From Prodrugs to Self-Assembling Prodrugs: Pros and ~~Cons~~

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Department of Oncology and Center for Nanomedicine, School of Medicine
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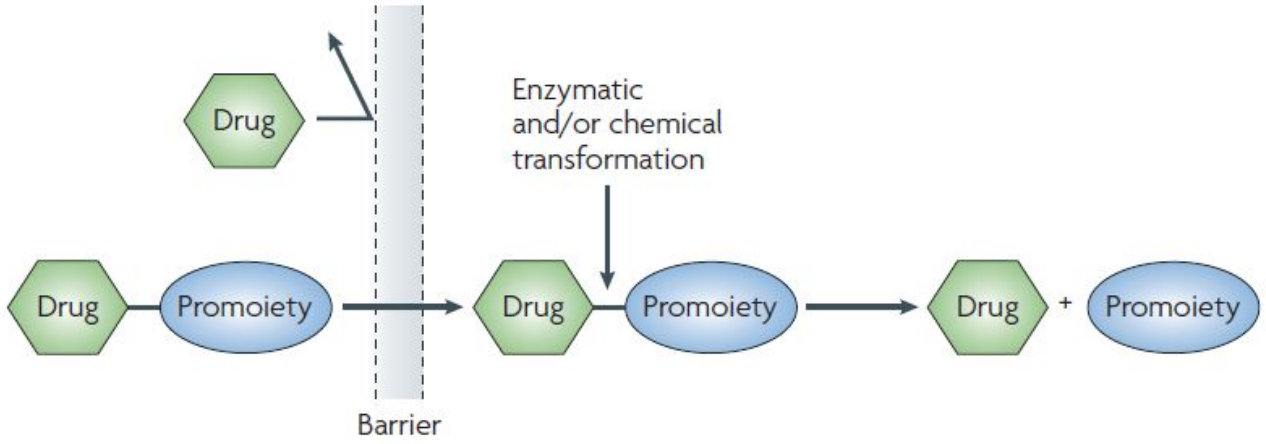
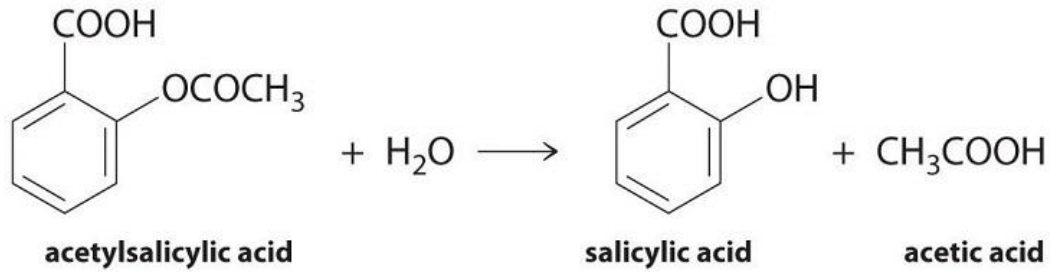
Controlled Release Society Annual Meeting, Montreal,
Canada
July 13, 2022

From Prodrugs to Self-Assembling Prodrugs

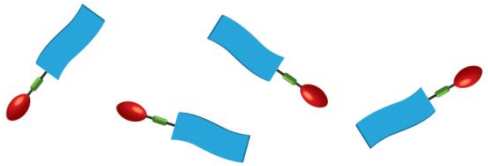


About 10% of marketed drugs are prodrugs



Aspirin hydrolysis

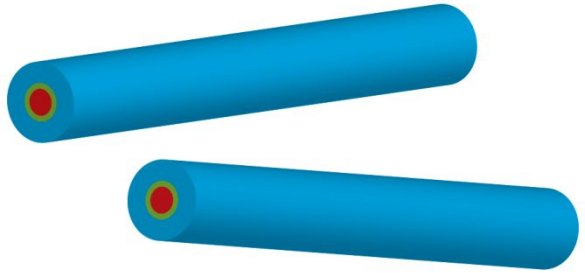
- **Help to overcome biological and pathological barriers and optimize the so-called "drug-like" properties. ADMET: absorption, distribution, metabolism, excretion, and toxicity.**
- **Aqueous solubility, instability, patient acceptability, formulation problems and site specificity.**



Self-Assembling Prodrugs

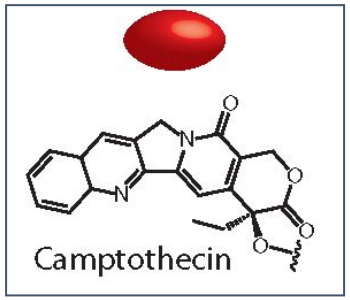
Assembly

Water

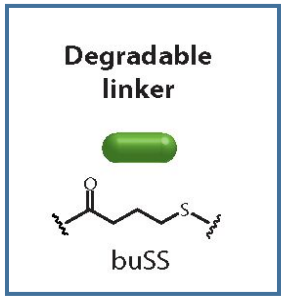


Journal of Controlled Release, 2015, 219, 383-395; ***Chemical Society Reviews***, 2017, 46 (21), 6638-6663;
Advanced Drug Delivery Reviews, 2017, 110-111, 112-126; ***Trends in Pharmacological Sciences,*** 2022, 43 (6) 510-521

