

Investigating the Tumor Immune Microenvironment using Cancer Genomics and Computational Pathology

Vésteinn Þórsson, Institute for Systems Biology
Frontiers of Predictive Oncology and Computing II; Oct 17, 2017; NYC

INSTITUTE FOR SYSTEMS BIOLOGY

Located in South Lake Union, Seattle

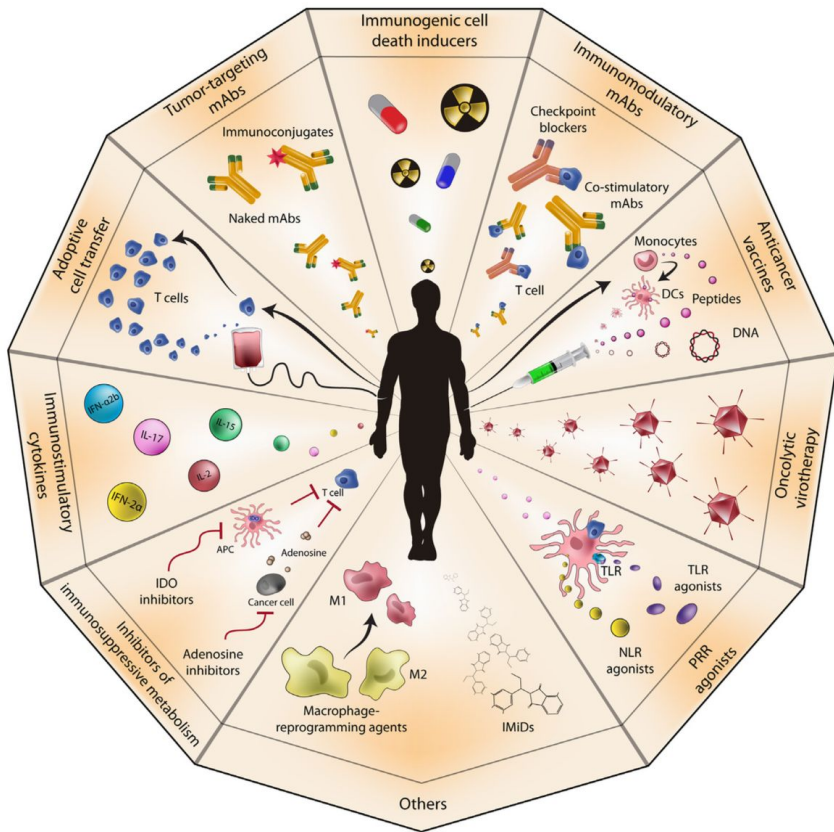
LEARN MORE



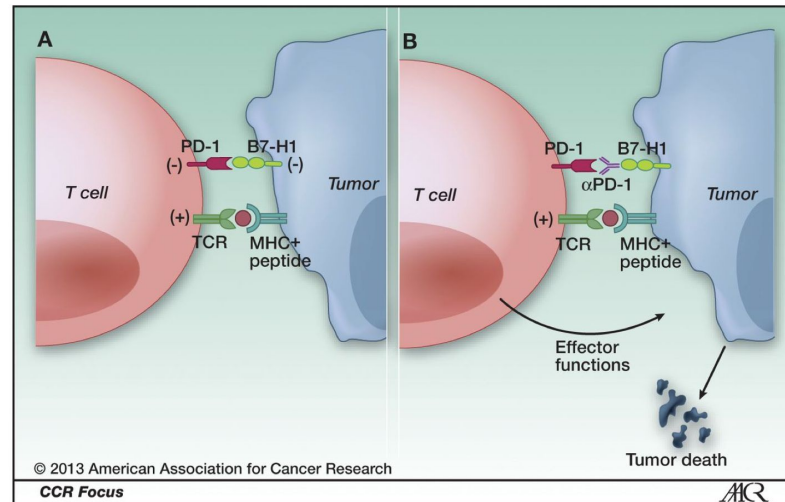
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Cancer Immunotherapy



Checkpoint Inhibition



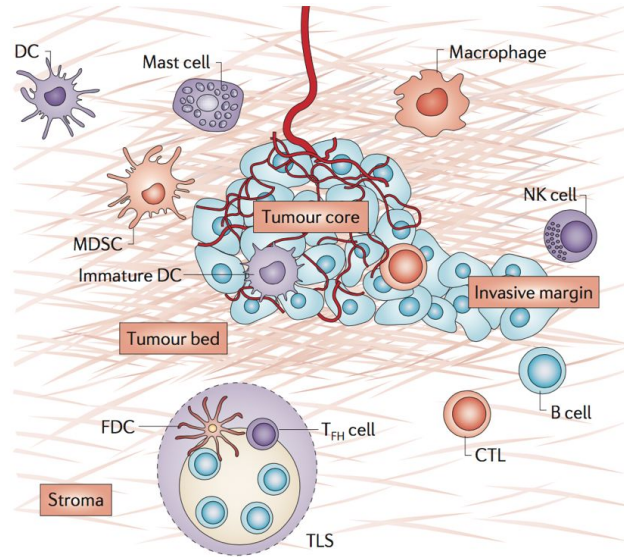
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CCR Focus
 Sznol M, and Chen L. *Clin Cancer Res* 2013;19:1021-1034

by American Association for Cancer Research



Classification of current anticancer immunotherapies.
 Oncotarget. 2014 Dec; 5(24): 12472–12508.

