

**Using omics to
determine endotypes;
patients with TIC/blood
failure**

Kirk Hansen PhD

**Professor, Biochemistry &
Molecular Genetics**

THOR 2024



Margot DeBot

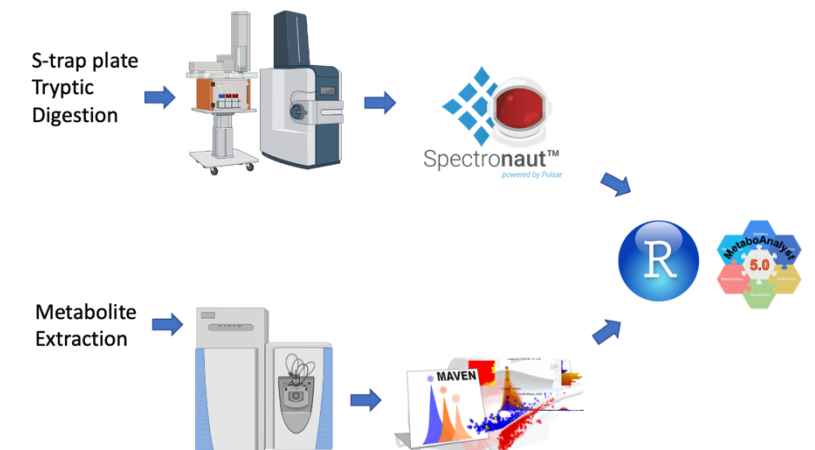
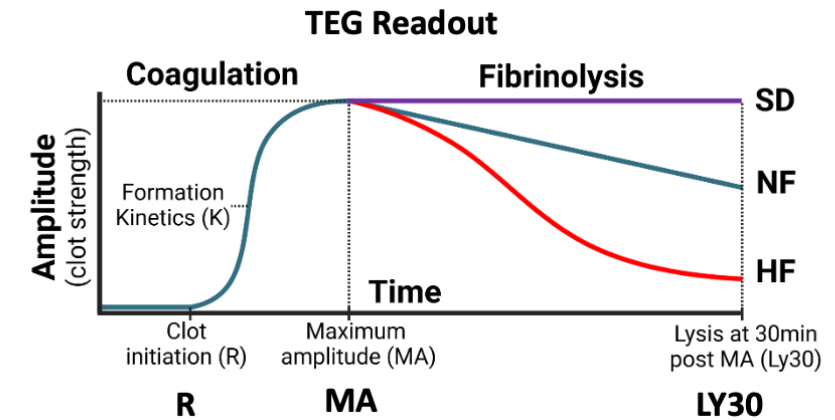
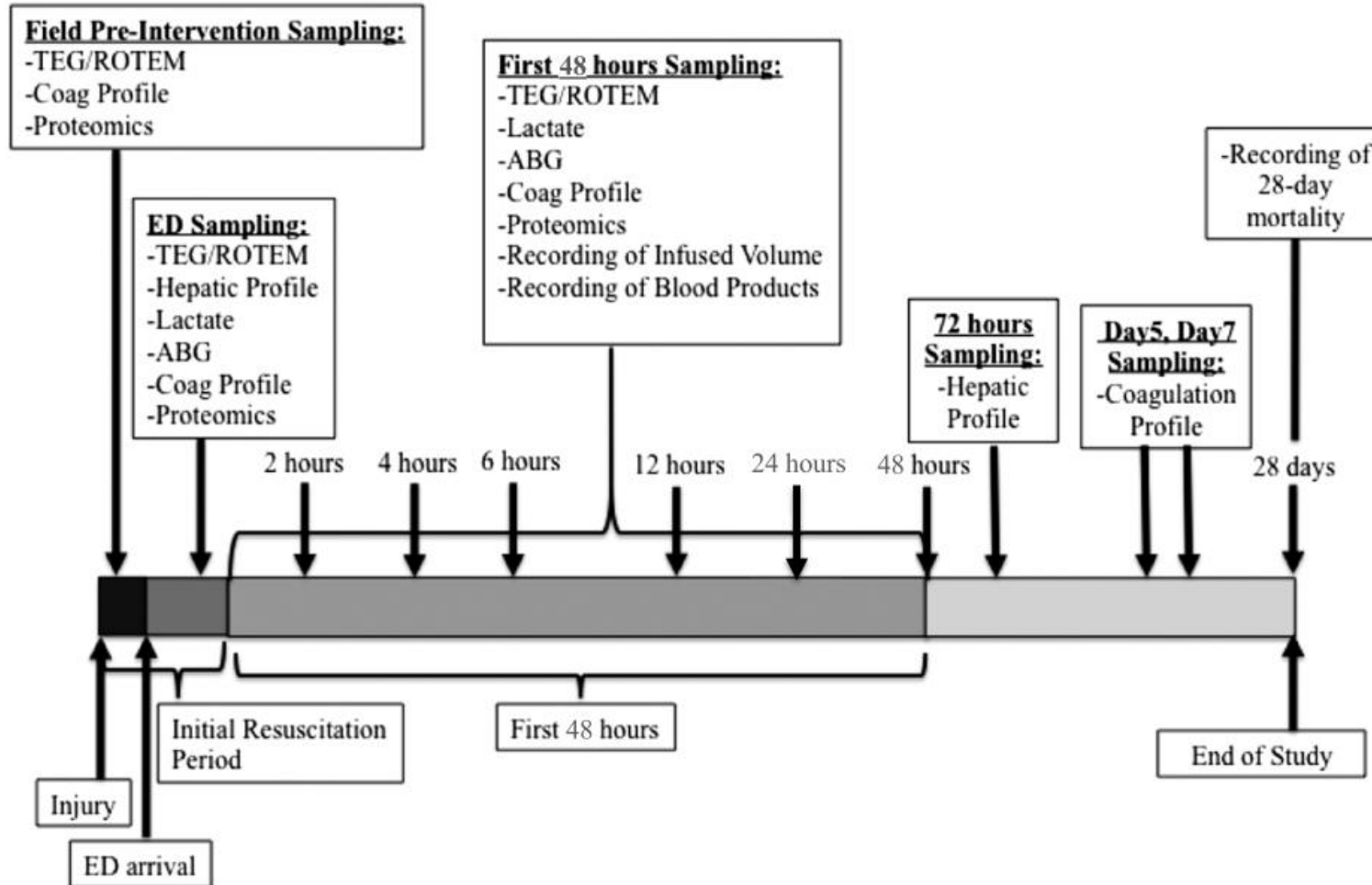


Chris Erickson

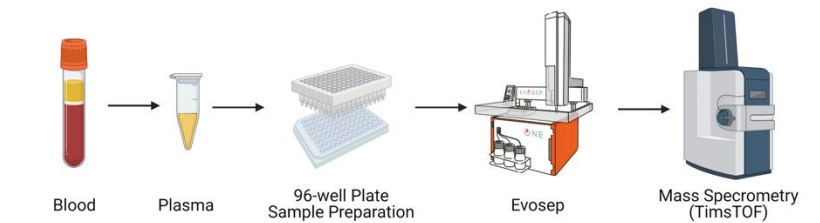
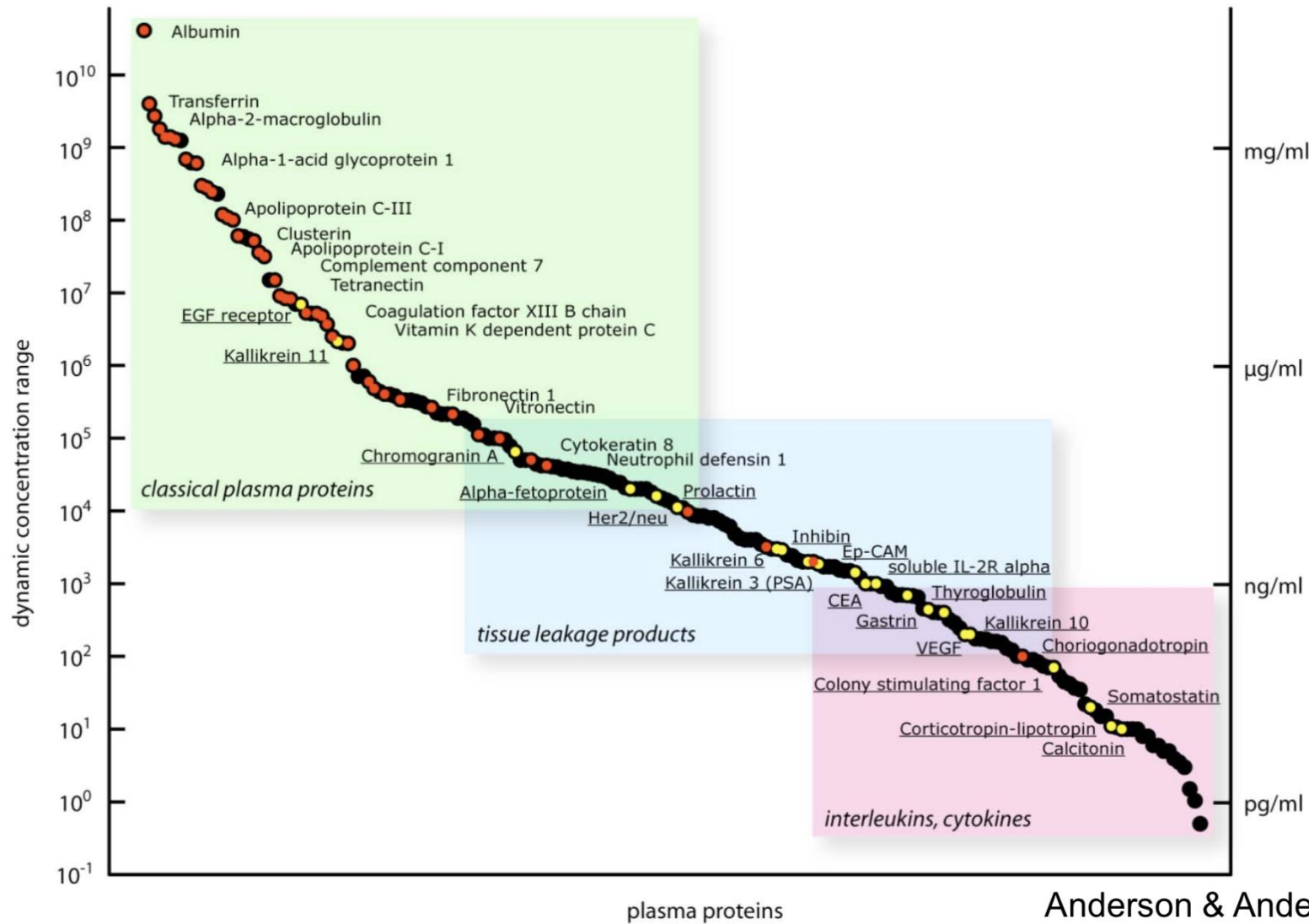


Monika Headrick

Control of Major Bleeding After Trauma (COMBAT)

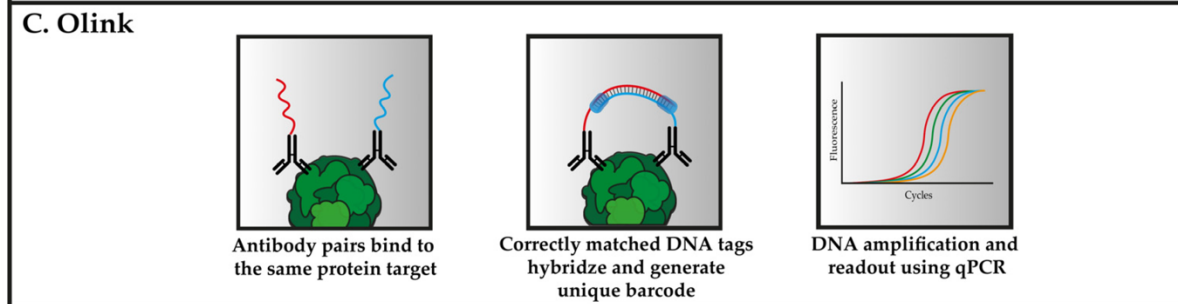
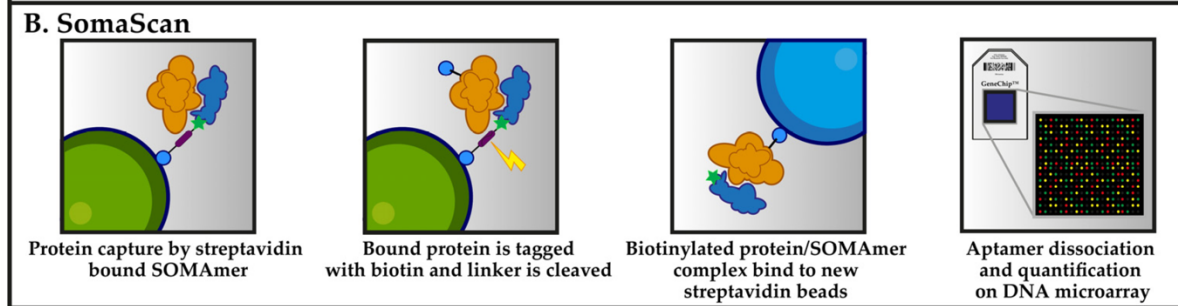
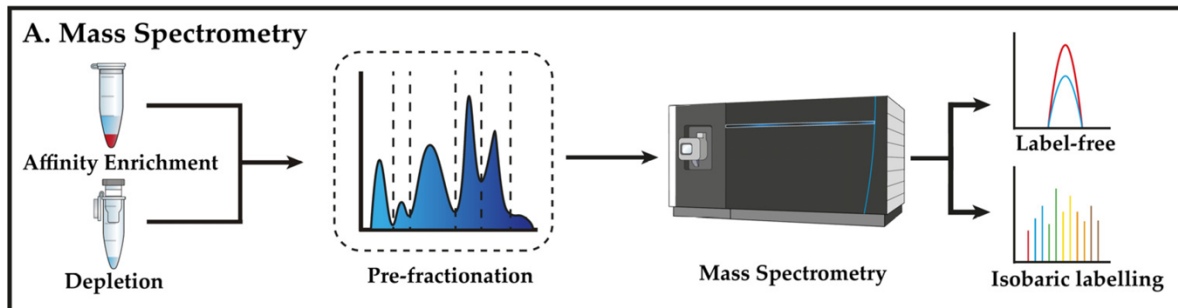


Plasma Proteomics



Current Proteomic Technologies

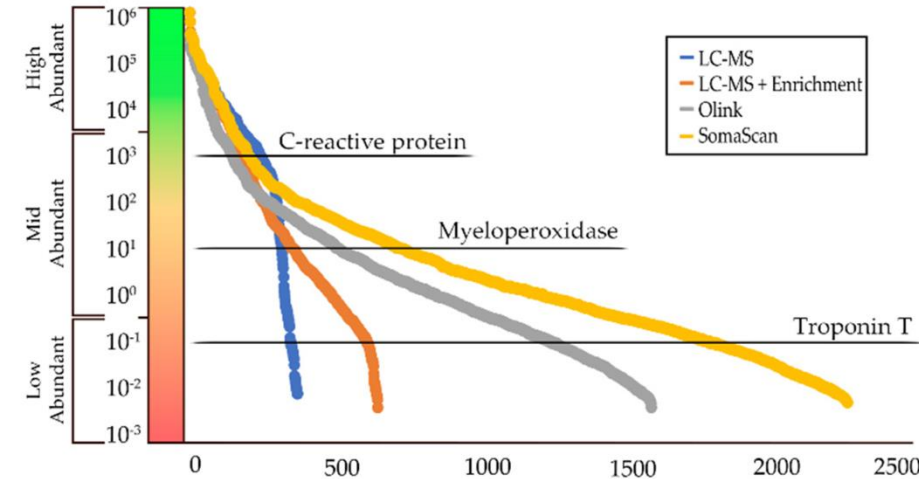
“Use top quality weapons”



1424 Proteins
(COMBAT)

1305 Proteins
(TACTIC)

~3000 Proteins
(JTDB)



