University of Pittsburgh | Trauma and Transfusion Medicine Research Center

UPMC TRAUMA 35 YEARS SAVING LIVES

Immune Effects of Tranexamic Acid

Matthew D. Neal, MD FACS

Watson Chair and Professor of Surgery

Vice Chair of Surgery, Academic Affairs
Director of Emergency General Surgery
Co-Director of the Pittsburgh Trauma and Transfusion Medicine Research Center
University of Pittsburgh and UPMC

@macky_neal

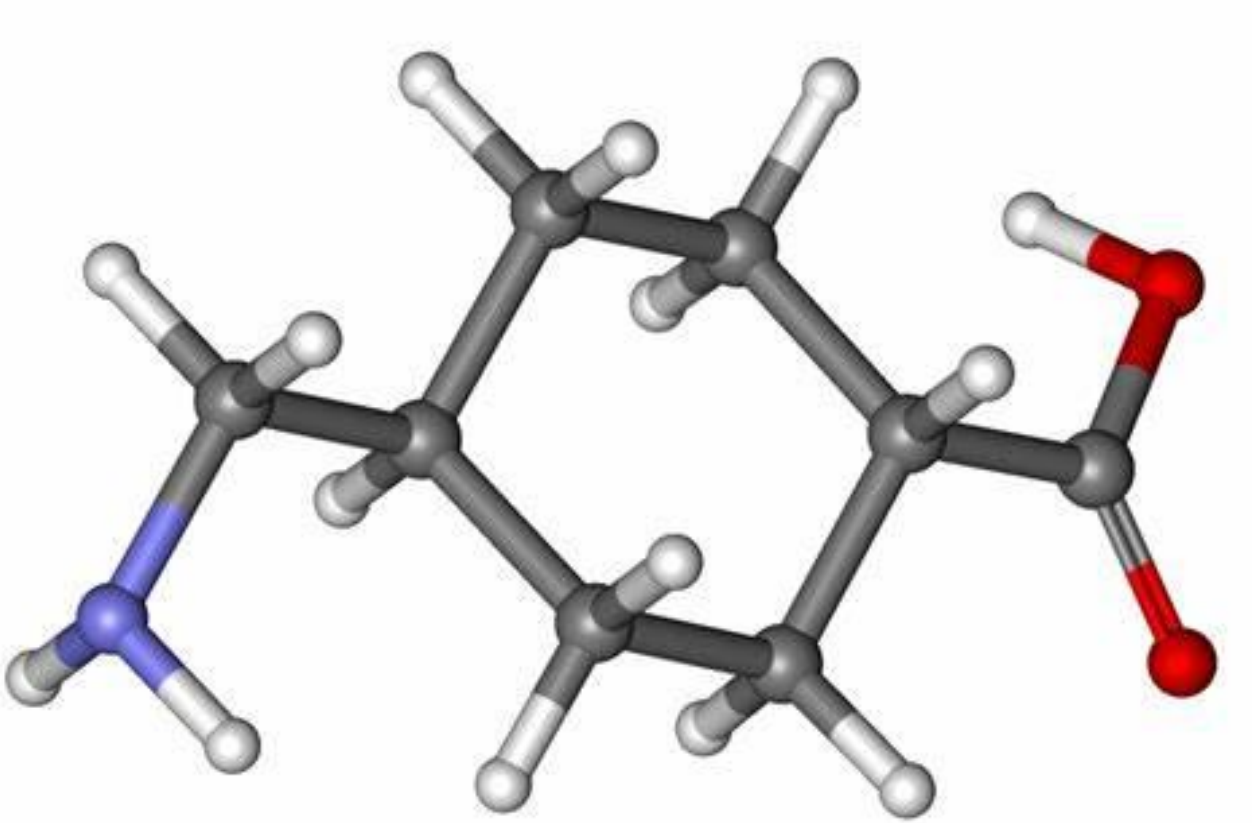
nealm2@upmc.edu

Disclosures

- Chief Medical Officer, Haima Therapeutics
- Research funding: NIH, DoD, DARPA, Haemonetics, Instrumentation Laboratories, Takeda
- Honoraria: Haemonetics, Takeda, Octapharma, Cellphire
- US Patents: DIELECTRIC SENSING TO CHARACTERIZE HEMOSTATIC DYSFUNCTION Serial Number: 16/837,704; NOVEL TLR4 INHIBITORS FOR THE TREATMENT OF HUMAN INFECTIOUS AND INFLAMMATORY DISORDERS Serial Number: 17/174,018

TXA.
i PUT
THAT
SHiT
ON EVERYTHiNG

But what really happens?



probably released later in trauma

released early in trauma (only with shock / hypoperfusion) from endothelial cells reacting on fibrin and venous occlusion

aPC ← trauma-induced endotheliopathy and sympathoadrenal activation

uPA

tPA

PAI 1/2 ← PAI1 → endothelium & platelets; PAI2 → placenta

plasminogen → **plasmin**

α2-antiplasmin

fibrin → **fibrin split products** (FSP, D-dimeres)

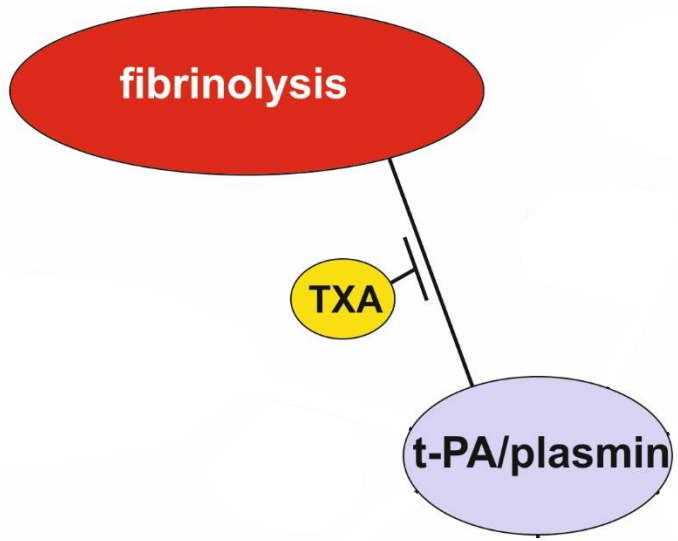
TAFI

Examples of immune consequences

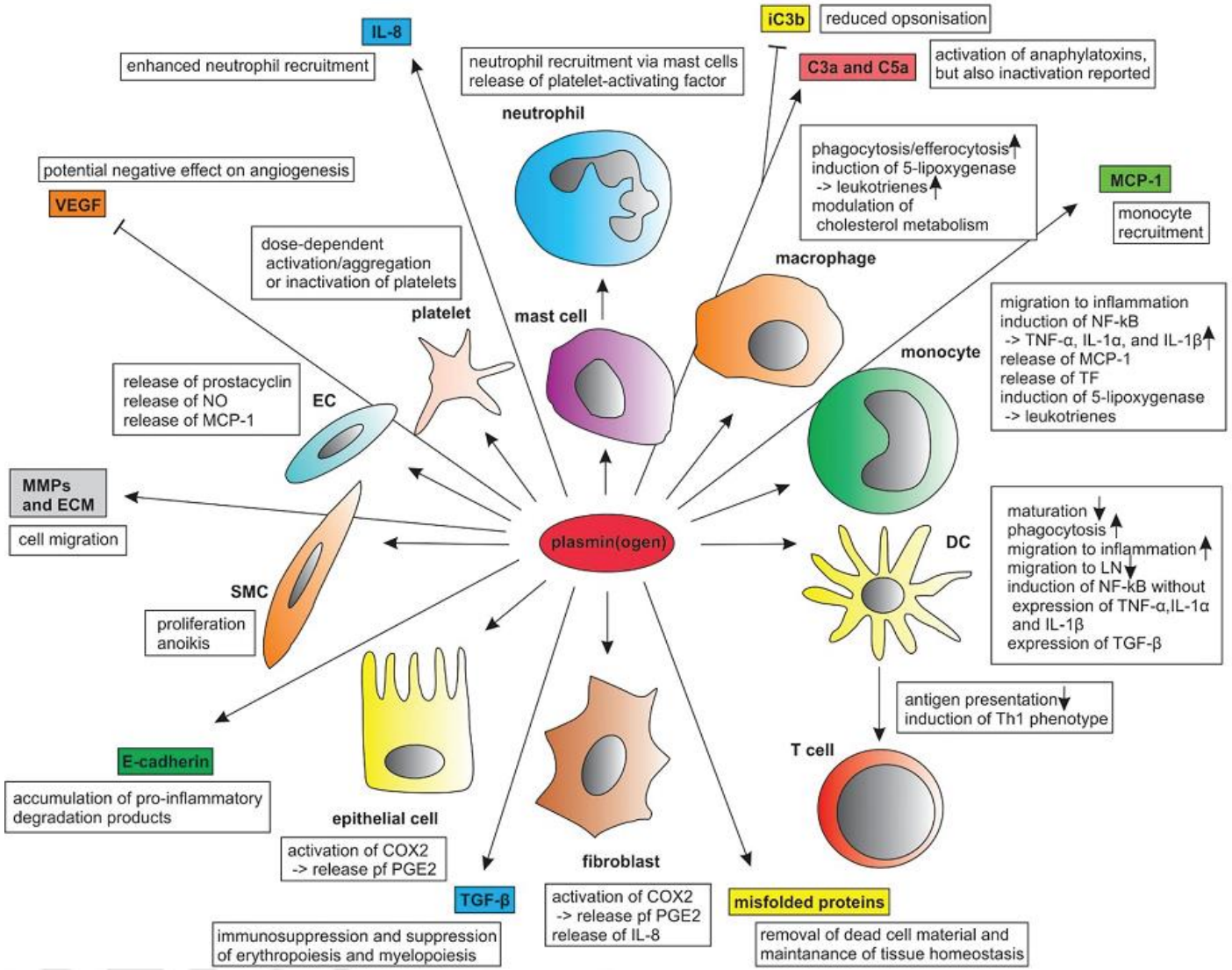
- Increased plasminogen
- Decreased plasmin (and downstream mediators)
- Tranexamic Acid independent effects (lysine)

