

# Engineering (metallo)prodrugs for cancer nano-(immuno)therapy

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RWTH Aachen University

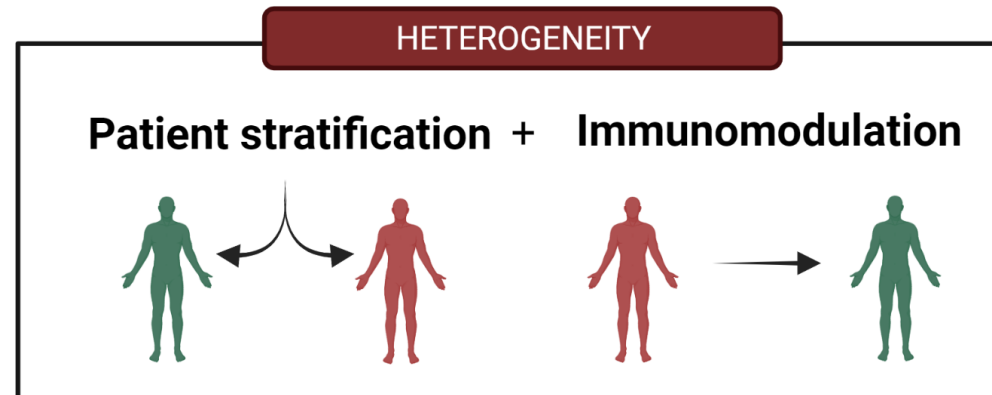
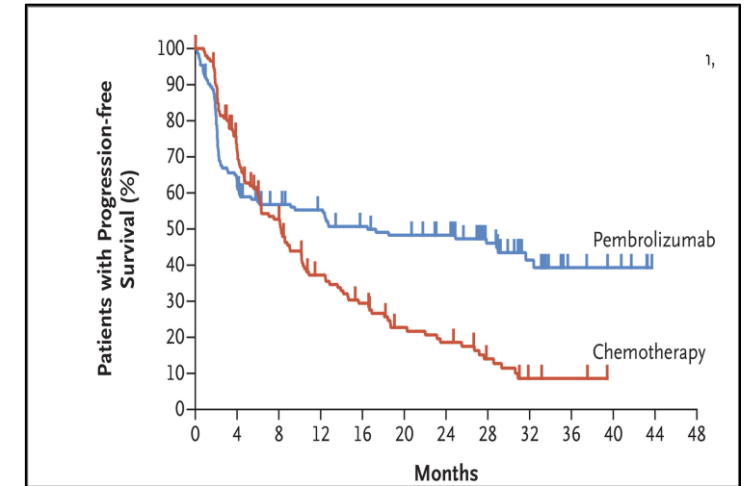
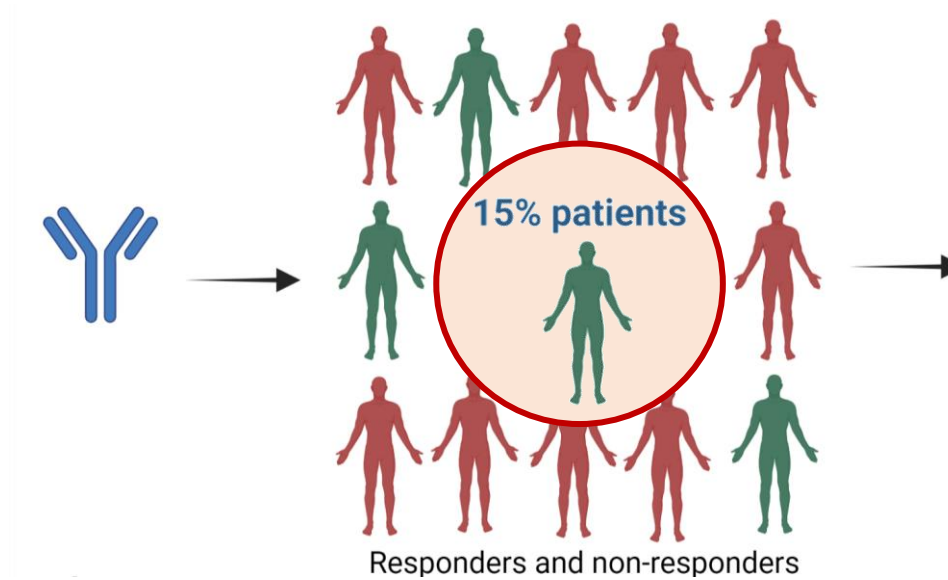
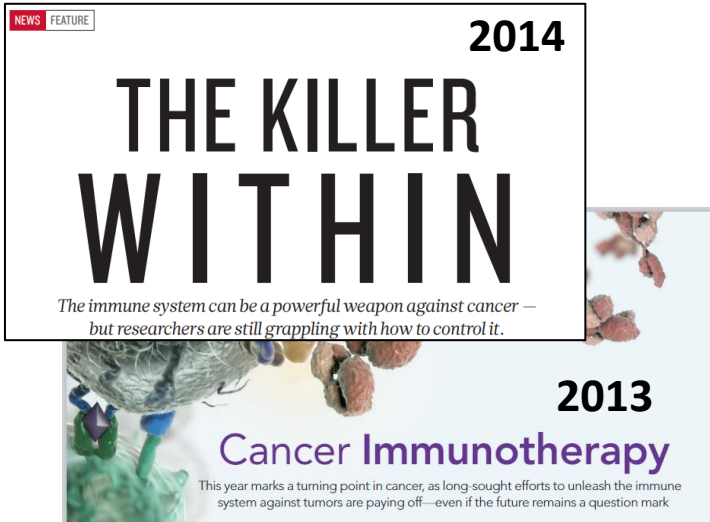
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***Advanced Delivery Science***

