Endophenotypes of Traumatic Brain Injury:
Biomarkers will Guide Novel Therapies

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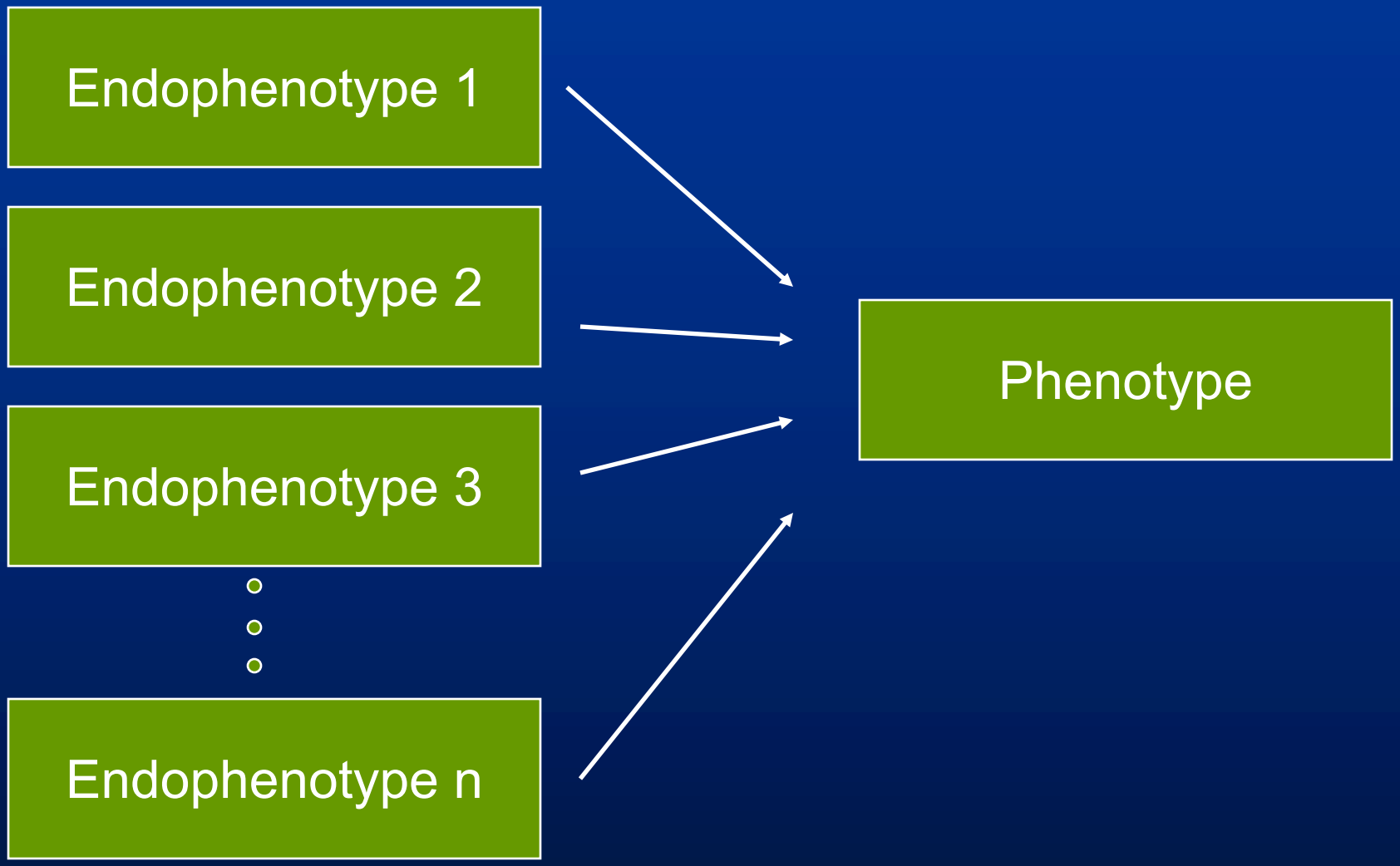
Endophenotype

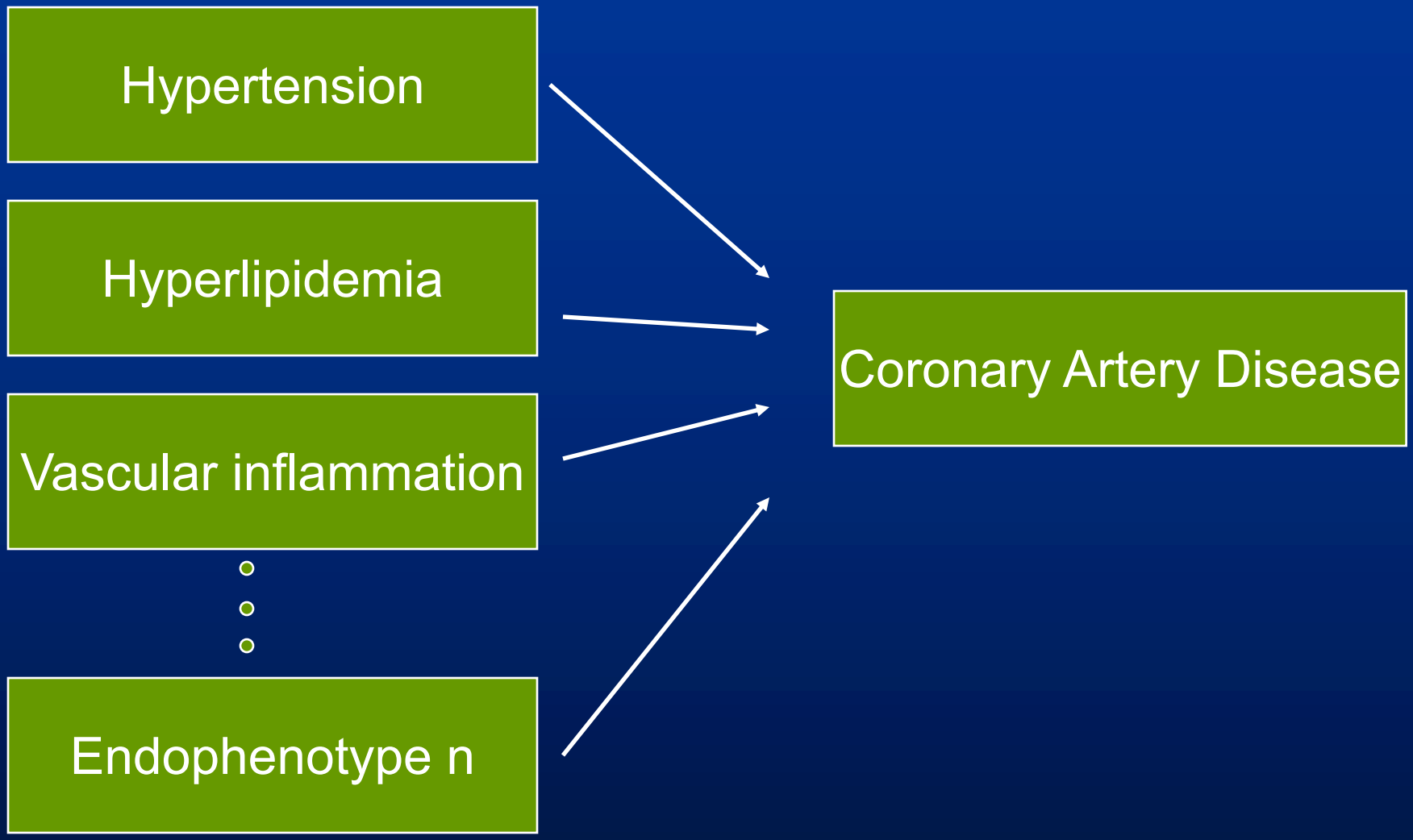
- An internal or intermediate phenotype that is closer to the underlying pathophysiology of disease (whether genetic or environmental)
- A continuous, quantitative variable (as opposed to phenotype which is usually a categorical variable)
- Measured quantitatively through physiologic, biochemical, or imaging technique.
- Synonyms: Endotype, subphenotype

