Applying Germ-line MicroRNA Mutations to Predict Response and Toxicity to Immune Therapy

Cancer Immune Responsiveness Workshop, May 2018

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Disclosure Information

Joanne B. Weidhaas

I have the following financial relationships to disclose:

Consultant for: MiraDx

Stockholder in: MiraDx

I will not discuss off label use and/or investigational use in my presentation.

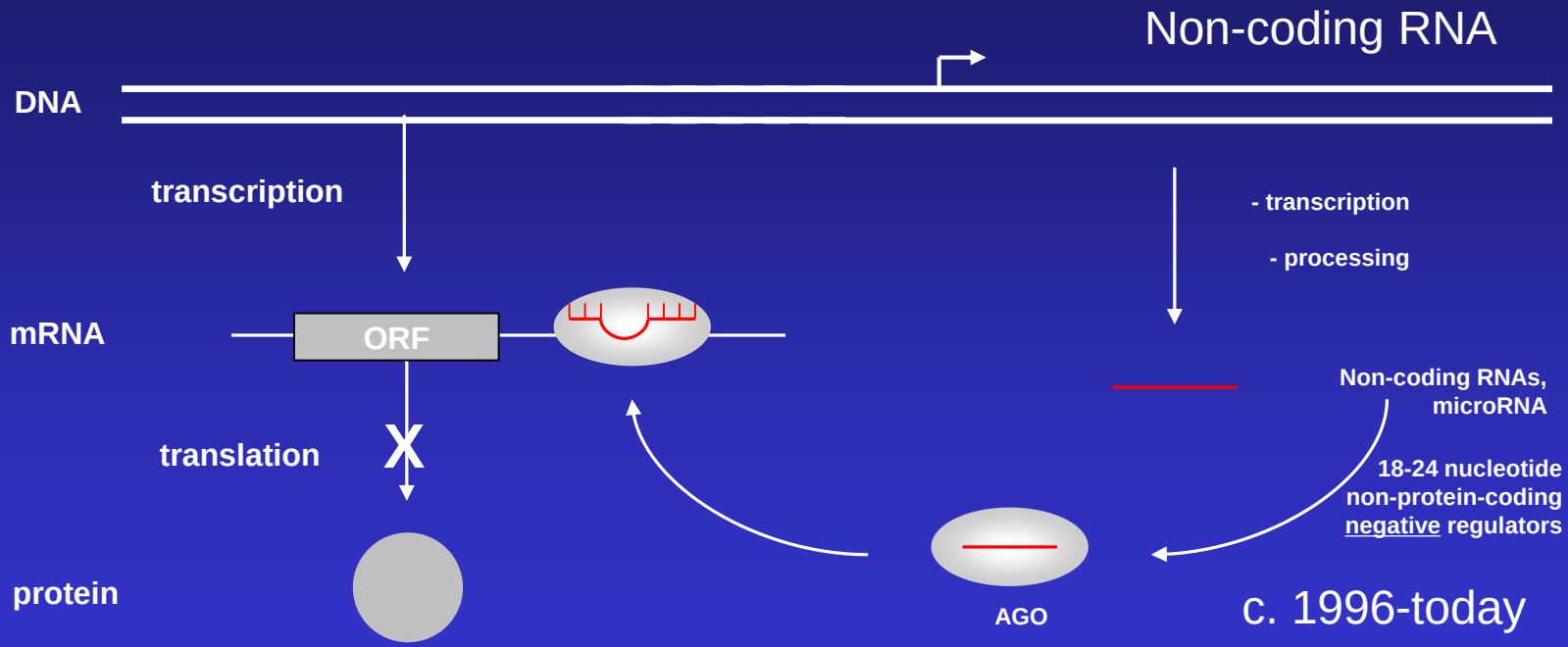
Hypothesis: Germ-line biomarkers will help

1. What You're Born With (Germ-line Genetics)

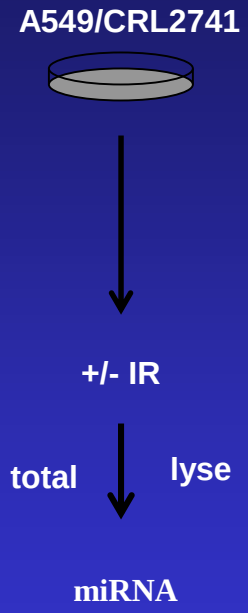
2. Same biomarkers predict systemic treatment response and toxicity

