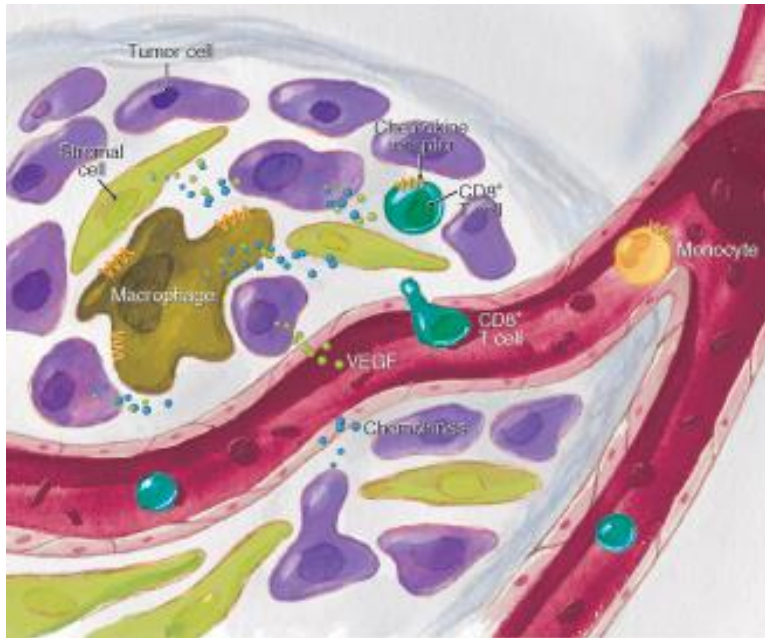


**A novel methylation signature that
reflects intratumoral lymphocyte
infiltration in breast cancer and
predicts for response to
anthracycline treatment**

J. Jeschke, M. Bizet, C. Desmedt, M. Defrance, S. Dedeurwaerder,
E. Calonne, G. Bontempi, C. Sotiriou, F. Fuks

No disclosures related to this presentation!

Tumor Infiltrating Lymphocytes (TIL)



TILs have prognostic and predictive value

VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

Carsten Denkert, Sibylle Loibl, Aurelia Noske, Marc Roller, Berit Maria Müller, Martina Komor, Jan Budczies, Silvia Darb-Esfahani, Ralf Kronenwett, Claus Hamsch, Christian von Törne, Wilko Weichert, Knut Engels, Christine Solbach, Iris Schrader, Manfred Dietel, and Gunter von Minckwitz

VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic and Predictive Value of Tumor-Infiltrating Lymphocytes in a Phase III Randomized Adjuvant Breast Cancer Trial in Node-Positive Breast Cancer Comparing the Addition of Docetaxel to Doxorubicin With Doxorubicin-Based Chemotherapy: BIG 02-98

Sherene Loi, Nicolas Sirtaine, Fanny Piette, Roberto Salgado, Giuseppe Viale, Françoise Van Eenoo, Ghizlane Rouas, Prudence Francis, John P.A. Crown, Erika Hitre, Evandro de Azambuja, Emmanuel Quinaux, Angelo Di Leo, Stefan Michiels, Martine J. Piccart, and Christos Sotiriou

RESEARCH ARTICLE

Open Access

Tumor-infiltrating lymphocytes predict response to anthracycline-based chemotherapy in estrogen receptor-negative breast cancer

Nathan R West^{1,2}, Katy Milne¹, Pauline T Truong³, Nicol Macpherson⁴, Brad H Nelson^{1,2,5,6} and Peter H Watson^{1,2,7*}

