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Commentary

Targeted drug delivery systems for pancreatic ductal adenocarcinoma: overcoming tumor microenvironment challenges with CAF-specific nanoparticles ☆

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) stands as a profoundly heterogeneous and aggressive malignancy, manifesting a discouragingly limited response to conventional therapeutic interventions. Within the intricate tapestry of the tumor microenvironment (TME), cancer-associated fibroblasts (CAFs) emerge as pivotal constituents, wielding the capacity to propel the malignant attributes of neoplastic cells while bolstering their deftness in thwarting treatments. The rapid evolution of nanomedicinal technologies ushers in fresh avenues for therapeutic paradigms meticulously honed to target CAFs. Notably, a recent proposition by Yuan et al. introduces a PDAC treatment strategy metaphorically akin to "shooting fish in a barrel." By adeptly capitalizing on the spatial distribution of the CAF barricade encircling the tumor, this innovative approach orchestrates a metamorphosis of CAFs, transitioning them from impediments to drug delivery into reservoirs of therapeutic agents. The resultant outcome, an augmentation of chemotherapy and immunotherapy efficacy, attests to the transformative potential of this concept. The study not only bequeaths novel insights and methodologies to surmount barriers in drug delivery for tumor treatment but also holds promise in elevating the precision, efficacy, and safety of tailored therapeutic regimens. Within this discourse, we meticulously evaluate Yuan et al.'s research, scrutinizing its merits and limitations, and cast a forward-looking gaze upon the formulation, validation of efficacy, and clinical translation of nanomedicines targeting CAFs.

Pancreatic ductal adenocarcinoma (PDAC) is a highly heterogeneous and aggressive form of cancer with poor prognosis.[1] Effective drug delivery is essential to overcome the numerous barriers within the body and achieve targeted, sustained, and controlled drug release for improved efficacy and reduced side effects.[2] The tumor microenvironment (TME), which consists of the extracellular matrix (ECM) and cancer-associated fibroblasts (CAFs), plays a significant role in cancer development and therapy resistance.[3]

In recent years, nanotechnology has revolutionized the field of medicine, giving rise to the development of nanomedicine and nano-delivery systems. Current research in targeting CAFs has primarily focused on CAF elimination. Through a meticulous perusal of the latest contributions disseminated across esteemed digital publication platforms, we unearthed a notable work authored by Yuan et al., as featured in *ACS Nano*. This scholarly exposition pertinently addressed the spatial dynamics of the CAF barricade encircling the neoplastic enclave. Termed the "shooting fish in a barrel" strategy, the authors ingeniously navigated the landscape of PDAC therapy.[4] The core thrust of their research resided in the transformation of CAFs, historically recognized as a formidable impediment to drug delivery, into an innate reservoir for therapeutic agents through the agency of nanomedicine.[4] By doing so, they charted an ambitious course towards the marked amplification of the therapeutic efficacy of chemotherapy and immunotherapy against PDAC.

In this study, the authors developed a novel composite nanoparticle named PI/JGC/L-A. Comprehensive characterization revealed excellent stability, high drug encapsulation efficiency, efficient escape from lysosomes, and controlled and targeted drug release of the particles. Notably, the study demonstrated the successful conjugation of the AEAA modification on PI/JGC/L-A with the Sigma non-opioid intracellular receptor 1 (Sigma 1R). The AEAA modification utilizes the binding site barrier (BSB) effect to capture nanoparticles non-specifically, thereby

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improving the targeted distribution and accumulation of drugs in CAFs. These findings provided a solid foundation for the efficient and targeted therapeutic effects of this nanoparticle system.

Based on their findings, the authors also demonstrated that the bromodomain-containing protein 4 (BRD4) inhibitor JQ1, encapsulated within the PI/JGC/L-A nanoparticle, has the ability to reprogram and normalize CAFs without causing their death or inactivation. To enhance drug targeting and efficacy while minimizing toxicity to normal cells and CAFs, the authors replaced gemcitabine with gemcitabine elaidate and IL-12 with IL-12 plasmid (pIL-12). The excellent transfection efficiency and efficient lysosome escape mediated by the BPEI proton sponge effect enable CAFs to act as an effective drug reservoir for PI/JGC/L-A. In order to investigate the release mechanism and effect of the drug from the CAF reservoir, the authors confirmed its successful release through *in vitro* and *in vivo* experiments. C18 ceramide facilitated the controlled release of exosomes loaded with gemcitabine elaidate by promoting the membrane localization of the drug. This promotes targeted drug transport from the CAF barrier to the tumor site, where it is effectively taken up by tumor cells and converted into gemcitabine, exerting its tumor-suppressive effects. Additionally, the high expression of pIL-12 in CAFs leads to the secretion of IL-12, activating infiltrating immune cells. Subsequently, the authors substantiated the enhanced anti-tumor efficacy of this formulation through a comprehensive array of both *in vivo* and *in vitro* assessments (Fig. 1).

