

New Results

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De novo design of protein nanoparticles with integrated functional motifs

 Cyrus M. Haas,  Sanela Rankovic,  Hanul K. Lewis,  Kenneth D. Carr,  Connor Weidle,
 Sophie S. Gerdes,  Lily R. Nuss,  Felicitas Ruiz, Syed Moiz,  Maggie Fiorelli,  Emily Grey,
 Jackson McGowan, Nikhila Kumar, Adrian Creanga,  Alex Kang,  Hannah Nguyen,  Yanqing Wang,
Banumathi Sankaran,  Annie Dosey,  Rashmi Ravichandran,  Asim K. Bera,  Elizabeth M. Leaf,
 Cole A. DeForest,  Masaru Kanekiyo,  Andrew J. Borst,  Neil P. King

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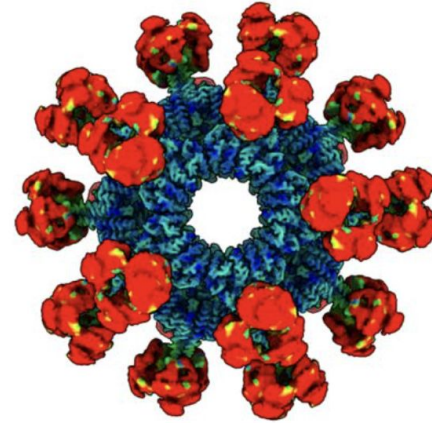
Abstract

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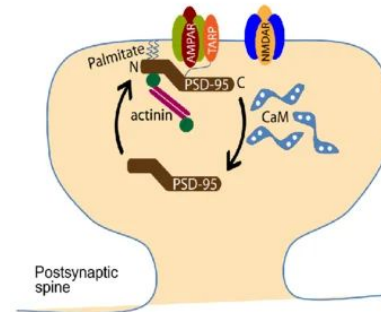
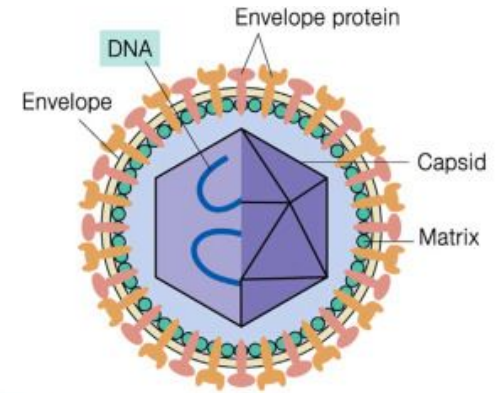
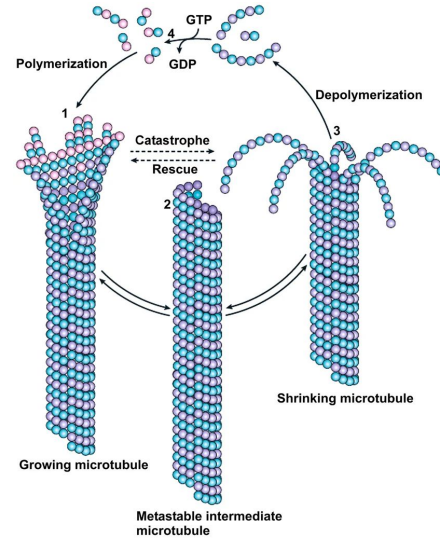


De novo design of protein nanoparticles with integrated functional motifs

Andrés and Barbara

Large self-assembling protein complexes are omnipresent in biology

- Examples:
 - Microtubules forming tracks
 - Viral capsids protecting viral genomes
 - Receptor scaffolding in neurons
- Developing de novo protein complexes is valuable for a variety of applications
- Hindered by the use of native structures as building blocks
 - Not enough generalizability











Challenge is to develop structures w/ functional motifs


- Want to develop a nanoparticle to fulfill a specialized function
- Some movement towards generating small de novo protein nanoparticles w/ various methods
- Could be more generalizable

🔒 | RESEARCH ARTICLE | PROTEIN DESIGN





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Top-down design of protein architectures with reinforcement learning

ISAAC D. LUTZ  SHUNZHI WANG  CHRISTOFFER NORN  ALEXIS COURBET  ANDREW J. BORST  YAN TING ZHAO  ANNIE DOSEY  LONGXING CAO 


JINWEI XU, [...] AND DAVID BAKER  +10 authors [Authors Info & Affiliations](#)

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De novo design of protein structure and function with RFDiffusion

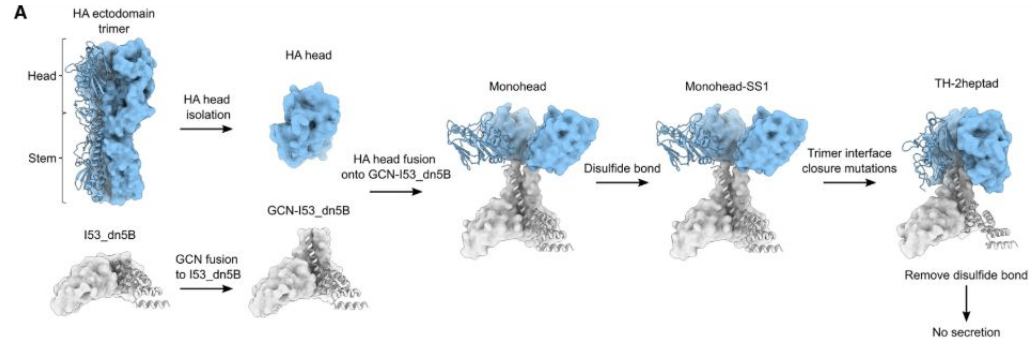
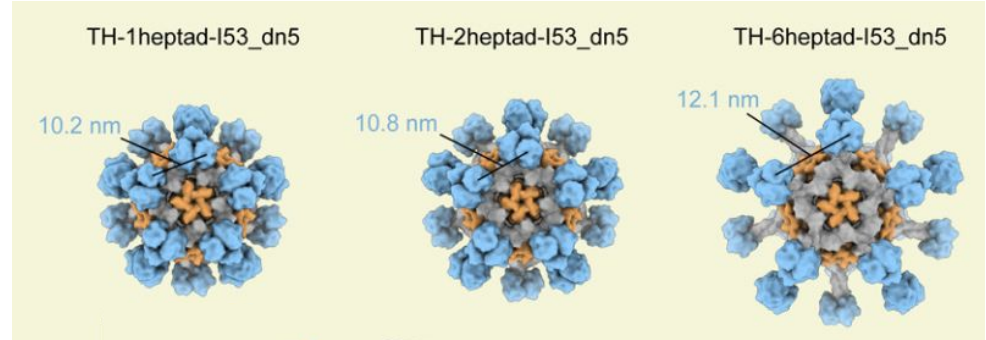
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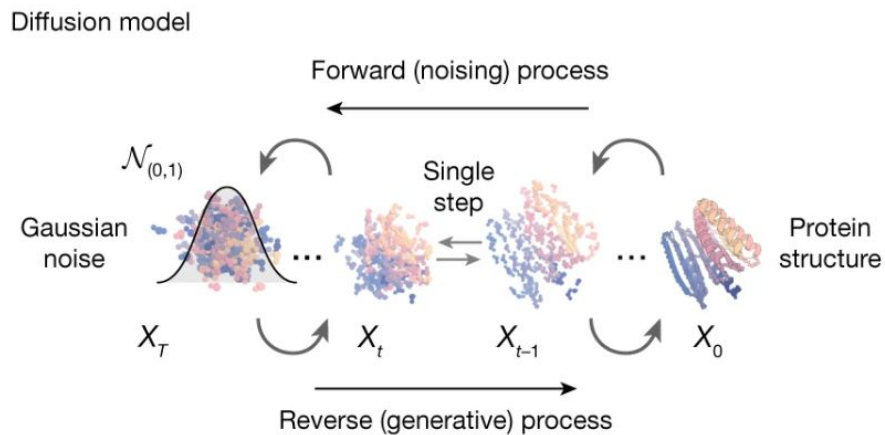
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Demanding test case - the design of antigen tailored nanoparticle immunogens

