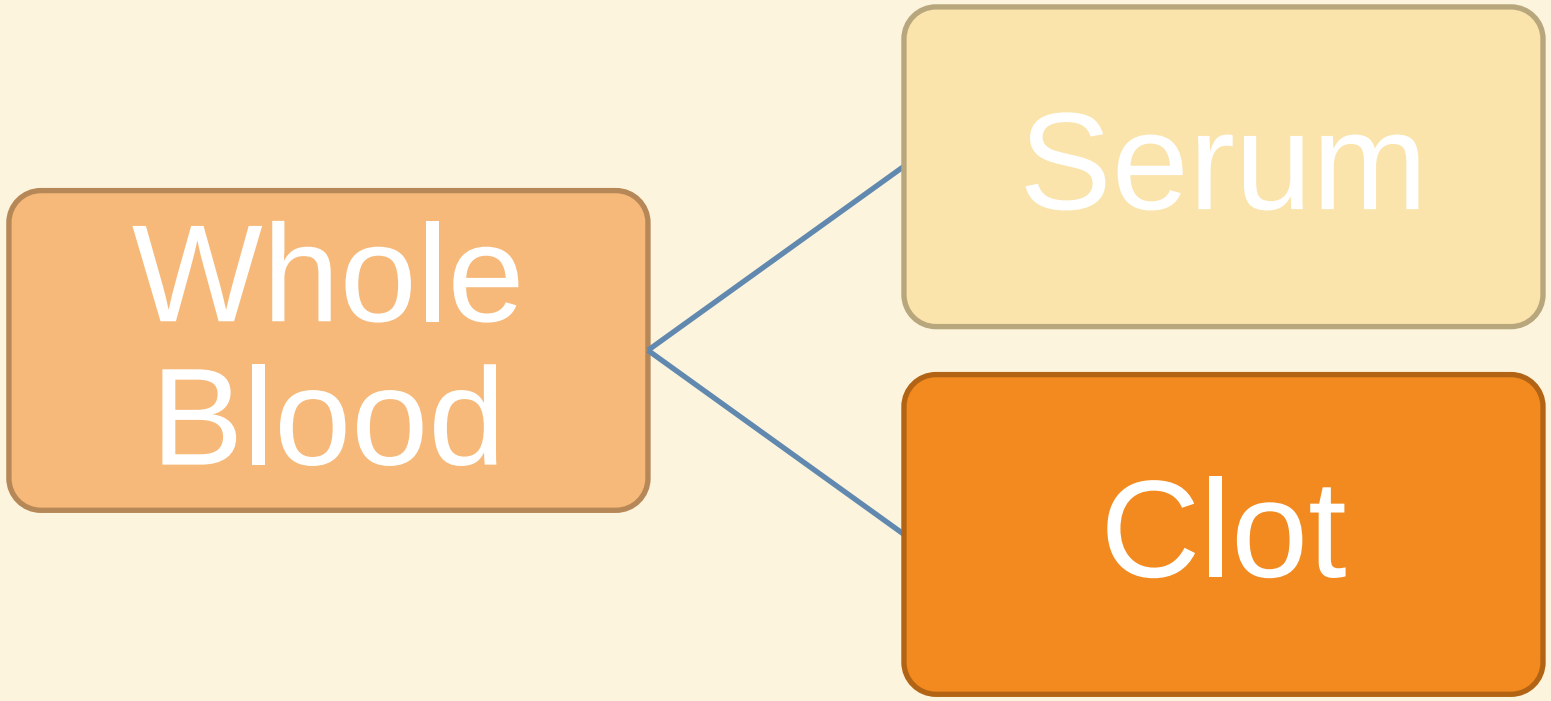
Monoclonal Antibody Therapeutics Partition to Serum



- Serum concentrations will be higher than whole blood
  - Hematocrit can approximate the partition factor
- Calculate conversion to include serum data sets in modeling
  - Historical data sets
  - Nonclinical efficacy models

