Presenter Disclosure Information

Mary L. Disis

The following relationships exist which may related to this presentation:

VentiRx, Roche, Bristol Meyers Squibb,
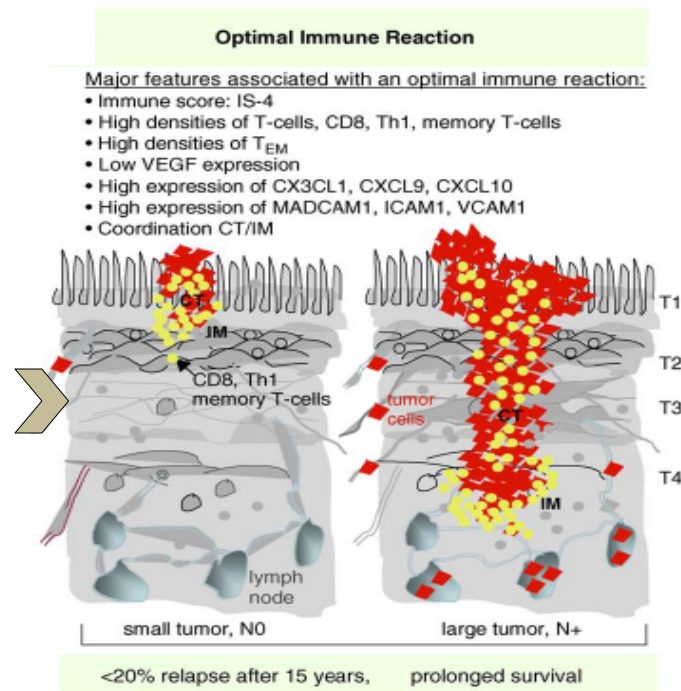*Immunovaccine, EMD-Serono*
Epigenomics

**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)

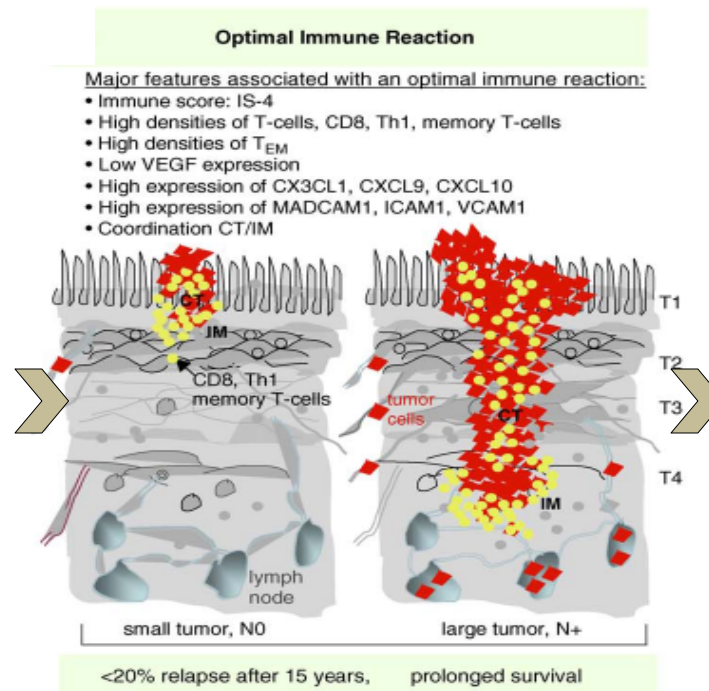- **Low density of regulatory cells** (e.g. Treg, Th2, MDSC)

Optimal Immune Reaction

Major features associated with an optimal immune reaction:
- Immune score: IS-4
- High densities of T-cells, CD8, Th1, memory T-cells
- High densities of T_{EM}
- Low VEGF expression
- High expression of CX3CL1, CXCL9, CXCL10
- High expression of MADCAM1, ICAM1, VCAM1
- Coordination CT/IM

small tumor, N0   large tumor, N+

<20% relapse after 15 years,   prolonged survival

Bindea et al, Curr Opin Immunol, 2010

Clinically effective anti-tumor immunity

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CD8, Th1 memory T-cells

tumor cells

lymph node

small tumor, N0   large tumor, N+

<20% relapse after 15 years,   prolonged survival
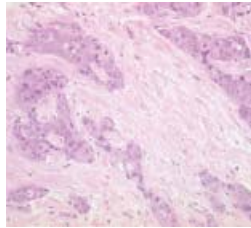
T1
T2
T3
T4

Bindea et al, Curr Opin Immunol, 2010

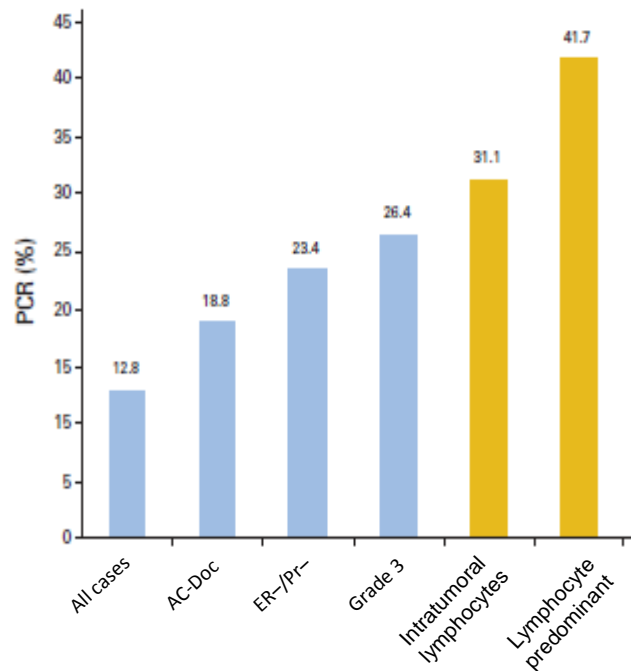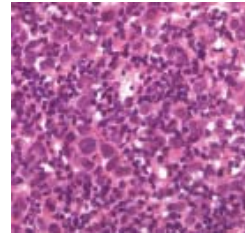**Environment supportive of clinically effective immunity**

- **Could the "immune score" be manipulated by immune –based therapy?**

- **Is there a potential for a blood-based "immune score"?**

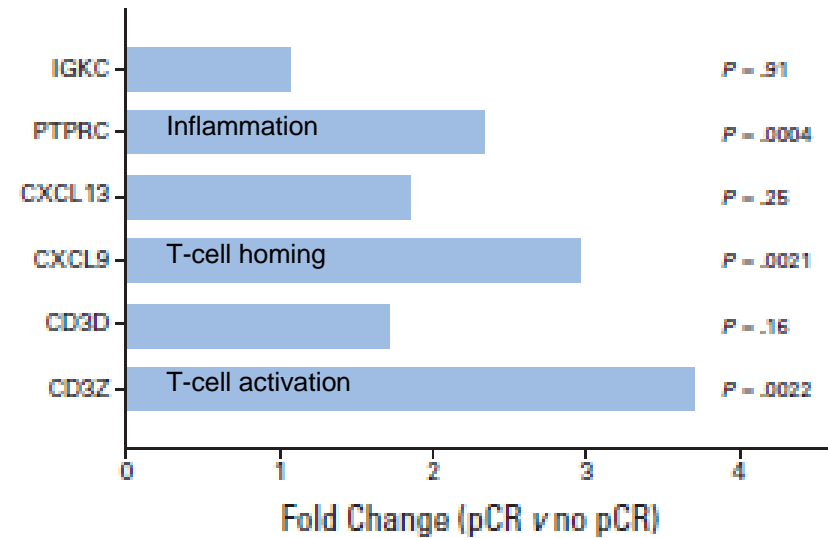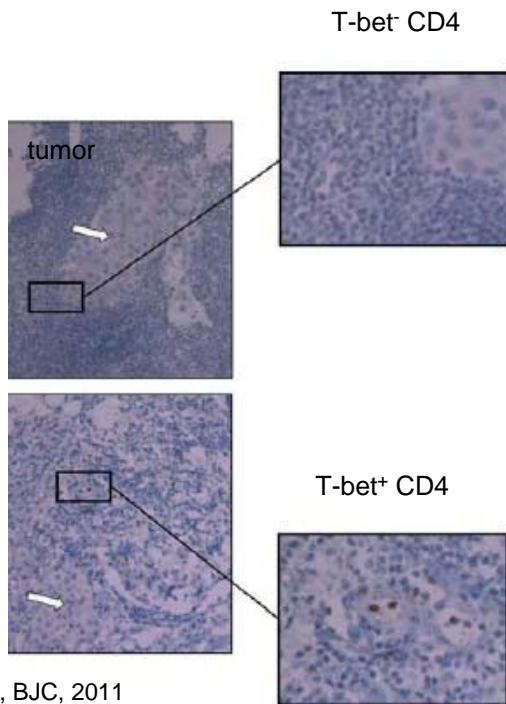# Breast cancer as a model: TIL predict response to chemotherapy

