

VITT: A pan-vaccine reaction in need for sensitive and *specific* diagnosis?

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Conflict of Interest

- Patents/Pending Patents: Mayo Clinic, Versiti BloodCenter of Wisconsin, Retham Technologies
- Equity Ownership and Officer: Retham Technologies
- Advisory Board: Veralox Therapeutics

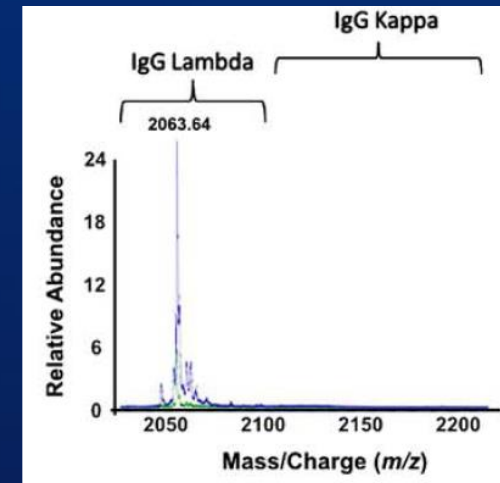
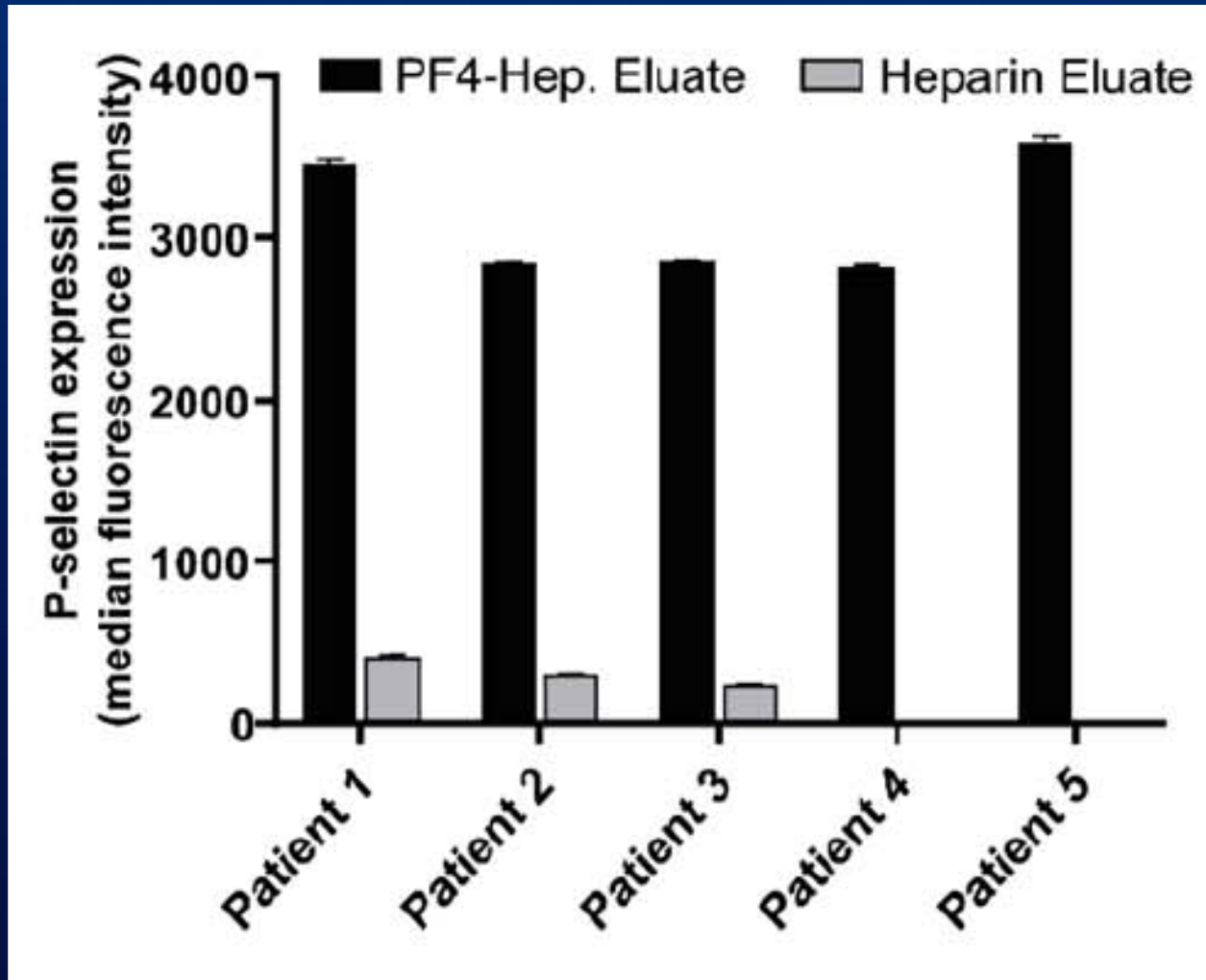
Introduction