Acknowledgements for slides:

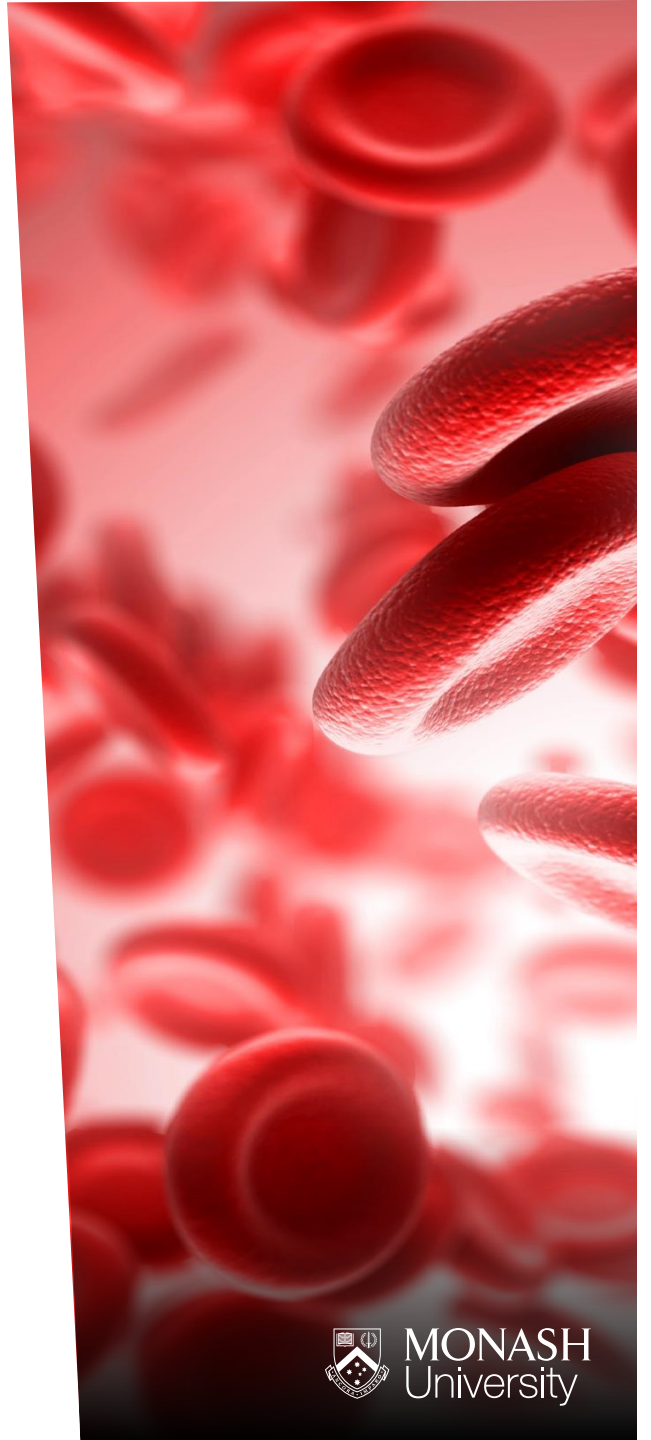
- Dominik Draxler
- Christopher Barrett


fibrinolysis
TXA
t-PA/plasmin

Plasmin, a potent modulator of immune function



Draxler et al., Semin Thromb Hemost. 2017 Mar;43(2):143-153.



TXA effects in healthy volunteers

Oral application of 1g TXA

Blood drawn preTXA, 2h, 4h, and 24h after TXA intake

Evaluation of plasma cytokines and flowcytometry

ORIGINAL ARTICLE

Cytometry PART A
Journal of the International Society for Advancement of Cytometry

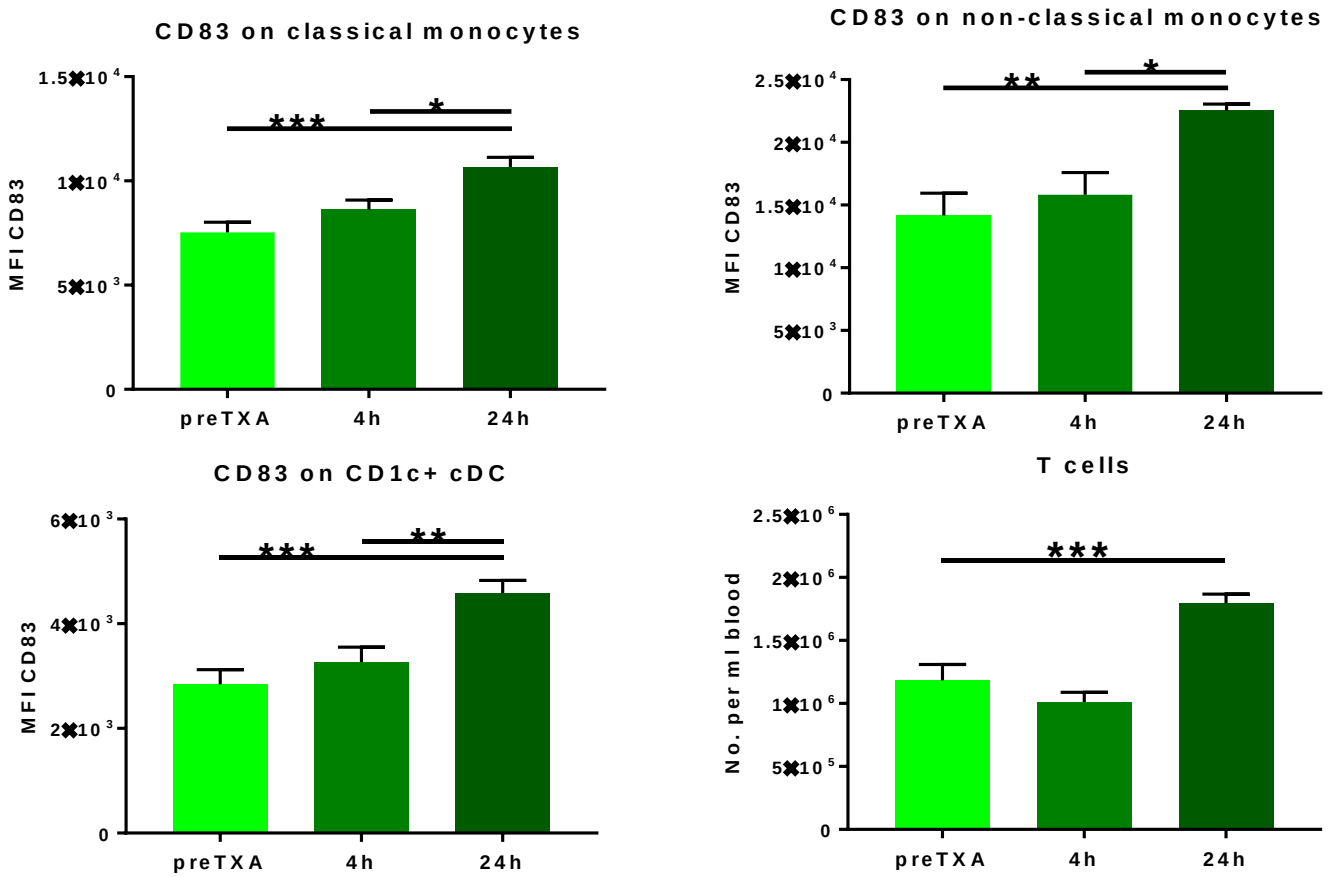
MIFlowCyt

A Flowcytometric Analysis to Efficiently Quantify Multiple Innate Immune Cells and T Cell Subsets in Human Blood

D.F. Draxler,[1] M.T. Madondo,[2] G. Hanafi,[1] M. Plebanski,[2†] R.L. Medcalf[1†*]

Baseline expression of CD83 is enhanced on various antigen-presenting cells by TXA

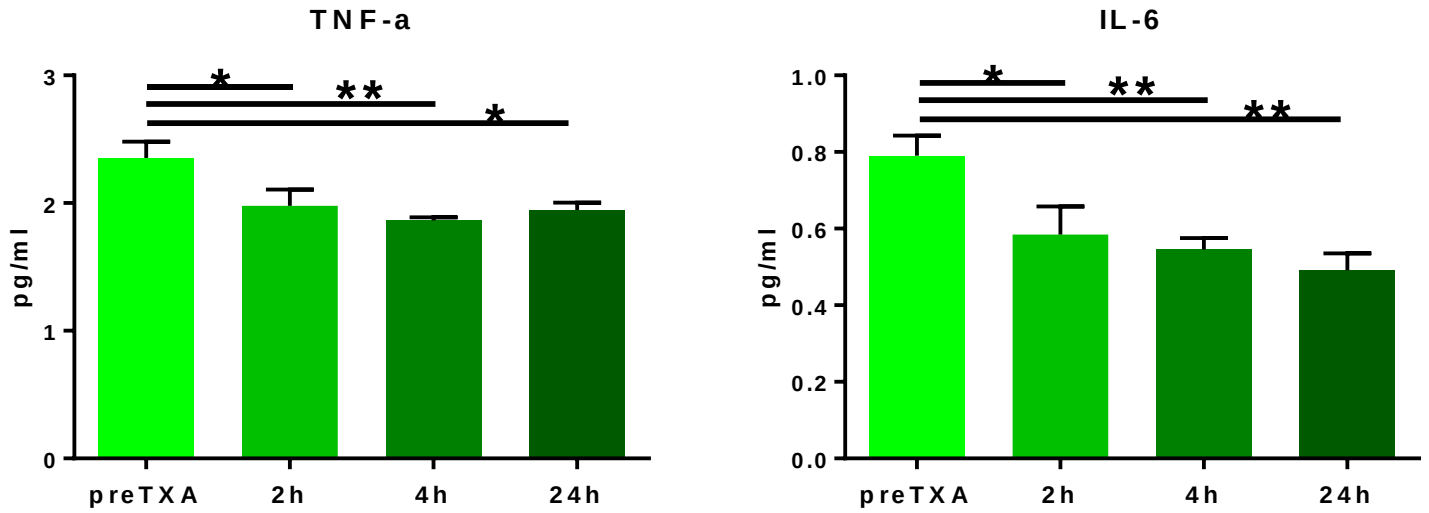
CD83 – activates DCs and regulates T cells



