

# Tumor Site Immune Modulation Therapy

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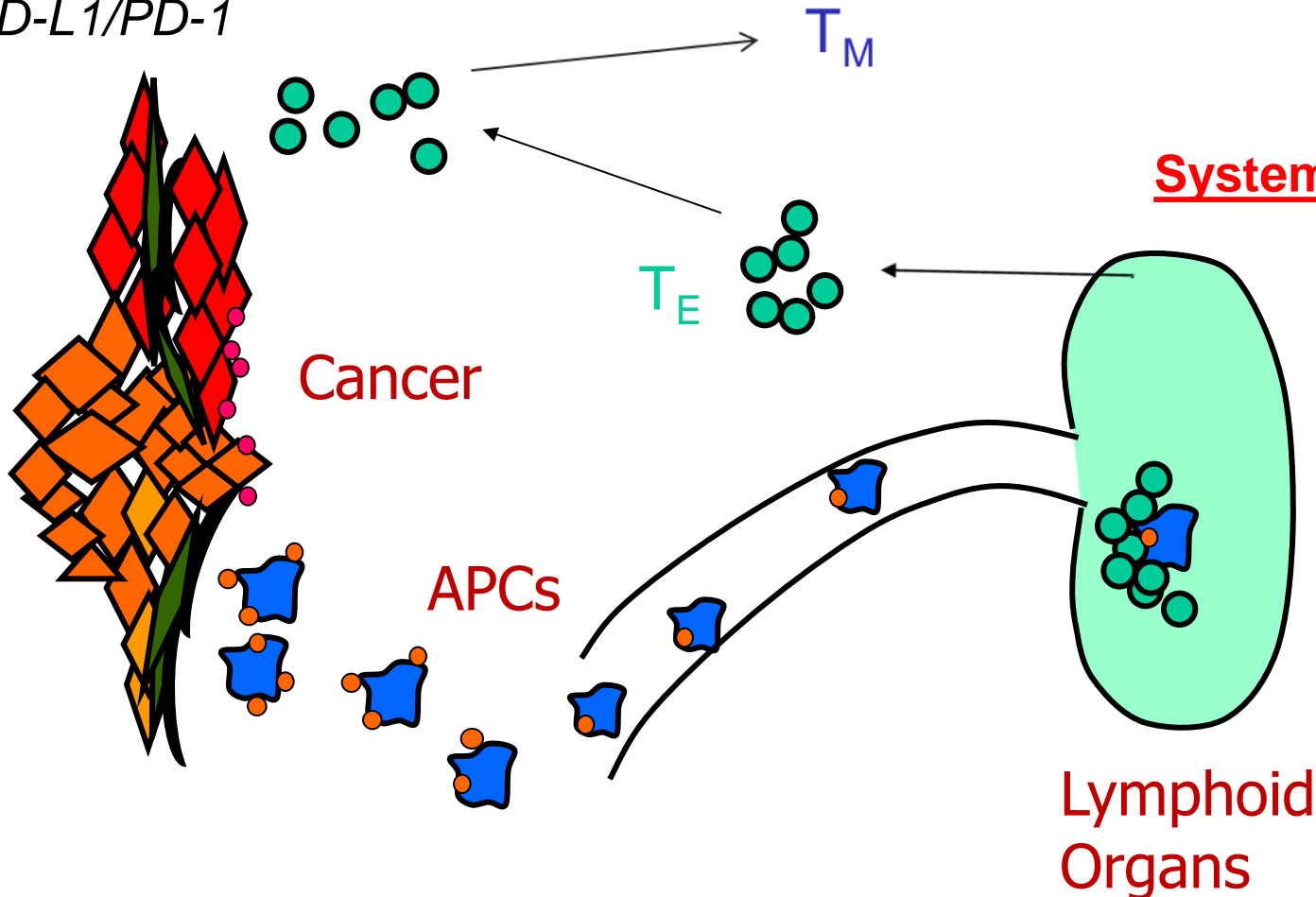
# Disclosures

- Consultant: MedImmune, Pfizer, Symphogen, Boehringer Ingelheim
- Sponsored research: Amplimmune, Eli Lilly

