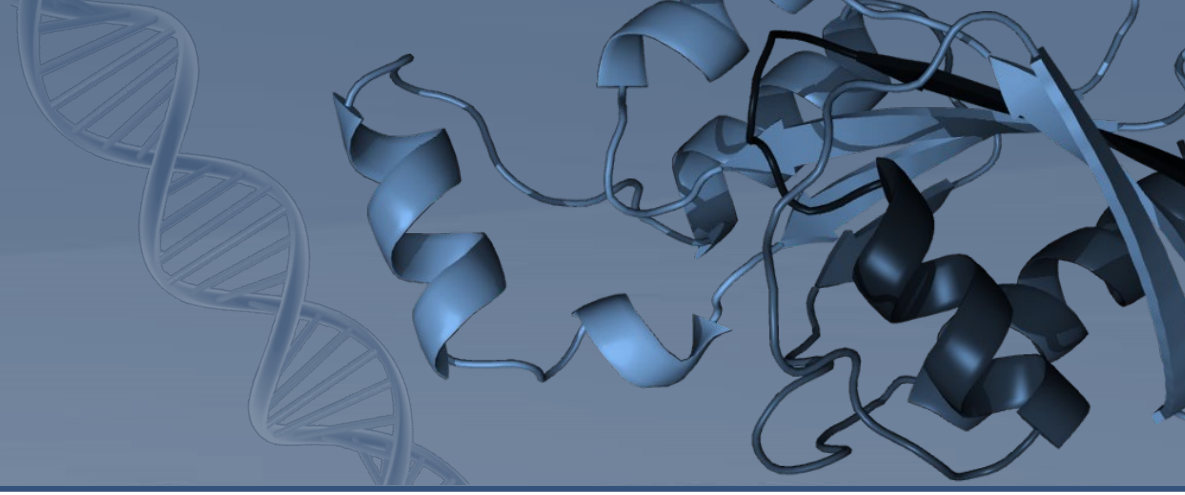
OFFICE OF CANCER CLINICAL PROTEOMICS RESEARCH



Deep Integrated Proteogenomic Characterization of Renal Cell Carcinoma

David J. Clark, PhD

TCIA Webinar

2.4.20

NIH NATIONAL CANCER INSTITUTE

ccRCC Proteogenomic Characterization Team

JHU

Dr. Daniel Chan
Dr. Hui Zhang
Dr. Zhen Zhang
Dr. Lori Sokoll
Dr. David Clark
Dr. Jianbo Pan
Dr. Yingwei Hu
Dr. Tung-Shing Lih
Dr. Shiyong Ma
Dr. Lijun Chen
Michael Schnaubelt
Minghui Ao
Dr. Kyung-Cho Cho
Dr. Qing Kay Li
Dr. Phillip Pierorazio
Dr. Christian P. Pavlovich
Dr. Jiang Qian

NCI

Dr. Henry Rodriguez
Dr. Mehdi Mesri
Dr. Emily Boja
Dr. Tara Hiltke
Dr. Chris R. Kinsinger
Dr. Mathangi Thiagarajan
Dr. Ana Robles
Dr. Christopher Ricketts
Dr. W. Marston Linehan

CPTAC ccRCC Working Group

Dr. A. Ari Hakimi
Dr. Gabriel Brominski
Dr. Andrzej Antczak
Dr. Tatiana Omelchenko
Dr. Jan Lubinski
Dr. Maciej Wiznerowicz

Renal Cell Carcinoma Statistics

Estimated New Cases

Males			Females		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**	**All Sites**	**878,980**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**	**All Sites**	**286,010**	**100%**

Cancer Statistics, 2018

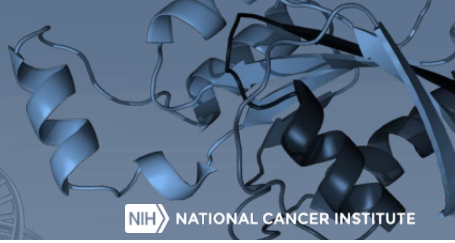
65,000 new renal cases annually

Predominant histology is ccRCC (75% of all renal cases)

30% of patient present with advanced disease at diagnosis

Surgical resection remains the only effective treatment for localized disease

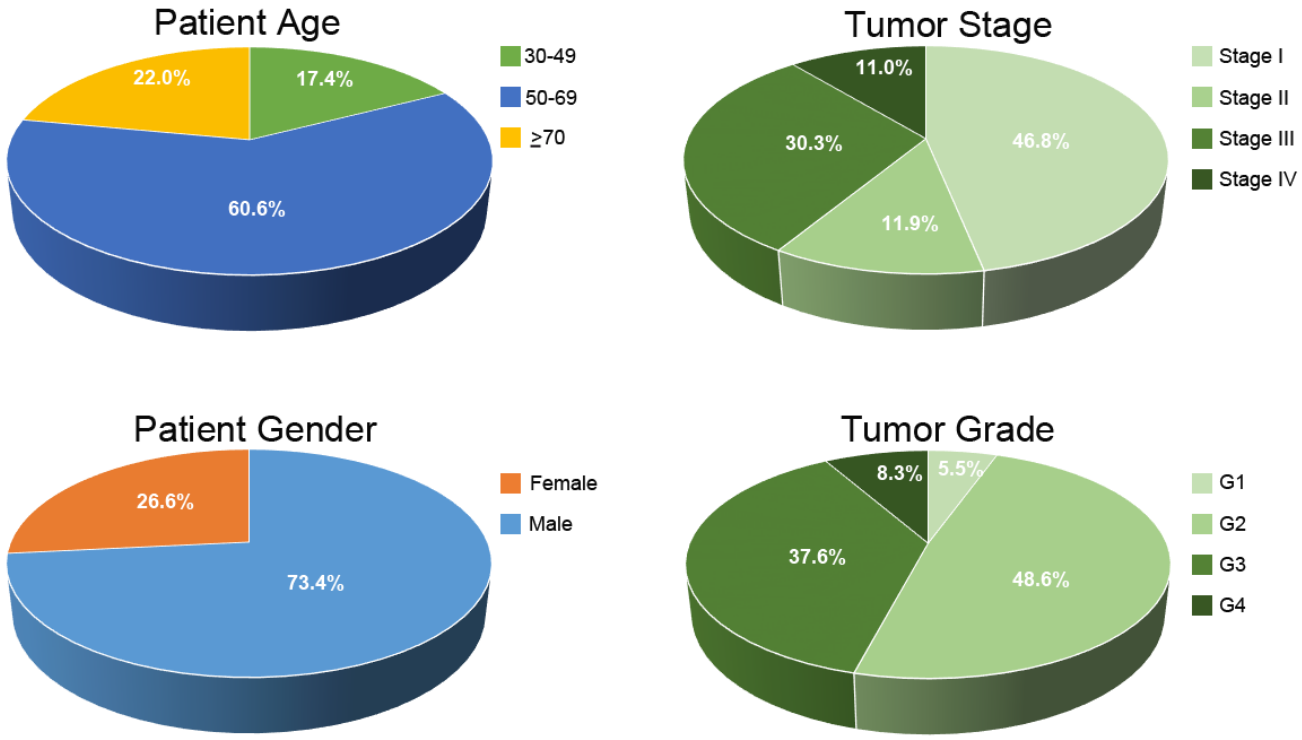
Goals of ccRCC Proteogenomic Characterization



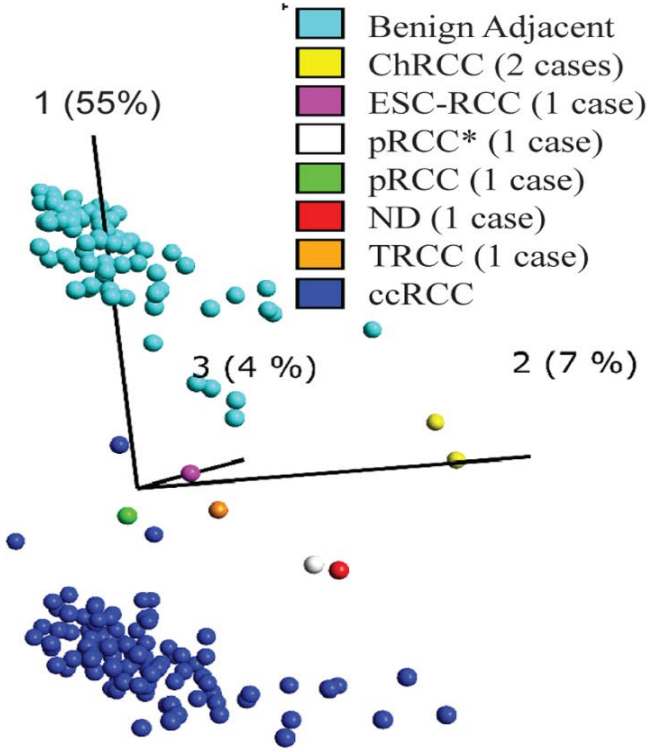
- Comprehensive molecular characterization of ccRCC
- Link genomic alterations to the functional mechanisms of ccRCC pathobiology.
- Delineate novel insights that are only captured utilizing integrated data analysis.

