Nanomedicine and Nanoscale Delivery III

Camilla Pegoraro

A mitochondria-targeted polypeptide-based nanoconjugate for breast cancer treatment

Camilla Pegoraro[1], Ekaterina Karpova[2], Yusuf Qutbuddin[3], Esther Masiá Sanchis[1], Pavels Dimitrijevs[4], Pavel Arsenyan[4], Petra Schwille[3], Carles Felip-León[2], Aroa Duro-Castaño[2], Inmaculada Conejos-Sánchez[1,*] and María J. Vicent[1,*]

[1]Príncipe Felipe Research Center and CIBERONC, Polymer Therapeutics Lab., Valencia, Spain
[2]Curapath, Valencia, Spain
[3]Max Planck Institute of Biochemistry, Martinsried, Germany
[4]Latvian Institute of Organic Synthesis, Riga, Latvia

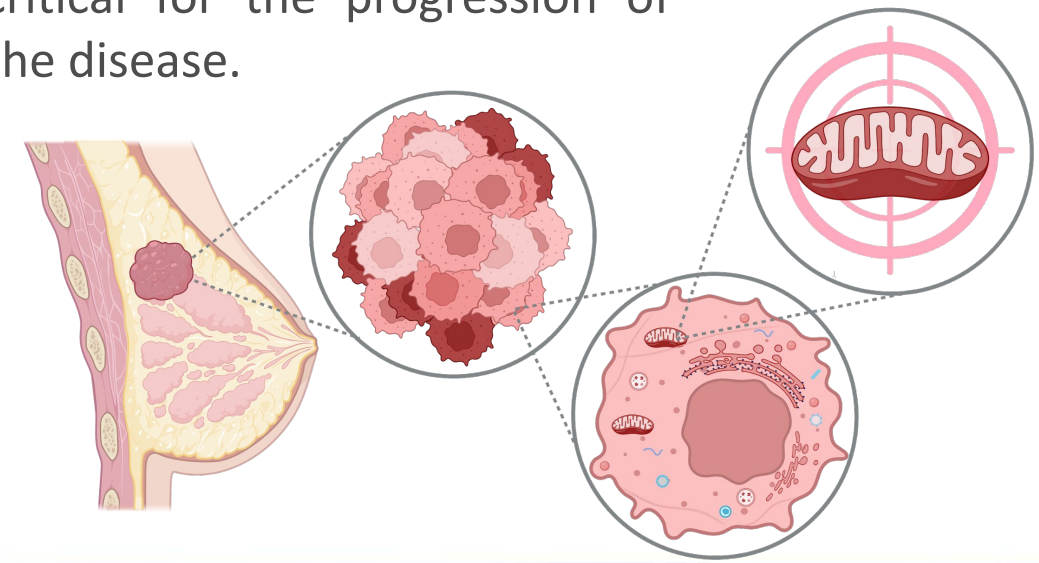
CONTROLLED RELEASE SOCIETY CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY
INTEGRATING Delivery Science ACROSS DISCIPLINES

Introduction

THE PROBLEM

Mitochondria's pivotal role in regulating cellular fate drives the pathogenesis of various diseases, including **cancer**.

In **breast cancer**, mitochondrial dynamics and metabolism are critical for the progression of the disease.



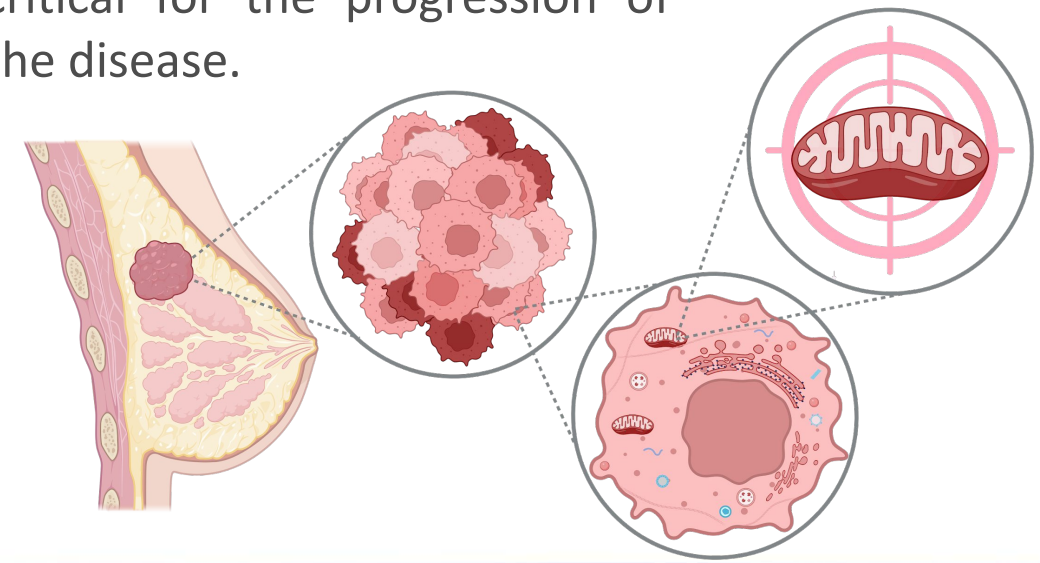
C. Pegoraro, et al., *Advanced Drug Delivery Reviews,* 2024, 207-115195

Introduction

THE PROBLEM

Mitochondria's pivotal role in regulating cellular fate drives the pathogenesis of various diseases, including **cancer**.
In **breast cancer**, mitochondrial dynamics and metabolism are critical for the progression of the disease.

