Zhen Xia, Ph.D.

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Educations

Ph.D. in Biology
Institution: Fudan University - Westlake University
Location: Hangzhou, China
Dates: Start Date: 01/09/2019 – Ph.D. Award Date: 20/01/2025
Thesis Title: Epi-transcriptomics on tumorigenesis and optimization of CAR T therapy.
Supervisor: Dr. Qi Xie

Bachelor of Science
Institution: Northwest A&F University
Dates: Start Date: 01/09/2015 – 30/06/2019

Publications

1. Lan, Y.#, **Xia, Z.#**, Shao, Q., et al. (2025). Synonymous mutations promote tumorigenesis by disrupting m^6A-dependent mRNA metabolism. ***Cell.*** **188**, 1–14 (2025). https://doi.org/10.1016/j.cell.2025.01.026

2. **Xia, Z.#**, Jin, Q.#, et al. Targeting overexpressed antigens in glioblastoma via CAR T cells with computationally designed high-affinity protein binders. ***Nat. Biomed. Eng.*** **8**, 1634–1650 (2024). https://doi.org/10.1038/s41551-024-01258-8

3. Ran, X.#, Zheng, J.#, Chen, L.#, **Xia, Z.#**, et al. (2024). Single-Cell Transcriptomics Reveals the Heterogeneity of the Immune Landscape of IDH-Wild-Type High-Grade Gliomas. ***Cancer Immunol. Res.*** **12**, 232-246. https://doi.org/10.1158/2326-6066.cir-23-0211

4. Lin, P., Chen, W., Long, Z., Yu, J., Yang, J., **Xia, Z.**, et al. (2024). RBBP6 maintains glioblastoma stem cells through CPSF3-dependent alternative polyadenylation. ***Cell Discov.*** **10**, 32. https://doi.org/10.1038/s41421-024-00654-3

5. **Xia, Z.**, et al. (2021). Epitranscriptomic editing of the RNA N6-methyladenosine modification by dCasRx conjugated methyltransferase and demethylase. ***Nucleic Acids Res.*** **49**, 7361-7374. https://doi.org/10.1093/nar/gkab517

Awards

1. China National Scholarship (2021)
2. Outstanding Student of Fudan University (2021)
3. Innovation Award of Westlake University (2023)
4. Su-Wu Scholarship of Westlake University (2023)
5. Dean's Award of Westlake University (2024)
6. Outstanding Graduates of ShangHai (2024)

Research summary

My name is Zhen Xia, and I obtained my Ph.D. degree in Biology at the School of Life Sciences, Westlake University. My supervisor is Dr. Qi Xie, whose lab focuses on the research of cancer immunotherapy and tumorigenesis. Under the esteemed mentorship of Dr. Qi Xie, I am immersed in research centered on the intricacies of epi-transcriptional regulation in tumorigenesis and the advancement of cancer immunotherapy.

My research focuses on the manipulation of epi-transcriptomics and cancer immunotherapy. In exploring the regulatory mechanisms of tumorigenesis, instead of employing conventional gene regulation methods like shRNA or Cas9-mediated gene editing, my work concentrated on the critical post-transcriptional modification, N^6-methyladenosine (m^6A), influencing RNA stability, splicing, translation, and localization. Due to the lack of suitable m^6A editing tools at the beginning, my first project was to develop a platform with high specificity for editing endogenous m^6A modifications. In this project, I achieved precise editing of endogenous m^6A in tumors by employing a strategy that linked CasRx, an enzyme naturally capable of targeting specific RNA sites, with methyltransferases or demethylases (PMID: 34181729, ***Nucleic Acids Research***, First Author).

