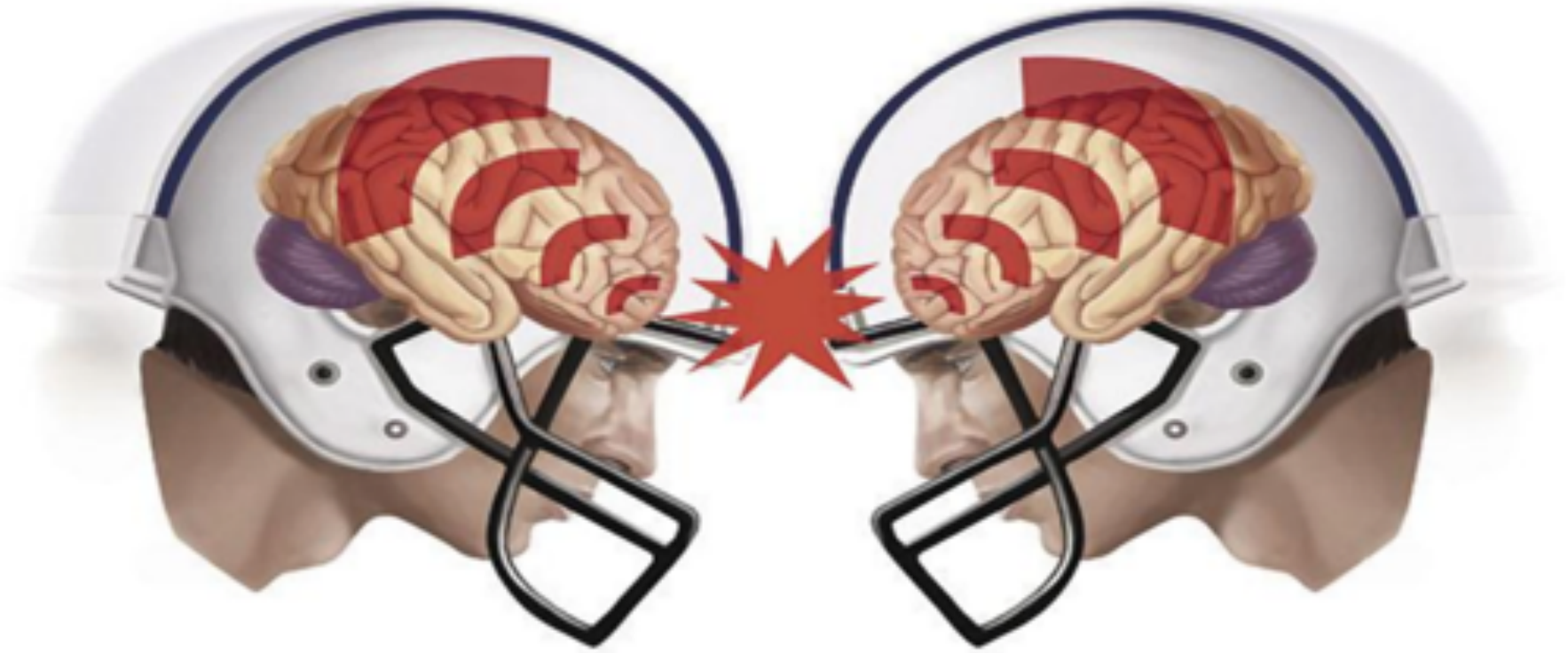
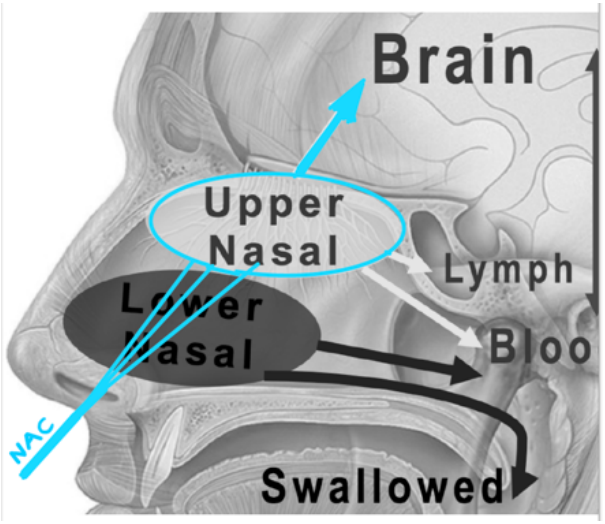
CONCUSSION: NO drug TREATMENT



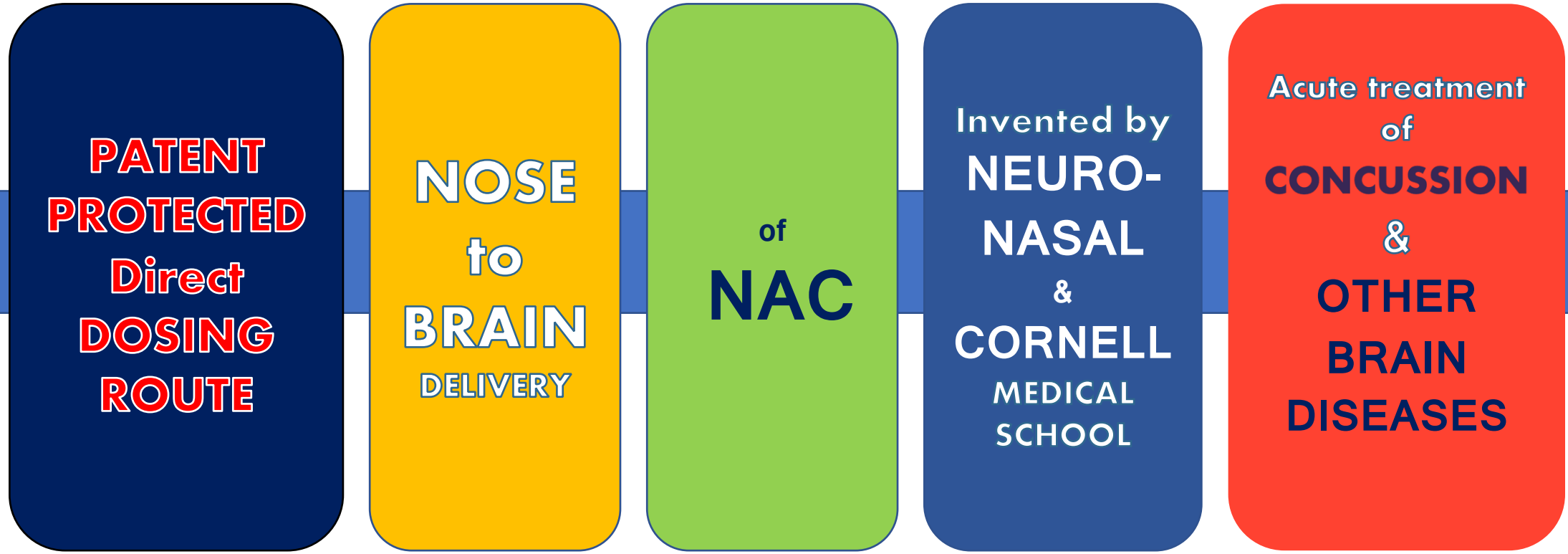
NeuroNasal Presents

A Paradigm Shift in Treating Concussion

NOSE-to-BRAIN DRUG DELIVERY TO TREAT CONCUSSION and PREVENT PERSISTENT SYMPTOMS



NEURONASAL LLC
IN (intranasal) dosing of NAC (N-Acetylcysteine)



WHAT IS CONCUSSION ?

