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"HSP90 Inhibition Drives GRP78 Relocalization to Enhance CAR-Based Immunotherapy During Tumor Evolution"

By

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Monday, April 27th, 2026
Cancer Center, G1196
1:00 P.M. EST

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ABSTRACT

Tumor evolution under therapeutic pressure frequently leads to drug resistance through adaptive proteostasis programs that buffer proteotoxic stress and stabilize oncogenic signaling. Heat Shock Protein 90 (HSP90) is a central molecular chaperone that supports tumor survival by maintaining mutated and overexpressed client proteins. However, whether disrupting this stress-buffering network can expose new vulnerabilities for immunotherapy remains largely unknown.

In this dissertation, we investigated proteostasis modulation using evolving models of multikinase inhibitor-resistant (MKIR) hepatocellular carcinoma (HCC) and patient-derived tumor samples. We demonstrate that low-dose HSP90 inhibition selectively induces relocalization of the endoplasmic reticulum chaperone Glucose-Regulated Protein 78 (GRP78) to the tumor cell surface, while sparing normal tissues. This inducible surface GRP78 functions as a Stress-Induced Tumor Antigen (**SITA**), converting a normally intracellular chaperone into a tumor-specific immunotherapeutic target.

Targeting this stress-exposed antigen significantly enhances susceptibility to GRP78-directed CAR-NK cells, leading to improved antitumor efficacy *in vivo* and increased infiltration of innate immune cells (e.g., NK cells and M1 macrophages) within GRP78-high tumor niches, as revealed by new spatial proteomics. Mechanistically, these findings identify the HSP90-GRP78 proteostasis axis as a modifiable regulator of tumor antigen exposure during tumor evolution.

Collectively, this work establishes a novel conceptual framework in which adaptive proteostasis can be therapeutically rewired to generate inducible tumor antigens. Furthermore, we describe the development of tumor-selective GRP78-targeting antibodies to enable next-generation CAR engineering and precision targeting of stress-adapted malignancies.