Comprehensive proteogenomic characterization of ccRCC

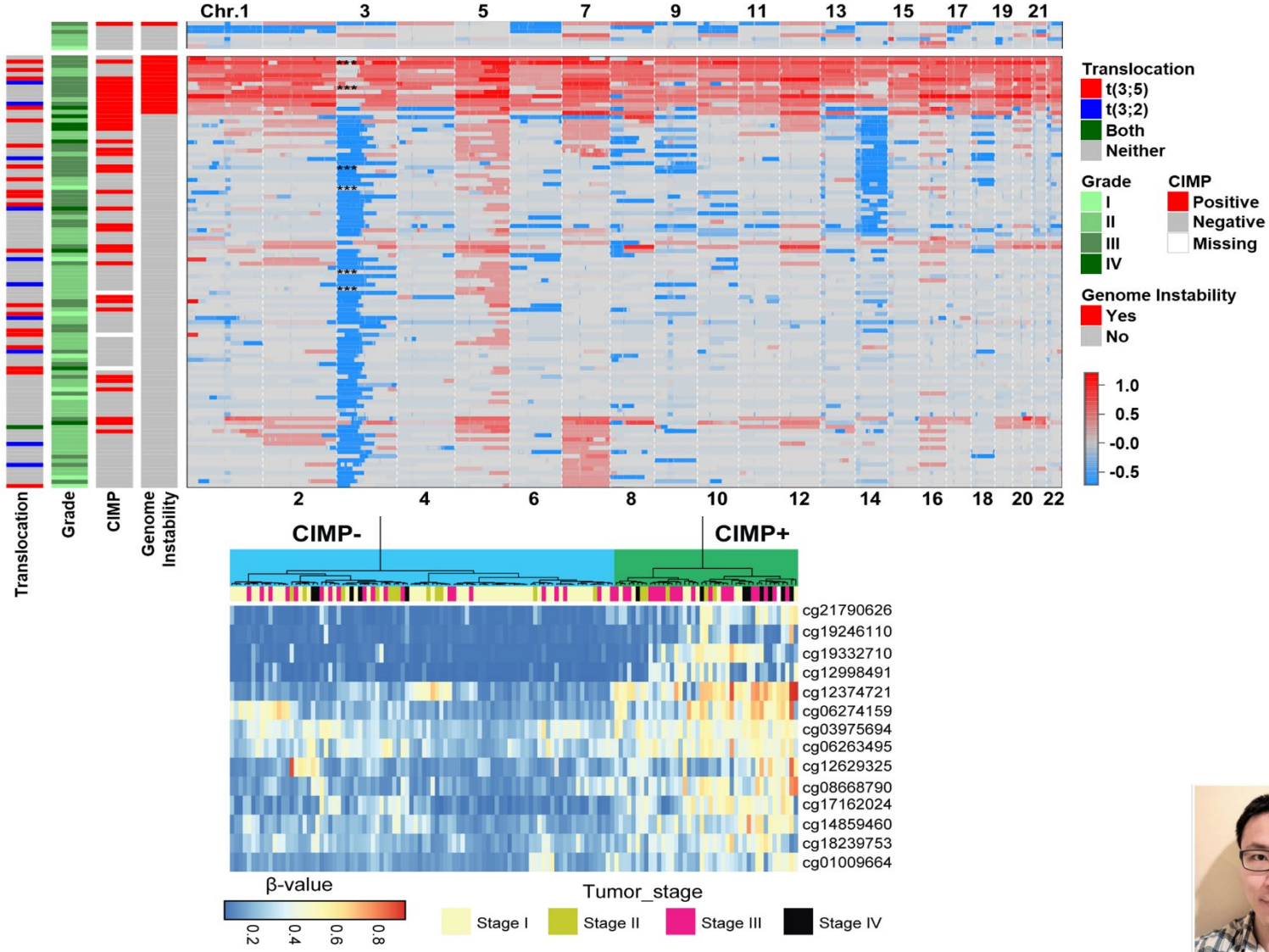
110 treatment-naive renal carcinoma and 84 NAT samples

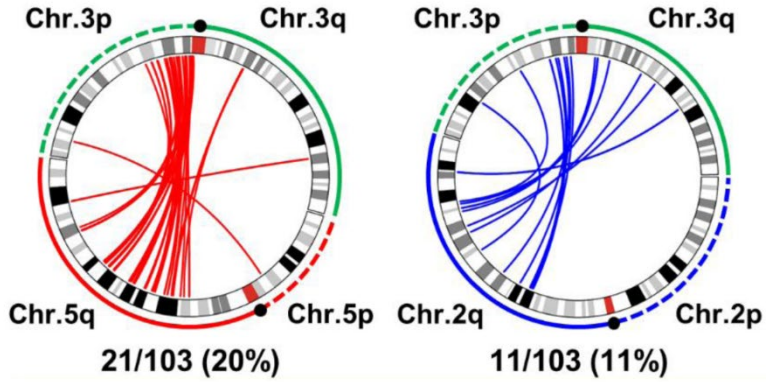


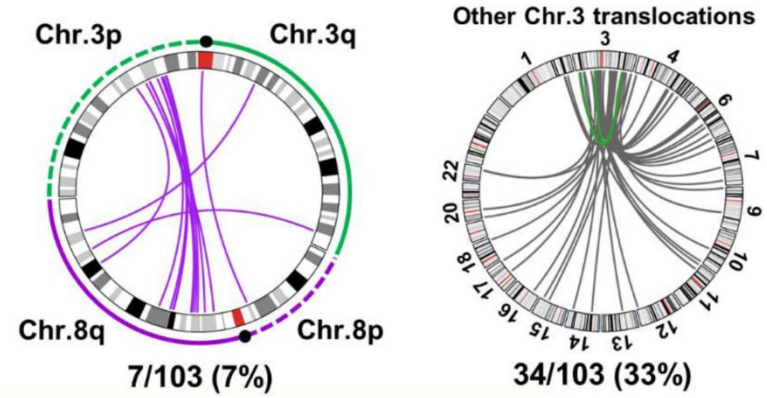
Transcriptomic signature of ccRCC



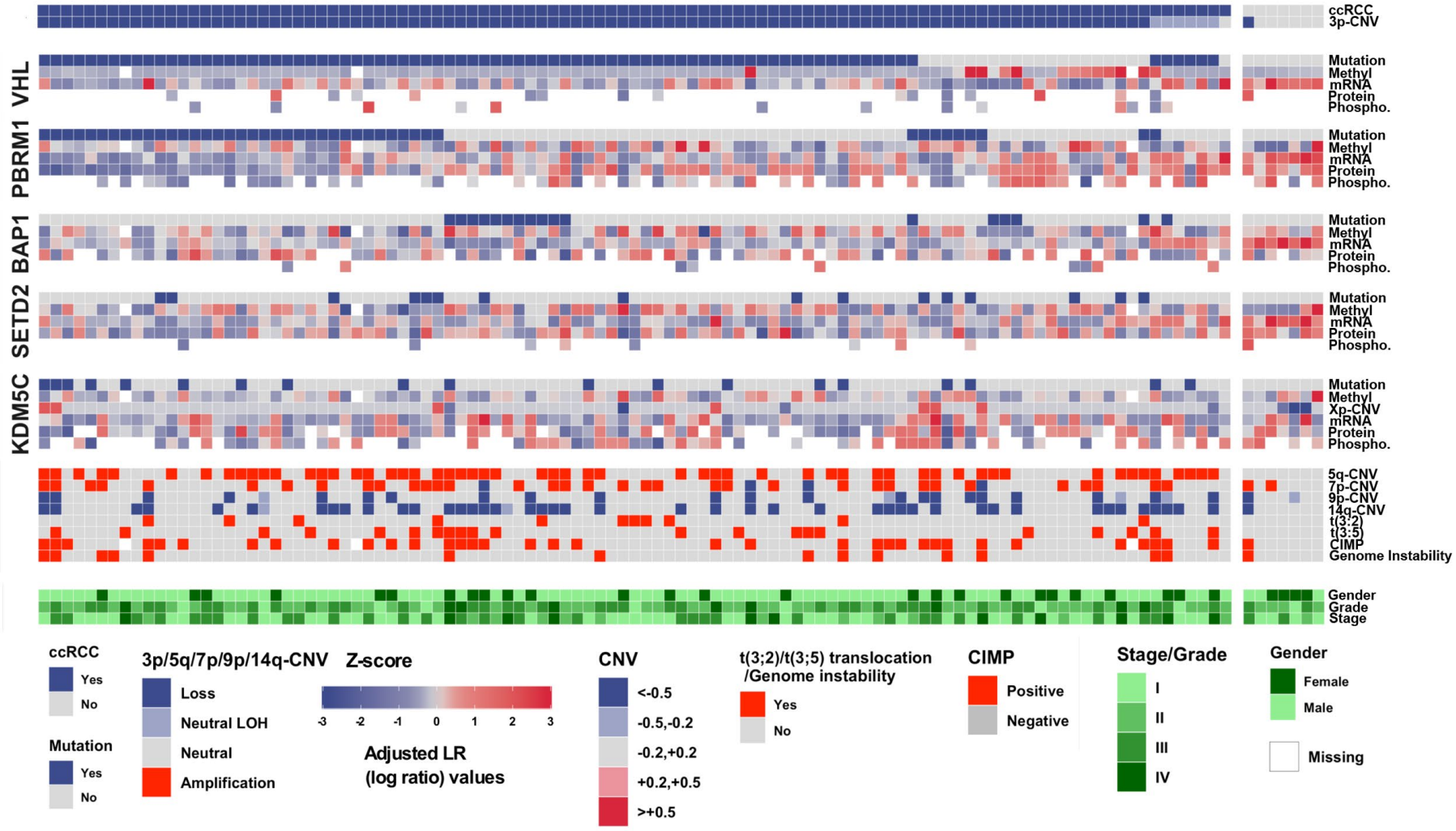
Genomic alteration analysis revealed 3p loss as a hallmark of ccRCC