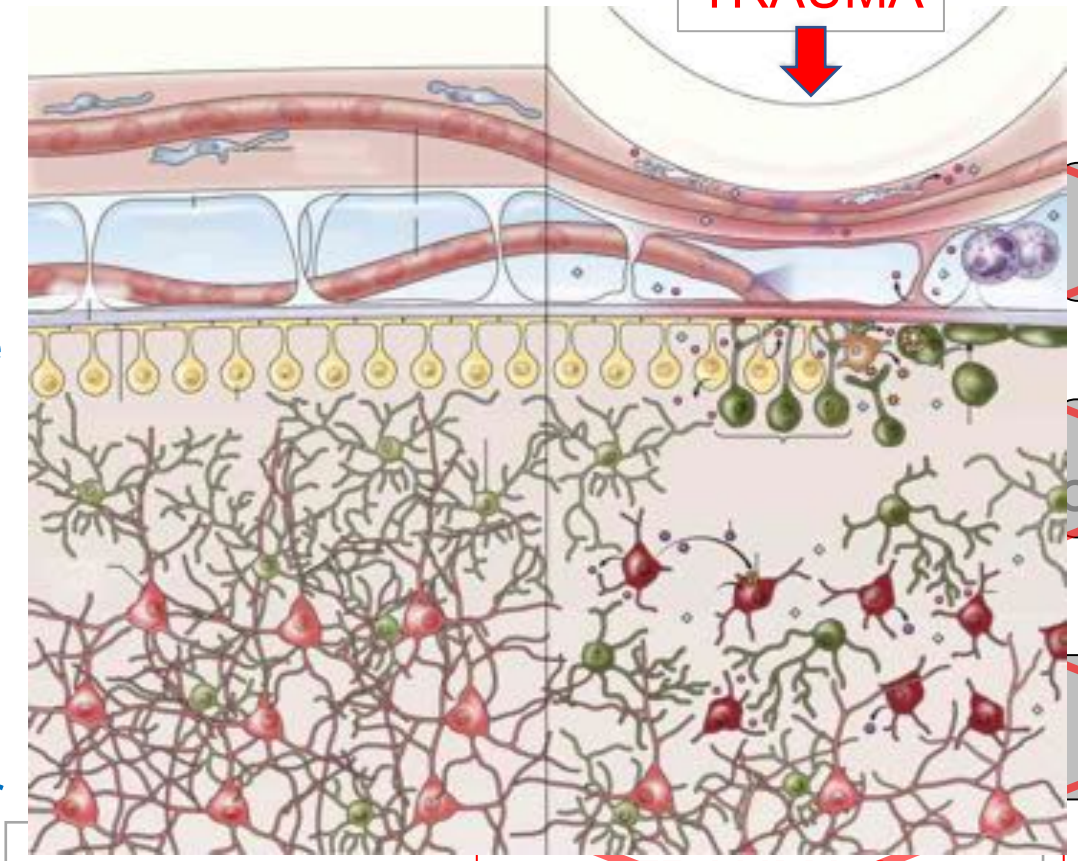
CONCUSSION IS A 2 STAGE INJURY

1st : IMPACT (the BANG): stretching and tearing of neurons and blood vessel

2nd STAGE : is biochemical damage caused by stretching

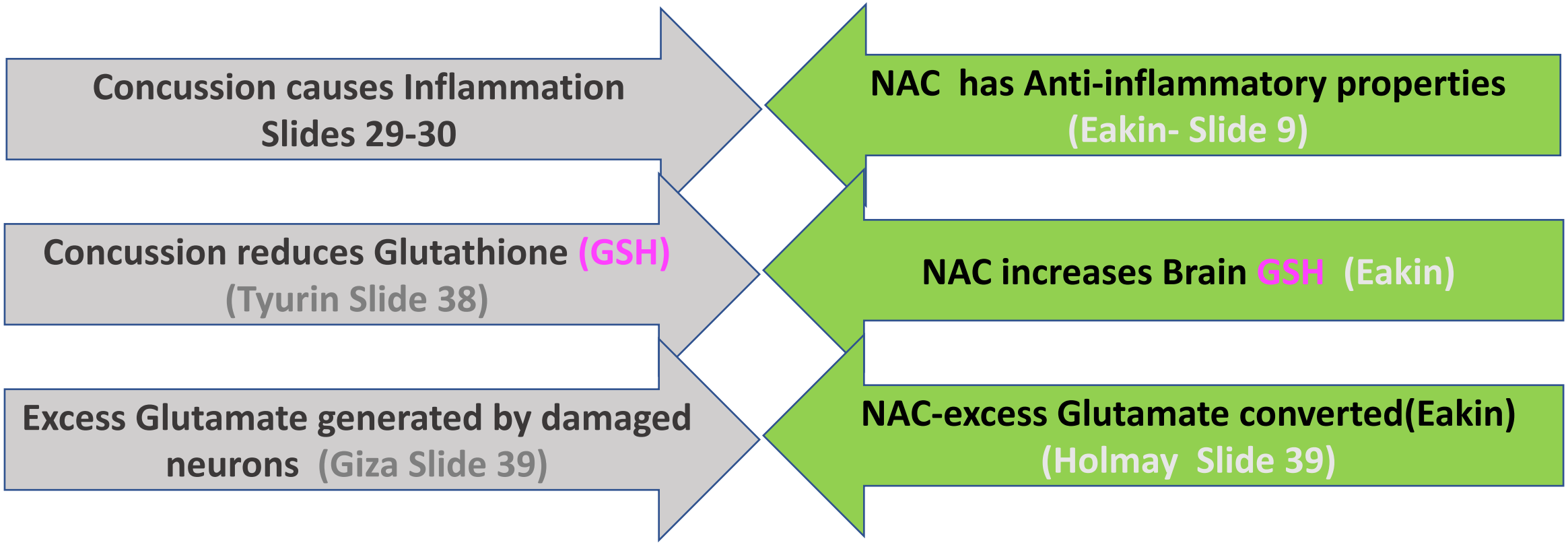
The second stage that NeuroNasal DRUG TREATMENT is treating-by addressing the three chemical routes of damage

PATHOBIOLOGY OF CONCUSSION & PHARMACOLOGY OF NAC

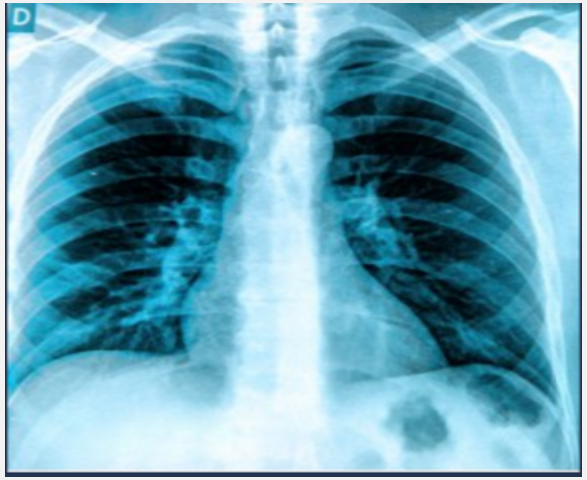


NEURONASAL IS USING NAC (N-Acetylcysteine) A PROVEN MEDICINE TO TREAT CONCUSSION by ORAL and IV ADMINISTRATION

N -acetylcysteine addresses the 3 major damage pathways above



N-ACETYLCYSTEINE (NAC) is SAFE - used for 40 years



TYLENOL OVERDOSE

and

as a MUCOLYTIC

NAC (N-ACETYLCYSTEINE) FOR BRAIN INJURY IN NEURONASAL'S SYSTEM

IP covering NOSE to BRAIN NAC

SAFE DRUG, PROVEN DEVICE

EFFICACY IS PROVEN

FDA APPROVED MEDICINE administered for several indications

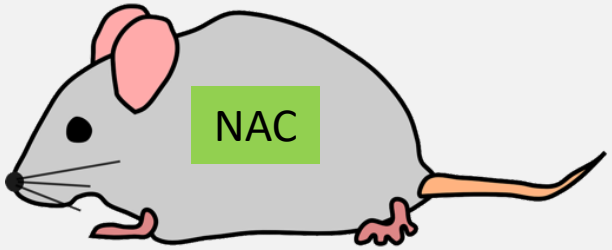
DEVICE (Drug Master File) Used with Narcan, & others.

EFFICACY of NAC is proven by several studies

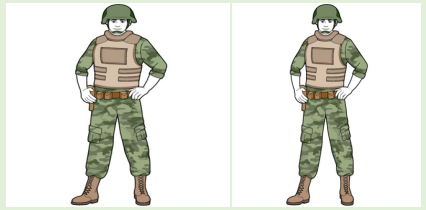
CONCUSSION MODEL SHOW IMPROVED PERFORMANCE WITH NAC VERSUS NO NAC

(Eakin K et al 2014 PLoS ONE 9(4): e90617.doi:10.1371/journal.pone.0090617)

RAT Intraperitoneal NAC study



SOLDIER STUDY: MEGA DOSE



HUMAN HIGH ORAL DOSE NAC SHOWS MORE THAN 85%

WERE SYMPTOM FREE IN STUDY DONE ON 81 US SOLDIERS.

(HOFFER Slide 39)

NAC WORKS : Clinical Data, Oral Administration

(Hoffer Study)

81 soldiers
Blast-exposed Military Service

7days > HIGH DOSE (4 gm loading then 2 gm twice daily→1.5 gm twice daily) compared with placebo

AFTER 7 DAYS those who were treated in 24 hours after injury 86% were Free of : impaired balance, sleep-disturbance, memory problems, confusion, head-ache, hearing/loss.

Three cohorts: placebo, initially treated within 24 hours of injury and initially treated after 24 hours. (Hoffer)

PROBLEM with MEGA Oral dosing

SIDE EFFECTS;

nausea, vomiting,
headache, dizziness,
diarrhea (Dean et al 2011.)

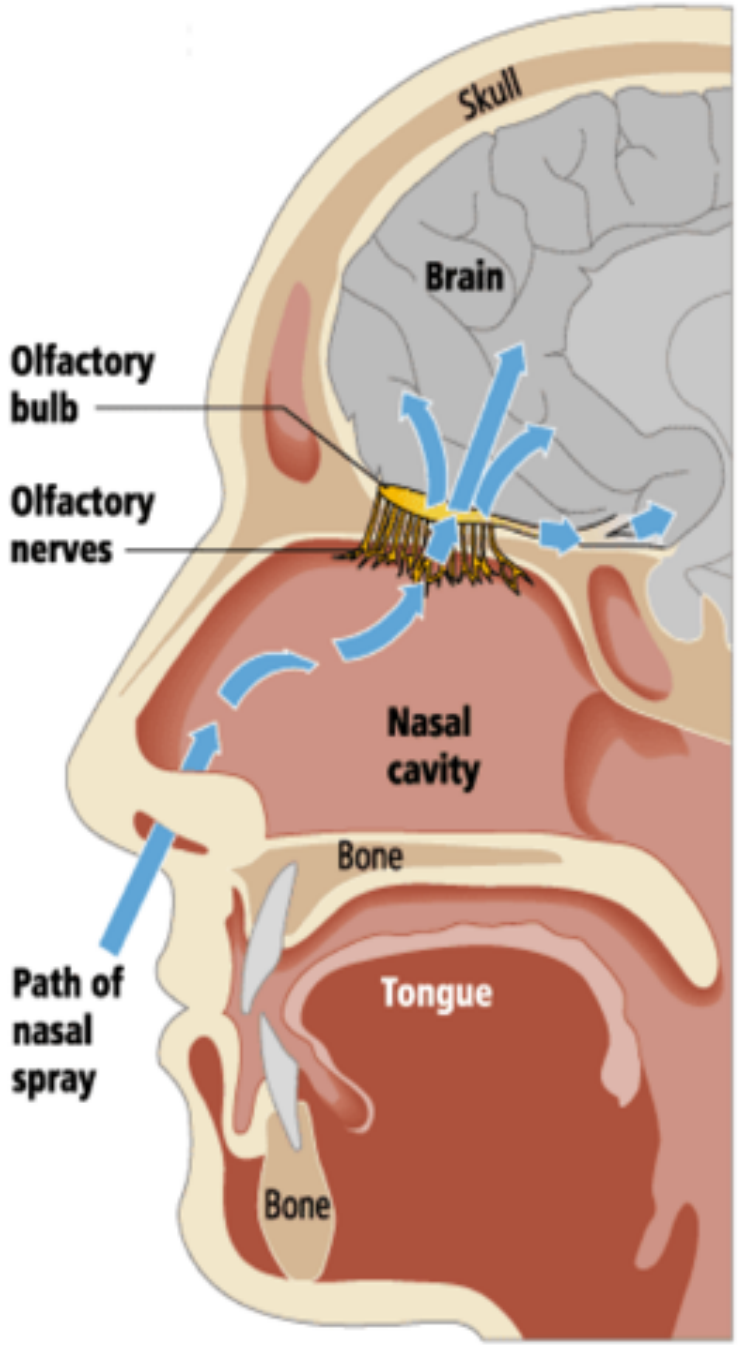
LOW BIOAVAILABILITY

IV, INTRAVENOUS NAC DELIVERY PROBLEM:

REQUIRES 5 DAYS HOSPITAL STAYS

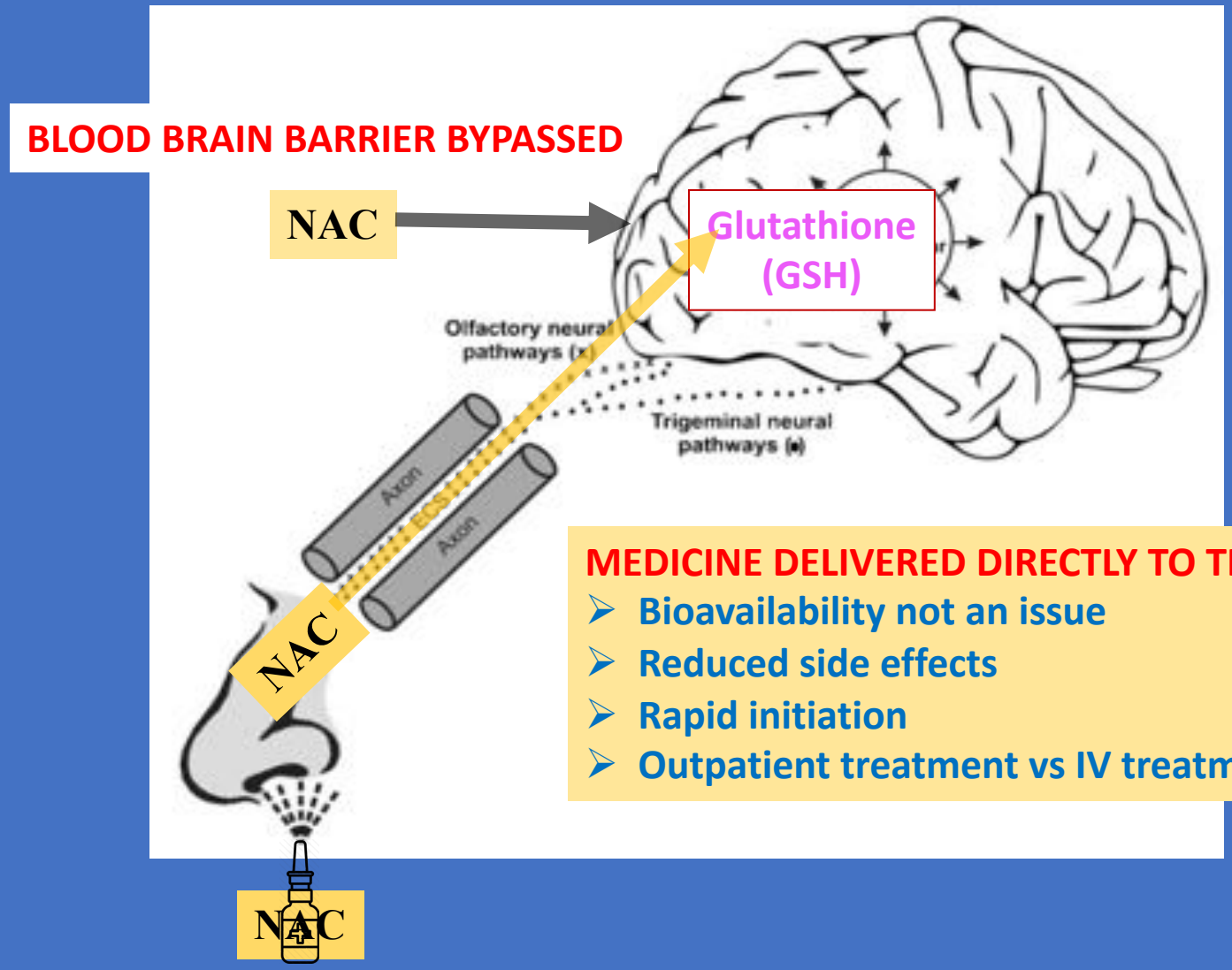
NEURONASAL DEVICE proven to deliver medicine to the upper 3rd of the nose - crucial to get to the brain