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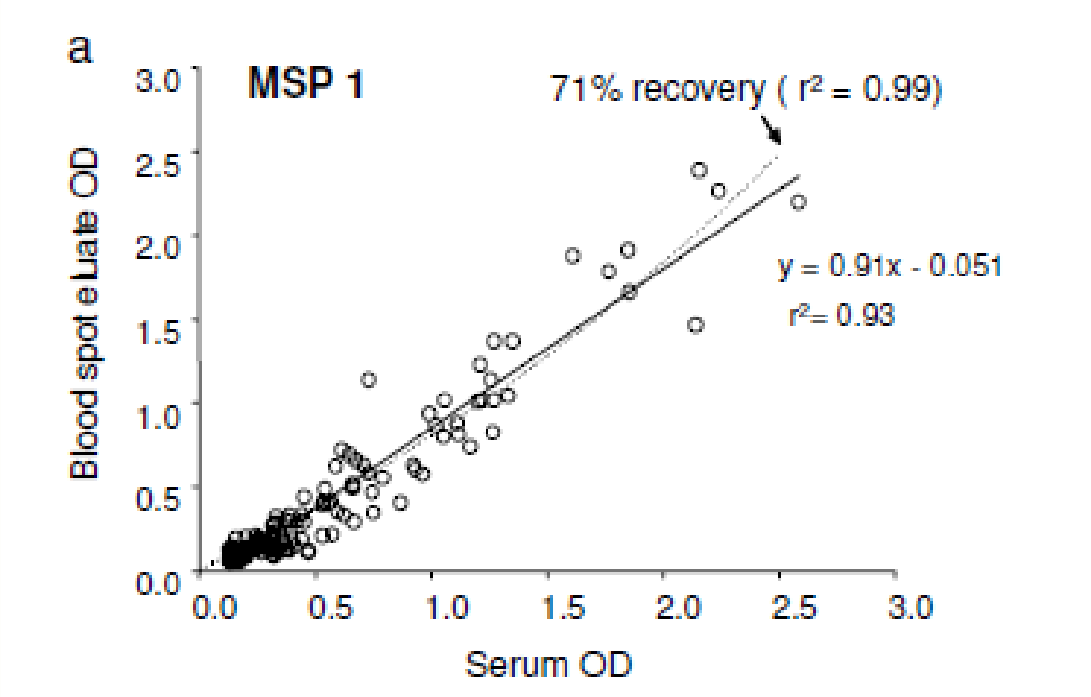
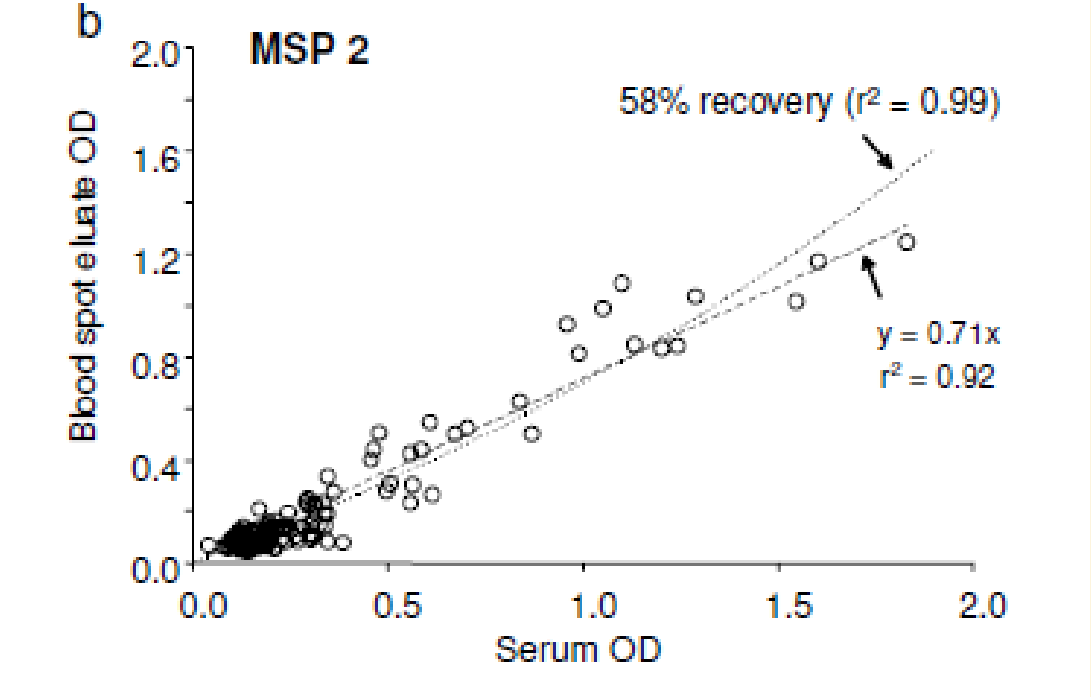
Serology (Anti-Malaria Antibodies)

