Presenter Disclosure Information

Mary L. Disis

The following relationships exist which may relate to this presentation:

VentiRx, Roche, Bristol Meyers Squibb, Immunovaccine, EMD-Serono Epigenomics
Immune response signatures and clinical outcome

I. Approach and models

II. Serologic signatures

III. Peripheral blood cell signatures
Clinically effective anti-tumor immunity

Population based, multiple tumor types

- Gene signature of a Type I cellular immune response (e.g. IFN-gamma, GZMB, CD3z)
- High density of infiltrating T cells (e.g. CD8, memory)
- Low density of regulatory cells (e.g. Treg, Th2, MDSC)

Bindea et al, Curr Opin Immunol, 2010
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Environment supportive of clinically effective immunity

- Could the “immune score” be manipulated by immune–based therapy?
- Is there a potential for a blood-based “immune score”?

Bindea et al, Curr Opin Immunol, 2010
Breast cancer as a model: TIL predict response to chemotherapy

3-7% pCR

40-42% pCR

Denkert et al, JCO, 2010

n=1,058 neoadjuvant Anthracycline/taxane

n=134 tumors
Breast cancer as a model: 
Tx induced Th1 predicts response

Ladoire et al, BJC, 2011

Samples from 1981-2000
Anthacyclines

T-bet+ CD4

Samples from 2001-2007
Trastuzumab–taxane

Prior to chemo Tbet+, p=0.99

n=44 HER2+ patients

50% T-bet+

n=58 HER2+ patients

16% T-bet+

Log-rank P=0.54

Independent predictor of improved RFS, p=0.04

Log-rank P=0.011
HR 4.76 (1.07-20)
Breast cancer as a model: Th diversity in tumor associated immunity

Cecil et al, 2012

IGFBP-2 and control antigens

Corrected spots/well (2x10^5)

IFN-g predominant

IL-10 predominant

Mixed Response

n=40

IGFBP-2

None

3%

IL-10

22%

Mix

53%

IFNg

22%

IGF-IR

IL-10

7%

Mix

53%

IFNg

40%
Data mining approaches to develop lead candidates

**Trial Designs**

- Phase I-II, HER2 Class II peptides
- Stage III and/or IV HER2* breast cancer
- Vaccine alone or concurrently with trastuzumab
- CR or SD (>2nd line tx)
- 6 vaccines, id, I month apart
- GM-CSF as an adjuvant

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**Phase I, n=66**

HR=0.598 (CI 95%, 0.41-0.85), p=0.004

- Vaccinated (n=52)
- SEER Age/stage matched controls (n=178)

Median F/U >10yr

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**Phase I/II, n=22**

- Median OS: 78m (6.5 yrs) *(8-23 mo)*
- Median PFS= 19m, 12% DFS *(7-12 mo)**

- Interim analysis: estimated 63% PFS at 4 yrs
- Expected: 44% at 4 yrs.

Median F/U >7yr

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**Phase II, n=38**

Interim analysis: estimated 63% PFS at 4 yrs

Expected: 44% at 4 yrs.

Median F/U >7yr

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*Disis et al, JCO, 2009*

*Schaller et al, ASCO, 2005*

**Yamamoto et al, Can Chemo Pharm, 2008*

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*Salazar et al, 2012*
Data mining approaches to develop lead candidates

**Trial Designs**
- Phase I-II, HER2 Class II peptides
- Stage III and/or IV HER2+ breast cancer
- Vaccine alone or concurrently with trastuzumab
- CR or SD (50% 2nd, 3rd line tx)
- SEER Age/stage matched controls (n=178)
- 6 vaccines, id, I month apart
- GM-CSF as an adjuvant

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Salazar et al, 2012
Development of epitope spreading associated with survival

Disis et al, JCO 2002

MVA: Stage, +/- chemo, CR, PR, SD
ES

HR=0.34 (CI 95%, 0.12-1.0), p=0.04

ES+, Median 84 mo
ES-, Median 24 mo

(n=52, Stage III/IV Breast Ca)
Environment supportive of clinically effective immunity

Cancer: Enhanced cross priming
Normal tissues: Autoimmunity

Epitope spreading: treatment induced change in the “immune score”?
Immune response signatures and clinical outcome

I. Approach and models

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Pilot study: Serologic signature of epitope spreading

- Stage IV
- Developed epitope spreading
- Alive greater than 10 years after vaccination
- Pre-vaccine and post-vaccine sera available
- n=8

HER2+ Breast Ca Library

Primary screen
- Pre-vaccine
- ES- sera

Secondary screen
- Pre-vaccine
- ES- sera

- 140K to 252K clones screened/patient
- 20-35 primary clones identified/patient
- 1-4 secondary clones confirmed for specificity
- Sequence the clones specific for ES developing after vaccination
Data mining approaches to develop lead candidates

**Trial Designs**

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Interim analysis: estimated 63% PFS at 4 yrs
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Salazar et al, 2012

Unique or shared responses? 
Magnitude elicited post vaccine is associated with survival

Disis et al, JCO, 2009
n=22 patients, 14 Ab responders

n=54
3 trials
Median follow-up 8yrs
Stage III/IV HER2+
Autoantibodies correlate with response after CTLA4 MoAb in prostate cancer

**SIMILAR**

- Responders: greater intensity
- greater # Ag

**DIFFERENT**

- Cell cycle associated
- Nuclear
- 30% are kinases

Kwek et al, JI, 2012
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Salazar et al, 2012
Type I IFN signature in autoimmune disease

Associated with disease severity: SLE

Limited response to rituximab: active RA

Bennett et al, JEM, 2003

Raterman et al, Arth Res Ther, 2012
Specific autoantibodies may stimulate TLR and Type I IFN production from DC

- Th1/CTL induced necrosis
- DC entry facilitated by Ab Fc
- Epitope spreading
- Necrosis associated autoantibodies: X-Chromatin (SUPT 16H), X-RNA/DNA (SON-EEF1A1), X-nucleosome

- IL-12, IFN-g, GM
- Stam2
- Dap-1

- Activate TLR via bound RNA/DNA
- Initiates Type I IFN cascade
- Requirement for T-cell mediated tumor rejection*

*Diamond et al, JEM, 2011

Theofilopoulos et al, Ann Rev Immunol, 2005
Immune response signatures and clinical outcome

• Predictive and prognostic signatures, many based on the immune score, are being evaluated in clinical trials

• Signatures modulated by immunotherapy and predictive of outcome are being developed

• Retrospective data mining on successful therapeutic studies or even selected unique patients may provide candidates

• Ideal therapeutic response signature:
  • Associated with mechanism; not specific therapy
  • Operative across disease types
Collaborators

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Mayo Clinic

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Karolina Palucka
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