Cohort selection for immunotherapy

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Select **molecularly & clinically** well defined & homogeneous candidates to:

(1) Identify ‘ideal’ patients

(2) Enrich for response to secondary/conjugate therapy

(3) Maximize insights from trial results analysis
1105 TCGA gliomas

• Single Nucleotide Alterations (SNAs) from exome-sequencing
• Copy Number Alterations (CNAs) from SNP6.0 arrays
• DNA methylation from Infinium 450K arrays
• mRNA-seq

• Clinical data, but
  ~ 2/3rd of lower grade gliomas were ‘alive’ at data collection
  ~ 1/5th have no status information
Tumors cluster by their sequence, methylation, mRNA and clinical characteristics.
Gliomas can be subdivided into 8 genomic subtypes.
Non-CIMP LGGs are GBM-like genomically and by survival.
Most GBM-like LGG fall in a tight genomic region defined by gain(7)/del(10)
84% of GBM-like LGGs with gain(7), del(10) have high HER2 expression.

Well-defined cohort for targeted therapy.

Levels of any given mRNA, protein, or protein state are noisy, but correlate with DNA-similarity.
A new patient’s tumor can be characterized by its similarity to other samples (sample leave-one-out experiment)

Sample locations vs. centroid of 3 nearest neighbors

Left out sample’s location estimated by 3-neighbor centroid

- Candidate sample
- Nearest neighbors
- Estimated location of new sample
Human glioma cells overexpress receptors for interleukin 13 and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and Pseudomonas exotoxin.

Receptor for Interleukin 13 Is a Marker and Therapeutic Target for Human High-Grade Gliomas

Waldemar Debinski, Denise M. Gibo, Stanley W. Hulett, James R. Connor, and G. Yancey Gillespie

Bioactivity and Safety of IL13Rα2-Redirected Chimeric Antigen Receptor CD8+ T Cells in Patients with Recurrent Glioblastoma

Christine E. Brown, Behnam Badie, Michael E. Barish, Lihong Weng, Julie R. Ostberg, Wen-Chung Chang, Araceli Naranjo, Renate Starr, Jamie Wagner, Christine Wright, Yubo Zhai, James R. Bading, Julie A. Ressler, Jana Portnow, Massimo D’Apuzzo, Stephen J. Forman, and Michael C. Jensen

Clinical Cancer Research


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IL13RA2 expression is fairly homogeneous, with [mRNA] \sim [protein]
Sample similarity by gene-set co-expression improves selection for high mRNA from noisy data

IL13RA2 expression quartiles

IL13RA2-high selected samples

Non-CIMP IL13RA2-high selected samples

Sample similarity by expression of the top 100 IL13RA2-correlated genes in 669 TCGA gliomas

samples selected

Genomic view of IL13RA2 expression
Selected non-CIMP ‘IL13RA2-high’ samples include some (but not all) samples with IL13RA2 mRNA in 2\textsuperscript{nd} quartile (blue)

149 (76\%) of 197 non-CIMP samples with expression data are selected
Selected IL13RA2-high samples are highly enriched in mesenchymal, classical, and LGr4 subtypes
Using genomic sample similarity, we can further refine cohort selection.

75% (79/105) of gain(7), del(10) gliomas are candidates for IL13RA2-directed therapy.
Technologies to Deliver Next Generation Cancer Therapies

Juno is exploring the potential of our CAR and TCR technologies to treat cancers not currently targeted by our CD19-directed and CD20-directed products in relapsed or refractory lymphoma, lung, and pancreatic cancers. We are advancing early-stage pre-clinical research of early stage CAR and TCR technologies.

MUC-16

MUC-16 is a protein that is overexpressed in cancers, including colorectal cancer. It is a potential target for our CAR and TCR technologies.

Safety of Targeting ROR1 in Primates with Chimeric Antigen Receptor–Modified T Cells

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ROR-1 is a protein expressed in the formation of embryos, but in normal adult cells its surface expression is predominantly found at low levels on adipocytes, or fat cells, and briefly on precursors to B cells, or pre-B cells, during normal B cell maturation. ROR-1 is overexpressed on a wide variety of cancers including a subset of non-small cell lung cancer, triple negative breast cancer, pancreatic cancer, prostate cancer, and ALL. It is expressed universally on B cell chronic lymphocytic leukemia and mantle cell lymphoma. Our ROR-1 product candidate was originally developed at FHCRC.
Cluster of 183 short-lived genomically highly similar tumors.

Expression data is available for 105 of these samples.

70 (67%) of 105 samples are selected ROR1-high samples.
Some gliomas express an ROR1 isoform missing its extra-cellular domain.

Isoform ‘a’

Isoform ‘b’

Ligand binding domain

Intra-cellular

Ligand binding domain

Intra-cellular

Balakrishnan & Riddell
ROR1 can be membrane-bound, cytoplasmic, or nuclear


Membrane-staining, mAb 6D4

Cytoplasmic-staining, mAb 4A5

Spatial heterogeneity of ROR1 staining in samples with low ROR1 mRNA

Low ROR1 RNA; One sample, example of tumor heterogeneity with variable intensities
Spatial heterogeneity of ROR1 staining in samples with high ROR1 mRNA

High truncated ROR1 RNA; One sample, example of tumor heterogeneity with variable intensities
Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma

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To come: Clustering tumors by immune cell composition and state