Air Force 711th Human Performance Wing – Application of NAMs

Prepared by Laura Stolle, PhD, Lead Research Toxicologist

Presented by Lisa Sweeney, Ph.D., Risk Assessment Toxicologist at UES, Inc.

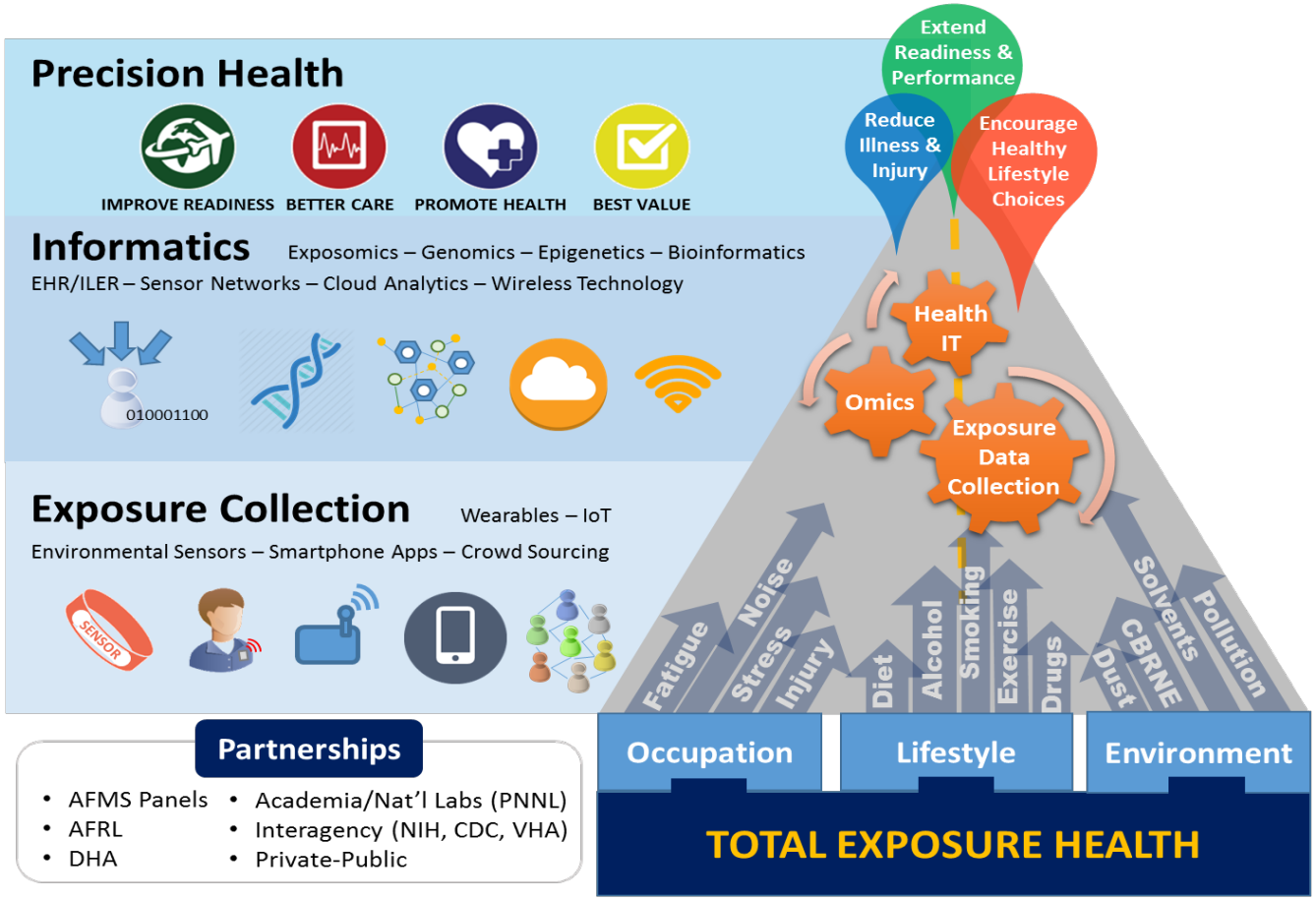
May 23, 2019

Total Exposure Health – Big Picture

AFMS CONOPS to enable capture of workplace, environmental, and lifestyle exposures experienced by an individual to prevent disease

- Emphasis is to leverage and advance:
  - Exposure Science
  - Sensor & data technologies
  - Health informatics
  - Clinical support systems

- Goals are to:
  - Obtain holistic health status
  - ID root causes of disease/injury
  - Provide innovative, accessible methods for primary prevention