# Tumor Site vs. Systemic Immune Modulation

## Tumor site modulation:

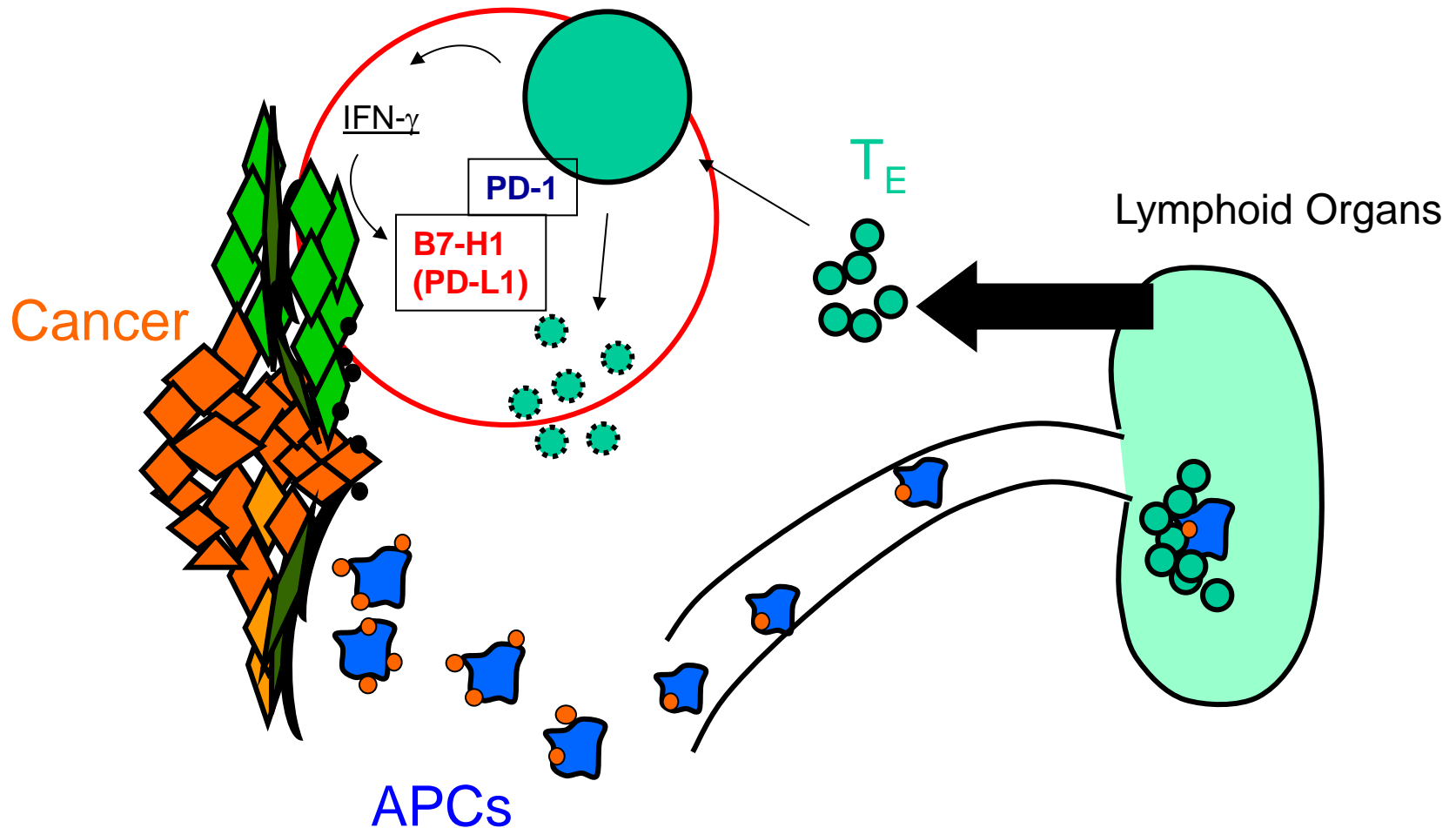
*PD-L1/PD-1*



## Systemic modulation:

*CTLA-4  
Lag-3  
Tim-3  
4-1BB  
OX40  
etc.*

# The B7-H1/PD-1 pathway in tumor site immune modulation



# **The B7-H1/PD-1: A “peace keeper” pathway**

- Low level of B7-H1 in normal cells and tissues
- Up-regulation of B7-H1 in tissues by neighboring T-cells via IFN- $\gamma$
- B7-H1 suppresses T cell activity via PD-1 to control inflammation
- Over-expression of B7-H1 by cells in tumor site to prevent immune attack

# **PD-1/PD-L1 antibody therapy**

- **Regression of large solid tumors**
- **A therapy for a broad spectrum of human cancer**
- **Durable response**
- **Tolerable toxicity**

# What are the next steps?

- A therapy for a broad spectrum of human cancer
- Predictive biomarkers to enrich responders
- Frontline therapy (chemo/radiation-free)
- Treatment of early diseases
- Mechanism-based combination therapy

# Overall Clinical Response rate to PD-1/PD-L1 antibody therapy

## Single agent:

Melanoma (n>2,000)	40-50%
Lung cancer (n>1,000)	20-35%
Renal cancer (n>200)	40-55%
Gastric cancer (n>50)	~30%
Bladder cancer (n>30)	~50%
Head & neck cancer (n>30)	~30%
Hodgkin's/non-Hodgkin's (n>50)	~50%
Colorectal cancer (n>50)	<10%
Prostate cancer (n>50)	<10%

#With durable clinical responses and <5% autoimmune toxicity

## Combination:

Melanoma (>100)	>60%
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# What are the next steps?

