# Aventuras y desventuras de la carrera investigadora

María Plaza Oliver

# Aventuras y desventuras de la carrera investigadora

María Plaza Oliver

Mi experiencia

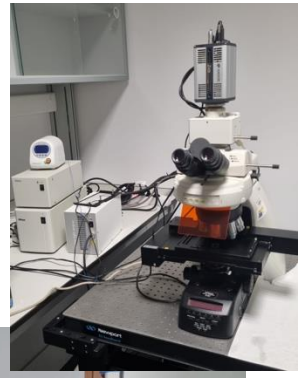
Grupo de investigación

Inconvenientes

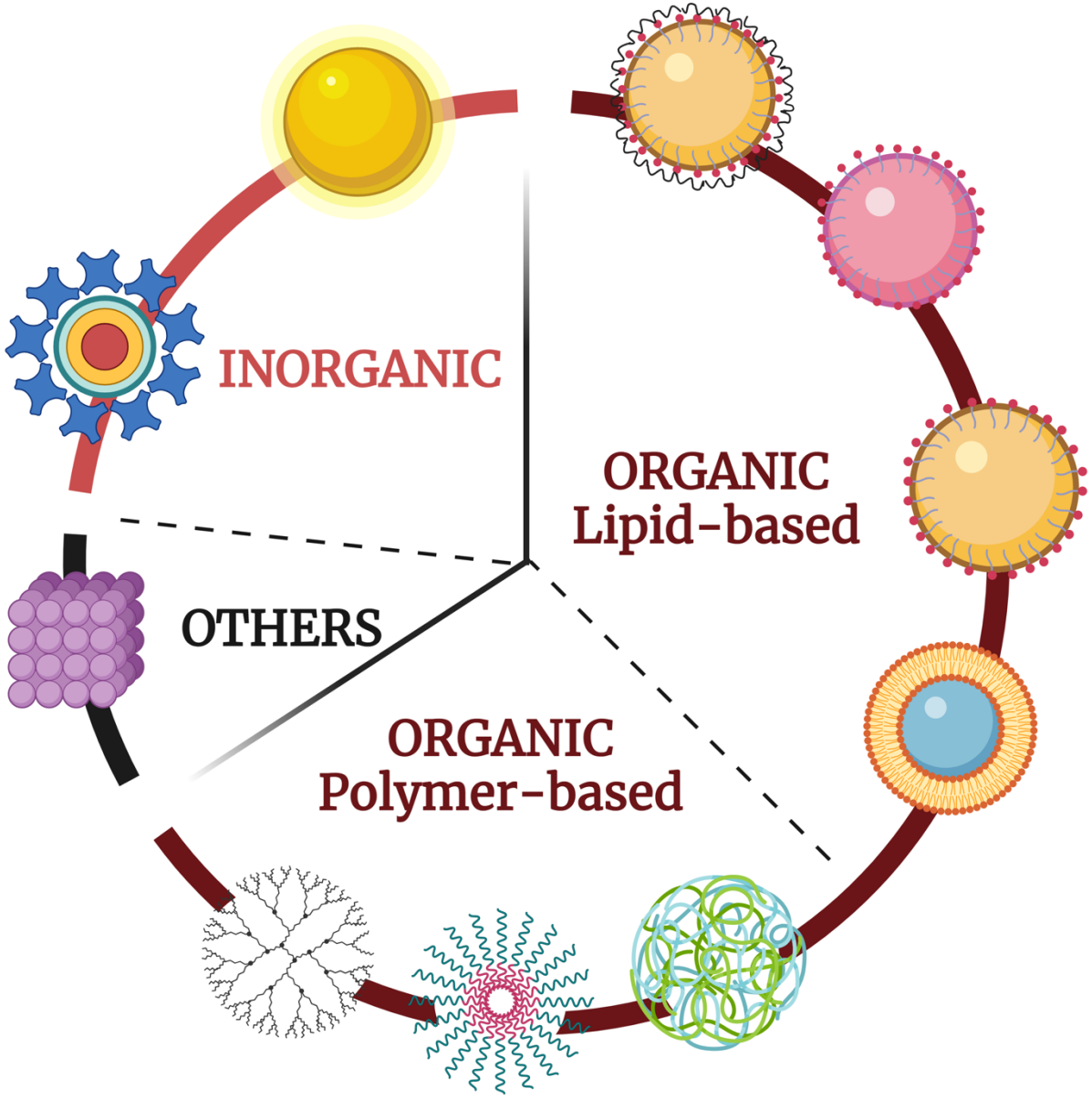
Ventajas

Ciencia

# Desarrollo y evaluación de nanomedicamentos (DEVANA)

# Nanocarriers to improve drug delivery

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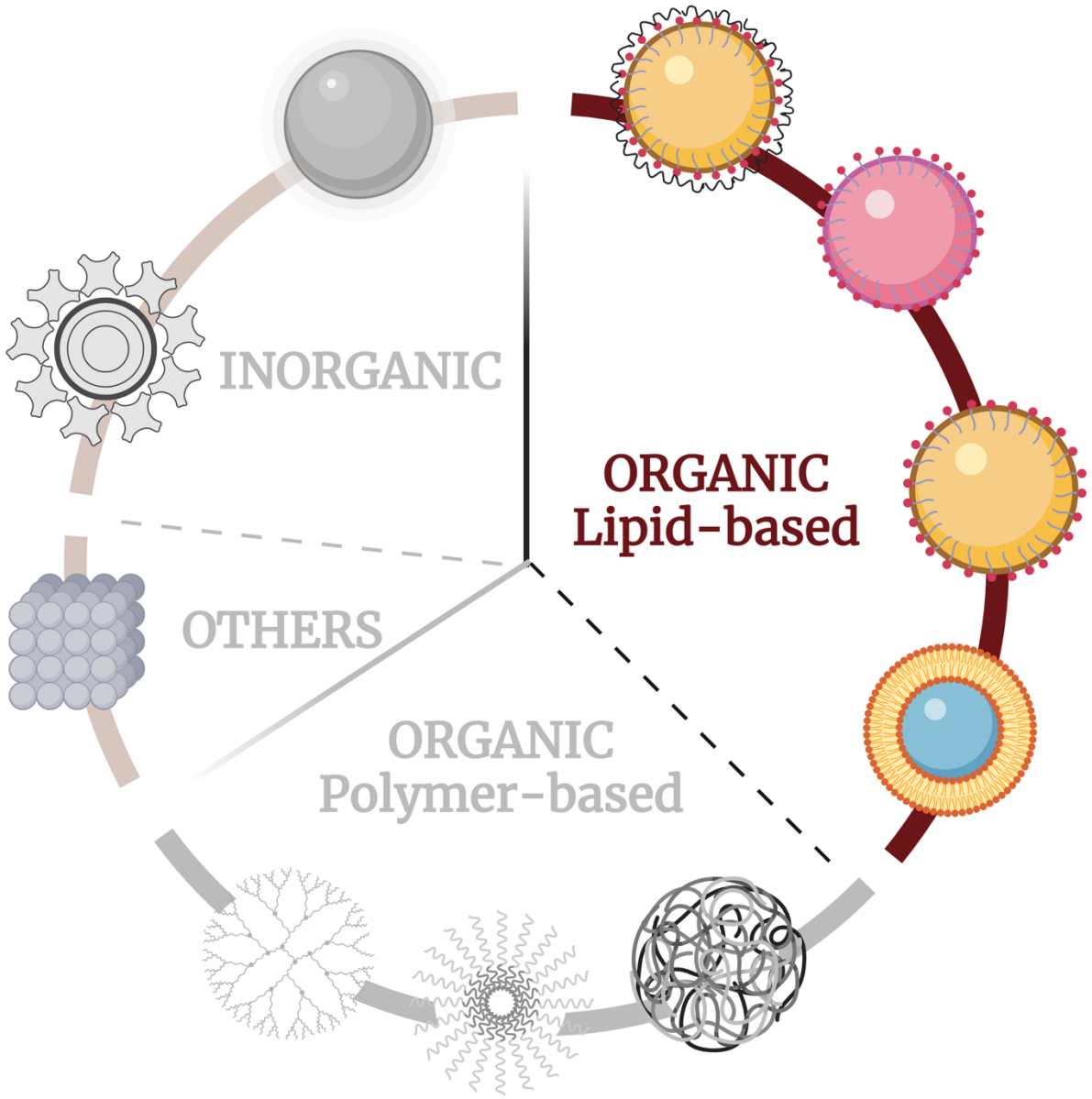
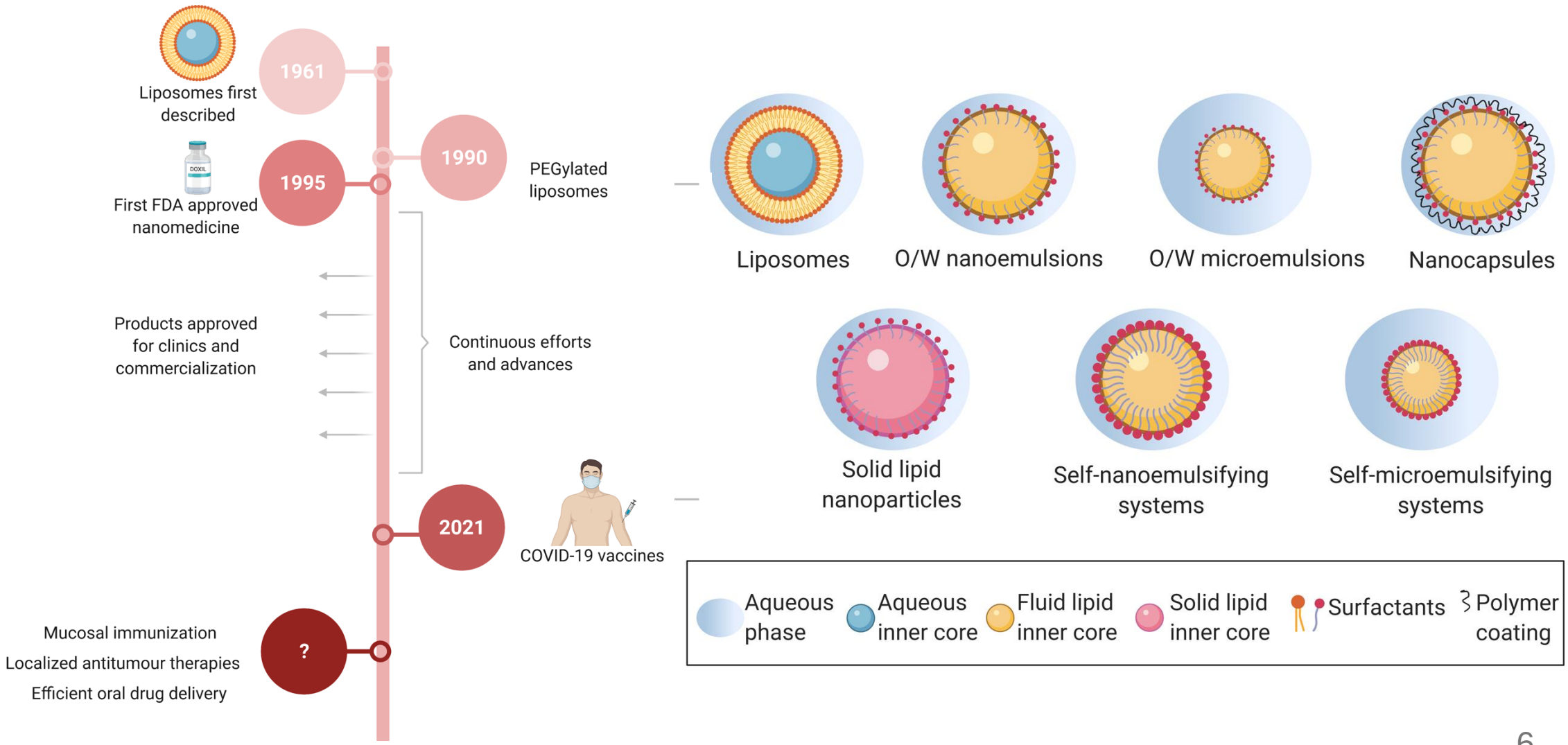
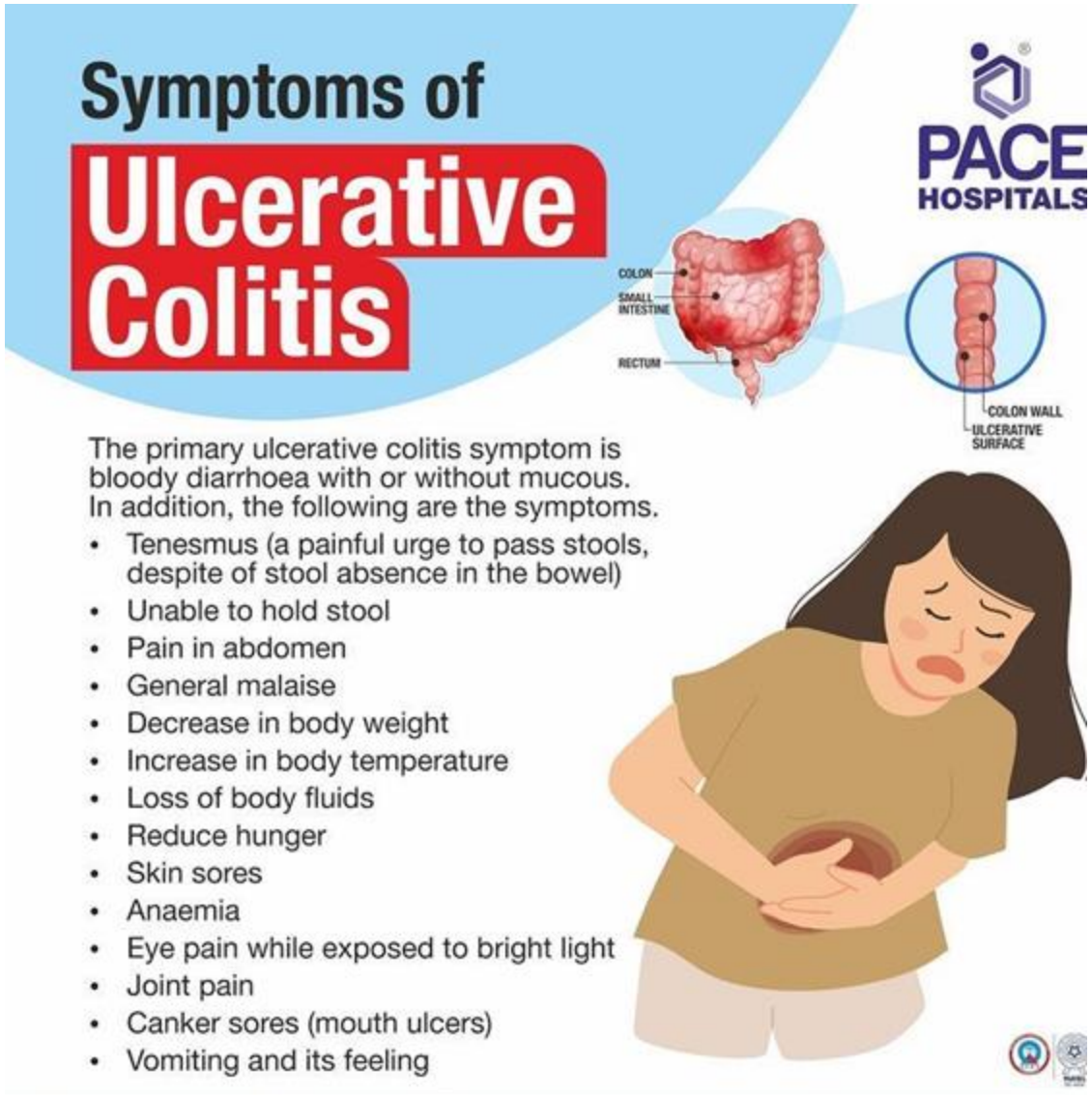



- Improved solubility
- Improved stability
- Controlled release
- Active cell targeting

# Evolution and impact of lipid-based nanocarriers in drug delivery



# Oral nanocarriers to treat ulcerative colitis




Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-024-01641-7

ORIGINAL ARTICLE

## Understanding the role of the structure of single-stimuli hybrid systems on their behaviour as platforms for colonic delivery

Joaquín González-Fuentes[1,2] · María Plaza-Oliver[1,2] · Manuel Jesús Santander-Ortega[1,2] · María Victoria Lozano[1,2]

Accepted: 20 May 2024


**Abstract**
The success of colon-targeted oral hybrid systems relies in the proper control over the release of the entrapped nanostructures at the colon. This work describes the design of hybrid systems for their colonic enzyme-triggered release. The hybrid systems were constituted by nanoemulsions, with adequate characteristics for the treatment of ulcerative colitis, included in a pectin hydrogel-like matrix. For that purpose, pectins with similar degrees of methylation (< 50%) and increasing degree of amidation, i.e. 0, 13 and 20%, were selected. Hybrid systems were formulated by a novel *aggregation induced gelation* method, using $Ca^{2+}$, $Ba^{2+}$ or $Zn^{2+}$ as aggregating agents, as well as by a polyelectrolyte condensation approach, obtaining structures in the micrometric range (< 10 μm). Despite the resistance of pectins to the upper gastrointestinal tract stimuli, the analysis of the behaviour of the different prototypes showed that the non-covalent crosslinks that allow the formation of the hybrid structure may play a relevant role on the performance of the formulation.

