#Drug delivery systems

For a treatment of osteosarcoma

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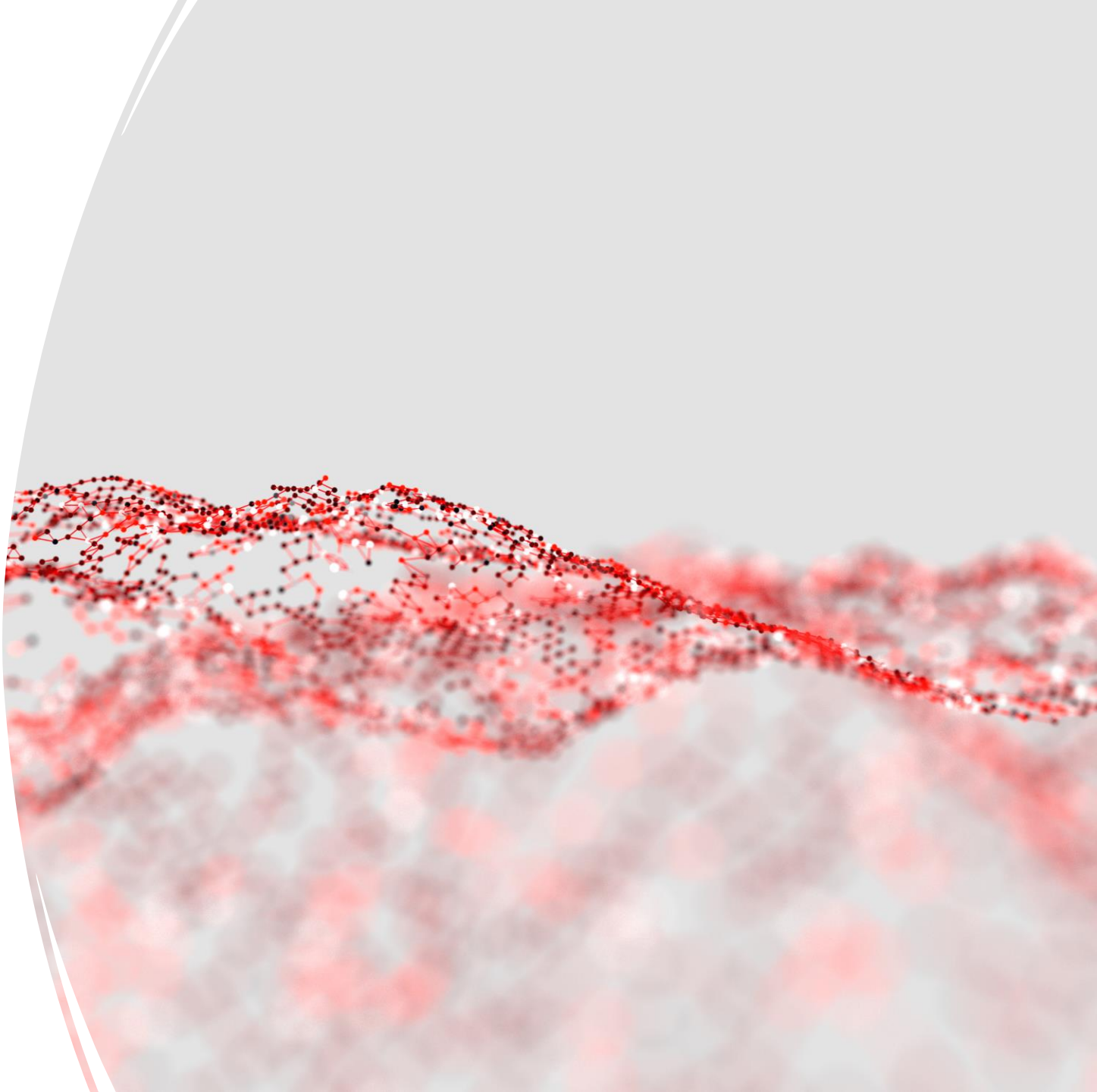
Outlook

- Osteosarcoma is the most common primary malignant bone tumor mainly occurred in children and adolescence, and chemotherapy is limited for the side effects and development of drug resistance.
- Advances in nanotechnology and knowledge of cancer biology have led to significant improvements in developing tumor-targeted drug delivery nanocarriers, and some have even entered clinically application.
- Various drug delivery nanocarriers have been designed and tested for osteosarcoma treatment, but most of them are still at experimental stage, and more further studies are needed before clinical application.