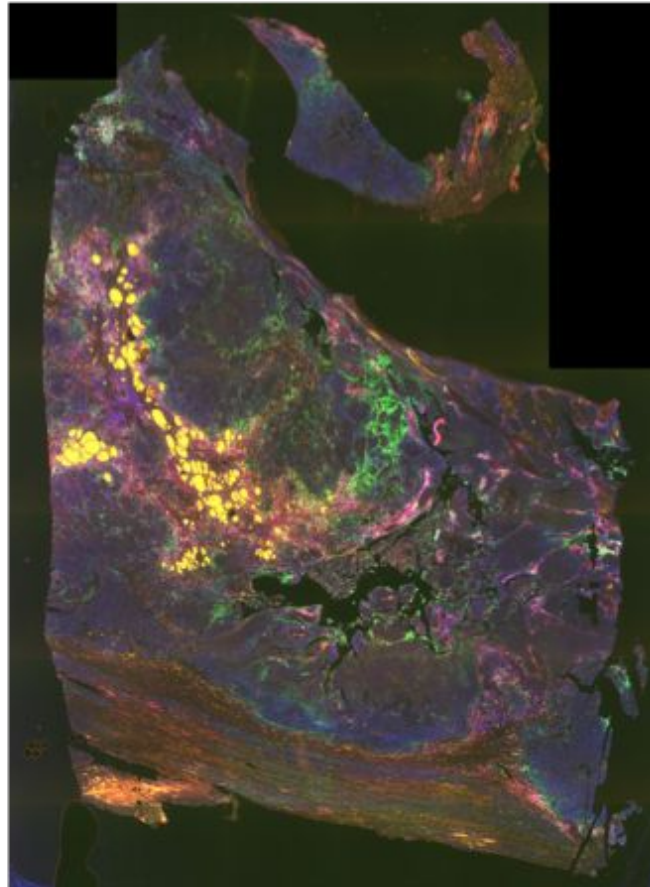
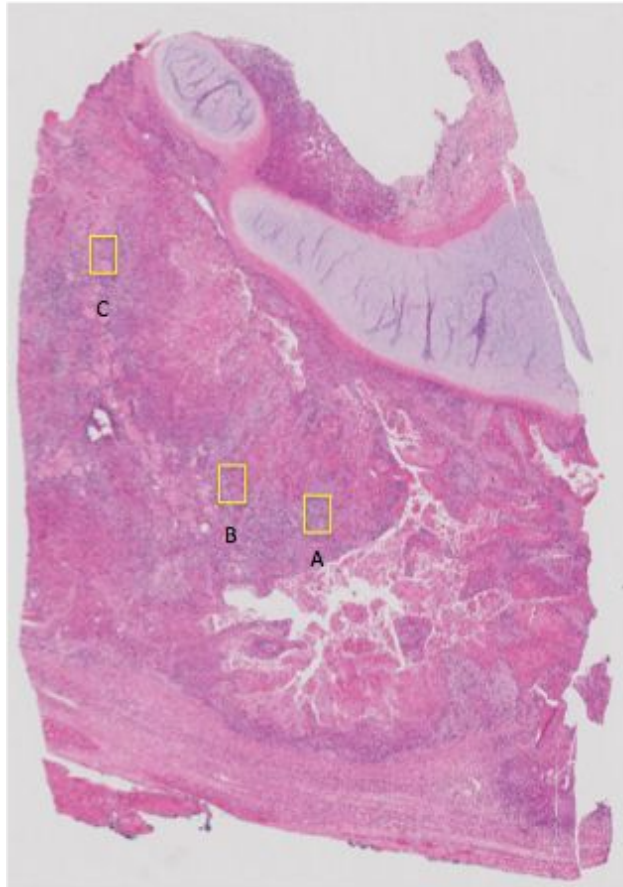
Constitution of Tumor Microenvironment Correlates with Prognosis



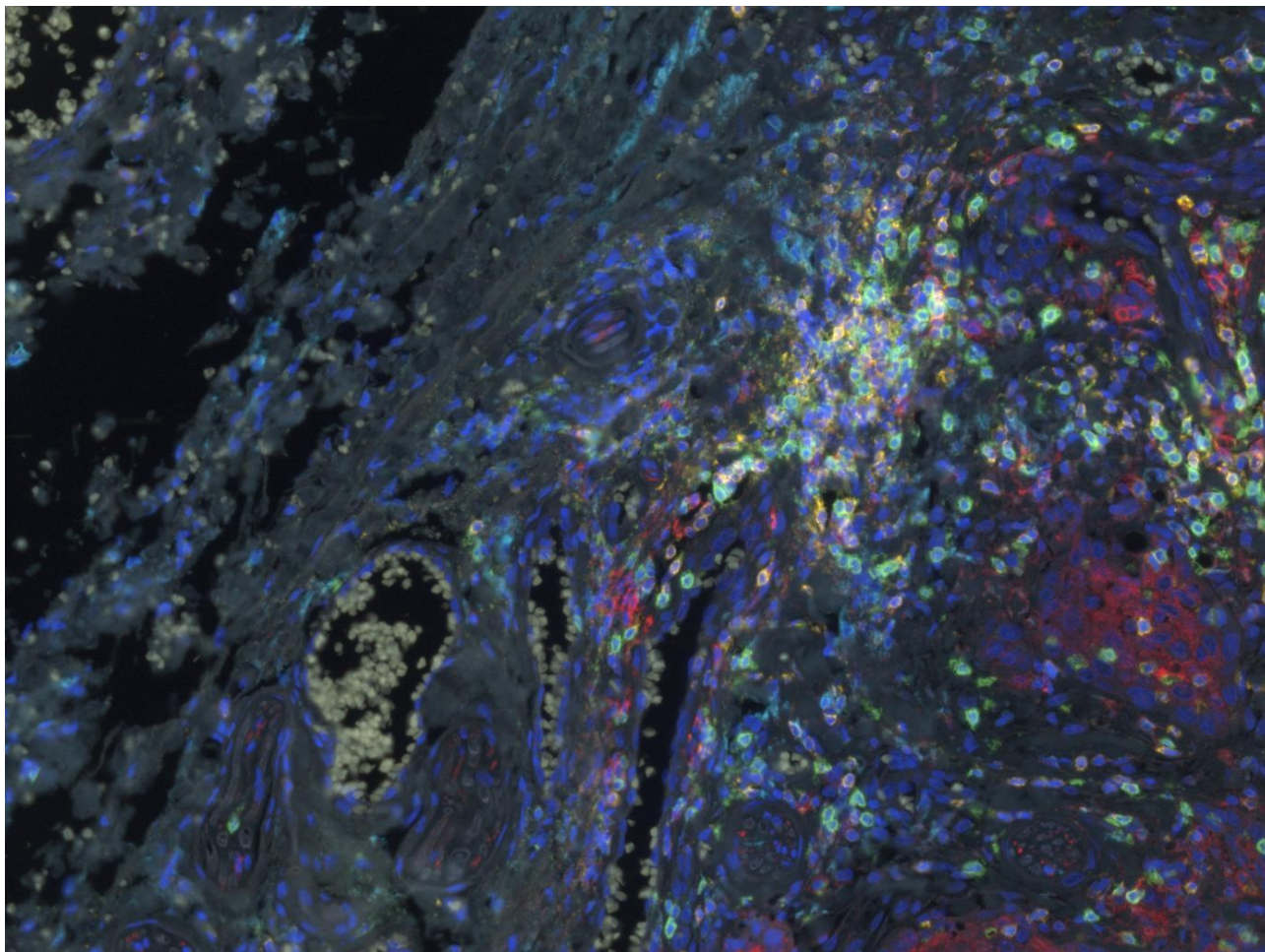
Fridman WH, Pagès F, Sautès-Fridman C, Galon J. *The immune contexture in human tumours: impact on clinical outcome*; Nat Rev Cancer. 2012 Mar 15;12(4):298-306