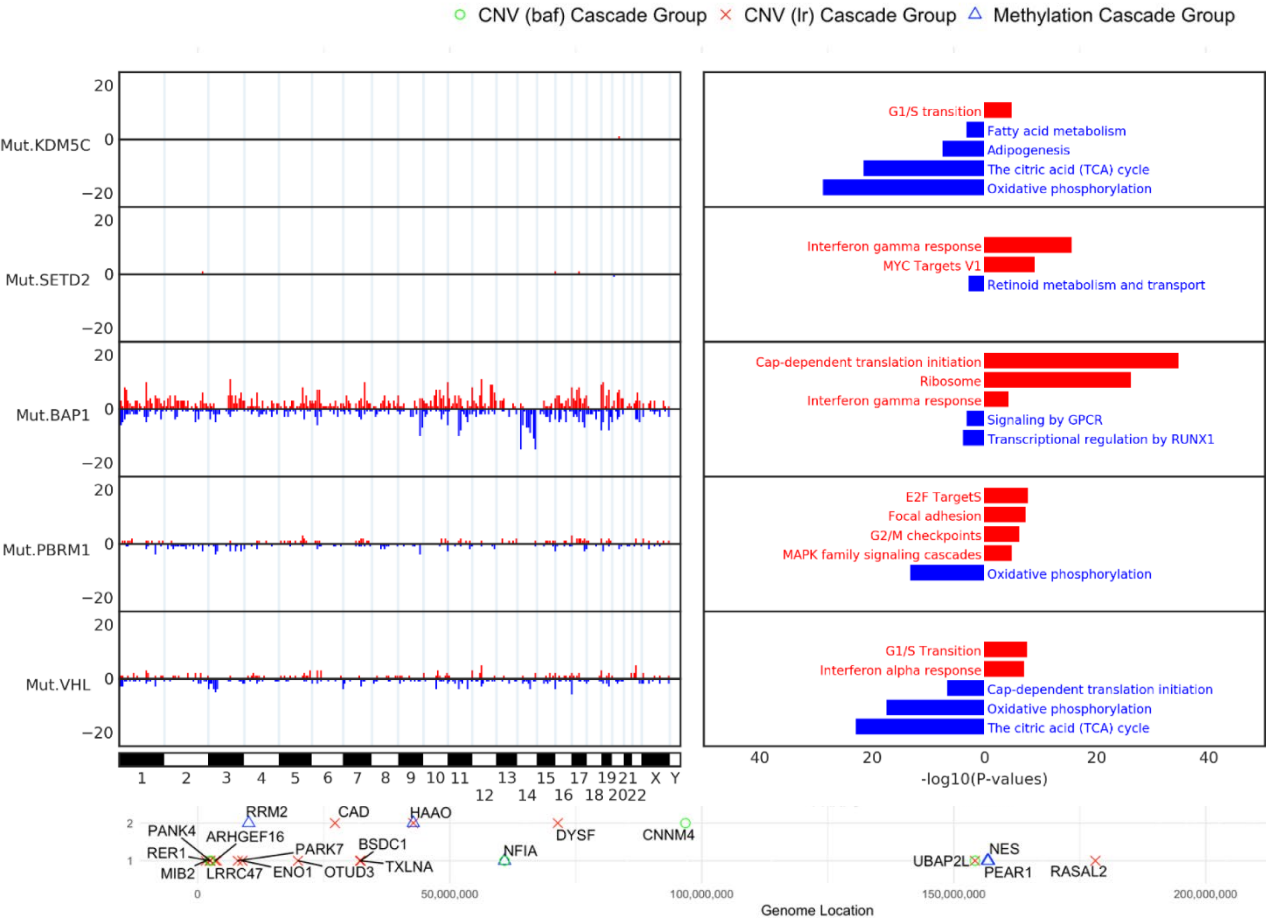


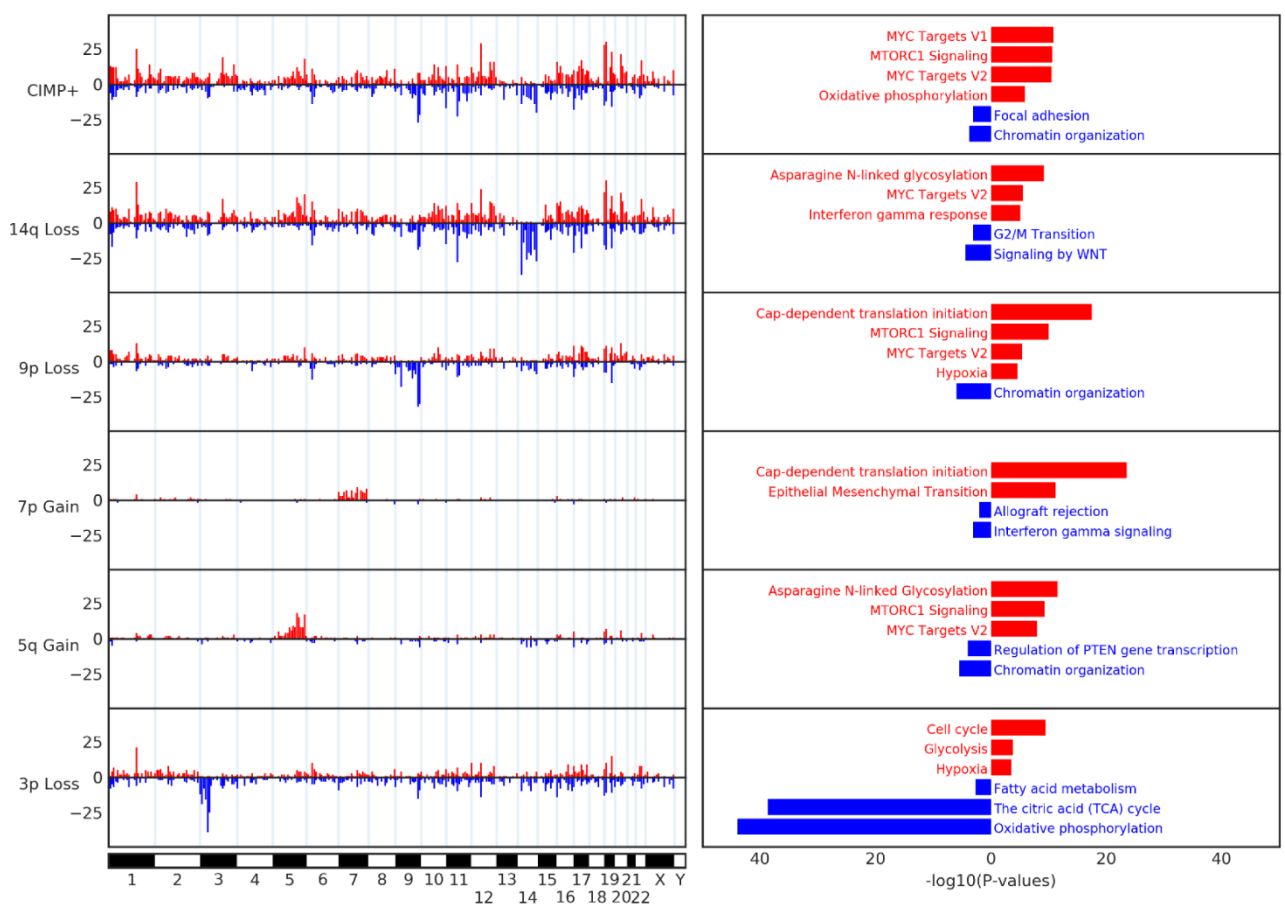
3p gene dysregulation impacts mRNA and protein levels

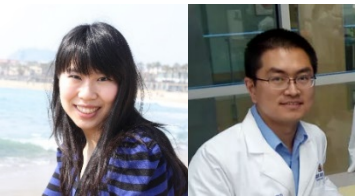


Interactive Software Tool: http://ccrcc.cptac-data-view.org

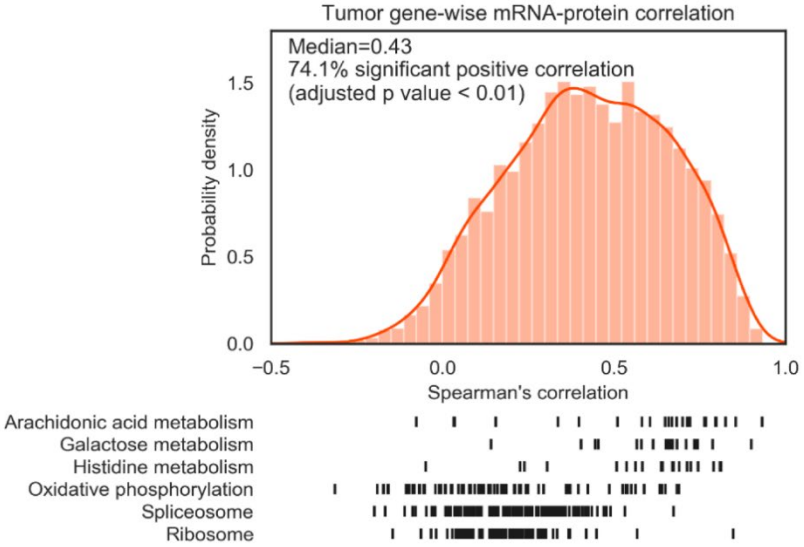
Protein-level *cis* and *trans* effect of CNV and epigenomic alterations

