Repetitive element-derived neoantigens are a potential source of highly tumor-specific cancer vaccine targets

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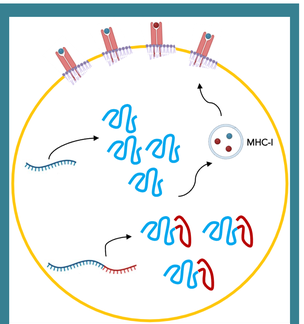
Background

Repetitive elements are commonly expressed in cancer, but they are suppressed in normal tissues. In cancer, changes in methylation can lead to repeat expression reactivation. Combined with dysregulation of splicing machinery, this leads to an increase in the number of RNA repeat-gene "fusions": transcripts derived from junctions between protein-coding genes and repetitive elements. These fusions have the potential to be a rich source of highly tumor-specific cancer vaccine targets.

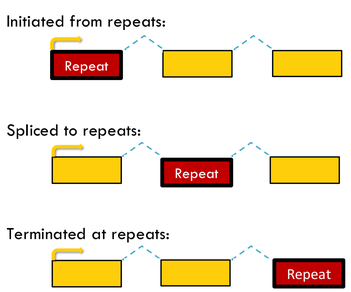
ROME has developed a state-of-the-art "repeatomics" machine learning platform designed to quantify the expression of highly repetitive elements with unparalleled sensitivity and specificity. This platform includes "ROMEFuse", which integrates short-read assembly and an alignment-based approach to detect RNA fusions between genes and repeat elements.



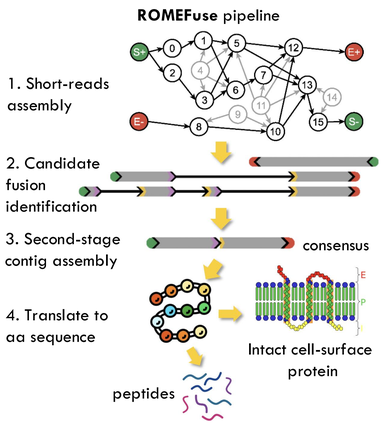
See also ROME's other poster on repeat antigens

ROMEFUSE IDENTIFIES GENE-REPEAT FUSIONS AS POTENTIAL VACCINE TARGETS

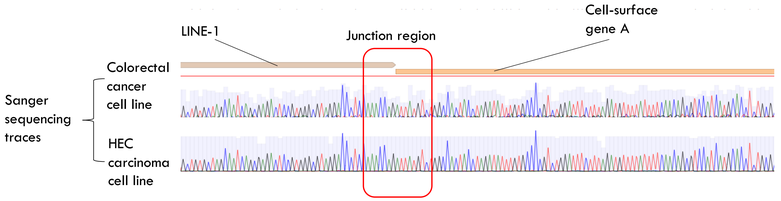
Different types of repeat-gene fusions:



ROMEFuse pipeline



Sanger sequencing validation of some of the identified fusions:



TUMOR-SPECIFIC REPEAT-GENE FUSIONS ARE IDENTIFIED ACROSS MULTIPLE TUMOR TYPES

Examples of repeat elements frequently found fused across multiple genes and tumor types in cancer:

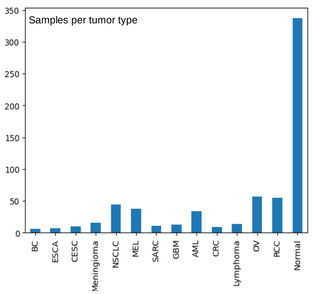
Showing fusions with a prevalence rate >20% in tumors in at least one tumor type in TCGA and <3% in any GTEx (normal) tissue

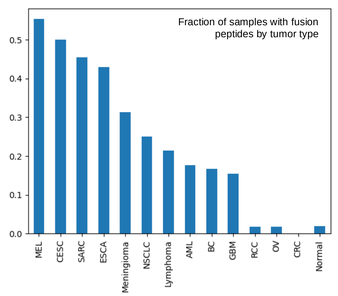
AN ANALYSIS OF PUBLIC IMMUNOPEPTIDOMICS DATA SUGGESTS FUSIONS ARE A PROMISING TARGET

Public data curation

Data collected from 40 studies in the public domain, including:

- Tumor (~1200 MS runs)
- Normal (~1000 MS runs)
- Cell line (~800 MS runs)





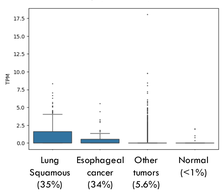
TUMOR-SPECIFIC FUSION PEPTIDES FROM A VARIETY OF CLASSES ARE FOUND TO BE PRESENTED BY MHC CLASS I

Top fusion peptides candidates

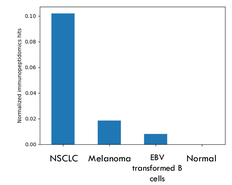
Fusion class	Tumor	Cell line	Normal
Fusion Y	12	2	0
Other fusion	12	0	0
Other fusion	11	0	0
Other fusion	9	31	0
Fusion Y	7	2	0
Other fusion	10	0	0
Other fusion	7	3	0
Other fusion	7	3	0
Other fusion	7	0	1
Fusion Y	5	5	0
Other fusion	6	0	0
Other fusion	6	1	0
Other fusion	5	2	0

Fusion Y is tumor-specific and has 3 peptides predicted

RNA-seq (TCGA)

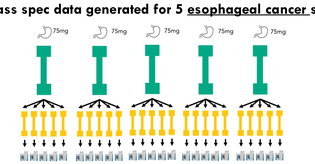


Immunopeptidomics



ROME TX HAS VALIDATED FUSION TARGETS WITH HIGHLY SENSITIVE IMMUNOPEPTIDOMICS ON ESOPHAGEAL CANCER SAMPLES

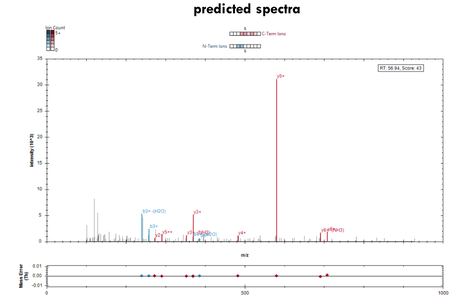
Mass spec data generated for 5 esophageal cancer samples



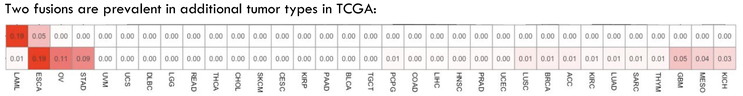
6 repeat fusion peptides are identified in at least one sample, with 2 identified across all 5 tumor samples

Peptide	Tumor 1	Tumor 2	Tumor 3	Tumor 4	Tumor 5
Peptide A	X	X	X	X	X
Peptide B	X	X	X	X	X
Peptide C	X				
Peptide D			X		
Peptide E			X		
Peptide F			X		

Example peptide with strong matching between observed and predicted spectra



Two fusions are prevalent in additional tumor types in TCGA:



Conclusion

Repetitive elements have been shown to be highly expressed in cancer. However, repeat-gene RNA fusions are less well studied due to the lack of efficient and accurate tools. Here, we present ROMEFuse, an RNA repeat-gene fusion detection platform, and identify a subset of tumor specific peptides also detected in publicly available and ROME internal immunopeptidomics data. Given the potentially large space of repeat-gene fusions, their tumor specificity, and patient prevalence, we believe that these elements could be a rich source of cancer vaccine targets.