

Palma Rocchi
Inserm Research Director



mRNA targeting Nanomedicine

“From cell signaling to personalized therapy”

COST ACTION CA 1714

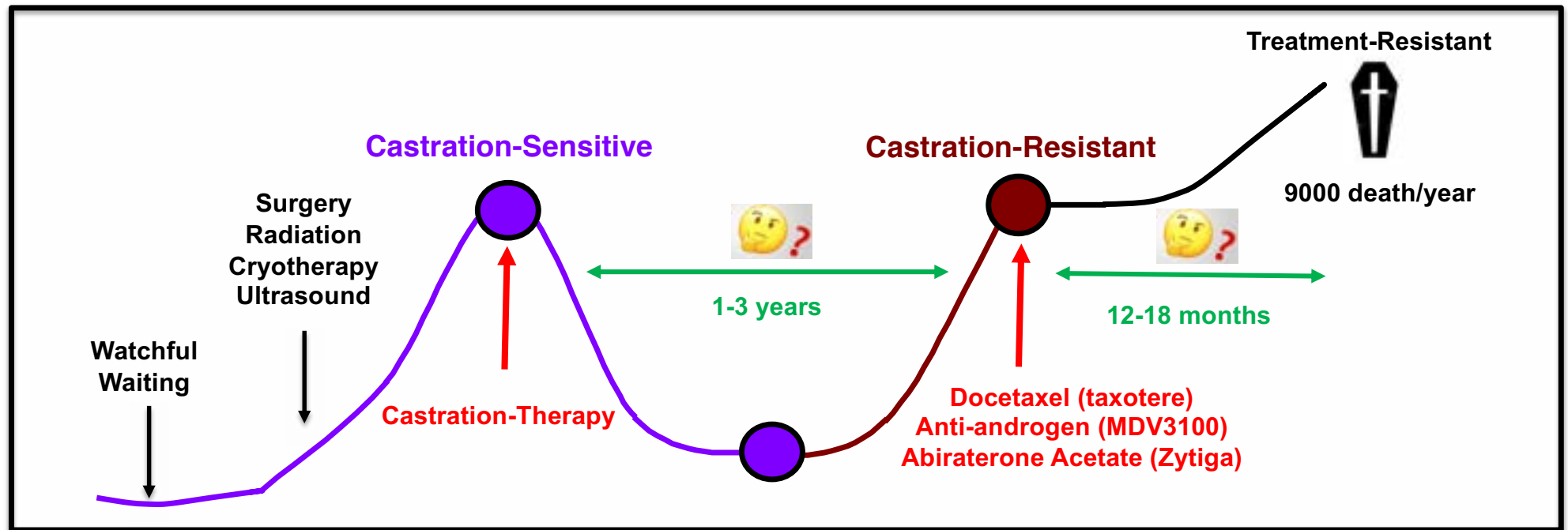
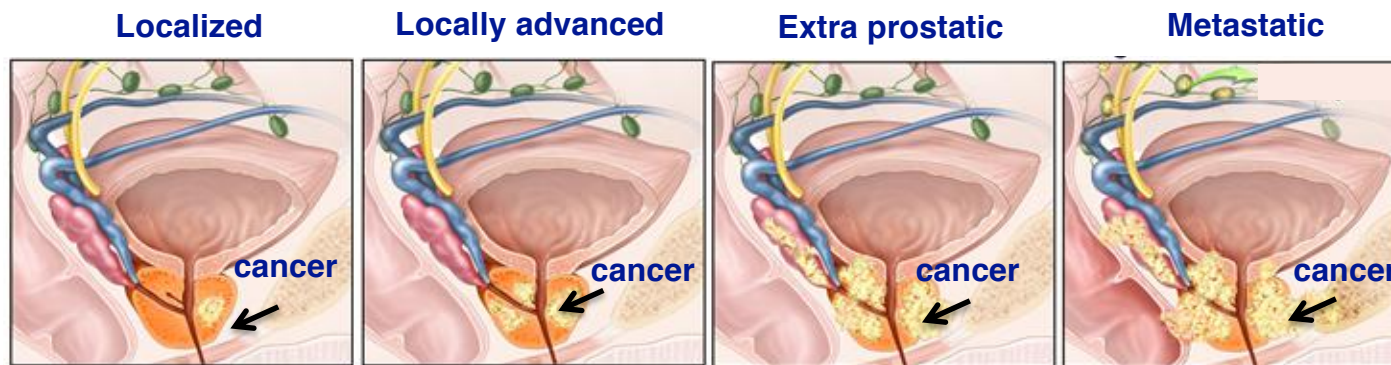
**NANO2CLINIC
CANCER NANOMEDICINE
FROM THE BENCH TO BEDSIDE**

March 25th, 2022

Prostate Cancer is the Most Frequent and third cause of mortality by Cancer in France

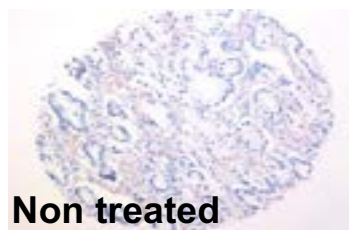
72000 new case/year

40% at diagnostic (43000 new case/year)



Previous Work

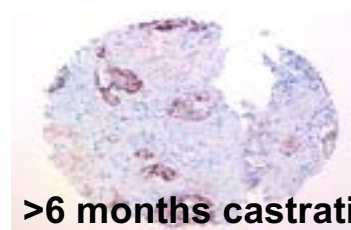
Heat Shock Protein 27 (Hsp27) is overexpressed in Castrate-Resistant Prostate Cancer (CRPC)



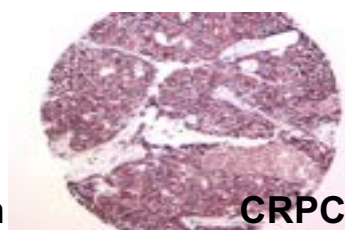
Non treated



3-6 months castration



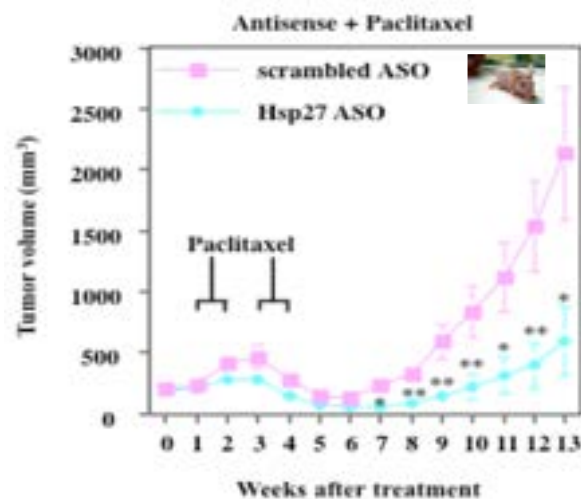
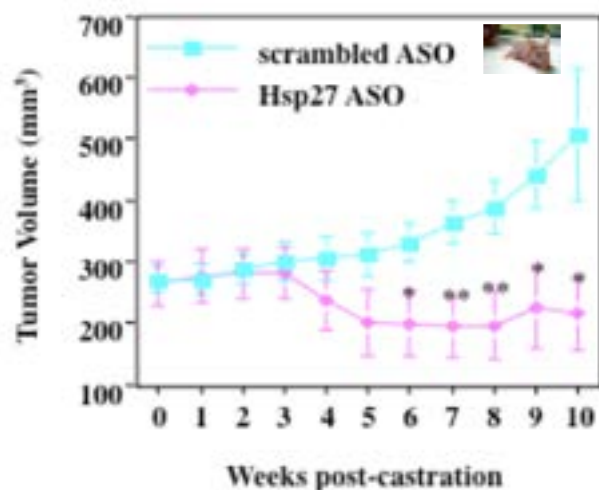
>6 months castration



CRPC



Oligonucleotide antisens (ASO) against HSP27 enhances castration- and docetaxel-therapy