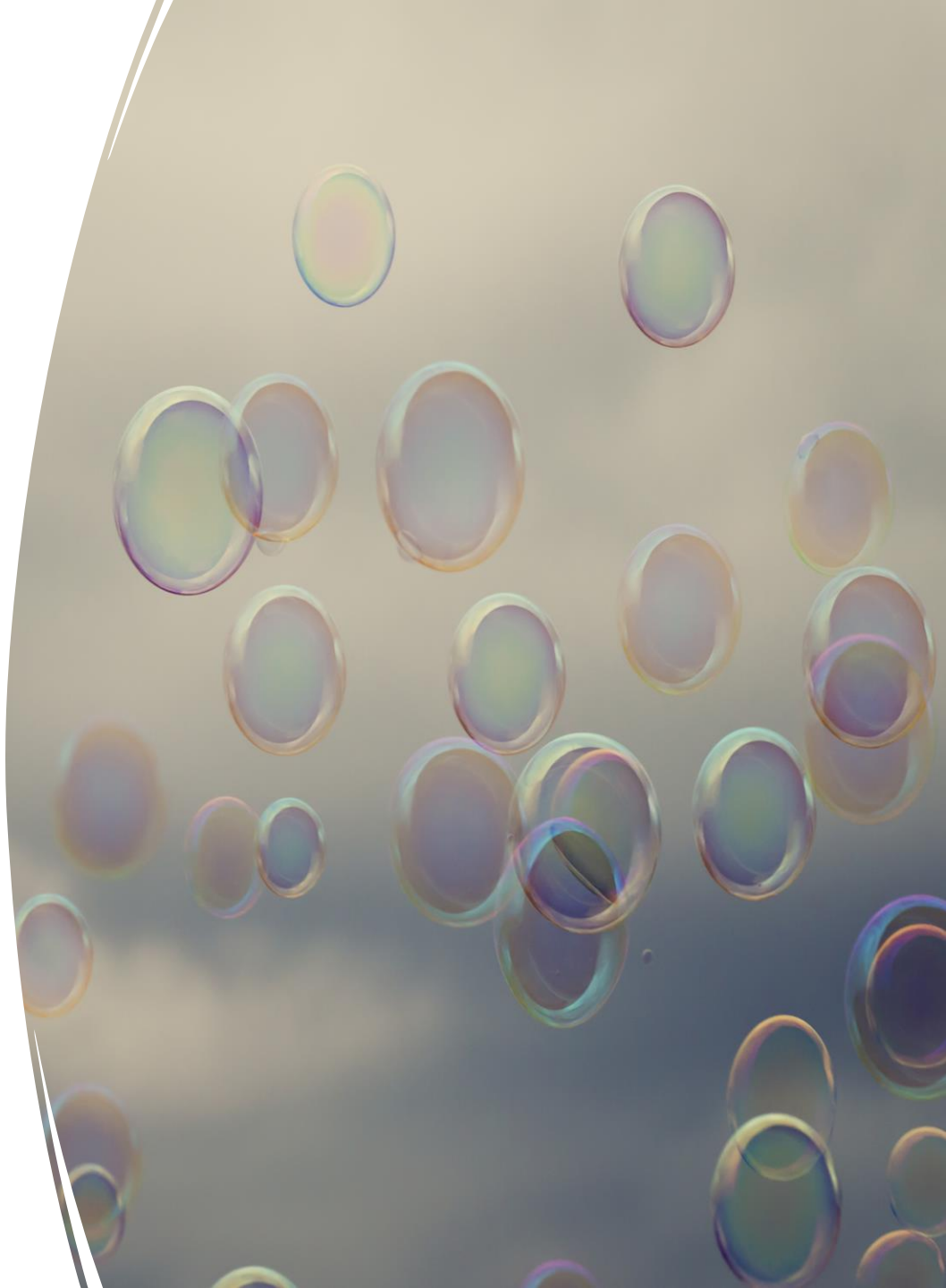
Introduction

- Nanosized drug delivery systems can be roughly classified into organic and inorganic carriers.
- Organic nanocarriers reported for osteosarcoma drug delivery mainly include liposomes, polymers, micelles, and dendrimers.
- Inorganic nanocarriers mainly include metallic nanoparticles, mesoporous silica nanomaterials, carbon-based nanomaterials, and calcium phosphates carriers.