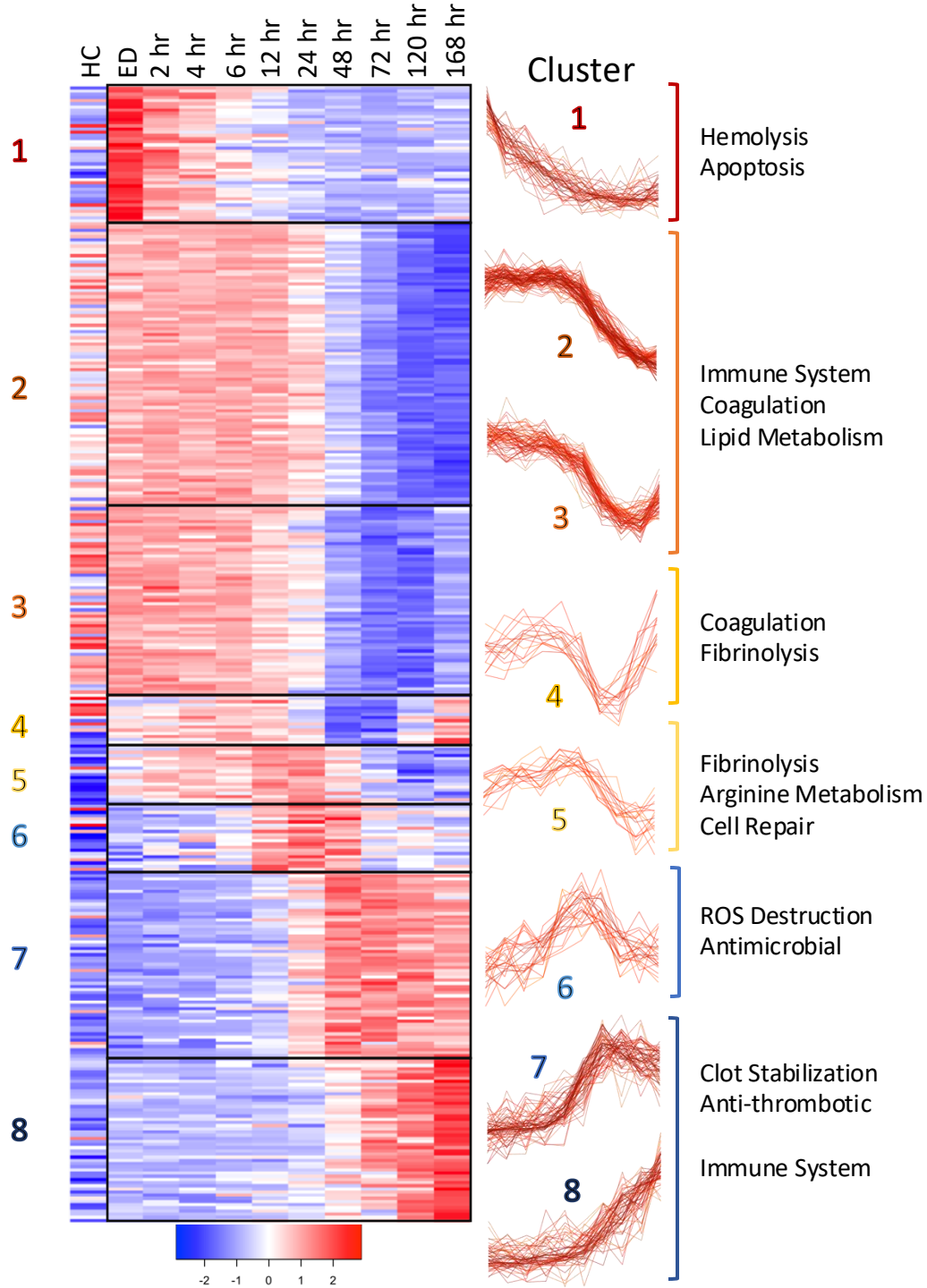
Plasma proteomics (average)



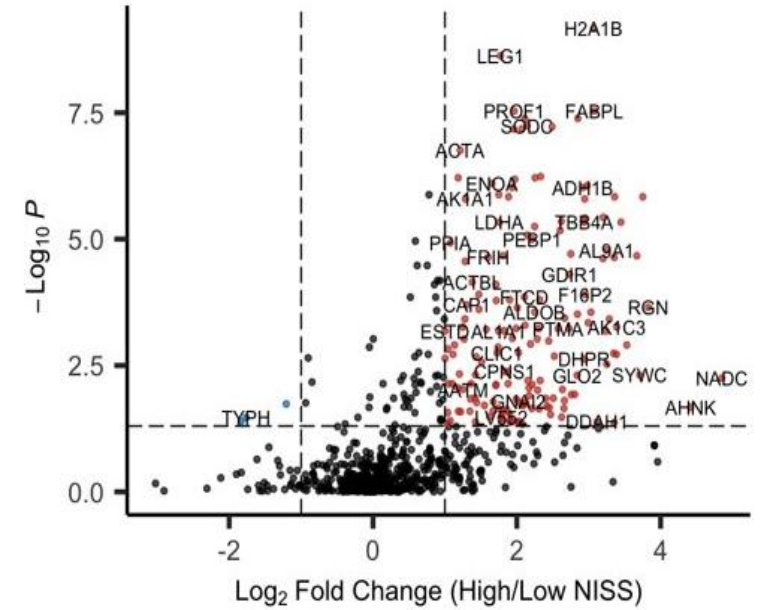
Healthy Controls
n = 100

- ED
- Hr2
- Hr4
- Hr6
- Hr12
- Hr24 Trauma
- Hr48 Hemorrhage
- Hr72 n = 118
- Hr120
- Hr168

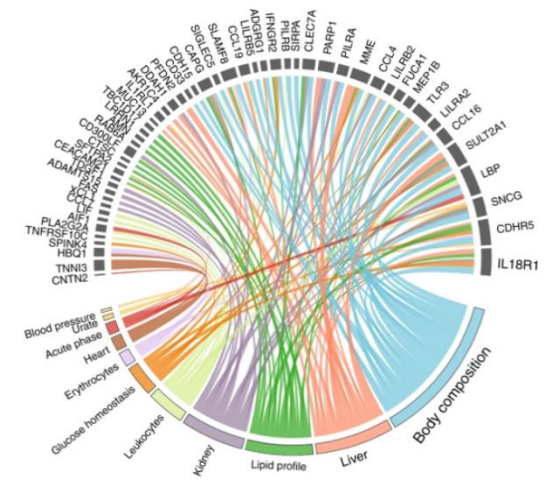
Total Samples: 943



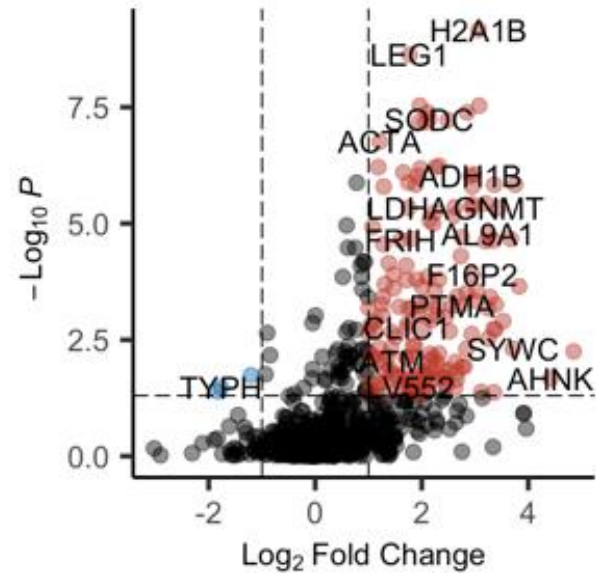
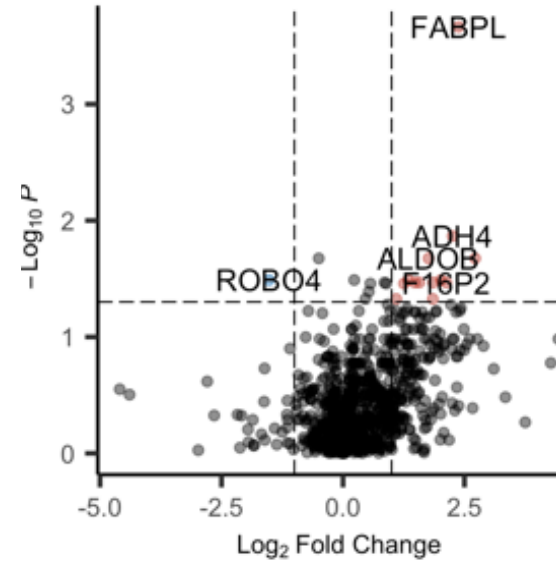
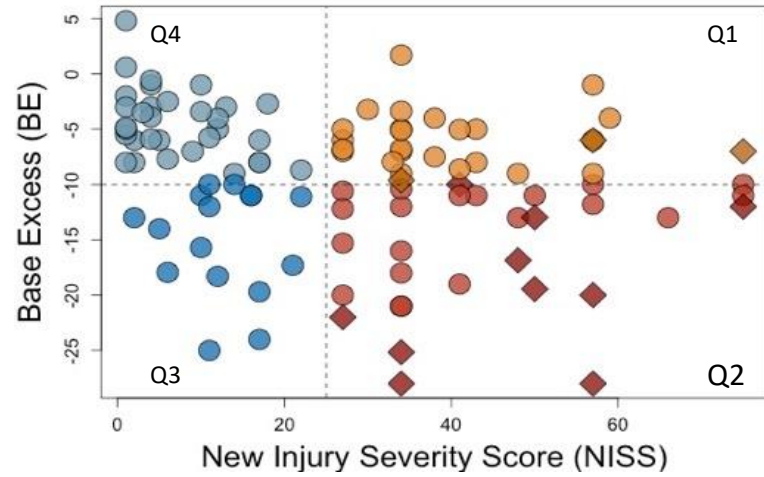
high versus low Injury score - ED



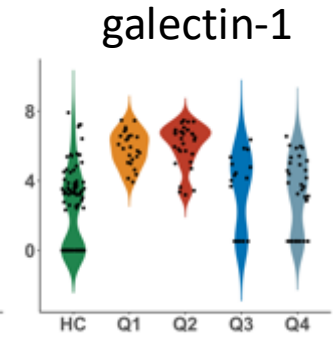
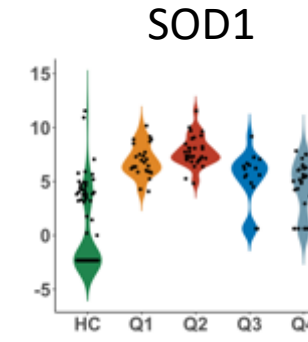
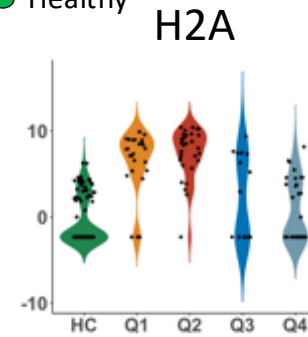
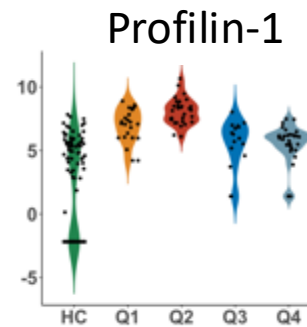
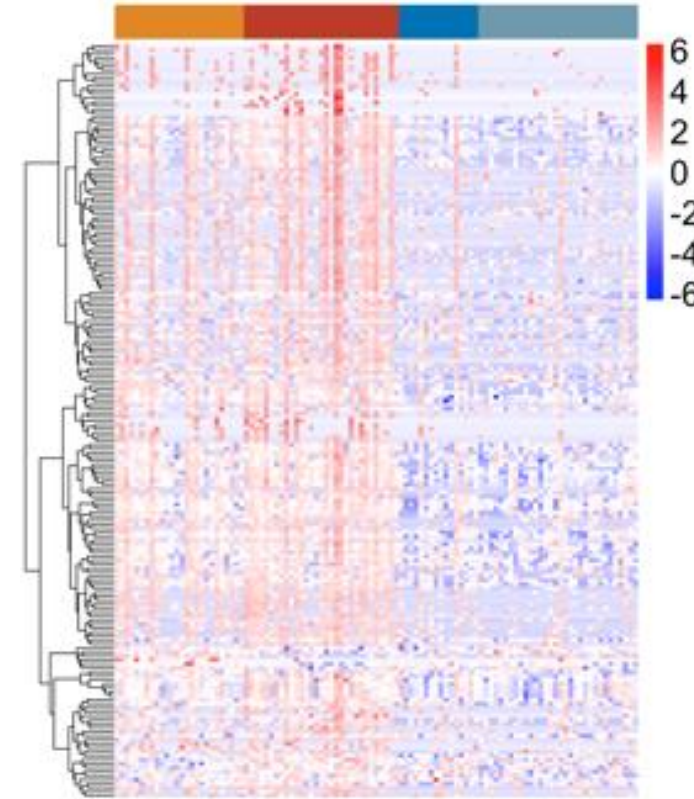
correlations with clinical parameters



Patient plasma proteome response to trauma and shock (ED)

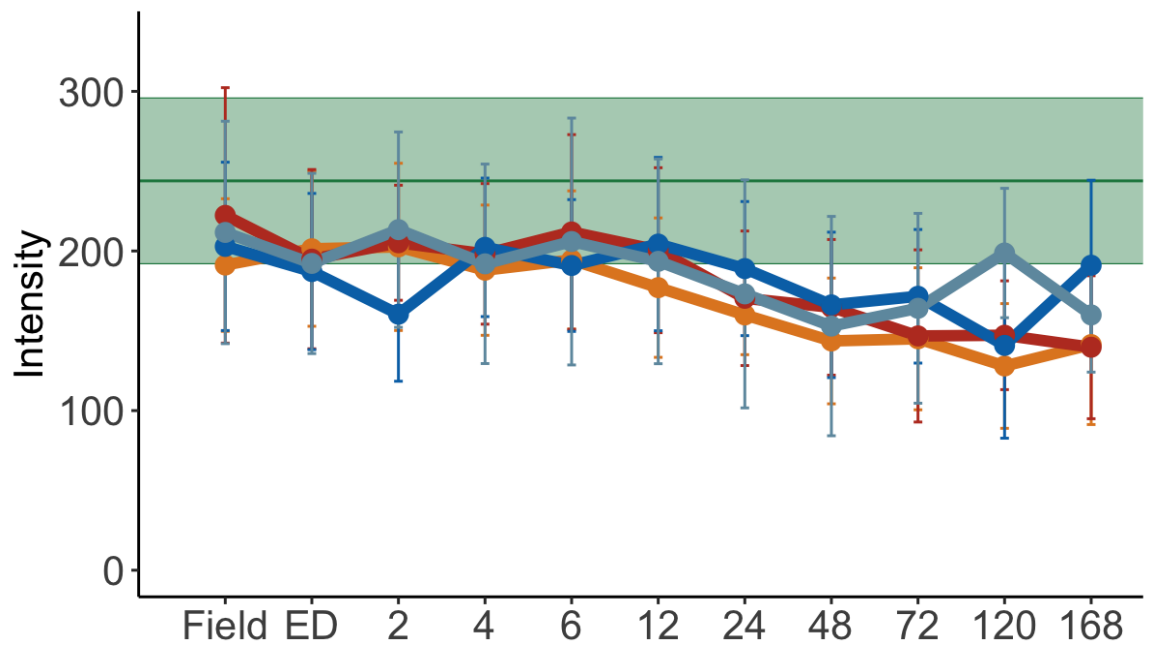


- High trauma, high shock
- High trauma, low shock
- Low trauma, high shock
- Low trauma, low shock
- Healthy

