# Nanomedicine Platform

# TRANS-INT consortium

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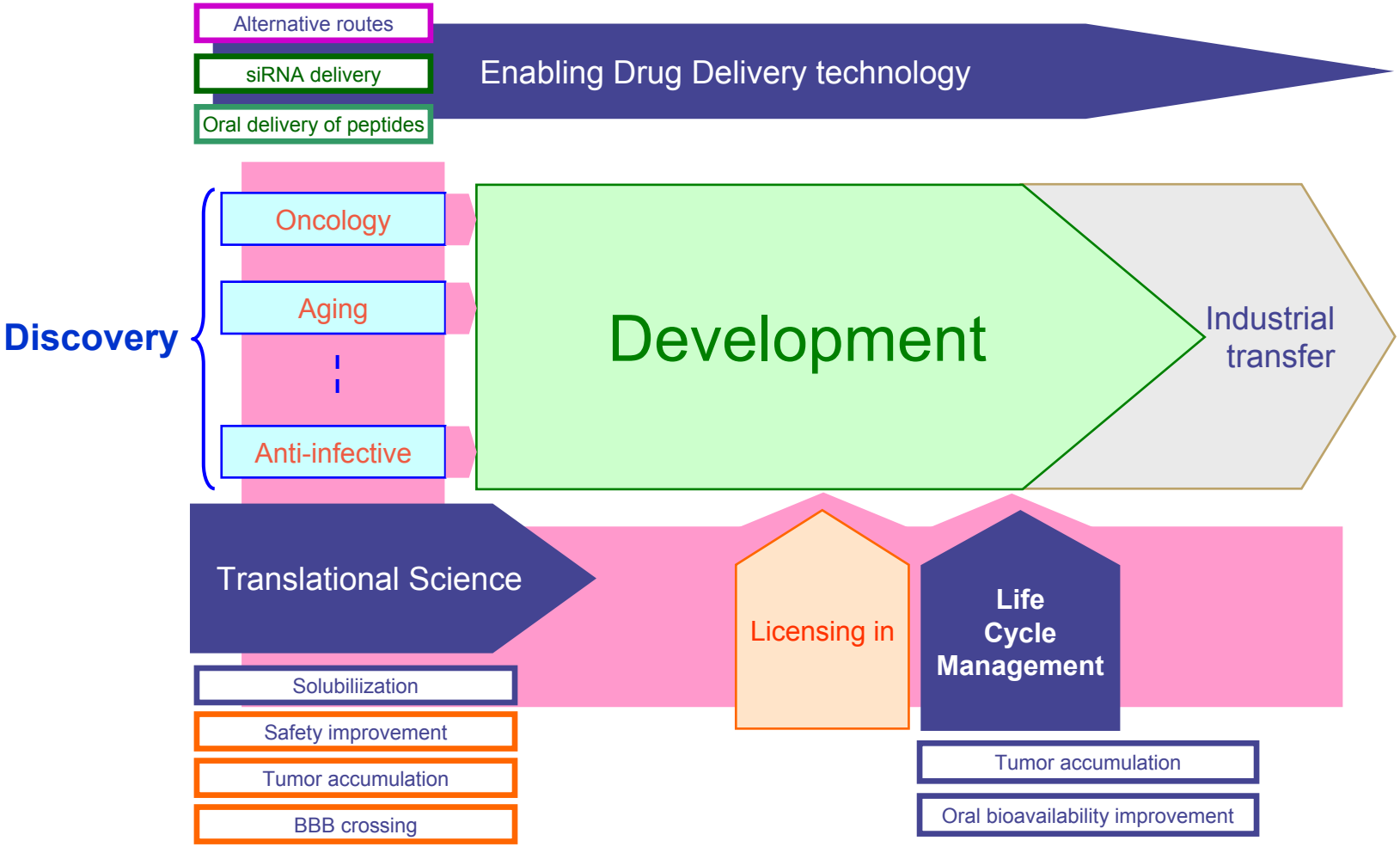
# Presentation objectives

- Focus on oral delivery of peptides/proteins.
- Share the views of a Pharmaceutical Scientist working in the Industry about the added value of nanomedicines, recent evolution and perspectives.
- Identify gaps to fill to unleash the potential of nanomedicines.
- Facilitate the “Open Innovation”, i.e. project-oriented collaborations between the public Research Institutions, the Start-ups and a “big Pharma” like Sanofi.

