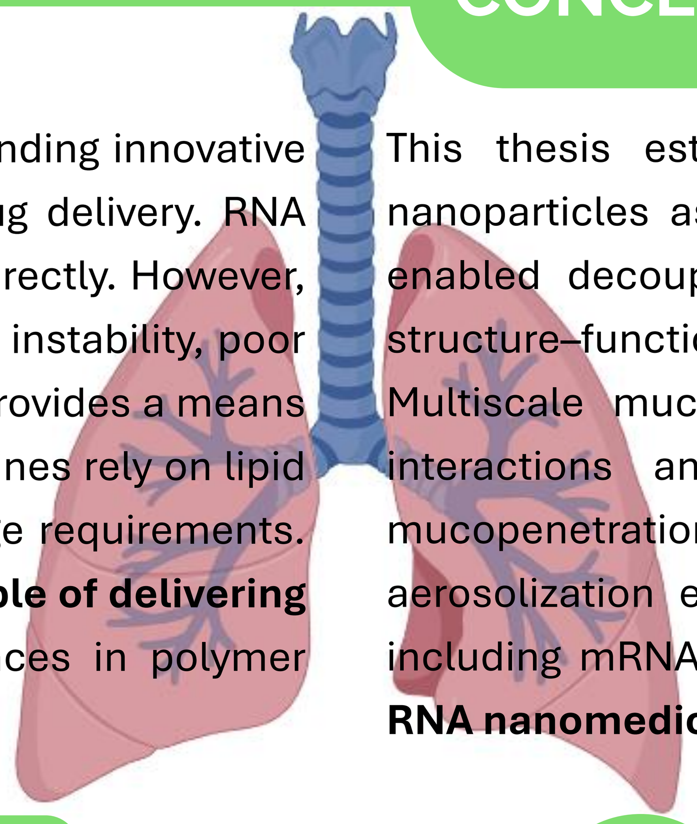
# From polymer design to inhalable RNA nanomedicine: poly(β-amino ester) nanoparticles for lung cancer treatment

Antoni Torres Coll, Dr. Cristina Fornaguera i Puigvert, Dr. Salvador Borrós Gómez.
*Grup d'Enginyeria de Materials (GEMAT), Institut Químic de Sarrià, Universitat Ramon Llull, Barcelona, Spain*

## ABSTRACT

Lung cancer remains one of the most lethal malignancies worldwide, demanding innovative therapeutic strategies that combine molecular precision with effective drug delivery. RNA therapeutics, offer a transformative platform to modulate gene expression directly. However, their clinical translation is hindered by biological barriers such as enzymatic instability, poor cellular uptake, and limited bioavailability in target tissues. **Nanomedicine** provides a means to overcome these challenges, yet most clinically approved RNA nanomedicines rely on lipid nanoparticles with restricted tissue tropism and stringent cold-chain storage requirements. This work **aims to develop a polymer-based nanomedicine platform capable of delivering RNA therapeutics safely and effectively to the lung**, integrating advances in polymer chemistry, nanotechnology, and pharmaceutical formulation.



## CONCLUSIONS

This thesis establishes an integrated framework for designing poly(β-amino ester) nanoparticles as inhalable carriers for RNA therapeutics. **(1)** Tailored pBAE chemistries enabled decoupled control of RNA condensation and surface functionality, revealing structure–function relationships that govern cellular uptake and targeted transfection. **(2)** Multiscale mucus analyses demonstrated that zwitterionic coatings minimize mucin interactions and preserve nanoparticle mobility, identifying key determinants of mucopenetration. **(3)** Finally, spray-dried nano-embedded microparticles achieved high aerosolization efficiency, structural stability, and full recovery of nanoparticle activity, including mRNA delivery. Together, **these findings advance the rational engineering of RNA nanomedicines toward clinically relevant pulmonary administration.**