Almasy & Blangero (2001) *Am J. Hum Genet* 105:42-44

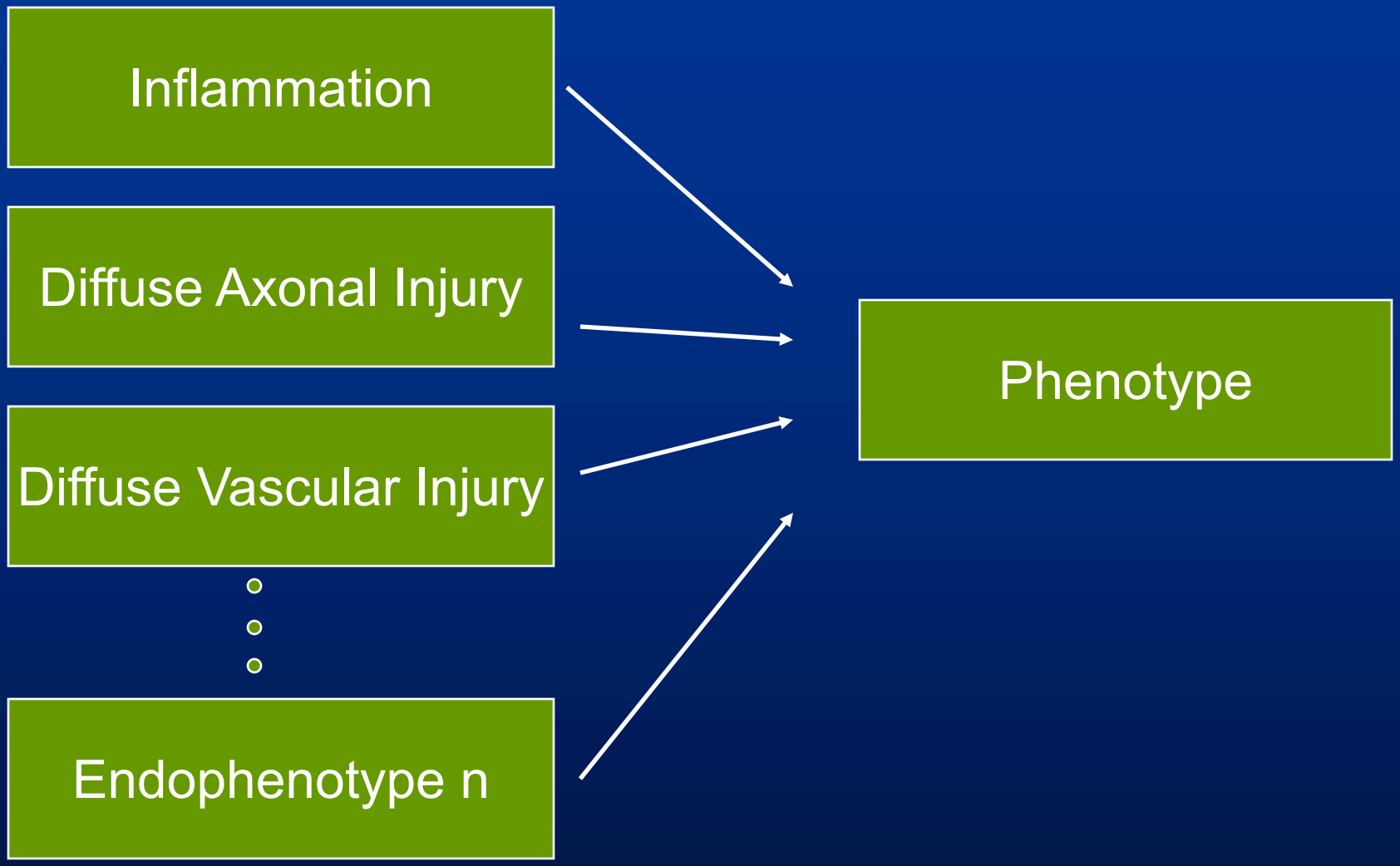
Endophenotypes



Endophenotypes of Coronary Artery Disease



Endophenotypes of TBI



Biomarkers in Clinical Research and Practice

- *FDA Definition:* Biomarkers are objectively measured indicators of a biologic process
  - Assessed by biochemical, radiologic, or other quantitative technique

FDA, Qualification Process for Drug Development Tools, 2010

Types of Biomarkers

- Diagnostic biomarker:
  - *Measure used to identify individuals with disease or condition of interest, or to define a subset of the disease*
- Prognostic biomarkers:
  - *Baseline measurements which categorize patients by degree of risk for disease progression, and informs about the natural history*
  - Used to select patients likely to have a problem that warrants therapy
- Predictive biomarkers:
  - *Baseline characteristics that categorize patients by their likelihood of response to a particular treatment.*
  - Used to measure the presence in the patient of the mechanism targeted by therapy
- Pharmacodynamic biomarkers:
  - *Dynamic measurements which show that biologic response has occurred in a patient after a therapeutic intervention.*
  - Used to demonstrate target engagement by therapy, and fine tune issues of dose, duration, timing of therapy

Robb et al, *JAMA* March 15, 2016 (315) :11

What do we need to know for the next generation of clinical trials?

- Biomarkers to measure endophenotypes should be developed iteratively between clinical and preclinical studies
  - *Observational studies humans*—Natural history of endophenotype in humans with TBI. Identify subset of patients likely to merit therapy
  - *Preclinical studies*—Confirm mechanistic benefit of therapy and establish pharmacodynamic relevance of biomarker
  - *Biomarker-driven Phase II clinical trials*—To establish optimal dose, timing, and duration of therapy

Outline

- Uses for biomarkers
  - Purposes
  - Context of use
- Biomarkers of Axonal Injury
- Biomarkers of Vascular Injury
- Biomarkers of Neuroinflammation

Clinical Needs: Pre-hospital

- Scene of accident; sidelines of sports event; combat setting
  - Inform decision to transfer to ED for medical evaluation
  - Inform decision to bypass nearest ED in favor of a neurosurgical specialty facility
- Need high sensitivity / moderate specificity
- Must be detectable in blood or other biologic fluid within minutes
- Impact:
  - Improve utilization of ED services
  - Accelerate transfer to specialized neurosurgical centers when such care needed

Clinical Needs: Emergency Department

- Identify patients in need of cranial CT
  - Excessive number of normal cranial CTs performed
- Identify subset of patients who may benefit from cranial MRI
- Inform counseling at ED discharge
  - Identify patients likely to develop PCS
- Select patients for clinical trials of neuroprotective/neurorestorative therapies