Methods for TIL Evaluation

TILs



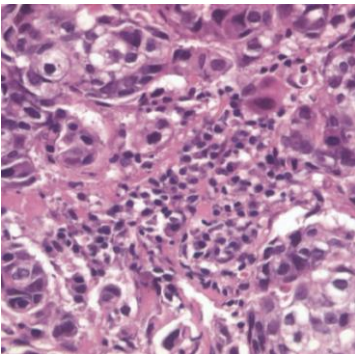
Staining/IHC

FACS

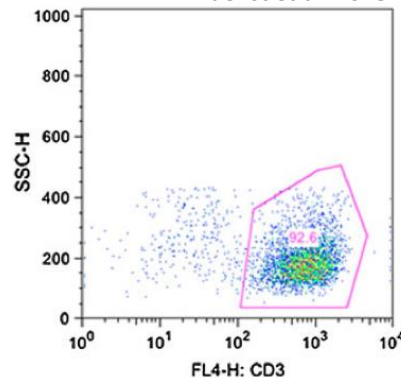
Gene
Expression

DNA
Methylation

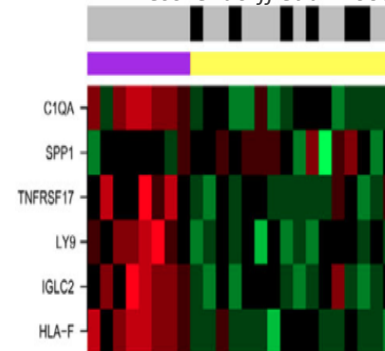
Denkert et al. 2010



Muenst et al. 2013



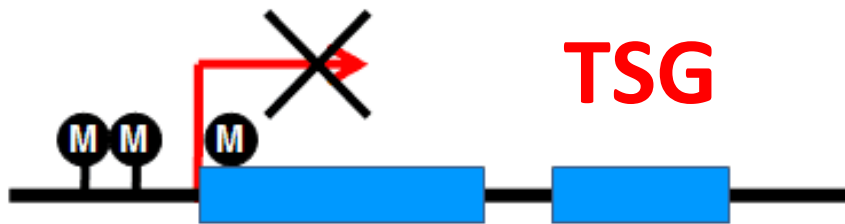
Teschendorff et al. 2008



DNA Methylation

5-Azacytidine

Vidaza®



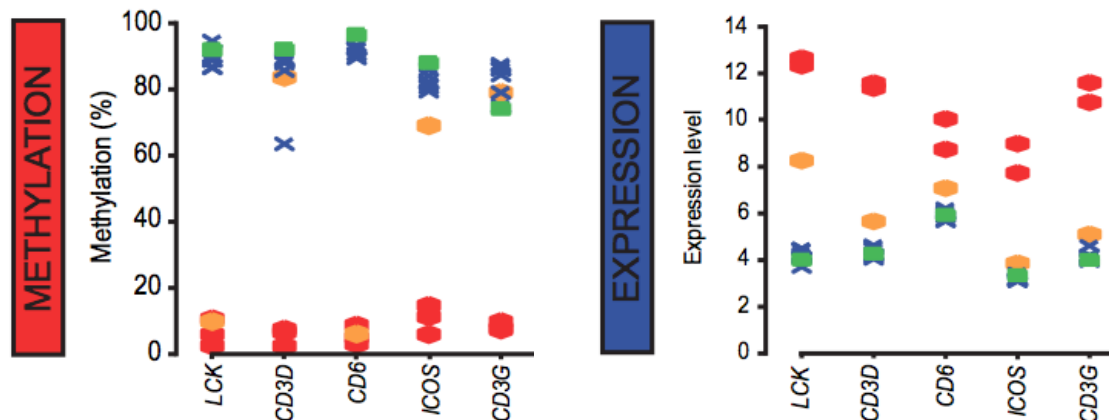
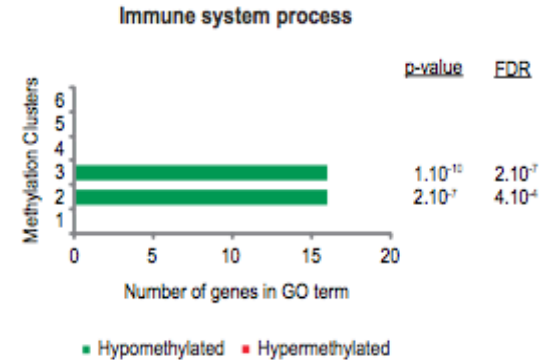
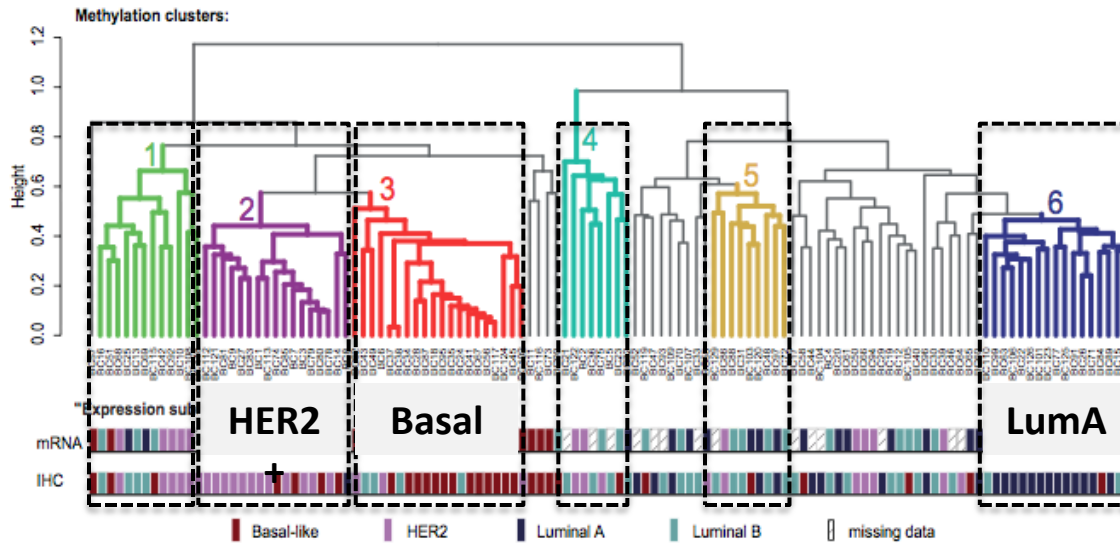
Infinium Methylation Arrays