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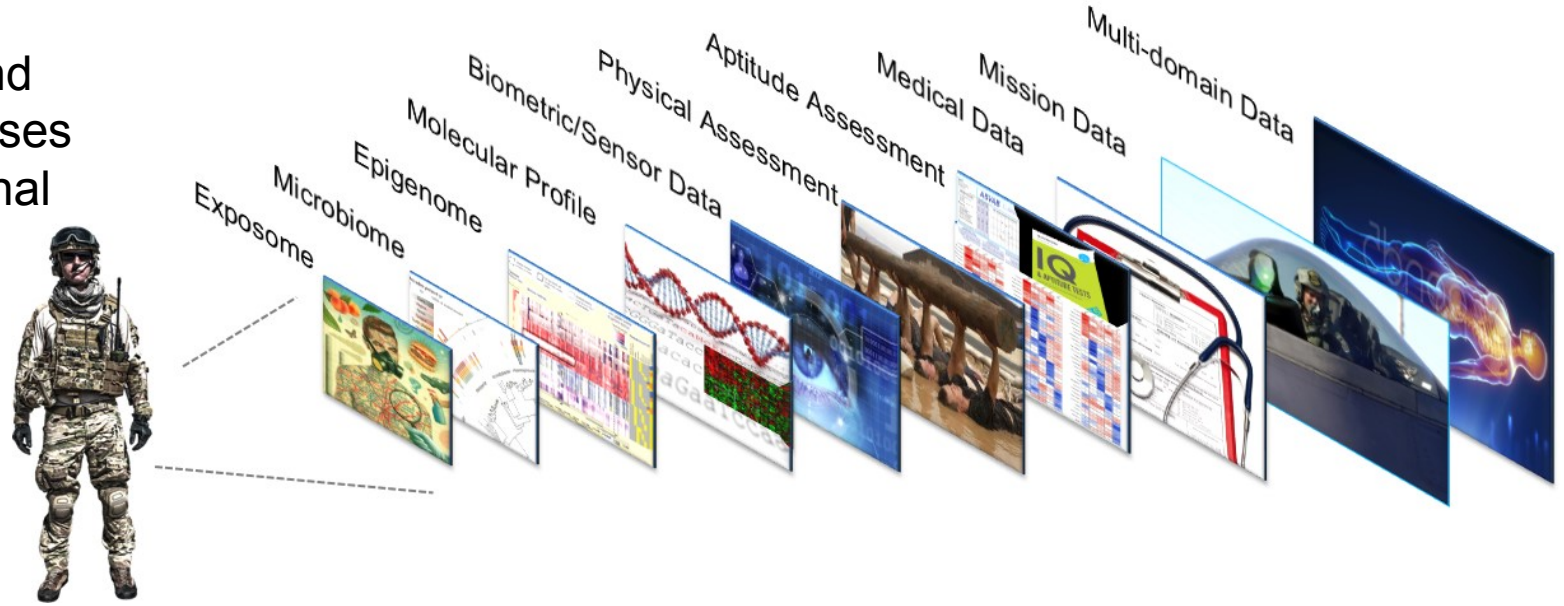
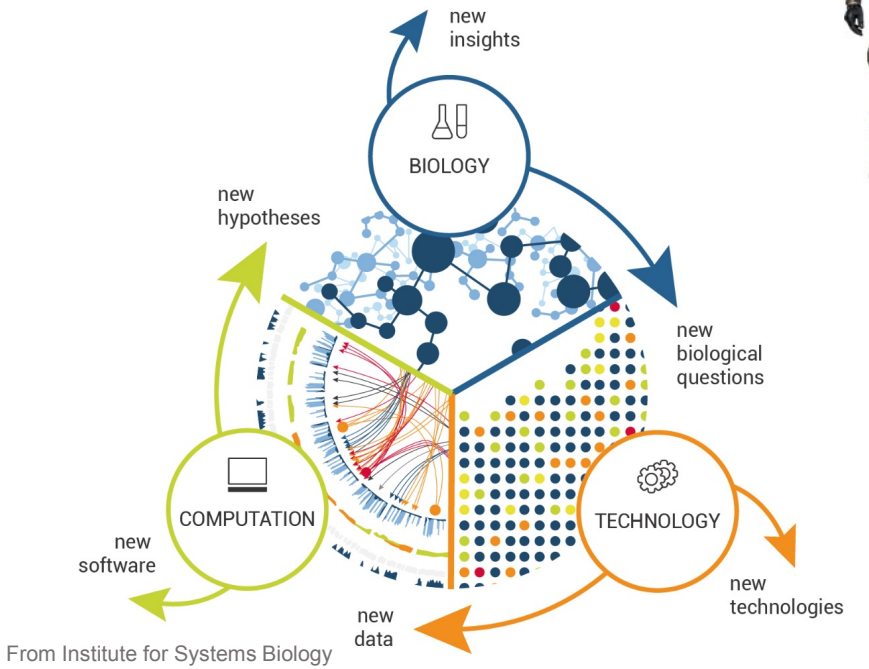
Systems Biology for Performance Vision

Elucidate warfighter biologic state and the underlying mechanism of responses such that we can build a computational model/"virtual warfighter" that recapitulates warfighter physiology in diverse operational environments