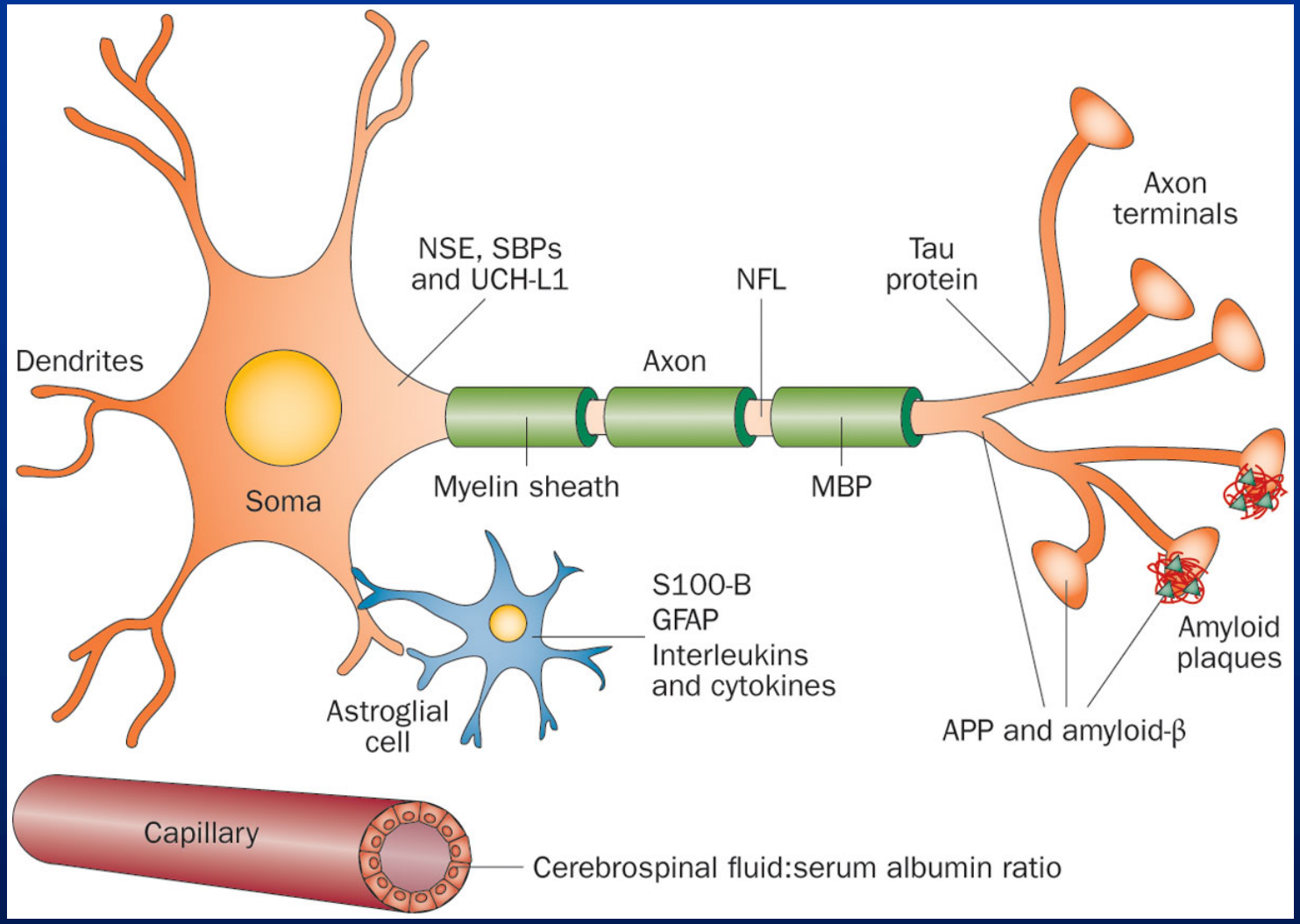
Clinical Needs: Intensive Care Unit

- Identify patients at risk for secondary neural injury
  - Ischemia
  - Intracranial hypertension
  - Inflammation
- Select patients for clinical trials of neuroprotective/neurorestorative therapies
- Inform decisions regarding intensity of care and benefit of rehabilitation services

Clinical Needs: Rehabilitation Unit and Chronic Care

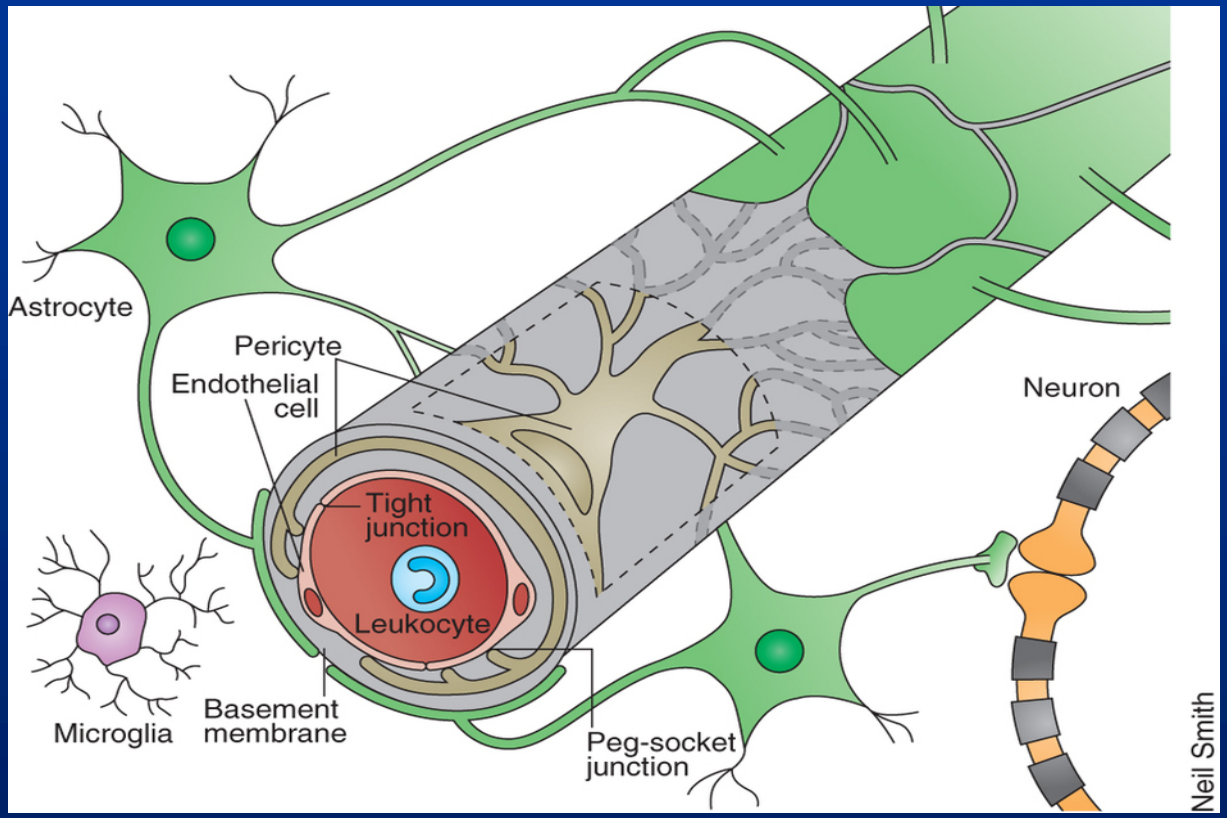
- Identify patients at risk for late complications of TBI
  - Post-traumatic epilepsy
  - Post-traumatic dementia / Chronic Traumatic Encephalopathy
- Identify mechanisms of post-TBI comorbidities
  - Post-traumatic headaches
  - Post-traumatic neuropsychiatric disorders
- Select patients for clinical trials of therapies designed to prevent late complications

Candidate biomarkers for TBI



Zetterberg et al, *Nat. Rev. Neurol*. 2013

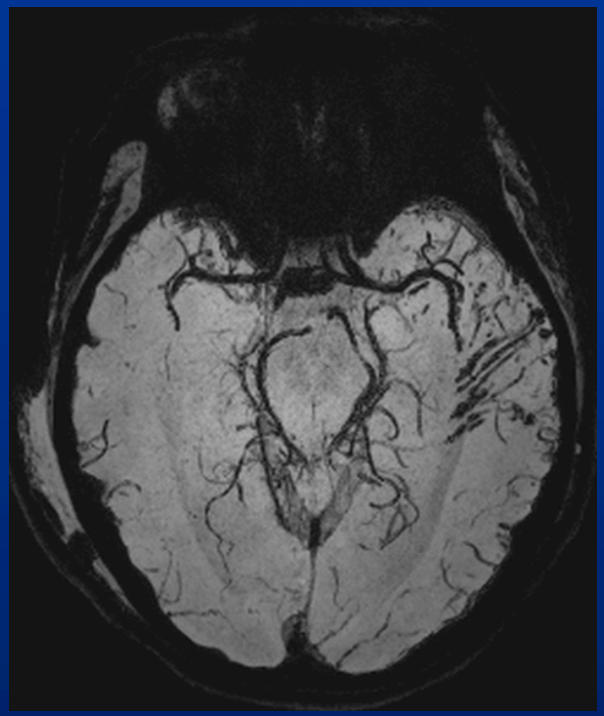
Blood Brain Barrier and Neurovascular Unit