The Concept of Self-Assembling Prodrugs: Camptothecin (CPT) as an Example

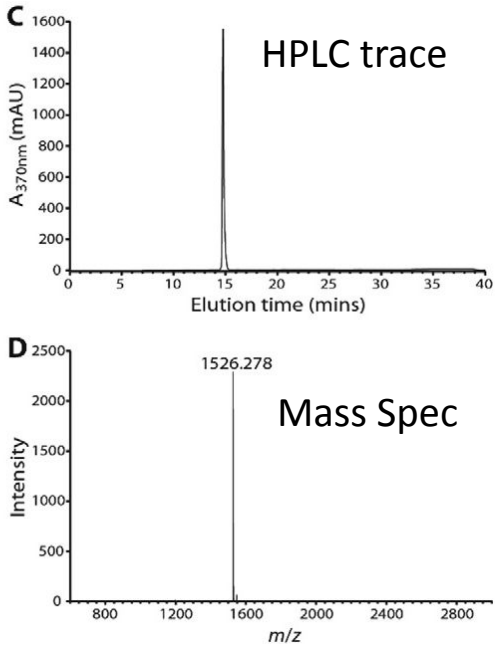


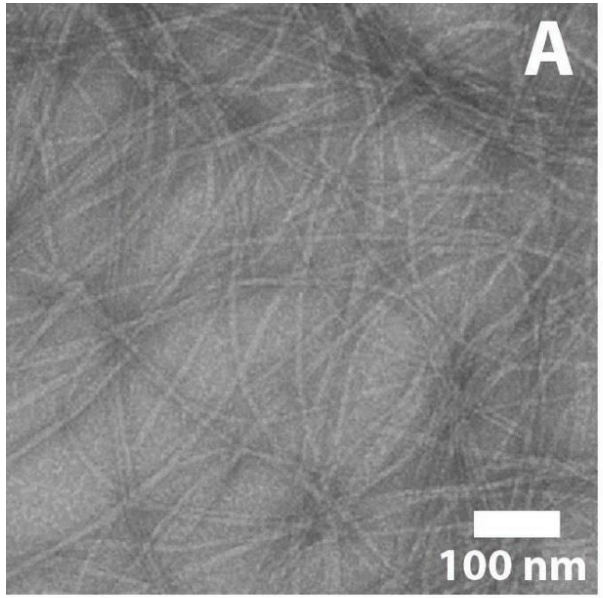
Drug:
hydrophobic

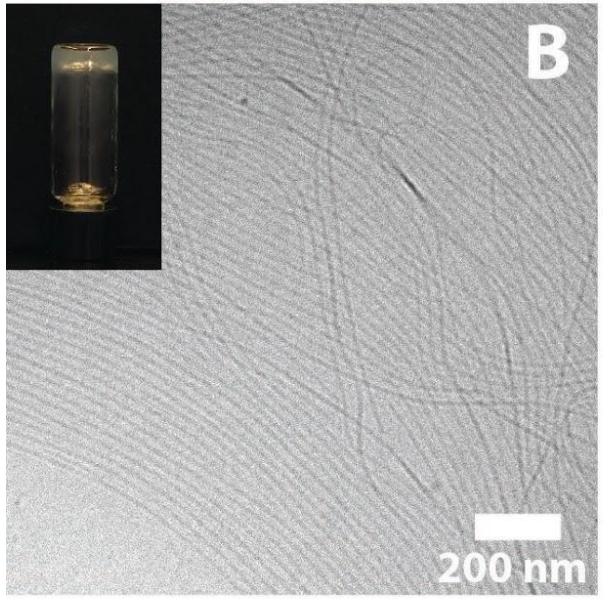


Linker:
Biodegradable

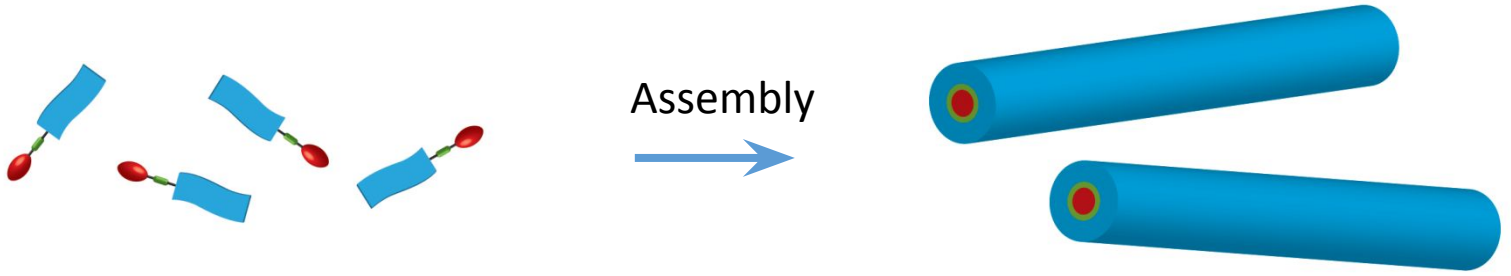
Peptide:
hydrophilic &
self-assembling





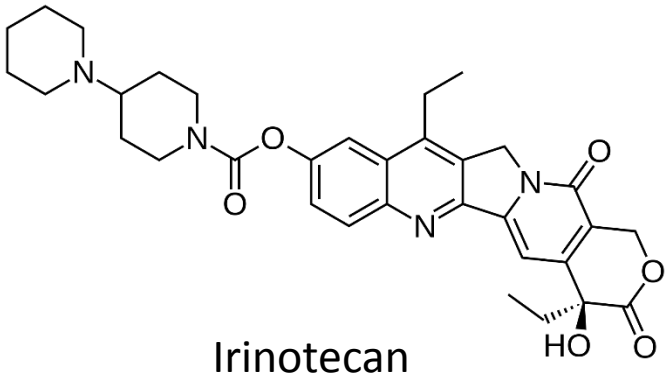


Self-assembly into nanostructures is promoted when dissolving in water

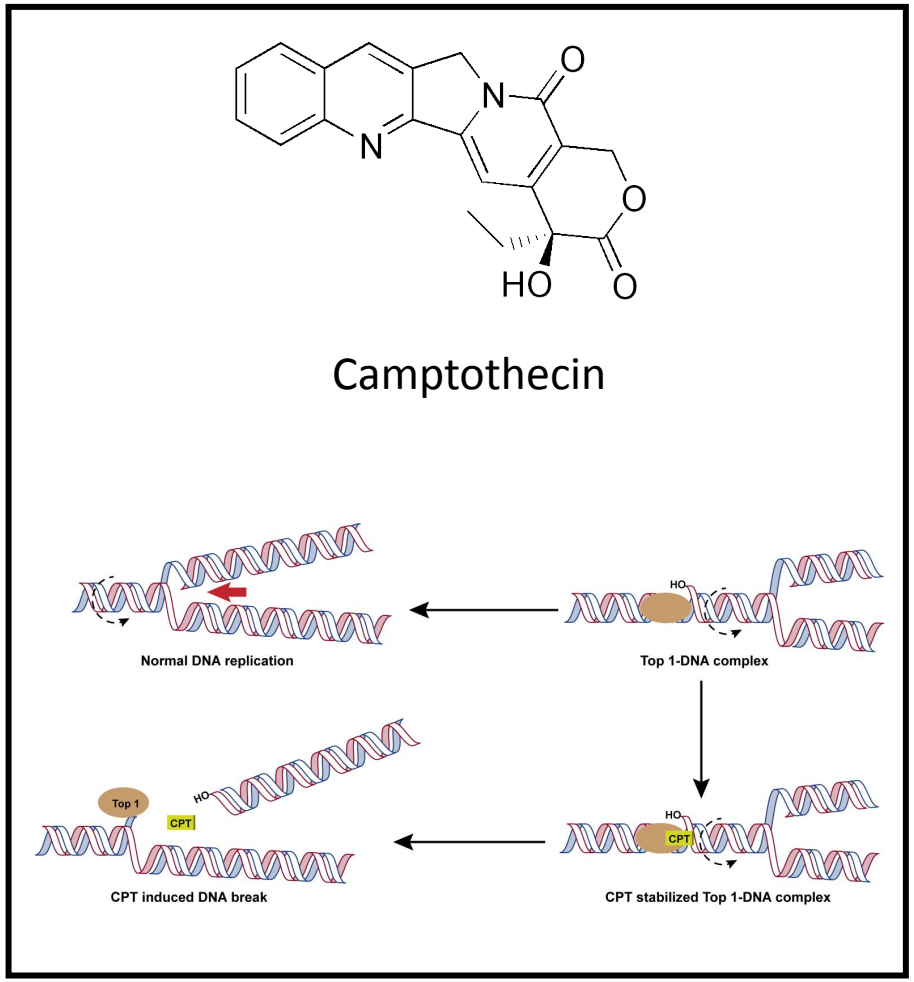


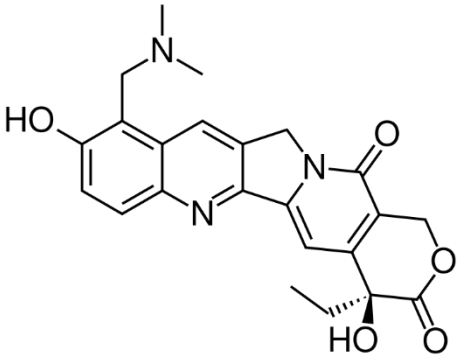
Cheetham, A. G.; Zhang, P.; Lin, Y.-A.; Lock, L. L.; Cui, H., *Journal of the American Chemical Society*, 2013, 135 (8), 2907-2910.

Camptothecin Prodrugs in Clinic



Irinotecan





Topotecan

Camptosar® (Pfizer)

FDA approval for **Metastatic Colorectal Cancer (1996)**

Annual Sale: $969 million (2007)

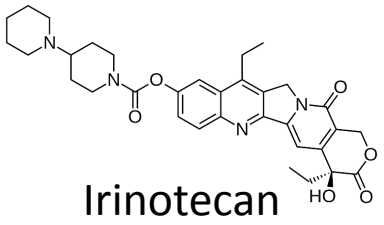
Hycamtin®

(GlaxoSmithKline)

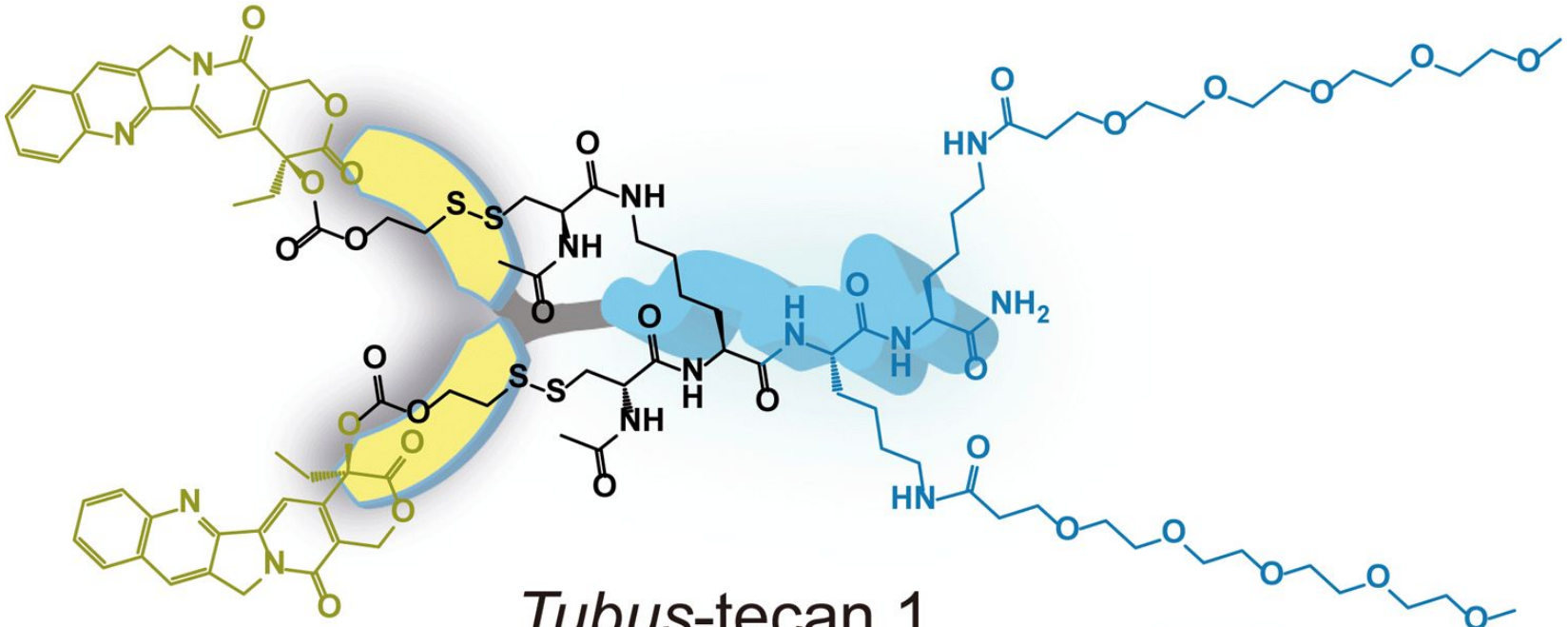
FDA approval for **Ovarian Cancer (1996), Cervical Cancer (2006),** and **Small Cell Lung Cancer (2007)**

Annul Sale: $ 140 million (2010)