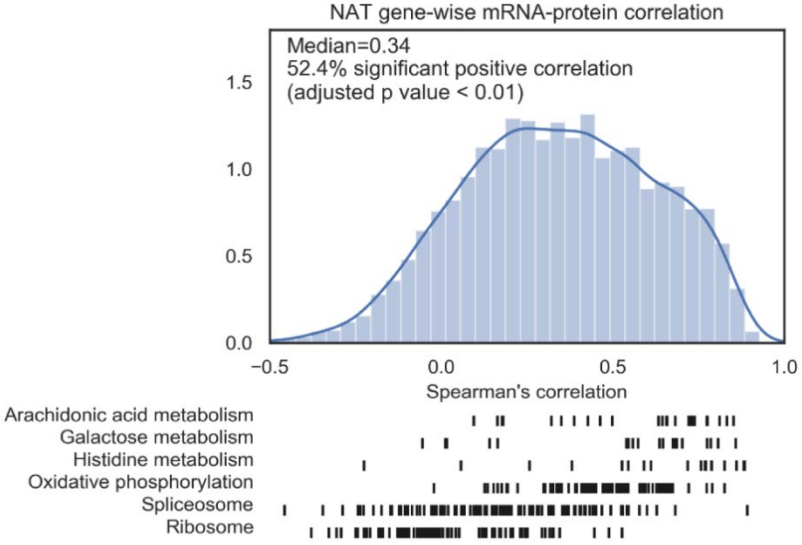




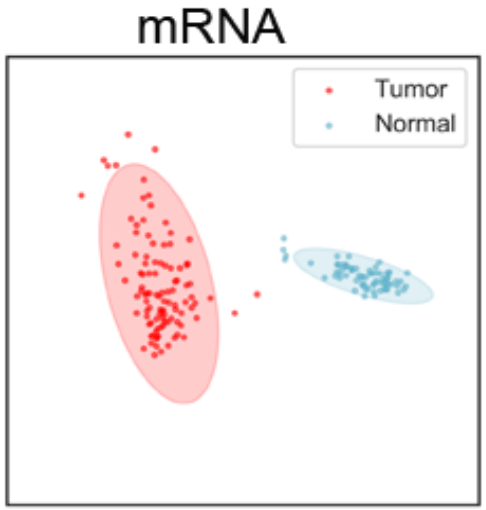


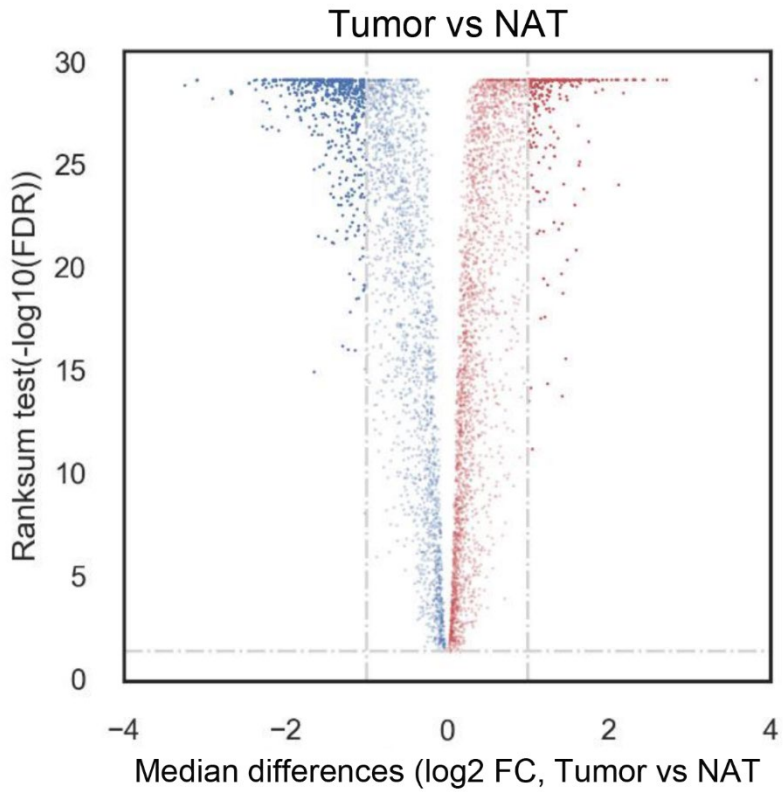
mRNA-protein correlation reveals uncoupling of protein translation machinery in tumors

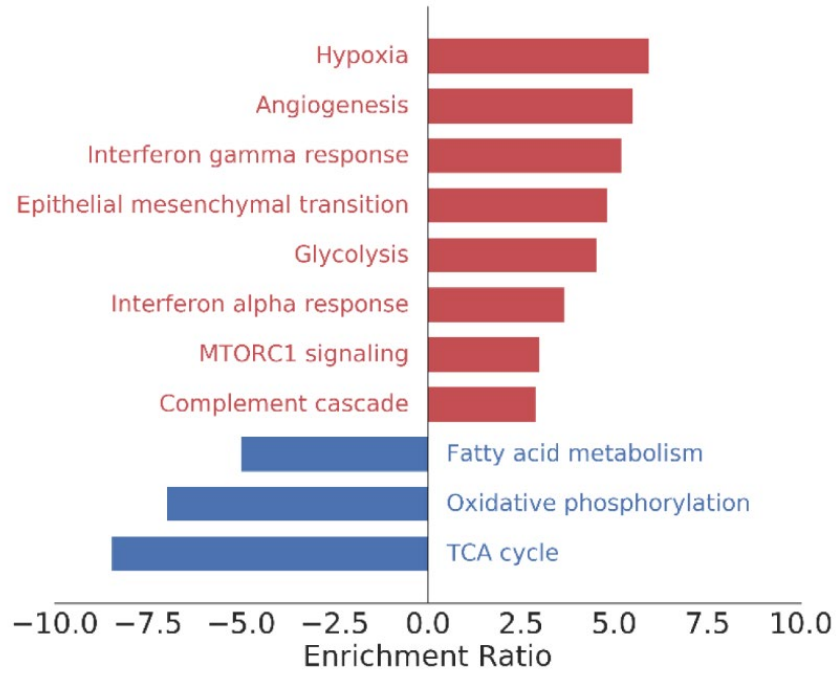


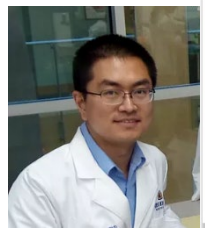


Differential proteomic analysis shows up-regulation of hypoxic-driven pathways in tumors