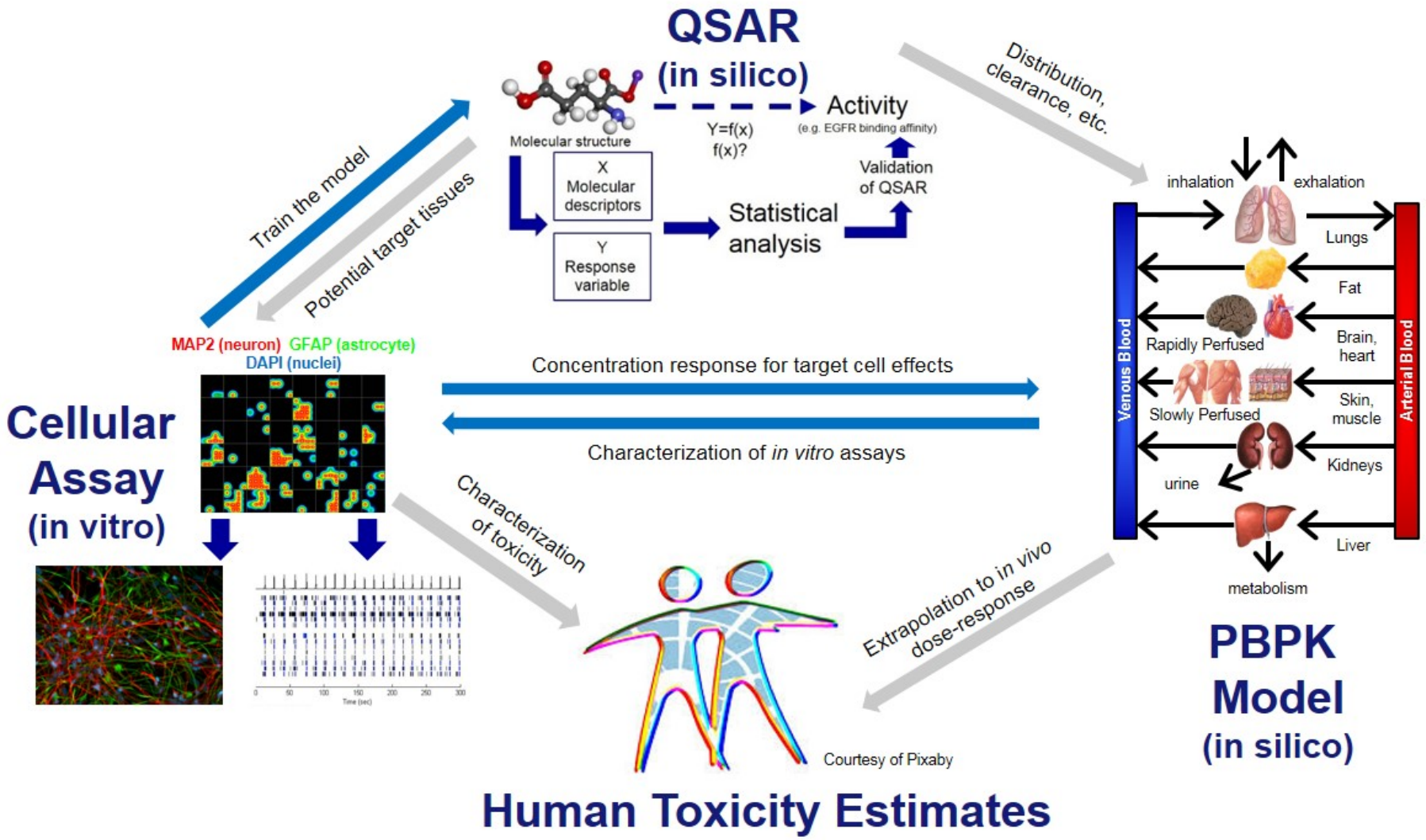




From Institute for Systems Biology

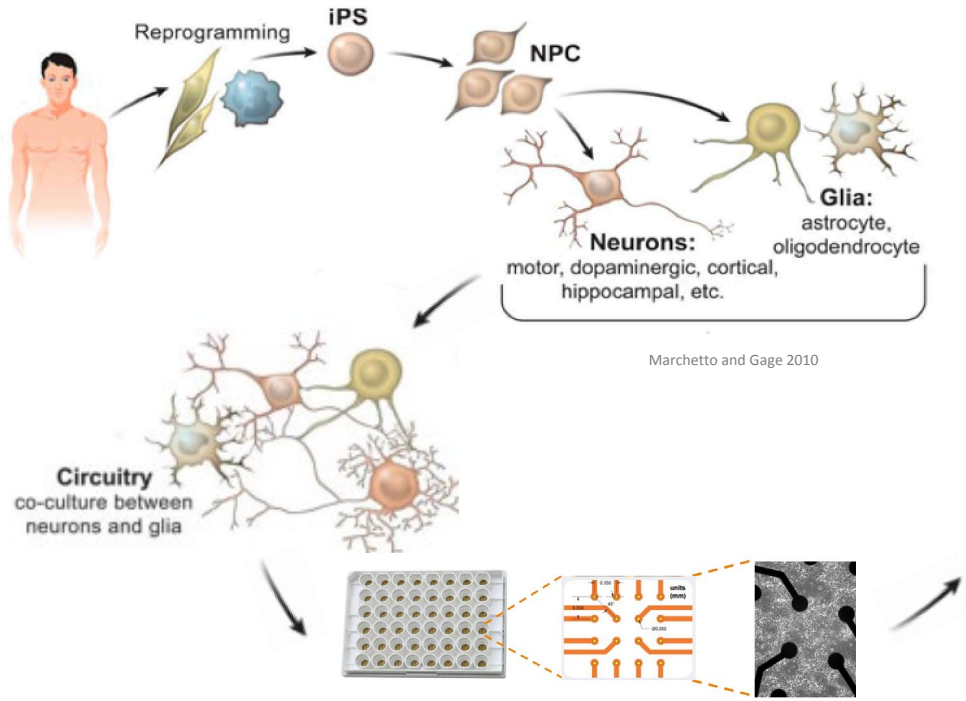
Enabling individual variable responses to any operational stressor/perturbation (hypoxia, hyperoxia, stress, fatigue, flight line operations, thermal stress, directed energy) to be predicted

In Vitro to In Vivo Extrapolation

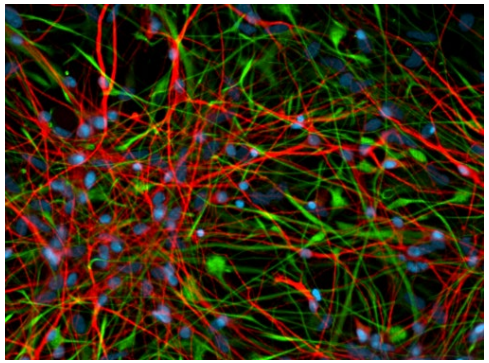


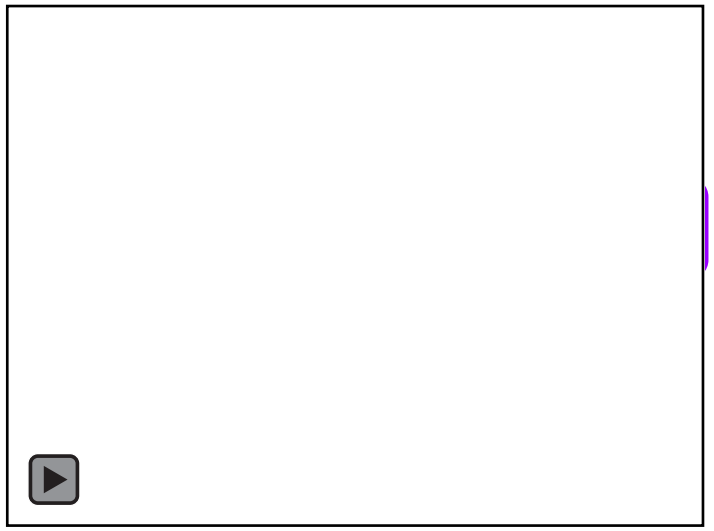
In Vitro Data Production

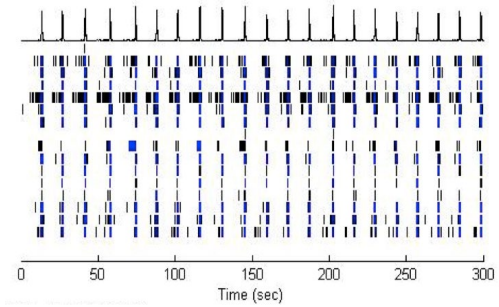
In Vitro – human stem cells



MAP2 (neuron); GFAP (astrocyte); DAPI (nuclei)