Liposomes

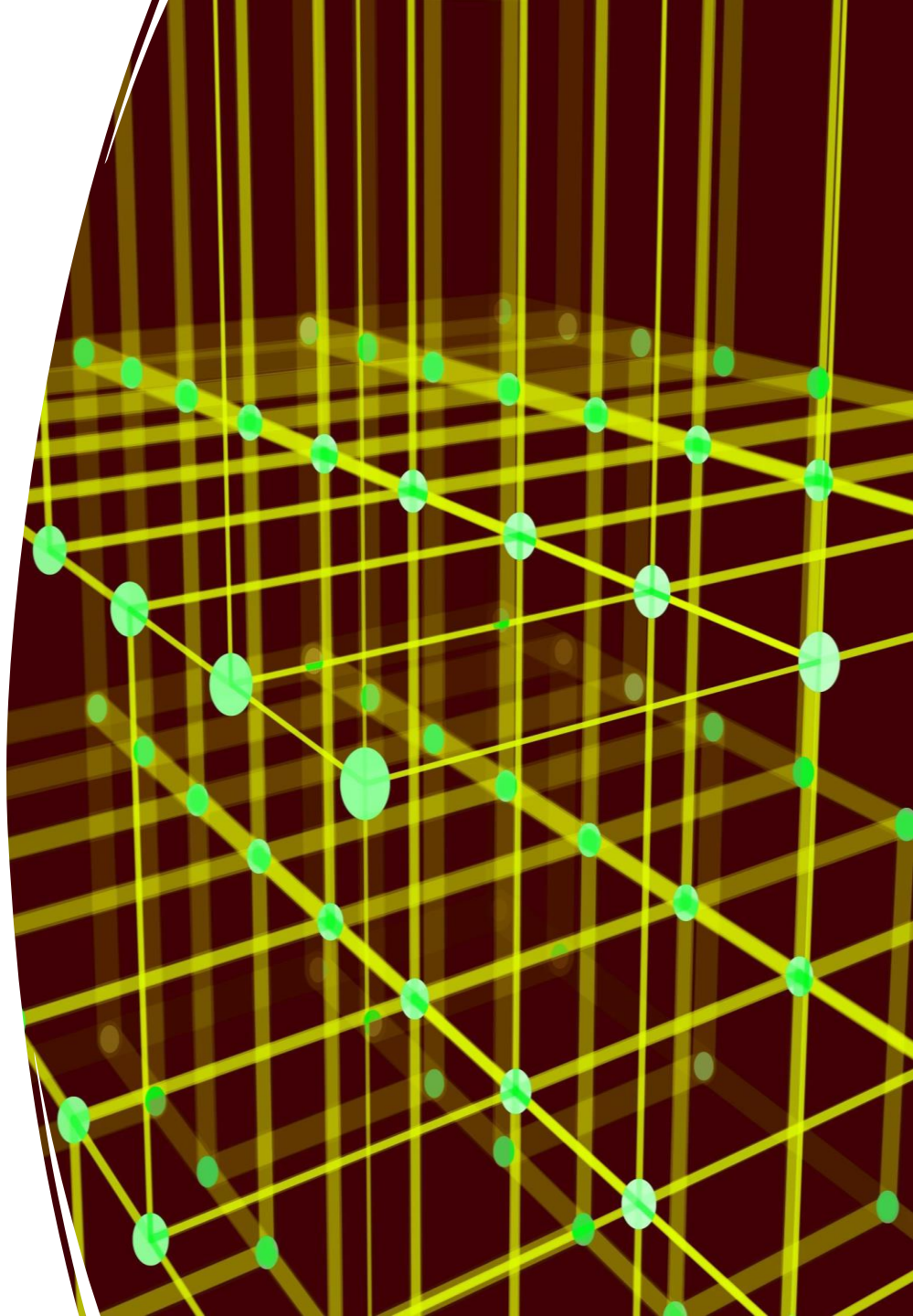
- Liposomes are spherical vesicles with a hydrophilic cavity surrounded by one or several lipid bilayers that allows the encapsulation of drugs with different solubility.
- Clinical trials have demonstrated that inclusion of liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE) could clinically and significantly improved the long-term survival of osteosarcoma patients.
- Surface modification with biocompatible hydrophilic polymers, such as polyethylene glycol (PEG), could help liposomes to escape from RES and prolong the circulation time.
- Other polymers such as chitooligosaccharides (COS) have been investigated for liposome modification