THE TARGET



Current limitations

- Crossing different biological barriers towards subcellular targeting
- Targeting mitochondrial membrane potential
  charge-based accumulation
- Cytosolic delivery by endosomal escape
  low efficiency
- Materials functionalization
  complex synthesis, poor scale-up

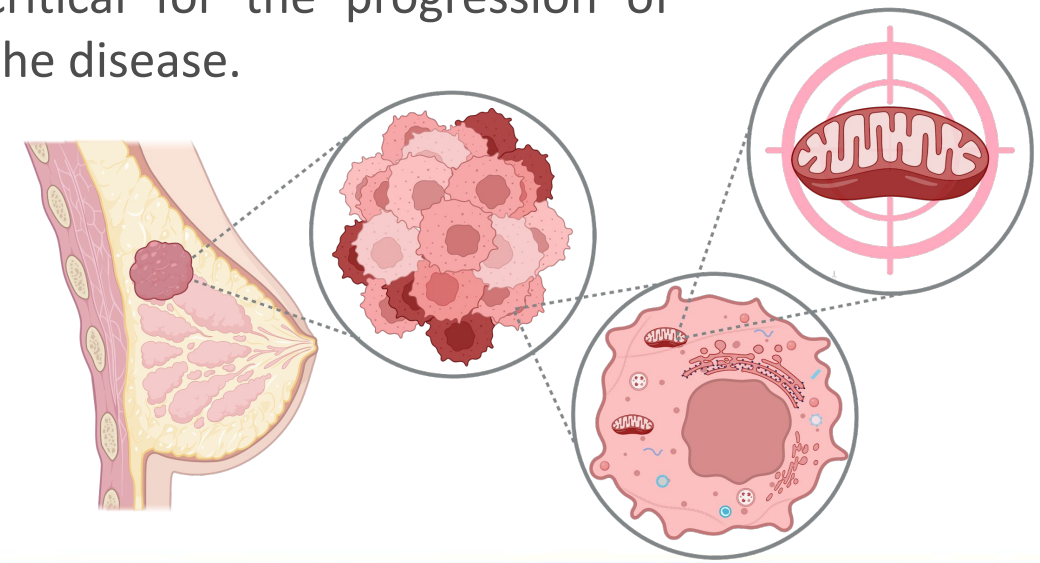
C. Pegoraro, et al., *Advanced Drug Delivery Reviews,* 2024, 207-115195

Introduction

THE PROBLEM

Mitochondria's pivotal role in regulating cellular fate drives the pathogenesis of various diseases, including **cancer**.
In **breast cancer**, mitochondrial dynamics and metabolism are critical for the progression of the disease.

THE TARGET



Current limitations

- Crossing different biological barriers towards subcellular targeting
- Targeting mitochondrial membrane potential
  charge-based accumulation
- Cytosolic delivery by endosomal escape
  low efficiency
- Materials functionalization
  complex synthesis, poor scale-up

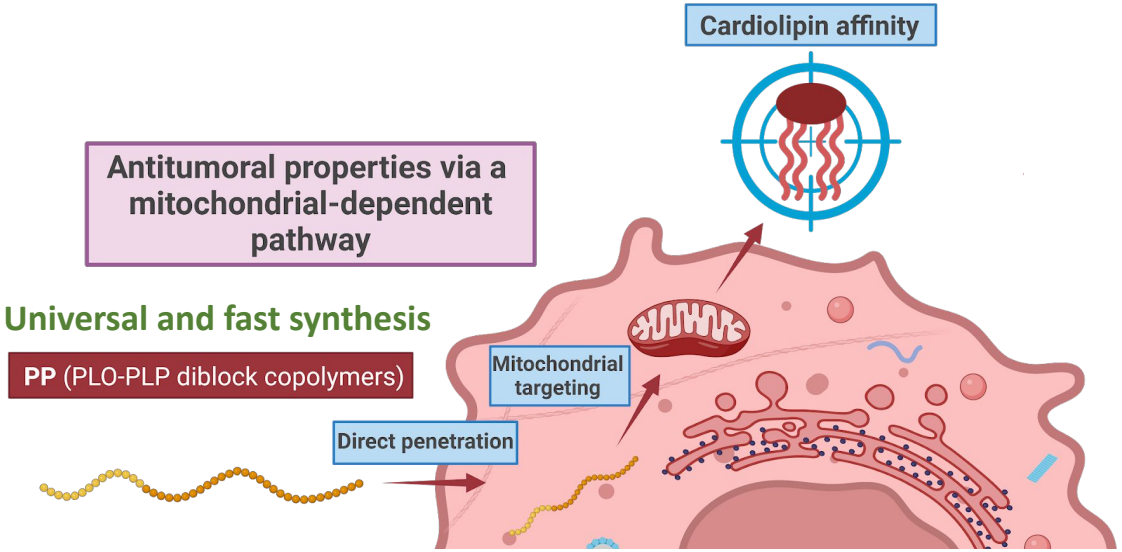
OUR SOLUTION

Nanocarriers with Mitochondria Tropism

Polypeptide-based Therapeutics

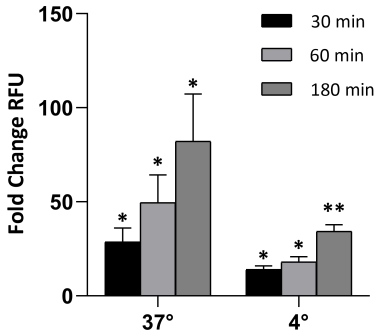
C. Pegoraro, et al., *Advanced Drug Delivery Reviews,* 2024, 207-115195

