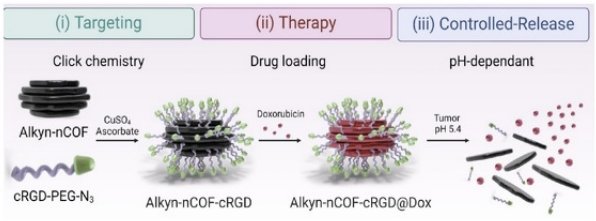
Tumor-Targeting Nanoparticles for Precision Chemotherapy in Cancer

Precision drug delivery system to enhance on-target drug potency while minimizing off-target effects and toxicity.



Schematic illustrating the formation and properties of COF-based NP drug delivery systems. Alkyn-nCOF is conjugated with cRGD-PEG-N3 peptides via click chemistry to form Alkyn-nCOF-cRGD, which can be subsequently loaded with a chemotherapeutic cargo (e.g., doxorubicin (Dox)) for pH-sensitive release in the acidic tumor microenvironment.

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Technology

The Trabolsi lab at NYU Abu Dhabi has developed pH-sensitive, covalent organic framework (nCOF) nanoparticles (NPs) that are externally conjugated with tumor-targeting RGD peptides for precise delivery of chemotherapeutics to tumor sites (see schematic). The enhanced NP specificity results from (i) selective payload release in acidic conditions common to tumor microenvironments and (ii) targeting by surface-conjugated RGD peptides to tumor cells overexpressing cell surface markers (such as αvβ3 integrins in triple negative breast cancer [TNBC]). The approx. 60nm diameter NPs were synthesized by conjugating alkyne-functionalized nCOFs (Alkyn-nCOFs) to azide-pegylated cyclic RGD peptides (cRGD-PEG-N3) by copper-mediated click chemistry to yield imine-linked Alkyn-nCOF-cRGD NPs. Such NPs loaded with the tool compound doxorubicin (Alkyn-nCOF-cRGD@Dox) showed Dox release at pH 5.4 within 24 hours, while remaining stable (<15% Dox release) at physiological pH 7.4. In proof-of-concept studies (*Benyettou et al., ACS Appl Mater Interfaces 2024*), the research team evaluated the efficacy and specificity of Alkyn-nCOF-cRGD@Dox NPs in a TNBC tumor model (NU/J mice with MDA-MB-231 tumors) by administering intraperitoneal injections of Alkyn-nCOF-cRGD@Dox, Alkyn-nCOF@Dox, Dox, or saline. The Alkyn-nCOF-cRGD@Dox-treated group showed a notable 95% reduction in tumor growth relative to the Alkyn-nCOF@Dox and free Dox control groups, which exhibited decreases of 65% and 67%, respectively. In conclusion, these Alkyn-nCOF-cRGD NPs provide several favorable characteristics for drug delivery (selective payload release, precision targeting, high tumor retention, and effective systemic elimination), which altogether can improve treatment efficacy and reduce off-target risks associated with conventional

nontargeted therapies for TNBC and other cancers.

Development Status

The NYU inventor plans on translating the promising proof-of-concept results into preclinical validation and potential clinical readiness. The specific goals include: 1) advanced PK, toxicity, and biodistribution studies; 2) mechanistic studies; 3) expansion to additional solid tumor cancer models; and 4) scale-up of COF synthesis and manufacturing.

Background

Breast cancer is one of the most prevalent cancers worldwide, with approximately 2.3 million new cases and 685,000 deaths reported in 2020, accounting for 11.7% of all cancer diagnoses and 15% of cancer-related deaths globally. In the United States, 1 in 8 women will develop invasive breast cancer during their lifetime, making it the second leading cause of cancer death among women, behind lung cancer. Additionally, approximately 20-30% of breast cancers are classified as triple-negative, characterized by an aggressive phenotype with conventional chemotherapy as the only viable treatment option, which often has severe side effects (nausea, hair loss, fatigue) and lower efficacy. The need for more targeted treatments has led to the exploration of novel approaches, such as nanoparticle-based drug delivery systems. COFs have recently emerged as promising candidates for drug delivery due to their uniform pore size, high surface area, customizable porosity, and pH-responsive behavior, which enable consistent drug loading, controlled release, and targeted delivery to acidic tumor environments, thereby optimizing treatment efficacy and minimizing impact on healthy tissue. By leveraging the unique properties of nanoparticles, such as their ability to enhance drug stability and targeting, researchers are developing new strategies to improve drug delivery precision and reduce side effects.

Applications

Solid tumor cancers such as:

- Breast cancer (triple negative), lung, cervical, pancreatic, colorectal, prostate, and ovarian

Advantages

- **Targeted delivery:** The surface-functionalized RGD peptides allow for precise targeting of NPs to cancer cells
- **Selective payload release:** NPs release cargo only in acid conditions, which are common to tumor microenvironments
- **Reduced side effects:** Precision delivery of chemotherapeutics by NPs to tumor cells minimizes adverse off-target effects
- **Tunable platform:** Structural properties of COF NPs can be readily customized to enable desired drug release characteristics.
- **Reliable delivery:** COF NP homogeneity (NP size, pore size, and porosity) affords consistent drug loading and controlled release profiles
- **Long-term biocompatibility:** NPs are composed of biodegradable COFs without known safety concerns

Intellectual Property

NYU has filed a PCT application covering the nanoparticle compositions (COFs variations functionalized with RGD peptides and loaded with various chemotherapeutic cargos) and the method of using such compositions for the treatment of cancer.

References

1. Benyettou, Farah et al. , https://pmc.ncbi.nlm.nih.gov/articles/PMC11503616/#sec3