APTAR UDS



DEVICE IS PROVEN-PRESENTLY USED FOR DELIVERY OF NALOXON FOR OPIOID OVERDOSE -NARCAN

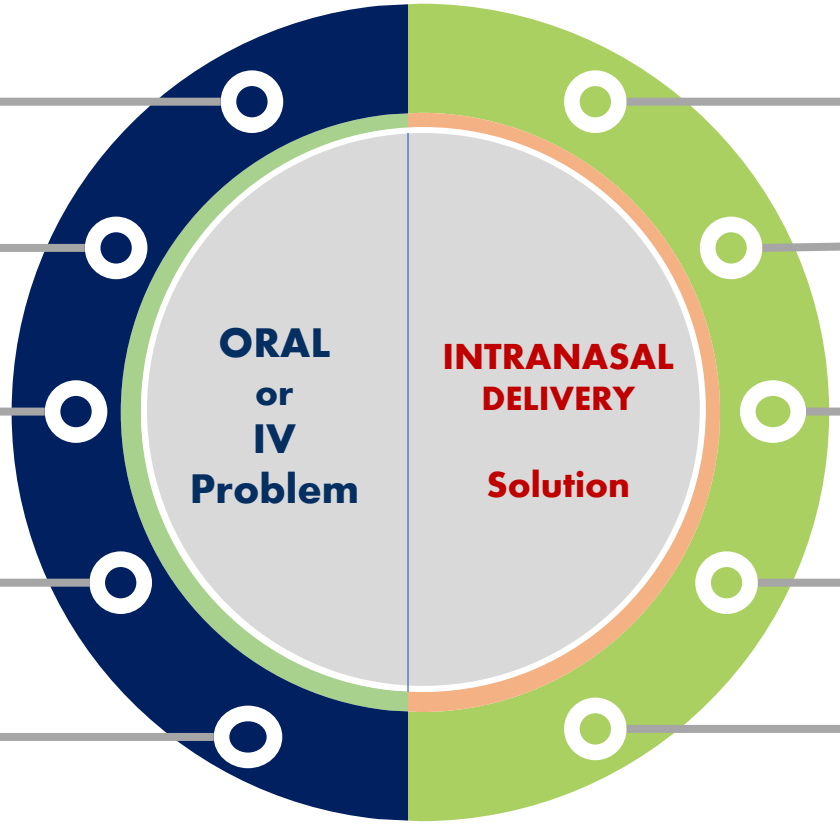
MEGA DOSE : Not needed with NEURONASAL's IN NAC DELIVERY SYSTEM



MEDICINE DELIVERED DIRECTLY TO THE BRAIN

- Bioavailability not an issue
- Reduced side effects
- Rapid initiation
- Outpatient treatment vs IV treatment

WHY IN (INTRANASAL) DELIVERY for BRAIN INJURY



Poor bioavailability

Mega dose needed

Mega Oral dose: dizziness, headache, vomiting

IV delivery: impractical - hospital stay

IV Not viable treatment

Superior bioavailability

Bypass Blood Brain Barrier

Reduced side effects

Out patient treatment

Rapid initiation of treatment

1st step: PILOT STUDY at Weill Cornell Medical School

OBJECT to PROVE that the MEDICINE GETS TO THE BRAIN

10 healthy volunteers

INTRANASAL NAC

Concentration of GSH in the Brain will be measured by MRS

COST: $150,000; duration 2 months; GO-NO-GO study

NEURONASAL HAS AN INCREDIBLE ADVANTAGE : HUMAN STUDY can be conducted (no animal trial needed)

IF GO : PILOT SUCCESS
2month;$150,000

PHASE I. will costs $3.5 M and take 1.5 YEARS

PHASE I. was designed with help of US ARMY

NEURONASAL HAS LETTER of SUPPORT from US ARMY indicating they will seek DOD funding for PHASE II.

Significant STEP UP IN VALUE Phase I and II; LOW COST

NEURONASAL

$150K PILOT FORETELLS SUCCESS IN PHASE I $3.5 MILLION

$3.5M RAISE
150K FIRST TRANCHE (go/no-go)

More complete presentation on our website (www.neuronasal.com)
White paper on science and clinical plan available

Strong Drug Development & IP Team

World-leading scientists in brain damage research
Highly experienced drug development team

Joseph Hulihan, MD
Chief Medical Officer

Thomas Argentieri, PhD
Senior Business Development and Commercialization Advisor

Thomas Bradshaw,
CEO / Co-Founder
Co-Inventor IN NAC

Rajiv Ratan,MD,PhD
Chair, Scientific Advisory Board
Co-Inventor IN NAC

Douglas Greene, MD
Head of R&D/ Senior Clinical Advisor

Legal/IP: Wilson, Sonsini, Goodrich & Rosati

2 MILLION PEOPLE IN THE USA AND 2 MILLION IN EU VISIT ER WITH CONCUSSION every year

50% OF CONCUSSION SUFFERERS HAVE PERSISTENT CONCUSSION EFFECTS

(McInnes slide 42)

5 MILLION PEOPLE (US) HAVE LONG TERM POST CONCUSSION SYMPTOMS

CONCUSSION MARKET IS A $3 BILLION target MARKET

NEURONASAL REVOLUTIONARY CONCUSSION TREATMENT brings incredible value for PARENTS, ATHELETS, INJURED and MILITARY all could be treated RIGHT AT THE SPOT.

NEURONASAL's SUCCESS: EVERYBODY WINS : SOCIETY and INVESTORS

APPENDIX

Licensing/Sale - after Phase II

- **The Drug device combination will be sold to ER and sports medicine initially**
  Near term: Companies serving hospital markets and emergency rooms are near term targets-especially those companies with neuroscience line;
  Longer term: Pharmas with over the counter businesses. The over the counter market will develop after the roll out to the hospital/ER market.

- **Target Companies**: J&J, Roche/Genentech, Novartis, Biogen, Merck, Takeda, Lilly, Amgen and Mallinckrodt.

DOD business may be built after Phase II

ADVANTAGES

Approach enables immediate initiation of therapy (essential for efficacy) and continued outpatient treatment.

Low technology risk, marketed delivery device, safe drug, validated biomarkers, proven clinical efficacy.

Strong supporting preclinical and clinical evidence to use 505(b)(2) regulatory pathway.

DoD support of program and ability to collaborate with CARE Consortium

Strong IP: Neuronasal- a proprietary drug-device combination & method of delivery claims.

NeuroNasal's FIRST TARGET: CONCUSSION

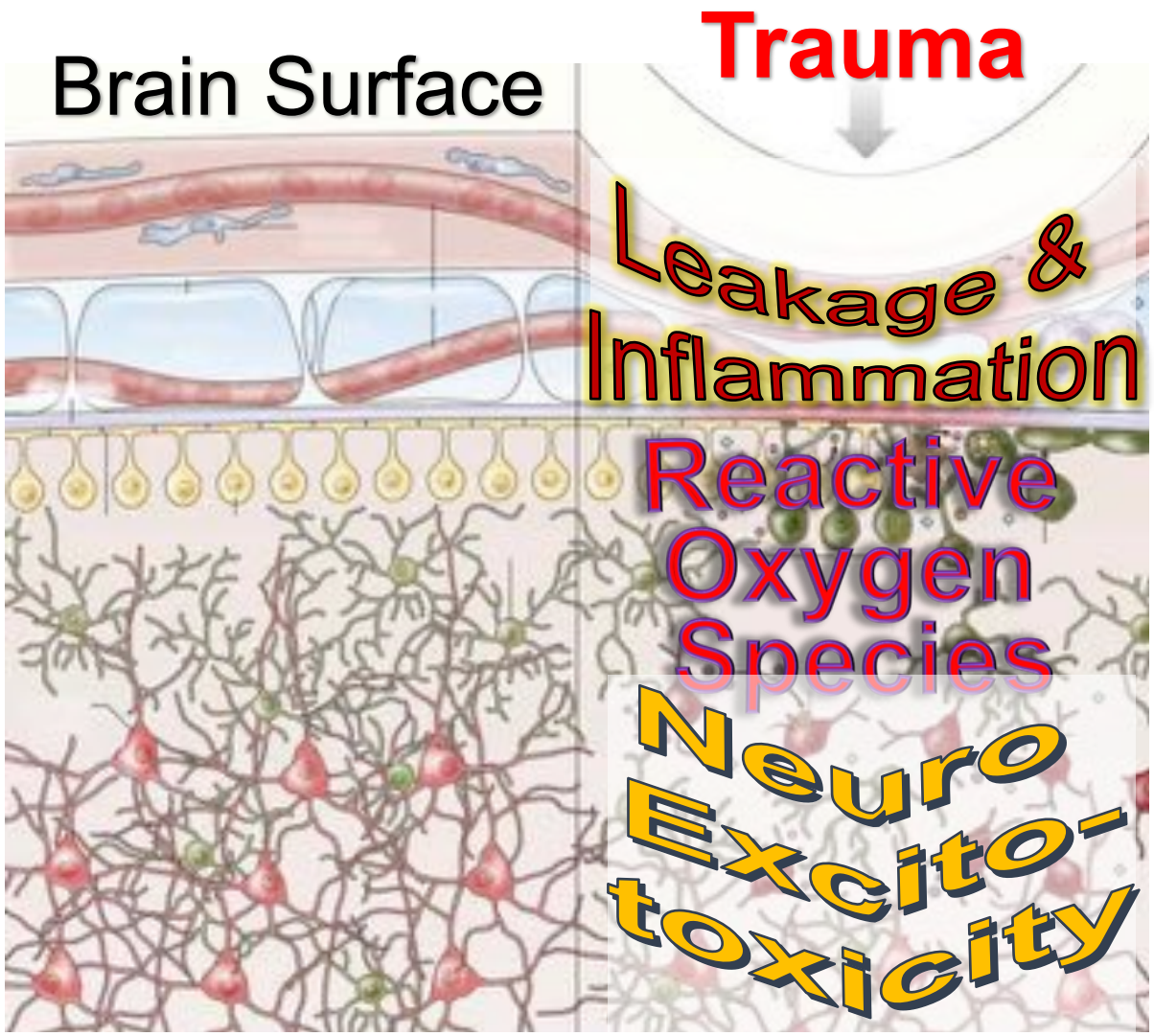
CURRENT TREATMENT	**NO DRUG TREATMENT for concussion, suggested treatment is rest. BUT with NeuroNasal's IN NAC, return to activity faster with fewer symptoms**
MARKET	**$3 Billion US and EU Concussion market-**reduced symptoms
2 Million New Patients In ED per Year in US	**For many - 50% - major disruption; approximately; 5 million patients in the US show long-term deficits from mild brain injuries (concussions).**
OUTPATIENT	**IN NAC can be applied on location right after injury, and at home Faster return to health, fewer persistent symptoms**