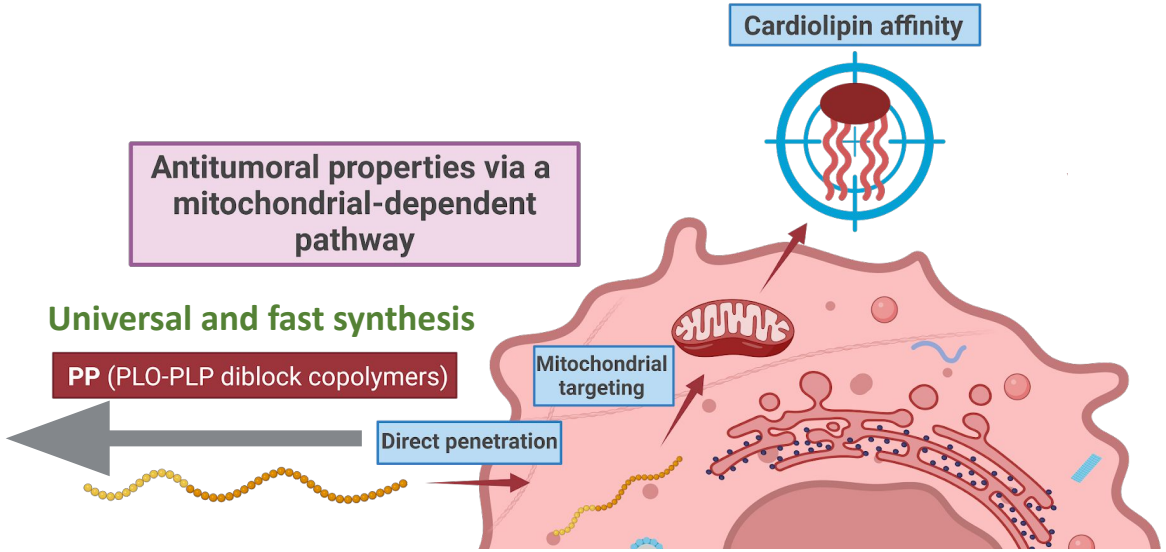
Results



C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

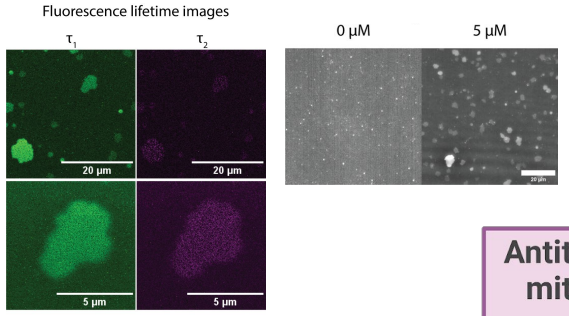
Results

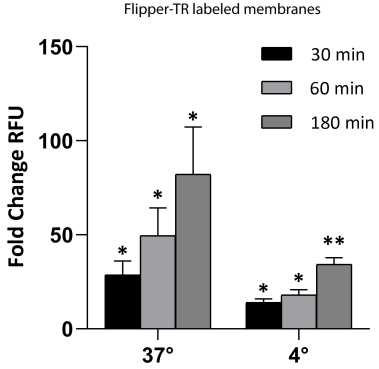




C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

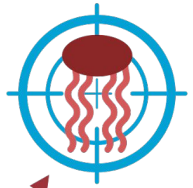
Results





Mitochondrial tropism

Cardiolipin affinity

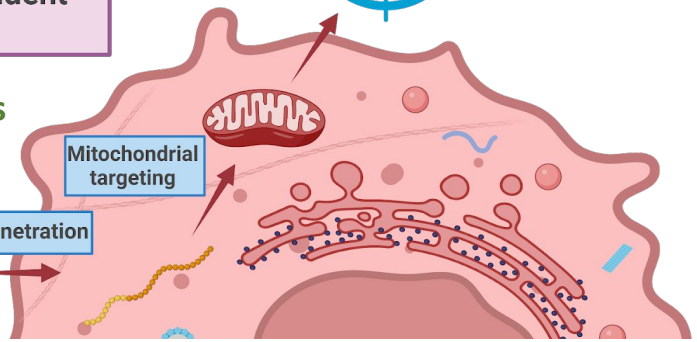


Antitumoral properties via a mitochondrial-dependent pathway

Universal and fast synthesis

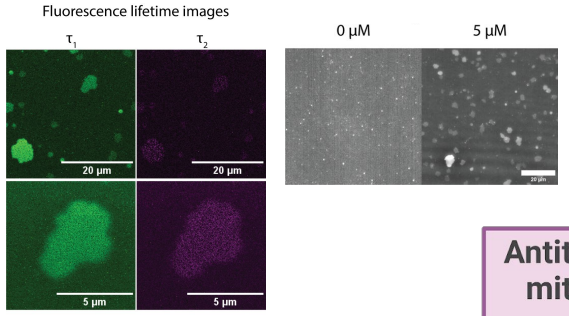
PP (PLO-PLP diblock copolymers)

