Blood-based Neurology biomarkers: a new approach for HIE diagnosis and prognosis

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Hypoxic Ischemic Encephalopathy (HIE)

- full-term infants------HIE occurs in approximately 3-20 per 1000 live births
- preterm infants------HIE occurs in up to 60% of live births

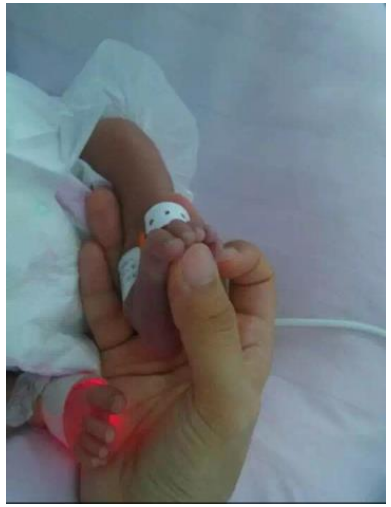
Criteria for cooling

- Clinical Evaluation:
  APGAR Score
- Physical exam
- EEG
- Laboratory Evaluation:
  Birth blood
  Umbilical cord
- Radiological Evaluation:
  Ultrasound, CT scans, MRI

Hypothermia Therapy

?

Lack of a standardized definition for mild HIE; How to accurately identify the hypothermia responder versus the non-responder?



How dose therapeutic hypothermia work?

Primary energy failure (minutes)

Hypoxia ---a shortage of oxygen in the blood
Ischemia --- a shortage of blood flow to the brain

O2
O2
O2

Immediate necrotic cell death

Failure of ATP-dependent Na+/K+ pump
Na+ overload, excitotoxicity

cooling

Secondary energy failure (hours to days)

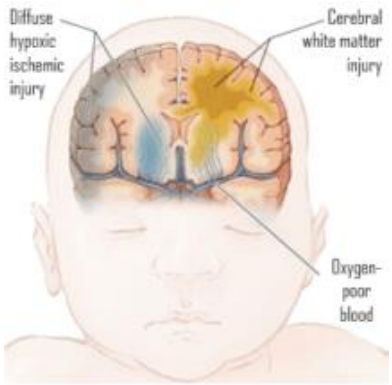
Restoration of blood flow

↓

Mitochondrial dysfunction
Caspases activation

Toxin released from damaged cells

Delated apoptotic cell death



Chronic brain injury (days to months)

↓

Cell loss, Cerebral atrophy

Astrogliosis, tissue repair remolding, inflammation

Encephalopathy

The current standard tools to predict outcome in perinatal asphyxia

Predictors of outcome	Pros	Cons
Acid-base balance	Widely available test, can be measured early by scalp and cord sampling	Cannot differentiate degree of severity of injury, invasive testing
pH	Responds early to HI	Low PPV for abnormal outcome
Lactate	Better reflects metabolic mechanism	No advantage over pH
Apgar score	Quick assessment of neonatal condition at birth, non-invasive	High inter-observer variability, poor predictor of long-term outcome
Sarnat staging system /Clinical examination	Non-invasive, good to track changes in clinical state as injury evolves, predictive at discharge	Requires clinical experience, affected by intubation and medications and hypothermia, poor predictor of long-term neurodevelopmental outcomes
Ultrasound	Bedside monitor, multiple times	Less sensitive than MRI
EEG/aEEG	early predictive value if normal, value of subclinical seizure detection, non-invasive	Requires resources, equipment to apply, clinical expertise to interpret, hypothermia itself affect the results
MRI/MRS	Specific patterns of injury aid prognosis, early changes apparent	Requires transfer of sick infant to MRI machine/department, requires infant to remain still for prolonged periods

CE Ahearne, et al. World J clin Pediatr. 2016 Feb 8; 5(1): 67–74

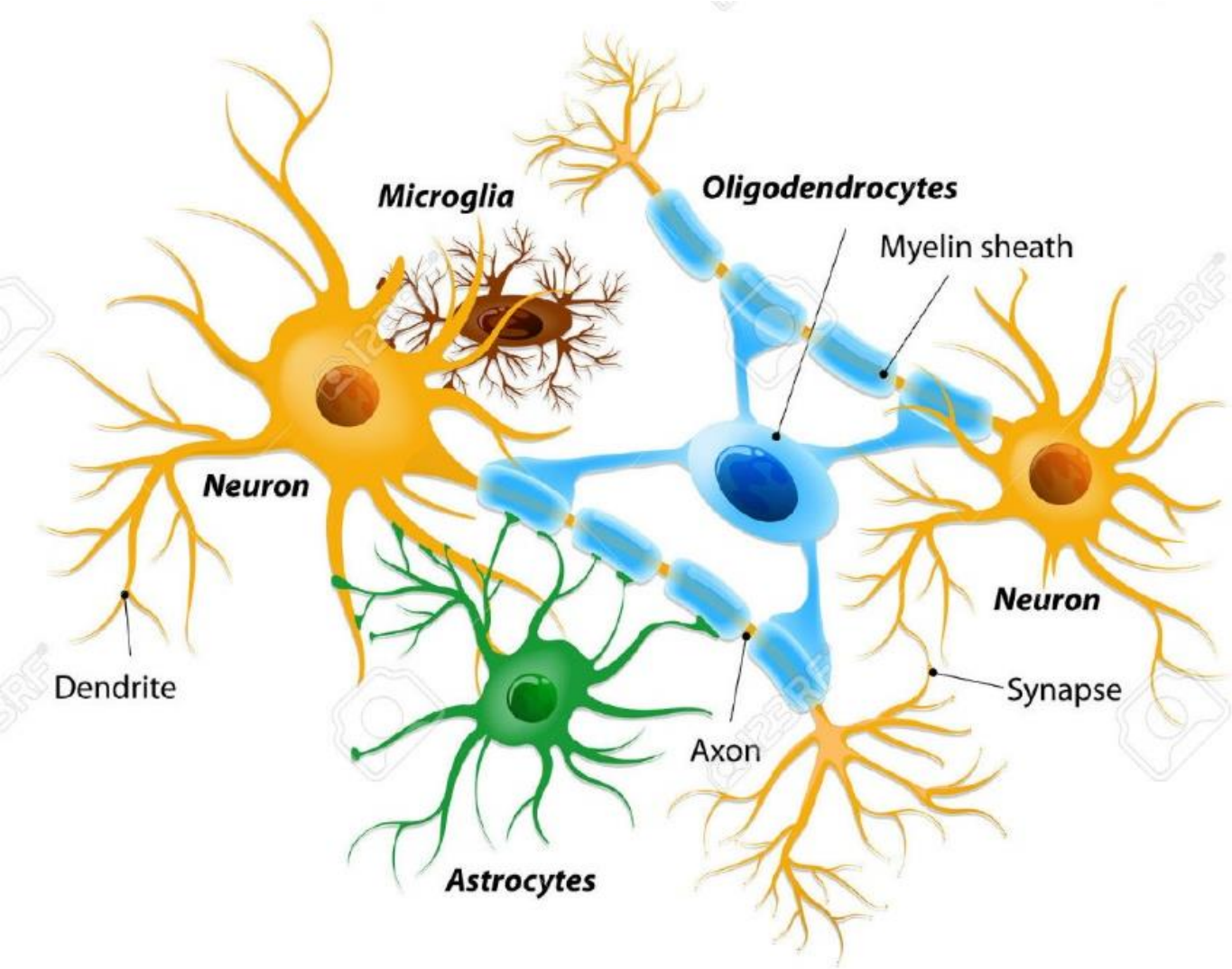
The novel emerging techniques to predict outcome in perinatal asphyxia

Predictors of outcome	Pros	Cons
HRV	Differentiates severity of HIE, non-invasive	Requires specialist equipment
Biomarkers	**Very promising in pilot studies**	**None validated for clinical use**
Serum	Reflects systemic biochemical state	Mixed markers from cerebral and other organ dysfunction, only small volumes available, invasive testing
Cord blood	Large volumes possible, available early	Mixture of fetal and placental blood
CSF	Reflects cerebral markers	Very difficult to sample
Urine	Relatively easy to sample	Affected if significant renal disease
Proteomics	Relatively stable and easy to test	Requires specialist equipment, response to injury may be delayed
Metabolomics	Rapidly responsive to changes in biochemical state	Requires specialist equipment, highly sensitive to environmental factors
Transcriptomics	Involved in critical processes of cell cycle and cell death, very stable	Requires specialist equipment, most markers are completely novel and difficult to identify, they may also regulate multiple pathways

CE Ahearne, et al. World J clin Pediatr. 2016 Feb 8; 5(1): 67–74

Major brain cell types and subcellular structures

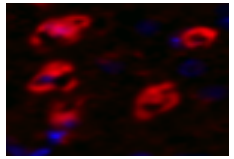
- **Neurons**
  - Cell body
  - Axons
  - Dendrites
  - Synaptic terminals
- **Astrocytes**
  - Glial intermediate filament
- **Oligodendrocytes**
  - Myelin sheath
- **Microglia cells**



https://www.sciencenewsforstudents.org/blog/scientists-say/scientists-say-glia

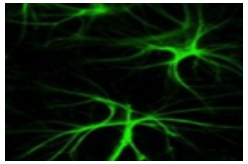
Major brain injury protein biomarkers linked to different pathophysiologic processes

UCH-L1



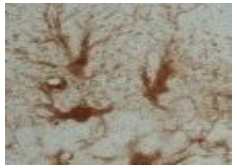
Cell body injury

GFAP & BDP



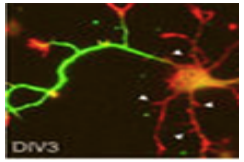
Gliosis/Glial Injury

S100B



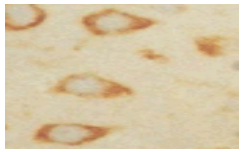
Glial/BBB damage

T-Tau & P-Tau



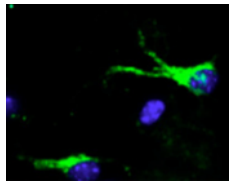
Tauopathy

NSE



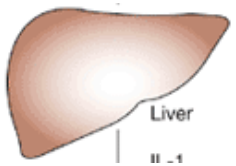
Cell body injury

IL-6

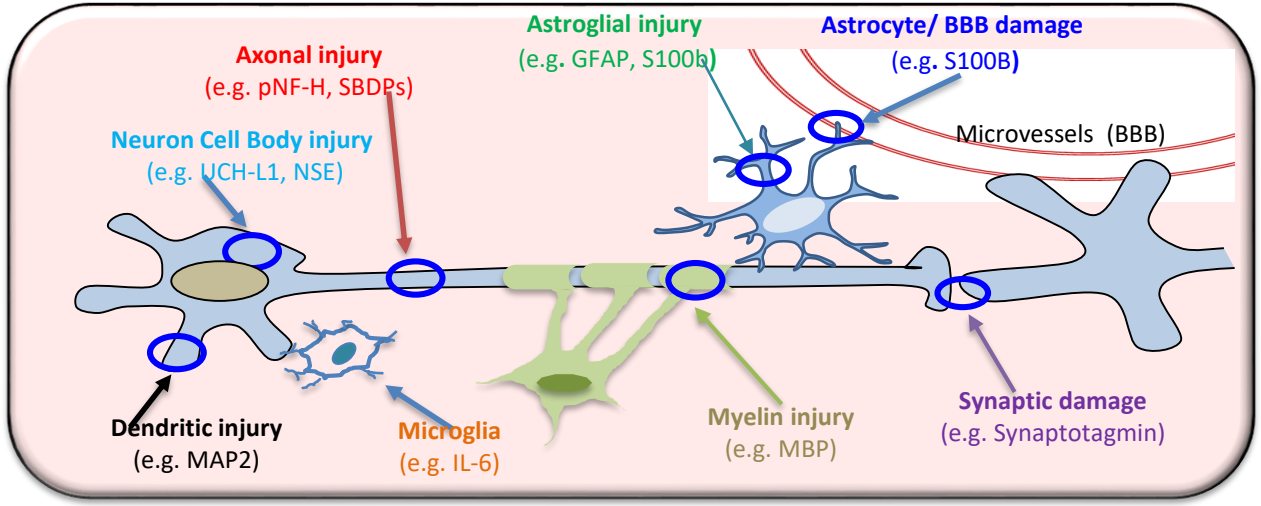


Neuroinflammation

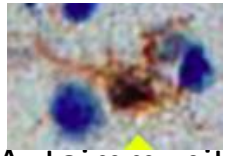
C-RP



Acute Phase Protein

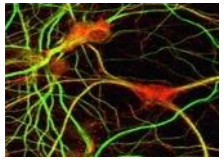


Anti-GFAP



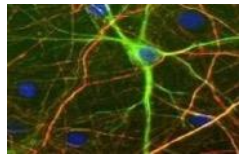
Autoimmunity

MAP2



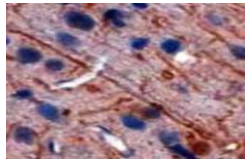
Dendritic injury

pNF-H/NF-L



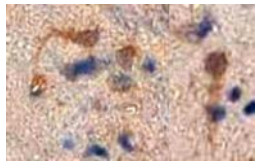
Axonal injury

SBDP150



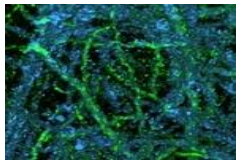
Necrosis

SBDP120



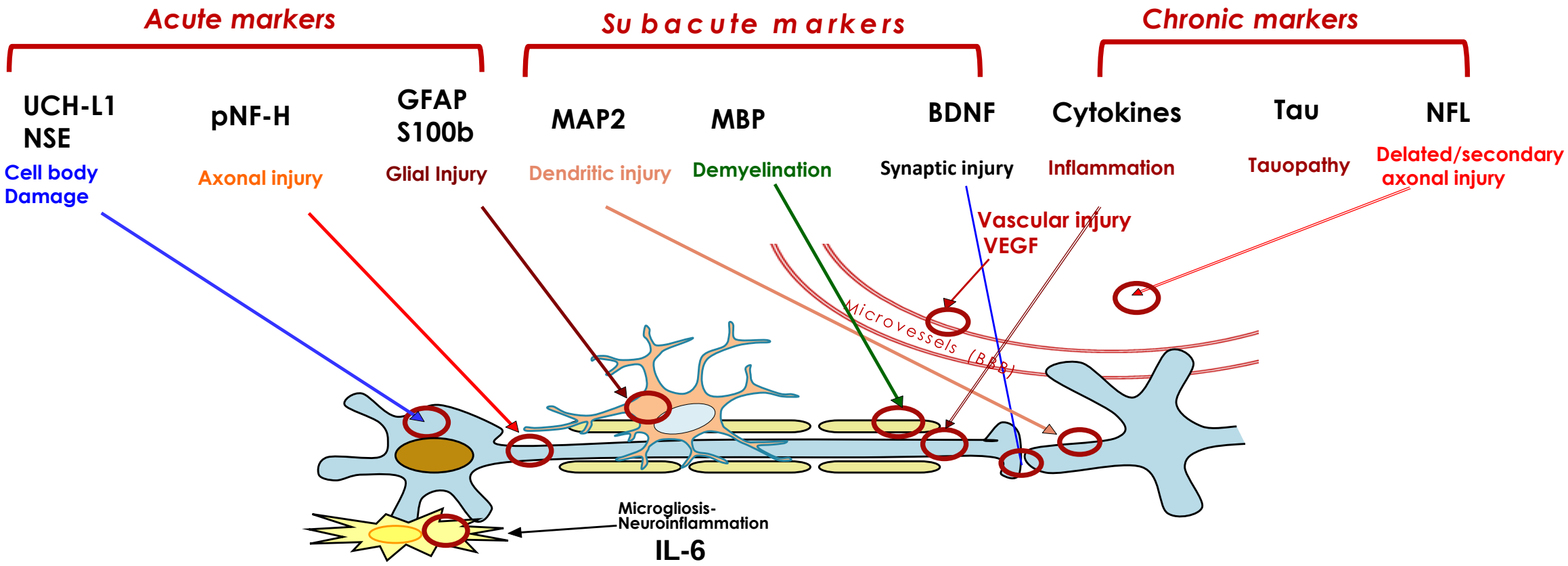
Apoptosis

MBP



Demyelination

Novel HIE protein biomarker candidates



Targeted Neuroprotein Biomarker Panel for HIE

protein	origin	Change in serum or CSF level	key reference	Biological fluid
NSE	Neuron/necrosis	↑	Celtik C, 2004	CS, C, P
GFAP	Astroglial injury	↑	Chalak LF, 2014	CS, C, P
UCHL-1	Neuronal cell body injury	↑	Douglas-Escobar M, 2014	CS, C, P
Tau	Neurodegeneration	↑	Massaro AN, 2018	CS, C, P
S100b	Astroglia /BBB damage	↑	Qian J, 2009	CS, C, P, A, U, S
NF-L	Axonal injury	↑	Shah DK, 2018	CS, C, P
BDNF	Neuroplasticity	↓paraventricular hypothalamus	Massaro AN, 2018	CS, C, P
		↑secretion neuron and astrocytes	Liu F 2013	CS, C, P
IL-6, IL-1b, TNF-a, IL8	neuroinflammation	↑	Chalak LF, 2014,Ramaswamy V, 2009	CS, C, P
MCP-1	neuroinflammation	↑		CS, C, P
MBP	White matter/necrosis	↑	Hu SJ, 2009	CS, C, P
Activin A	neurons differentiation and proliferation	↑	P. Florio, 2004	CS, C, P, A, U, S
AM(C-amidated peptide)	Neuroinflammation	↑	R. Di Iorio, 2004	CS, C, P, A
MAP2	Dendritic injury	↑ (rat tissue)	Minato K, 2013	CSF, C, P

