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Tumor microenvironment-targeted bacteriochlorophylls as theranostic agents for triple negative breast cancer

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Background & Purpose: Cytotoxic drugs that target specific receptors on cancer cells and supporting vasculature often fail to convey significant therapeutic benefit, despite their extensive tumor uptake and high toxicity in cell cultures. A recent example is provided by Cilengitide®, a cyclic Arg-Gly-Asp (cRGD) that accumulates in tumors but fails to delay cancer progression. In this study, we rationalized the current failure of cRGD based clinical trials by assessing the tumor heterogeneity, showing that significant populations of cancer and endothelial cells do not accumulate the cRGD agents.

Method: We further tested the hypothesis that bystander cell death propagation initiated by agents coupled to cRGD molecules can effectively eradicate the entire tumor even if taken by the limited cell populations. The new approach was applied to mice grafted with metastatic $4T_1$ tumors in their mammary pad. This model is considered good representative for triple Negative Breast Cancer (TNBC), a heterogeneous disease with distinct molecular subtypes that differentially respond to chemotherapy and targeted agents with high rate of treatment failure and mortality.

Result: Using STL-6014, a cRGD tagged with a fluorescing and photoactive bacteriochlorophyll derivative (Bchl-D), we showed that STL-6014 can specifically and non-invasively target orthotopic TNBC tumors as well as lung metastatic tumor lesions trough integrin receptors expressed on different cell populations. The apparent high tumor uptake reflects the integrin expression by these cells. High cRGD uptake confers death of cancer and stroma cells while cells lacking integrin expression remains alive and drive tumor proliferation. This therapeutic obstacle is solved by self-promoting death signal initiated by photo-activation of the Bchl-D tags in the β3 expressing cells. Rapid propagation of cell apoptosis/necrosis via bystander effect results 62% primary tumor ablation in mice bearing $4T_1$.

Conclusion: The study provides rationale and new means for paradigm shift in cell-targeted therapies, understanding and overcoming failures of therapies that target specific cell populations in the tumor microenvironment.

Biography

Lilach Agemy has her expertise in vascular biology and tumor/atherosclerosis microenvironment. Her current research focuses on using new targeted derivatives for photodynamic therapy with bacteriochlorophyll that were based on TOOKAD, which was recently approved by EMA. She is working in an extensively multidisciplinary environment involving biologists, chemists, physicists and bioengineers with participation ranging from designing, performing experiments, analyzing imaging and other biological data.

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