Data expressed as mean±SEM, n=7 * - 1way ANOVA with Tukey's multiple comparison

Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

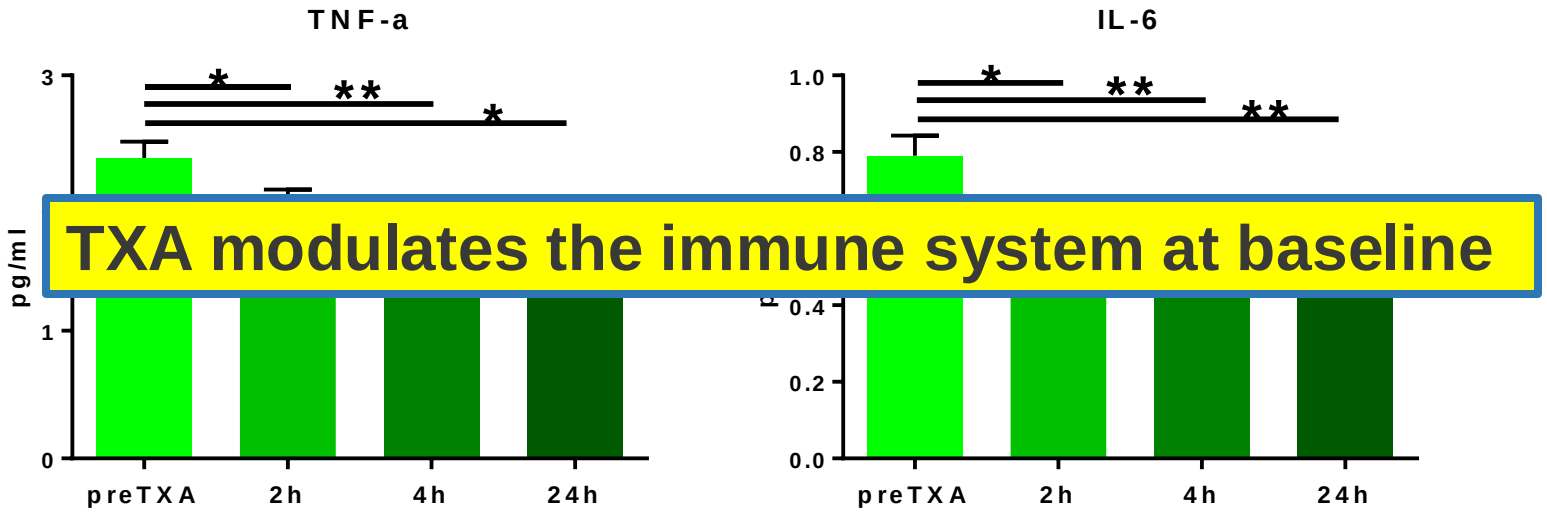
Baseline levels of pro-inflammatory cytokines are significantly reduced by TXA



Data expressed as mean±SEM, * - 1way ANOVA with Tukey's multiple comparison, n=10

Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

Baseline expression of CD83 is enhanced on various antigen-presenting cells by TXA



TXA modulates the immune system at baseline

Data expressed as mean±SEM, * - 1way ANOVA with Tukey's multiple comparison, n=10

Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

Immune effects of TXA in elective surgery

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

Paul S. Myles, M.P.H., M.D., Julian A. Smith, F.R.A.C.S., Andrew Forbes, Ph.D., Brendan Silbert, M.B., B.S., Mohandas Jayarajah, M.B., B.S., Thomas Painter, M.B., Ch.B., D. James Cooper, M.D., Silvana Marasco, Ph.D., John McNeil, Ph.D., Jean S. Bussières, M.D., Shay McGuinness, M.B., Ch.B., Kelly Byrne, M.B., Ch.B., Matthew T.V. Chan, M.B., B.S., Ph.D., Giovanni Landoni, M.D., and Sophie Wallace, M.P.H., for the ATACAS Investigators of the ANZCA Clinical Trials Network*

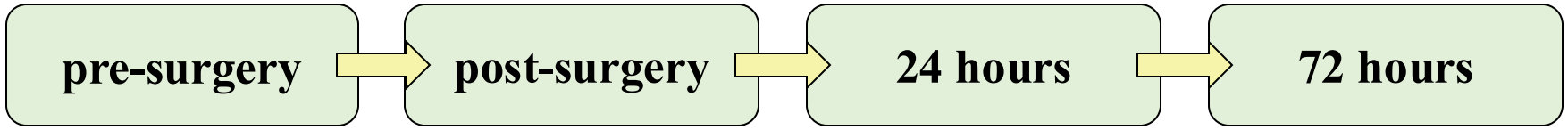
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

Paul S. Myles, M.P.H., M.D., Julian A. Smith, F.R.A.C.S., Andrew Forbes, Ph.D., Brendan Silbert, M.B., B.S., Mohandas Jayarajah, M.B., B.S., Thomas Painter, M.B., Ch.B., D. James Cooper, M.D., Silvana Marasco, Ph.D., John McNeil, Ph.D., Jean S. Bussières, M.D., Shay McGuinness, M.B., Ch.B., Kelly Byrne, M.B., Ch.B., Matthew T.V. Chan, M.B., B.S., Ph.D., Giovanni Landoni, M.D., and Sophie Wallace, M.P.H., for the ATACAS Investigators of the ANZCA Clinical Trials Network*

RCT, 4662 patients undergoing coronary artery bypass surgery, randomised to TXA (100mg/kg, later 50mg/kg) or placebo



Flowcytometry to evaluate myeloid and lymphoid cell populations and assessment of plasma proinflammatory and immunosuppressive cytokines

Single center analysis of immune/infection outcomes in cardiac surgery

Immune effects of TXA in cardiac surgery

Outcome measures	TXA (n = 204)	Placebo (n = 200)	RR (95% CI)	*P*
Primary end point				
Health care–associated infection	43 (21.1)	63 (31.5)	0.67 (0.48-0.94)	**.017**
Secondary end points*	23 (11.3)	22 (11.0)	1.03 (0.59-1.78)	.93
Pneumonia				
SSI	22 (10.8)	36 (18.0)	0.60 (0.37-0.98)	**.039**
Superficial	17 (8.3)	32 (16.0)	0.52 (0.30-0.91)	**.018**
Deep	4 (2.0)	4 (2.0)	0.98 (0.25-3.87)	.98
Organ space	1 (0.5)	2 (1.0)	0.49 (0.05-5.36)	.62†
Sepsis	21 (10.3)	31 (15.5)	0.66 (0.40-1.12)	.12
Bacteremia	2 (1.0)	1 (0.5)	1.96 (0.18-21.5)	.57†
Catheter line infection	2 (1.0)	0 (0.0)	—	.50†

Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

Immune effects of TXA in cardiac surgery

Outcome measures	TXA (n = 204)	Placebo (n = 200)	RR (95% CI)	*P*
Primary end point				
Health care–associated infection	43 (21.1)	63 (31.5)	0.67 (0.48-0.94)	**.017**
Secondary end points*	23 (11.3)	22 (11.0)	1.03 (0.59-1.78)	.93
Pneumonia				
SSI	22 (10.8)	36 (18.0)	0.60 (0.37-0.98)	**.039**
Superficial	17 (8.3)	32 (16.0)	0.52 (0.30-0.91)	**.018**
Deep	4 (2.0)	4 (2.0)	0.98 (0.25-3.87)	.98
Organ space	1 (0.5)	2 (1.0)	0.49 (0.05-5.36)	.62†
Sepsis	21 (10.3)	31 (15.5)	0.66 (0.40-1.12)	.12
Bacteremia	2 (1.0)	1 (0.5)	1.96 (0.18-21.5)	.57†
Catheter line infection	2 (1.0)	0 (0.0)	—	.50†

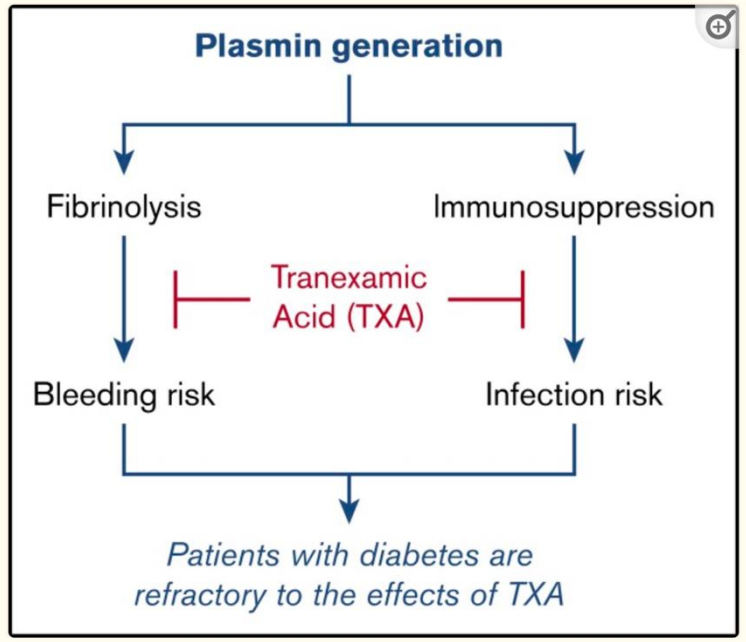
Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

Immune effects of TXA in cardiac surgery

Outcome measures	TXA (n = 204)	Placebo (n = 200)	RR (95% CI)	P
Primary end point				
Health care–associated infection	43 (21.1)	63 (31.5)	0.67 (0.48-0.94)	**.017**
Secondary end points*	23 (11.3)	22 (11.0)	1.03 (0.59-1.78)	.93
Pneumonia				
SSI	22 (10.8)	36 (18.0)	0.60 (0.37-0.98)	**.039**
Superficial	17 (8.3)	32 (16.0)	0.52 (0.30-0.91)	**.018**
Deep	4 (2.0)	4 (2.0)	0.98 (0.25-3.87)	.98
Organ space	1 (0.5)	2 (1.0)	0.49 (0.05-5.36)	.62†
Sepsis	21 (10.3)	31 (15.5)	0.66 (0.40-1.12)	.12
Bacteremia	2 (1.0)	1 (0.5)	1.96 (0.18-21.5)	.57†
Catheter line infection	2 (1.0)	0 (0.0)	—	.50†

Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

TXA reduces post-surgical infection rates indpendent of its blood-sparing effect (in patients without diabetes)

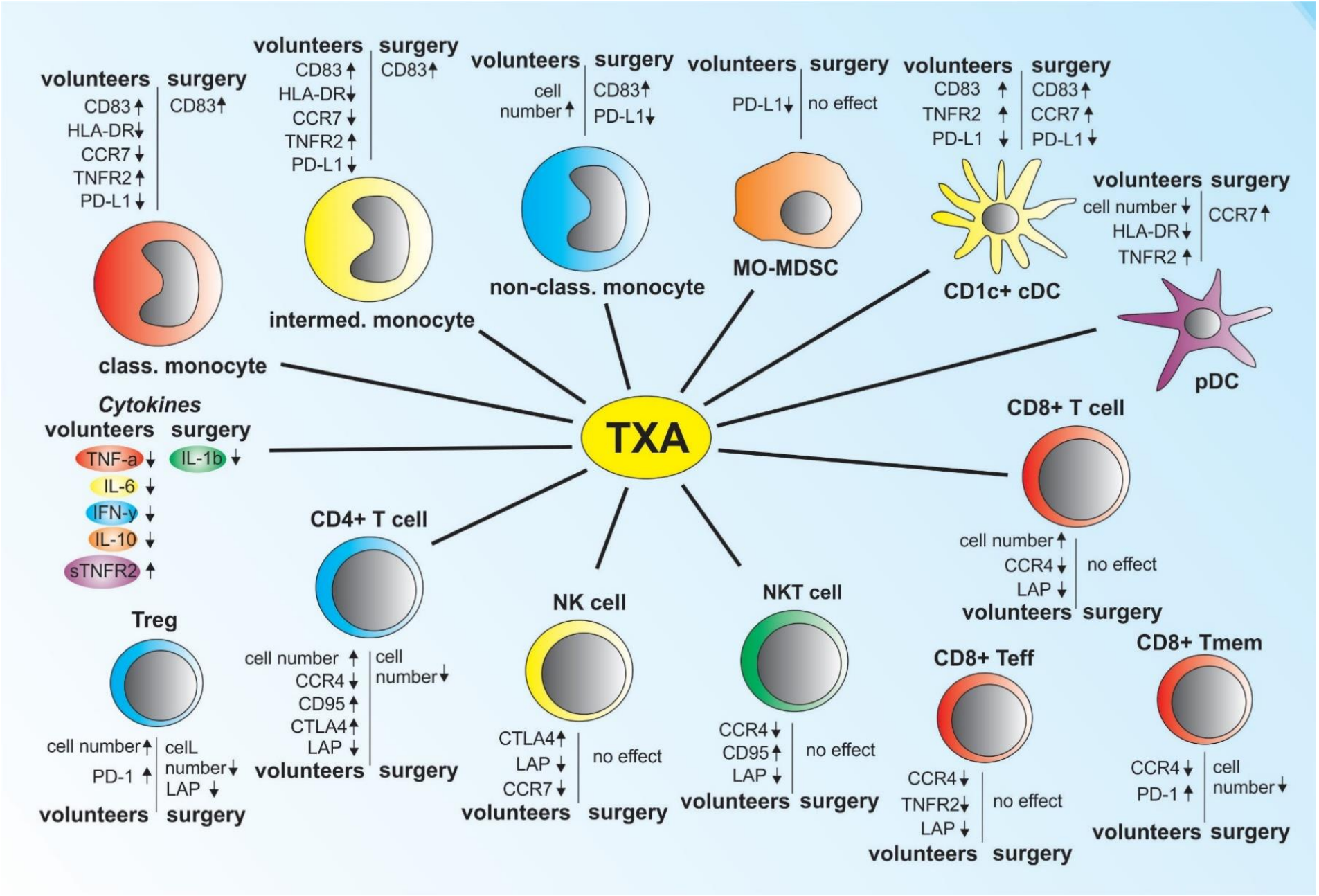


REGULAR ARTICLE

blood advances

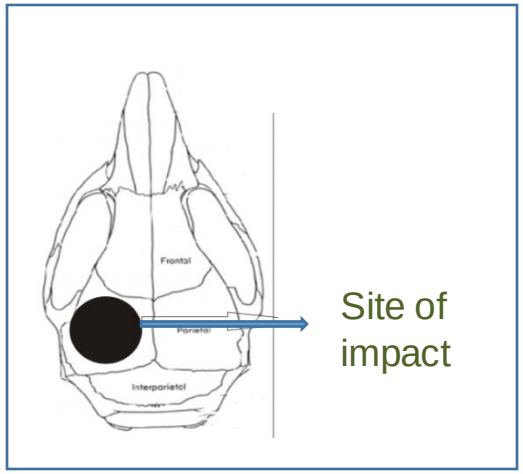
Tranexamic acid modulates the immune response and reduces postsurgical infection rates

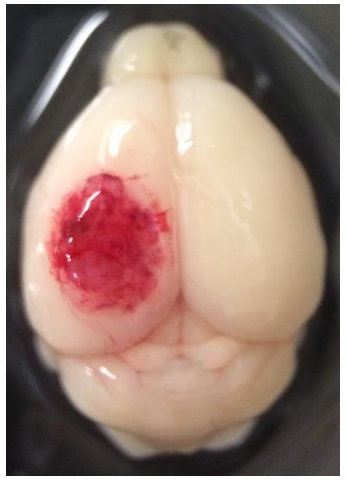
Dominik F. Draxler,[1] Kah Yep,[2] Gryselda Hanafi,[1] Anoushka Winton,[2] Maria Daglas,[1] Heidi Ho,[1] Maithili Sashindranath,[1] Lisa M. Wutzlhofer,[2] Andrew Forbes,[3] Isaac Goncalves,[1] Huyen A. Tran,[1] Sophia Wallace,[2] Magdalena Plebanski,[4] Paul S. Myles,[2,3,*] and Robert L. Medcalf[1,*]



Draxler et al., Blood Adv. 2019 May 28;3(10):1598-1609.

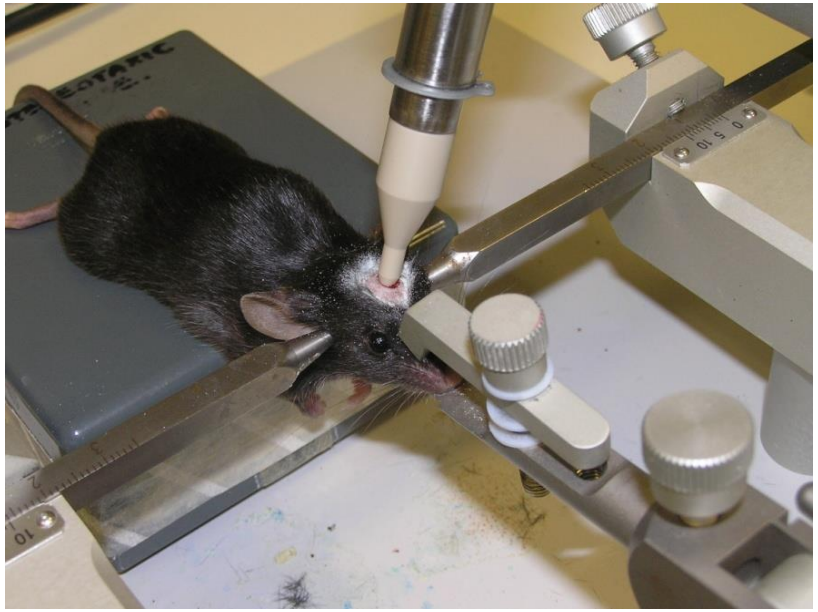
TXA effects in a mouse model of TBI





TXA administration

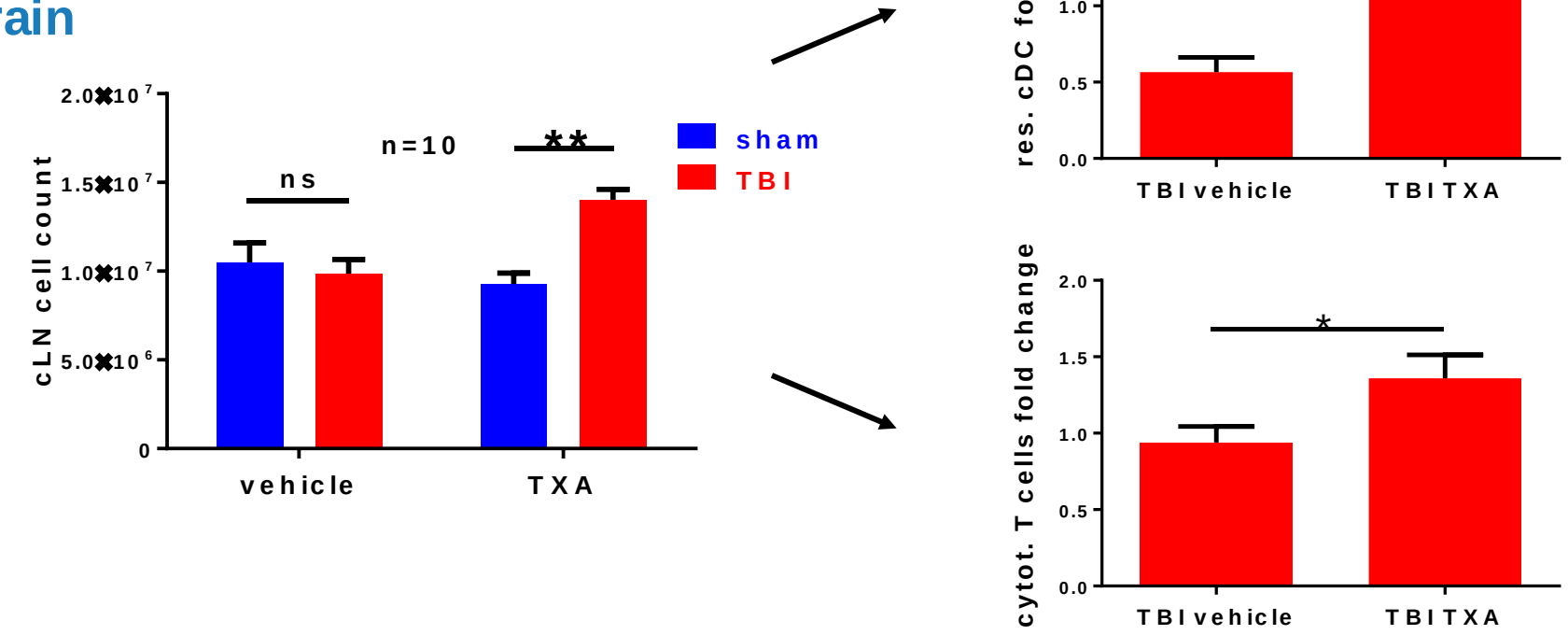
- 100mg/kg
- i.v. 20min after sham/TBI
- i.p. twice daily for 3 days



Draxler et al., J Thromb Haemost. 2019 Dec;17(12):2174-2187.