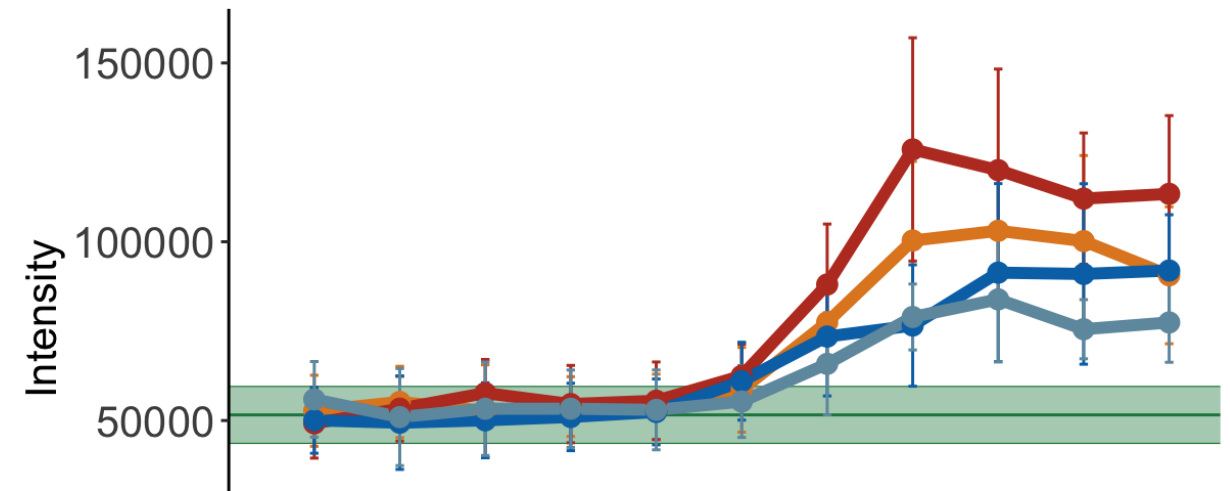


Dynamics of FBG & FXIII

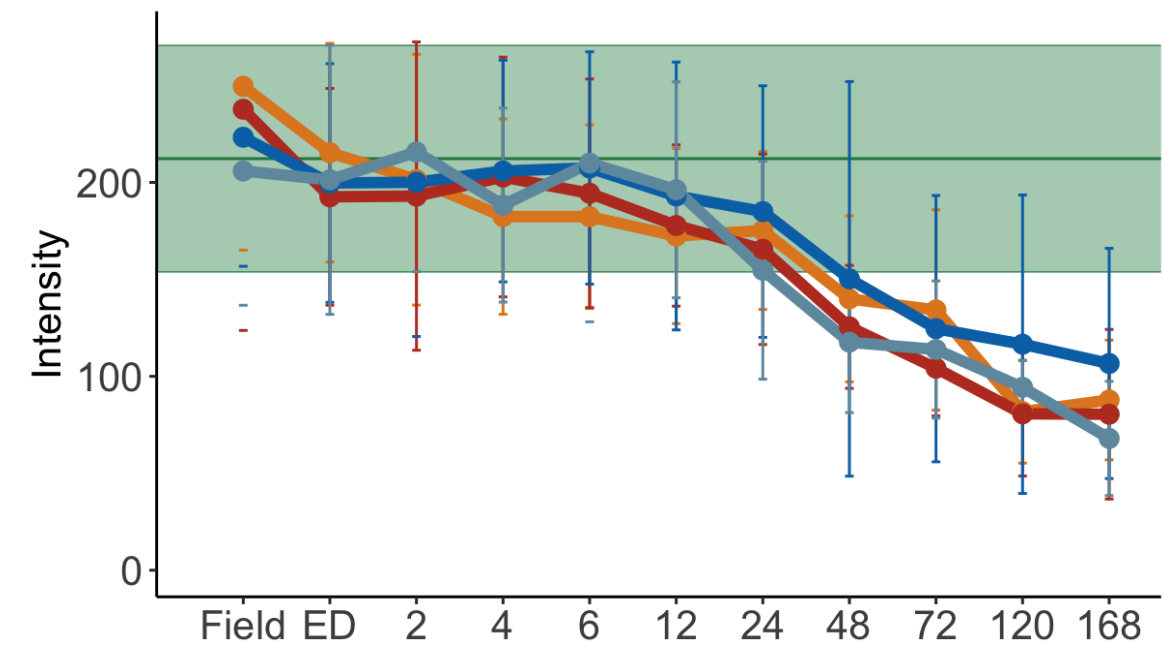
F13B



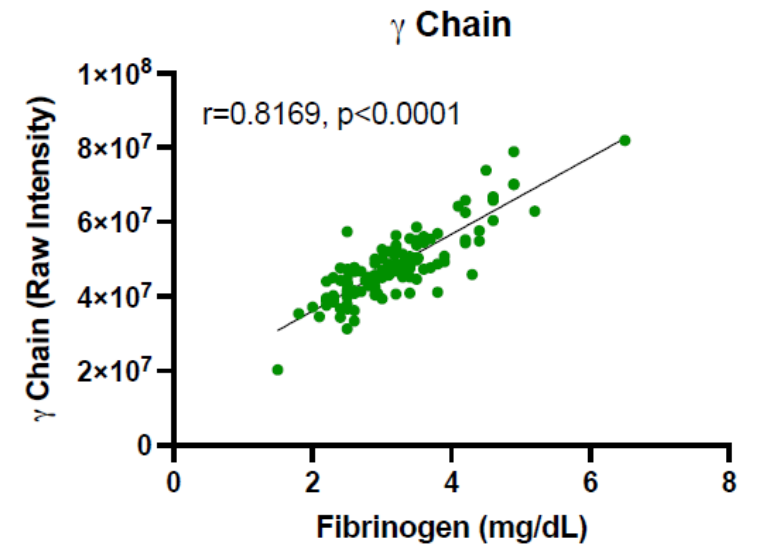
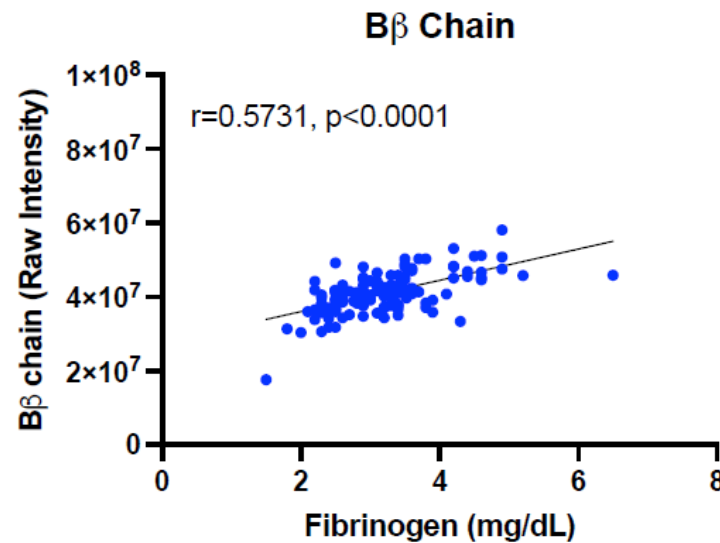
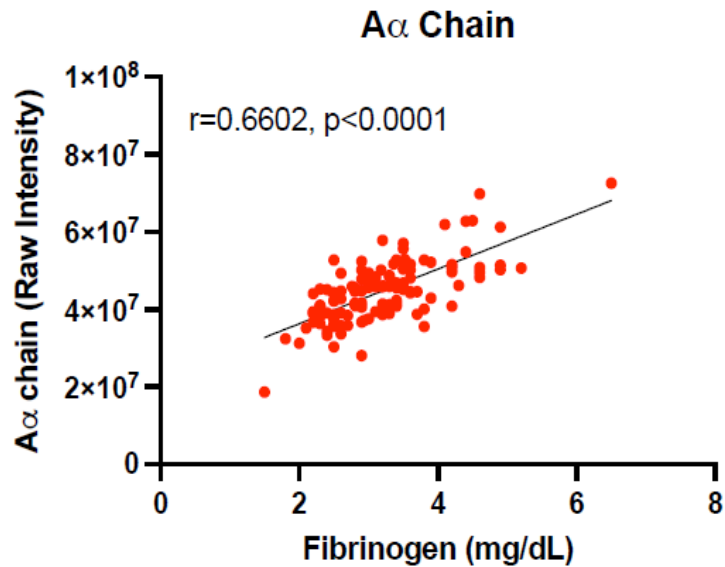
MS Fibrinogen



F13A



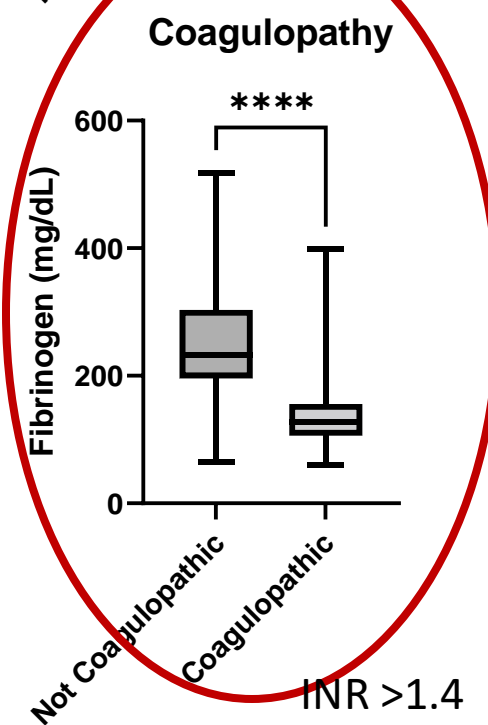
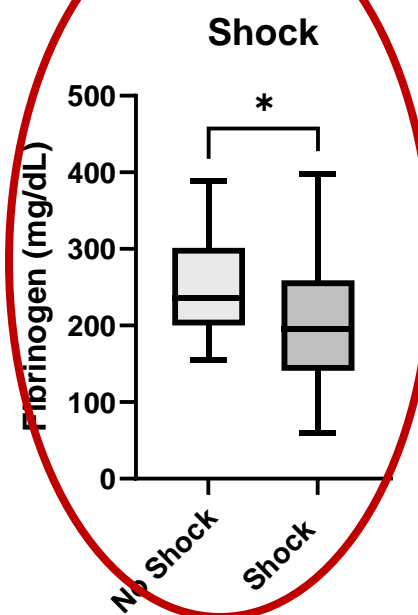
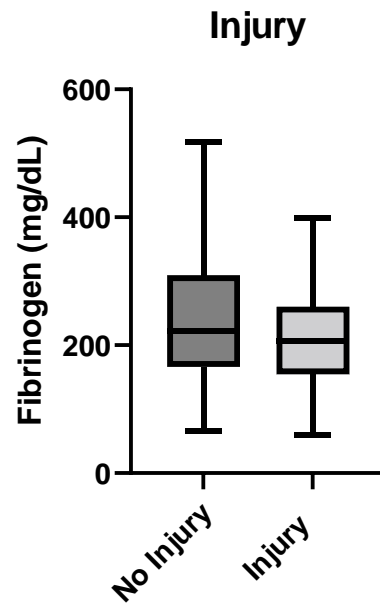
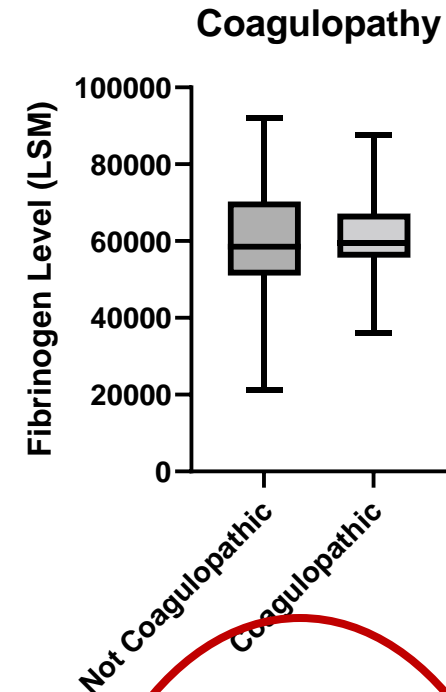
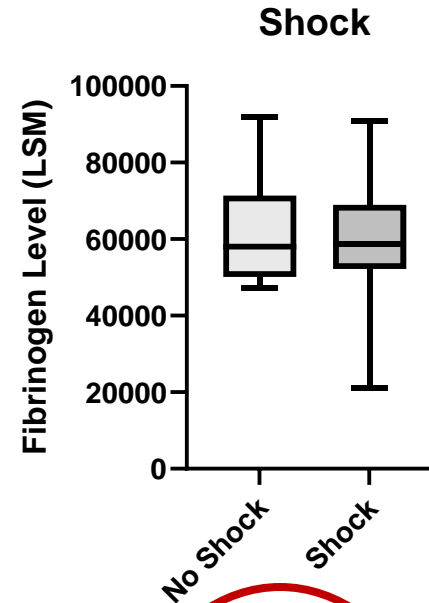
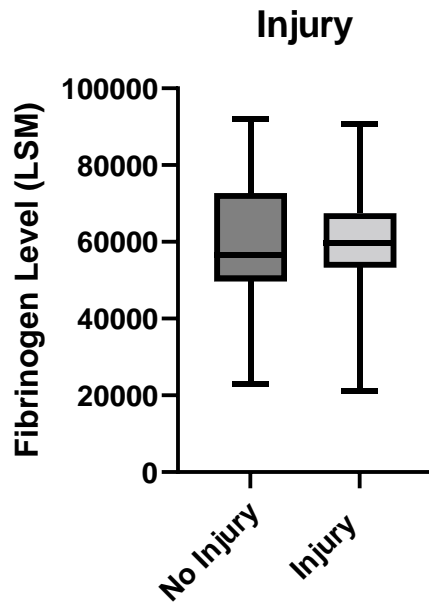
von Clauss to MS based correlations in FXI def healthy individuals



Fibrinogen Concentration
(Mass Spec)

VS.

Fibrinogen Activity
(von Clauss)