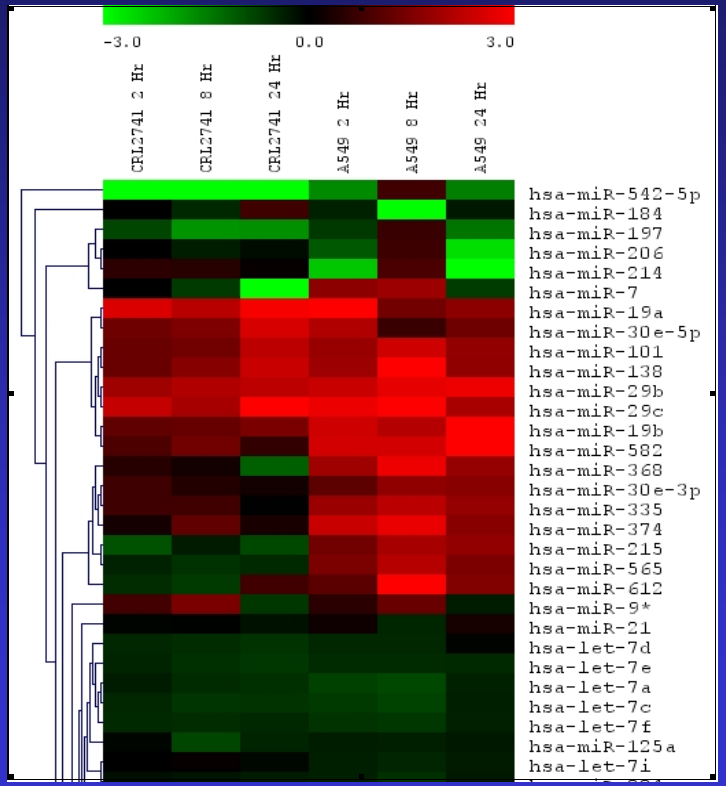
While accepted in most diseased states, not so in cancer