Meyers PA, Chou AJ. Muramyl tripeptide-phosphatidyl ethanolamine encapsulated in liposomes (L-MTP-PE) in the treatment of osteosarcoma. Adv Exp Med Biol. 2014;804:307–21.

Polymers

- Among others, preferably methotrexate, keratin, PEG-functionalized PLGA, HA are being evaluated.
- Due to its excellent biocompatibility and biodegradability, an *in situ* crosslinked nanogel based on HA has been synthesized for codelivery of DOX and cisplatin, two of the most widely clinically used chemo-drugs with proved synergistic effects, to osteosarcoma



Suksiriworapong J, Taresco V, Ivanov DP, Styliari ID, Sakchaisri K, Junyaprasert VB. et al. Synthesis and properties of a biodegradable polymer-drug conjugate: Methotrexate-poly(glycerol adipate) Colloids Surf B Biointerfaces. 2018;167:115–25.

Micelles

- Micelles are usually formed by amphiphilic polymers and have attracted considerable attention as promising nanocarriers for drug delivery.
- Polymeric micelles consist of a core and shell structure.
- In principle, the micelle core part is usually hydrophobic and can encapsulate poorly water-soluble agent, whereas the outer shell is able to stabilize the micelles in aqueous environment and can be modified with stimuli-responsive or tumor-targeting moieties.
- Delivery of DOX, ZnPc.
- Micelles are highly stable in aqueous environment due to their low critical micellar concentration; they may also tend to be dissociated in dilution or high ionic strength.

