Decoding Complexity: Insights into AI Explainability, Immune Repertoires, and Cancer Resistance

Authors: Rohita Biswas

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JOSHA presents a synthesis of recent research from the Collaborative Research Institute Intelligent Oncology (CRIION), highlighting advances in AI explainability, immune profiling, and cancer therapy resistance. The first study introduces Salvage, a Shapley-distribution–based method that improves interpretability in Vision Transformers through guided sampling. The second explores TRBC1/TRBC2 oligoclonality in T-cell lymphomas, revealing how tumor heterogeneity can drive primary resistance to TRBC-directed CAR T cell therapies. The third examines adenosine deaminase 2 deficiency, uncovering skewed T- and B-cell receptor repertoires that enable accurate patient identification via machine learning. Collectively, these works decode complexity across disciplines, offering new strategies to interpret AI models, map immune landscapes, and address therapeutic challenges, thereby advancing both research insight and clinical application in intelligent oncology and immunology.

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Decoding Complexity: Insights into AI Explainability, Immune Repertoires, and Cancer Resistance

Rohita Biswas
rohita.biswas23@gmail.com
University of Freiburg & Journal of Science, Humanities and Arts, (JOSHA), Freiburg im Breisgau, Germany

Abstract

JOSHA presents a synthesis of recent research from the Collaborative Research Institute Intelligent Oncology (CRIION), highlighting advances in AI explainability, immune profiling, and cancer therapy resistance. The first study introduces *Salvage*, a Shapley-distribution–based method that improves interpretability in Vision Transformers through guided sampling. The second explores TRBC1/TRBC2 oligoclonality in T-cell lymphomas, revealing how tumor heterogeneity can drive primary resistance to TRBC-directed CAR T cell therapies. The third examines adenosine deaminase 2 deficiency, uncovering skewed T- and B-cell receptor repertoires that enable accurate patient identification via machine learning. Collectively, these works decode complexity across disciplines, offering new strategies to interpret AI models, map immune landscapes, and address therapeutic challenges, thereby advancing both research insight and clinical application in intelligent oncology and immunology.

Keywords: AI Explainability; Vision Transformers; CAR T-cell Resistance; Immune Repertoire Profiling; Machine Learning.

1. Salvage: Shapley-distribution Approximation Learning Via Attribution Guided Exploration for Explainable Image Classification

By Mehdi Naouar *et al*.

Study and Purpose

This paper introduces Salvage, a novel removal-based explainability method for image classification, aimed at providing more accurate and interpretable predictions made by models, particularly Vision Transformers (ViTs). The purpose is to address the limitations of current explainability techniques by providing a more accurate assessment of feature significance using Shapley distributions and informed sampling strategies.

Hypotheses of the Study

The authors hypothesize that Salvage provides a better alternative to current explainability methods in both qualitative and quantitative metrics, thereby offering better insights into model predictions and feature importance.

Methods

The method involves training an explainer model to learn the classifier's prediction distribution on masked images, using Jensen-Shannon divergence for optimization. An attribution-guided sampling strategy balances the selection of important and unimportant features during training.

Result and Conclusion

The results indicate that Salvage significantly outperforms ten baseline explainability methods across multiple datasets, delivering higher-quality explanations while maintaining classification accuracy, which underscores its utility as both an explainer and a classifier.

Limitation

The most important limitation mentioned is that Salvage, like other methods based on Shapley values, relies on the assumption that all features are linearly

independent, which might be overly restrictive in real-world scenarios where feature interactions exist.

This article was previously published in *OpenReview.net* on January 22, 2025, and was presented at the *International Conference on Learning Representations (ICLR 2025)*.

Read the full article here

2. Oligoclonality of TRBC1 and TRBC2 in T cell lymphomas as mechanism of primary resistance to TRBC-directed CAR T cell therapies.

By Benjamin Thiele *et al*.

Study and Purpose

This study investigates why some T-cell lymphomas resist CAR T-cell therapies targeting TRBC1 or TRBC2 (specific markers on T cells). The purpose was to determine whether tumor heterogeneity—specifically, mixed or absent TRBC expression—could explain treatment failures observed in early clinical trials.

Hypothesis of the Study

The authors hypothesize that many T cell lymphomas may originate *before* the TRBC1 or TRBC2 segments are chosen during T cell development. As a result, the tumors can end up being oligoclonal, with different subclones expressing TRBC1, TRBC2, both, or neither. This diversity could make it easier for the tumor to escape TRBC-targeted CAR T cell therapies, which are designed to recognize only one of those forms.

Methods

They analyzed single-cell T-cell receptor (TCR) sequencing data from 12 T-cell lymphoma cases, focusing on TRBC1/TRBC2 expression in malignant clones while excluding non-cancerous bystander cells.

Result and Conclusion

The results indicate that oligoclonality in TRBC1 and TRBC2 is prevalent in T cell lymphomas, with certain cases exhibiting a complete lack of TRBC expression, revealing a complex clonal landscape that may lead to treatment failures in CAR T cell therapies.

Limitations

The small sample size (12 cases) and reliance on sequencing data—which may miss rare subclones or underestimate clonotype diversity—mean that broader studies are needed to confirm how common TRBC heterogeneity is in T-cell lymphomas.

This article was previously published in *Nature Communications* on February 21, 2024.

Read the full article here

3. Deficiency of adenosine deaminase 2 skews adaptive immune repertoires toward specific sets of T- and B-cell receptors

By Christoph Schultheiß *et al*.

Study and Purpose

This study investigated how *adenosine deaminase 2 deficiency (DADA2)*—a rare genetic disorder causing immune dysfunction—affects the adaptive immune system, particularly T and B cells. The goal was to identify disease-specific immune signatures and understand their link to DADA2 symptoms like autoimmunity, immunodeficiency, and inflammation.

Hypothesis of Study

The researchers hypothesized that DADA2 disrupts the diversity and function of immune cells, leading to skewed T- and B-cell receptor repertoires. Furthermore, they proposed that these varied immunogenic parameters could be detected using machine learning to distinguish DADA2 patients from healthy individuals.

Methods

The team performed flow cytometry, cytokine profiling, and next-generation immunosequencing on blood samples from 52 patients with DADA2 and healthy controls. They used machine learning (LightGBM classifier) to differentiate immune repertoires based on features like clonality, receptor diversity, and CDR3 characteristics.

Result and Conclusion

ADA2 deficiency leads to a unique, skewed immune receptor repertoire marked by restricted diversity and increased autoreactive elements—especially IGHV4-34 and TRBV29-1 usage—enabling highly accurate classification of DADA2 patients via machine learning.

Limitations

Although the immune signature is distinct, the study's reliance on cross-sectional data limits conclusions about disease progression and the long-term effects of therapy on immune repertoire normalization. Longitudinal data are needed.

This article was previously published online in *The Journal of Allergy and Clinical Immunology* on February 7, 2025.

Read the full article here

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