CS, cerebrospinal
A, amniotic
C, cord blood
P, peripheral blood
U, urine
S, saliva

Graham EM, et al. Curr Opin Pediatr. 2018 Apr;30(2):199-203
Satriano A, et al. Early Hum Dev. 2017 Feb;105:63-67.
Lv H, et al. World J Clin Pediatr. 2016 Feb 8;5(1):67-74

A Pilot Study of Novel Biomarkers in Neonates With HIE

Serum

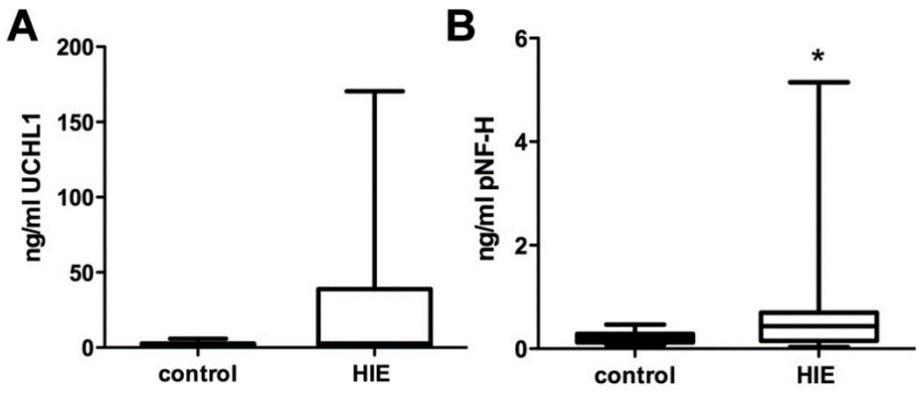


Fig 1. Serum biomarkers collected from the first blood sample of patients with HIE *vs* control subjects

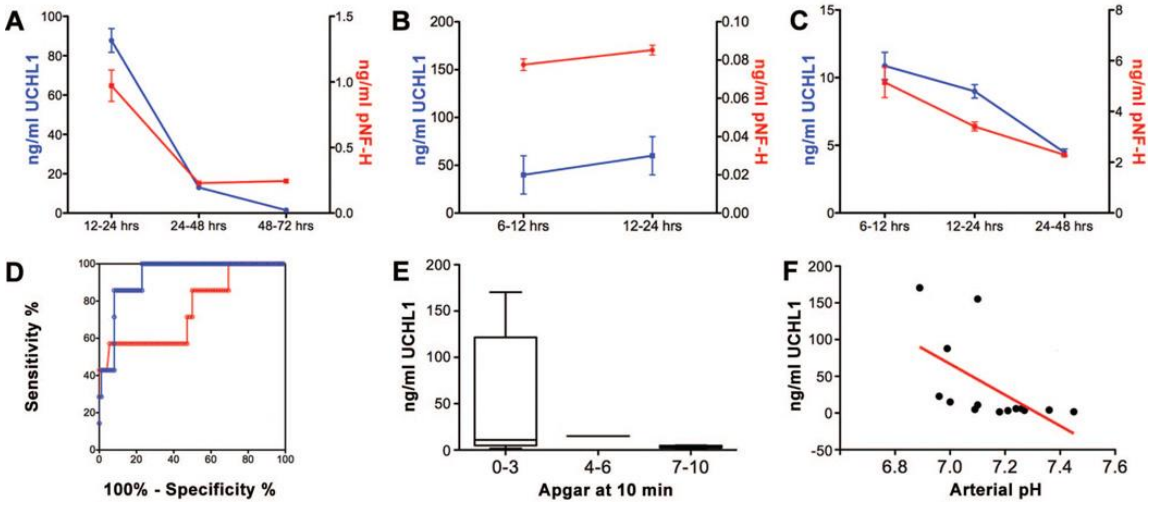


Fig 2 Selected data from individual patients, ROC curves, and relationship between initial serum UCHL1 level, Apgar score, and arterial pH

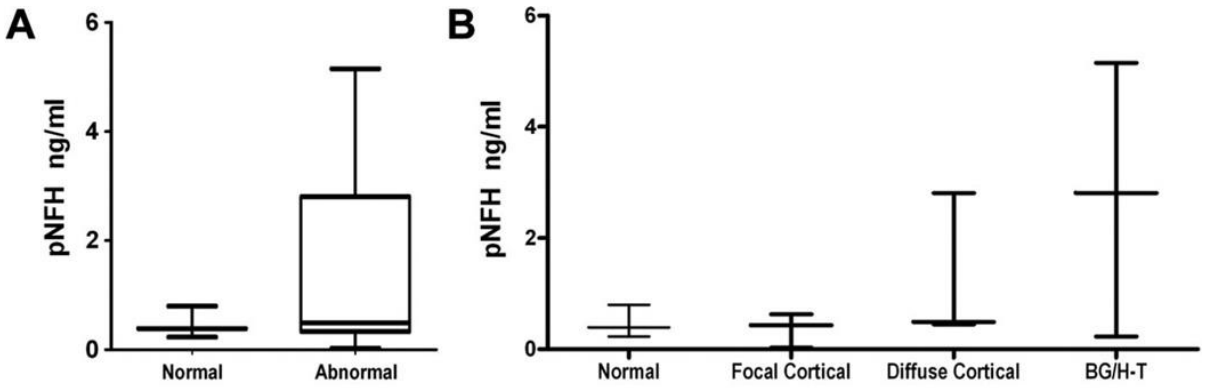
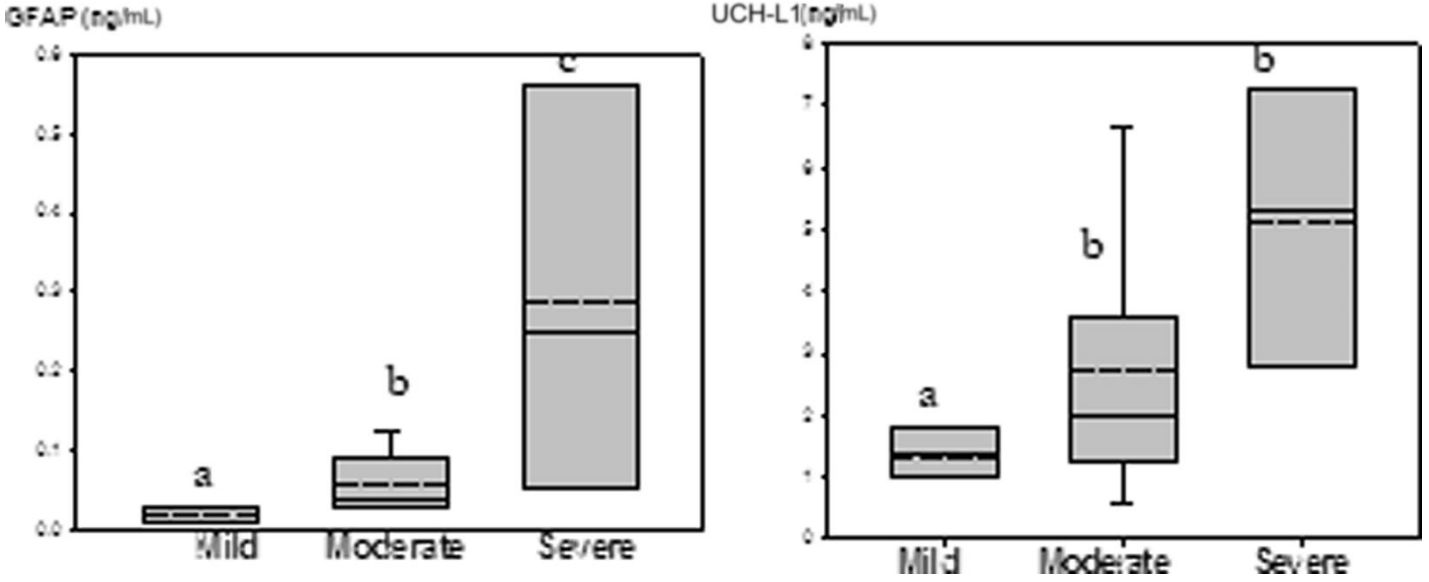


Fig 3 MRI and levels of serum pNF-H. Panel (*A*) shows pNF-H levels as a function of normal *vs* abnormal MRI

Douglas-Escobar M1, et al., Pediatr Res. 2010 Dec;68(6):531-6.

Umbilical cord plasma GFAP and UCH-L1 and severity of encephalopathy at birth

Cord blood



Serum biomarkers measured at 12 h and relationship to BSID III outcomes			
Serum biomarkers	Normal outcome (N = 22)	Abnormal outcome (N = 5)	P-value
GFAP	0.03 (0.03-0.05)	0.1 (0.08-0.6)	0.002
UCH-L1	1.88 (1.13-3.24)	2.38 (1.90-3.00)	0.45

Chalak LF, et al.,J Pediatr. 2014 Mar;164(3):468-74.e1

Saliva levels of S100B in newborns with perinatal asphyxia

saliva

A

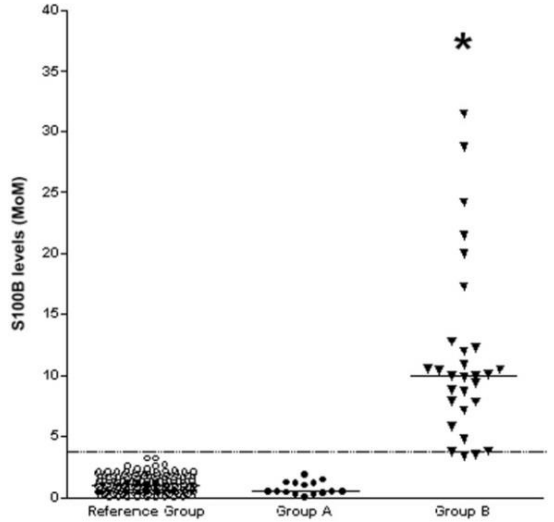


Fig 1. Saliva levels of S100B in asphyxiated full-term newborns.

B

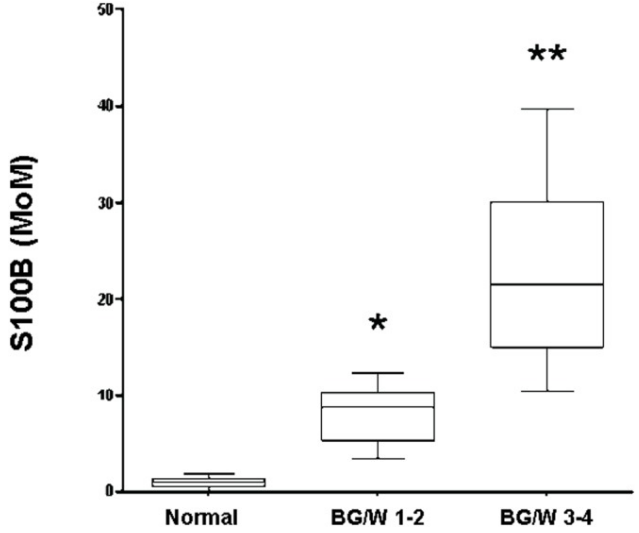


Fig 2. Saliva levels of S100B in neonates with normal, BG/W score 1–2 and BG/W score 3–4

C

S100B (MoM)	Reference Group (n = 244)			Group A (n = 15)			Group B (n = 33)		
	Mean	*Lower $CI_{95\%}$*	*Upper $CI_{95\%}$*	*Mean*	*Lower $CI_{95\%}$*	*Upper $CI_{95\%}$*	*Mean*	*Lower $CI_{95\%}$*	*Upper $CI_{95\%}$*
T0	1.10	1.02	1.20	0.80	0.50	1.08	23.6*	9.80	37.40
T1	1.00	1.01	1.10	1.00	0.90	1.10	26.4*	10.20	38.60
T2	1.00	1.01	1.10	1.00	0.90	1.10	26.4*	10.20	38.60
T3	1.10	1.02	1.20	0.80	0.60	1.00	24.8*	10.80	39.60
T4	0.98	0.96	1.00	1.00	0.90	1.10	23.8*	9.60	37.60
T5	1.00	0.9	1.10	1.10	1.02	1.20	23.0*	9.00	34.50
T6	1.10	1.02	1.20	1.10	1.02	1.20	18.2*	4.20	22.10
T7	1.10	1.02	1.20	1.10	1.02	1.20	1.00	0.90	1.10
T8	1.10	1.02	1.20	1.00	0.90	1.10	0.80	0.60	1.00
T9	1.10	1.02	1.20	1.00	0.90	1.10	1.10	1.02	1.20

Table 1. Time frame of saliva S100B concentration from birth to 9 days after born.

