Tech Session: Artificial Intelligence and Predictive Models

Leveraging High-Throughput Analytics and Predictive Models to Advance LNP Development

Yuchen Fan

Principal Scientist
Genentech

7/15/2025

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

High-throughput screening and analytics improve development efficiency of LNP formulations

HTS covers comprehensive formulation design space

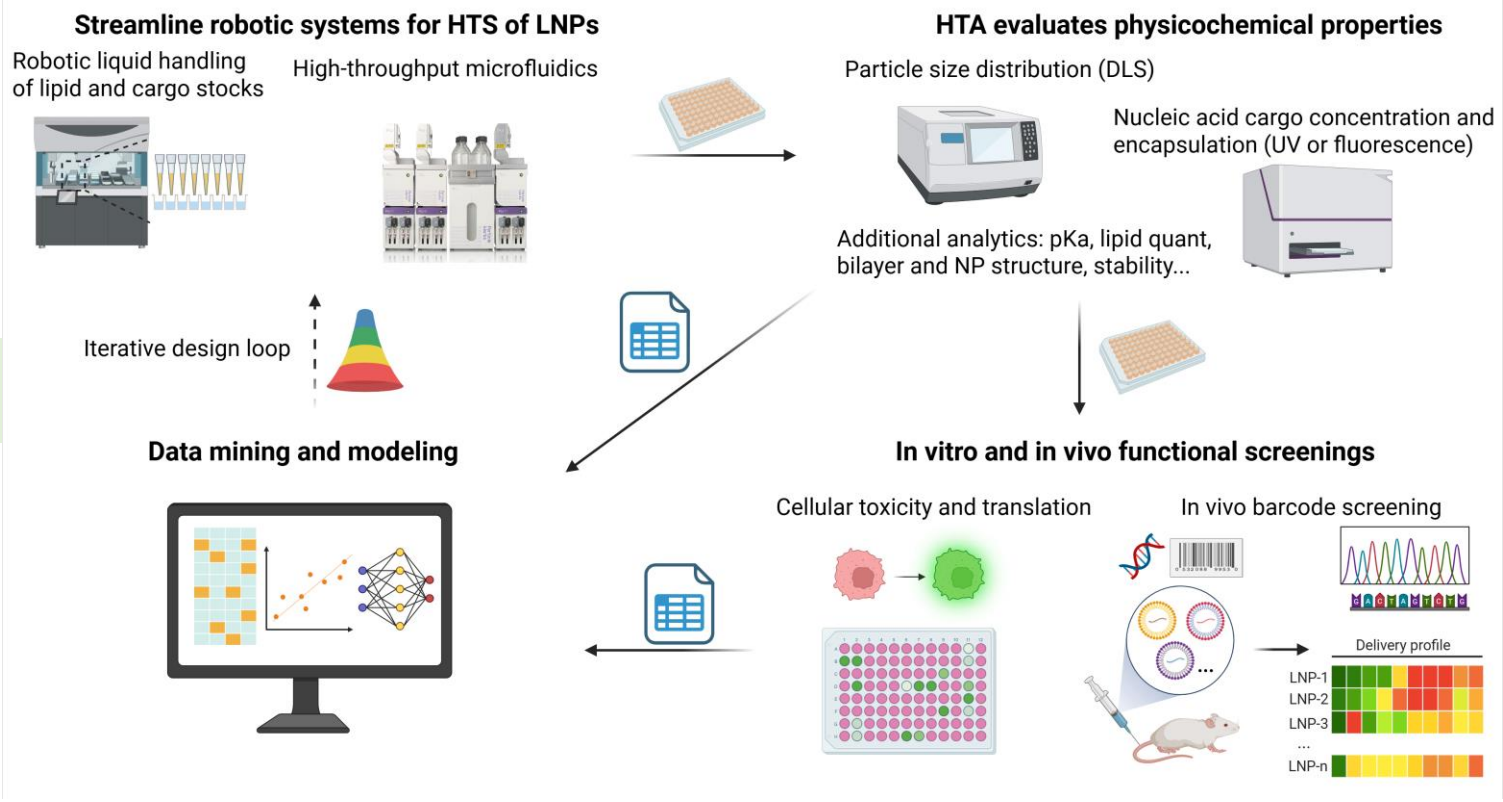
HTA (multi-parallel, spectroscopies) increases analytical throughput