## 1 Tailoring pBAE polymers for RNA delivery: a structure-function approach

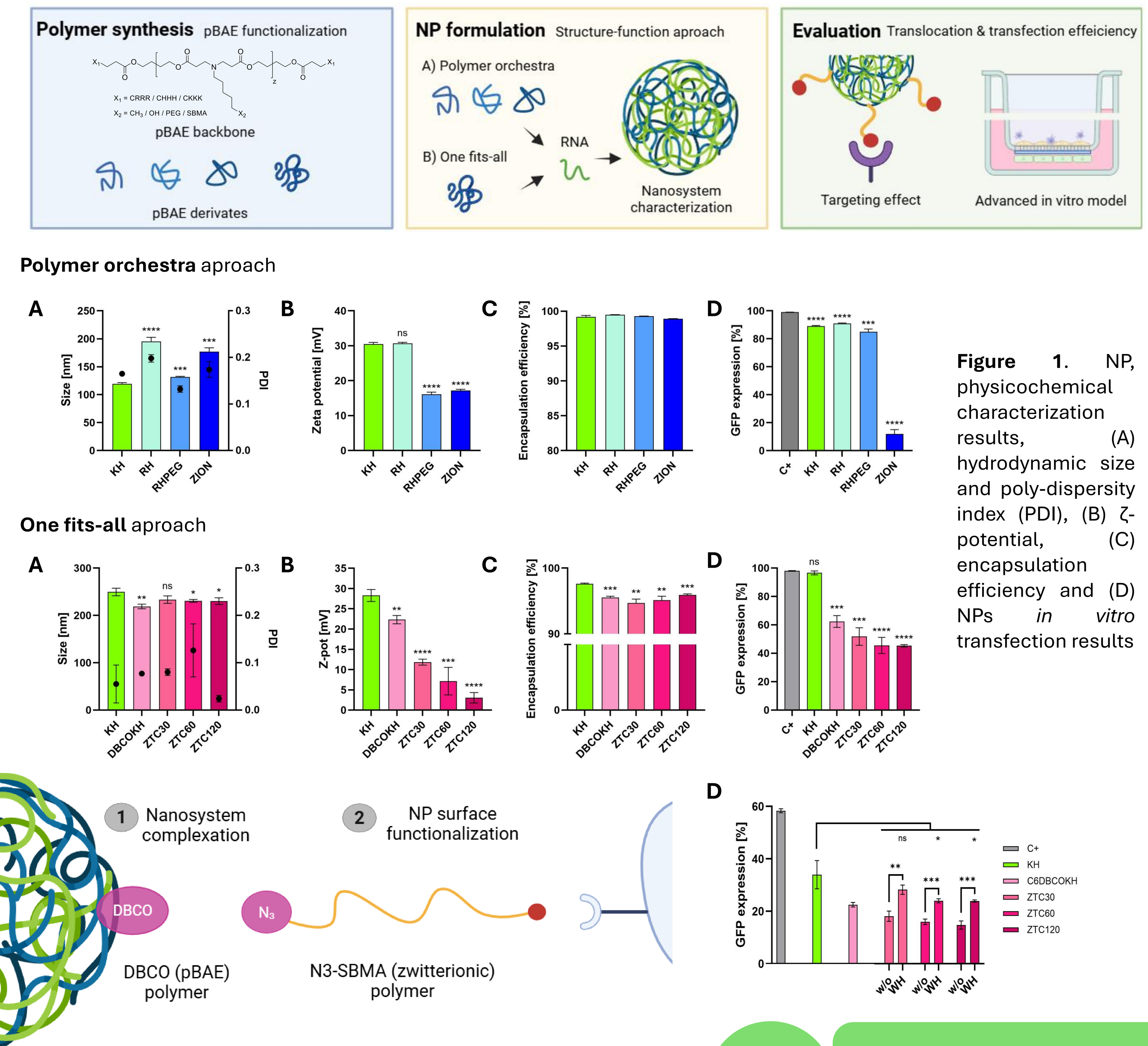
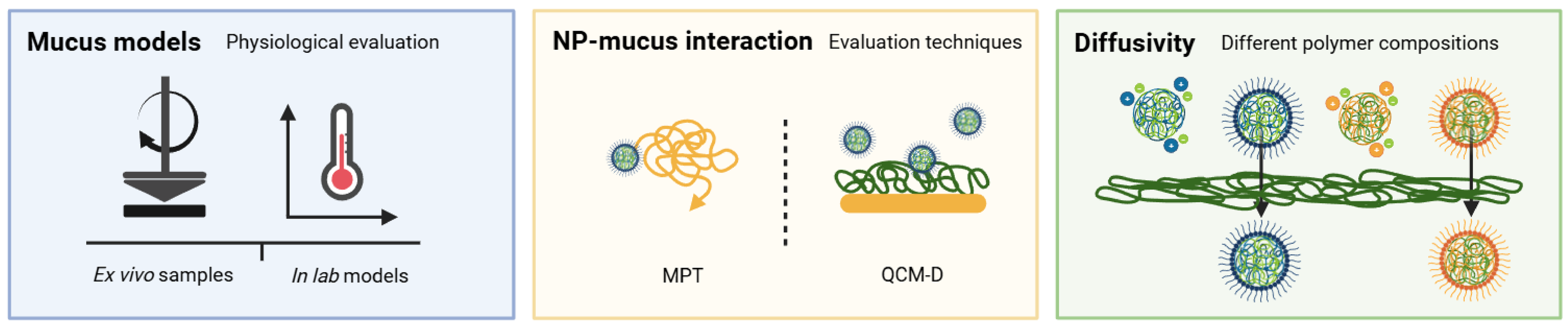