Gazzolo D et al., PLoS One. 2015 Jan 8;10(1):

Cohort from Shands University of Florida Teaching hospital

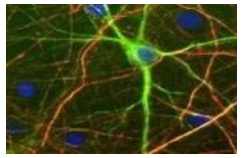
Demographics study population by cohort assignment

Patient Demographics	Total (n=49)	Cohort 1 (n=9)	Cohort 2 (n=40)
Sex – no. (%)			
Female	15 (30.6)	14 (35)	1(12.5)
Male	34 (69.4)	26 (65)	8(87.5)
Race – no.(%)			
White	29(59.2)	24(60)	5(55.6)
Black	12 (24.5)	9 (22.5)	3 (33.3)
Asian	1 (2.4)	1 (2.5)	0(0)
unknow	5(10.2)	4(10)	1(11.1)
other	2 (4.1)	2 (5)	0(0)
Birth weigh (g) *	3340 ± 791.07	3336 ± 839.9	3361 ± 560.5

Birth weight: values are means ± SD.
Cohort 1 = HIE; Cohort 2 =controls

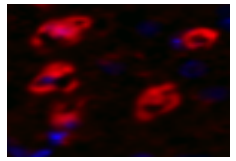
Agpar at 10 min
MRI_BG (basal ganglia)
MRI_W (watershed)
MI_BG_W(thalamus/basal ganglia/cortex)
Bayley_Cogcognitive
Bayley_language
Bayley_motor

NF-L



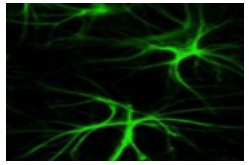
Axonal injury

UCH-L1



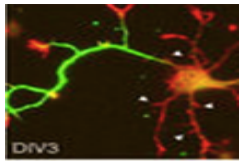
Cell body injury

GFAP



Gliosis/Glial Injury

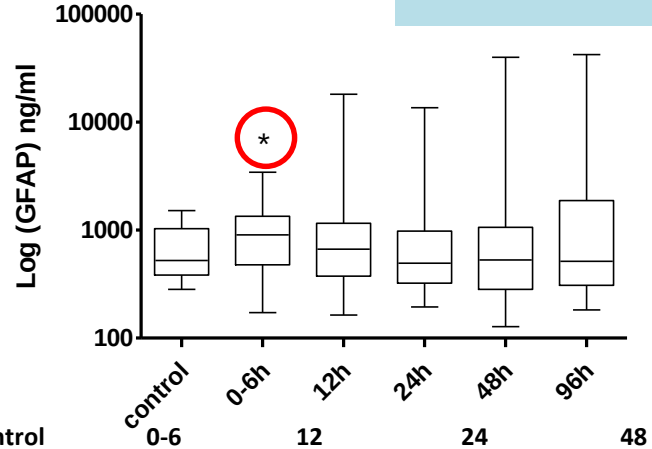
T-Tau



Tauopathy

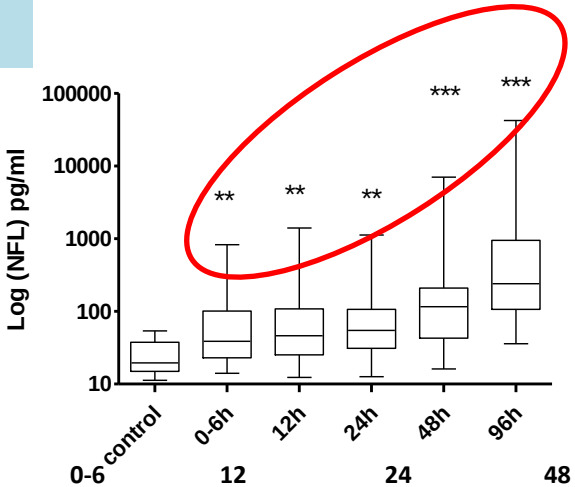
The temporal profile within 96h

GFAP



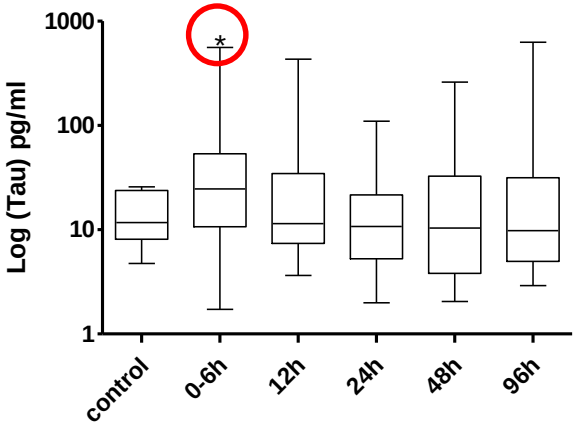
	Control	0-6	12	24	48	96
25% Percentile	383.0	476.8	374.4	323.2	282.5	309.0
Median	**522.1**	**904.0**	**666.8**	**494.2**	**530.4**	**515.1**
75% Percentile	1030	1342	1157	982.8	1061	1876

NFL



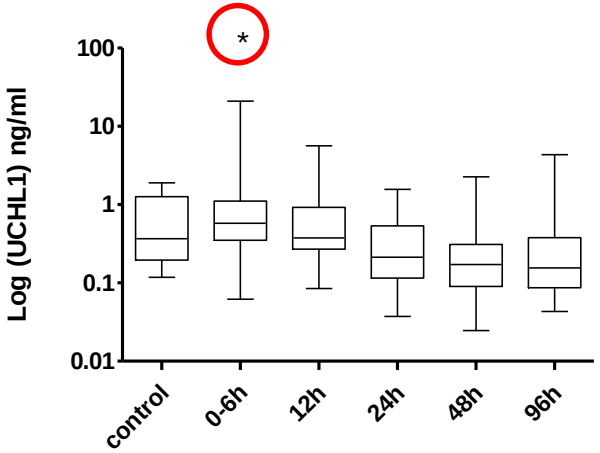
	Control	0-6	12	24	48	96
25% Percentile	14.93	23.01	25.27	30.94	42.94	107.1
Median	**19.65**	**38.63**	**46.38**	**54.73**	**115.9**	**241.3**
75% Percentile	37.60	100.9	108.7	106.7	210.0	948.0

Tau



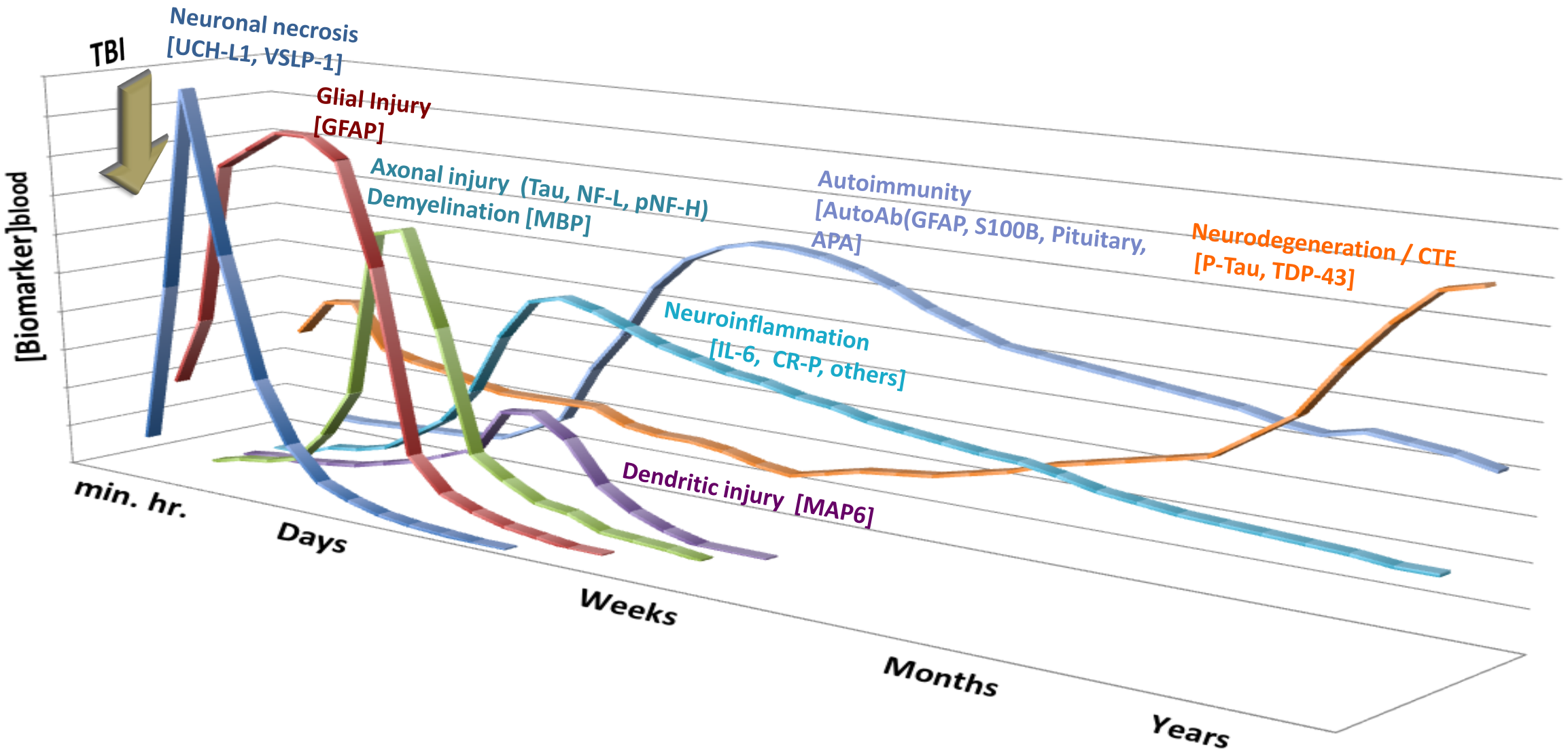
	Control	0-6	12	24	48	96
25% Percentile	8.114	10.66	7.407	5.264	3.815	4.967
Median	**11.72**	**24.62**	**11.42**	**10.75**	**10.36**	**9.788**
75% Percentile	23.81	53.62	34.62	21.53	32.64	31.56

UCHL1

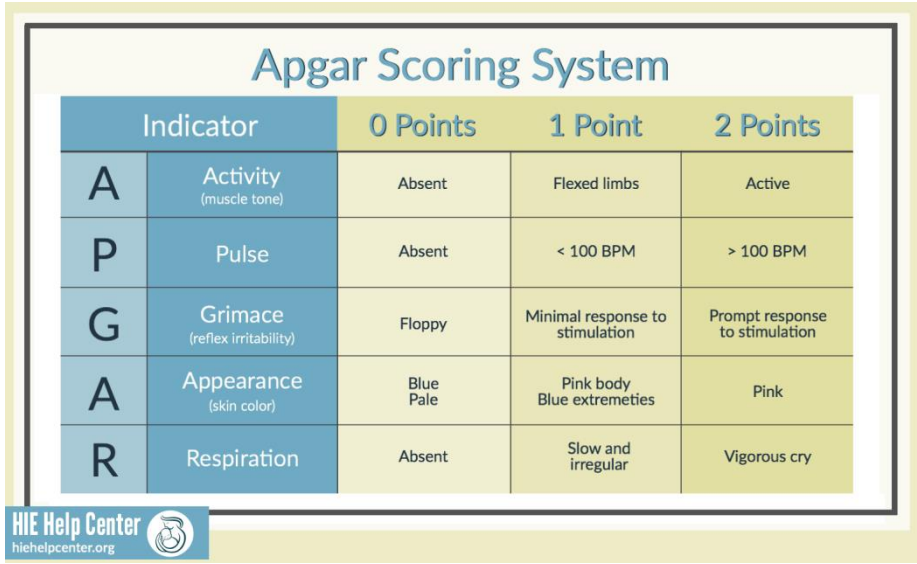


	Control	0-6	12	24	48	96
25% Percentile	195.9	349.8	271.2	114.9	90.05	86.43
Median	**367.5**	**579.2**	**376.4**	**213.4**	**172.2**	**155.9**
75% Percentile	1268	1113	922.3	533.5	309.2	379.2

A continuum of Precision Biomarkers based Temporal Biomarkers



Agpar_10 min

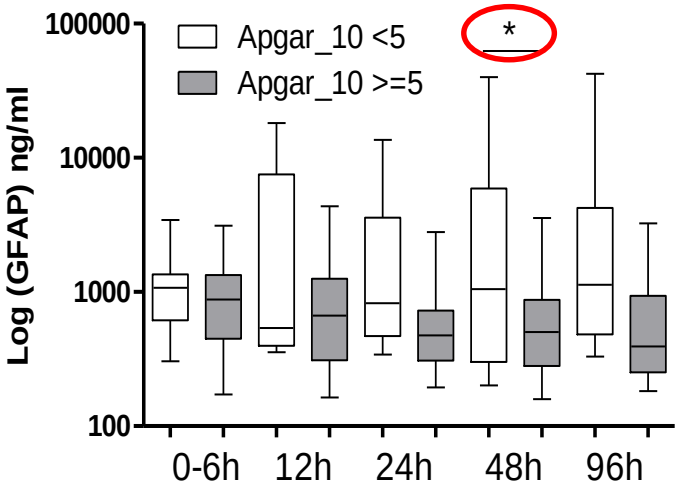


Apgar Scoring System

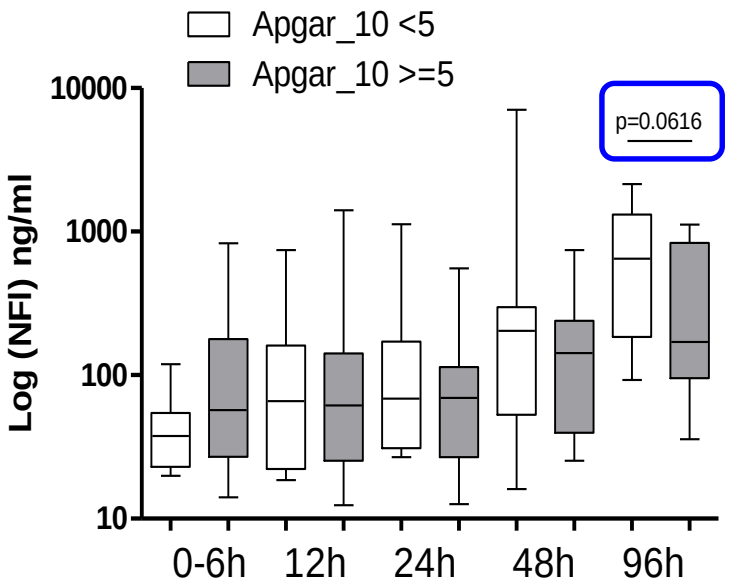
Indicator		0 Points	1 Point	2 Points
A	Activity (muscle tone)	Absent	Flexed limbs	Active
P	Pulse	Absent	< 100 BPM	> 100 BPM
G	Grimace (reflex irritability)	Floppy	Minimal response to stimulation	Prompt response to stimulation
A	Appearance (skin color)	Blue Pale	Pink body Blue extremeties	Pink
R	Respiration	Absent	Slow and irregular	Vigorous cry

HIE Help Center
hiehelpcenter.org

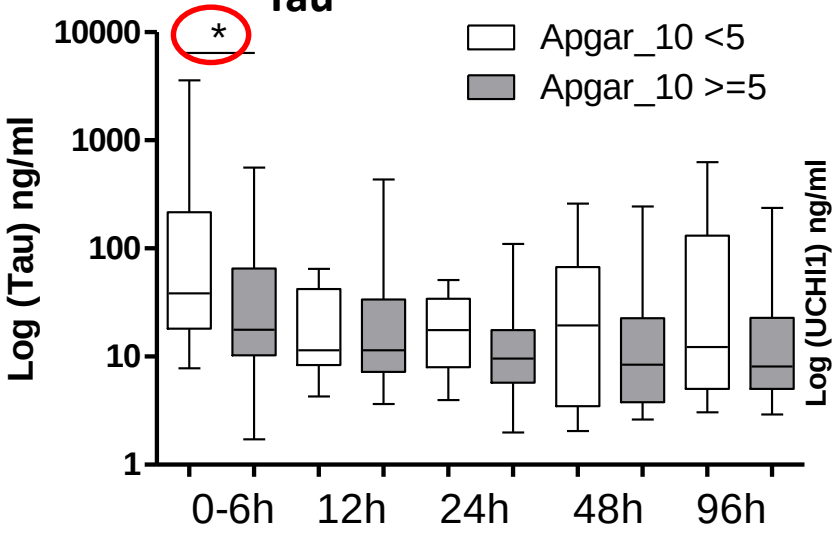
GFAP



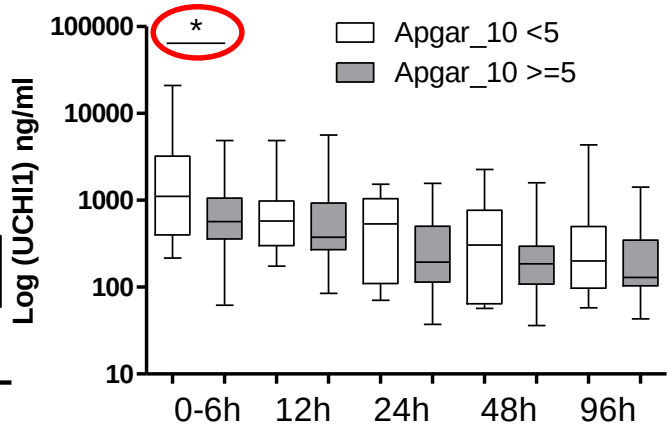
NFL



Tau

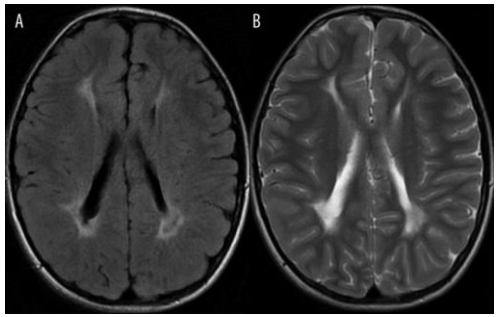


UCHL1

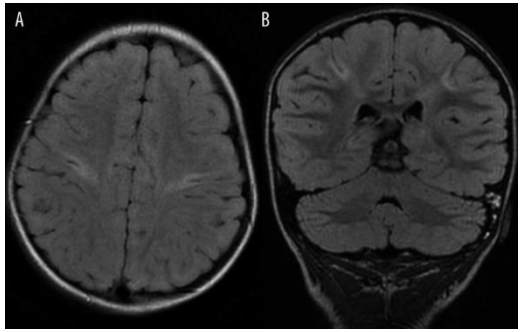


Three main MR patterns of hypoxic-ischemic lesions

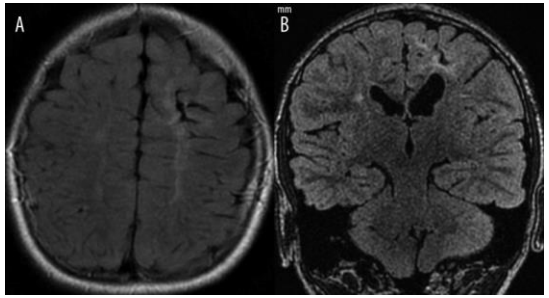
* Periventricular leukomalacia– PVL
* Basal ganglia and/or thalamus lesions – BGTL,
* Multicystic encephalopathy – MCE accompanied by injury to the basal ganglia, thalamus and/or cerebral cortex



