



Biomarker Strategies for Exposure and Response

October 11, 2019

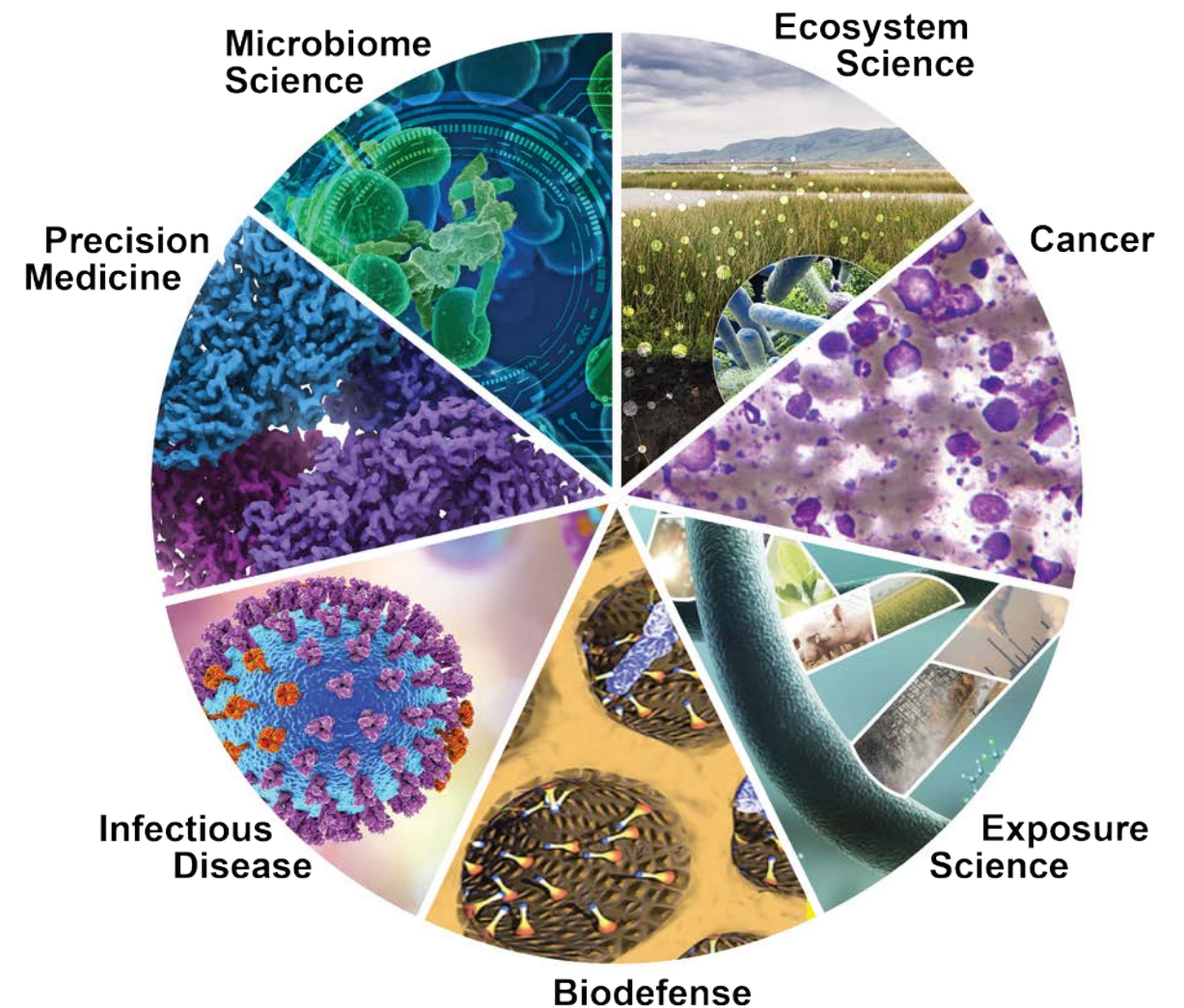
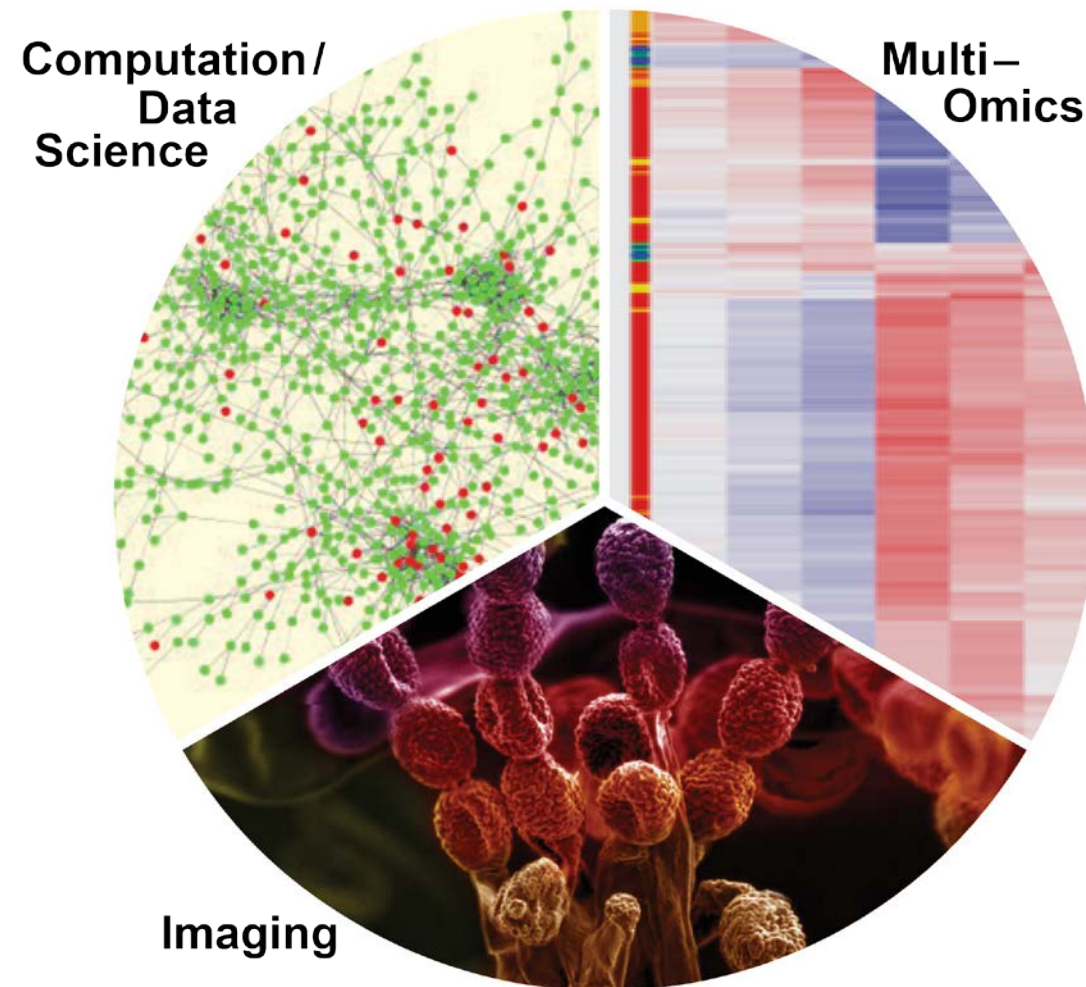
Katrina Waters, PhD

