

23. – 24. MAI 2017

Schloß Schönbrunn, Wien
Apothekertrakt und Orangerie

The search for biomarkers to predict response to immunotherapies in NSCLC patients

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Präsentiert von



DISCLOSURE

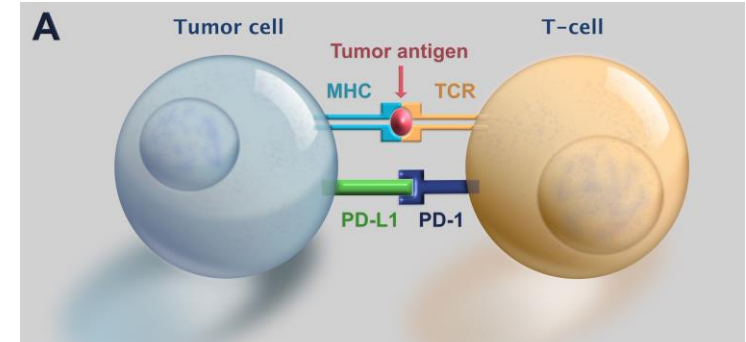
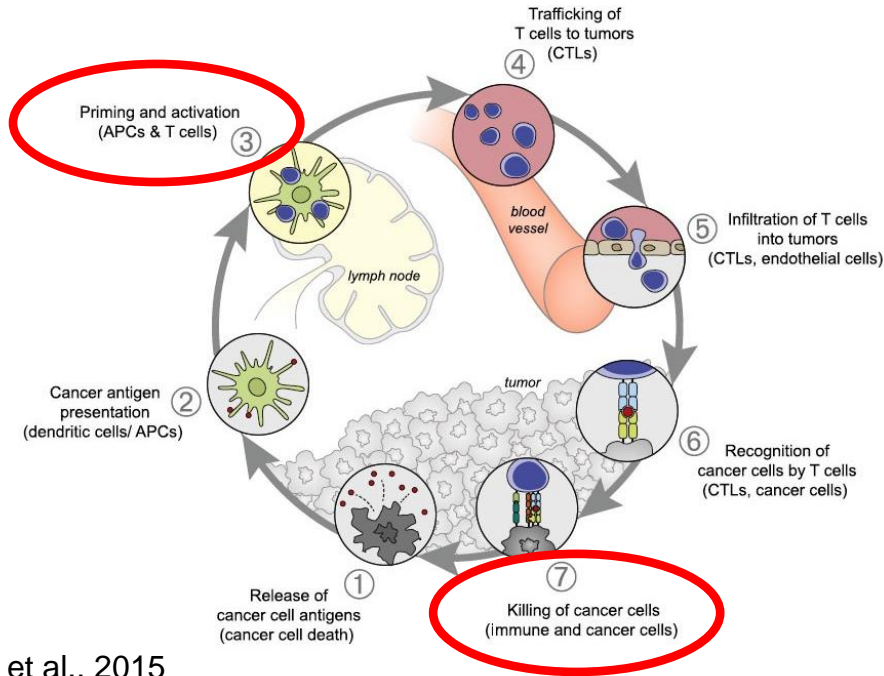
Relevant financial relationship:

Research fund by BMS (CA209-894)

CONTENT

- Background
- Mutation burden and response to immunotherapies
- Gene/pathway alterations associated with response to immunotherapies
- Epigenetics – DNA methylation
- Link between epigenetics and immunotherapies

PRINCIPLE OF ANTI-TUMOR IMMUNITY



Chen et al., 2015

IMMUNOTHERAPIES ARE ...