- Multivalent display of antigens on nanoparticle scaffold
- Fixed structures limits generalizability
 - Mismatches in symmetry or geometric constraints
- Authors decided to build nanoparticle scaffold for influenza virus hemagglutinin (HA) “tri-head” antigen

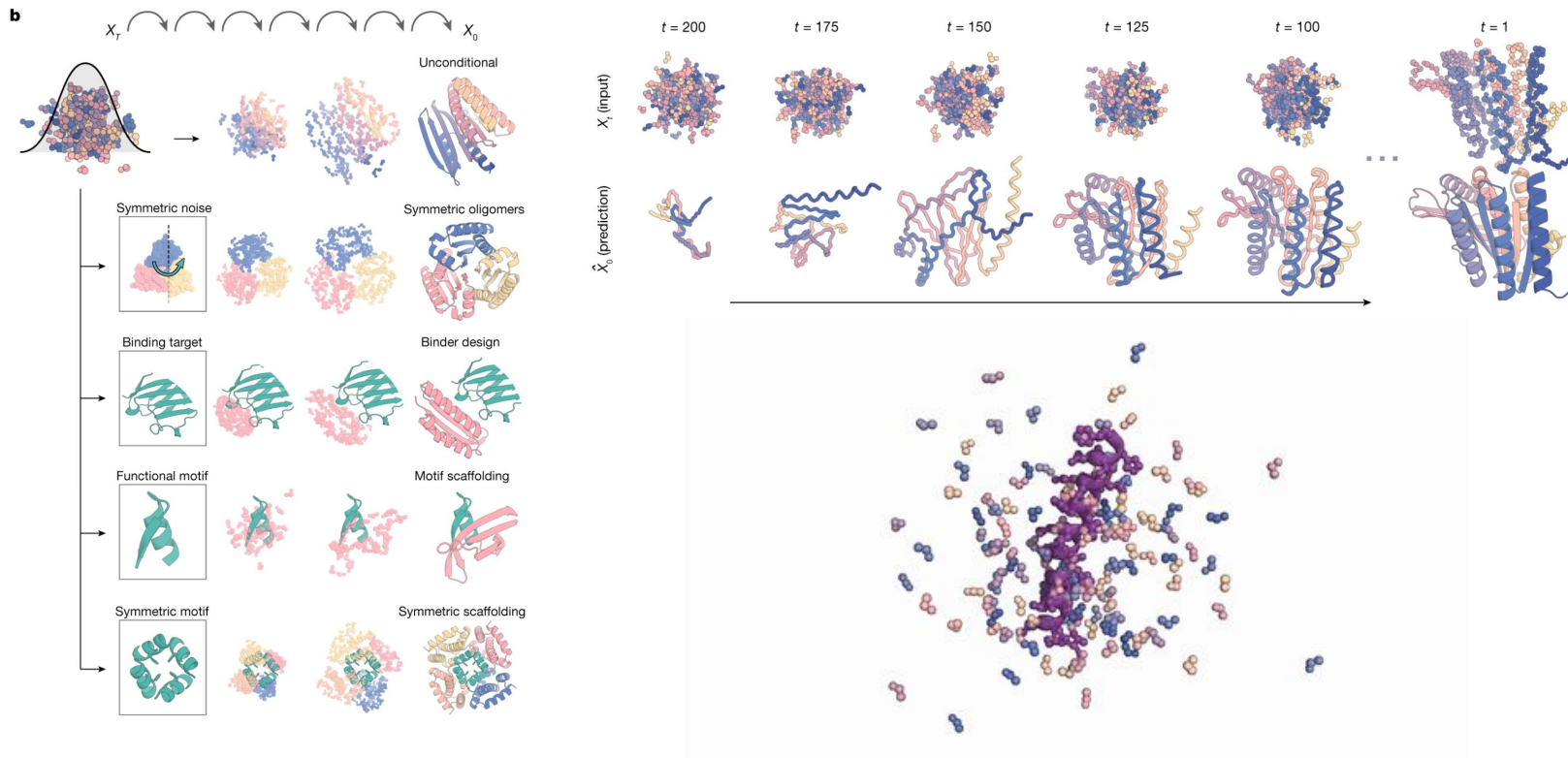


Protein design using RFdiffusion

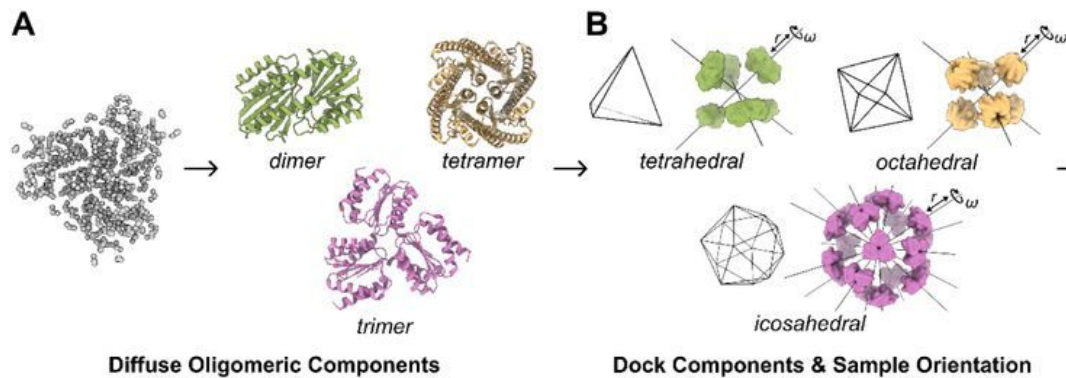


generated ~30,000 cyclic trimers (150/200aa)