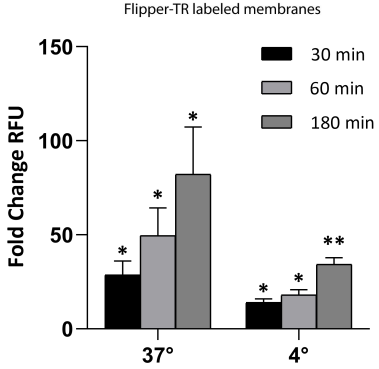
Direct penetration



C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

Results





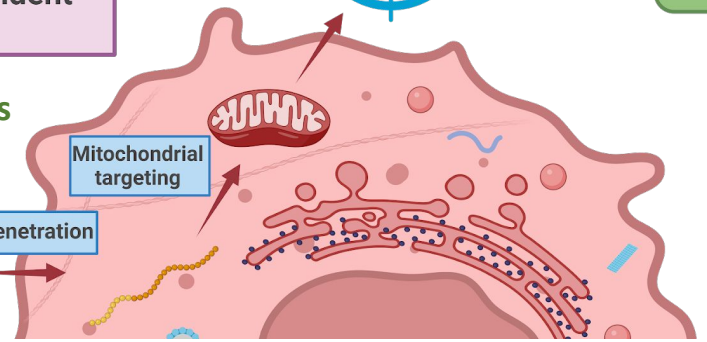
Mitochondrial tropism

Antitumoral properties via a mitochondrial-dependent pathway

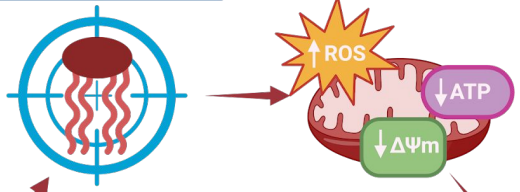
Universal and fast synthesis

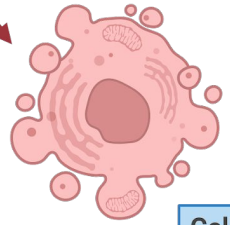
PP (PLO-PLP diblock copolymers)