3-7% pCR

40-42% pCR

n=1,058 neoadjuvant
Anthracycline/taxane

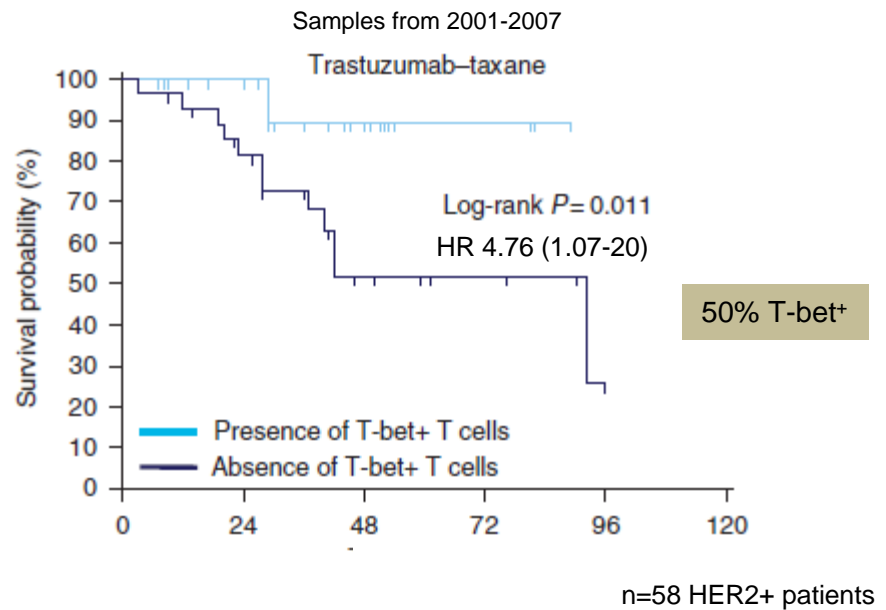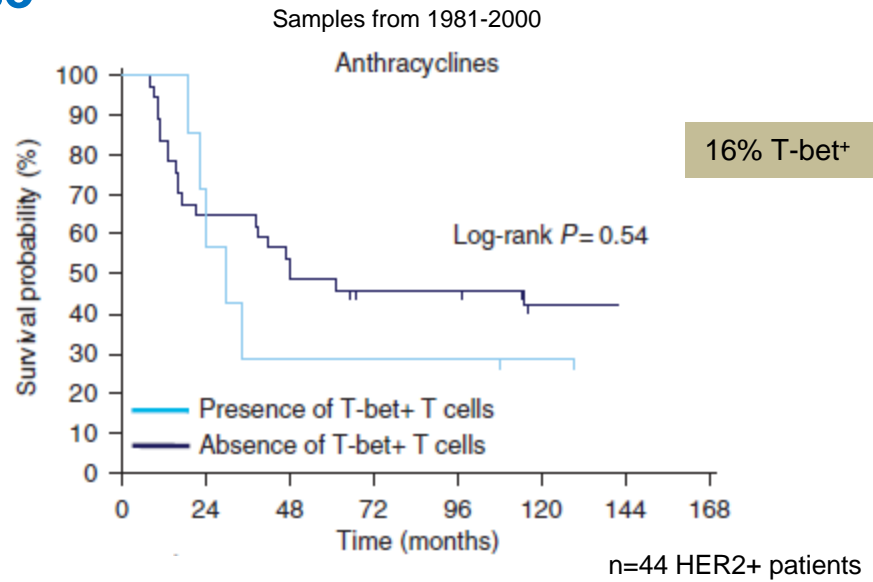|	Fold Change (pCR v no pCR)	P value
IGKC		P = .91
PTPRC	Inflammation	P = .0004
CXCL13		P = .25
CXCL9	T-cell homing	P = .0021
CD3D		P = .16
CD3Z	T-cell activation	P = .0022

n=134 tumors

Denkert et al, JCO, 2010

Breast cancer as a model:
Tx induced Th1 predicts response

Samples from 1981-2000

Anthracyclines

16% T-bet+

Log-rank $P= 0.54$

Survival probability (%)

Time (months)

n=44 HER2+ patients

Presence of T-bet+ T cells
Absence of T-bet+ T cells

T-bet- CD4

tumor

T-bet+ CD4

Ladoire et al, BJC, 2011

Samples from 2001-2007

Trastuzumab–taxane

Log-rank $P= 0.011$

HR 4.76 (1.07-20)

50% T-bet+

Survival probability (%)