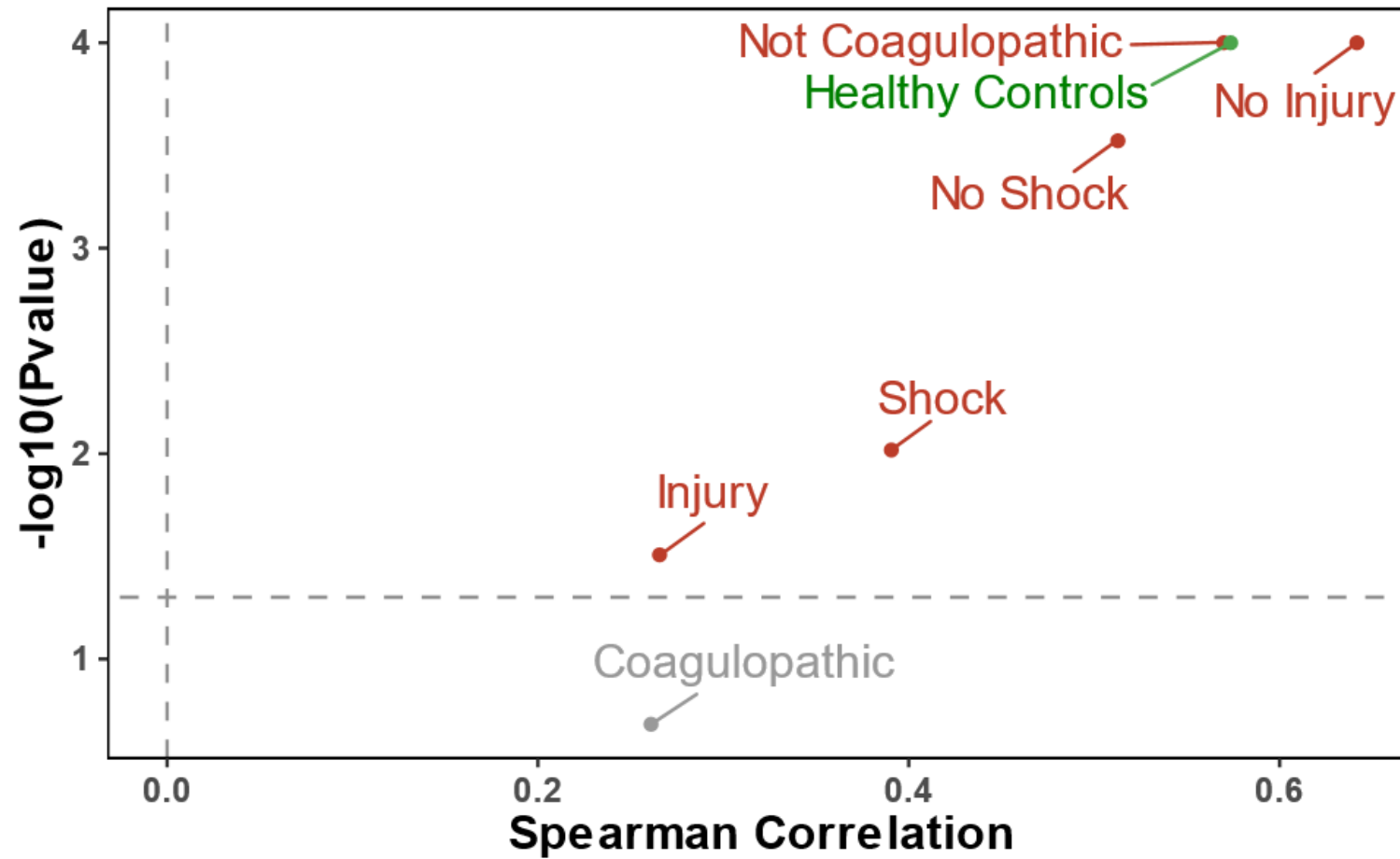


NISS >15

BE <-6

INR >1.4

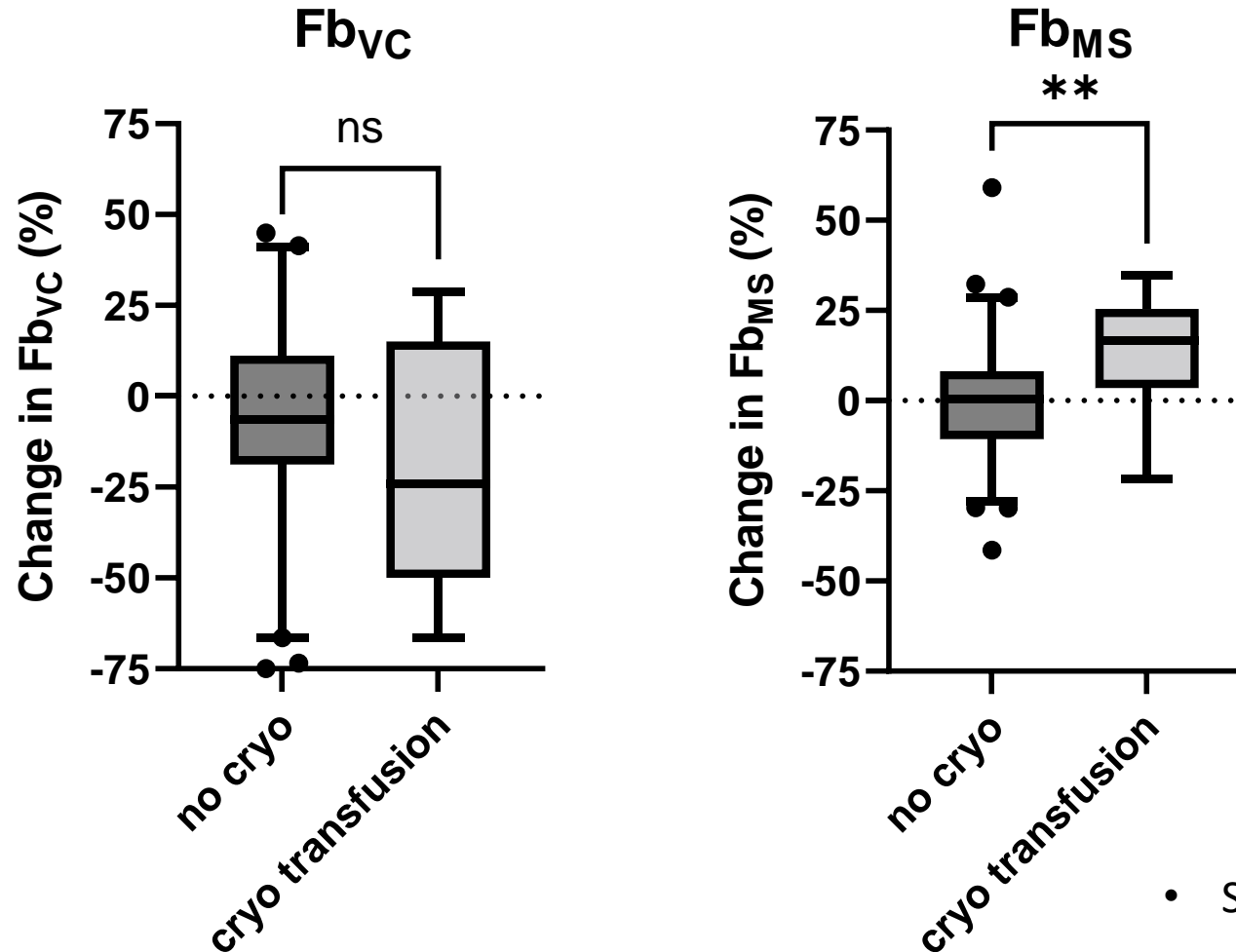
von Clauss to MS based correlations

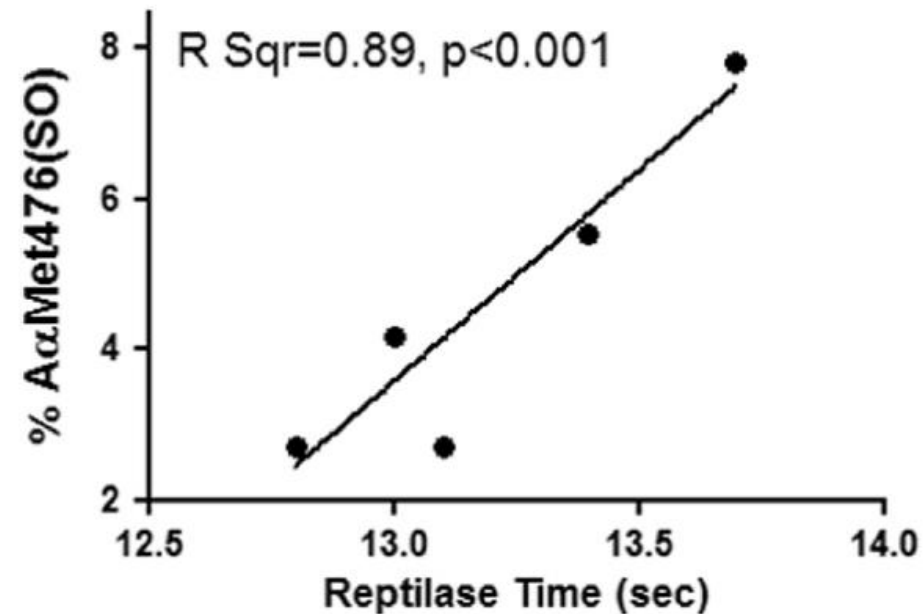
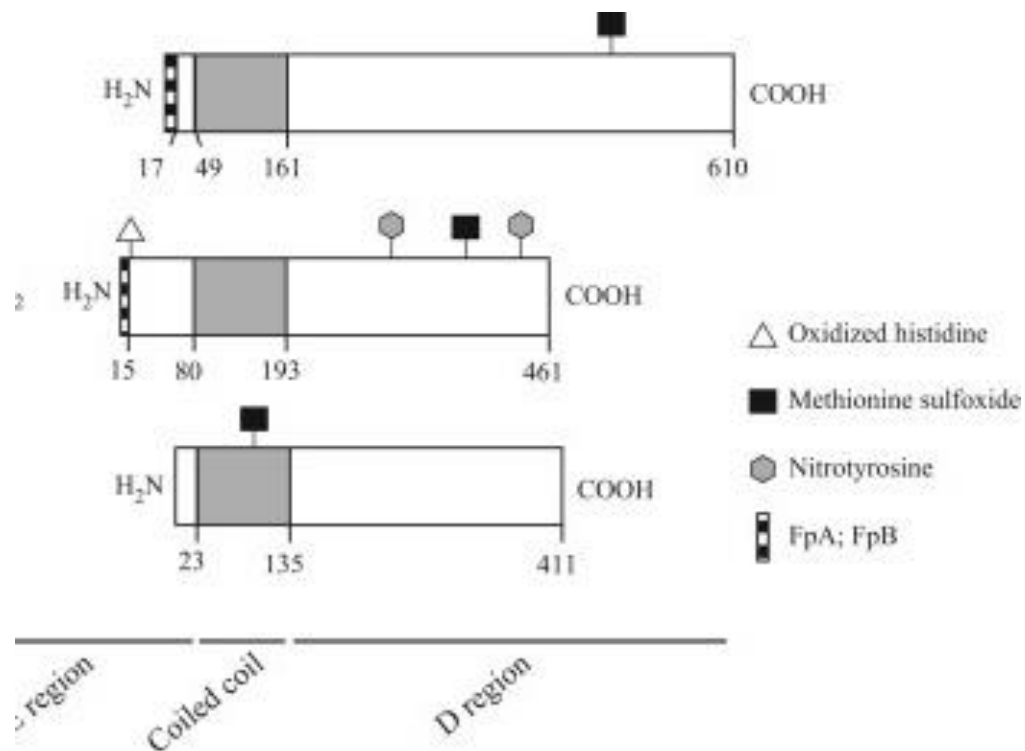


ED Fb _{VC} vs. ED Fb _{MS}	No Injury	Injury	No Shock	Shock	Not Coagulopathic	Coagulopathic	Healthy controls
Spearman R	0.64	0.27	0.51	0.39	0.57	0.26	0.57
p value	<0.0001	0.03	<0.01	0.01	<0.0001	0.21	<0.0001

von Clauss to MS based correlations

Fibrinogen function is not corrected with cryo





Functional impact of oxidative posttranslational modifications on fibrinogen and fibrin clots (2013)

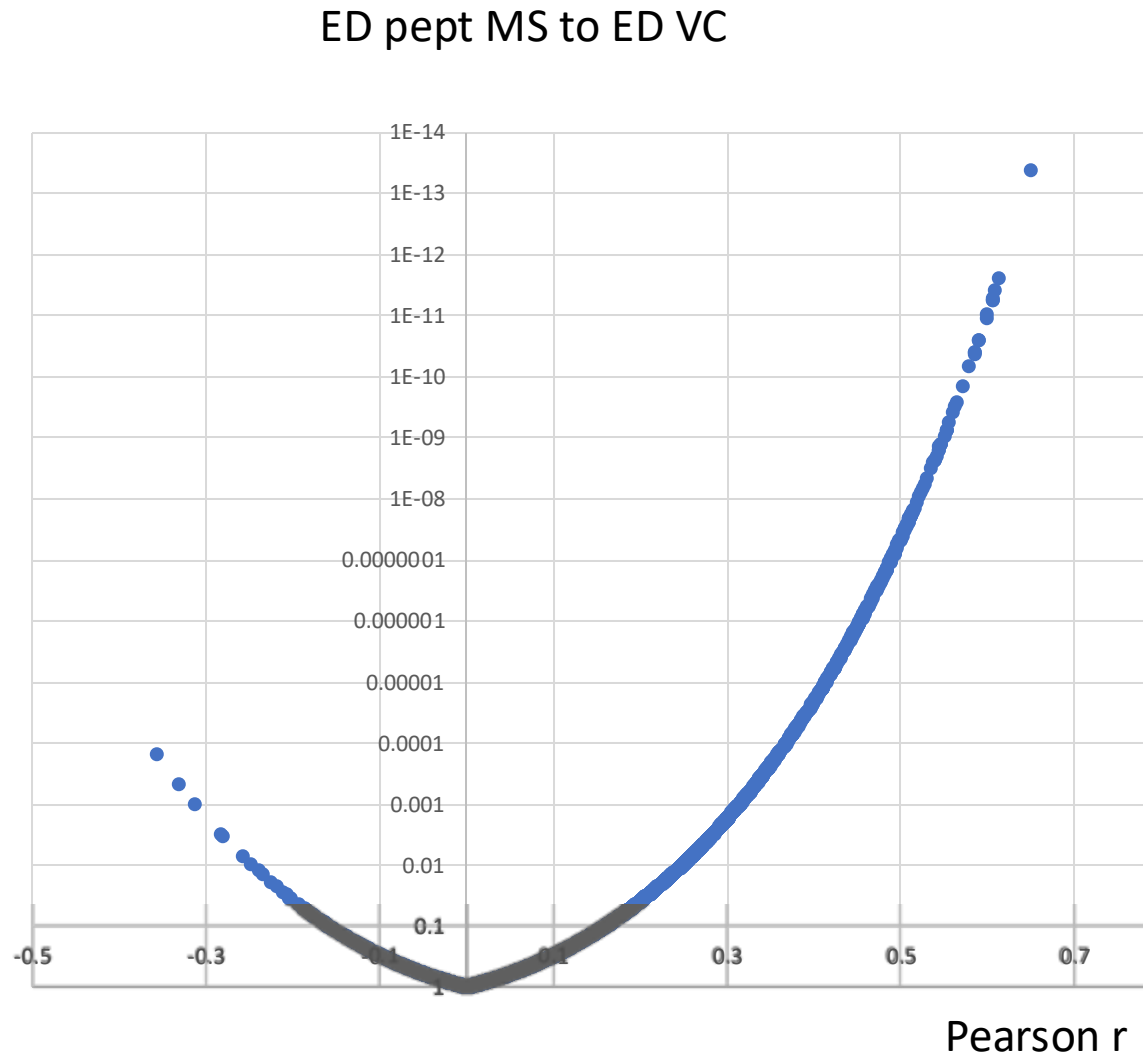
Marissa Martinez, John W Weisel, Harry Ischiropoulos

White NJ, Wang Y, Fu X, et al. Post-translational oxidative modification of fibrinogen is associated with coagulopathy after traumatic injury. *Free Radic Biol Med.* 2016;96:181-189.

- Fibrinogen oxidation impairs fibrin polymerization measured by reptilase time
- Oxidated fibrinogen levels impair polymerization at 2-8% of total fibrinogen, levels found in trauma patients

Correlations between MS and von Clauss measurements at the Emergency department time point (~45 min post injury)

-0.36	FIBG-89-AIQd
-0.33	NLy30
-0.28	FIBB-142-SSSox
-0.28	FIBB-33-VNDd
-0.26	FIBA-481-EVVpox
-0.25	FIBA-550-ESGd
-0.24	FIBG-339-STWdox
-0.23	NISS
-0.23	FIBG-334-NGM
-0.22	FIBG-168-TVQ
-0.19	FIBB-161-QVKq
-0.19	FIBA-23-GEG
-0.18	FIBG-96-PDEd
-0.18	FIBB-399-IHN
-0.18	FIBB-268-VYC2d
-0.18	FIBG-172-HDI
-0.18	FIBB-57-PSL
-0.17	FIBG-140-YNS
-0.17	FIBA-388-SES
-0.17	FIBA-347-QNPp
-0.17	FIBB-33-VNDd
-0.16	FIBB-54-EEA



FIBB-54-EEA	0.65
FIBG-96-PDE	0.61
FIBA-259-MEL	0.61
FIBA-226-MKPd	0.6
FIBA-259-MEL	0.6
FIBA-259-MELd	0.6
FIBA-256-QMRd2ox	0.6
FIBA-226-MKP	0.6
FIBG-259-IHL	0.59
FIBG-259-IHLd	0.59
FIBA-559-ESS	0.58
FIBB-212-LES	0.58
FIBB-61-PAP	0.58
FIBB-33-VND	0.58
FIBG-89-AIQ	0.57
FIBB-258-QPDq	0.56
FIBA-259-MELd	0.56
FIBB-484-IRP	0.56
FIBG-274-VELd	0.55
FIBB-53-REE	0.55
FIBB-258-QPD	0.55
FIBA-511-HRH	0.55

Peptide level-based correlations

Fba 481-510 (462-491)

EVVTSEdGSDcPEAMdLGtLSGIGtLDGFR

FIBA-481-EVV3

ED

0.39

EVVTSEdGSDcPEAmDLGtLSGIGtLDGFR

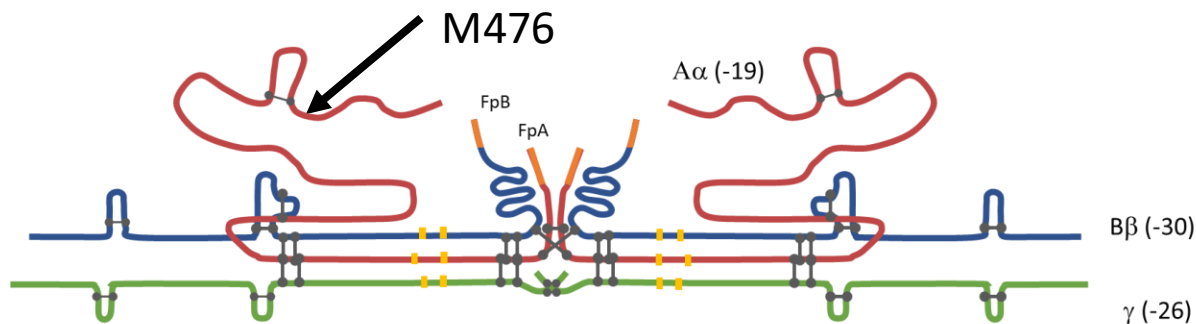
FIBA-481-EVVox4

-0.02

EVVTSEdGSDcPEAmDLGtLSGIGtLDGFR

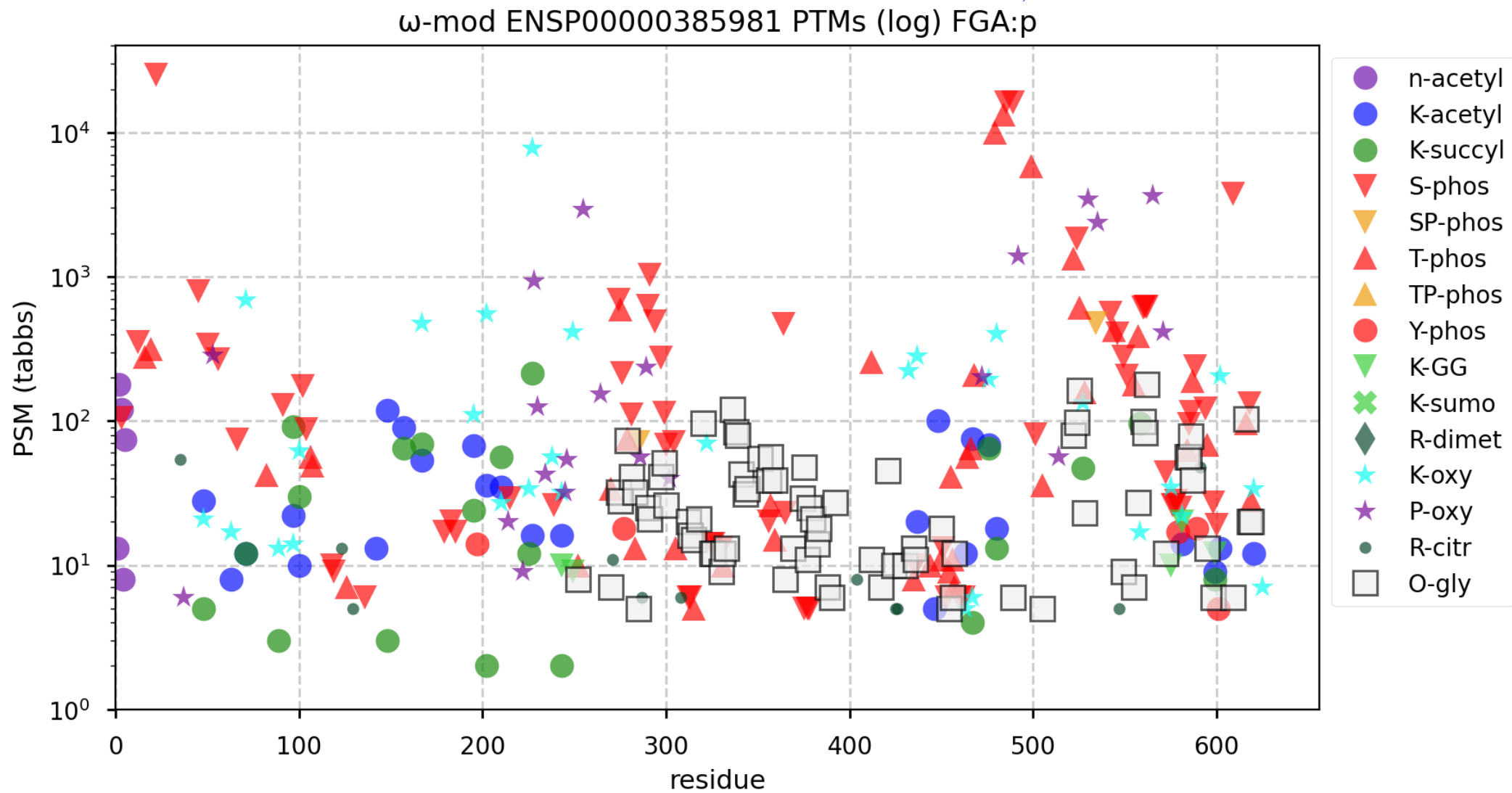
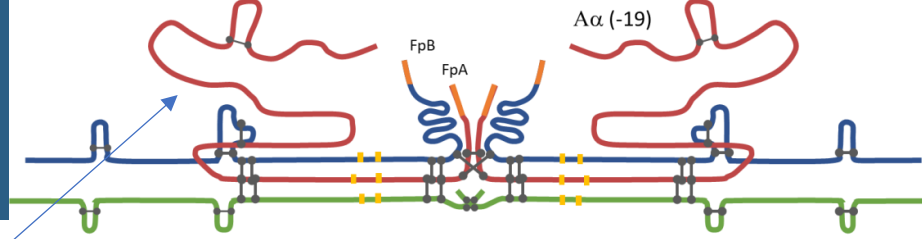
FIBA-481-EVVpox4