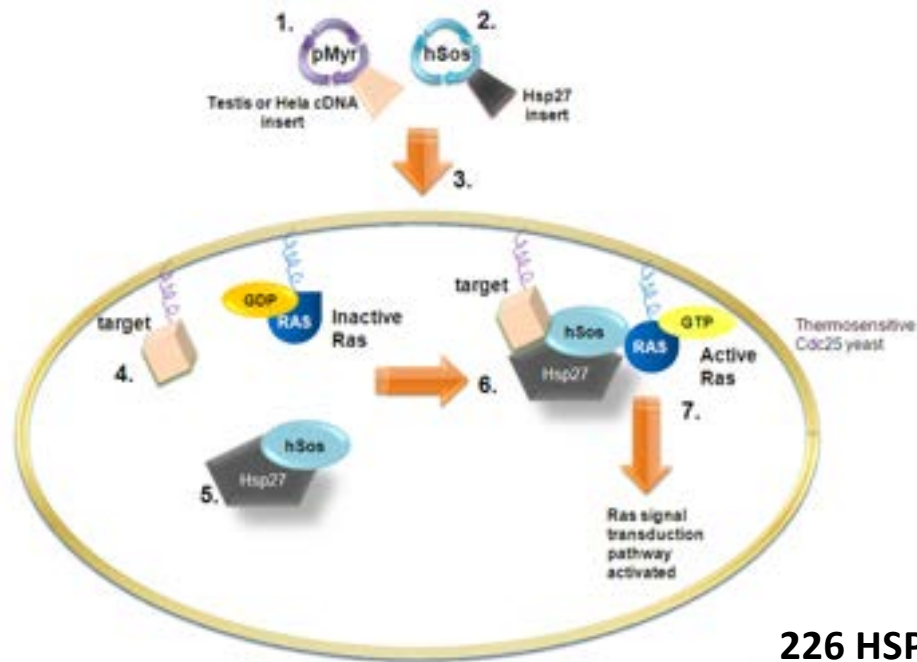
HSP27 ASO has been patented by UBC and licenced by Oncogenex (OGX-427, Apatorsen)



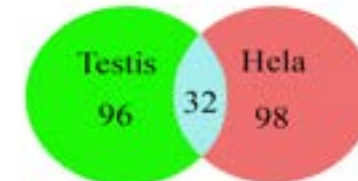
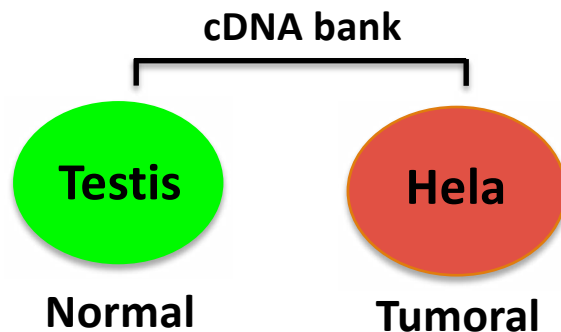
OGX-427 has been tested in clinical trial phase II on CRPC.

Rocchi, P., Cancer Res., 2004 and 2005; International Patent PCT no 10/605

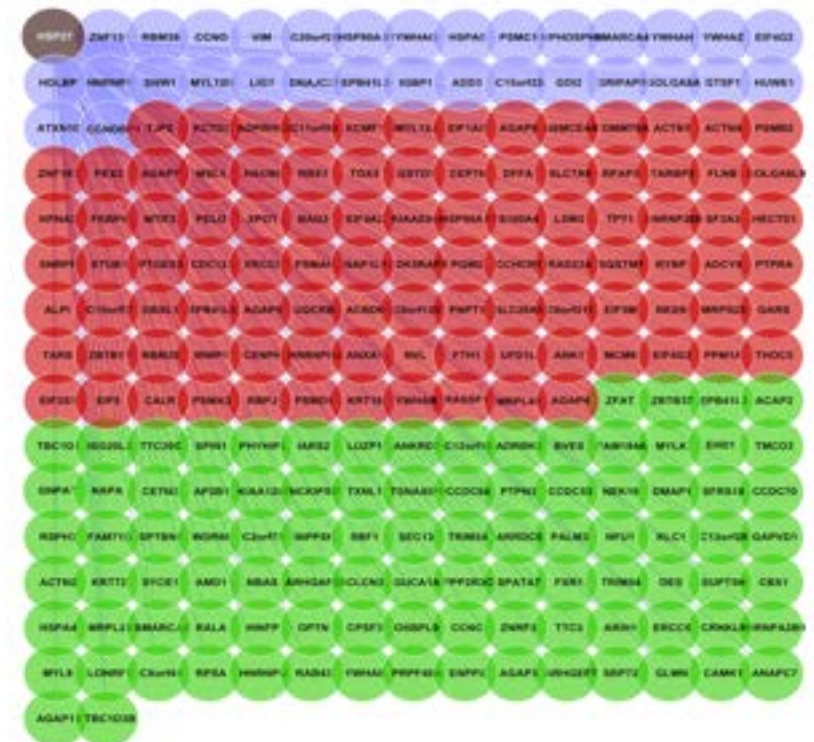
Large scale Hsp27 protein partner identification using cyrotrap two hybrid system



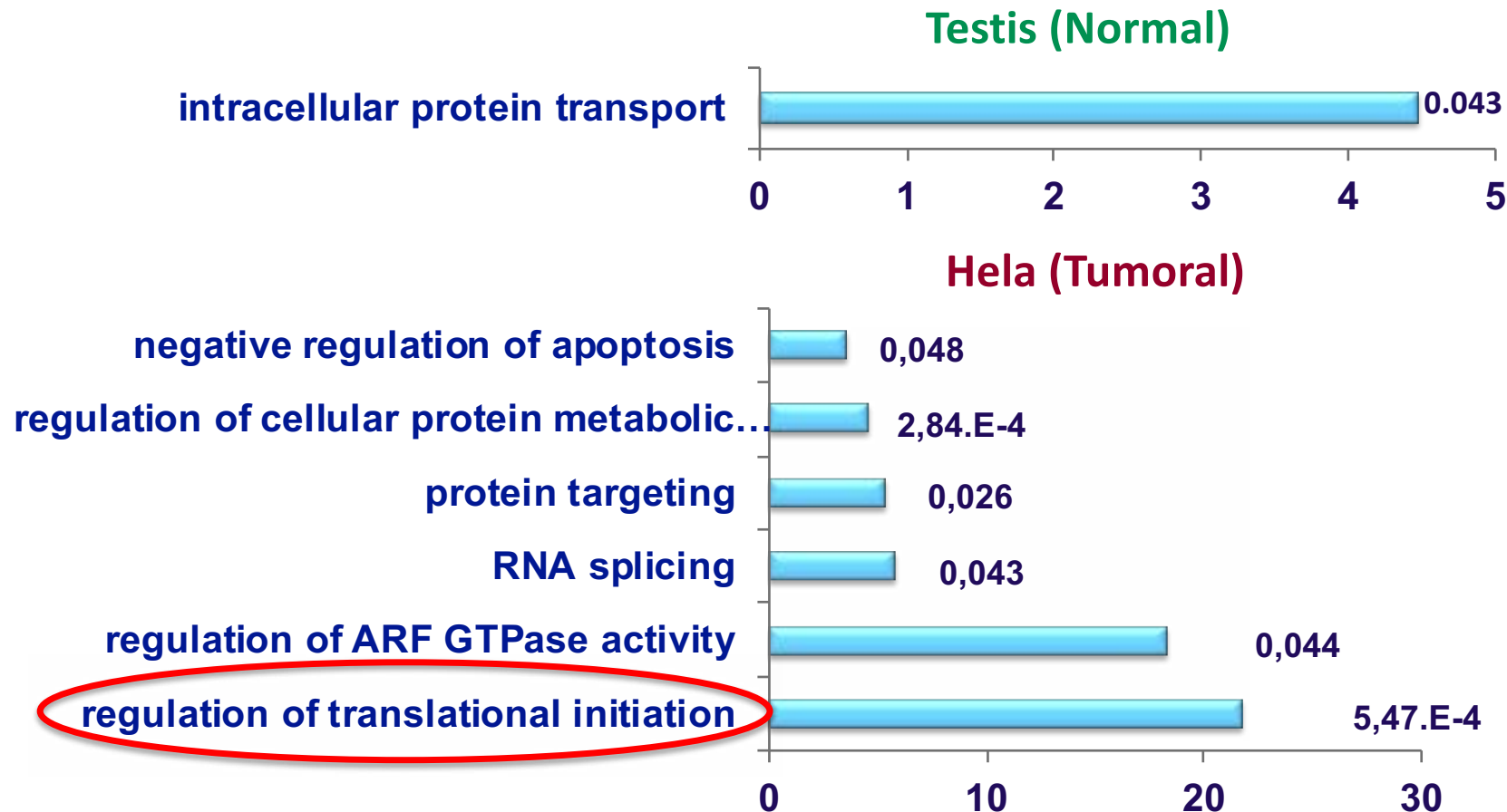
**226 HSP27 partner
proteins**



5 x 10⁶ clones tested



Hsp27 partner proteins functions analysis using DAVID



DAVID Bioinformatics Database (<http://david.abcc.ncifcrf.gov/>)