Laboratory Fellow and Division Director



PNNL is operated by Battelle for the U.S. Department of Energy

Biomarker Discovery is a Multi-disciplinary Contact Sport

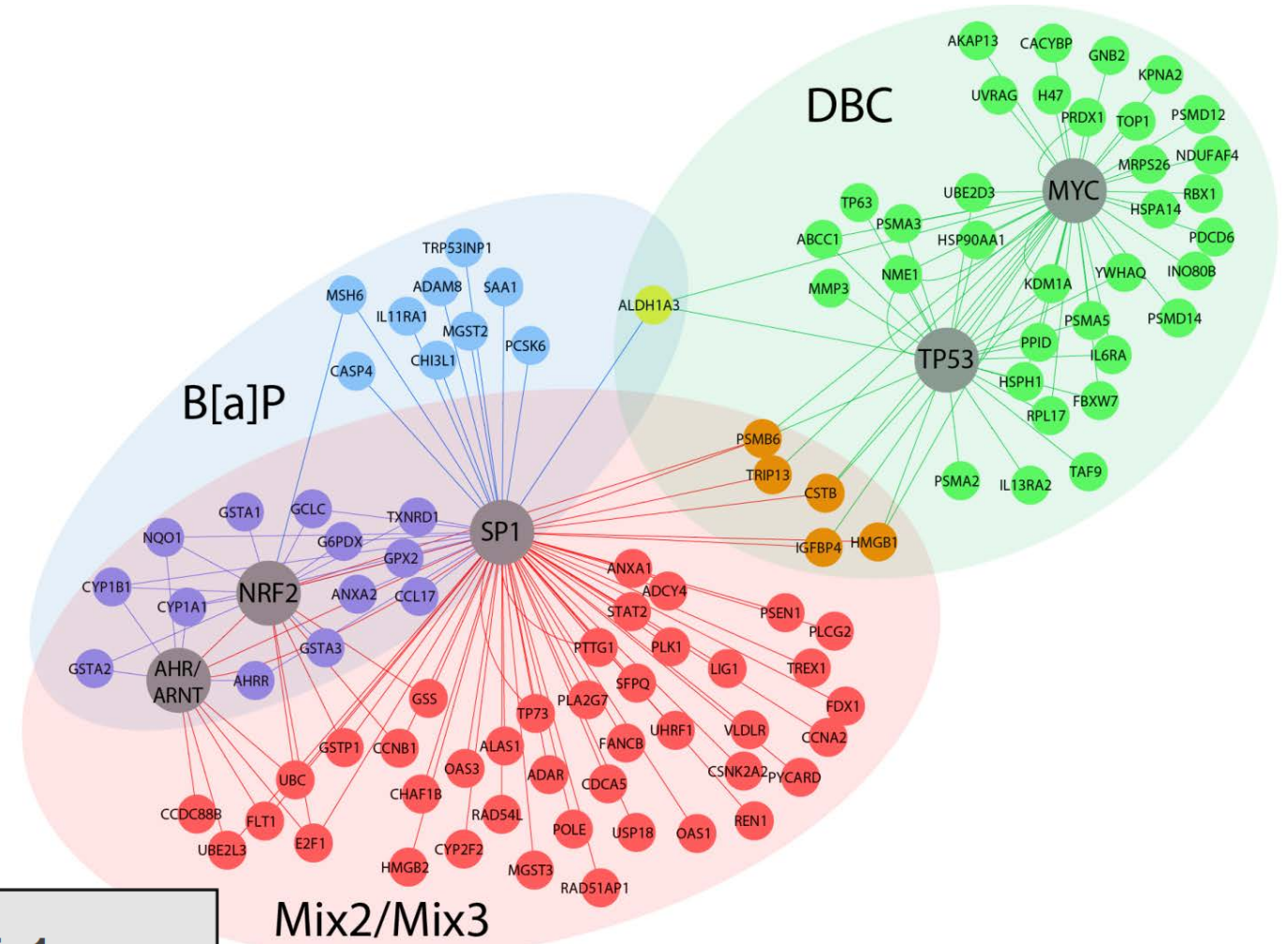
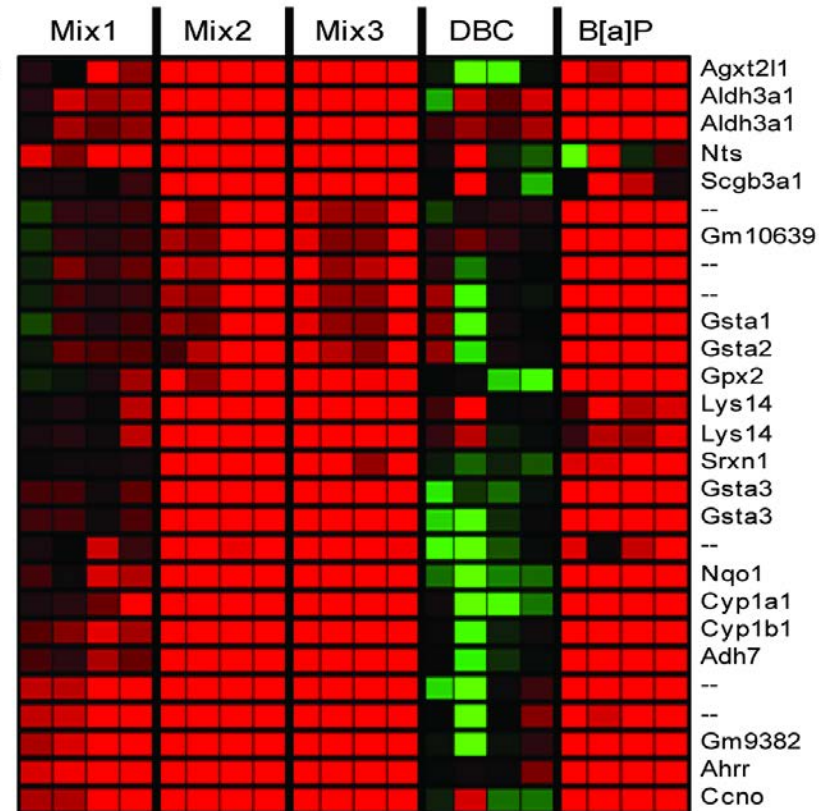


Biomarkers: Bridging Human Exposure and Precision Medicine

- Exposure vs response
- Diagnosis of health conditions
- Prognosis and risk stratification
- Mechanisms of response leading to therapeutic strategies
- Treatment stratification
- New therapeutics and countermeasure strategies



Mechanism-based classification to predict carcinogenic potential of PAHs & mixtures

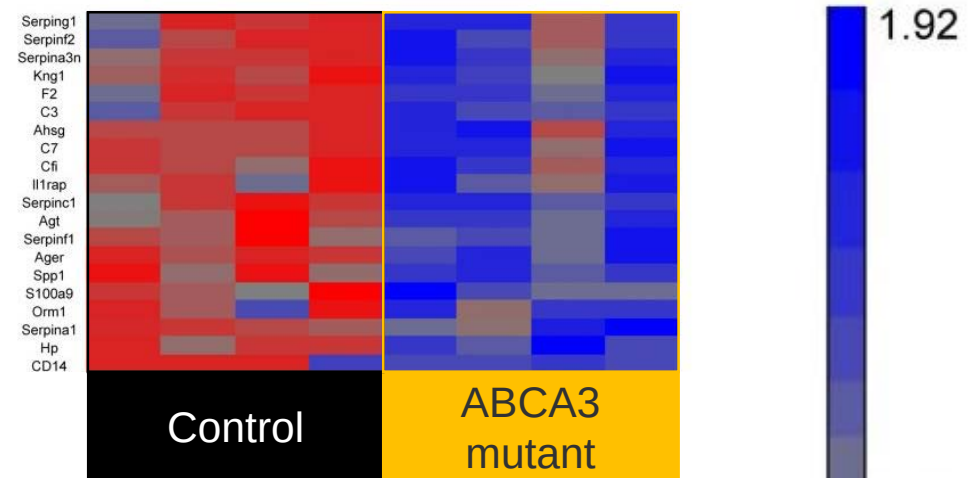


Tumor Outcome: DBC >>> B[a]P = Mix2 = Mix3 >> Mix1

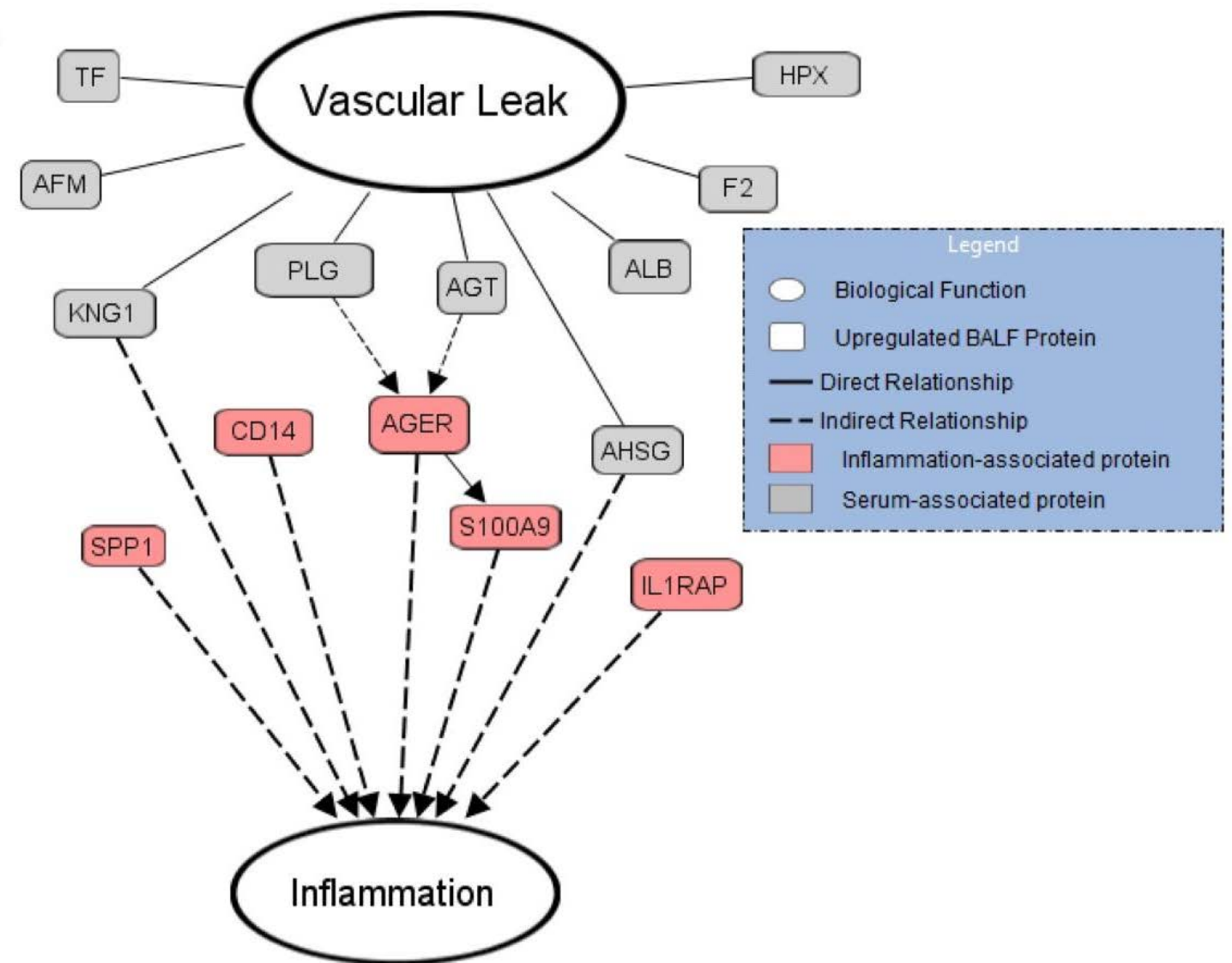
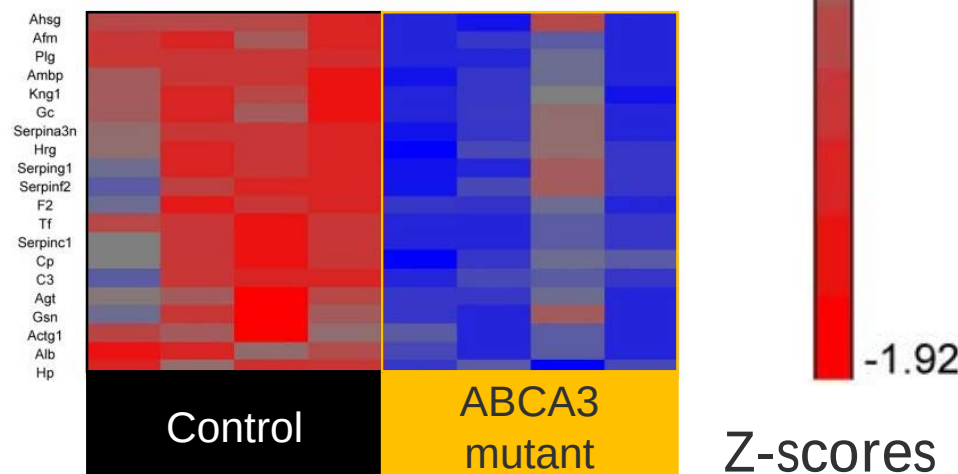
Classification: High Moderate Low