Breast Cancer
Methylomes

DNA Methylation Reflects TIL

UNSUPERVISED CLUSTERING ON THE MAIN SET



DNA methylation of immune related genes may be a quantitative marker for TIL

Approach

Infinium Methylation Arrays



**8 Breast Cancer Epithelial and
3 T- Lymphocyte Cell Lines**

Highly (>80%) differential methylated
probes between T cells and breast cancer
cells

**MeT
Signature**

Test MeT Signature for prediction of
response in TOP cohort

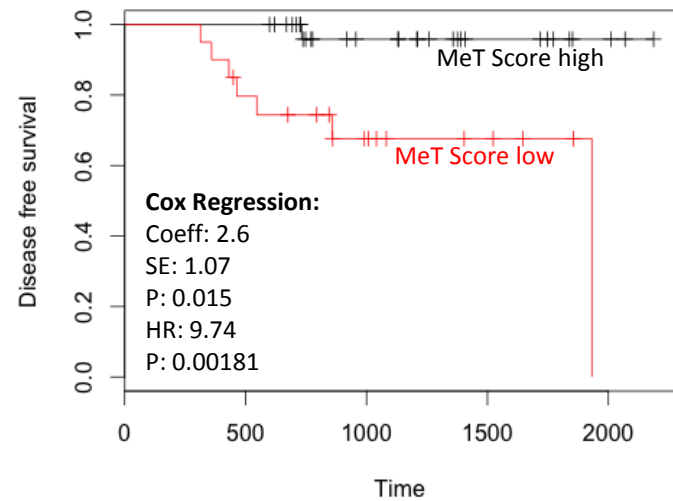
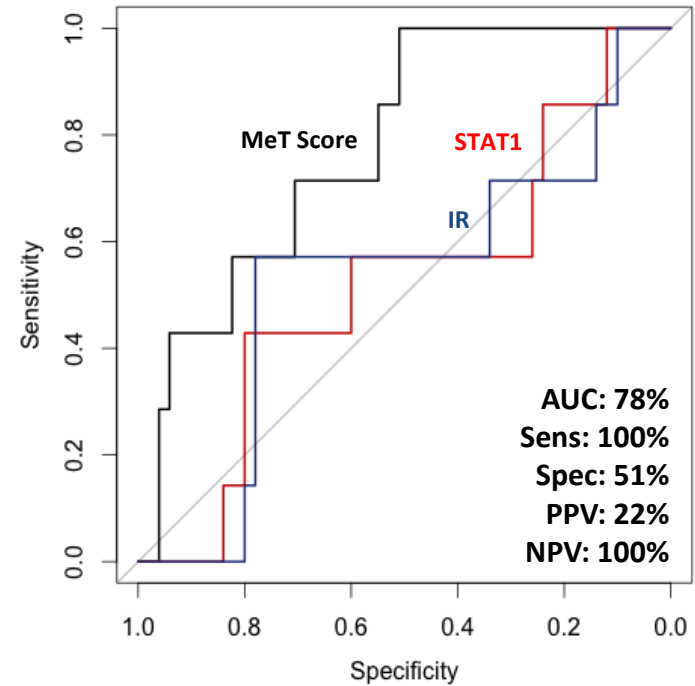
**TOP Cohort:
51 Non-Responders & 7 Responders**

Optimize/reduce MeT signature based on
anthracycline response in TOP cohort
using a **Machine Learning Approach**

