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2017
November 8-12
NATIONAL HARBOR
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November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Biomarkers for Primary Immunotherapy Resistance Based on the Circulating Proteome

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Presenter Disclosure Information

Heinrich Roder

The following relationships exist related to this presentation:

I am an officer of Biodesix

Introduction

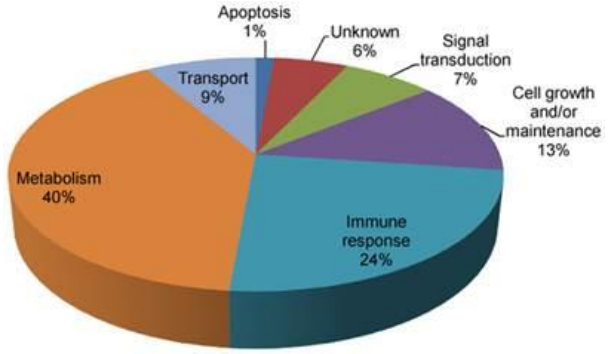
- Immune therapies have revolutionized the treatment of cancer
  - With spectacular benefit to some patients, but…..
- Not all patients respond
  - Different combination therapies are being evaluated in multiple clinical studies
- Many biomarker approaches are being investigated
  - To identify patients who do well on mono-immunotherapies
  - To identify patients who require additional treatment beyond monotherapy
  - To identify patients likely to experience adverse events …

Here we show how to use highly multiplexed protein expression measurements in combination with modern machine learning techniques to address these challenges. In this presentation we focus on identifying patients where mono-immunotherapy may be insufficient.

The Circulating Proteome and Cancer Immunology

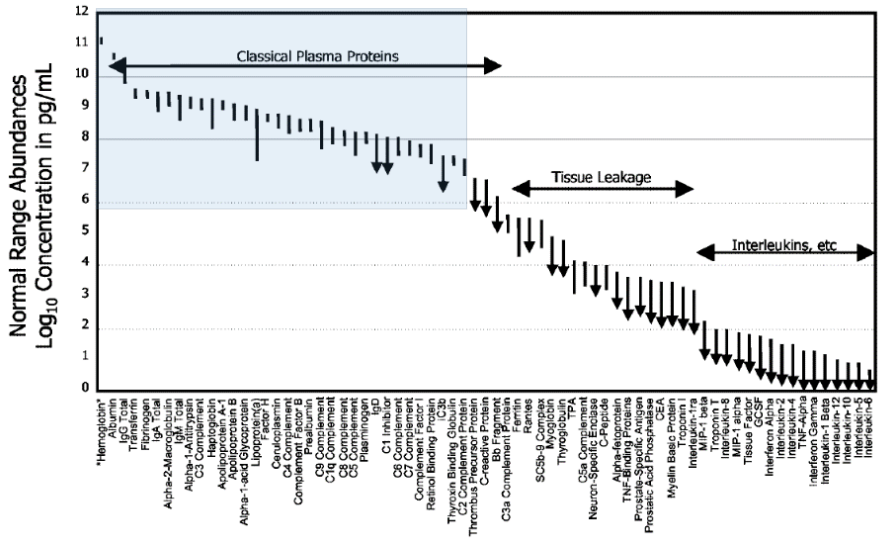
- The circulating proteome is derived from tumor, tumor microenvironment, and normal host tissues[1]
- The circulating proteome changes during tumor development and as a result of treatment
- Circulating proteins have direct regulatory effects on the immune system

Biological functions of classical plasma proteins[3]



Biodesix' test development depends on reliable measurements of classical plasma/serum protein abundance which can be connected to important immune related functions.

Dynamic range of circulating proteins[2]