Galon et al , ASCO 2016 *Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients.*

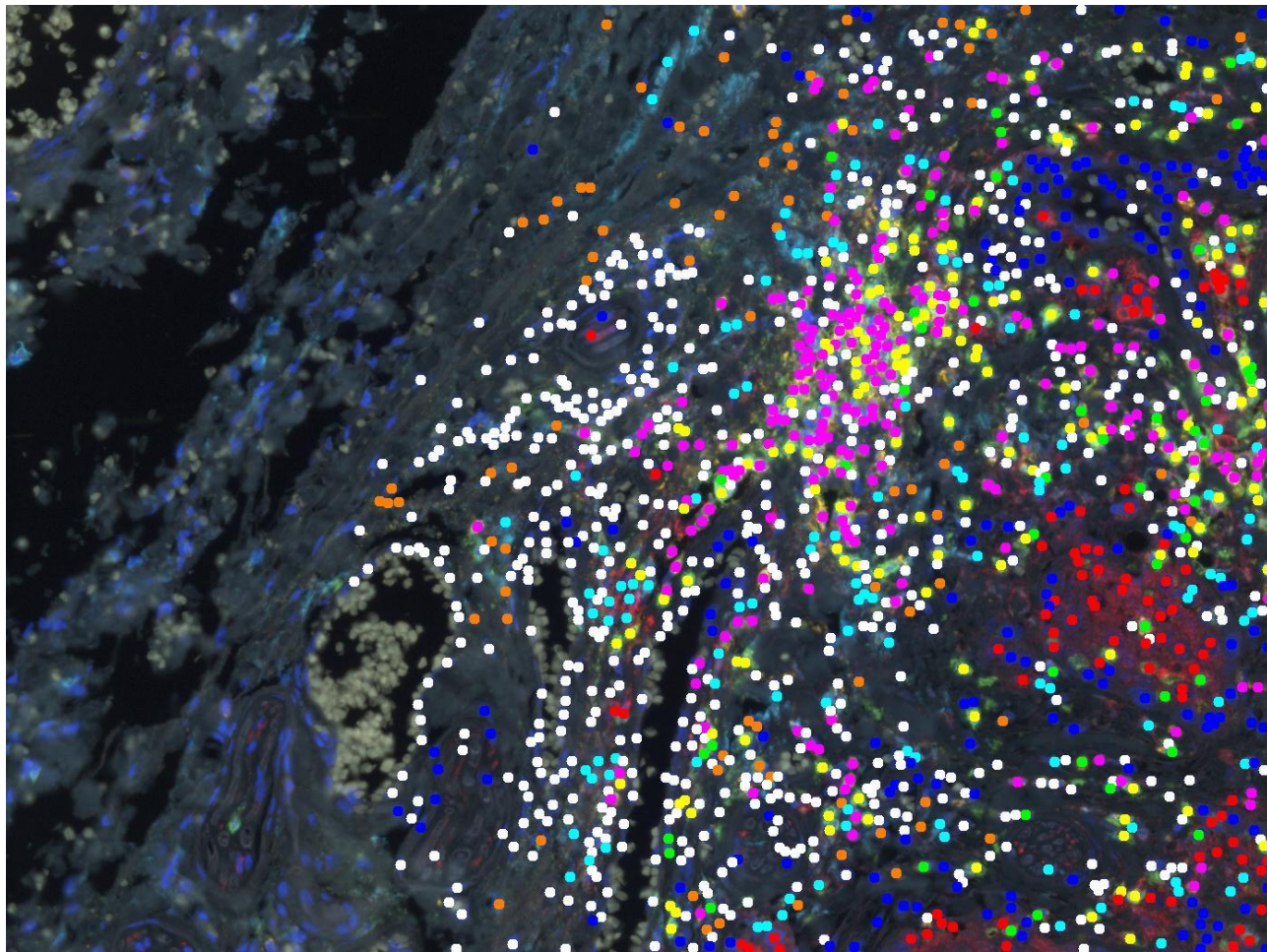
<http://meetinglibrary.asco.org/record/123627/abstract>



