The potential use of peptides in pancreatic cancer

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Pancreatic ductal adenocarcinoma (**PDAC**) is the most common type of pancreatic cancer and is among the most aggressive and still incurable cancers. Innovative and successful therapeutic strategies are extremely needed. Many approaches are under investigation to improve PDAC therapy. **The use of peptides is one of the possible delivery strategies to achieve tumor targeting.**

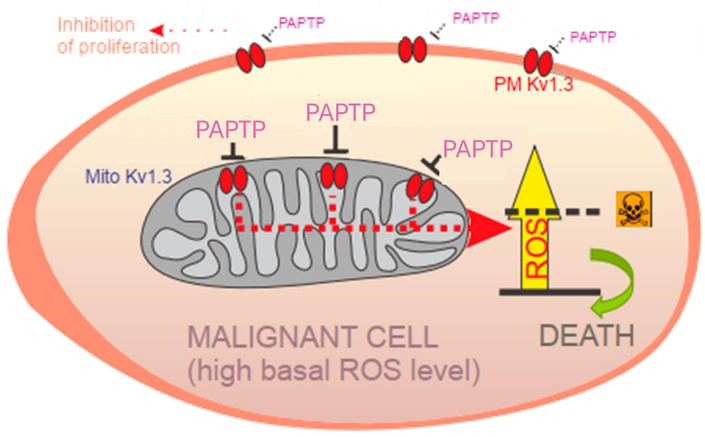
In recent decades, peptide-drug conjugates (**PDCs**) have been studied as new targeted therapies. PDCs combine a monoclonal peptide, a cytotoxic payload, and a linker, optimizing drug specificity and reducing adverse effects. These systems, composed of cyclic or linear peptides with low molecular weight, could allow for payload loading and better penetration into tumor tissues.

BACKGROUND

We found that several receptors capable of interacting with different peptides are overexpressed in pancreatic cancer cells, such as:

- The **CCK2R** receptor
- The **GRPR** receptor
- The **LDL-R** receptor
- The **Neuropilin-1**

Successively, the **Pan02** cell line, a murine pancreatic adenocarcinoma cell line, were selected to be tested.



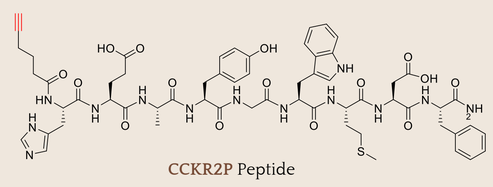
Among the various cargoes that could be tested for delivery to the cells, we opted for **PAPTP**, a mitochondria-targeted compound with promising anticancer effects. Mitochondria are emerging as a crucial target for cancer therapy and our derivative binds to and inhibits the **Kv1.3 channel** residing in the inner mitochondrial membrane, causing oxidative stress and selectively killing cancer cells while sparing normal ones.

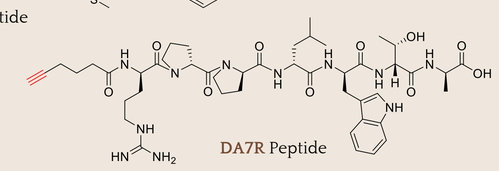
SYNTHESIZED CONJUGATES

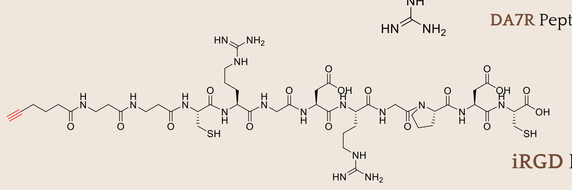
PEPTIDES

Elongated with a spacer containing an *alkyne group*

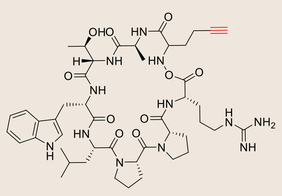
Linear Peptides

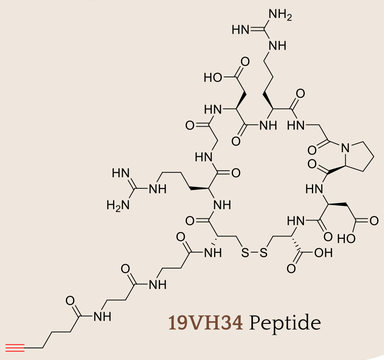

CCKR2P Peptide


DA7R Peptide


iRGD Peptide

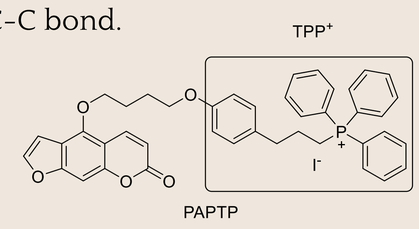
Cyclic Peptides


cA7R Peptide

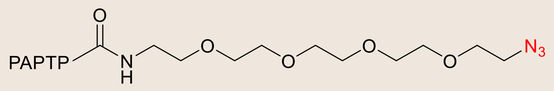

19VH34 Peptide

PAPTP

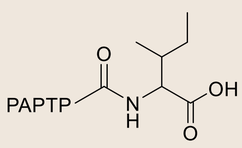
PAPTP is an antitumor drug derived from the psoralenic compound PAP-1. Its accumulation in the mitochondria is due to the presence of a permanent lipophilic cation, triphenylphosphonium (TPP+), attached to the molecule via a stable C-C bond.