- A severe thrombotic and thrombocytopenic reaction was described (first in 2021) in response to certain covid-19 vaccines (ChAdOx-1 nCoV-19 and Ad26.COV2.S)
- Multiple reports suggested that antibodies to Platelet Factor 4 (PF4) mediate this syndrome
- Our research effort were focused on to further characterizing anti-PF4 antibodies (abs) in VITT patients

Characterizing VITT Abs

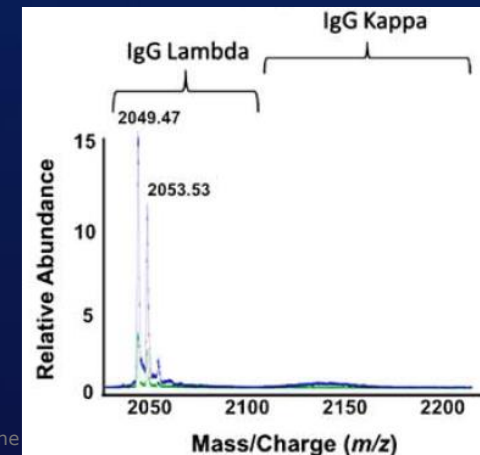
Antibody isolation coupled to Mass Spectrometry

Anti-PF4 abs are Monoclonal or Oligoclonal

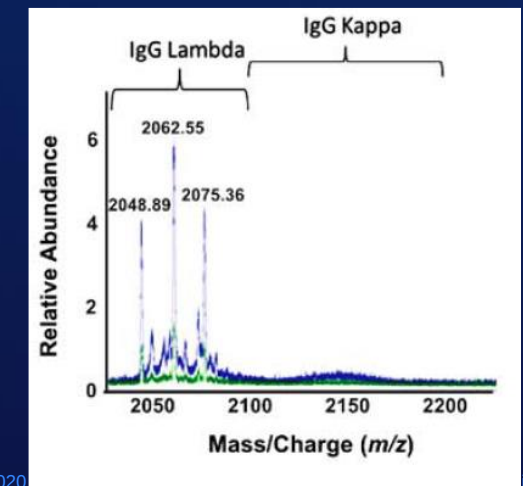