Our results indicated that the partial disassembling of the hybrid system's microstructure due to the intestinal conditions may facilitate the stimuli-triggered release of the nanoemulsions at the colon. More interestingly, the particle tracking experiments showed that the condensation process that occurs during the formation of the system may affect to the enzymatic degradation of pectin. In this sense, the effect of the high degree of amidation of pectin may be more prevalent as structural feature rather than as a promoter of the enzyme-triggered release.

**Keywords** Nanoemulsion · Hybrid system · Pectin · Particle tracking · Colon-targeted oral drug delivery

### Introduction

Since the conception of the first formulations based on pH-sensitive methacrylate for colonic drug delivery, the advances achieved in the field have opened the possibility of new therapies aiming the enteric immune system or the treatment of local diseases like ulcerative colitis. Colon-targeted drug delivery is one of the approaches for ulcerative colitis therapies, as the localization of the drugs at the damaged tissue may improve the efficacy/toxicity balance of the treatments [1]. The advances achieved in Nanotechnology have significantly contributed to this approach by providing new platforms [2], able to achieve longer retention times at the colonic mucosa due to their small size or to obtain more homogenous drug absorption, decreasing individual variability [3–6]. Within this context, our research group has reported that curcumin-loaded nanoemulsions (NE) constituted by ascorbate and antioxidant cores were able to retain the antioxidant molecule intracellularly in a monoculture of Caco-2 and avoid its permeation across the barrier, promoting the intracellular antioxidant activity of curcumin [7].

In order to transport the nanosystems to the damaged tissue, they are often formulated in colon targeted microstructures like hybrid systems. These systems are constituted by drug-loaded nanostructures entrapped in an external hydrogel-like matrix. The formulation of hybrid systems allows the protection of the nanostructures along the gastrointestinal tract (GIT), preventing their instability, premature drug leakage or non-optimal interaction with the intestinal epithelium [2, 8]. Once hybrid systems reach the

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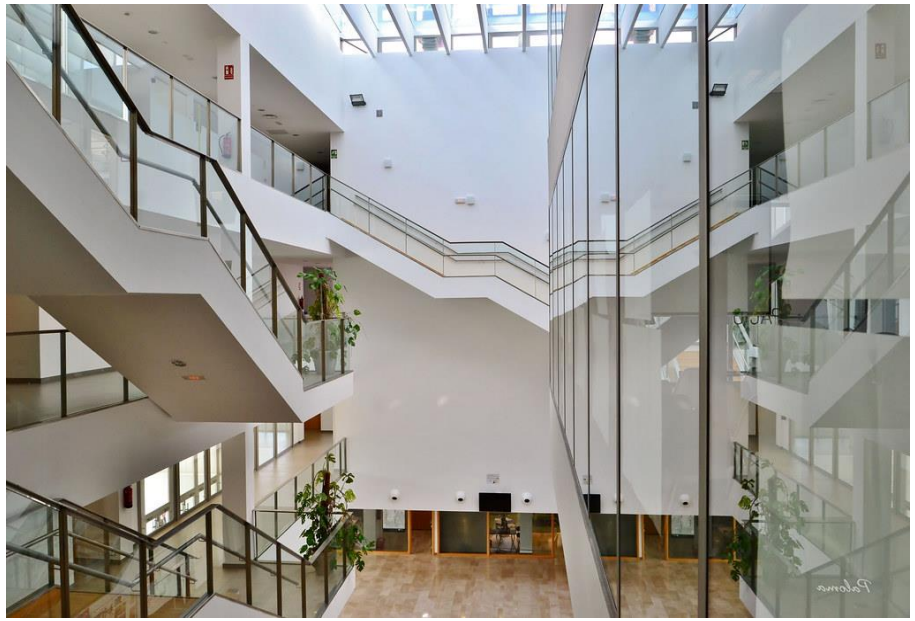
Published online: 10 June 2024

# (Mis) aventuras y desventuras en la carrera investigadora



Grado en Farmacia (2012-2017)



Estancias de iniciación a la investigación (2013)

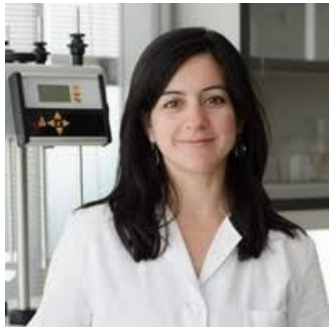
Estancias de iniciación a la investigación (2014)

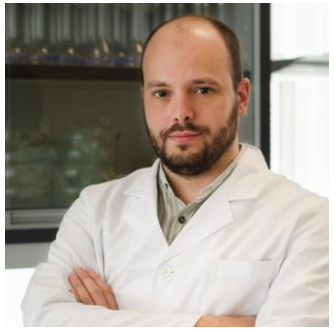
Becas de colaboración, MECD… (2015-2017)

DIPUTACIÓN DE ALBACETE

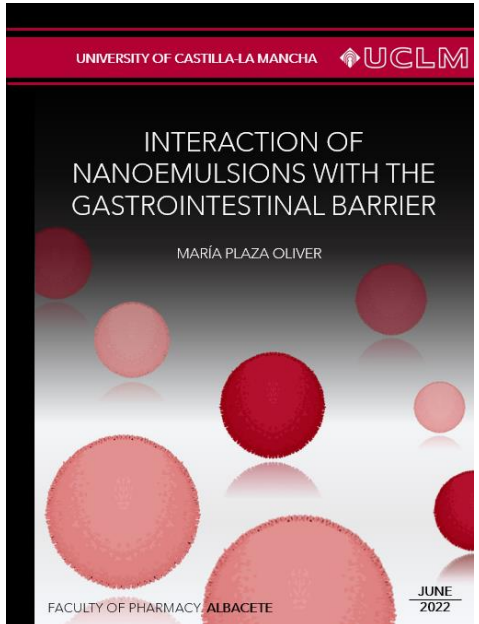
# (Mis) aventuras y desventuras en la carrera investigadora

Directores





Profs. Victoria Lozano y Manuel Santander




Tesis Doctoral (2017-2022)

- Beca asociada a Proyecto (2017 3 meses)
- Contrato Predoctoral (2018 9 meses)
  Estancia en Bruselas (2018 3 meses)
- Contrato Predoctoral Plan Propio UCLM ( 2019-2022 3.5 años)
  Estancia Predoctoral en Boston (2021, 6 meses)

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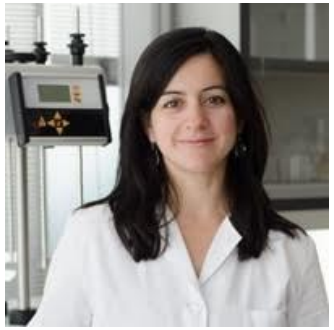