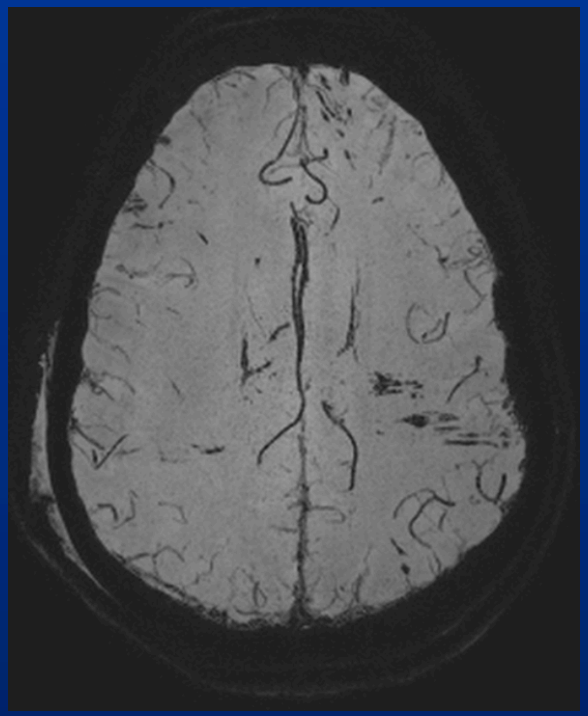


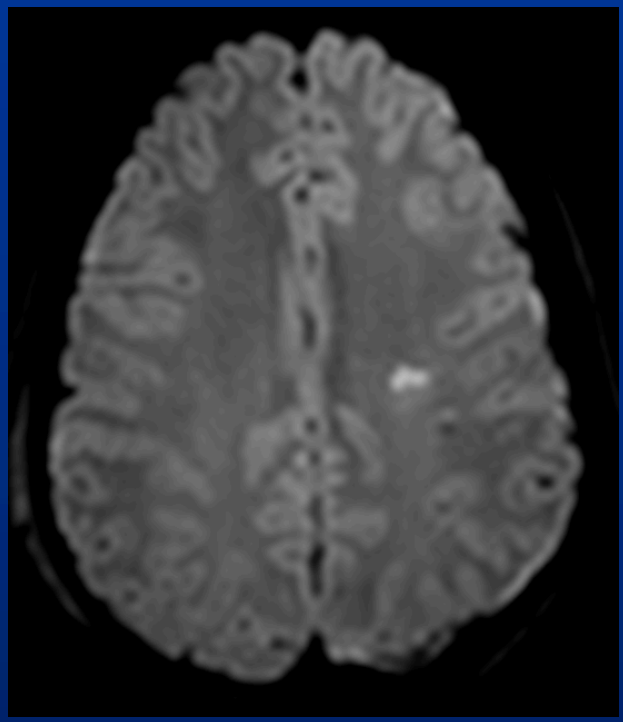
- Endothelial cells and Pericytes are components of BBB
- Neurofilaments maintain integrity of axons and dendrites

Obermeier Nat Medicine 19 1584–1596 (2013))

MRI of Diffuse Vascular Injury after TBI

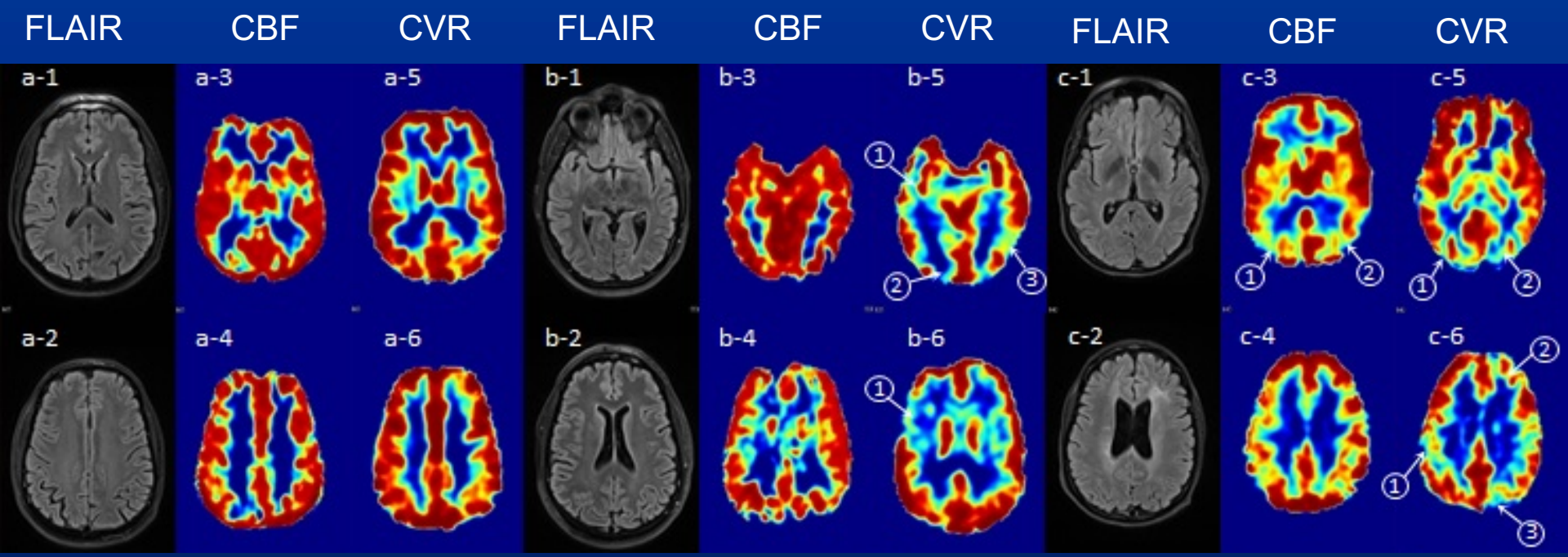






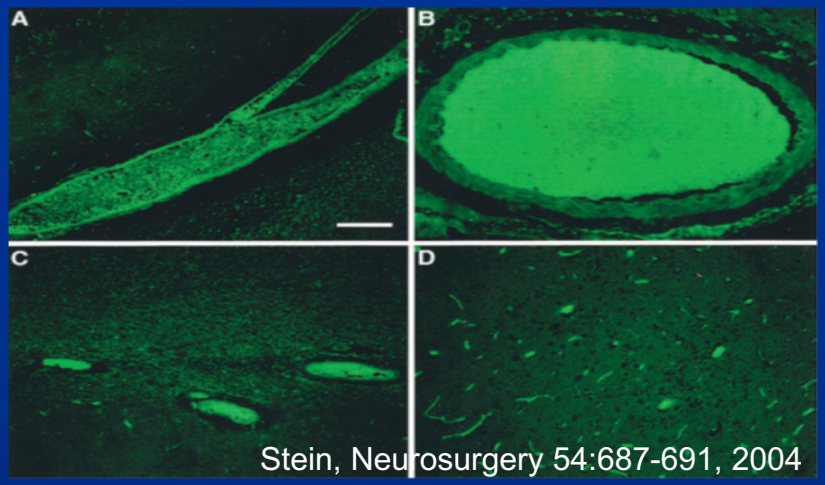
Courtesy of Larry Latour, PhD, NINDS/CNRM

Assessment of CBF (ASL) and CVR (hypercapnia-BOLD)