Monoclonal x3

Biclonal x 1

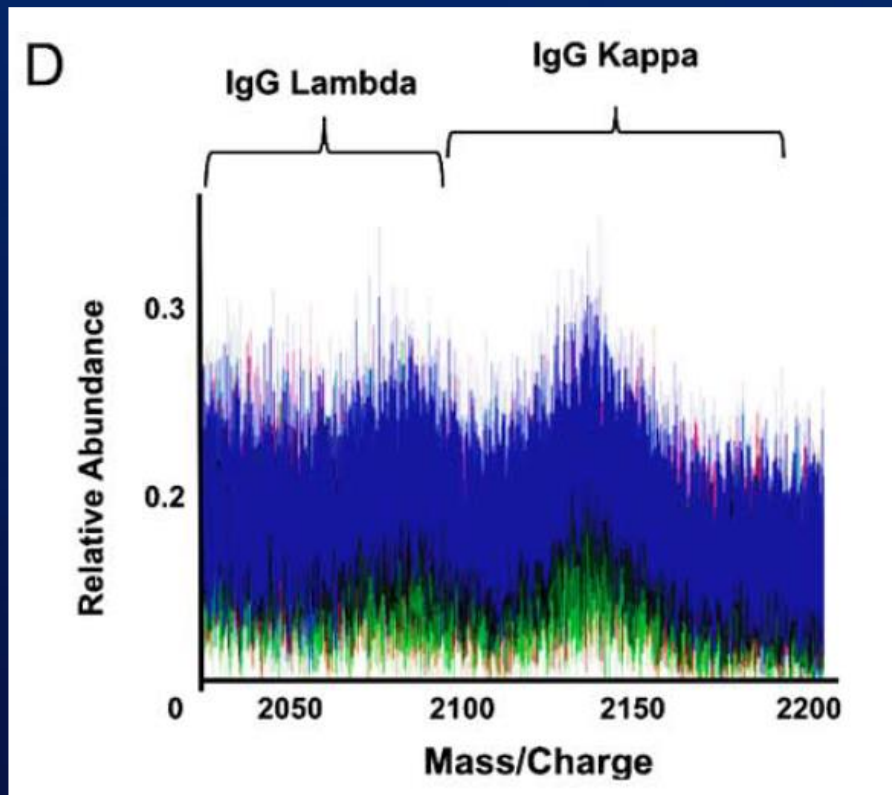


Triclonal x 1

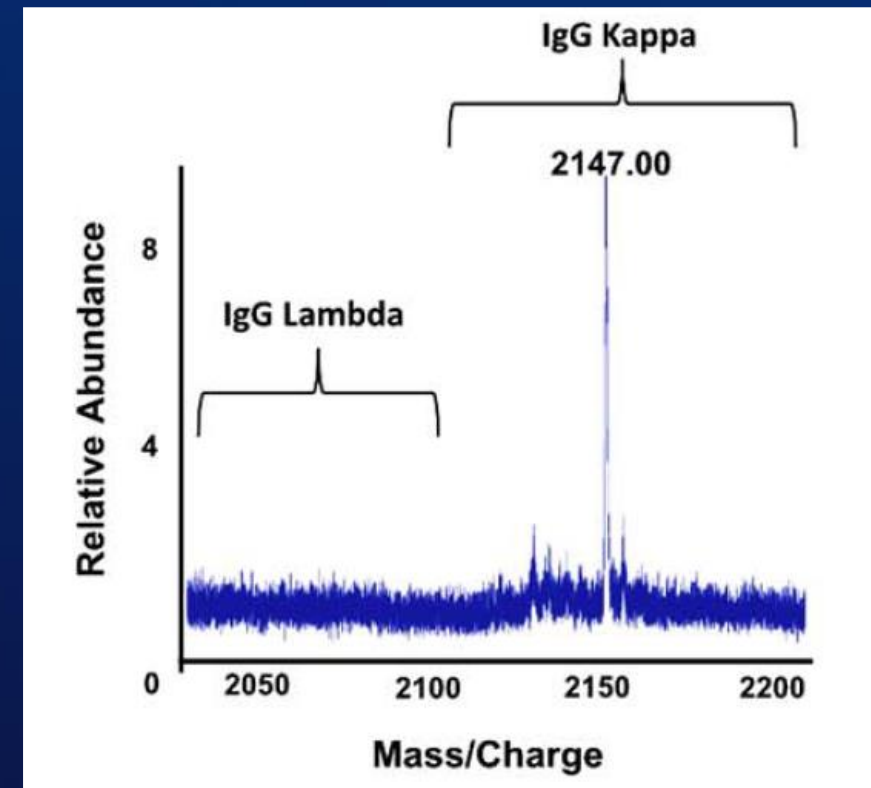


HIT antibodies: Polyclonal Spontaneous HIT: Monoclonal

HIT



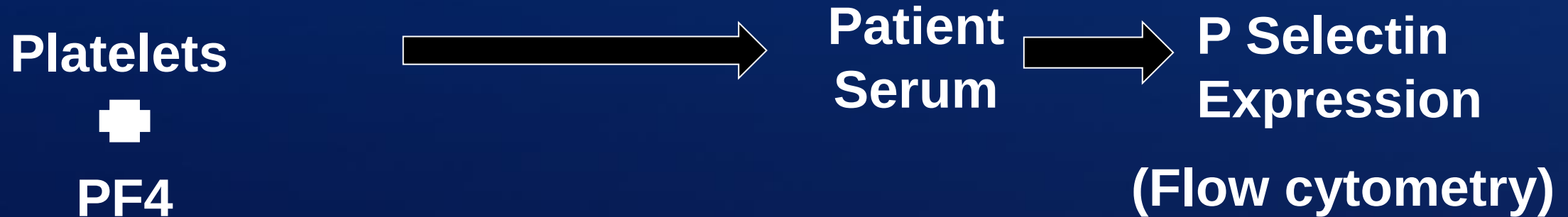
Spontaneous HIT



Identification of VITT antibodies

PF4-Dependent Functional Testing

Basis: PF4 bound to platelets is the target recognized by activating (“pathogenic”) HIT antibodies



Sep, 2016



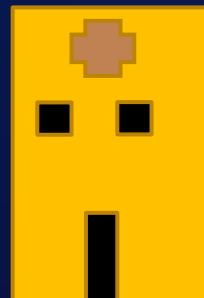
Feb, 2021

Solely performed in Specialized Reference Labs

Decentralize Functional Testing?