Tubustecan 1-OEGylated Camptothecin Prodrug



Irinotecan



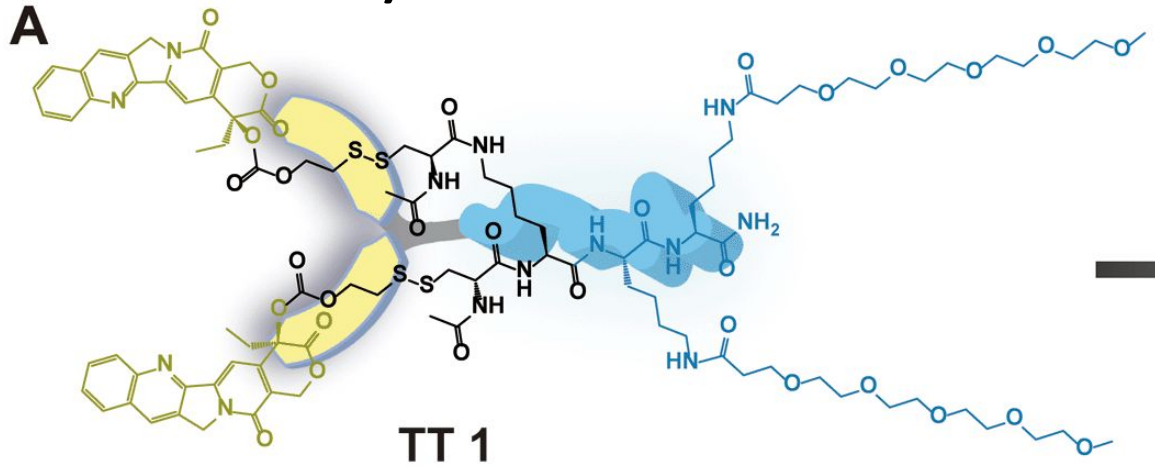
Hydrophobic drug

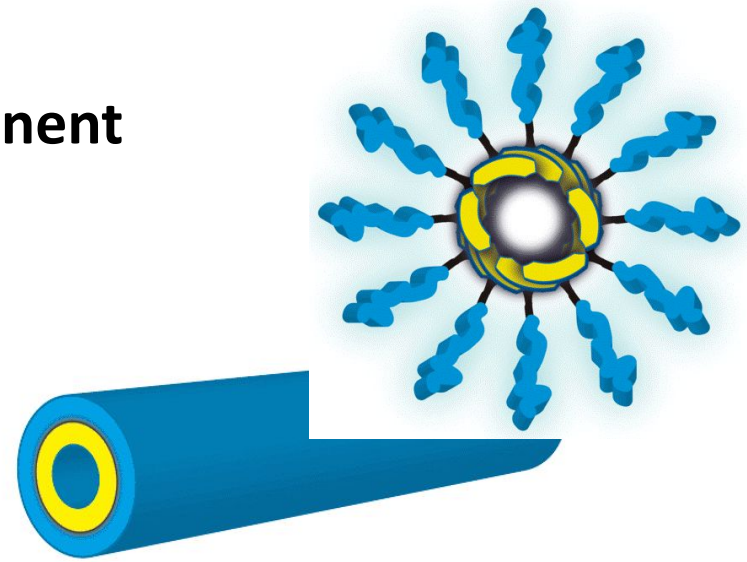
Biodegradable linker

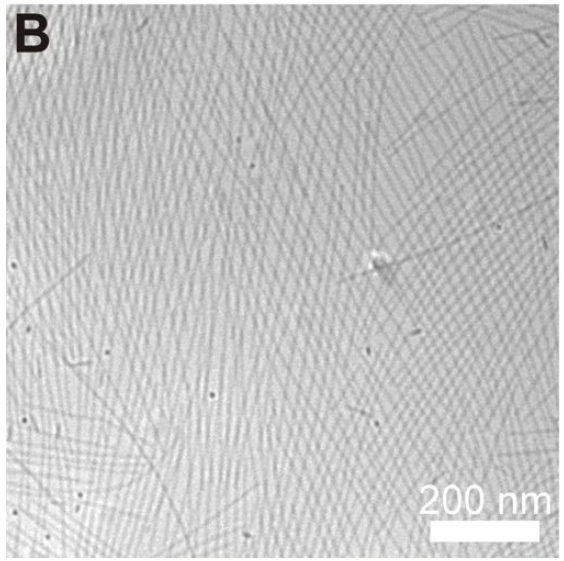
Hydrophilic auxiliary

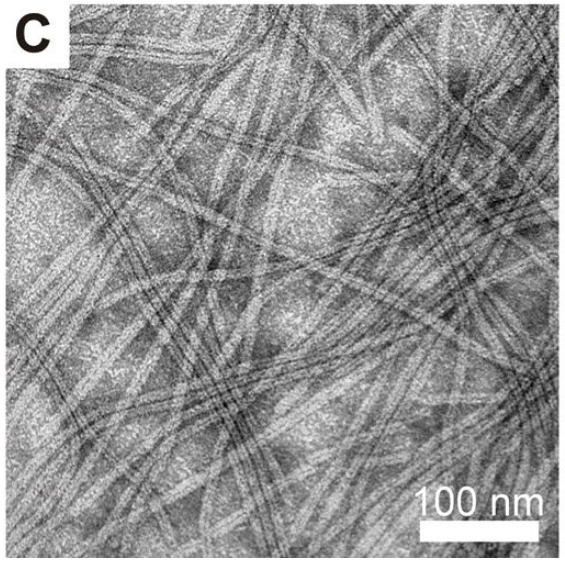
Cheetham, A. G.; Zhang, P.; Lin, Y.-A.; Lock, L. L.; Cui, H., *JACS*, 2013, 135 (8), 2907-2910.
Su, H.; Wang, F.; Wang, Y.; Cheetham, A.G.; Cui, H., *JACS,* 2019, 141 (43), 17107-17111
Su, H.; Wang, F.; Ran, W.; Zhang, W.; Dai, W.; Wang, H.; Anderson, C.F.; Wang, Z.; Zheng, C.; Zhang, P.; Li, Y.; Cui, H., **PNAS**, 2020, 117 (9) 4518-4526.

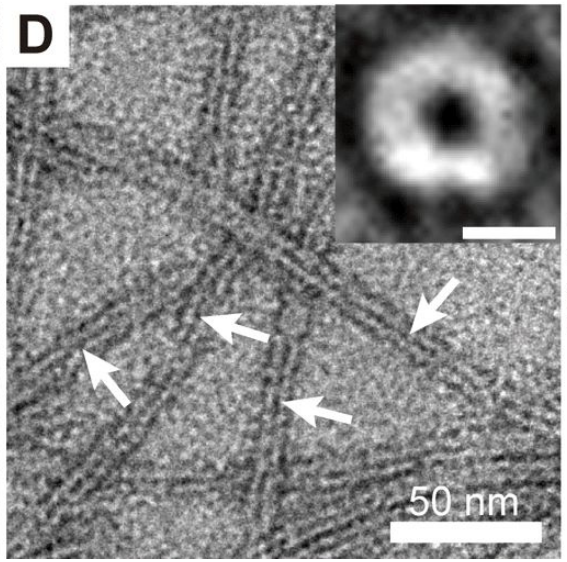
From hydrophobic anticancer drugs to prodrugs that can *self-assemble*, *self-deliver* and *self-formulate* (a.k.a. one-component nanomedicine)