- ... revolutionizing anti-cancer therapy
- ... active in multiple tumor types
- ... characterized by durable clinical benefit **in a subset of patients**



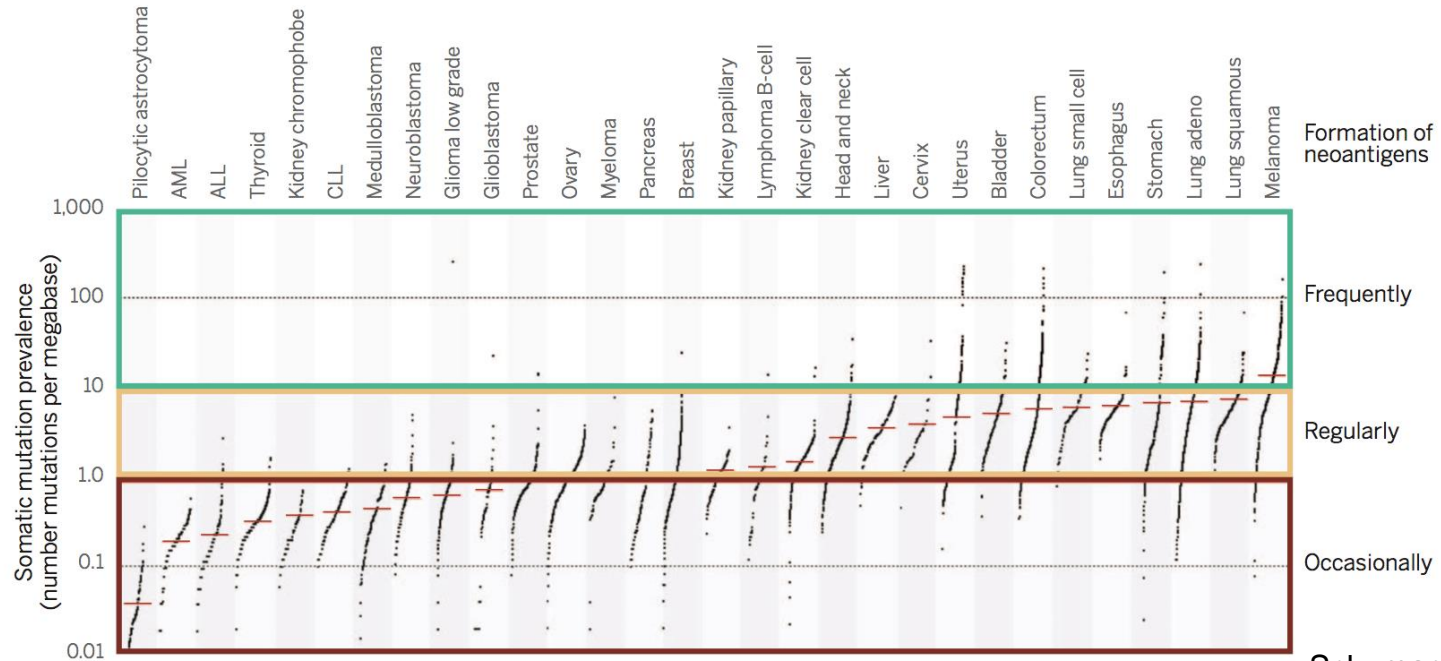
20 - 30%

Urgent need for predictive biomarkers

- PD-L1 expression (tumor cells / immune cells)
- Mutation burden / neoantigen expression
- Individual genes / pathways
- Epigenetic markers

MUTATION BURDEN - PREDICTIVE MARKER OF RESPONSE TO IMMUNOTHERAPIES?