# Cancer immunotherapy: hype or hope?

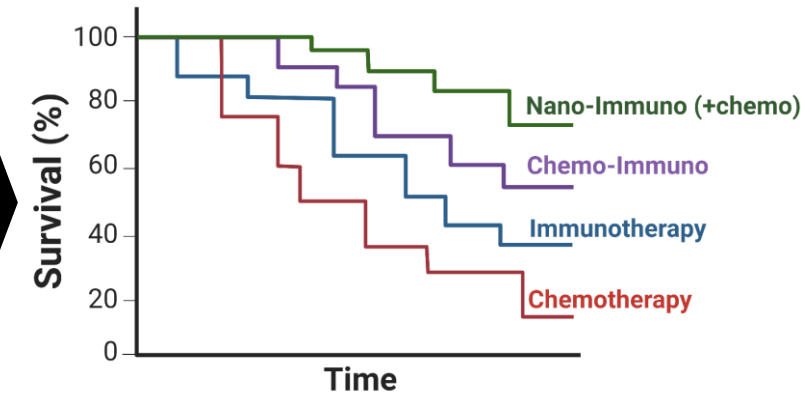
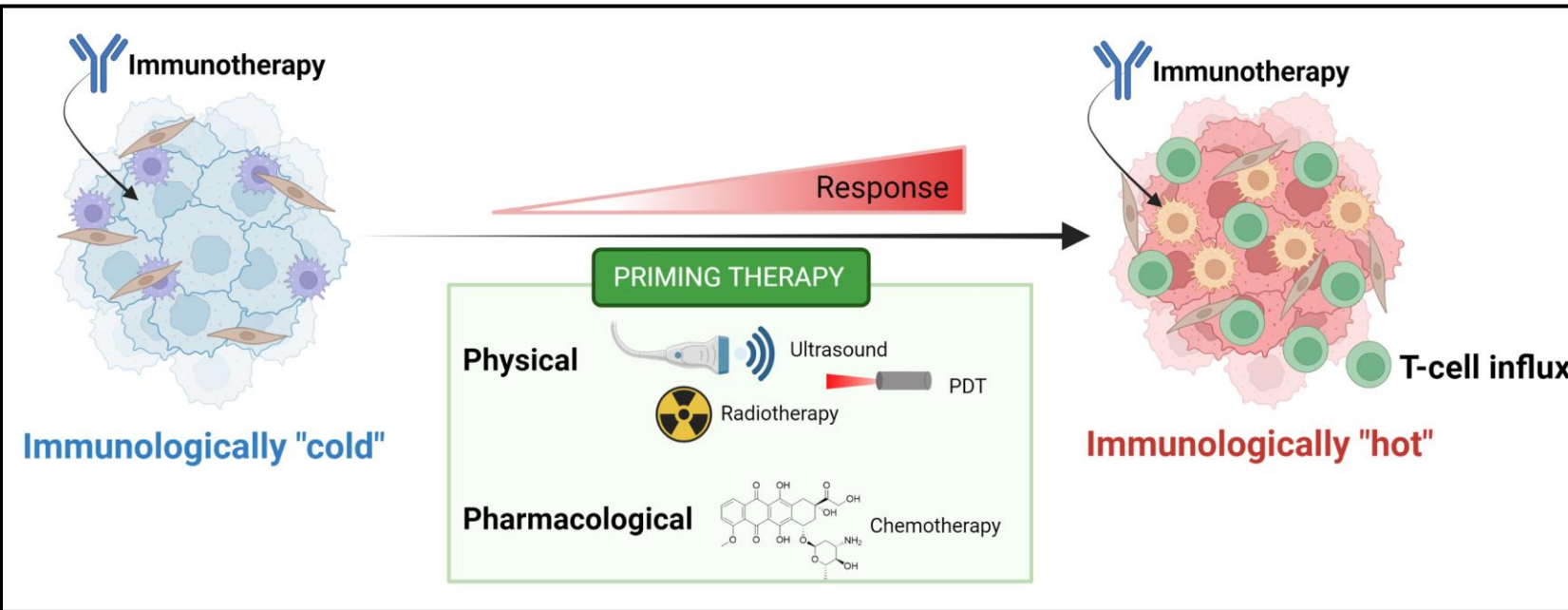


We can increase response rate by decreasing heterogeneity

Hegde et al., *Immunity*, 2020, 52, 17-35



# Nanomedicine boosts immunomodulation



## Enhancing cancer immunotherapy with nanomedicine

Darrell J. Irvine<sup>1,2,3,4,5\*</sup> and Eric L. Dane<sup>1</sup>

to reduce their off-target toxicity. Here, we discuss how nanomedicine-based treatment strategies are well suited to immunotherapy on the basis of nanomaterials' ability to direct immunomodulators to tumours and lymphoid organs, to alter the way biologics engage with target immune cells and to accumulate in myeloid cells in tumours and systemic compartments.

Irvine et al., Nat. Rev. Immunol., 2020, 20, 321-334.

## Combining Nanomedicine and Immunotherapy

Published as part of the Accounts of Chemical Research special issue "Nanomedicine and Beyond".