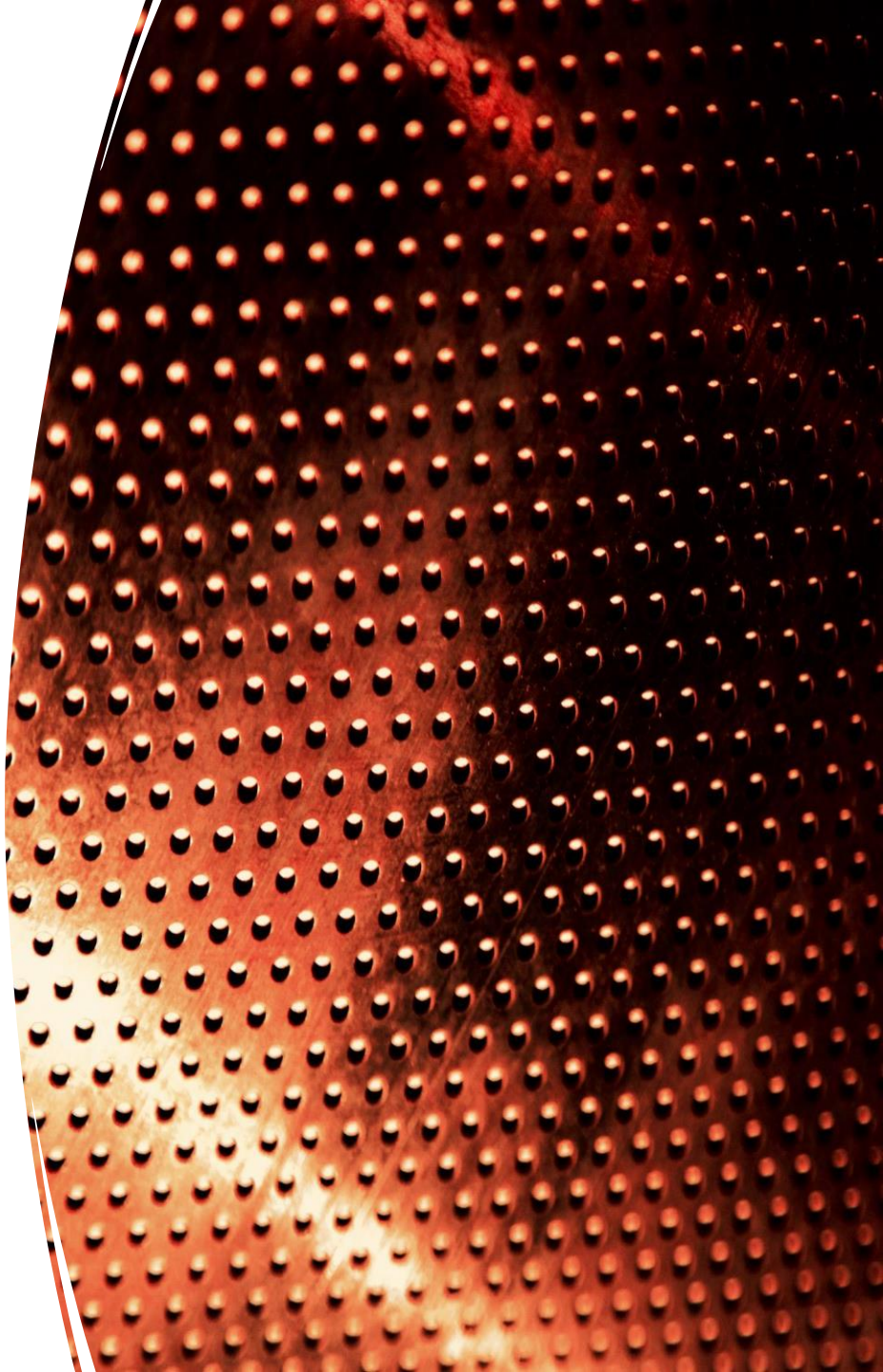
Dendrimers

- Dendrimers are nanoscale, globular, radially symmetric, water-soluble macromolecules with well-defined sizes, branched structures, and high density of modifiable functional groups.
- Nanogels containing DOX was synthesized by incorporating generation 5 (G5) PAMAM dendrimers and DOX into alginate (AG) nanogels.
- A triazine-modified dendrimer G5-DAT66 has been prepared and used for TRAIL gene delivery.

Wang Y, Li L, Shao N, Hu Z, Chen H, Xu L. et al. Triazine-modified dendrimer for efficient TRAIL gene therapy in osteosarcoma. Acta Biomater. 2015;17:115–24.