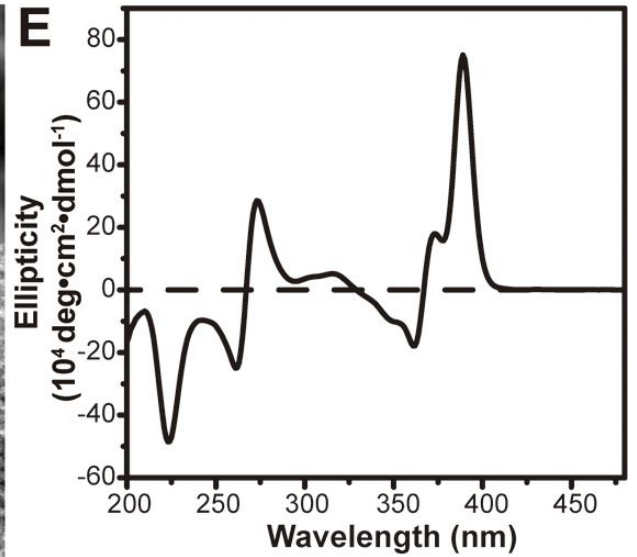








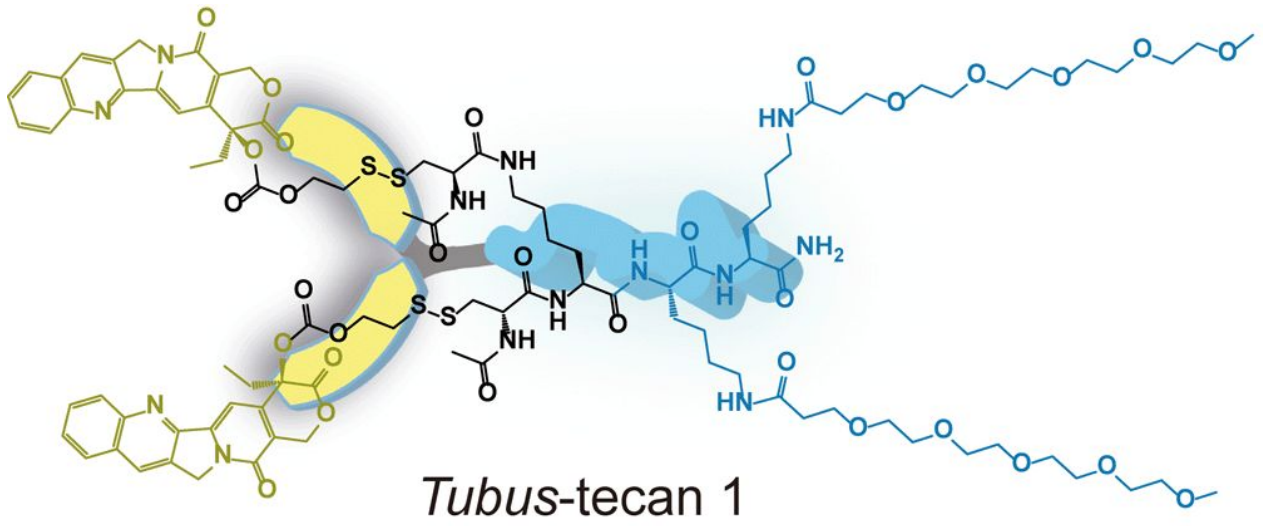


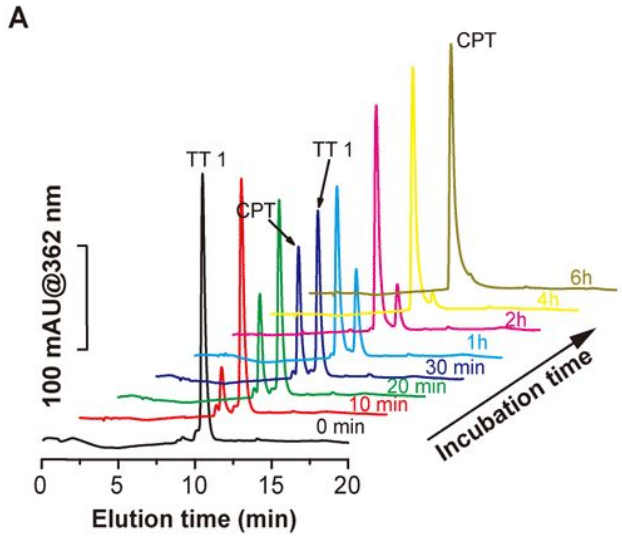


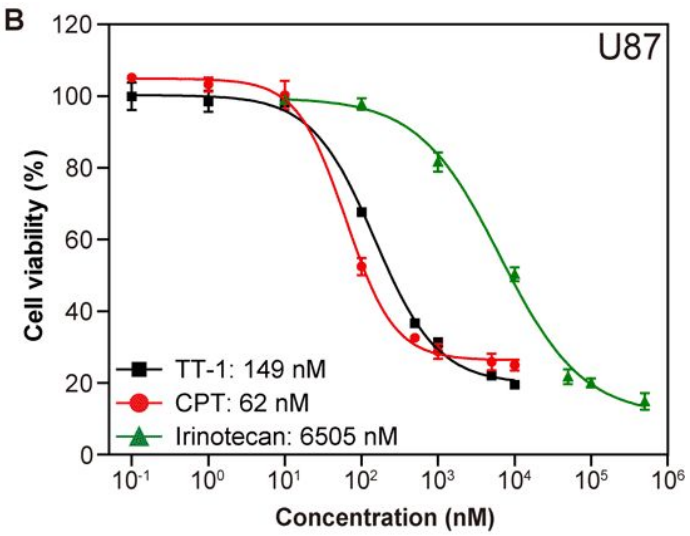
Su, H.; Wang, F.; Wang, Y.; Cheetham, A.G.; Cui, H., ***Journal of the American Chemical Society*** 2019, 141 (43), 17107-17111

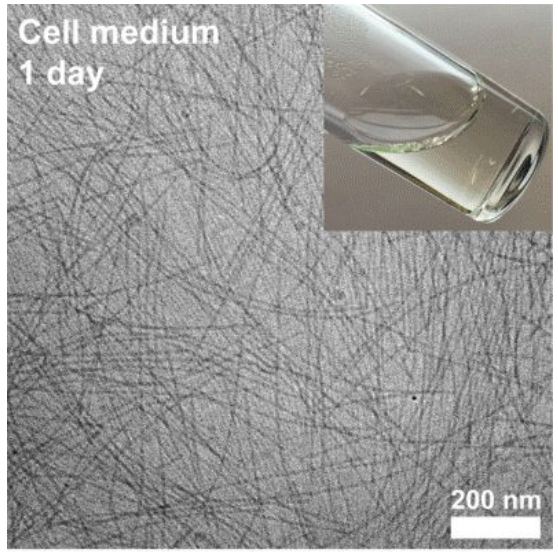
Su, H.; Wang, F.; Ran, W.; Zhang, W.; Dai, W.; Wang, H.; Anderson, C.F.; Wang, Z.; Zheng, C.; Zhang, P.; Li, Y.; Cui, H., **PNAS**, 2020, 117 (9) 4518-4526.

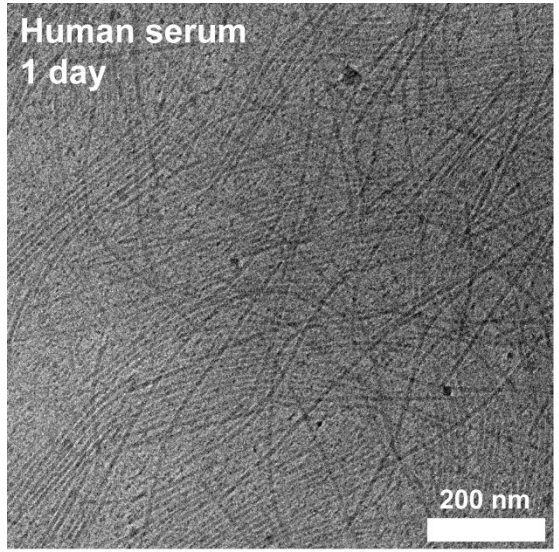
Tubustecan 1 can effectively release free CPT, show great efficacy against cancer cells and exhibit an excellent stability in human serum

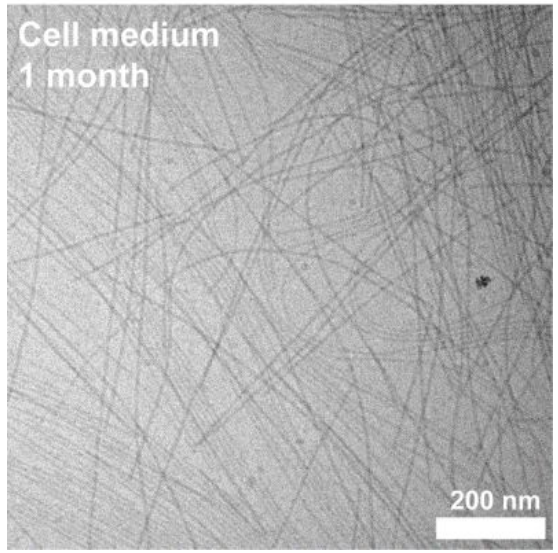


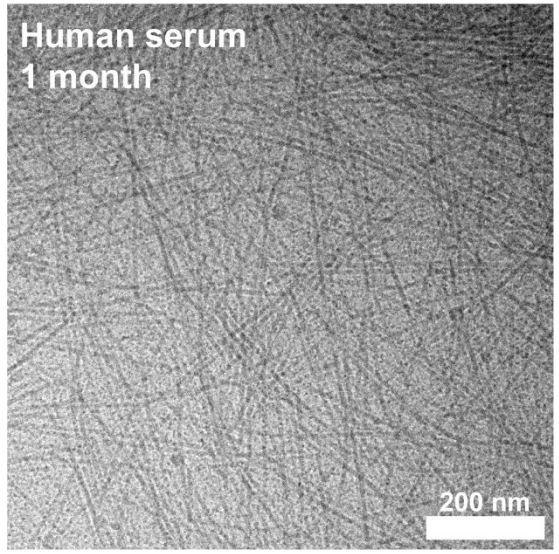




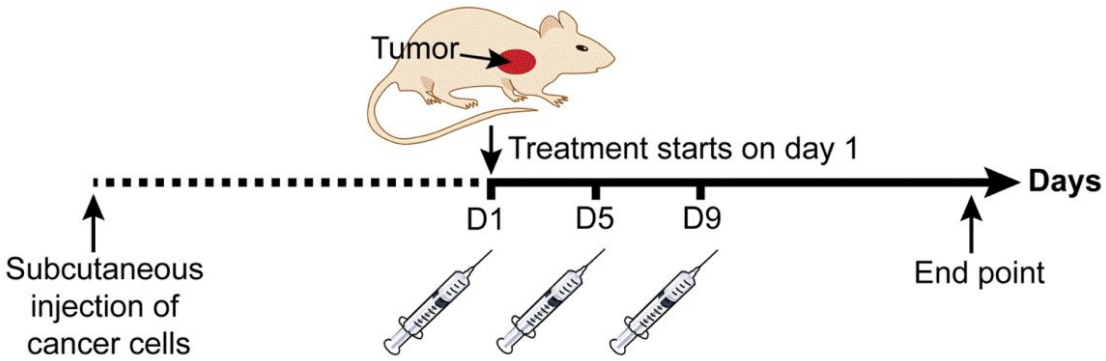


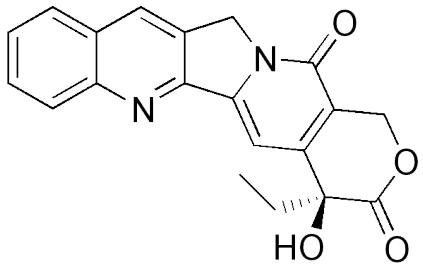




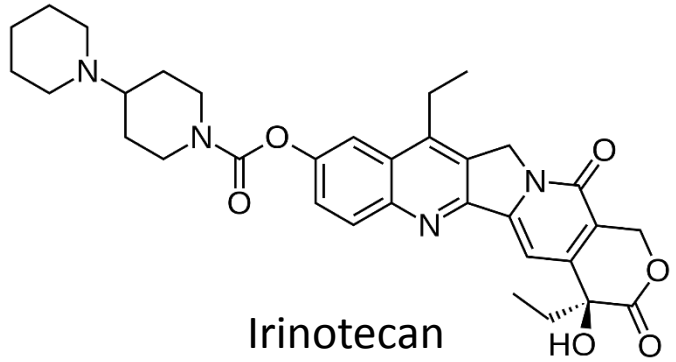


Tubustecan outperforms irinotecan: assembly into tubular nanostructures improves *maximal tolerated dose*, and results in *greater tumor suppression* and *prolonged survival*.