Presence of T-bet+ T cells
Absence of T-bet+ T cells

n=58 HER2+ patients
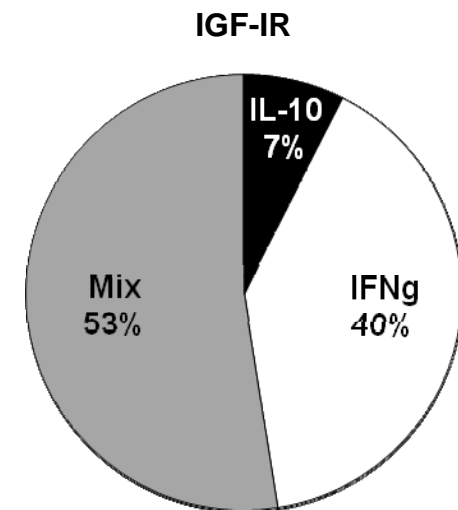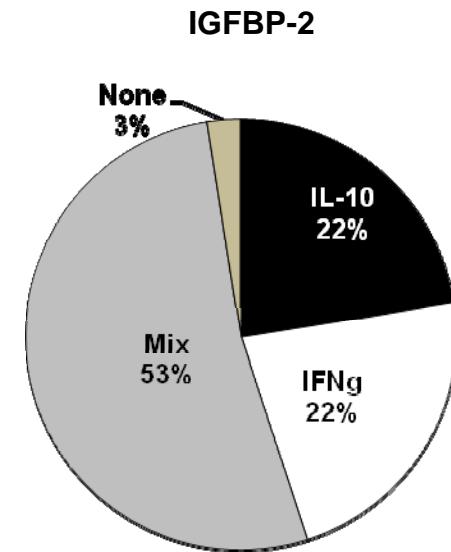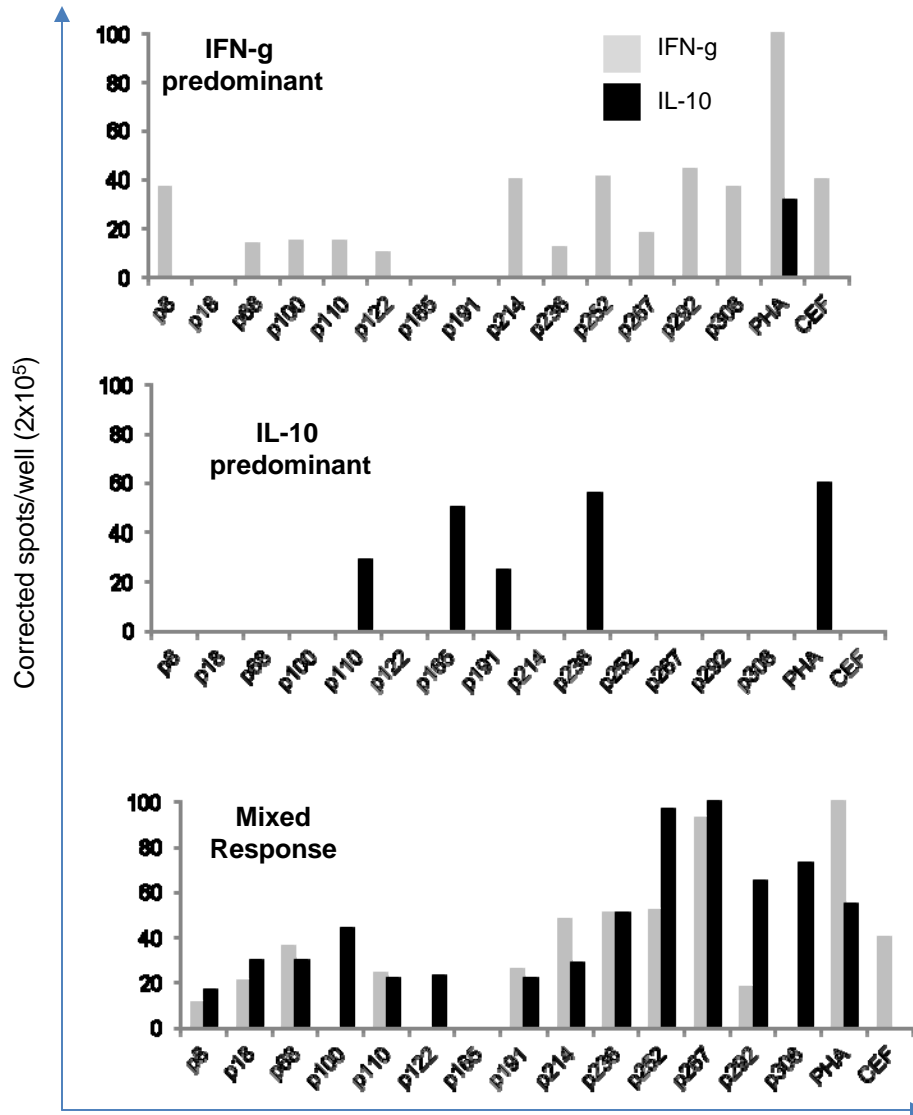
Prior to chemo Tbet $^+$,p=0.99

Independent predictor of improved RFS, p=0.04

Breast cancer as a model:
Th diversity in tumor associated immunity

Cecil et al, 2012

IGFBP-2 and control antigens

IGFBP-2

IGF-IR

n=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
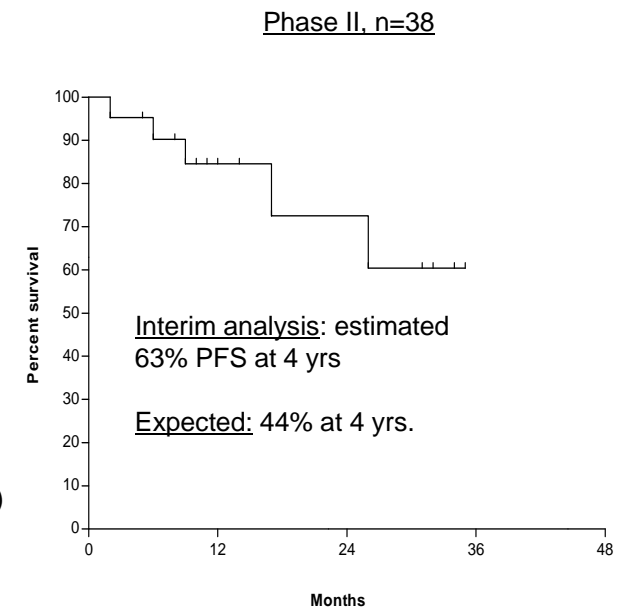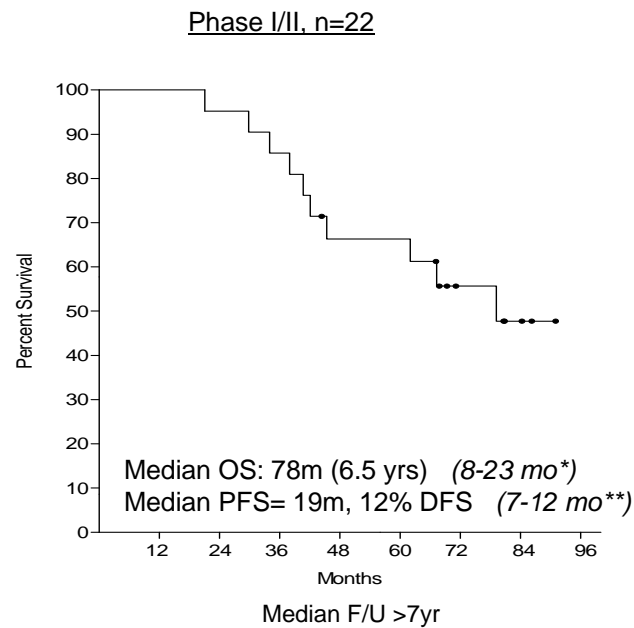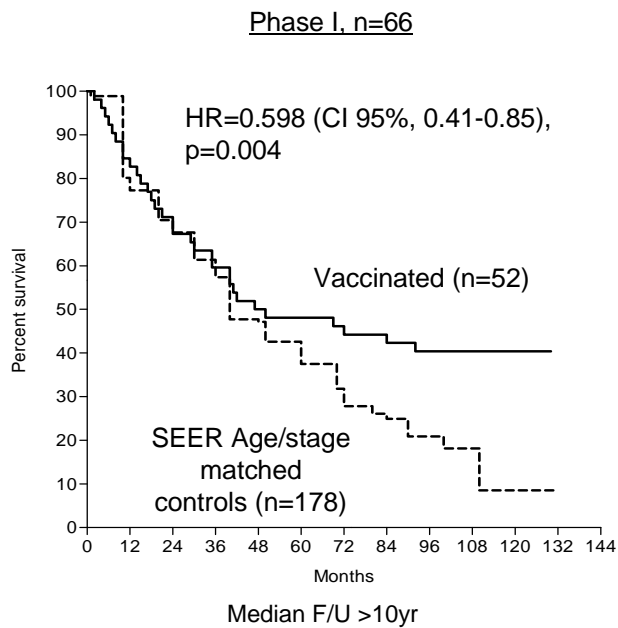
Phase I, n=66

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

Vaccinated (n=52)

SEER Age/stage matched controls (n=178)

Percent survival

Months

Median F/U >10yr

Disis et al, JCO, 2002
Salazar et al, ASCO, 2009

Phase I/II, n=22

Percent Survival

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

Months

Median F/U >7yr

Disis et al, JCO, 2009
*Schaller et al, ASCO, 2005
**Yamamoto et al, Can Chemo Pharm, 2008

Phase II, n=38

Percent survival

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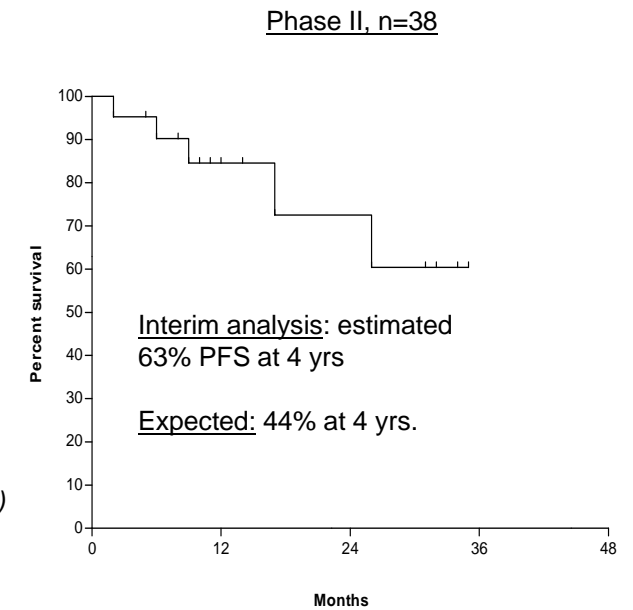
Expected: 44% at 4 yrs.