Previous studies have reported that cancer cells acquire numerous mutations during tumorigenesis. While there is substantial evidence suggesting that deleterious coding mutations are involved in tumorigenesis, the functions of high-frequency synonymous mutations are rarely reported. Our newly developed epi-transcriptomic editing tool laid the groundwork for us to identify and define a novel class of synonymous mutations within coding region, synonymous termed m^6A Disruption Mutations (sm^6A-DMs). In this project, we identified these sm^6A-DMs, although not altering the encoded amino acid sequence, significantly affect mRNA stability due to the loss of m^6A, driving tumor cells towards more malignant phenotypes (PMID: 39952247, ***Cell***, Co-first Author, rank second).

Another pivotal direction of my research is the optimization of immunotherapy. Chimeric Antigen Receptor (CAR) T cell therapy, heralded as one of the most hopeful modalities for cancer therapies, has achieved substantial success in hematological malignancies but remains less effective against solid tumors. A critical limitation is the inherent instability of the single-chain variable fragment (scFv) employed for antigen recognition in conventional CAR constructs. Through collaboration with Dr. Longxing Cao's Lab, we have enabled the computational design of binders with high affinity for target proteins, thereby facilitating the development of novel CAR structures, named de novo designed binder (DNDB) CAR T. In our study, we used high-binding affinity mini-protein binders instead of scFvs as antigen binding domains for efficient recognition of tumor surface antigens. These computationally designed 55–65-residue binders can bind to the target protein and activate T cells, and our subsequent in vitro and in vivo studies robustly demonstrated the enhanced efficacies of these DNDB CAR T cells in glioblastoma therapy compared with traditional scFv CAR T cells (PMID: 39420062, ***Nature Biomedical Engineering***, Co-first Author, rank first). Owing to the substantial therapeutic advancements observed, we are vigorously pursuing investigator-initiated clinical trials (IIT) to substantiate the translational potential and clinical

efficacy of this innovative approach.

Additionally, to enhance the efficacy of cancer immunotherapy, we constructed a single-cell transcriptome landscape of immune cells from tumor tissue and matching peripheral blood mononuclear cells (PBMC) from 9 IDH-WT high-grade glioma patients. In this study, we investigated the T-cell trajectory and identified the aryl hydrocarbon receptor (AHR) as a regulator of T-cell dysfunction, providing a potential target for glioma immunotherapy. We further demonstrated that knockout of AHR decreased chimeric antigen receptor (CAR) T cell exhaustion and improved CAR T cell antitumor efficacy both in vitro and in vivo. (PMID: 38091354, ***Cancer Immunology Research***, Co-first Author, rank fourth).

Conference attendance

1. Cell Symposia: Myeloid cells: From development to function and dysfunction. Poster: 'Single-cell transcriptomics reveals the heterogeneity and plasticity of the immune landscape of IDH-wildtype high-grade gliomas' (2023, Shanghai, China).

2. Nature conferences: Cancer Immunotherapy: From bench to bedside and back. Poster: 'De novo-designed binder-based CAR T cells enable effective targeting of glioblastoma' (2024, Boston, USA).

3. Cell Symposia: Hallmarks of cancer. Poster: 'Targeting overexpressed antigens in glioblastoma via CAR T cells with computationally designed high-affinity protein binders' (2024, Guangzhou, China).

Technical and professional skills

Molecular Biology Techniques:

CRISPR/Cas9 gene editing / screening, Knockout / overexpression library construction, single-cell sequencing, Screening library construction, Site-specific base editing (ABE, CBE), Site-specific m^6A editing, m^6A-RNA immunoprecipitation, m^6A detection (SELECT, GLORI), PCR, RT-PCR, qPCR, DNA/RNA extraction and purification, cloning techniques.

Cell Biology Techniques:

Gel-based 3D organoid culture, Primary CAR T cell generation, Flow cytometry, Immunofluorescence microscopy, Lentiviral packaging, Retroviral packaging, Cell electroporation, Regular cell culture and transfection.

Biochemistry Techniques:

Protein purification and quantification, SDS-PAGE, Western blotting, ELISA.

Animal Models and Experiments:

Intracranial orthotopic injection of brain tumor in mice, Subcutaneous injection, Intraperitoneal injection, Small animal imaging.