Recovery from paper dried blood spots





Corran, P. H., Cook, J., Lynch, C., Leendertse, H., Manjurano, A., Griffin, J., . . . Riley, E. (2008). Dried blood spots as a source of anti-malarial antibodies for epidemiological studies. *7*(1), 195. doi:10.1186/1475-2875-7-195

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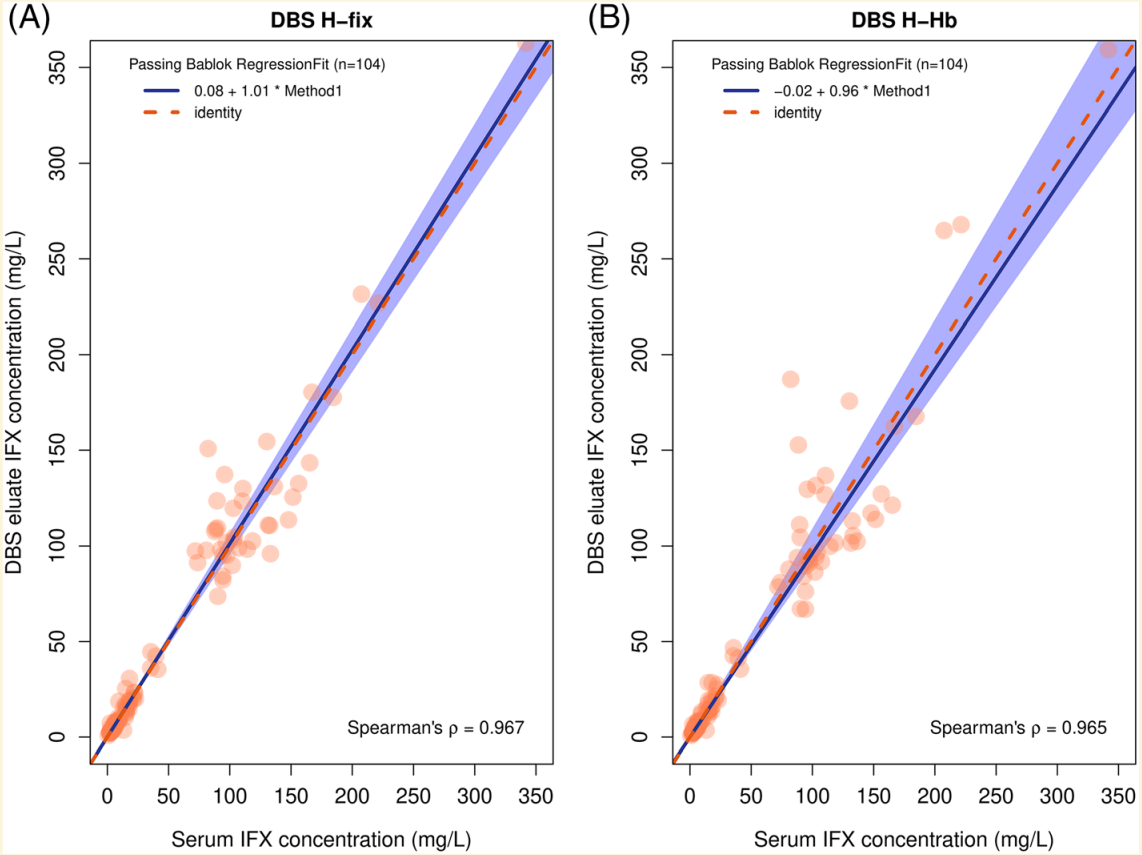
Improved Recovery Using Plastic Substrate

