Bridging early academic research & clinical development on polypeptide-based nanomedicines

Lessons learnt with PTS

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CRS 2022 Annual Meeting & Expo

July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science

MOTIVATION OF RESEARCH IN INNOVATIVE DRUG DELIVERY SYSTEMS

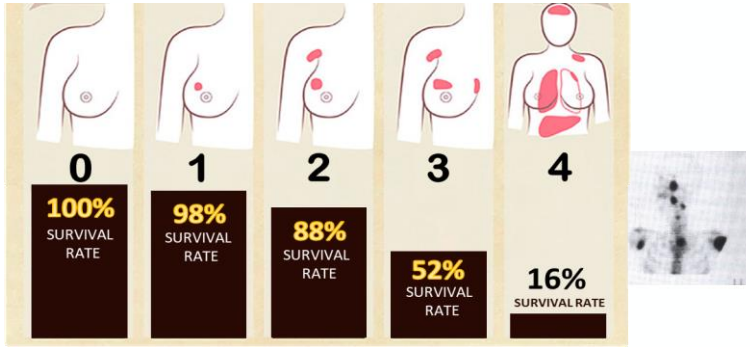
Design of Polymer Therapeutics for Unmet Clinical Needs

Continued Challenges to be addressed

Treating/Preventing

Metastatic Cancer

Stages of Breast cancer and related survival



American Cancer Society, 2018

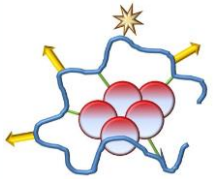
Drug Attrition Rates > 95%

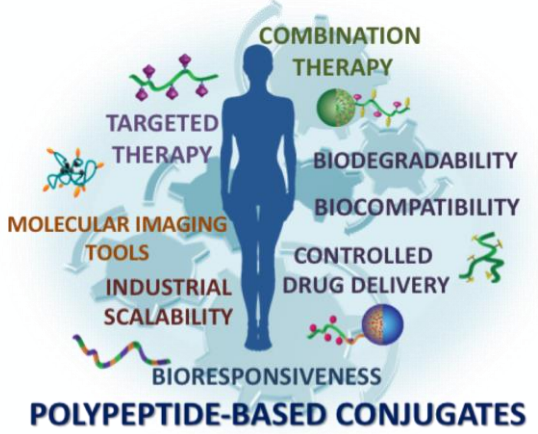
CNS Disorders

Healthy Brain Severe AD

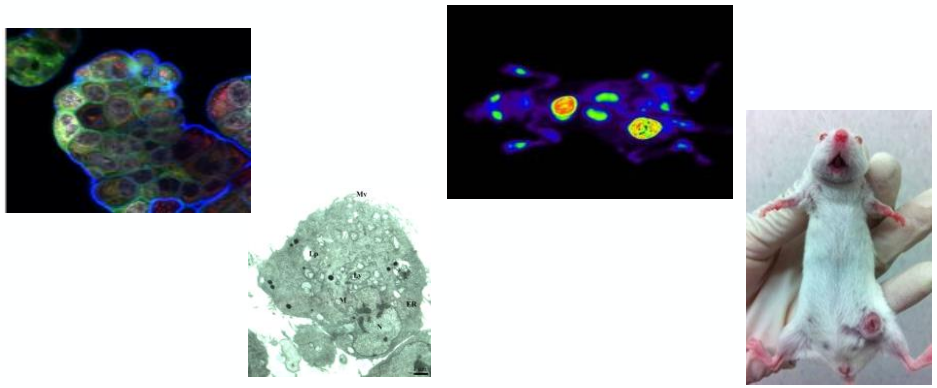
https://www.nia.nih.gov/alzheimers/

Control and Full Characterization of Complex Nanostructures



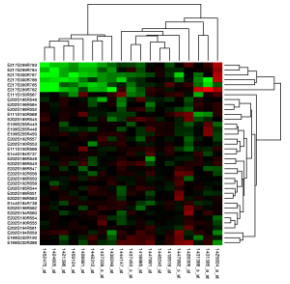


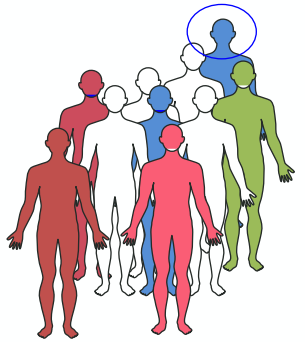
To use Adequate Preclinical Models



Patient Heterogeneity: Functional Biomarker

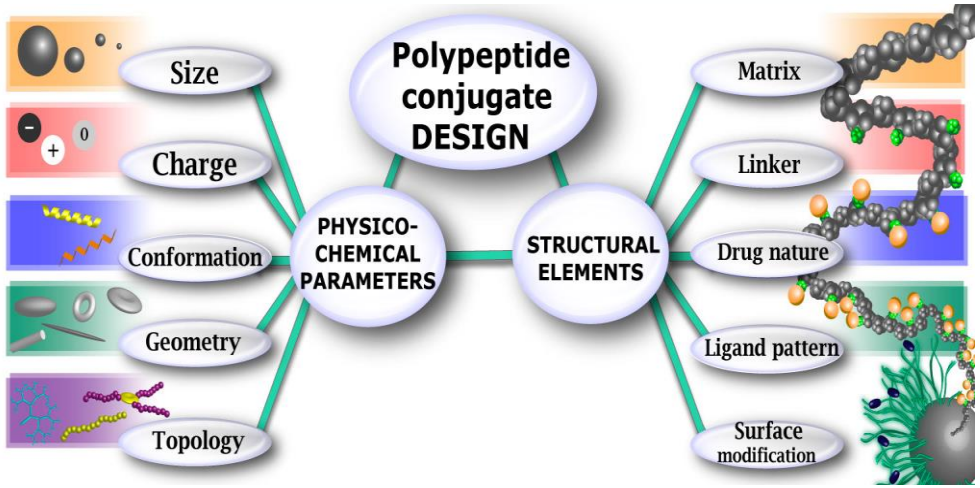
the patients/clinical setting disease, stage of disease



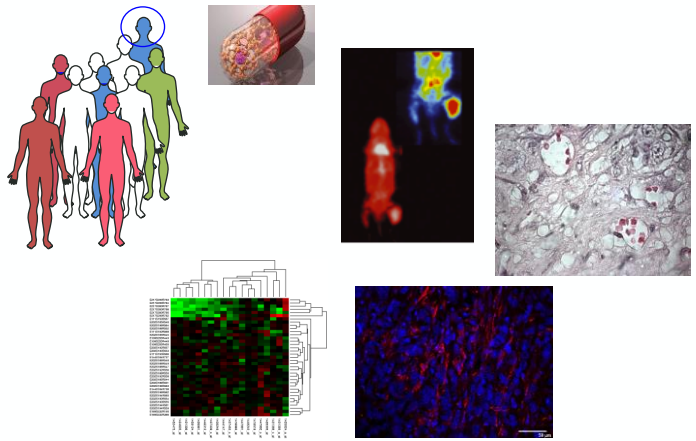


Our Motivation:
Polypeptide-based Drug Delivery Systems for Unmet Clinical Needs

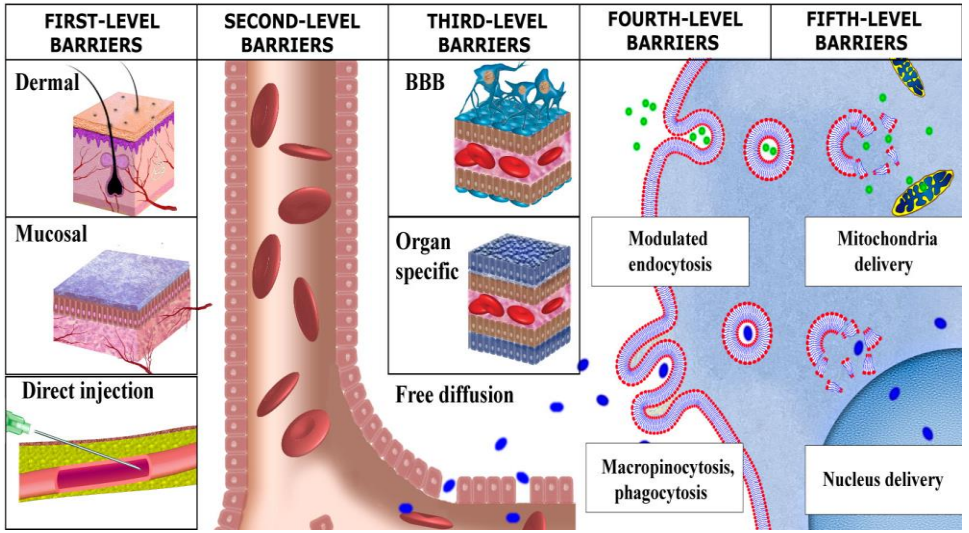
Molecular Design – Physical Parameters



Biological output – Therapeutic performance

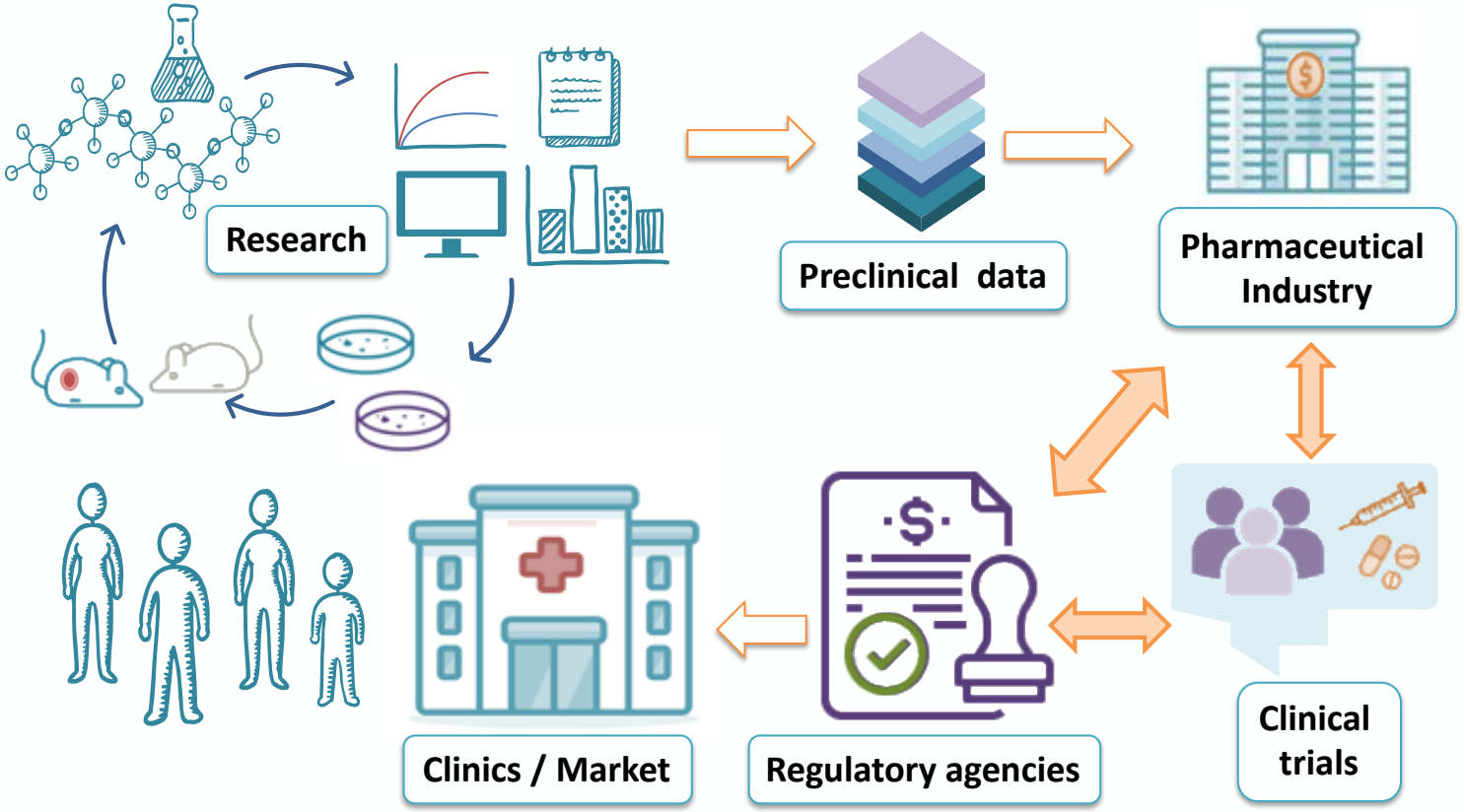


Bio-Nano Interface – Biological Barriers



O. Zagorodko, J.J. Arroyo-Crespo, V, J. Nebot, M. J. Vicent, *Macromolecular Bioscience* **2016.**
A. Niño-Pariente, V.J. Nebot, M. J. Vicent, *Current Pharmaceutical Design*, **2016.**