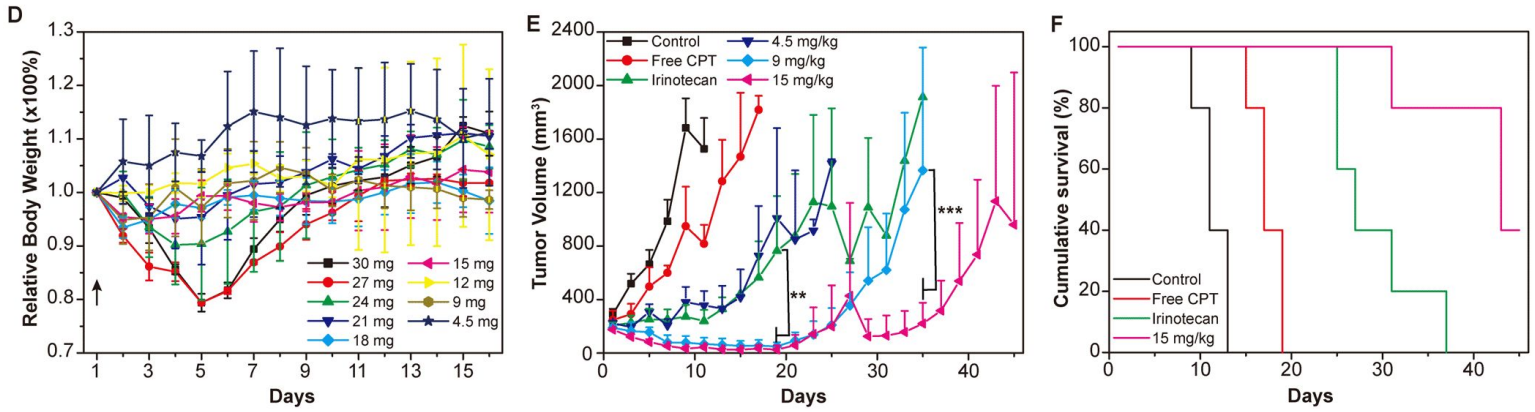




Camptothecin



Irinotecan



Camptosar® (Pfizer)

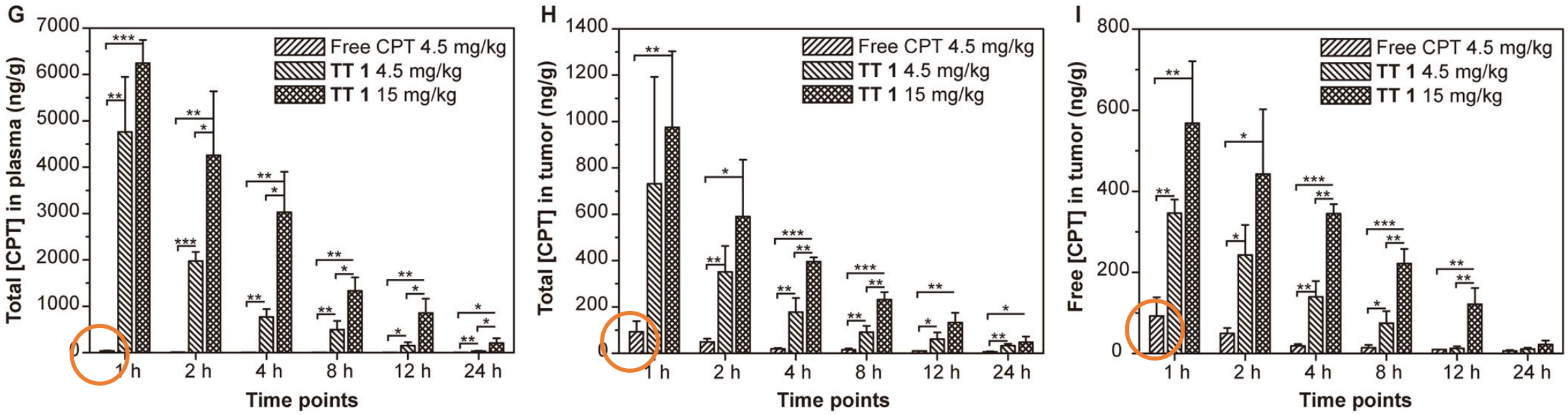
Improved Maximal tolerated dose (from ~4.5mg/kg for CPT to 24 mg/kg for TT1.

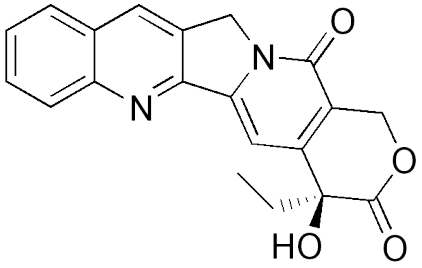
Enhanced tumor suppression, Prolonged survival with more injected TT1 creating better therapeutic outcome

FDA approval for **Metastatic Colorectal Cancer** (**1996**)

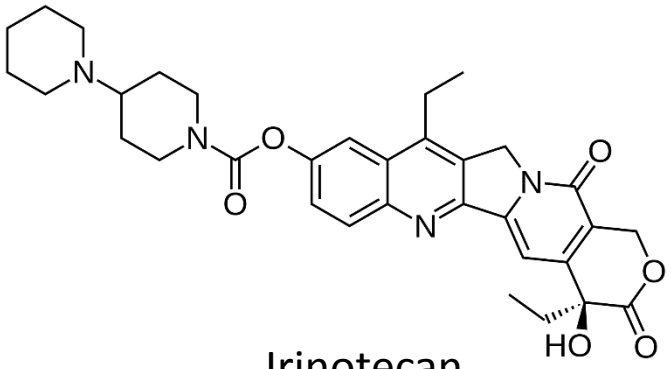
Su, H.; Wang, F.; Wang, Y.; Cheetham, A.G.; Cui, H., ***Journal of the American Chemical Society*** 2019, 141 (43), 17107-17111

Assembly into tubular nanostructures increases *circulation time in plasma and improves tumor accumulation*.





Camptothecin



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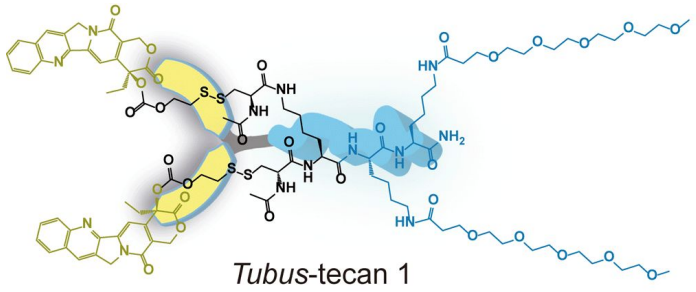
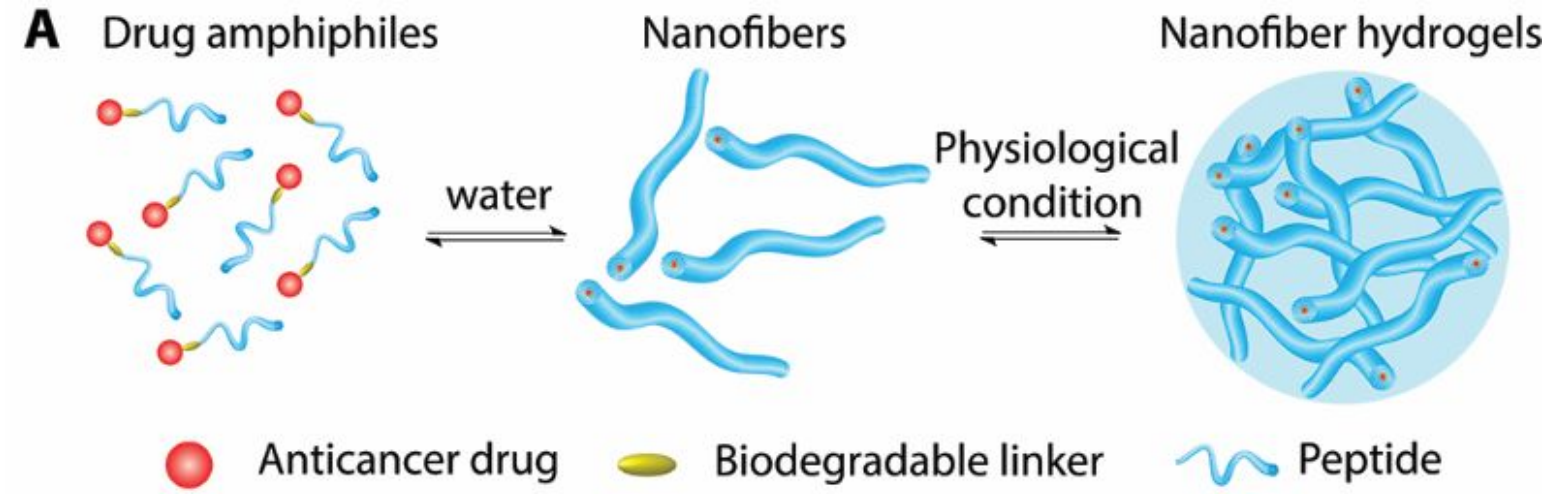
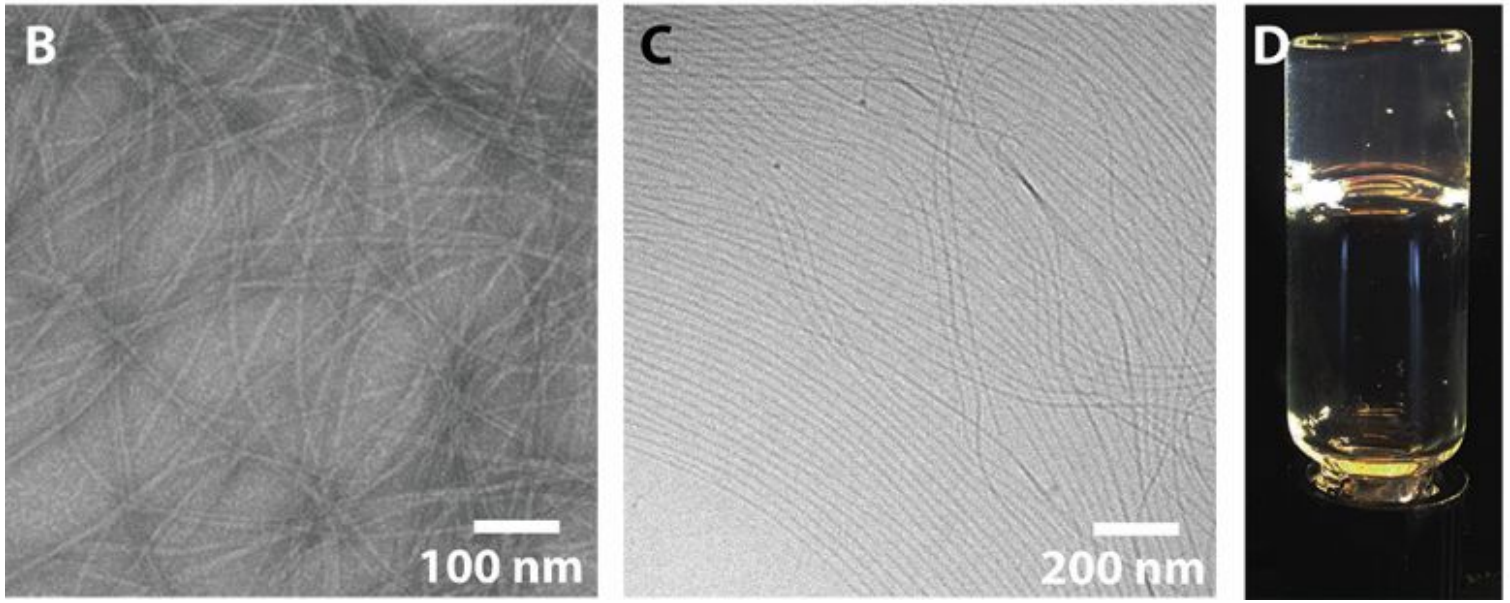