BAL Analysis of proteins and lipids identifies mechanism for genetic cause of respiratory failure

Inflammation-associated proteins

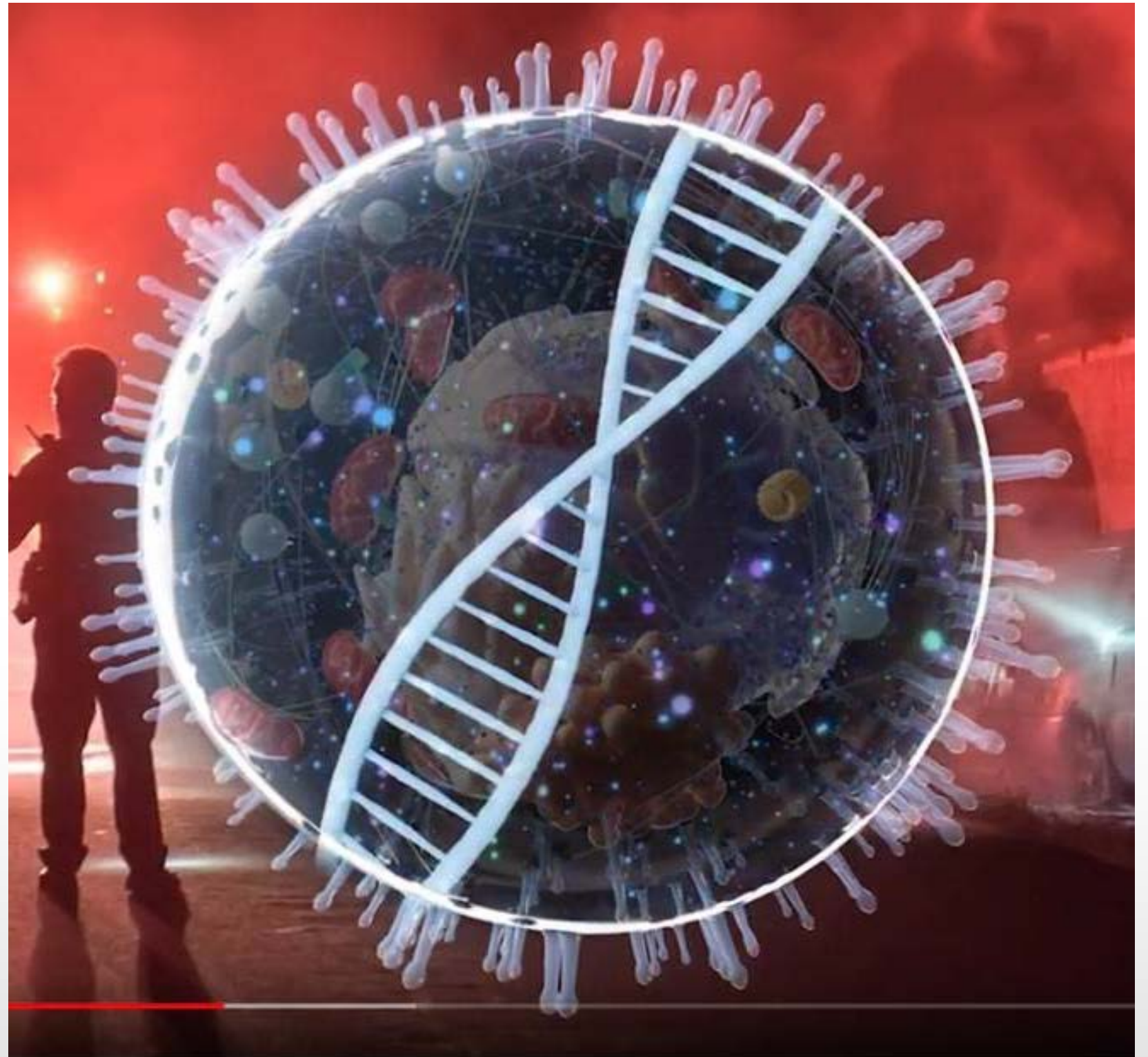


Serum-associated proteins

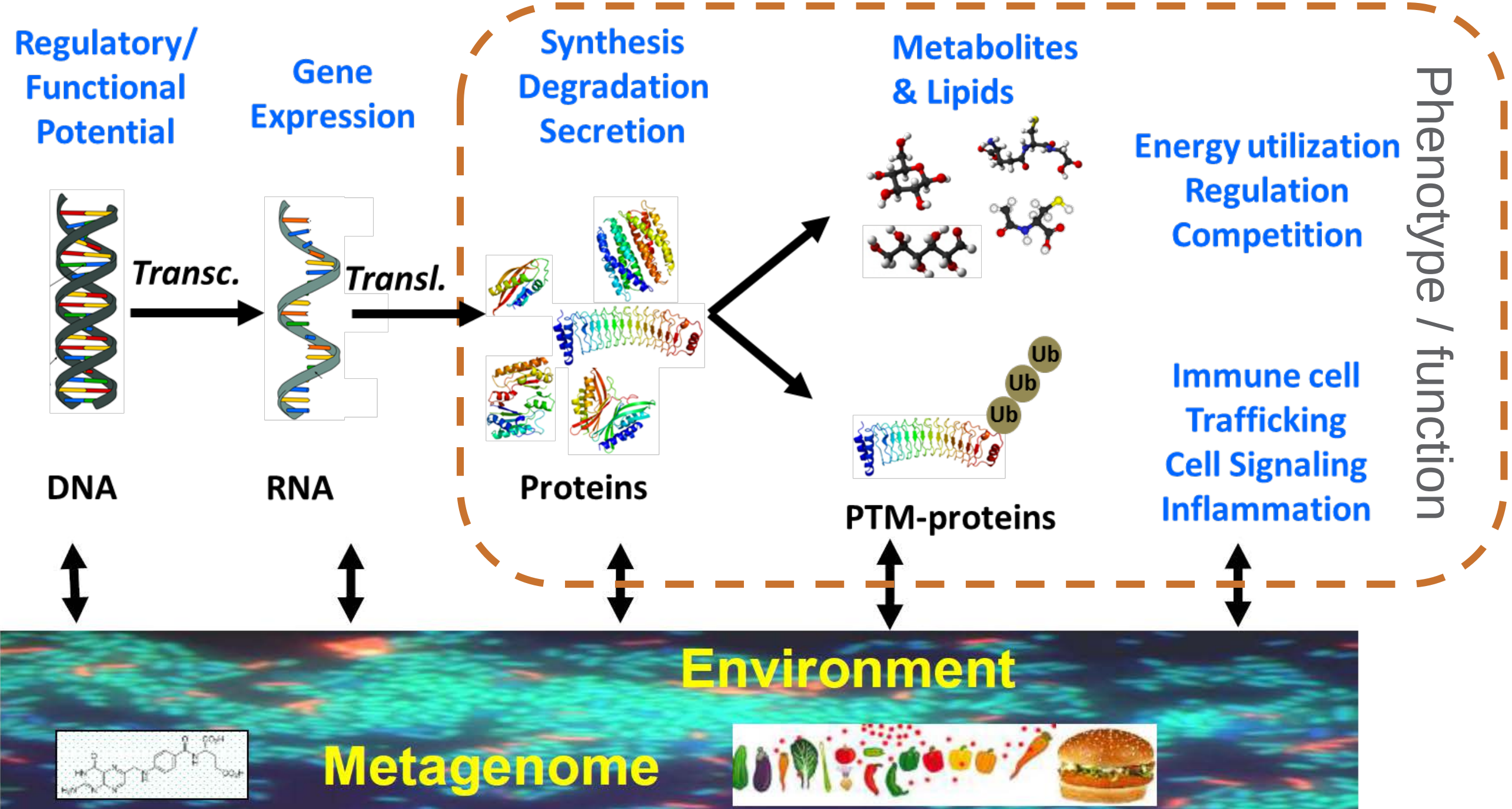


Specific considerations for veteran populations

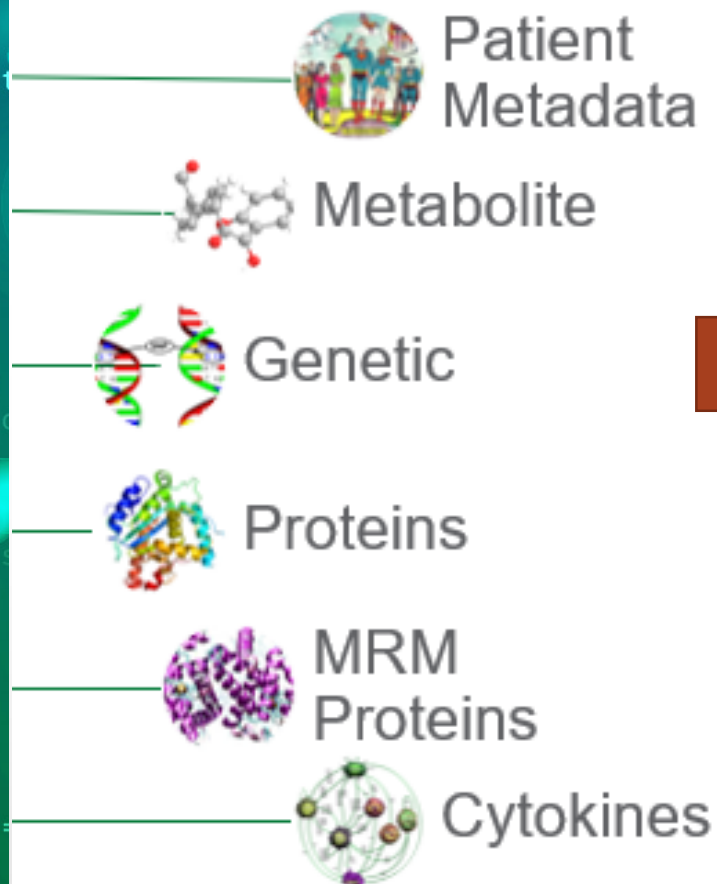
- Acute and chronic health effects of chemical & particulate exposures
- Multiple co-exposures, including infectious agents
- Influence of genetics on exposure and response