Deliver the formulation hits with higher efficiency and less resource

Fuel database to enable AI/ML-assisted formulation development

Low volume and microplate scale reduce material consumption

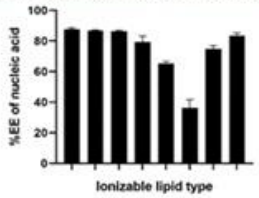
Automation saves labor and reduces human error



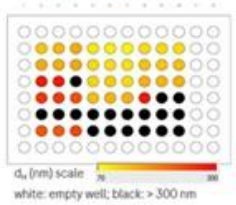
Schemes are assisted by BioRender

HTS and HTA workflows address critical physicochemical attributes of LNPs

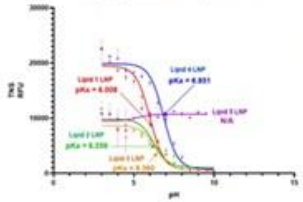
Encapsulation efficiency



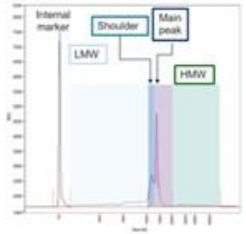
Size distribution



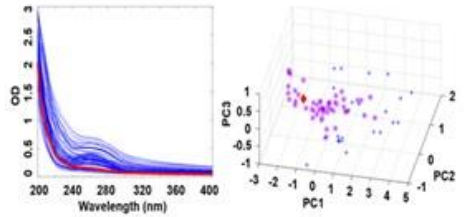
Apparent pKa



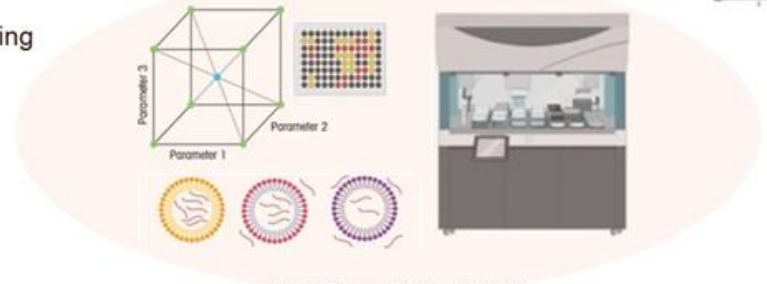
Cargo stability (mRNA integrity)



Predictive spectroscopy model for cargo loading

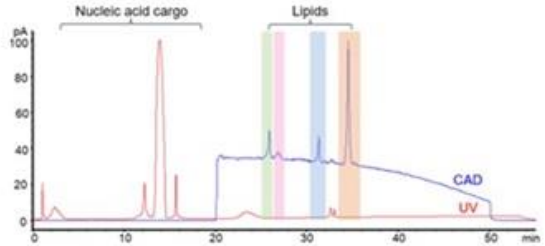


Anal Chem. 2022, 9081-9090.



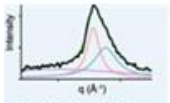
Int J Pharm. 2021, 120392.

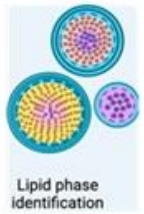
Platform IPRP for content of cargo and lipid excipients

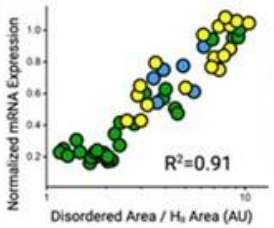


J Chromatogr A. 2025, 465788.

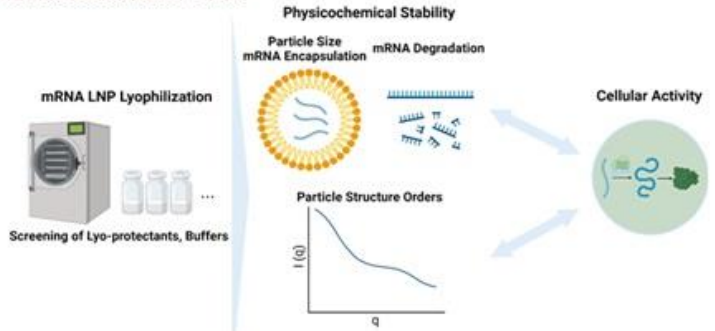
High-throughput LNP structure elucidation and SAR





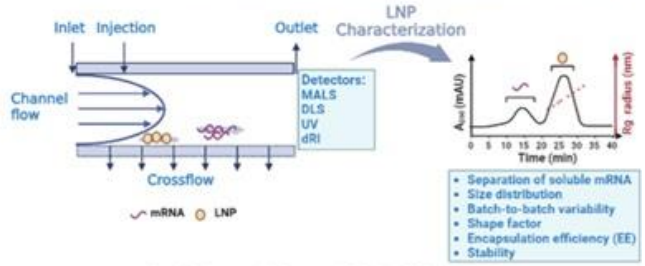


ACS Nano. 2023, 11454-11465.