**Figure 1.** NP, physicochemical characterization results, (A) hydrodynamic size and poly-dispersity index (PDI), (B) ζ-potential, (C) encapsulation efficiency and (D) NPs *in vitro* transfection results

## 2 Assessing nanoparticle permeability across mucus barriers



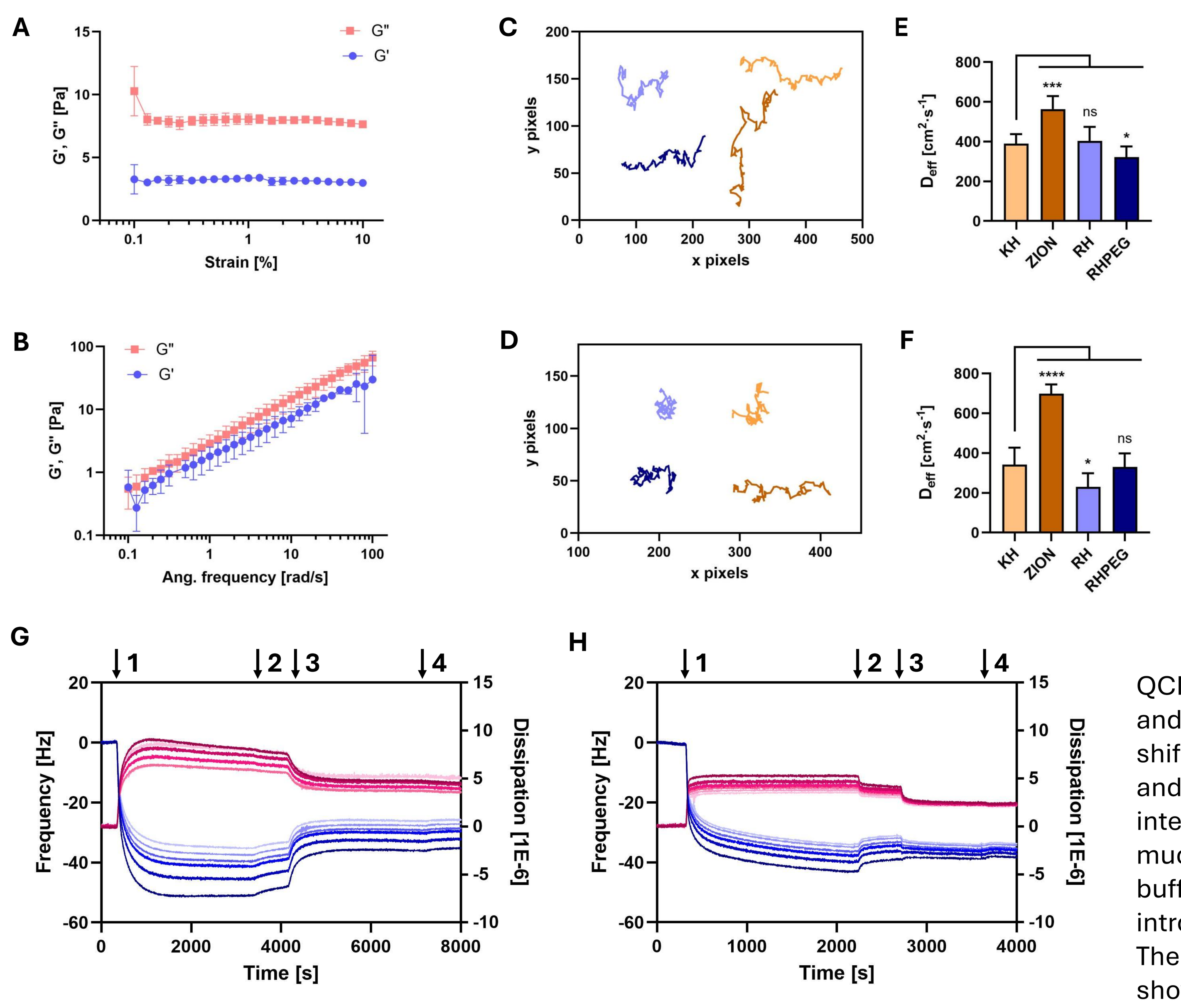
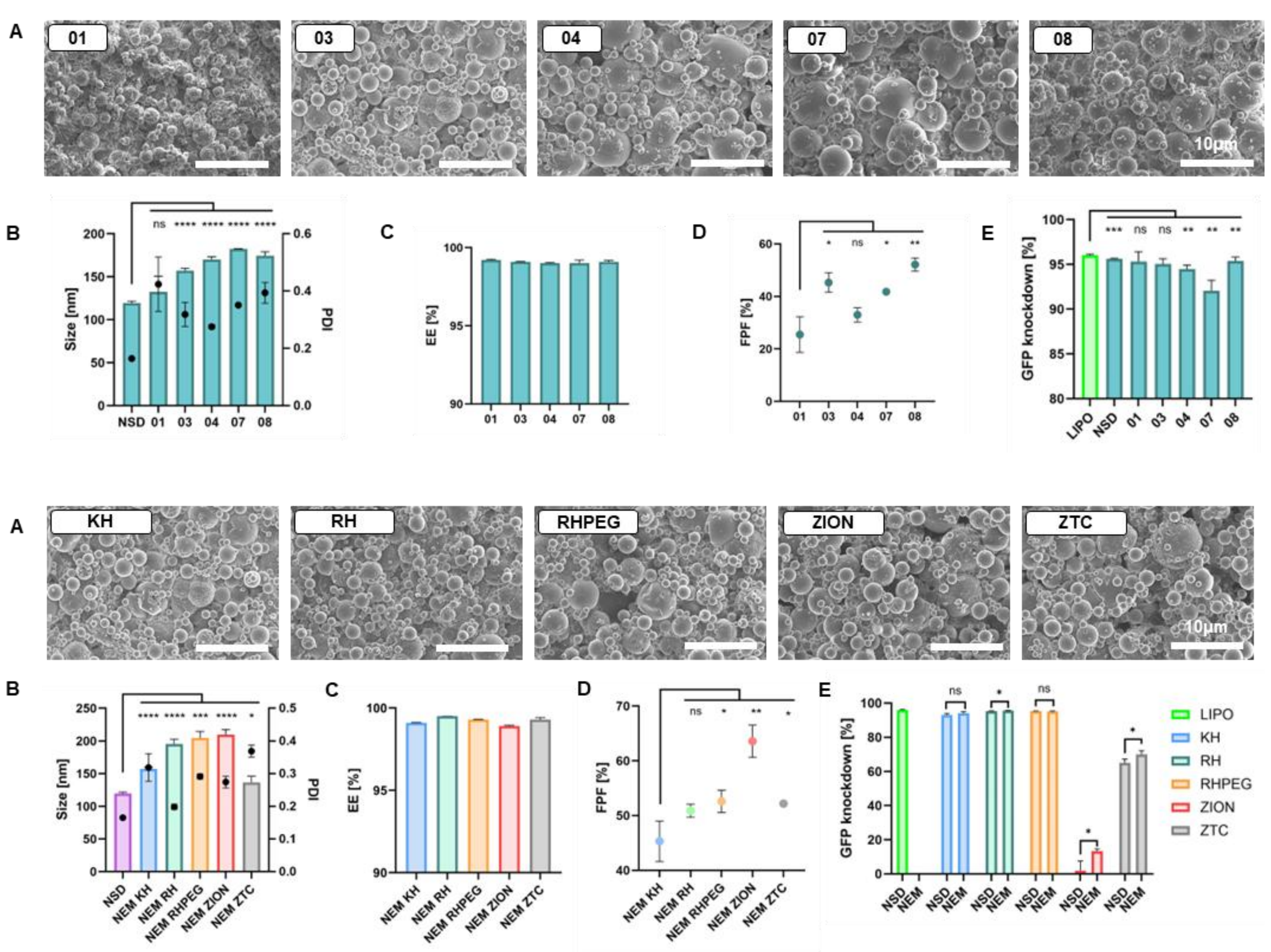
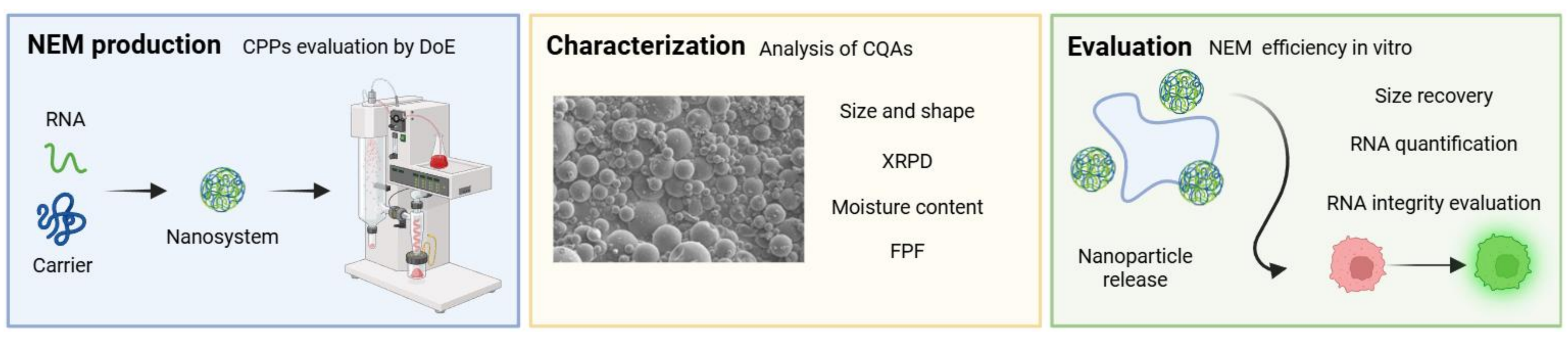