- Confounding impacts of lifestyle, stress, fatigue, mental health



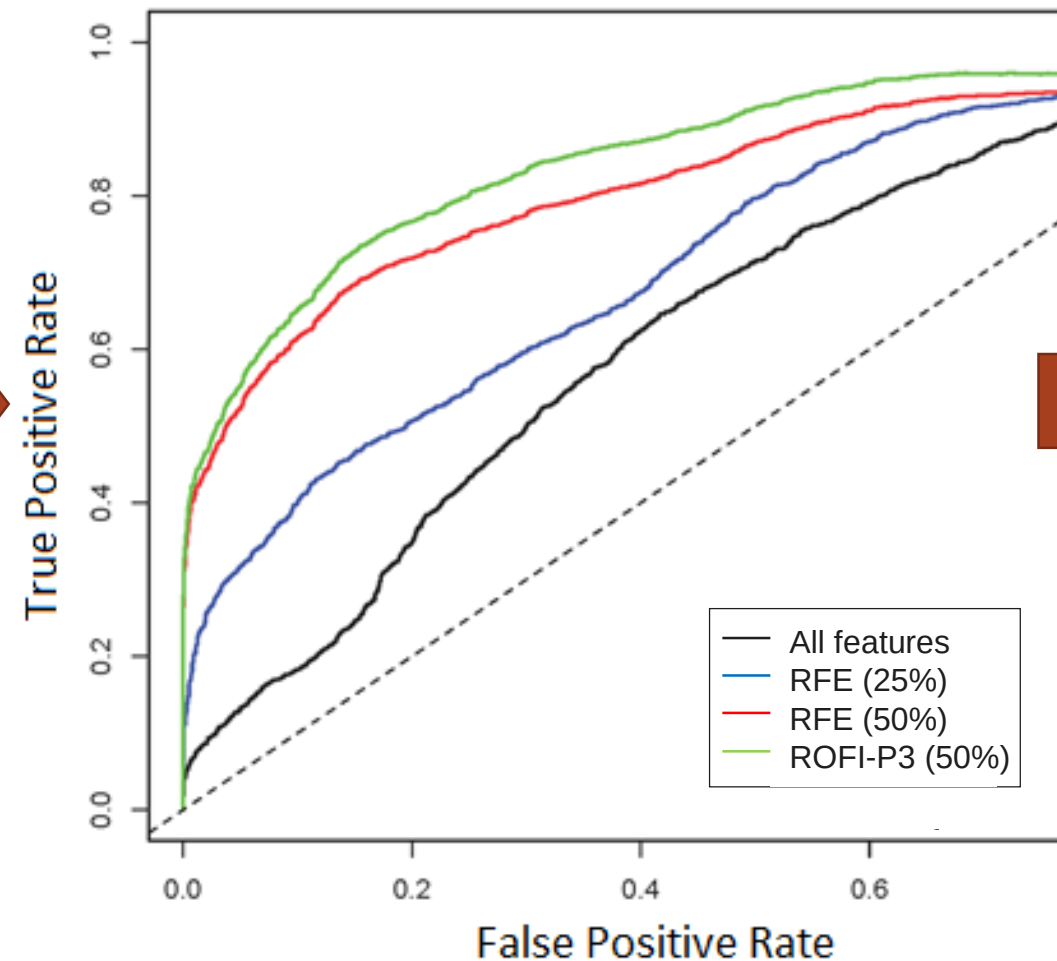
Systems-level analyses are needed to capture mechanism and phenotype



Biomarker panels can predict the development of type 1 diabetes prior to onset of clinical symptoms



>5K potential markers



Good Performance

Progression to T1D	
Feature	% Selected
Feature A	100
Feature B	100
Feature C	100
Feature D	99
Feature E	98
Feature F	98
Feature G	97
Feature H	92
Feature I	91
Feature J	90
Feature K	89