Direct penetration



Cardiolipin affinity

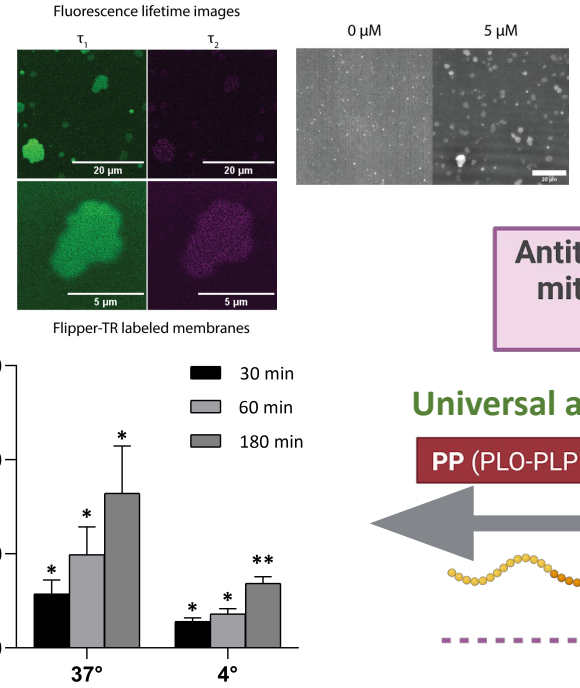


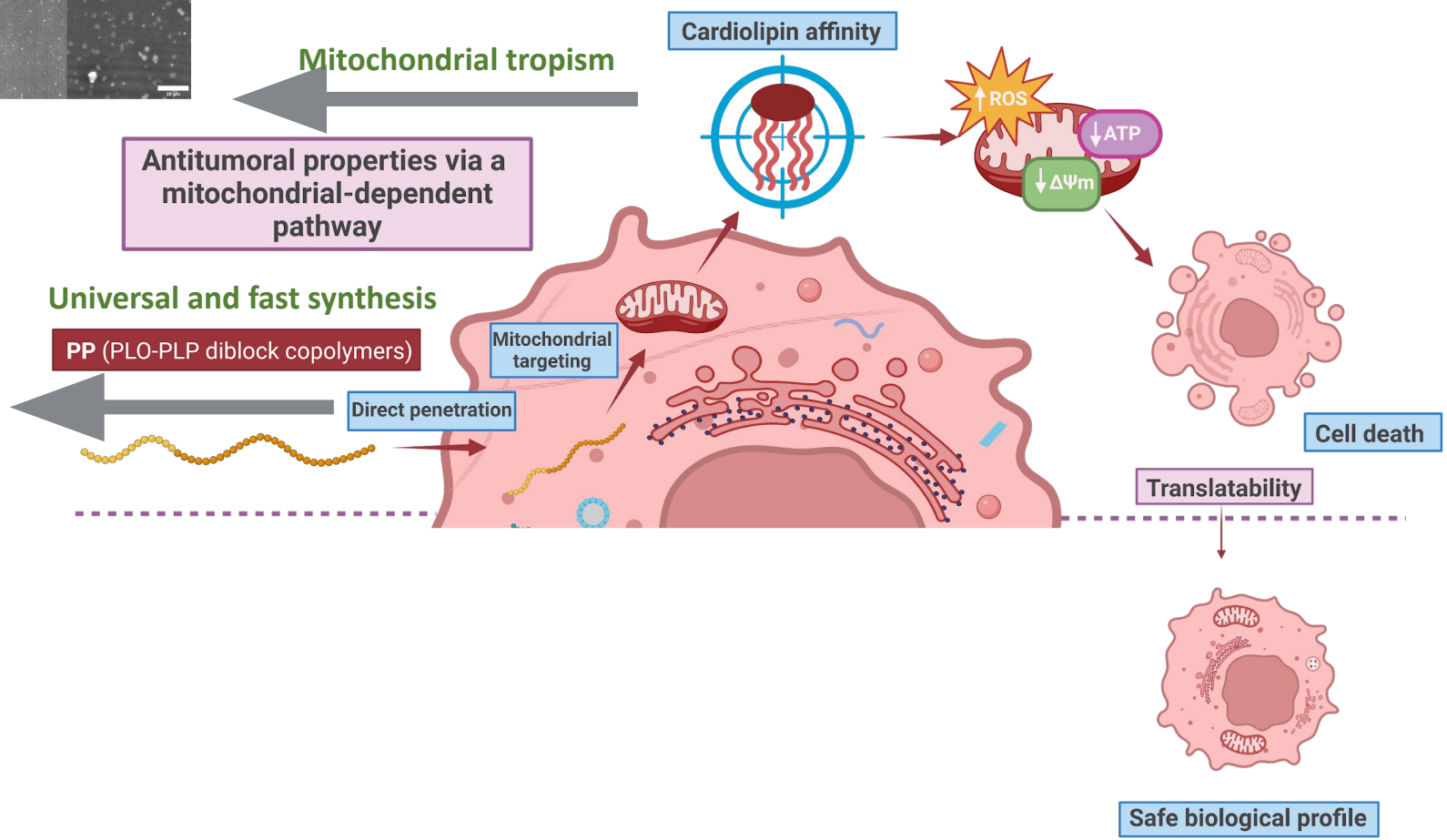


Cell death

C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

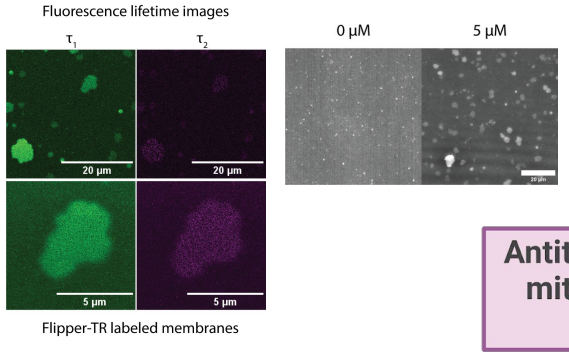
Results

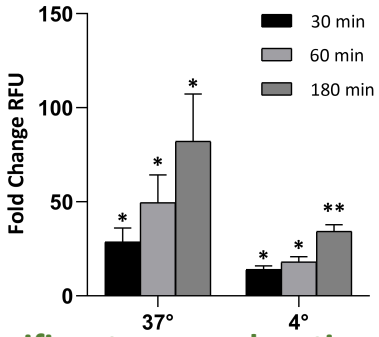




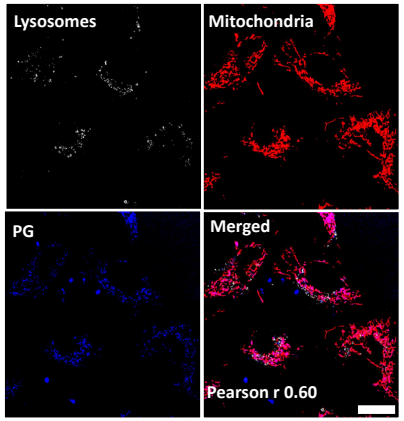
C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