Protein design using RFdiffusion



RPXdock



Deep learning–based sequence design with ProteinMPNN

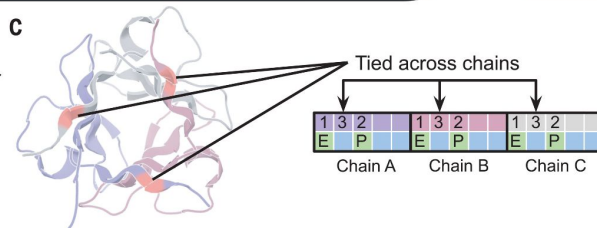
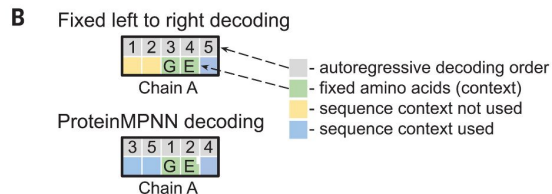
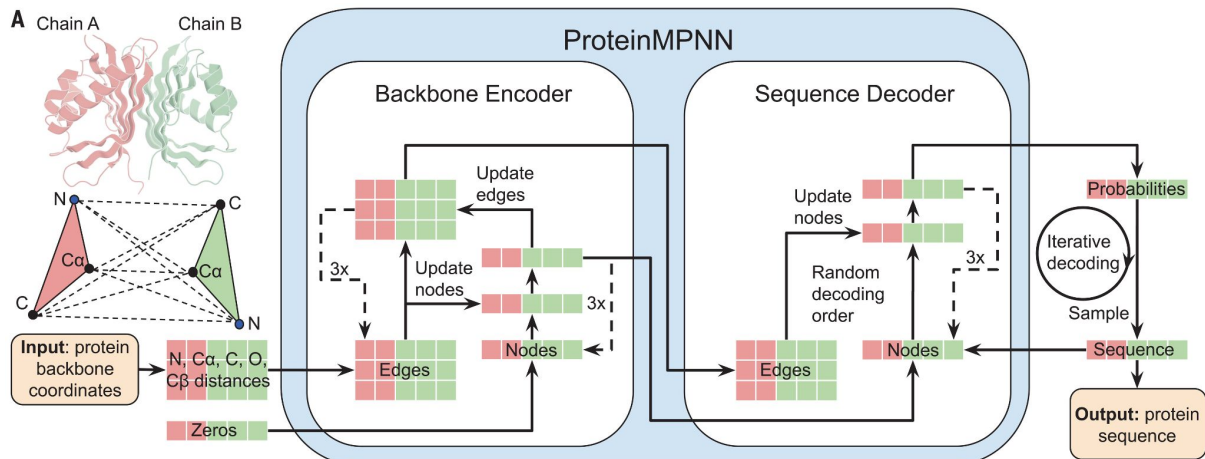
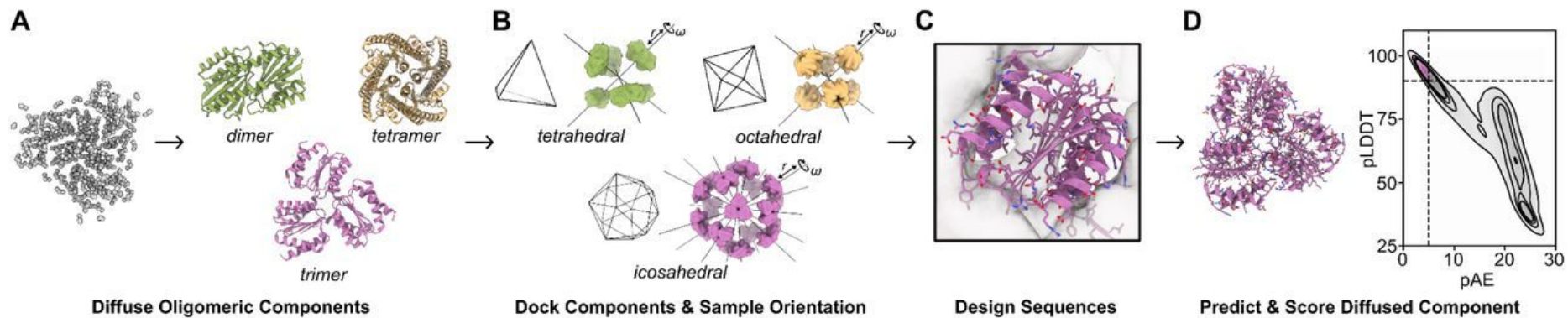
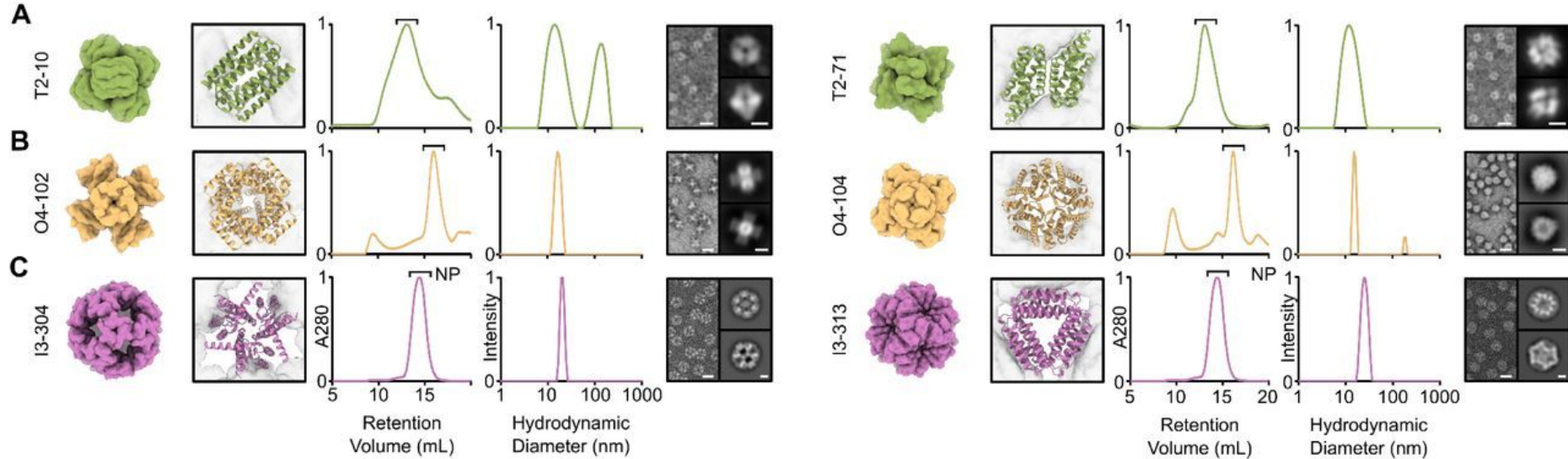


Figure 1



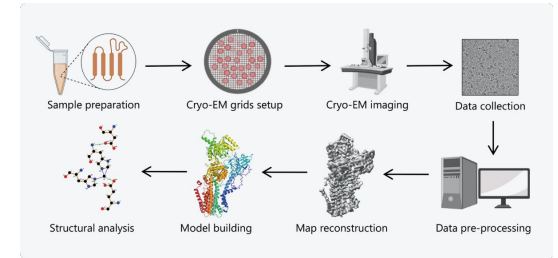
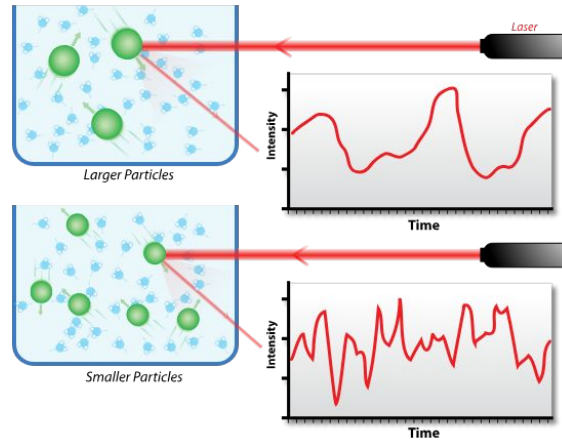
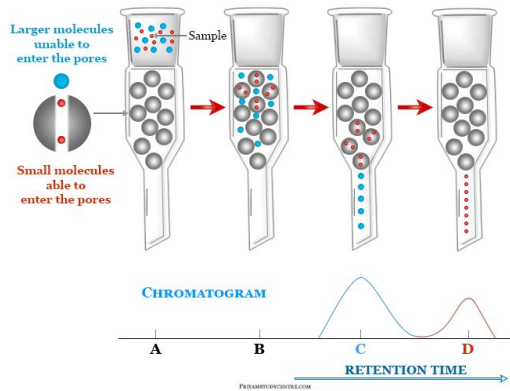
Use the method to actually generate nanoparticles