Months

Salazar et al, 2012

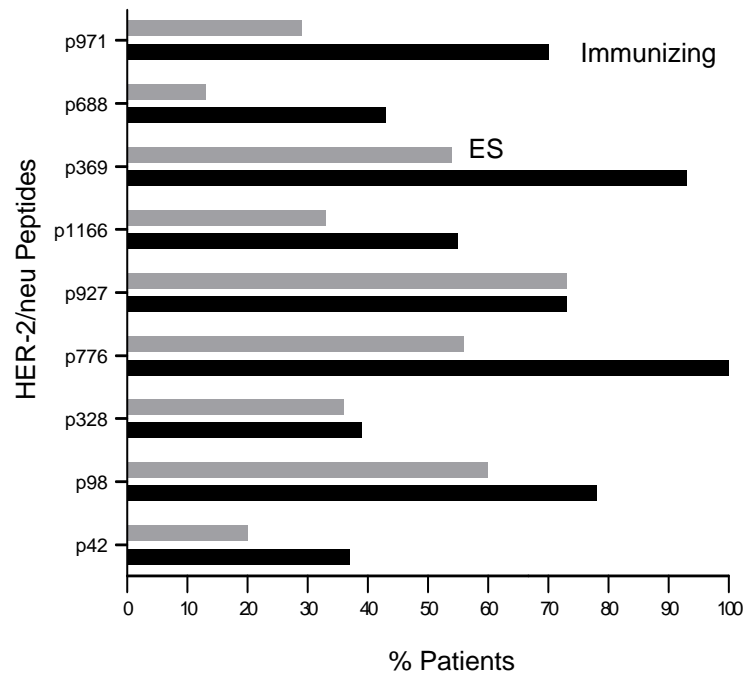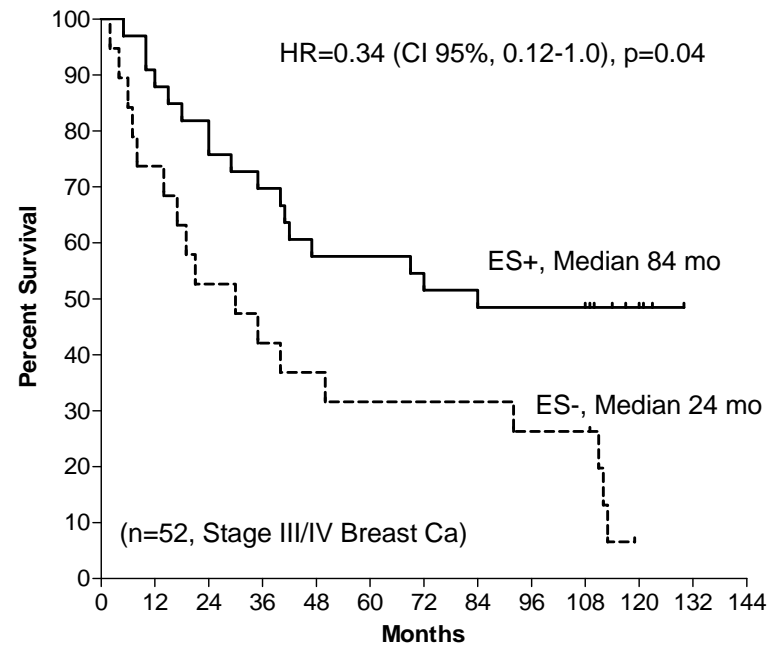# Data mining approaches to develop lead candidates
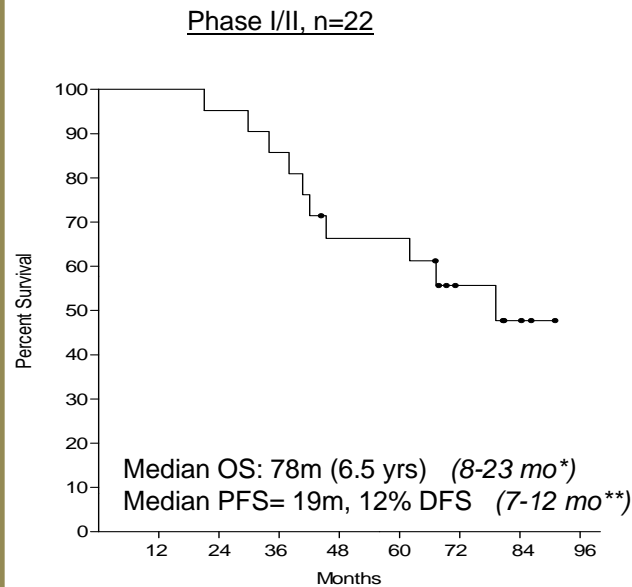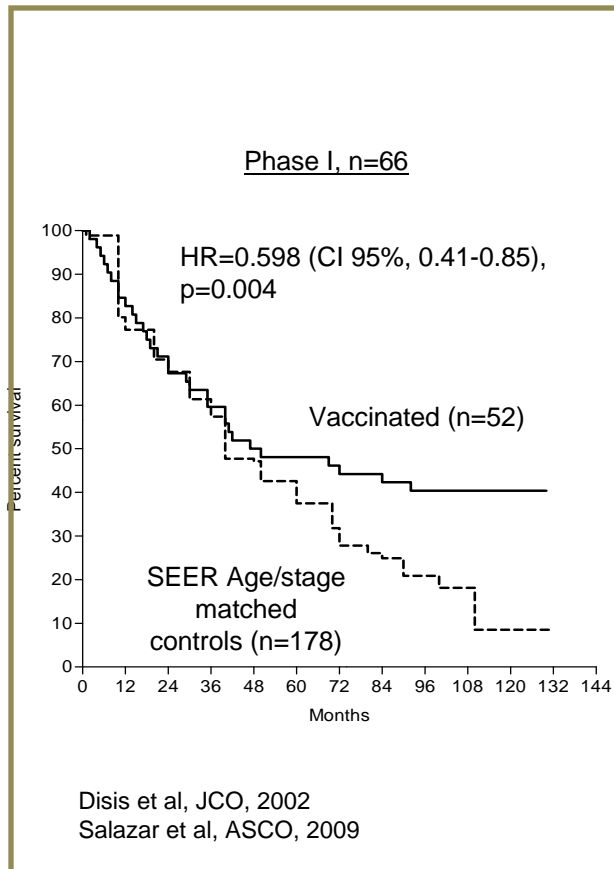
Trial Designs
Phase I-II, HER2 Class II peptides
Stage III and/or IV HER2+ breast cancer
Vaccine alone or concurrently with trastuzumab
CR or SD (50% 2nd, 3rd line tx)
6 vaccines, id, I month apart
GM-CSF as an adjuvant

Generate hypothesis

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Phase II, n=38

Percent survival

Months

Interim analysis: estimated 63% PFS at 4 yrs

Expected: 44% at 4 yrs.

