Translational validation of genetic and gene expression networks determining the phenotypic switch and therapy resistance of tumor cells

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In project 8 of this joint research effort we intend to use comprehensive biosampling combined with 'big data' analyses for uncovering phenotypic switch mechanisms behind therapy resistance. Melanoma resistance to current immune checkpoint inhibition is our main research focus. Utilizing high quality clinical data with survival endpoints and large-scale analyses incorporating exome and transcriptome data, we want to clarify why these advanced therapies fail in a subset of patients. Bio samples are prepared for genetic, epigenetic, and proteomic analyses. In-house, the skin cancer samples are streamed to automated protein staining and high-throughput sequencing of 29 selected melanoma genes. We then integrate comprehensive bioinformatic analyses of our own genetically and transcriptionally profiled samples and of publicly available datasets. Analyses of our in-hose datasets comprise univariate and multivariate survival analyses with overall and progression-free survival as well as best response endpoints. We perform differential gene expression analysis of responders and non-responders of anti-PD-1/PD-L1 treated patients. Beyond in-house data, public datasets provide great opportunities for discovery approaches as well as hypothesis testing when candidate markers exist. Single cell RNAseq data of melanoma tumors for instance tell us about the many different cells that make up a tumor's phenotype, including closely associated cells. Also, TCGA data provide information on gene-associated survival for a variety of cancer entities.

Projekt-related publications (selection):

Izar, Benjamin; Jerby-Arnon, Livnat; Rotem, Asaf; Shah, Parin; Liu, David; Zhang, Gao … **Schadendorf, Dirk**, et al. (2018), "Single-cell RNA-sequencing and-imaging of melanoma ecosystems reveals sources of resistance to immune checkpoint blockade." (2018): 3074-3074.

Horn, Susanne; Leonardelli, Sonia; Sucker, Antje; **Schadendorf, Dirk**; Griewank, Klaus G.; Paschen, Annette (2017), "Tumor CDKN2A-Associated JAK2 Loss and Susceptibility to Immunotherapy Resistance." JNCI: Journal of the National Cancer Institute 110.6 (2017): 677-681.

Sucker A, Zhao F, Pieper N, Heeke C, Maltaner R, Stadtler N, Real B, Bielefeld N, Howe S, Weide B, Gutzmer R, Utikal J, Loquai C, Gogas H, Klein-Hitpass L, Zeschnigk M, Westendorf AM, Trilling M, **Horn S**, Schilling B, **Schadendorf D**, Griewank KG, Paschen A. (2017), Acquired IFNγ resistance impairs anti-tumor immunity and gives rise to T-cell-resistant melanoma lesions. Nat Commun. 31;8:15440.

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Candidate's profile:

- Bachelor's degree in computer sciences or Master's degree in any of the following or equivalent disciplines: bioinformatics, epidemiology, biology, molecular biology
- Experience in statistical analysis of biomedical or clinical data
- Proficiency programming, bioinformatics, and handling of '-omics' datasets
- Strong statistical skills as evidenced by participation in publications or presentations in areas relevant to biomedical analysis
- Experience in Bayesian statistics or machine learning would be an advantage
- Proficiency with working in an unix/linux based server environment
- Excellent communication, presentation, interpersonal skills, both written and spoken

Project tasks & Training:

- Perform statistical programming activities, handling large datasets
- Generate summary tables, data listings, graphs and derived datasets as specified in the statistical analysis plan
- Analyses of DNA and RNA sequencing, proteomics and clinical data
- Survival analyses, testing multi-level data associations
- Create and maintain programming tracking documentation
- Provide statistical programming liaison to other members of the research initiative