Carmen Ballesteros-Merino and Bernard FoxEarl A. Chiles Research Institute



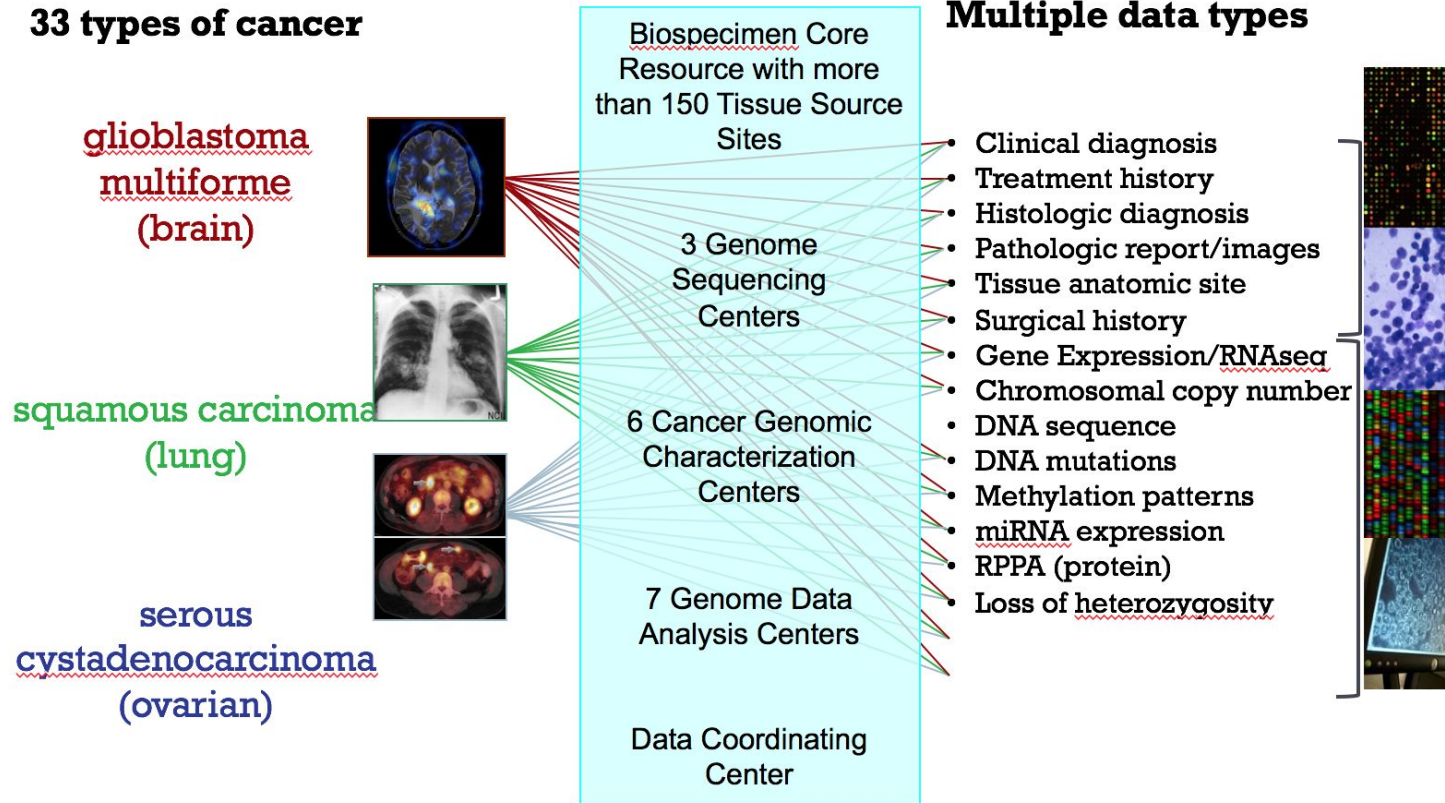
Bernard Fox lab, Earl A. Chiles Research Institute



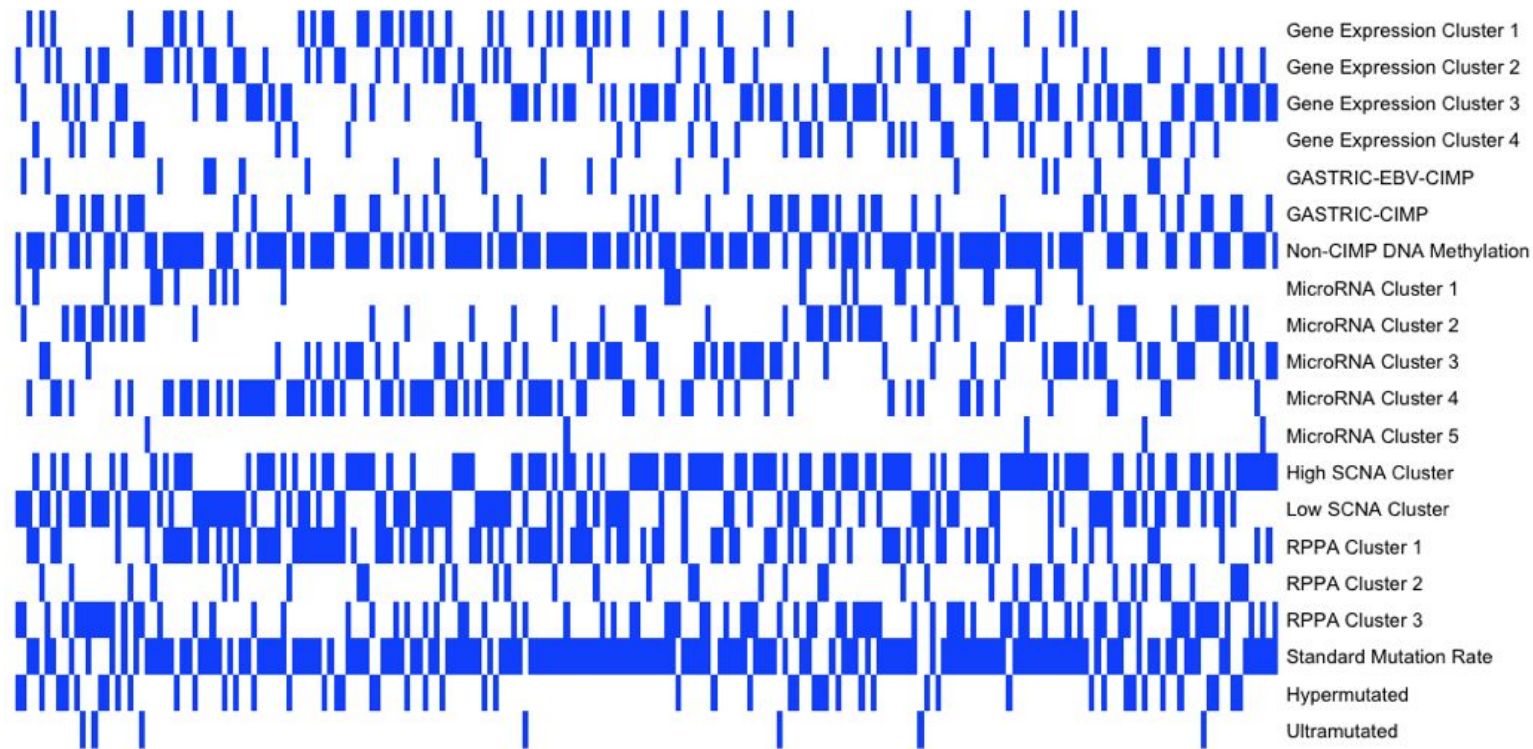
Bernard Fox lab, Earl A. Chiles Research Institute

	Spatial	Molecular	Cellular	Tissue	Organism
H&E	✓	✗	✓	✓	
IHC	✓	✓	✓	✓	
Cancer Genomics	✗	✓	✓	✓	