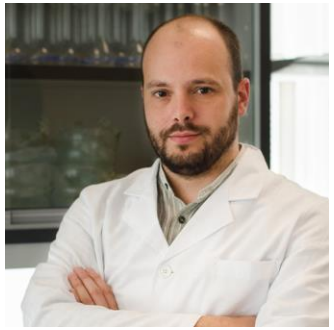

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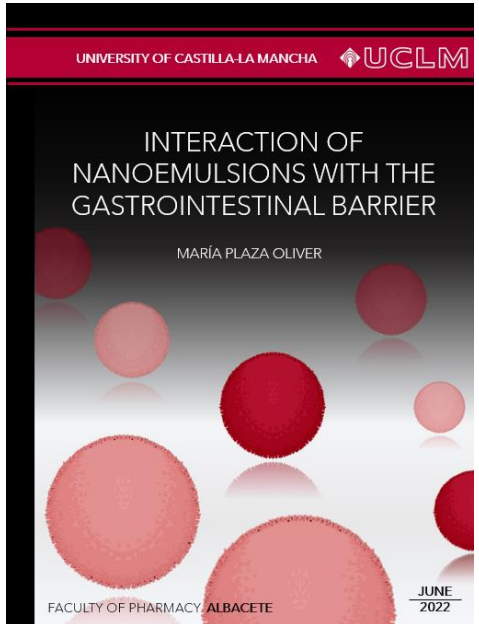


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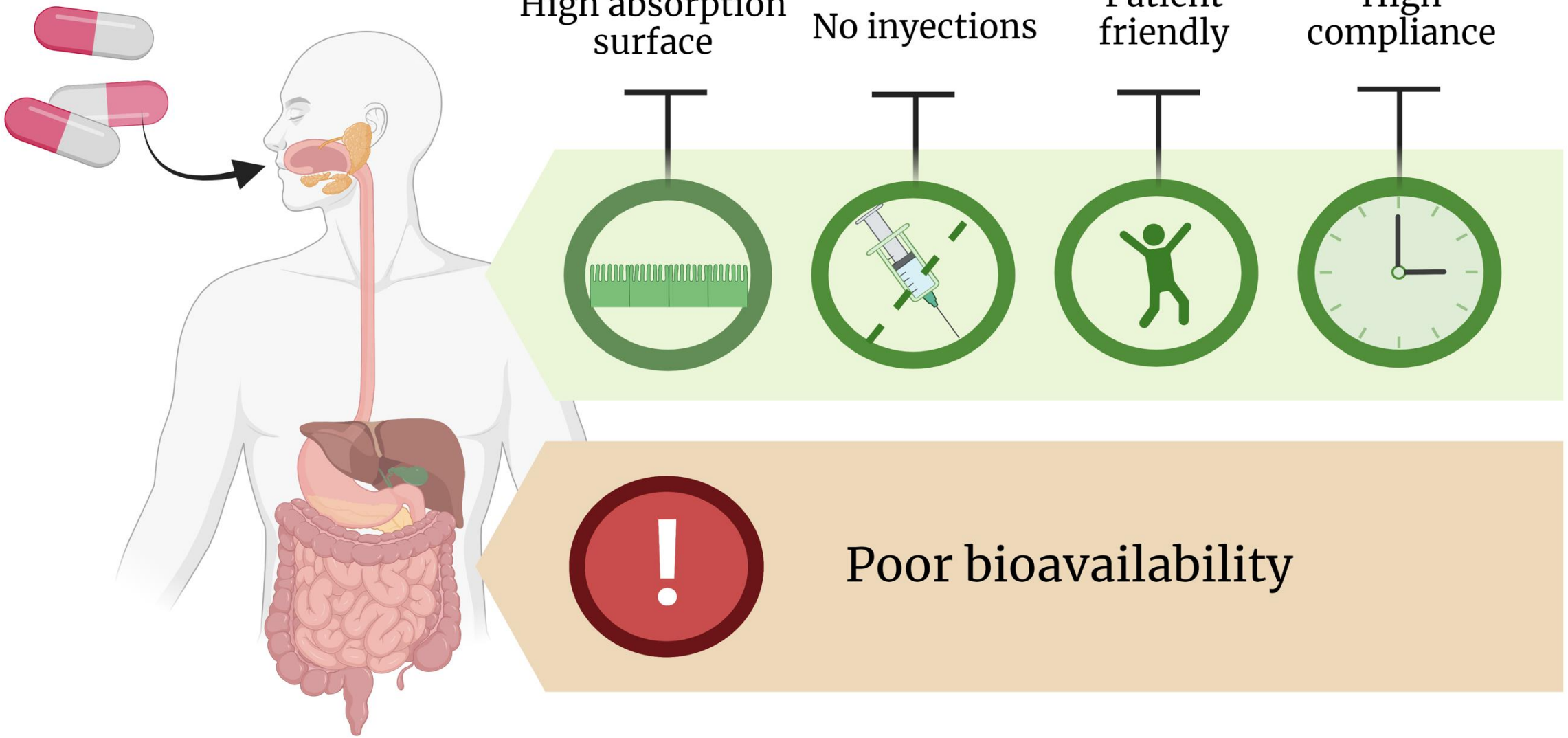
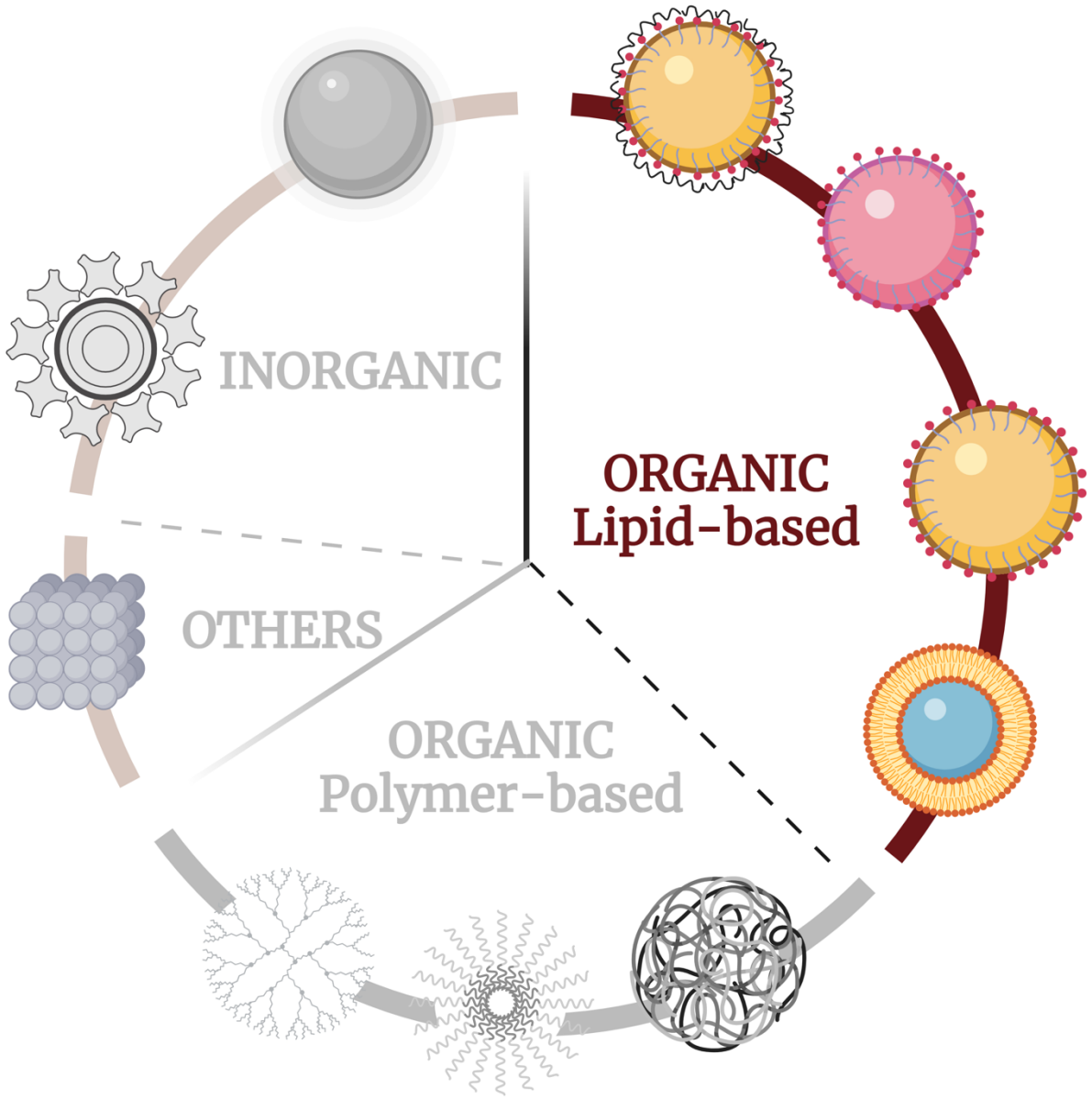
  Estancia Predoctoral en Boston (2021, 6 meses)
- Contrato Postdoctoral Margarita Salas (2022-2024, 2 años)
  Estancia Postdoctoral en Boston (2023, 1 año)