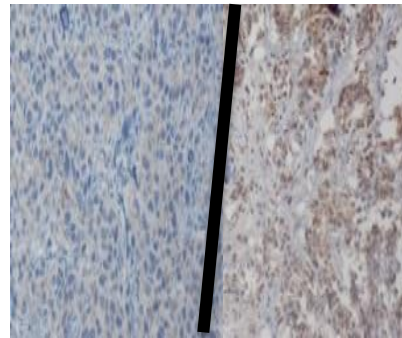
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# Membrane PD-L1 on Tumor Is A Potential Predictive Biomarker for Response to Anti-PD-1/PD-L1 therapy

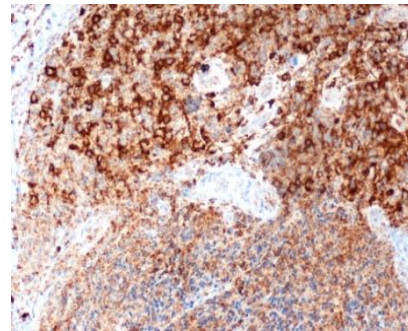
## PD-L1 staining patterns

NSCLC (17)  
Mel (30)  
RCC (9)  
**CRC (8)**  
CRPC (4)  
(n=41)

Negative or  
Cytosolic only  
(n=18)



Membranous  
(n=23)



Clinical Benefit  
Rate (CR+PR+SD)

= **6%**  
1/18 responders

= **48%**  
11/23 responders

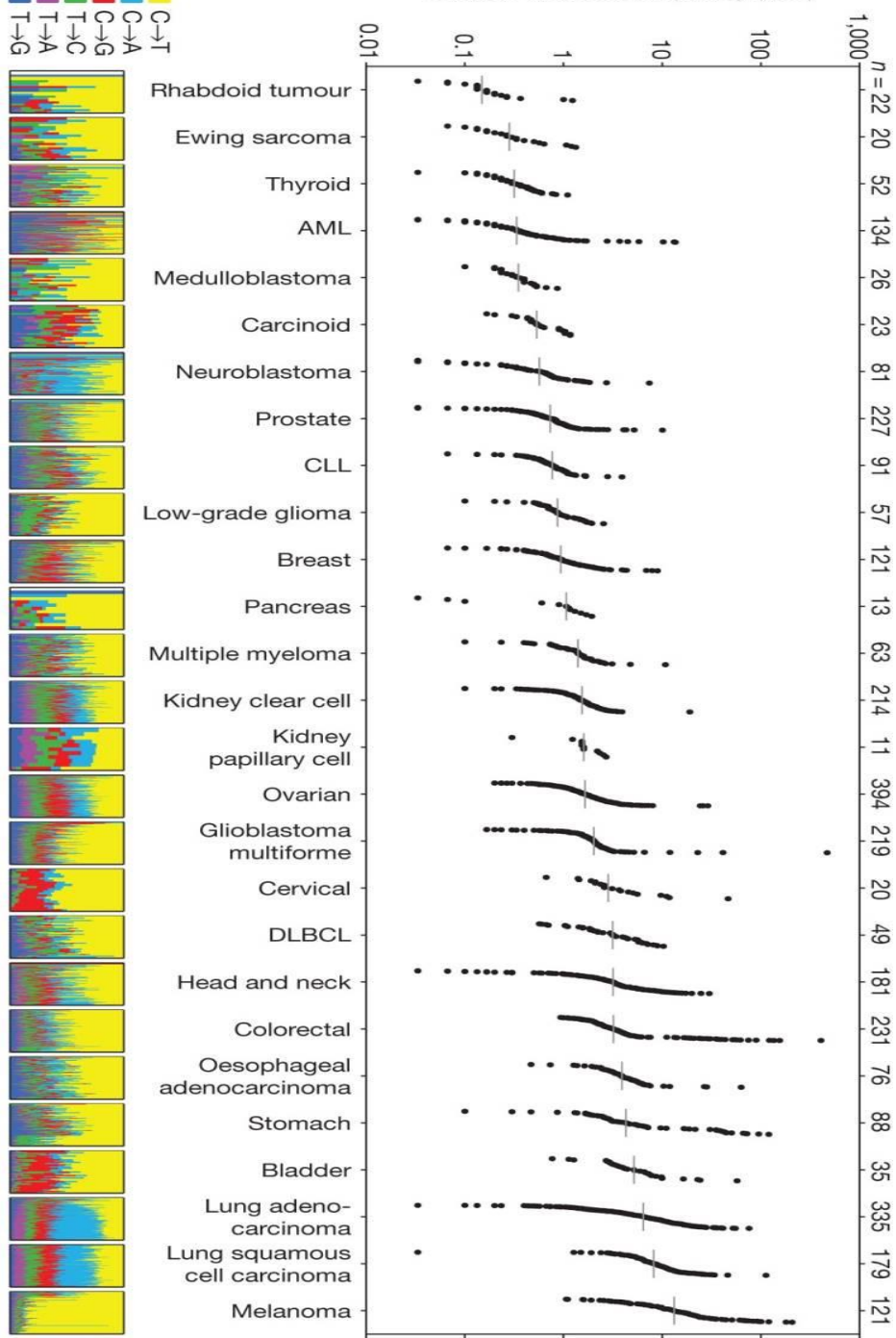
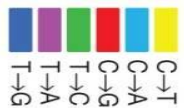
# Challenges to use B7-H1 expression in tumor site as a biomarker