-0.26

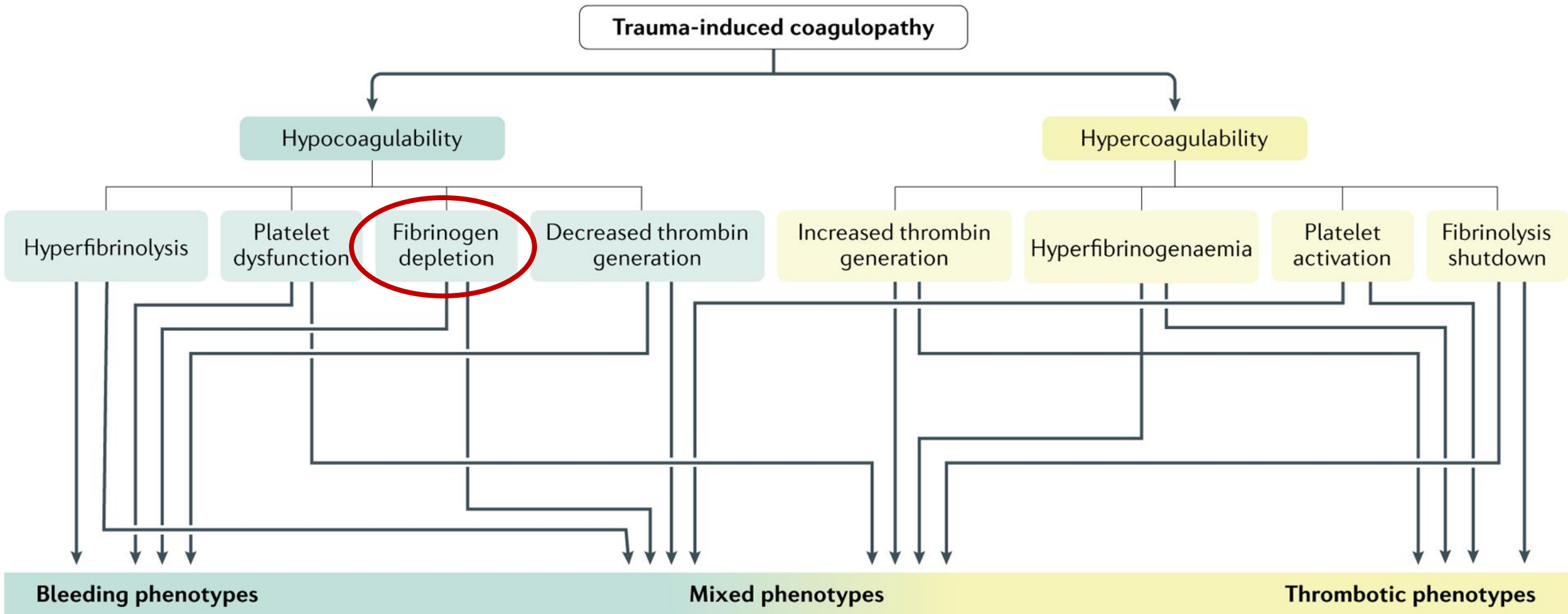


-0.36	FIBG-89-AIQd	FIBB-54-EEA	0.65
-0.33	NLy30	FIBG-96-PDE	0.61
-0.28	FIBB-142-SSSox	FIBA-259-MEL	0.61
-0.28	FIBB-33-VNDd	FIBA-226-MKPd	0.6
-0.26	FIBA-481-EVVpox	FIBA-259-MEL	0.6
-0.25	FIBA-550-ESGd	FIBA-259-MELd	0.6
-0.24	FIBG-339-STWdox	FIBA-256-QMRd2ox	0.6
-0.23	NISS	FIBA-226-MKP	0.6
-0.23	FIBG-334-NGM	FIBG-259-IHL	0.59
-0.22	FIBG-168-TVQ	FIBG-259-IHLd	0.59
-0.19	FIBB-161-QVKq	FIBA-559-ESS	0.58
-0.19	FIBA-23-GEG	FIBB-212-LES	0.58
-0.18	FIBG-96-PDEd	FIBB-61-PAP	0.58
-0.18	FIBB-399-IHN	FIBB-33-VND	0.58
-0.18	FIBB-268-VYC2d	FIBG-89-AIQ	0.57
-0.18	FIBG-172-HDI	FIBB-258-QPDq	0.56
-0.18	FIBB-57-PSL	FIBA-259-MELd	0.56
-0.17	FIBG-140-YNS	FIBB-484-IRP	0.56
-0.17	FIBA-388-SES	FIBG-274-VELd	0.55
-0.17	FIBA-347-QNPp	FIBB-53-REE	0.55
-0.17	FIBB-33-VNDd	FIBB-258-QPD	0.55
-0.16	FIBB-54-EEA	FIBA-511-HRH	0.55

Community wide PTM landscape

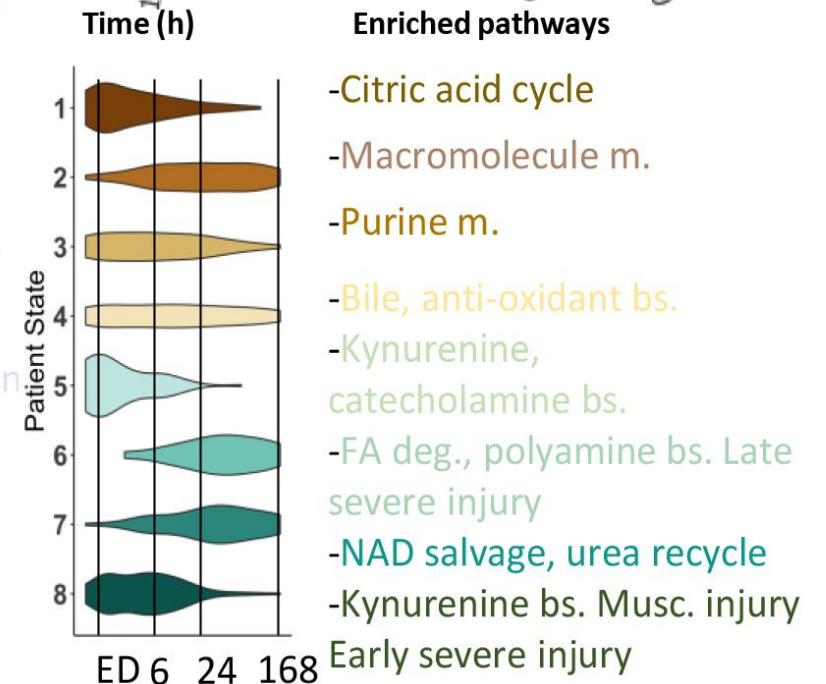
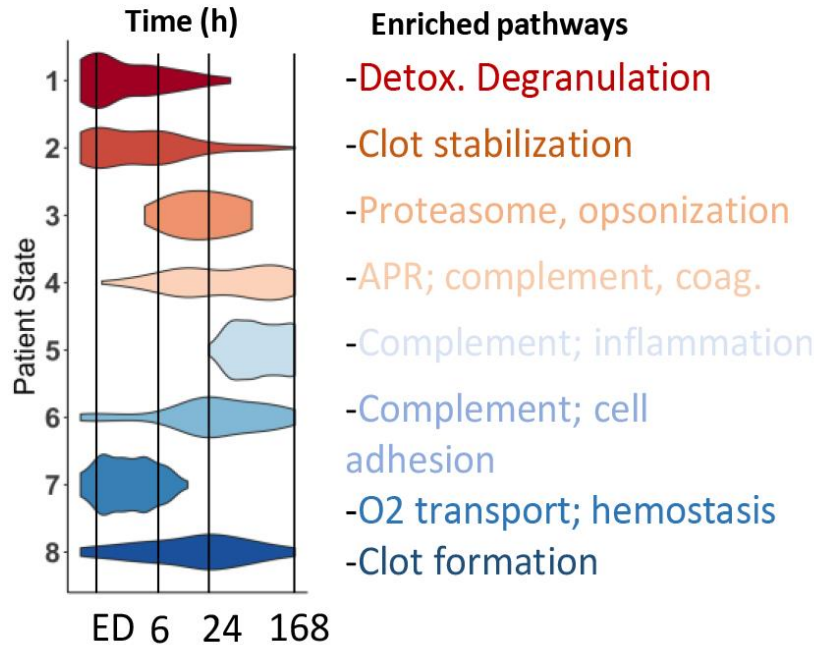
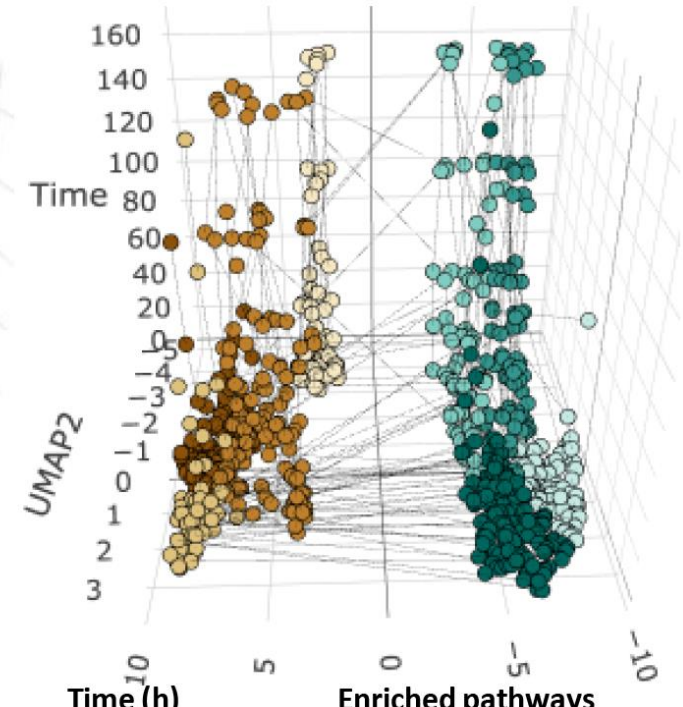
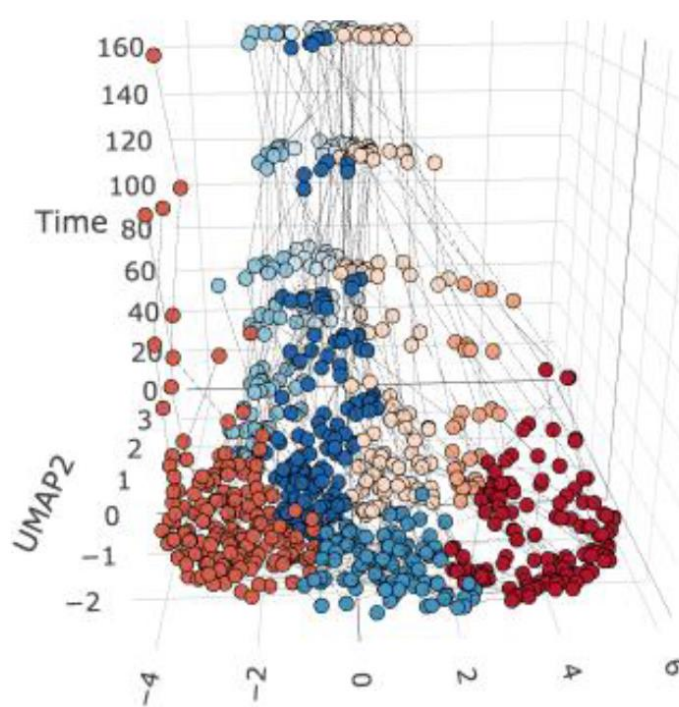


Trauma-Induced Coagulopathy

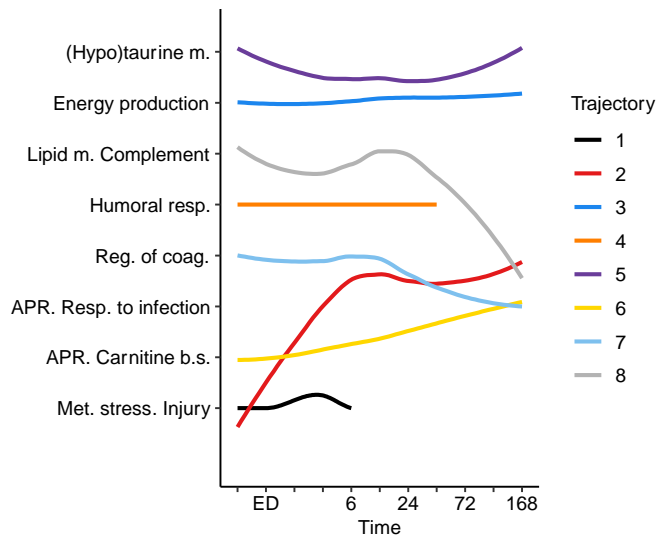
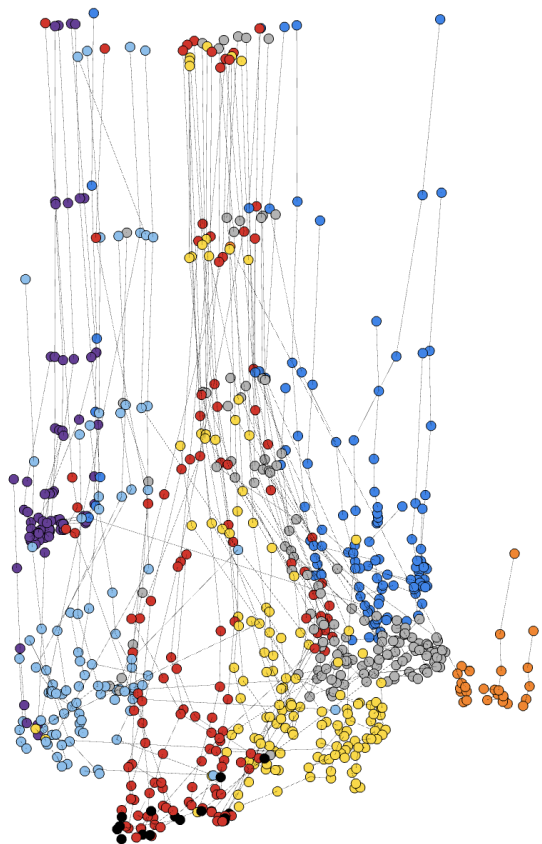


Patient States

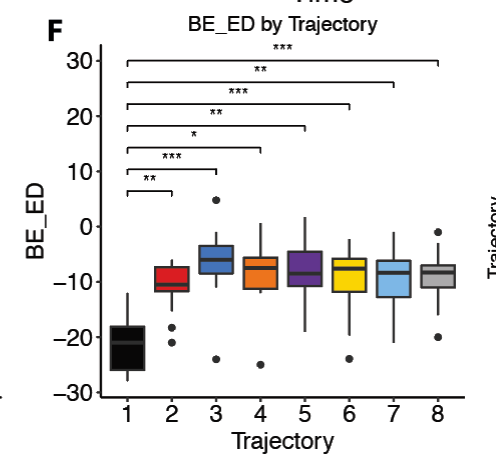
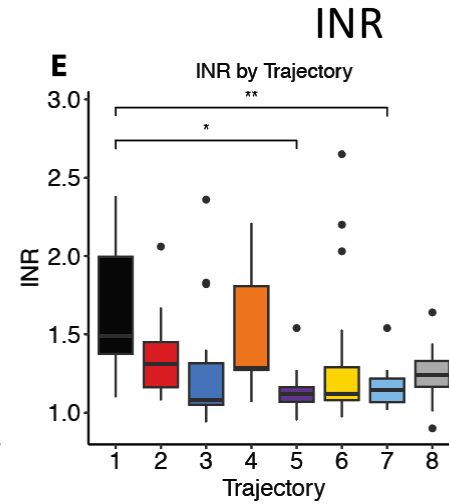
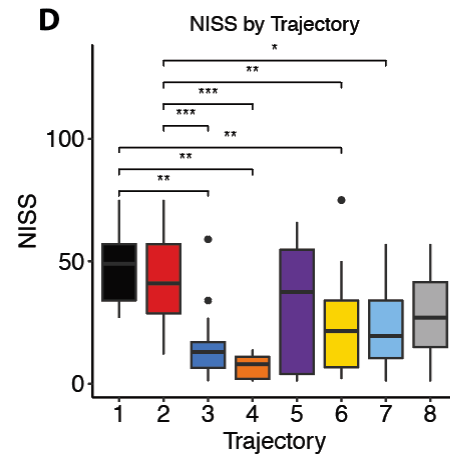
proteomic and metabolomic trajectories following trauma revealing distinct biological responses that can be used to personalize patient care