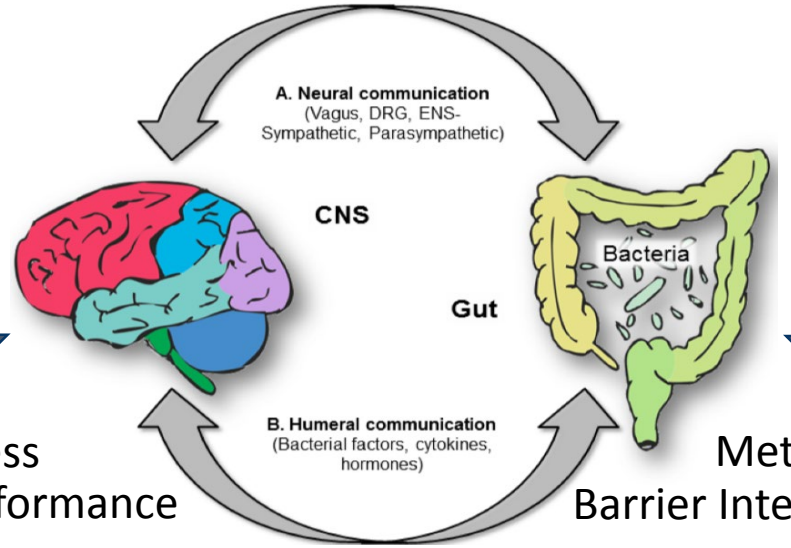


In collaboration with Anne Bang at Sanford Burnham Prebys

Airman-on-a-Chip: Gut-Microbiome-Brain Axis Work-Flow

Operational Stressors

- Fatigue
- Sleep deprivation
- Oxygen content



Cognition
Awareness
Performance

Homeostasis
Metabolism
Barrier Integrity

Environmental Stressors

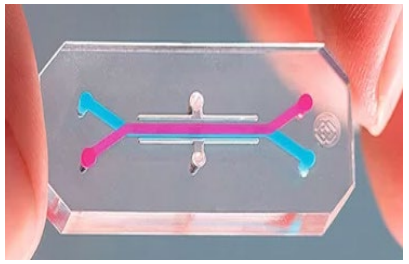
- Extreme temperatures
- High elevation
- Bacteria / viruses

Jenkins et al. Nutrients 2016, 8(1), 56; https://doi.org/10.3390/nu8010056

3D Extracellular Matrix

Cells: Gut/Endo./iPSC

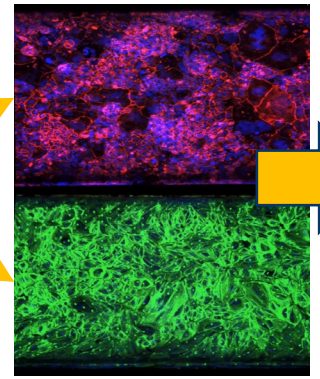
Gut – Microbiome – Brain Axis Organ Systems: Homeostasis, Dysbiosis, Countermeasure Development



Microfluidic Device

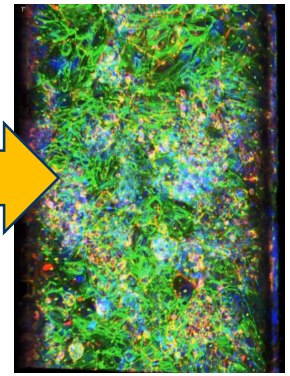
Shear Stress + Mechanical Forces

GUT



Endothelium

GUT Tissue



Tyler Nelson

Gut-Organ Axis Discovery/Evaluation

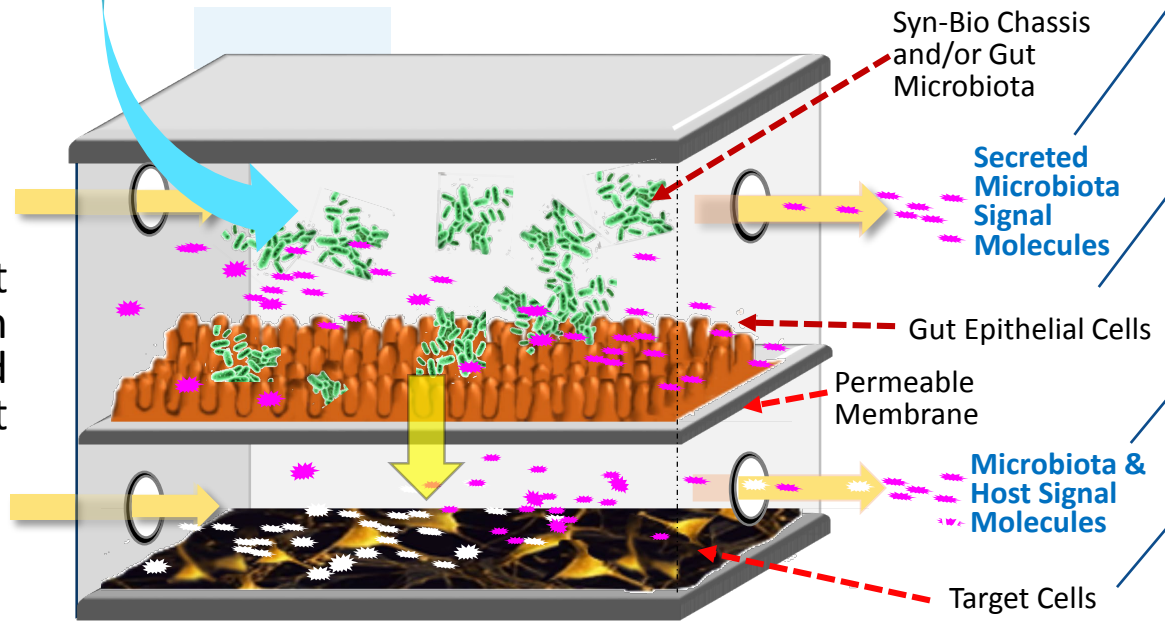
Scan of Bacterial-Host-Target Using Monoculture and Complex Bacterial Population

Bacteria – Host Cell Contact for Signal Transfer

Microbiome Surface & Excreted Signal Analyses

Platform Use:

- SynBio Engineered Chassis
- Single Bacterial Component (Monoculture)
- Single Bacterial Component + Mock Community
- Cecum/Fecal Full Microbiome



Camilla Mauzy

Microbiome (MB): Culture & Biofilm (= MAM)
16S rRNA Sequencing – Population Dynamics
qPCR quantitation of specific species
Meta transcriptomics
Meta proteomics

MB Output Molecules:
Metabolomics – bacterial excreted metabolites
Lipidomics – SCFA fatty acid chains

Gut Epithelial (GE) Response:
Transcriptomics
Targeted qRT-PCR
Cytokines
MALDI Imaging for global Omic Analysis
MAFFs