Results





Significant non-endocytic uptake



Mitochondrial tropism

Antitumoral properties via a mitochondrial-dependent pathway

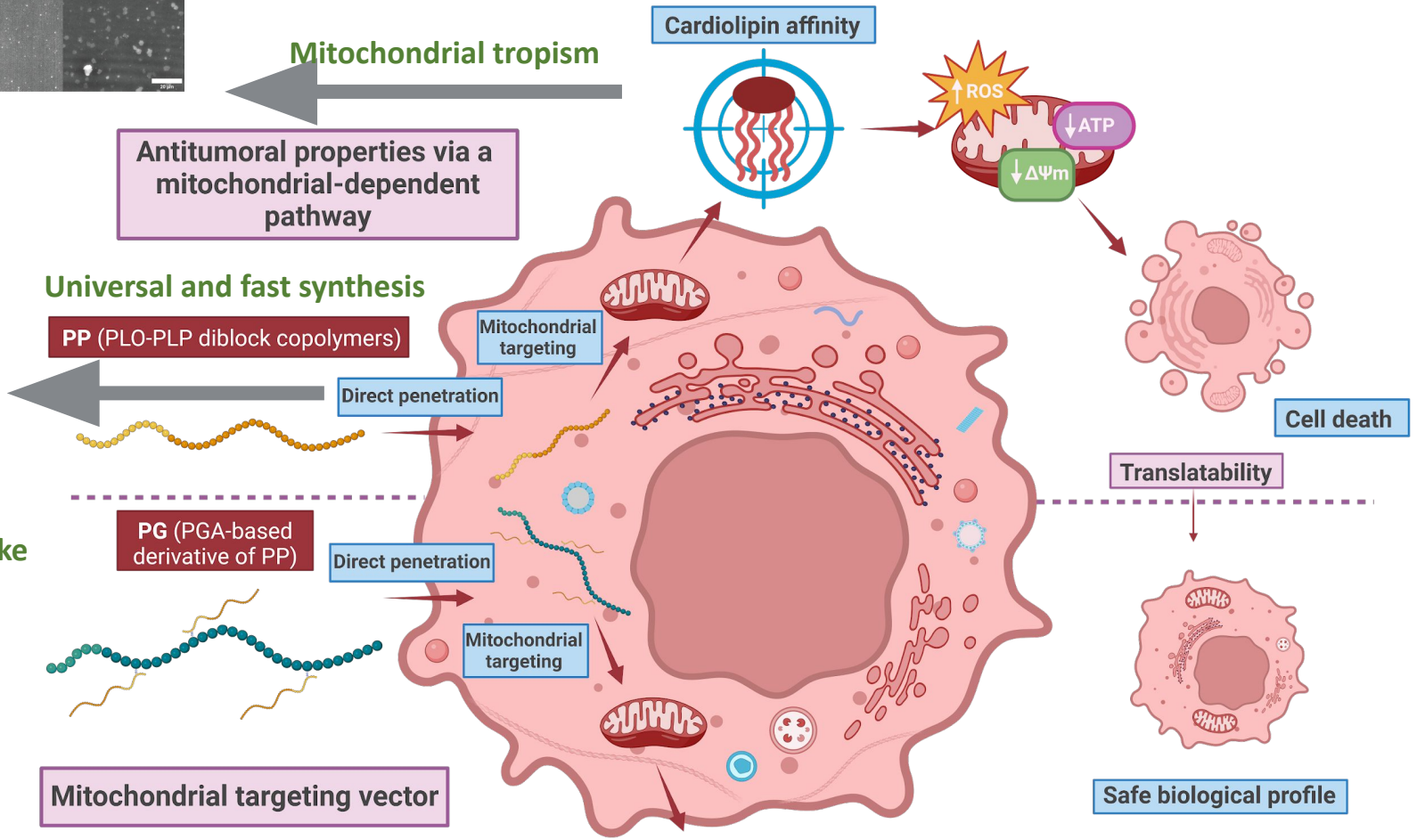
Universal and fast synthesis

PP (PLO-PLP diblock copolymers)

PG (PGA-based derivative of PP)

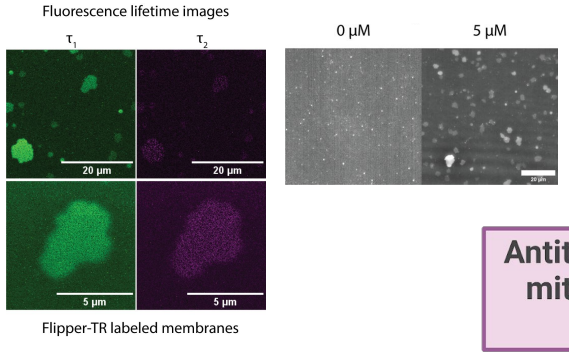
Mitochondrial targeting vector

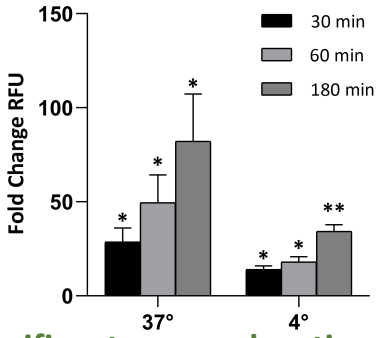
Mitochondrial targeting retained after PP conjugation (PG)



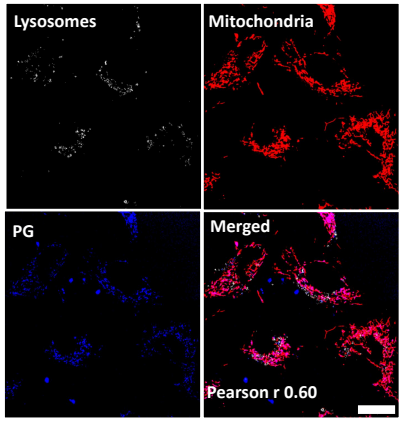
C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