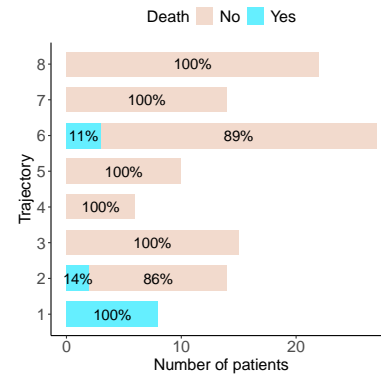
Omics trajectories



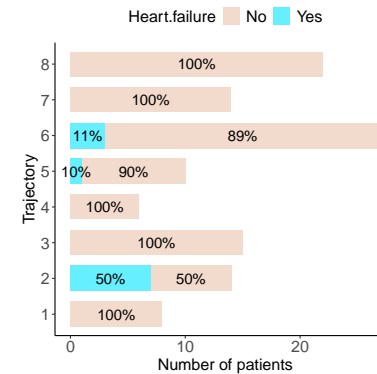
Injury patterns



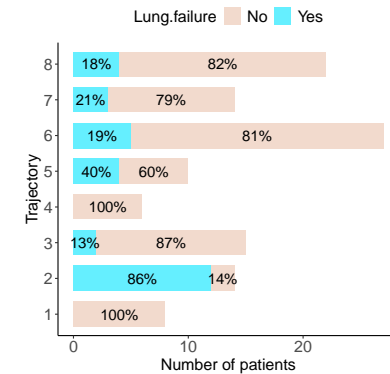
Death



Heart failure



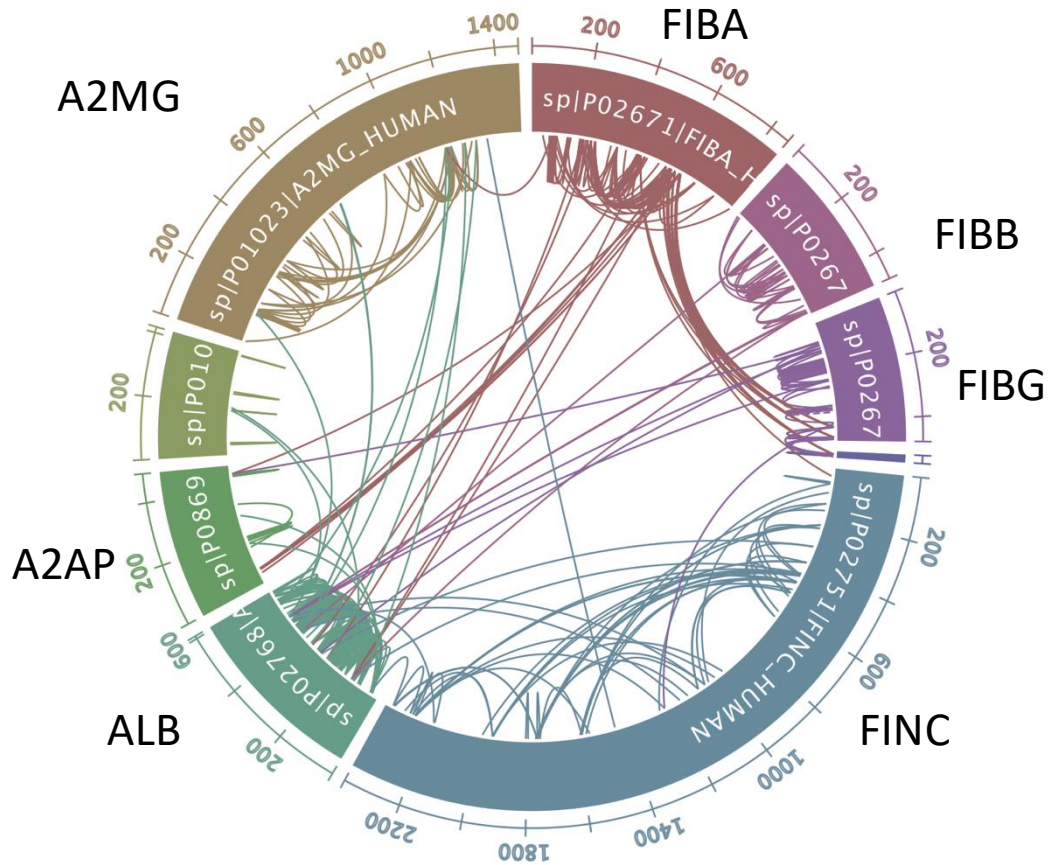
Lung failure



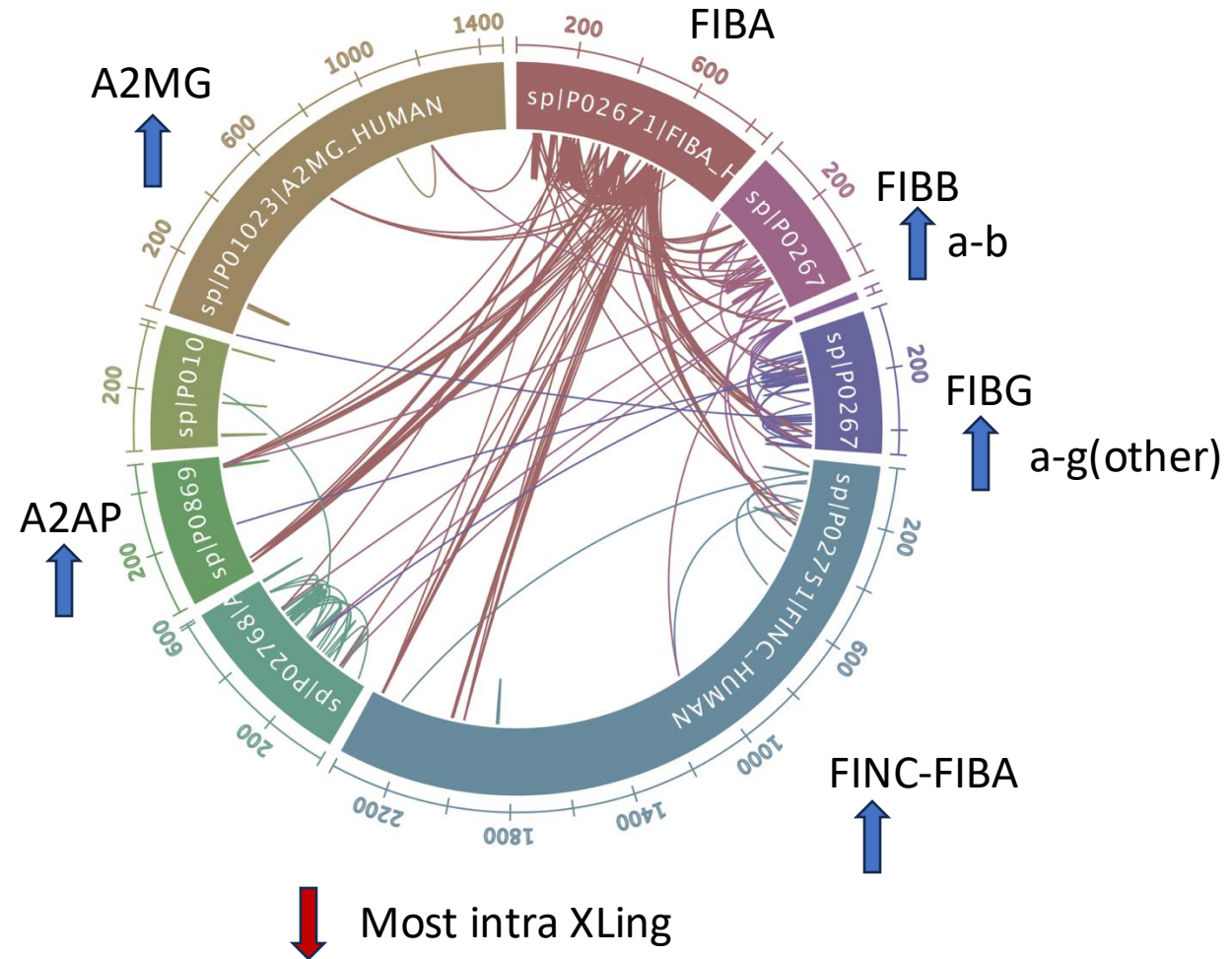
divergent patient outcomes among similarly injured patients.

Fibrin crosslink profiles in Truama

Healthy volunteers N=10



Trauma patients (field) N=3

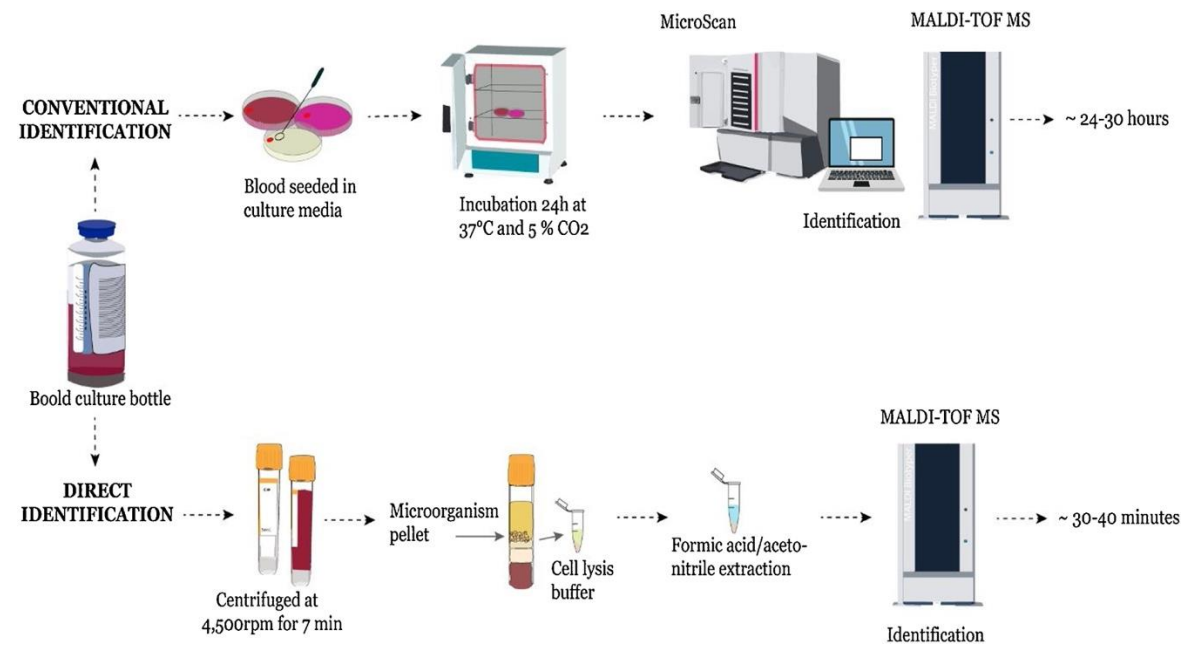


Will omic readouts make it to the trauma bay?

Barriers to clinical use of MS

- Complexity
- Cost
- Expertise required
- Robustness

Success case: clinical microbiology



Acknowledgements

- Margot DeBot
- Chris Erickson
- Monika Dzieciatkowska
- Ian Lacroix
- Lauren Schmitt

Trauma Research Team

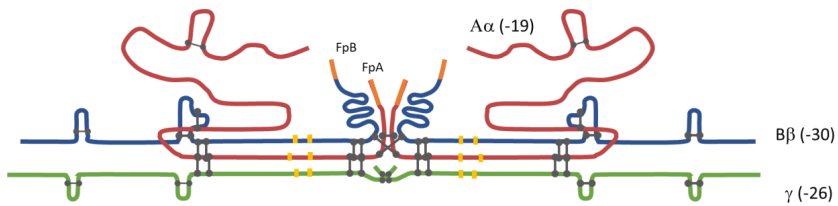
Mitch Cohen

Angelo D'Alessandro

Ernest Moore

Chris Silliman

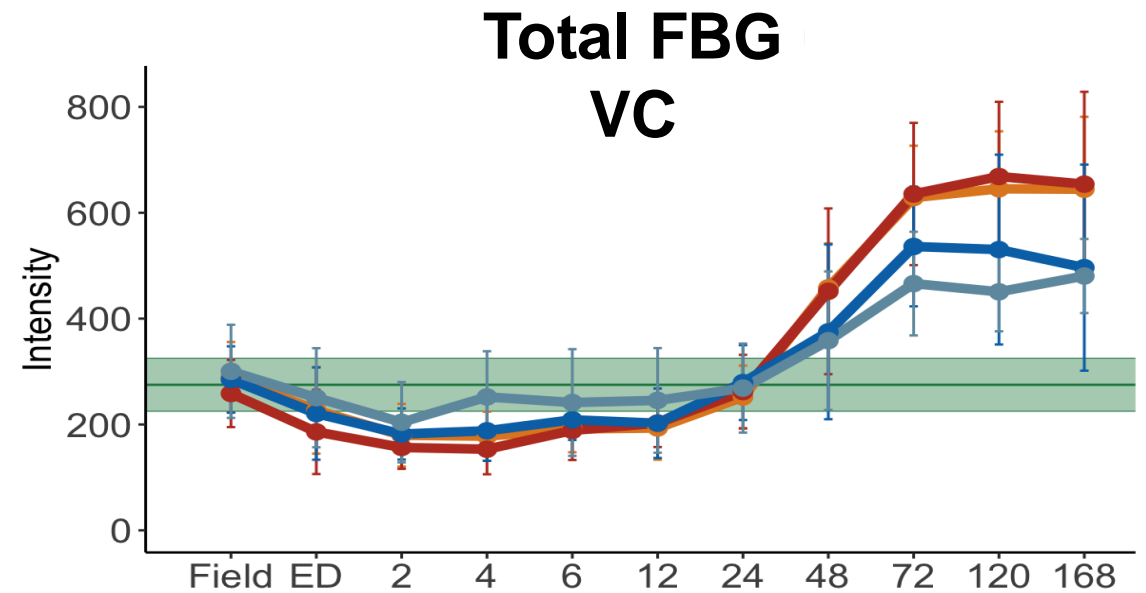
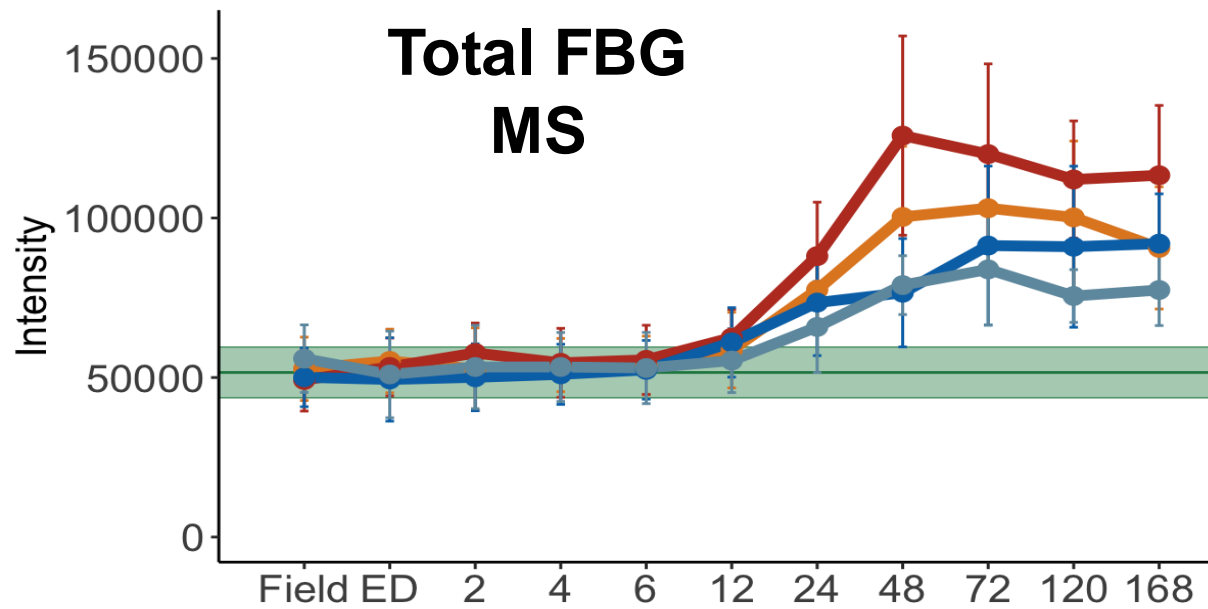