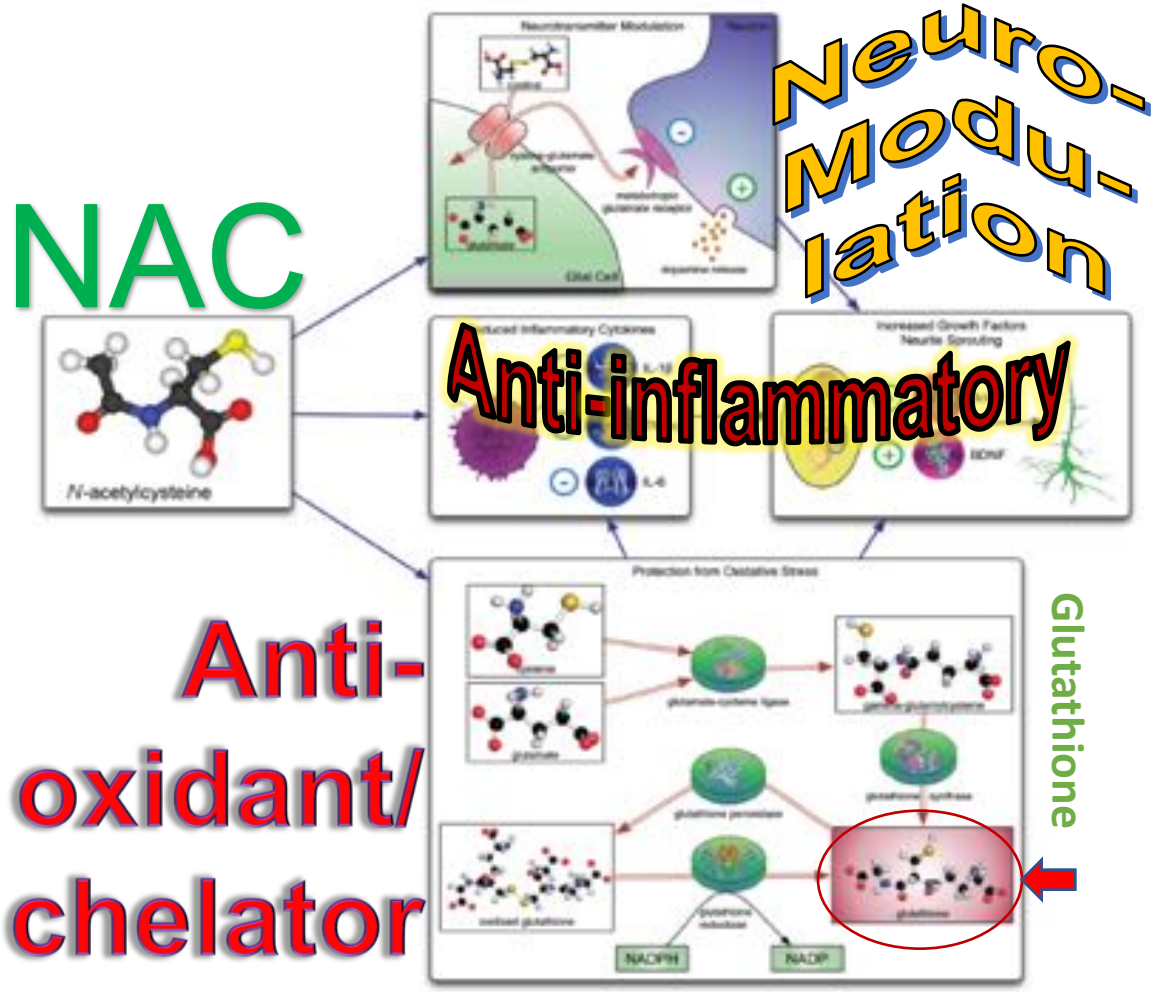
NEURONASAL IS A REDUCED RISK DEVELOPMENT PROJECT

- **First tranche ($150K) will be used for human pilot study of nose to brain on IN NAC on ten subjects at Weill Cornell Medical School, a collaboration partner with Neuronasal**
- **The pilot study will**
  - **utilize INTRANASAL (IN) NAC and monitor the increase in brain Glutathione 10 subject human study**
  - **completed within 2 months**

- **Success with the pilot study greatly reduces program risk**
- **Parkinson's Disease and other opportunities**