In-hospital testing: Functional VITT Testing

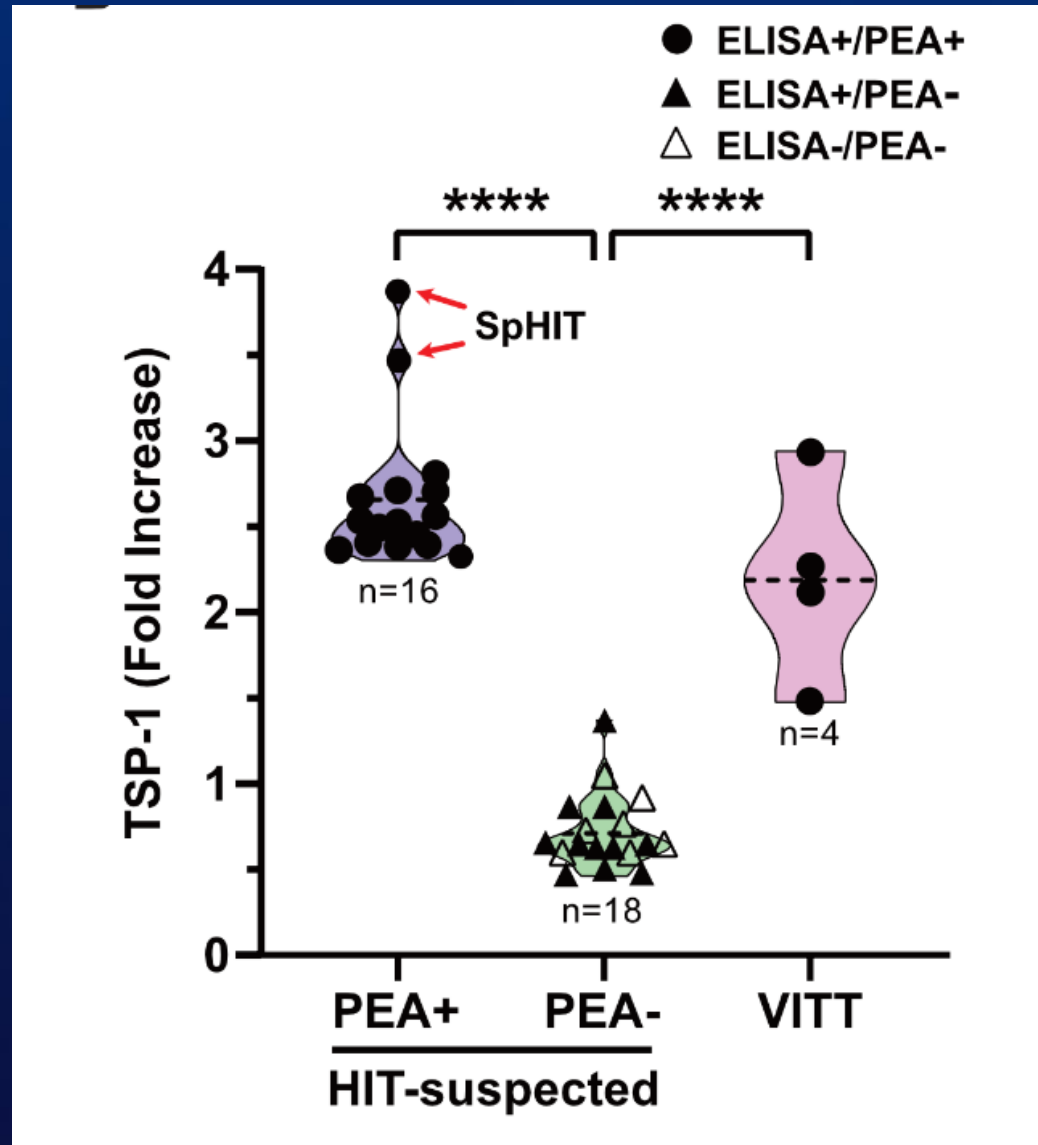


(1)
Long-term
Stable
Platelets

(2)
PF4

(3)
Assess Platelet
Activation

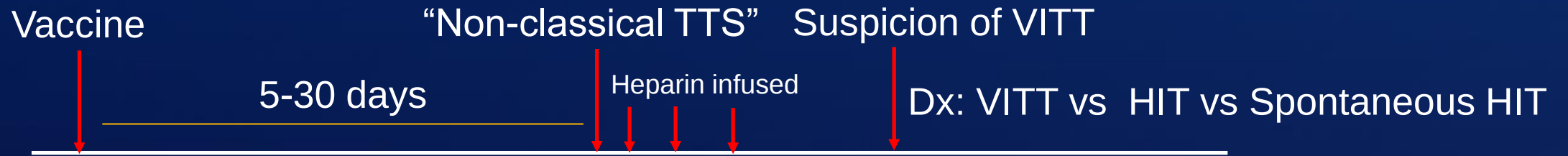
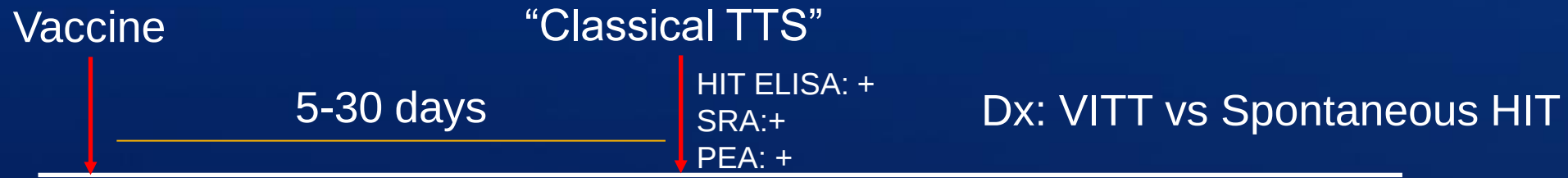
