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Imaging of c-Met aberrant cancers with Gallium-68 chelators for positron emission tomography

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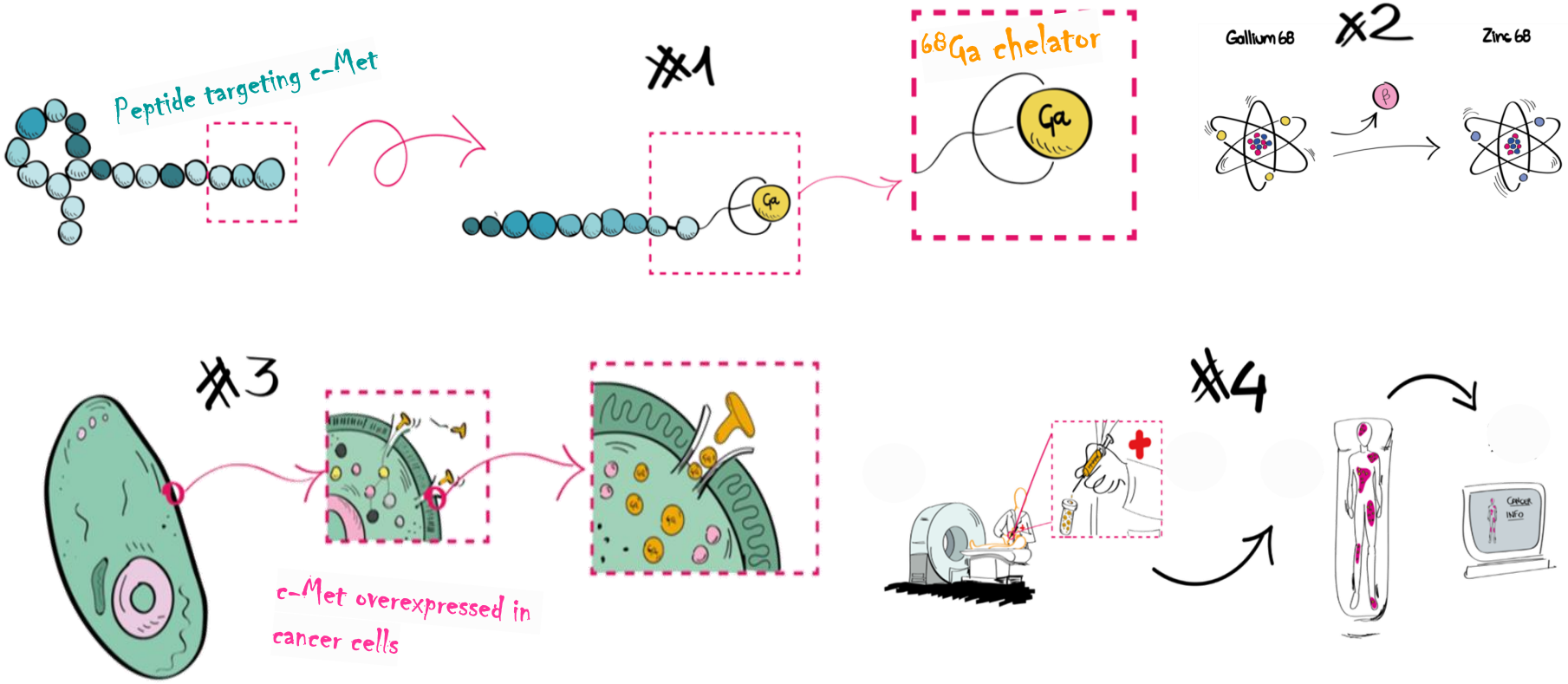
Graphical Abstract