Pathobiology of Concussion & Pharmacology of NAC

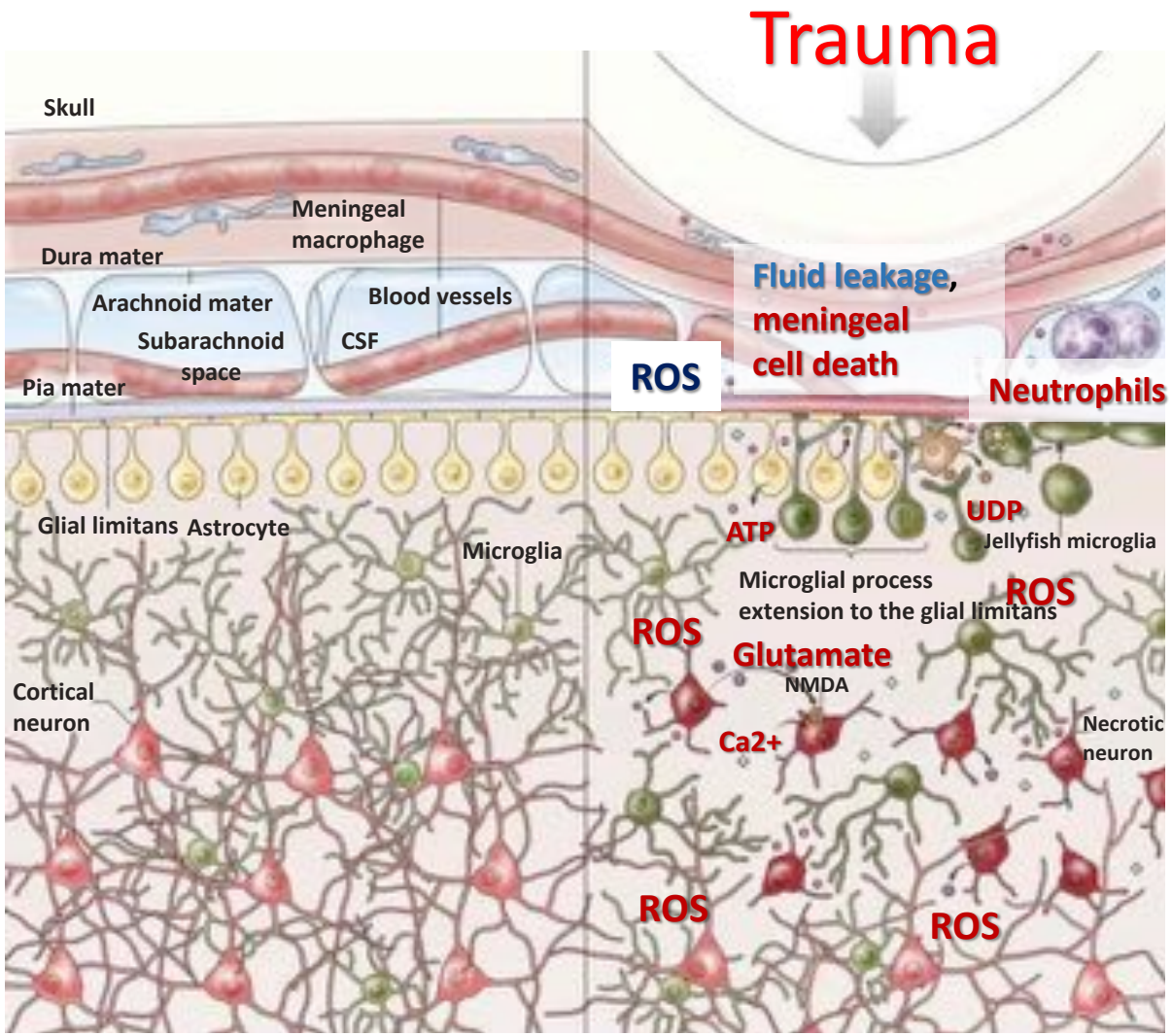




Adapted from Corps KN et al 2015. JAMA Neurol 72:355-362

Adapted from Dean O et al 2011. J Psych Neurosci 36:78-86

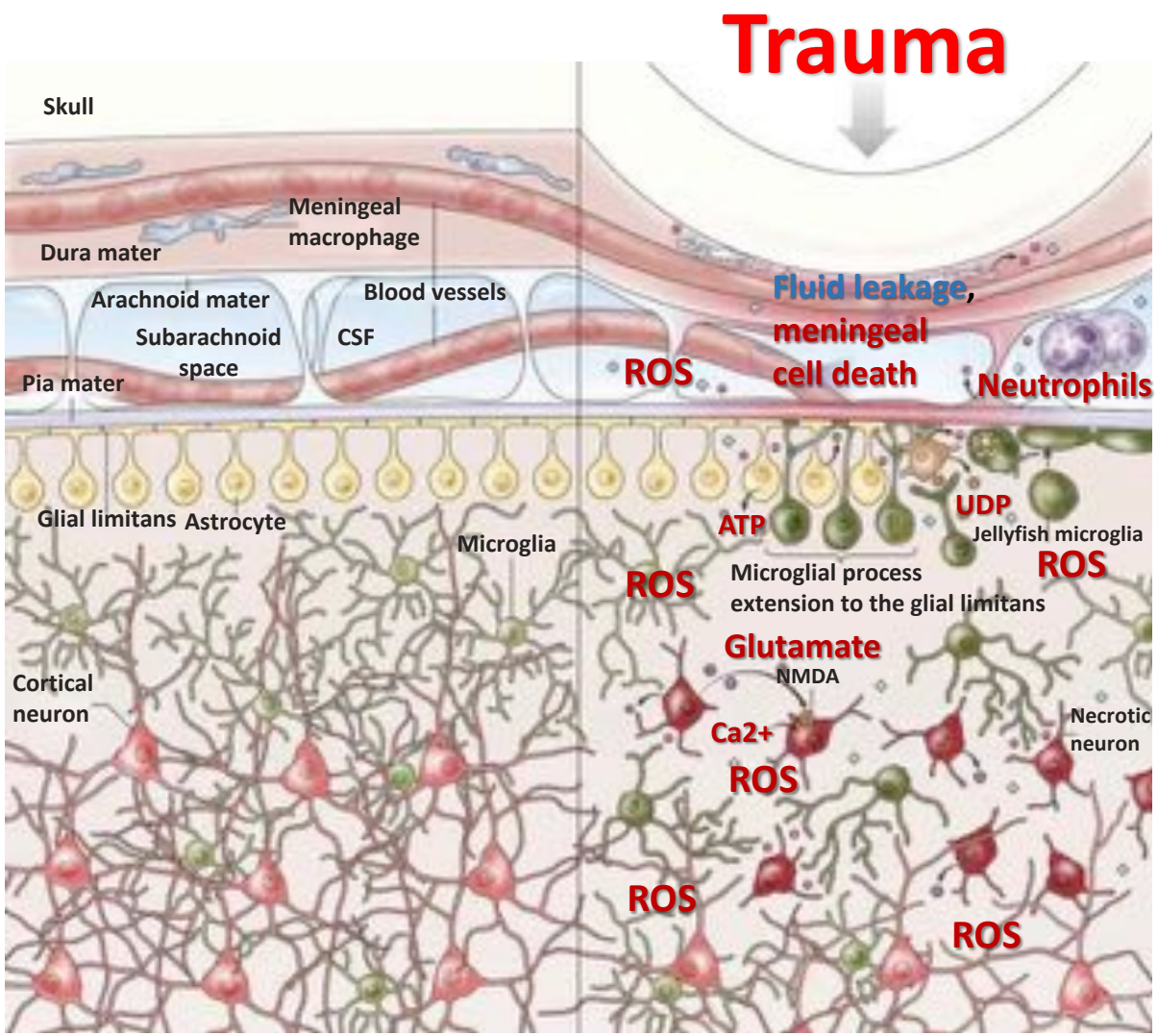
PATHOBIOLOGY OF CONCUSSION at the BRAIN SURFACE



Adapted from Corps KN et al 2015. JAMA Neurol 72:355-362

- **Brain anatomy before focal trauma.** The dura mater has small blood vessels lined by thin meningeal macrophages. The subarachnoid space contains vessels, stromal cells, and cerebrospinal fluid (CSF). The glial limitans, composed of astrocytic foot processes, lies beneath the pia mater and separates the CSF from underlying parenchyma.
- **Mild focal trauma** compresses the meningeal space, compromising vascular integrity and inducing rapid necrosis of meningeal macrophages and structural cells. Leakage of fluid from meningeal blood vessels results in edema, and damaged meningeal cells release reactive oxygen species **(ROS)** and adenosine triphosphate (ATP), triggering a sterile immune reaction, glutamate release and neuro-excitotoxicity.

TRANSMISSION OF TRAUMA TO DEEPER BRAIN STRUCTURES



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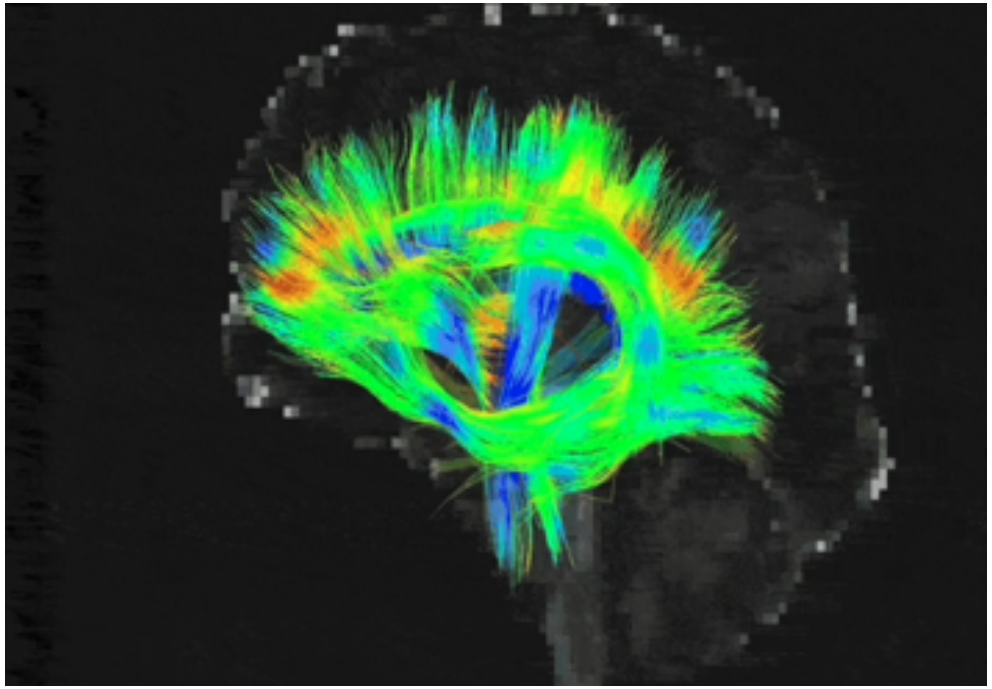


Concussive force transmitted deeper in the brain causes microstructural distortion and disruption of long nerve fiber tracts (red and yellow above) and blood vessels, causing a cascade of ischemia reperfusion injury, neuro-excitotoxicity, inflammation and **ROS**. Amount of fiber damage parallels post-concussion brain impairment

Niogi SN et al 2008. Am J Neuroradiol 10.3174/ajnr.A0970

Concussion Effects on Brain Glutathione

Concussion reduces brain Glutathione in RAT by 33% 24 hours following injury.

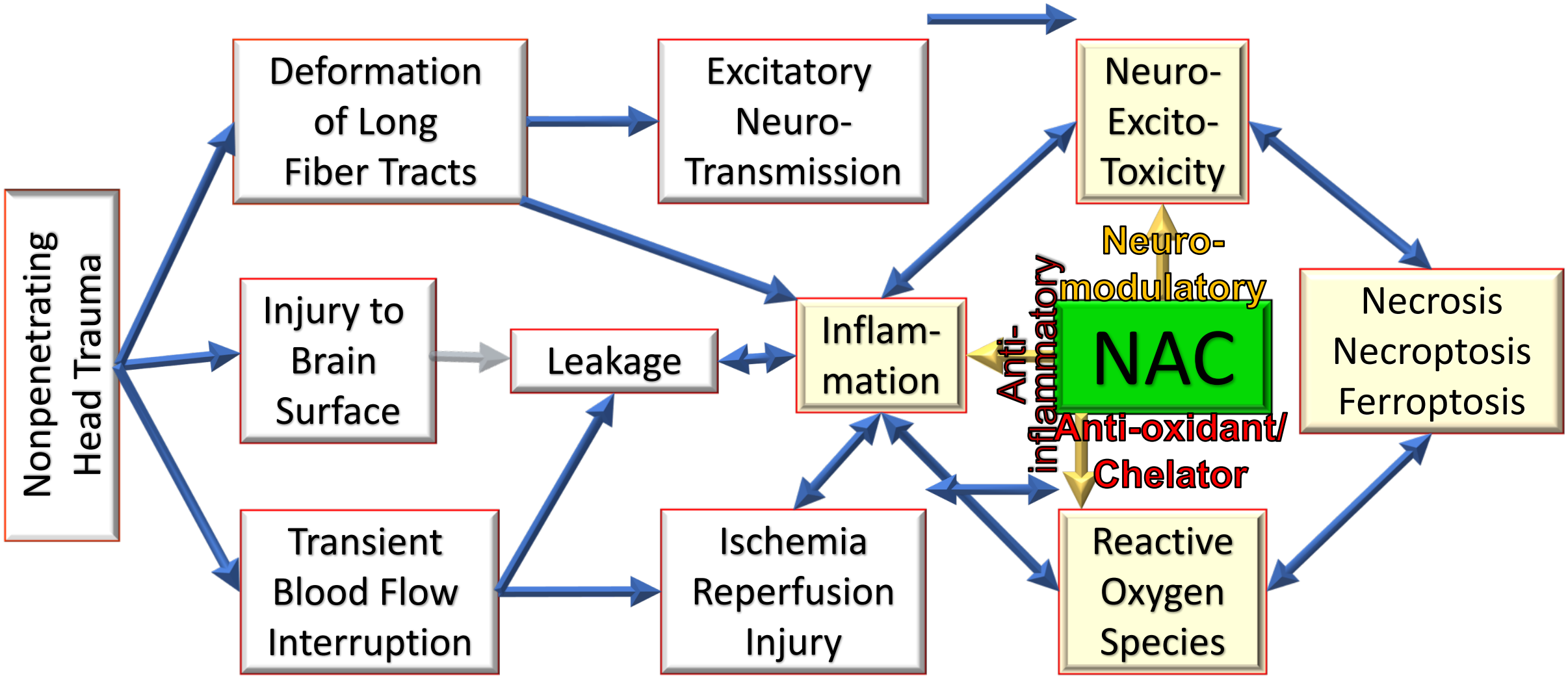
Oxidative Stress Following Traumatic Brain Injury in Rats: Quantitation of Biomarkers and Detection of Free Radical Intermediates *†Vl.Tyurin, *†Y. Tyurina, *G. Borisenko, *†T V. Sokolova, *V. Ritov, †P.Quinn, §Marie Rose, \P.Kochanek, §¶S.Graham, and V. Kagan

J Neurochemistry. 2000. 2178-2189

Direct brain delivery of Glutathione reduces concussion sequelae in rodents.
"GSH when applied continuously starting at 15 min or 3 hrs post-injury reduced parenchymal cell death at 12 hrs by 67% and 51%, respectively."

TRANSCRANIAL AMELIORATION OF INFLAMMATION AND CELL DEATH FOLLOWING BRAIN INJURY Theodore L. Roth, et al. National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD Nature. 2014 January 9; 505(7482): 223–228. doi:10.1038/nature12808.