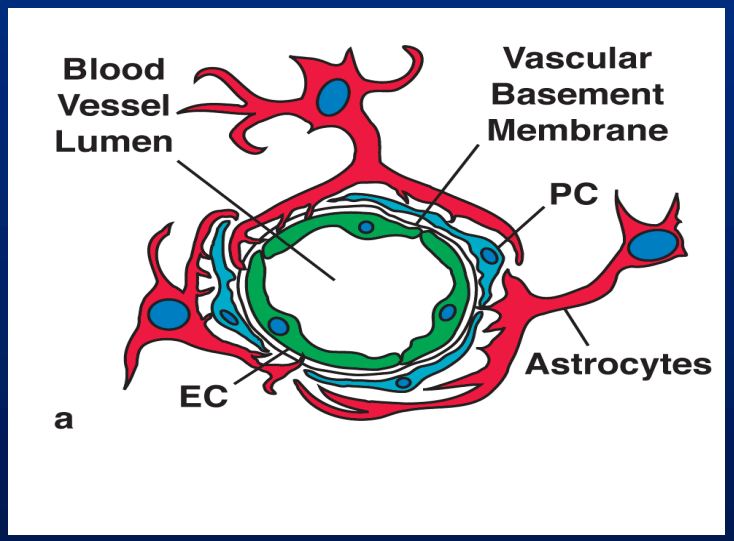
Amyot et al, *J Neurotrauma* 2017

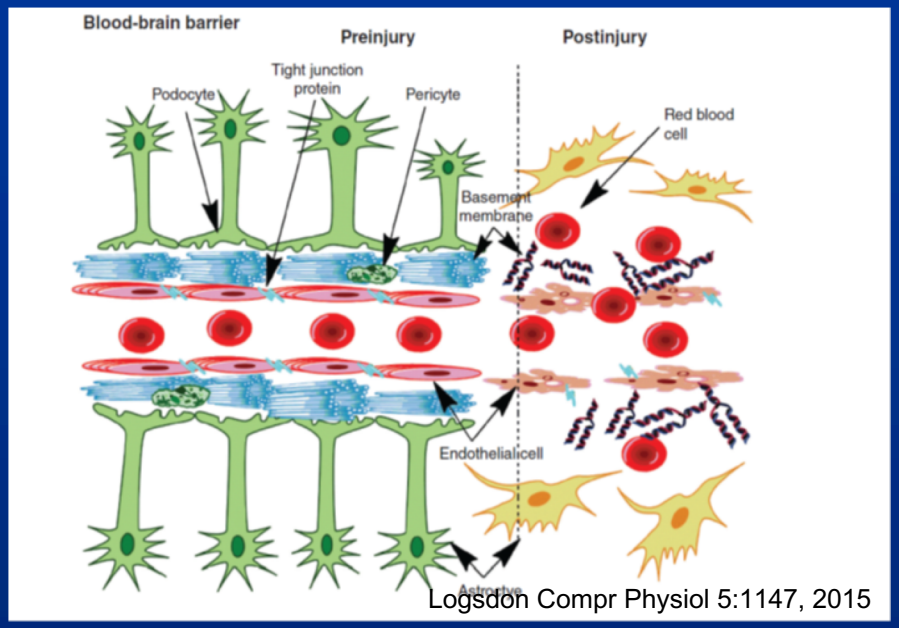
von Willebrand factor and Cellular Fibronectin are candidate biomarkers of endothelial injury



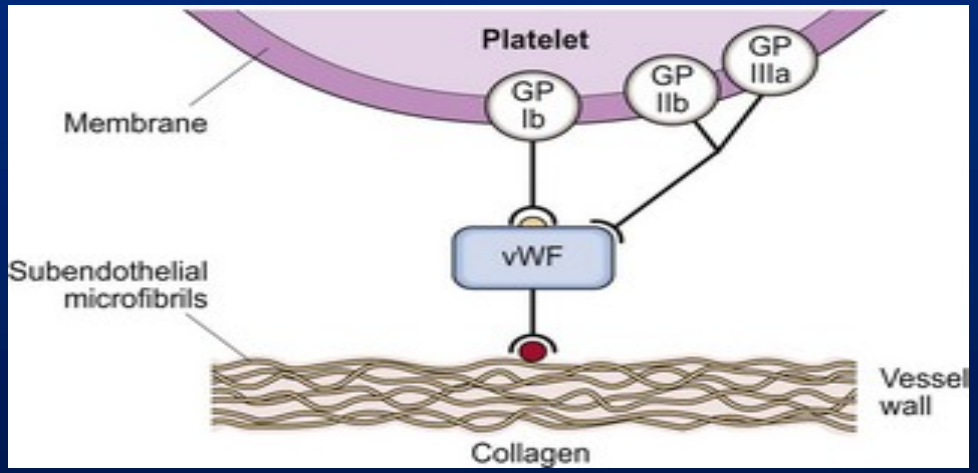
Stein, Neurosurgery 54:687-691, 2004

Diffuse microthrombosis after TBI



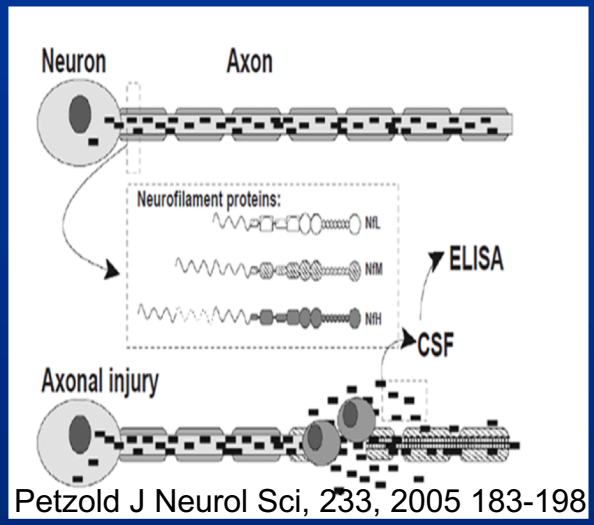


Logsdon Compr Physiol 5:1147, 2015

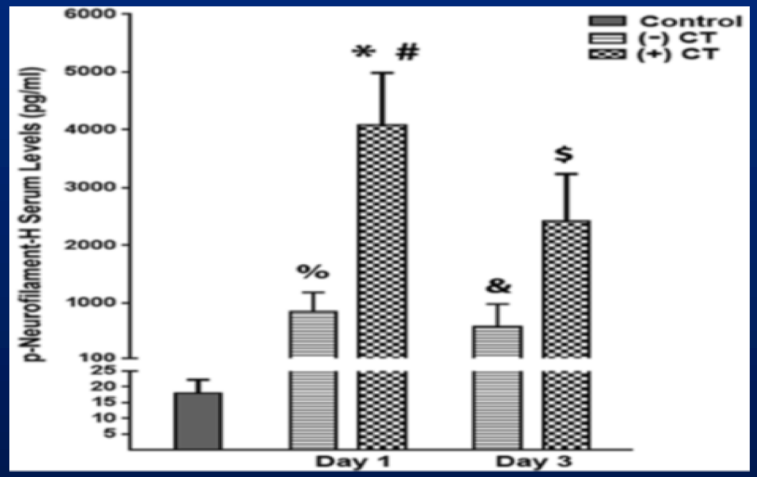


pNF–H is a candidate biomarker of axonal injury after TBI

NF proteins are component of axonal cytoskeleton and are shed into extracelluar space after injury



