LDL receptor-peptide conjugate as *in vivo* tool for specific targeting of pancreatic ductal adenocarcinoma

Angélina Acier[1,2], Magali Godard[2], Fanny Gassiot[2], Pascal Finetti[1], Marion Rubis[1], Jonathan Nowak[2], François Bertucci[1], Juan Iovanna[1], Richard Tomasini[1], Pascaline Lécorché[2], Guillaume Jacquot[2], Michel Khrestchatisky[3], Jamal Temsamani[2], Cédric Malicet[2], Sophie Vasseur[1] and Fabienne Guillaumond[1]

[1]CRCM, Aix-Marseille Univ, CNRS, INSERM, Institut Paoli-Calmettes, Marseille, France; [2]Vect-Horus, Marseille, France; [3]Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, Marseille, France

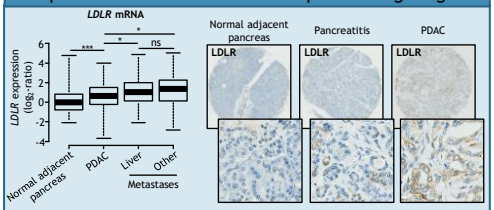
PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

One of the five deadliest cancers, characterized by a:

- late diagnosis with frequent metastases leading to a poor prognosis
- low efficiency of current chemotherapies
- dense and hypoxic stroma that constrains cancer cells to reprogram their metabolism

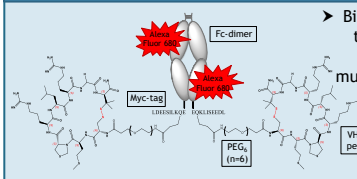
Aims: using its high cholesterol dependency, filled by LDLR, as a promising delivery route for imaging agents in PDAC.

LOW-DENSITY LIPOPROTEIN RECEPTOR (LDLR): a powerful candidate for PDAC-specific targeting



➤ In patients, *LDLR* mRNA increases with PDAC progression and LDLR is highly represented in the epithelial compartment.

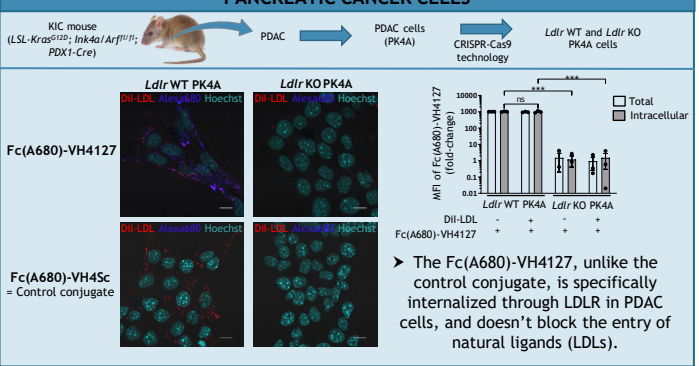
THE LDLR-TARGETING CONJUGATE



➤ Binds with high affinity to the extra-cellular EGF-like domain of murine and human LDLR.

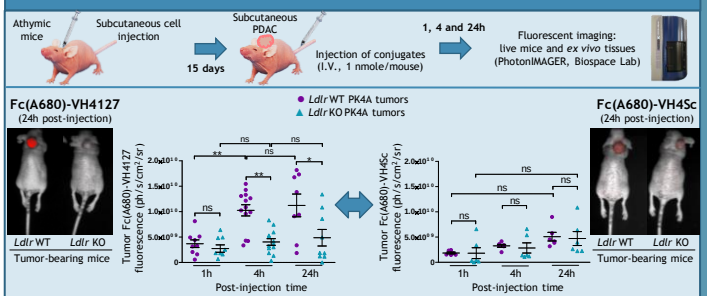
Fluorescent conjugate	Peptide sequence	K_D (hLDLR)	K_D (mLDLR)	Plasma half-life
Fc(A680)-VH4127 (Target: LDLR)	Pr-[cM"Thz"RLRG"Pen"]$_c$-NH_2	0.0607 nM (± 0.025)	0.0918 nM (± 0.051)	4.27 h

LDLR-TARGETING CONJUGATE INTERNALIZED BY PANCREATIC CANCER CELLS



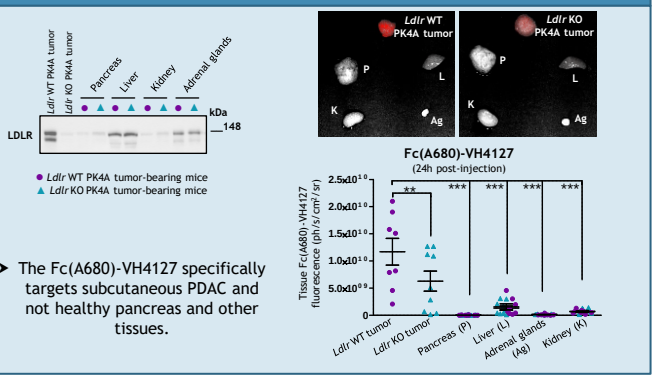
➤ The Fc(A680)-VH4127, unlike the control conjugate, is specifically internalized through LDLR in PDAC cells, and doesn't block the entry of natural ligands (LDLs).

