The Importance of Multi-organ Response in Blast-induced Neurotrauma

Biomedicine Business Area;
National Security Technology Department

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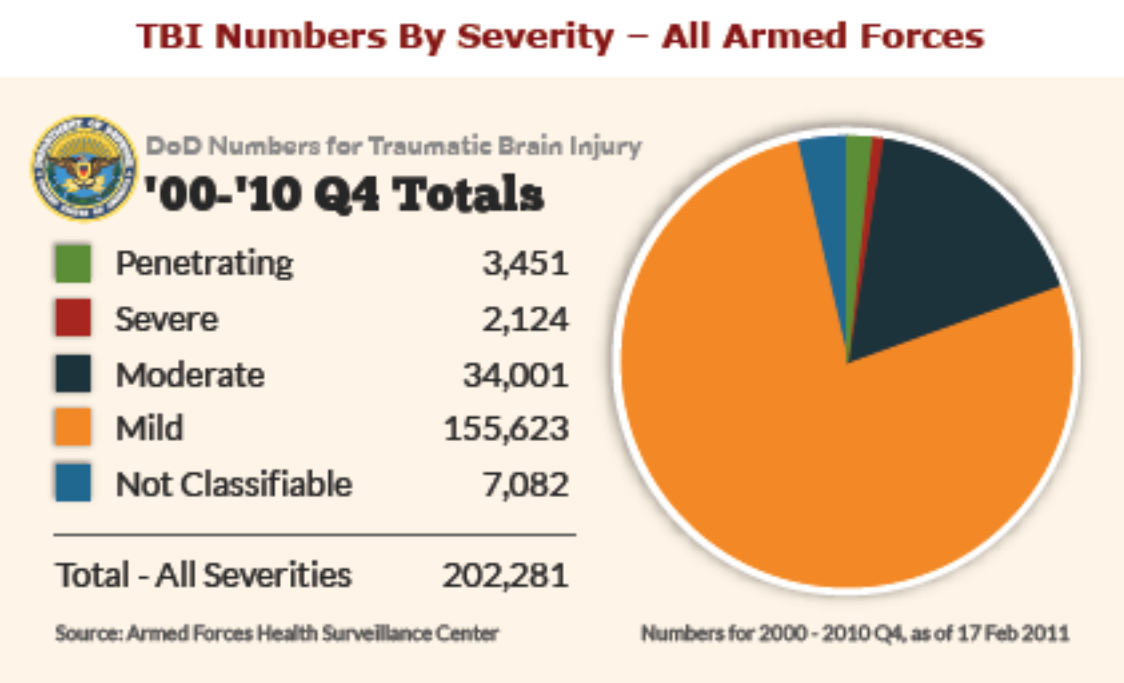
APL
The Johns Hopkins University
APPLIED PHYSICS LABORATORY

Challenge:
Military TBI Numbers



A trend toward mild TBI:

1) better body armor reducing penetrating TBI;
2) improved evacuation; and
3) improved immediate care.

The Defense and Veterans Brain Injury Center (DVBIC) estimates that 202,281 service personnel were diagnosed with traumatic brain injury (TBI) between 2000 and 2010 (as of February 17, 2011), with the overwhelming distribution of mild TBI (155,623, i.e., approximately 77%).

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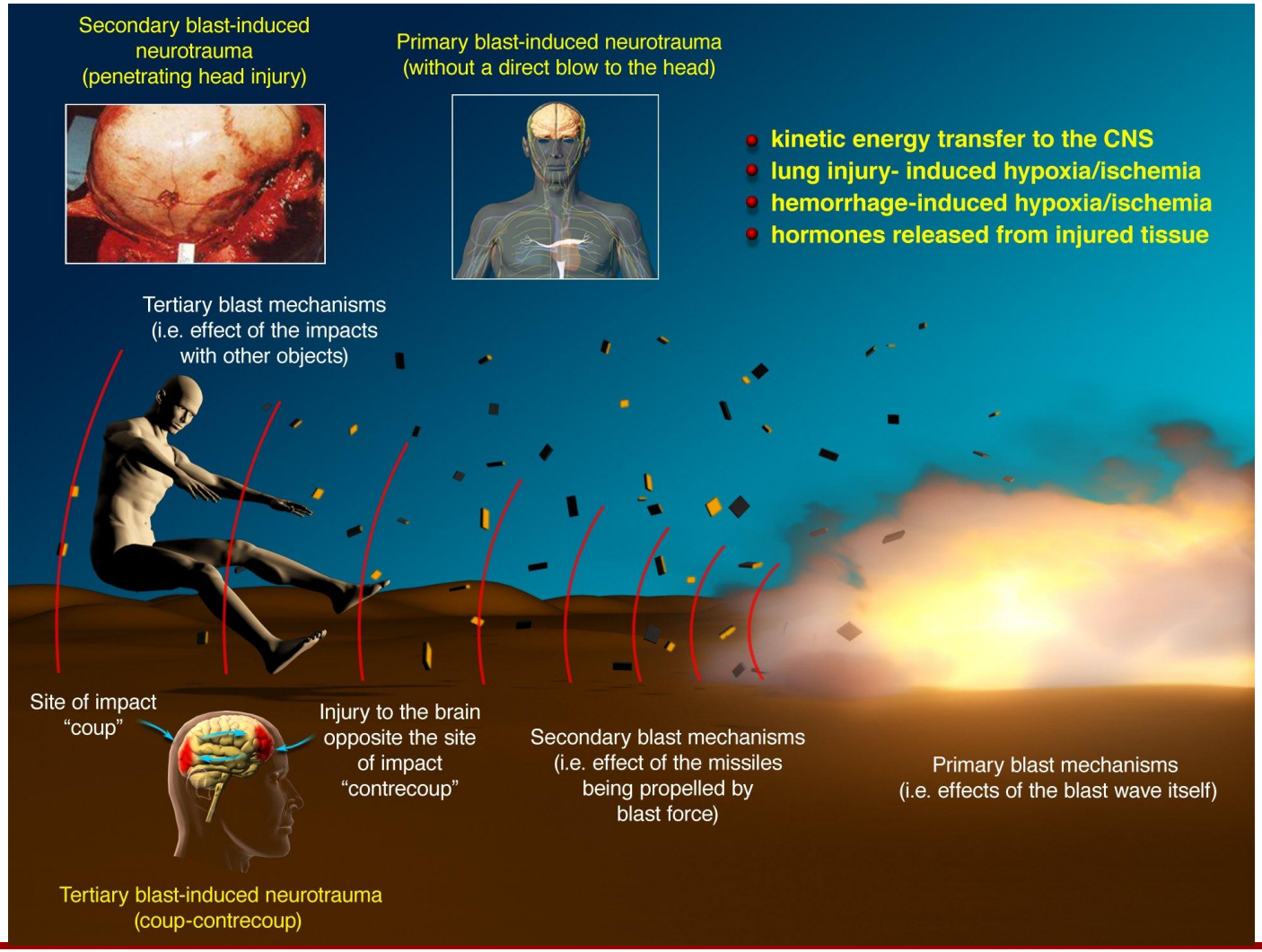
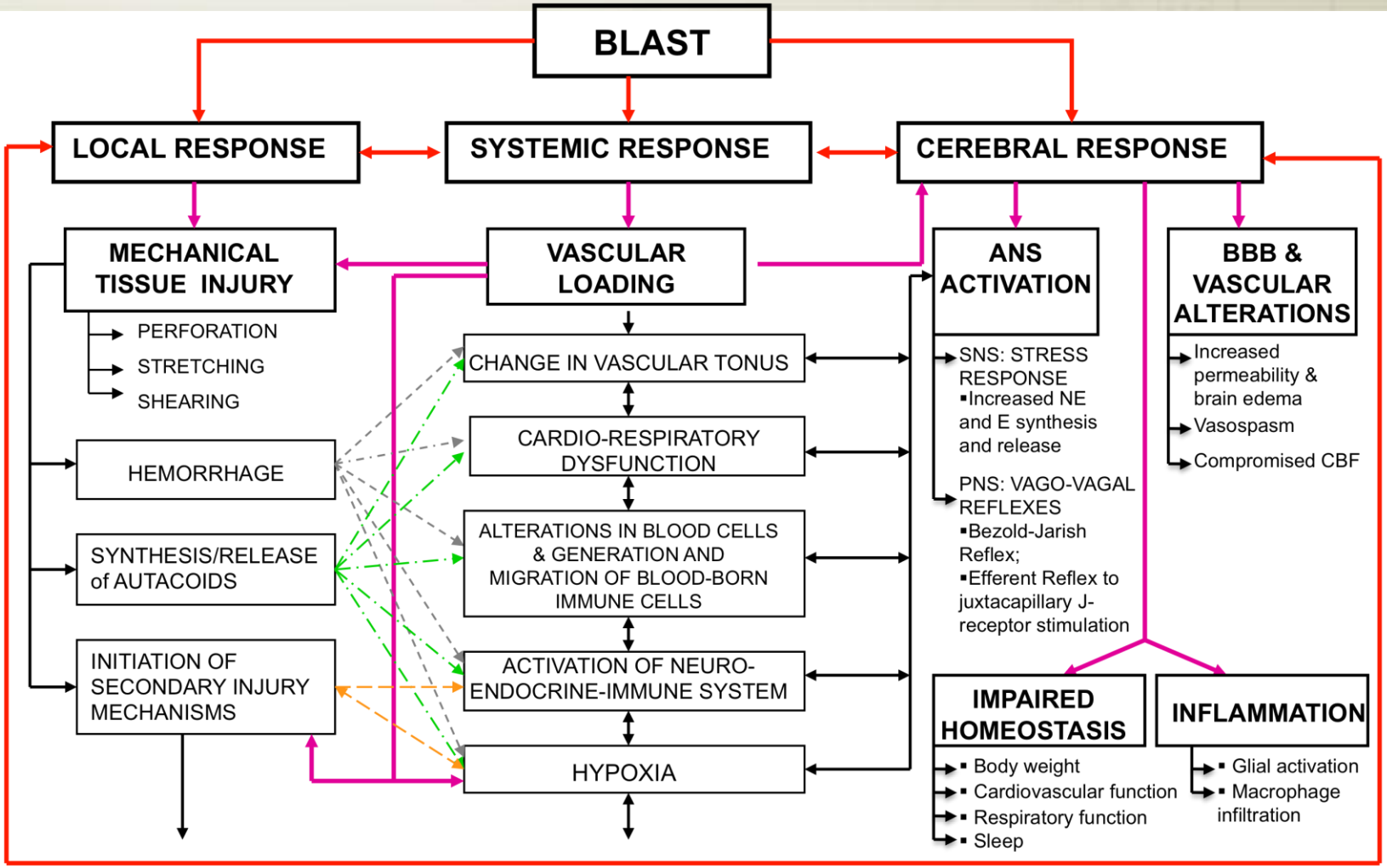
Challenge:
Complexity of Blast Effects