# Nanotechnologies – Applications



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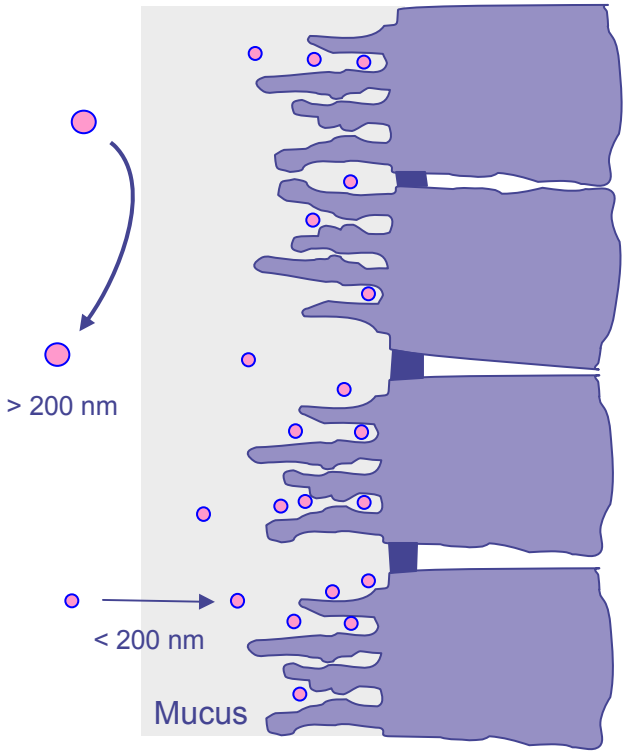
# Why small ?

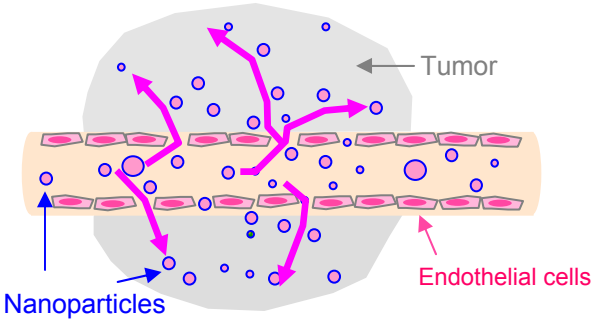
## Oral route



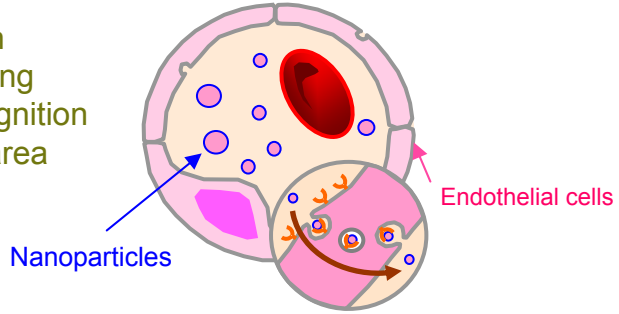

Carry the drug through the mucus in the vicinity of the enterocyte membrane

## Intravenous route

Tumor accumulation (EPR effect)




Blood Brain Barrier crossing through R/L recognition High surface area



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# Expected performances of Nanotechnologies for oral and i.v. routes

| | Dispersion of poorly water soluble drugs | Encapsulation. Protection of fragile drugs from (bio)degradation | Performance expected from small size | Performance expected from surface properties |
|---|---|---|---|---|
| Oral | Small molecules<br>• Crystalline nanoparticles | Peptides/proteins<br>(proteins, nucleic acids) | Carry the drug through the mucus in the vicinity of the membrane of the enterocyte | Bioadhesion: increased residence time in the window of absorption |
| Intravenous | Small molecules<br>• Crystalline nanoparticles<br>• Dispersion at the molecular state in lipids (liposomes) and polymeric nano-carriers | Oligonucleotides siRNA | Enhanced Permation Retention (EPR) effect (tumor accumulation) | Long circulating properties.<br>Blood brain barrier crossing based on R/L recognition. |