Results





Significant non-endocytic uptake



Mitochondrial tropism

Antitumoral properties via a mitochondrial-dependent pathway

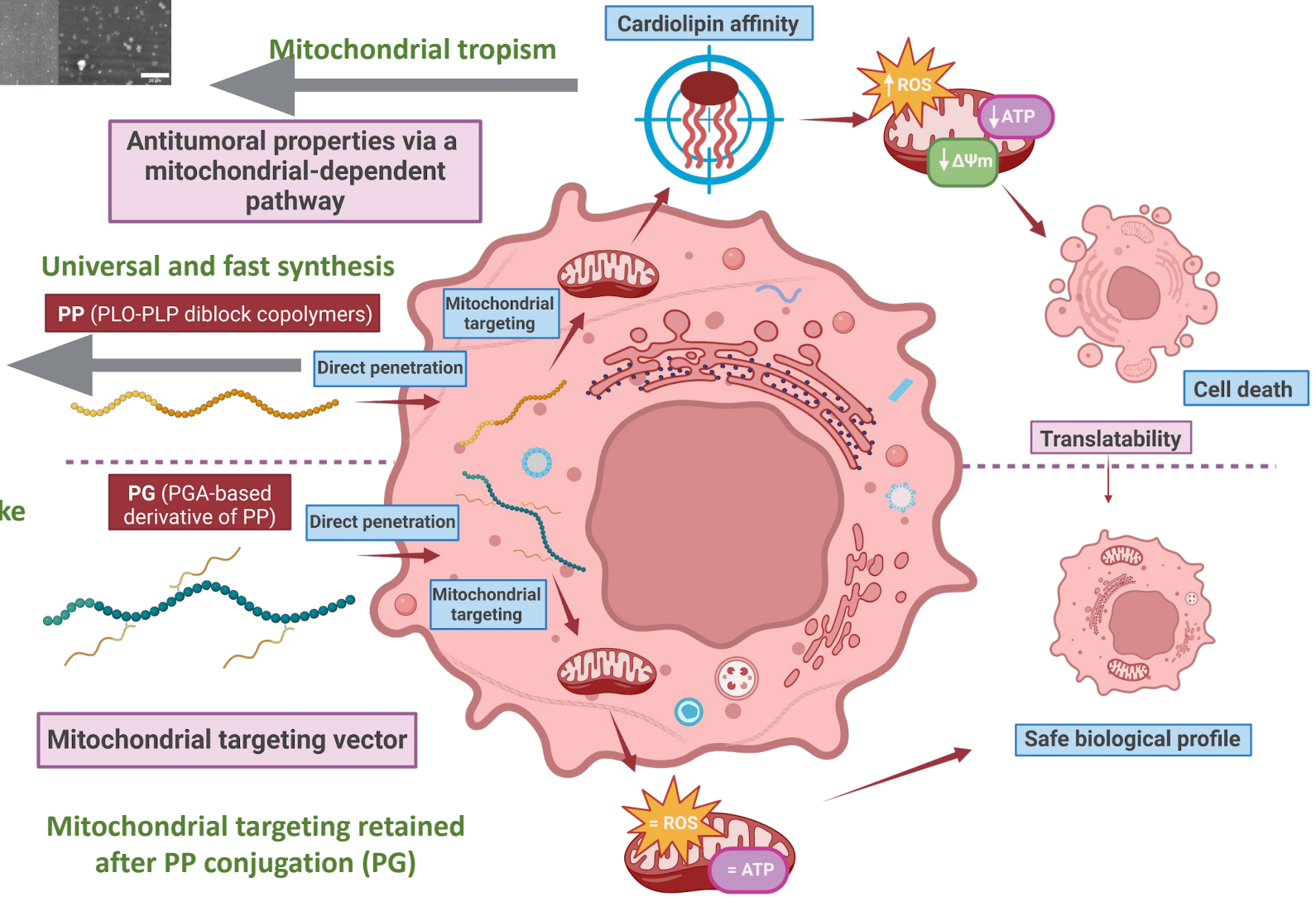
Universal and fast synthesis

PP (PLO-PLP diblock copolymers)

PG (PGA-based derivative of PP)

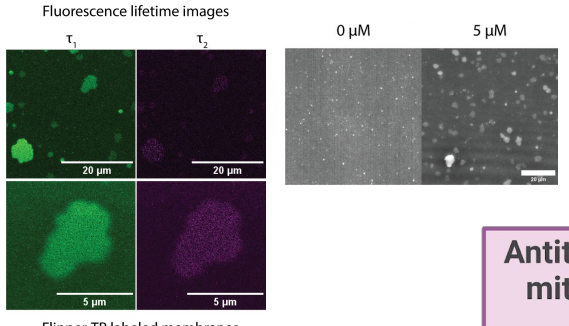
Mitochondrial targeting vector

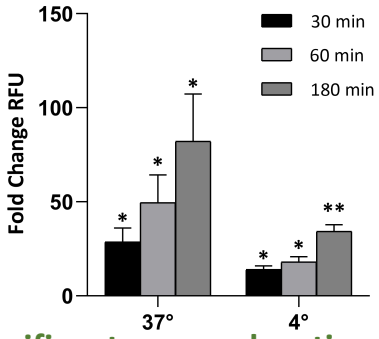
Mitochondrial targeting retained after PP conjugation (PG)



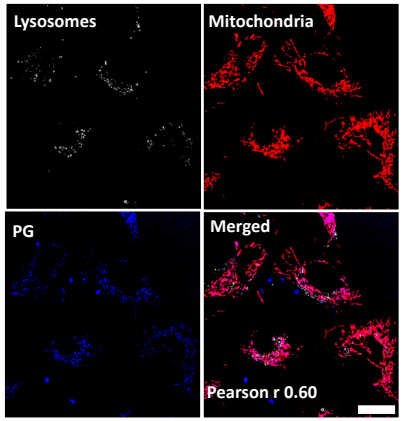
C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

Results





Significant non-endocytic uptake



Mitochondrial tropism

Antitumoral properties via a mitochondrial-dependent pathway

Cardiolipin affinity

Concentration-dependent antitumoral activity

ROS
ATP
ΔΨm

Universal and fast synthesis

PP (PLO-PLP diblock copolymers)

Direct penetration

Mitochondrial targeting

PG (PGA-based derivative of PP)

Direct penetration

Mitochondrial targeting

Mitochondrial targeting vector

Mitochondrial targeting retained after PP conjugation (PG)