TXA facilitates increased cellularity involving resident cDC as well as cytotoxic T cells in the cervical lymph nodes (cLN) 1 week post TBI

cLN:
draining lymph node system of the brain

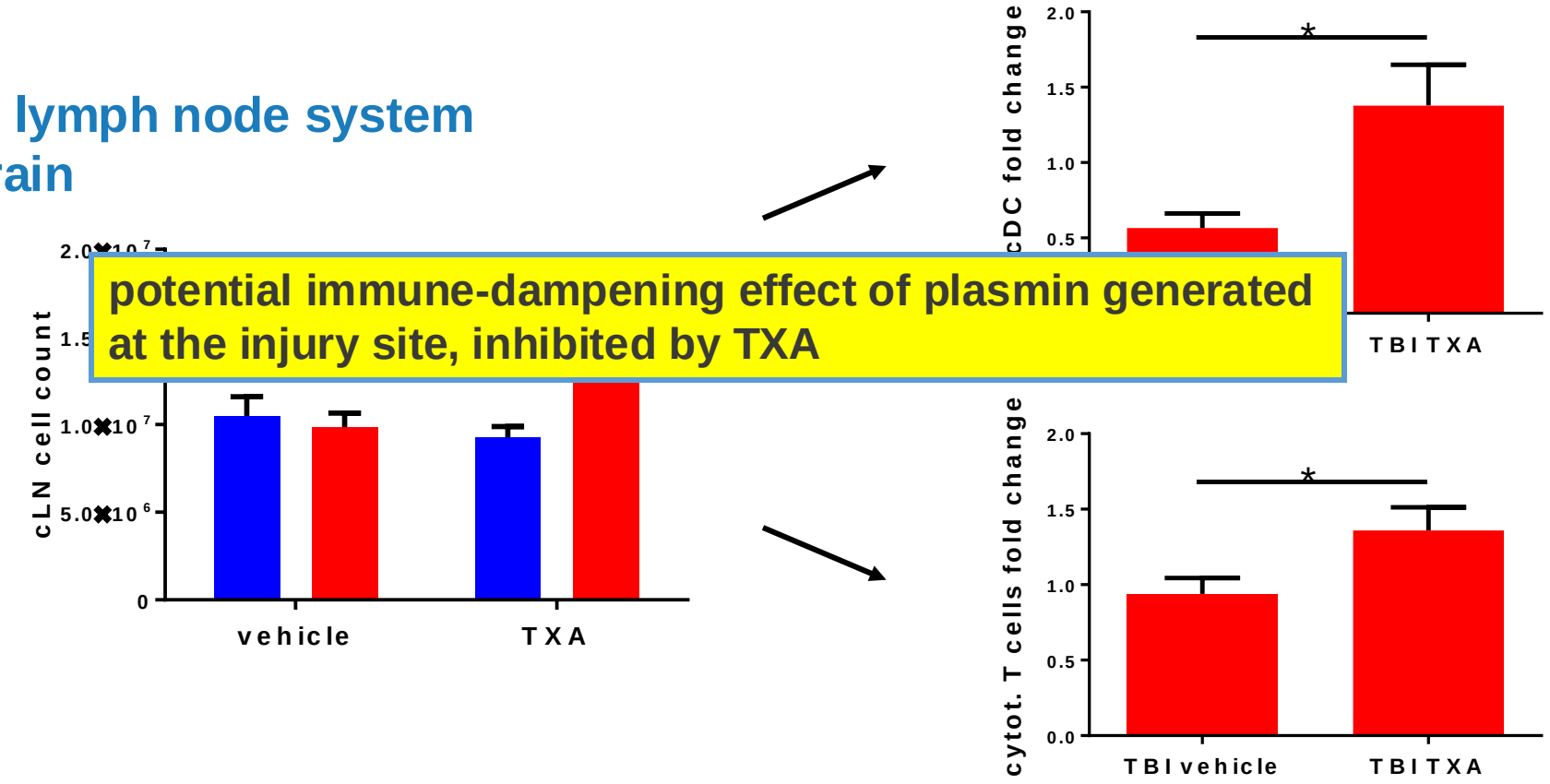


Data expressed as mean±SEM; 2way-ANOVA with Tukey correction

Draxler et al., J Thromb Haemost. 2019 Dec;17(12):2174-2187.

TXA facilitates increased cellularity involving resident cDC as well as cytotoxic T cells in the cervical lymph nodes (cLN) 1 week post TBI

cLN:
draining lymph node system of the brain



potential immune-dampening effect of plasmin generated at the injury site, inhibited by TXA

Data expressed as mean±SEM; 2way-ANOVA with Tukey correction

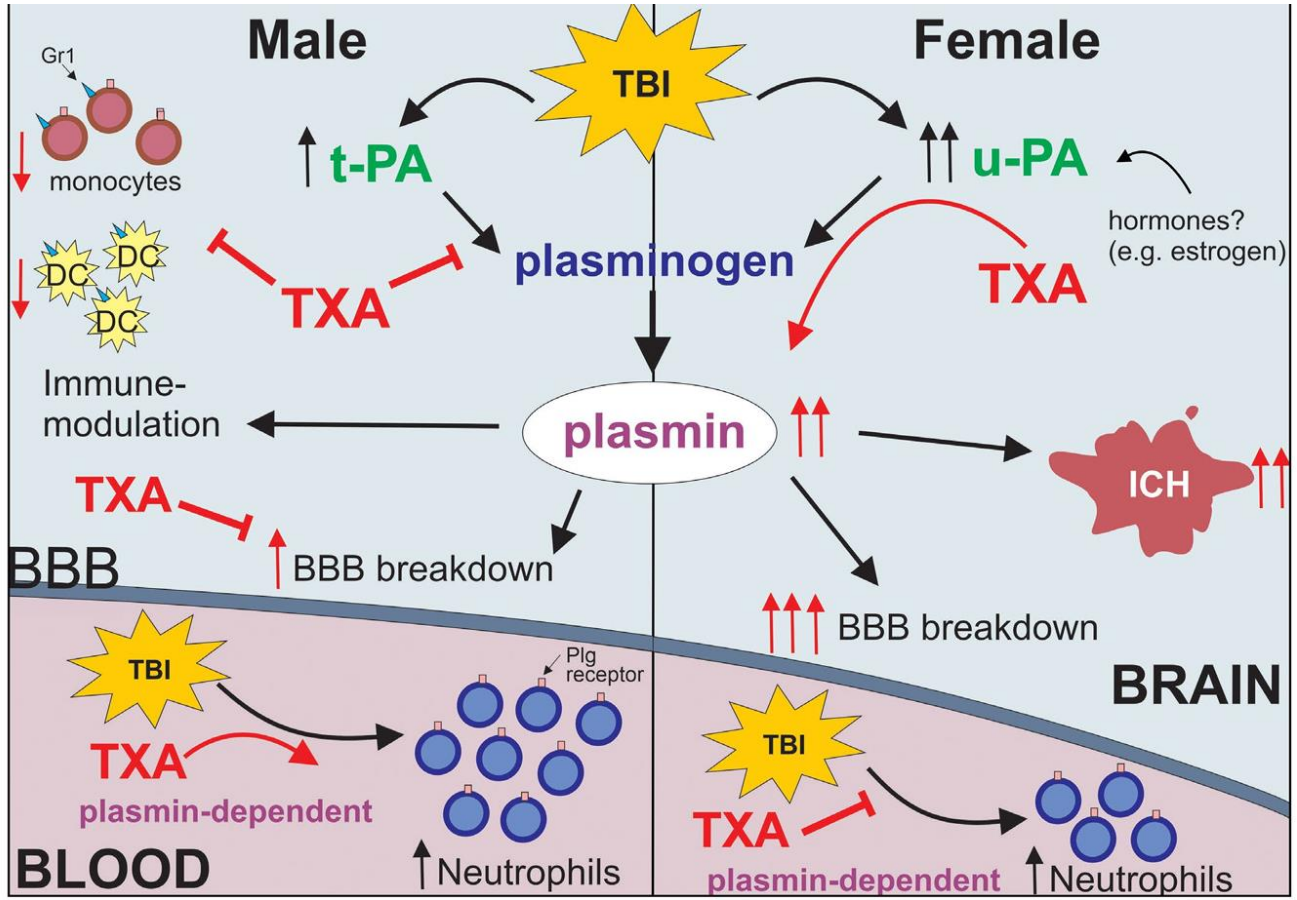
Draxler et al., J Thromb Haemost. 2019 Dec;17(12):2174-2187.