MUTATION BURDEN (MB) IN VARIOUS HUMAN TUMOR ENTITIES

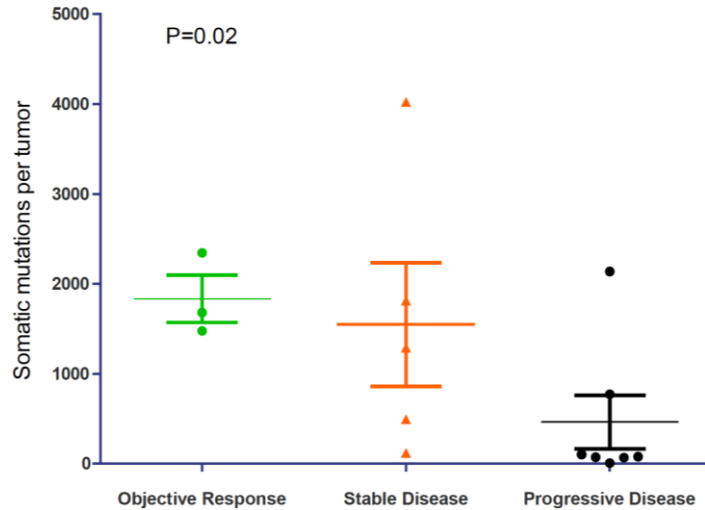


Schumacher et al., 2015

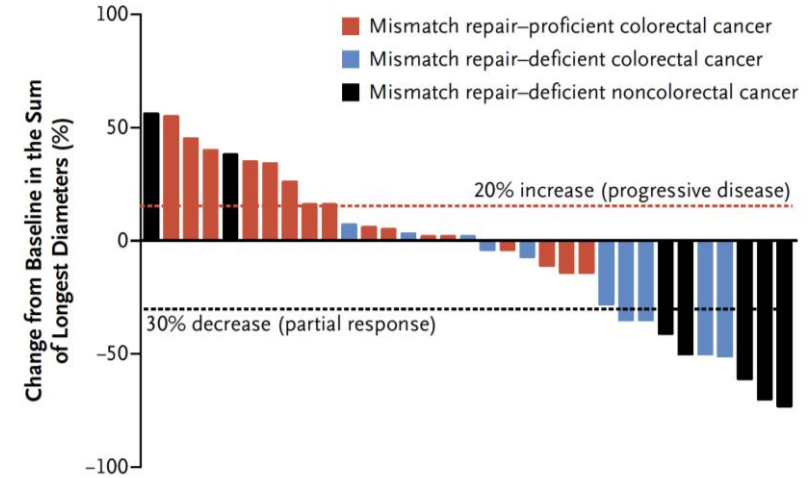
DETECTION OF MB: WHOLE EXOME SEQUENCING



PEMBROLIZUMAB - MISMATCH-REPAIR DEFICIENT TUMORS



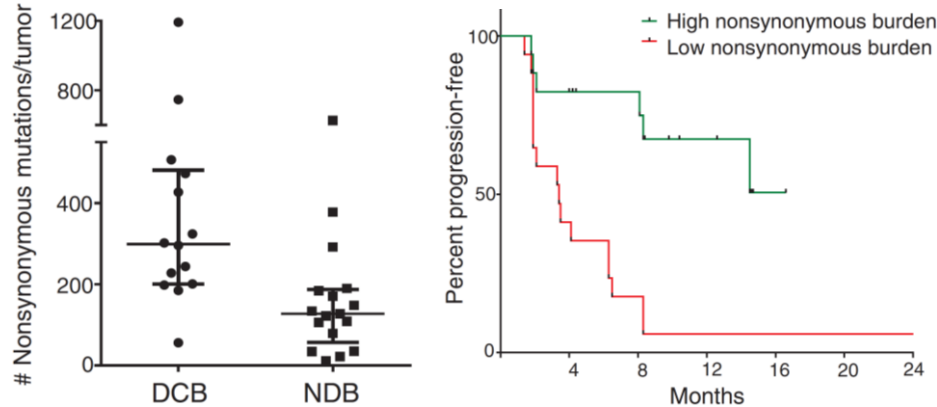
B Radiographic Response



High number of somatic mutations correlates with response to treatment

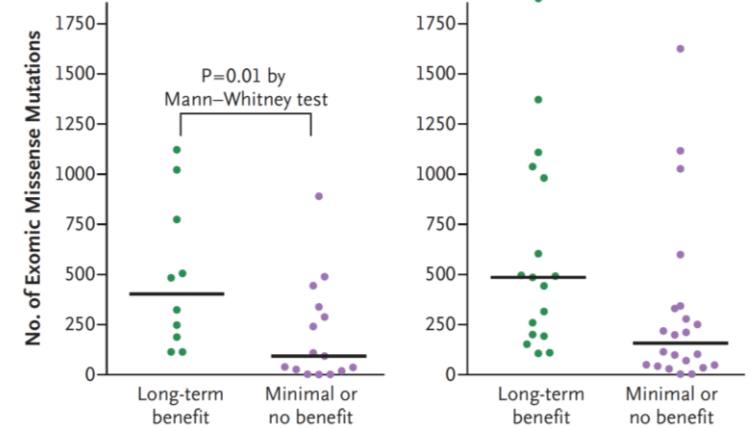
Le et al., 2015

PEMBROLIZUMAB - NSCLC



Rizvi et al., 2015