From Bench to Clinics

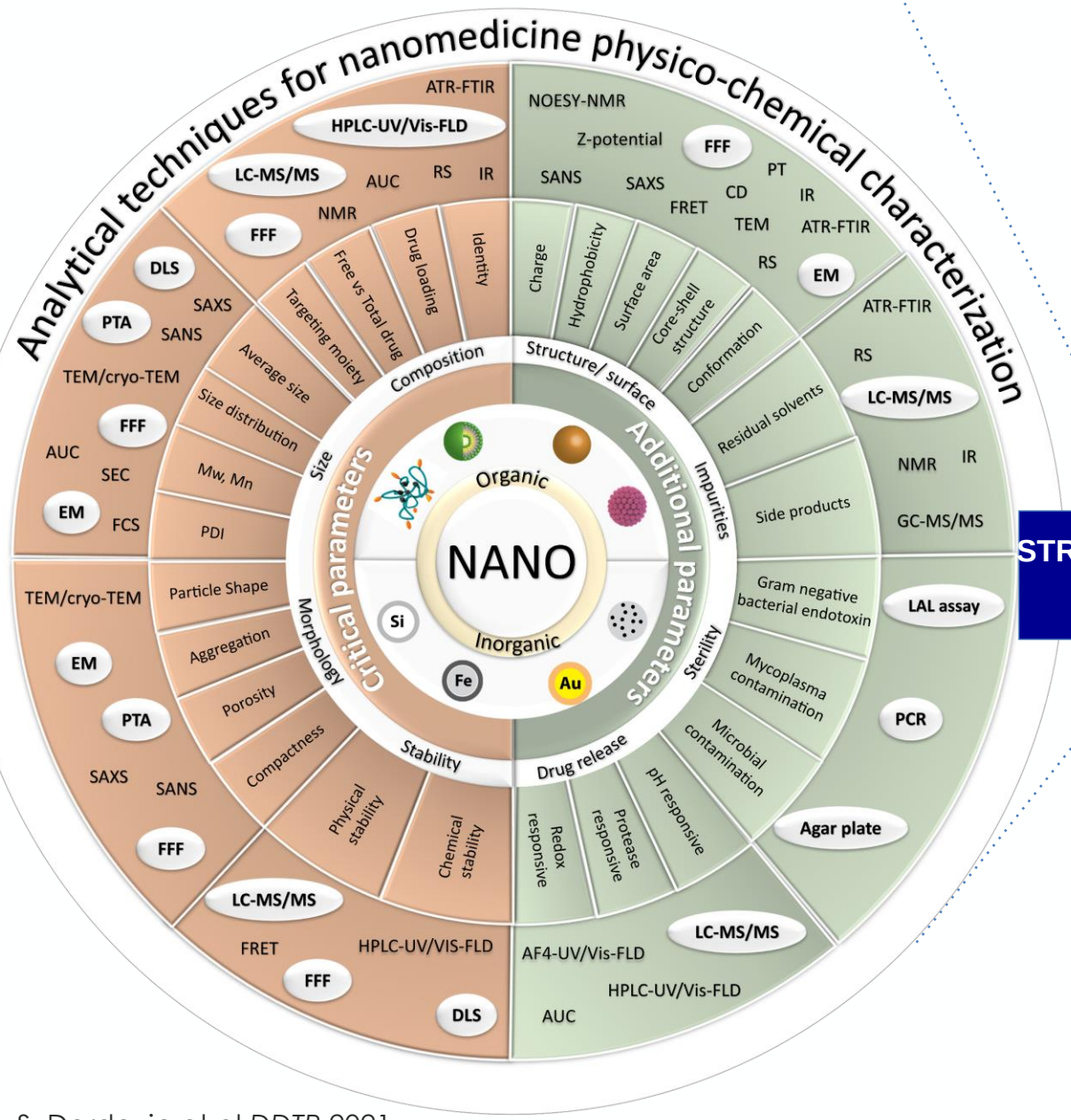


Features and pathways crucial to the clinical translation of DDS:

1. Identifying those critical quality attributes of the drug product essential for activity and safety.
2. Appropriate analytical methods (physical, chemical, biological) for characterization, important process parameters,
3. Adequate pre-clinical models.
4. Evaluation of batch-to-batch consistency and considerations regarding scaling up that will ensure a successful reproducible manufacturing process.
5. Close collaboration with regulatory agencies from the early stages of development to assure an aligned position to accelerate the development of future DDS.

S. Dordevic et al DDTR 2021

Physico-chemical Descriptors & Functional Biomarkers. Personalised Therapy



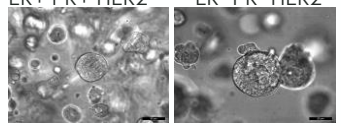
S. Dordevic et al *DDTR* 2021

STRUCTURE-ACTIVITY RELATIONSHIP

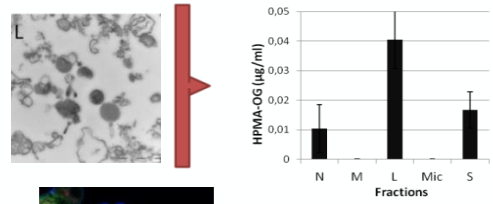
- ***Endocytosis and Cell Trafficking 2D and 3D models***

Patient Derived BCa Organoids

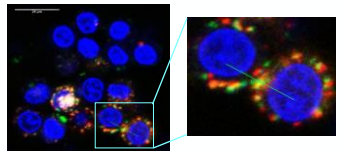
ER+ PR+ HER2- ER- PR- HER2-

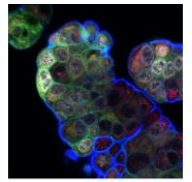


Subcellular fractionation



'Live-cell' confocal microscopy

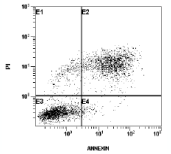




Cell morphology
Cell Painting

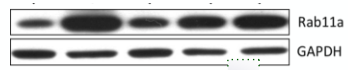
- ***Activity***

Toxicity, Annexin V, Cell cycle…

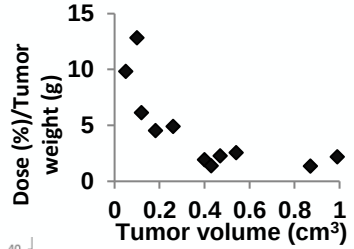


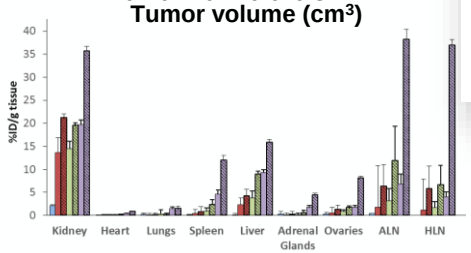
Exosome release-Biogenesis Markers

Protein levels
(Rabs, Rho/Rock , MAPkinases, PI3K/AKT…)

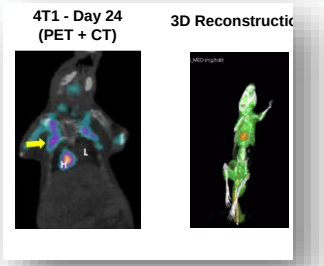


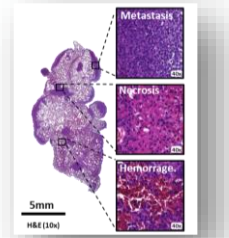
- ***EPR/Vascularisation vs. Tumour size***





- ***Metastasis progression***





- ***Toxicology***
- ***Biodistribution, PK, Fate***

Polypeptide-based Drug Delivery Systems

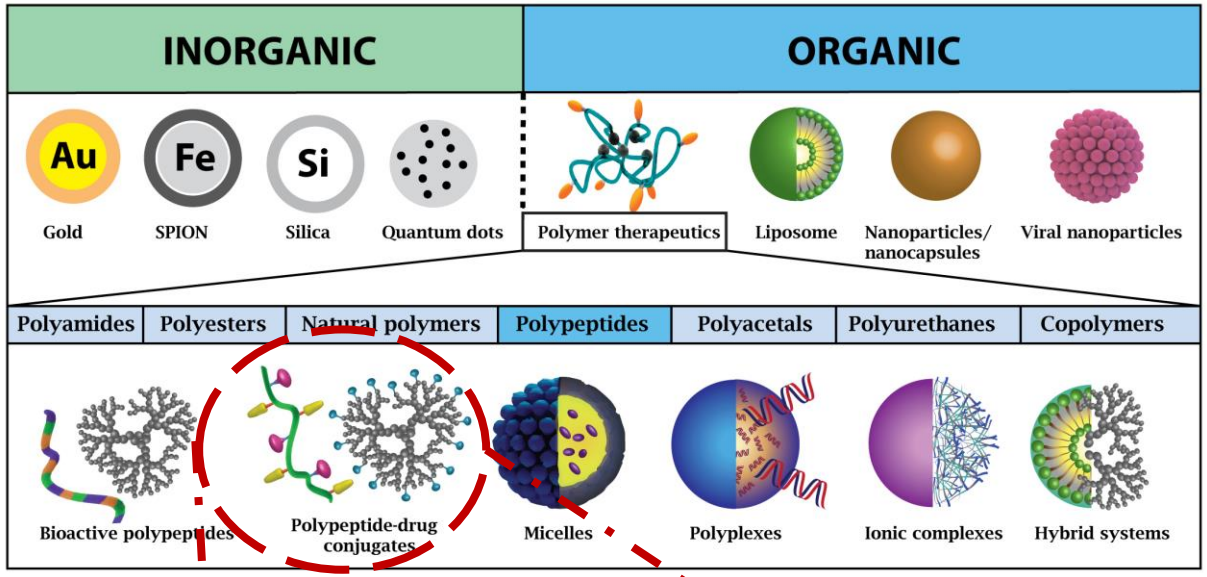
Challenges towards Clinical Translation

- Shift to **biodegradable polymeric** systems with **well-defined** architectures.
- **Controlled manufacture** processes to boost translation into clinics.
- **Development of instrumental tools** allowing for the characterization under relevant physiological environment.
- Use body **stimuli gradients for rational design** of adaptive systems towards body-site specific delivery of cargoes.
- Maximize the output of **preclinical data** towards personalized medicine.