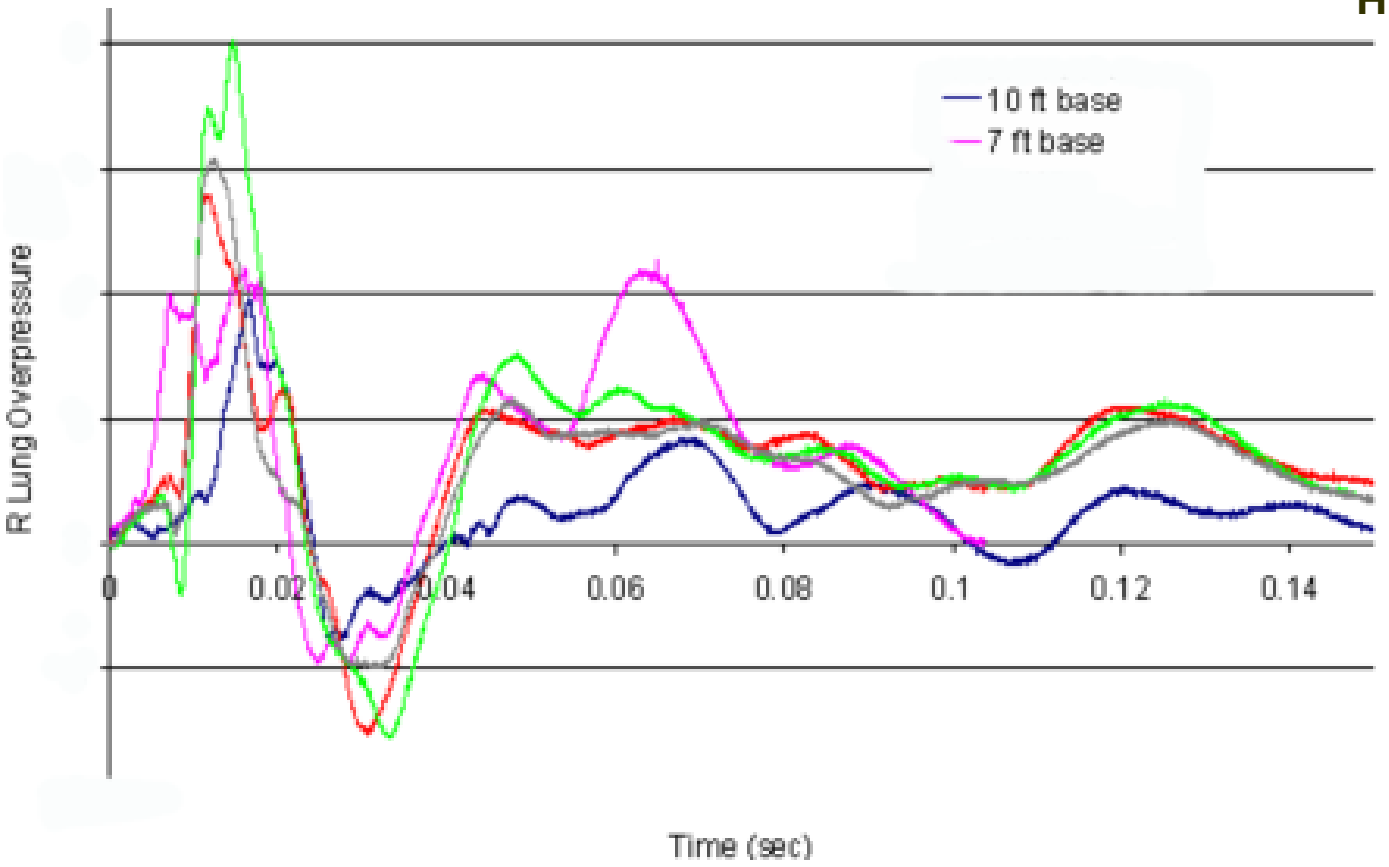


Challenge:
Primary Blast Effects & Whole Body Exposure

Challenge:
Complexity of Physiological Responses to Blast



Blast Exposure Increases Pressure in the Lungs

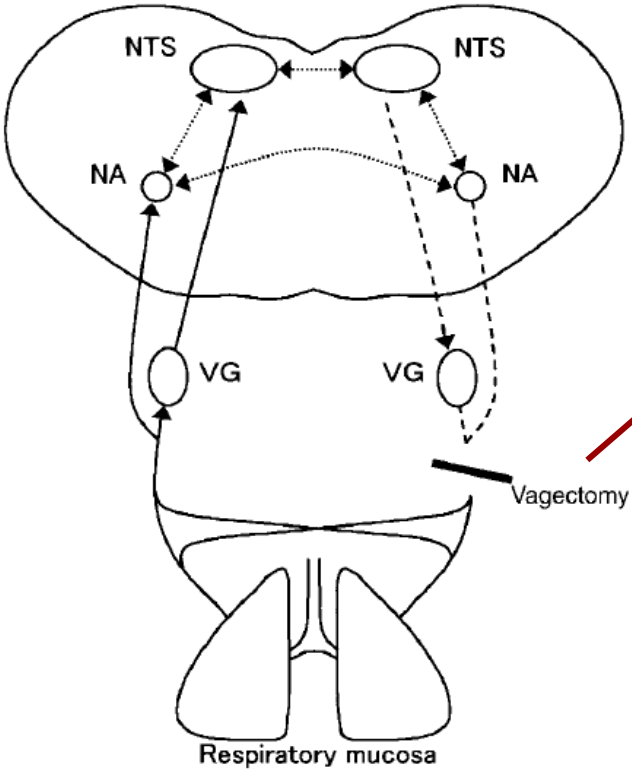


Human Surrogate Torso

JHU/APL Biomechanics & Injury Mitigation Systems (BIMS);
Program Manager:
Andrew Merkle

Reducing PNS Activation Improves Early BINT

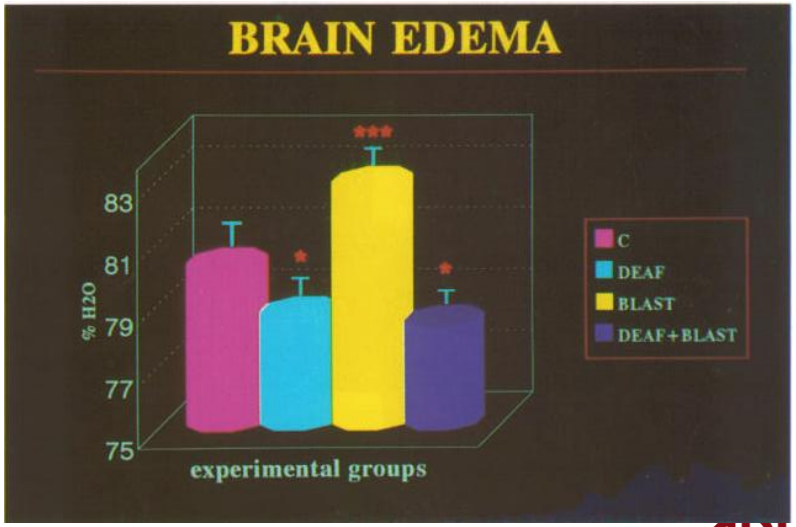
- Rabbit experiments; compressed air-generated shock wave with nominal peak pressure 304 kPa (i.e., 40 psi);
- Bilateral dissections of the vagus (DEAF), 2 hours before the blast;
- Animals sacrificed 30 minutes after blast)



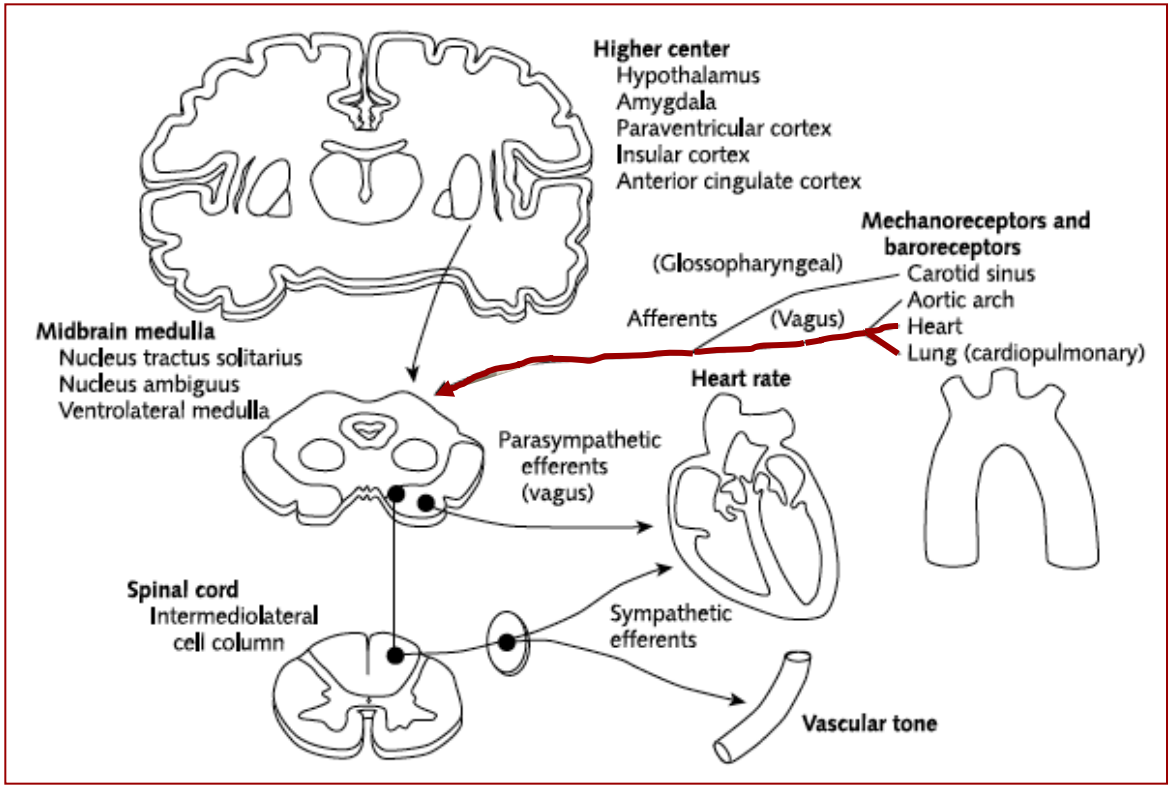
Bold, dotted, and broken lines indicate afferent pathways to VG, NTS, and NA; pathways between vagal medullary centers; and an efferent pathway to VG of the vagectomized side, respectively. VG, vagal (nodose) ganglion; NTS, nucleus of the solitary tract; NA, nucleus ambiguus.

		Metabolic Changes		Electrolyte/Mineral Changes	
Blast	LP	↑		Edema	↑
	Glucose	↑		Ca^{2+}	NORM
	Lactate	↑		Mg^{2+}	↑
	L/P ratio	↑		Zn^{2+}	NORM
	PCr/ATP ratio	↓			
Deaf. + blast	LP	↑		Edema	↑
	Glucose	NORM		Ca^{2+}	↑
	Lactate	↑		Mg^{2+}	NORM
	L/P ratio	NORM		Zn^{2+}	↑
	PCr/ATP ratio	NORM			

Blast, responses of group B compared with those of group A; Deaf. + blast, responses of group C compared with those of group C.