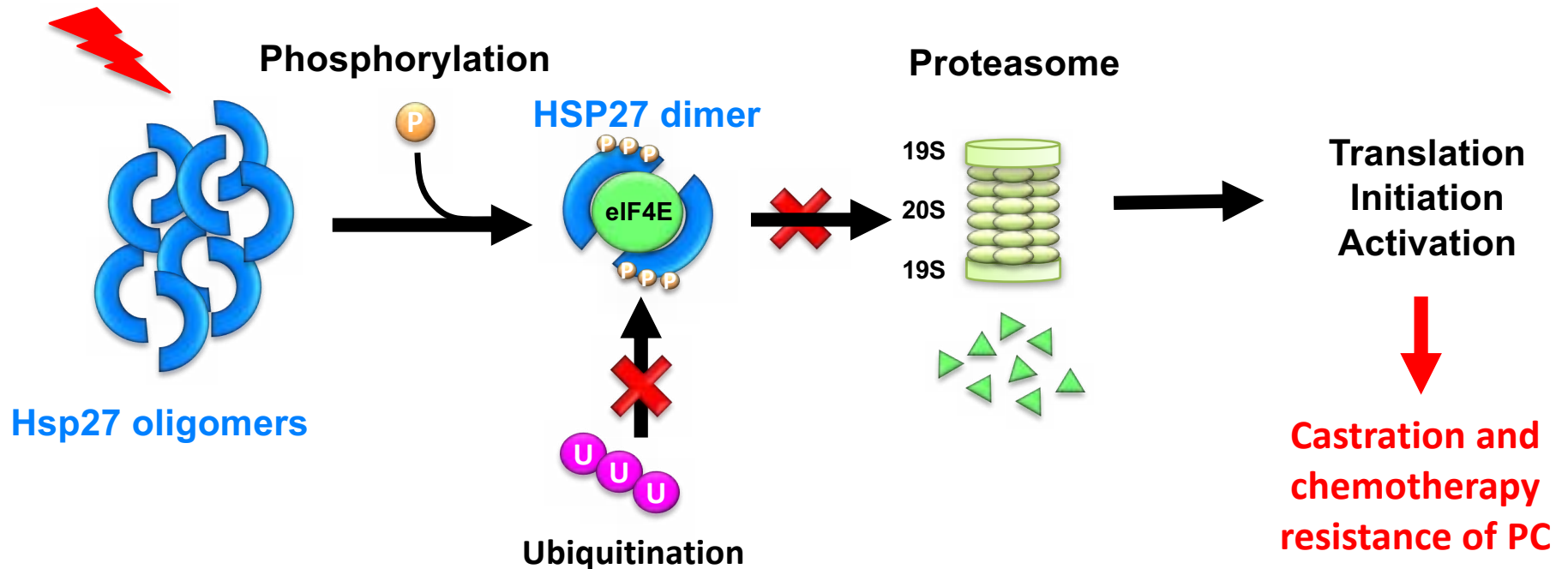


Y2H Hsp27

Katsogiannou M., Molecular and Cellular Proteomics, 2015

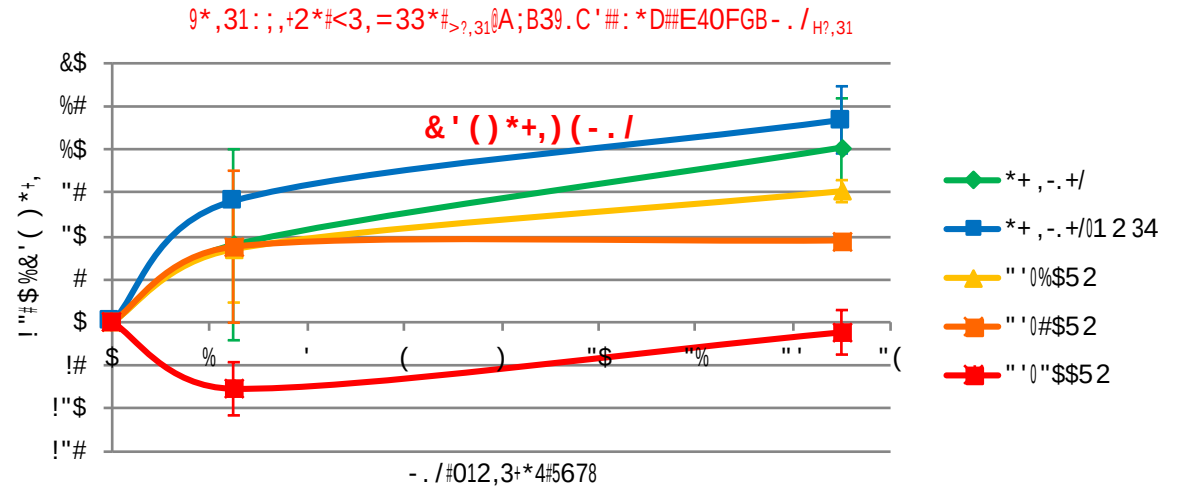
HSP27 activates protein translation initiation and treatment resistance of CRPC

**Cellular Stress:
Castration,
Chemotherapy**

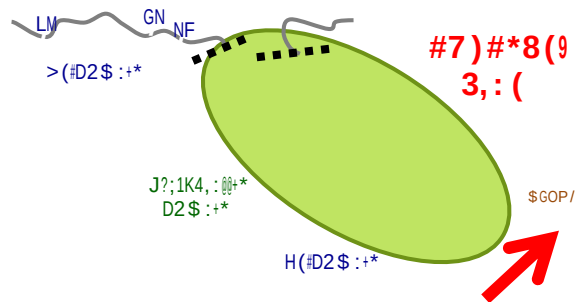


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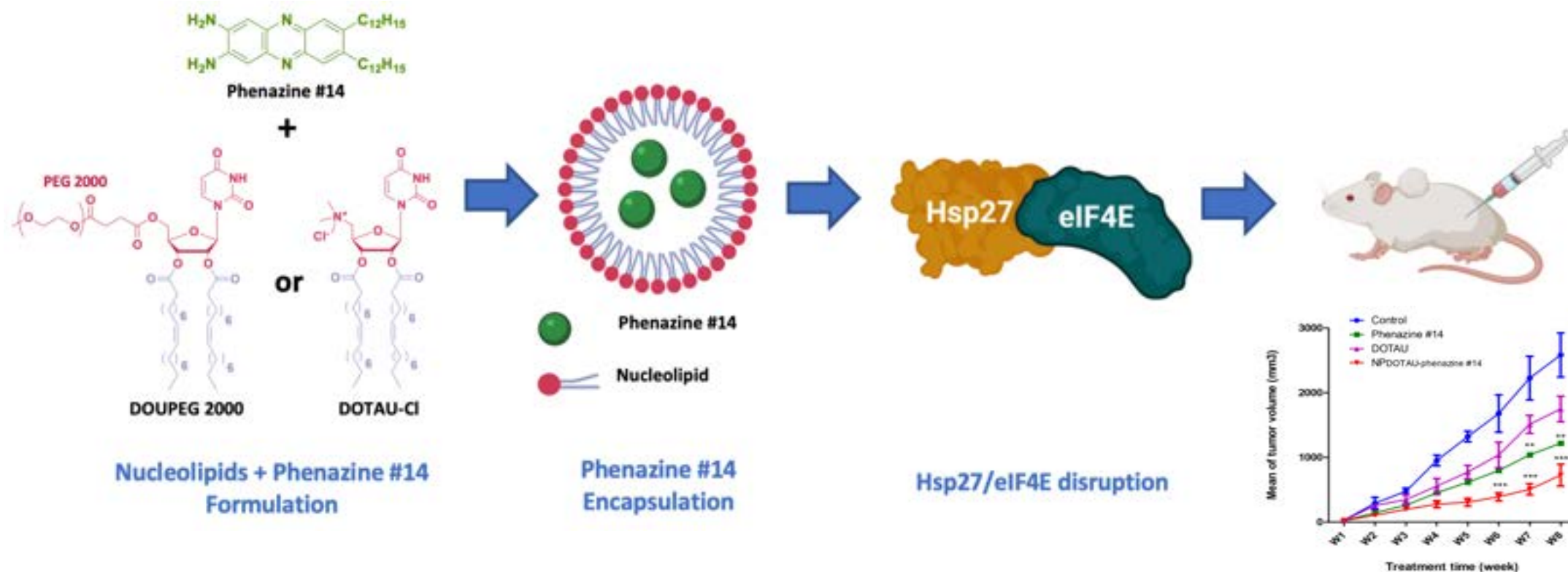