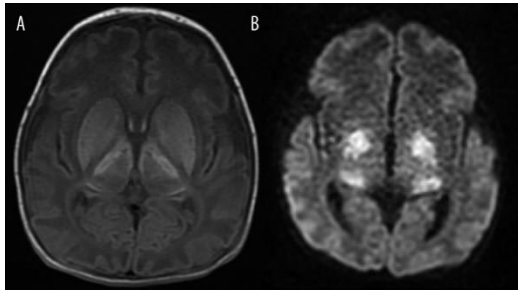
Symmetrical paraventricular gliosis



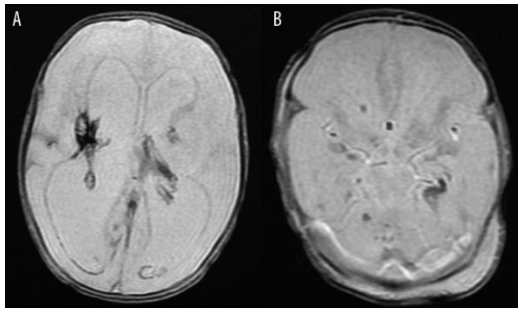
Cerebral cortex and white matter injury



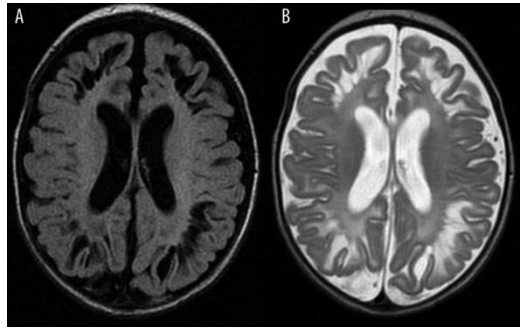
subcortical white matter injury



Injury of basal ganglia and thalamus



Intraventricular or intraparenchymal hemorrhage

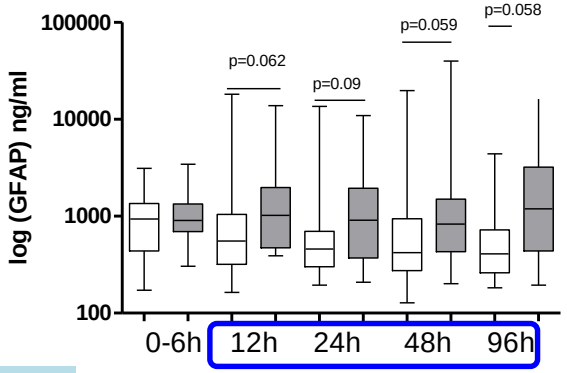


Multicystic encephalopathy

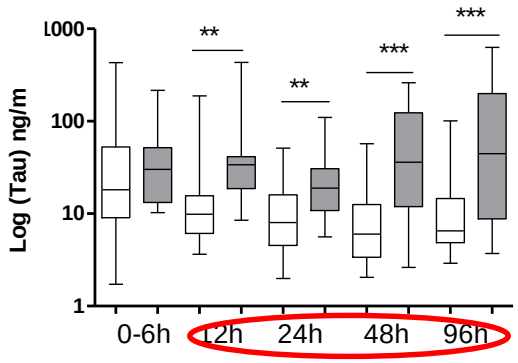
Cabaj A, et al. Pol J Radiol. 2012 Jul;77(3):71-6

MRI-BG

GFAP



NFL



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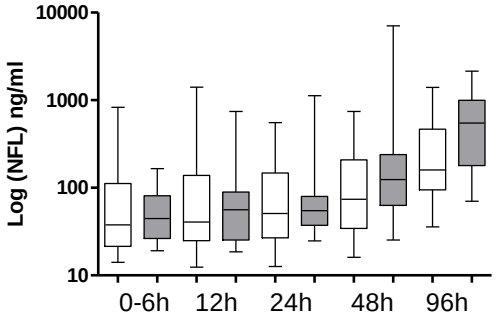
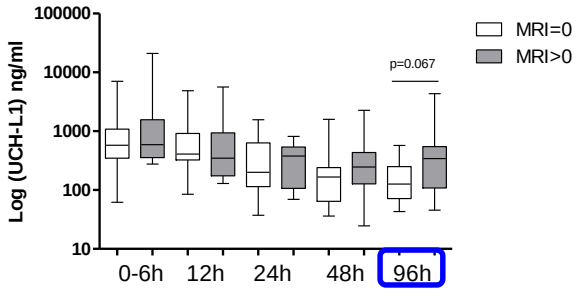
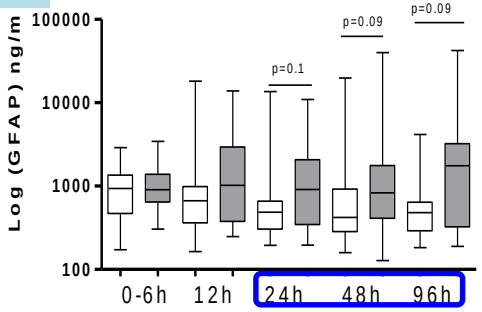
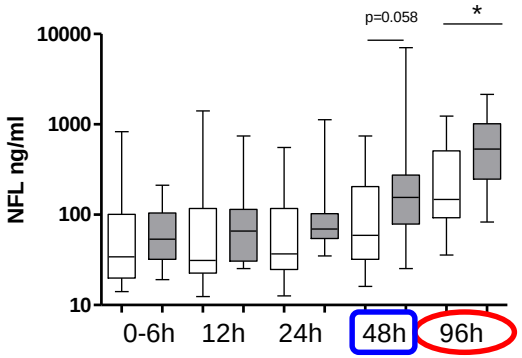


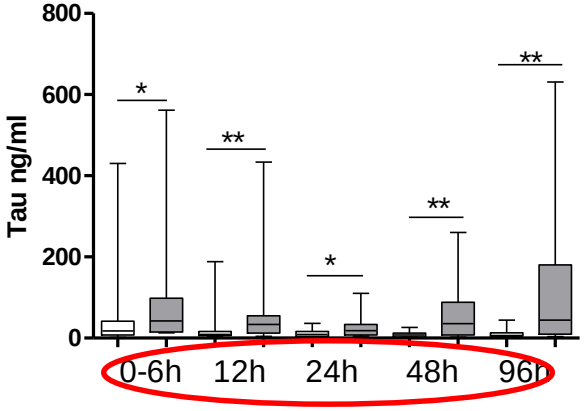
UCHL1

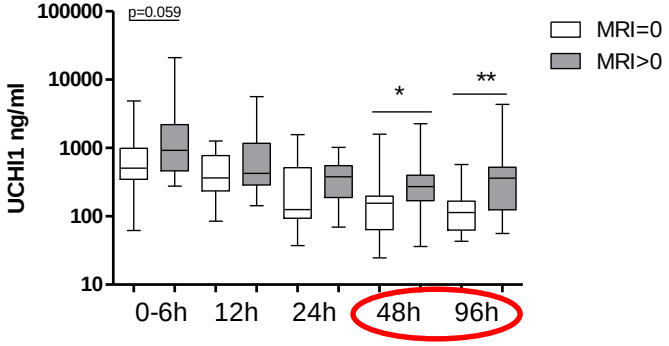


MRI-W

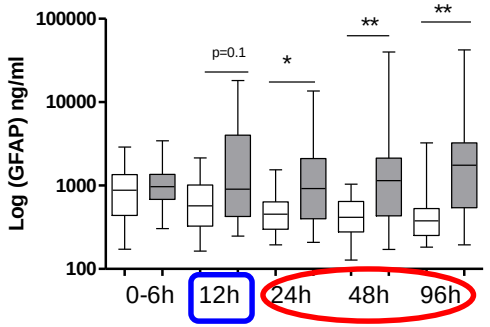


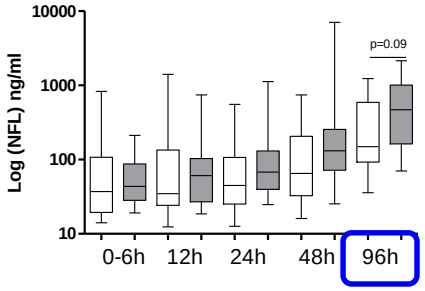


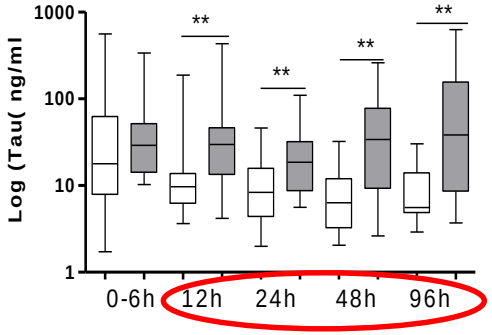


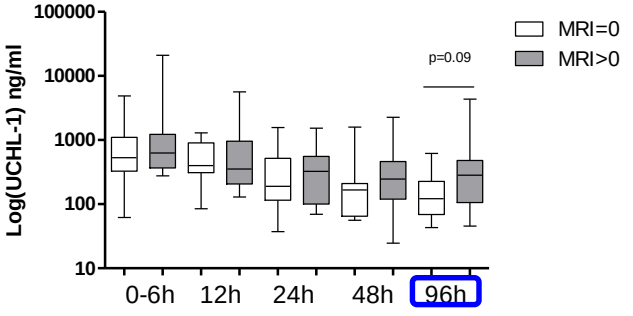


MRI_BG_W





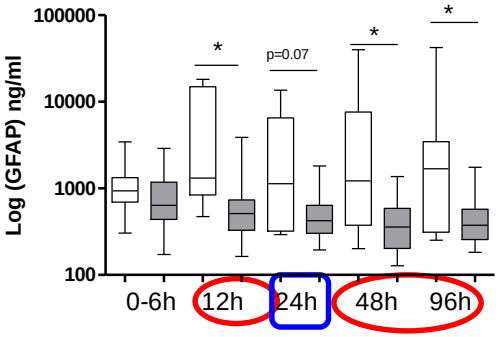




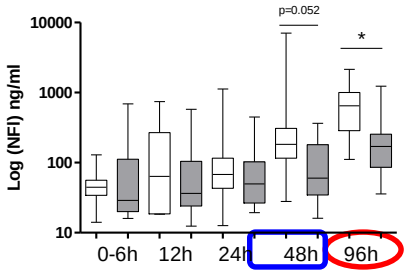
Bayley Scales

Cognitive function

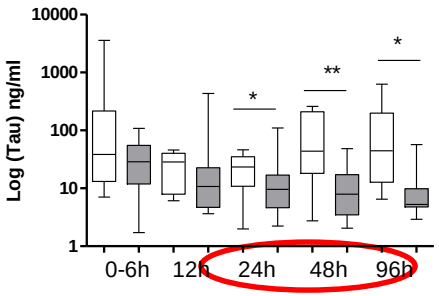
GFAP



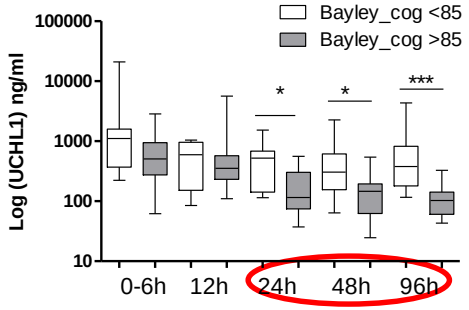
NFL



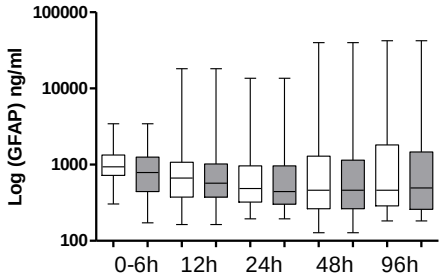
Tau

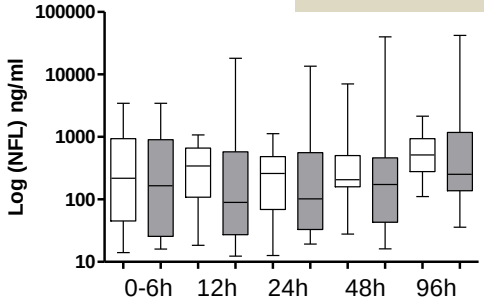


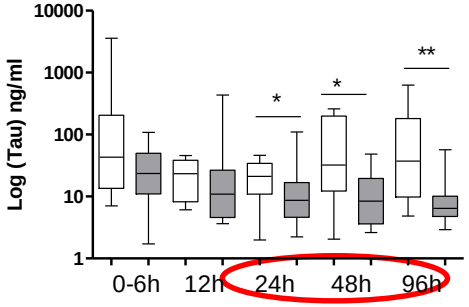
UCHL1

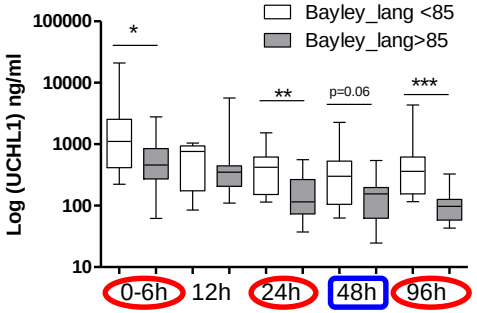


language

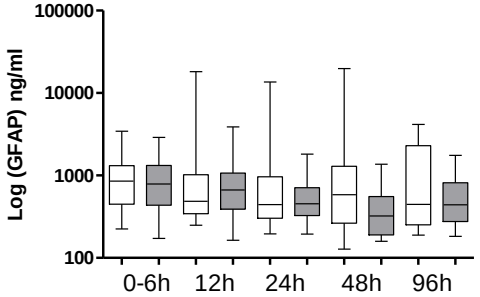


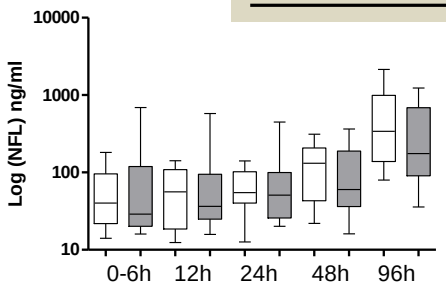


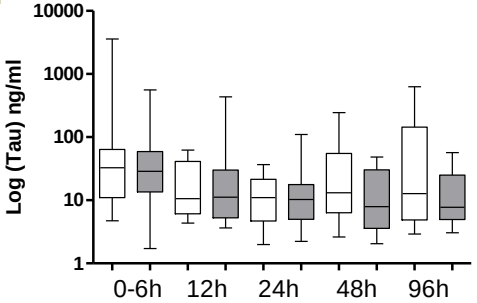


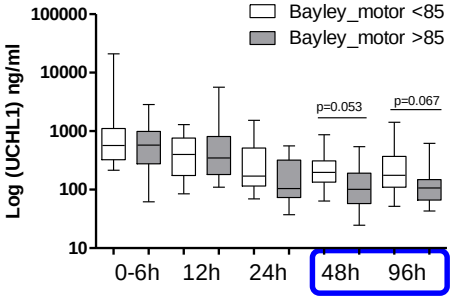


Motor function









Receiver operating characteristic curve

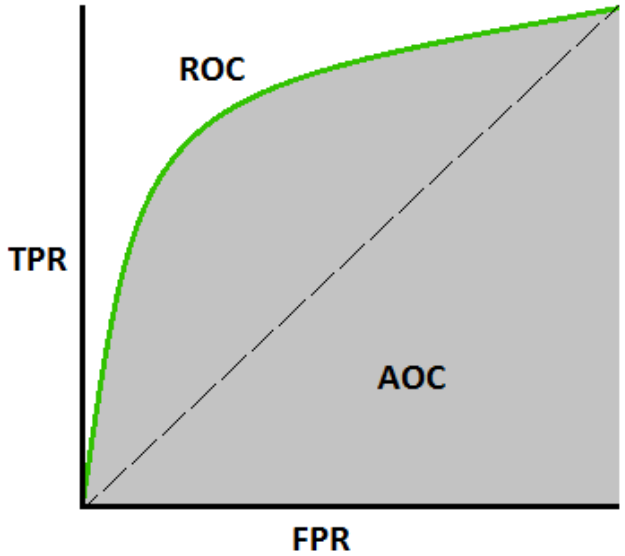
sensitivity, **recall**, **hit rate**, or **true positive rate** (TPR)

$$\mathrm{TPR} = \frac{\mathrm{TP}}{P} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}$$