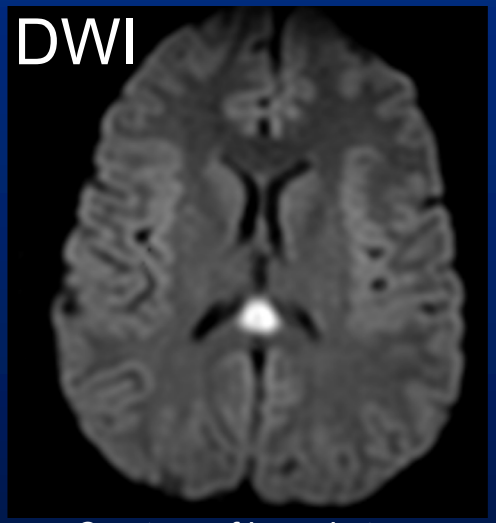
Petzold J Neurol Sci, 233, 2005 183-198



Gatson J Neurosurg 121:1232–1238, 2014

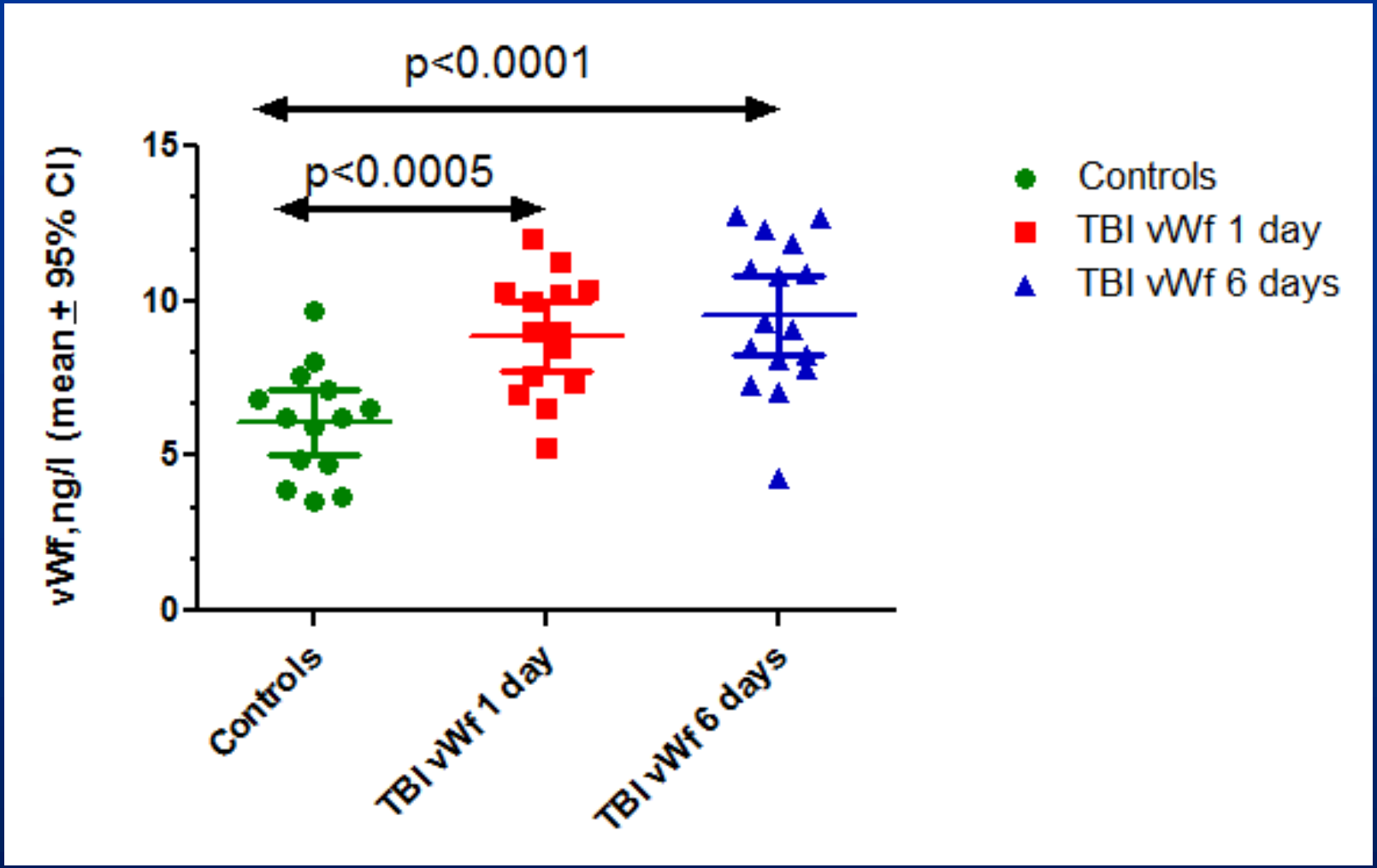
Axonal injury is universal in severe TBI, and also common in mTBI

Nat. Rev. Neurol. 10, 156–166 (2014)