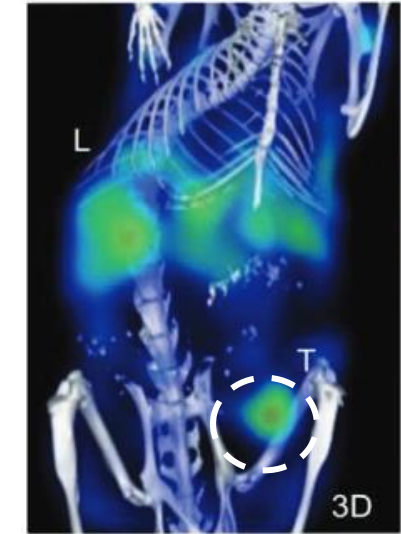
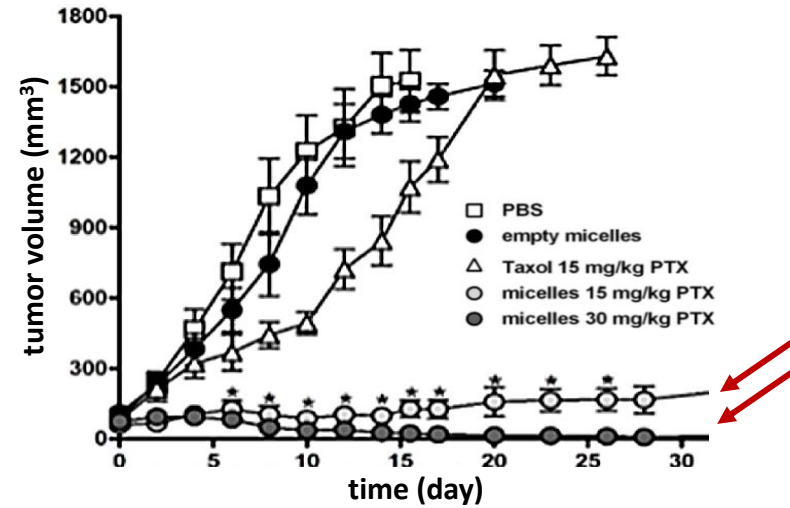
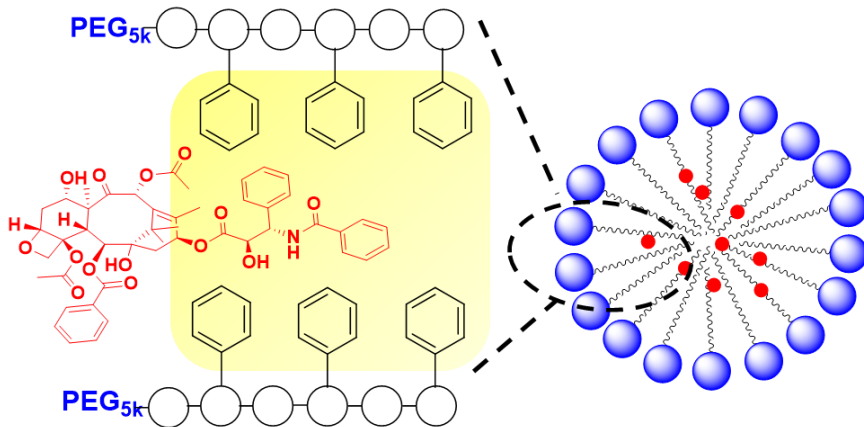
Yang Shi<sup>\*,†,§</sup> and Twan Lammers<sup>\*,†,‡,§</sup>

Shi, Y.; Lammers, T., Acc. Chem. Res., 2019, 52, 1543-1554.

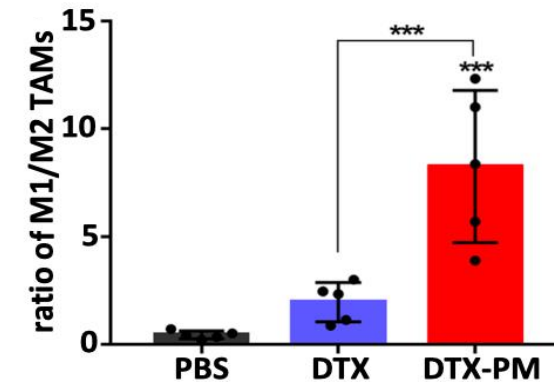
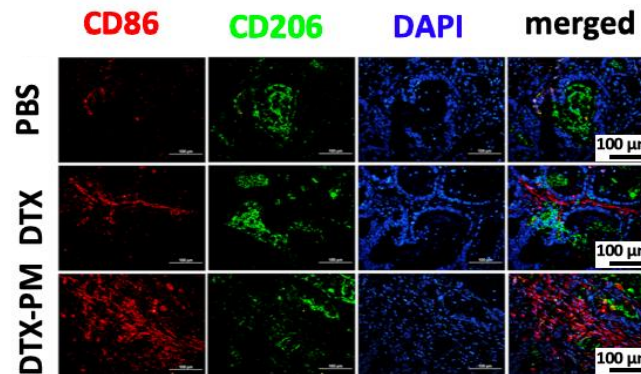
# $\Pi$ -electron-stabilized polymeric micelles

