# TuNa-AI: A Hybrid Kernel Machine to Design Tunable Nanoparticles for Drug Delivery

Zilu Zhang[1], Yan Xiang[1], Joe Laforet Jr.[1], Ivan Spasojevic[2,3], Ping Fan[3], Ava Heffernan[4], Christine E. Eyler[4], Kris C. Wood[5], Zachary C. Hartman[6], Daniel Reker[1,7,✉]

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## 1 Technology Exposition

- **Drug-excipient nanoparticles** are an emerging drug delivery platform.
- They are known for facile synthesis through **self-assembly**, **high drug-loading** capacity, and a rational design process informed by **machine learning**[1,2].
- However, their simple synthesis (**Fig. 1**) also prevents **tuning of material composition**.

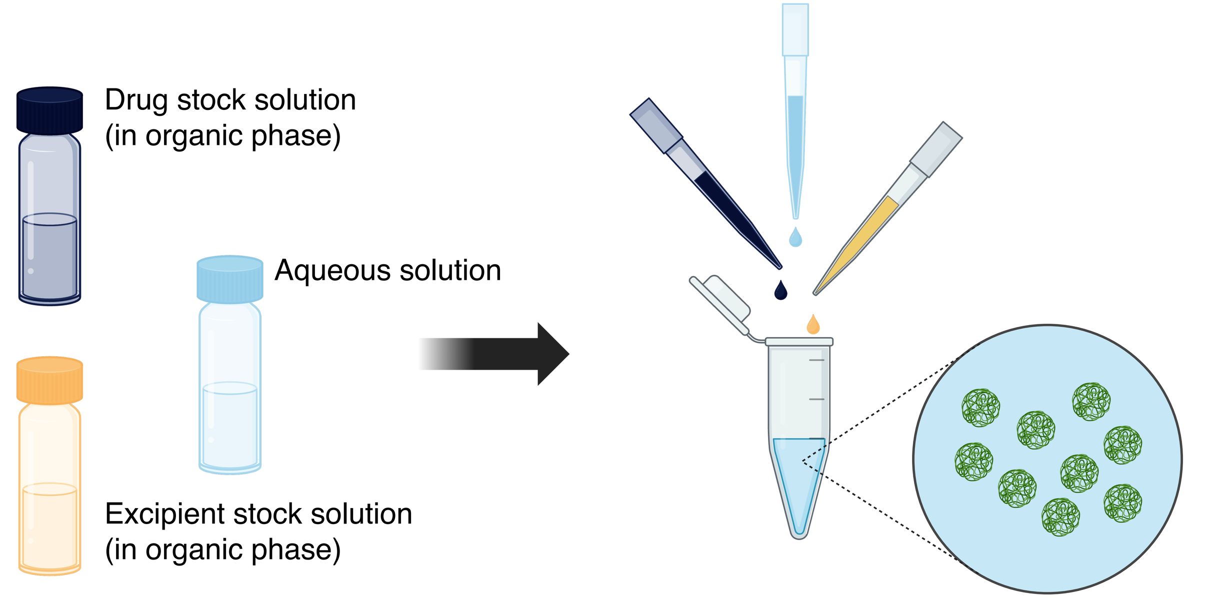


**Figure 1.** Schematic of the drug-excipient nanoparticle **synthesis protocol**. The **drug** and **excipient** are dissolved in an organic solvent (e.g., DMSO) and mixed in **equimolar amounts**. The mixture undergoes phase reversal upon the addition of an **aqueous solution**, leading to the self-assembly of **nanoparticles**.

### Aim

- Devise a **robotic-assisted synthesis protocol** to create nanodrugs at various excipient/drug molar ratios.
- Design a **hybrid kernel machine** approach to prediction nanoparticle formation.
- Apply the computational model to **identify novel drug-excipient nanoparticles**.

