Inverse Biomarker Exploring Technology (IBMET)

Mathematical Identification of Cancer-Specific Epitopes and Novel Targets (Biomarkers) from Big Data of Single-Domain Antibodies Recognizing Higher Structures

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Summary

We release a new method for discovering biomarkers expressed on unmet cancers. IBMET, which is the mathematical mining of the specific antibodies among a large dataset of VHH coding genes from immunized alpacas with cancer cells, predicted a VHH recognizing novel molecular complex.

The novelty and advantages of IBMET are described as

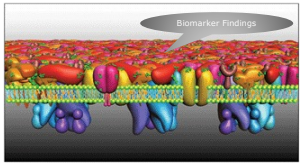
1. The ability to identify abnormalities (features) in post-translational modifications or complex formation, which are not detectable by genome or mRNA expression analysis, by converting antibodies that recognize target molecule structures into amino acid sequence information.
2. Immediate formulation into ADCs and other drugs upon biomarker discovery, as antibodies are already available.
3. Instant response to necessary companion diagnostics in parallel with drug formulation.

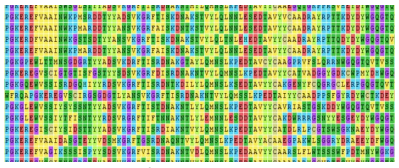
This enables the provision of a super-rapid and highly probable next-generation antibody drug development platform. With IBMET, we have successfully identified similar marker molecules in not only pancreatic cancer but also cholangiocarcinoma and TNBC and are currently aiming to pipeline multiple targets.

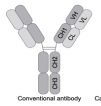
Antigen (Target) **Antibody** (Drug)

Background

- Currently, candidate molecules such as MUC1, Mesothelin, CEACAM6, and Claudin18.2 have been proposed as immunotherapy targets in pancreatic cancer. These molecules are significantly overexpressed in cancer cells, allowing differentiation from normal cells, and are being targeted for drug development using immunotherapy modalities like antibody drug conjugate (ADC), T cell bispecific (TCB), and CAR-T.
- To accelerate therapeutic biomarker discovery, computational methods, especially **statistics** and **machine learning**, have attracted interest for predicting antigen-antibody interactions.
- The Inverse Biomarker Exploring Technology (**IBMET**) is a bio−AI fusion technology that comprehensively converts biologically generated single−domain antibodies into a digital library to discover new biomarker molecules by using features correlated with epitopes.







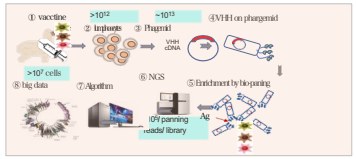
AVIDa-hIL6 Project Page: https://avida-hil6.cognanous.com

Full paper: https://arxiv.org/abs/2306.0332

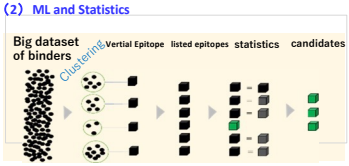
IBMET: Biomarker-VHH Interaction Dataset

IBMET

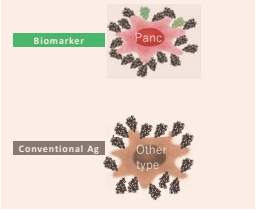
(1) Construction of a large dataset of Ab