Dr Olivier Siri
chimiste



Nucleoside-Lipid-Based Nanoparticles for Phenazine Delivery: A New Therapeutic Strategy to Disrupt Hsp27-eIF4E Interaction in Castration Resistant Prostate Cancer

Dr Michel Camplo
Marseille



Pr. Philippe Barthélémy
Chimiste des ON
Université de Bordeaux

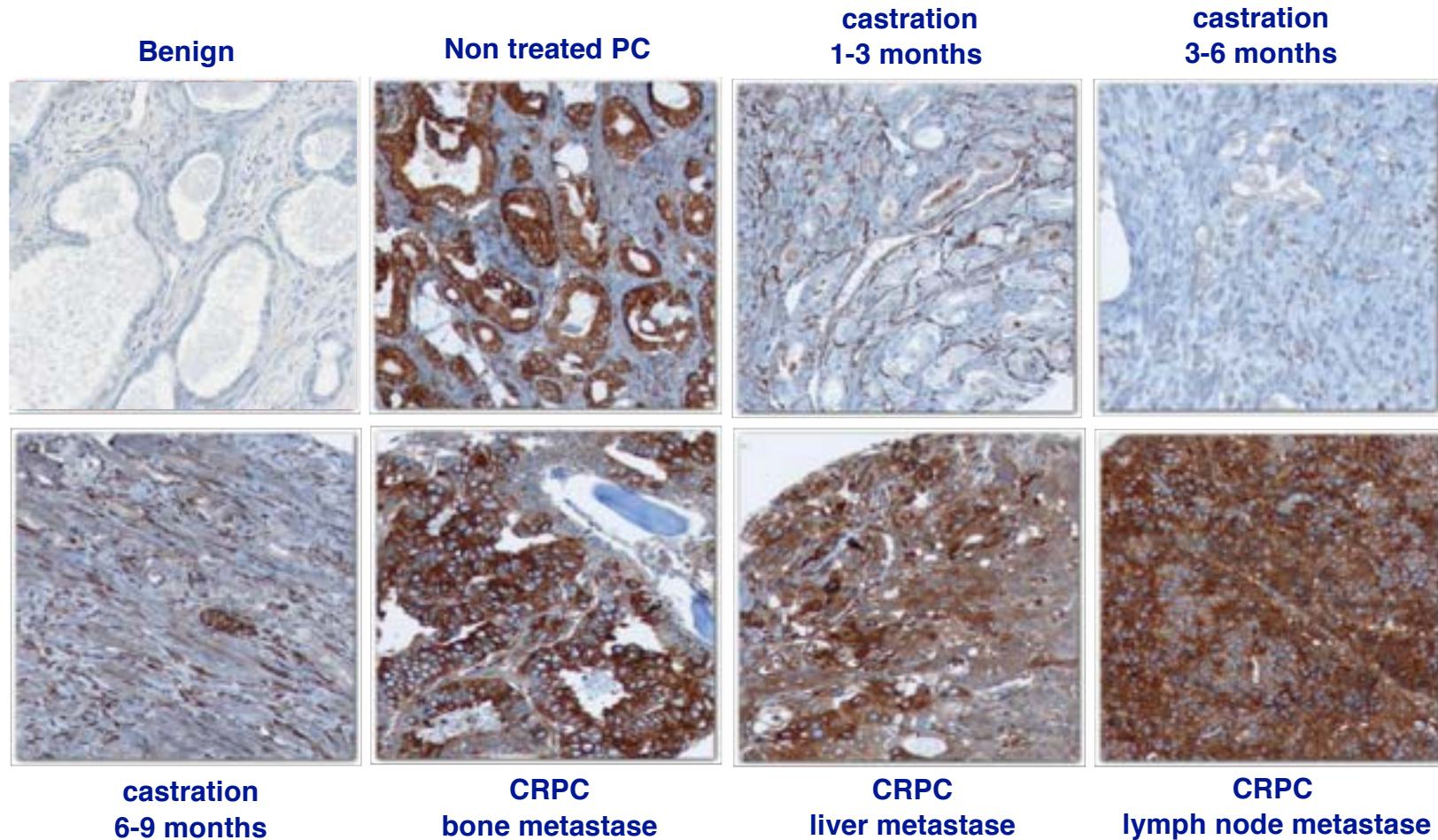


Projet PAIR prostate
Coordonateur (1 050 K€)

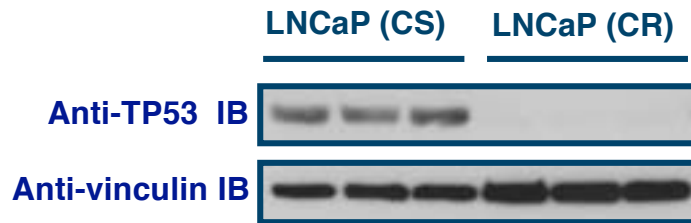
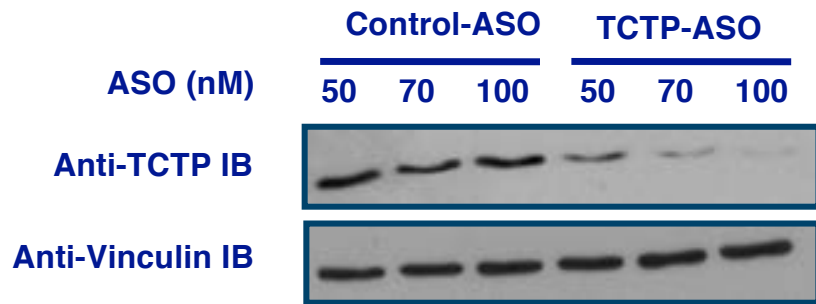
Ziouziou, H., Pharmaceutics 2021; Patent BET 16P0495 (3)

Hsp27 interactome analysis identify TCTP as novel therapeutic target in CRPC

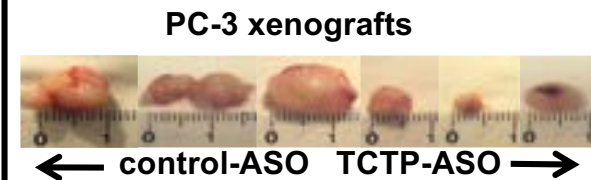
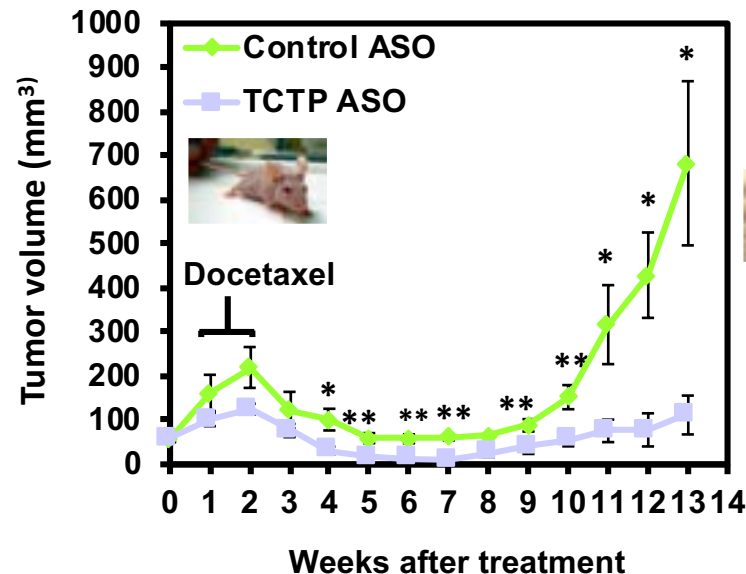
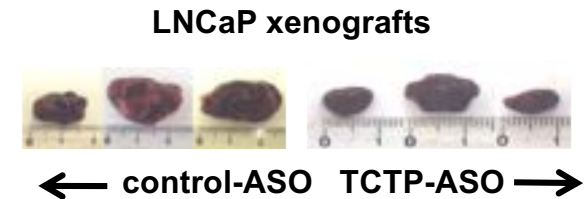
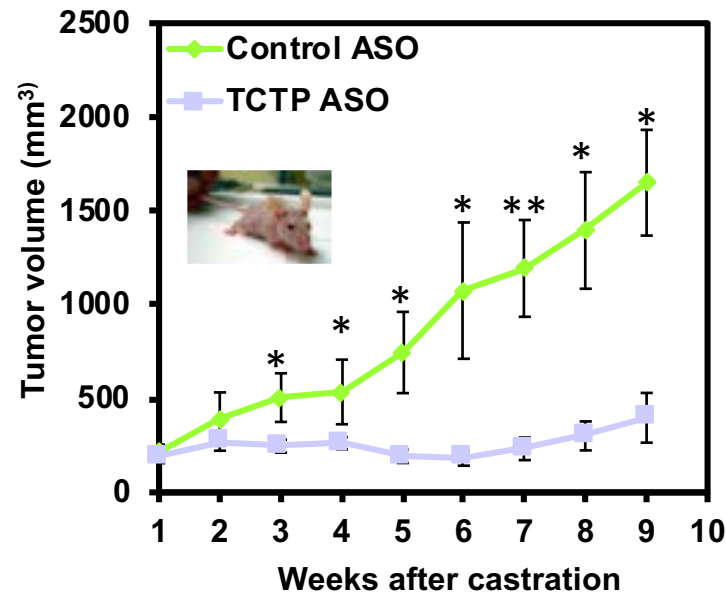
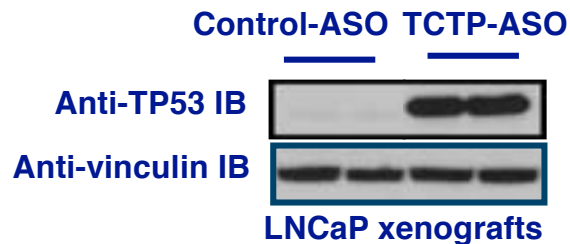
Tissue Micro Array of 212 **castration-treated specimens**