Sex-dependent effects on immune function

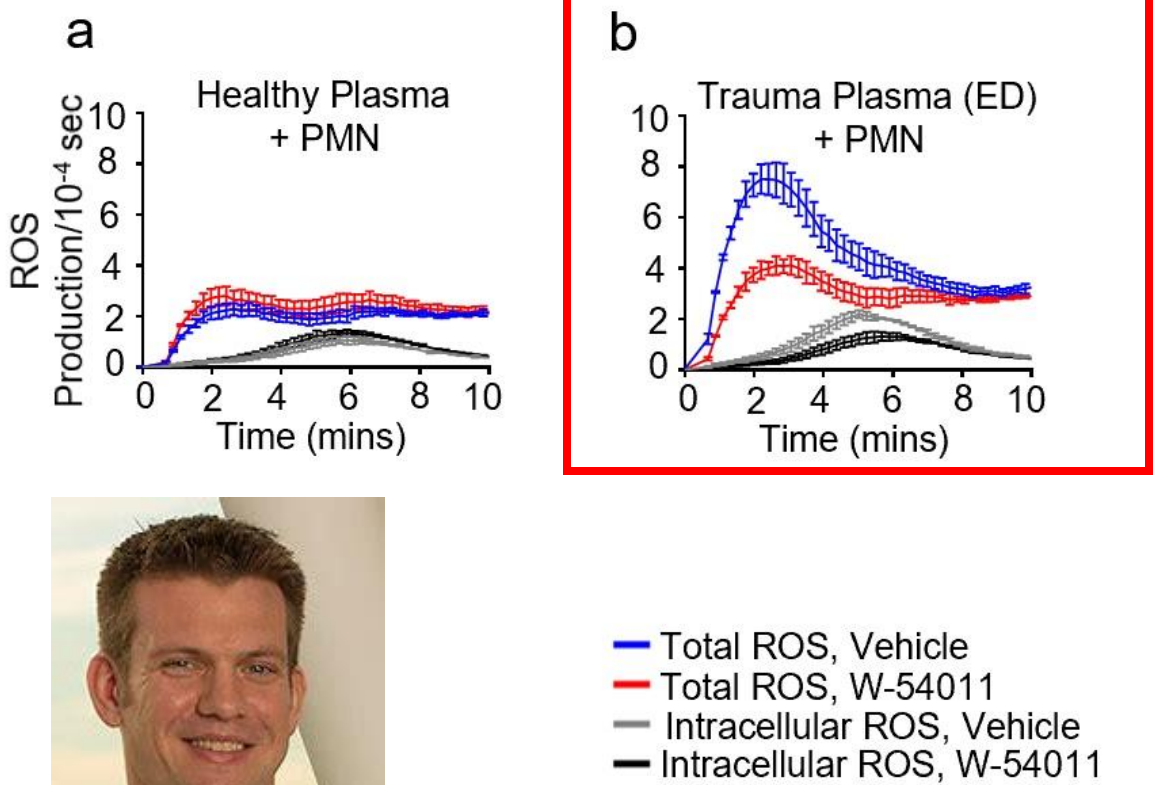
ORIGINAL ARTICLE

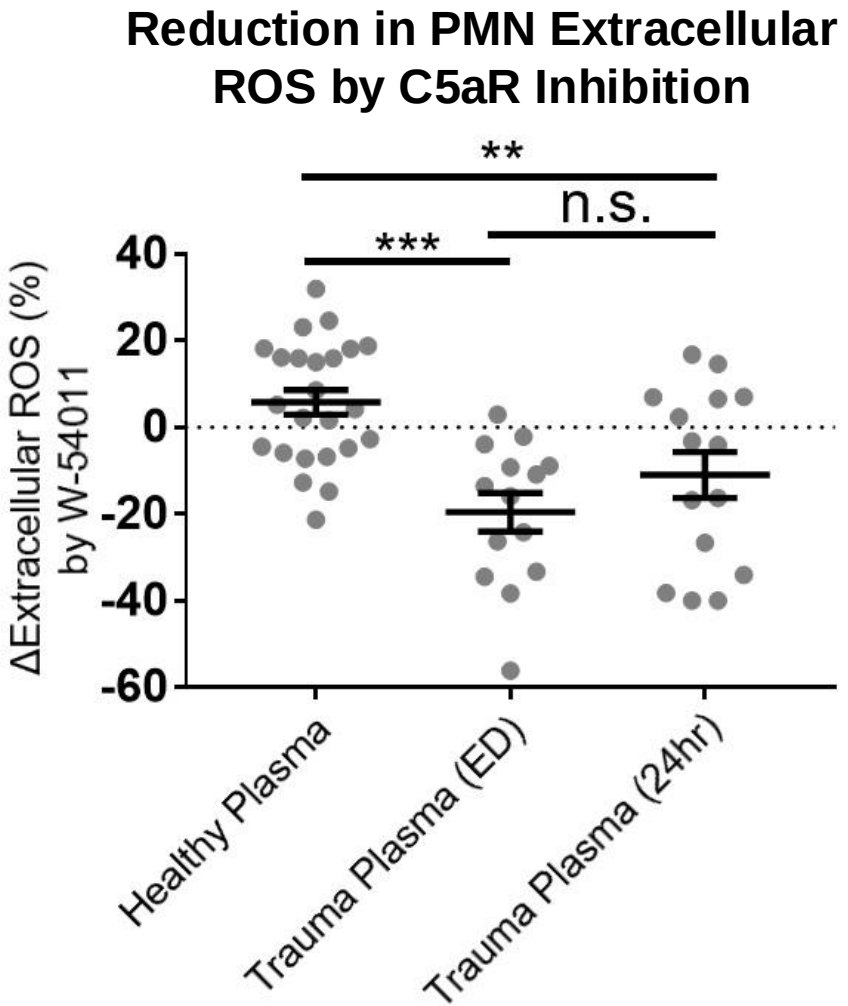
Sex-dependent effects of tranexamic acid on blood-brain barrier permeability and the immune response following traumatic brain injury in mice

Maria Daglas | Adam Galle | Dominik F. Draxler | Heidi Ho | Zikou Liu | Maithili Sashindranath | Robert L. Medcalf



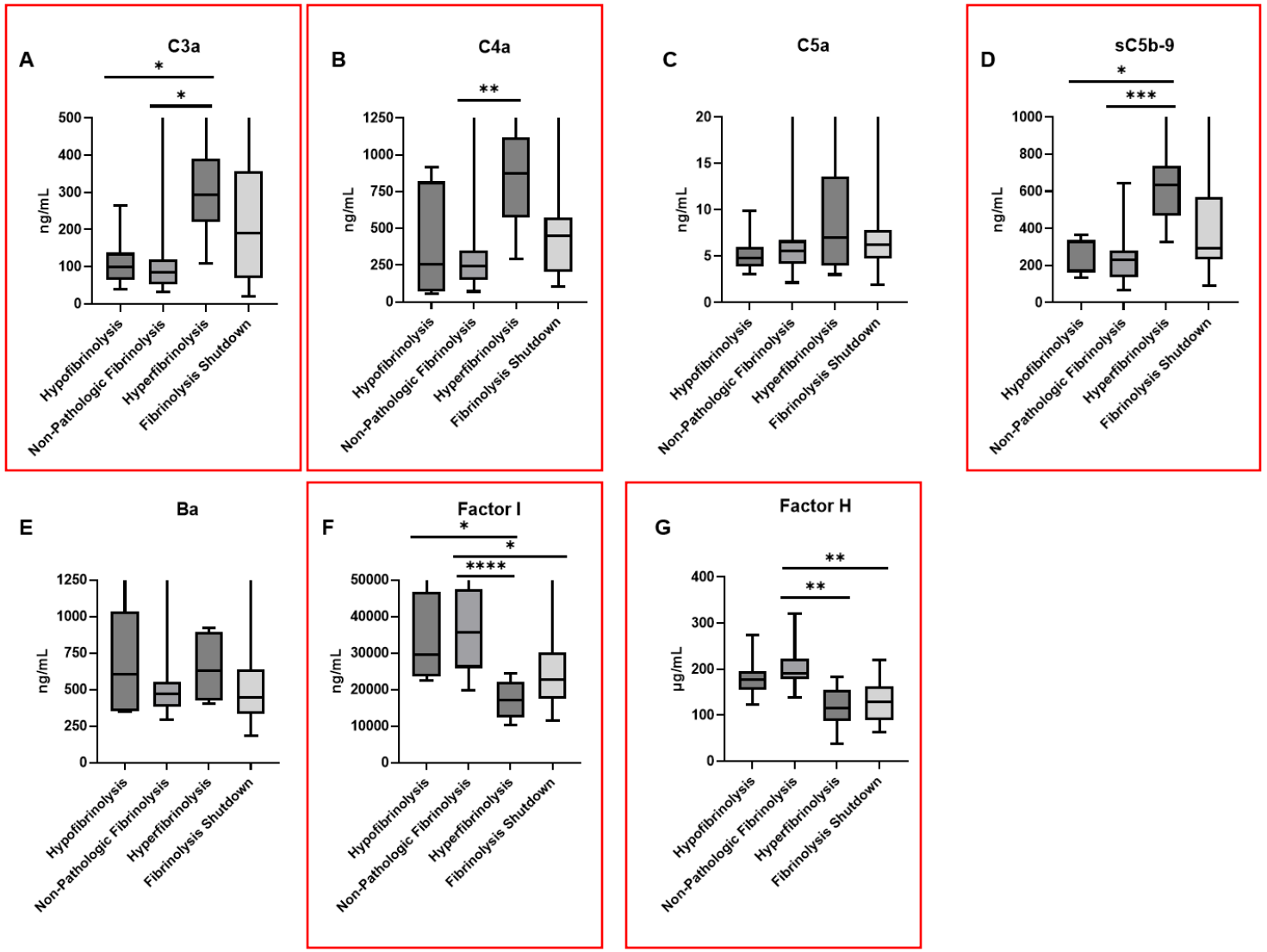
Trauma Patient Plasma Primes PMN for Extracellular ROS in C5a-Dependent Manner