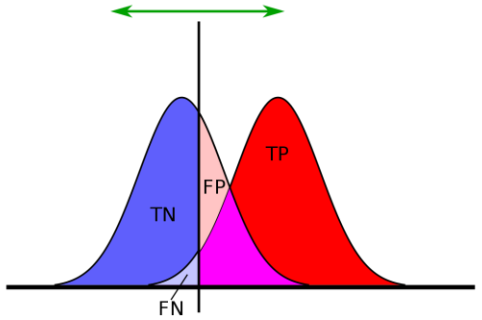
specificity, **selectivity** or **true negative rate** (TNR)

$$\mathrm{TNR} = \frac{\mathrm{TN}}{N} = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FP}}$$

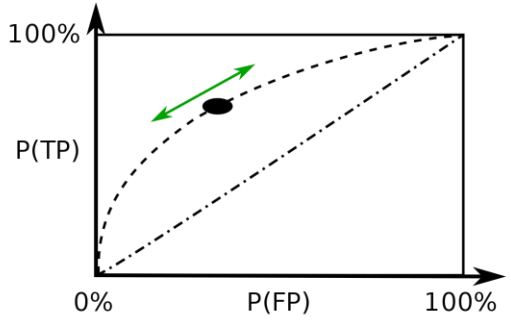
		True condition	
	Total population	Condition positive	Condition negative
Predicted condition	Predicted condition positive	**True positive**	**False positive**, Type I error
	Predicted condition negative	**False negative**, Type II error	**True negative**



ROC AUC
.90-1 = excellent (A)
.80-.90 = good (B)
.70-.80 = fair (C)
.60-.70 = poor (D)
.50-.60 = fail (F)



TP	FP
FN	TN



Area under ROC curve performance using biomarker concentrations for prognosticating 18-24 month outcome

Cognitive function

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
GFAP_12	0.865	0.093	0.010	0.682	1.000
GFAP_24	0.854	0.134	0.012	0.591	1.000
GFAP_48	0.854	0.087	0.012	0.683	1.000
Tau_96	0.863	0.090	0.017	0.685	1.000
UCHL1_24	0.854	0.097	0.012	0.664	1.000
UCHL1_48	0.760	0.126	0.065	0.513	1.000
UCHL1_96	0.917	0.060	0.003	0.799	1.000

Motor function

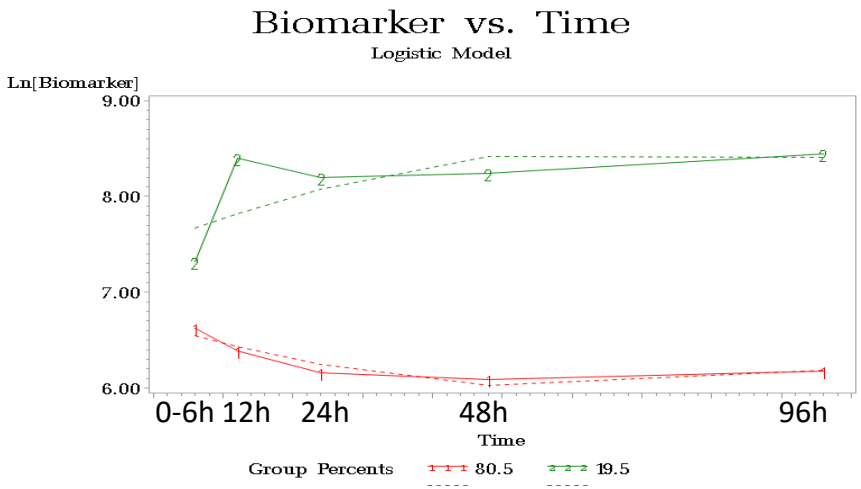
Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
GFAP_48	0.827	0.095	0.011	0.641	1.000

language

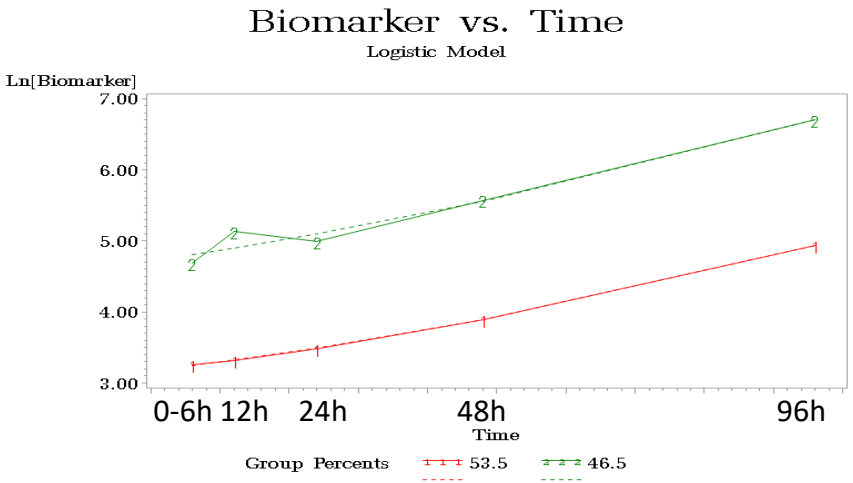
Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
GFAP_12	0.905	0.077	0.003	0.754	1.000
GFAP_24	0.867	0.116	0.007	0.640	1.000
GFAP_48	0.781	0.106	0.038	0.573	0.989
NFL_96	0.800	0.113	0.036	0.579	1.000
Tau_96	0.756	0.125	0.073	0.510	1.000
UCHL1_0_6	0.771	0.125	0.045	0.526	1.000
UCHL1_24	0.876	0.081	0.005	0.717	1.000
UCHL1_96	0.905	0.064	0.003	0.779	1.000

Two-group biomarker trajectories profiles

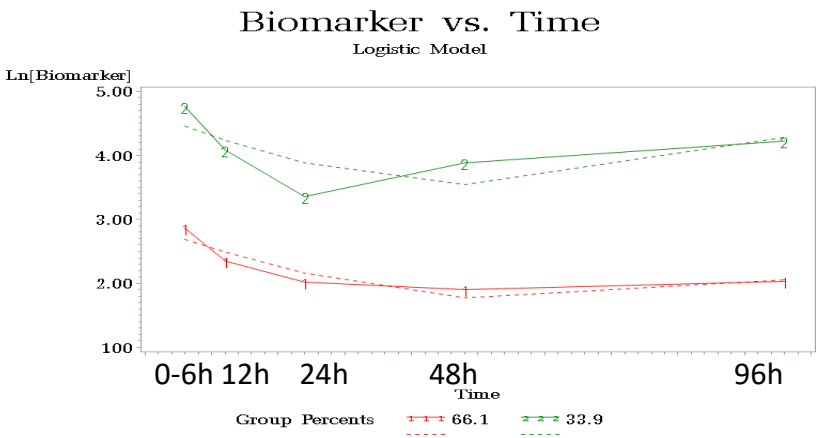
GFAP



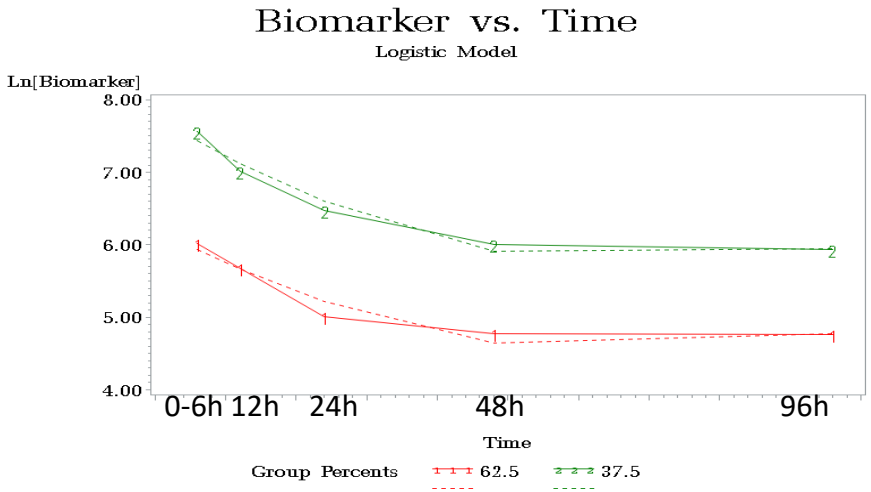
NFL



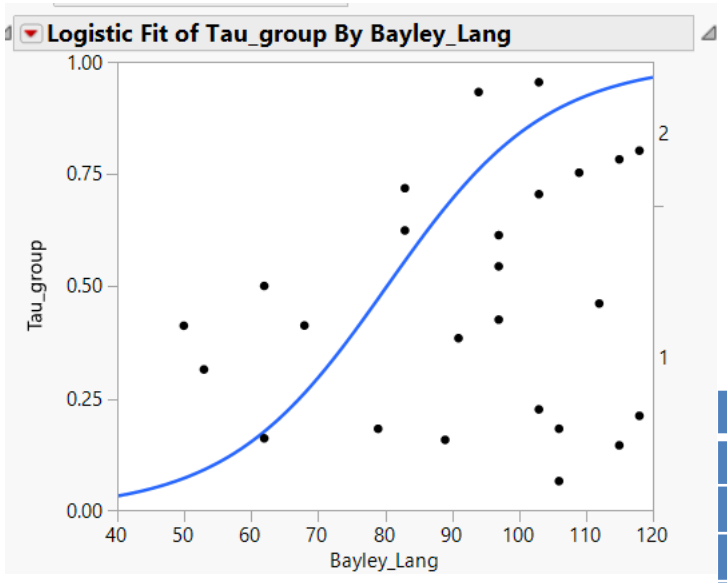
Tau



UCHL1

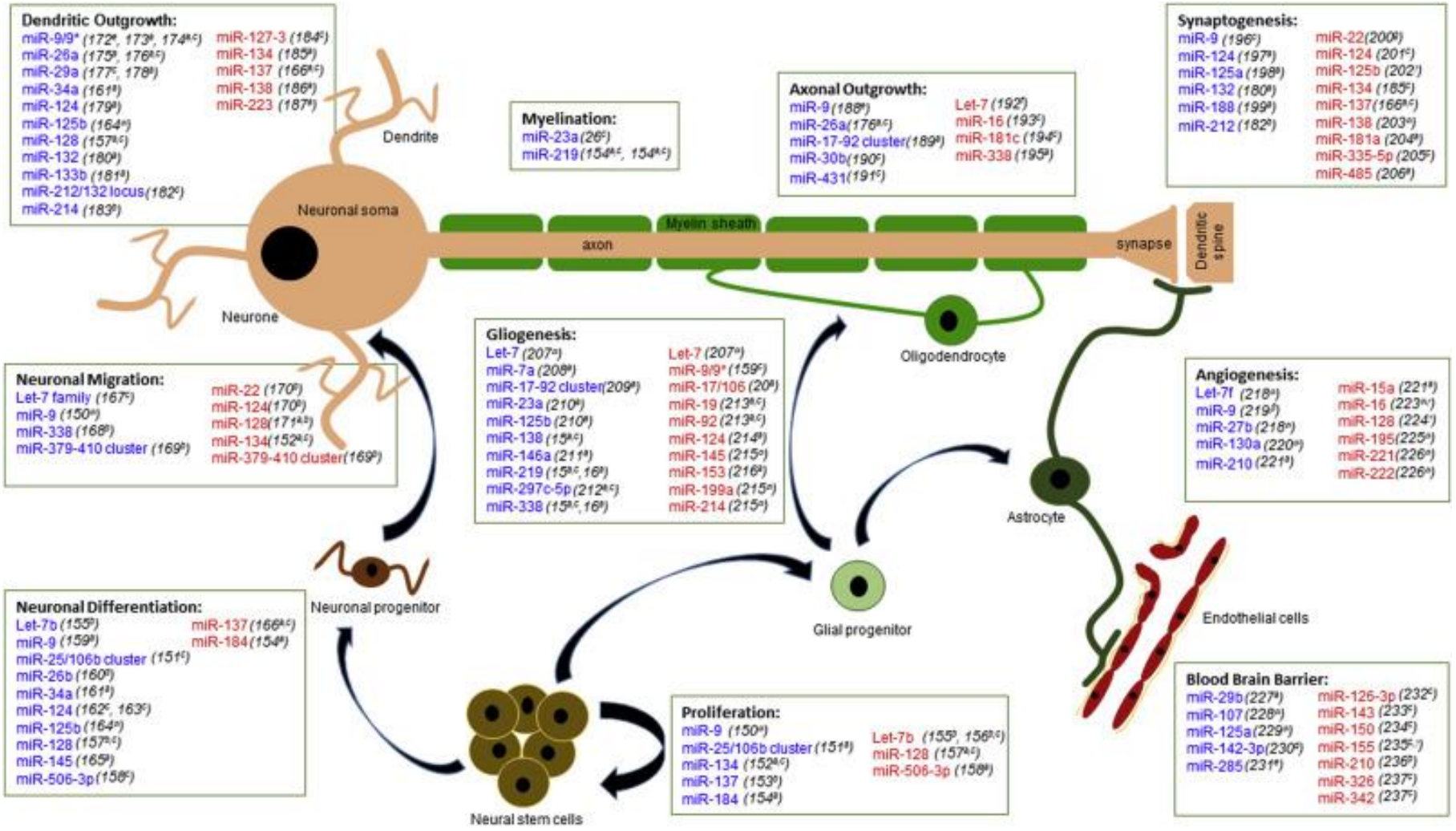


Area under ROC curve performance to predict HIE outcomes using biomarker trajectory groups