## 2 Automated Exploration

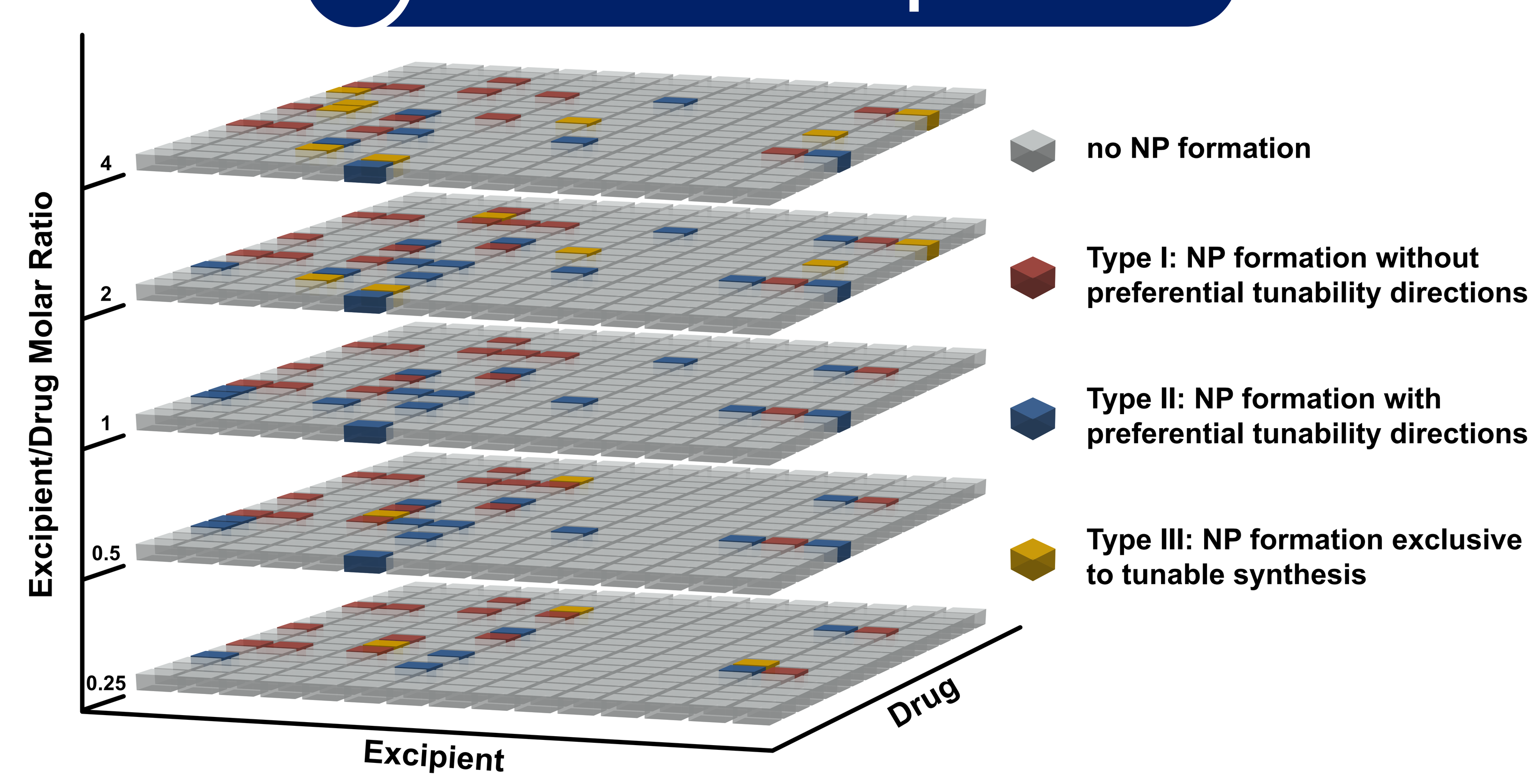


**Figure 2.** Robot-assistant **screening results of nanoparticle formation** experiments. The full data matrix includes 17 drugs and 15 excipients. The optimized synthesis protocol investigated five different excipient/drug molar ratios (0.25, 0.5, 1, 2 and 4) in order to expand the nanoparticle searching space.