TCGA: Tumor analysis on multiple platforms

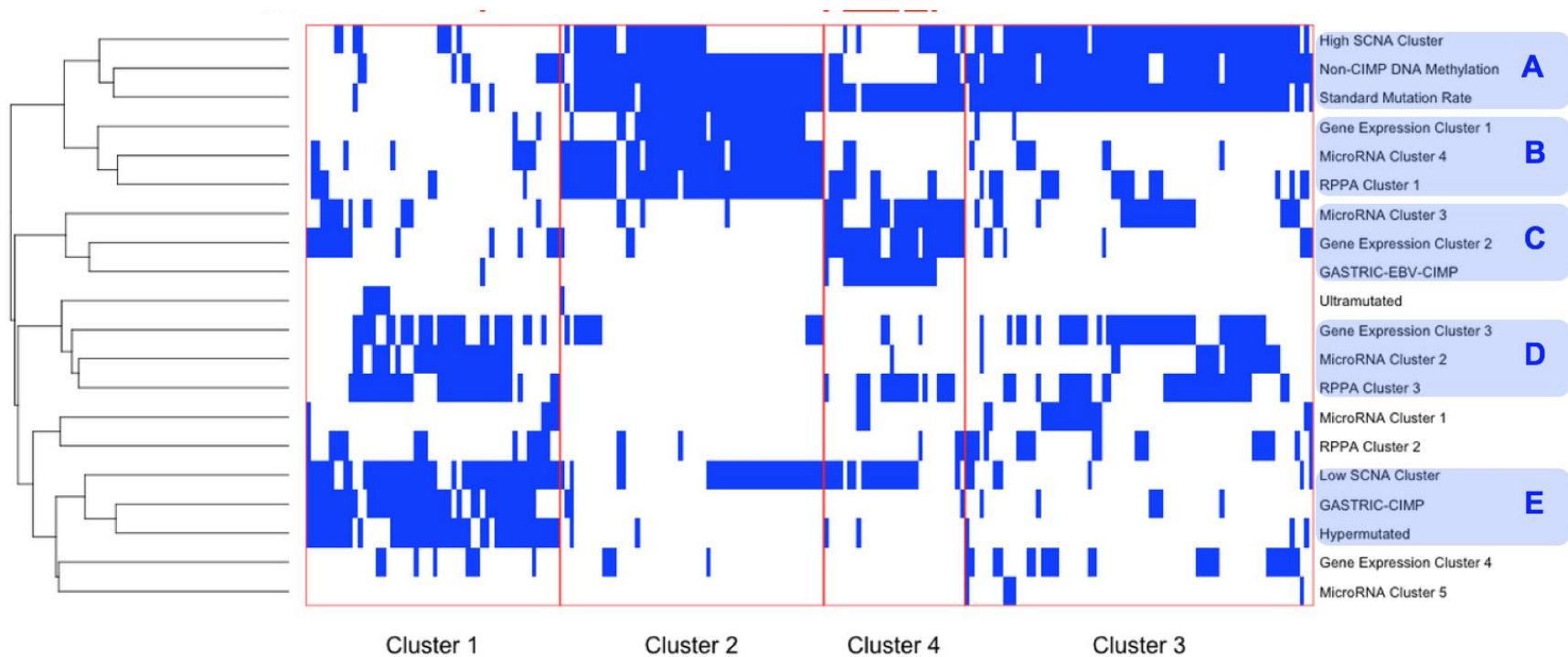


Gastric Cancer - Platform-Specific Clusters

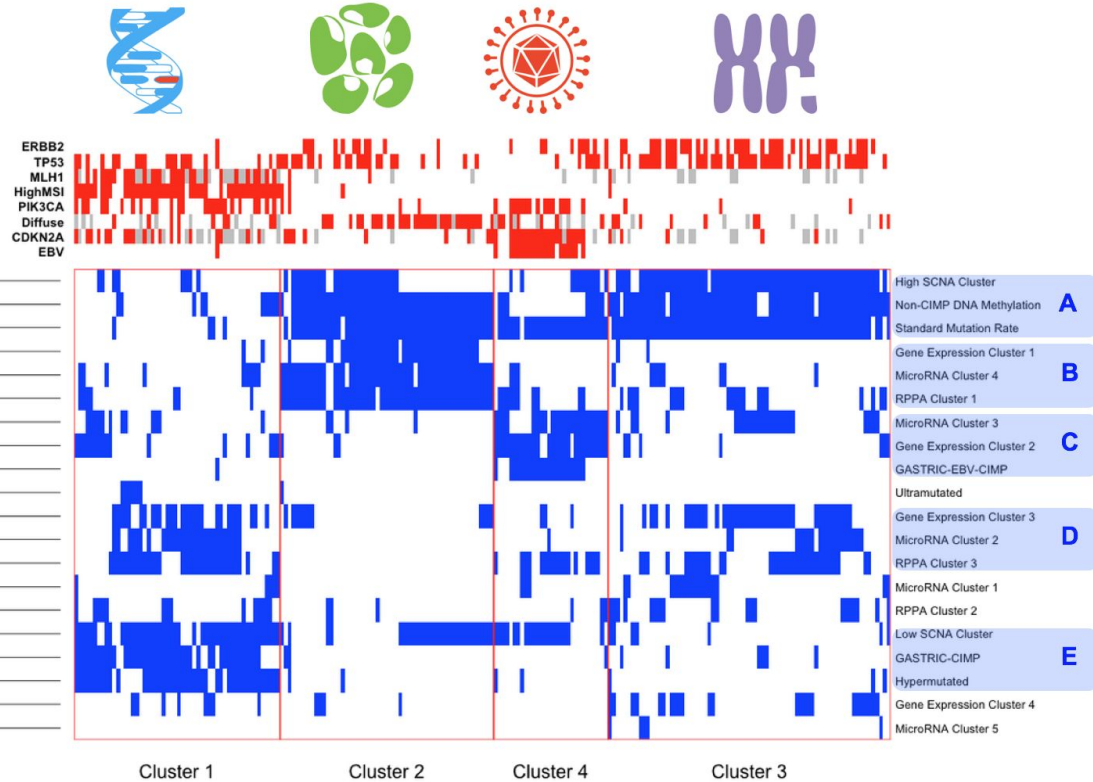


295 Tumor Samples

**Subtypes defined by
the 6 different platforms**



Subtypes defined by
the 6 different platforms



Gastric-CIMP
Hypermut
MSI-H
PIK3CA mut.
Low SCNAs

Diffuse
Expression-1
MicroRNA-4
RPPA-1

EBV
EBV-CIMP
Expression-2
Low SCNAs

Aneuploid (ERBB2 amp)
TP53 mutations
Non-CIMP



CIN

- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

Cardia
GE Junction
Fundus



EBV

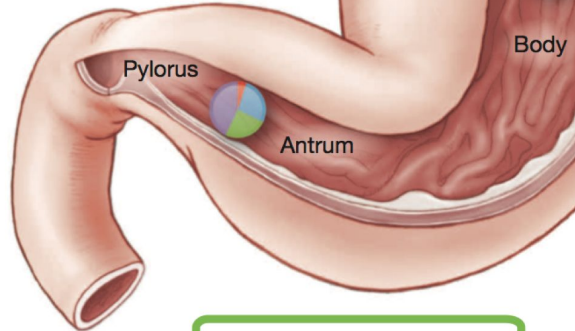
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI

- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

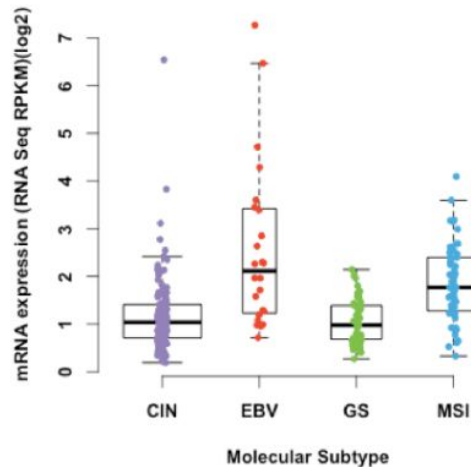
GS

- Diffuse histology
- *CDH1*, *RHOA* mutations
- *CLDN18-ARHGAP* fusion
- Cell adhesion



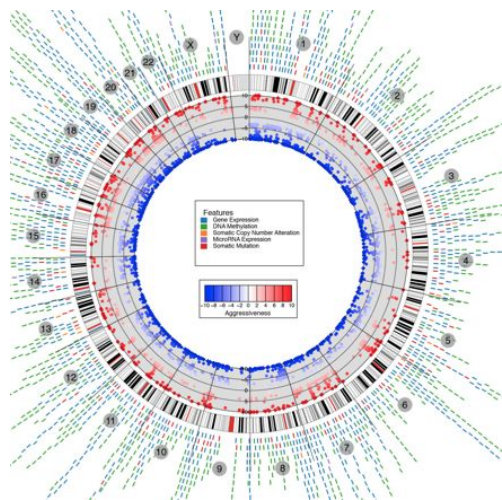
	Spatial	Molecular	Cellular	Tissue
H&E	✓	✗	✓	✓
IHC	✓	✓	✓	✓
Cancer Genomics	✗	✓	✓	✓

PD-L1 / CD274

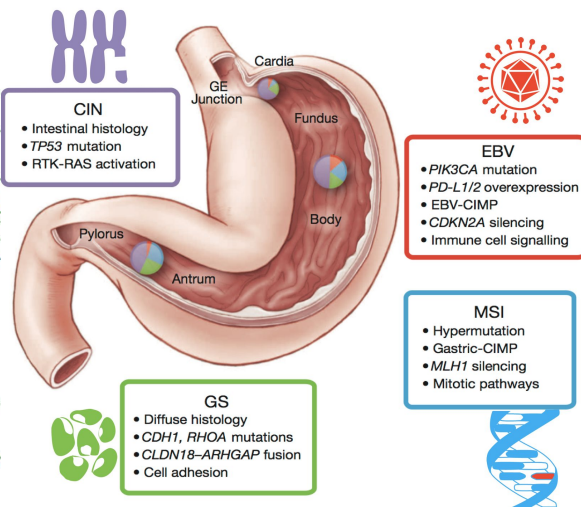


Research on Tumors of the Gastrointestinal Tract by the TCGA

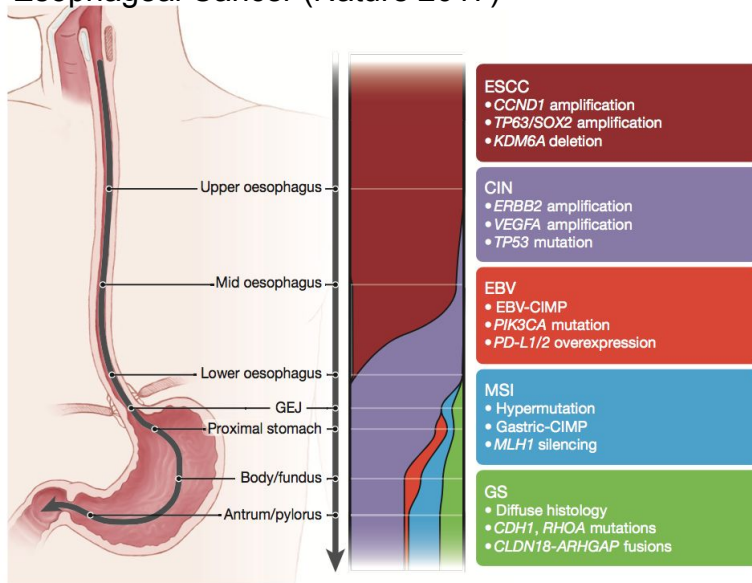
Colorectal Cancer (Nature 2012)



Gastric Cancer (Nature 2014)



Esophageal Cancer (Nature 2017)