MB/GE Output Molecules:
Metabolomics
Lipidomics
Proteomics - neuropeptides

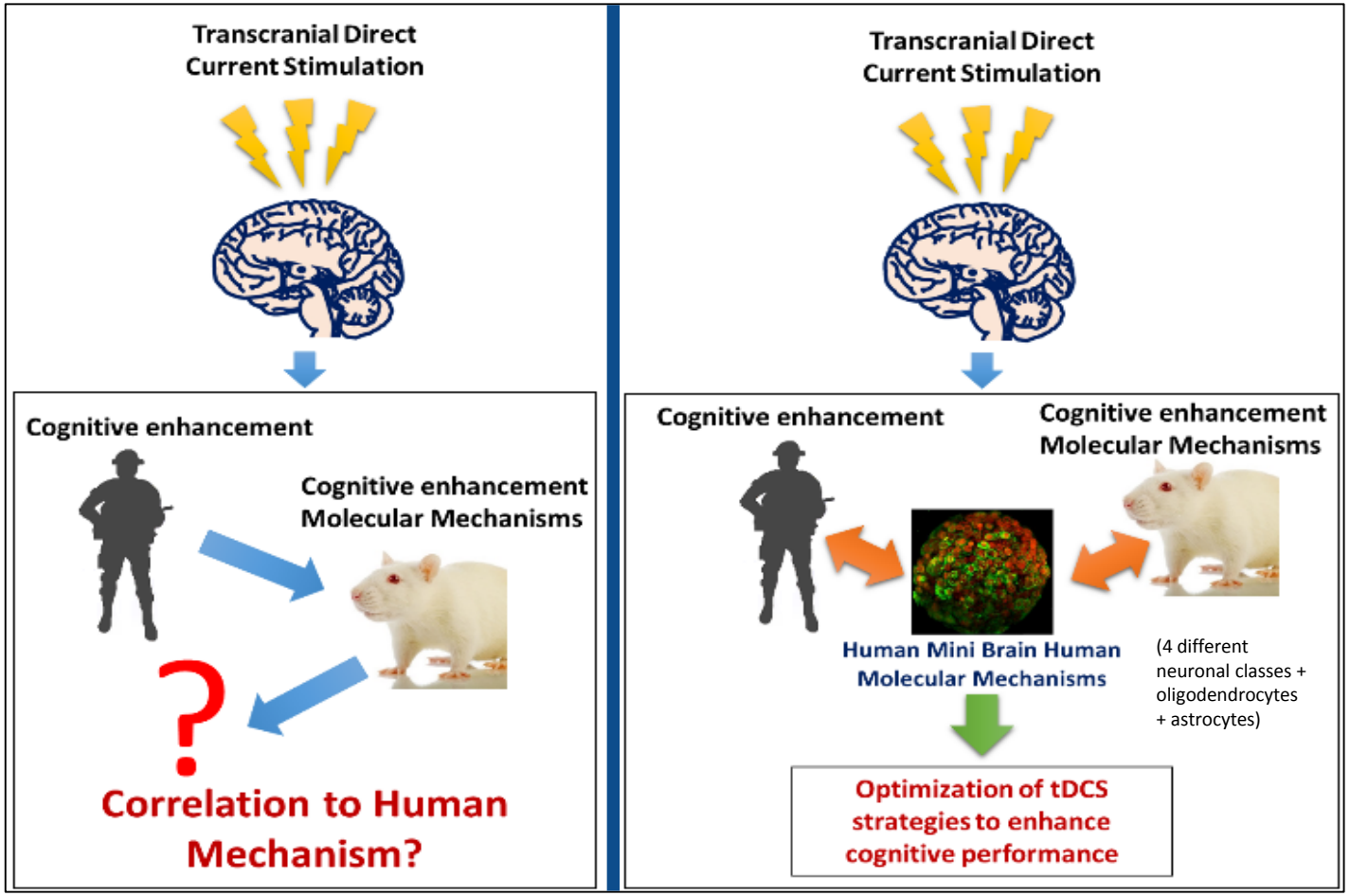
Target Cell (TC):
Transcriptomics
qRT-PCR Key Pathway Genes

TC (Neuronal):
Metabolomics, Lipidomics, Proteomics

TC (Skeletal Muscle):
Metabolomics, Lipidomics, Proteomics
Markers of Damage, Energy Metabolism
Contraction

Modeling Performance Enhancement/Protection-tDCS Using Human Mini Brains

Q: What molecular changes are initiated by direct current stimulation?



Pathways of Interest: Angiogenesis, Neurogenesis, Synaptic Plasticity

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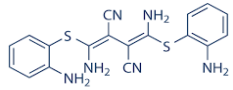
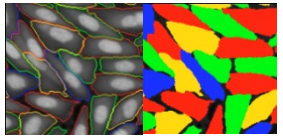
In Vitro – Personalized Risk

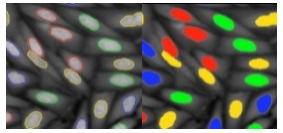


Chemical exposure

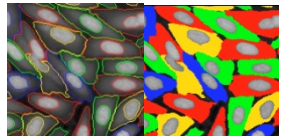
Commercially available genetically defined cells



Cytoplasmic Volume



Nuclear Envelope Determination



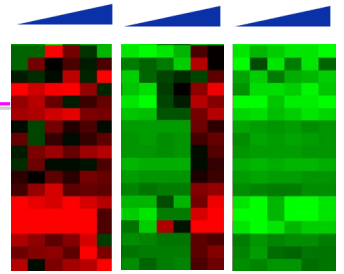
Nuclear Area / Cell Area

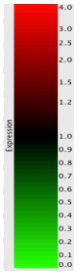
Phenotypic ID

Phenotypic features that characterize response of cells to chemicals

correlate

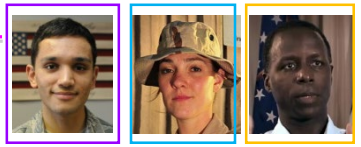
Chemical "X" concentration





sensitive

resistant



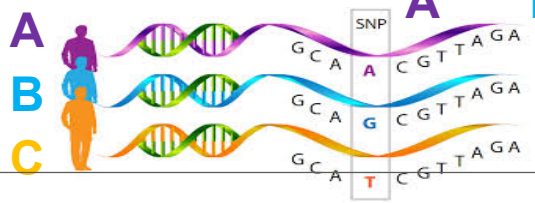
A B C

HCA features

ID correlation between genetic makeup and differential phenotypic responses

predict

- Toxin sensitivity
- Disease susceptibility
- Therapeutic response
- Therapeutic optimization