$\Pi$ -electron-stabilized micelles prime the tumor (immune) microenvironment

**Taxane-loaded**  
(paclitaxel (PTX), docetaxel (DTX))



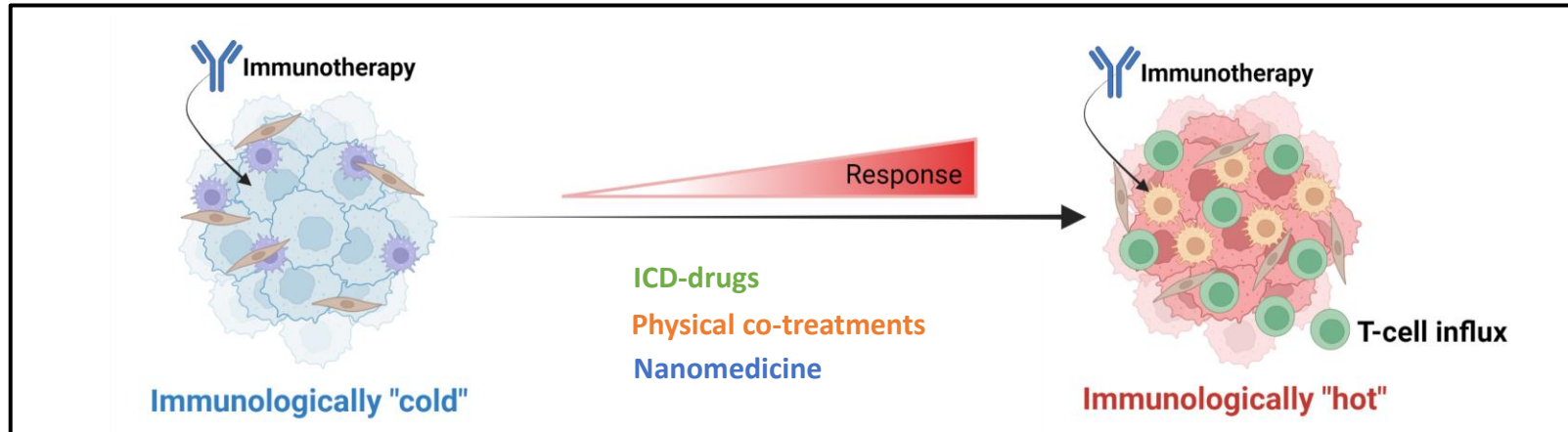
GI PDX



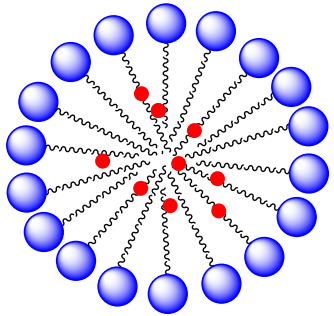
**M1 / M2  
Ratio ↑**

Shi et al., *ACS Nano* **2015**, 9, 3740-3752  
Liang et al., *Biomaterials*, **2021**, 266, 120432  
I. Biancacci et al., *Adv. Sci.*, **2022**, 9, e2103745,

# Smart (nano-)immunomodulation combinations



## Nanomedicine

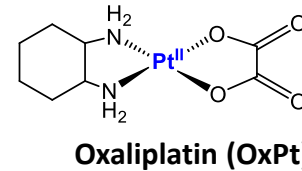
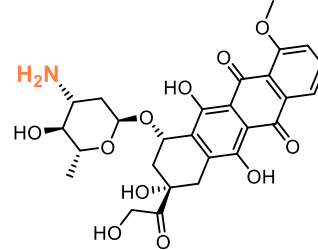