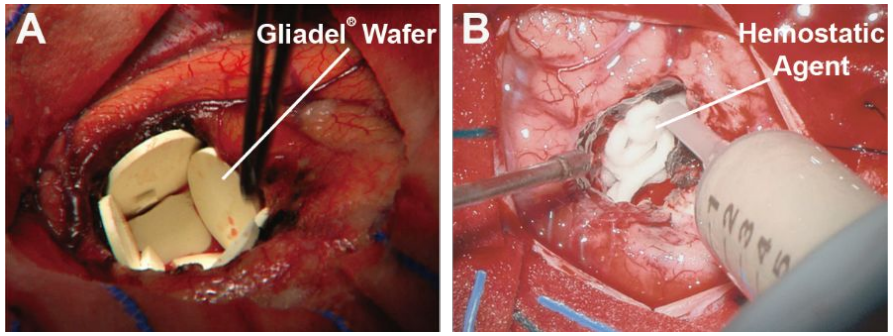
Tubustecan

Self-Assembling Camptothecin Prodrug Hydrogels for Local Chemotherapy (injectablity and long-acting release)



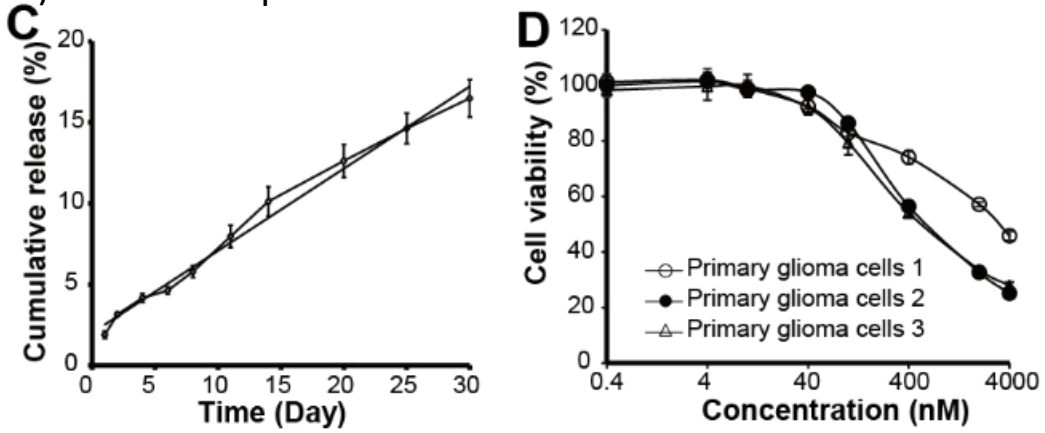


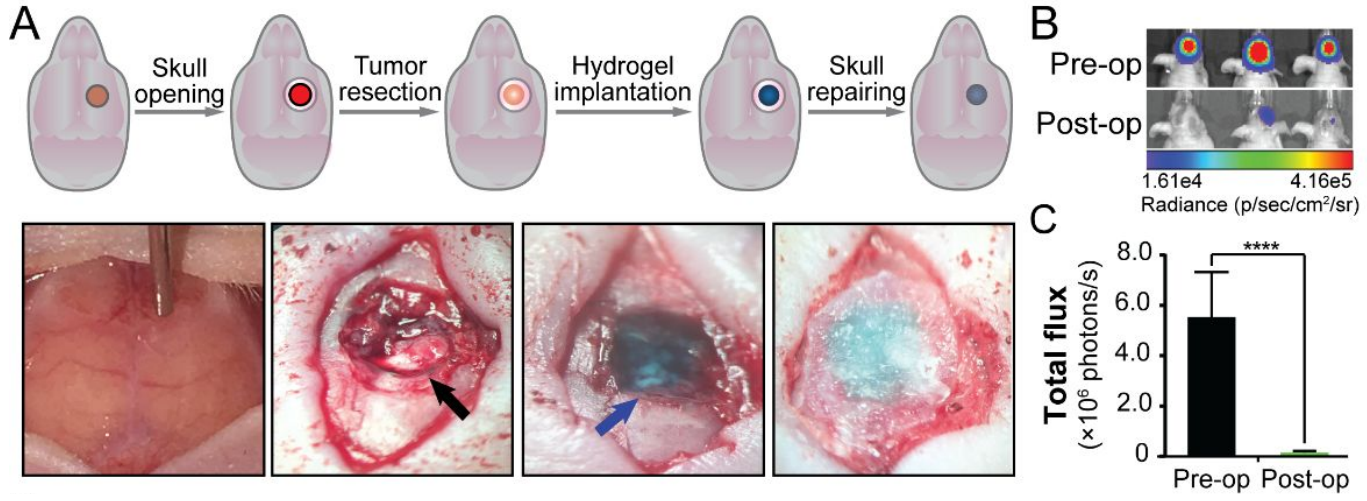
Injectable Nanofiber Hydrogels for Improved Glioblastoma Multiforme (GBM) Treatment

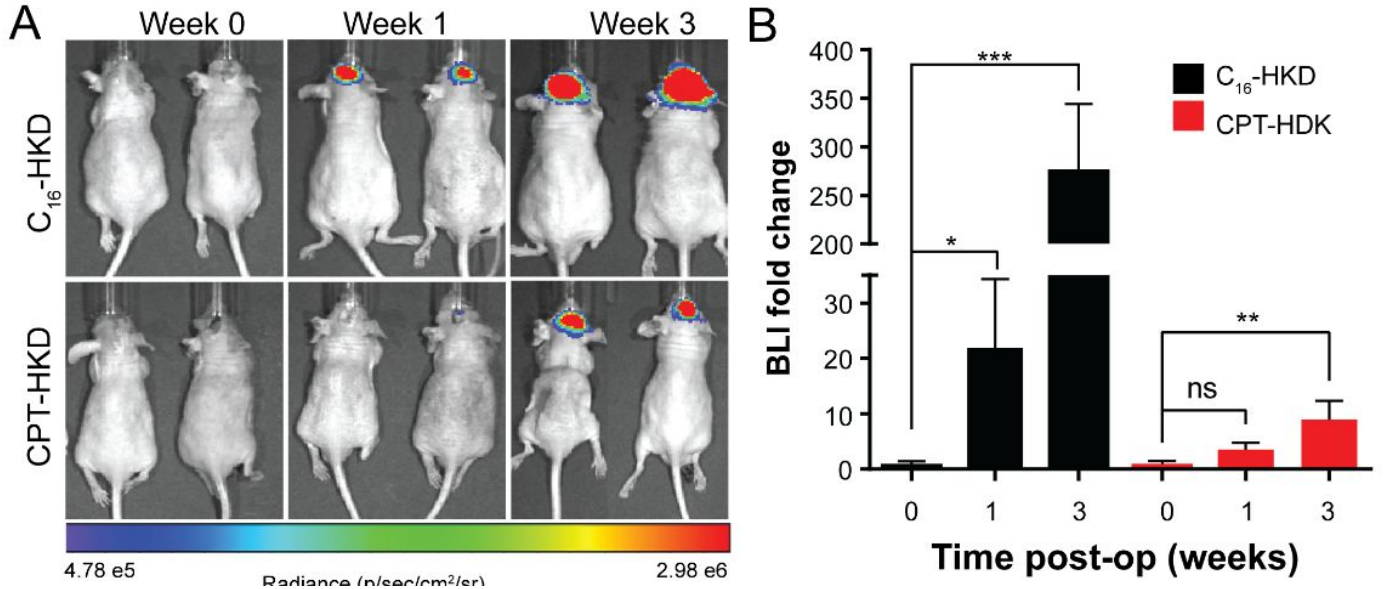


Key properties:

1) Seamless cavity filling (gelation upon tissue contact)
2) Sustainable and linear drug release
3) Mechanisms to overcome drug resistance
4) One-component feature