Full recovery with hematocrit correction



- Influximab pharmacokinetic
  - Linear fit
  - Aligned with identity
  - (Lower recovery with home collection)

Berends, S. E., D'Haens, G. R. A. M., Schaap, T., Vries, A., Rispens, T., Bloem, K., & Mathôt, R. A. A. (2019). Dried blood samples can support monitoring of infliximab concentrations in patients with inflammatory bowel disease: A clinical validation. *British Journal of Clinical Pharmacology, 85*(7), 1544-1551. doi:10.1111/bcp.13939

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Case Study

- Monoclonal antibody against Respiratory Syncytial Virus (RSV) fusion protein
- Prophylactic treatment in infant population at highest risk of mortality

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Respiratory Syncytial Virus (RSV) is a major global health concern, primarily affecting young children

- In 2015, an estimated 1.4 million hospital admissions were due to RSV
- There were approximately 273,000 in-hospital deaths among infants less than 6 months old, and more than 99% of these deaths occurred in developing countries [Shi 2017]*
- There is an urgent need for affordable, safe, and effective prevention against RSV, especially in low- and middle-income countries (LMICs)
- The goal of the RSM01 development program is to develop a safe and effective mAb to prevent RSV disease in infants, with a focus on accessibility in LMIC

*DOI: 10.1016/S0140-6736(17)30938-8

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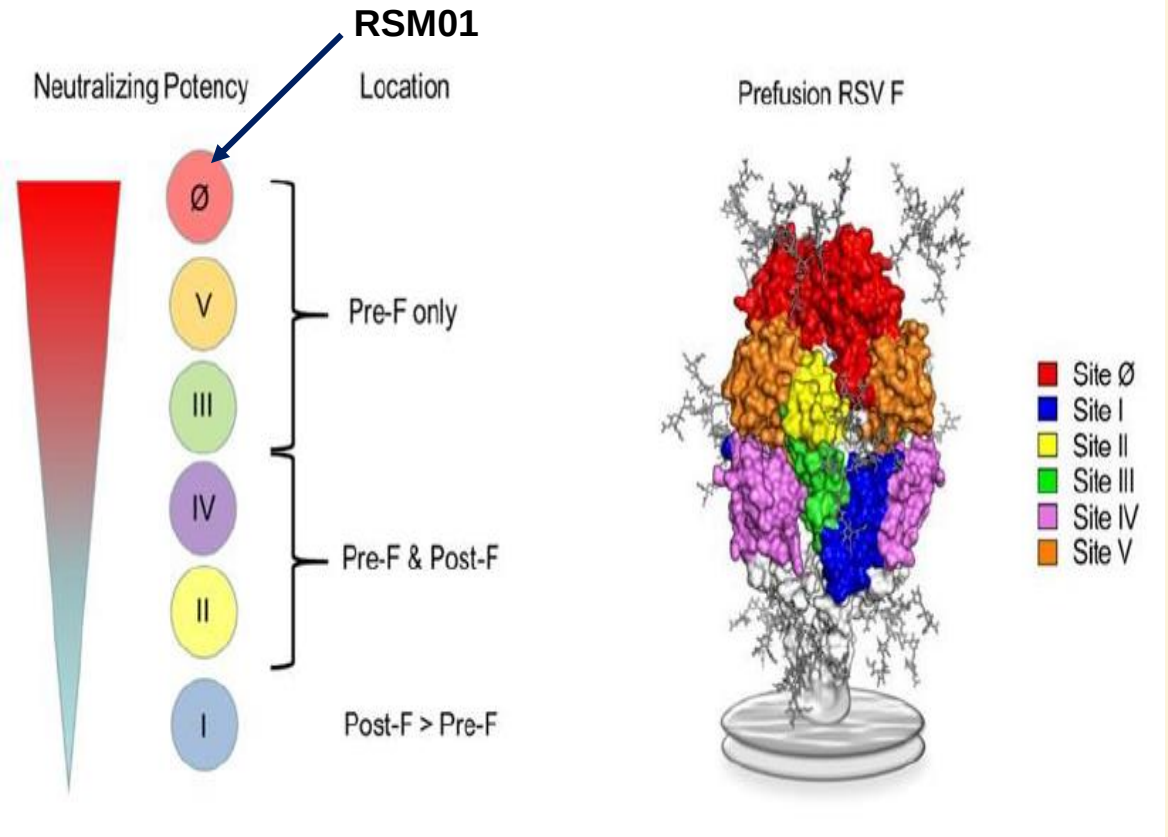
RSM01: A long-acting, potent neutralizing RSV mAB