Also apply new insights into DNA



Why? MiRNAs lead the systemic stress response

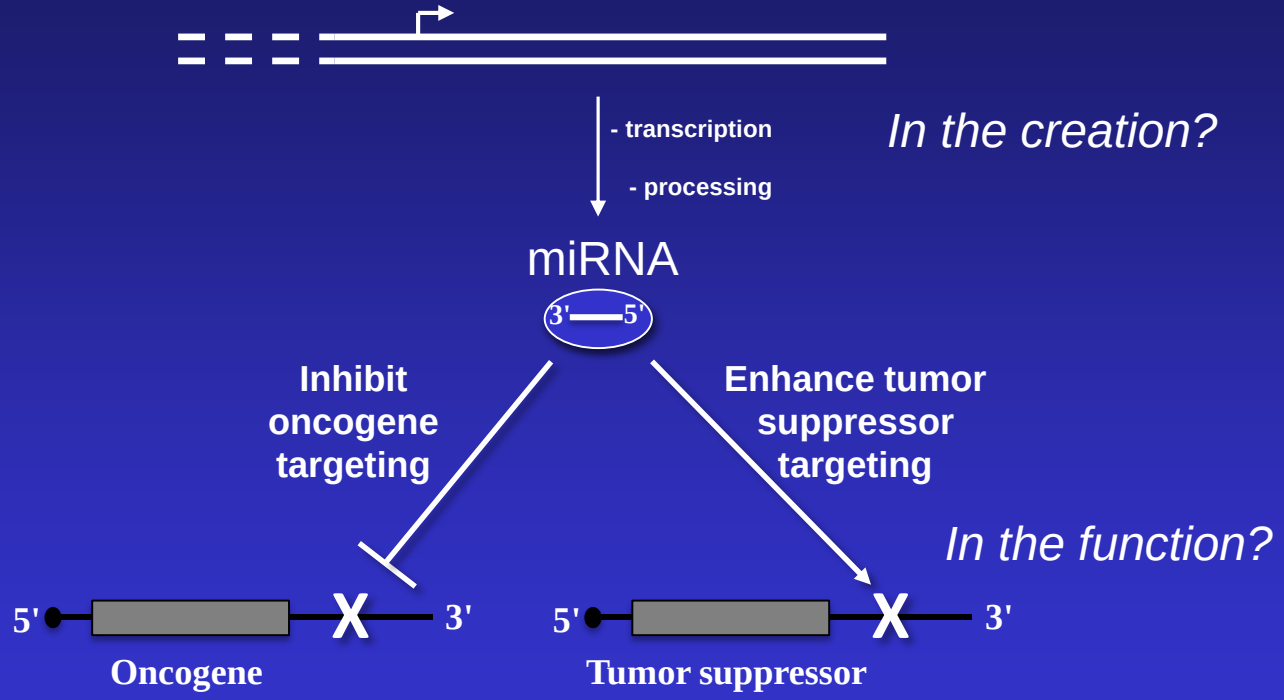




- Immediate
- Conserved
- Systemic

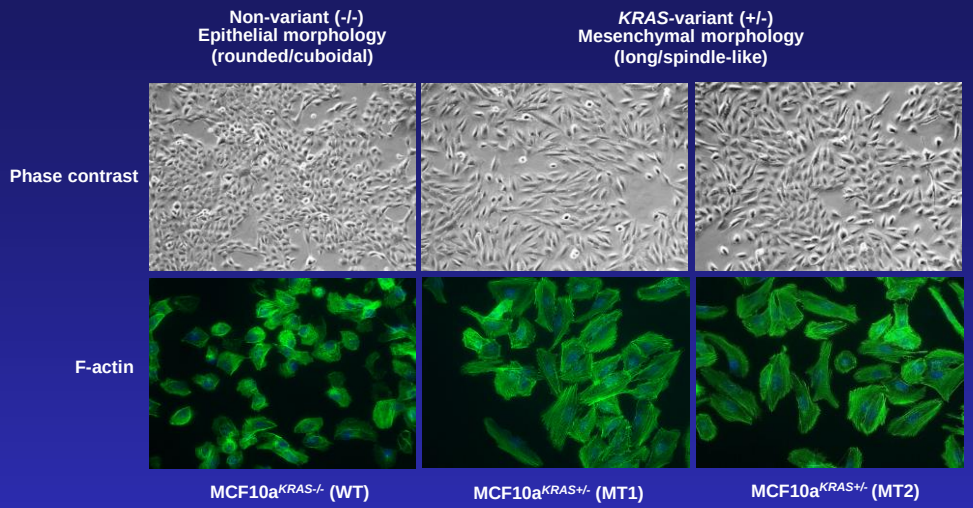
Weidhaas et al., Cancer Research, (2008)

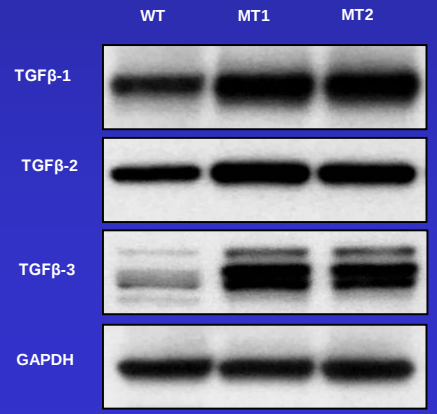
Are there germ-line differences in microRNAs?