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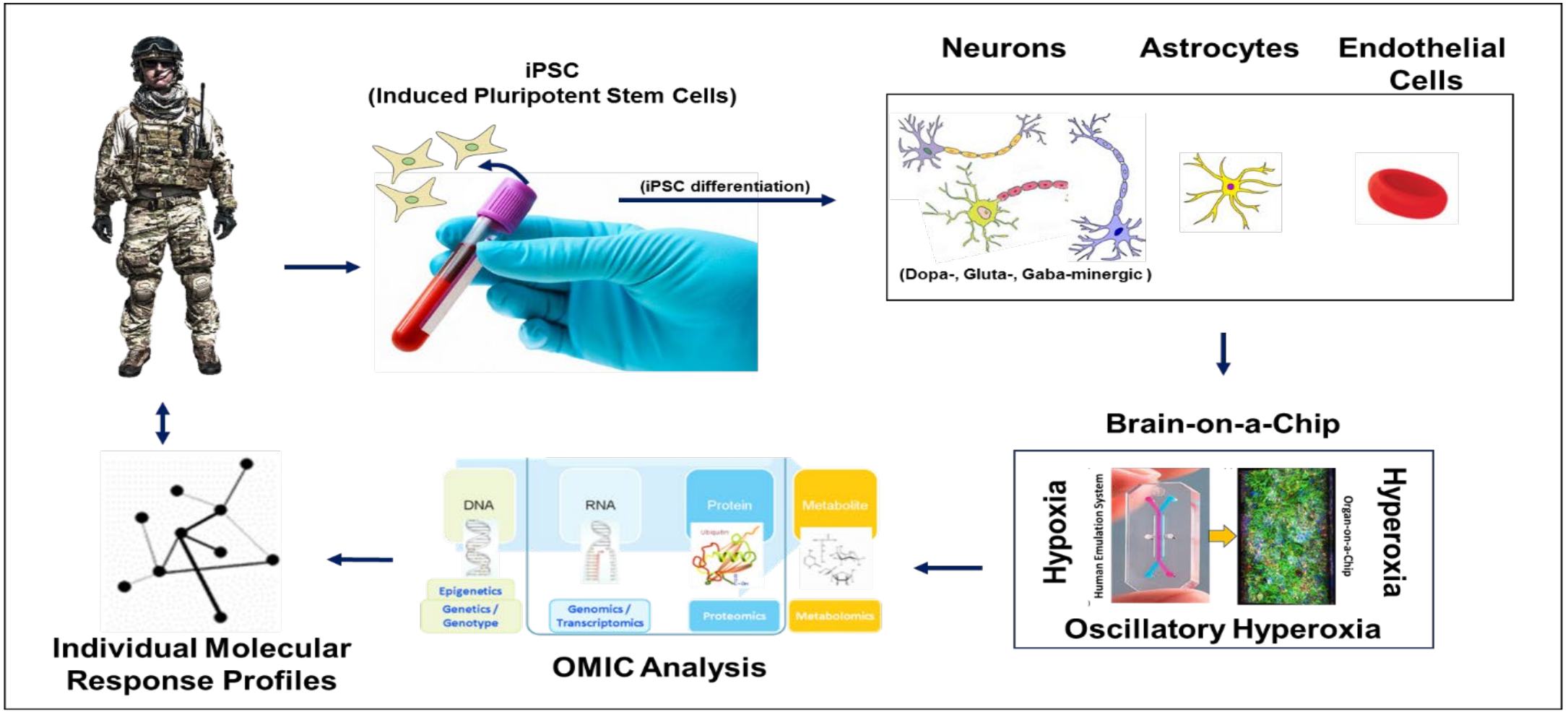
Assessment of Neuro-Vascular Responses to Hyperoxic Oscillations in Airman: A Systems Biology Approach



Tyler Nelson

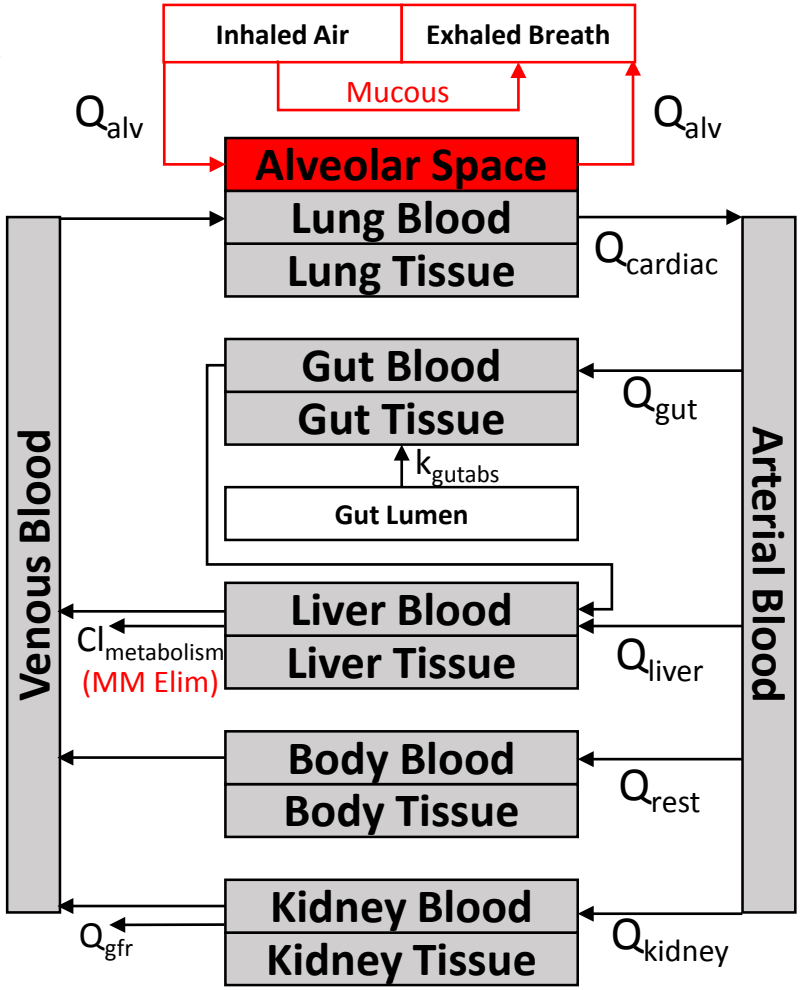
Biological Systems Modeling

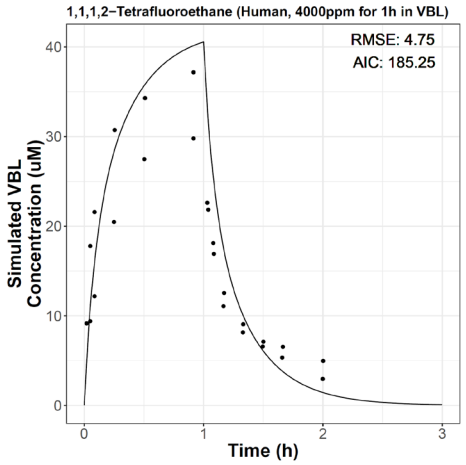
Development of a Generalized Inhalation Model for Use with the High-Throughput Toxicokinetics (*httk*) Package in R