Our solution

- **POLYPEPTIDES**
- **REPRODUCIBILITY**
- **MODERN TECHNIQUES**
- **LINKING CHEMISTRY**
- **ADEQUATE PRECLINICAL MODELS**

Key Features for a Rational Design of Polypeptide-drug Conjugates

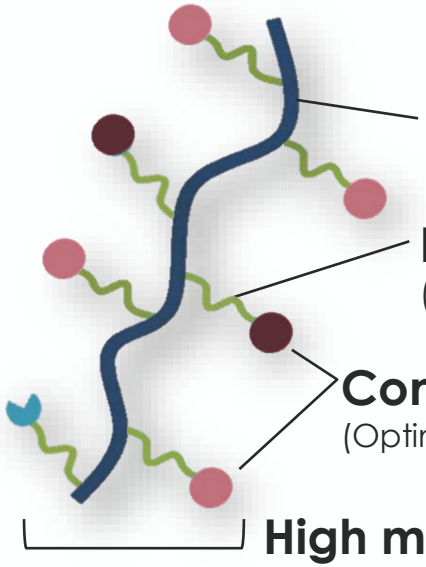


Key Features:

I. Choice of the polymeric carrier
II. Choice of the proper linking chemistry
III. Characteristics of drugs suitable for conjugation
IV. Targeting moieties (CMT through BBB)

T Melnyk, S Dordevic, I Conejos-Sánchez, MJ Vicent, Adv Drug Deliv Rev 2020

Active Targeting



Water soluble biodegradable backbone: POLYPEPTIDES
(Increased drug solubility- Topicity-Architecture- control size-shape)

Bioresponsive drug-linkers
(Controlled, site-specific, delivery)

Conjugation of synergistic drugs: COMBINATION THERAPY
(Optimized synergism)

High molecular weight: Passive Targeting
(Increased accumulation via EPR effect)

Polypeptides as Drug Carriers

PRECLINICAL	POLYPEPTIDE BASE MULTIPLE DRUGS CONJUGATED	COMBINATION
PRECLINICAL	DNA/RNA + CONJUGATION/ENCAPSULATION POLYMERIC MICELLES CONJUGATION + ENCAPSULATION	COMBINATION
PRECLINICAL	Au HYBRID MATERIALS	COMBINATION
PRECLINICAL	TARGETED SYSTEMS (FA, CPP, HA, Ab)	MONOTHERAPY
OPAXIO CT-2106 DEP techn.	POLYPEPTIDE-DRUG CONJUGATE	MONOTHERAPY
COPAXONE (1996) VIVAGEL (2019)	POLYPEPTIDIC DRUG	MONOTHERAPY
NK-911 (Ph I) NC-4016 (Ph I) NC-6004 (Ph III)	METAL COMPLEXATION POLYMERIC MICELLES ENCAPSULATION + CONJUGATION	MONOTHERAPY

WHY POLYPEPTIDES??

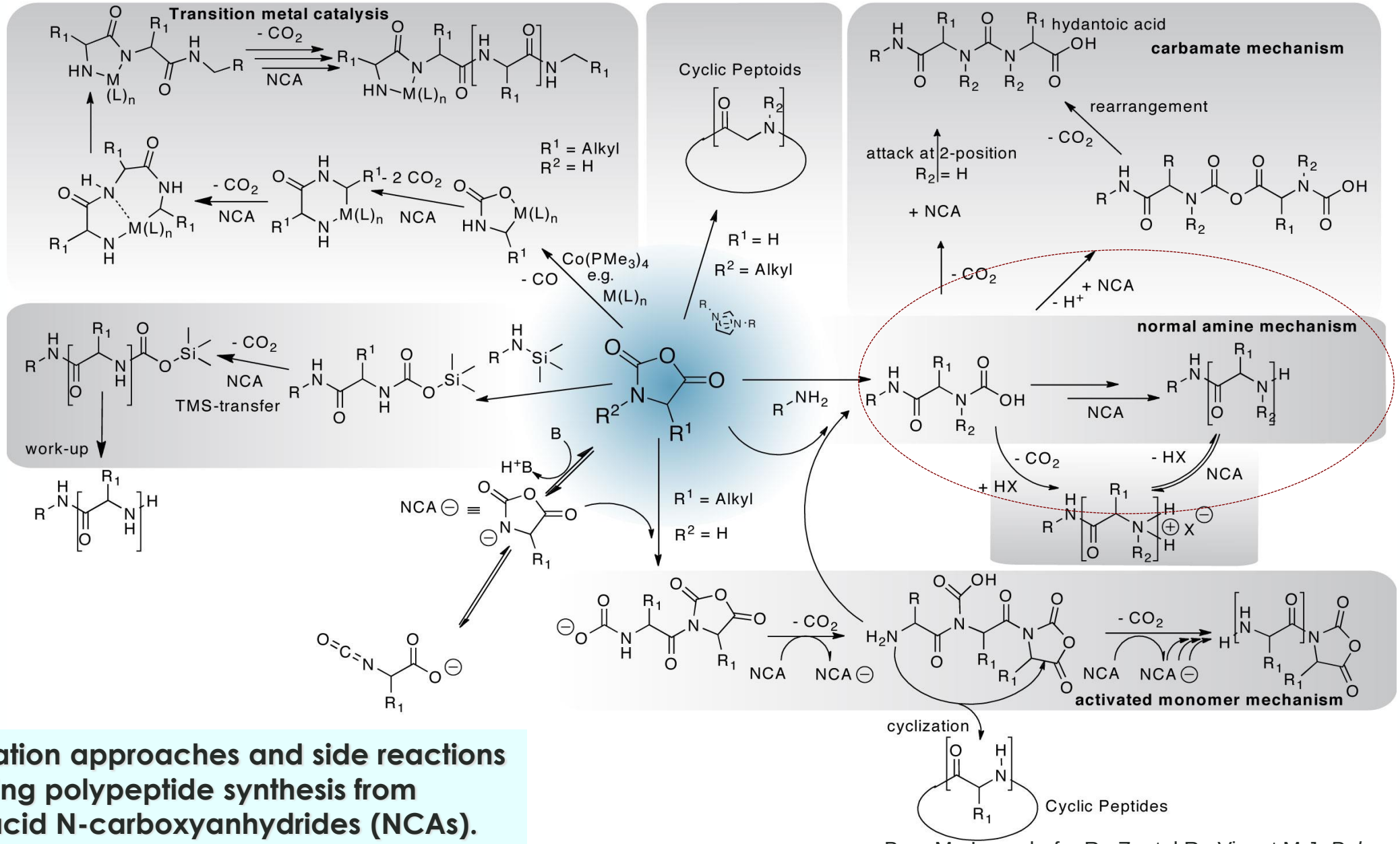
- Biodegradability
- Higher Molecular Weigth
- High water solubility
- Reduced immunogenicity
- Multivalency
- Enhanced loading capacity
- Examples in the market and in advanced Clinical trials

Copaxone®. Top 10 selling Drug
Sales 2013: $3600

T Melnyk, S Dordevic, I Conejos-Sánchez, MJ Vicent, Adv Drug Deliv Rev 2020

A. Duro-Castano et al Polymers 2014

Versatile Polypeptides. NCA Polymerization

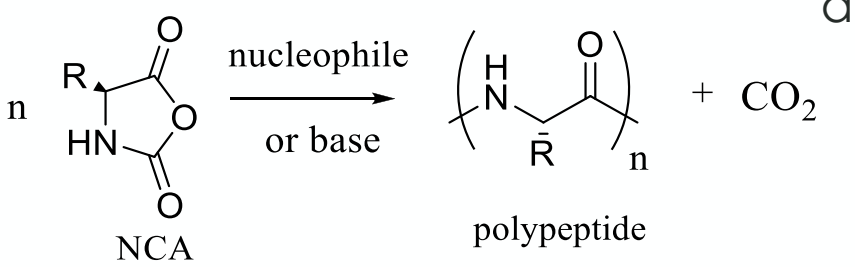


Polymerization approaches and side reactions during polypeptide synthesis from amino acid N-carboxyanhydrides (NCAs).

Barz M., Luxenhofer R., Zentel R., Vicent M.J. *Polym. Chem.* 2011

Versatile Polypeptides by NCA polymerization

Living ROP of NCA



Really demanding synthesis: highly pure solvents, NCAs and system in general.

Two main

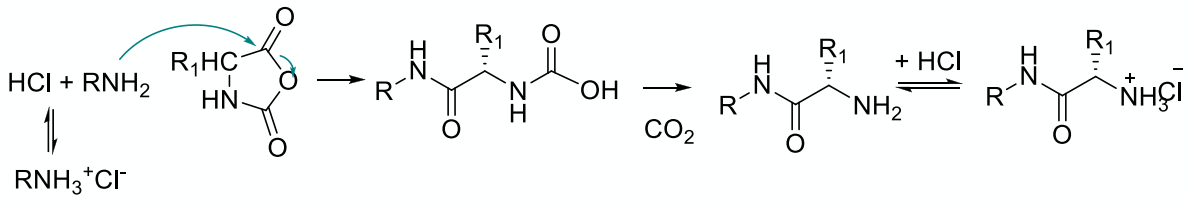
NAM: Nucleophilic attack of the initiator
AMM: Basic character of the initiator

- ❑NAM Initiation faster than Prop. →PDI ↓
- ❑AMM Prop. Faster than Initiation → PDI ↑

AVOID AMM

FACTORS TO TAKE INTO ACCOUNT
● Critical Purity of NCAs
● Critical Purity of solvents
● Presence of water/moisture
● Removal of CO_2 (Carbamic/acid equilibrium)
● pH, Temperature
● Bulkiness of substituents
● Unwanted terminations and secondary reactions

Schlaad Method



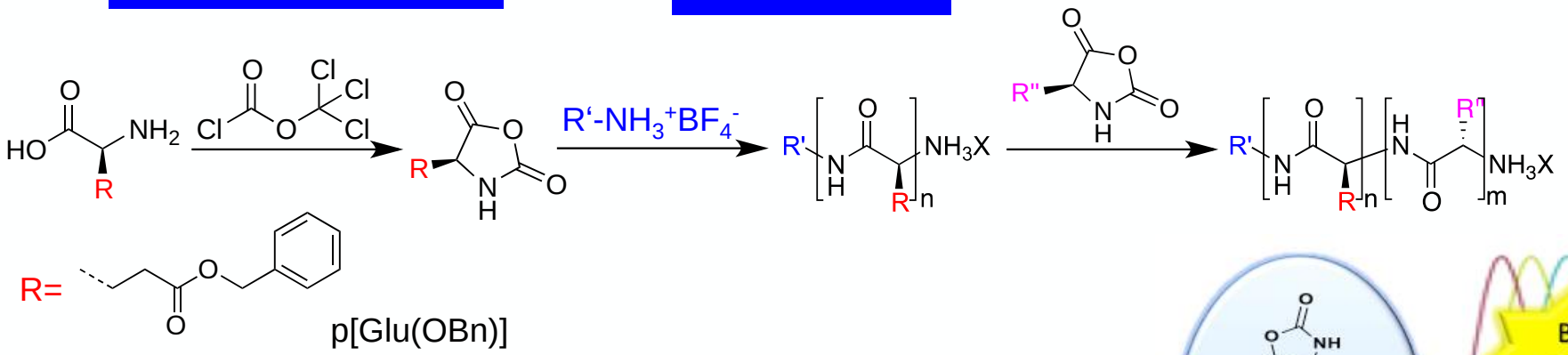
To Avoid AMM mechanism

Versatile Polypeptides by NCA polymerization

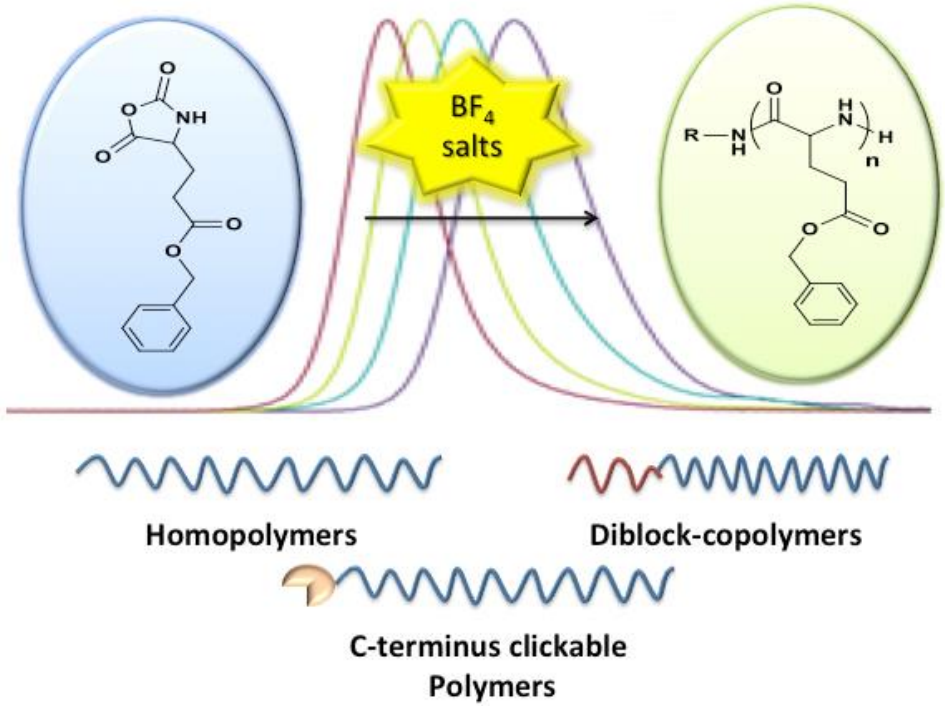
Polymer Therapeutics Lab

Monomer synthesis

ROP of NCAs



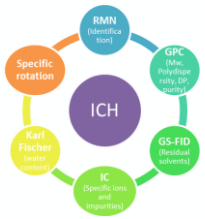
Living Polymerization can be achieved by using ammonium salts of primary amines with non nucleophilic counter ions as initiators.