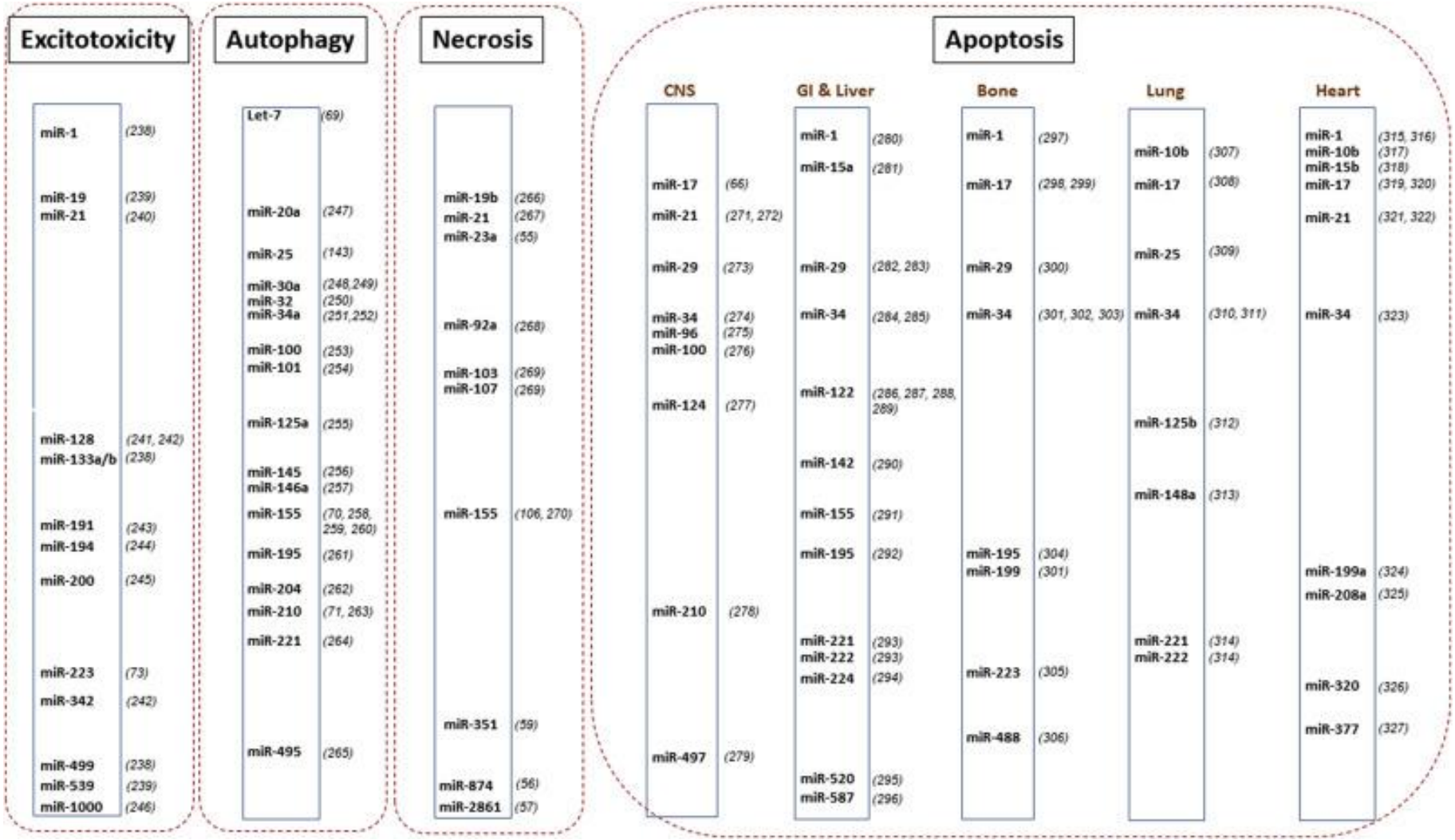
	AUC(95CI)	P-value
Poor Neurologic Function at Discharge (Bayley_cog)		
GFAP	0.924 (0.803-0.999)	0.019
NF-L	0792(0.604-0.98)	0.014
Tau	0.871(0.728-0.999)	0.003
UCHL1	0.713(0.497-0.93)	0.0913
Poor Neurologic Function at Discharge (Bayley_lang)		
GFAP	0.894(0.758-0.999)	0.03
NF-L	00656(0.418-0.894)	0.189
Tau	0.871(0.728-0.999)	0.003
UCHL1	0.783(0.604-0.962)	0.025
Poor Neurologic Function at Discharge (Bayley_lang)		
GFAP	0.939(0.604-0.98)	0.014
NF-L	0.734(0.536-0.932)	0.049
Tau	0.824(0.65-0.997)	0.010
UCHL1	0.643(0.426-0.86)	0.256

miRNAs involvement in normal neonatal brain development



Ponnusamy V, Yip PK. Neuropharmacology. 2019 May 1;149:55-65.

miRNAs in cellular death



Ponnusamy V, Yip PK. Neuropharmacology. 2019 May 1;149:55-65.

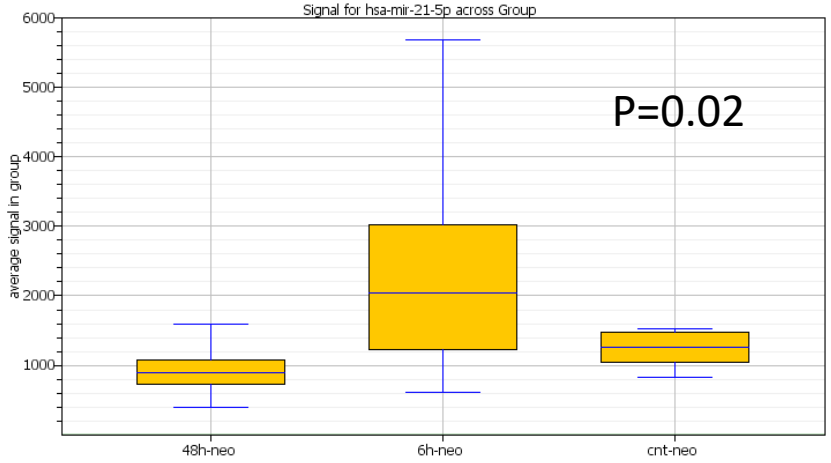
Tentative miRNA markers for HIE

Table 2. Examples of Targeted miRNA in HIE			
miRNA	origin	changes in serum or CSF level	key reference
miRNA-21	Astrocytes injury-linked	↑	Chen, 2015
miRNA181b	Regulator of UCHL-1	↓	Looney AM, 2018
miRNA-124	Astrocytes-enriched	↓	Oikawa, 2015
miRNA-155	microglia/astrocytes modulation	↑	Billeter, 2014
miRNA-374a-5p	??	↓	Looney AM, 2015
miRNA210	neuronal apoptosis-linked	↓	Wang ZS, 2018

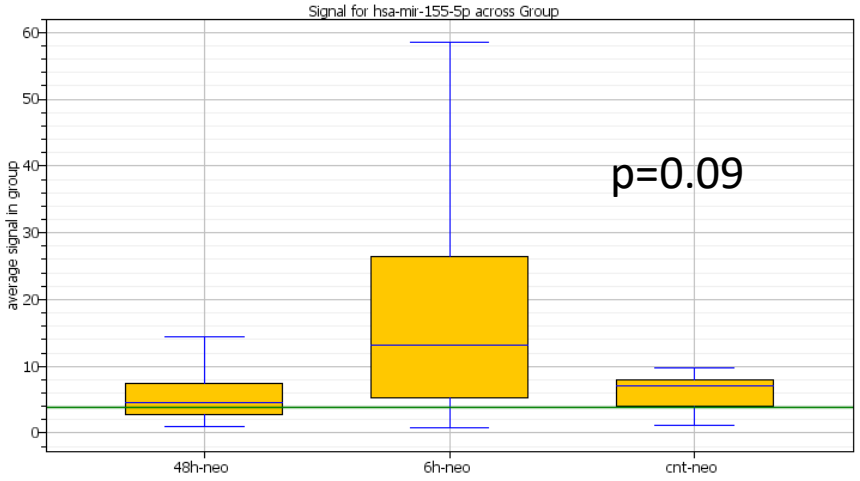
Cohort from Shands University of Florida Teaching hospital

181b-5p

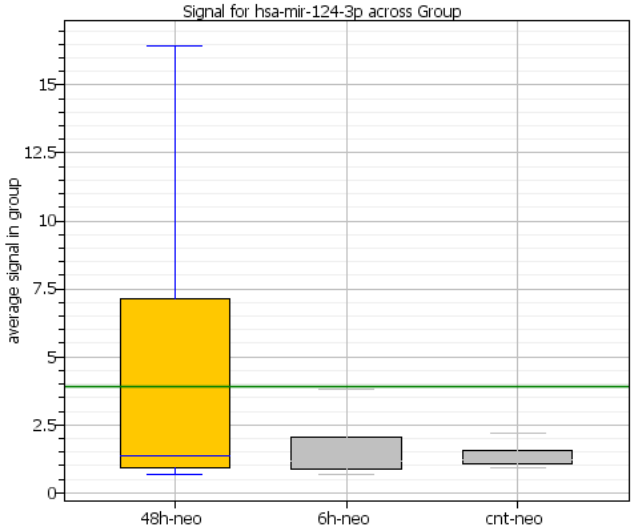
21-5p



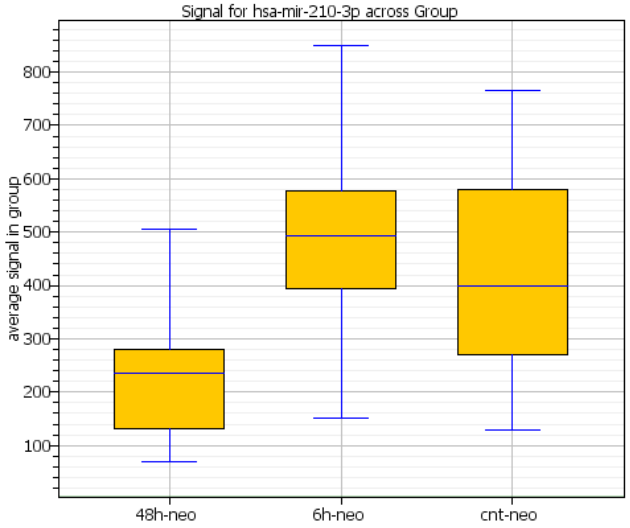
155-5p



124-3p

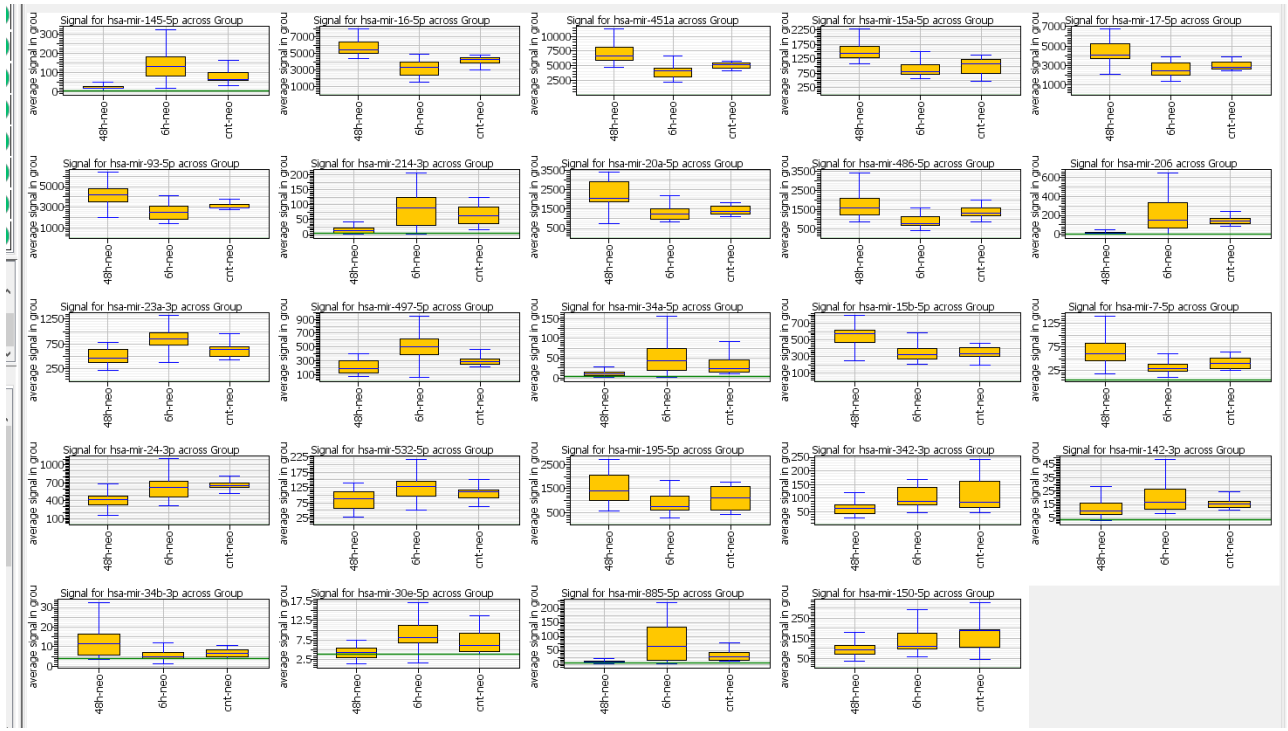


210-3p



Screened additional 24 significant changed miRNA

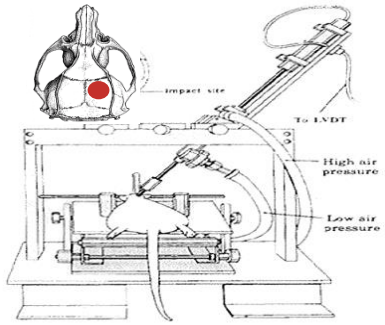
probe	fold	adj p	raw p	high	low	fold-spread	inter-group CV
hsa-mir-145-5p	6.054	2.50E-06	3.84E-08	117.423	19.397	2.008	0.56
hsa-mir-16-5p	1.841	8.16E-06	1.26E-07	5635.018	3061.506	1.17	0.249
hsa-mir-451a	1.766	0.000226	3.48E-06	6932.014	3924.662	1.281	0.236
hsa-mir-15a-5p	1.718	0.000413	6.35E-06	1510.058	878.95	1.317	0.258
hsa-mir-17-5p	1.712	0.000418	6.44E-06	4192.916	2449.504	1.305	0.228
hsa-mir-93-5p	1.639	0.00206	3.17E-05	3988.792	2433.882	1.298	0.199
hsa-mir-214-3p	5.805	0.00304	4.69E-05	56.565	9.744	2.538	0.536
hsa-mir-20a-5p	1.739	0.00364	5.61E-05	2142.398	1231.887	1.328	0.246
hsa-mir-486-5p	1.907	0.00378	5.82E-05	1646.459	863.316	1.442	0.251
hsa-mir-206	12.042	0.00748	0.000115	141.89	11.783	2.931	0.651
hsa-mir-23a-3p	1.743	0.0558	0.000883	807.076	463.083	1.402	0.222
hsa-mir-497-5p	2.516	0.0623	0.000989	444.061	176.518	1.682	0.348
hsa-mir-34a-5p	3.991	0.147	0.00244	39.399	9.872	2.951	0.476
hsa-mir-15b-5p	1.588	0.164	0.00275	528.796	332.895	1.343	0.217
hsa-mir-7-5p	2.105	0.169	0.00285	60.09	28.549	1.738	0.307
hsa-mir-24-3p	1.743	0.237	0.00416	692.561	397.262	1.425	0.219
hsa-mir-532-5p	1.623	0.331	0.00617	122.841	75.678	1.458	0.192
hsa-mir-195-5p	1.802	0.383	0.00741	1429.389	793.08	1.638	0.255
hsa-mir-342-3p	1.652	0.412	0.00814	100.044	60.576	1.555	0.208
hsa-mir-142-3p	1.88	0.537	0.0118	18.965	10.088	1.8	0.246
hsa-mir-34b-3p	1.979	0.726	0.0197	10.721	5.416	1.831	0.302
hsa-mir-30e-5p	2.046	0.758	0.0216	7.909	3.865	1.584	0.275
hsa-mir-885-5p	3.106	0.935	0.0411	38.569	12.416	3.051	0.415
hsa-mir-150-5p	1.757	0.96	0.0483	153.056	87.129	1.781	0.223



Translating research into practice--from bench to bedside

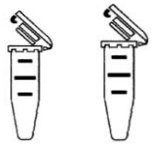
A MS/MS based proteomic biomarker discovery