Activation of the Parasympathetic Nervous System by Blast Exposure



Bezold – Jarisch Reflex

- A cardiovascular depressor reflex involving a **marked increase in vagal (parasympathetic)** efferent discharge to the heart;
- Elicited by stimulation of chemoreceptors, primarily in the left ventricle;
- Causing a slowing of the heart beat (**bradycardia**) and dilatation of the peripheral blood vessels with resulting **lowering of the blood pressure**;
- The concept was originated by Bezold in 1867, later revised by Jarisch in 1937.

Juxtacapillary J-receptors

- Located in the alveolar walls and in close contact with the capillaries;
- Stimulated by hyperinflation of the lungs, accumulation of interstitial fluid in the lung parenchyma (lung edema) and pulmonary capillary engorgement;
- Impulses travel up the vagus nerve via slowly conducting unmyelinated C-fibers and may induce **rapid shallow breathing**, and sensation of **dyspnoea.**

Requirements for a Reliable Experimental Model of Traumatic Brain Injury

- The mechanical force used to induce injury is controlled, reproducible, and quantifiable;
- The inflicted injury is reproducible, quantifiable, and mimics components of human conditions;
- The injury outcome, measured by morphological, physiological, biochemical, or behavioral parameters, is related to the mechanical force causing the injury;
- The intensity of the mechanical force used to inflict injury should predict the outcome severity.

Cernak I, 2005, NeuroRx 2: 410-422

▪The **JHU/APL model of primary blast injury and primary BINT** utilizes well-defined mechanical factors inducing injury, based on physics of field explosions;

▪It reproduces essential hallmarks of blast injuries and BINT:

- •Position-dependent injury severity and injury pattern;
- •Graded functional (motor, cognitive, and behavioral) deficits;
- •Graded induction of inflammatory response in the brain;
- •Importance of systemic response in BINT.

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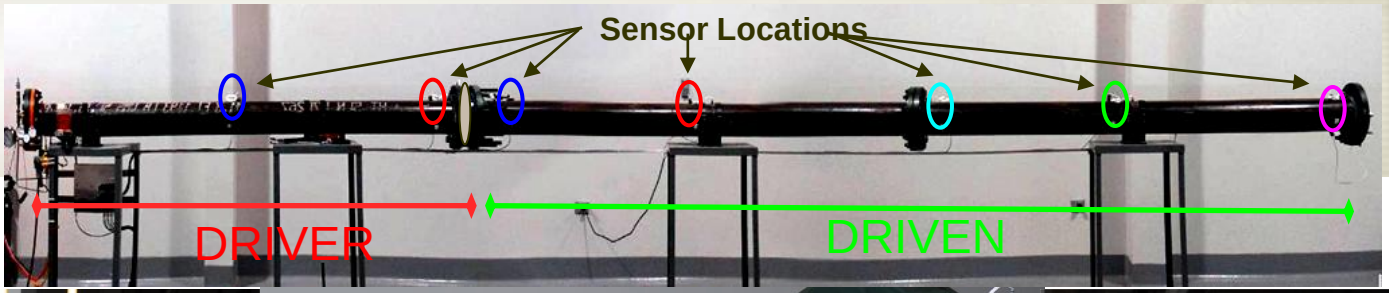
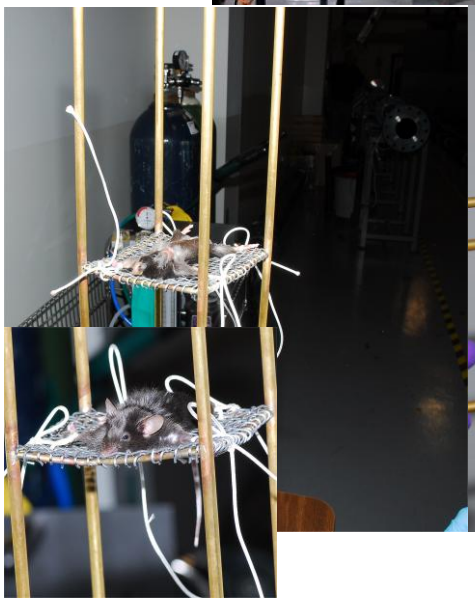
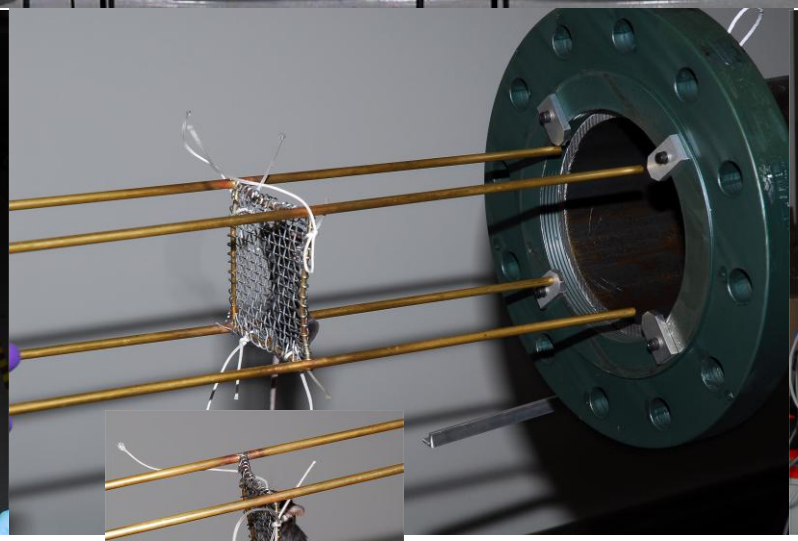
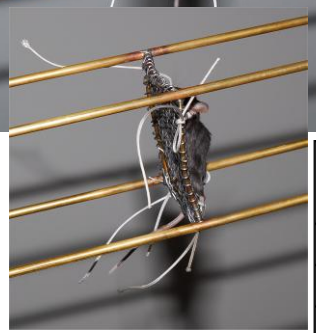
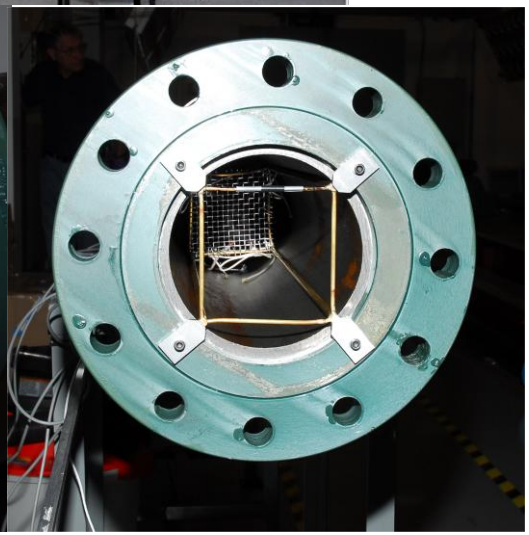
JHU/APL Mouse BINT Model