**Figure 2.** Mucus evaluation results, (A) Strain sweep analysis of $N_2$-dried mucus samples, (B) Frequency sweep analysis of $N_2$-dried mucus samples, MPT of the 2D movements of the NPs formulations in (C) water media and (D) mucus, Effective Diffusion Coefficient (Deff) of the formulations in (E) water and (F) mucin media.

QCM-D frequency (blue) and dissipation (purple) shifts over time for (G) KH and (H) ZION NPs–mucin interactions. Steps: (1) mucin adsorption, (2) buffer rinse, (3) NP introduction, (4) final rinse. The 3rd–13th overtones are shown with progressively decreasing intensity.

## 3 Pharmaceutical development of inhalable NEM for RNA pulmonary delivery





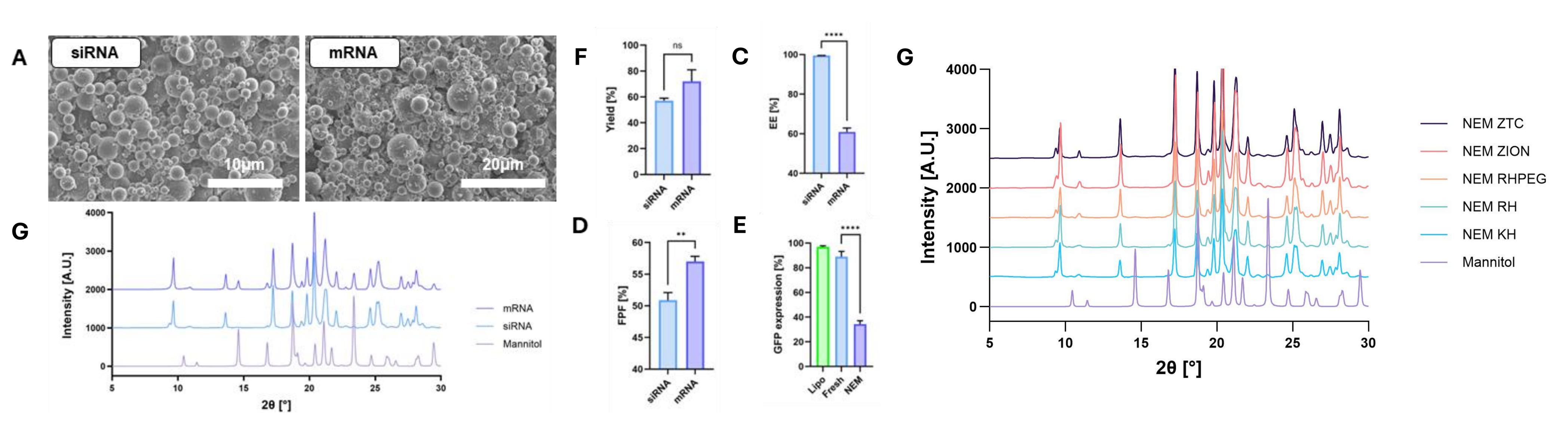



**Figure 3.** NEM results. (A) SEM images of pBAE NEM formulations, (B) NP size of pBAE NEM after redispersion in HPW, (C) EE quantification of pBAE NEM, (D) Fine particle fraction (FPF) of pBAE NEM, (E) GFP knockdown evaluation in the H1299 GFP+ cell line after 48 h, (F) Yield quantification of NEM during spray-drying production, (G) NEM XRPD analysis. (01 – 08) Spray drying mannitol only DoE conditions.

## ACKNOWLEDGEMENTS

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## CONTACT

Antoni Torres Coll
**Antoni.torres@iqs.url.edu**
https://orcid.org/0000-0003-0240-9101

Dr. Cristina Fornaguera