In summation, the work presented by Yuan et al. introduced a groundbreaking stratagem poised to surmount drug delivery obstacles intrinsic to PDAC therapy, thereby amplifying the potential of chemoimmunotherapy—a prospect with broader implications across a spectrum of tumors grappling with comparable delivery hindrances. Nonetheless, while the merits of biomedical applications are discernible, an ample body of evidence to substantiate the efficacy and safety of this strategy is presently wanting.

The complexity and heterogeneity of CAFs in the TME pose challenges for understanding their mechanisms and limit treatment efficacy.[3] Prominent CAF biomarkers encompass not only α-SMA, but also palladin, S100A4 and FAP, among others.[3] Distinct subpopulations of CAFs are delineated by one or more such biomarkers, where biological contours interlace while avoiding perfect concordance.[3] Thus, this study solely employed α-SMA and collagen I as biomarkers, which may not comprehensively encapsulate the entire CAF spectrum. Exploration into the functional characterization of CAF subpopulations postulates their potential as targets to heighten the effectiveness of cancer therapeutics. It merits attention that the intricacies and variances of CAFs transcend singular histological cancer types, with distinct CAF subtype compositions and proportions potentially divergent even within similar cancer categories. Prospective investigations should encompass expanded sample types and sizes, delving further into the organ-specific and spatiotemporal attributes of CAF subtypes, thus confirming the scope of applicability for cancer treatment modalities hinging upon CAF-facilitated drug delivery.

The foundation of nanomaterial delivery lies in the use of nanoparticles as carriers. Previous studies have extensively demonstrated that the composition, particle size, morphology, and surface properties of nanoparticles play a crucial role in their tissue distribution, absorption, and elimination, and ultimately impact the efficacy and safety of pharmaceuticals.[5] In future research, increased attention should be devoted to the selection of excipients to ensure effective encapsulation and protection of the drug before reaching the target site, controlled release of the drug upon uptake by target cells, and precise spatiotemporal delivery of multiple drugs.

The specific spatial structure and inherent properties of nanomaterials dictate the need for careful consideration when selecting their payload. In their study, Yuan et al. selected three drugs with distinct effects and demonstrated their individual anti-tumor efficacy as well as their synergistic effects when combined. However, further investigation is required to determine the optimal types and dosages of the loaded drugs. Combination strategies in targeted therapy often prevent cancer cells from developing resistance and achieve effective and durable therapeutic effects.[6] Hence, when selecting and characterizing therapeutic drugs, attention must be given not only to the effects of individual drugs but also to potential drug interactions. Furthermore, careful fine-tuning and comprehensive evaluation of the types, doses, and proportions of therapeutic drugs are essential to achieve the optimal therapeutic effect. Simultaneously, the attainment of efficacious drug encapsulation emerges as a pivotal determinant warranting contemplation during the design of drug types and dosages. Considerations encompassing the physical and chemical attributes, along with the mass ratio, intrinsic to both nanocarriers and drugs, can profoundly influence encapsulation efficiency and loading capacity.[7] Concomitantly, with an escalation in the number of incorporated drugs, the synthesis trajectory of nano-medicines burgeons in complexity, invariably augmenting both preparatory intricacy and cost.

The stability, controllability, and precision of nanomaterials throughout their delivery within the body fundamentally underpin the efficacy and safety of therapeutic agents. Nano-drug delivery systems characterized by orchestrated drug comportment necessitate a comprehensive assessment spanning multiple biological barriers encompassing tissues, cells, and organelles, a strategic imperative to ensure an optimized drug therapeutic index.[8] In this context, the employed method of tail vein injection to administer PI/JGC/L-A holds potential drawbacks, potentially triggering loss and non-specific dispersion of the drug, thereby incurring unavoidable drug wastage and consequential biological toxicity in normal tissues. Consequently, future research imperatives pivot around the strategic design of nano-drug delivery systems, the formulation of effective delivery modalities, and the accomplishment of refined and calibrated drug release profiles. This requisite progress mandates upholding drug stability, circumventing assorted biological barriers across diverse drug delivery pathways.