# Oral drug delivery



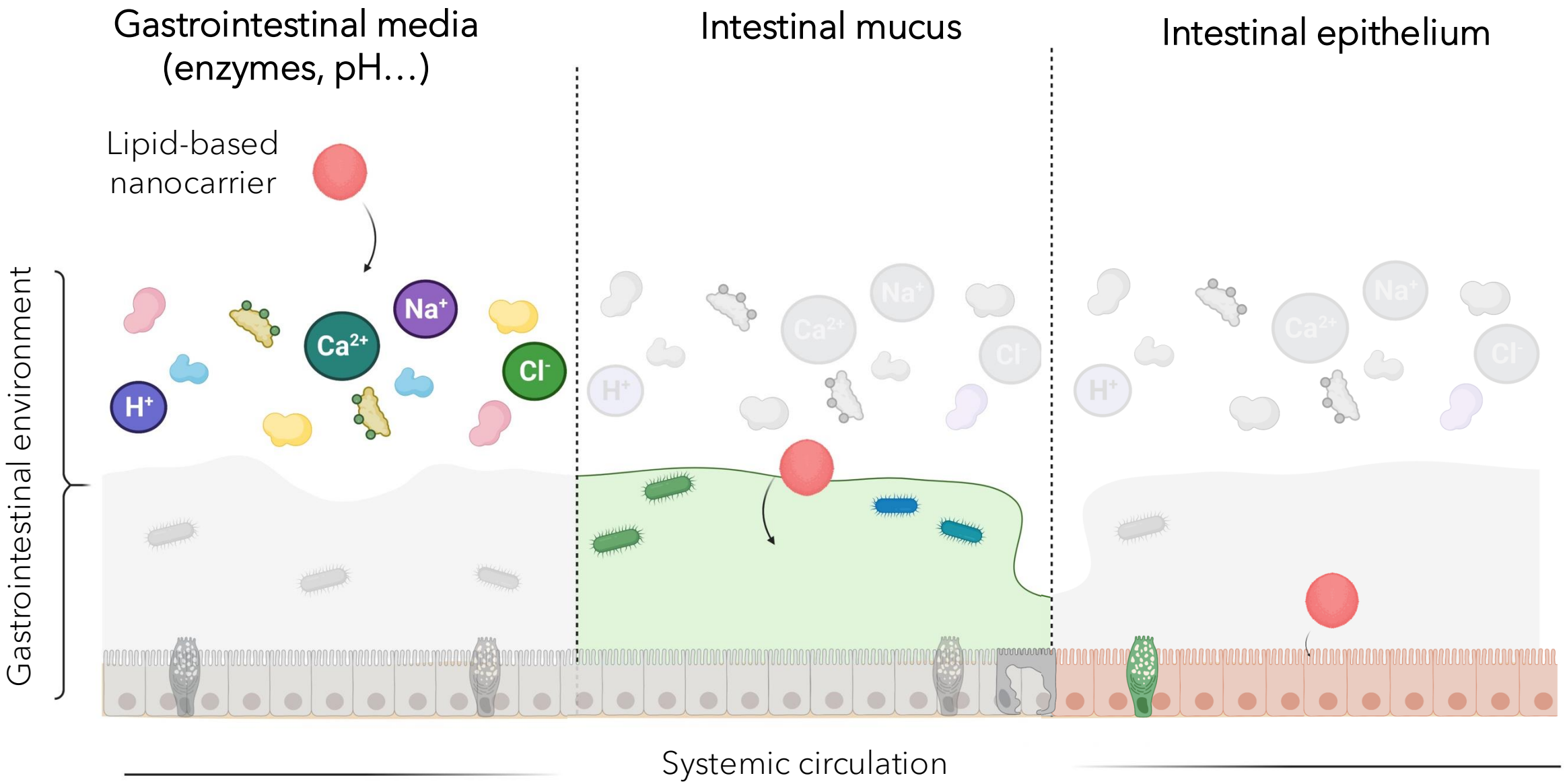
# Lipid-based nanocarriers to improve oral drug delivery




- Improved solubility
- Improved stability
- Controlled release
- Active cell targeting