TCTP-ASO treatment inhibits CR LNCaP progression after castration *in vivo* by restoring p53 expression



Xenografts



Challenge in ASO therapy

Although **clinical relevance** of ASO has been **demonstrated**

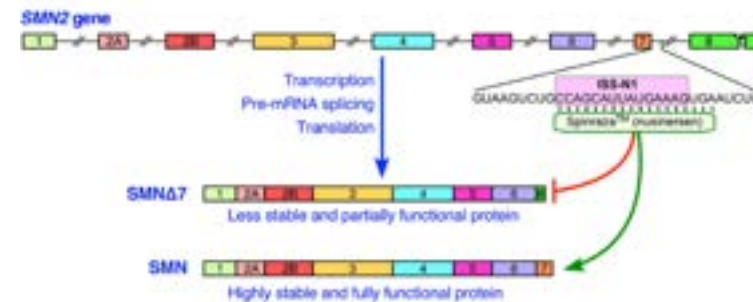


Spinraza/Nusinersen (Biogen) in neurologic muscular dystrophy (SMA=spinal muscular atrophy) against mutated SMN gene (survival motor neuron)



Antisense rescues babies from killer disease

Meredith Wadman (Science, December 15, 2016)



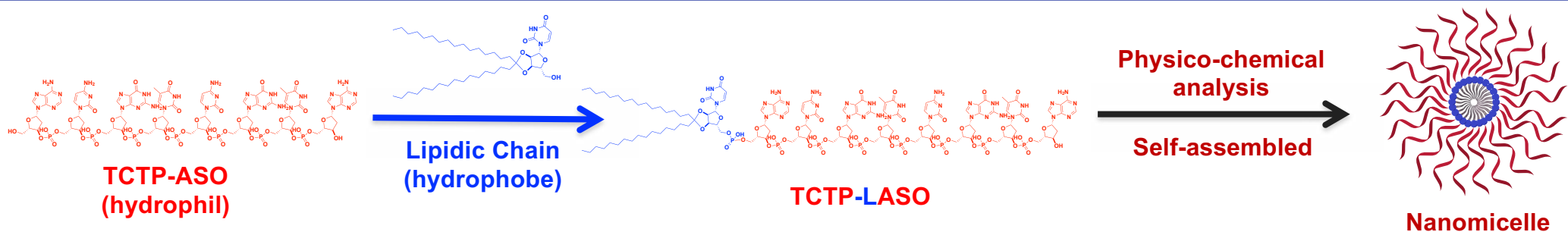
Poor intracellular delivery limits its efficacy



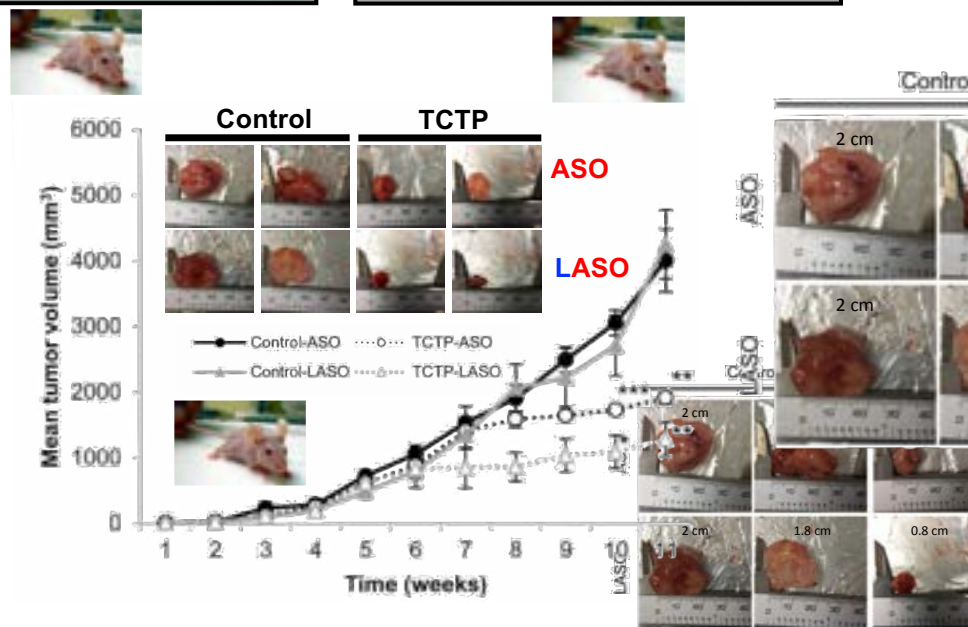
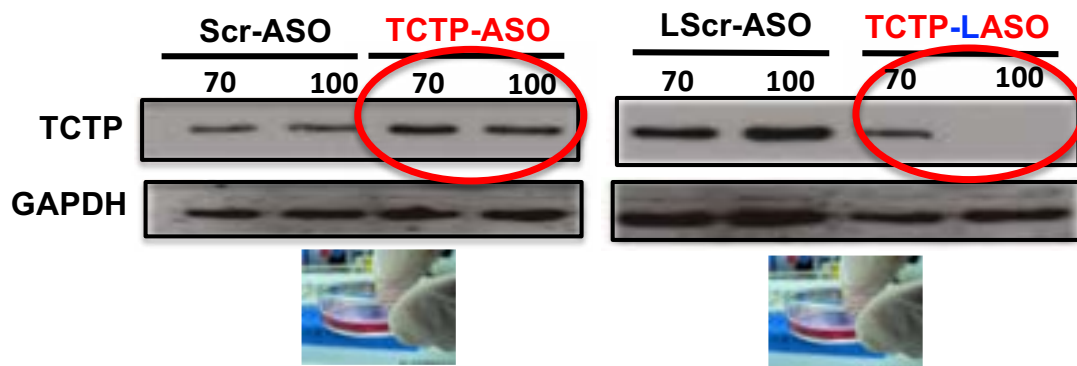
Pr Philippe Barthelemy
Bordeaux



TCTP-ASO Efficacy Improvement



Transfection
without oligofectamin



Karaki, S., Journal of Controlled Release 2017
Patent PCT001517, 2013 (5)



Emergence



Animals: mice xenografted with PC3 (hormono- res
animals/ group
Treatment: IP injection; 10mg/kg; daily injection