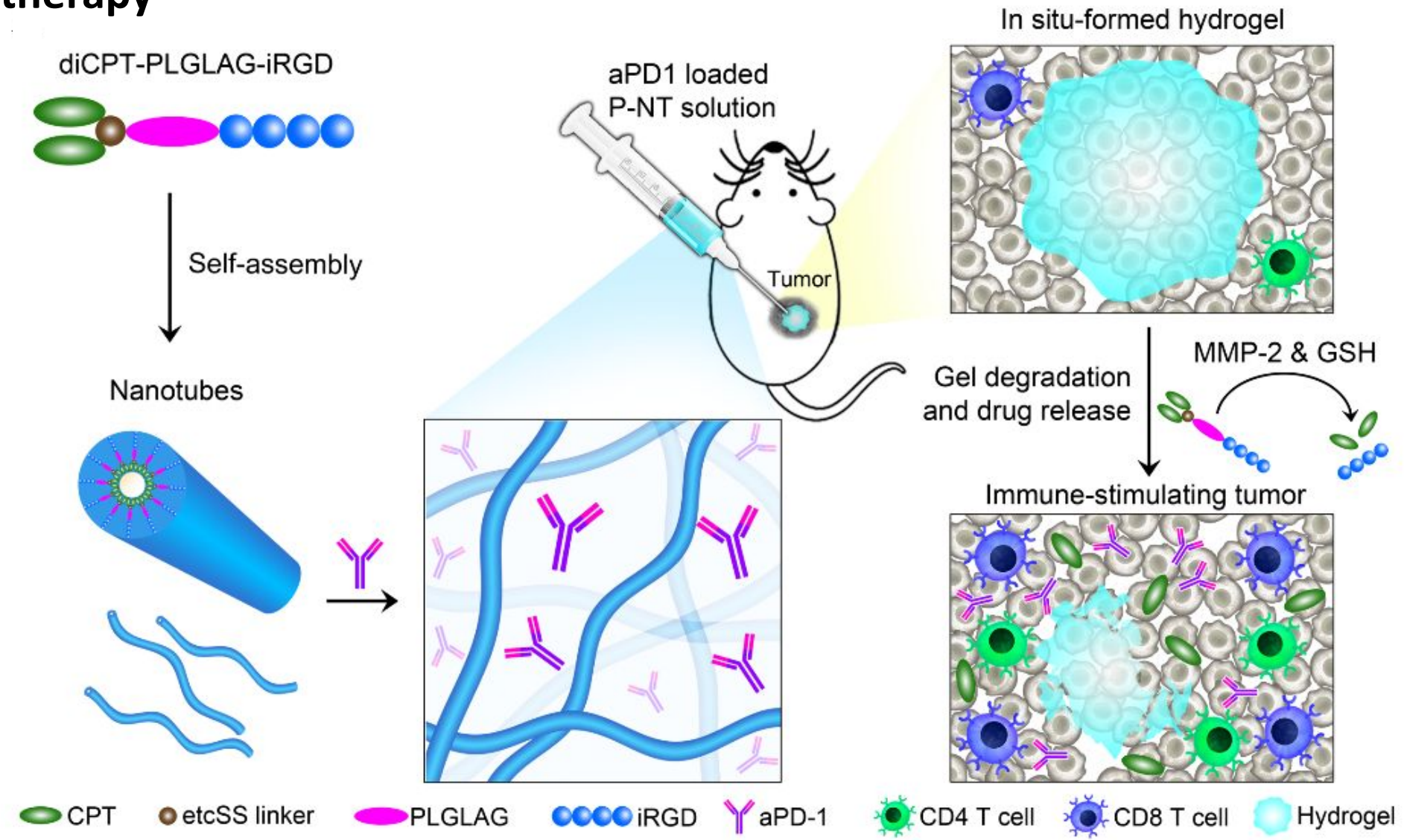






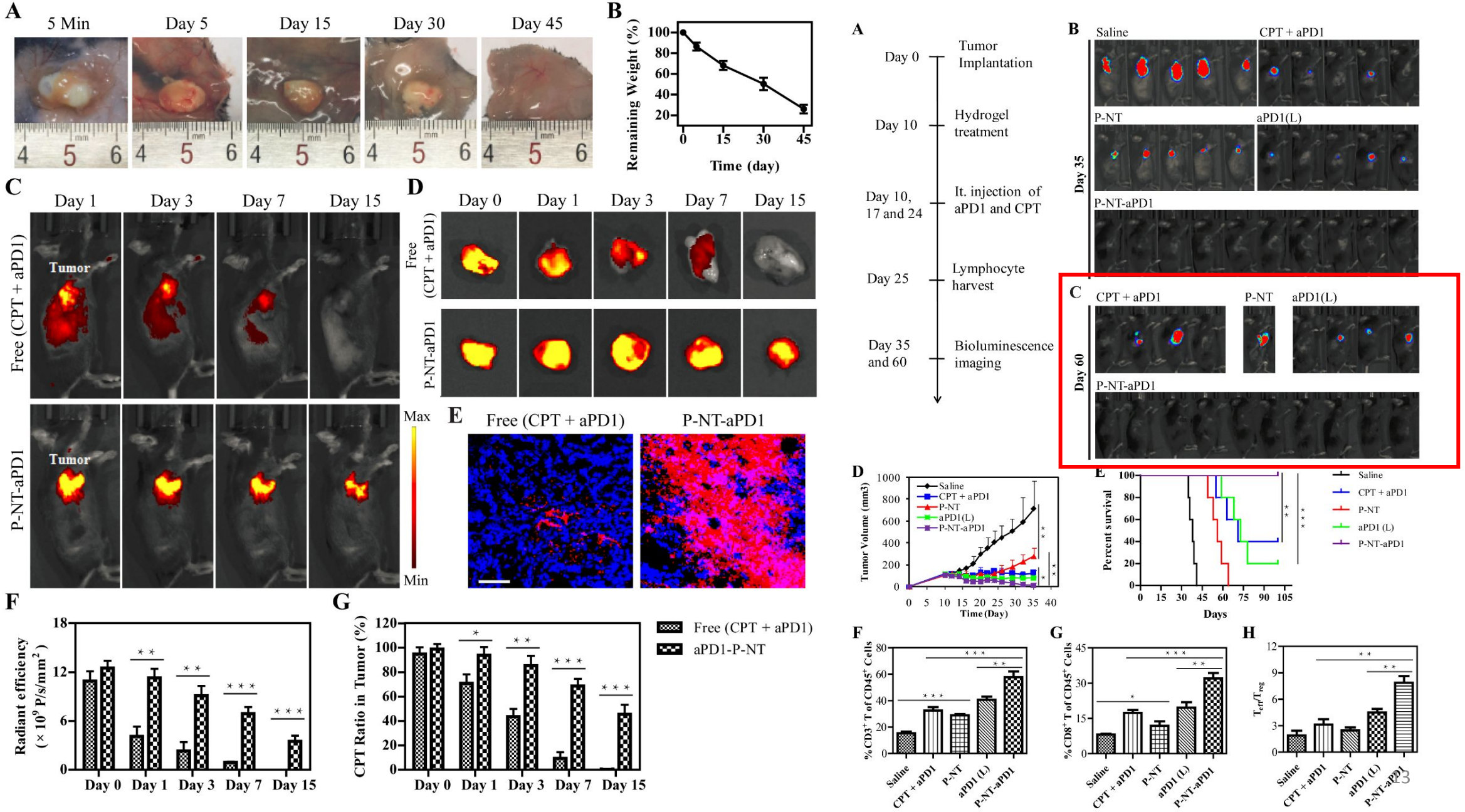
Journal of Controlled Release 2020, 319, 311-321.

CPT Prodrug as an Immune Booster/delivery vehicle for Combined Chemotherapy and Immunotherapy

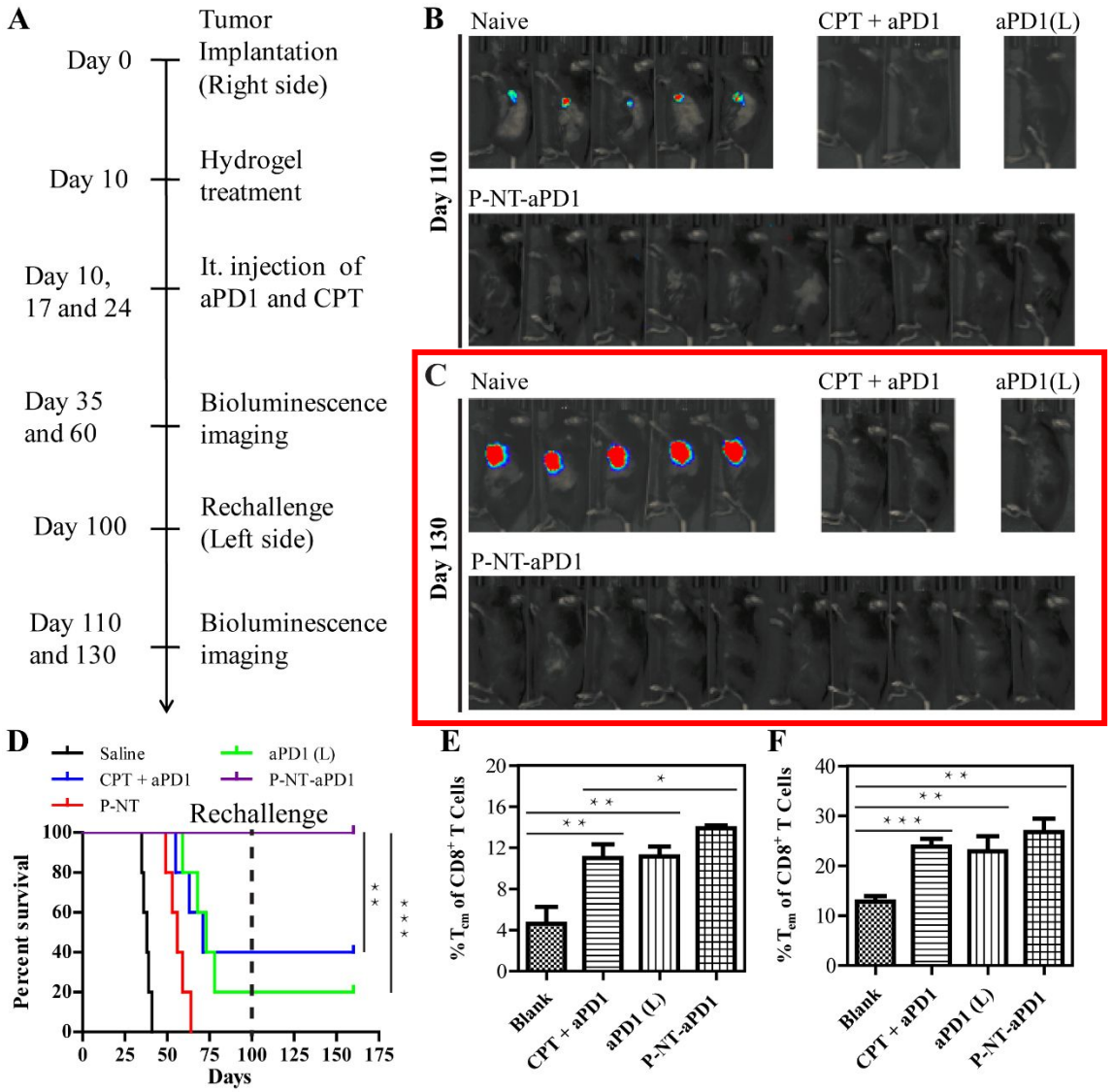


Science Advances 2020, 6, eaaz8985; ***Nature Biomedical Engineering***, 2020, 4, 1090–1101