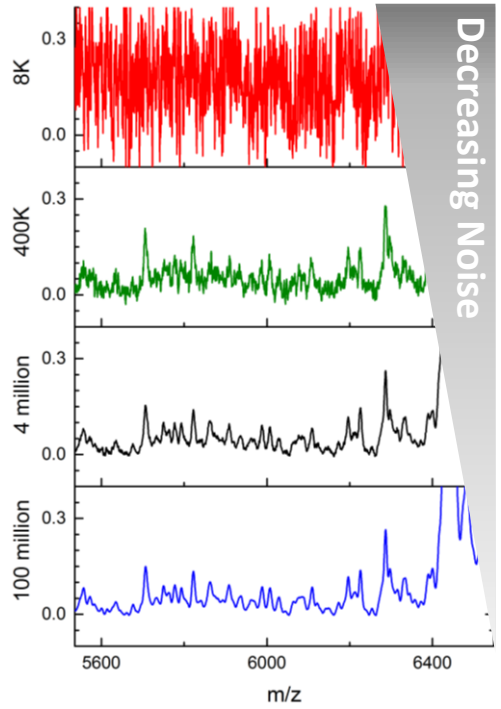


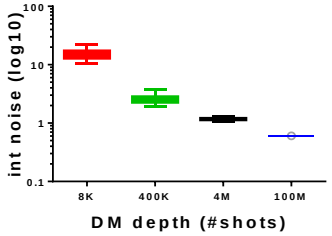
[1]*S. Pitteri et al. Cancer Research (2011)* ; [2]This research was originally published in Molecular & Cellular Proteomics. N.L. Anderson and N.G. Anderson. The Human Plasma Proteome. *Molecular and Cellular Proteomics (2002)*; 1:845-867. © the American Society for Biochemistry and Molecular Biology. [3]Gautam P, Nair SC, Ramamoorthy K, Swamy CVB, Nagaraj R (2013) Analysis of Human Blood Plasma Proteome from Ten Healthy Volunteers from Indian Population. *PLOS ONE* 8(8): e72584. doi:10.1371/journal.pone.0072584

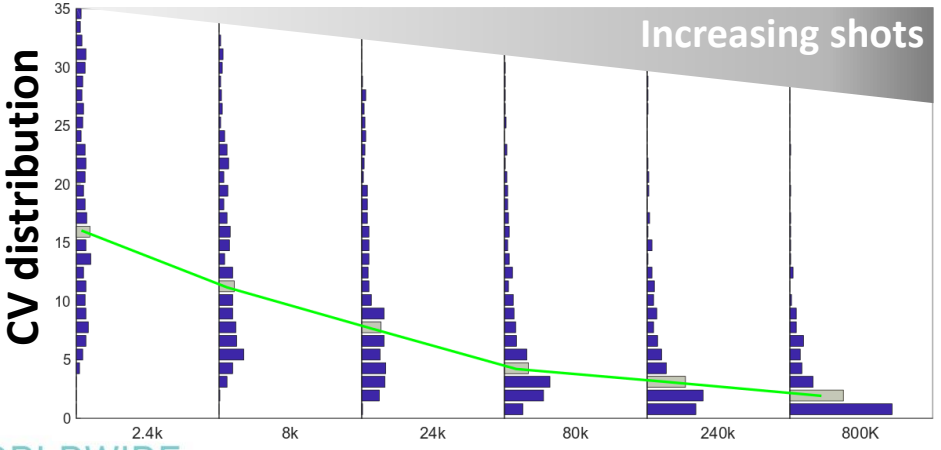
Deep MALDI ToF MS of Serum

High throughput, reproducible, validated, multiplexed measurements

- No fractionation: avoids bias and does not limit measurement
- Large abundance range requires sensitive measurements
  - Increase S/N ratio by dramatically increasing the number of laser shots, reducing noise
  - Reduce CV of observable peaks (proteins)
- Practical considerations
  - Small amounts of serum < 2µl
  - Serum cards for easy logistics in clinical practice
  - QC control through reference samples per batch