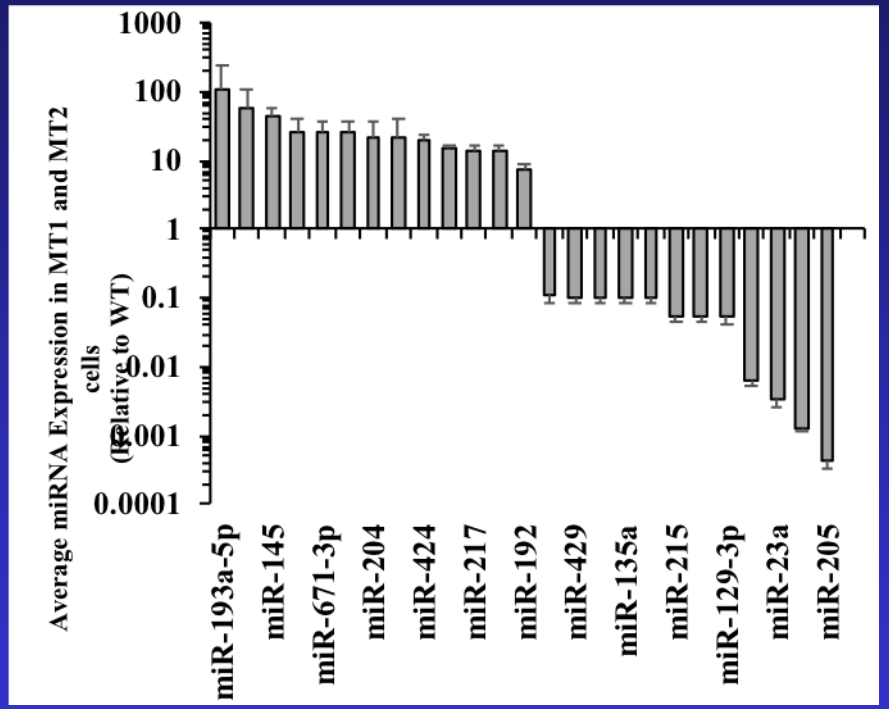


Are missed on RNA seq, exon sequencing, and SNP platforms

First example: *KRAS*-variant impacts normal biology

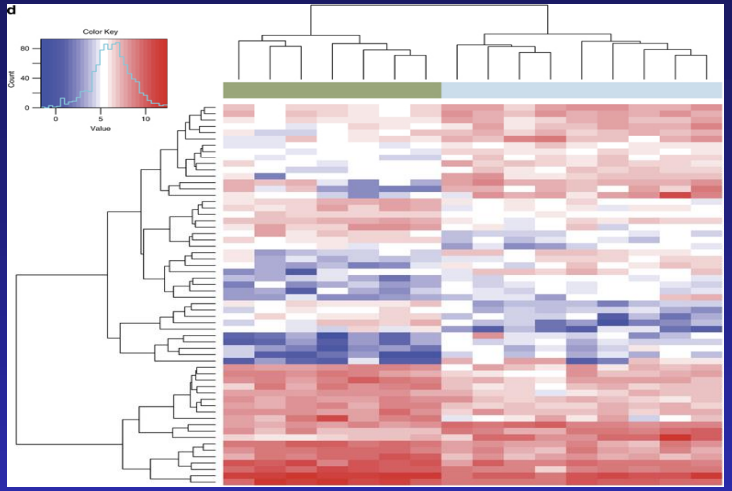




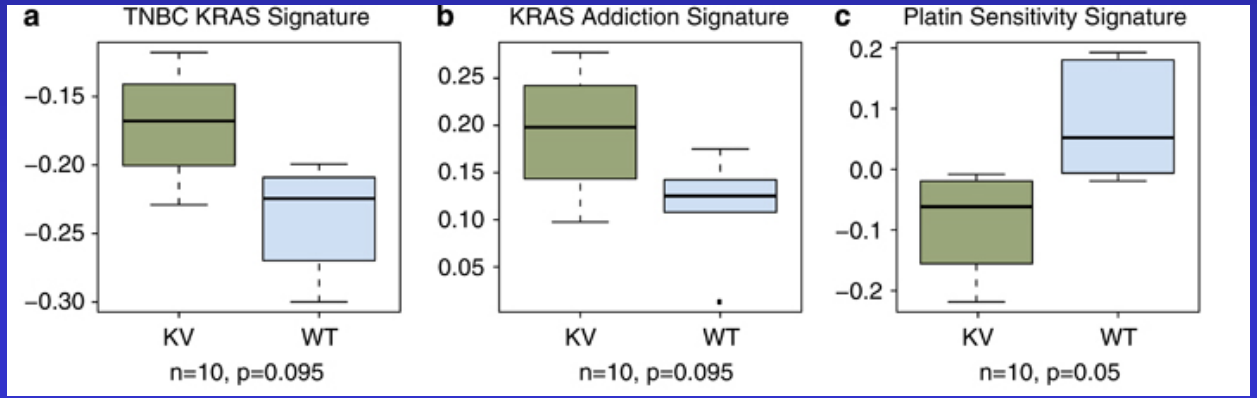


Jung et al., submitted, (2018)

KRAS-variant impacts tumor biology



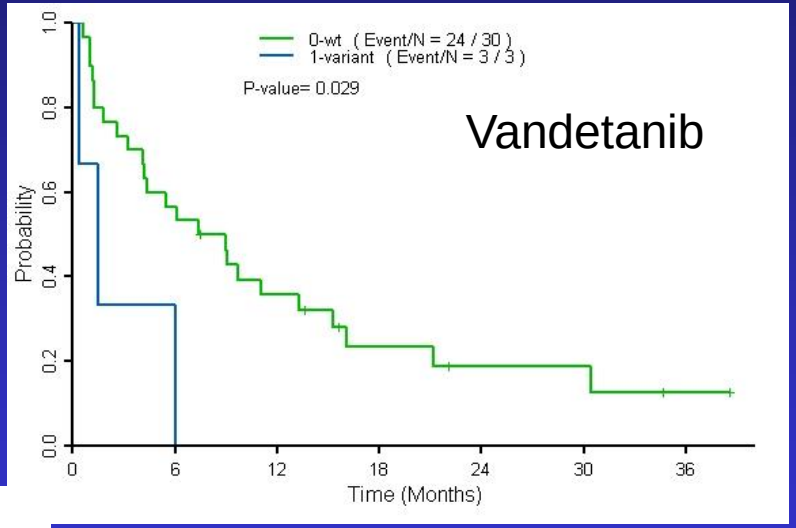
Expression Signature	TT vs TG/GG TNBC Tumor	*p*K-S Test
NRAS	up	*0.02*
BRCA mutant-like	up	*0.04*
Luminal Progenitor	up	*0.04*
MAPK Creighton	up	*0.06*
PCA Estrogen	down	*0.04*