Polymeric micelles

+

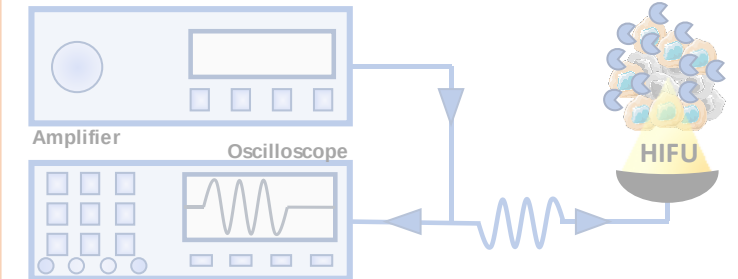
## ICD-(metallo)drugs

### Doxorubicin (Dox)



+

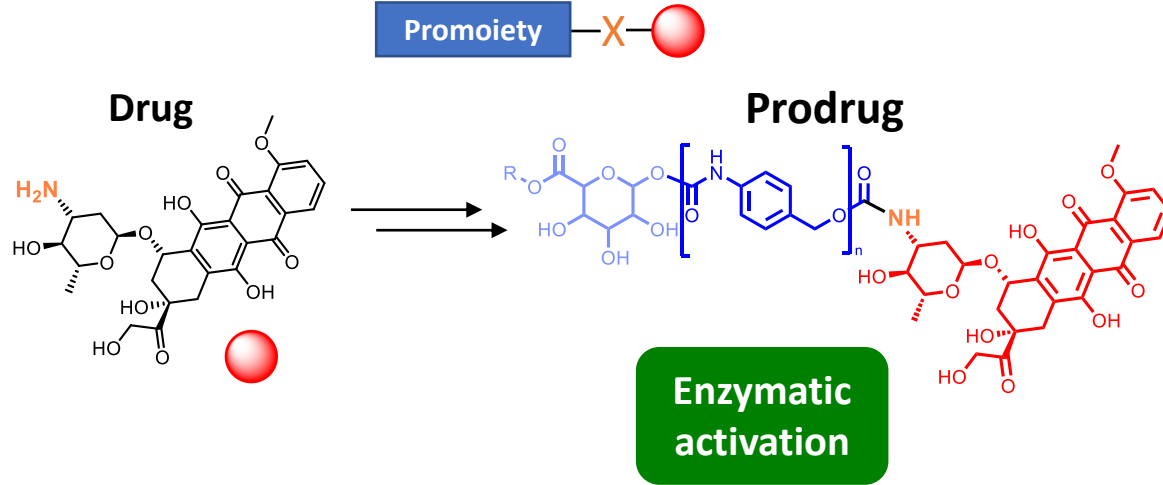
## High-intensity focused ultrasound



# (Metallo)prodrug chemistry

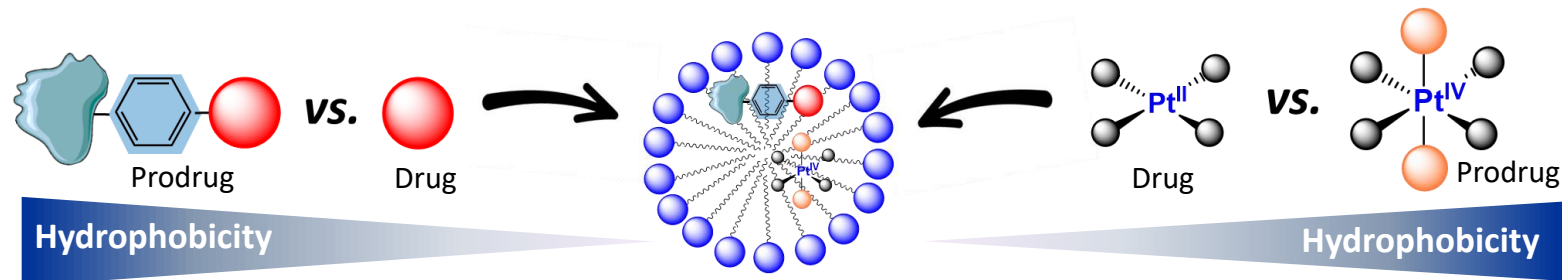
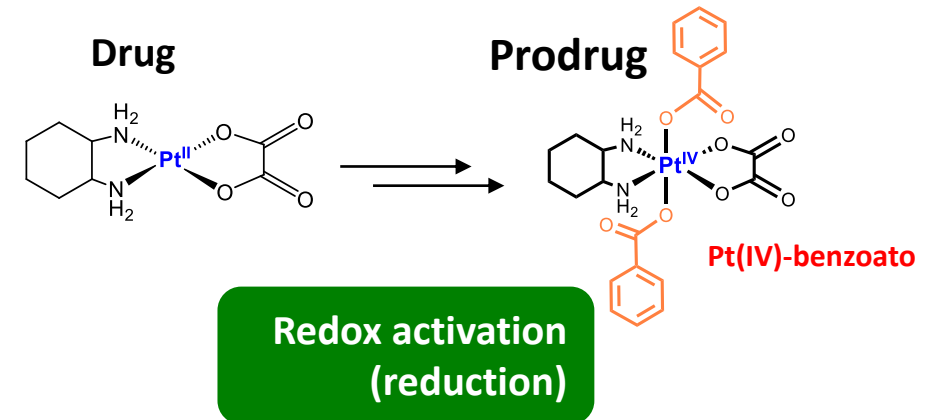
Smart modifications of pharmacological and/or physicochemical properties

## Organic-based drugs

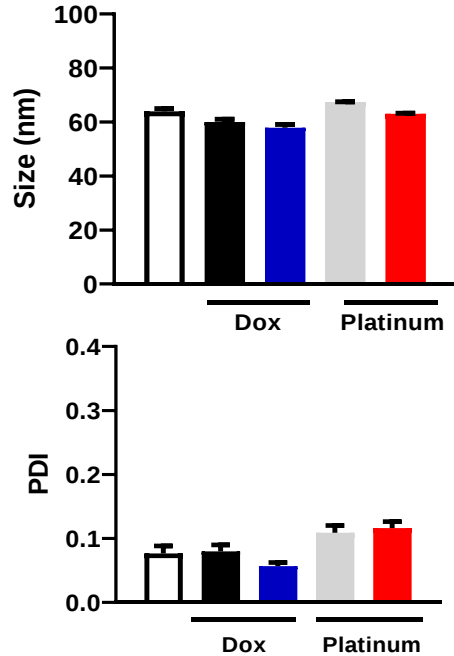
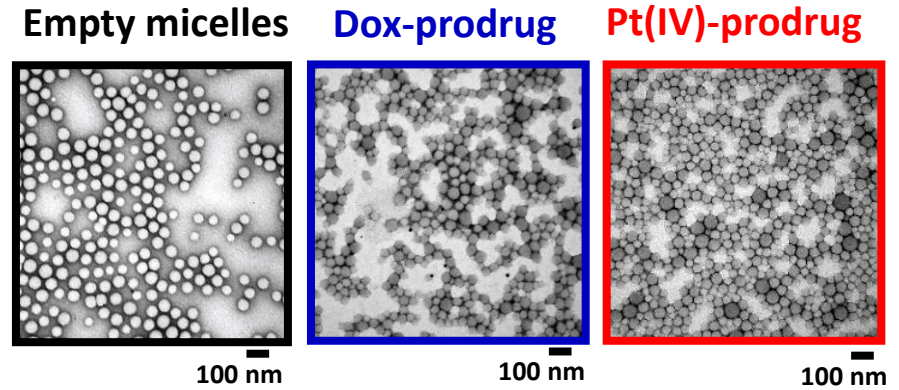
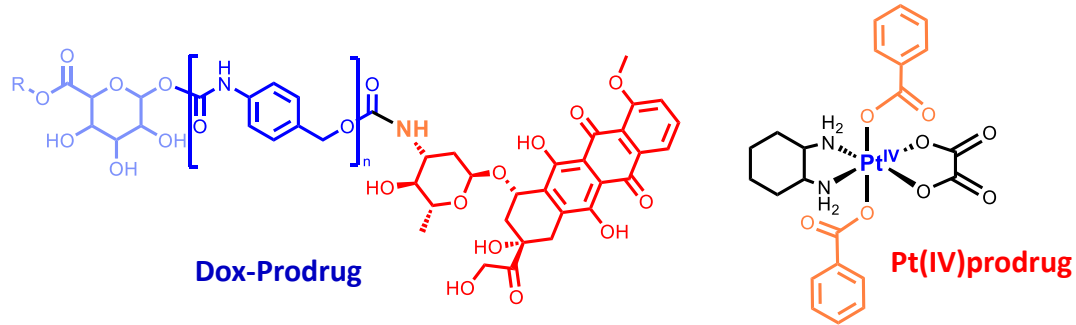


