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AI-Driven Discovery of Selectively Cytotoxic Nanoparticles for Cancer Therapy

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Metal and metal oxide nanoparticles (NPs) have emerged as promising candidates for cancer therapy due to their potential dual functionality: they can serve as passive drug carriers, protecting toxic drugs from adverse side effects while ensuring targeted delivery, and they can exhibit selective cytotoxicity, directly eliminating cancer cells[1]. However, designing NPs that selectively target cancer cells while sparing healthy ones remains a major challenge due to the vast chemical space and complex interactions between NP physicochemical properties and biological systems. Existing experimental approaches are labor-intensive and time-consuming, underscoring the need for computational frameworks to efficiently screen and optimize NPs for selective cytotoxicity[2].

To address this, we developed a machine learning (ML)-reinforced genetic algorithm (GA) platform designed to identify and optimize metal and metal oxide NPs with selective toxicity toward user-defined cell lines[3]. Our approach integrates a light gradient boosting machine (LGBM) regressor with a GA, enabling efficient exploration of the NP chemical space and predicting cytotoxicity profiles based on NP size, shape, surface charge, and composition. By leveraging existing cytotoxicity datasets, this platform can generate optimized NP candidates with enhanced selectivity.

As a proof of concept, we applied this framework to identify NPs selectively toxic to HEK293 cells while sparing BJ cells. The model predicted spherical Au NPs (45 nm, zeta potential: +44 mV) and irregularly shaped ZnO NPs (120 nm, zeta potential: +51 mV) as top candidates. These NPs were synthesized with varying sizes and morphologies, characterized using UV-Vis spectroscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Zetasizer to validate their physicochemical properties. Experimental characterization revealed slight deviations from predictions, with Au NPs synthesized at 15 nm, 25 nm, and 35 nm, while ZnO NPs exhibited diverse morphologies, including sheet, short petal, javelin, and star-like structures. To account for these variations, we reran our model, incorporating updated characterization data to refine toxicity predictions.

Cytotoxicity was experimentally evaluated using CCK-8 and Crystal Violet assays to assess cell viability. Results showed that ZnO NPs demonstrated strong selective toxicity toward HEK293 cells while sparing BJ cells, aligning well with the model's predictions. In contrast, Au NPs unexpectedly promoted HEK293 cell proliferation rather than exhibiting cytotoxic effects, suggesting complex bio-nano interactions that require further investigation. This discrepancy highlights the necessity of integrating mechanistic studies to improve the predictive power of ML models in nanotoxicology.

Our study underscores the capability of ML-guided approaches to accelerate the discovery of selectively toxic NPs and optimize their physicochemical properties for targeted cancer therapy. By combining predictive modeling with experimental validation, our framework provides a powerful tool for designing next-generation NPs with enhanced therapeutic precision. Future work will focus on elucidating the molecular mechanisms governing NP-cell interactions, refining toxicity predictions, and expanding this approach to a broader range of nanomaterials and

cancer cell models. This research paves the way for AI-driven nanomedicine, offering a scalable solution for developing safe and effective nanotherapeutics with minimal off-target effects.

References

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