**Poor clinical translation**

# Gastrointestinal barriers: obstacles to oral nanocarriers

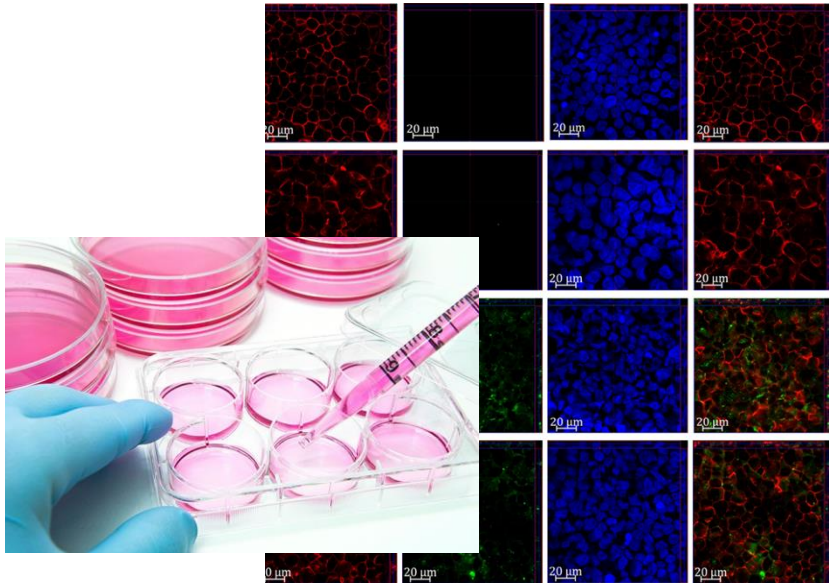


# Louvain Drug Research Institute. University of Louvain

UCL Université catholique de Louvain

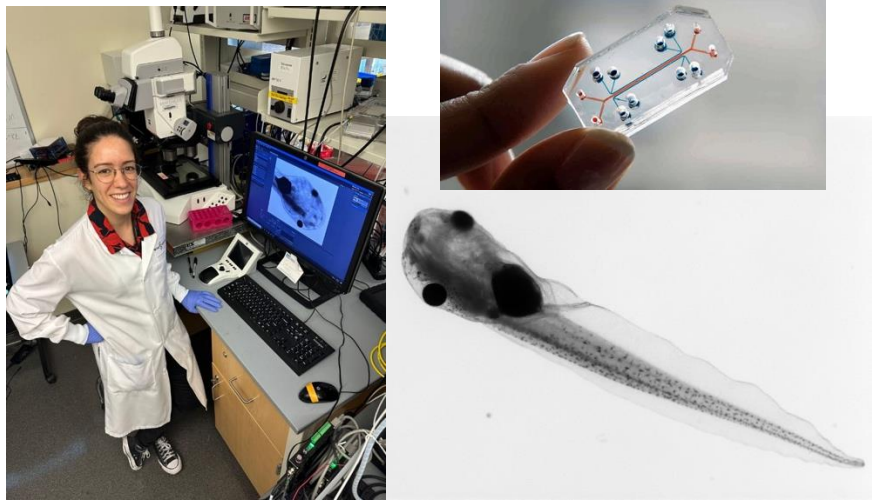
LDRI LOUVAIN DRUG RESEARCH INSTITUTE

Profs. Ana Beloqui y Véronique Préat



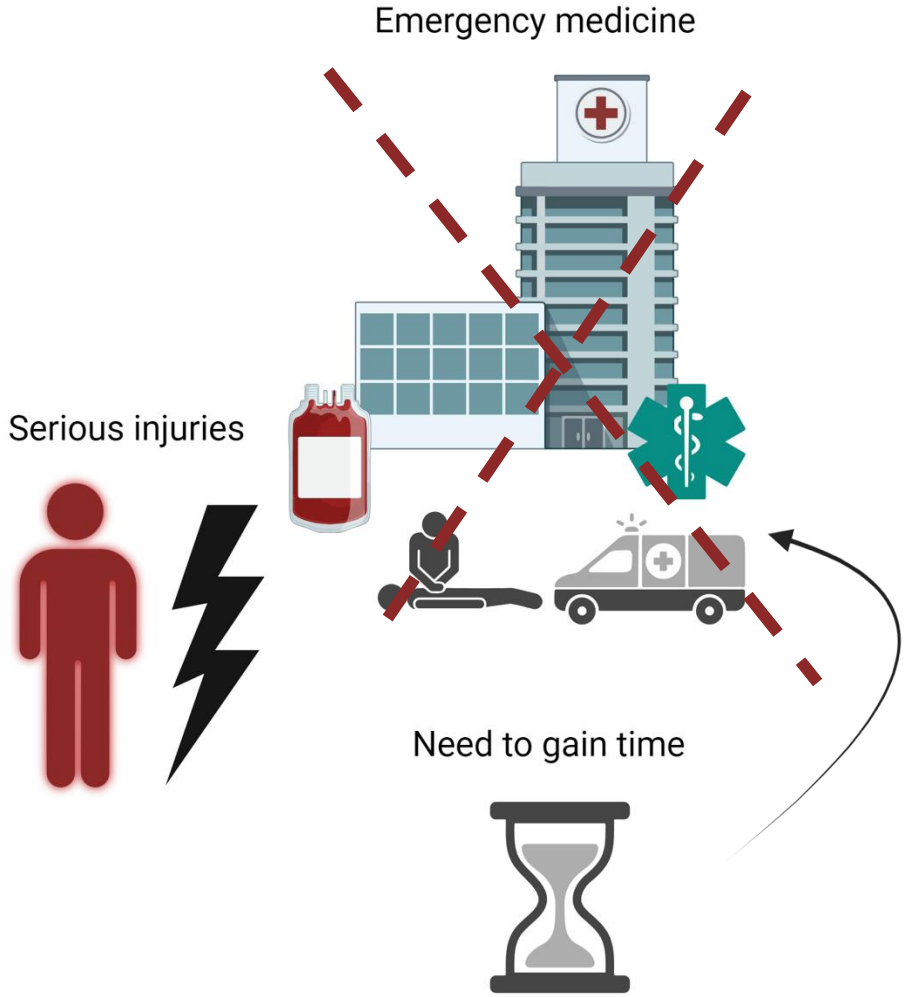
# Wyss Institute at Harvard University

Profs. Michael Super, Richard Novak, Donald Ingber

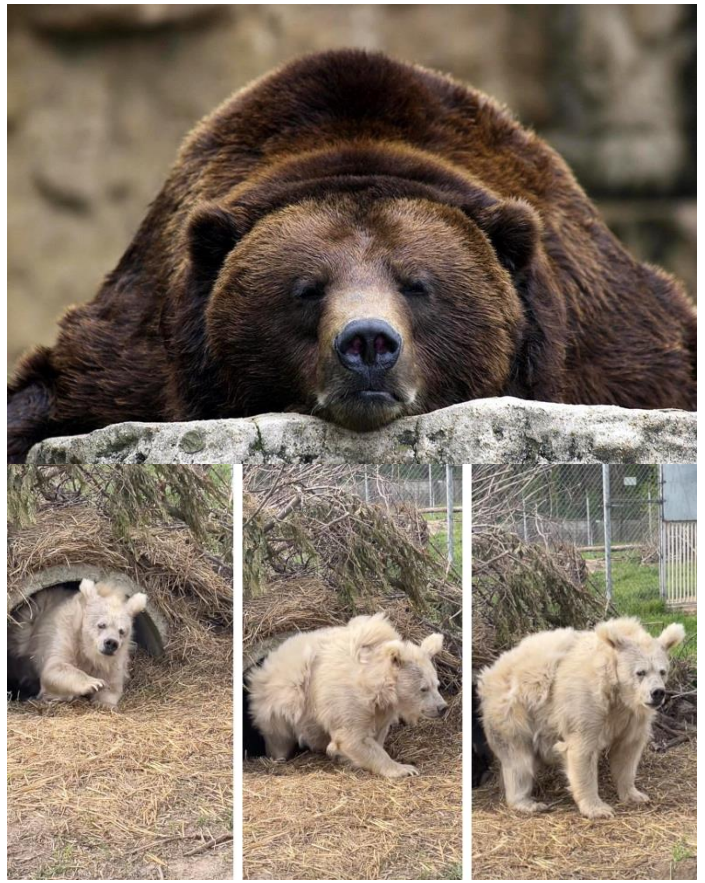



# Biostasis project

DEFENSE ADVANCED RESEARCH PROJECTS AGENCY





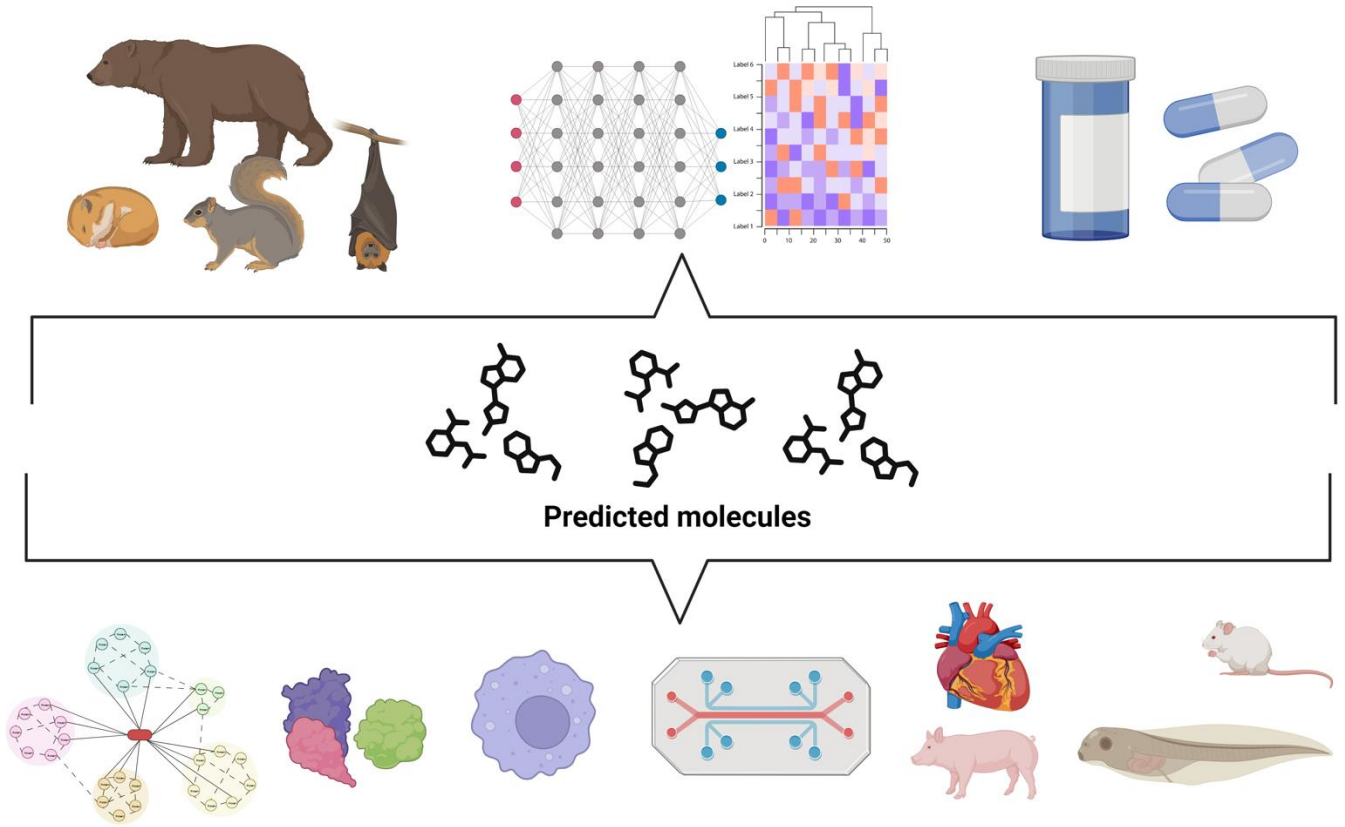


Example in nature: hibernating animals

# Biostasis project

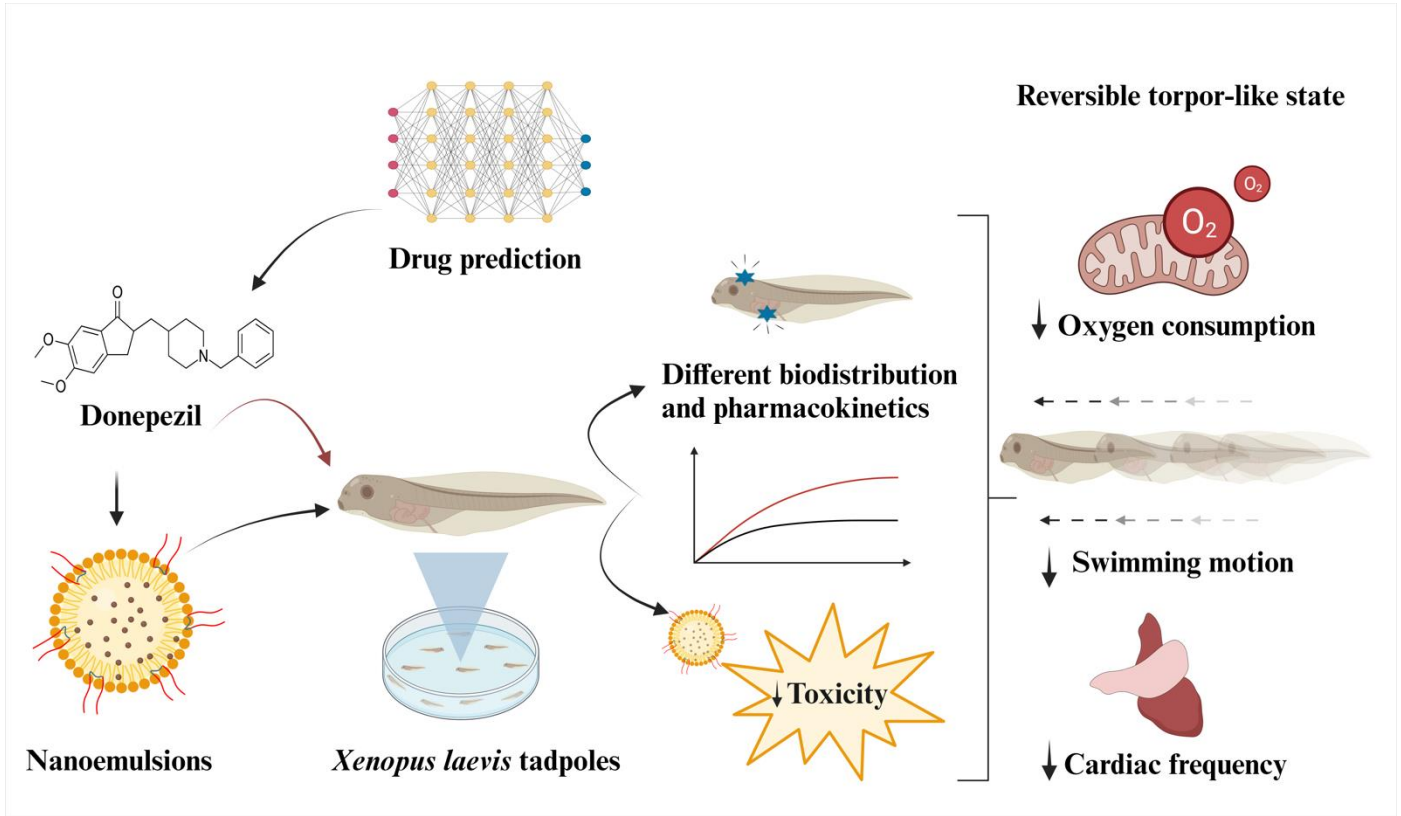
DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

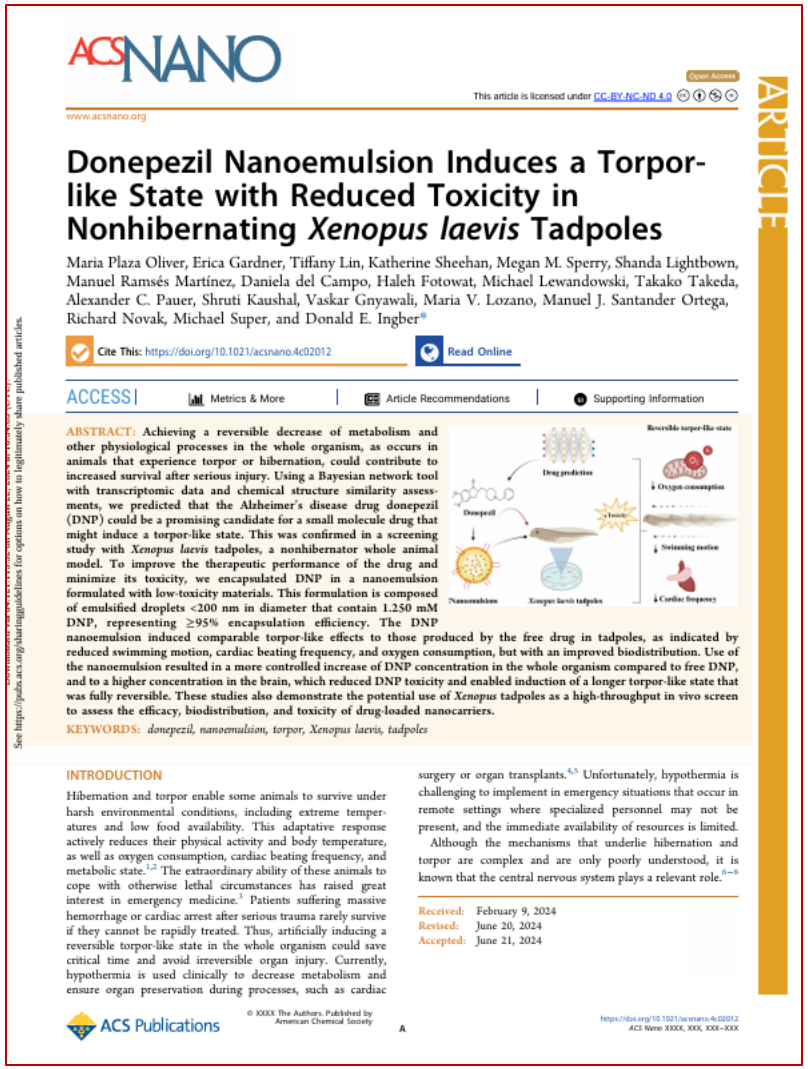
**Development of therapeutics that slow biochemical activities while preserving molecule, cell, tissue, organ, and organism viability**



# Biostasis project

DARPA DEFENSE ADVANCED RESEARCH PROJECTS AGENCY



ACS NANO

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Donepezil Nanoemulsion Induces a Torpor-like State with Reduced Toxicity in Nonhibernating *Xenopus laevis* Tadpoles

Maria Plaza Oliver, Erica Gardner, Tiffany Lin, Katherine Sheehan, Megan M. Sperry, Shanda Lightbown, Manuel Ramsés Martínez, Daniela del Campo, Haleh Fotowat, Michael Lewandowski, Takako Takeda, Alexander C. Pauer, Shruti Kaushal, Vaskar Gnyawali, Maria V. Lozano, Manuel J. Santander Ortega, Richard Novak, Michael Super, and Donald E. Ingber*

Cite This: https://doi.org/10.1021/acsnano.4c02012 Read Online