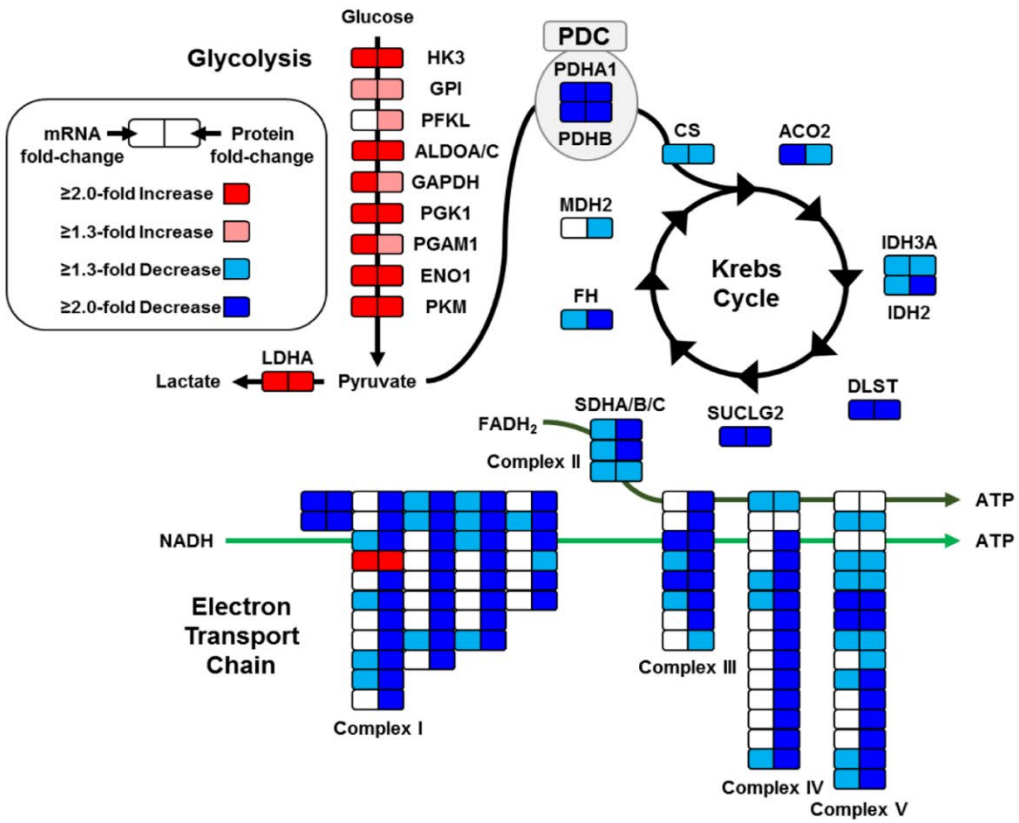


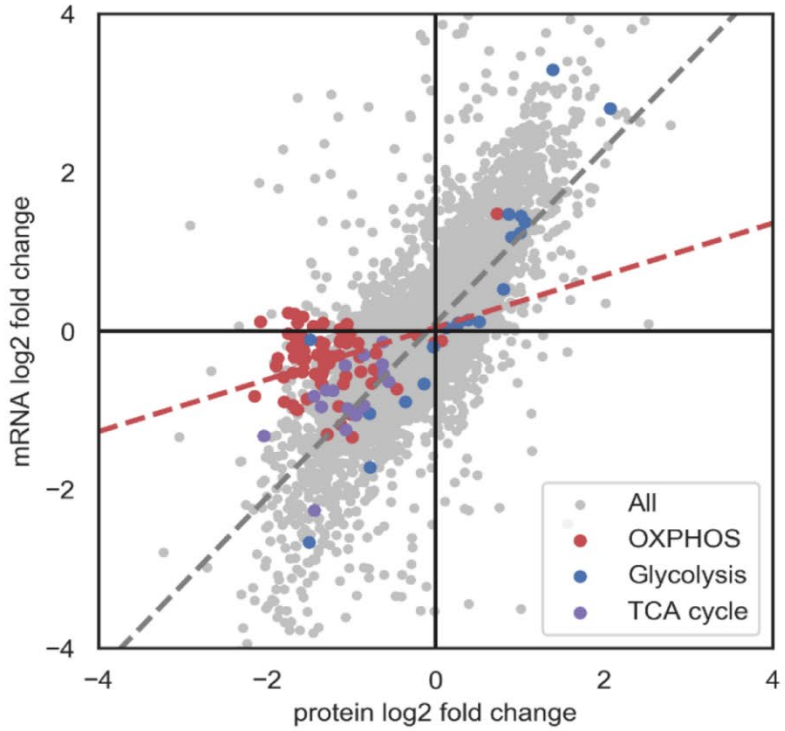




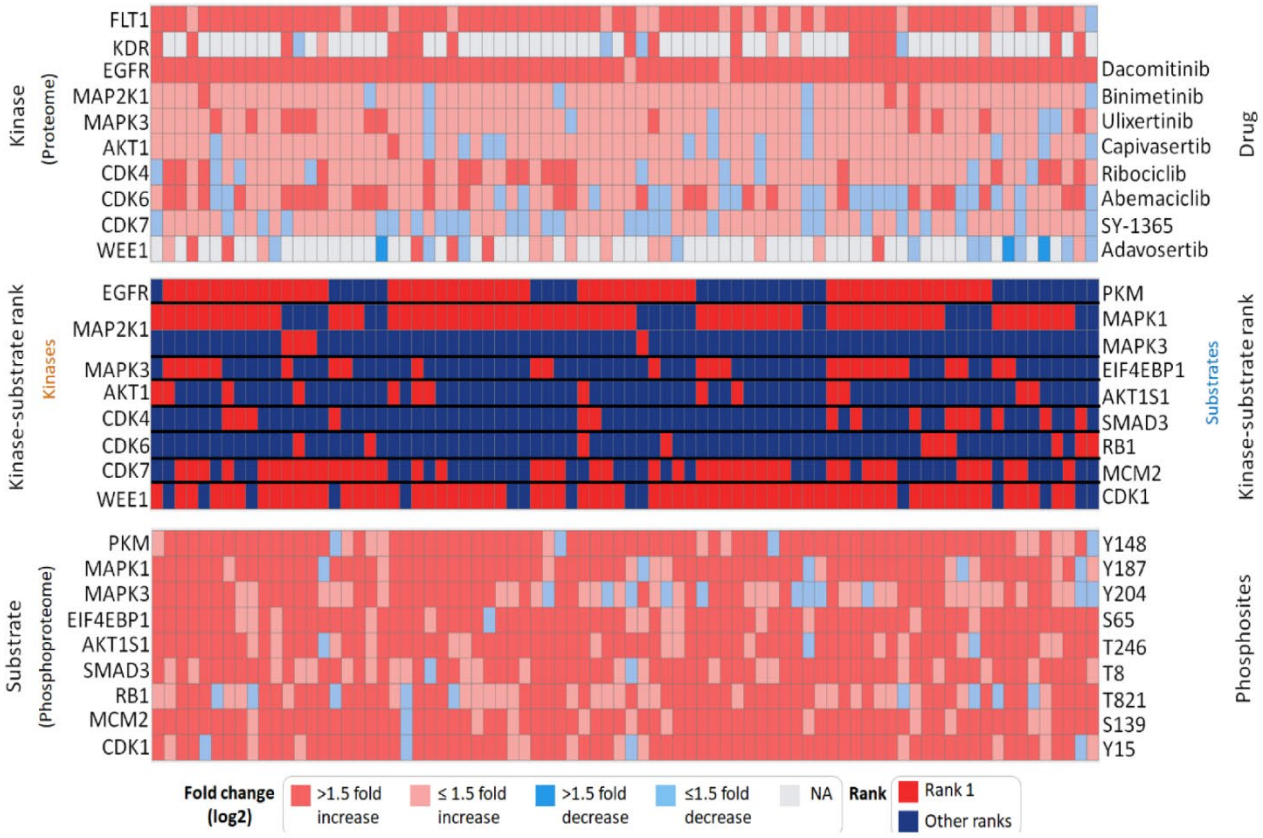


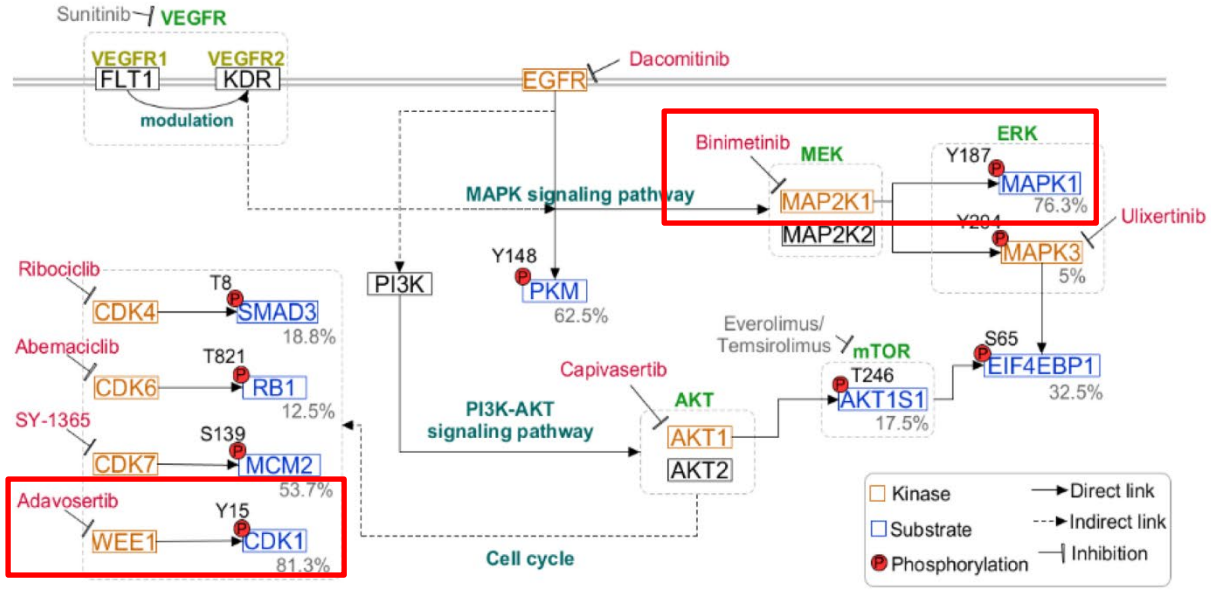
Canonical Warburg effect only captured at the protein level in ccRCC



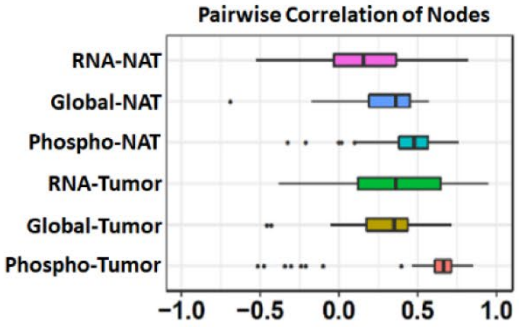


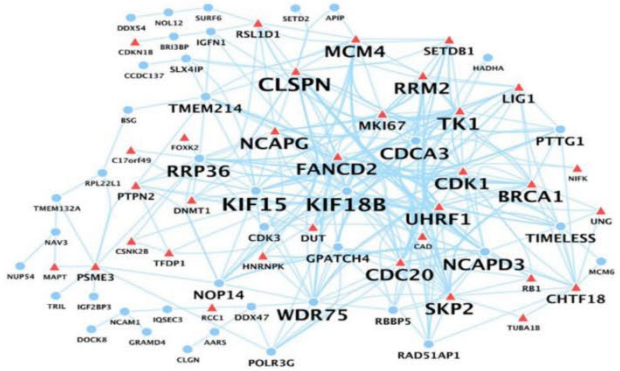
Phosphoproteomics identifies phospho-substrate targets for kinase inhibition in ccRCC