Salazar et al, 2012

Development of epitope spreading associated with survival

Disis et al, JCO 2002

HR=0.34 (CI 95%, 0.12-1.0), p=0.04
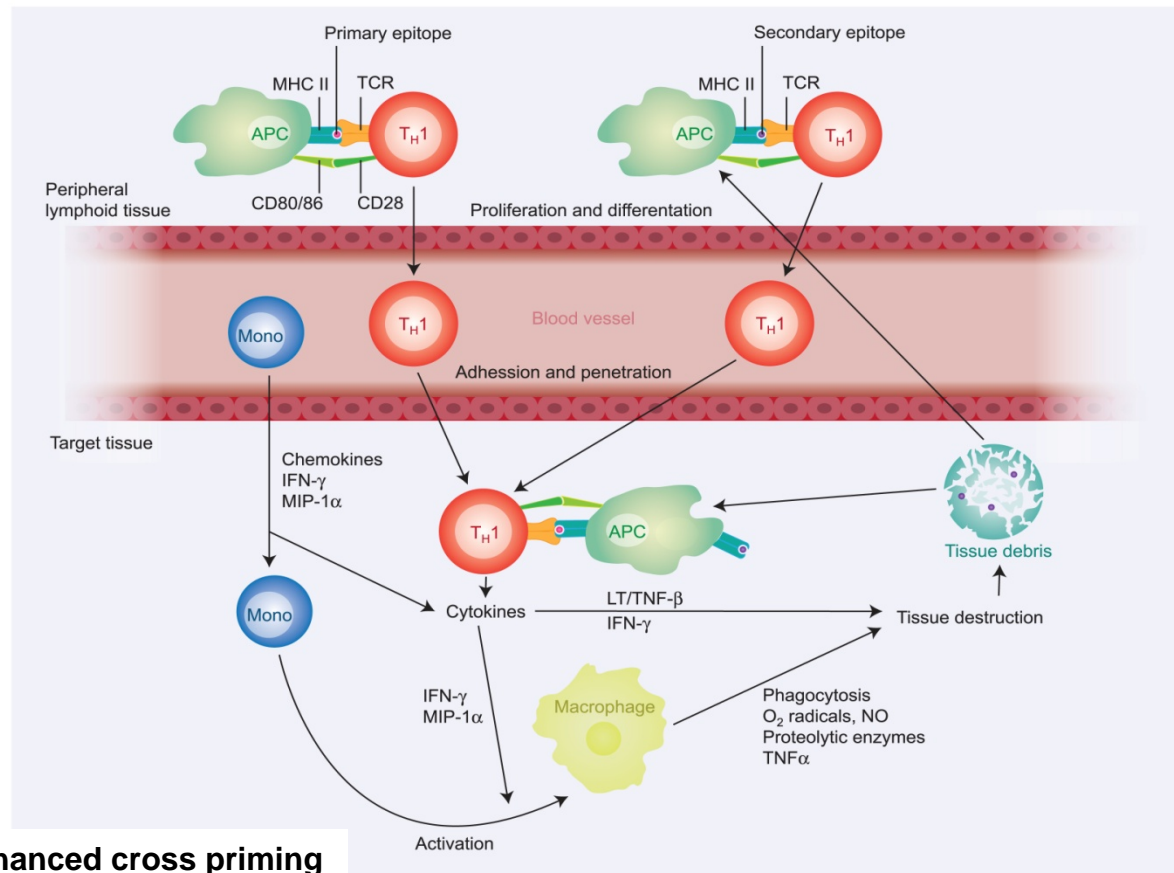
ES+, Median 84 mo

ES-, Median 24 mo

(n=52, Stage III/IV Breast Ca)

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

Salazar et al, ASCO, 2009

Environment supportive of clinically effective immunity

Primary epitope

MHC II | TCR

APC | T$_H$1

Peripheral lymphoid tissue

CD80/86 | CD28

Secondary epitope

MHC II | TCR

APC | T$_H$1

Proliferation and differentation

Mono | T$_H$1 | Blood vessel | T$_H$1

Adhession and penetration

Target tissue

Chemokines
IFN-γ
MIP-1α

Mono

T$_H$1 | APC

Tissue debris

Cytokines | LT/TNF-β | Tissue destruction
IFN-γ

IFN-γ
MIP-1α

Macrophage

Phagocytosis
O$_2$ radicals, NO
Proteolytic enzymes
TNFα

Activation

Cancer: Enhanced cross priming
Normal tissues: Autoimmunity

Vanderlught et al, Nat Rev Immunol, 2002

Epitope spreading: treatment induced change in the "immune score"?

Immune response signatures and clinical outcome

I.   Approach and models

II. Serologic signatures

III. Peripheral blood cell signatures

Pilot study: Serologic signature of epitope spreading

HER2+ Breast Ca Library

Primary screen

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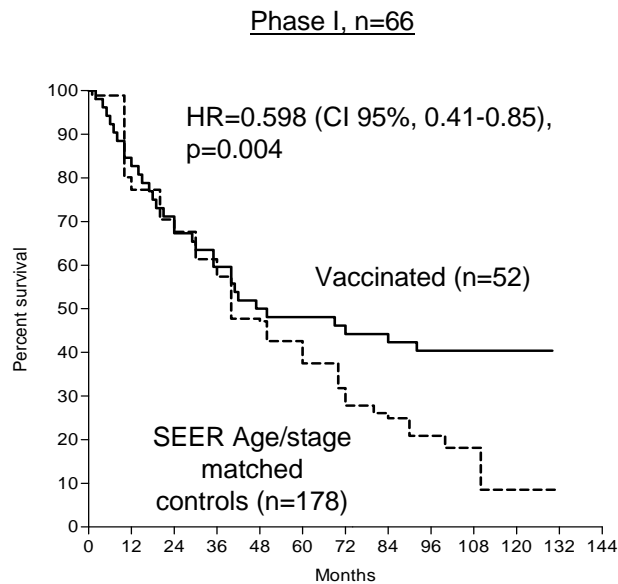- n=8

Secondary screen

- Pre-vaccine
- ES- sera
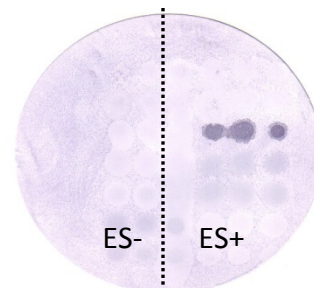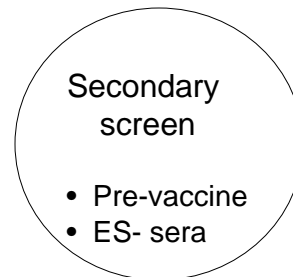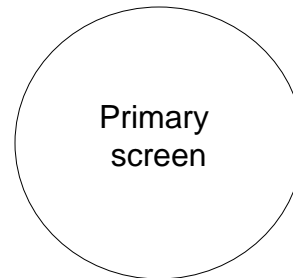
- 140K to 252K clones screened/patient
- 20-35 primary clones identified/patient
- 1-4 secondary clones confirmed for specificity
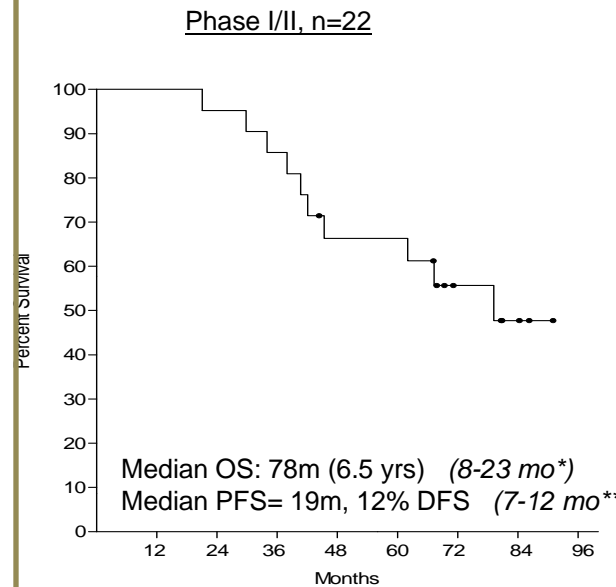- Sequence the clones specific for ES developing after vaccination