IPIILIMUMAB - MELANOMA



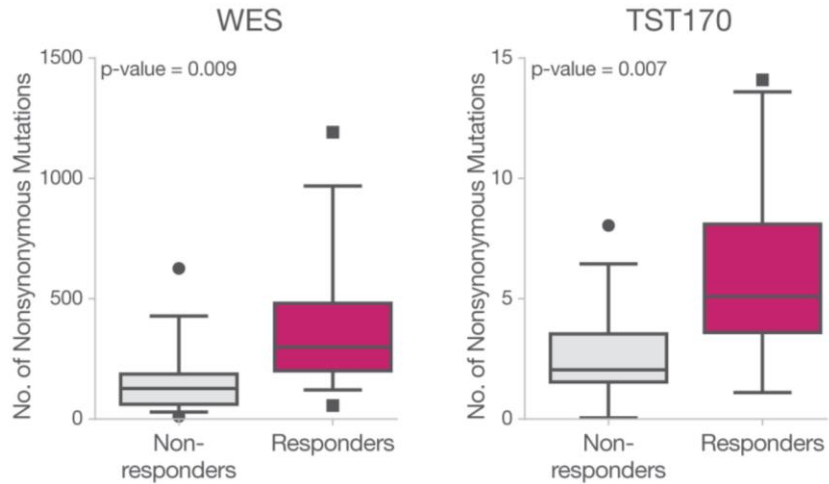
Snyder et al., 2014

High number of somatic mutations correlates with response to treatment

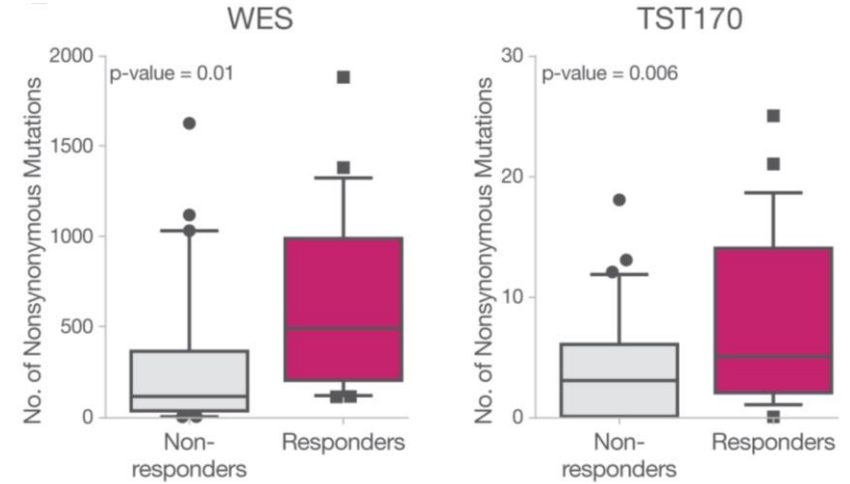
Feasible biomarker in clinical routine??

WHOLE EXOME SEQUENCING VS TARGETED SEQUENCING

Rizvi cohort



Snyder cohort

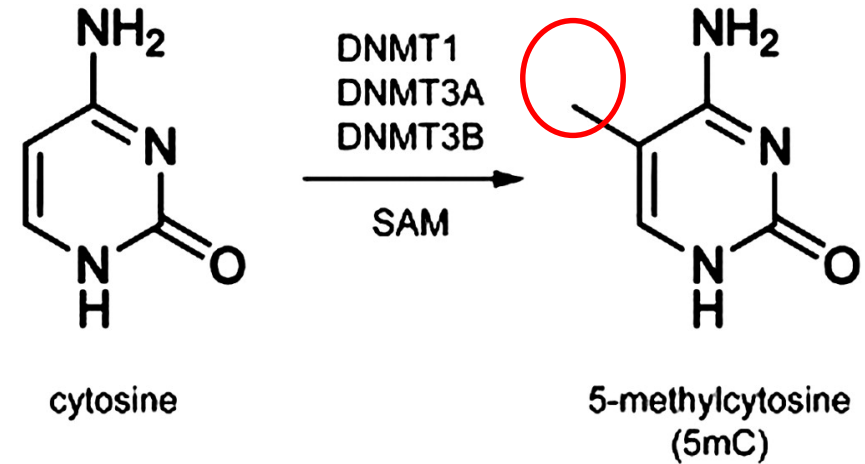


Highly comparable data between WES and Illumina TruSight Tumor 170 panel

DNA METHYLATION - PREDICTIVE MARKER OF RESPONSE TO IMMUNOTHERAPIES?