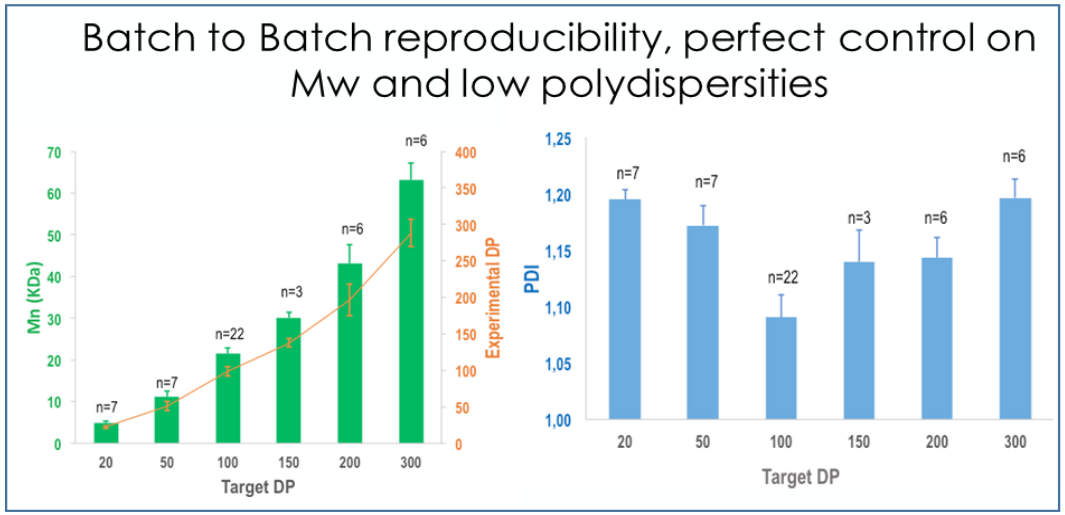
I. Conejos-Sánchez, A. Duro-Castano et al. *Polymer Chemistry* **2013;** Patent PCT/ES2012/070740

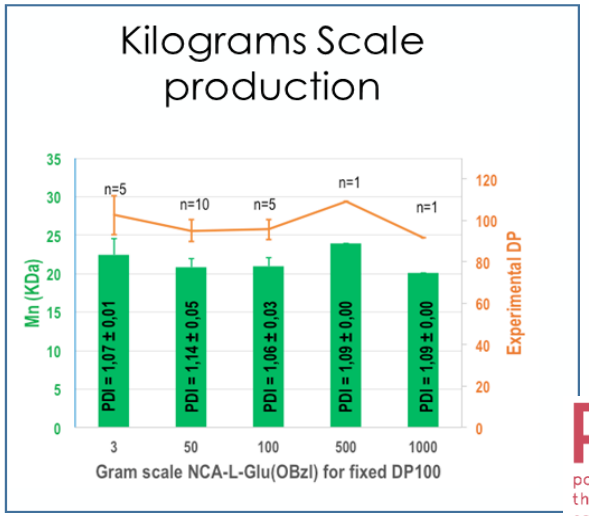
Versatile Polypeptides as Carriers

- Controlled molecular weight
- Batch-to batch reproducibility
- At the lab: up to 100 g scale.
  At SME at Kg Scale under GMP



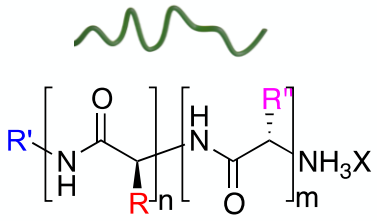
- Minimized heterogeneity
- Different architectures
- Undetectable racemization

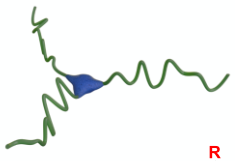




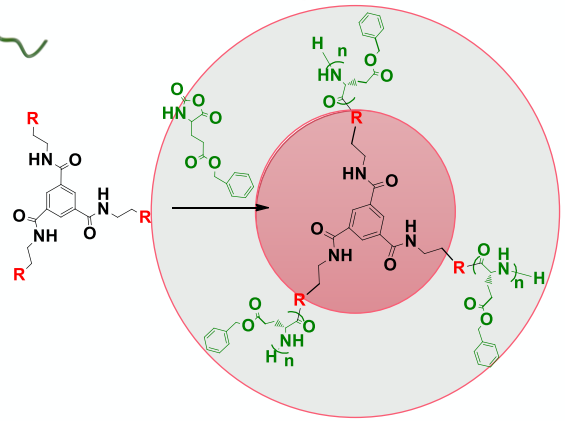
P+S polypeptide therapeutic solutions

Linear PGA

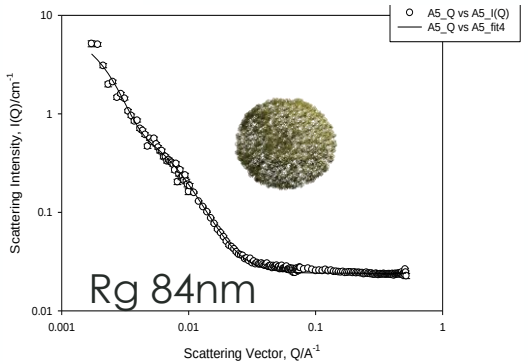




Star-Shaped PGA



By SANS (10 mg/ml)



I. Conejos-Sánchez, A. Duro-Castano,ert al. *Polym Chem*. 2013.
M.J. Vicent et al. US PATENT: 9623125. Licenced to PTS
M. Barz, A. Duro-Castaño et al *Polym Chem* 2013
A. Duro-Castaño et al Polymer 2014
A. Duro-Castaño et al. *Mol Pharm* 2015

The Importance of the LINKING Chemistry

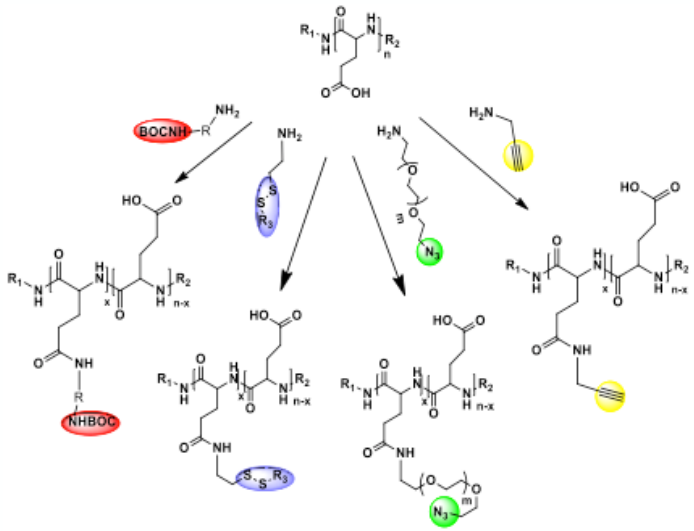
Post-polymerization modification on amino acid side groups

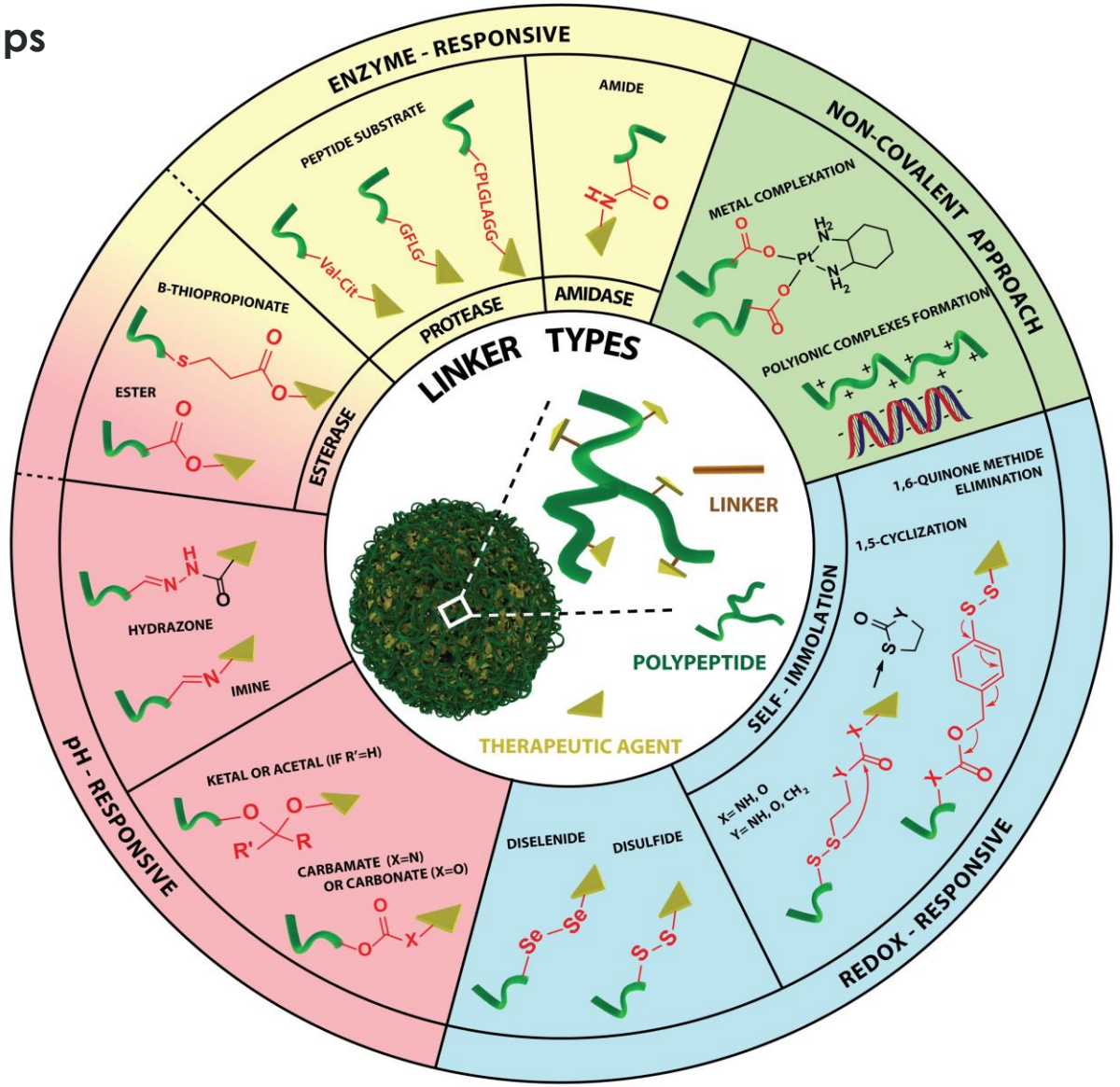
Controlled molar substitution

High functional capacity

Orthogonal functionalities towards:

- Bioconjugation (Imaging moieties, targeting moieties, active agents)
- Surface coatings/stealth properties