TCGA PanCancer Atlas

Cells-Of-Origin

Oncogenic Processes

Squamous

Stemness

Gastro

Gyn

Kidney

Pathways /
Therapies

Mutation

Signatures

Germline

Immune

Drivers /
Essentials

Aneuploidy

MYC

NOTCH

HIPPO

RAS

TGFB

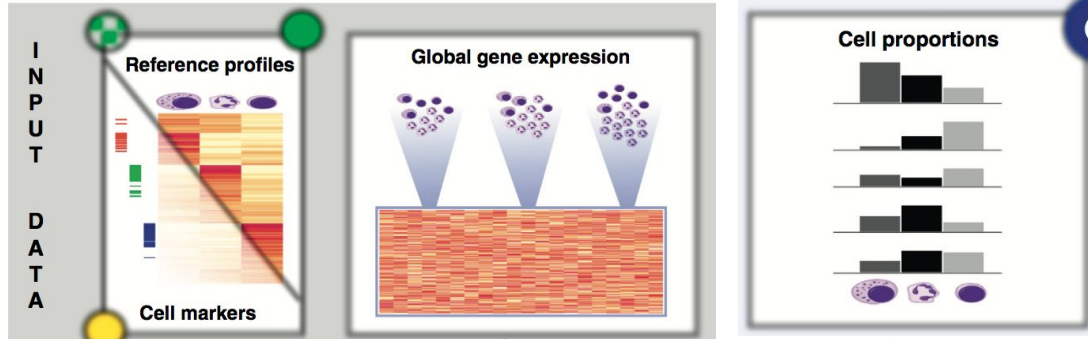
DDR

Spliceosome

SWI/SNF

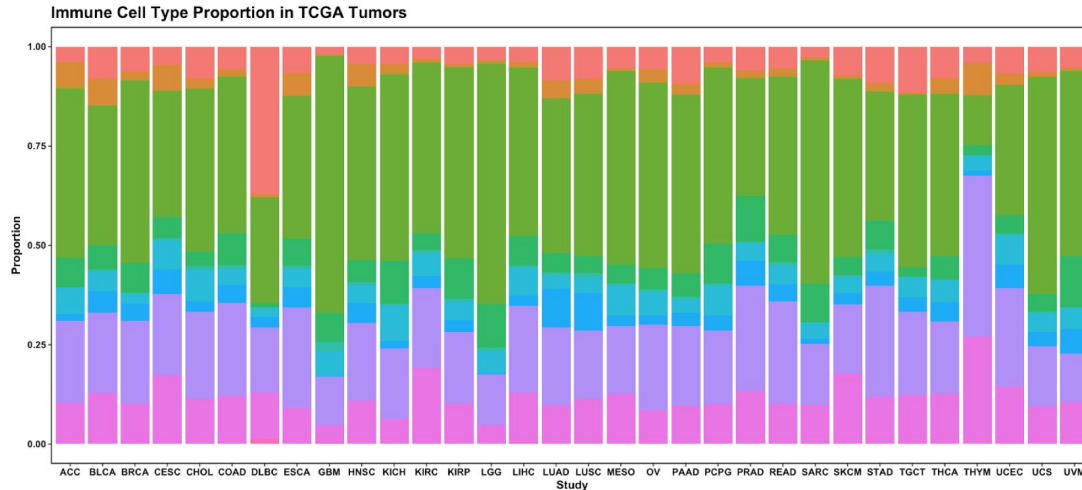
PI3K

Expression deconvolution



Shen-Orr and Gaujoux, *Curr. Op. Immunology* 2013

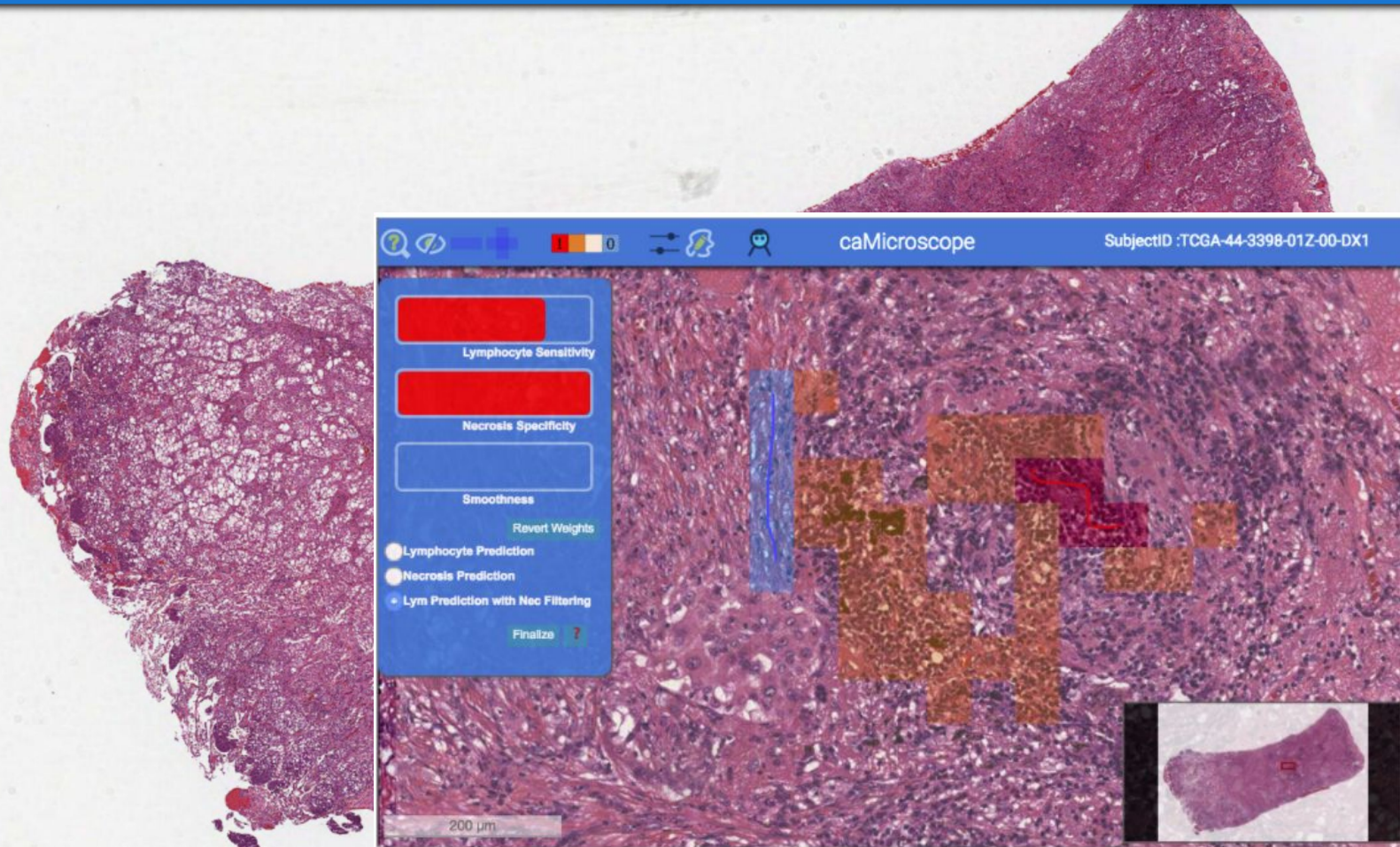
	Spatial	Molecular	Cellular	Tissue
H&E	✓	✗	✓	✓
IHC	✓	✓	✓	✓
Cancer Genomics	✗	✓	✓	✓



Cell_Type

- B_cells
- Dendritic_cells
- Eosinophils
- Macrophage
- Mast_cells
- Neutrophils
- NK_cells
- Plasma_cells
- T_cells_CD4
- T_cells_CD8
- T_cells_gamma_delta

TCGA Immune Response Working Group



Lymphocyte Sensitivity



Necrosis Specificity



Smoothness

Revert Weights

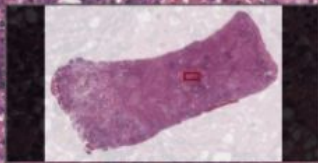
Lymphocyte Prediction

Necrosis Prediction

Lym Prediction with Nec Filtering

Finalize ?