DNA METHYLATION

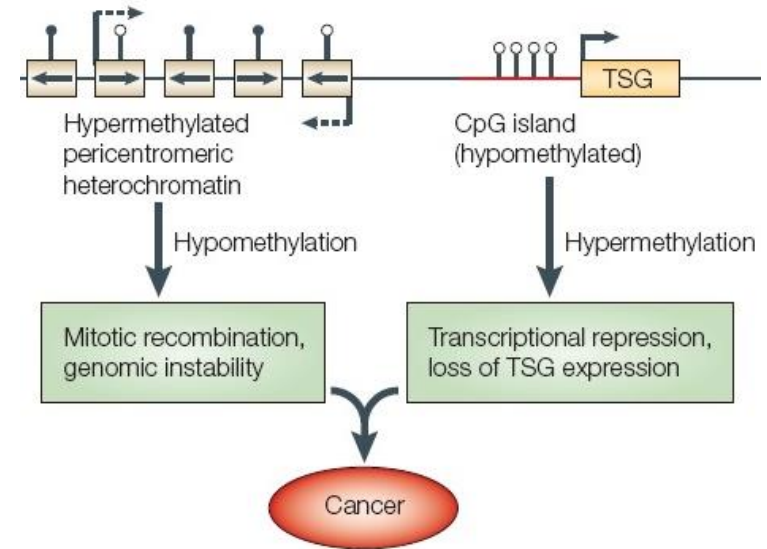
- Covalent addition of $-CH_3$ to carbon 5 of cytosine within CpG dinucleotide
- Reaction catalyzed by DNA methyltransferases (DNMT)
- Co-factor: S-adenosyl-L-methionine (SAM)
- Reversible process



Ku et al., 2011

CPG ISLANDS

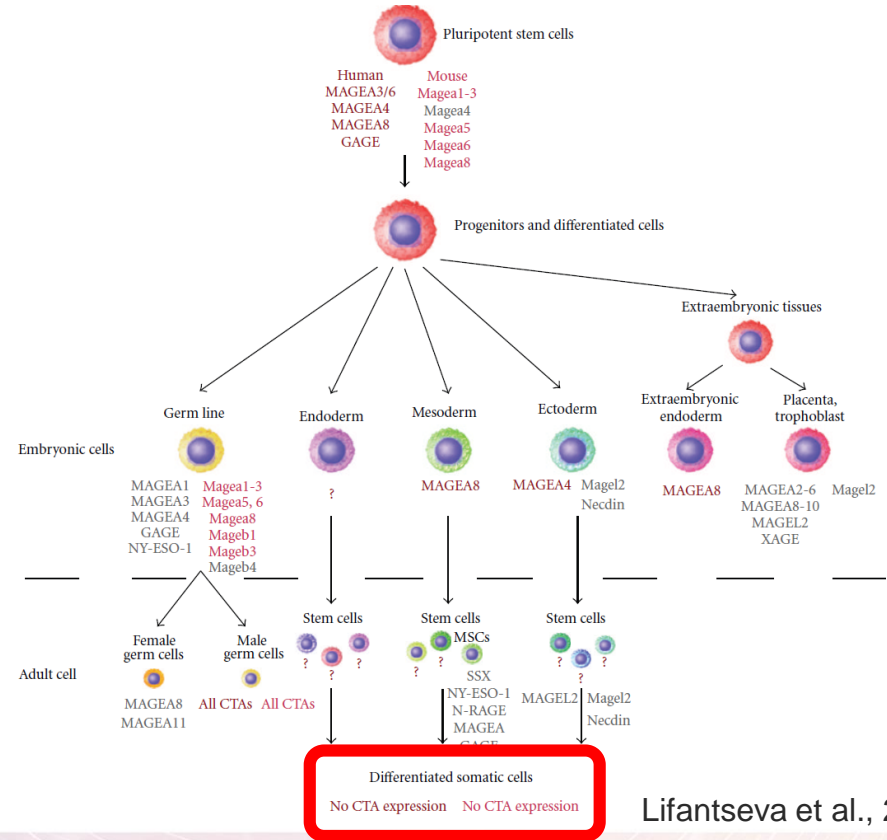
- CpG-rich genomic regions of 0.5-4 kb in length
- Located in promoter region of ~ 60% of mammalian genes
- Usually unmethylated (exceptions: e.g. x-linked, imprinted genes)
- Tissue specific e.g. Cancer Testis Antigens