Workflow

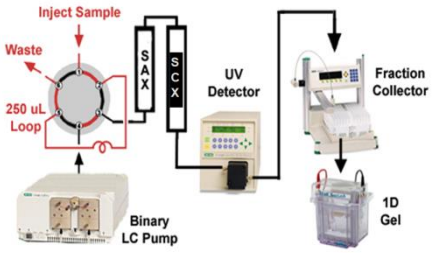


Animal model (CCI)

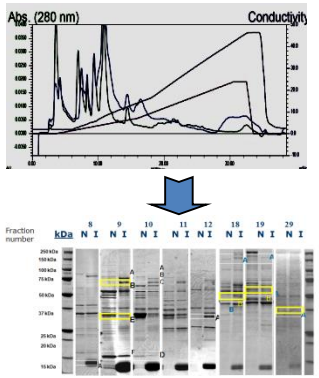
Extracted Homogenized Protein



Con TBI



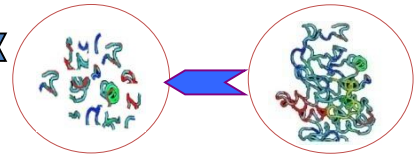
1D-CAX Chromatography (1st D Separation)

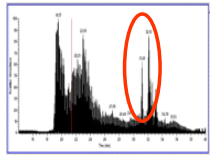


1D-SDS PAGE (2nd D Separation)

Differentially protein bands cut out

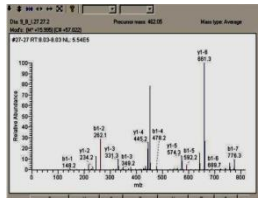
In-Gel digestion (Injured-Ctrl Peptides)

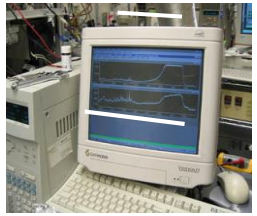




RPLC (3rd dimension Separation)

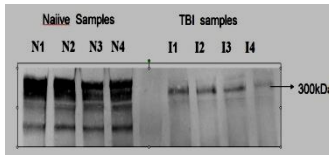
Tandem MS (LCQ)





Protoeme Database Search (Sequest)

Differential Protein Hit list



Confirmation via western blotting

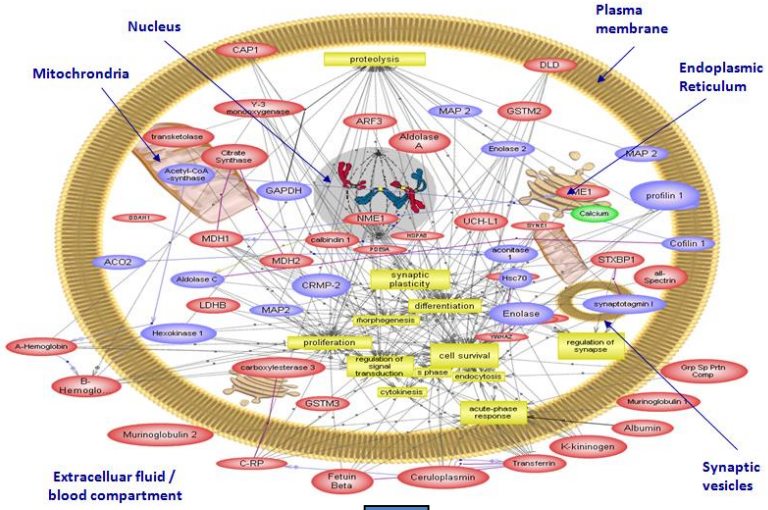
Kobeissy, et al. . Mol. Cell. Proteomics 5: 1887-1898.

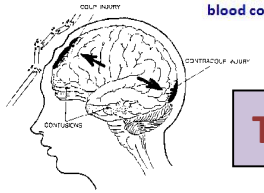
Systems Biology based analysis: identifying non-redundant pathways or convergent hot spots and top biomarkers

TBI insult

Neuroproteomics

Systems Biology Analysis





TBI pathology dynamics

(1) Proteolyitc Cell death markers
- SBDP150, SBDP145: Necrosis /
- SBDP120: Apoptosis
T-Bax

(2) Cytoskeleton damage markers
- MAP2-dendirtic
- Tau – axonal (calp, casp)
- NF-H,M, L –axonal

(3)Glia/ Microglia Injury Markers
- Gliosis: GFAP
- Microgliosis: EMAP-II

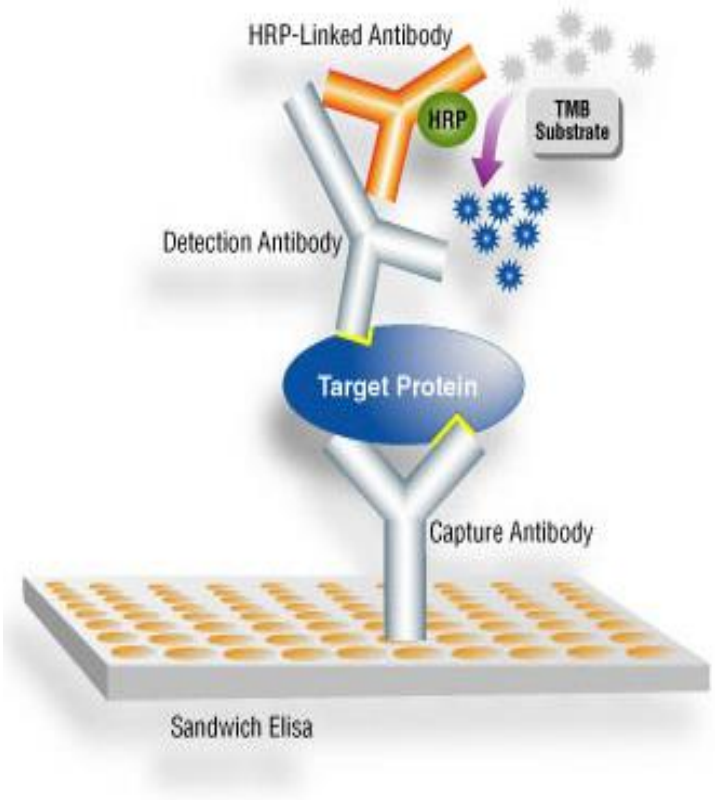
(4) Synaptic dysfunction markers
- Synaptotagmin
Synaptojanin

(5) Cell Body /nucleus
UCH-L1, PrP

(6) Neuroregeneration markers
- CRMP-2 (axonal + Dendritic)

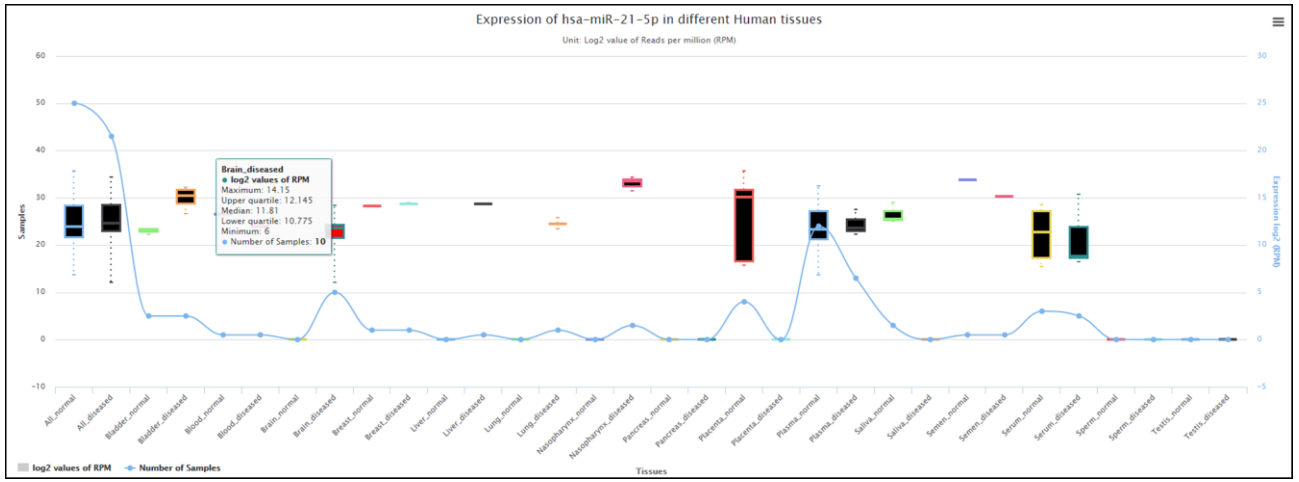
Kobeissy, et al. (2008) Proteomics: Clinical Applications, 2: 1467-1483.

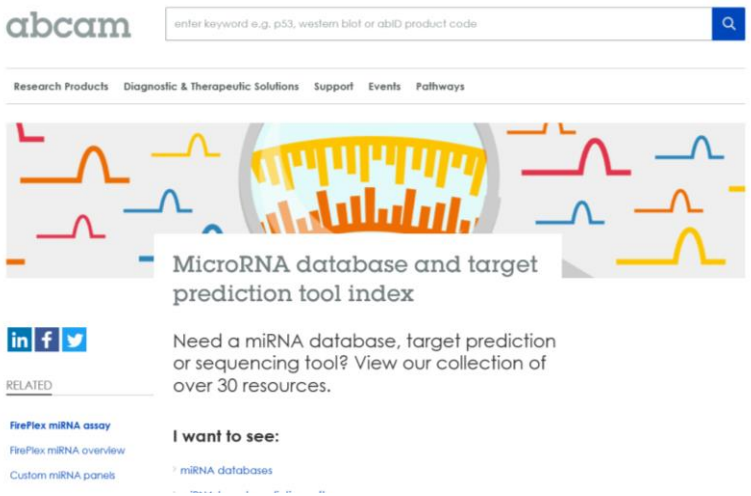
Sandwich ELISA Test



- **Antibody binds with antigen to confirm presence of biomarkers**
- **Commercially available swELISA kits**
  - **Quanterix Neurology 4-Plex**
  - **Neuromic**
  - **Lifespan**
- **Home-brew**

miRNA discovery





https://www.abcam.com/kits/microrna-database-and-target-predictor-resources

http://www.mirbase.org/

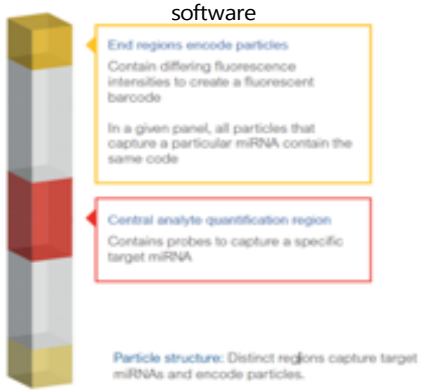
http://guanlab.ccmb.med.umich.edu/mirmine/help.html

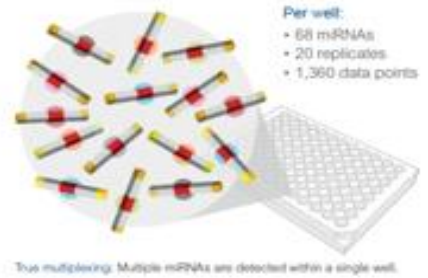
Firefly™ particle technology for multiplex miRNA assays

- Particles are made from a porous bio-inert hydrogel that allows target capture throughout the 3D volume. Compared with the leading bead-based platform

- Particles contain three distinct functional regions each separated from the other by inert spacer regions.
  - The central analyte quantification region contains probes that capture target miRNAs.
  - The two end regions function as two halves of a barcode to distinguish different particles

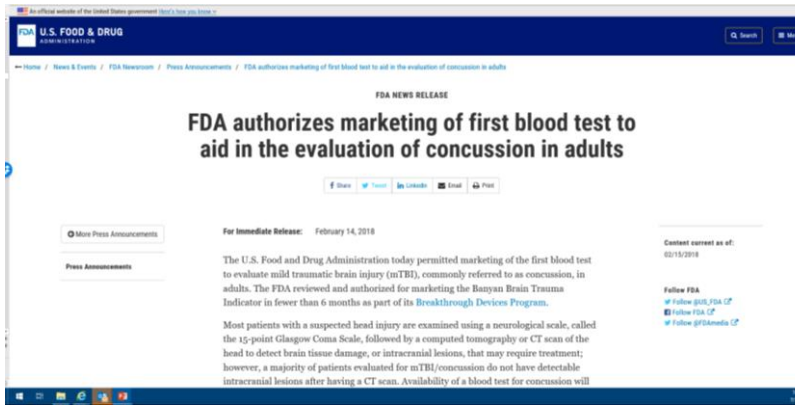
- Sample Hybridizes with Firefly miRNA capture particles
  ↓
- PCR amplification with labeling mix
  ↓
- rinse PCR product on firefly articles
  ↓
- Add reporter mix
  ↓
- Scan samples on Millipore guava easyCyte 6HT flow cytometer
  ↓
- Firfly Analysis Workbench software





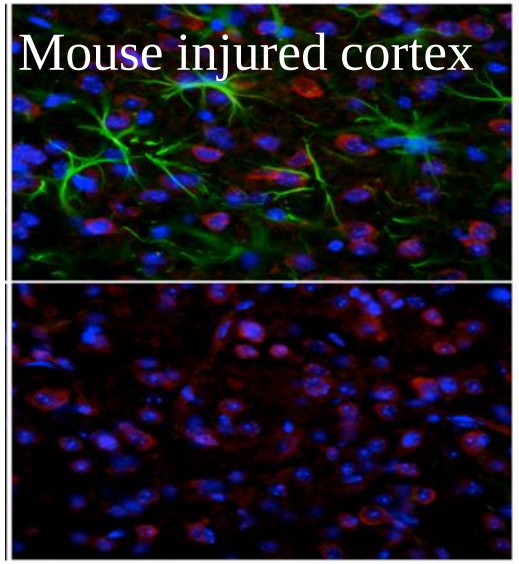
Guava easyCyte™ 6HT cytometer

UCH-L1/ GFAP - Brain Necrosis markers ?