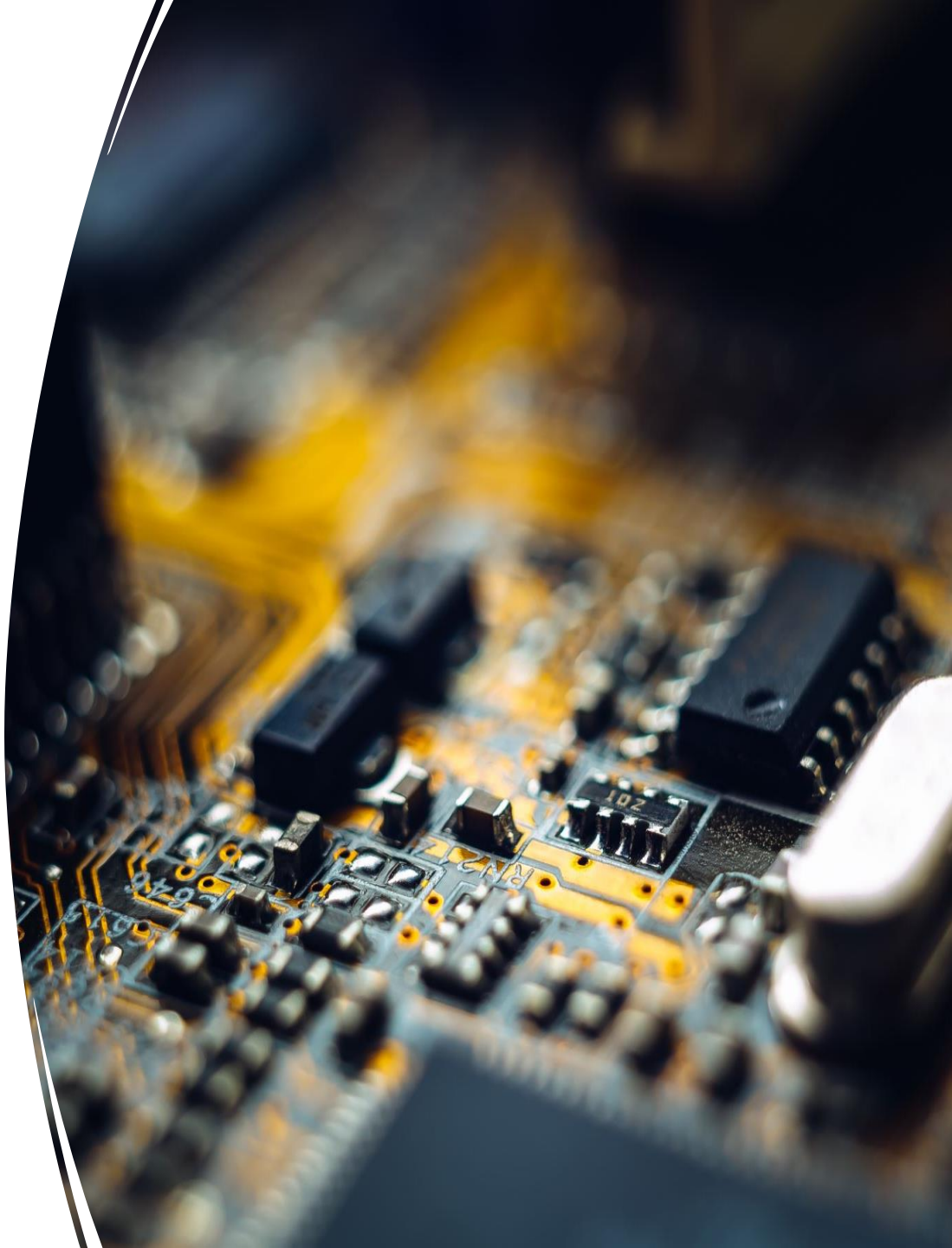
Metalic nanocarriers

- Metallic nanocarriers can be pure metallic particles such as gold, silver, and copper; or metallic compound such as oxides and Mxene; or hybrid polymers that consist of metal ions or clusters such as metal organic frameworks (MOFs)
- AuNPs are the most used due to their photothermal properties.
- Fabricated Gemcitabine conjugated magnetite nanoparticles.
- However, Fe_3O_4 nanoparticles were reported to tend to agglomerate in biological conditions.



Mesoporous silica nanocarriers

- FDA recognized biosafety.
- The large surface area and the porous structure enable MSNs to have high loading capacity with different agents.
- Surface modification with different functional groups allows MSNs to realize tumor targeting and controlled drug release.
- Delivery of siRNA, DOX.
- Combination with PEG – ultrasound detachment.
- MSNs are considered to have the potential to be a more promising platform for cancer therapy compared to other inorganic nanocarriers such as copper, gold, and silver which exhibit some cytotoxicity.



Kesse S, Boakye-Yiadom KO, Ochete BO, Opoku-Damoah Y, Akhtar F, Filli MS, Mesoporous Silica Nanomaterials: Versatile Nanocarriers for Cancer Theranostics and Drug and Gene Delivery. Pharmaceutics; 2019. p. 11.

Carbon-based nanocarriers

- GO and CNTs are being applied.
- Good physicochemical properties including easily-modified surface, excellent photo-thermal conversion ability, supramolecular π-π stacking, and high adsorption ability.
- Delivery of DOX, TRA, siRNA, cis-Pt, caspase-3 and others.