## Metal-based drugs

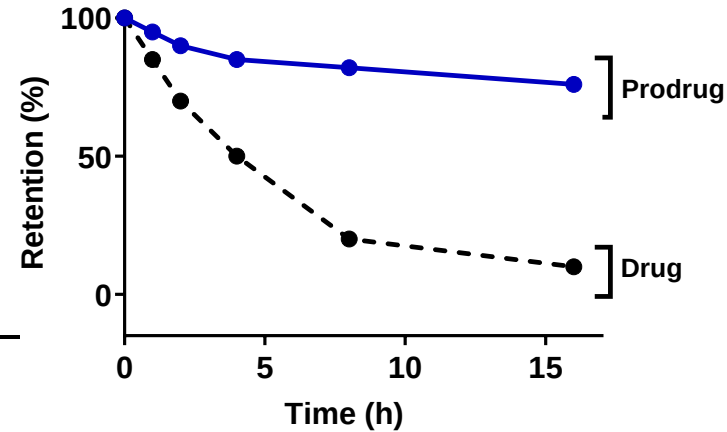
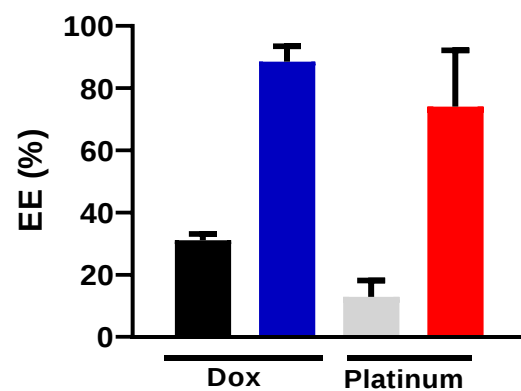
Ligand nature   **Oxidation state**   Geometry   Isomerism



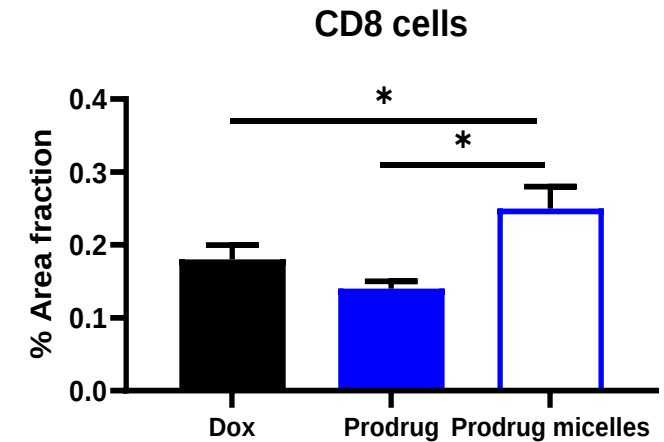
# (Metallo)prodrug-loaded micelles



Enhanced prodrug encapsulation and retention in micelles



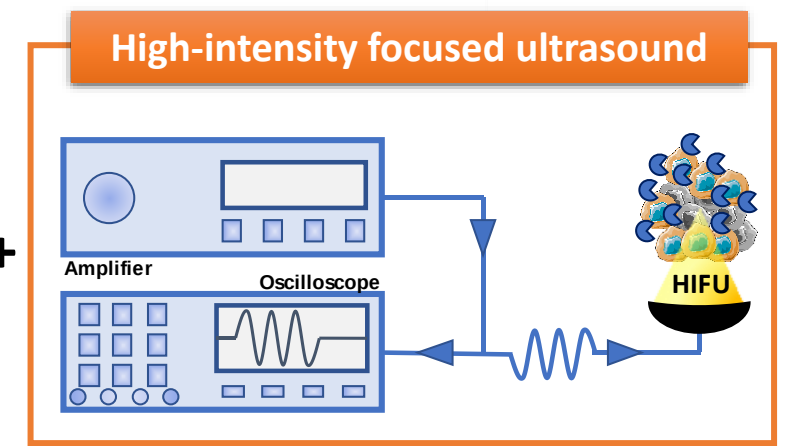
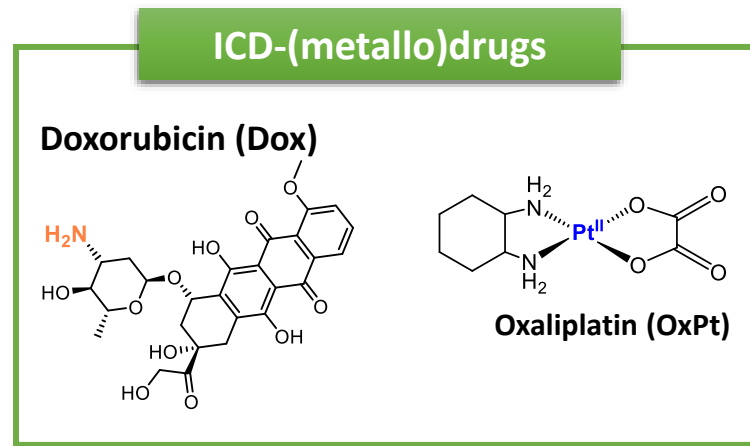
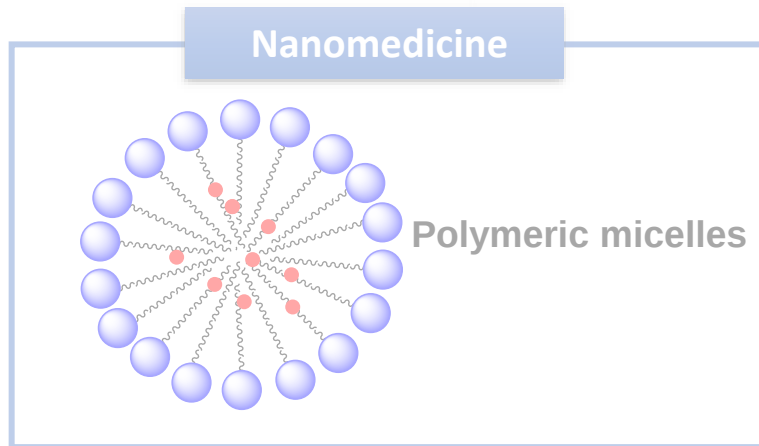
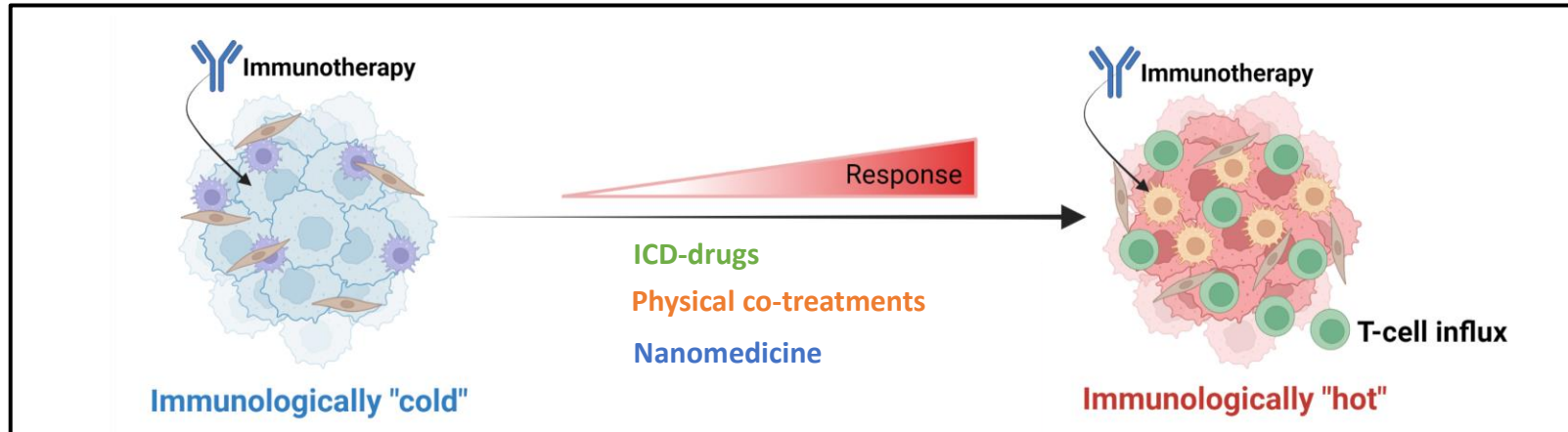
Increased immunogenicity when combined with micelles