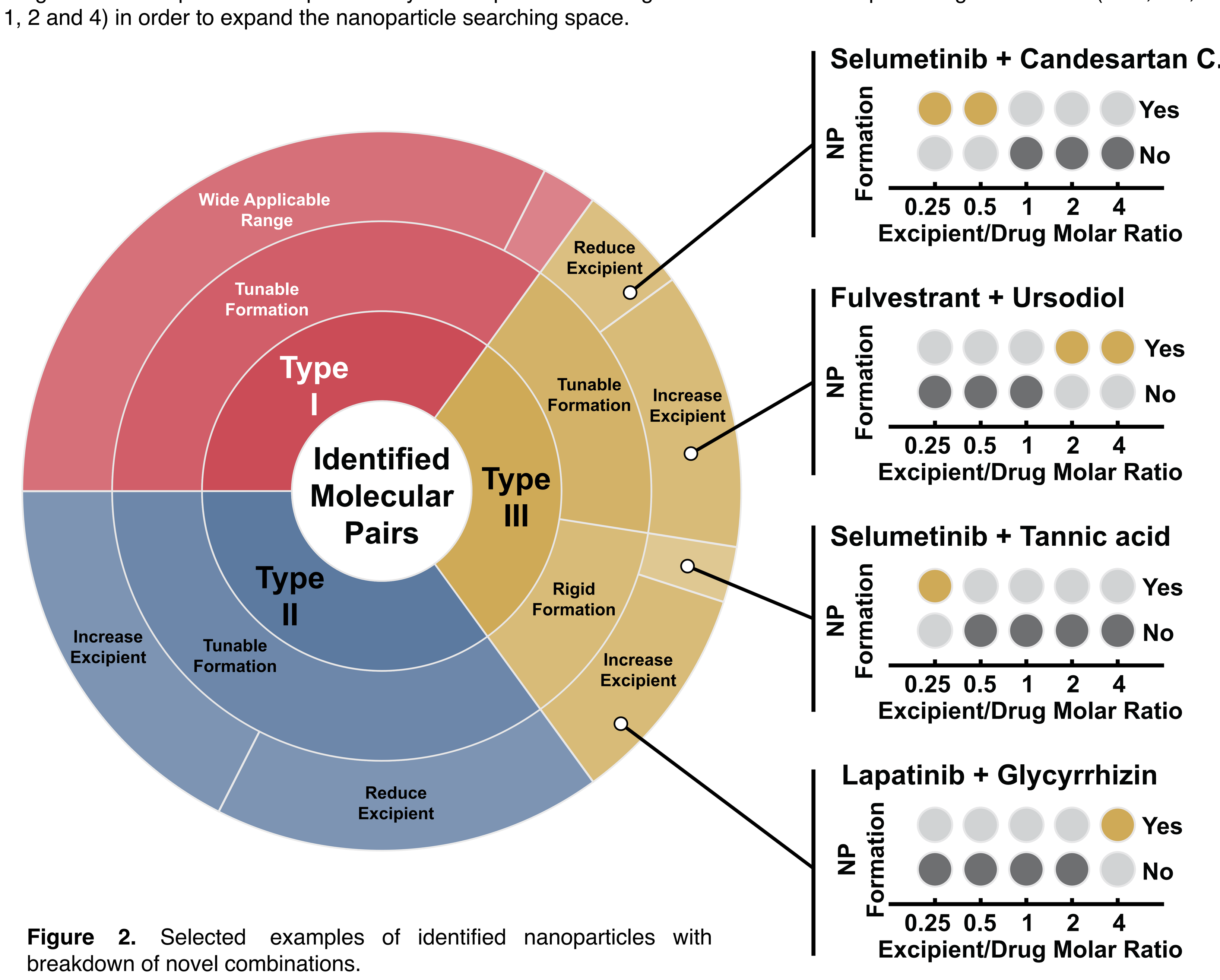


**Figure 2.** Selected examples of identified nanoparticles with breakdown of novel combinations.

## 3 Kernel Hybridization

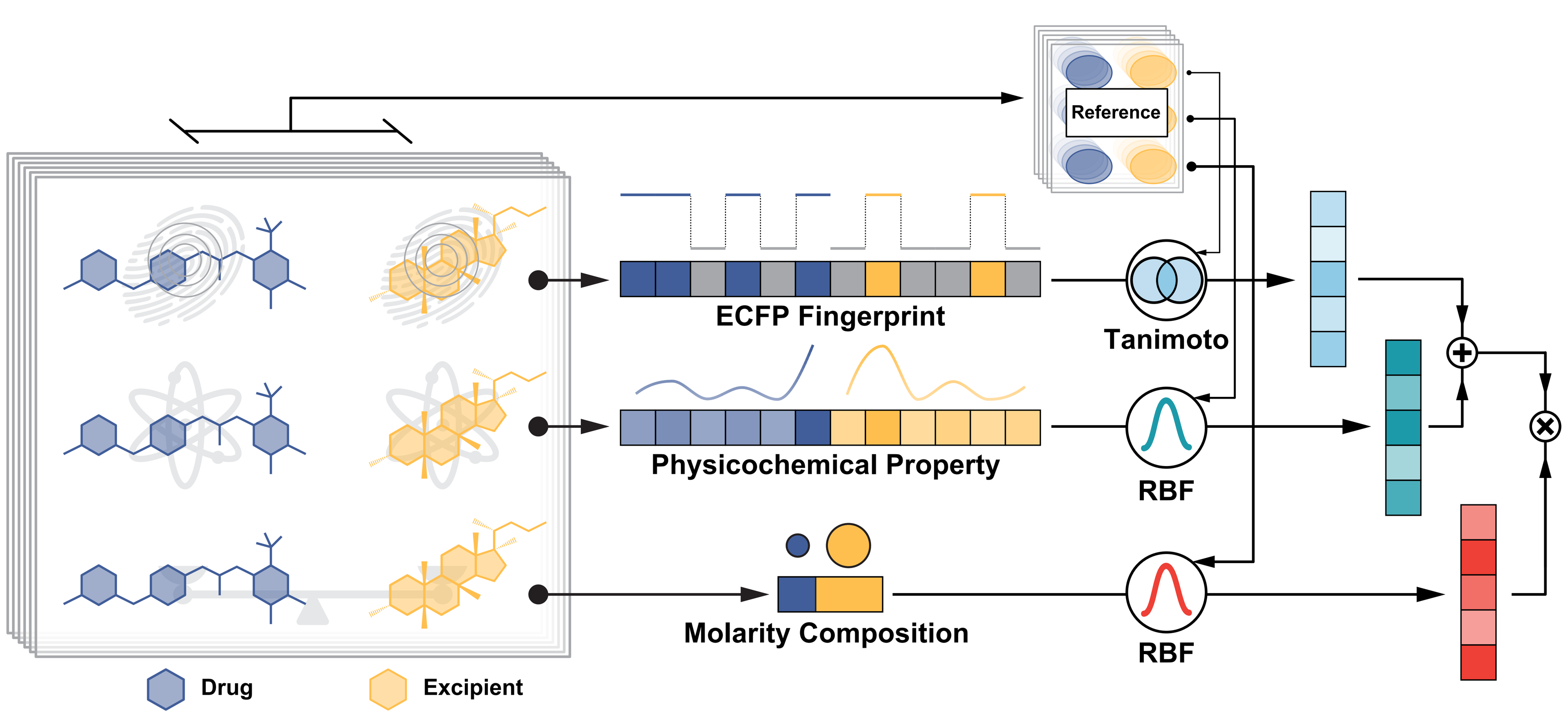


**Figure 3. Schematic of the hybrid kernel machine design.** Hybrid kernel machine architecture, featuring inputs from binary ECFP fingerprints, continuous physicochemical properties, and molarity ratios of drug and excipient during synthesis. RBF, radial basis function.