J Control Release. 2024, 727-737.

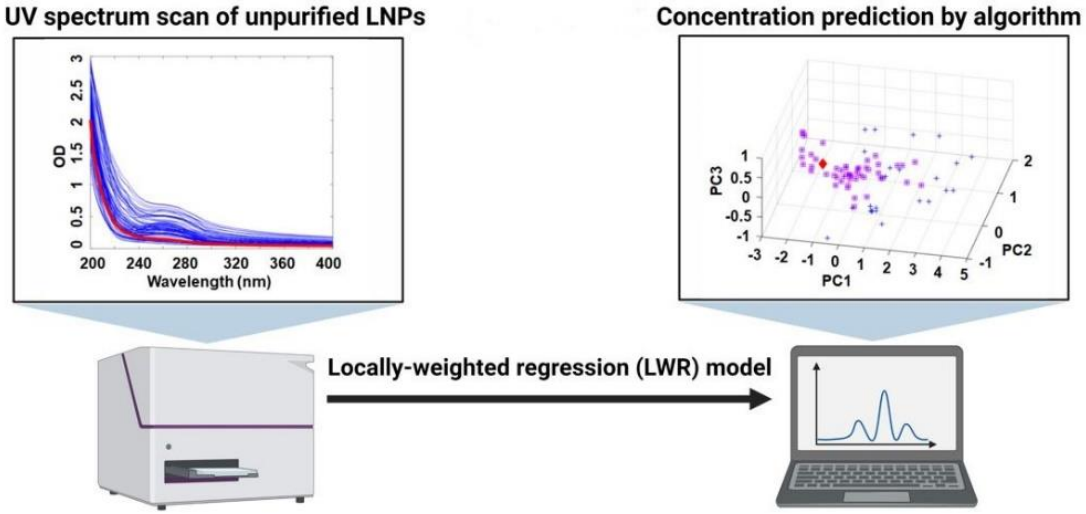
Platform FFF for multi-attribute characterizations

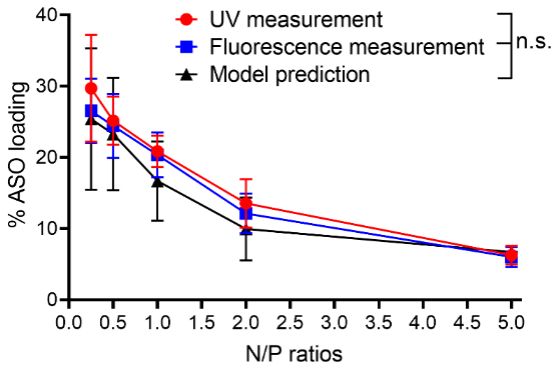


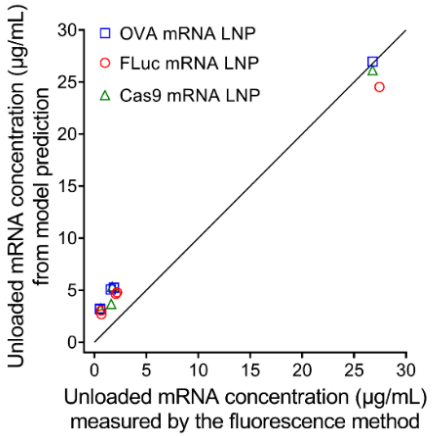
Anal Bioanal Chem. 2024, 5281-5293.