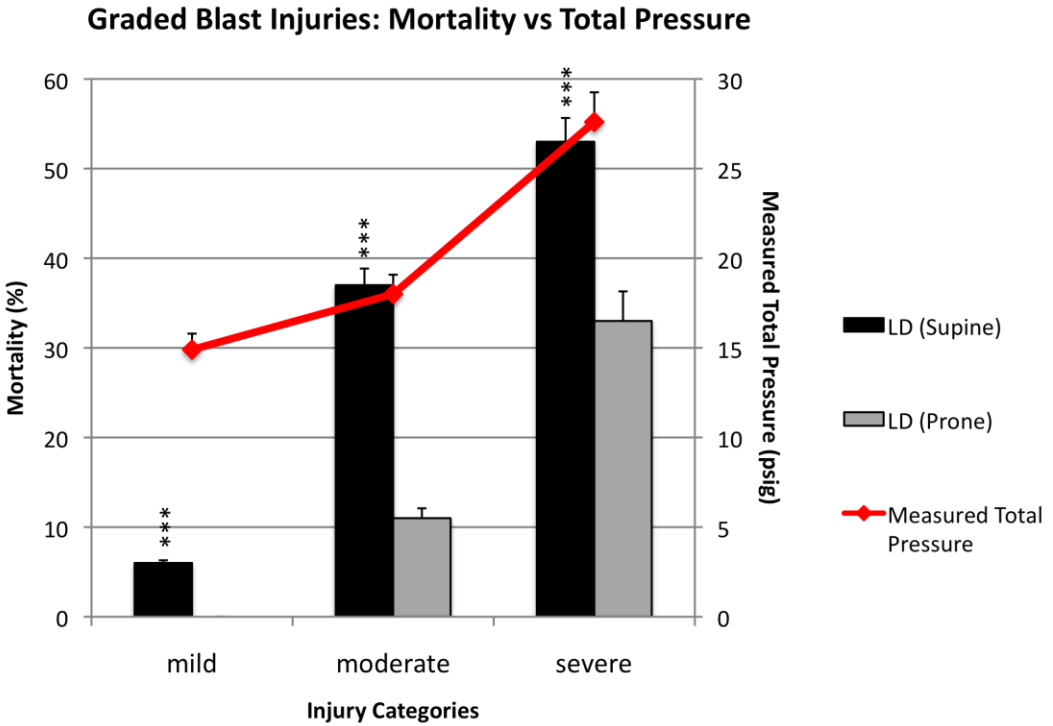


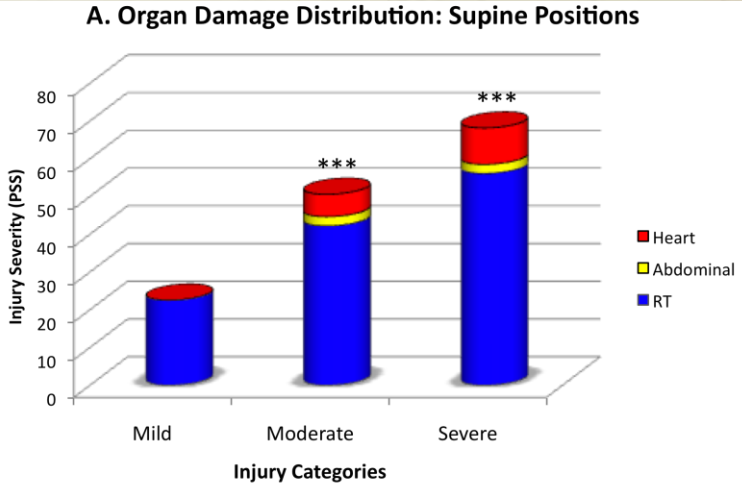


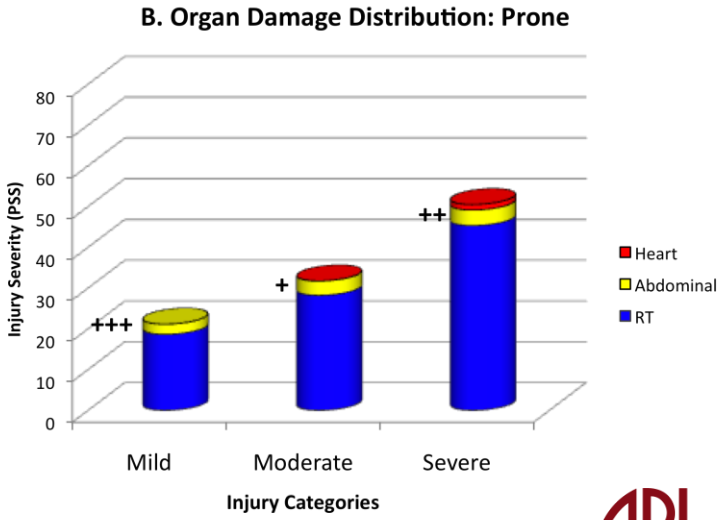


	Mild		Moderate		Severe	
	Mean	SD	Mean	SD	Mean	SD
Measured Rupture Pressure (psig)	26.5	2.1	30.9	2.5	42.8	4.6
Measured Static Pressure (psig)	9.9	1.2	11.0	1.4	15.3	2.4
Calculated Static Pressure (psig)	11.9	N/A	13.7	N/A	18.3	N/A
Measured Total Pressure (psig)	14.9	N/A	18.0	N/A	27.6	N/A
Calculated Total Pressure (psig)	15.1	N/A	17.9	N/A	25.7	N/A
Measured Impulse (psig-ms)	50	5	51	21	72	17

Position-dependence of injury severities







Type, Severity and Frequency of Blast-induced Microscopic Lesions in Key Thoracic and Abdominal Organs

LUNGS	Severe-Supine	Severe-Prone	Moderate-Supine	Moderate-Prone	Mild-Supine	Mild-Prone	Total*
Superficial hemorrhages	0.0%	0.0%	5.3%	50.0%	33.3%	25.0%	20.7%
Hematomas	0.0%	33.3%	10.5%	0.0%	22.2%	25.0%	12.1%
Hemorrhagic consolidation	100.0%	66.6%	84.2%	50.0%	44.4%	37.5%	65.5%
							98.3%

LIVER	Severe-Supine	Severe-Prone	Moderate-Supine	Moderate-Prone	Mild-Supine	Mild-Prone	Total*
Infarcts	14.3%	100.0%	52.6%	50.0%	0.0%	50.0%	41.4%

HEART	Severe-Supine	Severe-Prone	Moderate-Supine	Moderate-Prone	Mild-Supine	Mild-Prone	Total*
Right ventricle dilatation	57.1%	33.3%	21.0%	0.0%	11.1%	0.0%	17.2%
Left ventricle dilatation	28.6%	33.3%	21.0%	0.0%	11.1%	0.0%	12.0%
							29.3%

SPLEEN	Severe-Supine	Severe-Prone	Moderate-Supine	Moderate-Prone	Mild-Supine	Mild-Prone	Total*
Red infarcts	28.6%	0.0%	10.5%	16.6%	0.0%	12.5%	12.1%

KIDNEY	Severe-Supine	Severe-Prone	Moderate-Supine	Moderate-Prone	Mild-Supine	Mild-Prone	Total*
Red infarcts	14.3%	0.0%	26.3%	8.3%	0.0%	0.0%	12.1%

* Percentiles represent rates of cases with indicated lesion in the total number of cases of the first group.