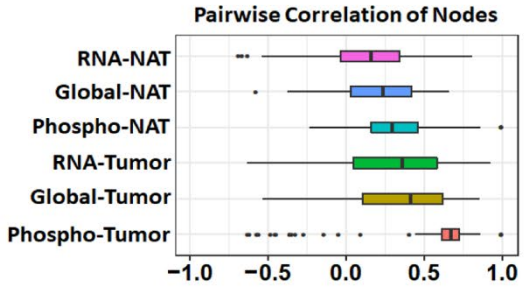


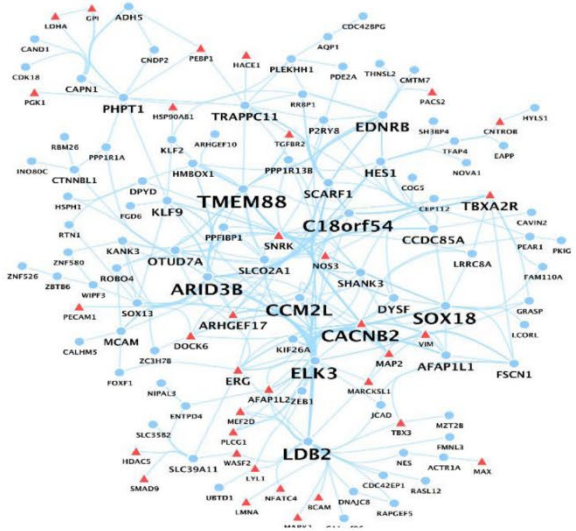


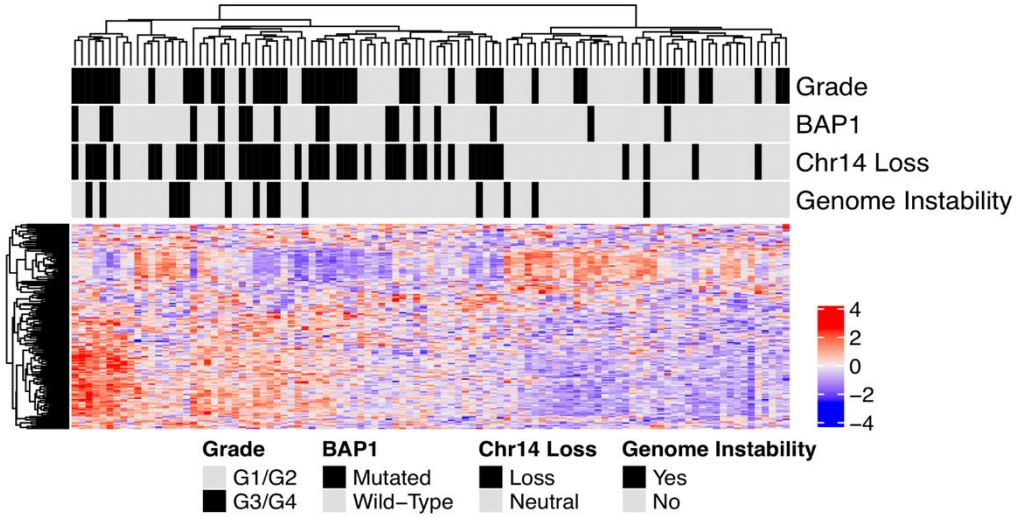
Phosphopeptide analysis identifies co-expression networks in ccRCC