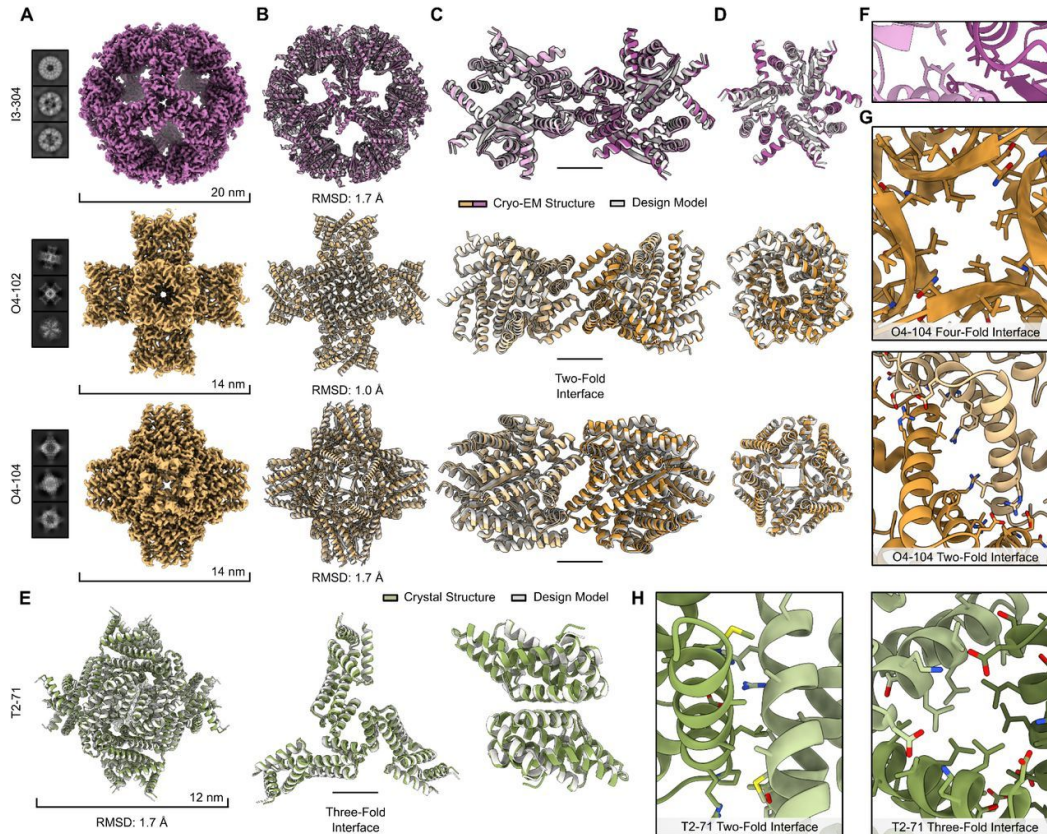
Strengths: robust characterization, try different geometries and oligomeric states - speaks to the “generalizability” of their method
On-target densities obtained by 3D reconstruction closely match design models

Validation of nanoparticle targets using SEC, DLS, CryoEM

Size Exclusion Chromatography (SEC)



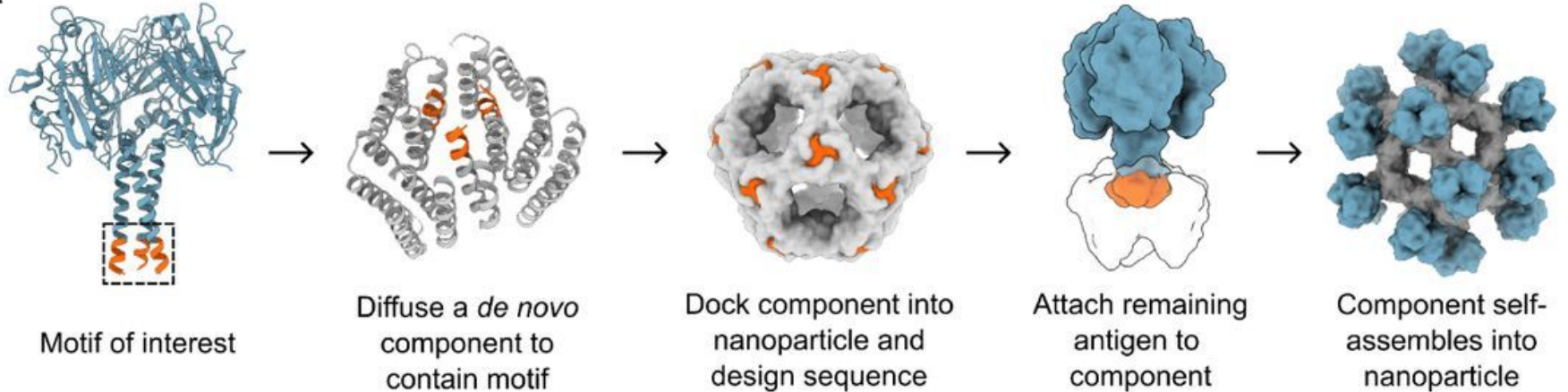
Further characterization of a subset of nanoparticles



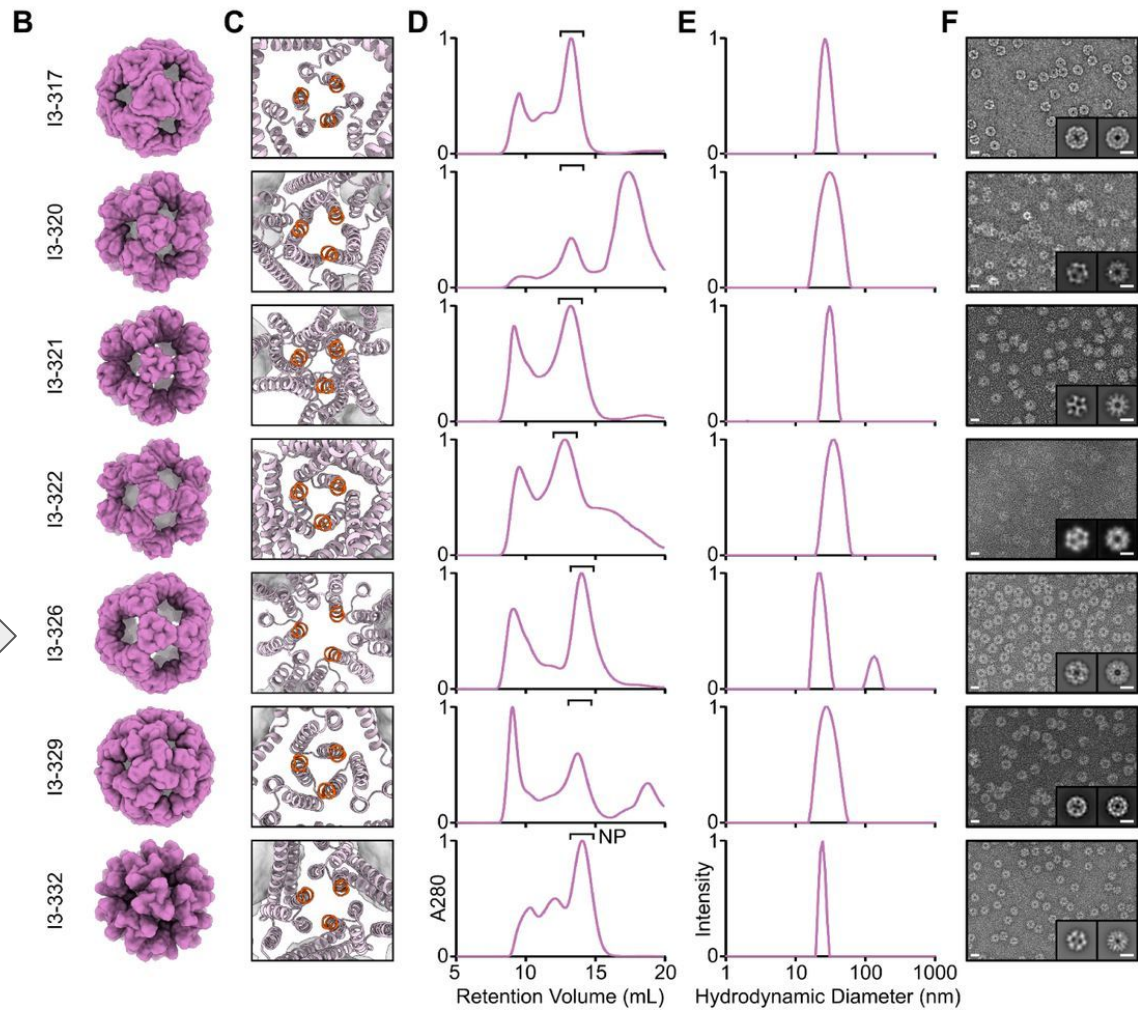
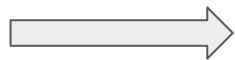
- Measure the difference between design and produced nanoparticle
- Would love to know the rationale for why they moved forward with this specific group of candidates
- Would've loved better labeling of what to look at/legend
- Unclear if the variation in interactions is a limitation of their methodology?