□ Empty ■ Dox ■ Dox-Prodrug ■ OxPt ■ Pt(IV)prodrug

Manuscript in preparation

# Smart (nano-)immunomodulation combinations

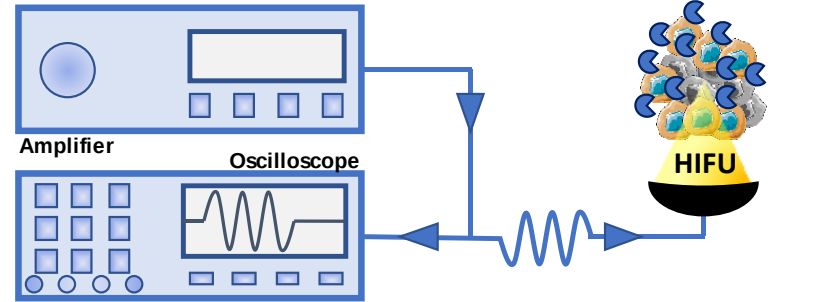
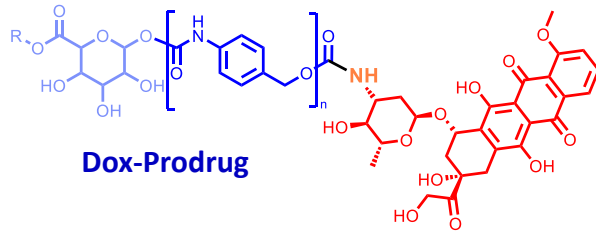