- **FDA cleared** for acute phase detection of CT-detectable pathoanatomical lesions
- **Mainly tracking tissue necrosis**
- **= Contusion injury (?)**
- **4-6 h Manual/ Semi-automated ELISA assay**
- **NEXT**
- **Abbott Laboratories (i-STAT Alinity / ARCHITECT)**
  - UCH-L1/GFAP
  - (FDA approved devices)

Neuron-astroglia biomarker tandem
GFAP (green)
UCHL1 (red)



TRACK-TBI Phase 1 analysis: UCH-L1, GFAP, NSE, C-RP, S100B

DESIGN, SETTING, AND PARTICIPANTS

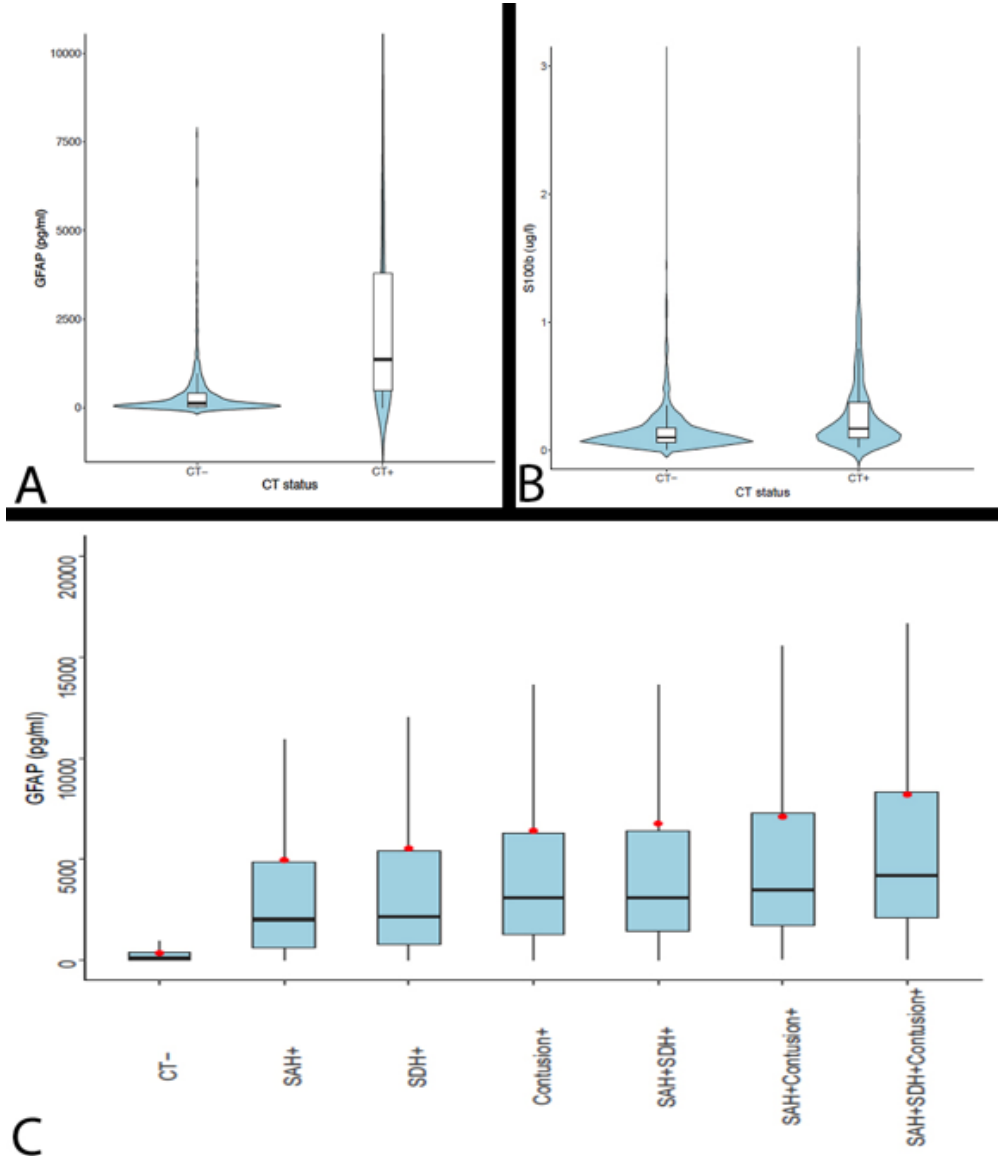
At the interim analysis point (Phase 1) of the TRACK-TBI study, we enrolled **1,375** participants with TBI across injury (GCS 3-15) and demographic spectra, along with **122** orthopedic injury and **209** healthy controls. Matching blood samples collected within 25 h post-injury were assayed with 2 clinical platforms: the Roche Elecsys® automated NSE and S100B assay and the novel Abbott i-STAT® point-of-care prototype UCH-L1 and GFAP assay; and Abbott Alinity ARCHITECT hsC-RP assay

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

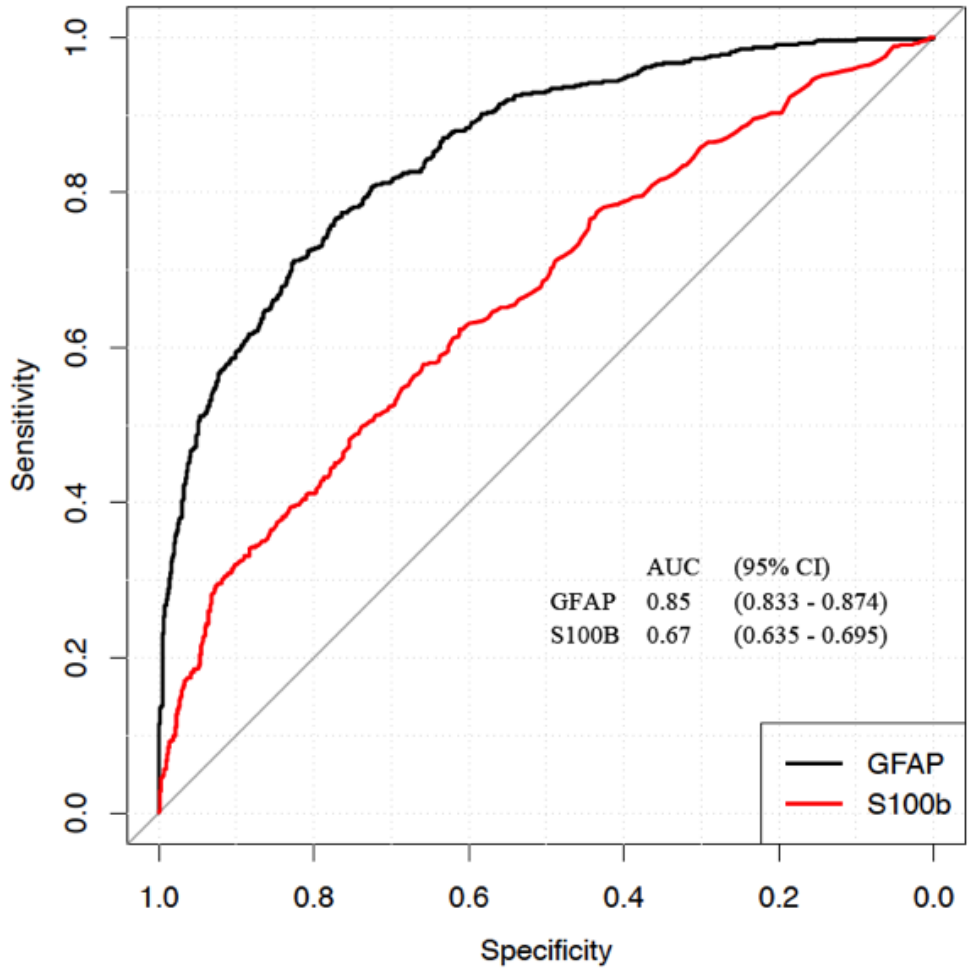
Abbott

Roche

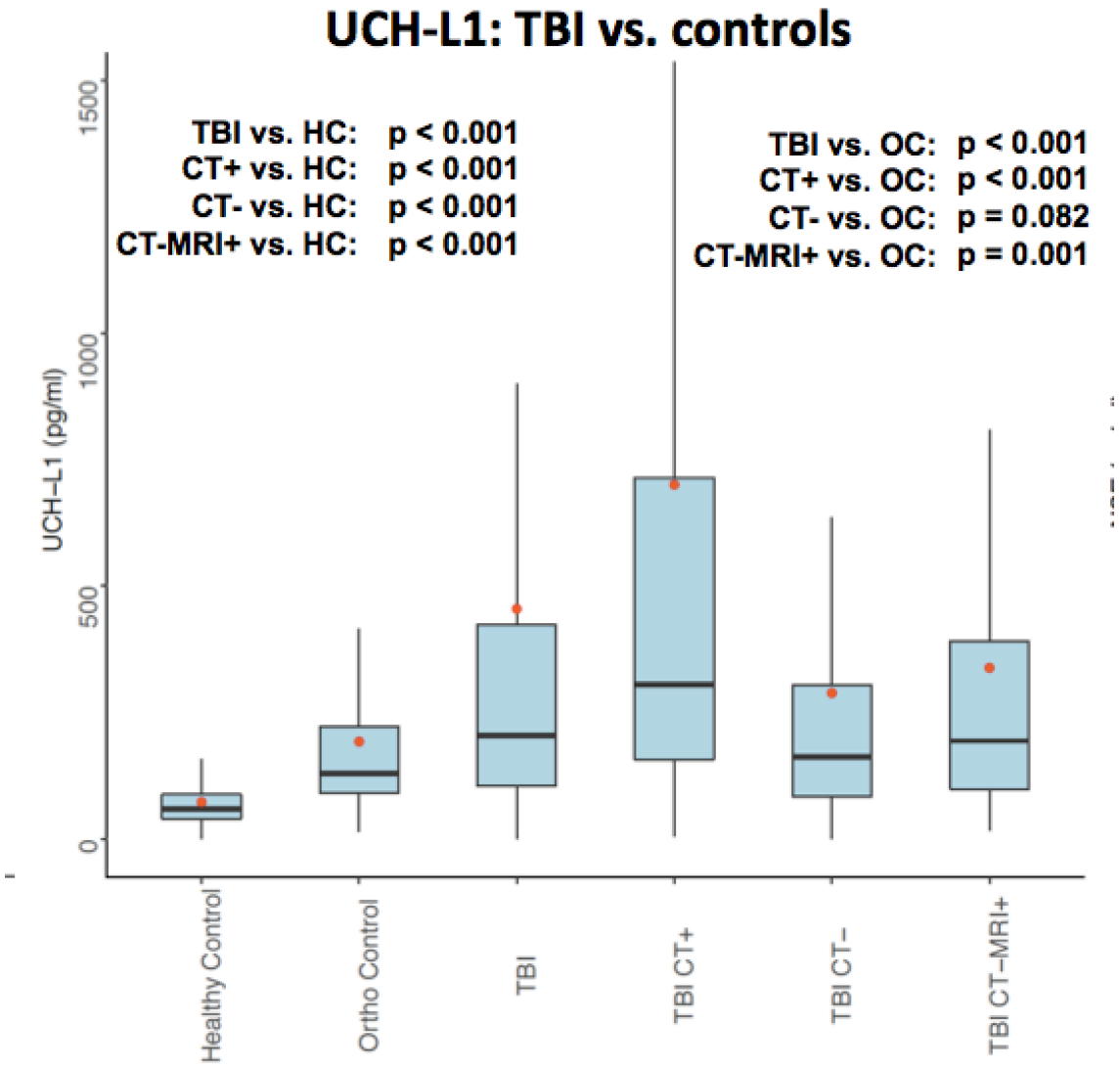
GFAP vs. S100B, NSE Diagnosing TBI by CT status



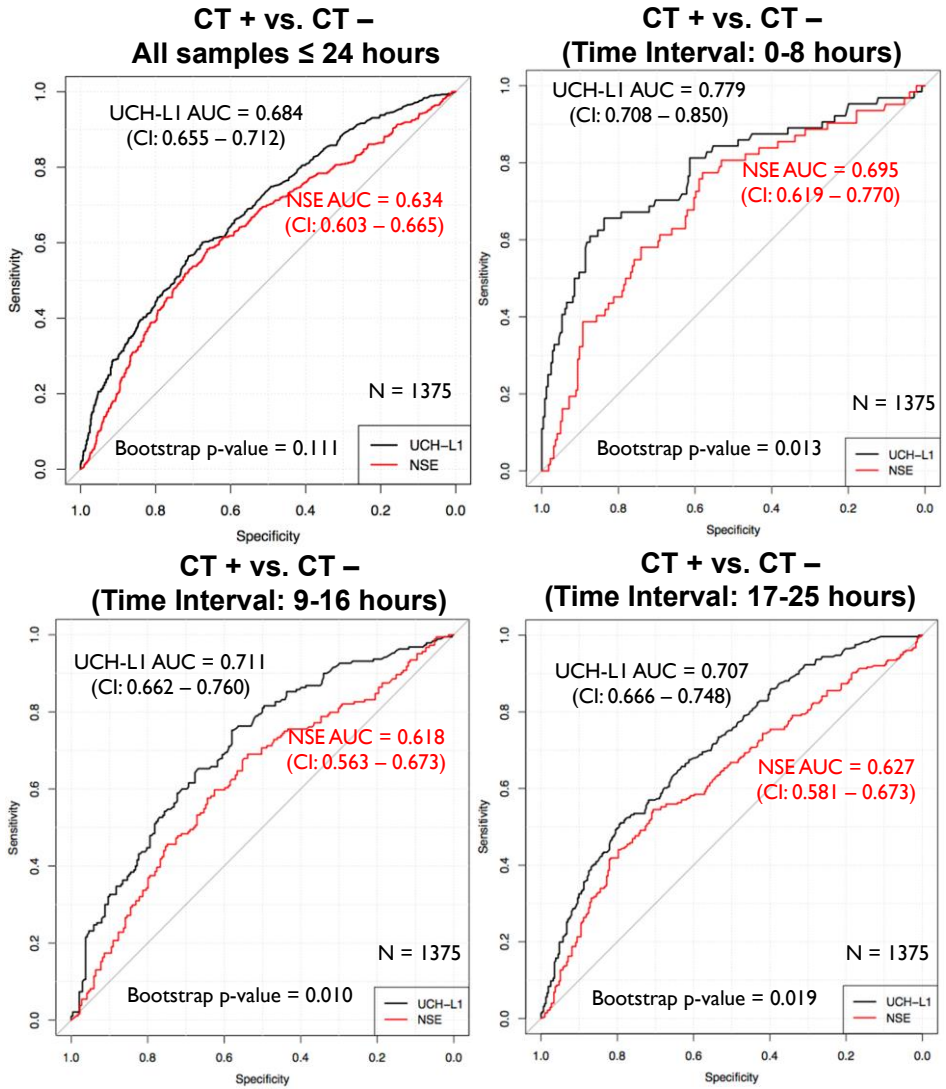
CT+ vs. CT -

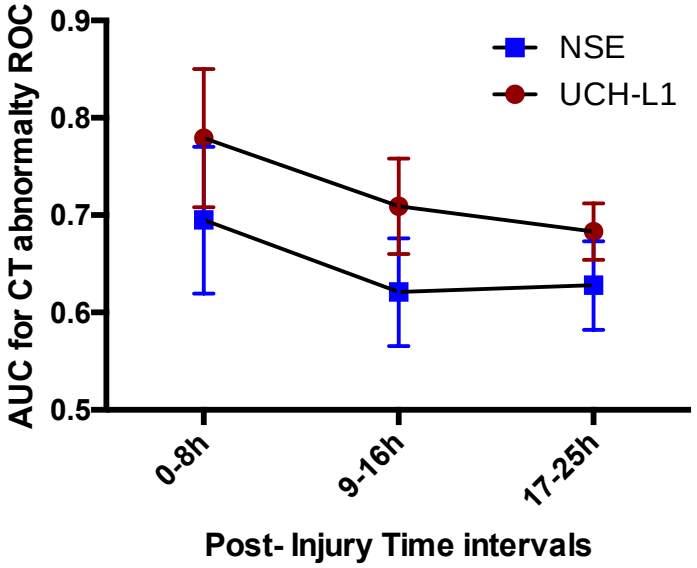


UCH-L1 blood levels by CT/MRI status among TBI subjects



UCH-L1 and NSE ROC Analysis for CT+ vs. CT- TBI subjects at different time intervals.





	UCH-L1	NSE
0-8h vs 9-16h	0.128	0.096
0-8h vs 17-25h	0.089	0.136
9-16h vs 17-25h	0.904	0.806

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

POSSIBLE Diagnostic devices : from Core Lab to POC

- **Abbott Laboratories (i-STAT Alinity / ARCHITECT)**
  - UCH-L1/GFAP (Device approved)
- **Roche (Cobas)**
  - **S100b, NSE**
  - TBI markers
- **Phillips (Minicare)**
  - TBI biomarkers / Device approved
- **BioDirection (Tbit)**
  - GFAP / S100B
  - Device in development

OUR GOAL-----multiple platforms as "Fit for Purpose" HIE diagnostics/prognosis

Civilian Medicine

Major Hospitals – Core Lab

Emergency Room/ Neurointensive Care

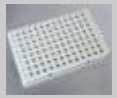
Reference Lab

QUEST, etc.

Doctor's office; Clinics

HIE Diagnostic Test Platforms

(A) ELISA plates & Microplate-Readers



(B) Semi-automated high sensitivity multiplex workstation

(C) Automated ELISA stations

(D) POC Platforms

(F) Handheld Devices

Research

Animal studies

Human studies

Family Support

Acknowledgements

Department of Emergency Medicine---Kevin Wang, Haiyan Xu, J. Adrian Tyndall
Department of Pediatrics---Michael Weiss, Livia Sura, Candace C Rossignal

SUNY-DOWNSTATE

Baylor College of Medicine

University of Miami

Orlando Regional Medical Center

Uniformed Services Univ. of the Health Sciences

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

University of California
San Francisco

University of Pécs

Chinese Univ. of Hong Kong

Walter Reed Army Institute of Res.

University of Pittsburgh

Banyan Biomarkers

CENTER-TBI

Antwerp University /
Univ. Cambridge

ICON-TBI

Univ. Cambridge
Mario Negri Institute, etc.