Leveraging predictive spectroscopy model to quantify nucleic acid cargo loading in high throughput

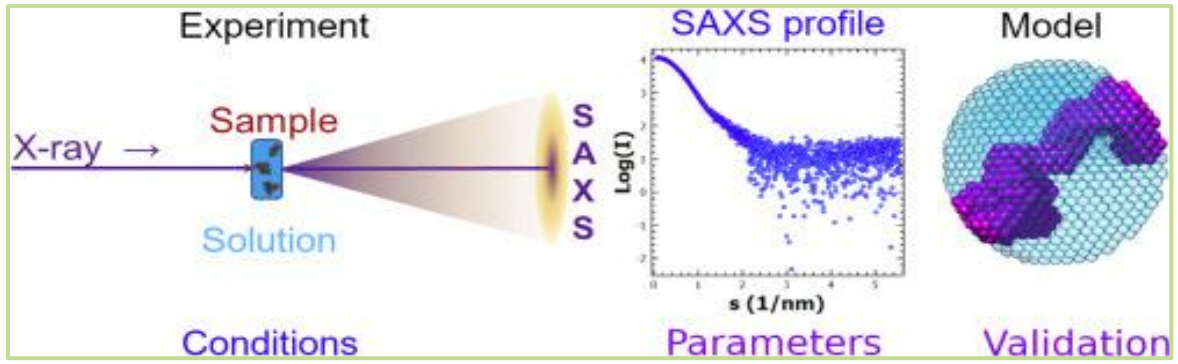
- In situ, non-label HTA is preferred
- Conventional UV or fluorophore labeling approaches are limited by pre-separation processes and/or additional external standards
- Nucleic acids share unique UV spectrum features, with peak absorbance at 260 nm
- Collect spectra of historical LNPs from HTS, apply PCA and statistical algorithms to deconvolve the unloaded and/or loaded cargo information
- Build PLS models to quantitatively predict cargo loading
- **An in situ, non-label, and evolving approach**: prediction performance could be further improved by more data feeding from screened samples



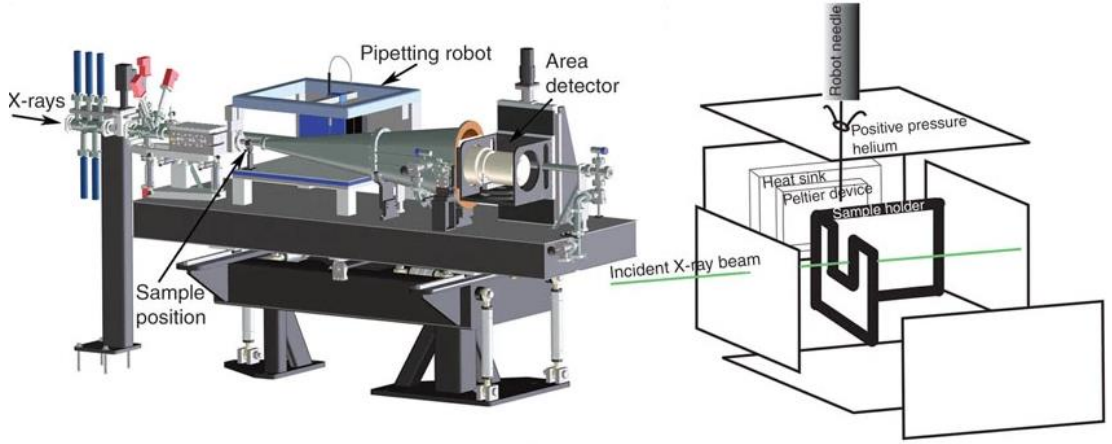




High-throughput SAXS for LNP structure elucidation

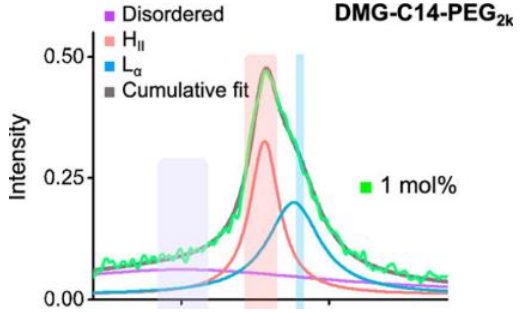


Screening of LNP structural features (1 hr / 96-well plate)