## 4 Computational Evaluation

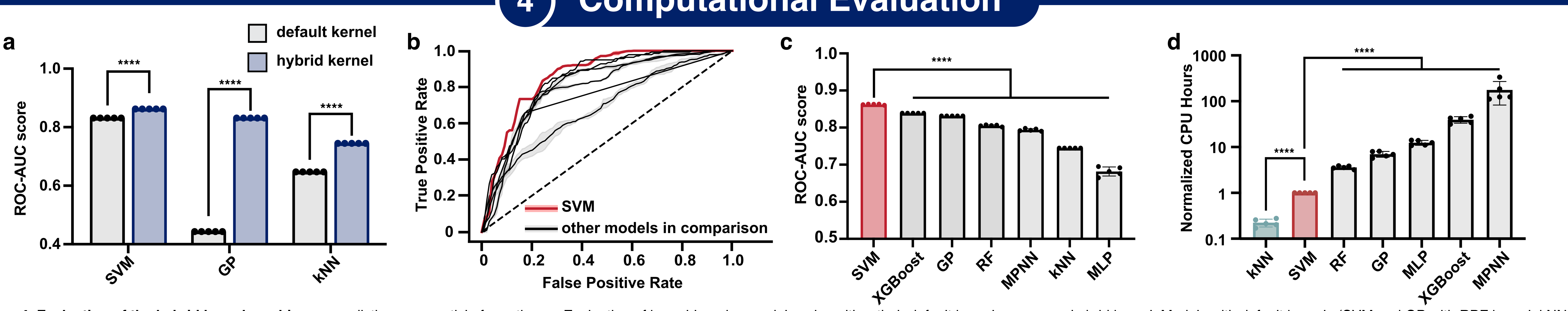


**Figure 4. Evaluation of the hybrid kernel machine** on predicting nanoparticle formation**. a**, Evaluation of kernel-learning models using either their default kernel or our new hybrid kernel. Models with default kernels (SVM and GP with RBF kernel; kNN with Minkowski distance) are shown in gray, while hybrid kernel models are highlighted in blue. **b,c,** ROC curves and AUC scores of all surveyed models. The best-performing support vector machine (SVM) model is shown in red, while all other models are shown in shades of gray. The dashed diagonal represents random guessing (ROC-AUC = 0.5), and the shaded areas indicate one standard deviation across five independent cross-validation results for each model. SVM, support vector machine; GP, Gaussian process; RF, random forest; MPNN, message-passing neural network; kNN, k-nearest neighbors; MLP, multi-layer perceptron. **d,** Computational cost comparison (normalized to SVM CPU time, except the MPNN which uses GPU acceleration). Unpaired t-test (α = 0.05); ****p < 0.0001.