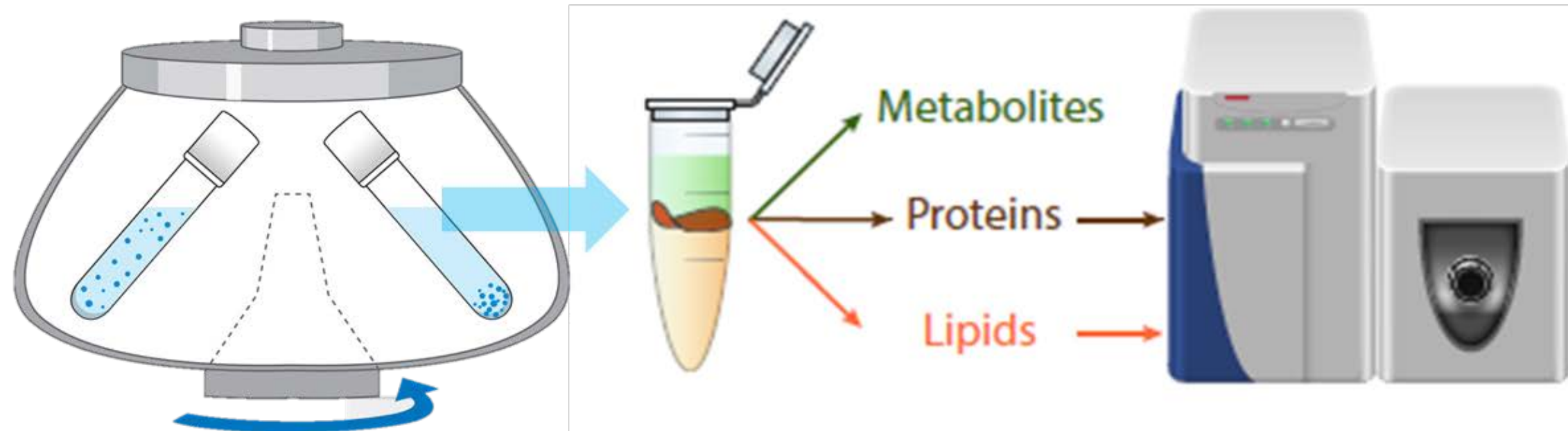
Clinical Markers

MPLEx: Single-sample Integrative Proteomic, Metabolomic and Lipidomic Analyses

Centrifugation

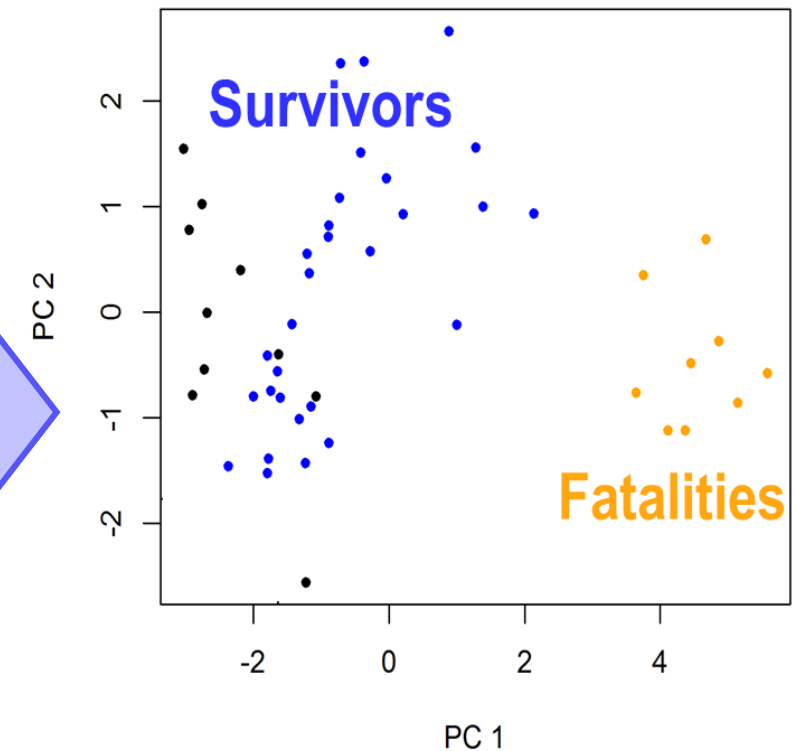
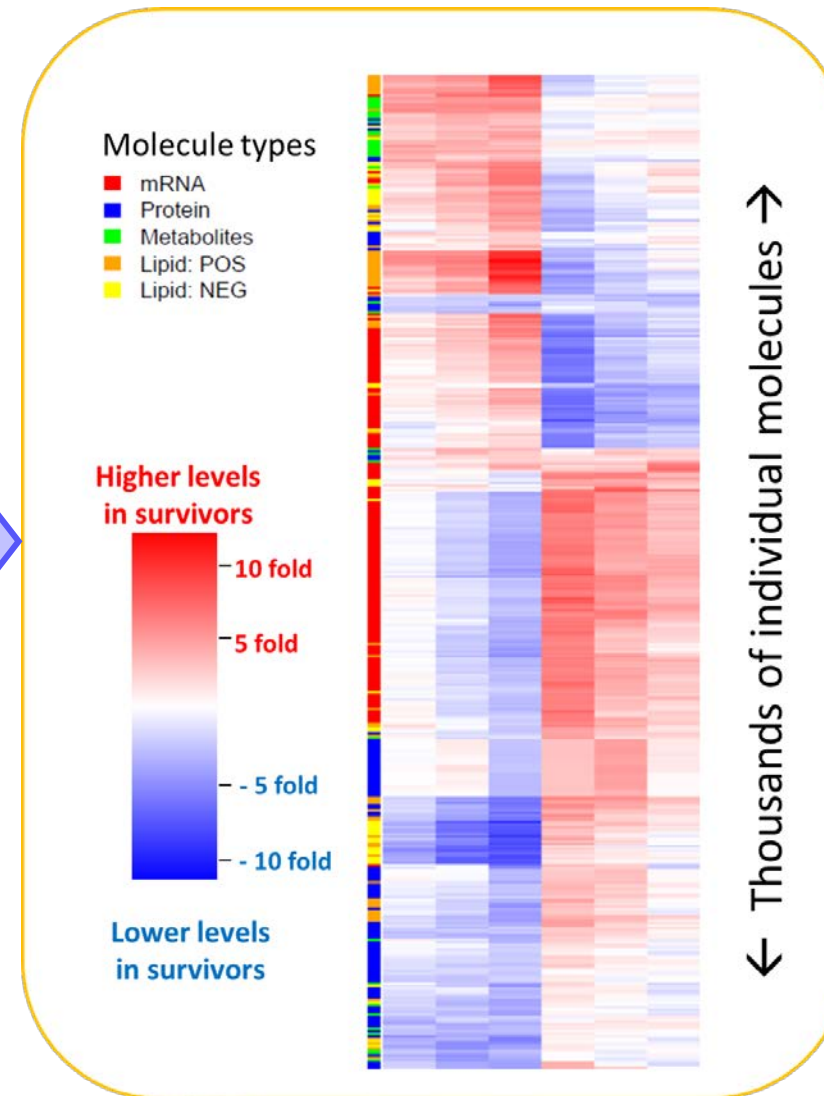
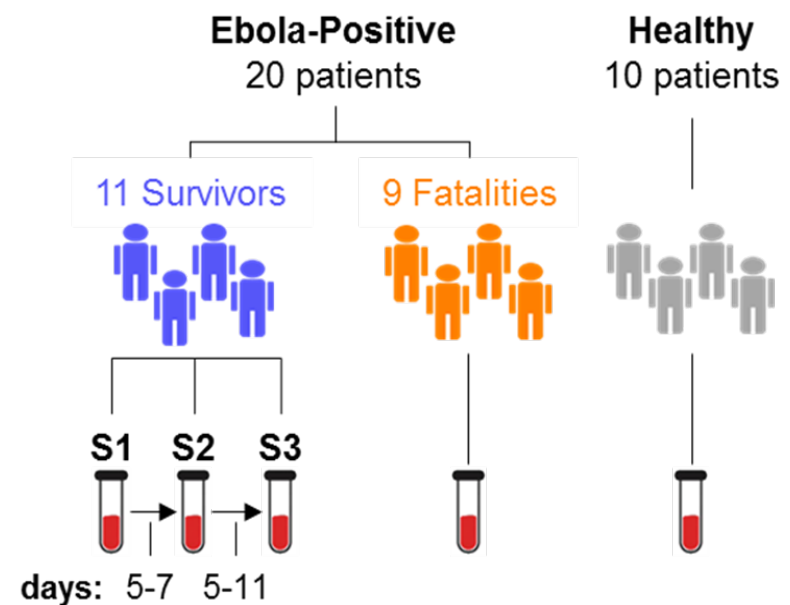
MPLEx

LC-MS/MS



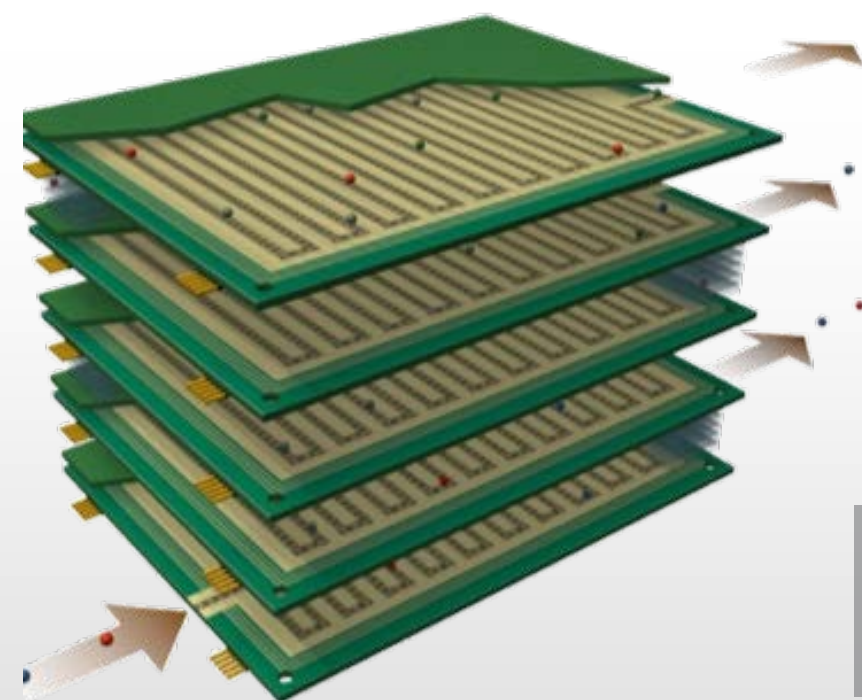
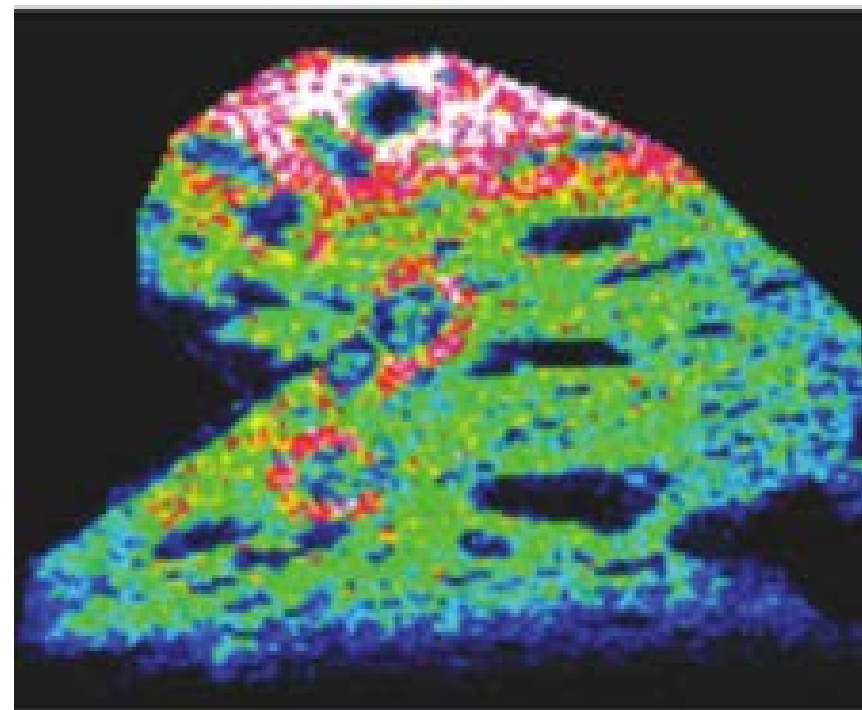
Nakayasu et al, mSystems 2016 DOI: 10.1128/mSystems.00043-16
Burnum-Johnson et al, Analyst. 2017 Jan 26; 142(3): 442–448.