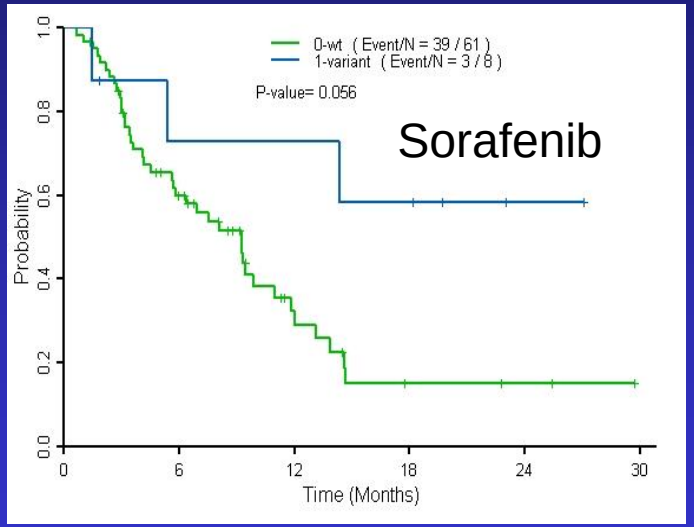


Paranjape et al., Lancet Oncology (2011); Ratner et al., Oncogene (2012)

KRAS-variant predictive biomarker of response

- Metastatic NSCLC patients
- Two phase II trials





Weidhaas et al., ASCO (2014)

KRAS-variant
Pan-Cancer, Drug Specific

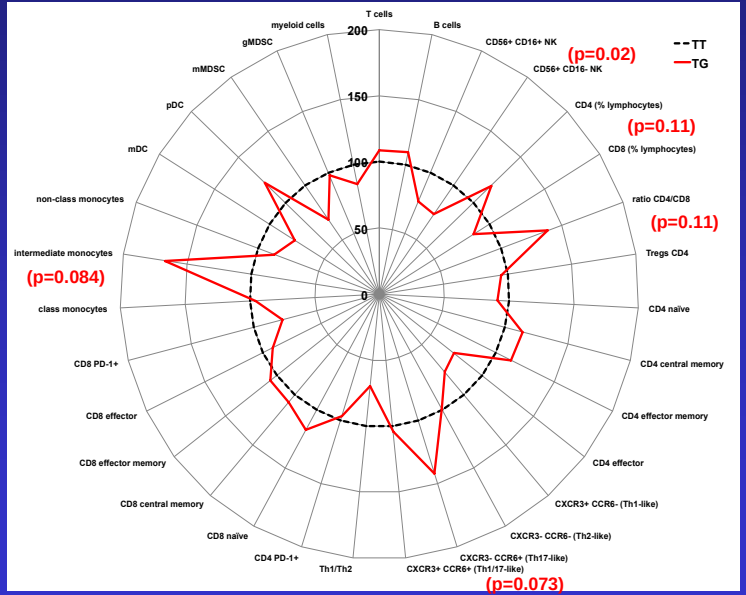
- Over 11,000 patients, including 3 phase III trials

Agents	Cancer types	Phase Trial	Improvement in Progression Free Survival (PFS)	Improvement in Overall Survival (OS)
Sorafenib	NSCLC trials	Two Phase II	**2x increase** in PFS	**>3x increase** in OS
MK2206	NSCLC trail	One Phase II	**1.3x increase** in PFS	**6x increase in OS** when combined with Erlotinib
Cetuximab	Colon, Head & Neck, Lung	Phase II and III	**2x increase** in PFS	**2x increase** in OS
Cisplatin	Ovarian, Head & Neck, Lung	Phase II and III	**3x decrease** in PFS	**2x decrease** in OS
Erlotinib	NSCLC trials	Two Phase II	**2x decrease** in PFS	**3x decrease** in OS
Vandetanib	NSCLC trial	One Phase II	**1.2x decrease** in PFS	**8x decrease** in OS

THERAPY specific not TUMOR type specific

KRAS-variant patients are immunologically altered

- Depressed NK cells and altered monocytes
- Immunologically suppressed (*high TGFB*), DNA repair deficient