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ABSTRACT: Achieving a reversible decrease of metabolism and other physiological processes in the whole organism, as occurs in animals that experience torpor or hibernation, could contribute to increased survival after serious injury. Using a Bayesian network tool with transcriptomic data and chemical structure similarity assessments, we predicted that the Alzheimer's disease drug donepezil (DNP) could be a promising candidate for a small molecule drug that might induce a torpor-like state. This was confirmed in a screening study with *Xenopus laevis* tadpoles, a nonhibernator whole animal model. To improve the therapeutic performance of the drug and minimize its toxicity, we encapsulated DNP in a nanoemulsion formulated with low-toxicity materials. This formulation is composed of emulsified droplets <200 nm in diameter that contain 1.250 mM DNP, representing ≥95% encapsulation efficiency. The DNP nanoemulsion induced comparable torpor-like effects to those produced by the free drug in tadpoles, as indicated by reduced swimming motion, cardiac beating frequency, and oxygen consumption, but with an improved biodistribution. Use of the nanoemulsion resulted in a more controlled increase of DNP concentration in the whole organism compared to free DNP, and to a higher concentration in the brain, which reduced DNP toxicity and enabled induction of a longer torpor-like state that was fully reversible. These studies also demonstrate the potential use of *Xenopus* tadpoles as a high-throughput in vivo screen to assess the efficacy, biodistribution, and toxicity of drug-loaded nanocarriers.