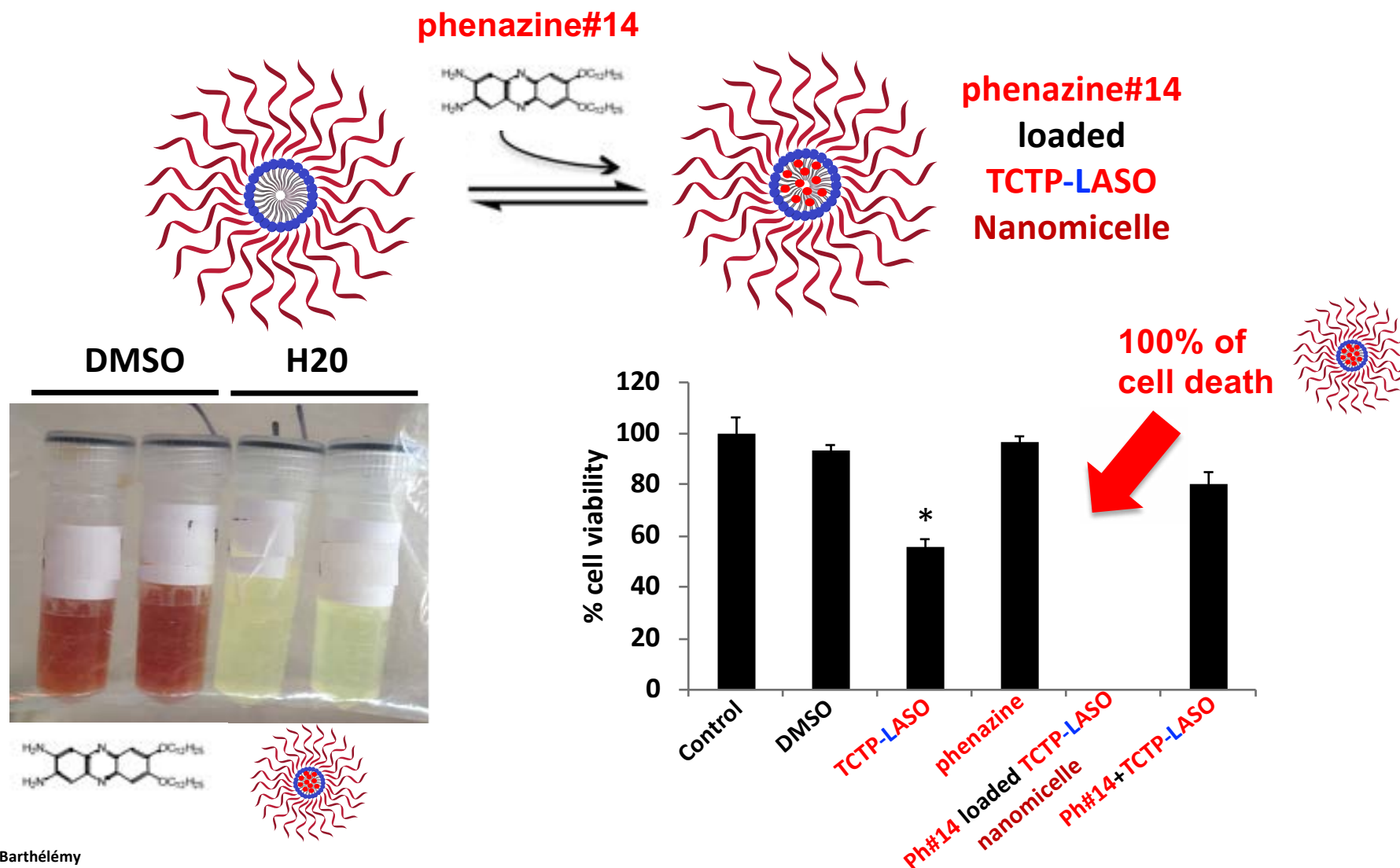
Dr Olivier Siri
Marseille



Dr Michel Camplo
Marseille



ASO nanomicelle can serve as delivery system



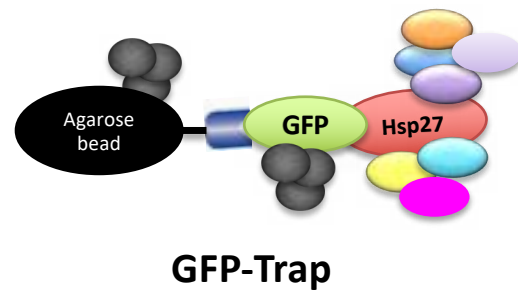
Pr. Philippe Barthélémy
Chimiste des ON
Université de Bordeaux



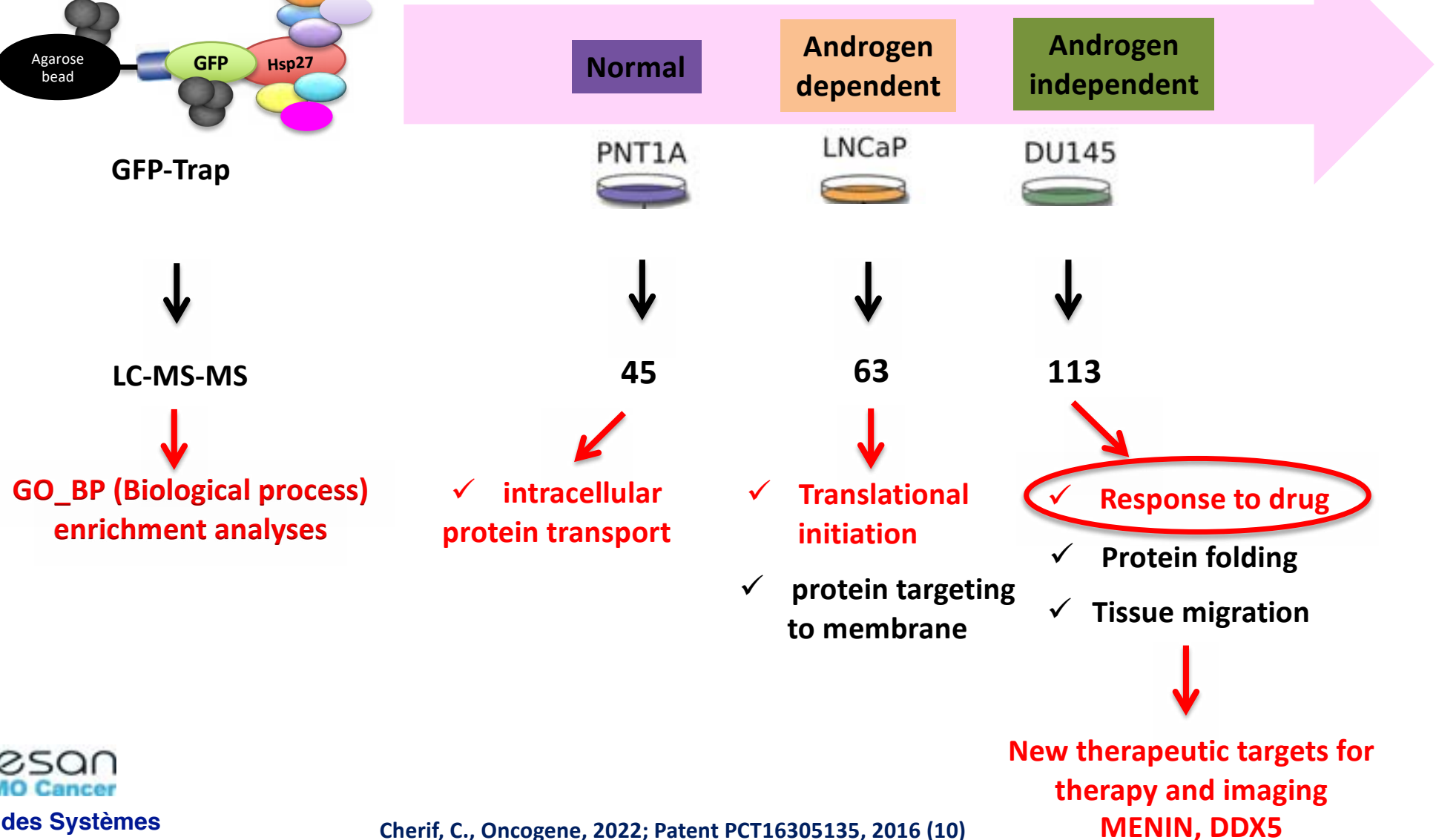
maturation

Branger, N., Patent PCT16349, 2018 (6)

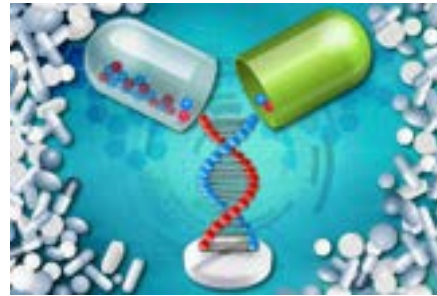
Project 1: Hsp27 interactome identification during PC progression using GFP-Trap