ES- ES+

Data mining approaches to develop lead candidates

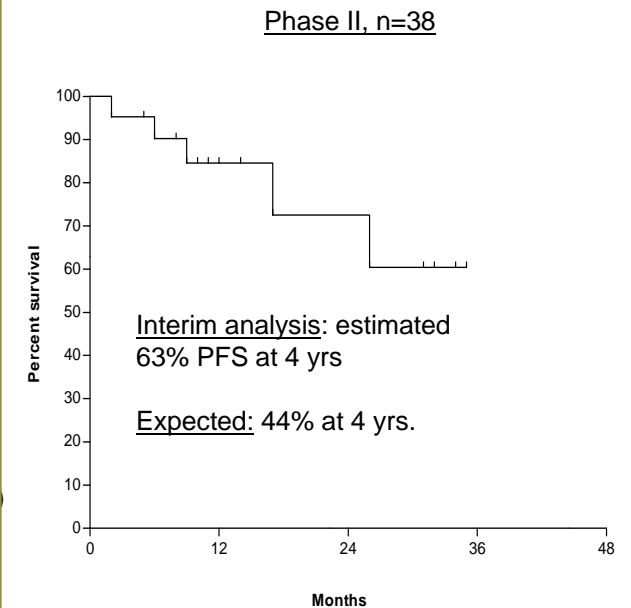| Trial Designs |
| --- |
| Phase I-II, HER2 Class II peptides |
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| Vaccine alone or concurrently with trastuzumab |
| CR or SD (50% 2nd, 3rd line tx) |
| 6 vaccines, id, I month apart |
| GM-CSF as an adjuvant |

Unique or shared responses?

Phase I, n=66

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

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SEER Age/stage matched controls (n=178)

Disis et al, JCO, 2002
Salazar et al, ASCO, 2009

Phase I/II, n=22

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

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*Schaller et al, ASCO, 2005
**Yamamoto et al, Can Chemo Pharm, 2008

Phase II, n=38

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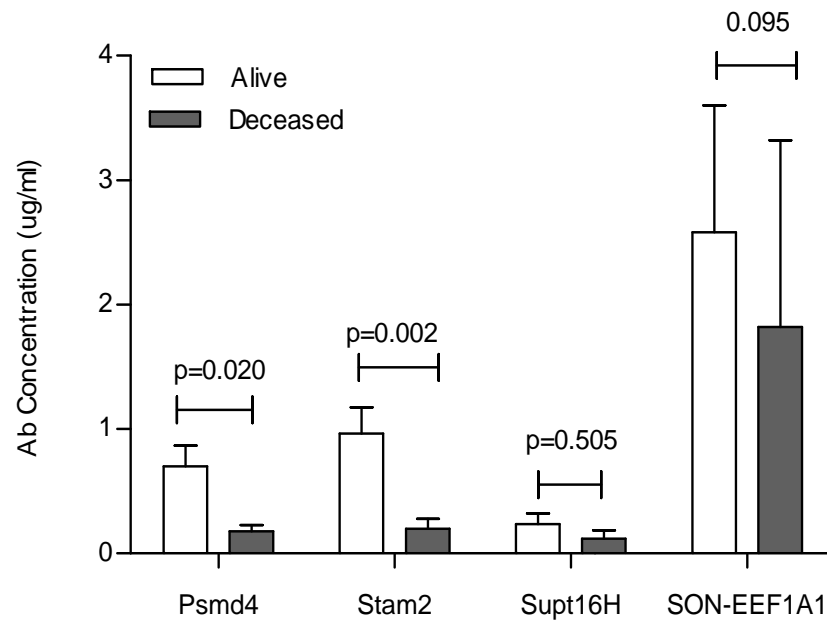
Expected: 44% at 4 yrs.

Salazar et al, 2012

Magnitude elicited post vaccine is associated with survival

R=0.592
p=0.026
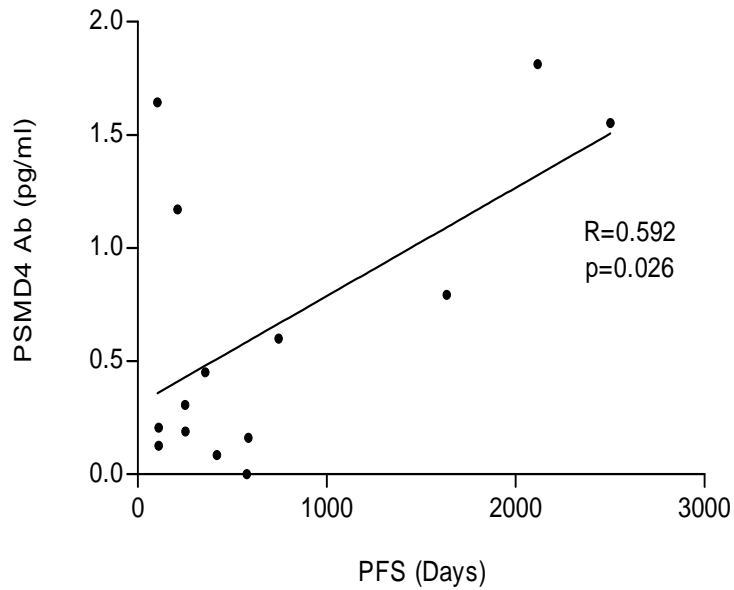
Disis et al, JCO, 2009
n=22 patients, 14 Ab responders

p=0.020
p=0.002
p=0.505
0.095

n=54
3 trials
Median follow-up 8yrs
Stage III/IV HER2+

Autoantibodies correlate with response after CTLA4 MoAb in prostate cancer

SIMILAR

p<0.05
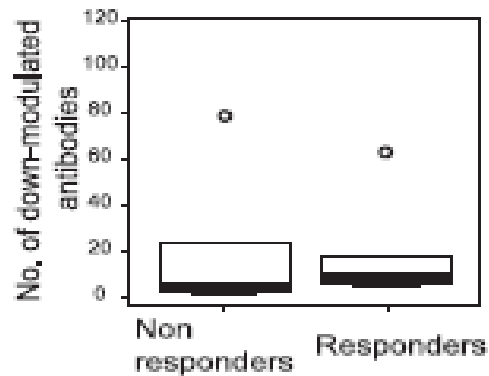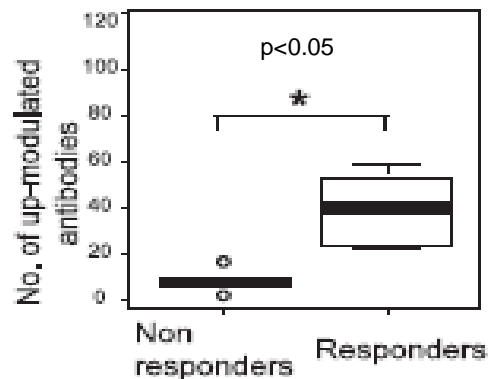
Responders: greater intensity
greater # Ag