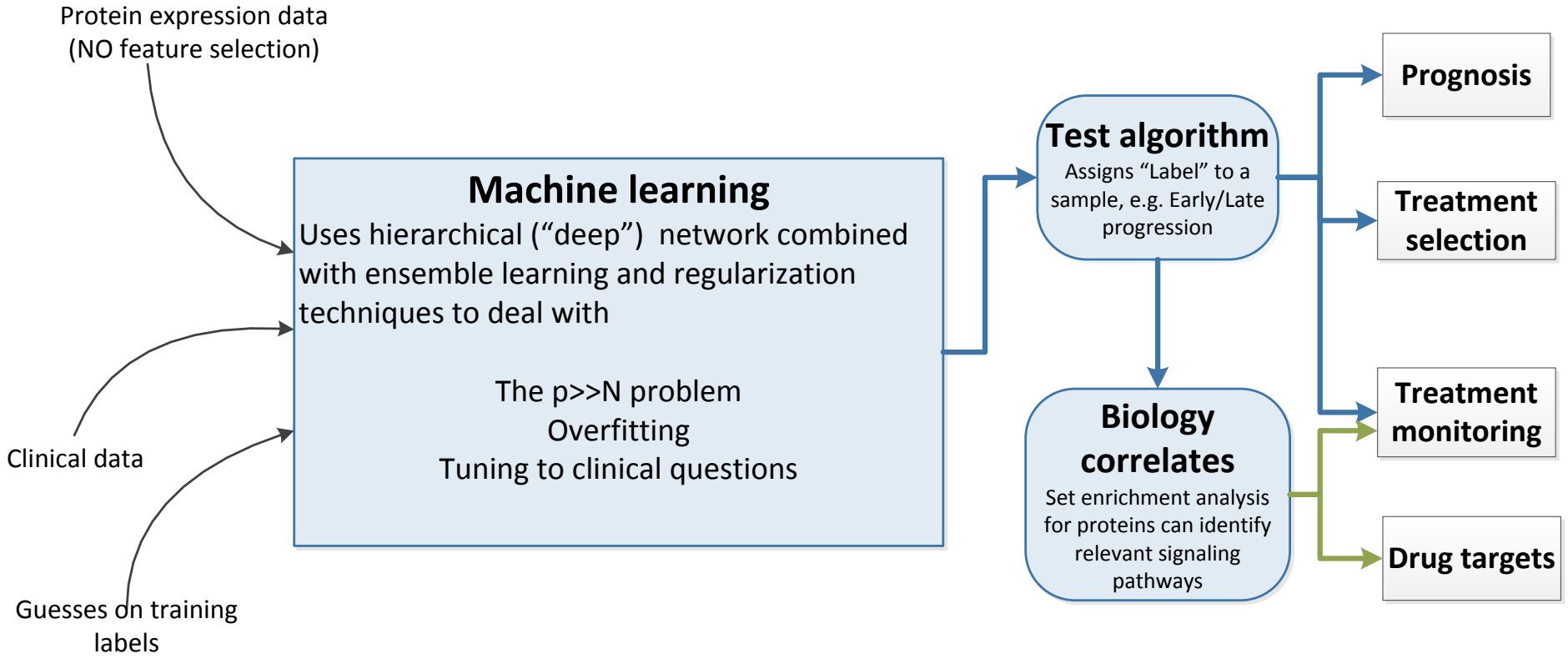






Test Development Platform

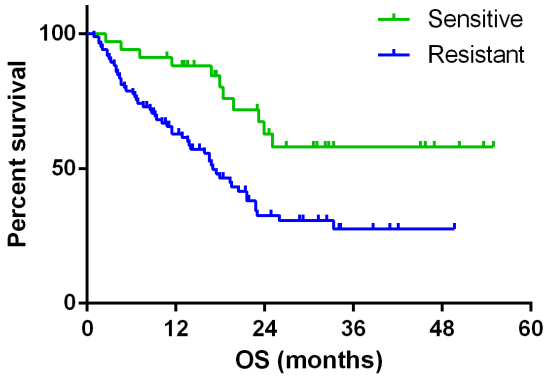
Samples + Data → Unbiased Tests → Biology



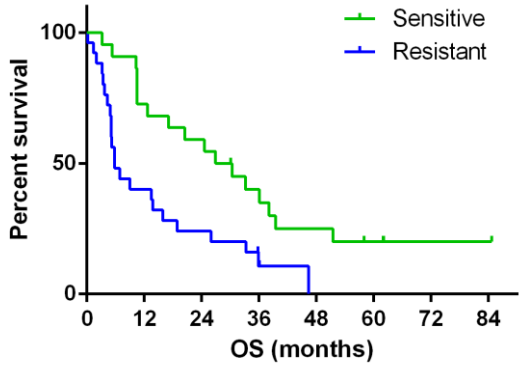
Results: Some Patients may be Resistant to Immunotherapy

Across different immune therapies in melanoma

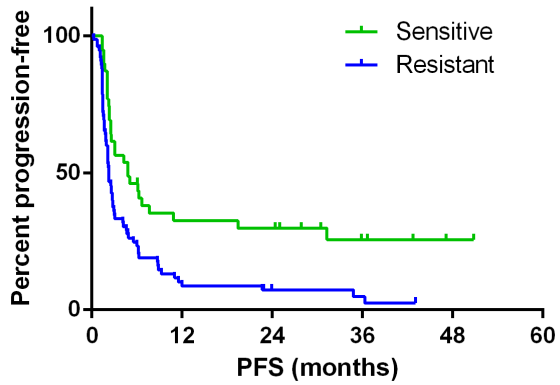
CP test in Anti-PD1 (N=119)



CP test in anti-CTLA4 (N=48)



HD-IL2 (N=114)



Two separate tests developed for checkpoint efficacy (CP) and HD-IL2 benefit identify a group of patients that may obtain little long term benefit from anti-PD1, anti-CTLA4, and HD-IL2 treatment.