Thrombospondin-1 release assay (TRA) using controlled-rate cryopreserved platelets



Platelets: Months or Years old

Stable with shipping on dry ice

VITT Diagnostic Challenges

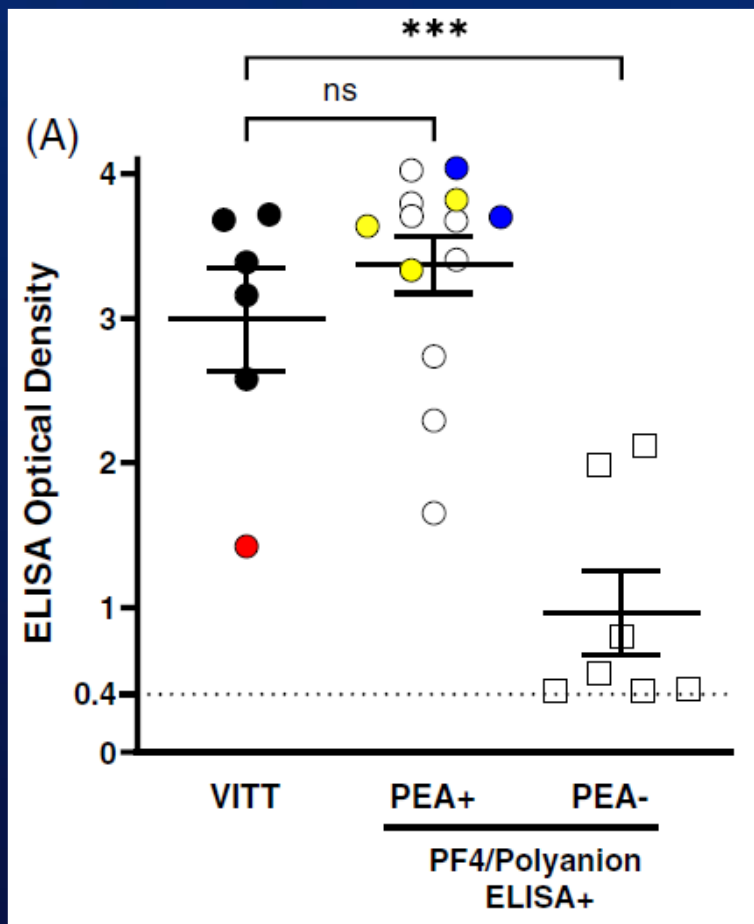


Some current assays are highly *sensitive* for VITT: HIT (PF4/polyanion) ELISA; PEA/PIPA/PF4-SRA