# HIFU + Enzyme Prodrug Therapy

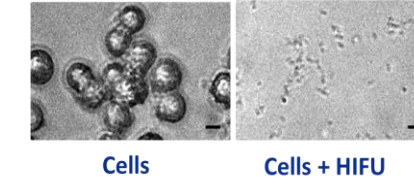
ICD-inducing prodrugs

+

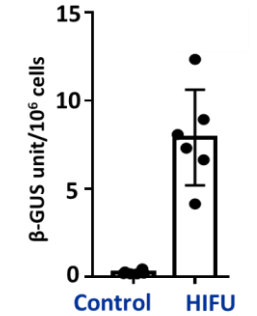
High-intensity focused ultrasound



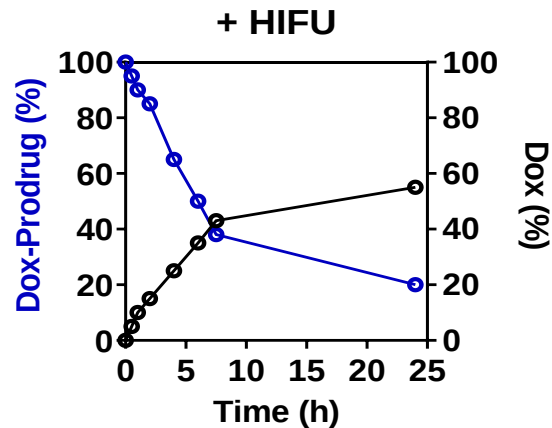
Microscopy



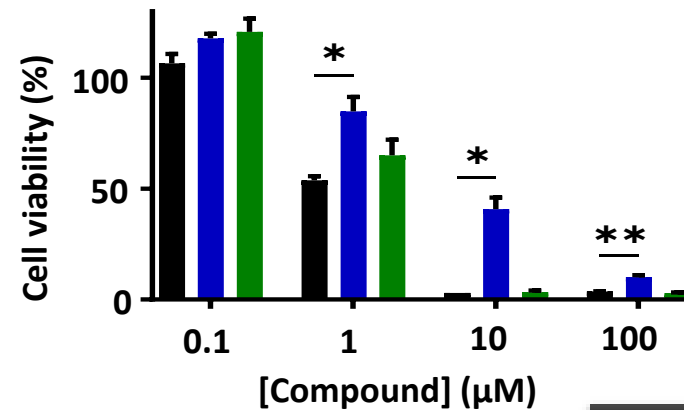
Release of enzyme



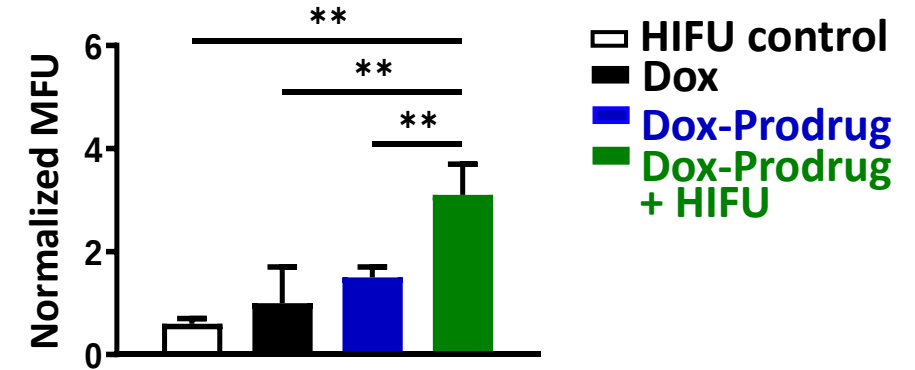
(a) Enzymatic activation



(b) *In vitro* cytotoxicity



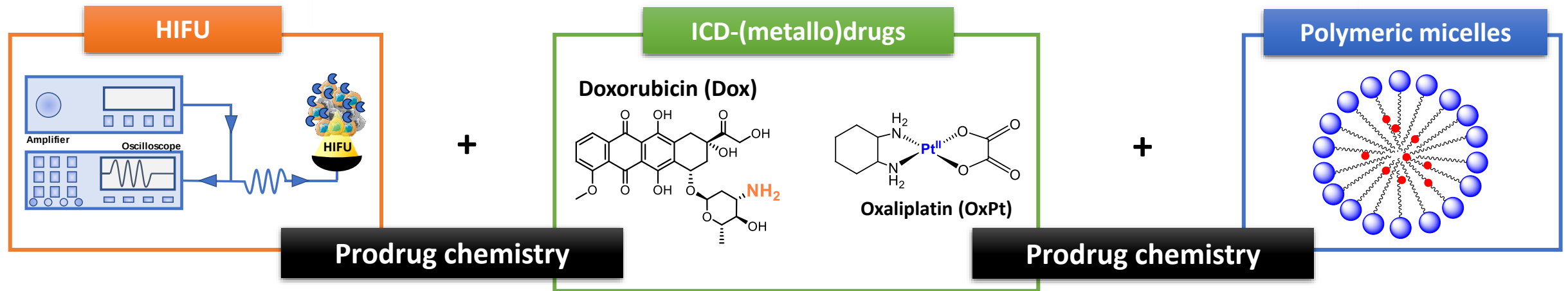
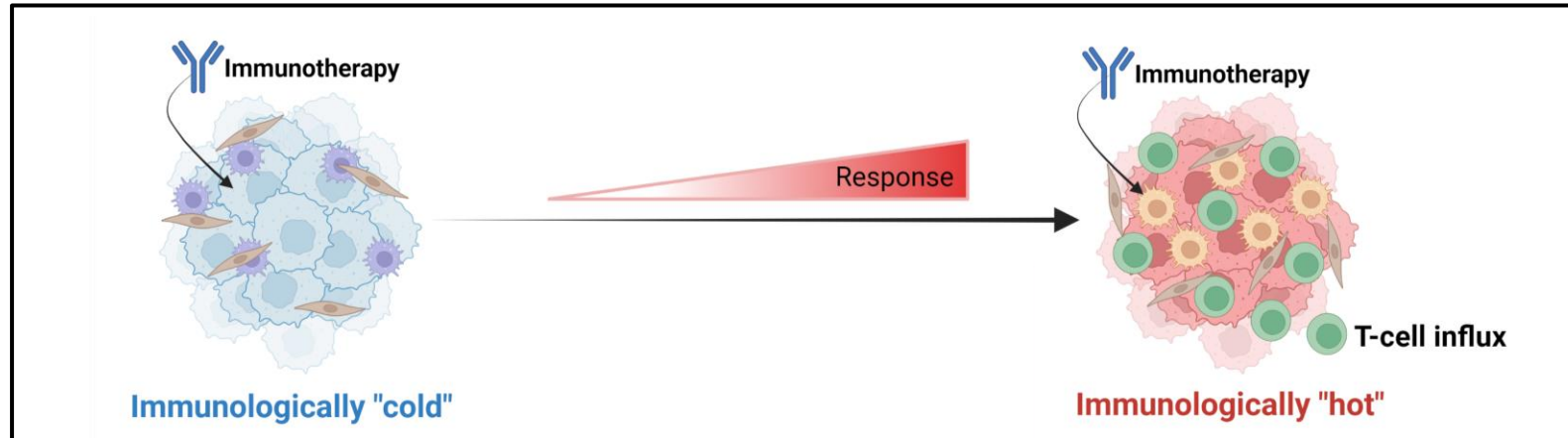
(c) Calreticulin translocation (ICD marker)



K.Roemhild et al., *Theranostics* 2022, 12, 4791-4801

HIFU synergizes with enzyme-responsive (ICD-inducing) prodrugs

# Conclusion: modular prodrug chemistry is a key player



Enzyme **prodrug** therapy (EPT) (poster 349)

(**Metallo**)prodrug-loaded polymeric micelles (poster 348)

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