Integrated omics signatures can predict survivors from non-survivors of Ebola infection



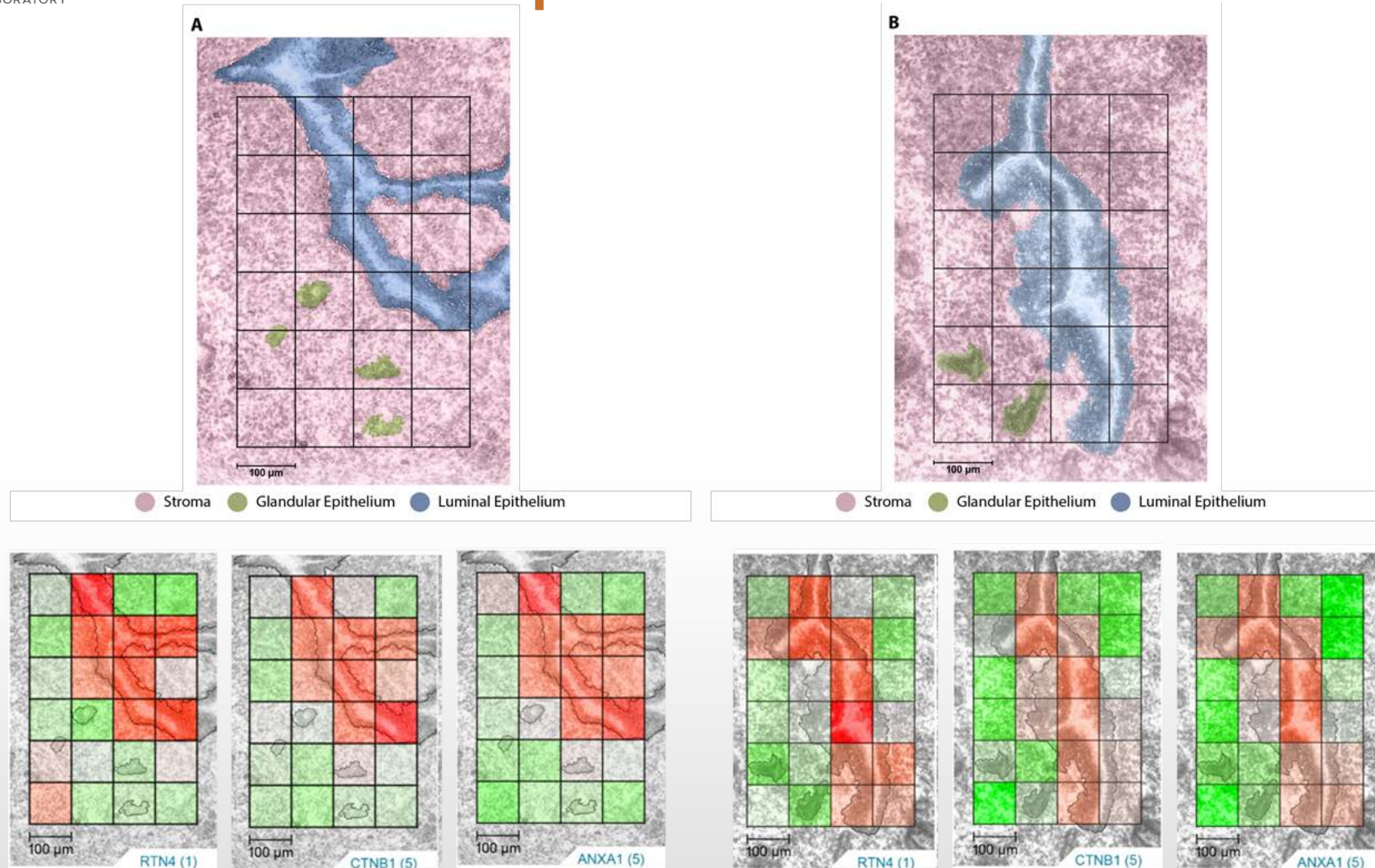
Advanced technologies for biomarker discovery

- Spatial resolution
- Single(s) cell resolution
- High throughput specialized separations
- High resolution detection and accuracy
- Standards-free global small molecule profiling



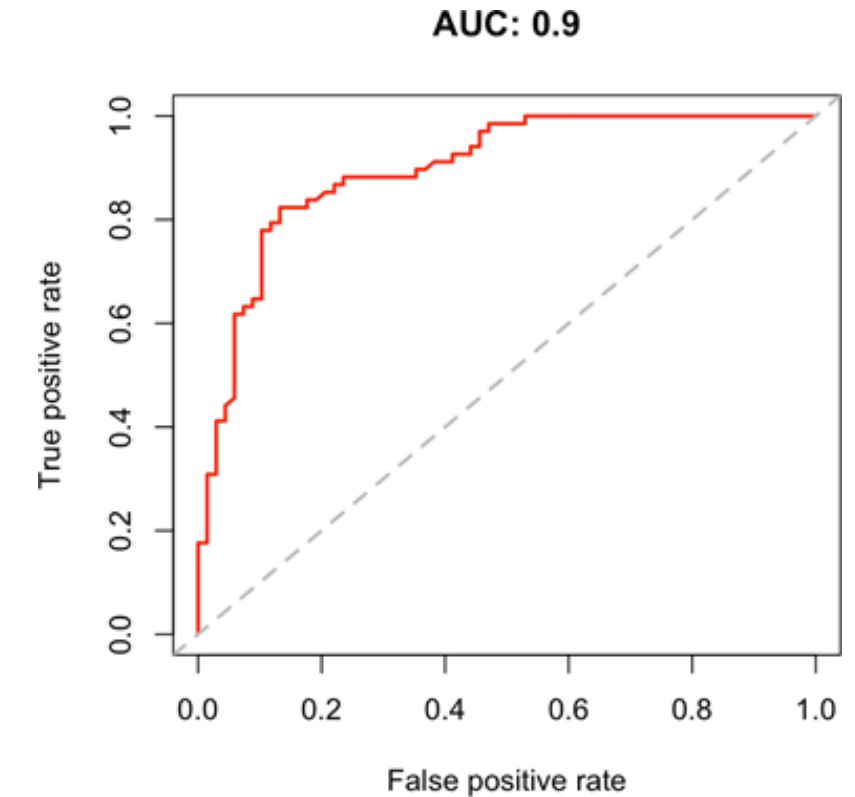
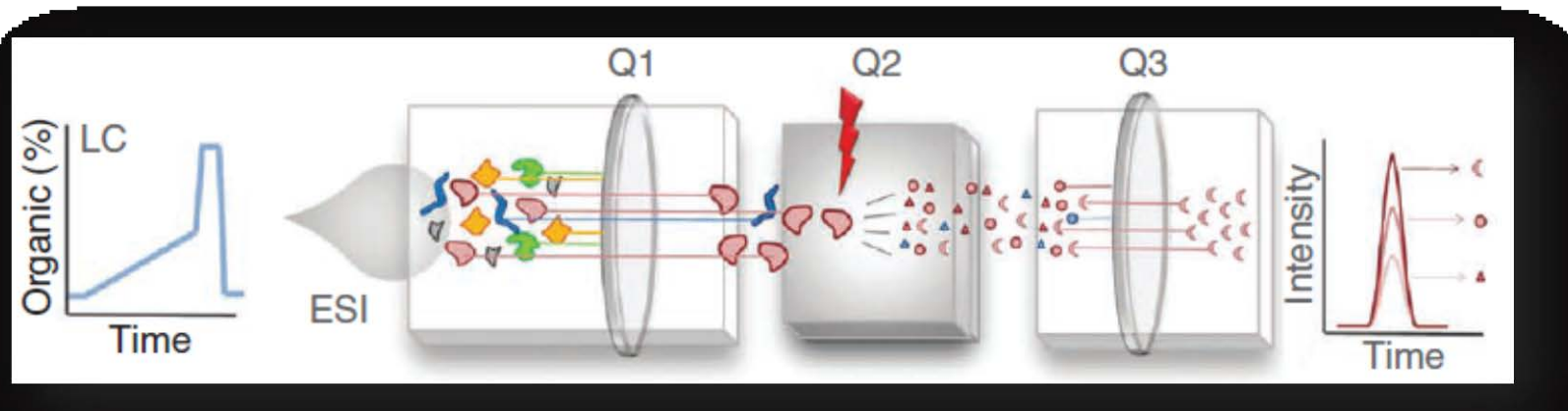
• High resolution & accuracy

nanoPOTS: Protein Imaging of >2000 proteins with 100um spatial resolution



Multiplexed SRM enables early detection of HNSCC in DOD Serum Repository samples

Liquid Chromatography –Selected Reaction Monitoring (LC-SRM)