Prostate Cancer Progression



Project 2: ASO nanomicelle development for personalized medicine of PC



Projet PerMed
100K€/an



Projet Nano-S
PI (300K€)



Pr François Bertucci
IPC



Dr Gwenaëlle Gravis
IPC



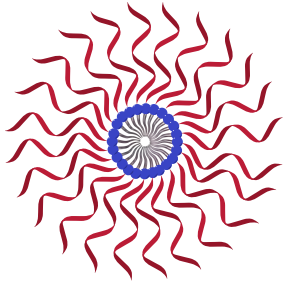
Pr Cyril Bastide
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Michaël Baboudjan
MD Urologist
PhD student



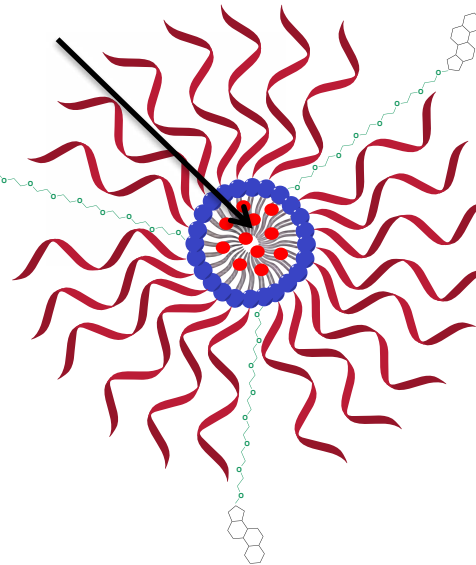
Project 3: ASO nanomicelle optimization for active delivery of chemotherapy



ARNm thérapeutique
Projet mRNAnanoPC
Coordonateur (478K€)

● small molecules:
Phénazine 14...

Active targeting:
PSMA peptide ...



Project NanoTRAFFIC
PI (25K€)



Projet SmartPSMA
Coordonateur (499K€)



Project NucleoTher
PI (460K€)



Projet NucleoTher
PI (20K€)