- Fully human IgG1 mAb
- Targets antigenic site zero of the prefusion F protein (a region considered to be highly neutralization sensitive).
- Acts by binding to and inhibiting the pre-fusion form of RSV glycoprotein F on the surface of the virus, blocking a critical step in the membrane fusion process.
- YTE mutation in Fc region increases serum $t_{1/2}$
- Potential for a single dose for RSV season coverage



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RSM01 VAMS® Implementation

- Support microsampling as the **primary** matrix for mAb pharmacokinetics (PK) in **clinical** development
- Analytical Method Development
  - Use volume absorptive microsampling (VAMS) with plastic substrate
  - 100% recovery versus whole blood spike
- Clinical bridging study
  - Enable modeling to include nonclinical and nirsevimab serum data
  - Fully matched profiles for venous serum vs capillary blood VAMS
    - Far exceeds the requirements for a bridging study
    - Enables comparison of PK parameters in addition to raw drug concentration from samples

Selected references to small molecule matched plasma and blood:
https://doi.org/10.1016/j.jchromb.2021.122556; https://doi.org/10.1016/j.jpba.2023.115688

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Method Validation Highlights

Parameter	Blood	Serum
MRD	1:200 (including extraction)	1:200
Precision	≤ 13.6%	≤ 18.9%
Accuracy	≤ 6.5%	≤ 4.2%
Total Error	≤ 20.1%	≤ 22.2%
Selectivity	100% Unspiked 90% LLOQ 100% HQC	100% Unspiked 100% LLOQ 100% HQC
In-study Precision	≤ 7.6%	≤ 11.4%
In-study Accuracy	≤ 5.7%	≤ 7.7%

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Gates MRI-RSM01-101 Study Design

Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and PK of Single Ascending Doses of RSM01in Healthy Adults (NCT05118386)