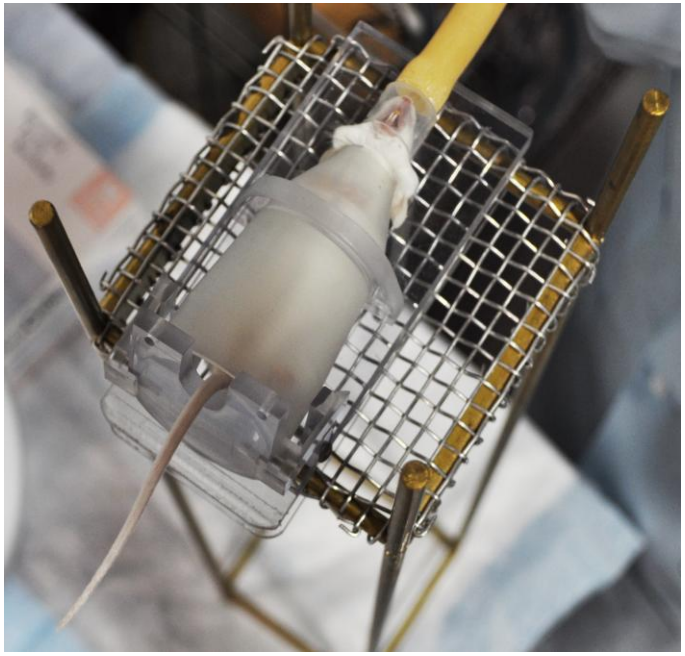
→ Supine > Prone

← Prone > Supine

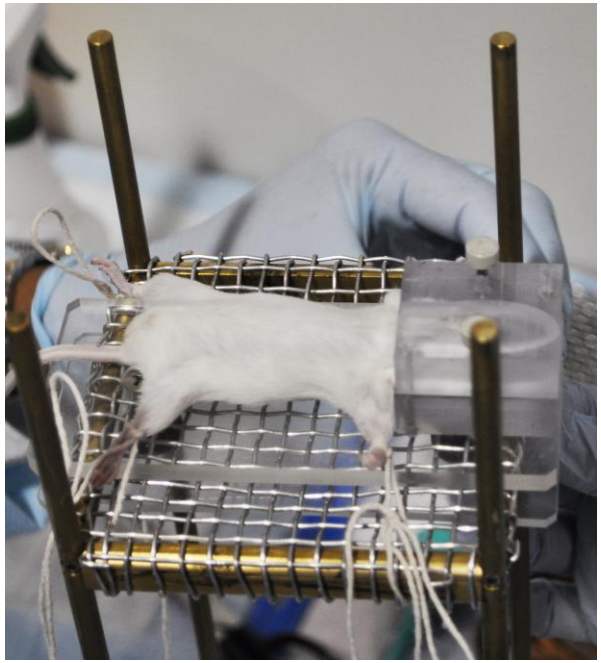
Importance of Blast Transmission Pathways

Whole-body exposure

Torso protection & Head exposure



Head protection & Torso exposure



In Vivo Imaging of Inflammation

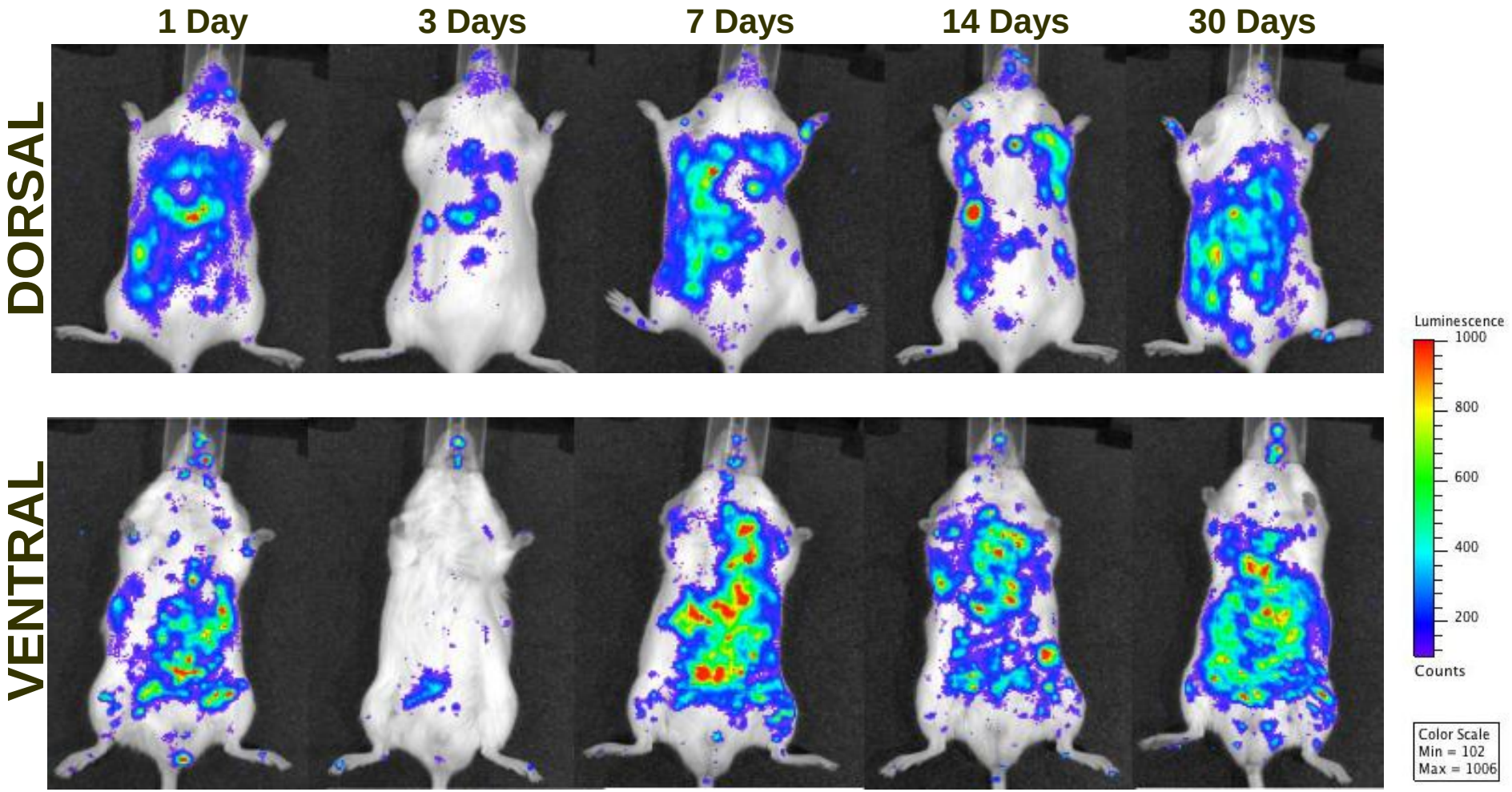
- **XenoLight Rediject Inflammation probe** is a chemiluminescent reagent for in vivo monitoring of inflammation using the IVIS bioluminescence / fluorescence camera;

- This probe is offered in a ready-to-use format and measures **myeloperoxidase (MPO) activity of activated phagocytes allowing for longitudinal tracking of MPO level and inflammation status** in vivo;