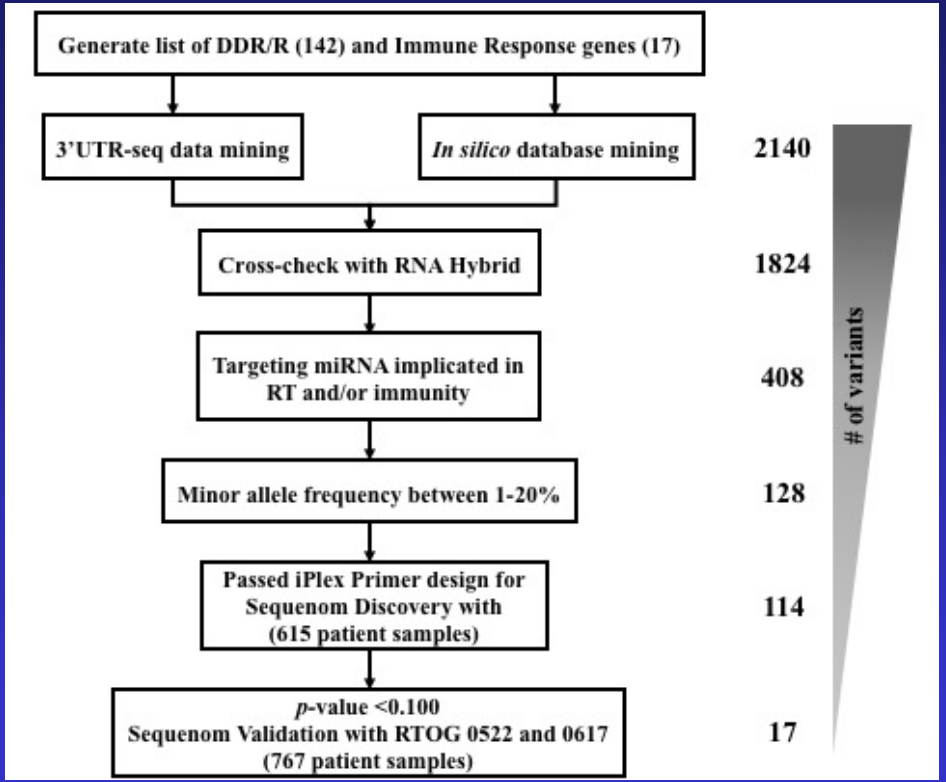


	n	Min	Q1	Median	Q3	Max
KRAS-non-variant	311	2261.42	8837.00	18476.52	32379.43	123264.70
KRAS-variant	65	5034.35	12574.03	23376.49	44809.10	109759.72

Weidhaas et al., JAMA Oncology, (2016)

Identification of Additional Mutations

- Sequencing all 3'UTRs, promoter regions and miRNAs
- Identified novel and known variants
- Validated for function in silico
- ~2100 for additional study
- Confirm disrupt miRNAs relevant in response
- Common enough to be clinically relevant
- Apply to relevant well vetted clinical data sets



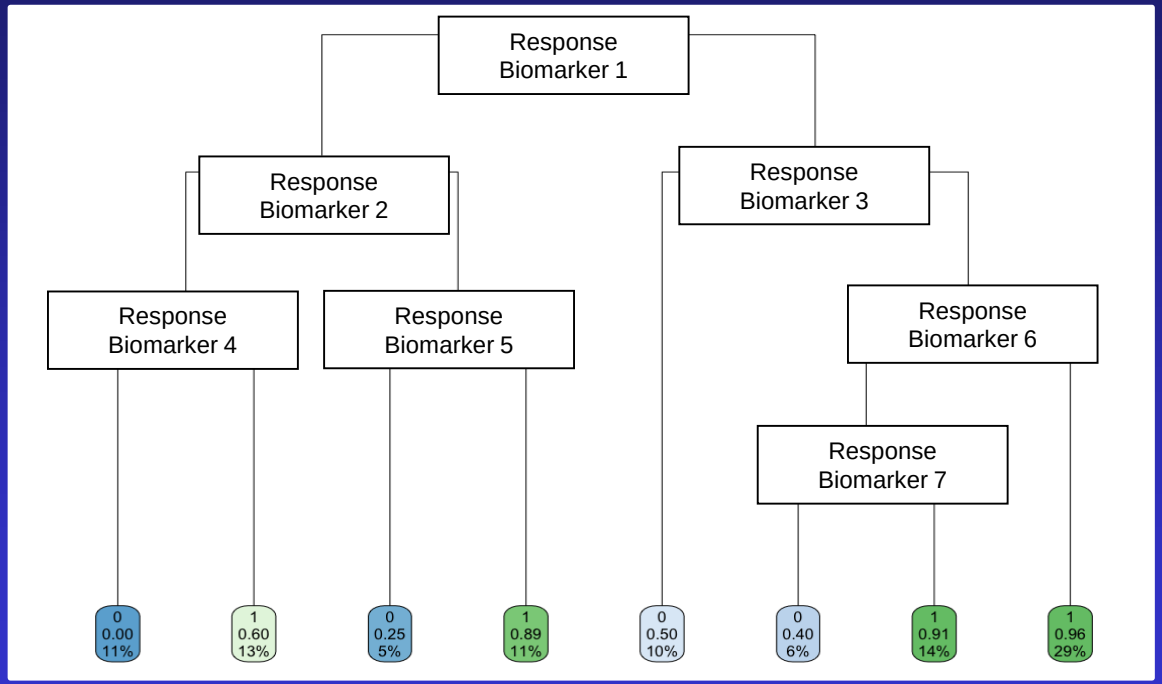
Chen et al., Oncogene, (2014)