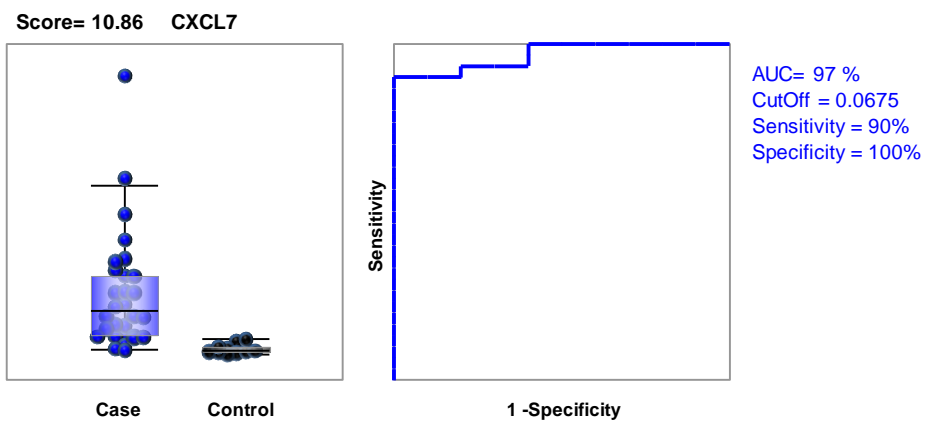
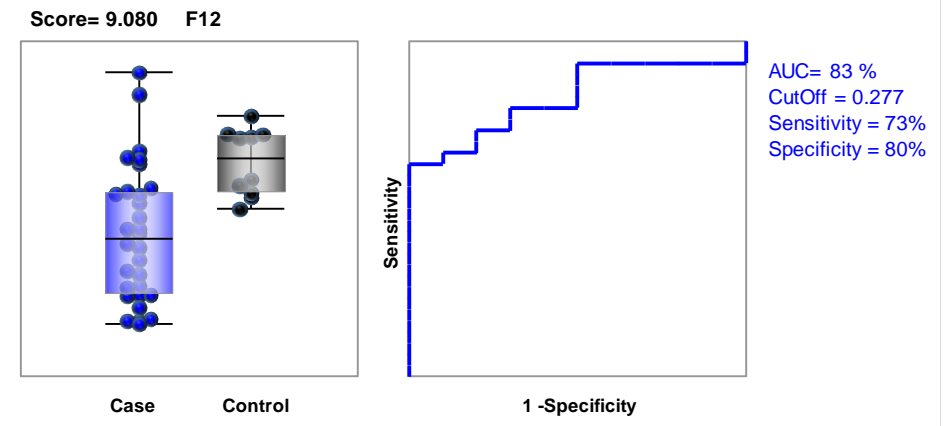
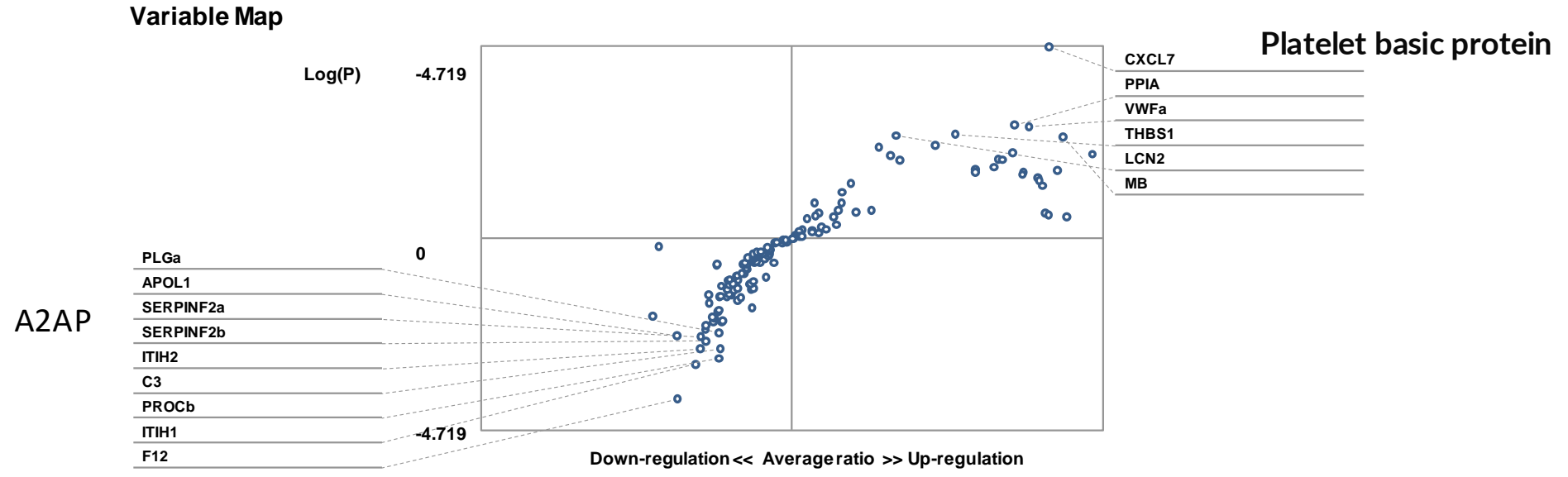
MS corr	Field	ED	2h	4h	6h	12h	24h
0.6	0	6	12	24	79	0	11
0.55	0	22	34	81	142	5	23
0.5	14	66	97	130	216	38	51
0.4	87	266	254	282	389	163	169
-0.25	18	4	15	6	7	26	61
-0.35	2	1	0	0	2	1	11
-0.4	0	0	0	0	0	0	3
-0.5	0	0	0	0	0	0	0
-0.6	0	0	0	0	0	0	0

-0.36	FIBG-89-AIQd	FIBB-54-EEA	0.65	-0.36	FIBG-89-AIQd	FIBB-54-EEA	0.65	-0.36	FIBG-89-AIQd	FIBB-54-EEA	0.65
-0.33	NLy30	FIBG-96-PDE	0.61	-0.33	NLy30	FIBG-96-PDE	0.61	-0.33	NLy30	FIBG-96-PDE	0.61
-0.28	FIBB-142-SSSox	FIBA-259-MEL	0.61	-0.28	FIBB-142-SSSox	FIBA-259-MEL	0.61	-0.28	FIBB-142-SSSox	FIBA-259-MEL	0.61
-0.28	FIBB-33-VNDd	FIBA-226-MKPd	0.6	-0.28	FIBB-33-VNDd	FIBA-226-MKPd	0.6	-0.28	FIBB-33-VNDd	FIBA-226-MKPd	0.6
-0.26	FIBA-481-EVVpox	FIBA-259-MEL	0.6	-0.26	FIBA-481-EVVpox	FIBA-259-MEL	0.6	-0.26	FIBA-481-EVVpox	FIBA-259-MEL	0.6
-0.25	FIBA-550-ESGd	FIBA-259-MELd	0.6	-0.25	FIBA-550-ESGd	FIBA-259-MELd	0.6	-0.25	FIBA-550-ESGd	FIBA-259-MELd	0.6
-0.24	FIBG-339-STWdox	FIBA-256-QMRd2ox	0.6	-0.24	FIBG-339-STWdox	FIBA-256-QMRd2ox	0.6	-0.24	FIBG-339-STWdox	FIBA-256-QMRd2ox	0.6
-0.23	NISS	FIBA-226-MKP	0.6	-0.23	NISS	FIBA-226-MKP	0.6	-0.23	NISS	FIBA-226-MKP	0.6
-0.23	FIBG-334-NGM	FIBG-259-IHL	0.59	-0.23	FIBG-334-NGM	FIBG-259-IHL	0.59	-0.23	FIBG-334-NGM	FIBG-259-IHL	0.59
-0.22	FIBG-168-TVQ	FIBG-259-IHLd	0.59	-0.22	FIBG-168-TVQ	FIBG-259-IHLd	0.59	-0.22	FIBG-168-TVQ	FIBG-259-IHLd	0.59
-0.19	FIBB-161-QVKq	FIBA-559-ESS	0.58	-0.19	FIBB-161-QVKq	FIBA-559-ESS	0.58	-0.19	FIBB-161-QVKq	FIBA-559-ESS	0.58
-0.19	FIBA-23-GEG	FIBB-212-LES	0.58	-0.19	FIBA-23-GEG	FIBB-212-LES	0.58	-0.19	FIBA-23-GEG	FIBB-212-LES	0.58
-0.18	FIBG-96-PDEd	FIBB-61-PAP	0.58	-0.18	FIBG-96-PDEd	FIBB-61-PAP	0.58	-0.18	FIBG-96-PDEd	FIBB-61-PAP	0.58
-0.18	FIBB-399-IHN	FIBB-33-VND	0.58	-0.18	FIBB-399-IHN	FIBB-33-VND	0.58	-0.18	FIBB-399-IHN	FIBB-33-VND	0.58
-0.18	FIBB-268-VYC2d	FIBG-89-AIQ	0.57	-0.18	FIBB-268-VYC2d	FIBG-89-AIQ	0.57	-0.18	FIBB-268-VYC2d	FIBG-89-AIQ	0.57
-0.18	FIBG-172-HDI	FIBB-258-QPDq	0.56	-0.18	FIBG-172-HDI	FIBB-258-QPDq	0.56	-0.18	FIBG-172-HDI	FIBB-258-QPDq	0.56
-0.18	FIBB-57-PSL	FIBA-259-MELd	0.56	-0.18	FIBB-57-PSL	FIBA-259-MELd	0.56	-0.18	FIBB-57-PSL	FIBA-259-MELd	0.56
-0.17	FIBG-140-YNS	FIBB-484-IRP	0.56	-0.17	FIBG-140-YNS	FIBB-484-IRP	0.56	-0.17	FIBG-140-YNS	FIBB-484-IRP	0.56
-0.17	FIBA-388-SES	FIBG-274-VELd	0.55	-0.17	FIBA-388-SES	FIBG-274-VELd	0.55	-0.17	FIBA-388-SES	FIBG-274-VELd	0.55
-0.17	FIBA-347-QNPp	FIBB-53-REE	0.55	-0.17	FIBA-347-QNPp	FIBB-53-REE	0.55	-0.17	FIBA-347-QNPp	FIBB-53-REE	0.55
-0.17	FIBB-33-VNDd	FIBB-258-QPD	0.55	-0.17	FIBB-33-VNDd	FIBB-258-QPD	0.55	-0.17	FIBB-33-VNDd	FIBB-258-QPD	0.55
-0.16	FIBB-54-EEA	FIBA-511-HRH	0.55	-0.16	FIBB-54-EEA	FIBA-511-HRH	0.55	-0.16	FIBB-54-EEA	FIBA-511-HRH	0.55

Time course by Injury and shock grouping

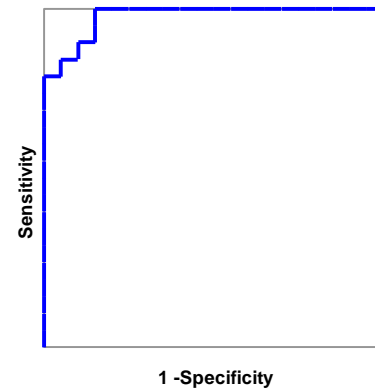
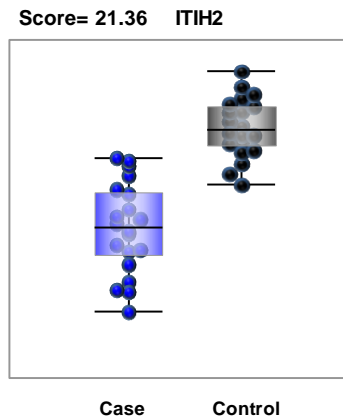
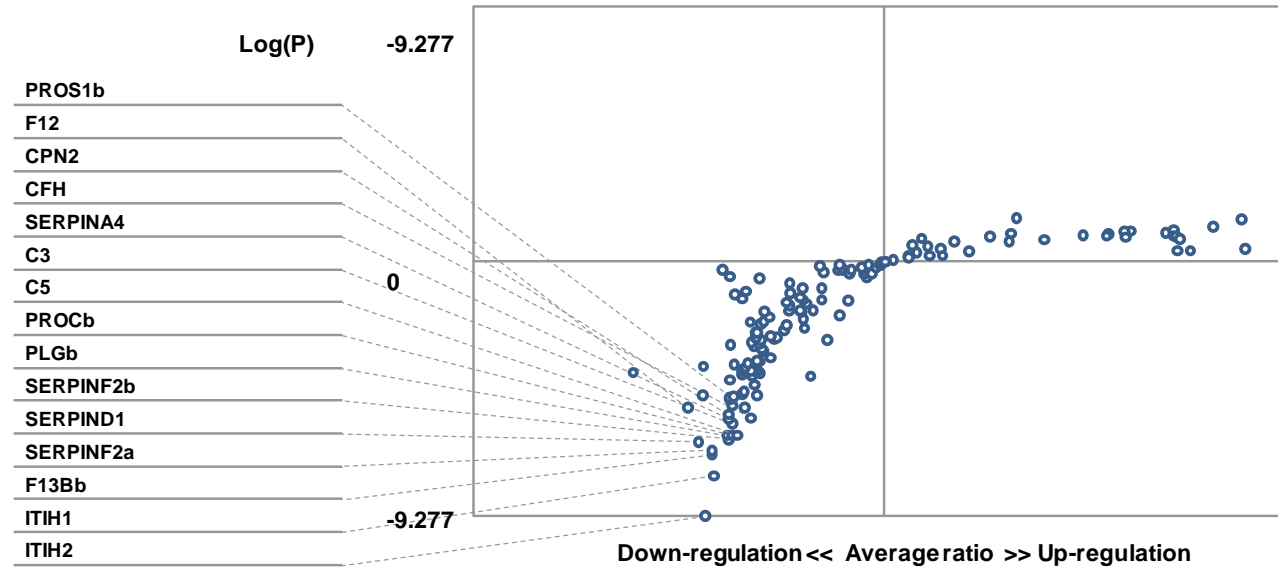


Trauma vs Control (HF, NF, SD vs HC)

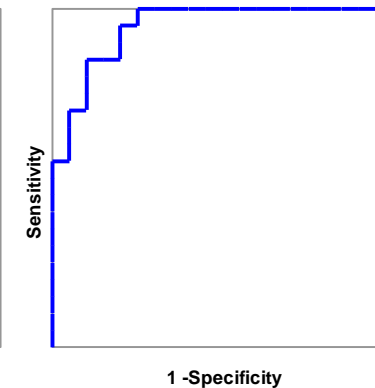
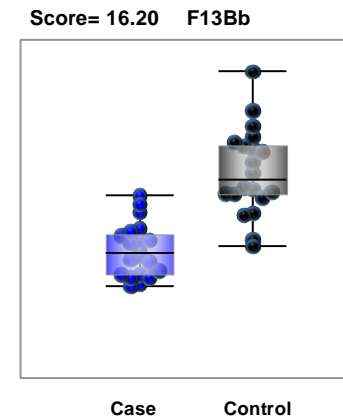


Coagulopathic vs Normal* (SD, HF vs NF, HC)

Variable Map



AUC= 98 %
CutOff = 1.51
Sensitivity = 90%
Specificity = 90%



AUC= 95 %
CutOff = 0.263
Sensitivity = 85%
Specificity = 90%

FpB 31-44 (1-14)

(MKRMVSWSFH KLKTMKHL LLLCVFLVKS)QGVNDNEEGFFSAR

FBB 3-14

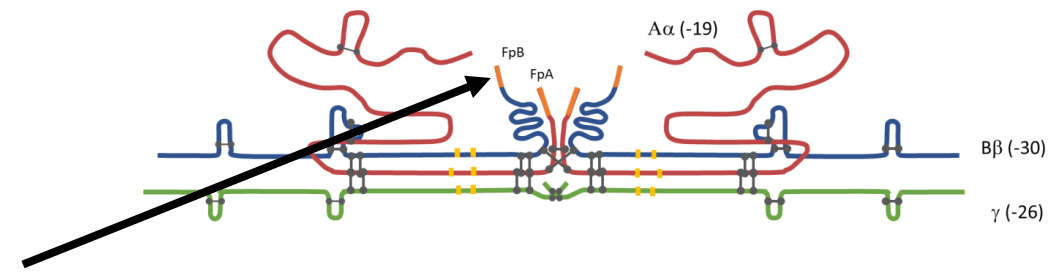
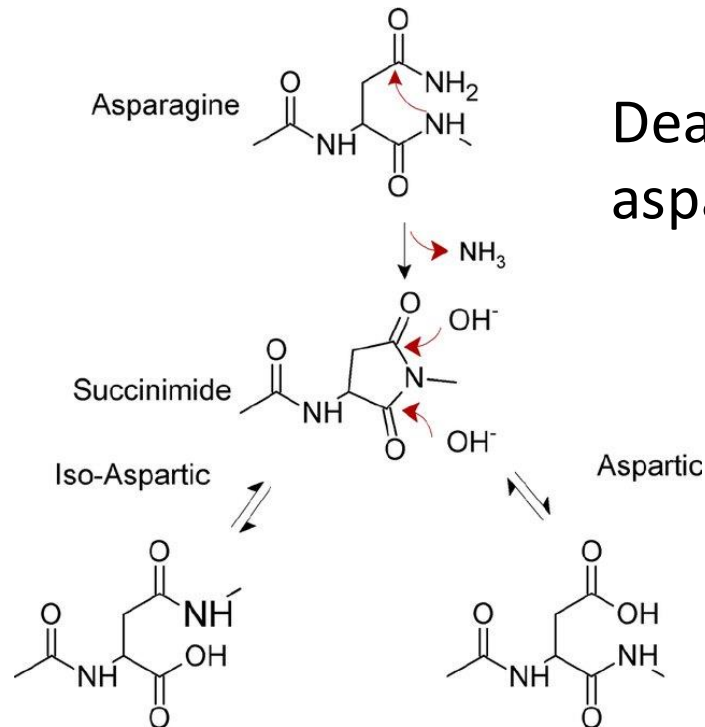
		Field	ED	4h	6h	12h	24h
VNDNEEGFFSAR	FIBB-33-VND2	0.32	0.58	0.37	0.69	0.37	0.40
VnDnEEGFFSAR	FIBB-33-VND2d2	-0.06	0.12	0.15	0.20	0.09	0.01
VnDNEEGFFSAR	FIBB-33-VNDd2	-0.05	-0.17	0.20	0.04	-0.13	0.07
VNDnEEGFFSAR	FIBB-33-VNDd2	-0.02	-0.28	-0.24	-0.04	-0.23	0.10