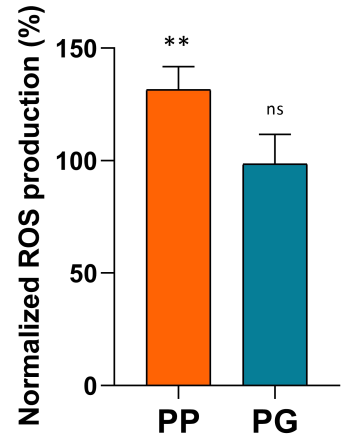
Cell death

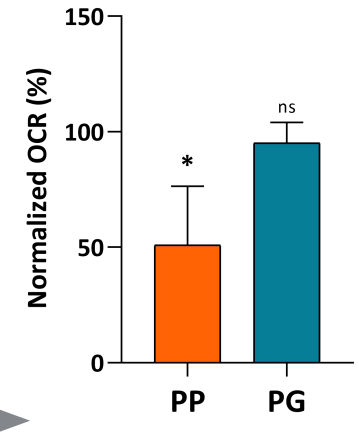
Translatability

Safe biological profile

= ROS
= ATP

Potential translation for non-cancer applications

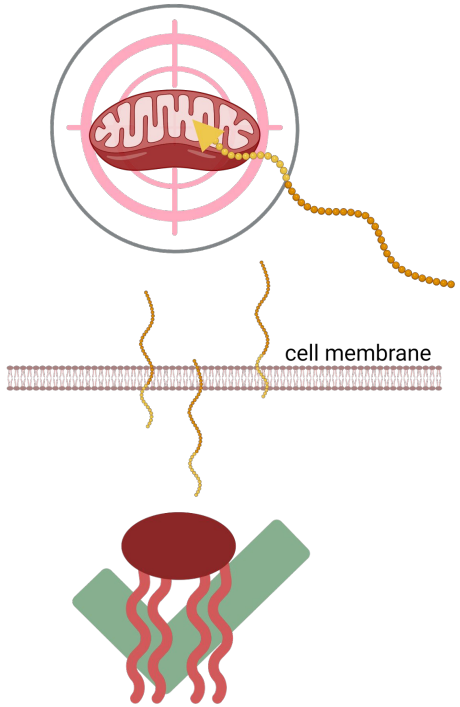




C. Pegoraro, I. Conejos Sánchez; M. J. Vicent, et al., Patent Application no. EP23382668.4; Filing date: June 29, 2023

Conclusions

- We developed a **universal, fast** (2-steps) **and easy to scale-up synthesis method** for a family of **diblock copolymers (PP) based on Polyornithine (PLO) and Polyproline (PLP)** that **inherently targets mitochondria** without the need of moiety functionalization
- We demonstrated that our selected carrier (PP) can enter cells through an **energy-independent uptake mechanism**
- We proved that our selected carrier (PP) targets mitochondria through a **cardiolipin-specific potential-independent mechanism**

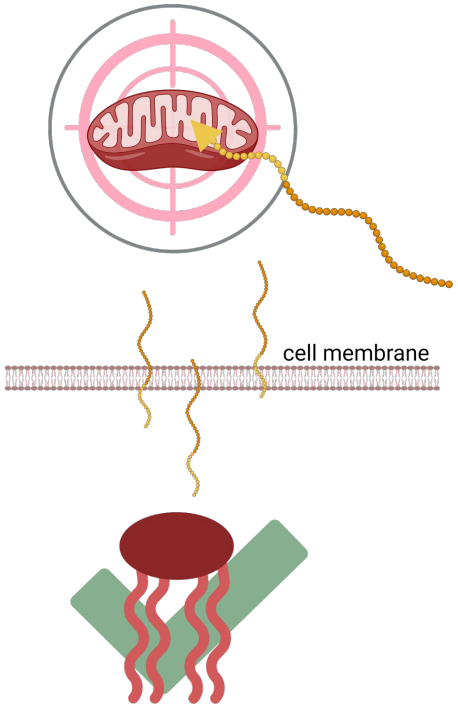


Conclusions

- We developed a **universal, fast** (2-steps) **and easy to scale-up synthesis method** for a family of **diblock copolymers (PP) based on Polyornithine (PLO) and Polyproline (PLP)** that **inherently targets mitochondria** without the need of moiety functionalization

- We demonstrated that our selected carrier (PP) can enter cells through an **energy-independent uptake mechanism**

- We proved that our selected carrier (PP) targets mitochondria through a **cardiolipin-specific potential-independent mechanism**

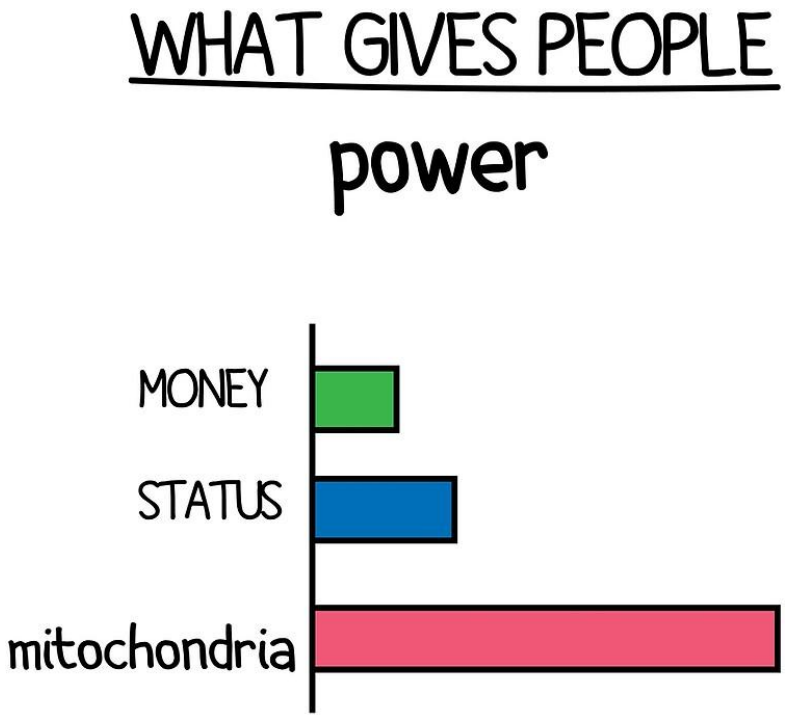


In addition:

We demonstrated that our selected carrier has **concentration-dependent antitumoral activity** at the mitochondria level, making it a potential anti-cancer polypeptidic drug.

We designed and synthesized **a non-toxic conjugate (PG) derivative of PP** as a proof of concept for the **translation of the diblocks to preclinical models**

Thanks for your attention!



Visit poster number 339 and scan the QR code for more information and get in touch!

This project is supported by the H2020-MSCA-ITN-2019 BIOMOLMACS (proposal n° 859416) and NextGeneration EU i+d+I funding through GVA Conselleria Innovació. Materiales con funcionalidades avanzadas para la nueva transformación tecnológica. Pol@Mets. Ref. MFA/2022/065