(2) ML and Statistics



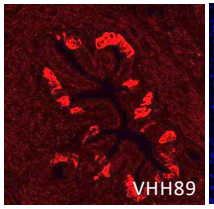
(3) Check by immunostaining on cells

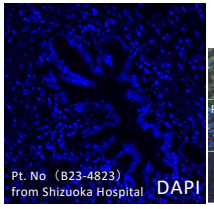


(4) Pathological check by immunostaining

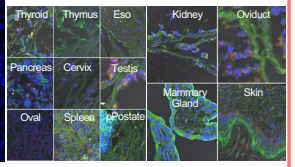
	control1	control 2	OCUG-1	MIA PaCa-2	KP-2	KP-3	KP-4	QGP-1	SUIT-2	TYPK-1	HuCCA-1	HuCCT1	HuH28
Cluster611	-0.12	-0.62	-12.31	-1.90	-1.44	0.53	7.32	-0.40	2.69	-2.31	13.97	23.18	14.81
Cluster1021	0.00	0.00	-3.07	-0.87	-1.51	0.00	-2.31	-0.45	3.81	-1.54	-3.20	6.81	-3.72
Cluster1388	-0.67	0.00	-3.48	0.00	-0.62	0.00	-1.33	-1.23	0.00	0.00	0.00	4.32	-1.74
Cluster1475	0.00	-0.55	-2.41	0.00	0.00	0.00	-0.98	0.00	-1.69	0.00	-1.41	-1.91	-1.39
Cluster2384	0.00	0.00	-2.08	-0.62	-0.62	0.00	-1.33	0.00	-0.46	-0.48	0.00	-0.68	-0.62
Cluster2596	-0.67	0.00	-0.62	0.00	0.00	0.00	0.00	-0.45	0.00	0.00	0.00	-1.52	-0.62
Cluster3081	0.00	-0.55	-1.74	-0.62	-12.83	0.00	0.00	0.00	0.00	-0.78	0.00	-0.68	-1.02
Cluster3409	0.00	0.00	-1.02	0.00	6.92	0.00	0.00	0.00	-0.77	0.00	0.00	-1.91	-0.62
Cluster3776	0.00	0.00	-1.02	0.00	-4.06	0.00	0.00	0.00	0.00	-0.48	-0.84	-0.68	-0.62
Cluster4086	0.00	0.00	-1.02	0.00	5.66	0.00	0.00	0.00	0.00	0.00	0.00	-0.68	0.00
Cluster4453	0.00	0.00	0.00	-0.48	-0.68	0.00	0.00	-4.71	0.00	0.00	-0.52	-0.68	0.00
Cluster5912	0.00	0.00	-0.62	-0.48	-0.68	0.00	0.00	-3.09	0.00	0.00	0.00	-1.11	0.00
Cluster7124	0.00	0.00	0.00	-4.12	0.00	0.00	0.00	-3.42	0.00	-0.48	0.00	-1.52	0.00
Cluster8166	0.00	0.00	-0.62	-1.91	0.00	6.61	0.00	0.00	0.00	-0.48	0.00	-0.68	-0.62
Cluster68875	0.00	0.00	0.00	0.00	0.00	-4.12	0.00	0.00	0.00	0.00	-4.06	0.00	0.00
Cluster10251	0.00	0.00	0.00	0.00	0.00	-1.91	-0.62	0.00	-0.48	0.00	0.00	0.00	-0.62
Cluster10483	0.00	0.00	-0.62	0.00	0.00	-0.68	0.00	0.00	-0.48	-4.06	0.00	0.00	0.00
Cluster13625	0.00	0.00	-0.62	0.00	-4.12	-1.52	-0.62	0.00	0.00	0.00	-0.52	-0.68	-4.12

Enrichment Score by the bio-panning using the cancer cell lines(Blue: PDAC, green: Cholangiocarcinoma)



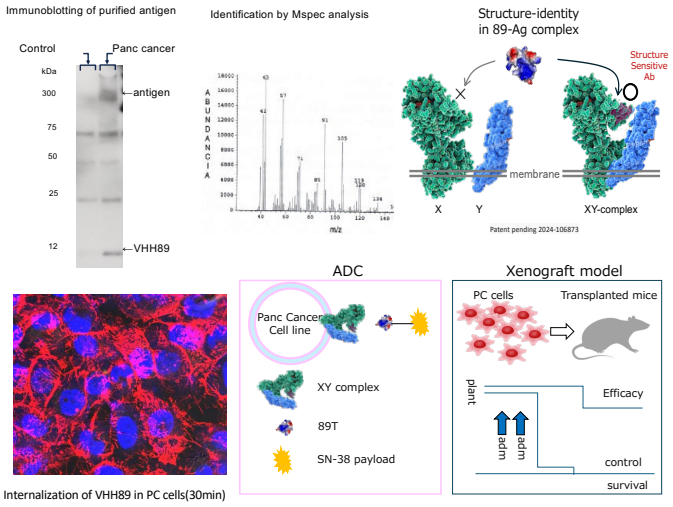


Normal human tissue array Biochain)



Green: Her2, Red: VHH89

Identification of the biomarkers



Future Works

Reference

[1] Advances in biomarkers and techniques for pancreatic cancer diagnosis (2022).
[2] Proteomic biomarkers in body fluids associated with pancreatic cancer (2018).
[3] KRAS Mutations in Solid Tumors: Characteristics, Current Therapeutic Strategy, and Potential Treatment Exploration (2023).
[4] The Role of Circular RNAs in Pancreatic Ductal Adenocarcinoma and Biliary-Tract Cancers (2020).
[5] *NTRK* gene fusions as novel targets of cancer therapy across multiple tumour types (2016).
[6] AVIDa-hIL6: A Large-Scale VHH Dataset Produced from an Immunized Alpaca for Predicting Antigen-Antibody Interactions (2022).
[7] A SARS-CoV-2 Interaction Dataset and VHH Sequence Corpus for Antibody Language Models (2023).
[8] A panel of nanobodies recognizing conserved hidden clefts of all SARS-CoV-2 spike variants including Omicron (2022).