KEYWORDS: *donepezil, nanoemulsion, torpor, Xenopus laevis, tadpoles*

INTRODUCTION

Hibernation and torpor enable some animals to survive under harsh environmental conditions, including extreme temperatures and low food availability. This adaptative response actively reduces their physical activity and body temperature, as well as oxygen consumption, cardiac beating frequency, and metabolic state.[1,2] The extraordinary ability of these animals to cope with otherwise lethal circumstances has raised great interest in emergency medicine.[3] Patients suffering massive hemorrhage or cardiac arrest after serious trauma rarely survive if they cannot be rapidly treated. Thus, artificially inducing a reversible torpor-like state in the whole organism could save critical time and avoid irreversible organ injury. Currently, hypothermia is used clinically to decrease metabolism and ensure organ preservation during processes, such as cardiac surgery or organ transplants.[4,5] Unfortunately, hypothermia is challenging to implement in emergency situations that occur in remote settings where specialized personnel may not be present, and the immediate availability of resources is limited.

Although the mechanisms that underlie hibernation and torpor are complex and are only poorly understood, it is known that the central nervous system plays a relevant role.[6−8]

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Accepted: June 21, 2024

ACS Publications





ARTICLE

# Oral nanocarriers to treat ulcerative colitis



Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-024-01641-7

ORIGINAL ARTICLE

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### Introduction

Since the conception of the first formulations based on pH-sensitive methacrylate for colonic drug delivery, the advances achieved in the field have opened the possibility of new therapies aiming the enteric immune system or the treatment of local diseases like ulcerative colitis. Colon-targeted drug delivery is one of the approaches for ulcerative colitis therapies, as the localization of the drugs at the damaged tissue may improve the efficacy/toxicity balance of the treatments [1]. The advances achieved in Nanotechnology have significantly contributed to this approach by providing new platforms [2], able to achieve longer retention times at the colonic mucosa due to their small size or to obtain more homogenous drug absorption, decreasing individual variability [3–6]. Within this context, our research group has reported that curcumin-loaded nanoemulsions (NE) constituted by ascorbate and antioxidant cores were able to retain the antioxidant molecule intracellularly in a monoculture of Caco-2 and avoid its permeation across the barrier, promoting the intracellular antioxidant activity of curcumin [7].

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[2] Instituto de Biomedicina (IB), Universidad de Castilla-La Mancha (UCLM), Albacete 02008, Spain

Published online: 10 June 2024
Springer

# ¿Qué se necesita para ser investigador?

# ¿Qué se necesita para ser **un buen** investigador?

Motivación y capacidad de motivar

Organización

Escucha activa

comprensión

Trabajo en equipo

Toma de decisiones

Curiosidad

Respeto

Capacidad de síntesis y concreción

Pensamiento crítico

## HABILIDADES INTRA E INTERPERSONALES

Capacidad de adaptación

Empatía

Resiliencia

disciplina

Gestión del tiempo

Tolerancia

Desenvolverse en situaciones de estrés

Comunicación Oral y Escrita

Liderazgo

Resolución de conflictos

# Ventajas de la carrera investigadora


# Aventuras y desventuras de la carrera investigadora

# Aventuras y desventuras de la carrera investigadora

OPINION

# La ciencia y la precariedad laboral de los investigadores

# La precariedad doblega a los científicos españoles, que pasan de emigrar a abandonar la investigación

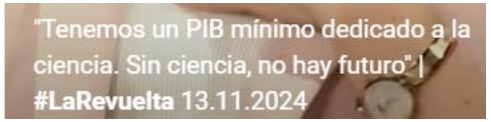
Siete de cada diez investigadores han considerado en alguna ocasión dejar la ciencia, según una encuesta de Ciencia con Futuro

» Ciencia y tecnología

Comisión Europea, que **España ha perdido unos 12.000 científicos desde el inicio de esta década**.

Más información

**La ciencia española no para de quedarse atrasada tras nueve años de recortes**


# Mariano Barbacid lamenta la "absoluta precariedad" de la investigación en España

- Alude a "una década de recortes" y pide al nuevo Gobierno que "realmente invierta en ciencia"

EDUCACIÓN Y UNIVERSIDAD

## Años de investigación excelente para terminar "mendigando una mesa": la precariedad de los investigadores en España

investigadores en el trabajo. Algunos de ellos tienen que ver con la **precariedad laboral**: un salario menos competitivo que en profesiones que requieren una cualificación similar, la incertidumbre de los contratos de corta duración o la necesidad, en muchas ocasiones, de mudarse a otra ciudad, o incluso a otro país, cuando el contrato se termina... Otro factor es el **alto nivel de exigencia** que impone el sistema de publicaciones por el cual se evalúan los méritos científicos (de ellos puede depender el próximo contrato). Otros **condicionantes más sutiles** que pueden entrar en el cómputo del bienestar tienen que ver con la barrera tan difusa que existe entre lo personal y lo profesional, desvaneciéndose así los límites de lo que conocemos como jornada laboral –y que los éxitos y desventuras profesionales se


**Figura 1**. Resultados de la evaluación del trastorno mental en una muestra poblacional. Gráfico basado en los datos publicados por **Levecque et al., 2017**.

## Situación precaria en la investigación predoctoral

# Los científicos: respetados, pero precarios

- La complejidad temática y la incertidumbre laboral desincentiva que los jóvenes se dediquen a la ciencia

Coronavirus

## Jóvenes investigadores denuncian la falta de financiación tras la pandemia: "Hay mucha precariedad"

- RTVE.es pone rostro a la generación de doctorandos en España en diversos ámbitos
- Piden más recursos para continuar con sus proyectos y reducir la incertidumbre laboral

## El líder de los investigadores 'precarios' deja la ciencia y emigra a Bruselas

José Manuel Fernández, exportavoz de la Federación de Jóvenes Investigadores, ha dejado la investigación por un puesto administrativo

# Bruselas llama a paliar la precariedad laboral de los investigadores jóvenes

# Aventuras y desventuras de la carrera investigadora

## Ventajas de la carrera investigadora




OPINION

**La ciencia y la precariedad laboral de los investigadores**

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La ciencia española no para de quedarse atrasada tras nueve años de recortes


"Tenemos un PIB mínimo dedicado a la ciencia. Sin ciencia, no hay futuro". #LaRevuelta 13.11.2024

Años de investigación excelente para terminar "mendigando una mesa": la precariedad de los investigadores en España

Figura 1. Resultados de la evaluación del trastorno mental en una muestra poblacional. Gráfico basado en los datos publicados por Levecque et al., 2017.

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**Los científicos: respetados, pero precarios**

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**Jóvenes investigadores denuncian la falta de financiación tras la pandemia: "Hay mucha precariedad"**

RTVE.es pone rostro a la generación de doctorandos en España en diversos ámbitos

Piden más recursos para continuar con sus proyectos y reducir la incertidumbre laboral

**El líder de los investigadores 'precarios' deja la ciencia y emigra a Bruselas**

José Manuel Fernández, exportavoz de la Federación de Jóvenes Investigadores, ha dejado la investigación por un puesto administrativo

**Bruselas llama a paliar la precariedad laboral de los investigadores jóvenes**