Applying these biomarkers to systemic response

- Cohorts:
  - anti-PD1/PDL1 treated melanoma patients with known response and toxicity (n=55)
  - anti-PD1/PDL1 NSCLC, GU, prostate, GYN, sarcoma (n~100)
- Screened a panel of ~325 vetted biomarkers
- Model response
- Model toxicity

Anti-PD1/PDL1 biomarkers of response

- Melanoma only training set, 55 patients
- Progressive and relapsed versus sustained responders



71% accuracy, 80% sensitivity and 65% specificity

How does this compare to PDL1 and TMB?

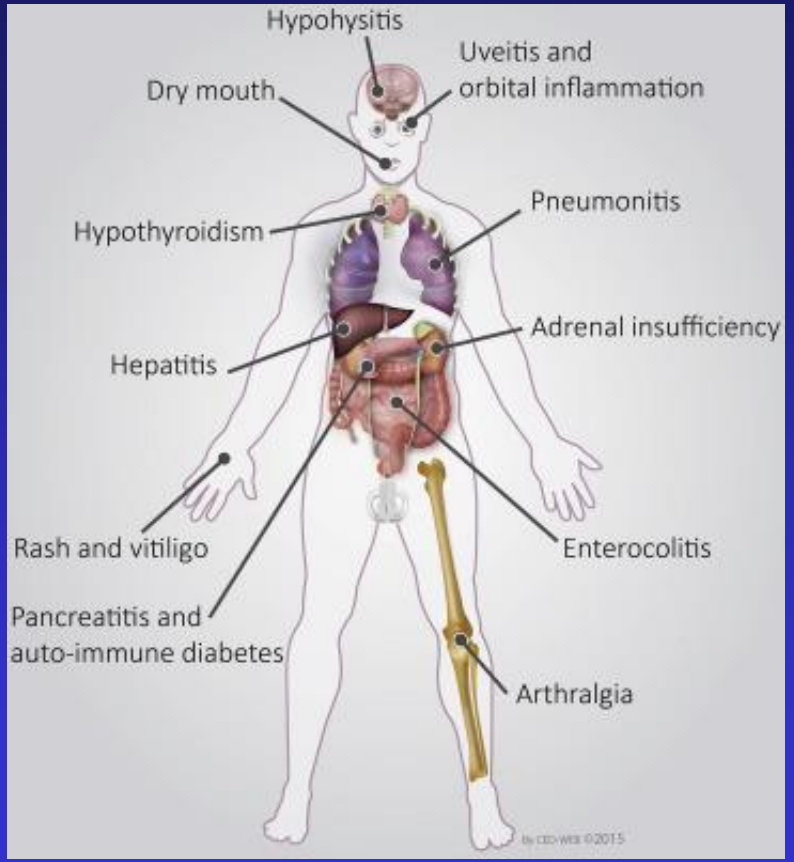
- In this cohort, PDL1 staining performed in ~50%
- TMB on ~90% of patients
- Compared head to head

	Accuracy	Sensitivity	Specificity
PDL1>=50	33%	0%	67%
TMB>10	60%	69%	50%
TMB>20	52%	31%	75%
Mir-variants	68%	77%	58%