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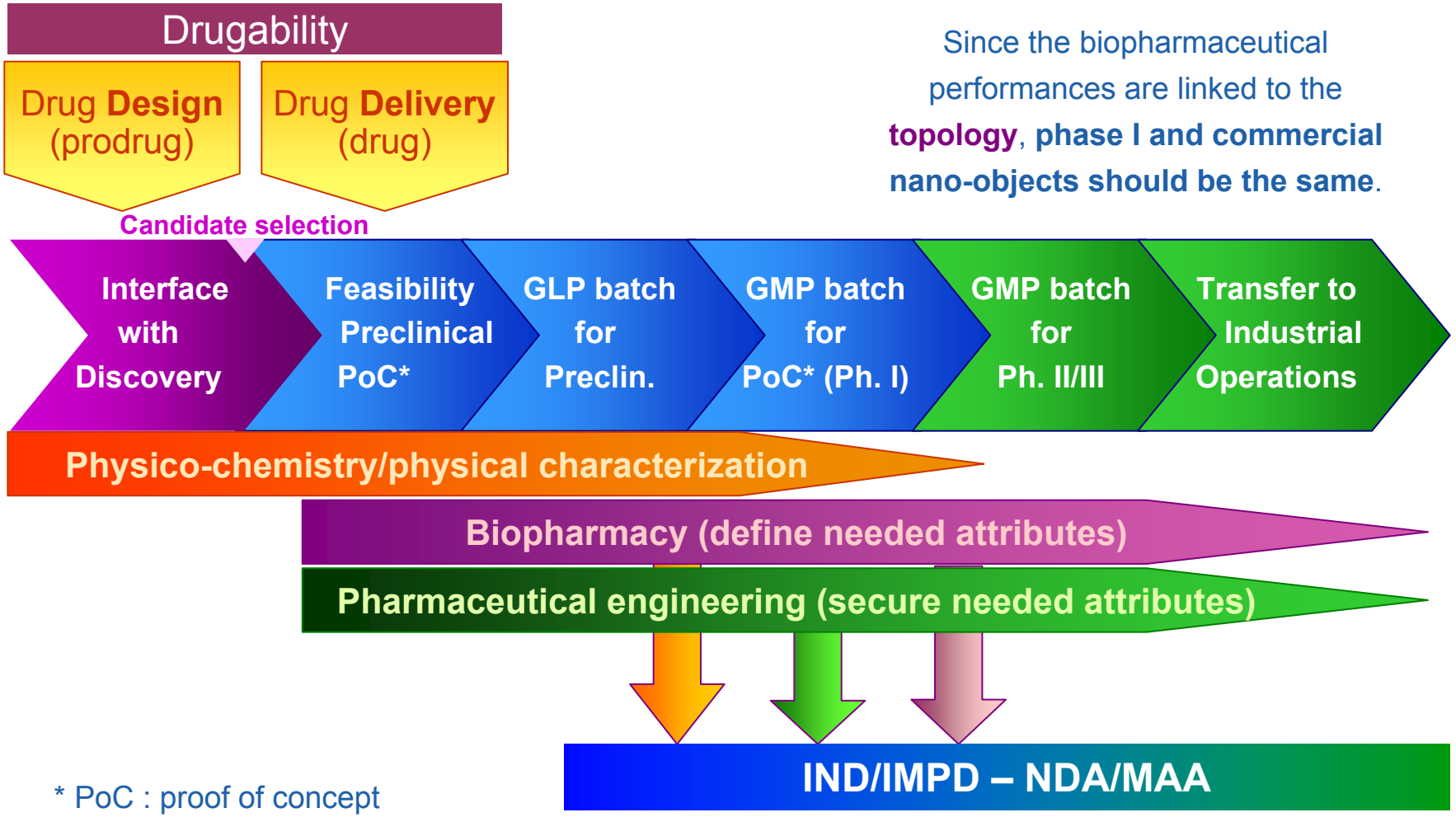
# Biopharmacy – Oral route (peptides/proteins)

- Points documented
  - Nano-encapsulation allows oral bioavailability increase of peptides and proteins (insulin).
  - Oral bioavailability increase is based on a combination of (i) protection against degradation in the GI fluids, (ii) mucoadhesion increasing the residence time in the window of absorption, (iii) stable dispersed (colloidal) state promoting diffusion through the mucus to the vicinity of the enterocytes, (iv) paracellular and (v) trancellular transports.
- Points to be further explored
  - Contribution of paracellular and transcellular transports to BA increase.
  - Contribution of the increased concentration gradient (i + ii + iii) in the vicinity of the enterocyte membrane on BA increase.
  - Is the drug still encapsulated when it crosses the intestinal epithelium ?
  - Mechanisms and site of release (desorption by ion pairing displacement in the GI lumen, biodegradation of the nano-objects before or after intestinal barrier crossing),
  - Fraction of drug delivered in the Gut-Associated –Lymphoid Tissue (M-cells of Peyer's patches) and potential "vaccine-like" sensitization.
  - Impact of the mechanism of oral BA improvement on dose ranging.

# Manufacturing of nano-objects

- Points documented
  - **Description of a variety of preparation processes based on precipitation, emulsification, milling, hot-melt.**
  - **Influence of the manufacturing process on the structure of the drug/excipients nano-assembly.**
- Points to be further explored
  - **Physico-chemistry of nano-assembly. Relationships between the characteristics of raw materials (polymer, lipids) and the process parameters (polymer and surfactant concentrations, viscosity of the dispersed phase, kinetics of solvent evaporation) on the structure of the nano-object.**
  - **Prediction of the quality of dried/resuspended nano-object (including under storage).**
  - **Batch size limitations according to the physico-chemical principles of nano-assembly, drying.**
  - **Is long term stability of key attributes dependent upon the process ?**

# Nano-objects development process



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# Conclusion – Status and perspectives

- Status
  - **A lot of progress and achievements in the design of nano-objects and the understanding of their biopharmacy over the past 20 years.**
  - **However, some methodological gaps remain (structure properties relationships, drug encapsulation and release, etc).**
- Perspectives – Quality (TRANS-INT)
  - **Adaptation of the level of control of the physico-chemistry and key attributes to the degree of complexity of the expected performance (from colloidal dispersion to functionalities based on ligand/receptor recognition).**
- Perspectives – Biopharmacy (TRANS-INT)
  - **Need to better integrate the "desired" and "undesired" functions of nano-objects in the context of the route of administration (after single and repeated administrations),**
  - **Development of specific DMPK approaches and tools (mathematical models, imaging) supporting Drug Delivery strategies based on accumulation of a small fraction of the dose in desired (and undesired) compartments,**
  - **Better identification and control of the sources of variability linked to patient ("nanomics") and materials (CMC) .**