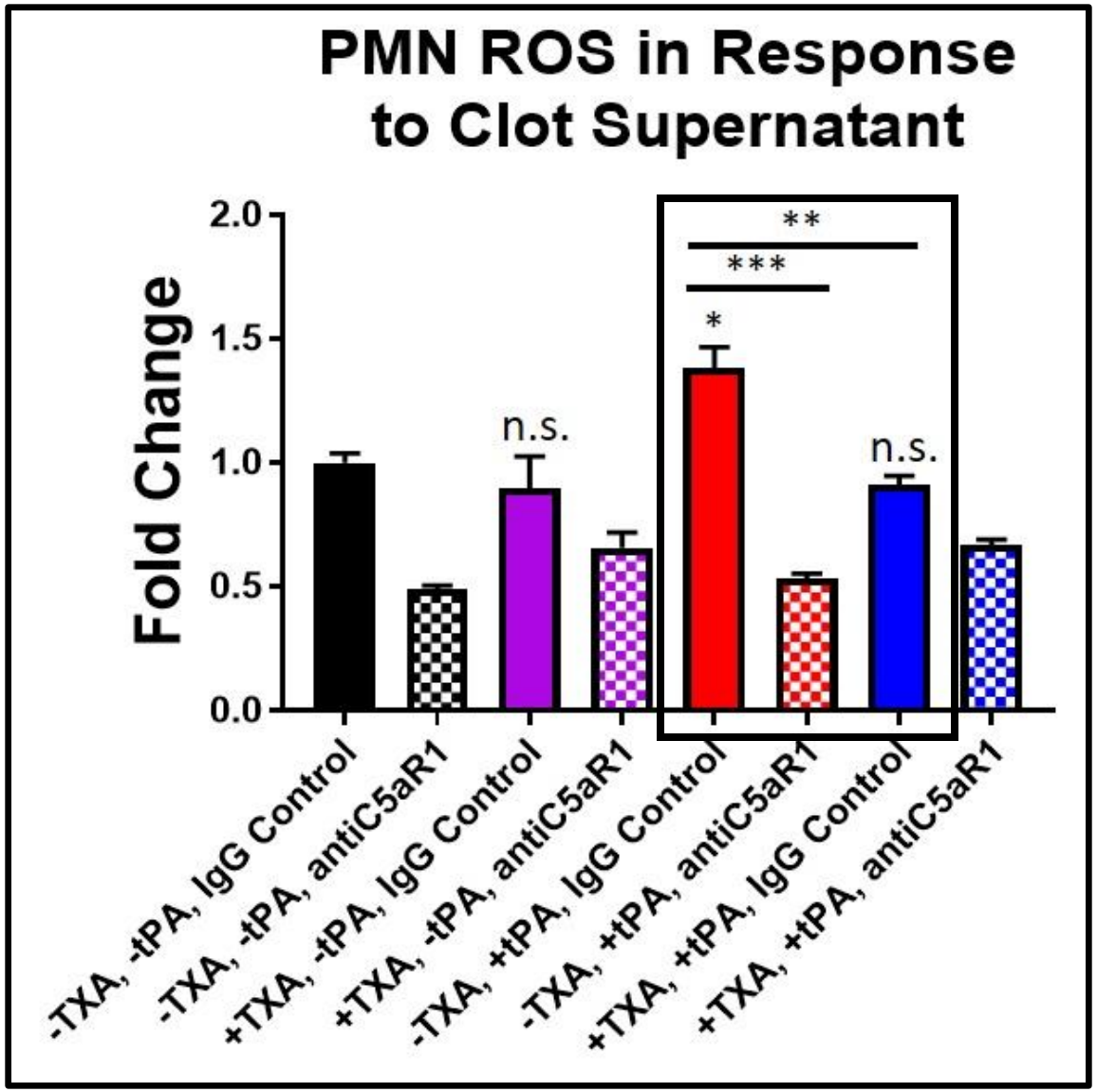
Barrett et al. *Clin Exp Immunol*. 2018;194(1):103-117

Hyperfibrinolysis Appears to be Associated with Complement Activation (N=56)



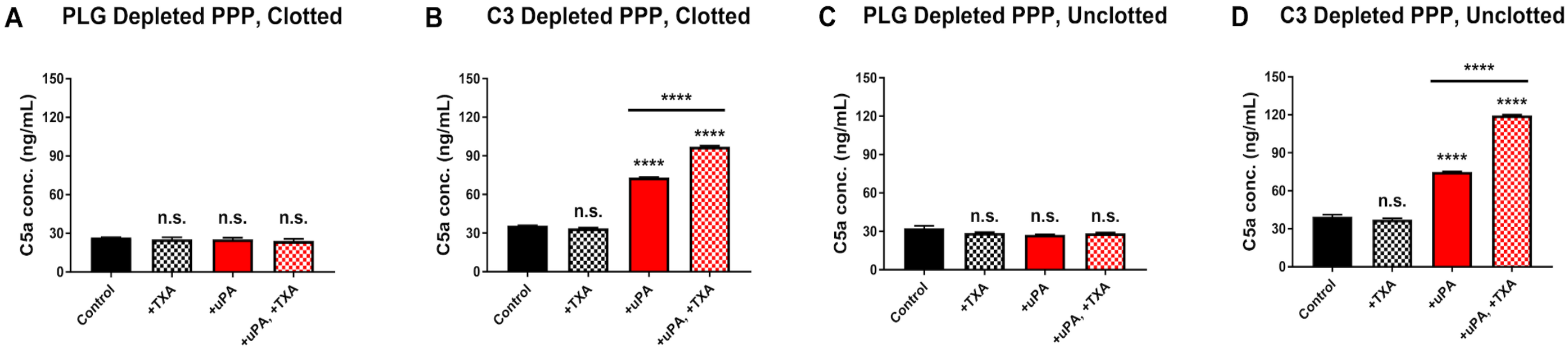
Barrett lab, unpublished

tPA-mediated fibrinolysis promotes pro-inflammatory complement activation that primes PMN for ROS Generation



Can inhibit PMN ROS with TXA or C5aR1 inhibition (or target PI3K P110*B* or PLD1)!!

TXA paradoxically augments plasmin-mediated complement activation when uPA is the plasminogen activator



READ MORE:

Page S11 of the *Transfusion* supplement in front of you!

With respect to uPA + TXA leading to C5 cleavage (i.e. plasmin generation), this phenomena is largely fibrin-independent!

Barrett et al. *J Trauma Acute Care Surg*. 2019;86(1):101-107

frontiers in Immunology

CLINICAL TRIAL
published: 08 September 2020
doi: 10.3389/fimmu.2020.02085

The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI): A Randomized, Double-Blind, Placebo-Controlled, Single-Center Trial

Philip C. Spinella[1†‡], Kimberly A. Thomas[1†‡], Isaiah R. Turnbull[2], Anja Fuchs[2], Kelly Bochicchio[2], Douglas Schuerer[2], Stacey Reese[2], Adrian A. Coleoglou Centeno[2], Christopher B. Horn[2‡], Jack Baty[3‡], Susan M. Shea[1‡], M. Adam Meledeo[4‡], Anthony E. Pusateri[4], Jerrold H. Levy[5‡], Andrew P. Cap[4‡] and Grant V. Bochicchio[2] for the TAMPITI Investigators*

OPEN ACCESS

Edited by:
Matthew D. Neal,
University of Pittsburgh, United States

Reviewed by:
Hunter Moore,
University of Colorado, United States
Christopher Barrett,
Massachusetts Institute of Technology, United States
Dominik Ferdinand Draxler,
Bern University Hospital, Switzerland