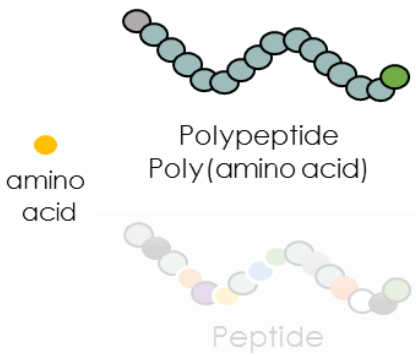




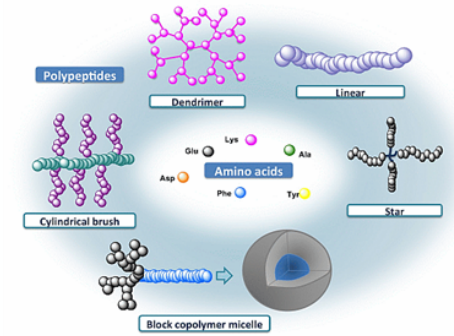
M Barz, A Duro-Castano, MJ Vicent - Polymer Chemistry, ***2013***

T Melyk, S Dordevic, I Conejos-Sánchez, MJ Vicent, Adv Drug Deliv Rev ***2020***

POLYPEPTIDE



Drug Delivery Systems



Polypeptide Carrier Armoury

- STRONG EXPERTISE IN POLYPEPTIDE-BASED DRUG DELIVERY SYSTEMS DESIGN
- PROPRIETARY KNOW-HOW ON HIGH QUALITY POLYPEPTIDE MANUFACTURING
- EXPERTS IN PHYSICO-CHEMICAL CHARACTERIZATION & ANALYTICAL DEVELOPMENT
- CHEMISTRY, MANUFACTURING & CONTROL

THERAPEUTIC

Stability of active components

Control on Biological barriers interface

Increased bioavailability

Increased efficacy

Increased Stability

Reduced side effects

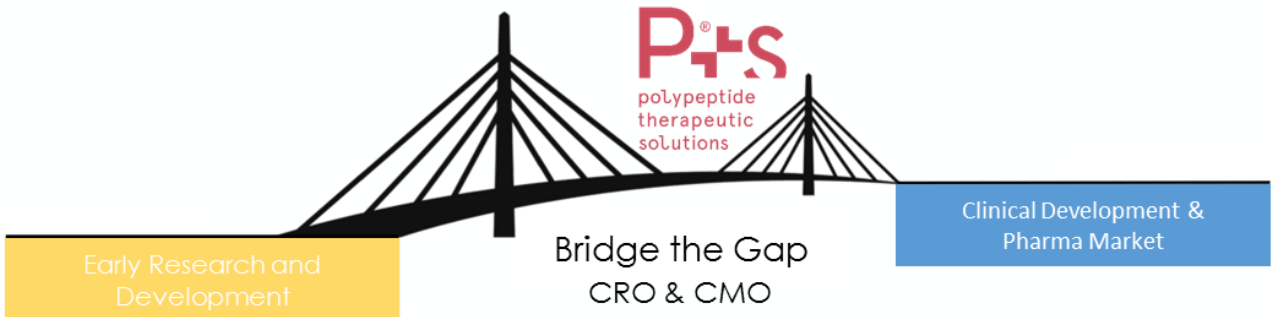
Multivalency/ High loading capacity

Stealth properties

Biocompatibility

- STRONG BACKGROUND IN STUDYING INTERFACE WITH BIOLOGICAL BARRIERS
- SOLID KNOW-HOW ON BIOLOGICAL EVALUATION (in vitro / in vivo)

SOLUTIONS



Polymer Therapeutics
Vicent Lab

Versatile Polypeptides as Carriers

- Biodegradability
- High water solubility
- Multivalency- High Loading capacity
- Examples in the market and in advanced Clinical trials
- Living Polymerization Controlled molecular weigth
- Batch-to batch reproducibility
- At the lab: up to 100 g scale. At SME at Kg Scale under GMP
- Minimized heterogeneity
- Different architectures
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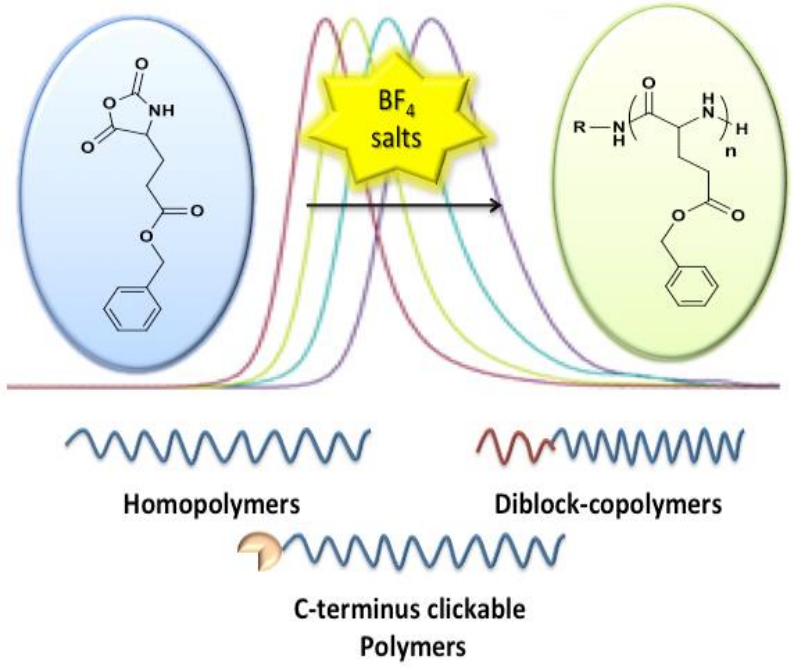
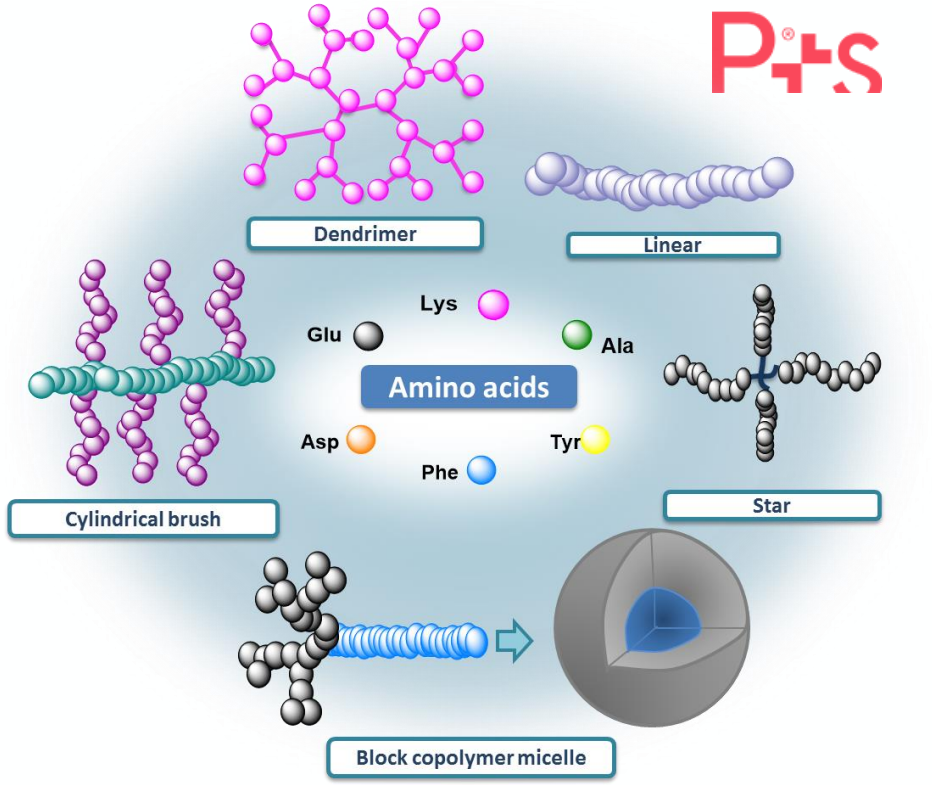
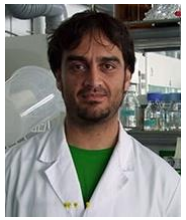


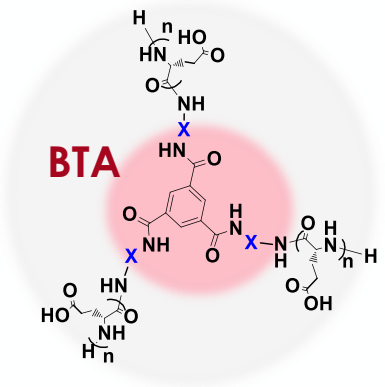


High quality NCA and precise control on polymerization processes allows accurate PAA engineering at large scale following ICH guidelines and under GMP

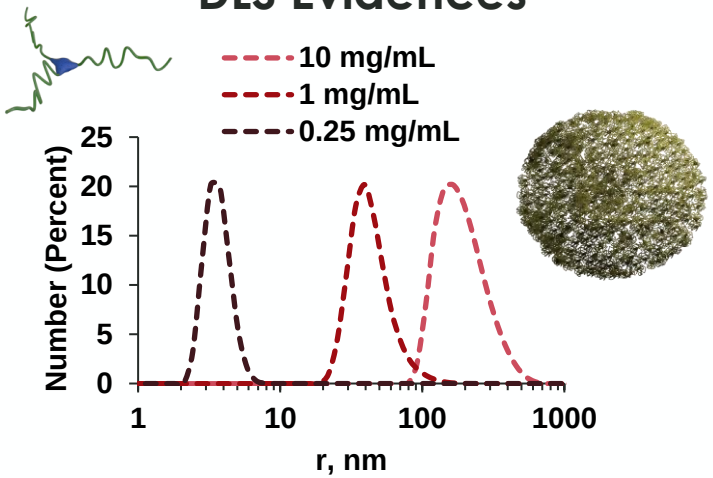
[1]Conejos-Sanchez, I. et a., Polymer Chemistry, **2013**, 4, 3182; M.J. Vicent et al. US PATENT: 9623125. Licenced to PTS [2]Deming T. J., Chem. Rev., **2016**, 116, 786; [3]González-Henríquez C.M. et al., Polymers, **2017**, 9, 551; [4]Byrne M. et al., Macromol. Rapid Commun. **2015**, 36, 1862; [5]Duro-Castaño A., Biomater. Sci., **2015**, 3, 1321; [6]Habraken G. J. M. et al., Macromol. Rapid Commun. **2011**, 33, 272−286; [7] Heise A., Chem. Soc. Rev., **2013**, 42, 7373; O. Zagorodko, *Macromolecular Bioscience,* **2017,** 17 , 1600316**;** A. Duro-Castaño et al Polymer 2014**,**

