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Haas Laboratory

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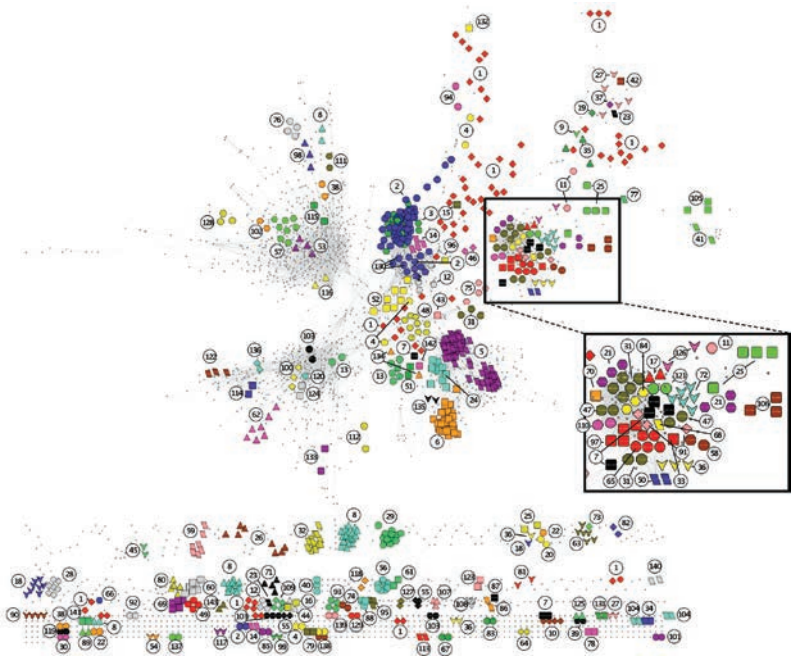
The Haas laboratory uses quantitative mass spectrometry-based proteomics to characterize cancer cells and their vulnerabilities in a comprehensive proteome-wide manner. This is fueled by recent discoveries that have enhanced the depth and throughput of proteomics in quantifying proteins and their post-translational modification. These improvements have put us at a pivotal point in the field of mass spectrometry, where, for the first time, we are able to handle the analysis of the large number of samples that have to be examined to generate the basis for understanding a disease that displays the heterogeneity found in cancer. We are specifically interested in mapping changes in the global landscape of protein-protein interactions - the interactome - that occur in cancer cells, and we have shown that dysregulations in the interactome are enabling the prediction of cancer vulnerabilities. Another focus in the lab is to develop high-throughput plasma proteome mapping technologies to enable early detection of cancer across multiple cancer types in an unbiased manner. We believe that our proteomics technologies have the potential to become a powerful tool in basic and clinical cancer research and may be used to diagnose cancer, predict its susceptibility, and monitor its progression.

Cancer is based on dynamic changes of the genome that ultimately translate into an altered proteome, optimized for uncontrolled cell growth and division. In addition, many pathways, initially causing cancer further promote the propagation of altered genetic information, accelerating the adaption of cancer cells to new environments. This dynamic process becomes even more complex if taking into account the dynamic state of the cellular proteome that is regulated by protein synthesis and degradation, posttranslational modifications, protein localization, and the interaction of proteins with other proteins as well as with different classes of biomolecules. While the “cancer genome” can now be easily accessed due to advances in DNA sequencing technology, the information contained in the “cancer proteome” has remained largely untapped due to technical challenges in quantifying the large number of proteins expressed in mammalian cells. Yet, the proteome holds enormous potential to improve our understanding of the basic principles underlying cancer to revolutionize the early diagnosis of the disease and to improve patient care. Up to date, virtually all targeted therapeutics in cancer treatment are targeting proteins. Understanding how these drugs alter the proteome and the interactome – the global map of protein-protein interactions – has the potential to help us refine our approaches to drug design.

The core technology used in our research group is high-throughput quantitative proteomics enabled through multiplexed mass spectrometry. This technology allows us to map the proteome of a cancer cell line or tumor tissue at high throughput. Analyzing the proteome maps across a panel of cancer cell lines, we recently made the observation that the concentration of proteins in known complexes is accurately correlated across all analyzed cell lines. We showed that protein co-regulation analysis allows the genome-wide mapping



A Map of Protein-Protein Interactions Identified Using the IMAHP Technology Based on Protein Concentration Co-Regulation across Cancer Cell Lines.

of protein-protein interactions with an accuracy ten-times larger than when using co-expression analysis based on RNAseq data. We further found that deviations from co-regulation of two interacting proteins in specific cancer cell lines reflect perturbed cellular circuitry, and it remarkably predicts sensitization to therapeutics targeting regulatory modules in the associated pathway. We have termed this approach to fast, in-depth characterization of protein-protein interaction landscapes interactome dysregulation (DysReg) mapping. This novel method enables an interactome-wide mapping of protein-protein interaction dysregulation and inferred cancer vulnerabilities of any cancer sample based on a proteome map that is acquired at high throughput.

Our goals are to apply these technologies to (i) identify novel cancer vulnerabilities that direct new treatment strategies, to (ii) map cancer vulnerability dynamics, such as those occurring in the development of therapy resistance, to identify novel targets that enable to overcome the treatment resistance, and to (iii) use our technology in a clinical setting for mapping tumor vulnerabilities to inform treatment strategies in a patient-specific manner.

We also recently identified the E3 ligase UBR4 as a key regulator in adjusting the concentration level of interacting proteins – the molecular mechanism enabling our interactome mapping – and we have shown that this role presents UBR4 as a target for treating aneuploid cancer.

Another goal of our group is to develop a novel high-throughput proteomics platform including an artificial intelligence (AI)-powered mass spectrometry data acquisition method to enable unbiased deep proteome mapping of plasma proteomes to enable early detection of cancer. Unbiased screening of more than 2000 plasma proteins (in 10 minutes per sample) rather than mapping a small of number of biomarkers will allow to enable a multi-biomarker assay for multiple cancer types that is constantly improved through adaptation to the detection accuracy.

Selected Publications:

Kathiresan M, Animesh S, Morris R, Kreuzer J, Patra KC, Shi L, Merritt J, Yin X, Benes CH, Bardeesy N, **Haas W**. Protein interactome homeostasis through an N-recognin E3 ligase is a vulnerability in aneuploid cancer. *bioRxiv*. 2023 May 4: 2023.05.04.539299.

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McAlister GC, Nusinow DP, Jedrychowski MP, Wühr M, Huttlin EL, Erickson BK, Rad R, **Haas W**, Gygi SP. MultiNotch MS3 enables accurate, sensitive, and multiplexed detection of differential expression across cancer cell line proteomes. *Anal Chem*. 2014; 86, 7150-7158.

Ting L, Rad R, Gygi SP*, **Haas W***. MS3 eliminates ratio distortion in isobaric multiplexed quantitative proteomics, *Nat. Methods*. 2011; 8, 937-940.

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