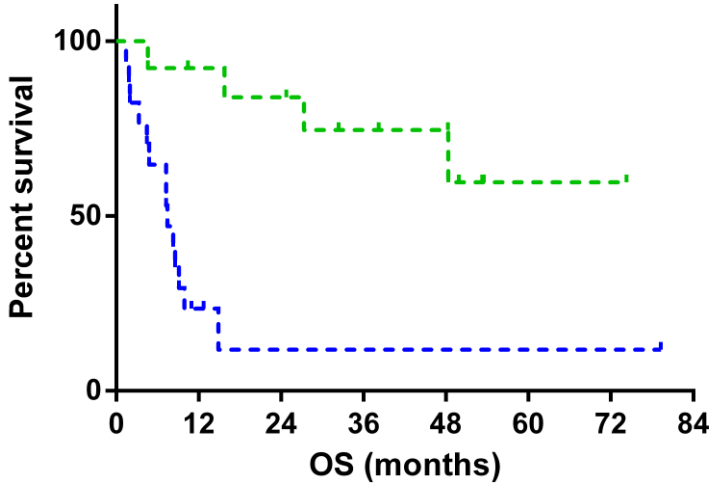
- Test classifications are independent predictors of outcomes when adjusted for other markers, such as LDH and PD-L1 expression

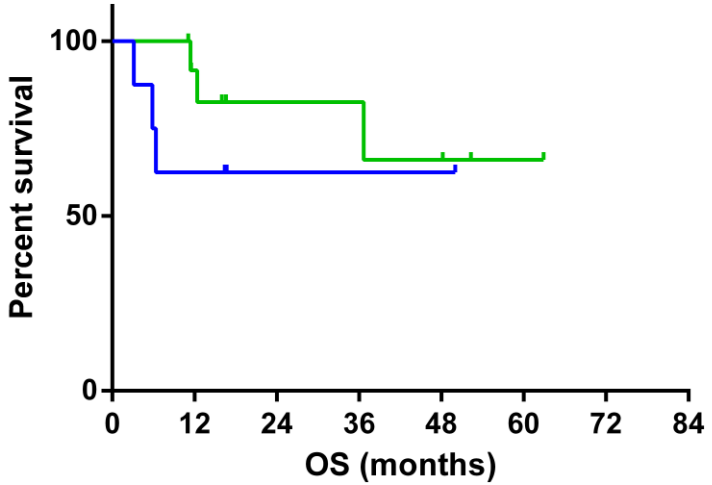
The pre-treatment circulating proteome contains information that can predict durable benefit from immunotherapies.

Validation and Utility

Anti-PD1 ± Anti-CTLA4 | Melanoma

Can we identify the patients who will benefit from combination therapy?



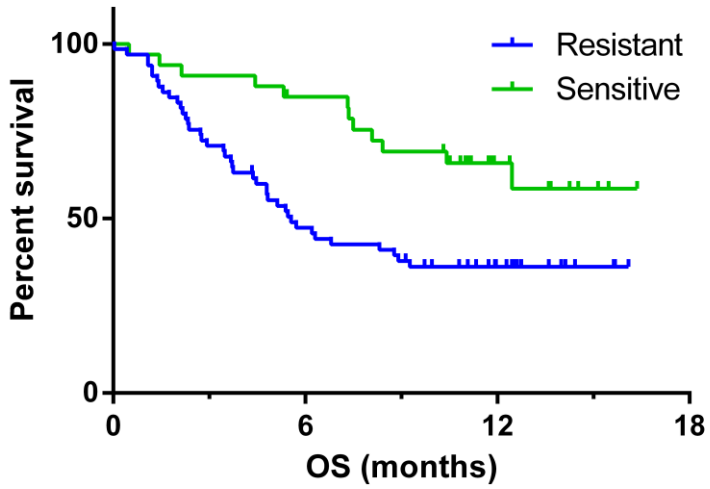


BDX Test Result	Treatment	n
Sensitive	Combination	13
Sensitive	Single agent	13
Resistant	Combination	8
Resistant	Single Agent	17