Putting it into practice - tackling a difficult design task with their design method

A

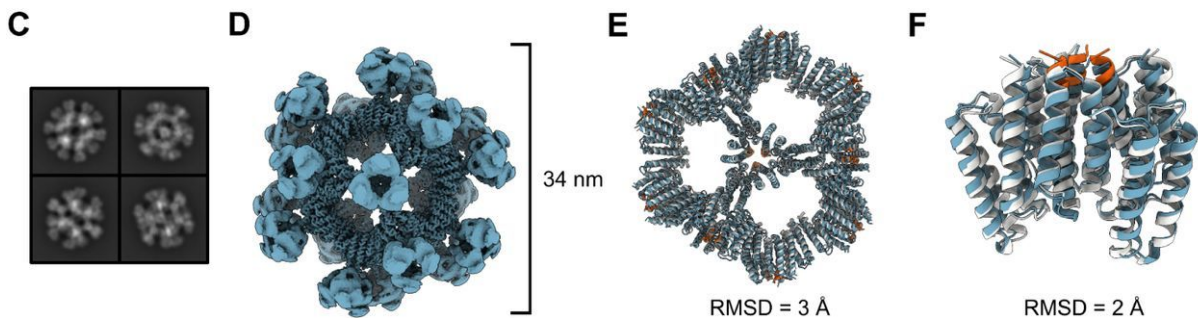
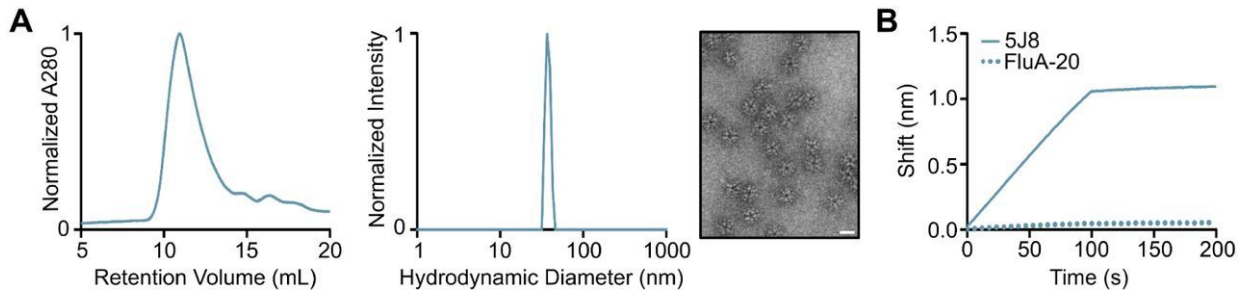