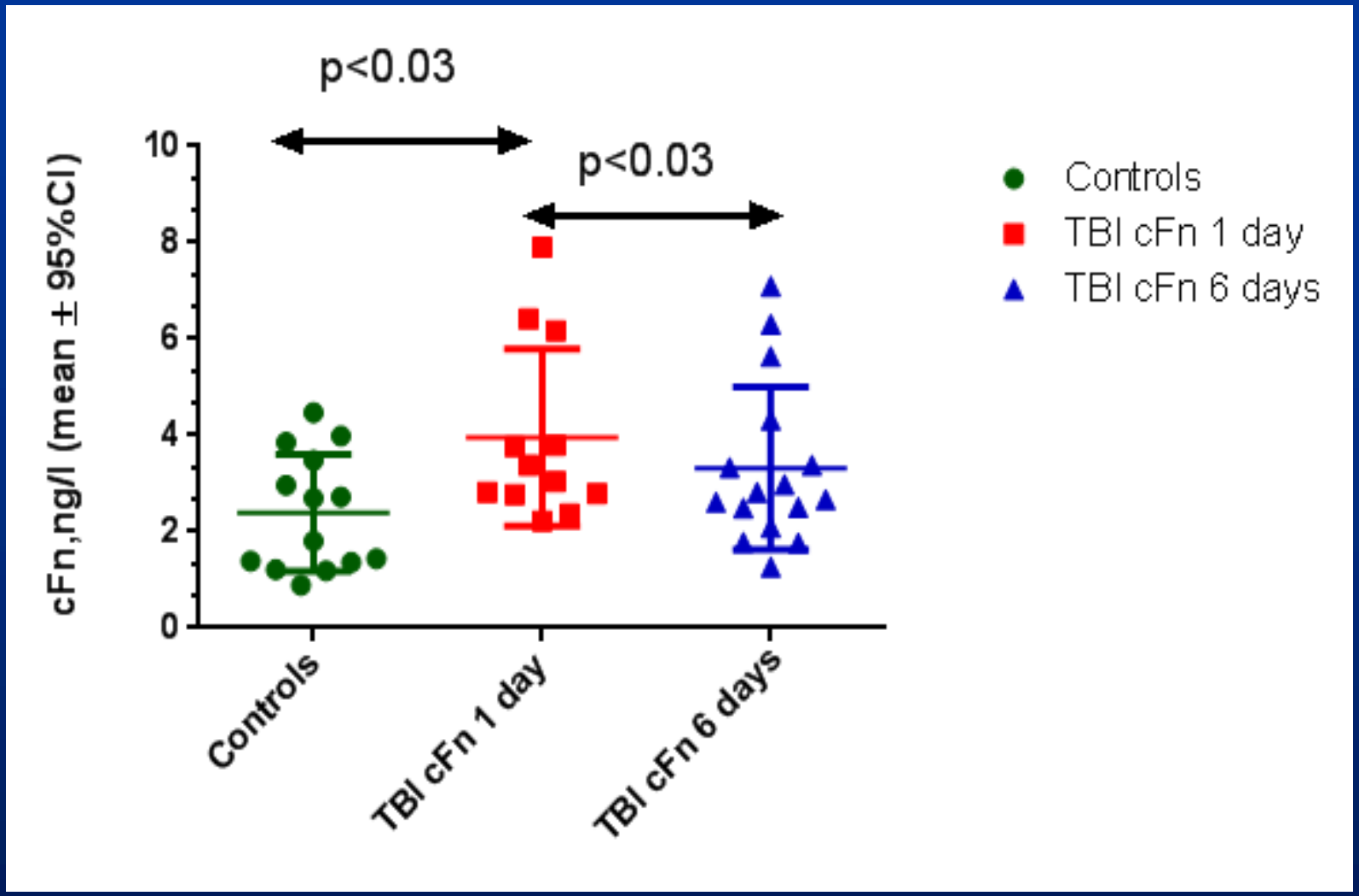
Courtesy of Larry Latour

Plasma vWF in Traumatic Vascular Injury



Bogoslovsky et al, Under Review

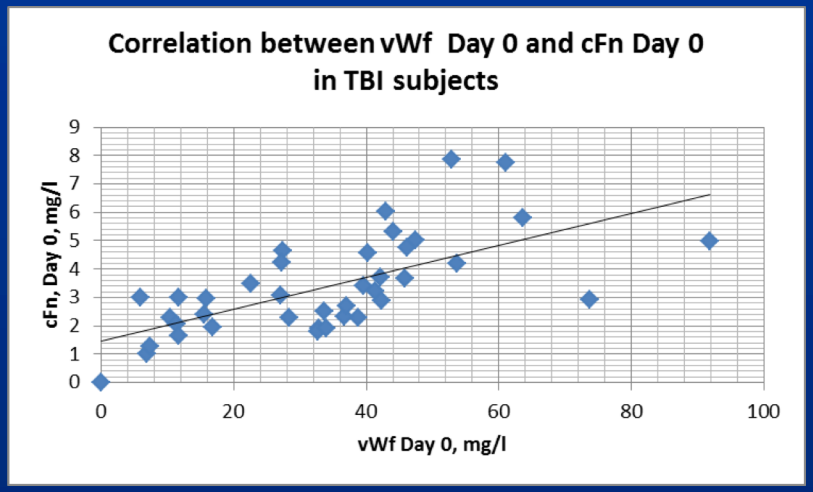
Plasma cFn in Traumatic Vascular Injury



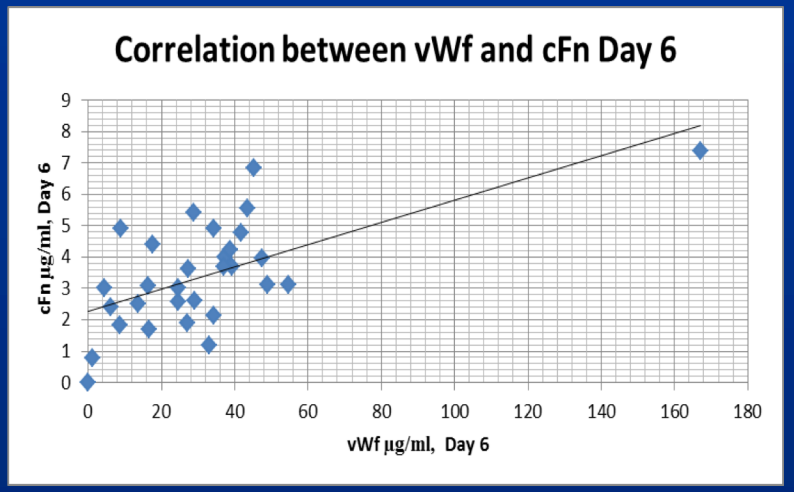
Bogoslovsky et al, Under Review

vWF and cFN are moderately correlated

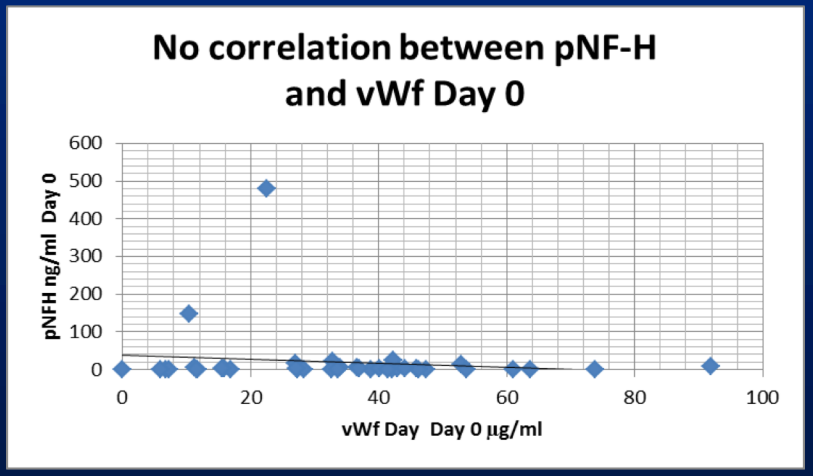
pNF-H is not correlated to either vascular injury biomarker

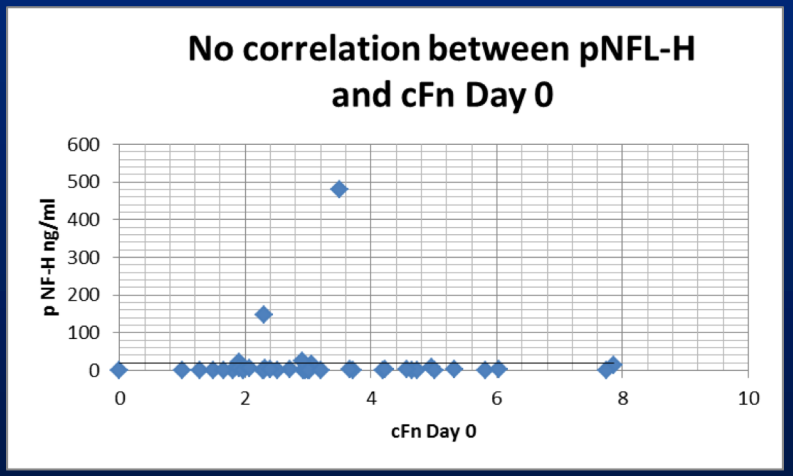


Spearman r = 0.496, p=0.0085



Spearman r = 0.566, p=0.001



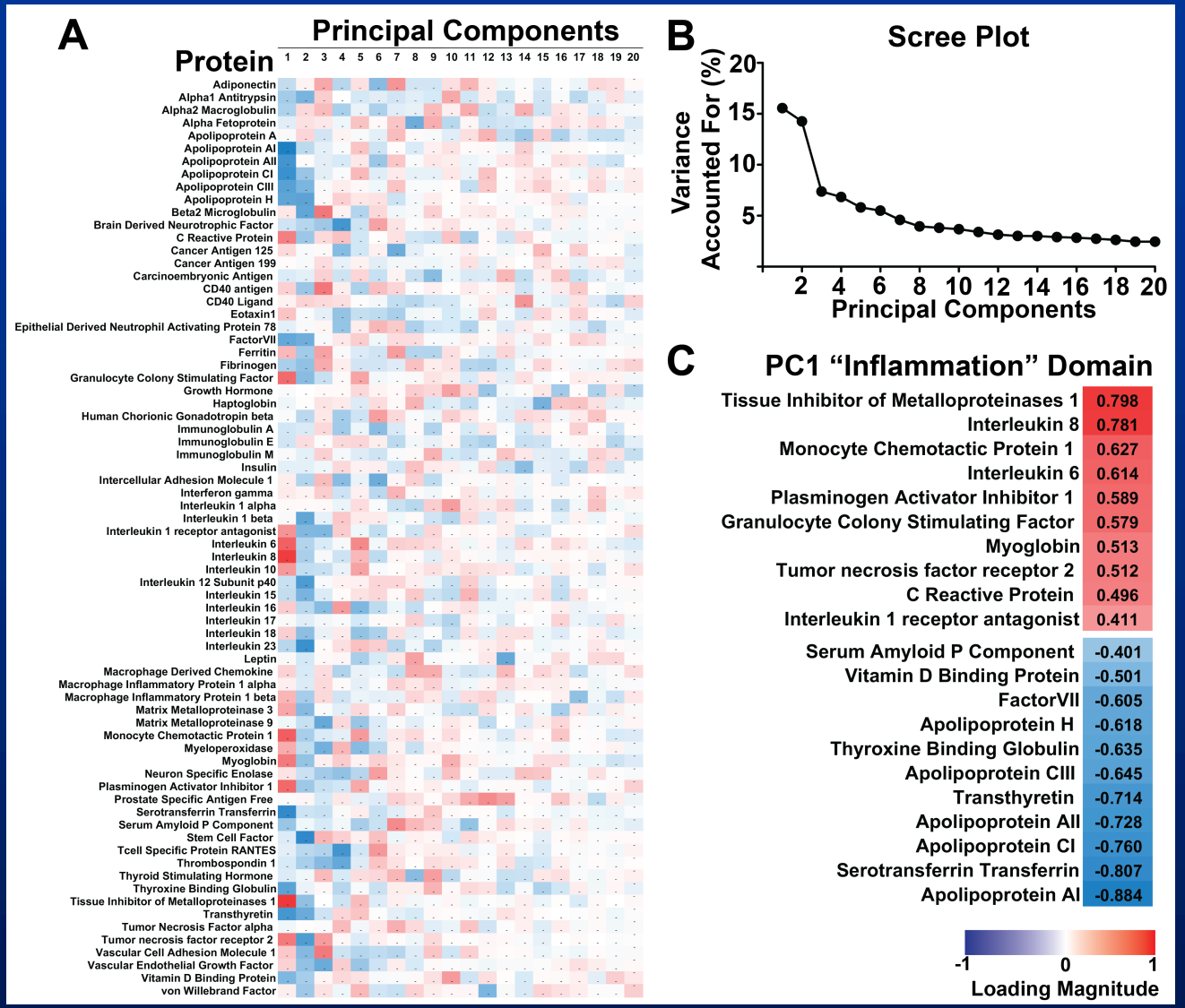


Addition of vWf, cFn and pNF-H improves prediction of outcome over MRI, Age, Gender and Arrival GCS

Model for prediction of 30 day GOSE	R^2 (Nagelkerke)	Significance (Hosmer and Lemeshow)	Correctly classified Poor Outcome (GOSE 1-6)	Correctly classified Good Outcome (GOSE 7-8)
Age, Gender, Arrival GCS	.102	.843	**30.0**	**88.0**
Age, Gender, Arrival GCS + MRI	.146	.709	**45.0**	**80.0**
Age, Gender, Arrival GCS + MRI + Day 0 BM	.427	.616	**58.3**	**76.5**
Age, Gender, Arrival GCS + MRI + Day 6 BM	.441	.406	**62.5**	**92.9**