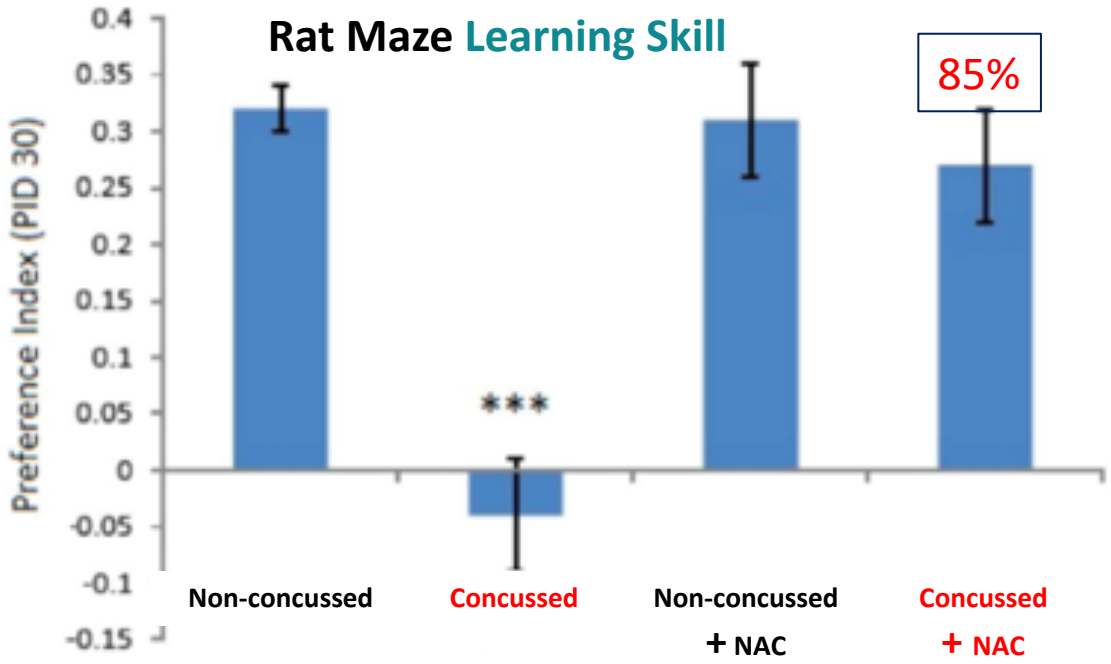
N-ACETYLCYSTEINE (NAC) ATTENUATES POST-CONCUSSIVE INJURY CASCADE



Corps KN et al 2015. JAMA Neurol 72:355-362; Roth TL et al 2014. Nature 505: 323-228. Cornelius C et al 2013. Antioxidants & Redox Signaling DOI: 10.1089/ans.2012.4981; Barkhoudarian G et al 2011. Clin Sports Med 30:33-48; Dean O et al 2011. J Psych Neurosci 36:78-86; Shahripour RB et al 2014. Brain & Behavior 4:108-122; Zille M et al 2015. Stroke 48:1033-1043

Experimental Data Concussed Rat Model using NAC

Cognitive Function



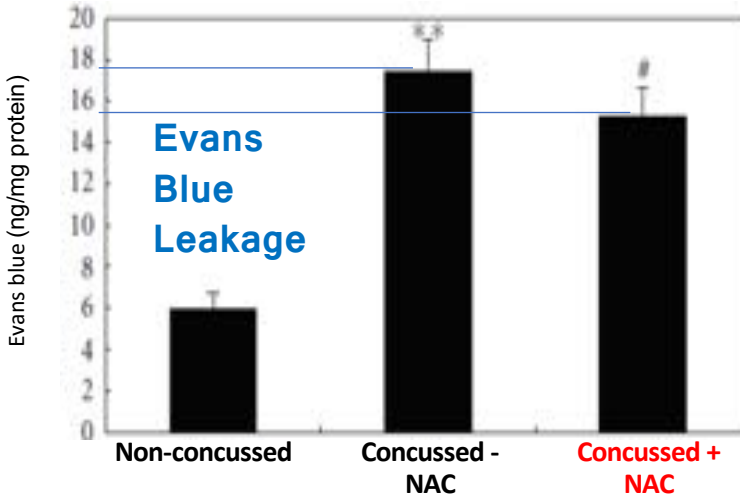
Eakin K et al 2014 PLoS ONE 9(4): e90617. doi:10.1371/journal.pone.0090617

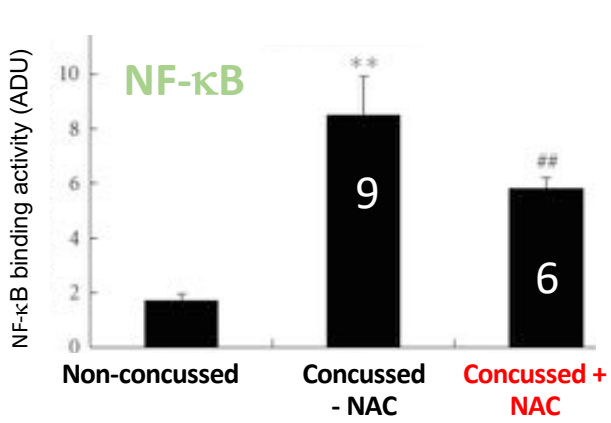
Concussed Rats treated with NAC 85% of them showed similar performance to rats with no concussion, NAC got the concussed rats back, close to the same performance level as rats with had no concussion

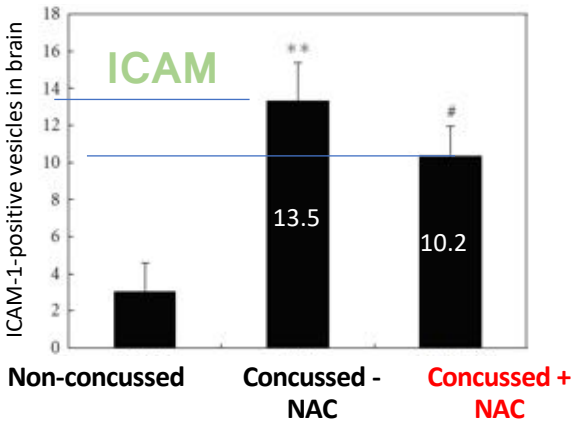
Experimental Data Concussed Rat Model Using NAC

NEURO-INFLAMMATORY RESPONSE

Results show that BBB leakage and inflammatory markers are elevated after concussion (concussed -NAC) but not as elevated when treated with NAC (concussed +NAC)





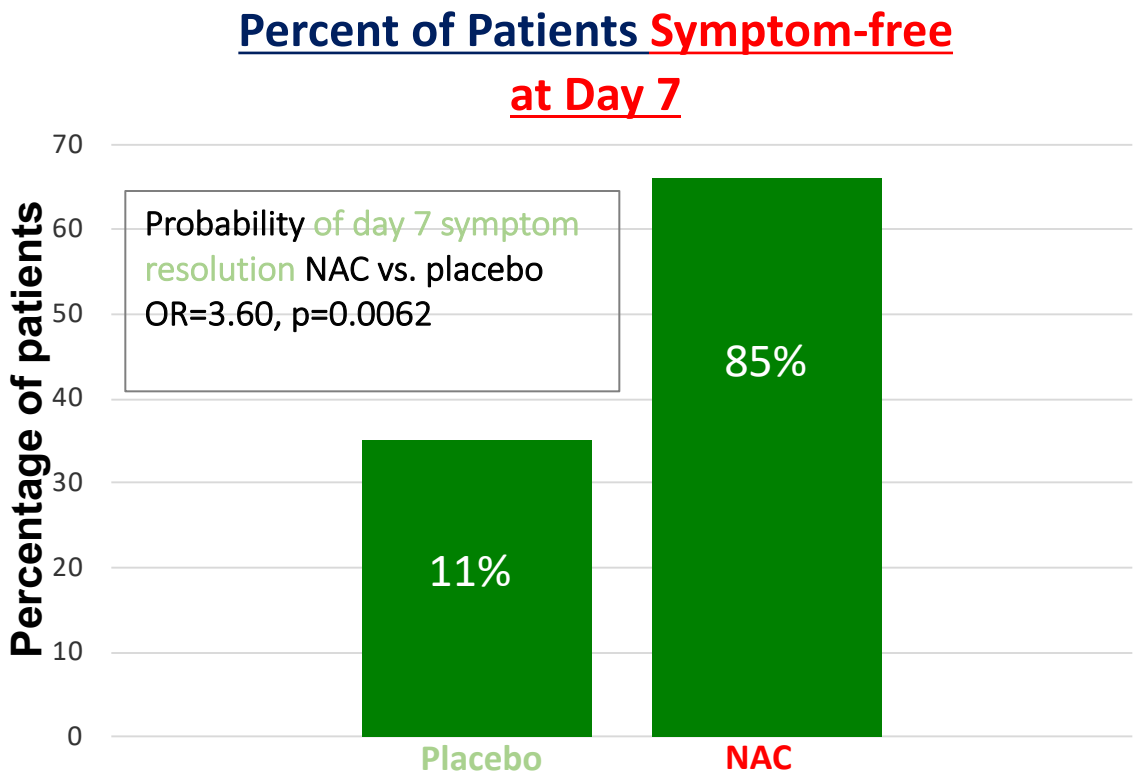


Blood-brain-barrier(BBB) leakage Is reduced by +NAC application

Inflammatory markers : are reduced using +NAC compared to no -NAC application

Eakin K et al 2014 PLoS ONE 9(4): e90617. doi:10.1371/journal.pone.0090617

CLINICAL DATA
NAC Reduced Post-concussive Symptoms in Blast-exposed US Military Service Personnel Compared to Placebo



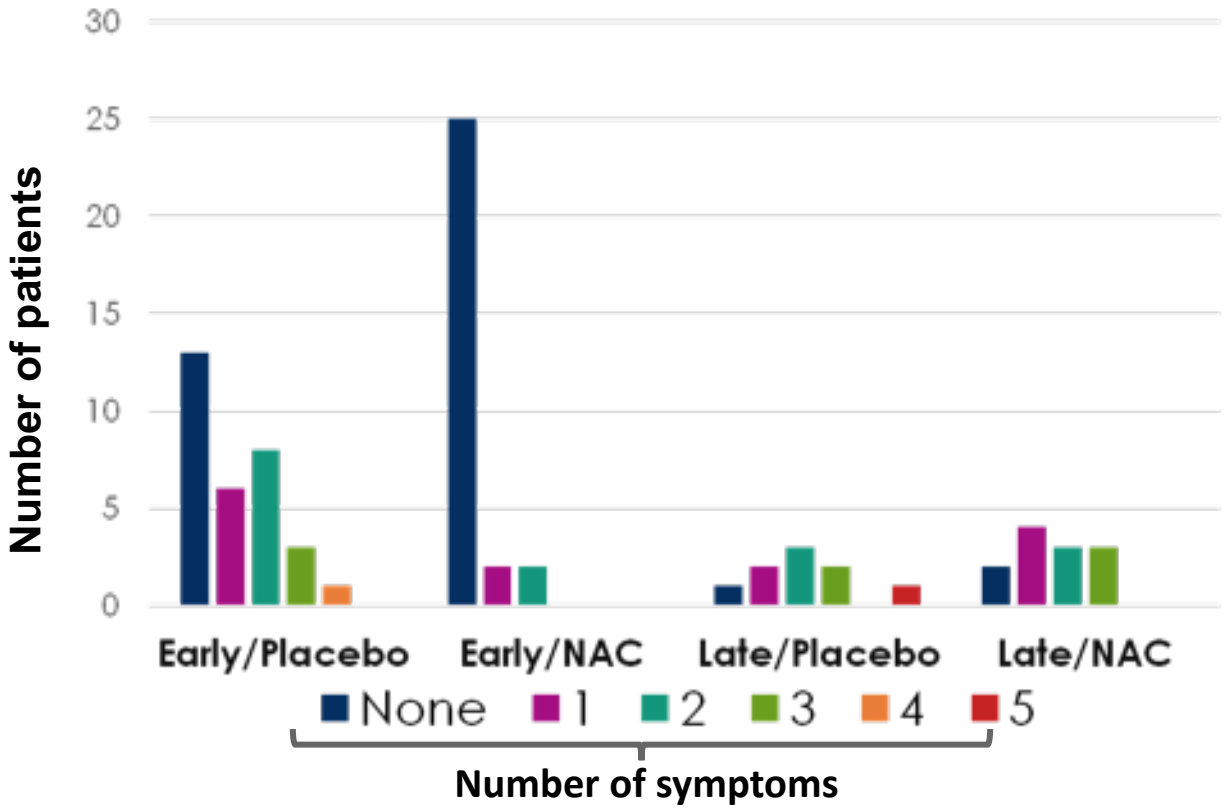
- Symptoms included impaired balance, sleep disturbance, memory problems, confusion, headache, hearing loss.
- Neuropsychological tests also improved with NAC (COWA word association & trail making tests).
- Oral NAC dosing 4 gm loading then 2 gm twice daily→1.5 gm twice daily for 7 days under supervision.
- Oral dosing not well tolerated in general population due to nausea, vomiting, diarrhea (Dean et al 2011).