Nepomuceno et al., 2013

CANCER TESTIS ANTIGENS

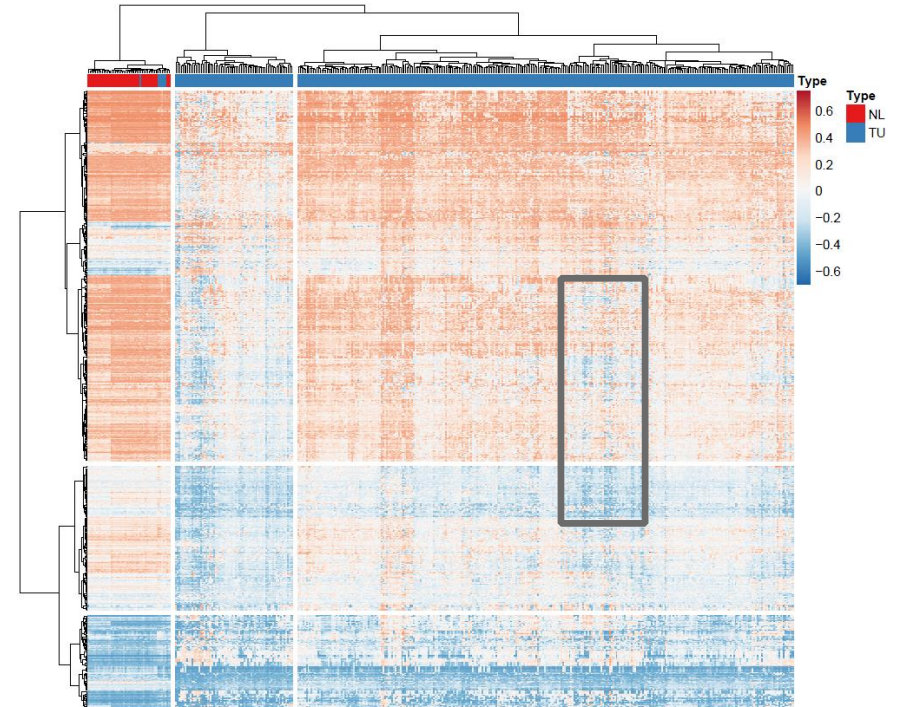
- Large family of testis/placenta specific proteins
- Silenced by methylation in differentiated somatic cells
- Re-expressed various malignancies
- Recognized as non-self structures
- Induce immune response