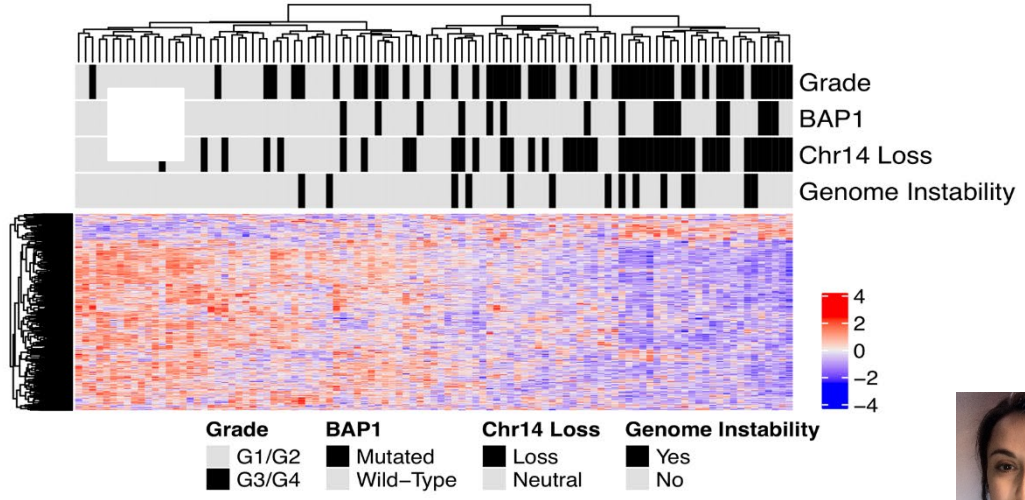






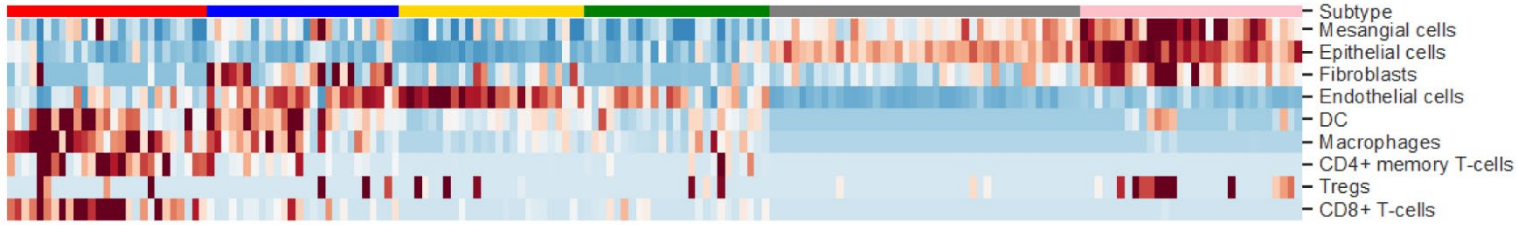


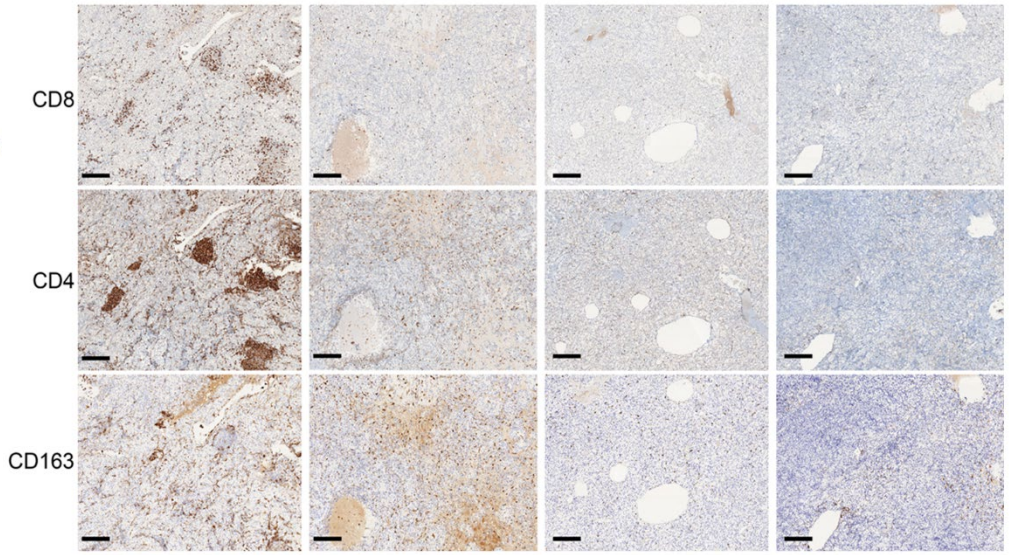


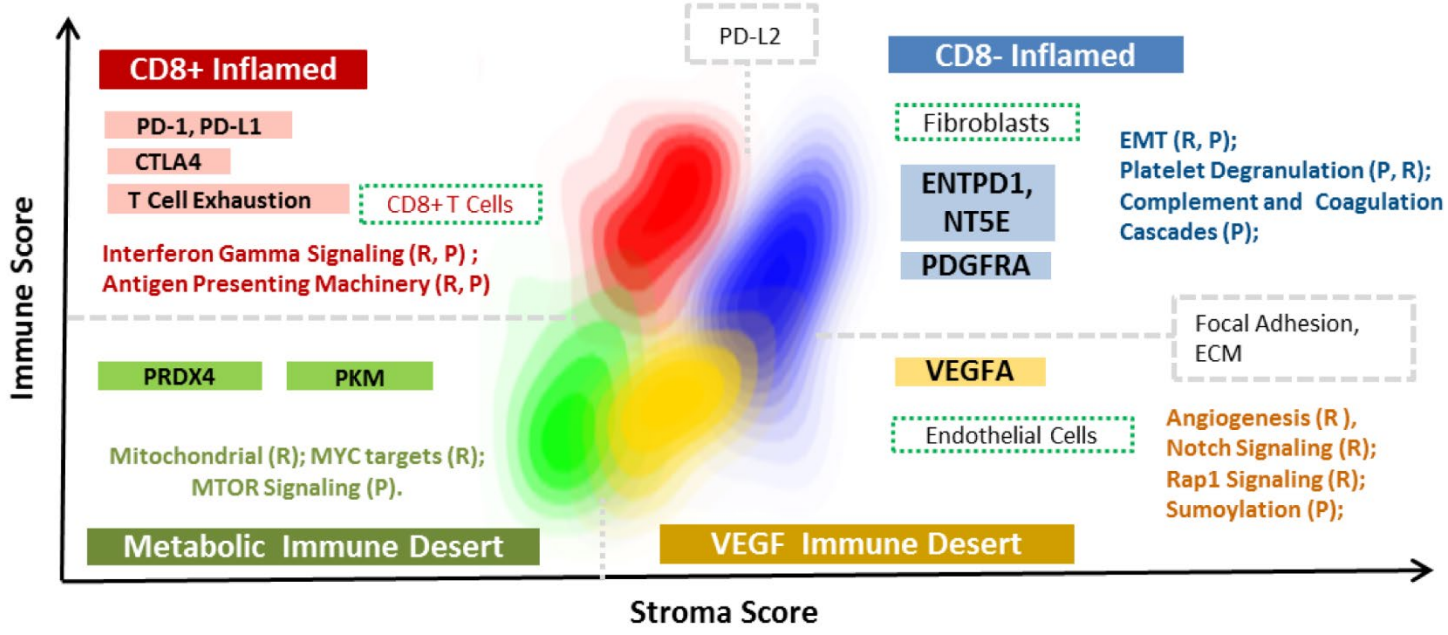


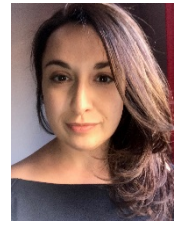
Interactive Software Tool: http://ccrcc.cptac-network-view.org/

TME analysis identifies four subtypes of immune infiltration in ccRCC

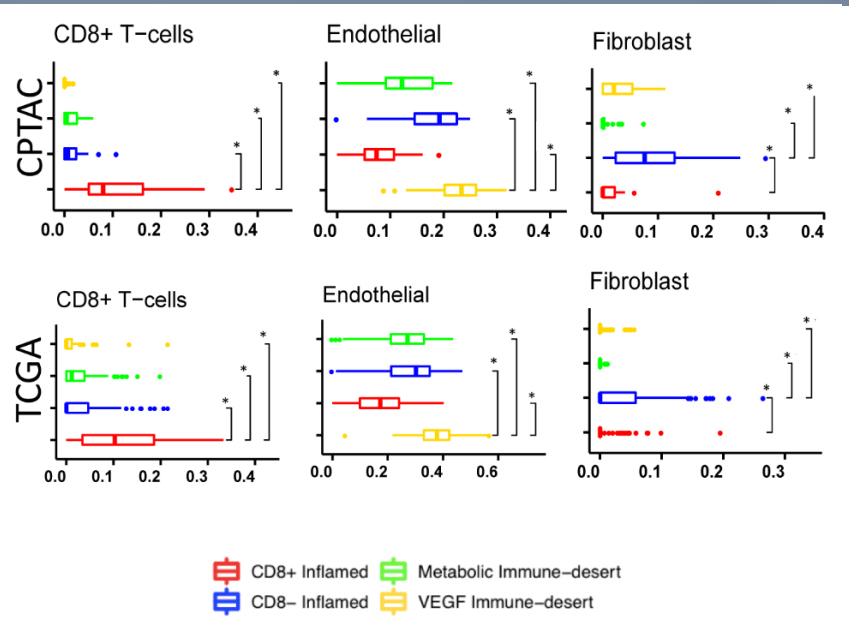


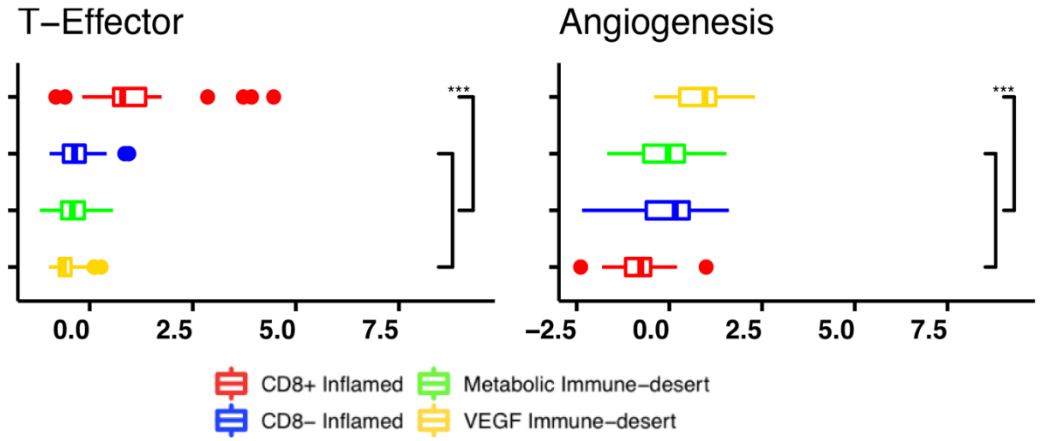






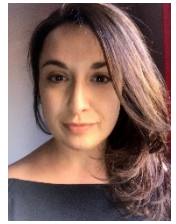
Subtypes correlated to predicted survival and therapeutic response