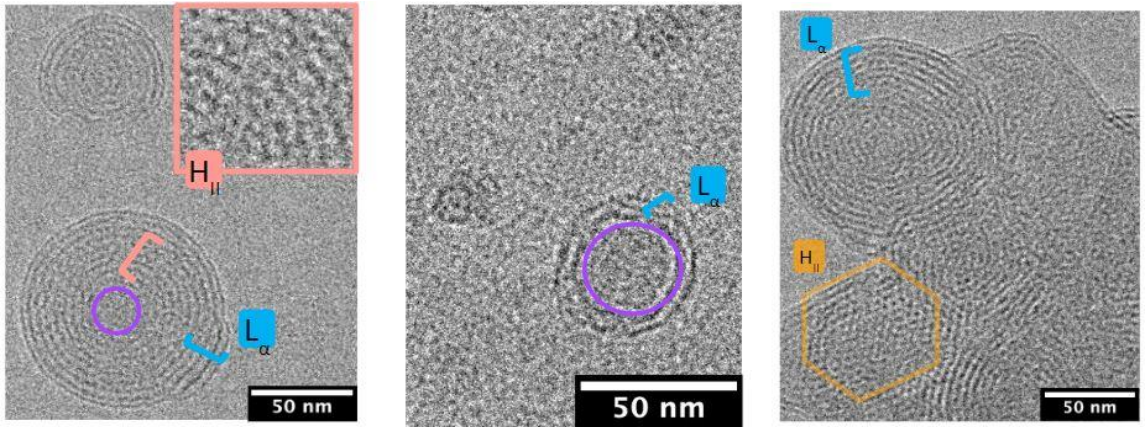


Nat Methods. 2009, 606-612.

- Based on cryo-TEM and HT-SAXS results, deconvolve LNP into different core structure features: **hexagonal, lamellar, and amorphous phases**
- Prescence and abundance of different internal structural phases are affected by different lipid compositions and formulation processes