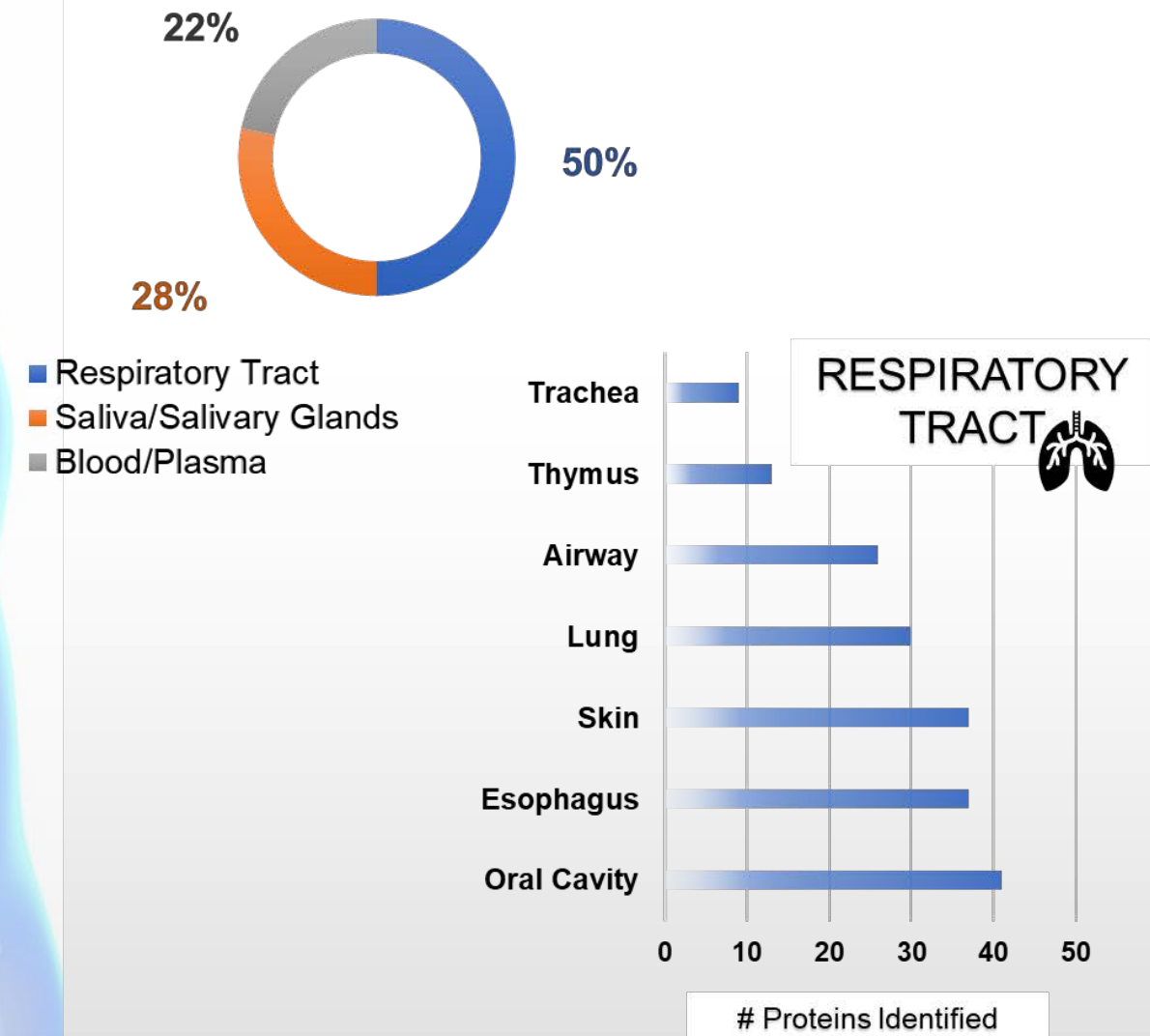


978 DODSR Sera	HNSCC cases diagnosed between 2003 and 2013, and healthy controls matched for age at the time of diagnosis, gender and ethnicity			
	Pre 2	Pre 1	Post 1 (at diagnosis)	Post 2
Cases (175)	4 ± 1 years	2 ± 1 years	1 ± 1 year	2 ± 1 years
Controls* (175)	4 ± 1 years	2 ± 1 years	1 ± 1 year	2 ± 1 years

Exhaled breath analysis detects biomarkers from the trachea, lung and esophagus



EBC TISSUE-SPECIFIC PROTEOMIC COVERAGE



Getting beyond the reliance on reference libraries with computational approaches for chemical ID

The Molecular Universe

Known
Molecules

Available for
Purchase

- Expensive & slow
- <1% of known chemicals and <20% of metabolites in the Human Metabolome Database are available for purchase
- Reference libraries will never be sufficient

Most compounds are not available as standards and never will be



DarkChem
Deep
Learning

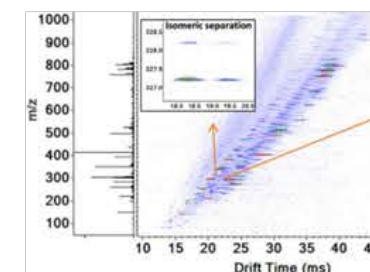
arXiv:1905.08411



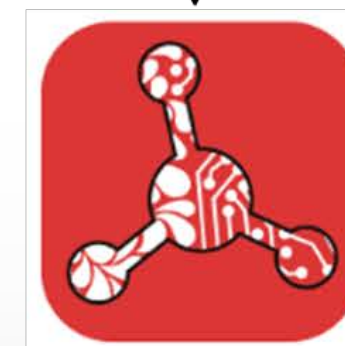
ISiCLE
Quantum
Chemistry

acs.analchem.8b04567

Library



Data

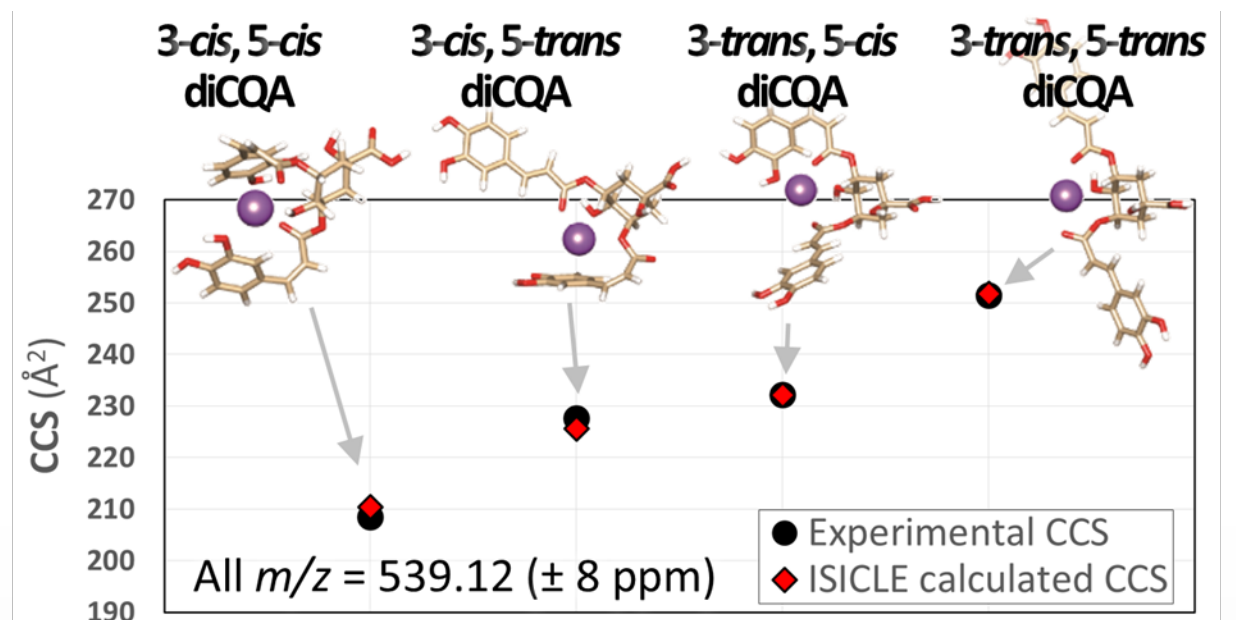


MAME
Scored
Identifications

acs.jcim.9b00444

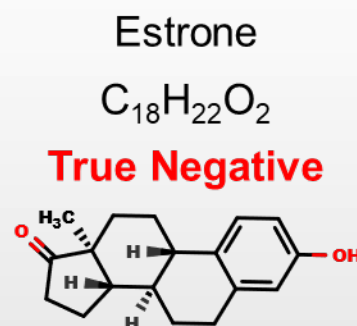
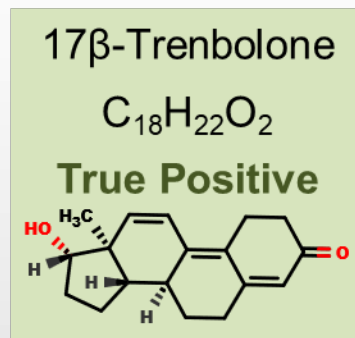
github.com/pnnl

Computational approaches combined with IMS correctly identify isomers and unknowns in blinded samples

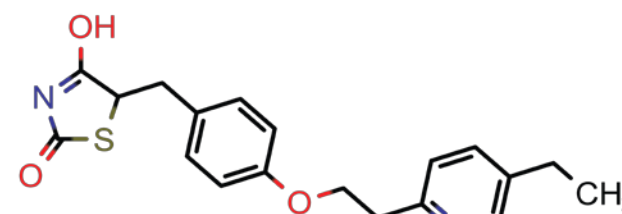


acs.jpcllett.6b03015

ENTACT:
Chemical
Identification
Challenge by
the EPA

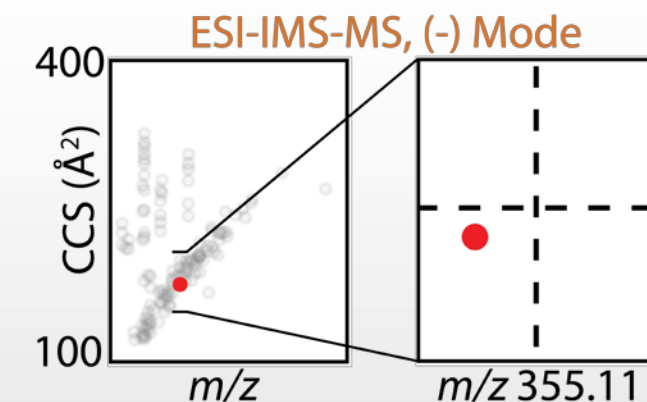
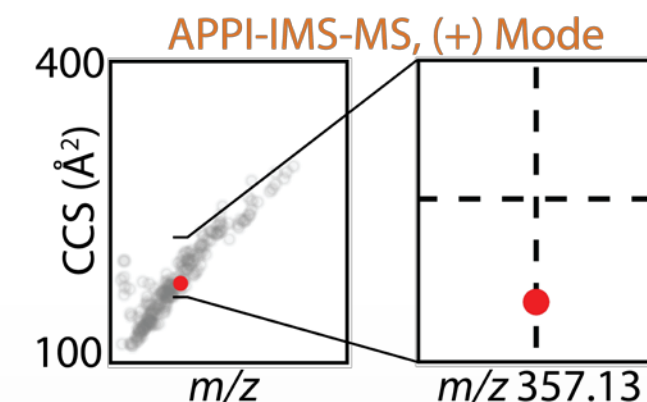
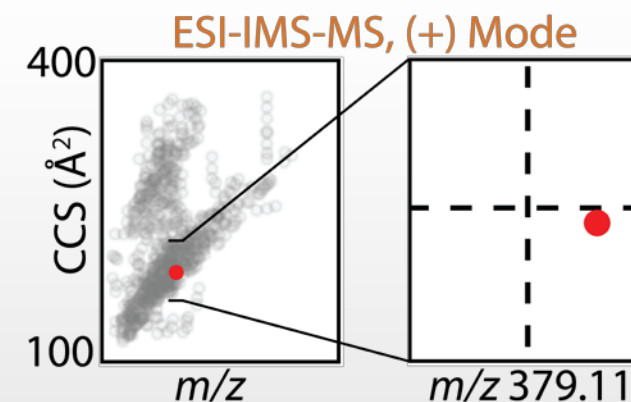
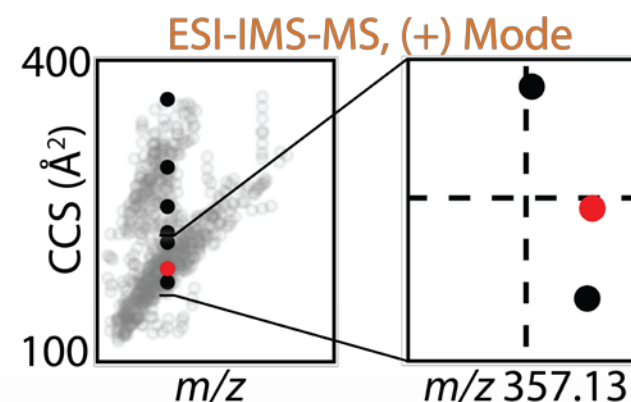