- **Heterogenic expression**
  - Limited size of biopsy specimens
  - Timing
  - Denatured B7-H1 protein in FFPE
- **Future approaches**
  - In vivo imaging
  - CTC









# Somatic mutation frequencies in exomes from 3,083 tumor–normal pairs

Lawrence *et al. Nature* 499:214, 2013



High ORR

Low ORR



# What are the next steps?

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# B7-H1 expression and TILs in lung cancer by disease stages

Stage	N	TILs	B7-H1 <sup>hi</sup>
I	169	44%	33%
II	102	40%	34%
III	129	35%	21%*
IV	44	24%	23%*

# Total 444 patients with non-small cell and small cell lung cancer in both Yale and Greece cohort were analyzed

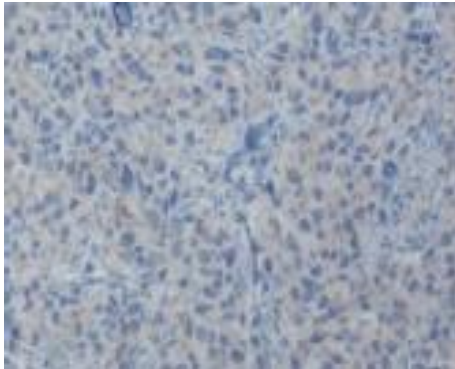


# What are the next steps?

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- Combination (mechanism-based)

# PD-L1 expression/TIL infiltration in 110 human melanoma and their functional implications

I

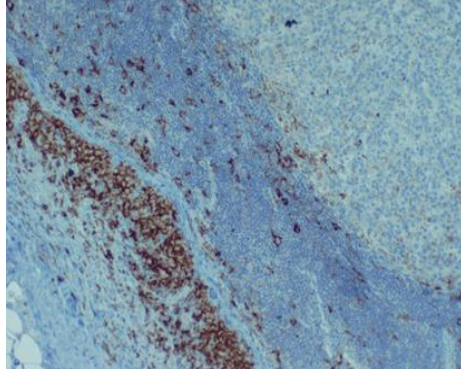


B7-H1 -  
TIL-

41%

Lack of  
inflammation

II

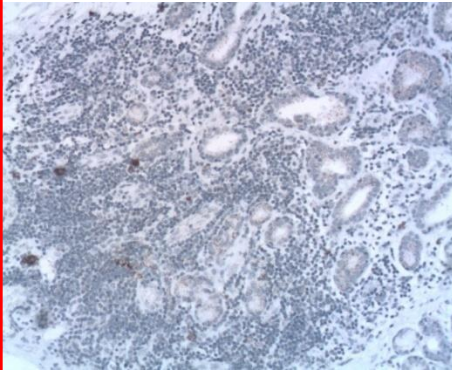


B7-H1+  
TIL+

38%

Adaptive  
resistance

III

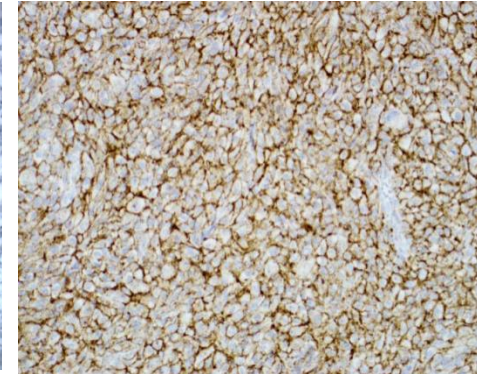


B7-H1-  
TIL+

20%

other inhibitors?