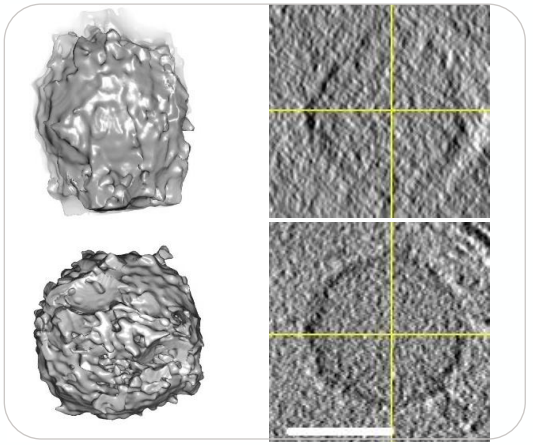


The importance of Controlling Carrier Architecture



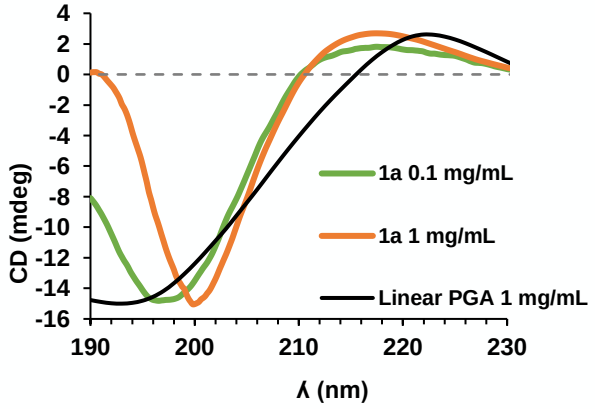
DLS Evidences



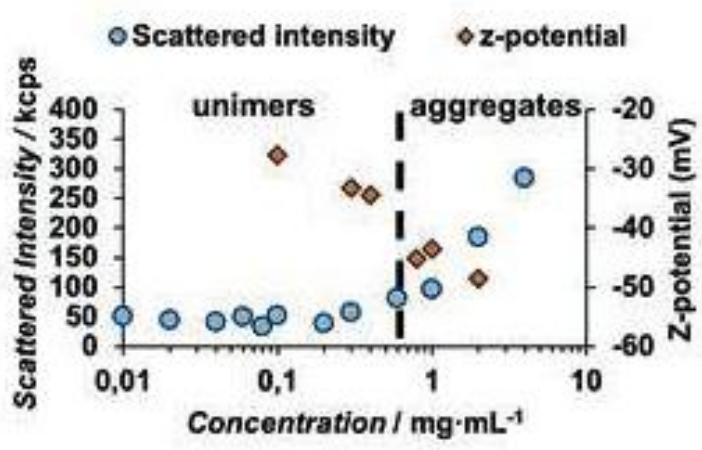


3D reconstructed tomograms by Cryo-TEM (scale bar is 50 nm)

Size, z-pot and secondary structure dependence on different physico-chemical stimuli

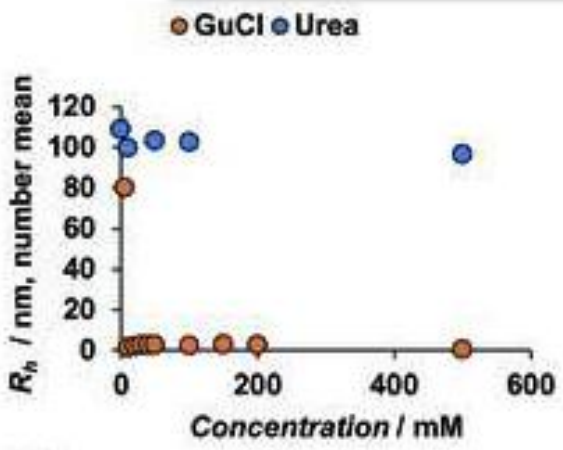


Concentration



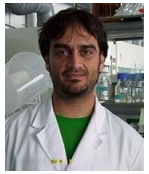
DLS analysis in ddH_2O

Ionic Strength

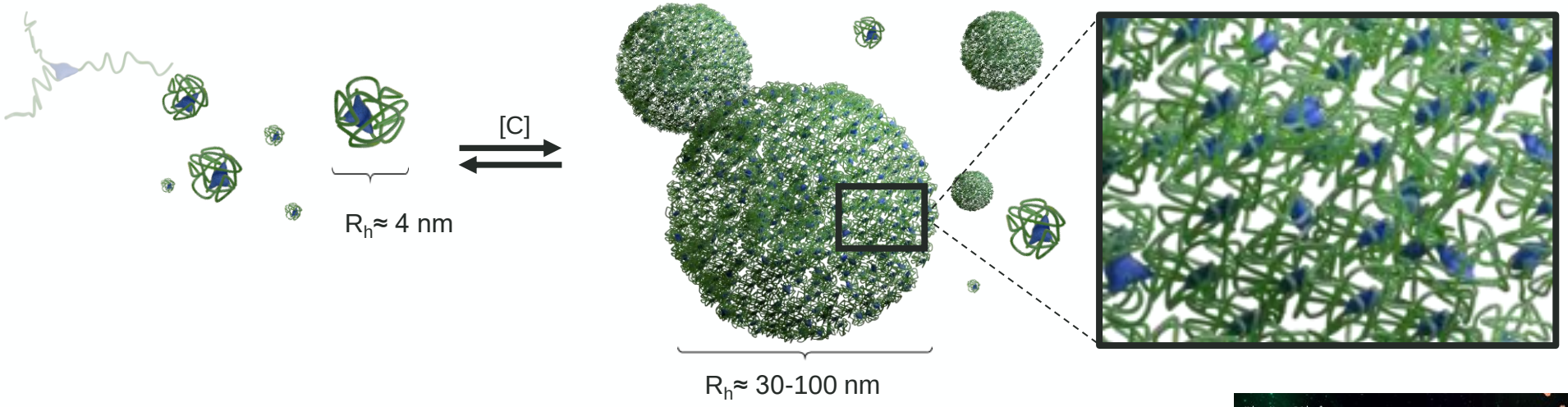


Presence of Ionic Denaturant (GuCl) or nonionic denaturant (Urea)

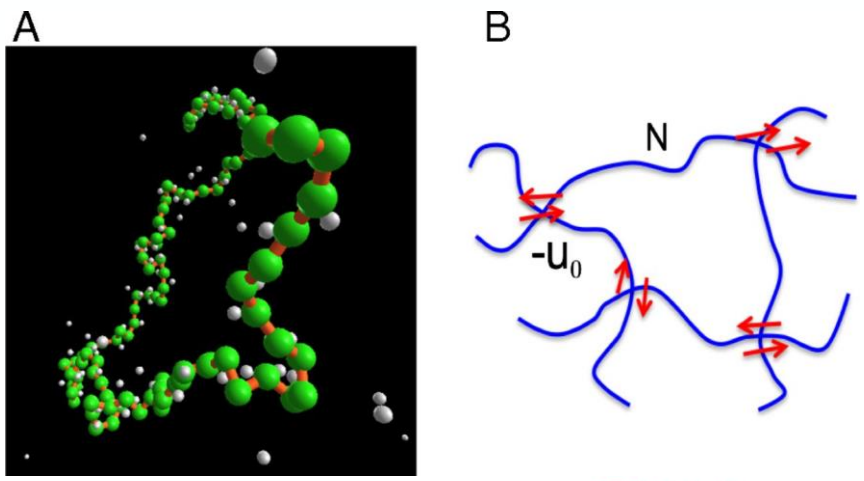
Vicent et al WO2017/025298 A1; Duro-Castaño et al Adv. Mater 2017

‘Ordinary–extraordinary’ transition. Versatile Nanoconstructs

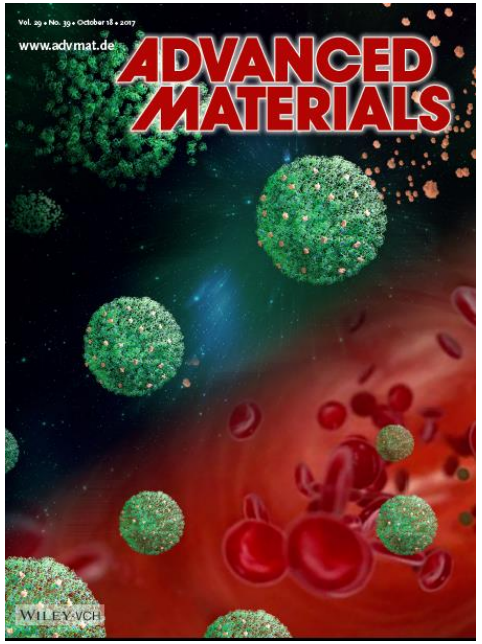


(A) Counterion cloud (white) surrounding a polyelectrolyte chain (green).
(B) Transient dipoles originated from adsorbed and shared counterions creating cross-linking points



Murugappan Muthukumar *PNAS 2016, 113, 12627*

PNAS



M.J. Vicent et al., **WO2017025298A1;**
Duro-Castaño et al. *Advanced Materials*, **2017**

COMPANY OVERVIEW- Timeline

2012-2015

- 2012 PTS Founded as spin-off from Polymer Therapeutics Lab at CIPF (Valencia, Spain), PI: MJ. Vicent
- Distribution of PAAs to Academic labs
- IRIS BIOTECH partnership

2016-2017

- Columbus VP
- 2000 sqft at CIPF
- QA/QC Departments
- GLP Certification
- First Pharma Customer
- Full CMC development package presented to FDA

Iris Biotech

Polymer Therapeutics Vicent Lab

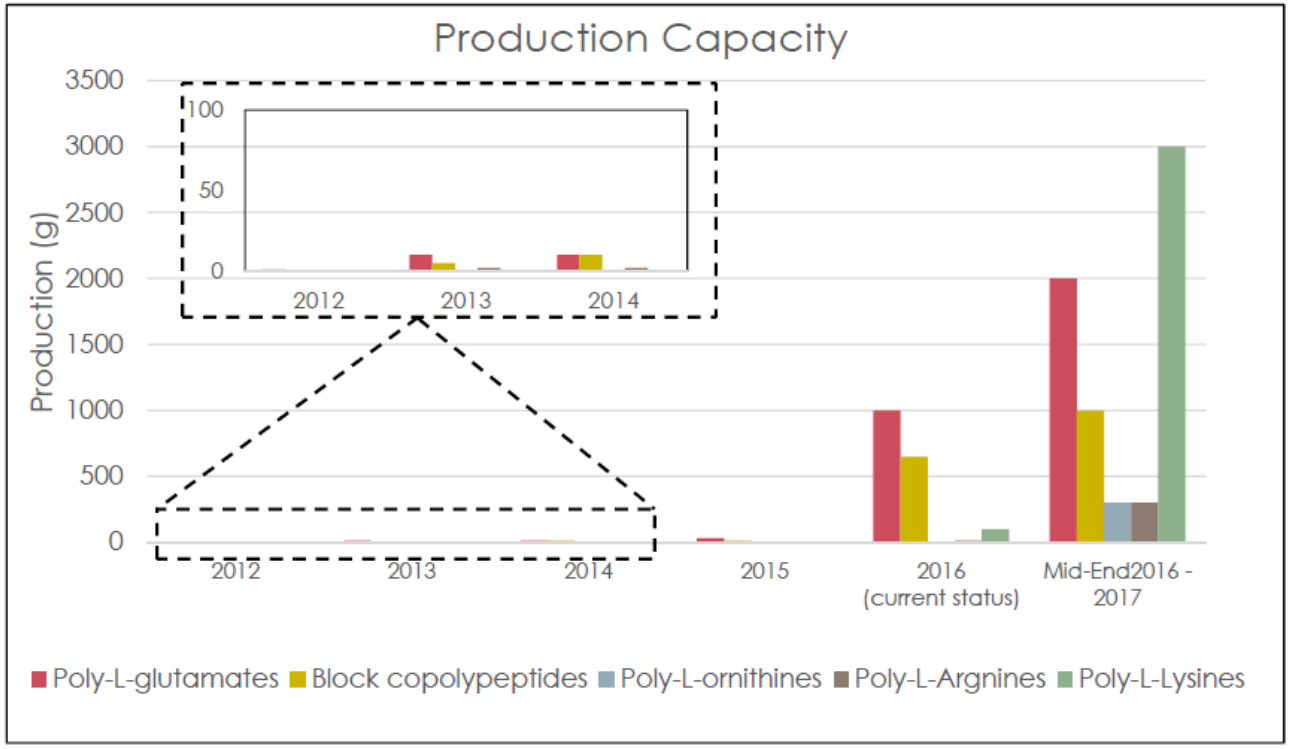
Lab in 2009

Lab in 2013

Lab&PTS in 2016

R&D lab, preclinical suits and GLP certified QC lab.