US Soldiers treated with high oral dose NAC- Hoffer study (see appendix references #12)

CLINICAL DATA

NAC Reduced Post-concussive Symptoms in Blast-exposed US Military Service Personnel Compared to Placebo

Distribution of Symptoms at Day 7:

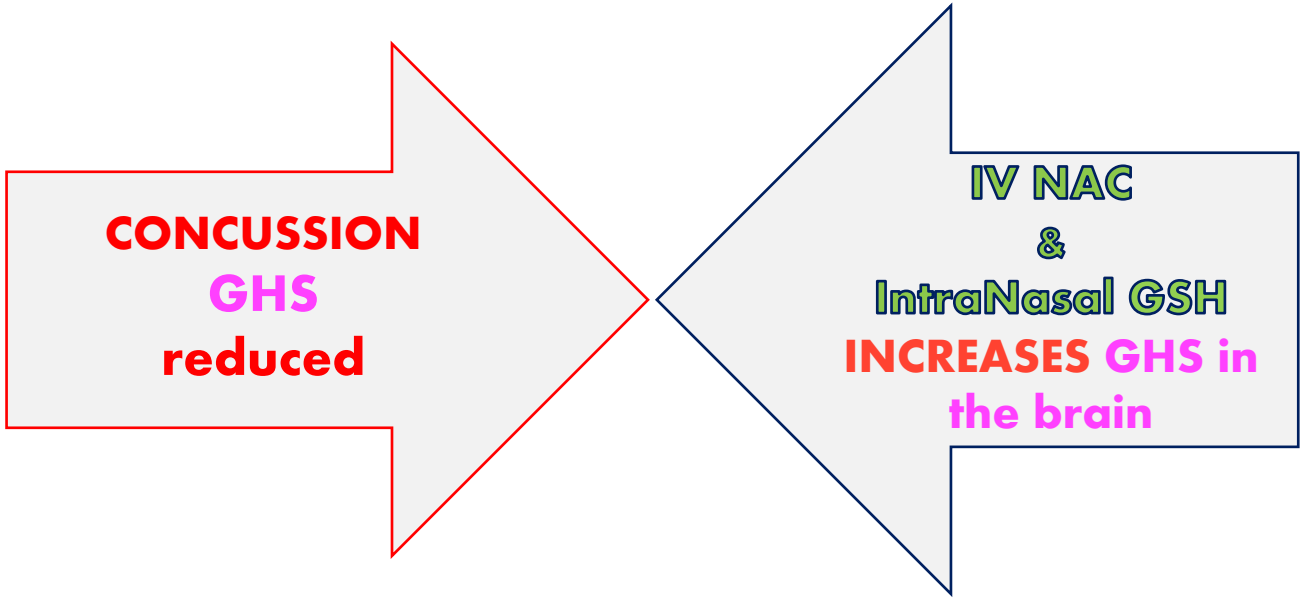


US Soldiers treated with high oral dose NAC-

Hoffer study (see appendix references)

Early treatment (within the first 24 hours) leads to significantly fewer subjects with post blast symptoms (both single symptoms and multiple symptoms)

Scientific Rationale for IntraNasal NAC



MOA

CONCUSSION DECREASES BRAIN GSH (Tyurin)

INCREASES BRAIN GSH

- IV NAC (Holmay)
- INTRANASAL GSH (Mischley)

We will demonstrate that IN NAC gets to Brain and increases GSH- Our pilot study - $150 thousand - done at Weill Cornell, collaboration partner

EFFICACY

RAT Intraperitoneal NAC study

CONCUSSION MODEL SHOW IMPROVED PERFORMANCE WITH NAC VERSUS NO NAC

(Eakin K et al 2014 PLoS ONE 9(4): e90617.doi:10.1371/journal.pone.0090617)

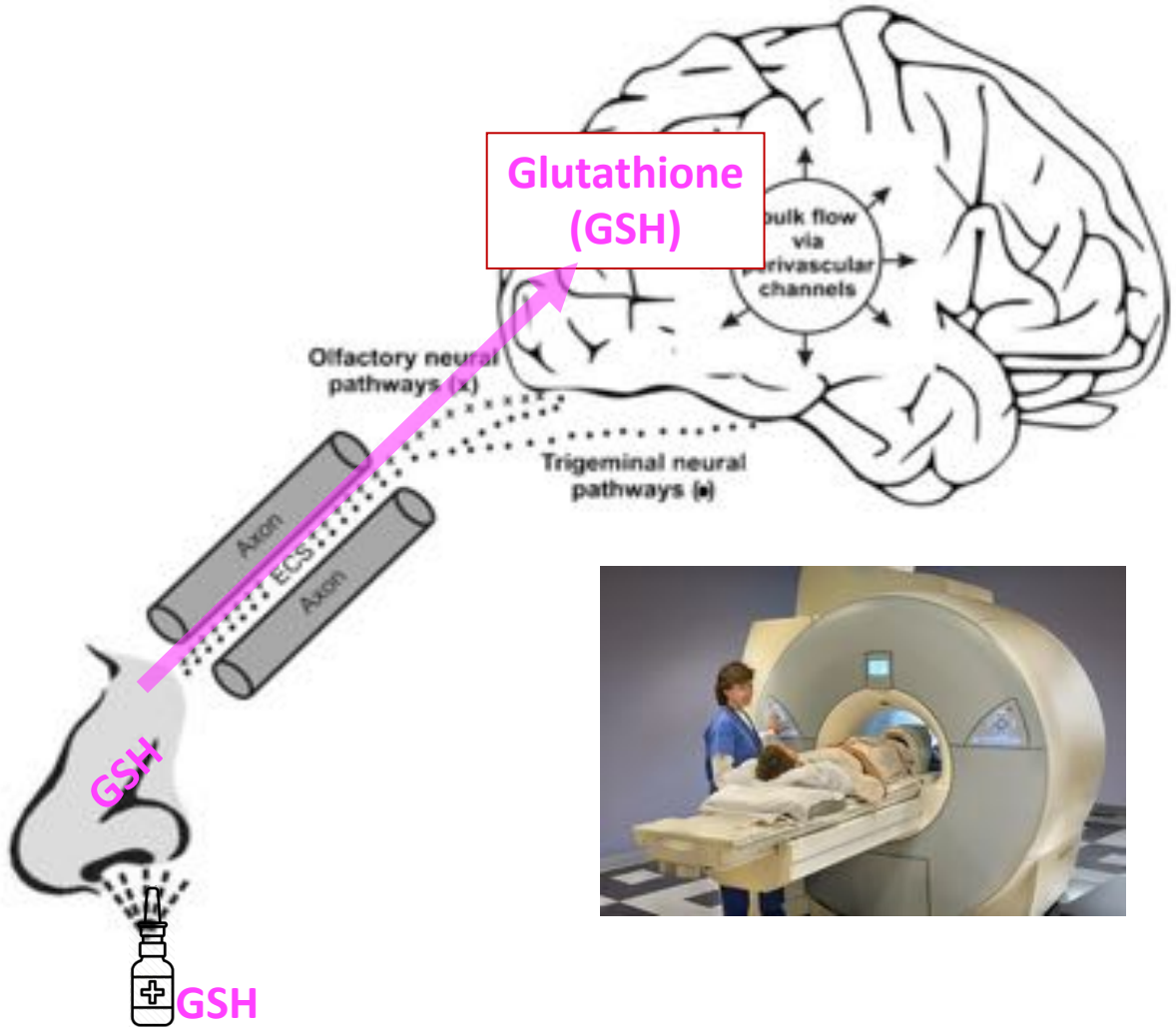
SOLDIER STUDY:

HUMAN HIGH ORAL DOSE NAC SHOW MORE THAN 50% REDUCTION IN POST BLAST SYMPTOMS IN STUDY DONE ON 81 US SOLDIERS (HOFFER)

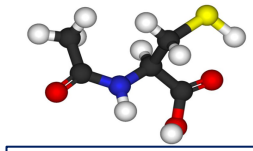
Reason to expect NAC to travel nose to Brain