IV



B7-H1+  
TIL-

1%

Intrinsic  
induction

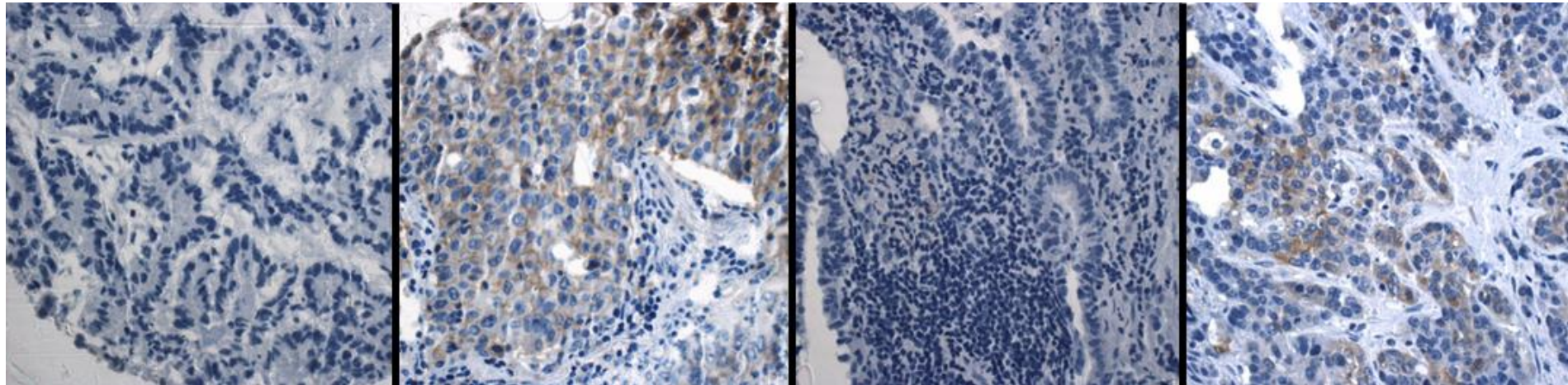
# PD-L1 expression pattern in 457 lung cancer (tissue microarray analysis)

**B7-H1-TIL-**

**B7-H1+TIL+**

**B7-H1-TIL+**

**B7-H1+TIL-**



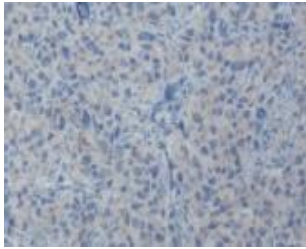
**45%**

**17%**

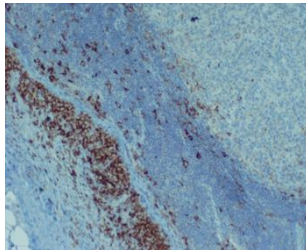
**26%**

**12%**

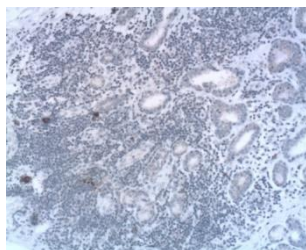
# Mechanism-based combination therapy



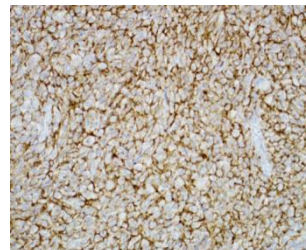
**TIL-/PD-L1-** (**lack of inflammation**): anti-CTLA-4, local radiation, chemoattraction, cancer vaccine, adoptive T cell therapy



**TIL+/PD-L1+** (**adaptive resistance**): Anti-PD-1 +/- anti-PD-L1, new inhibitory pathways



**TIL+/PD-L1-** (**non-PD-L1 mediated immune tolerance**): New inhibitory pathways



**TIL-/PD-L1+** (**intrinsic induction of PD-L1**): EGFR inhibitors etc.

# Platforms for discovery of tumor site T-Cell inhibitory pathways

**Over-expressed molecules of human cancer**  
(identified by microarray, proteomics and bioinformatics)



**T-Cell Activity Array**



**The Receptor Array**



**Immunobiology *in vitro* and *in vivo***



**Mouse tumor /PDX models**





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