**Optimized MeT
Signature**

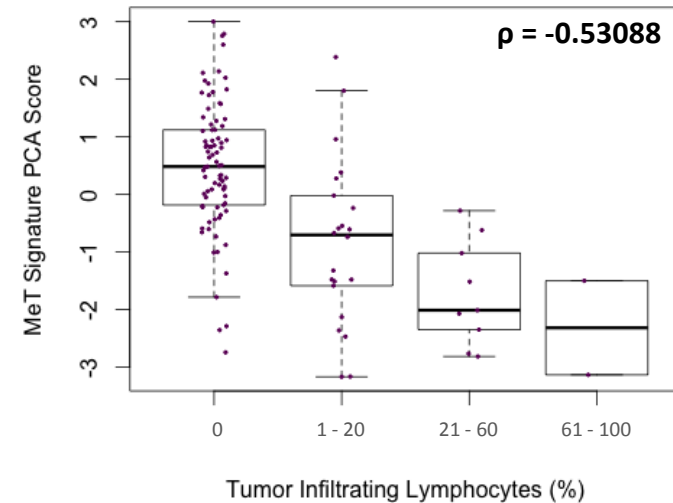
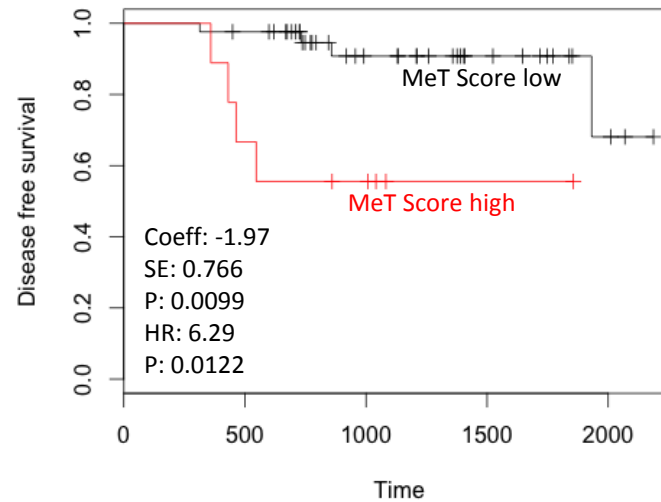
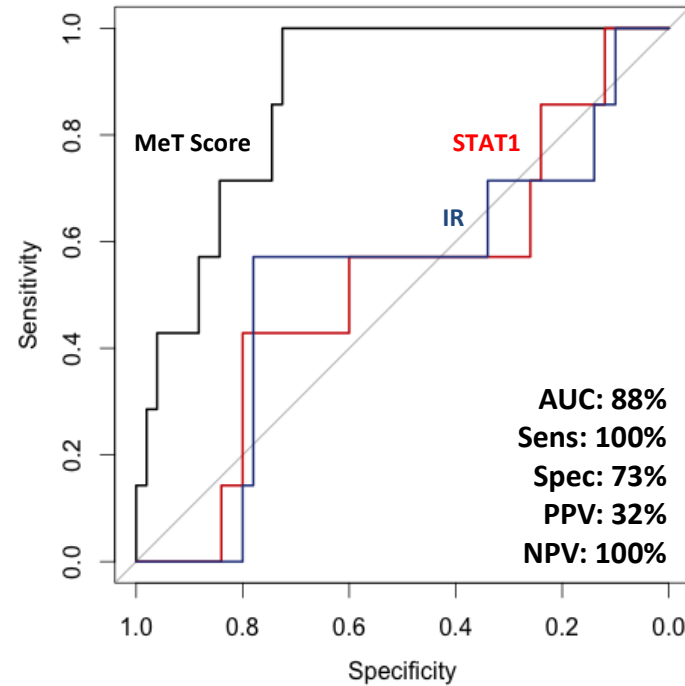
MeT Signature

PCA Analysis



Optimized MeT Signature

PCA Analysis



Conclusions

DNA methylation of T cell-related genes (MeT Signature) reflects lymphocyte infiltration of tumors (TIL) and predicts response to anthracyclines



- Stability of DNA methylation mark
- Sensitivity of DNA methylation detection assays
- Nature of DNA methylation signal in T cell-related genes (on/off)

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Sarah Dedeurwaerder
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Francois Fuks
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Francoise Rothe
Benjamin Haibe-Kains
Christos Sotiriou
- **(IB)²:** Gianluca Bontempi