The transformation of CAFs into a repository of therapeutic agents presents an alluring and auspicious concept, yet its realization necessitates extensive and protracted preclinical as well as clinical investigations prior to widespread clinical deployment. The distinctive physical and chemical attributes intrinsic to nano-medicines engender a therapeutic landscape distinctly divergent from that of traditional drugs, thereby introducing a distinct realm of potential safety concerns.[9] Of paramount concern, disparities observed between preclinical and clinical trial outcomes underscore the challenges arising from variances between animal tumor models and their human counterparts.[10] Addressing this quandary mandates diligent patient population screening, judicious selection of drug modality (encompassing controlled release mechanisms, routes of administration, and delivery durations), along with rigorous clinical investigations.

The trajectory toward nanomedicine industrialization necessitates the refinement of production processes, encapsulating a comprehensive analysis of nanocarrier material properties and the institution of standardized evaluation protocols. Herein, the adoption of precise and reproducible detection methodologies emerges as indispensable, ensuring formulation uniformity across production batches. Concurrently, timely equipment process updates are imperative to streamline production and curtail costs. The journey towards clinical implementation is undeniably arduous and uncertain, demanding persistent efforts. A future replete with nanomedicinal triumphs in the realm of actual cancer treatment hinges upon arduous endeavors aimed at surmounting multifarious obstacles.

The study by Yuan and colleagues presented valuable insights for future research on targeting CAFs in the TME for cancer therapy. Their approach not only eliminates the harmful effects of CAFs but also harnesses their potential as adjunct tools in cancer treatment. With the rapid advancements in nanomedicine, the precision and effectiveness of targeting CAFs for cancer therapy are expected to instill new hope in a greater number of cancer patients.