200 µm



	Spatial	Molecular	Cellular	Tissue
H&E	✓	✗	✓	✓
IHC	✓	✓	✓	✓
Cancer Genomics	✗	✓	✓	✓

Data Management and Integration

NCI Cloud Resources

Bringing data and computation together to create knowledge that accelerates cancer research and enables precision medicine



Broad Institute



Seven Bridges

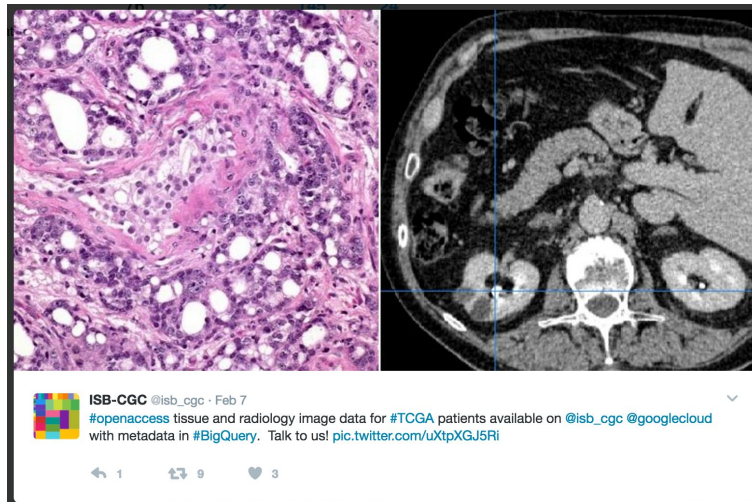


Institute for Systems Biology



QuIP

caMicroscope



CANCER RESEARCH INSTITUTE

iATLAS

Harnessing bioinformatics to speed discovery in cancer immunotherapy.



Example Query: CTLA-4 Gene Expression

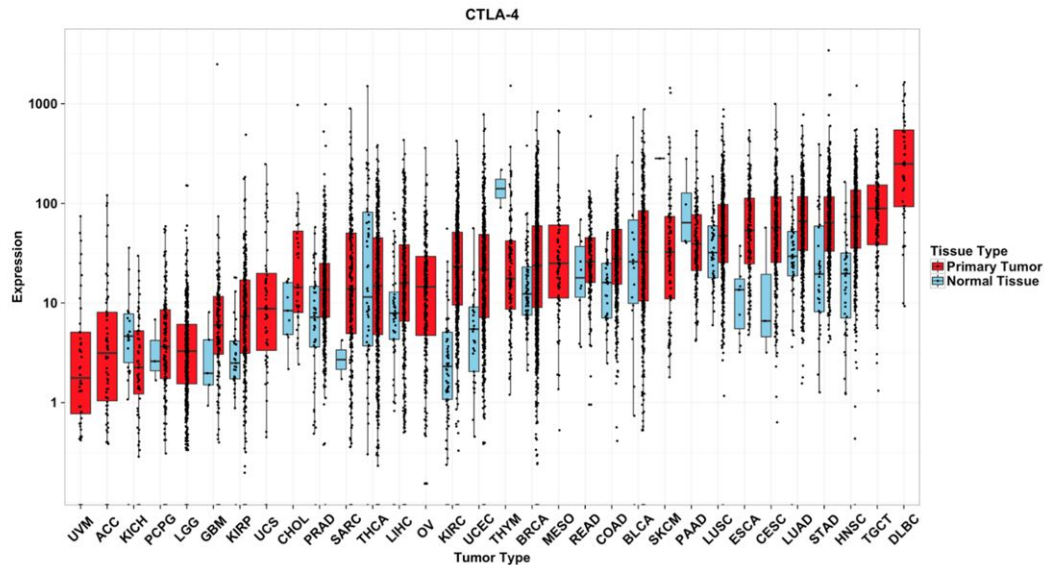
```
select * from [isb-cgc-01-0008:Filtered.EBpp_AdjustPANCAN_RNASeqV2_filtered] where Symbol="CTLA4"
```

Row	ParticipantBarcode	SampleBarcode	AliquotBarcode	SampleTypeLetterCode	SampleType	Study	Symbol	Entrez	normalized_count
1	TCGA-OR-A5JB	TCGA-OR-A5JB-01A	TCGA-OR-A5JB-01A-11R-A29S-07	TP	Primary solid Tumor	ACC	CTLA4	1493	60.1537
2	TCGA-OR-A5LG	TCGA-OR-A5LG-01A	TCGA-OR-A5LG-01A-11R-A29S-07	TP	Primary solid Tumor	ACC	CTLA4	1493	1.365
3	TCGA-4Z-AA7N	TCGA-4Z-AA7N-01A	TCGA-4Z-AA7N-01A-11R-A39I-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	346.102
4	TCGA-DK-A6AV	TCGA-DK-A6AV-01A	TCGA-DK-A6AV-01A-12R-A30C-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	55.1331
5	TCGA-FD-A5BR	TCGA-FD-A5BR-01A	TCGA-FD-A5BR-01A-11R-A26T-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	105.179

Can query directly from R using the

biarquery

library, then do a plot



Thank you

ISB Team David Gibbs, Sheila M. Reynolds, Michael Miller, Ilya Shmulevich

TCGA Gastroesophageal Cancer Working Group Adam J. Bass (Dana Farber Cancer Institute), Peter W. Laird (Van Andel Research Institute), Ilya Shmulevich (ISB), Francisco Sánchez-Vega (MSKCC), Barbara G. Schneider (Vanderbilt), Toshinori Hinoue (Van Andel),...

TCGA Immune Response Working Group Benjamin Vincent (UNC), Ilya Shmulevich (ISB),...

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TCGA Research Network, TCGA Patients and Families

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