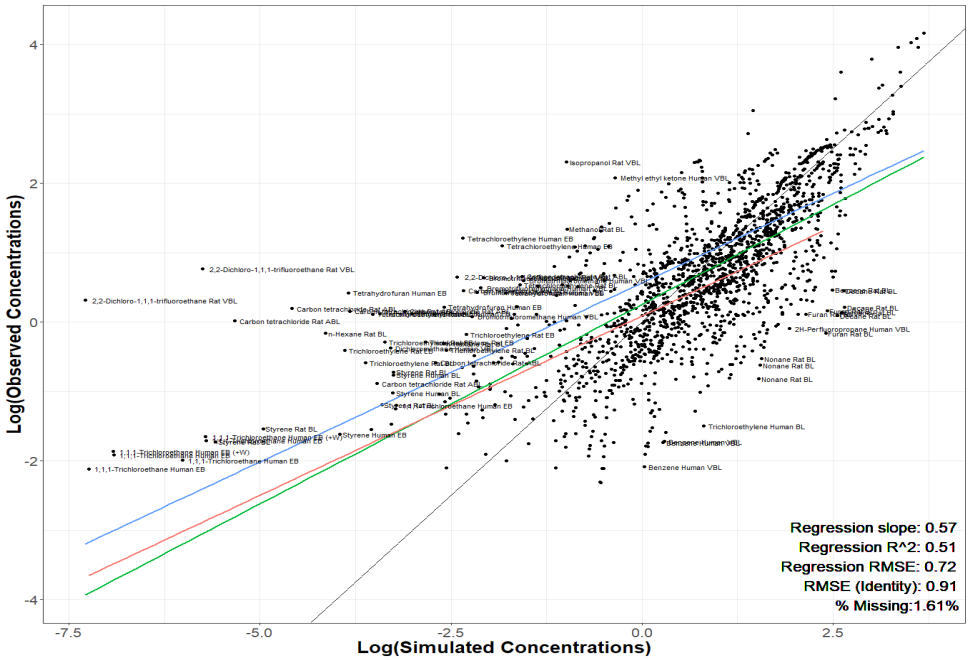
Dr. Matt Linakis

- Recent collaborative work with the USEPA

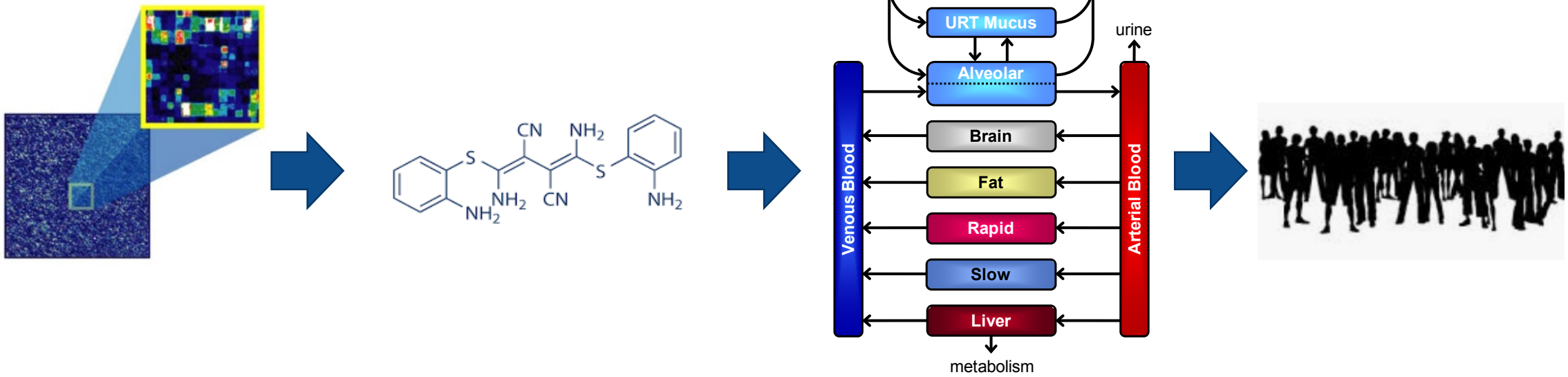
- 42 chemicals for model building/training
- Input:
  - Gas inhalation
- Output:
  - Blood and other tissue concentrations
  - Exhaled breath concentrations
- Under Development:
  - Aerosol inhalation







The Potential for Genetic Variation to Impact Risk Estimates from Chemical Exposures in a United States Air Force Population



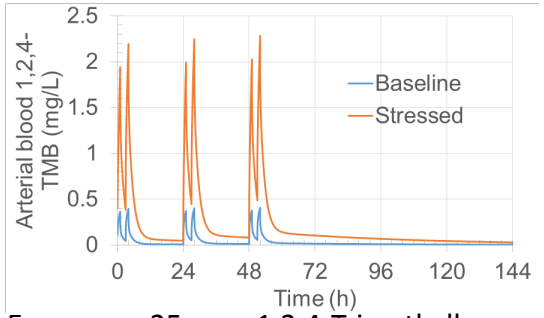
Jeffery Gearhart and Joseph Jarvis

Drs. Lisa Sweeney,
Matt Linakis

Development of Exposure Limits for Chemicals Encountered During Aircraft Operation

Aircrew Problem Formulation—In-flight airborne chemical contaminants

- Population: healthy adults
- Exposure
  - Assume 2 flights (1 h/flight) per day with 2 h separation on three consecutive days
  - Several stressors possible (heat, exertion, altitude, +Gz forces, vibration)
- Comparator
  - Same exposure concentration and schedule, lack of stressors (modified value)
- Outcome
  - Critical effect(s) for toxicity reference value derivation

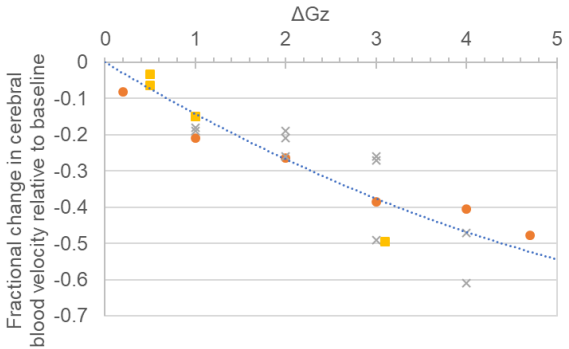


Predicted peak blood concentrations of 1,2,4-TMB are ~5-fold higher under physiological stress (heart rate = 120 bpm) vs. baseline.