## 5 Nanodrug Innovation

### 5.1 increasing excipients – formulate hard-to-load drug

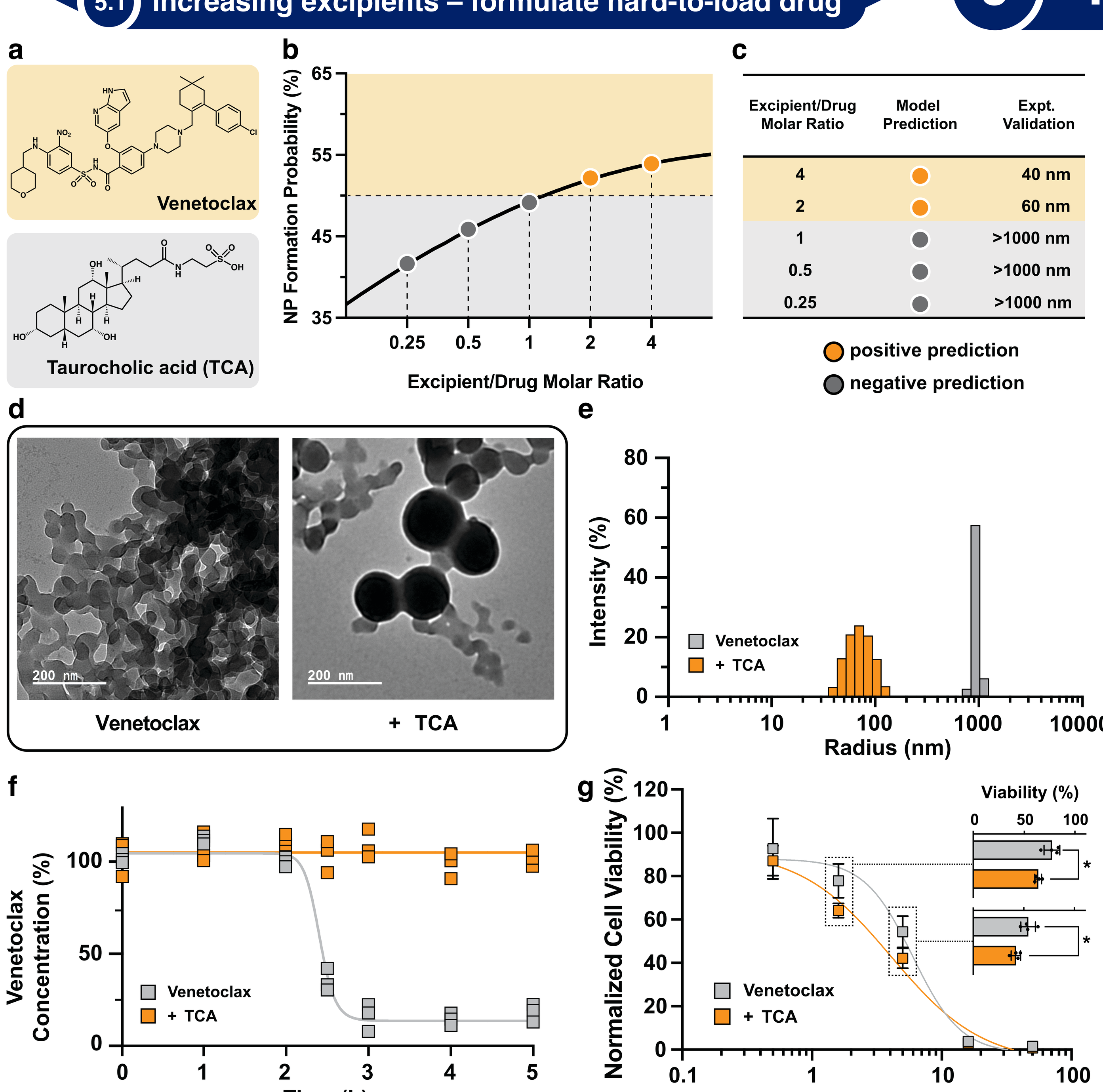


**Figure 5. Venetoclax-Taurocholic Acid (TCA) nanoparticles form when TCA is added more than Venetoclax. a,** Chemical structures of venetoclax and taurocholic acid (TCA). **b,c,** Model predictions and experimental validation (hydrodynamic radius) of venetoclax-TCA nanoparticles at different molar ratios. **d-f,** Transmission electron microscope (TEM) images, size distribution, and dispersion stability of 500 µM venetoclax, both unformulated and TCA-formulated (venetoclax:TCA = 2, molar ratio). **g,** Venetoclax nanoparticles exhibit improved cytotoxicity over free drugs on Kasumi-1 acute myeloblastic leukemia (AML) cells.