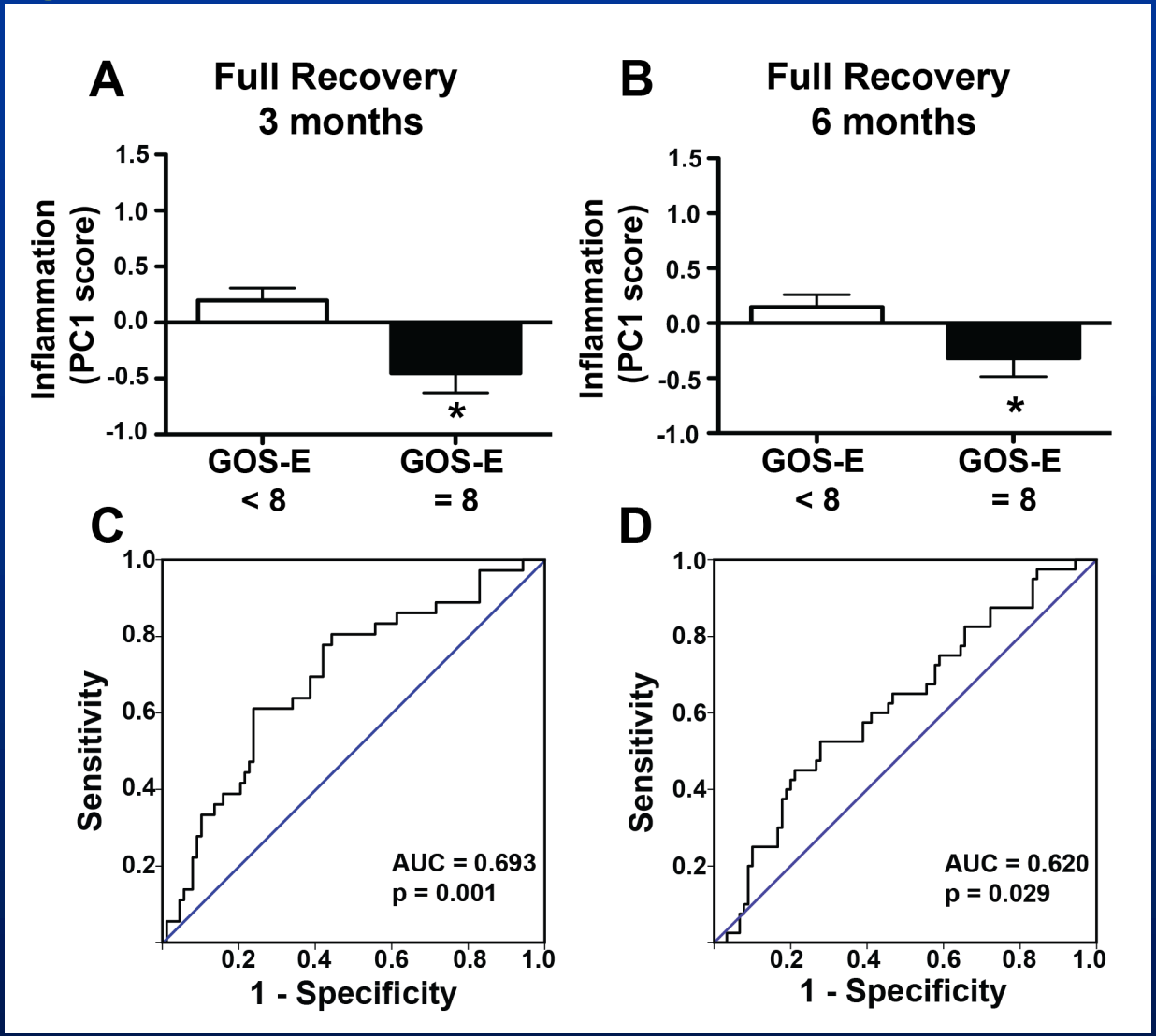
Bogoslovsky et al, Under Review

Inflammatory Biomarkers



Huie et al and TRACK-TBI Investigators, Under Review

Inflammatory Biomarkers are Prognostic for outcome after TBI



Huie et al and TRACK-TBI Investigators, Under Review

Inflammatory Cytokines as Prognostic Biomarkers

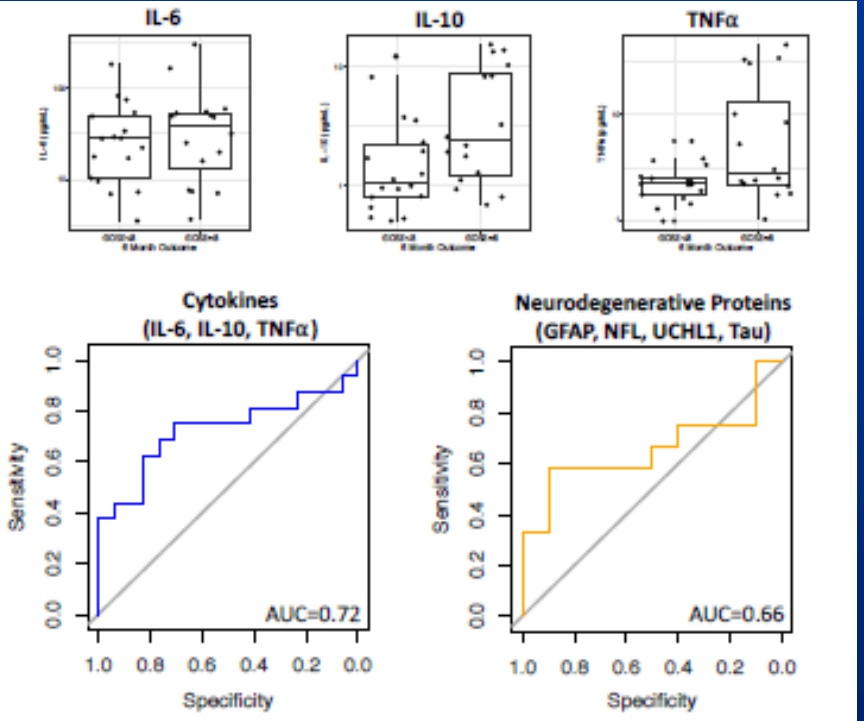


Figure 4. *ROC for cytokines and neurodegenerative proteins separately as predictors of 6 month outcome after TBI.* Logistic regression performed with all three cytokines predicted 6 month GOSE score (GOSE<8 or GOSE=8) better than logistic regression performed with all four neurodegenerative proteins for the same outcome.

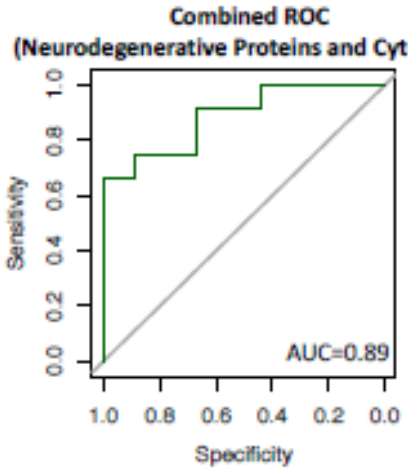


Figure 5. *ROC for neurodegenerative and inflammatory proteins combined as predictors of 6 month outcome after TBI.* The strongest predictive model for 6 month GOSE was generated by adding all four neurodegenerative proteins and all three cytokines to the logistic regression model.

Haber et al, INTS 2018

TRACK-TBI Precision Medicine Initiative

Candidate Endophenotype-directed Biomarkers

Measuring neuroinflammation

- Free water fraction
- DCE-MRI
- IL-1-β, IL-6, IL-10, TNF-α

Measuring diffuse axonal injury

- Diffusion Tensor Imaging
- Regional brain volumes
- NfL, Tau, SNTF

Measuring diffuse vascular injury

- Cerebral Blood Flow (CBF)
- Cerebrovascular Reactivity (CVR)
- vWF, cFN, PDGFR-β

TRACK-TBI Clinical Trials Network (TRACK-TBI NET)

Candidate Phase 2 acute TBI drug candidates

Targeting neuroinflammation

- IL-1 receptor antagonist
- Minocycline/NAC
- Imatinib

Targeting diffuse axonal injury

- Cyclosporine A
- Omega-3 FA
- Dronabinol

Targeting diffuse vascular injury

- Simvastatin
- Glyburide
- Losartan
- CN-105 (ApoE mimetic)

Penn TBI Clinical Research Initiative