Intranasal GSH, a Similar but Larger Molecule, Reaches the Brain

NAC, a (GSH) precursor, is much smaller but similar chemically to GSH

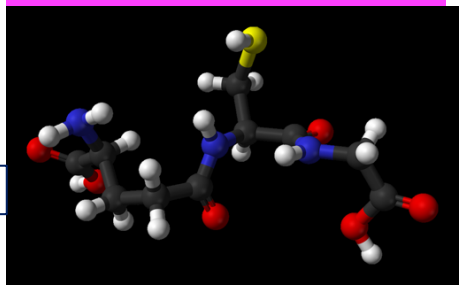


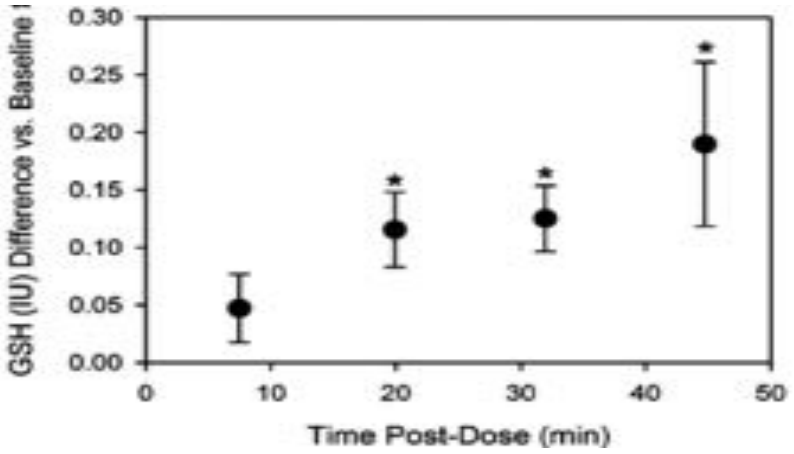
NAC:$C_5H_{10}N_2O_2S$



NAC IS CONVERTED TO GSH IN THE BRAIN

GSH:$C_{10}H_{17}N_3O_6S$

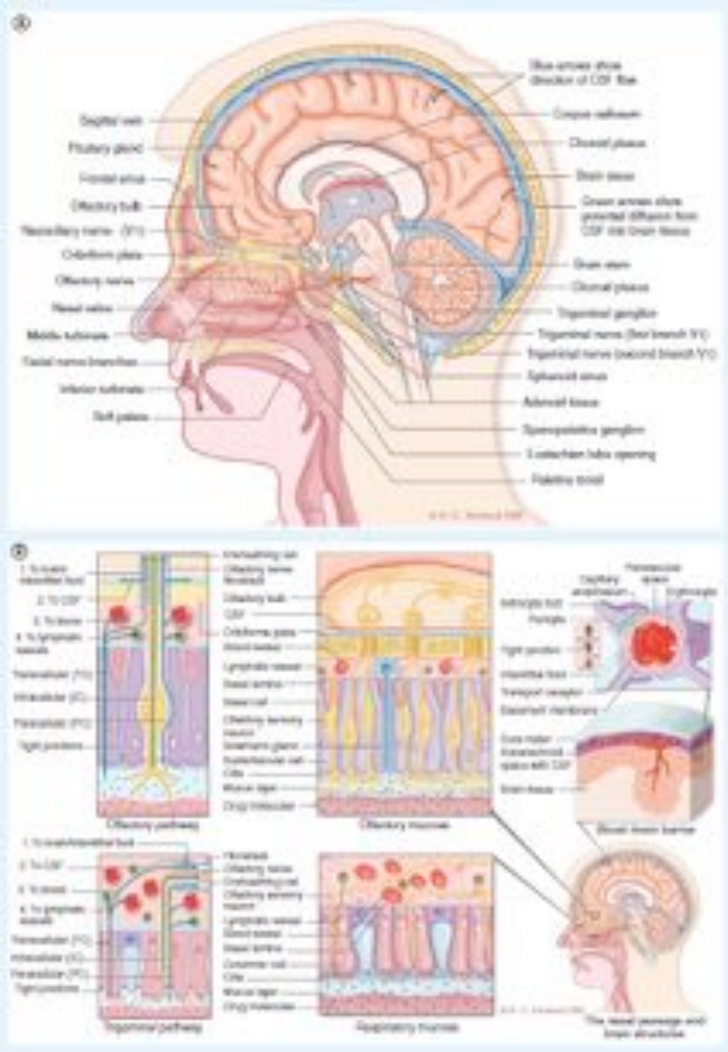


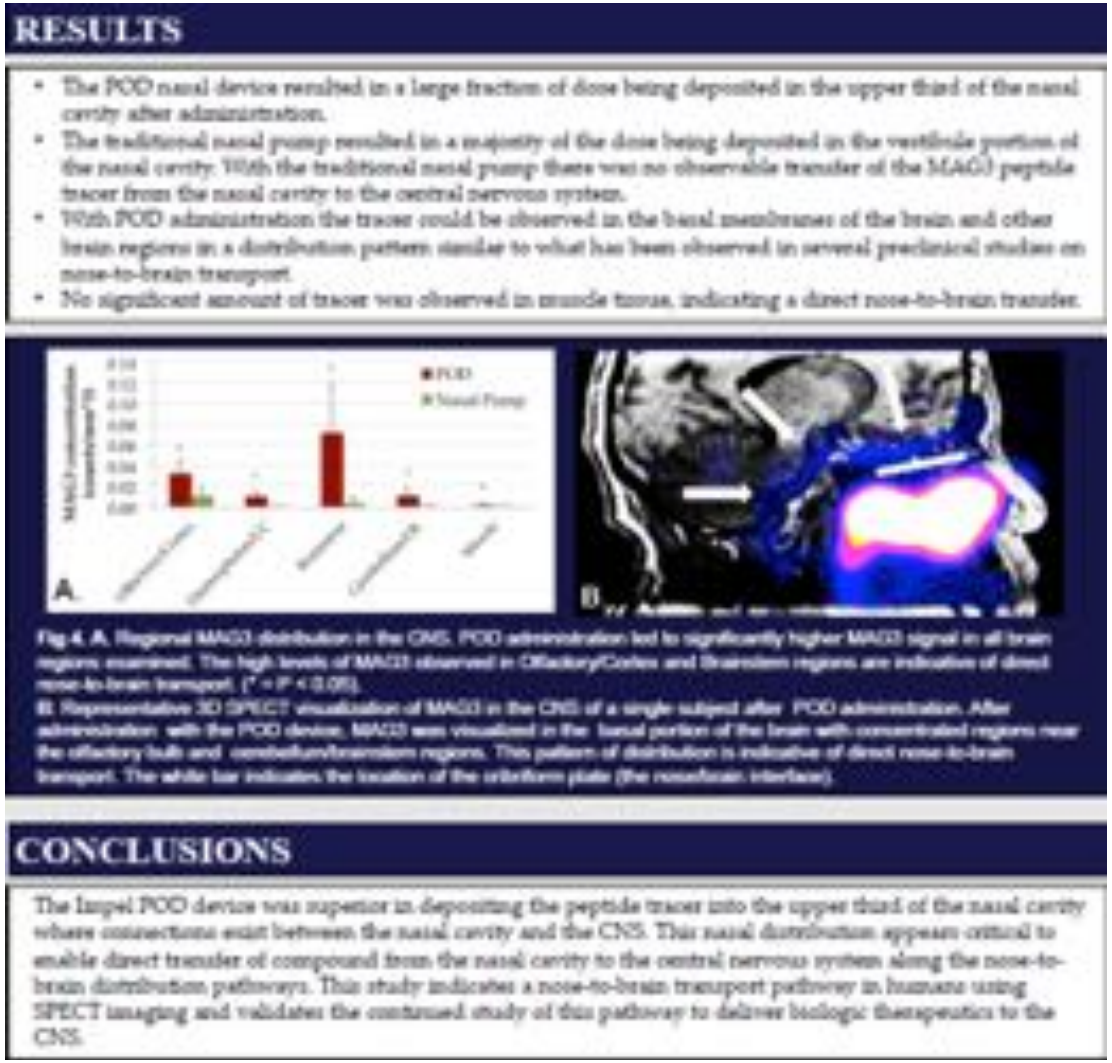


Mischley L et al. npj Parkinson's Disease (2016) 2, 16002; doi:10.1038/npjparkd.2016.2

DIRECT NOSE-TO-BRAIN DRUG DELIVERY

Anatomically Diverse and Specific Nose-to-Brain Pathways
Nose-to-Brain Transport Directly Demonstrated in Man





- LEFT: Diverse nose-to-brain pathways include trigeminal and olfactory nerve axonal and para-axonal, counter-current vascular and, trans-cribiform plate transport (Djupesland 2014).
- RIGHT: Direct SPECT imaging of nose-to-brain delivery of MAG-3 in human subject (Hoekman 2016).

Why NAC and IN (intra-nasal) delivery of NAC

WHILE HIGH ORAL DOSE OF NAC DID NOT SHOW ADVERSE EFFECTS IN HOFFER STUDY, SUBSTANTIAL EVIDENCE THAT HIGH ORAL DOSE WILL CAUSE NAUSEA:

1) Holdiness MR Clinical Pharmacokinetics of N-Acetylcysteine. Clin Pharmacokinetics 20:123-134,1991

2) Millea PJ N-Acetylcysteine Multiple Clinical Applications. Am. Fam Physician 80(3):265-269, 2009

3) Prescott L Oral or Intravenous N-Acetylcysteine for Acetaminophen Poisoning. Ann Emerg Med 45:409-413, 2005

Because high oral NAC dose could cause symptoms exacerbating concussion symptoms, it is unlikely to be developed or used as replacement for IN NAC.

Why NAC and IN (intra-nasal) delivery of NAC

NAC administered in high dose - efficacy in human trial but

ORAL	**NAC high dose poorly tolerated – nausea, vomiting**
INTRAVENOUS	**NAC - would require 7 day hospital stay**

NAC administered by NEURONASAL INTRA-NASAL dosing permits

- Outpatient treatment for concussion
- Rapid initiation of therapy and continued outpatient treatment
- Could be administered prior to formal concussion diagnosis by school MD/EMT's and then by the patient as outpatient
- Same advantage on battlefield, immediate access to treatment

TARGET PRODUCT PROFILE

Target Product Profile: N-Acetylcysteine Intranasal Administration Device for the Treatment of Concussion			
Product Description	[TRADENAME] is a drug-device combination product consisting of xxx mg of N-acetylcysteine in prefilled devices for intranasal administration to be used twice daily for 7 days following mild traumatic brain injury (mTBI).		
Mechanism of Action (MOA)	Intranasal administration delivers N-acetylcysteine to the brain, where it has been demonstrated to exert antioxidant, anti-inflammatory and neuromodulatory actions that diminish spreading neural damage following mechanical trauma to the head. It thereby reduces the symptoms of concussion within the first week and also prevents long-term sequelae, including cognitive impairment, mood disturbances and headache.		
Clinical Pharmacology	Magnetic resonance spectroscopy has demonstrated that Glutathione, when administered intranasally, rapidly reaches the CNS to elevate brain glutathione levels. N acetylcysteine systemic bioavailability is poor when administered orally (for acetaminophen overdose) or via inhalation (as a mucolytic).		
Indication	[TRADENAME] is indicated for the treatment of symptoms of concussion following mild traumatic brain injury. It has been shown to reduce the severity and duration of cognitive impairment, dizziness, imbalance, mood disturbance and headache, as well as improve functioning and quality of life, in patients with concussion. [TRADENAME] is administered twice daily for 7 days, with the first dose administered as soon as possible, preferably within 24 hours, of injury.		
Efficacy	***Primary endpoint:*** *Percent change in the Post-Concussion Symptom Scale (PCSS)* from day 0 (day of injury) to day 7 (highest possible score =132, assume placebo rate of 35%)*		
	Optimistic: 80% improvement in PCSS ($p<0.05$) with CGI statistically superior to placebo	***Target:*** 65% improvement in PCSS ($p<0.05$) with CGI statistically superior to placebo	***Minimal:*** 50% improvement in PCSS ($p<0.05$) without CGI statistically superior to placebo
	Secondary endpoints Superior to placebo on: • Symptom resolution at day 2 (placebo rate=20%) • Symptom resolution (PCSS < 7) at day 7 (placebo rate=40%) [key secondary endpoint], Day 30, Day 60 and Day 90 • Reduction in concussion-related disability • PCSS sub-scores and symptoms of headache, dizziness, imbalance, mood disturbance • Improvement in cognitive function at Day 7, Day 28 and at 3 months compared to baseline (ImPACT test)		
Safety/tolerability	• No serious adverse events; acceptable tolerability (adverse event discontinuations similar to placebo). • Favorable safety profile permits initiation of dosing immediately after injury; can be administered prior to obtaining CT scan		
Formulation	• Single-dose, prefilled device for intranasal administration with xxx mg of N-acetylcysteine in xx mL solution • Each package contains 14 devices providing twice daily dosing for 7 days • Product is stable at room temperature and does not require refrigeration		
Market size	US market $3B @ $XXX per course of treatment†		

Few concussion drugs in clinical development

VA has two drugs in trial at two VA centers:

- Tolcapone- a COMT inhibitor used to treat Parkinsons's (VA Northern CA)
- Pregnenolone- schizopheria drug (VA Durham)

Other Drugs

- ❑ Pain medications for post concussion headaches
- ❑ Sildenafil Citrate (U of Texas Southwestern Med Center)
- ❑ Atorvastatin (Baylor)
- ❑ Astrocyte small molecule pre clinical

Prevalence of Persistent Concussion Symptoms

APPROXIMATELY 50% OF INDIVIDUALS WITH MILD TRAUMATIC BRAIN INJURY SHOWED LONG TERM COGNITIVE DEFICITS: MILD TRAUMATIC BRAIN INJURY (MTBI) AND CHRONIC COGNITIVE IMPAIRMENT:

(A survey of 45 studies of cognitive impairment post concussion showed that

A scoping review. K.McInnes, et al . https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5388340/)

In contrast with prevailing views that most concussions resolve within 3 months,

APPROXIMATELY 225,000 NEW PATIENTS IN THE US EACH YEAR SHOW LONG-TERM DEFICITS FROM MILD BRAIN INJURIES (CONCUSSIONS).

This is approximately equal to the number of patients diagnosed annually with breast cancer, multiple sclerosis, and traumatic spinal cord injury combined.

Sports Medicine

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