### 5.2 reducing excipients – maintain bioequivalence

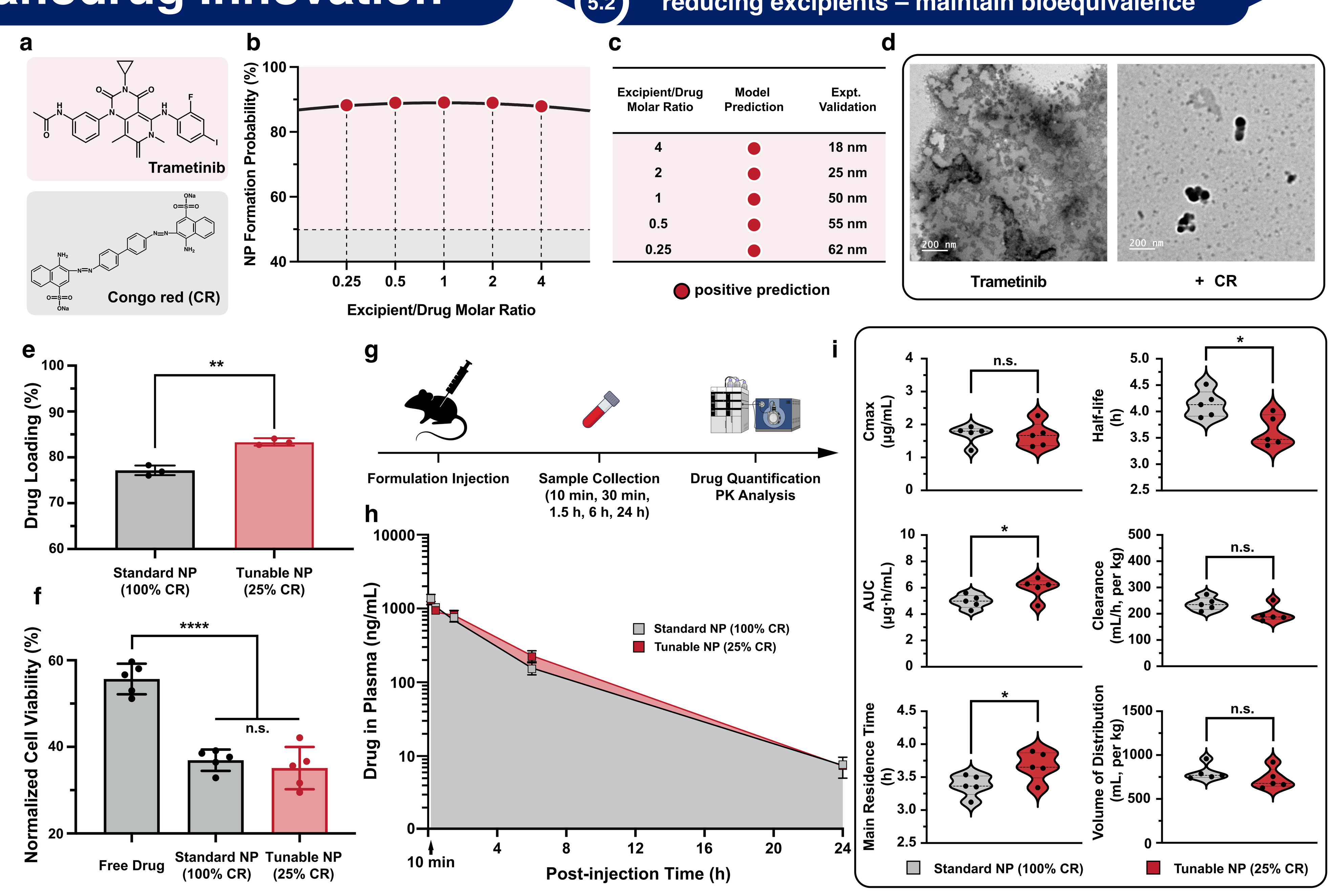


**Figure 6. Synthesizing bio-equivalent trametinib nanoparticles using less Congo red (CR). a,** Chemical structures of trametinib and Congo red (CR). **b,c,** Model predictions and experimental validation of Trametinib-CR nanoparticles. **d,** TEM images of 500 µM trametinib. **e,** Drug loading of trametinib nanoparticles at CR/trametinib molar ratios of 1:1 (standard nanoparticles, 100% CR) and 1:4 (tunable nanoparticles, 25% CR). **f,** Standard and tunable trametinib nanoparticles (20 µM) exhibit comparable in vitro cytotoxicity against $HepG_2$ human liver cancer cells. **g,** Schematic of in vivo experiment. **h,** Plasma drug concentration following retro-orbital injection of equal doses of standard and tunable trametinib nanoparticles. **i,** Key pharmacokinetic parameters of standard and optimized trametinib nanoparticles derived from plasma drug concentration profiles show largely bioequivalent behavior. Unpaired t- test (α = 0.05); n.s., p ≥ 0.05, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.


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### Affiliated Institution

1. Department of Biomedical Engineering, Duke University, Durham, NC 27708
2. Department of Medicine, Duke University School of Medicine, Durham, NC 27710
3. Pharmacokinetics/Pharmacodynamics (PK/PD) Core Laboratory, Duke Cancer Institute, Durham, NC 27710
4. Department of Radiation Oncology, Duke University School of Medicine, Durham, NC 27710
5. Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, NC 27710
6. Department of Surgery, Pathology and Integrative Immunobiology, Duke University, Durham, NC 27708
7. Duke Cancer Institute, Duke University School of Medicine, Durham, NC 27710

✉ Correspondence: daniel.reker@duke.edu


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