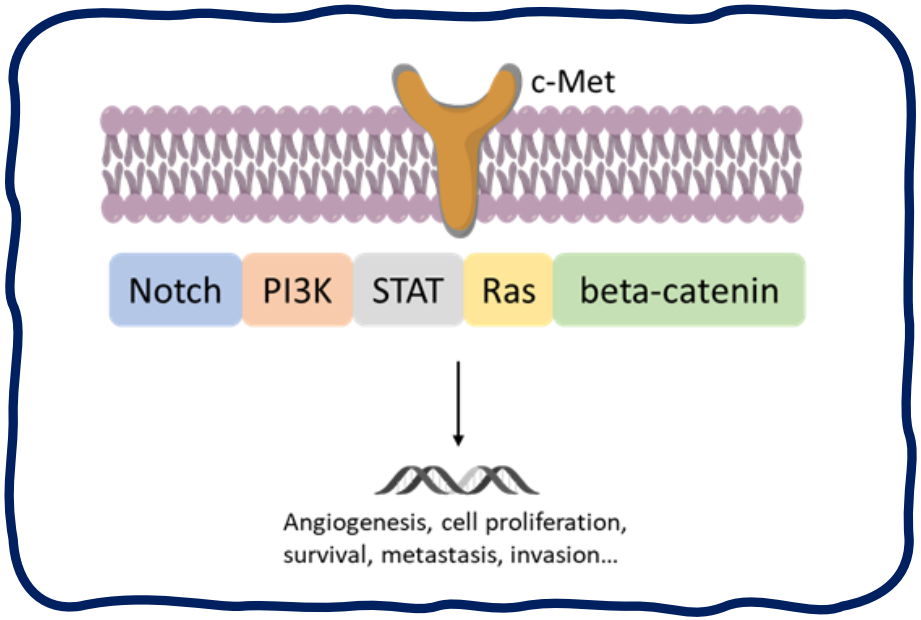


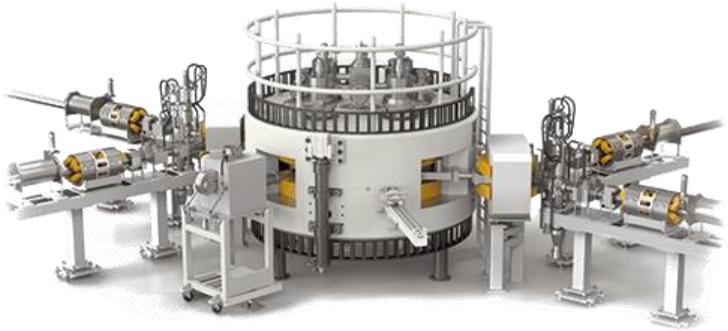
Abstract

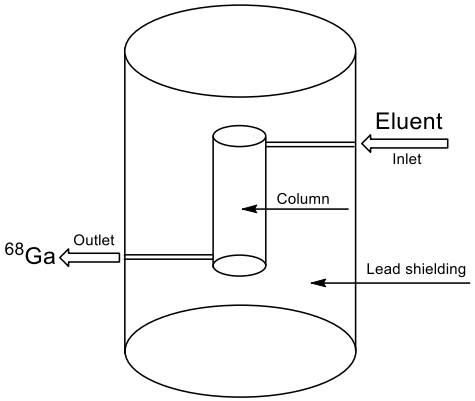
c-Met is a receptor tyrosine kinase which, after activation by its ligand, the hepatocyte growth factor (HGF), mediates a range of intracellular signalling pathways including some related to proliferation, motility, migration and invasion of cancer cells. Aberrant HGF/c-Met signalling is involved in the development and metastatic progression of several tumour types. Thus, this protein receptor is a key player in cancer initiation and progression. For this reason, monitoring of c-Met expression in real time is likely to assist in the diagnosis and the monitoring of response to therapy. Positron emission tomography (PET) imaging represents one of the most promising clinical tools for the *in vivo* real-time monitoring of abnormal alterations of c-Met and for the diagnosis of c-Met related cancers. Here we present the rational design and synthesis of a library of novel peptide-chelator bioconjugates potentially able to effectively target c-Met and to efficiently bind gallium-68, and therefore to make the cells visible in the positron emission tomography. In fact, the main feature of ^{68}Ga is that it undergoes a spontaneous radioactive decay, becoming a different element by releasing a positron, which is then measured by common hospital PET scanner. Moreover, the use of ^{68}Ga as radioactive species would abolish the costly infrastructures related with ^{18}F and ^{11}C production and the more complex synthetic chemistry procedures involved in radiolabeling. Non-invasive PET imaging with the developed tracers will support will create powerful tools for the detection and monitoring of the most common and lethal cancers among Europe and worldwide.