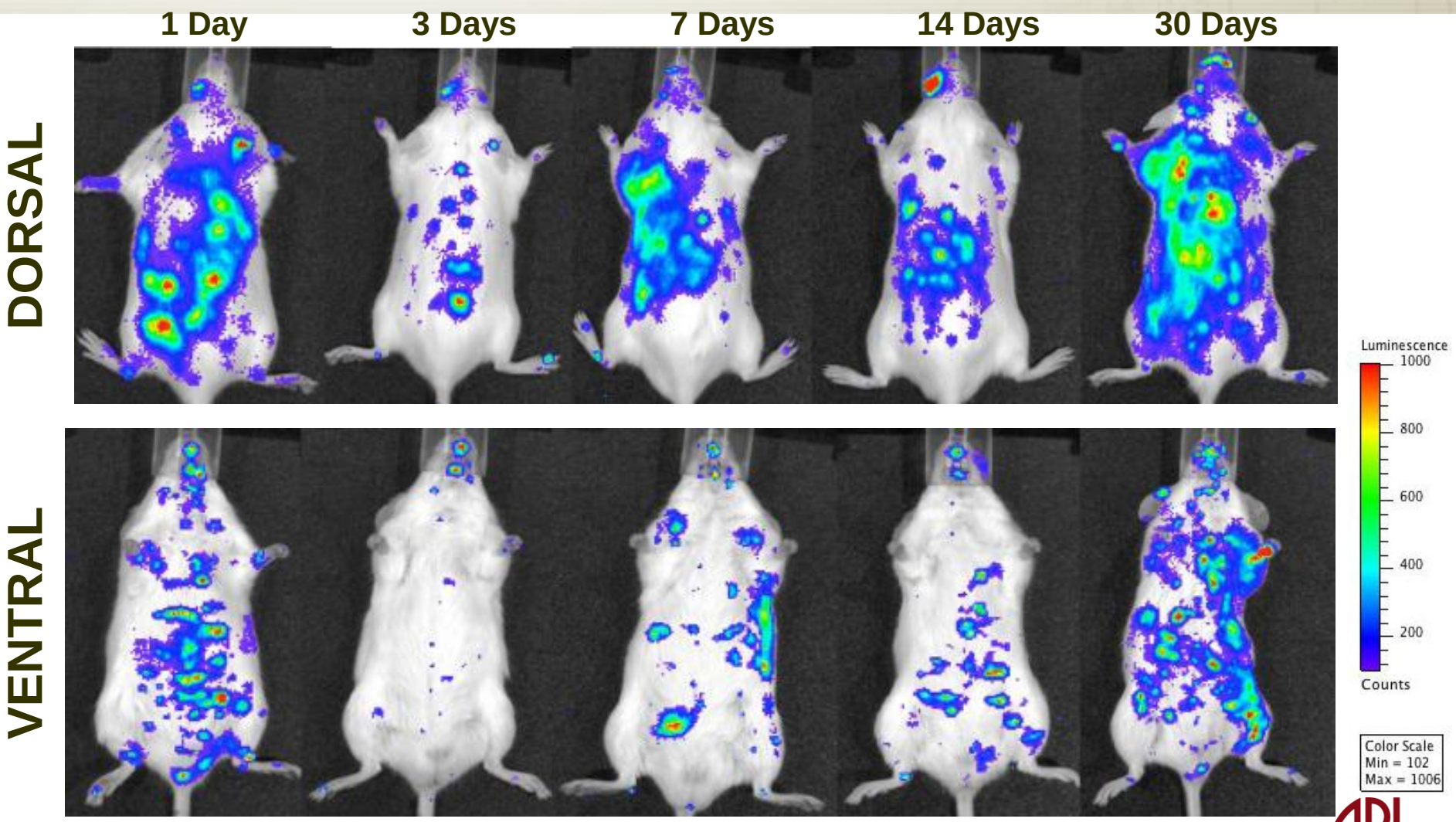
- Intraperitoneal (i.p.) injection at 200 mg/kg (150 µL /mouse*) and imaging 10 minutes post i.p. injection of the probe with exposure time of 5 minutes for better sensitivity.

IVIS® Imaging System 3D Series Components: Thermoelectrically cooled CCD camera with water chiller, patented optomechanical imaging chamber for multi-view imaging, acquisition computer, high-resolution monitor, integrated gas anesthesia, and Living Image® software. Fluorescence option available.

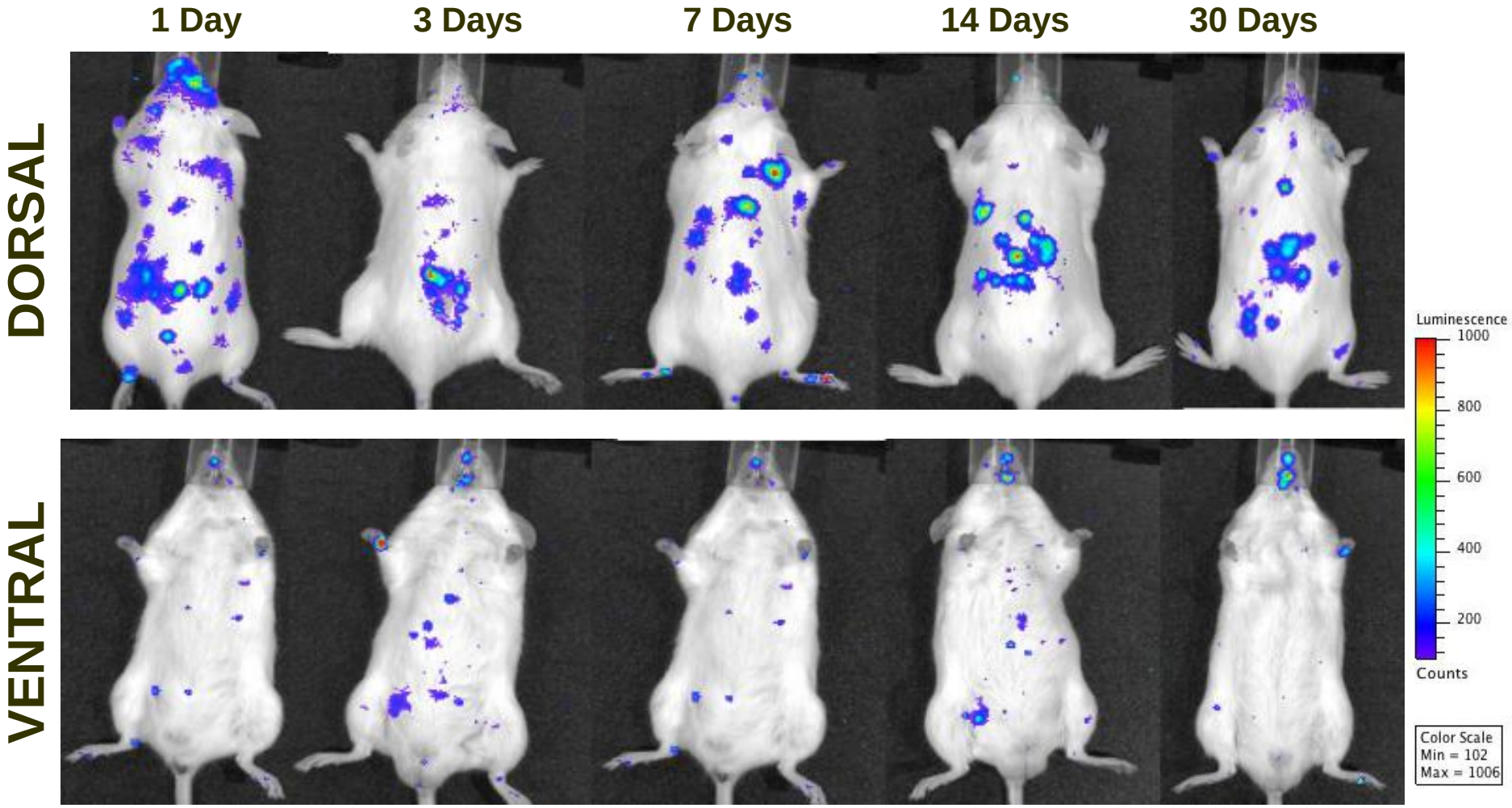
Whole-body Blast (No Protection)



Blast with Head Protection



Blast with Body Protection



Axonal Pathology in Distinct CNS Tracts Based on Silver Degeneration Staining

0 – no pathology
1 – mild pathology (scattered axons)
2 – moderate pathology
3 – severe pathology (confluent axons)