Reproducibility, robustness & scalability



Large resources (human & economic) invested during the last year to Up-scale our methodology

GMP-compliant quality system Impementation

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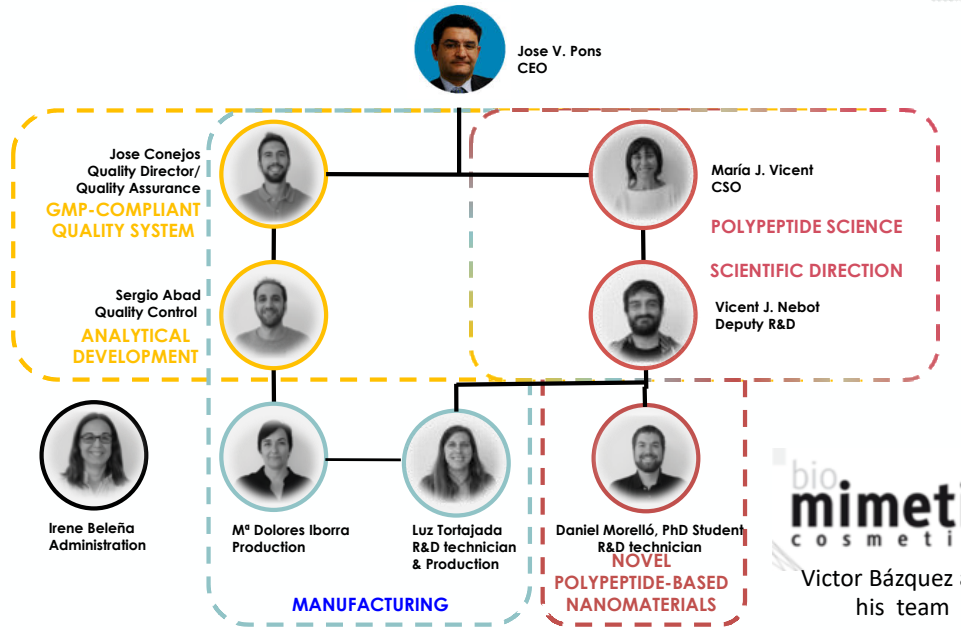
2018-2019

- 24000 sqft GMP clinical DS Facility in Paterna
  - 4000 sqft GMP area
  - 2 GMP suits for DS
  - GMP QC Lab
  - PD, R&D ad analytical dev. Lab
- First 2 GMP productions

THE TEAM at PTS



www.pts-polypeptides.com / www.pds-dermatology.com

Victor Bázquez and his team

Polymer Therapeutics Vicent Lab

Lab in 2009

Lab in 2013

Lab&PTS in 2016

R&D lab, preclinical suits and GLP certified QC lab.

Clinical GMP facility for Polymer& Lipid excipients, (Bio) conjugates

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2020-2021

- ARCLINE Acquisition
- US TEAM (R. Shaw, CEO)
- Expansion of facility:
  - Added 1500 sqft for Clinical Drug Product
- > 30 GMP batches
- > 150 NC QC methods developed > 80 validated

2022

- PTS GLOBAL
- Customer Fast track, BLA filling preparation for 2024
- Lipid & Polymer Nanoparticle Formulation capacity
- Partnership with Knauer (COMIRNATY LNP production mixing technology)
- > 50 GMP batches produced

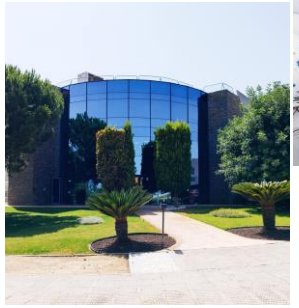
Polymer Therapeutics Vicent Lab

Lab in 2009

Lab in 2013

Lab&PTS in 2016

R&D lab, preclinical suits and GLP certified QC lab.



Clinical GMP facility for Polymer& Lipid excipients, (Bio) conjugates

Clinical GMP facility for Formulation and F&F

KNAUER

LNP production IJM mixing technology

COMPANY **OVERVIEW**

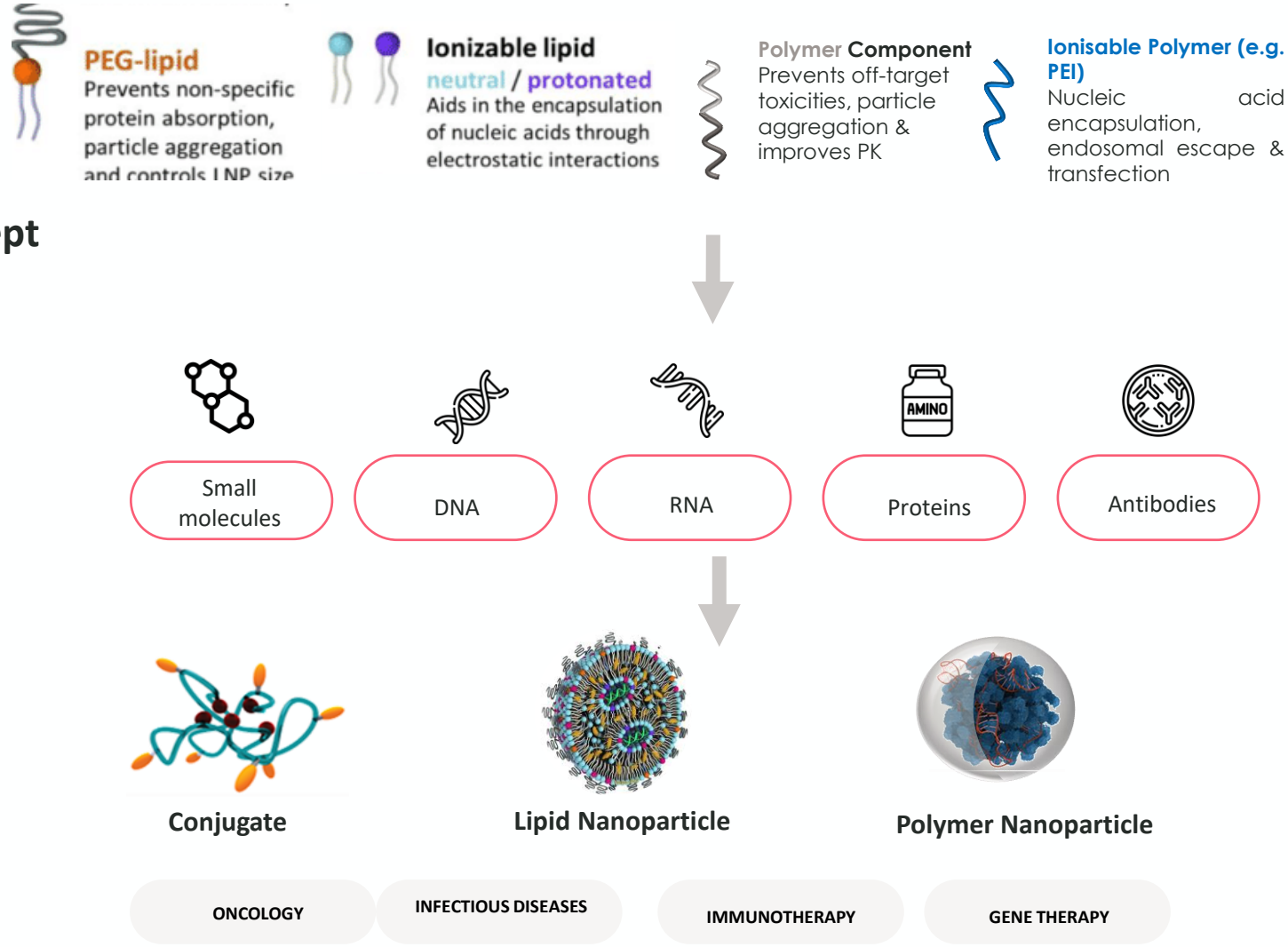
Experts in Complex Nanomedicine Development and GMP Manufacturing

*PTS is a **Customer Product & Technology Enabler** providing unique technical expertise in custom design and end-to-end manufacture of polymer and lipid-based drug delivery systems. We provide hands-on guidance from preclinical development through commercial-scale GMP manufacturing – as a committed partner you can trust to move fast, manufacture smart, and provide integrated partnership along your drug development journey and beyond.*

- Polymer & Lipid Excipients
- Chemical and Biological Conjugation
- Lipid and Polymer Nanoparticle Formulation
- Aseptic Fill & Finish

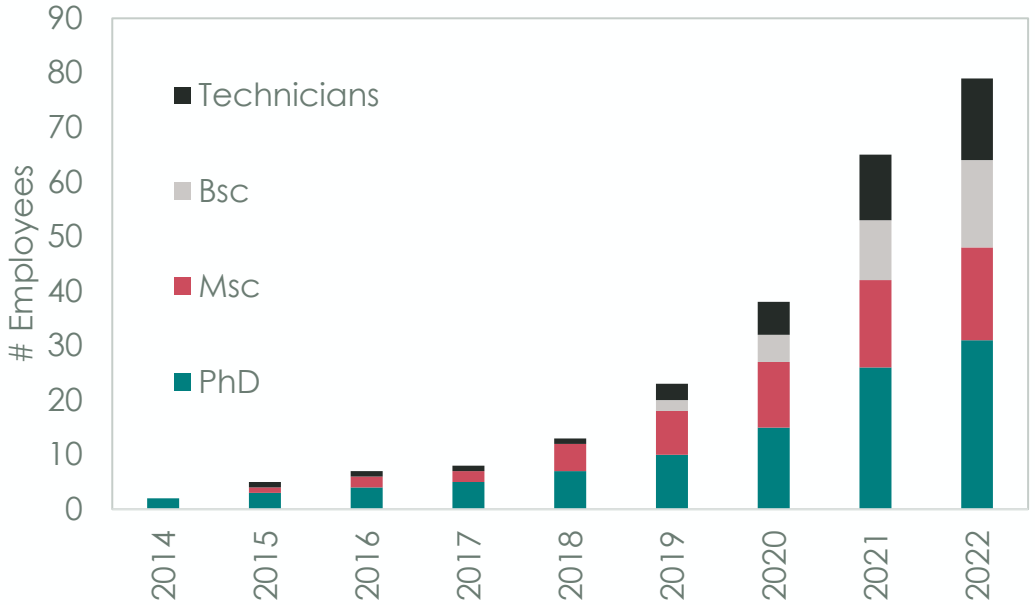
We are Nanoparticle, Conjugate & Functional Excipient Manufacturing Experts

- Formulation Development
- Analytical Method Development
- Manufacturing Process Development
- Preclinical Manufacturing & Proof-of-Concept
- Benchtop Scaleup to cGMP Suites
- Clinical Manufacturing
- Project Management & CMC
- Aseptic Fill/Finish
- Labeling, Inspection, & Packaging
- Supply Chain
- Quality Control
- Quality Assurance
- Technology Transfer