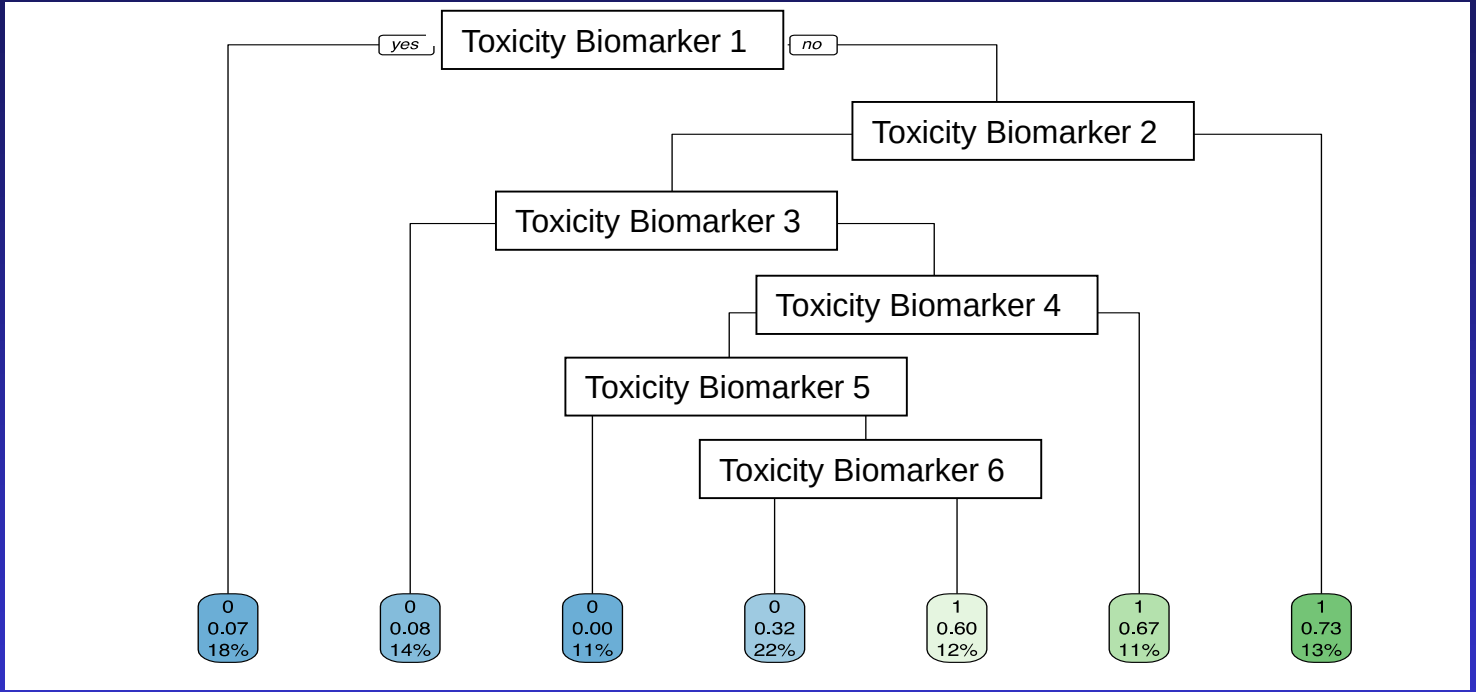
- Found independent from each other

iRAEs – immune related adverse events

- What is this?
  - Reflect “over-zealous” immune system
  - Grade 2 or > irAEs develop on 24-30% of patients treated with single agents
  - Can lead to significant morbidity
- Analysis
  - Training set 54 melanoma patients
  - Validation cohort 100 patients other cancer types (NSCLC, prostate, GU)
  - Pan-cancer signature



Anti-PD1/PDL1 biomarkers of toxicity



Accuracy of 75%, Sensitivity of 70%, Specificity of 86%

Independent validation: 80% accuracy (82% sensitivity and 87% specificity)

Pan cancer signature: 81% accuracy, 84% sensitivity and 75% specificity

Future Directions

- Validate response in the extended cohort

- For toxicity consider
  - Exposure
  - Toxicity type
  - Higher grades
  - Combinations

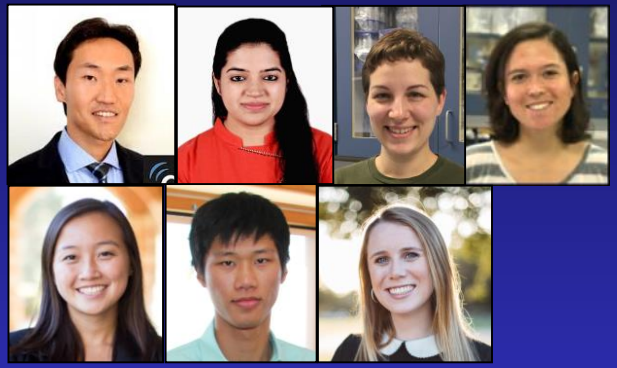
Conclusions

- Germ-line microRNA-based genetic variants can predict:
  - Different cellular biology
  - Tumor biology
  - Unique systemic reactions to cancer therapy (good or bad)
- Promising will predict response to immune therapy
- Strong evidence do predict toxicity to IOs
- Pan-cancer biomarkers of toxicity

Acknowledgements

The (Old) Weidhaas Yale Lab

The (Growing) Weidhaas UCLA Lab



Funding
CT State
NIH/NCI RO1 x 2
Shannon Foundation
CMCR
UCLA CTSI
UCLA Department of Radiation Oncology
NCI SBIR program

Great Collaborations
Department of Rad Onc UCLA
Toni Ribas UCLA
David Oh, City of Hope
NCI
NRG
Wolfgang Lilleby, Oslo University Hospital