No current assays are *specific* for VITT

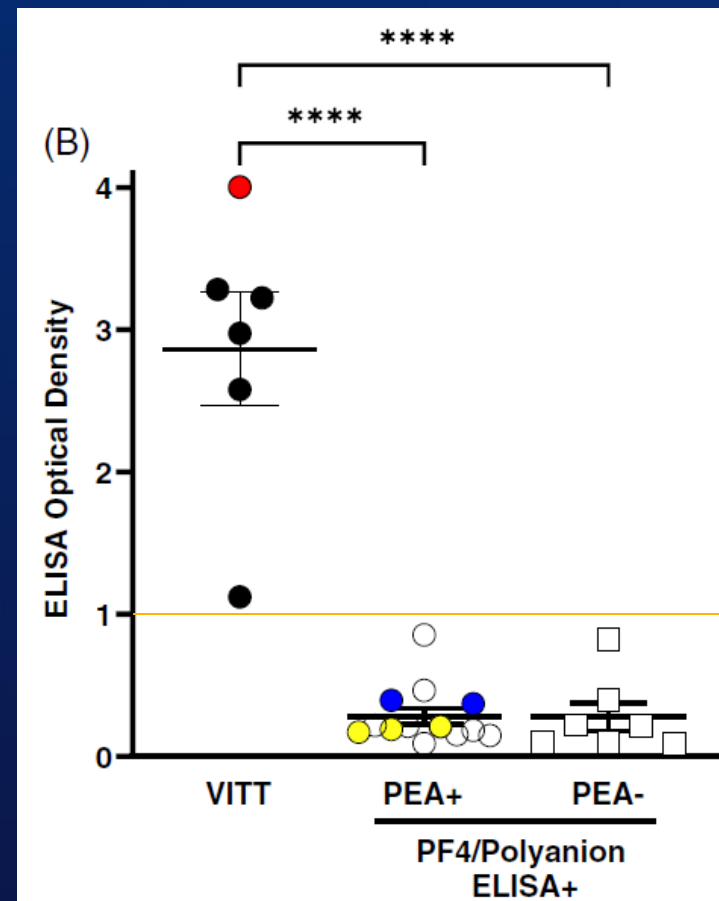
Can we specifically and sensitively detect VITT antibodies?