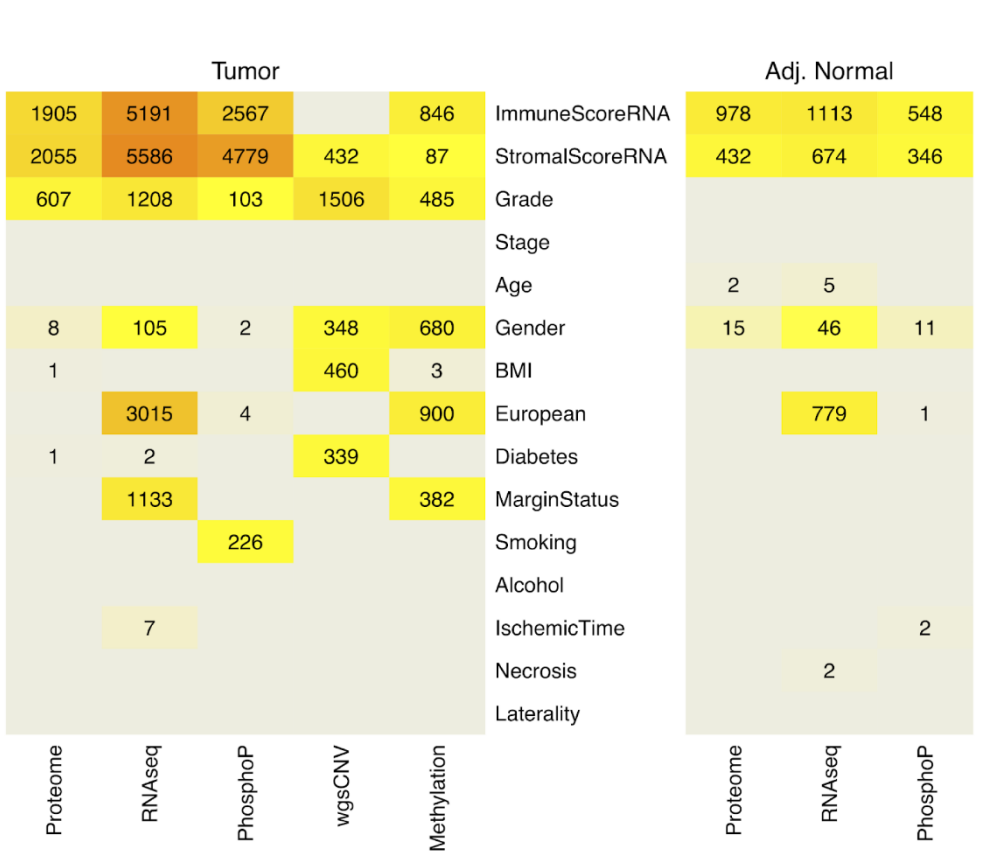


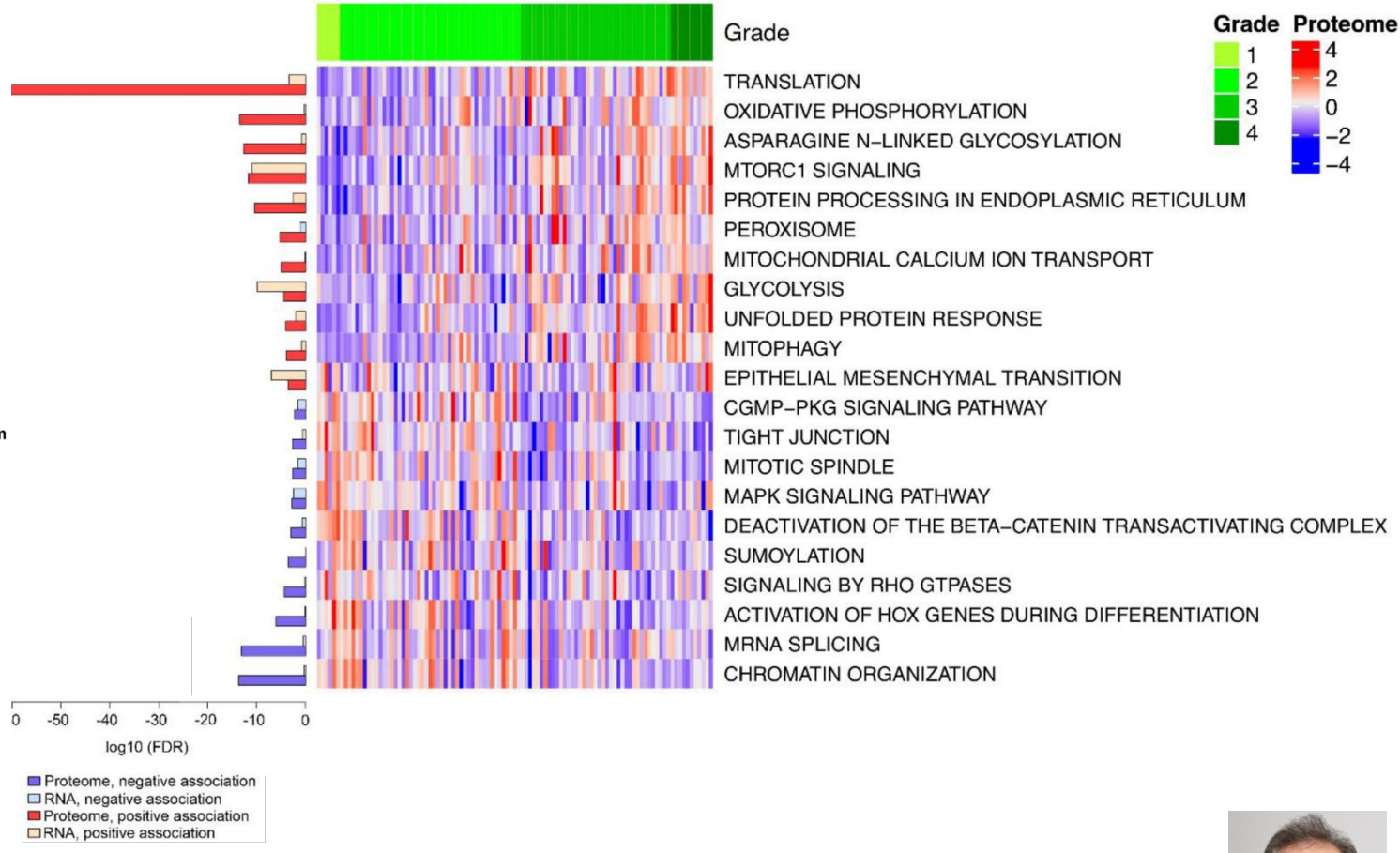
Gene signatures based on McDermott et al., *Nat. Med.* (2018)

TCGA Network, *Nature* (2013)

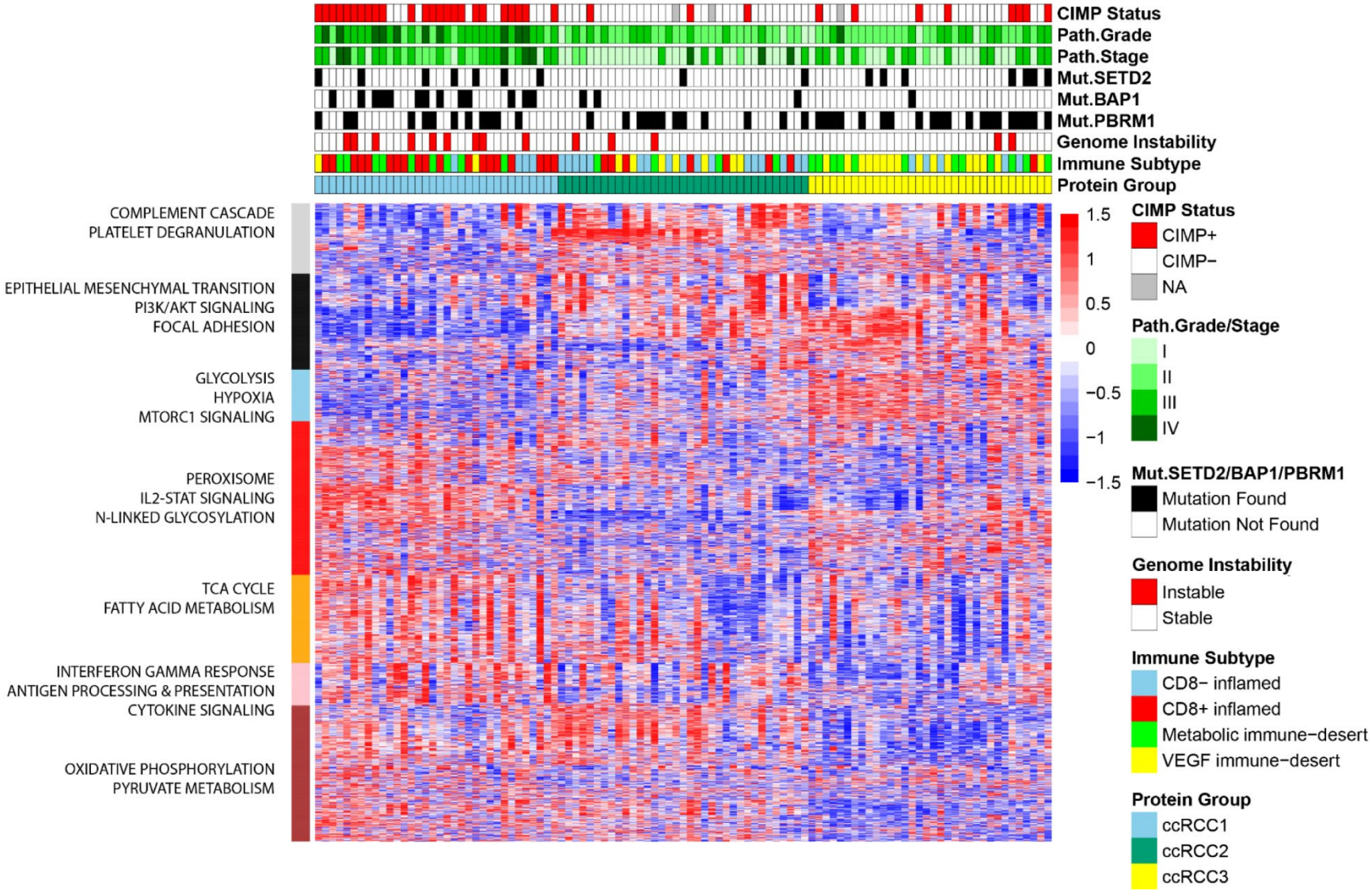


Differential protein expression between low- and high-grade tumors





Inter-tumor heterogeneity of ccRCC captured by proteomic analysis



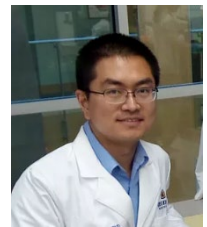
ccRCC1:

- CIMP+ status
- higher grade
- BAP1 mutation
- genome instability

ccRCC1 – CD8+ Inflamed

ccRCC2 – CD8- Inflamed

ccRCC3 – VEGF Immune Desert



Summary

- Most comprehensive genomic, proteomic and phosphoproteomic characterization of ccRCC to date.
- 3p loss is a hallmark of ccRCC; chromosomal translocation may be a major mechanism of 3p loss
- Warburg Effect is only captured at the protein level
- Phosphoproteomic analysis revealed up-regulation of ERK/MAPK signaling pathway and G2-M cell cycle stalling in the majority of ccRCC tumors
- Deconvolution of TME signatures delineated four subtypes of ccRCC defined by proteomic and transcriptomic pathways.

Future Directions

- Confirm global proteomic and phosphoproteomic signatures in an independent cohort.
  - Use orthogonal methodologies
- Evaluate the functional consequence of select kinase inhibitors in RCC cell models
- Assess the degree of intratumor heterogeneity at the protein level

Thanks

CPTAC Resources

RAW Data and Expression Matrices:
https://portal.gdc.cancer.gov/

https://cptac-data-portal.georgetown.edu/cptac/s/S044

https://cptac-data-portal.georgetown.edu/cptac/s/S050

Bioinformatician-friendly data download:
https://github.com/PayneLab/cptac

Interactive Software Tools:
http://ccrcc.cptac-data-view.org

http://ccrcc.cptac-network-view.org/