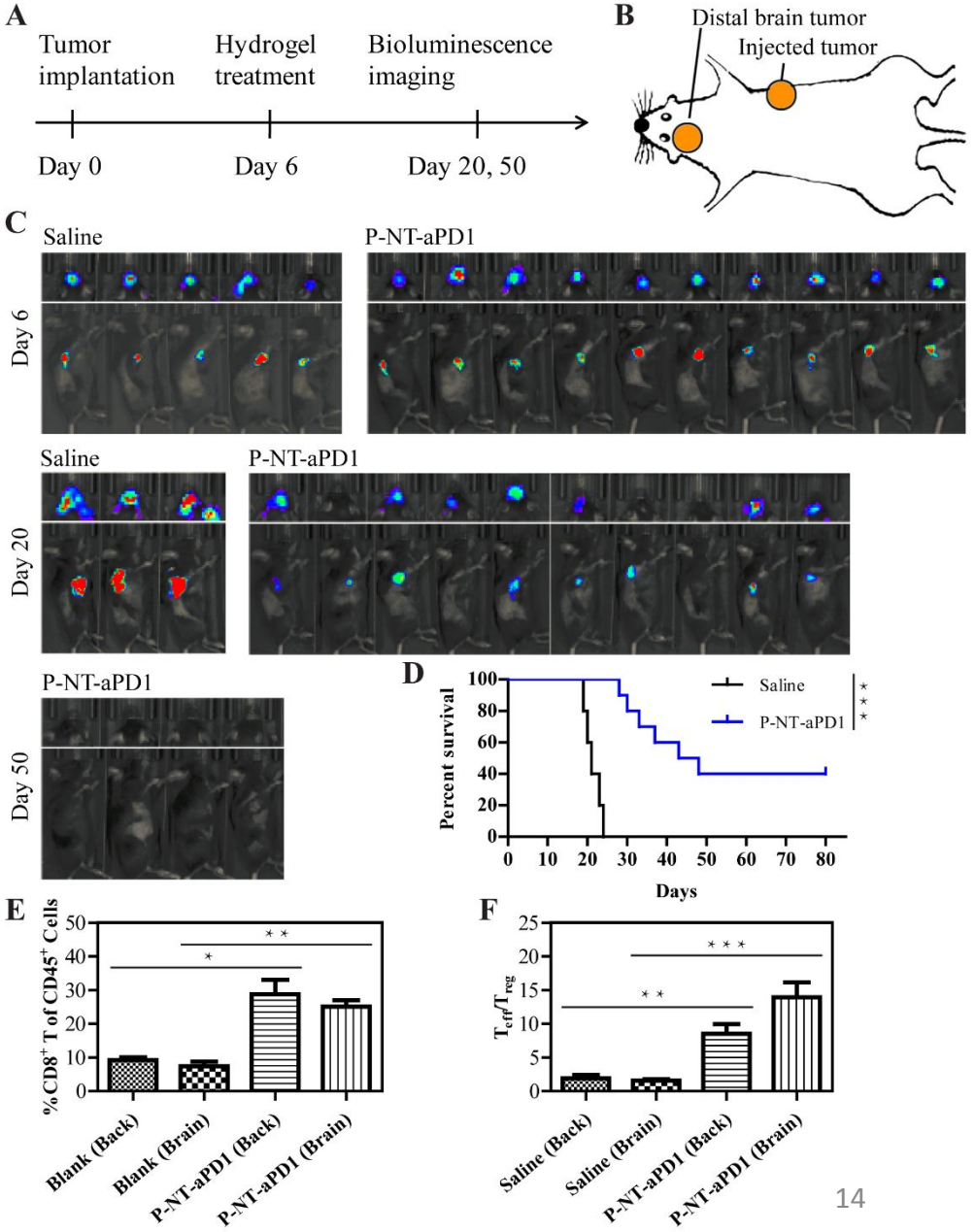
Long-acting release and effective tumor suppression



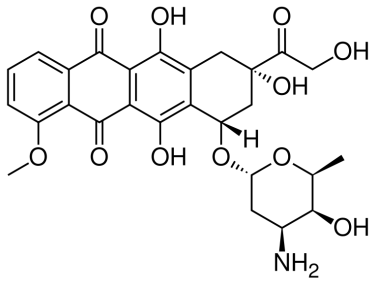
Rechallenge studies validate “Memory” effect



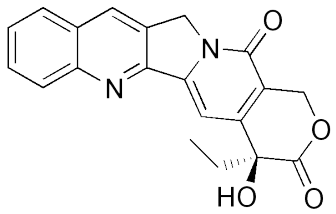
Local delivery led to systemic treatment



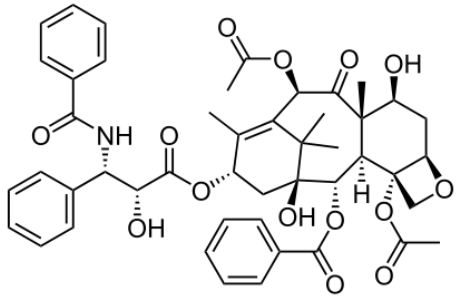
Self-Assembling Prodrugs



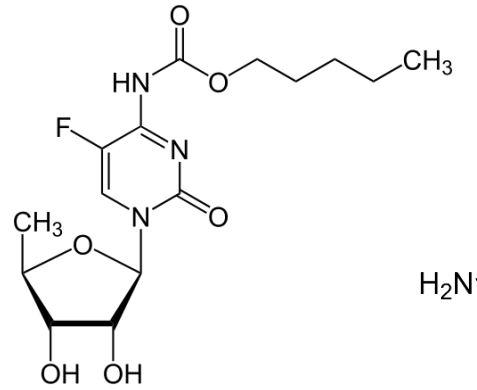
Doxorubicin



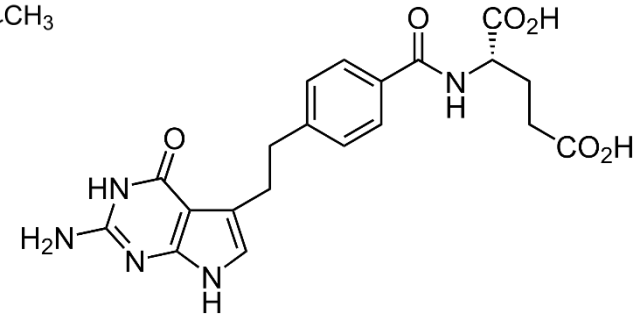
Camptothecin



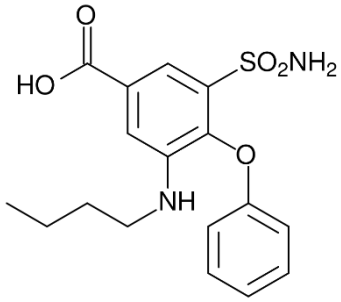
Paclitaxel



Capecitabine



Pemetrexed



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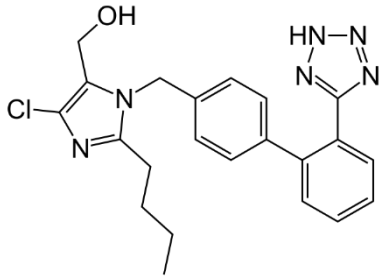

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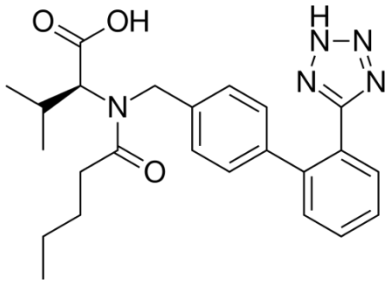
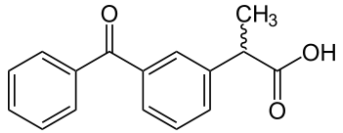
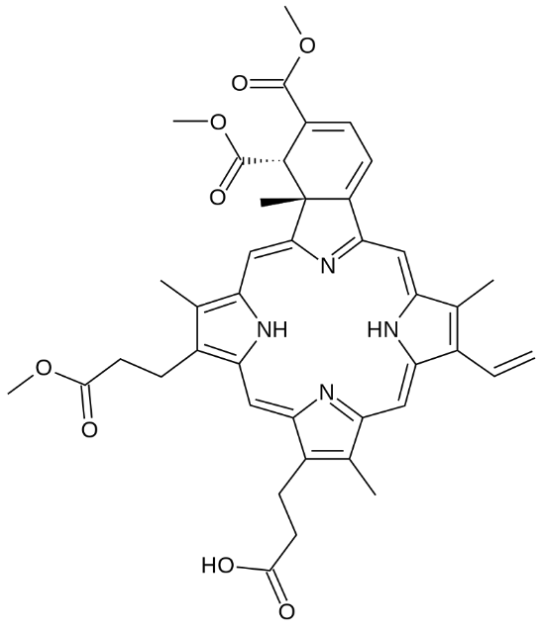


Valsartan



Ketoprofen



Verteporfin

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