“Standard” HIIT (PF4-polyanion) ELISA



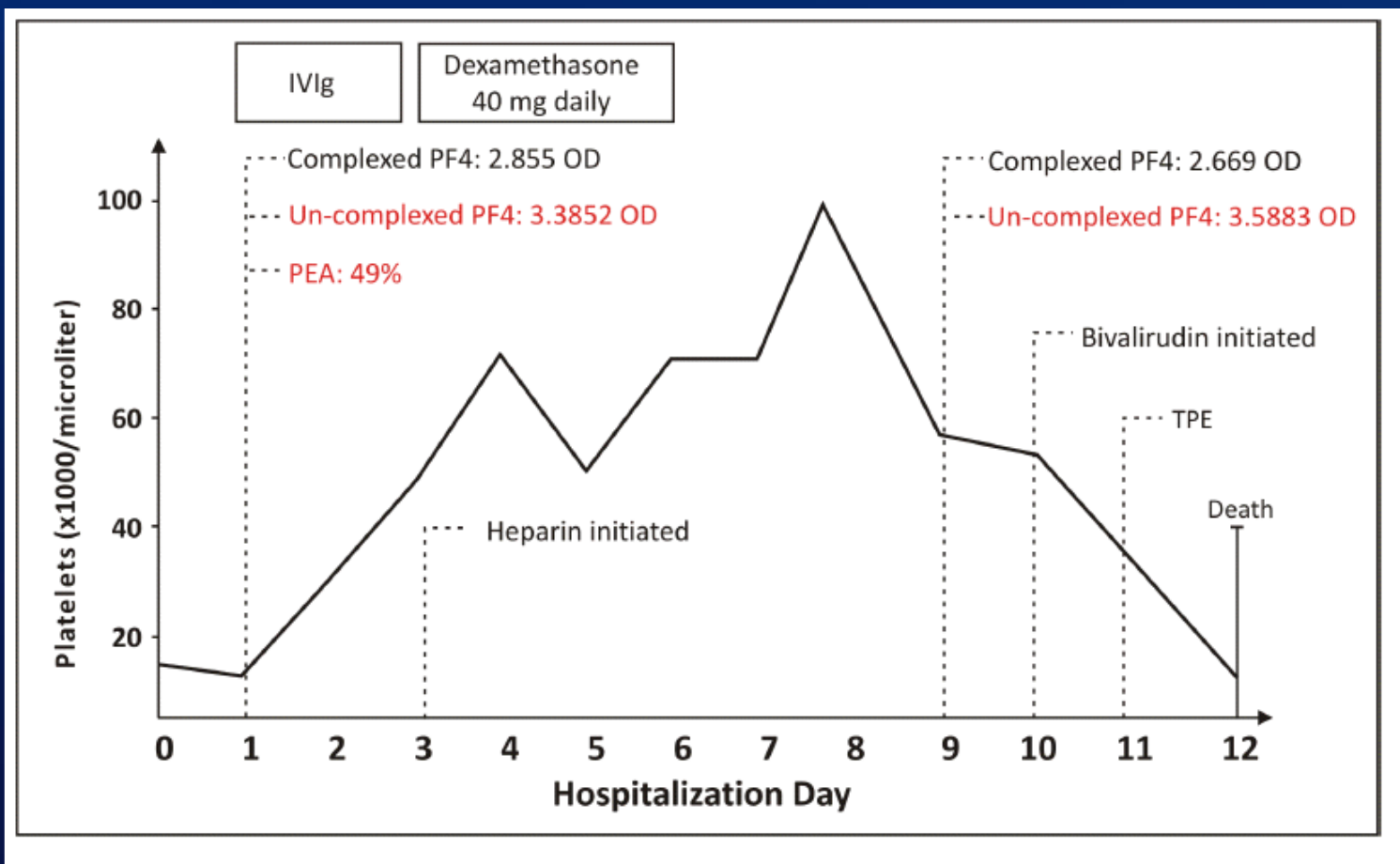
ROC AUC:
VITT vs. non-VITT: **0.5417**

Un-complexed PF4 ELISA



ROC AUC:
VITT vs. non-VITT: **1.0**

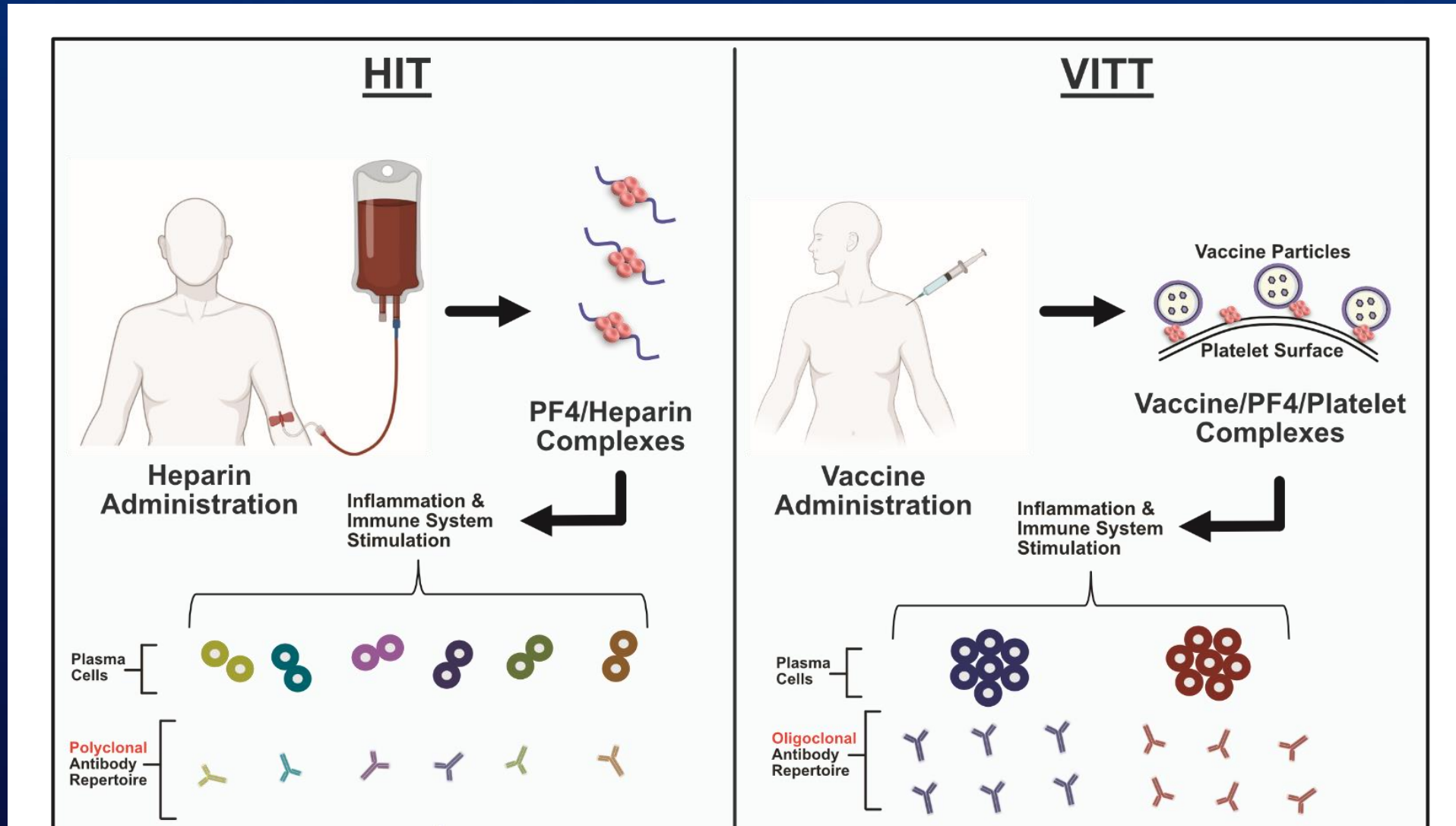
mRNA-1273-associated VITT?