Dr Olivier Siri
Chemist



Dr Michel Camplo
Chemist



Pr. David Taïeb
Nuclear Medicin
AMU-CRCM-Cerimed



Pr. Benjamin Guillet
Radiopharmacist
AMU-Cerimed



Pr. Philippe Barthélémy
ASO Chemist
Bordeaux University



2020-2022 Years of Nucleic Acids: Demand Growth and New Technology

Chemistry Nobel Prize, 2020



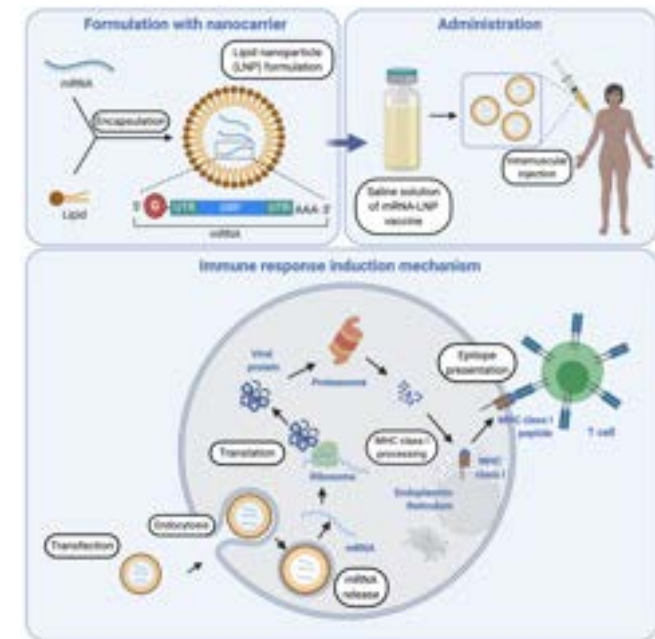
Emmanuelle Charpentier, Jennifer Doudna



Crispr Cas9

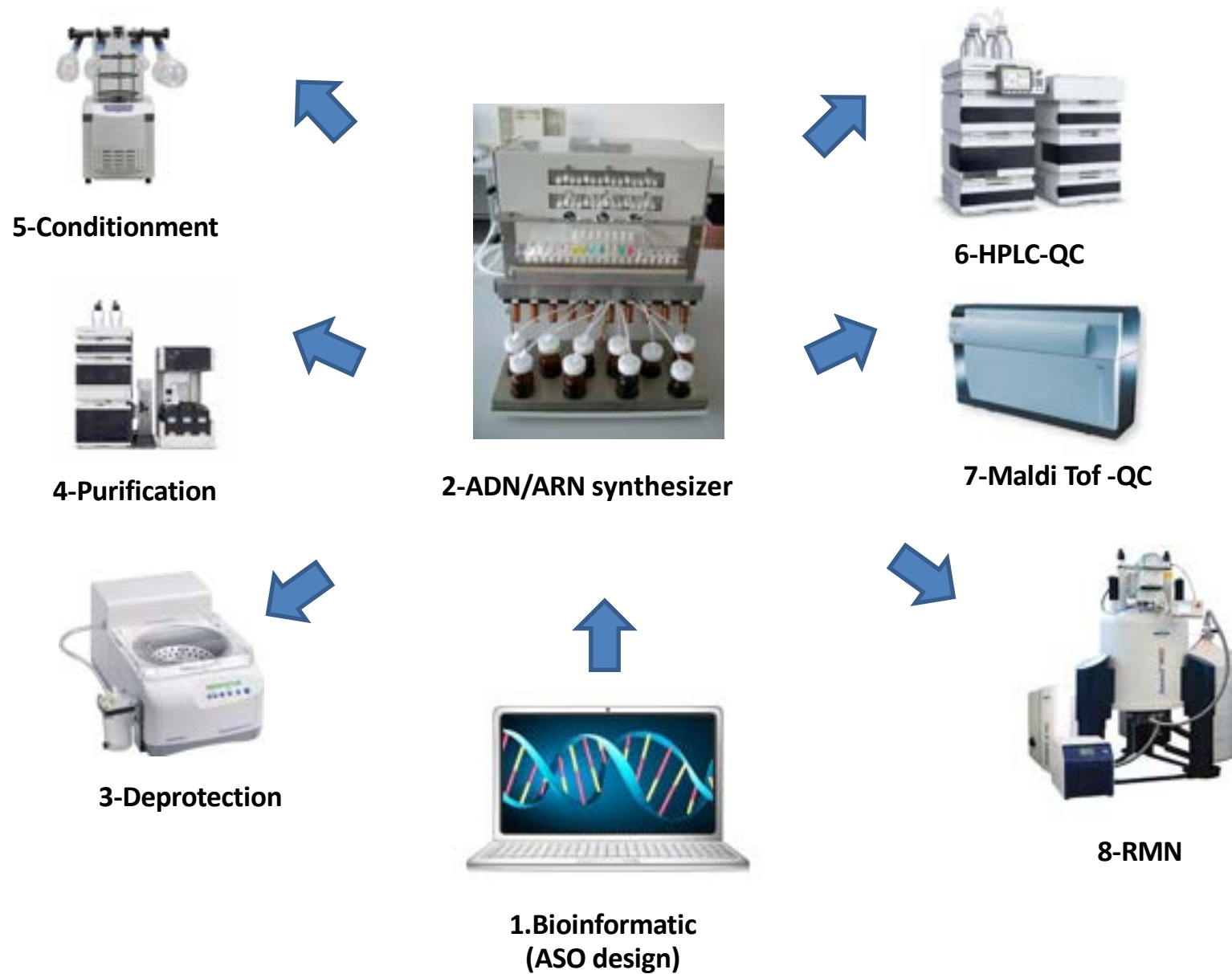


Katalin Kariko

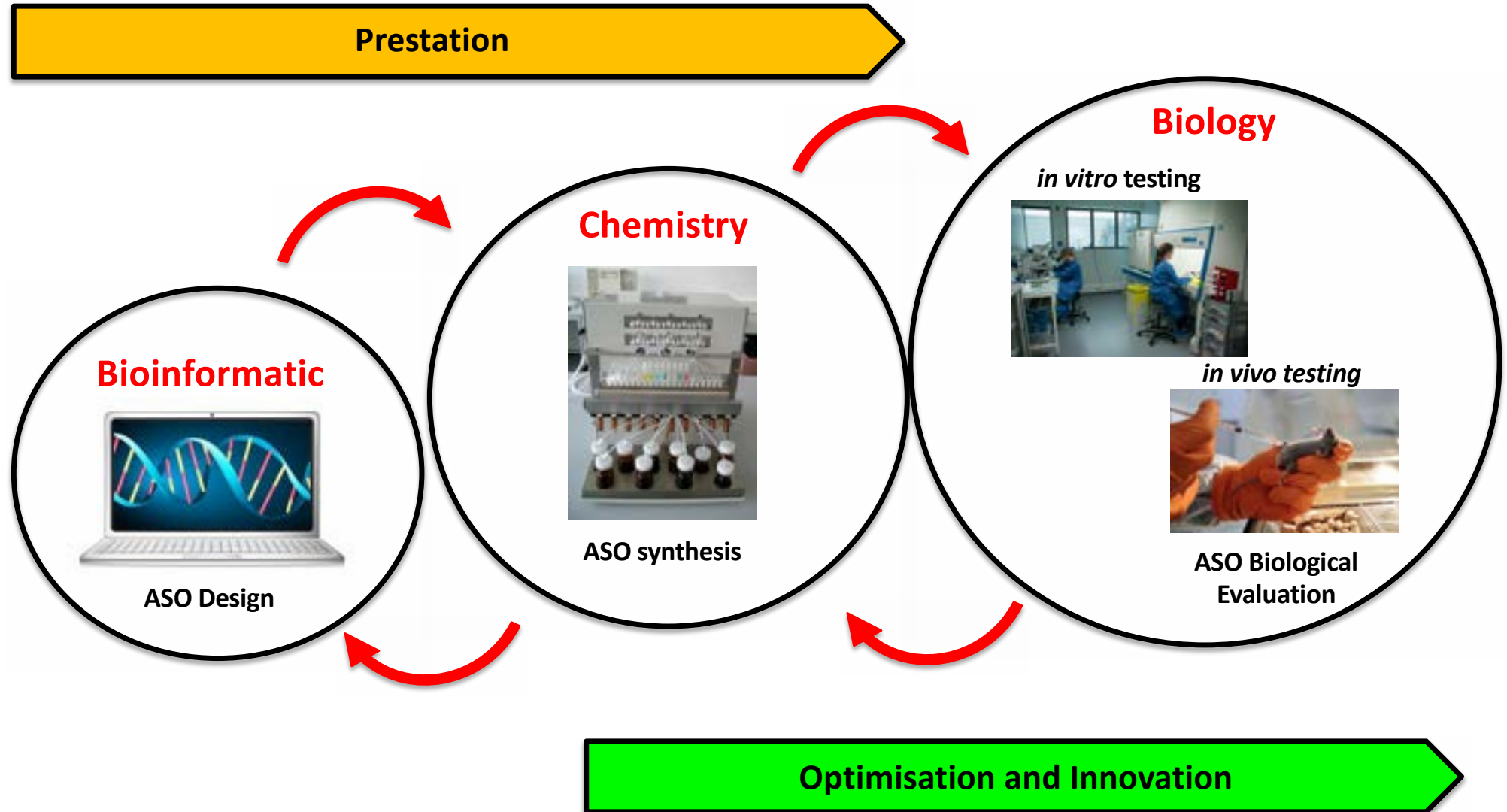


Covid-19 mRNA vaccine, moderna

Therapeutic ASO synthesis activity start in 2020



Startup “OligoNanoMed” pour le développement de Nanomédicaments ciblant l’ARN pour la thérapie et l’imagerie



Thanks to my team

From cell signaling to personalized therapy



Cyril Bastide
MD-PhD-HDR
PU-PH in
Urology



Sophie Giusiano
MD-PhD
MCU-PH in
Anatomo-Pathology



Khanh Le-Thi
PhD student
Viet Gov
PhD fellowship



Sandra Udu-Itum
PhD student
French Embassy and
Funai University scholarship



Souhaila Zaghdoudi
PhD
Tunisian Gov Fellowship



Clémentine Sarda
M2 Onco

mRNA targeting Nanomedicine



David Taïeb
MD-PhD-HDR
PU-PH in
Nuclear Medicine



Clément Paris
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Junior Scientist
Amidex



Kenneth Omabe
PhD student
French Embassy and
Funai University scholarship



Jerry Ombor
PhD student
French Embassy and
Funai University scholarship

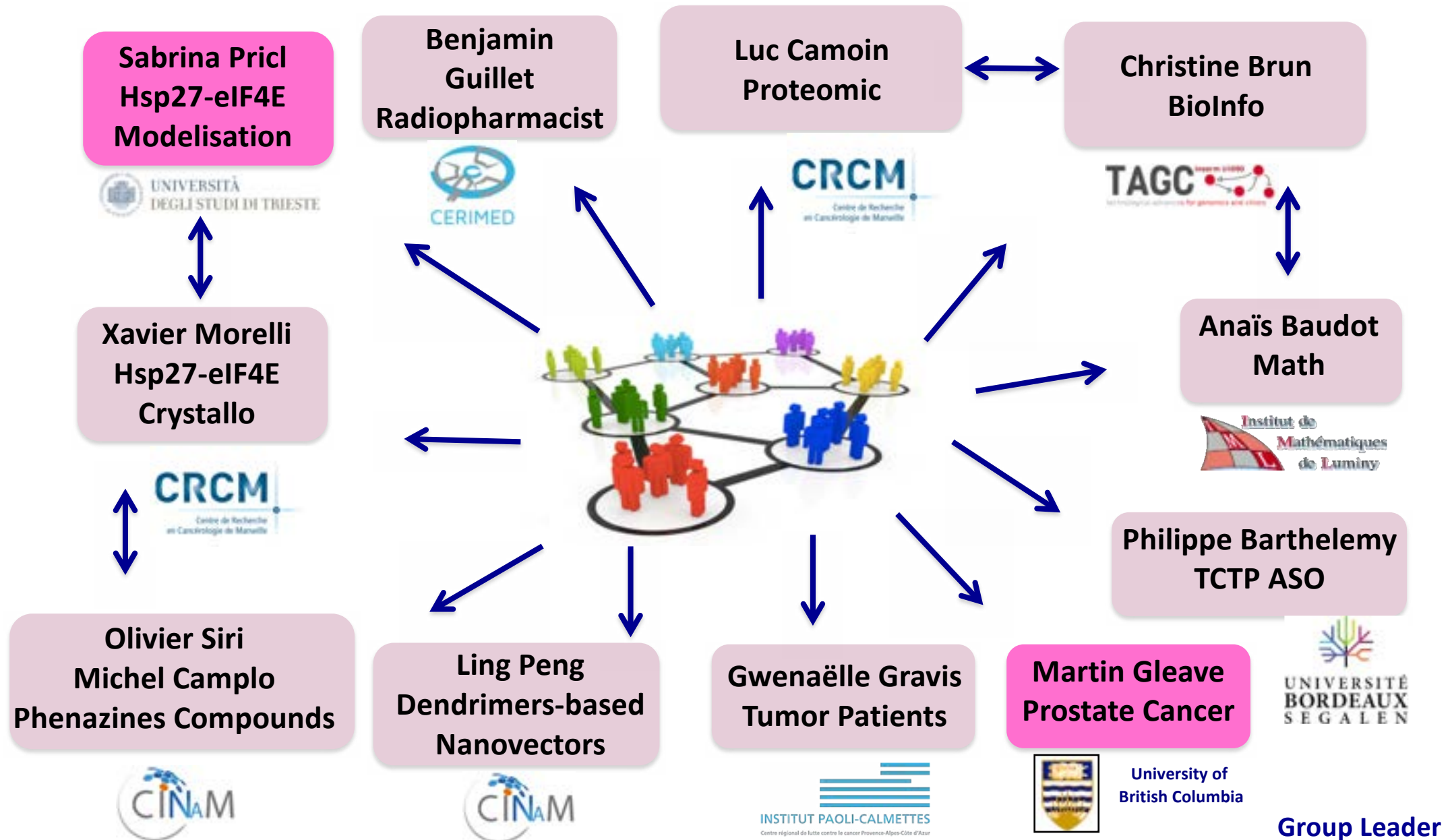


François Lannes
MD fellow
PhD student



Nicolas Sahakian
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Many thanks to my long time collaborators





Merci pour votre attention!