SUBCUTANEOUS & SYNGENEIC PDAC TRANSPLANTATION (*IN VIVO*)



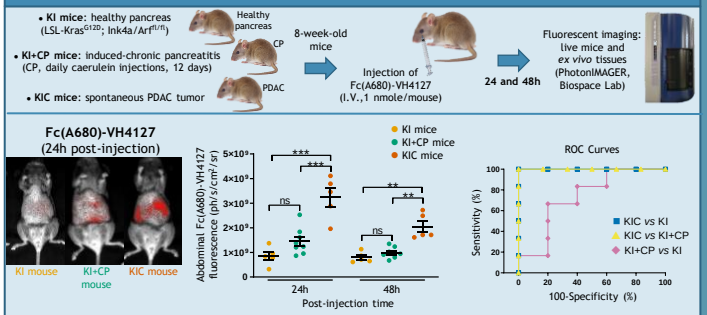
➤ The LDLR-targeting conjugate is selectively addressed and up-taken by PDAC *in vivo*, contrary to the control conjugate (Fc(A680)-VH4Sc).

SUBCUTANEOUS & SYNGENEIC PDAC TRANSPLANTATION (*EX VIVO*)



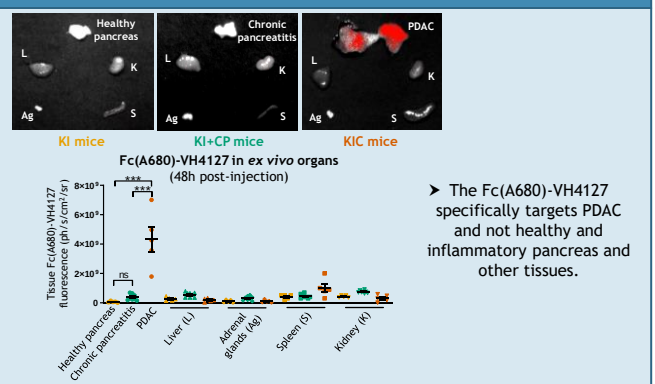
➤ The Fc(A680)-VH4127 specifically targets subcutaneous PDAC and not healthy pancreas and other tissues.

SPONTANEOUS PDAC & INDUCED-CHRONIC PANCREATITIS (*IN VIVO*)



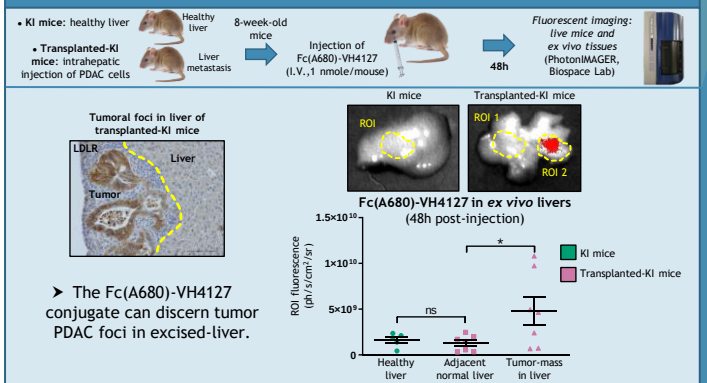
➤ The Fc(A680)-VH4127 specifically discriminates PDAC-bearing mice, from control and induced-CP mice with a high specificity and sensitivity.

SPONTANEOUS PDAC & INDUCED-CHRONIC PANCREATITIS (*EX VIVO*)



➤ The Fc(A680)-VH4127 specifically targets PDAC and not healthy and inflammatory pancreas and other tissues.

PDAC METASTASIS IN LIVER (*EX VIVO*)



➤ The Fc(A680)-VH4127 conjugate can discern tumor PDAC foci in excised-liver.

CONCLUSION/PERSPECTIVES

This proof-of-concept study showed that:

- *LDLR* is overexpressed in tumoral compartment of the primary pancreatic tumor, as well as in metastasis, making this receptor a good target to improve diagnosis of PDAC progression by imaging.
- Fc(A680)-VH4127 conjugate specifically binds to LDLR and targets pancreatic tumors, even stroma-rich PDAC and not healthy pancreas or other tissues. These results have been validated in both induced- and spontaneous PDAC mouse model.
- This conjugate can reliably discriminate PDAC from chronic pancreatitis, a well-known challenge, and allows the detection of tumoral foci in excised-liver.

This study highlights the powerful potential of LDLR-targeting peptides, as vehicles for nuclear imaging probes and/or drugs, and offers hopeful perspectives both in medical imaging for pre-operative diagnosis and in cancer treatments through fluorescence guided-surgery and targeted-drug delivery.