No.	Survival	CC	Cing	AC	Frnx	SM	MTT	IC	Low CST	Olf	Optic	ML	LL	Crbl WM	Crbl Pedn	Spt V	VSCT
1	D7	0+	0+	0+	0+	0+	0+	0+	3+	0+	0+	0+	0+	1+	2+	2+	0+
2		1+	2+	0+	0+	0+	0+	0+	2+	1+	3+	0+	0+	3+	1+	0+	0+
3		1+	0+	0+	0+	0+	0+	0+	1+	0+	2+	0+	0+	1+	0+	0+	0+
4		0+	0+	0+	0+	0+	0+	0+	1+	0+	3+	0+	0+	1+	1+	0+	0+
5		0+	0+	0+	0+	1+	0+	0+	1+	0+	2+	0+	1+	1+	1+	0+	0+
6		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	1+	0+	0+	0+
7		1+	2+	0+	1+	0+	0+	0+	2+	0+	3+	0+	1+	1+	1+	0+	0+
8		0+	0+	0+	0+	0+	0+	0+	2+	0+	2+	2+	2+	3+	3+	0+	1+
9		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
10		1+	0+	0+	0+	0+	0+	0+	0+	0+	2+	0+	1+	1+	1+	0+	0+
1	D7	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
2	Torso	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
3	Covered	0+	0+	0+	0+	0+	0+	0+	0+	0+	1+	0+	0+	0+	0+	0+	0+
4		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
5		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
6		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+
1	D7	0+	0+	0+	0+	0+	0+	0+	0+	0+	2+	0+	1+	2+	2+	2+	2+
2	Head	0+	0+	0+	0+	0+	0+	0+	2+	0+	0+	0+	2+	2+	2+	0+	0+
3	Covered	0+	0+	0+	0+	0+	0+	0+	0+	0+	3+	0+	1+	1+	0+	0+	0+
4		0+	0+	0+	0+	0+	0+	0+	1+	0+	0+	0+	1+	0+	1+	0+	0+
5		0+	0+	0+	0+	0+	0+	0+	2+	0+	0+	0+	1+	2+	0+	0+	0+
1	D14	1+	2+	2+	2+	2+	1+	2+	3+	3+	3+	1+	2+	2+	1+	0+	0+
2		0+	0+	0+	0+	0+	0+	0+	1+	0+	1+	0+	1+	1+	1+	0+	0+
3		0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	0+	1+	0+	0+	0+
4		0+	0+	0+	0+	1+	0+	0+	1+	0+	2+	0+	1+	1+	1+	0+	0+
5		0+	0+	0+	0+	0+	0+	0+	1+	0+	1+	0+	0+	3+	1+	0+	0+
6		2+	1+	0+	0+	0+	0+	1+	2+	0+	2+	0+	0+	1+	0+	0+	2+
7		0+	2+	0+	0+	1+	0+	1+	3+	1+	2+	1+	1+	2+	1+	0+	0+

Whole-body exposure
Torso protection & head exposure
Head protection & torso exposure

CC – corpus callosum
Cing – cingulum
AC – anterior commissure
Frnx – fornix
SM – stria medullaris
MTT – mammilothalamic tract
IC – internal capsule
Low CST – low corticospinal tract
Olf – olfactory tract
Optic – optic tract
ML – medial lemniscus
LL – lateral lemniscus
Crbl WM – cerebellar white matter
Crbl Pedn – cerebellar peduncles
Spt V – spinal tract of trigeminal nucleus
VSCT – ventral spinocerebellar tract

Blast-induced Neurotrauma: Essential Research Components

Resilience

Multi-phase, Multi-system Response to Injury

Stressors of Military Environment

Complexity of Blast Effects

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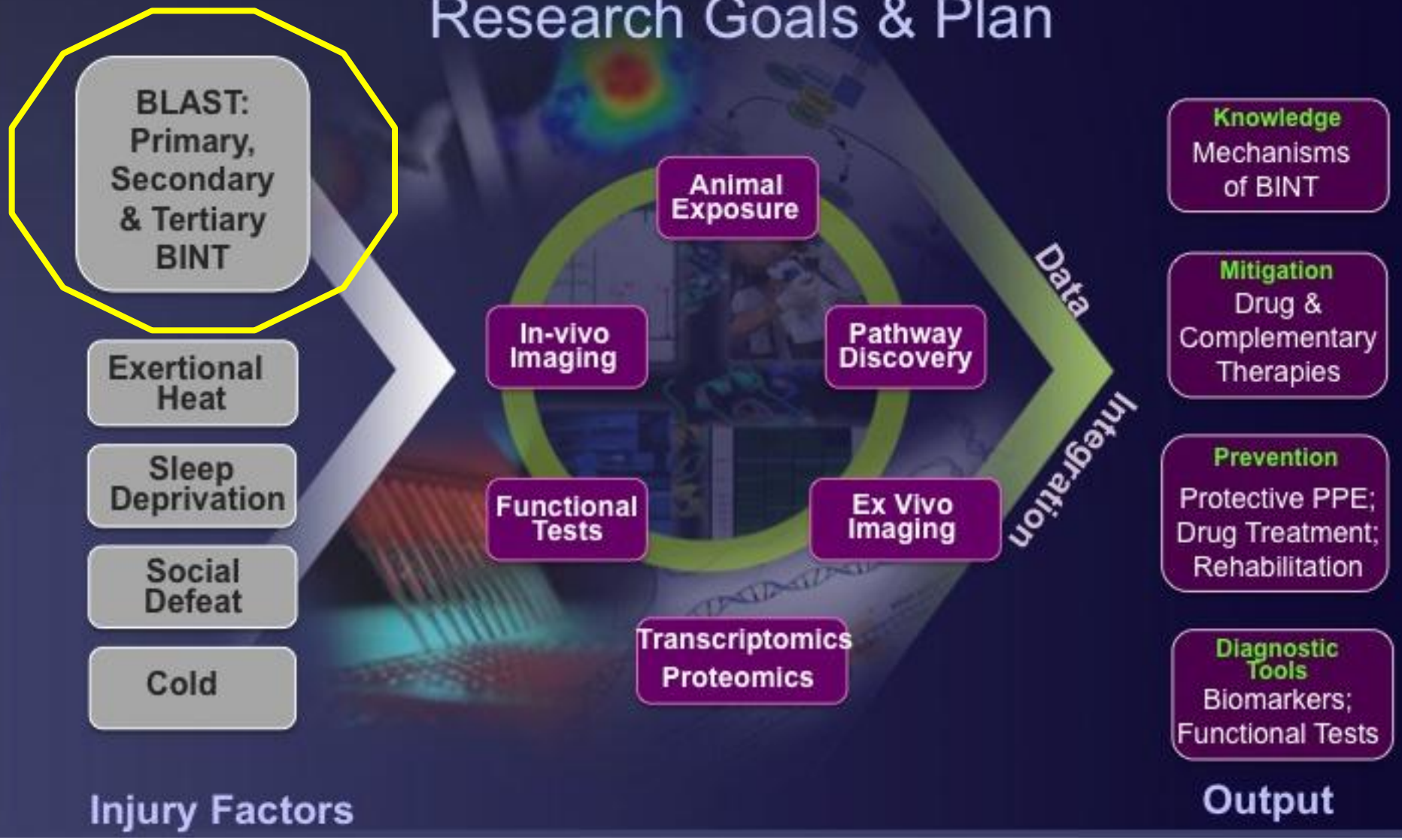
Research Goals & Plan



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- Vassilis Koliatsos (JHU SOM)
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- Stefan Plantman (KI, Stockholm)

Thank You & Questions

Black-eyed Susan (Rudbeckia Hirta)
has been the official Maryland flower since 1918 when it was designated the "Floral Emblem" of Maryland by the General Assembly
(Chapter 458, Acts of 1918; Code State Government Article, sec. 13-305).