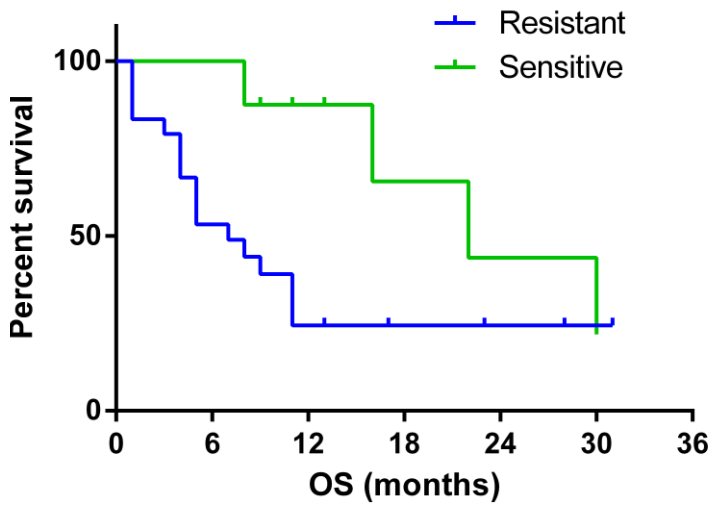
If validated in randomized data this suggests that the resistant group of patients derives most benefit from the addition of anti-CTLA4 to anti-PD1.

Similar Effects in NSCLC

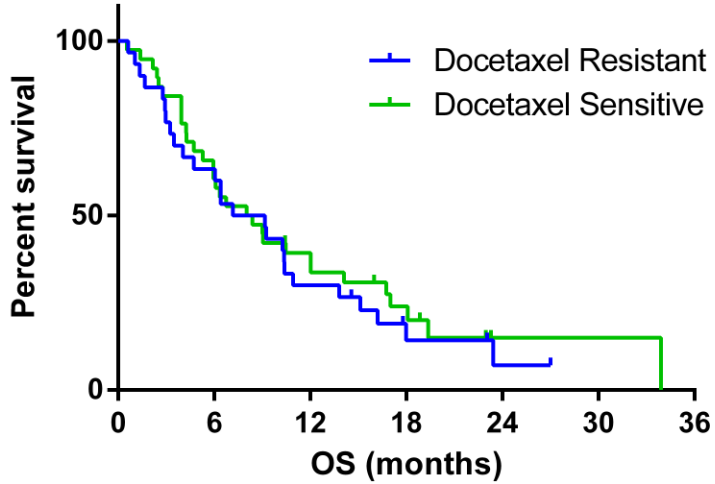
Development (nivolumab) [1] (N=98)



Validation (nivolumab)[1] (N=32)



Evaluation (chemotherapy) (N=68)



A test developed for anti-PD1 benefit in NSCLC identifies a group of patients not obtaining much long term benefit from nivolumab in 2nd line NSCLC, and is likely predictive for nivolumab vs. docetaxel.

[1]S. Goldberg et al, SITC2017, P30

What Characterizes Patients with Resistance?

Association of sensitive and resistant groups with biological processes

Signaling process	Checkpoint test	HD-IL2 test
Acute inflammatory response	NS	**p < 0.01**
Activation of innate immune response	NS	NS
Regulation of adaptive immune response	NS	NS
Positive regulation of glycolytic process	NS	NS
Immune T-cells	NS	NS
Immune B-cells	NS	NS
Cell cycle regulation	NS	NS
Natural killer regulation	NS	NS
Complement system	**p < 0.05**	**p < 0.01**
Acute response	NS	NS
Cytokine activity	NS	NS
Wound healing	**p < 0.01**	**p < 0.05**
Interferon	NS	NS
Interleukin-10	NS	NS
Growth factor receptor signaling	NS	NS
Immune Response Type 1	NS	NS
Immune Response Type 2	NS	NS
Acute phase	**p < 0.01**	**p < 0.01**
Hypoxia	NS	NS
Cancer	NS	NS