DIFFERENT

- Cell cycle associated
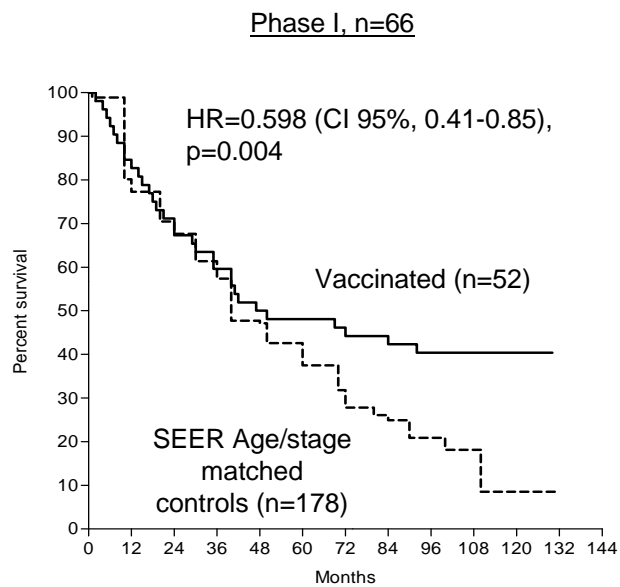- Nuclear
- 30% are kinases

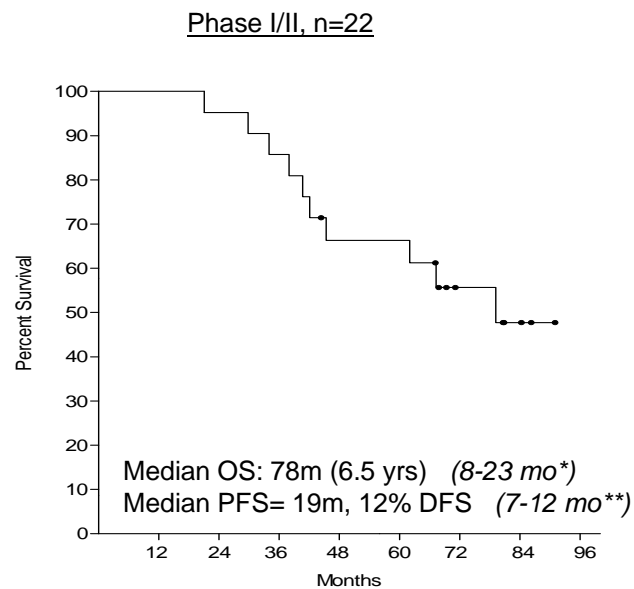| Gene Symbol	Description
AXL	AXL receptor tyrosine kinase
NTRK3	Neurotrophic tyrosine kinase, receptor, type 3
BTK	Bruton agammaglobulinemia tyrosine kinase
CSNK1G1	Casein kinase 1, γ 1
MPG	*N*-methylpurine-DNA glycosylase
CSNK1E	Casein kinase 1, ε
CCNT1	Cyclin T1
PAK6	p21 protein (Cdc42/Rac)-activated kinase 6
CSNK1G2	Casein kinase 1, γ 2
KIT	v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog
AIF1	Allograft inflammatory factor 1
DLX1	Distal-less homeobox 1
MATK	Megakaryocyte-associated tyrosine kinase
PLK1	Polo-like kinase 1
CSNK1D	Casein kinase 1, δ
GTSF1	Gametocyte specific factor 1
HN1	Hematological and neurologic expressed 1
LMCD1	LIM and cysteine-rich domains 1
KIR3DX1	Killer cell Ig-like receptor, three domains, X1
OR6N2	Olfactory receptor, family 6, subfamily N, member 2
FAM129A	Family with sequence similarity 129, member A
GABRA3	γ-Aminobutyric acid A receptor, α 3
MUSTN1	Musculoskeletal, embryonic nuclear protein 1

Kwek et al, JI, 2012

**Immune response signatures
and clinical outcome**

I.   Approach and models

II. Serologic signatures

III. Peripheral blood cell signatures
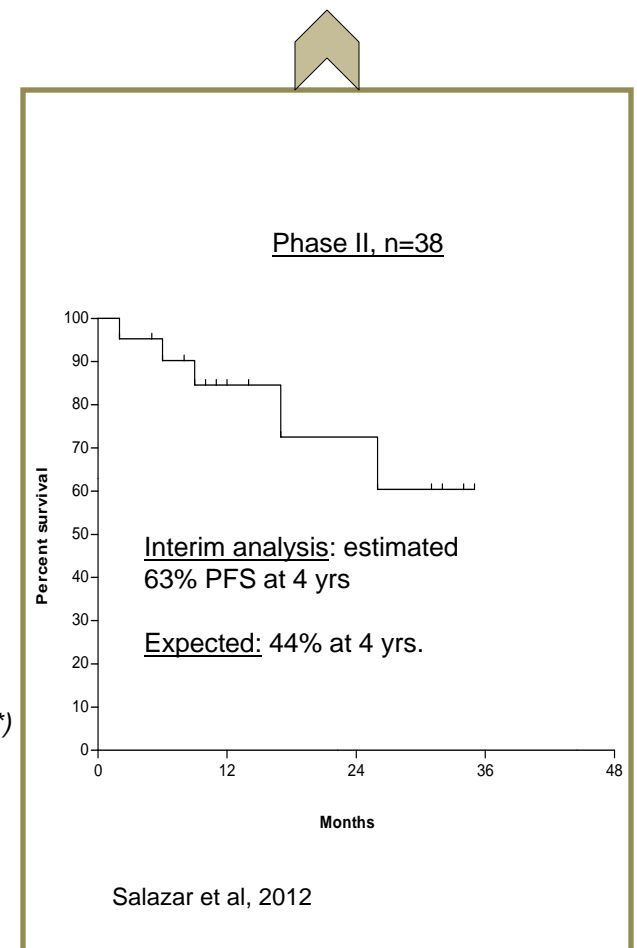
Data mining approaches to develop lead candidates

Discovery and validation

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)

Percent survival

Months

Disis et al, JCO, 2002
Salazar et al, ASCO, 2009

Phase I/II, n=22

Percent Survival

Median OS: 78m (6.5 yrs)   *(8-23 mo*)*
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Months

Disis et al, JCO, 2009
*Schaller et al, ASCO, 2005
**Yamamoto et al, Can Chemo Pharm, 2008

Phase II, n=38

Percent survival

Interim analysis: estimated 63% PFS at 4 yrs

Expected: 44% at 4 yrs.
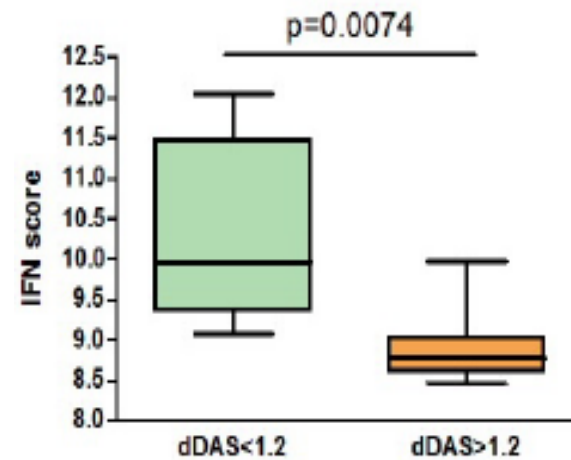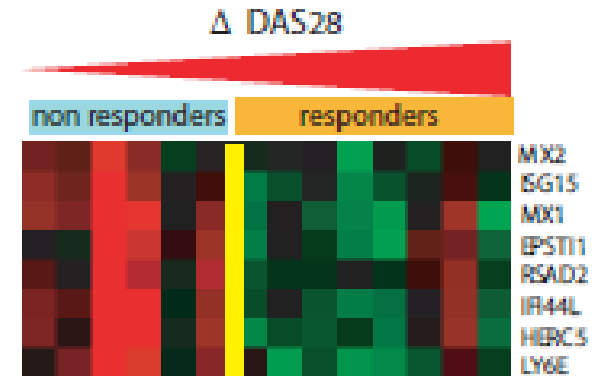
Months