Dose Escalation Phase

Cohort 1
300 mg IV
RSM01, n = 6;
PBO, n = 1

Cohort 2
300 mg IM
RSM01, n = 6;
PBO, n = 1

Cohort 3
1000 mg IV
RSM01, n = 6;
PBO, n = 1

Cohort 4
3000 mg IV
RSM01, n = 6;
PBO, n = 1

Dose Expansion

Cohort 5
600 mg IM
RSM01, n = 24;
PBO, n = 4

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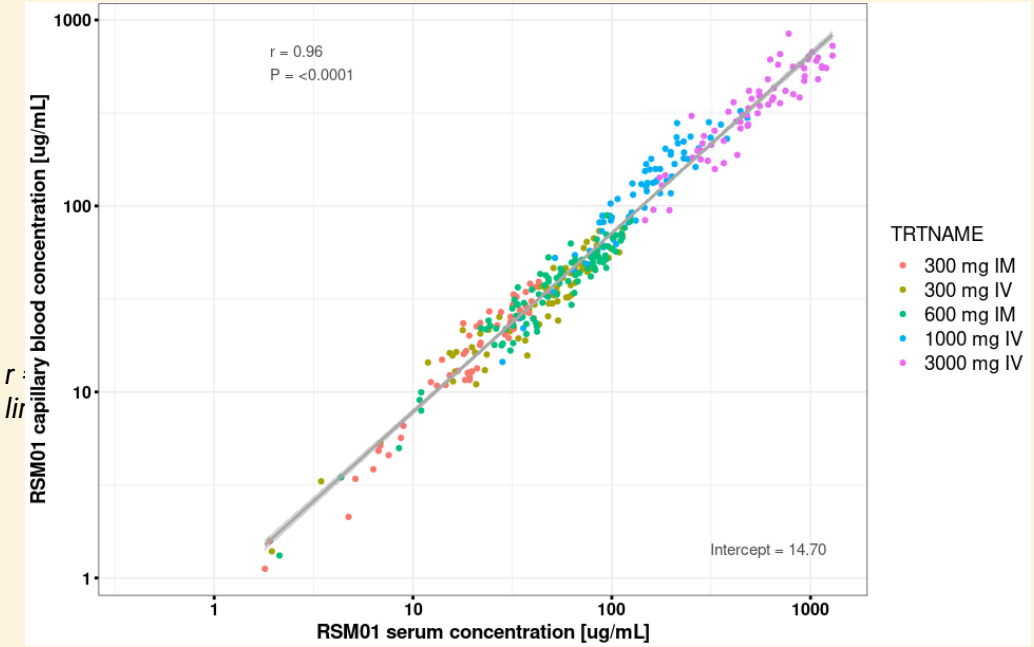
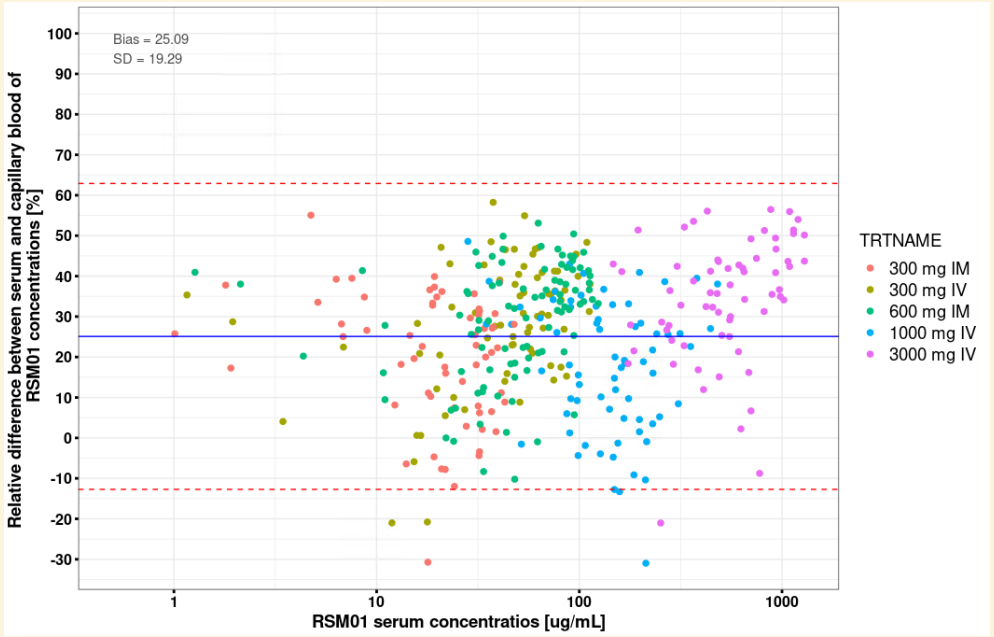
Gates MRI-RSM01-101:

High correlation and agreement between serum and blood concentrations

- All subjects show high correlations between the blood and plasma



- Generally, no discernable pattern emerges even when controlling for sex, race, or ethnicity



*Bias (mean of (Serum - Blood)/Serum*100%) as a solid blue line and the lower and upper limits of agreement (LOA) as dashed red lines*