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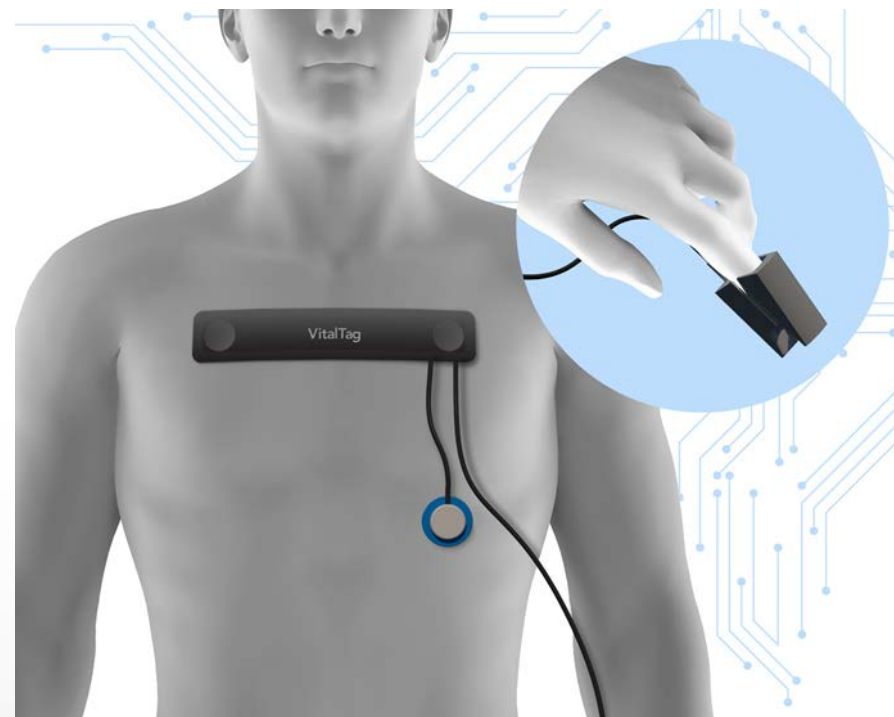


Pioglitazone

Exact Mass:	356.12 Da	
[M+H] ⁺	m/z 357.13	CCS 193 Å ²
[M+Na] ⁺	m/z 379.11	CCS 191 Å ²
[M-H] ⁻	m/z 355.11	CCS 181 Å ²

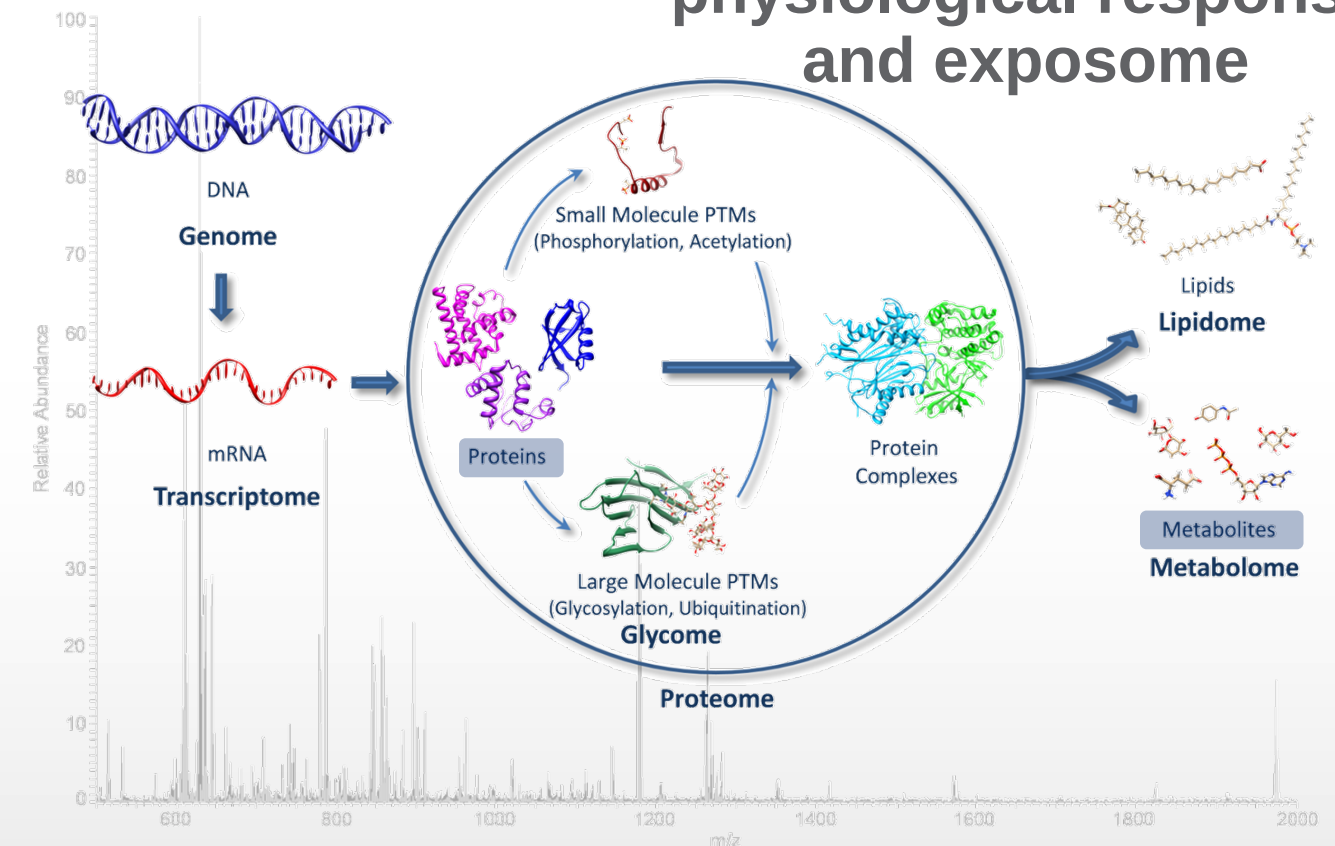


Simultaneous measurement of physiological stress, exposure and response



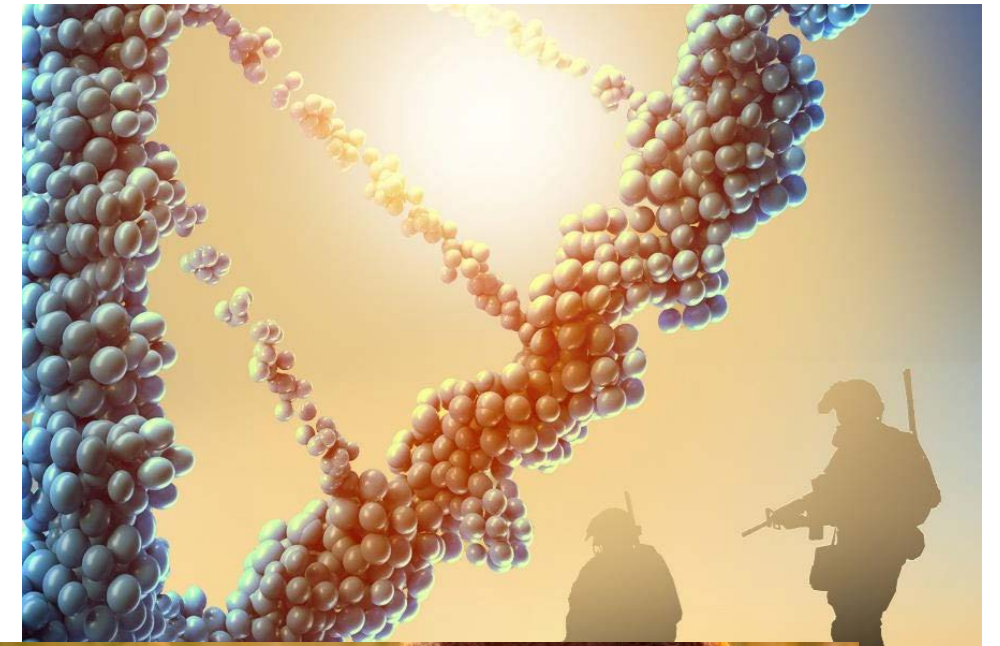
Physiological measures
of stress

Multi-omics profiling of
physiological response
and exposome



Summary

- Single biomarkers are unlikely, thus advanced technologies and data integration are becoming more important
- Response outcomes are multi-factorial and must consider genetic and psychosocial confounders
- Real-time or parallel exposure measurements are ideal for coupling exposure to response
- Biomarker panels can be designed for diagnosis, prognosis and countermeasure strategies





Thank you



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EARTH & BIOLOGICAL SCIENCES

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