FBB 3-14

N95D (N69D)

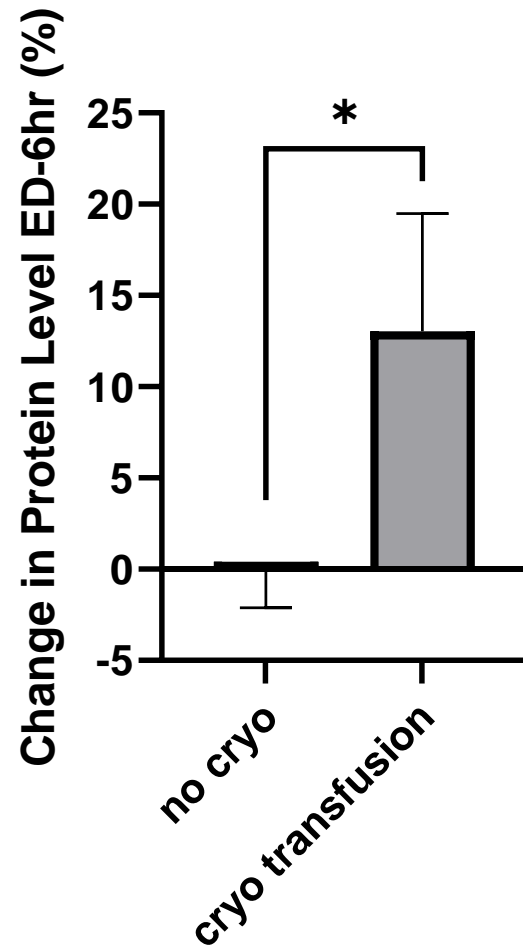
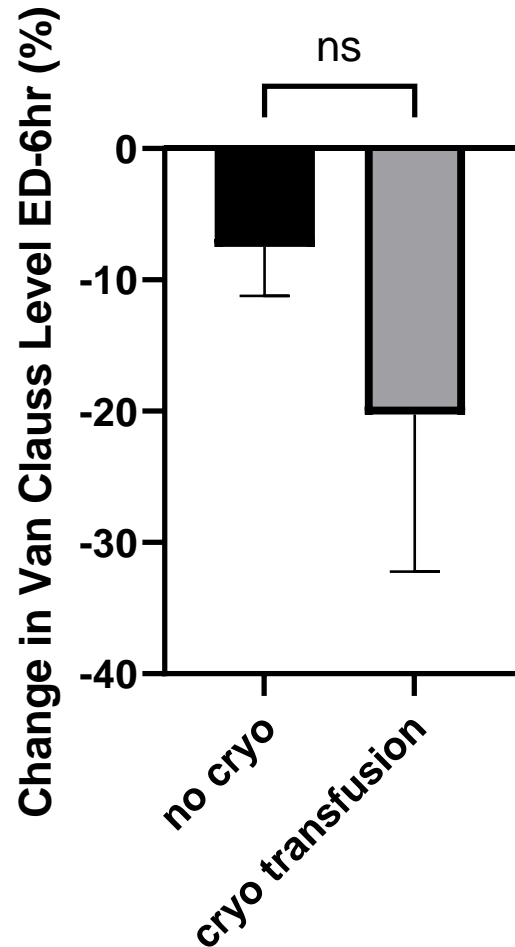
N103D (N77D)

M104m (M78m)

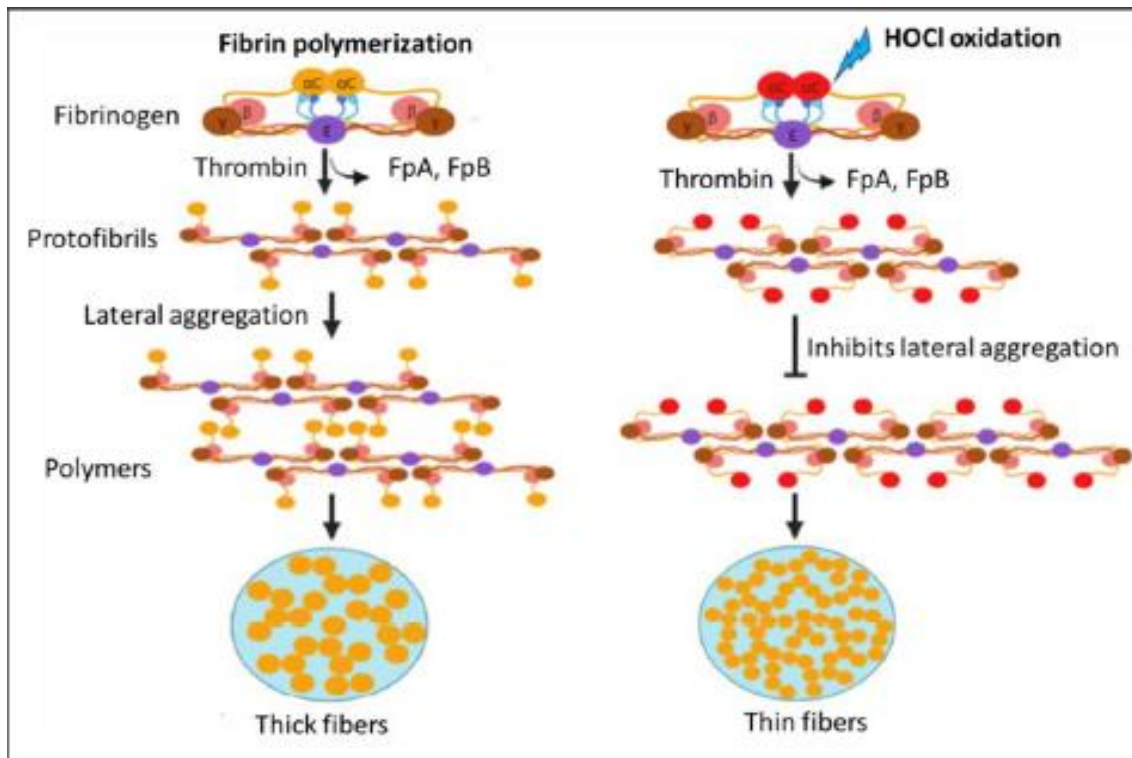


-0.36	FIBG-89-AIQd	FIBB-54-EEA	0.65
-0.33	NLy30	FIBG-96-PDE	0.61
-0.28	FIBB-142-SSSox	FIBA-259-MEL	0.61
-0.28	FIBB-33-VNDd	FIBA-226-MKPd	0.6
-0.26	FIBA-481-EVVpox	FIBA-259-MEL	0.6
-0.25	FIBA-550-ESGd	FIBA-259-MELd	0.6
-0.24	FIBG-339-STWdox	FIBA-256-QMRd2ox	0.6
-0.23	NISS	FIBA-226-MKP	0.6
-0.23	FIBG-334-NGM	FIBG-259-IHL	0.59
-0.22	FIBG-168-TVQ	FIBG-259-IHLd	0.59
-0.19	FIBB-161-QVKq	FIBA-559-ESS	0.58
-0.19	FIBA-23-GEG	FIBB-212-LES	0.58
-0.18	FIBG-96-PDEd	FIBB-61-PAP	0.58
-0.18	FIBB-399-IHN	FIBB-33-VND	0.58
-0.18	FIBB-268-VYC2d	FIBG-89-AIQ	0.57
-0.18	FIBG-172-HDI	FIBB-258-QPDq	0.56
-0.18	FIBB-57-PSL	FIBA-259-MELd	0.56
-0.17	FIBG-140-YSN	FIBB-484-IRP	0.56
-0.17	FIBA-388-SES	FIBG-274-VELd	0.55
-0.17	FIBA-347-QNPP	FIBB-53-REE	0.55
-0.17	FIBB-33-VNDd	FIBB-258-QPD	0.55
-0.16	FIBB-54-EEA	FIBA-511-HRH	0.55

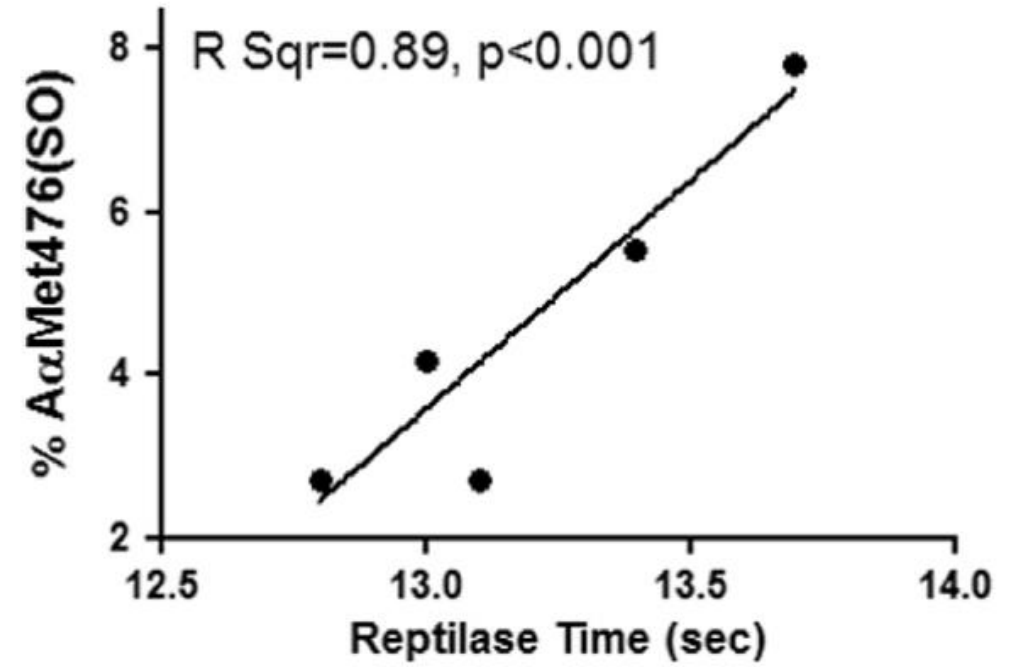
Cryo increases total fibrinogen, does not change VC



- 68 patient had Omics and VC data at both ED and 6hr
- 8/68 patients received a median of 2u cryo (range 1-8)
- No cryo no change, Cryo 13% increase (p=0.03).
- Van Clauss level decreased in both groups from the ED to 6hrs (p=0.27).
- Similar trend (not sig) with Plt, FFP



Lau, WH., White, N.J., Yeo, TW. *et al.* Tracking oxidation-induced alterations in fibrin clot formation by NMR-based methods. *Sci Rep* **11**, 15691 (2021).

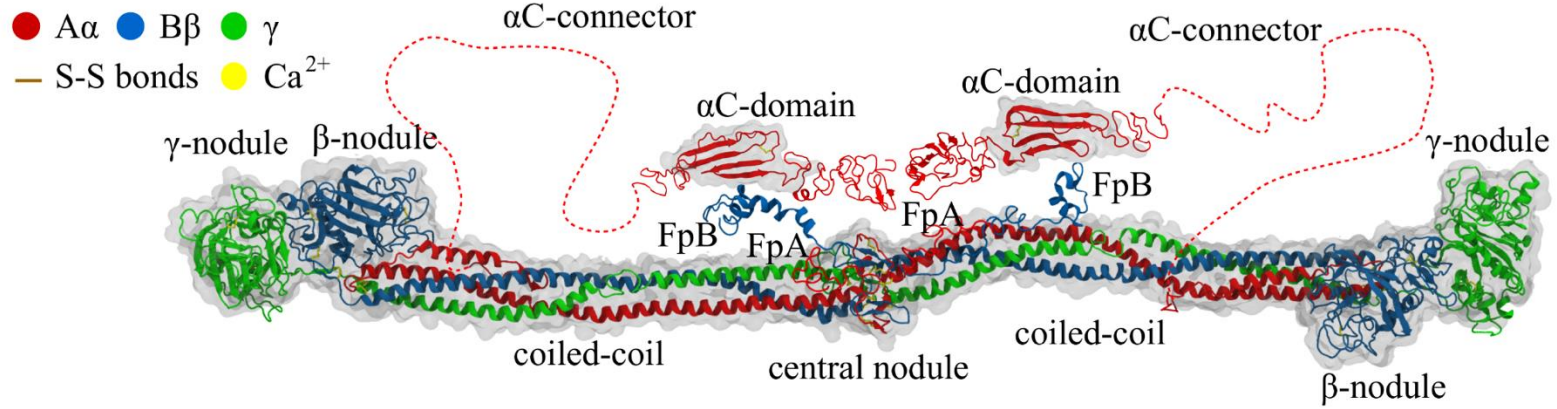


White NJ, Wang Y, Fu X, et al. Post-translational oxidative modification of fibrinogen is associated with coagulopathy after traumatic injury. *Free Radic Biol Med.* 2016;96:181-188

Fibrinogen monomer

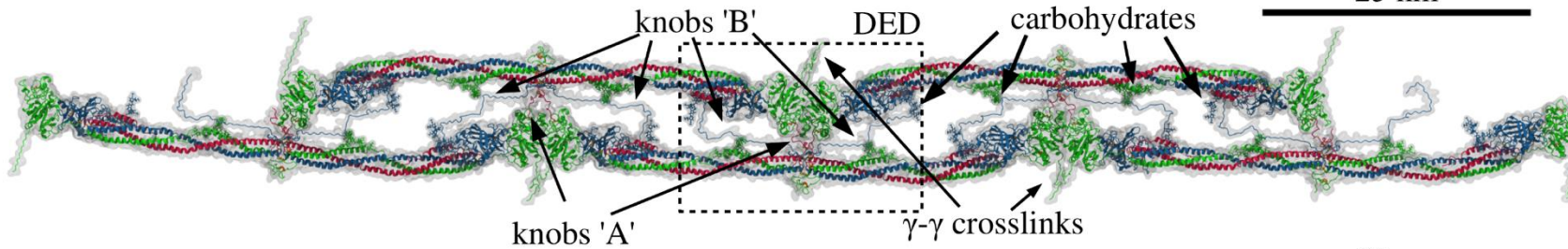
Several Fiber Models Have Been Proposed

10 nm



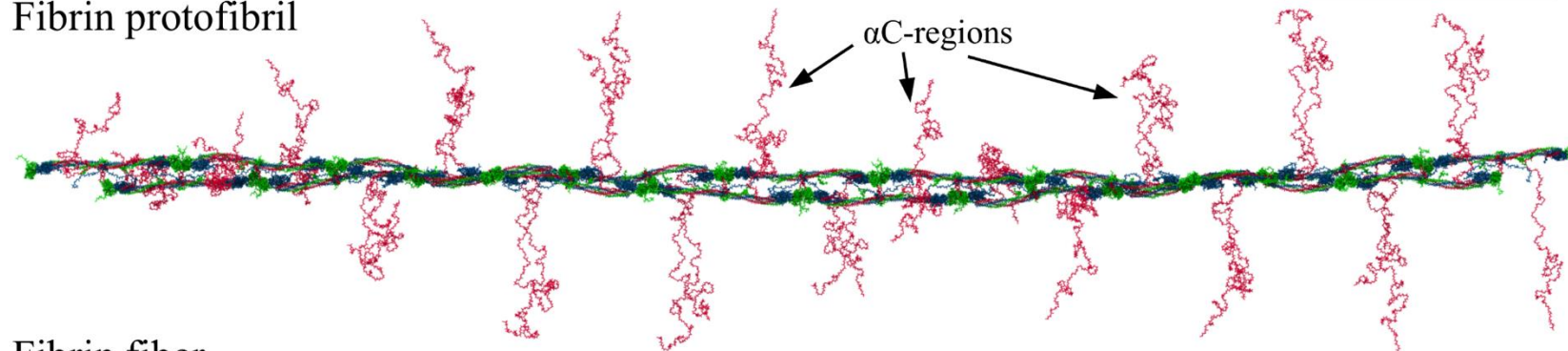
Double-stranded oligomer

25 nm



Fibrin protofibril

80 nm



Fibrin fiber

100 nm