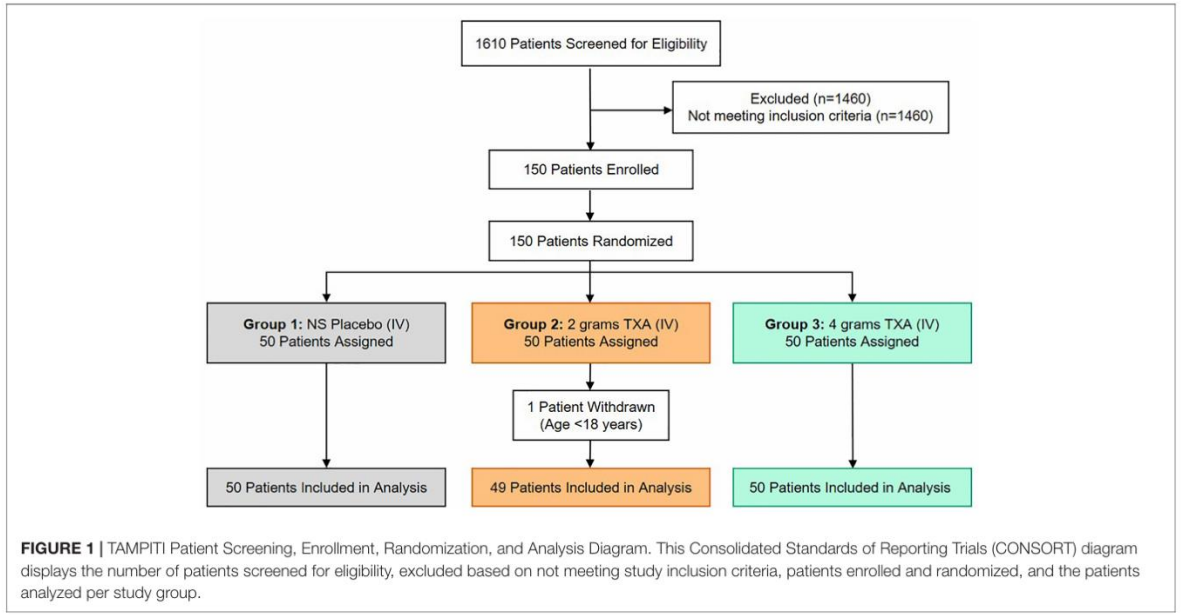
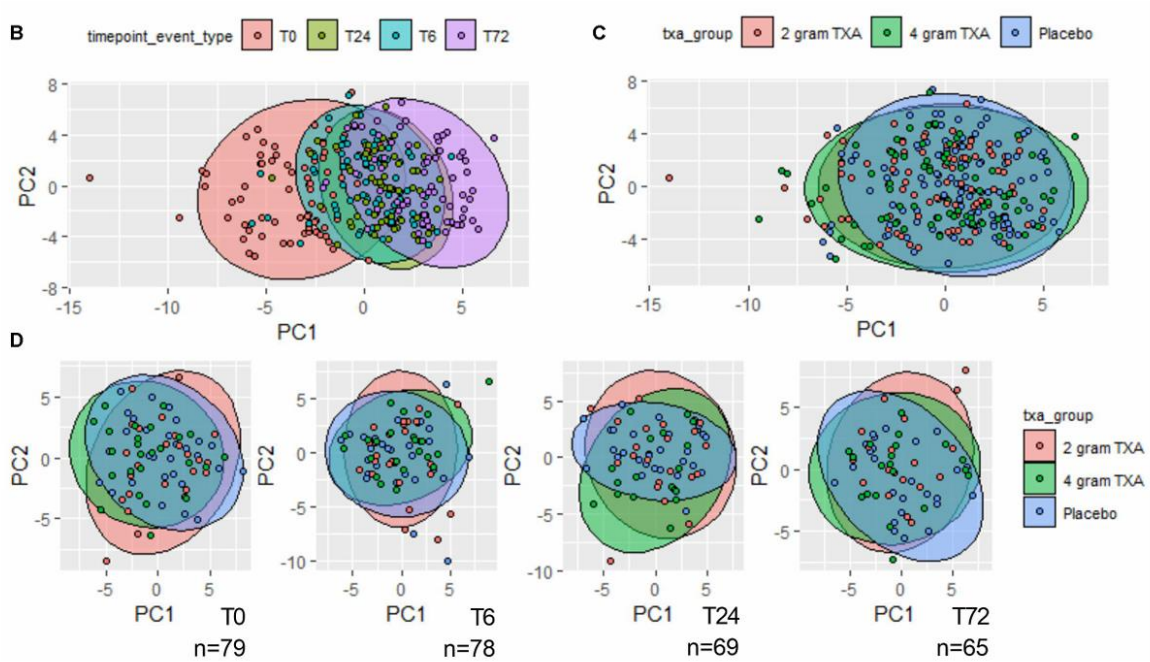
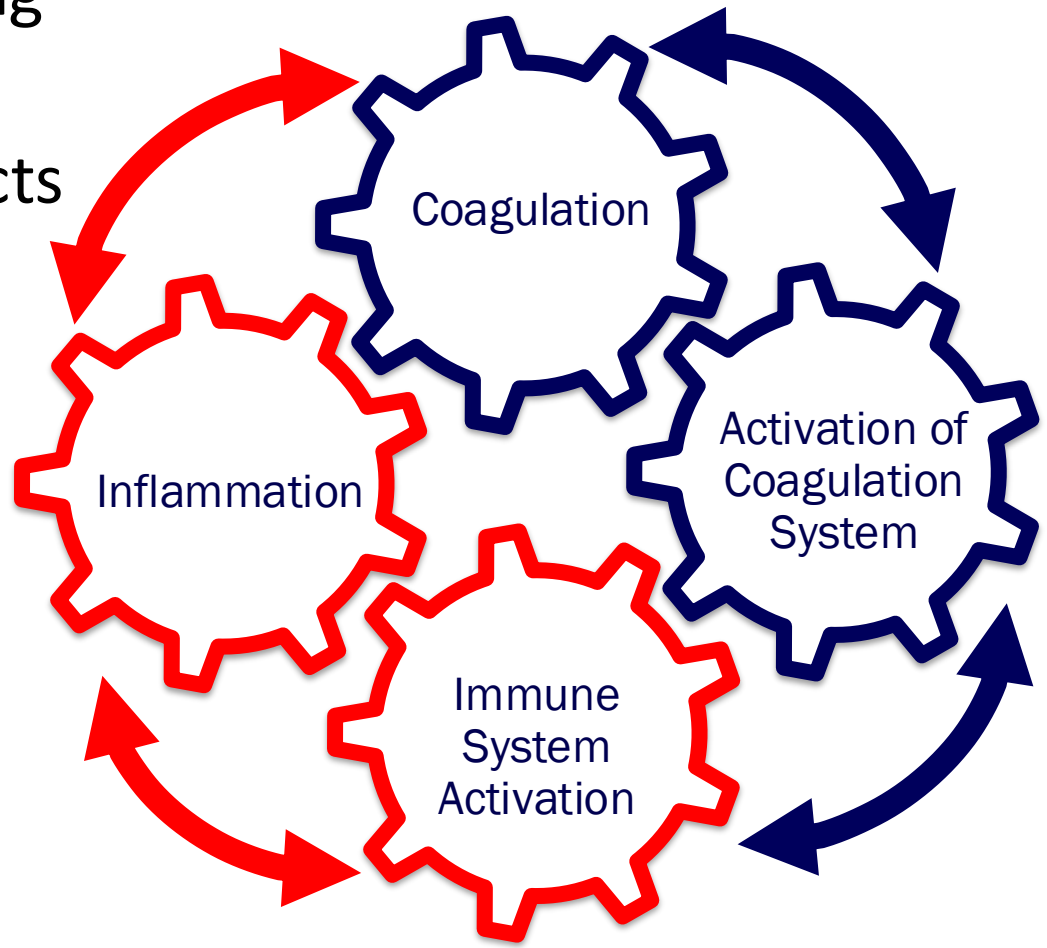


FIGURE 1 | TAMPITI Patient Screening, Enrollment, Randomization, and Analysis Diagram. This Consolidated Standards of Reporting Trials (CONSORT) diagram displays the number of patients screened for eligibility, excluded based on not meeting study inclusion criteria, patients enrolled and randomized, and the patients analyzed per study group.

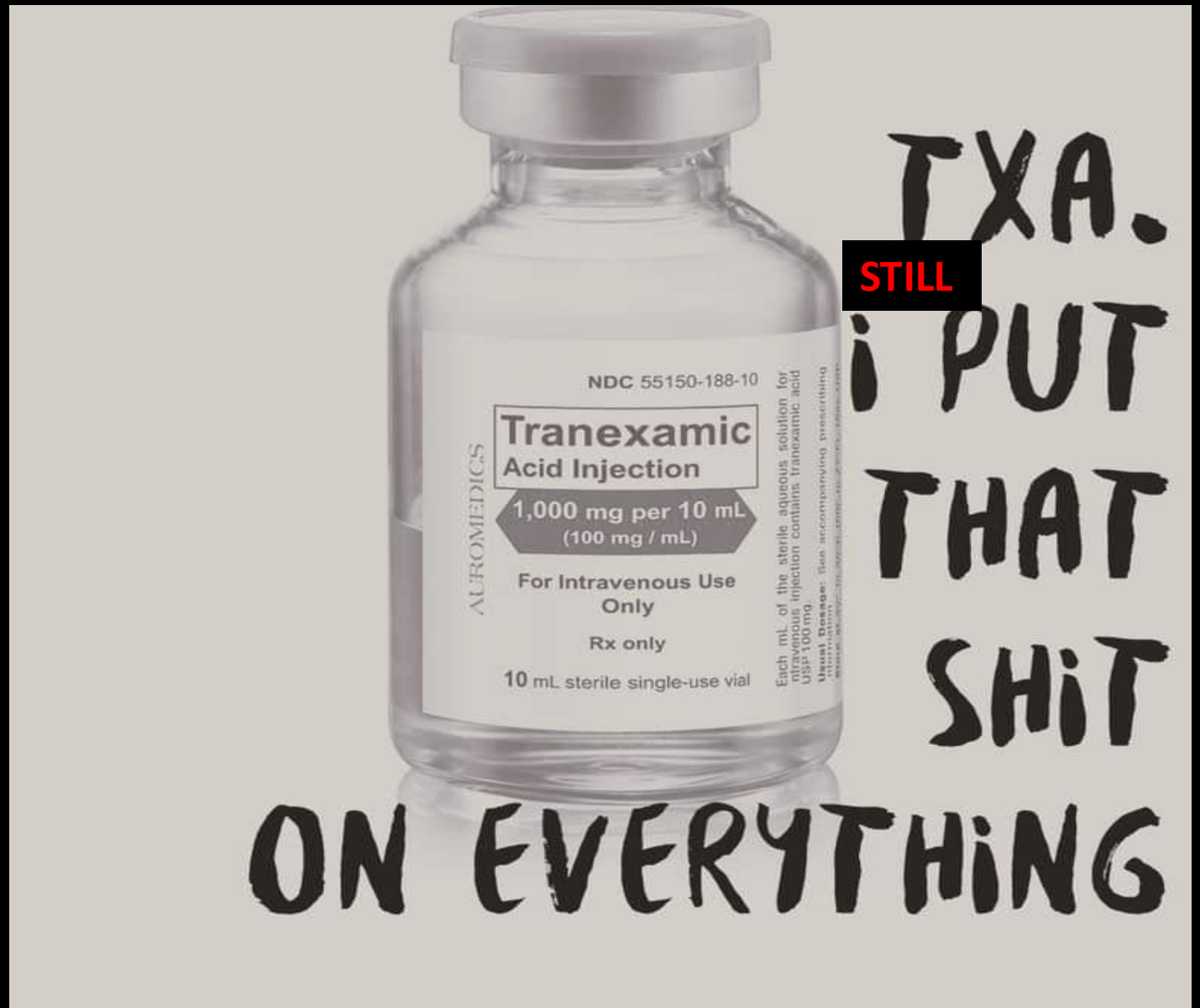


Summary

- Tranexamic acid is an immunomodulating pro-hemostatic agent
- Plasmin, plasminogen, TXA specific effects
- Hard to uncouple immune/hemostatic effects
- Immunothrombosis
- Differential effects based on indication for use (cardiac, trauma, etc)



Even considering the immune effects….




University of Pittsburgh
Trauma and Transfusion Medicine Research Center
YOU!!

Questions?

- nealm2@upmc.edu
- @macky_neal
- Cell: 412 848 2134

Neal lab funding

- R35GM119526-07 NIGMS
- R01HL166944-01A1 NHLBI
- OTA # 1OT2HL156812-01 NHLBI
- DM160354 Department of Defense JPC-6 Combat Casualty Care Research Program
- Department of Defense CDMRP JPC-6 Combat Casualty Care Research Program
- Department of Defense W81XWH21107810
- DARPA N66001-23-9-4005

DEPARTMENT OF DEFENSE · UNITED STATES OF AMERICA

DARPA

NIH National Institute of General Medical Sciences

NIH National Heart, Lung, and Blood Institute