Salazar et al, 2012

Type I IFN signature in autoimmune disease
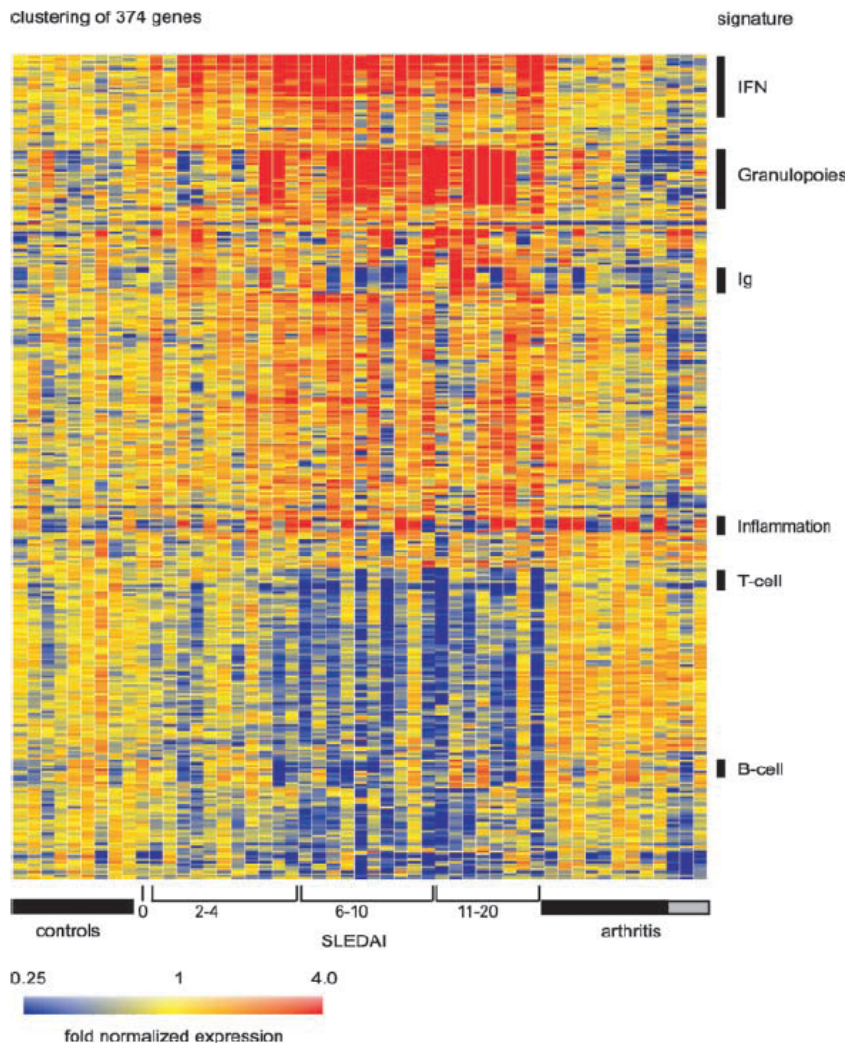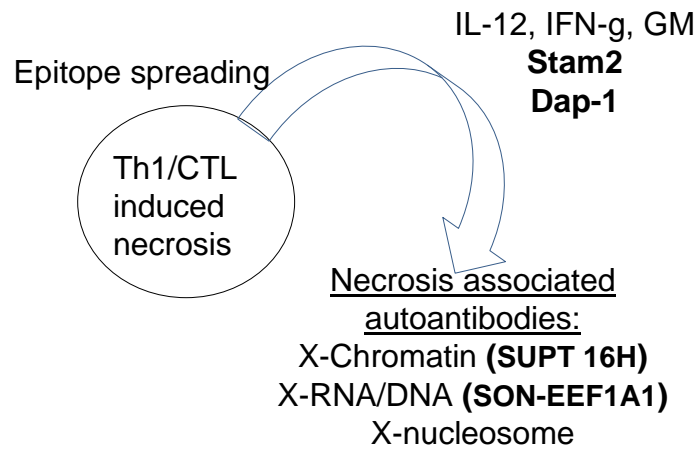

Associated with disease severity: SLE
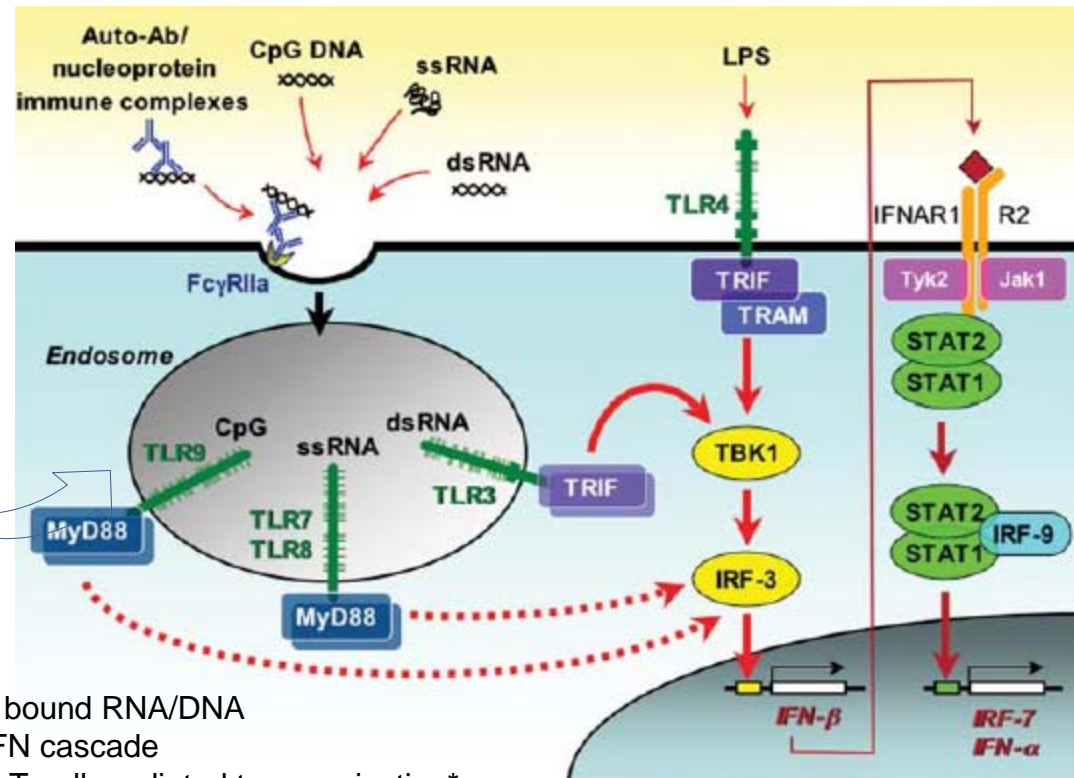
Bennett et al, JEM, 2003

Limited response to rituximab: active RA

Raterman et al, Arth Res Ther, 2012

Specific autoantibodies may stimulate TLR and Type I IFN production from DC

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

Epitope spreading

Th1/CTL induced necrosis

Necrosis associated autoantibodies:
X-Chromatin **(SUPT 16H)**
X-RNA/DNA **(SON-EEF1A1)**
X-nucleosome

DC entry facilitated by Ab Fc

Auto-Ab/ nucleoprotein immune complexes · CpG DNA · ssRNA · LPS · dsRNA · TLR4 · IFNAR1 · R2 · FcγRIIa · TRIF · TRAM · Tyk2 · Jak1 · STAT2 · STAT1 · Endosome · CpG · dsRNA · TBK1 · TLR9 · ssRNA · TLR3 · TRIF · STAT2 · STAT1 · IRF-9 · TLR7 TLR8 · MyD88 · IRF-3 · MyD88 · IFN-β · IRF-7 IFN-α

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

Theofilopoulos et al, Ann Rev Immunol, 2005

*Diamond et al, JEM, 2011

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

www.tumorvaccinegroup.org

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Yi Yang

Catherine Coy

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Korea University

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