This one
secreted



They pick one and show that it does what they say it does

I3-326-MI15-TH



They only did this in female mice - BAD

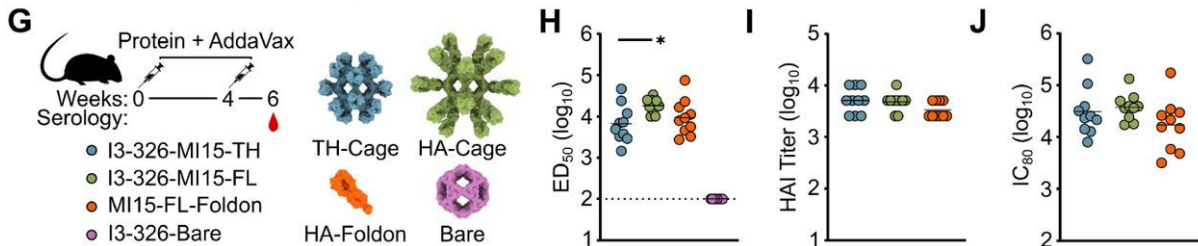


Figure S1

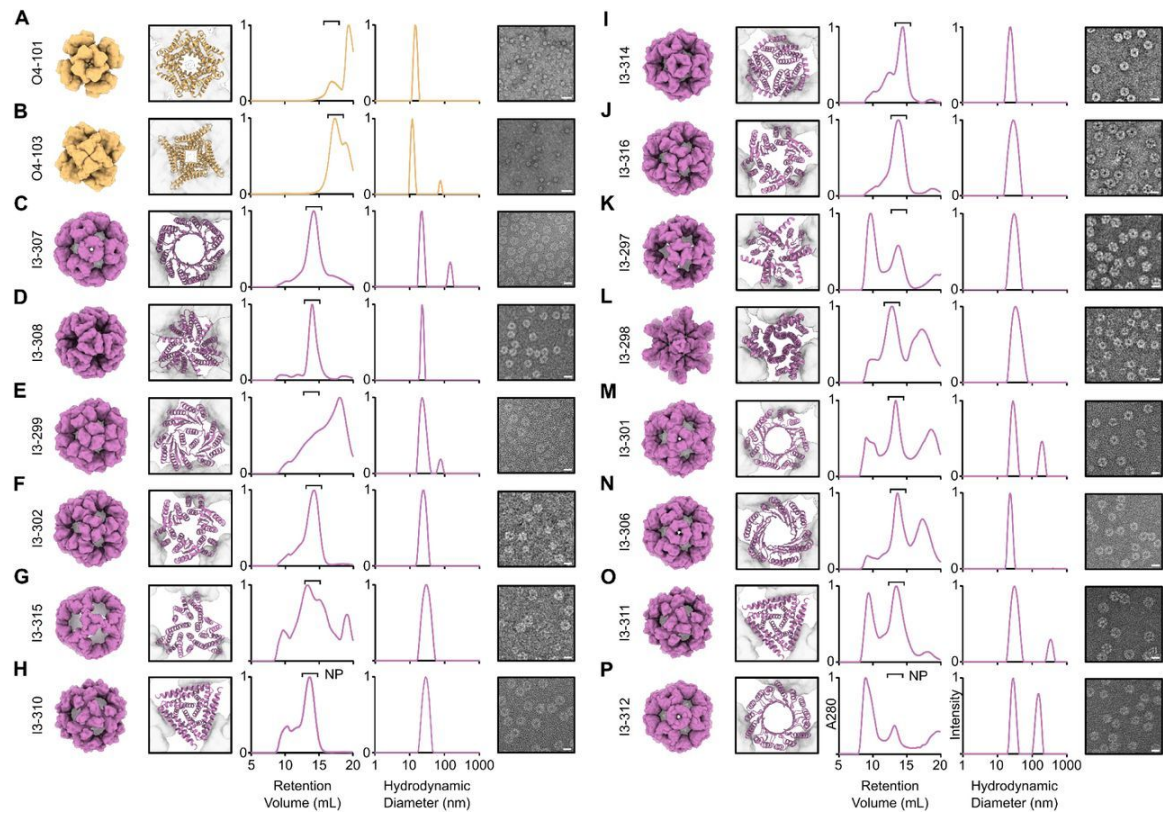


Figure S3

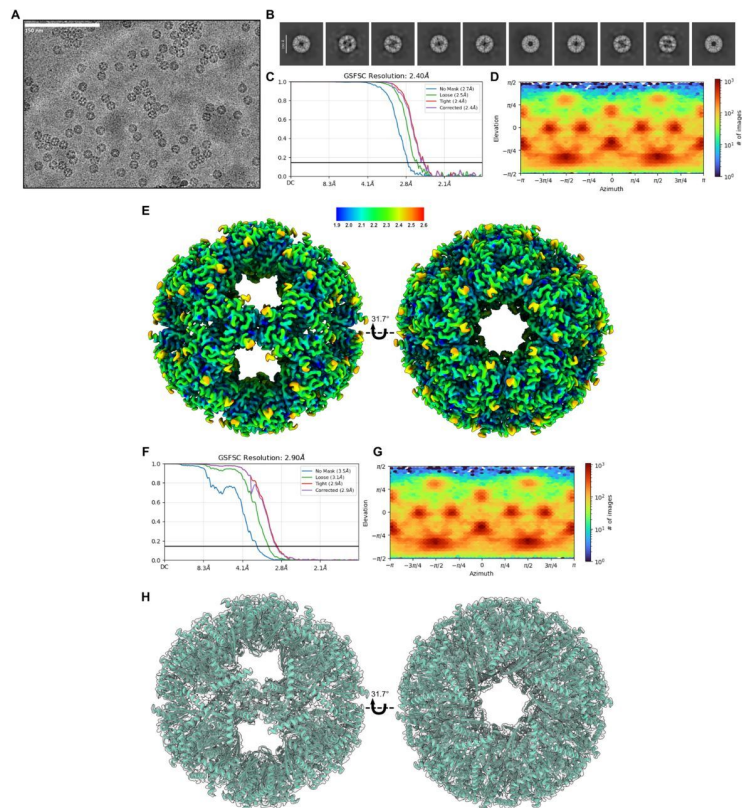


Figure S4