Lifantseva et al., 2011

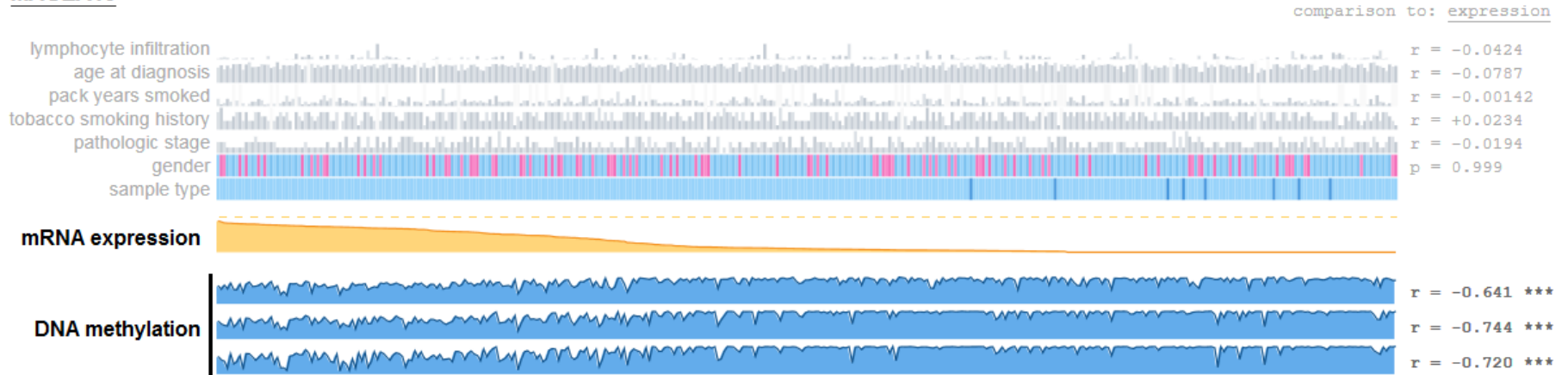
REDUCED CTA METHYLATION IN LUSC

- TCGA data
- Lung squamous cell carcinomas
- 372 primary TUs
- 43 matching NLs
- Infinium HumanMethylation450 BeadChip

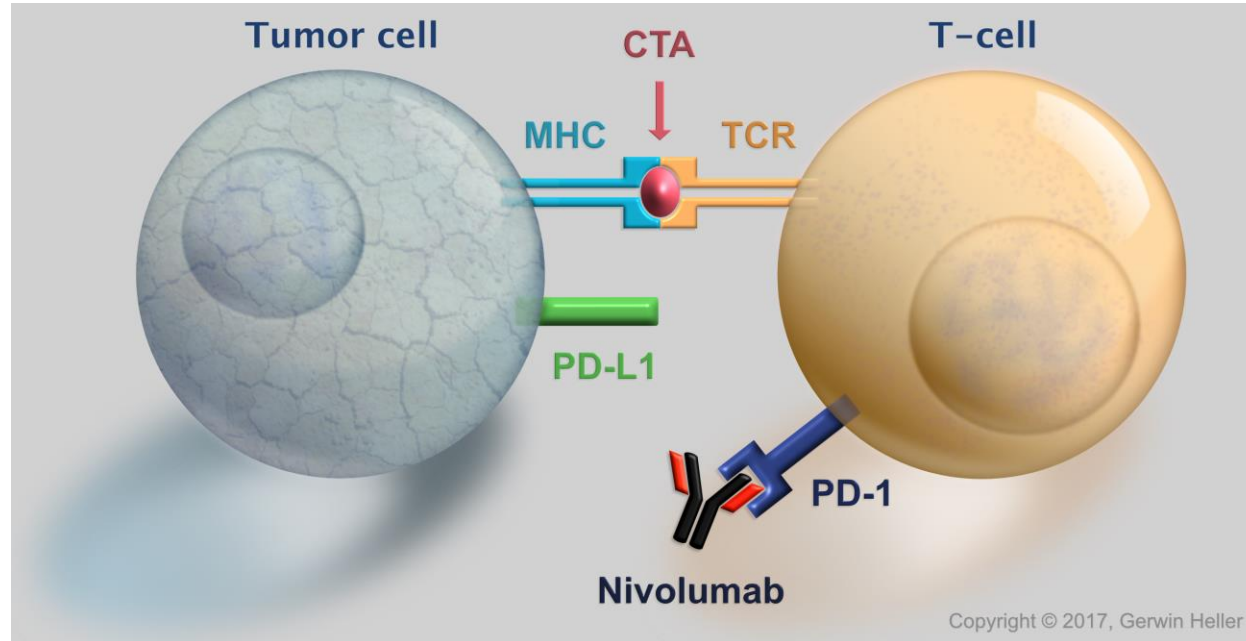


CTA METHYLATION VS. EXPRESSION IN LUSC

MAGEA10



IS REDUCED CTA METHYLATION / INCREASED CTA EXPRESSION A PREDICTIVE MARKER?



THANK YOU VERY MUCH FOR YOUR ATTENTION!!