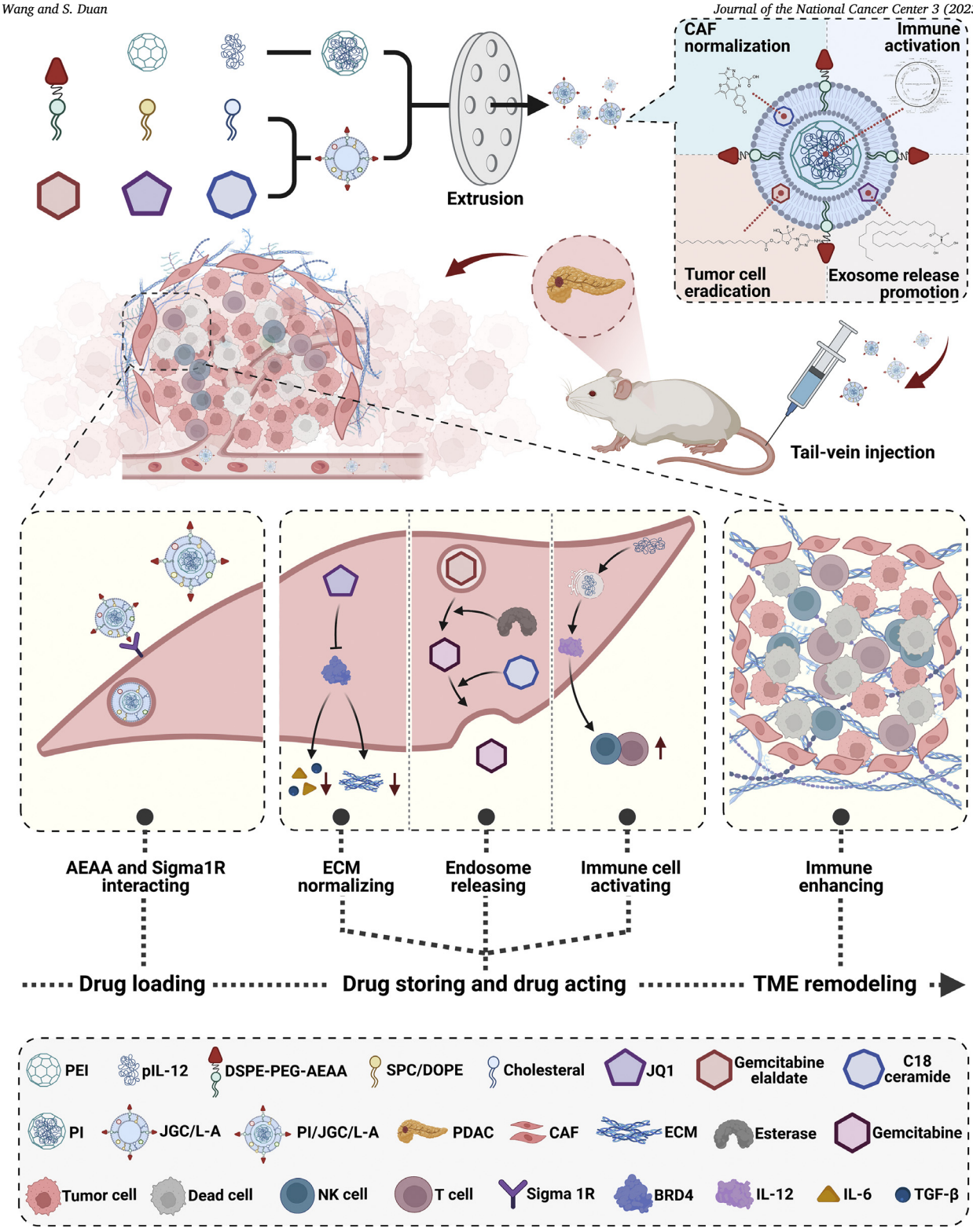

Fig. 1. Preparation, characterization, and mechanism of action of PI/JGC/L-A nanoparticles in targeting CAFs and enhancing antitumor efficacy. PI/JGC/L-A nanoparticles are formulated by combining JGC/L-A, composed of CHEMS, DOPE, SPC, and DSPE-PEG-AEAA, with PI, composed of BPEI and pIL-12. These nanoparticles are designed to encapsulate three drugs, namely, JQ1, C18 ceramide, and gemcitabine elaidate. Intravenous administration of PI/JGC/L-A allows its delivery to the TME of PDAC via the circulatory system. Within the TME, the DSPE-PEG-AEAA surface modification of PI/JGC/L-A enables its targeting of CAFs by binding to the Sigma 1R receptor present on their surface. Subsequently, the nanoparticles enter the CAFs and release the loaded drugs. JQ1 facilitates the formation of drug-loaded "barrels" and normalizes CAFs by promoting ECM remodeling. Under the influence of C18, gemcitabine elaidate is converted to gemcitabine, which is then loaded onto CAF exosomes and released, leading to cancer cell death within the "barrel". Moreover, pIL-12 expression results in the secretion of IL-12, stimulating immune cell activity and proliferation within the "barrel". The synergistic effect of these active ingredients promotes TME remodeling, while the combination of chemotherapy and immunotherapy achieves a superior antitumor effect. CAFs, cancer-associated fibroblasts; CHEMS, cholesteryl hemisuccinate; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DSPE-PEG-AEAA, 1,2-distearoyl-sn-glycero-3-phosphoe-thanolamine-poly(ethylene glycol)-aminoethyl anisamide; ECM, extracellular matrix; PDAC, pancreatic ductal adenocarcinoma; PI, cationic inner core; pIL-12, IL-12 plasmid; SPC, soybean lecithin; TME, tumor microenvironment.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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Author contributions

X.S. conducted the original draft. X.S. and Z.W. performed the visualization. S.D. conducted the revision.

References

1. Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer – clinical challenges and opportunities. *Nat Rev Clin Oncol*. 2020;17:527–540. doi:10.1038/s41571-020-0363-5.
2. Wang J, Ni Q, Wang Y, et al. Nanoscale drug delivery systems for controllable drug behaviors by multi-stage barrier penetration. *J Control Release*. 2021;331:282–295. doi:10.1016/j.jconrel.2020.08.045.
3. Lavie D, Ben-Shmuel A, Erez N, et al. Cancer-associated fibroblasts in the single-cell era. *Nat Cancer*. 2022;3:793–807. doi:10.1038/s43018-022-00411-z.
4. Yuan S, Mu W, Liu S, et al. Transforming cancer-associated fibroblast barrier into drug depots to boost chemo-immunotherapy in “shooting fish in a barrel” pattern. *ACS Nano*. 2023. doi:10.1021/acsnano.3c02272.
5. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015;33:941–951. doi:10.1038/nbt.3330.
6. Jin H, Wang L, Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nat Rev Drug Discov*. 2023;22:213–234. doi:10.1038/s41573-022-00615-z.
7. Liao LY, Liu J, Dreaden EC, et al. A convergent synthetic platform for single-nanoparticle combination cancer therapy: ratiometric loading and controlled release of cisplatin, doxorubicin, and camptothecin. *J Am Chem Soc*. 2014;136:5896–5899. doi:10.1021/ja502011g.
8. Wang JJ, Ni QK, Wang YF, et al. Nanoscale drug delivery systems for controllable drug behaviors by multi-stage barrier penetration. *J Control Release*. 2021;331:282–295. doi:10.1016/j.jconrel.2020.08.045.
9. Shi JJ, Kantoff PW, Wooster R, et al. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer*. 2017;17:20–37. doi:10.1038/nrc.2016.108.
10. Li W, Tang J, Lee D, et al. Clinical translation of long-acting drug delivery formulations. *Nat Rev Mater*. 2022;7:406–420. doi:10.1038/s41578-021-00405-w.