PAPTP was modified with the addition of a short linker containing an *azido moiety* to allow conjugation with the peptide in a position not interfering with binding to and inhibition of Kv1.3

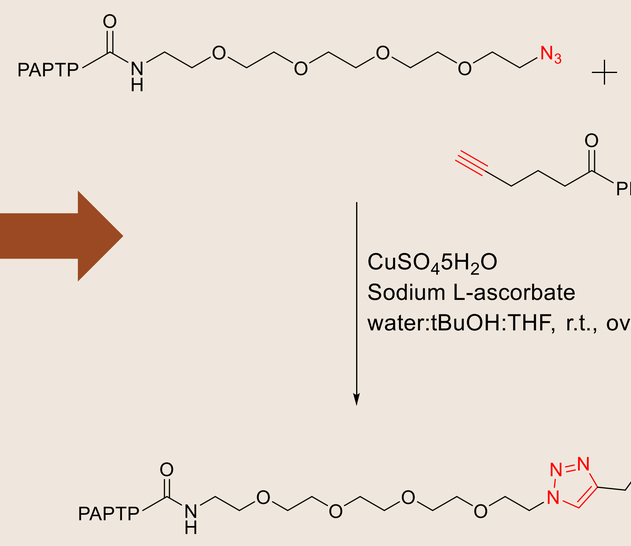


Other linkers have been used, such as the amino acid isoleucine (I), which allows peptide conjugation through an amide bond.



CLICK REACTION

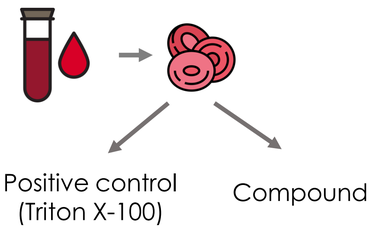
- biologically compatible conditions (aqueous environment, room temperature, and physiological pH)
- limited or no production of by-products.



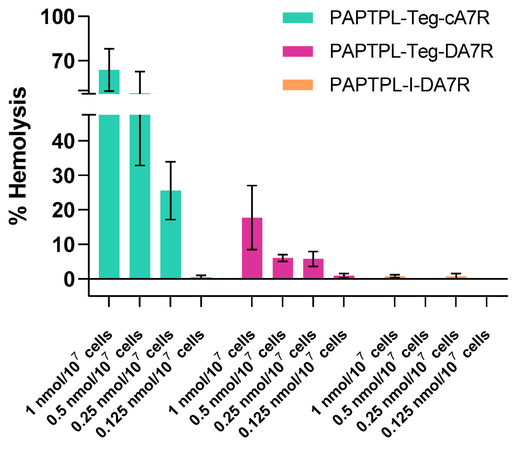
BIOLOGICAL TEST

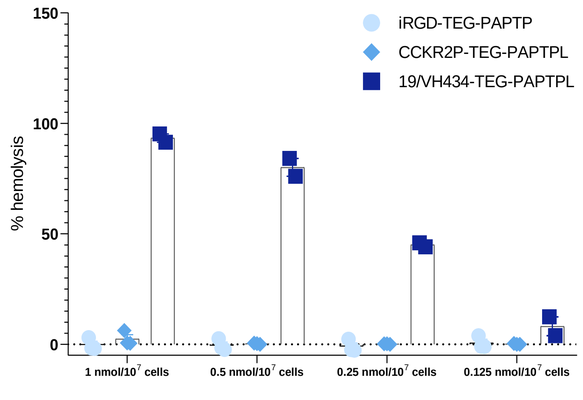
Some of the peptides, when conjugated with PAPTPL, become haemolytic. This renders the PAPTPL-peptide construct unsuitable for *in vivo* applications, since the derivatives are expected to reach the bloodstream upon administration.

Haemolysis studies performed with red blood cells isolated from blood from mice. Data expressed as % haemolysis in comparison to that induced by Triton X -100.



A7R variants:
(Parrasia S. et al, Pharmaceutics 2023)





CONCLUSION

- The SPPS technique produced few by-products, avoiding the need for purification for most peptides.
- The CuAAC coupling reaction was effective under mild conditions for most peptides. The use of microwaves is suggested for future syntheses.
- Conjugation of peptides with PAPTP may cause unexpected properties of the resulting derivative, such as emolytic properties.
- *In vivo* experiments with a PDAC orthotopic mouse model are under way to test phramacokinetic and antitumoral properties of non-hemolytic derivatives.
- Non-hemolytic constructs are under study in mice, for their tissue distribution profiles, their ability to accumulate in the pancreas and PDAC, and their efficacy in reducing tumor mass in an orthotopic PDAC mouse model.