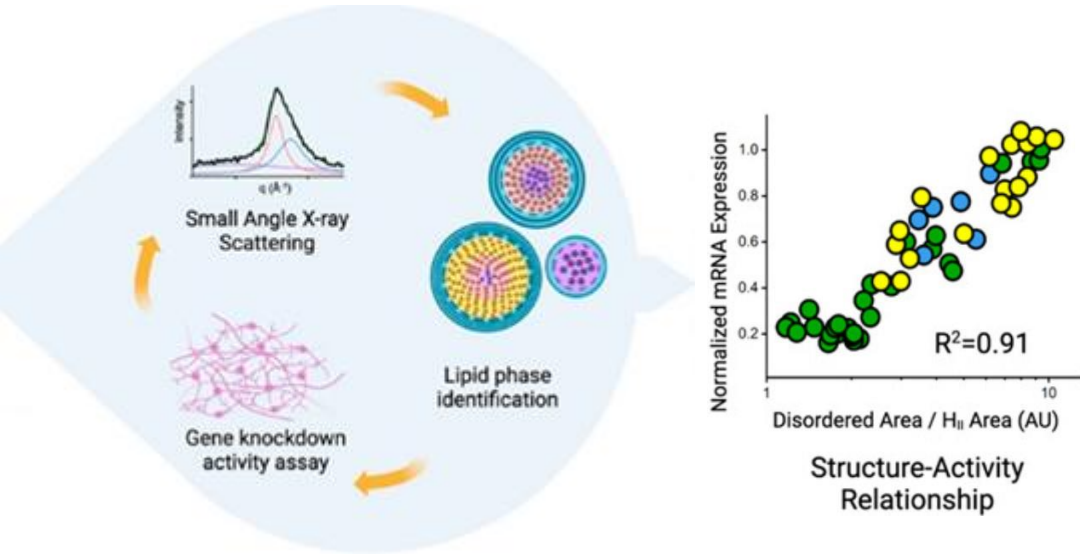


1% DMG (C14:0)-PEG$_{2k}$ | 5% DSPE (C18:0)-PEG$_{2k}$ | 1% DOPE (C18:1)-PEG$_{0.55k}$

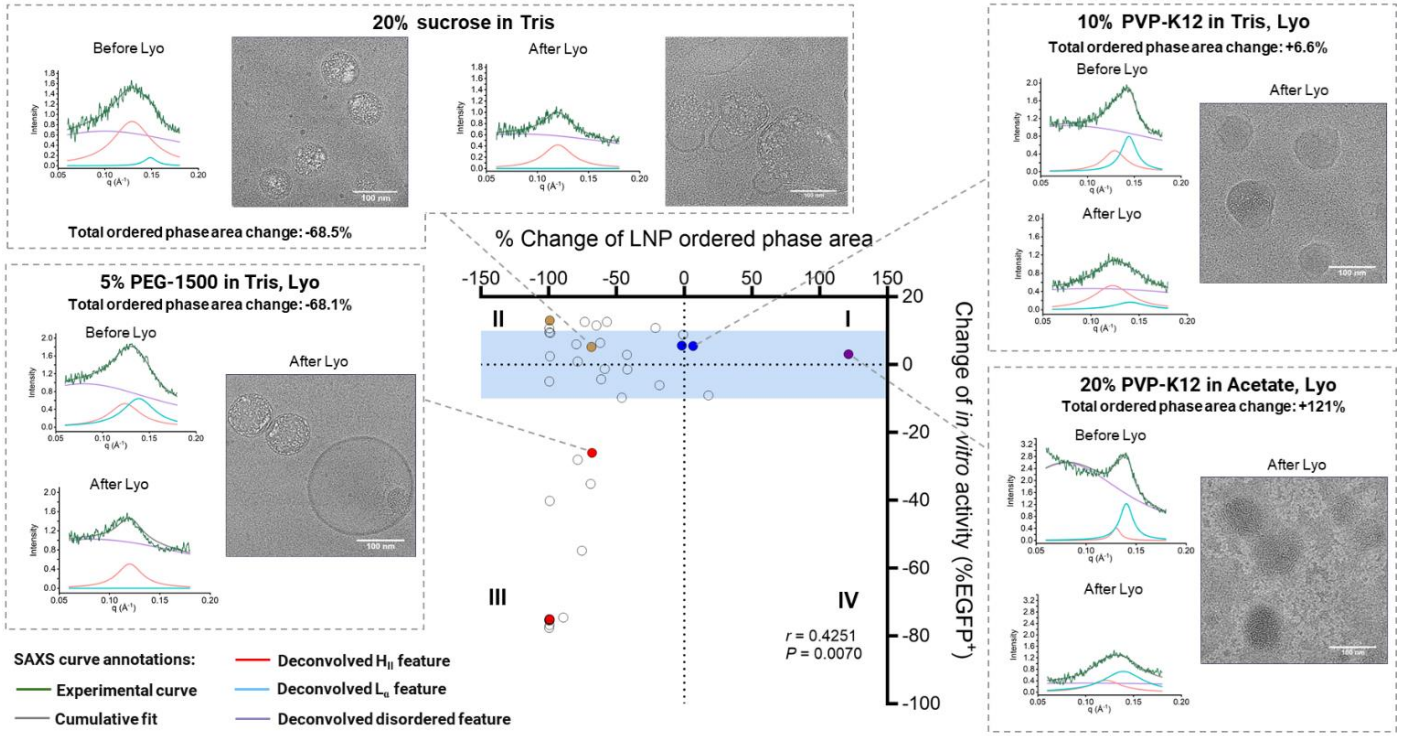


High-throughput LNP structure elucidation allows SAR

In a screening library of ASO-LNPs: higher relative abundance of (hexagonal) ordered phase / amorphous phase correlates with stronger cellular knockdown efficacy



In a screening library of lyophilized mRNA-LNPs: in vitro efficacy is preserved after lyophilization if the ordered structure is preserved or if there is structural transition into amorphous bleb features



HTS and HTA for LNPs

❖ Automation-enabled HTS workflow:

- Examine vast design spaces with reduced material consumption and increased efficiency
- Customizable and translatable scales support both in vitro and in vivo evaluations

❖ HTA toolbox:

- Address quality attributes of LNPs, employ stage-tailored specifications and criteria
- Build and mine dataset to innovate predictive models to further increase throughput

❖ Lab-in-the-loop:

- Correlate multi-attributes to propose SAR to guide formulation design
- Fuel AI/ML models to advance next-generation formulation development

Acknowledgment

Automation
Wan-Chih Su
Raymond Lieu
Tao Chen
Samantha Yu*
Pascal Winkler*
Daisy Fu*
Weijia Hou*

Analytical
Alexandre Goyon
Zhenqi Shi
Zeenat Razvi
Shengli Ma*
Nanzhi Zang
Ziting Gao
Juan Bian
Jessica Lin
Kelly Zhang
Peter Yehl

Pharmaceutics
Apoorva Sarode
Kristina McKee
Yimin Gu
Feng-Peng Chang*
Hsiu-Chao Lin*
Chun-Wan Yen
Dennis Leung
Karthik Nagapudi

In vitro/in vivo
Amy Byrnes*
Diamanda Rigas
Christopher Kemball
Whitney Binder

Lawrence Berkeley National Laboratory
Lee Joon Kim*
Michal Hammel
Gregory Hura

*Previous member