NS: Not significant

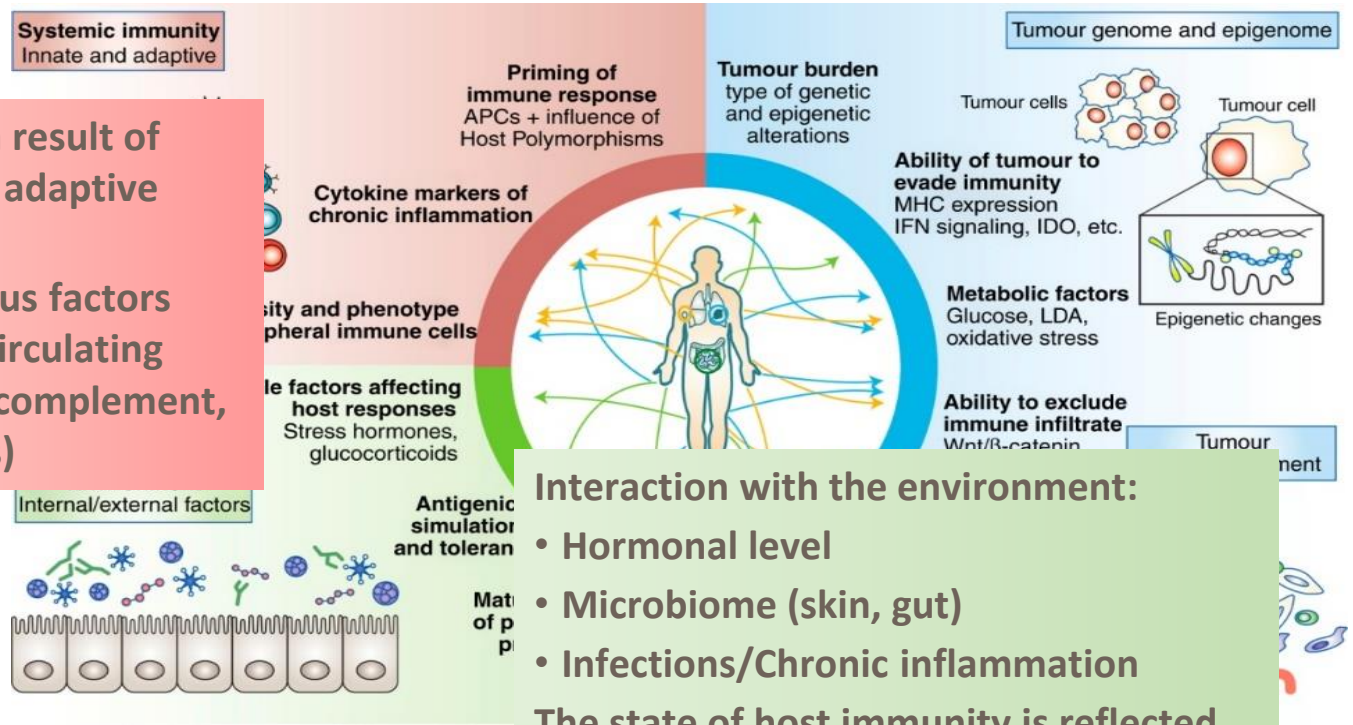
Both anti-PD1 and HD-IL2 resistant groups of patients are characterized by elevated levels of complement, acute phase reactants, and wound healing.

Independent confirmation by orthogonal experimental techniques

- Combined blockade of **complement** signaling and anti-PD-1 can enhance anti-PD-1 efficacy; Y. Wang et al, Cancer Discovery 6 (9) :1022-35 June 2017
- A transcriptional signature (IPRES) identified related to innate anti-PD-1 resistance; **wound healing** is one of the pathways; W. Hugo et al, Cell 168 (3), 542, 2017

Biodesix Tests are Relevant to Aspects of Anti-Tumor Immunity

- Systemic immunity is a result of Interplay of innate and adaptive immune systems
- Is regulated by numerous factors including some major circulating proteins (acute phase, complement, wound healing systems)



Interaction with the environment:
- Hormonal level
- Microbiome (skin, gut)
- Infections/Chronic inflammation

The state of host immunity is reflected in the plasma proteome.

Response and resistance to immunotherapy is defined by
- ❑ Systemic host immunity
- ❑ Environmental factors
- ❑ Tumor characteristics
- ❑ Tumor microenvironment

[1]Cogdill *et al.* Hallmarks of response to immune checkpoint blockade. *British Journal of Cancer* (2017) 117, 1–7. doi:10.1038/bjc.2017.136

Summary

- The pre-treatment circulating proteome can help to identify a group of patients that derives little durable benefit from immunotherapies
  - Across tumor types and therapies
- These patients have elevated acute phase, complement and wound healing signaling
  - New treatment options for this group of patients are needed

- This test development platform can be used to develop tests for
  - Prognosis
  - Patient selection
  - Treatment monitoring
  - Drug target discovery

References

And many thanks to all patients, their families, and our collaborators

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