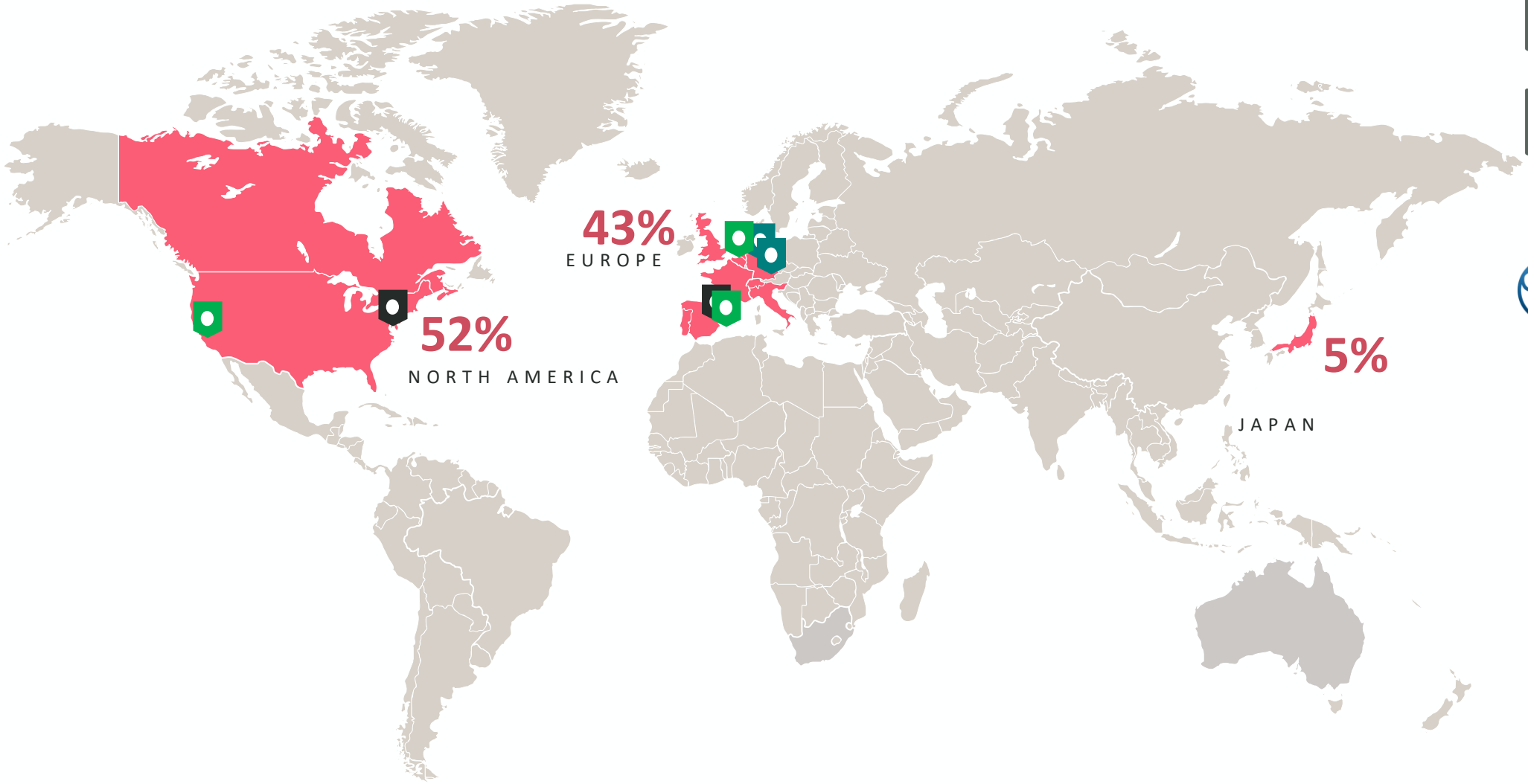
COMPANY OVERVIEW - Team

A highly motivated, talented and technically skilled team is the most important asset at PTS. Our team combines Academic background on PAA delivery systems, Industrial knowledge and track record in Pharmaceutical field.



COMPANY OVERVIEW

>500 projects with >60 Pharma and Biotech companies Worldwide



PTS LOCATIONS

PTS US Comercial Office
Cambridge, Boston

PTS EU Development &
Clinical GMP Manufacturing
Valencia, Spain

PARTNERS

Iris Biotech

KNAUER

ACADEMIC COLLABORATIONS

Polymer Therapeutics Vicent Lab — Maria J. Vicent Lab, Valencia - Spain

BARZLAB — Matthias Barz Lab, Leiden - Netherlands

UCLA — Tim Deming Lab, Los Angeles - US

U LISBOA — Helena Florindo Lab, Lisbone- PT

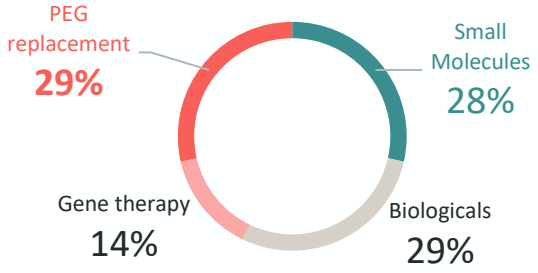
COMPANY OVERVIEW - GMP Manufacturing

> 50 GMP BATCHES MANUFACTURED

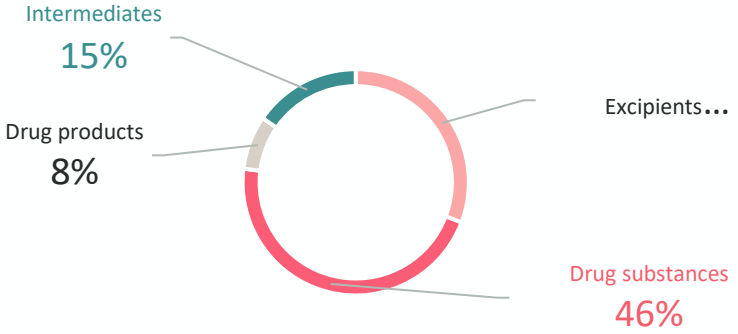
100 % CUSTOMER AUDIT COMPLIANCE

4 CMC PACKAGES DELIVERED for IND FILLING, APPROVED BY FDA/EMA, 4 MORE ONGOING IN 2022

Delivery Payload / modality



Regulatory Status



30-60 Days I POC-Feasibility

- Custom Synthesis and Prototype development / matching
- Basic QC to assess prototype performance
- Synthetic route scouting & selection
- Tech transfer

80-150 Days I Preclinical

- Bench Scale Process Characterisation (CQAs to pCPPs)
- Scale-up process (each operation unit)
- Method evaluation and Development (RM, IPC, release)
- Development Transfer Protocol to GMP operations
- GLP TOX Batches

120 Days I IND Enabling

- Process Transfer/Development
- Initial cGMP Process Characterization
- Method Qualification, Validation at demand Equipment & Process qualification
- Qualification of Sterility Assurance
- ICH Stability programs
- GMP Clinical Trial Material supply
- Continuous regulatory support
- IND filling support, CMC part module Q3

120-200 Days I Phase I

120-200 Days I Phase II

COMPANY OVERVIEW – QC

> 150 NON COMPEDIAL ANALYTICAL METHODS DEVELOPED

> 80 ANALYTICAL METHODS VALIDATION (ICH Q2)

>10 FORMAL ICH STABILITY PROGRAMS

- Routine characterizations
- In-process and quality control
- Identity, quantitative, and limit tests
- Impurity profiles
- Analysis according to current monographs (e.g., Ph. Eur., USP)
- Method development and validation (RM, IPC, Release, cleaning)
- Comprehensive cGMP documents and release certificates
- ICH Formal Stability studies

Polymer & Lipid Excipients (Bulk solid)

- Lipid Identity – UPLC-ELSD/CAD
- Lipid Purity – UPLC-ELSD/CAD
- Polymer Purity, Mw and PDI – SEC-RI-MALS
- Residual Solvents – USP
- Water Content – Karl Fischer
- Mw & DP by End Group Analysis – HPLC-MS-UV
- Enantiomeric excess – HPIC-MS-UV
- Endotoxin, Bioburden
- Cleaning Verification/Validation – HPLC/TOC
- Raw Material ID – RPIP
- Stability

Polymer Conjugates Drug Product

- API Identity – HPLC-UV/MS
- API Concentration – HPLC-UV/MS
- Conjugation ratio % – SEC-RI-UV / qNMR
- Appearance, Viscosity, Osmolality, pH, VIC – USP
- Residual Solvents – USP
- Endotoxin, Bioburden, Sterility, SVP – USP
- Content Uniformity – USP
- Cleaning Verification/Validation – HPLC/TOC
- Raw Material ID – RPIP
- Stability

Lipid Nanoparticle & Polymer Nanoparticle Drug Products

- Particle Size and Distribution – Malvern DLS
- Zeta Potential – Malvern DLS
- API Identity – RPIP
- API Concentration – RPIP
- API % Encapsulation – Ribogreen
- API Ratio – SEC
- Total API (RNA) Purity – Fragment Analyzer
- Lipid Identity – UPLC-ELSD/CAD
- Lipid Concentration – UPLC-ELSD/CAD
- Appearance, Viscosity, Osmolality, pH, VIC – USP
- Residual Solvents – USP
- Endotoxin, Bioburden, Sterility, SVP – USP
- Content Uniformity – USP
- Cleaning Verification/Validation – HPLC/TOC
- Raw Material ID – RPIP
- Stability

Summary:
Lessons Learnt from PT Lab to PTS

1. Identify a need, the most simple idea could be the most needed

2. Take the chance, go for it!

3. But always with the adequate people. Trust is a must!

4. Science is not enough for a success story. Business and Market knowledge should go together with Scientific background.

5. But a Robust Science and IP protection makes a Solid Foundation.

PRECISION POLYMERS FOR DRUG DELIVERY

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+1-267-638-8910 (US)

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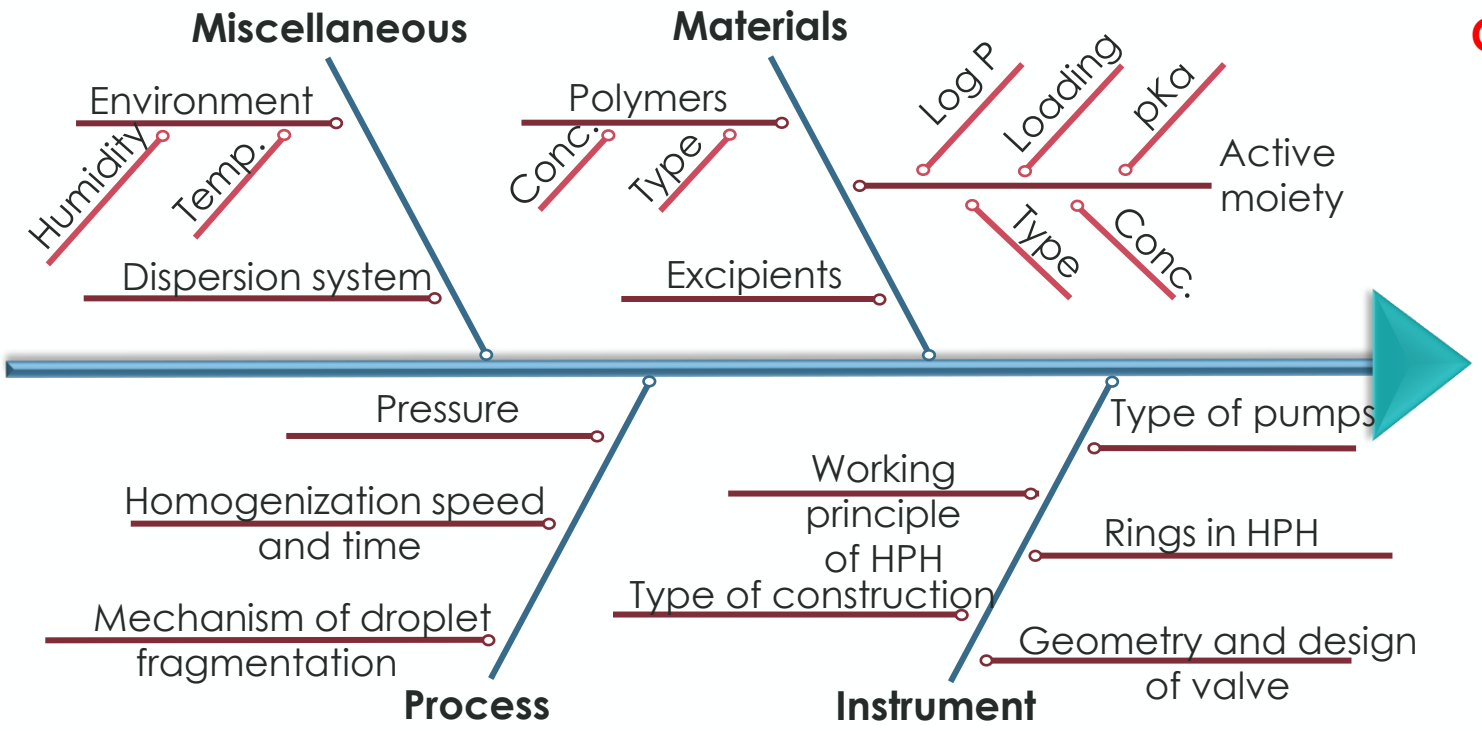
pts@pts-polypeptides.com

(+34) 963 769 080

Representation of those critical material attributes (CMA) and critical process parameters (CPP) that cause discrepancy and variability of critical quality attributes (CQAs) during the rational design and production of nanomedicines.

Critical Manufacturing Attributes



Critical Quality Attributes

- Size
- PDI
- Morphology
- Stability
- Surface charge
- Drug loading
- Drug release
- Encapsulation efficiency

Critical Process Parameters

S. Dordevic et al DDTR 2021