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Colocalized delivery of rapamycin and paclitaxel to tumors enhances synergistic targeting of the PI3K/Akt/mTOR pathway

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Ongoing clinical trials target the aberrant PI3K/Akt/mammalian target of rapamycin (mTOR) pathway in breast cancer through administration of rapamycin, an allosteric mTOR inhibitor, in combination with paclitaxel. However, synergy may not be fully exploited clinically because of distinct pharmacokinetic parameters of drugs. This study explores the synergistic potential of site-specific, colocalized delivery of rapamycin and paclitaxel through nanoparticle incorporation. Nanoparticle drug loading was accurately controlled, and synergistic drug ratios established in vitro. Precise drug ratios were maintained in tumors 48 hours after nanoparticle administration to mice, at levels twofold greater than liver and spleen, yielding superior antitumor activity compared to controls. Simultaneous and preferential in vivo delivery of rapamycin and paclitaxel to tumors yielded mechanistic insights into synergy involving suppression of feedback loop Akt phosphorylation and its downstream targets. Findings demonstrate that a same time, same place, and specific amount approach to combination chemotherapy by means of nanoparticle delivery has the potential to successfully translate in vitro synergistic findings in vivo. Predictive in vitro models can be used to determine optimum drug ratios for antitumor efficacy, while nanoparticle delivery of combination chemotherapies in preclinical animal models may lead to enhanced understanding of mechanisms of synergy, ultimately opening several avenues for personalized therapy. © The American Society of Gene & Cell Therapy.

SciVal Topic Prominence
Topic: Breast Neoplasms | Mutation | hormone receptor-positive
Prominence percentile: 98.765

Indexed keywords

EMTREE drug terms:	mammalian target of rapamycin; nanoparticle; paclitaxel; phosphatidylinositol 3 kinase; protein kinase B; rapamycin; paclitaxel; phosphatidylinositol 3 kinase; protein kinase B; rapamycintarget of rapamycin kinase
EMTREE medical terms:	animal experiment; animal model; animal tissue; antineoplastic activity; breast cancer; cancer inhibition; conference paper; controlled study; drug delivery system; drug potentiation; drug tumor level; femalein vitro study; livermouse; nanoencapsulation; nanopharmaceutics; nonhuman; particle size; protein phosphorylation; protein targeting; spleen; animal; apoptosis; cell proliferation; drug effects; human; Mammary Neoplasms, Animal; MCF 7 cell line; metabolism; nude mouse; signal transduction; tumor cell line

Species Index:	Animalia; Mus
MeSH:	Animals; Apoptosis; Cell Line, Tumor; Cell Proliferation; Female; Humans; Mammary Neoplasms, Animal; MCF-7 Cells; Mice; Mice, Nude; Paclitaxel; Phosphatidylinositol 3-Kinases; Proto-Oncogene Proteins c-akt; Signal Transduction; Sirolimus; TOR Serine-Threonine Kinases

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paclitaxel, 33069-62-4; phosphatidylinositol 3 kinase, 115926-52-8; protein kinase B, 148640-14-6; rapamycin, 53123-88-9; target of rapamycin kinase, 171715-28-9; Paclitaxel; Phosphatidylinositol 3-Kinases; Proto-Oncogene Proteins c-akt; Sirolimus; TOR Serine-Threonine Kinases

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LC, United States;
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