Note: Additional cases of TTS after mRNA vaccination have been noted*

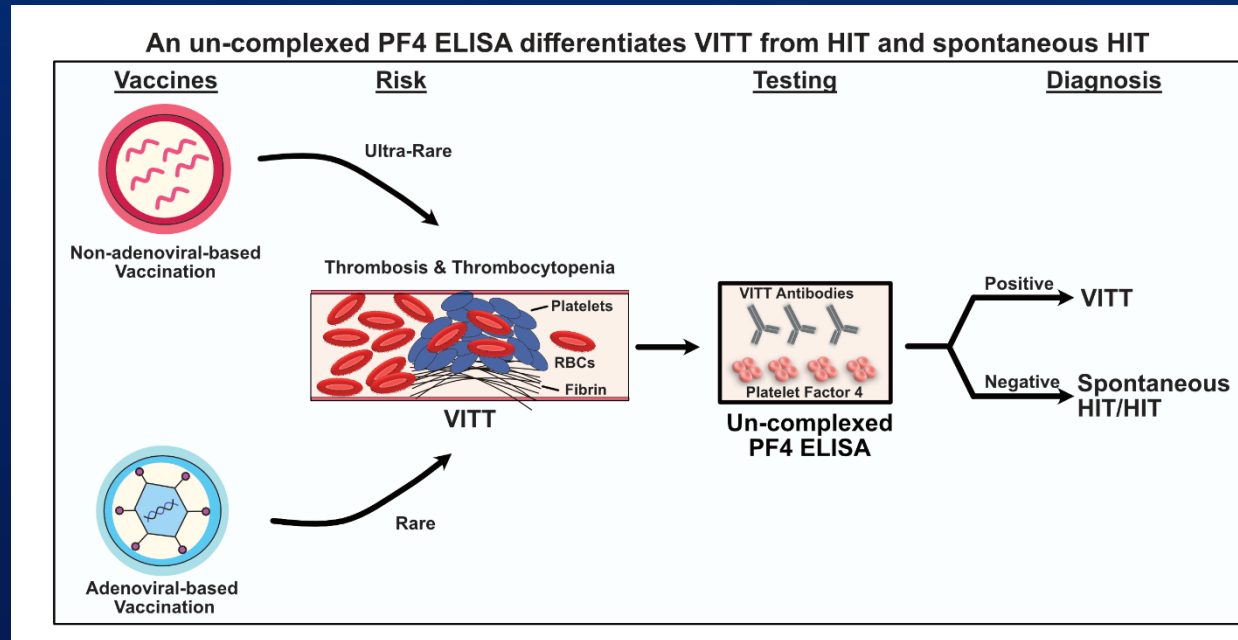
Padmanabhan et al, AJH 2022

VITT: A model



Art: A Kanack

Risk of VITT with covid-19/non-covid-19 vaccines



- *Could there be “VITT-like” Spontaneous HIT or HIT cases?*
- While the un-complexed PF4 ELISA appears much more specific for VITT than PF4-polyanion ELISAs currently available, we need to study more cases of spontaneous HIT/HIT to establish better estimates of test *specificity*

Key Conclusions

- Monoclonal and Oligoclonal anti-PF4 antibodies mediate VITT (and “Spontaneous HIT”)
- “Classical” HIT appears to be mediated by polyclonal anti-PF4 antibodies
- “Gold standard” functional testing using PF4-treated platelets is solely performed in the realm of specialized reference labs. For more rapid diagnosis, esp in challenging cases, decentralize testing using long-term stored platelets coupled to a technically-simple Thrombospondin-1 ELISA endpoint?

Key Conclusions

- The un-complexed PF4 ELISA appears to be highly sensitive for VITT antibody detection*
- *Preliminary data* suggests that antibody binding to un-complexed PF4 seems to be key differentiating feature of VITT (from HIT and spontaneous HIT). Its level of specificity needs to be evaluated in larger studies
- The scientific community should be open to the possibility that VITT may be a pan-vaccine reaction. Until this issue is clarified, VITT should be in the differential diagnosis of TTS after any type of vaccination

Mayo Clinic

Platelet Immunology Lab:

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David Murray Lab:

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Sangli group (Pittsburgh, PA)

Ahlen group (Norway)

Cryopreserved Platelet/TSP1 Studies:

Curtis Jones, Retham Technologies

Mayo Sp Coag Lab