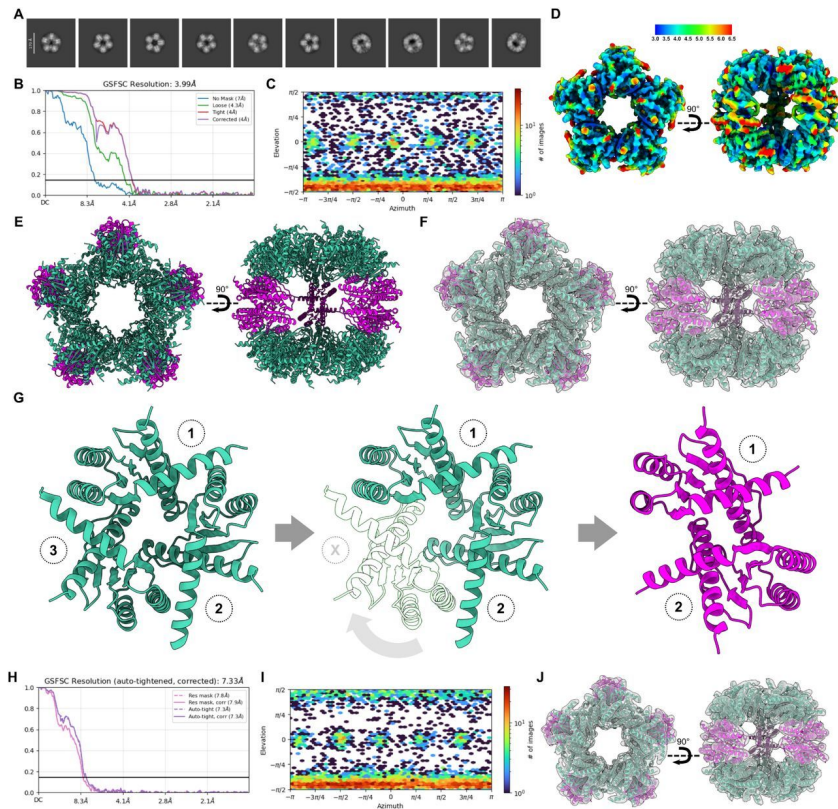


Figure S5

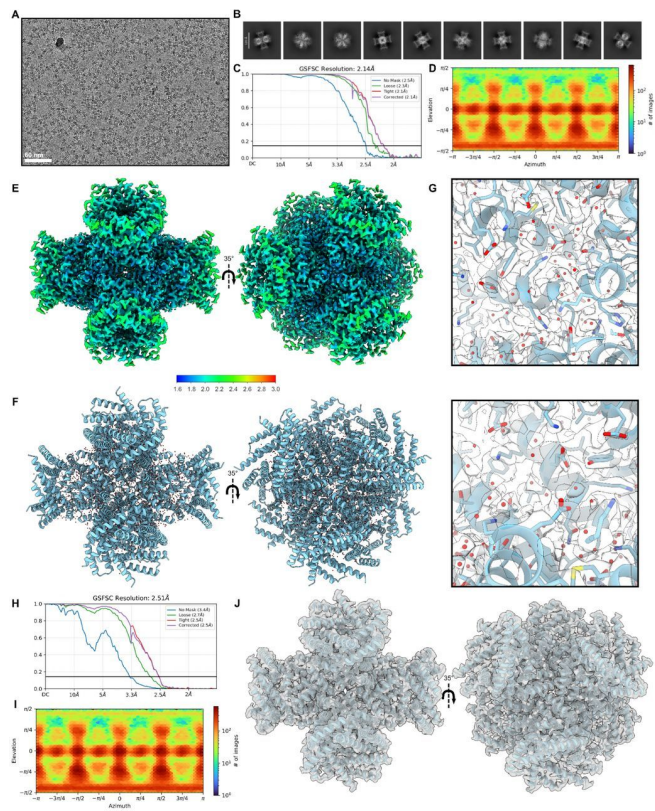


Figure S6

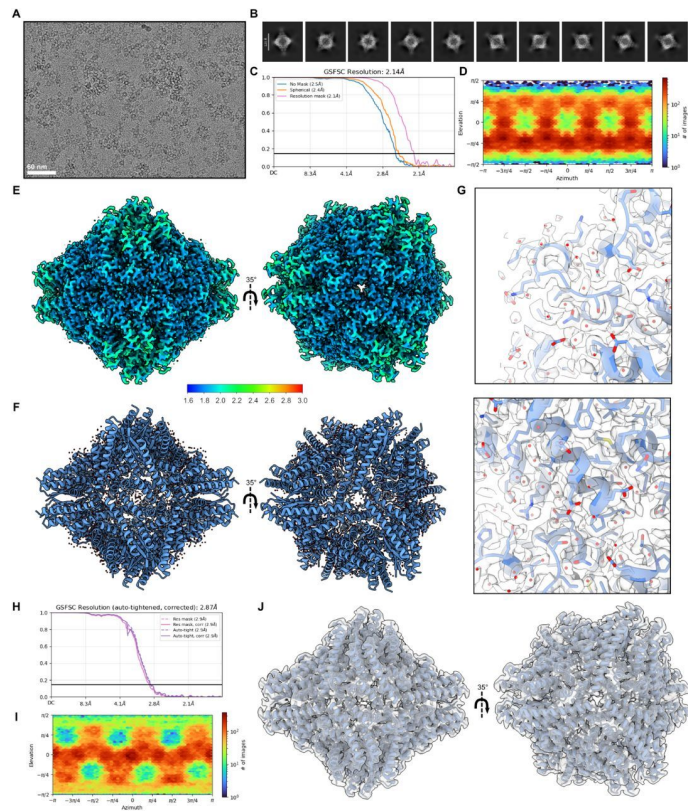


Figure S7

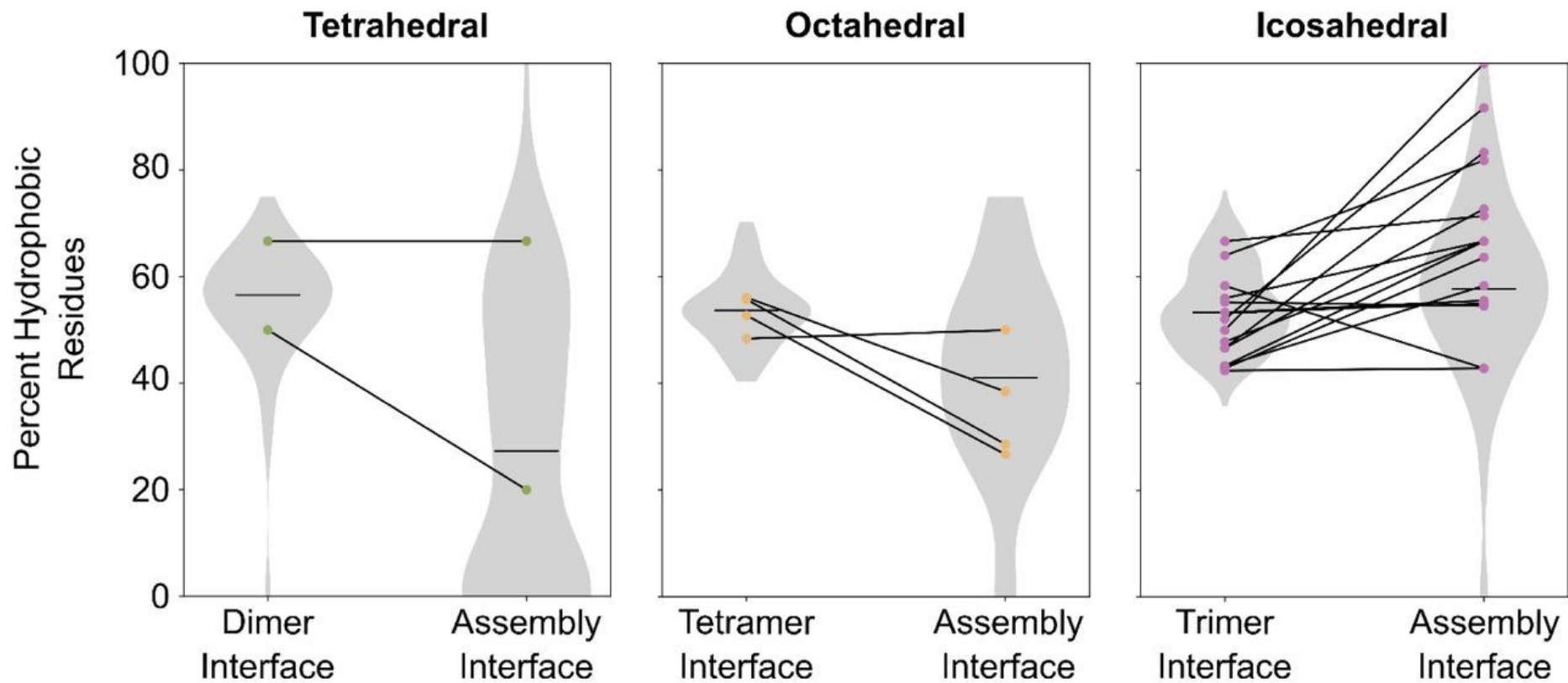


Figure S8

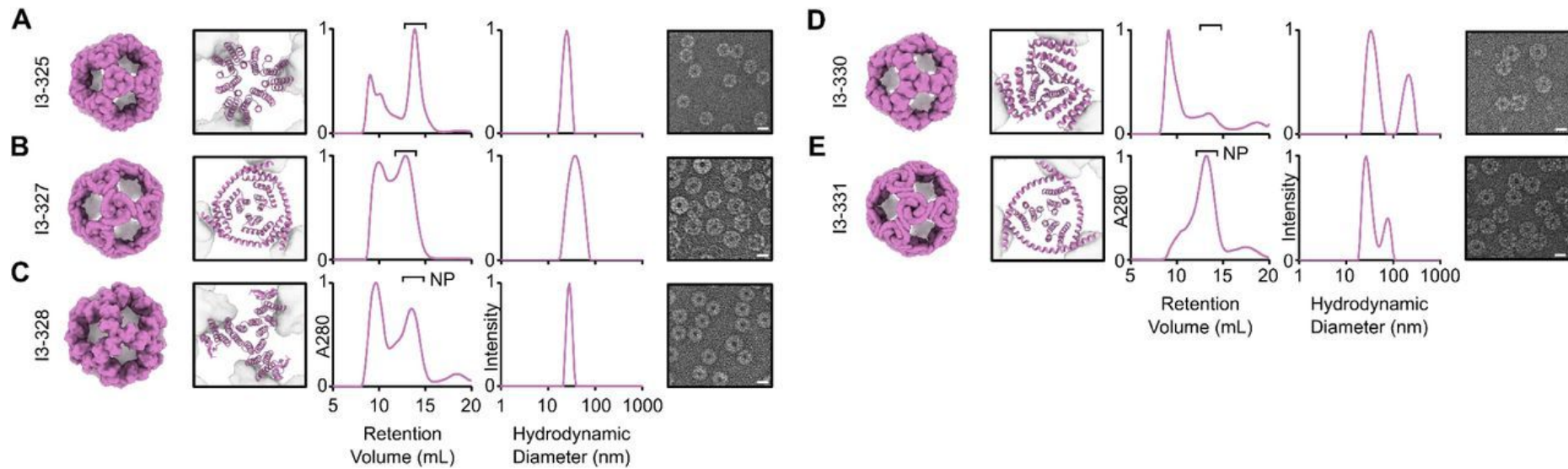


Figure S9

Conditional Nanoparticle nsEM Characterization:

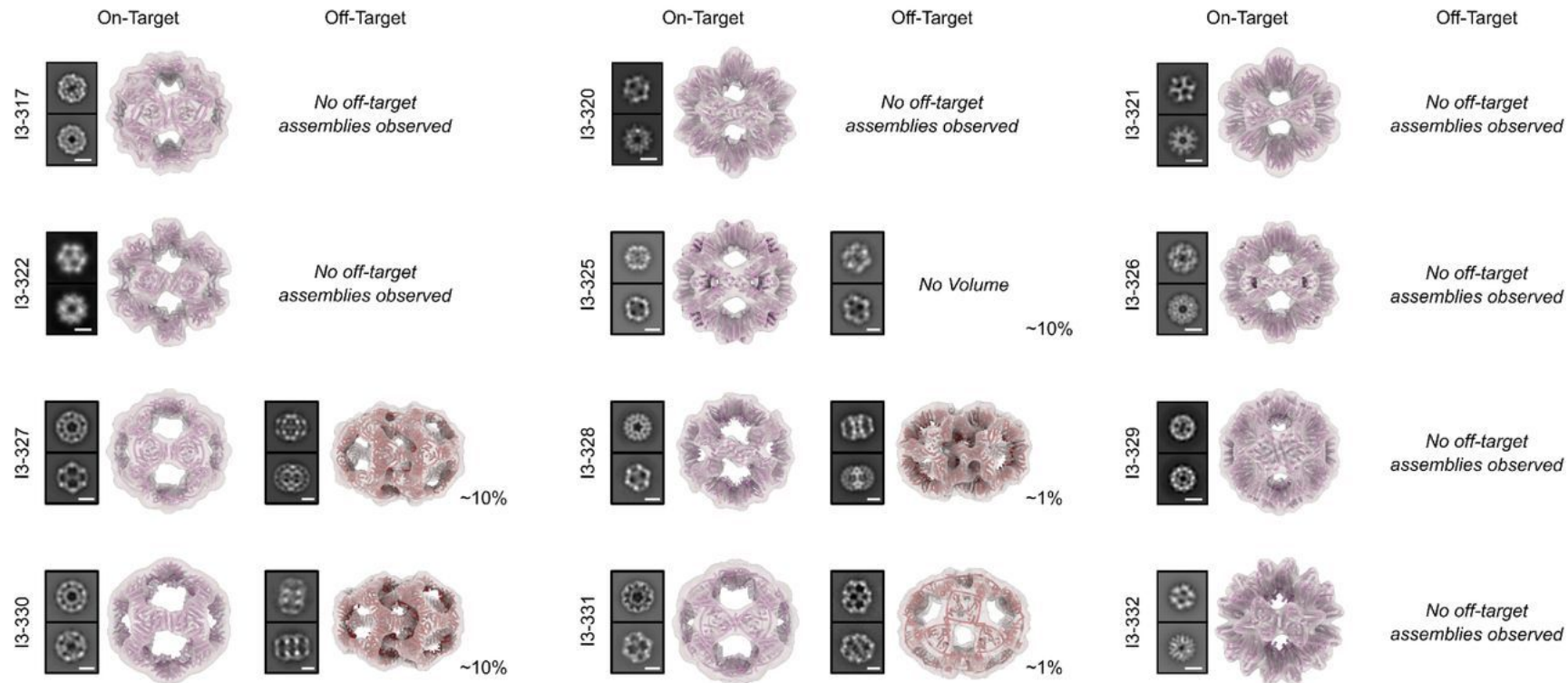


Figure S10

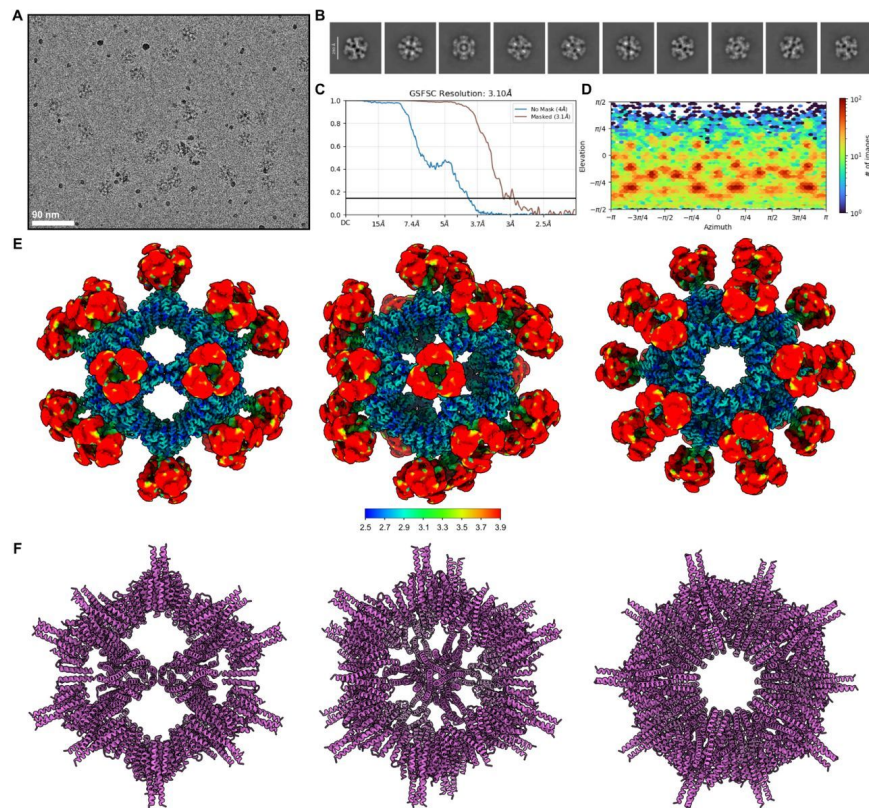


Figure S11

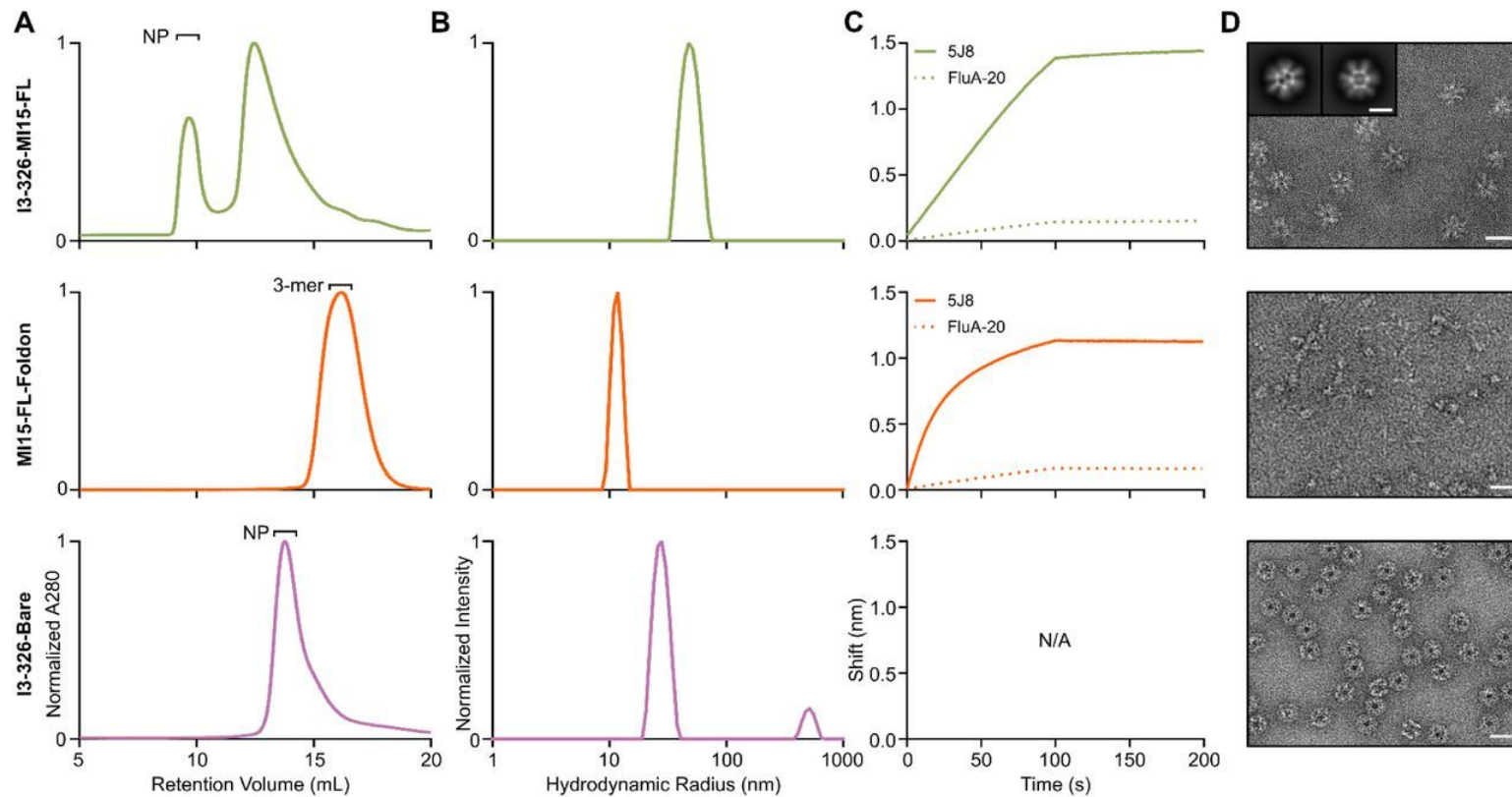


Figure S12

