

## Therapeutic strategies for targeting cancer stem cells

Yu Jeong Kim<sup>1#</sup>, Elizabeth L. Siegler<sup>2#</sup>, Natnaree Siriwon<sup>3</sup>, Pin Wang<sup>1,2,3</sup>

<sup>1</sup>Department of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA 90089, USA.

<sup>2</sup>Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089, USA.

<sup>3</sup>Mork Family Department of Chemical Engineering and Materials Science, University of Southern California, Los Angeles, CA 90089, USA.

<sup>#</sup>Authors contributed equally to this work

**Correspondence to:** Dr. Pin Wang, Mork Family Department of Chemical Engineering and Materials Science, University of Southern California, 3710 McClintock Ave, RTH509, Los Angeles, CA 90089, USA. E-mail: pinwang@usc.edu



Dr. Yu Jeong Kim is a PhD candidate in the Department of Pharmacology and Pharmaceutical Science at University of Southern California (USC) mentored by Dr. Pin Wang. Her research focuses on liposomal nanoparticle-based drug delivery for combination therapy such as co-delivering two inhibitors to target two distinct populations within tumor bulk. Current studies involve the combination of immunotherapy and existing chemotherapeutic drug by utilizing Chimeric Antigen Receptor (CAR)-engineered T cells and Natural Killer (NK) cells and pharmaceutical drugs loaded crosslinked multilayer liposome vesicles for targeted cancer therapy.

### ABSTRACT

The therapeutic limitations of conventional chemotherapeutic drugs present a challenge for cancer therapy; these shortcomings are largely attributed to the ability of cancer cells to repopulate and metastasize after initial therapies. Compelling evidence suggests that cancer stem cells (CSCs) have a crucial impact in current shortcomings of cancer therapy because they are largely responsible for tumor initiation, relapse, metastasis, and chemo-resistance. Thus, a better understanding of the properties and mechanisms underlying CSC resistance to treatments is necessary to improve patient outcomes and survival rates. In this review, the authors characterize and compare different CSC-specific biomarkers that are present in various types of tumors. We further discuss multiple targeting approaches currently in preclinical or clinical testing that show great potential for targeting CSCs. This review discusses numerous strategies to eliminate CSCs by targeting surface biomarkers, regulating CSC-associated oncogenes and signaling pathways, inhibiting drug-efflux pumps involved in drug resistance, modulating the tumor microenvironment and immune system, and applying drug combination therapy using nanomedicine.

**Key words:** Cancer stem cells; targeted cancer therapy; drug resistance

### INTRODUCTION

Cancer stem cells (CSCs) are a small subset of cancer cells with the ability to self-renew and initiate tumor growth. They were first discovered in acute myeloid leukemia (AML) in the late 1990s.<sup>[1]</sup> Since then, CSCs have been discovered in many solid tumors.<sup>[2-6]</sup> Within the last two decades, CSCs have become a subject of intense research as a potential target for cancer therapeutics.

The discovery of CSCs led to a major shift in cancer modeling. Previously, cancers were thought to be made up of equipotent malignant cells which either renewed or differentiated stochastically, giving rise to a heterogeneous tumor. In contrast, the CSC model suggests that a hierarchy

exists among tumor cells, with CSCs at the top, producing the bulk of the tumor cells while maintaining their own renewal.<sup>[5]</sup> A third model, clonal evolution, states that heterogeneity comes from genetic or epigenetic changes that arise during cancer progression. The CSC and clonal evolution models are not mutually exclusive, as CSCs can also evolve over time, generating different clonal subpopulations within the tumor.<sup>[6]</sup>

CSCs share a number of properties with normal stem cells (SCs). Both typically make up a small percentage of the total number of cells in a tissue, they are largely quiescent, and, most notably, they are multipotent and

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As discussed above, nanocarriers enhanced the delivery and cytotoxic activity of CSC-inhibitors. Several studies introduced active targeting strategies of nanoparticle surfaces to increase their specificity and cellular uptake by CSCs. Lastly, researchers have been focusing on nanoparticle-mediated drug combinatorial therapy. One important advantage of nanocarriers is their capability to incorporate multiple therapeutic agents in one carrier system, allowing co-delivery of cytotoxic drugs and CSC inhibitors to simultaneously target both bulk tumor and CSCs. Patient cures will rely on the ablation of the entire tumor. Ultimately, nanoparticle mediated combination therapy may prove to be the most successful in eradicating whole tumors.

The CSC field is relatively new, and CSC-targeting therapeutics is in their early stages. While many advances have been made in CSC research, many of these studies have been performed *in vitro* only, and none are past the early clinical stages. Important factors such as effective dosages and side effects must be elucidated before employing cancer treatment plans that target both differentiated tumor cells and CSCs. There is need to improve the existing methods to precisely isolate, identify and target CSCs. As mentioned, increasing amount of nanomedicine have been evaluated about their application potentials in CSC therapy, but only a small amount of them can be approved to translate to clinical treatment. With the fact that every cancer acts differently in different patients, the development of personalized combinational therapies may serve as a key to successful treatments. Furthermore, it is important to realize that the combination of nanomedicine and immunotherapy may present a novel direction which shows great potential in personalized cancer therapy.

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### Conflicts of interests

There are no conflicts of interest.

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