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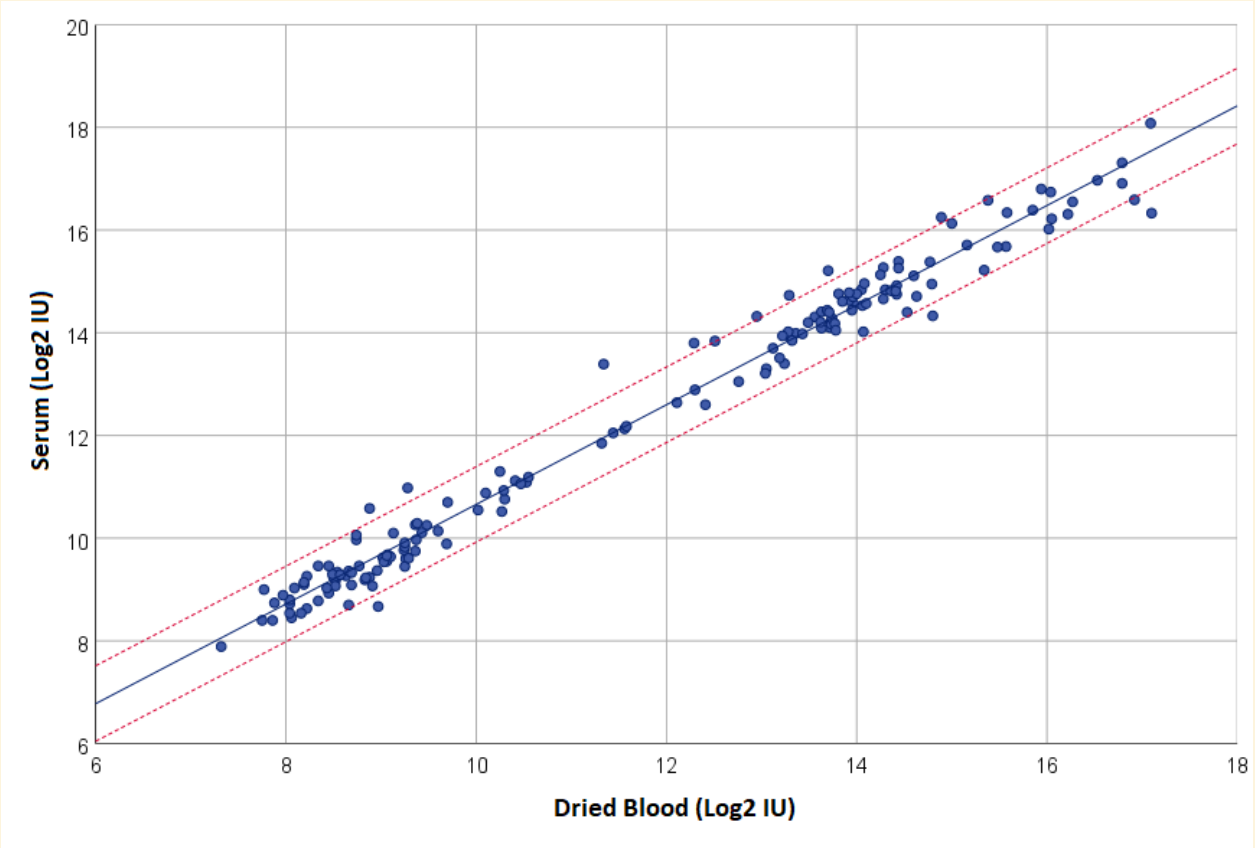
Gates MRI-RSM01-101 RSV Neutralizing Ab

Beyond binding to functional activity

- Simple methodology
  - PBS extraction overnight
  - Cell based assay with live viral stock
  - International Units based on WHO standard
- Correlation established
  - Extracted antibodies retained function
  - Spiked samples (not shown)
  - Study samples (D1, D91, D151)



Submitted manuscript pre-print: https://www.medrxiv.org/content/10.1101/2023.08.10.23293875v1

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Conclusions

- A patient-centric sampling strategy using dried blood collected on VAMS technology was successfully implemented for RSM01 in a first-in-human trial with adult participants
- The PK results in capillary blood from VAMS and serum samples were linearly correlated
- This approach is valuable in advancing global clinical drug development and is planned for use in future pediatric RSM01 trials in infants

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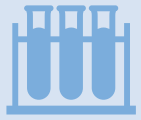
Aspirational Advances



Which safety labs can be converted to microsampling?

- Collaborate with central lab and non-interventional study
- Other nonprofit organizations focused on increasing diagnostic access
- PCSIG Diagnostics Working Group

Which exploratory biomarkers can be converted to microsampling?

- Serology already on DBS for some infectious diseases
- Published sequencing, genomics, proteomics
- Long shot to miniaturize deep sequencing (extractions currently use 2 mL)

Feasibility of other matrices even less invasive than capillary blood?

- Interstitial fluid
- Saliva
- Tears

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Acknowledgments

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  - http://www.pcsig.org
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Thank you!

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