Exposure: 25 ppm 1,2,4-Trimethylbenzene (TMB)

Impact of the flight-related stressors +Gz forces and altitude/barometric pressure on physiologically-based pharmacokinetic model parameters used for risk assessment

- ~170 articles reviewed, data extracted from ~70.
- >20 data synthesis figures have been prepared (see example below)



Fractional change in cerebral blood flow velocity due to increases in +Gz (baseline of +1 Gz). ○: Kawai et al. 1997; ×: Ossard et al. 1994, 1996; □: other sources (Iwasaki et al. 2012, Ogawa et al. 2016, Stevenson and Scott 2014). Trendline: $y = 0.0083 x^2 – 0.1505 x$; $r^2 = 0.805$

Current efforts:

- Incorporate stressor-related impacts into physiologically based pharmacokinetic models
- Literature review/data extraction for vibration

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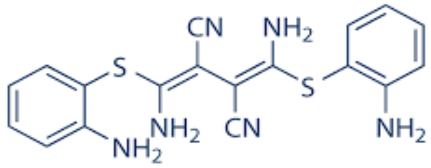
In Vivo Validation

In Vivo Validation



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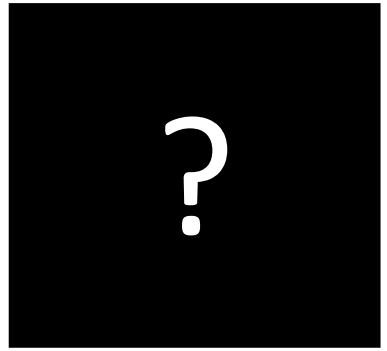
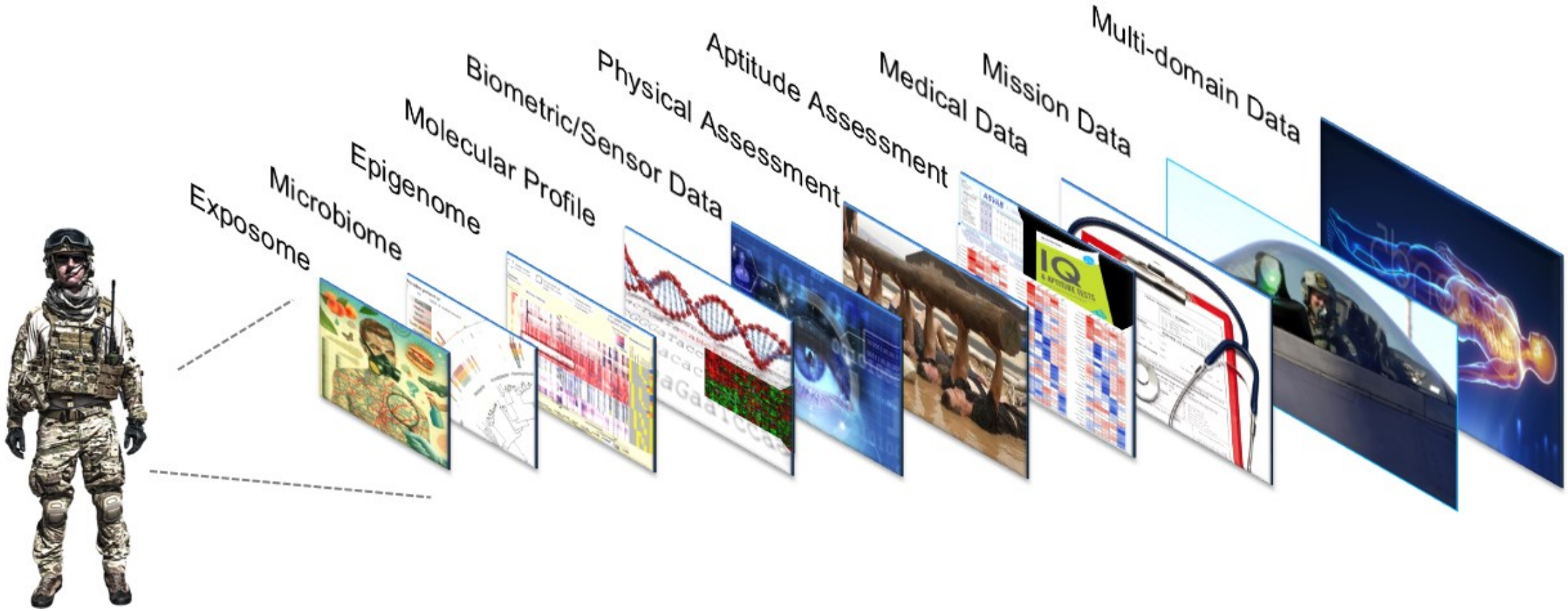


Low level exposure

operational features of flight

- G-forces
- Oxygenation
- Argon (and other air components)
- Hypobaric pressure
- Isometric workload
- Work of breathing



Acknowledgements

- Dr. Heather Pangburn, RHB, Systems Biology for Performance Core Research Area Lead
- Dr. Darrin Ott – RHM, Aerospace Operational Medicine Core Technical Competency Lead
- Dr. (Mark) Tyler Nelson – RHB, Organ on a Chip Team Lead
- Dr. Jeffery Gearhart – RHM, Biological Modeling Team Lead
- Dr. Patrick McLendon – RHM, In Vitro Modeling Team Lead
- Dr. Anne Bang – Sanford Burnham Prebys
- Dr. Joseph Jarvis – RHB, Bioinformatics Team Lead

Questions?