Keywords: c-Met; Gallium-68 chelators; HGF; peptides, PET imaging.

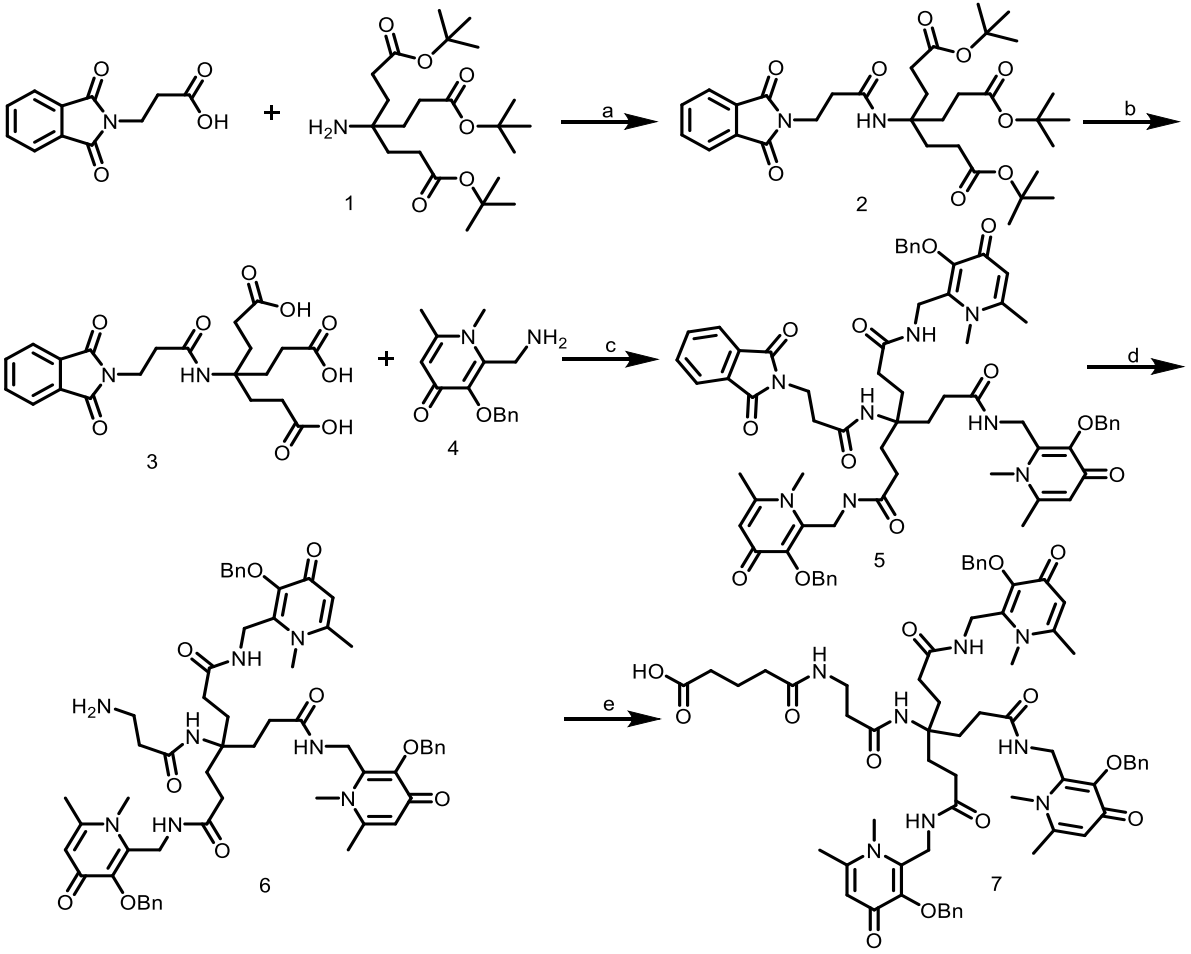
Introduction: c-Met, PET and ^{68}Ga

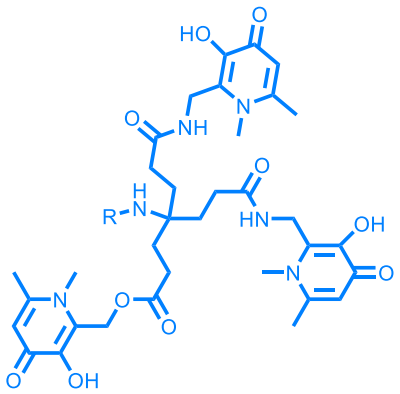






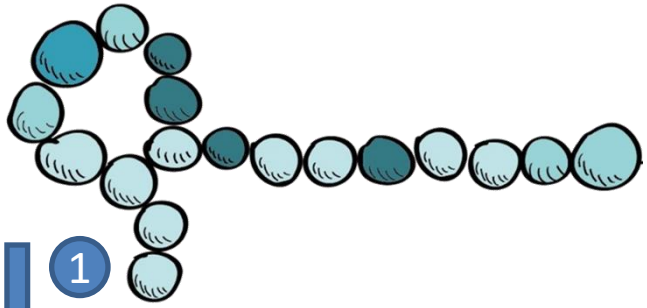
Results and Discussion: THP as ^{68}Ga chelator



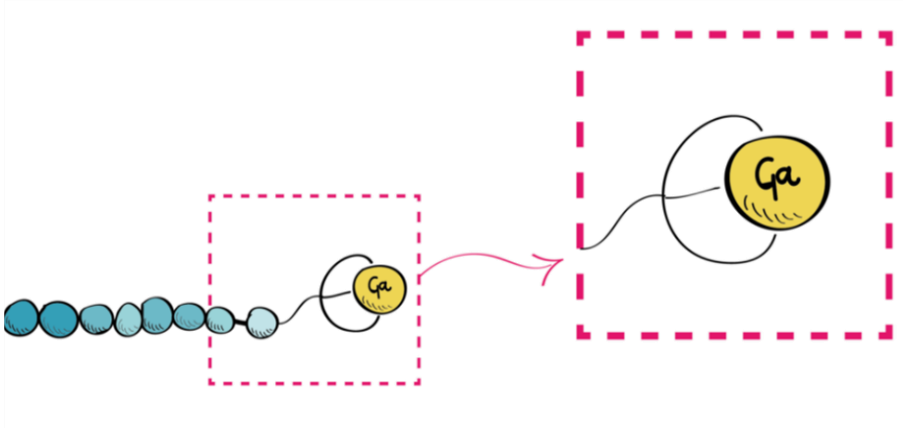


a) HOBt, DCC, dry DMF, 1 d, r.t., 66%; b) 96% HCOOH, 18 h, r.t., 97%; c) HOBt, DCC, dry DMF, 3 d, r.t., 82%; d) NH_2NH_2, EtOH, 3 h, reflux, 96%; e) glutaric anhydride, DIPEA, dry DMF, 18 h, r.t., 98%.

Results and Discussion: Synthesis of Peptides and their Bioconjugates

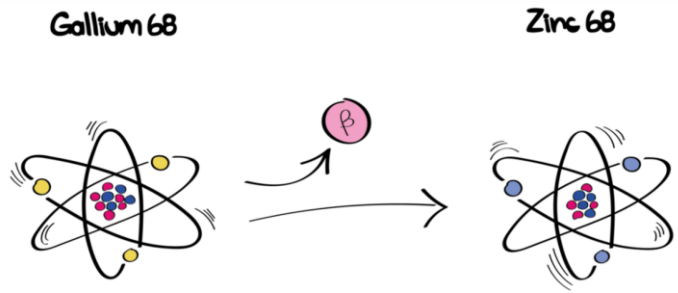


1 Synthesis of the peptide chain



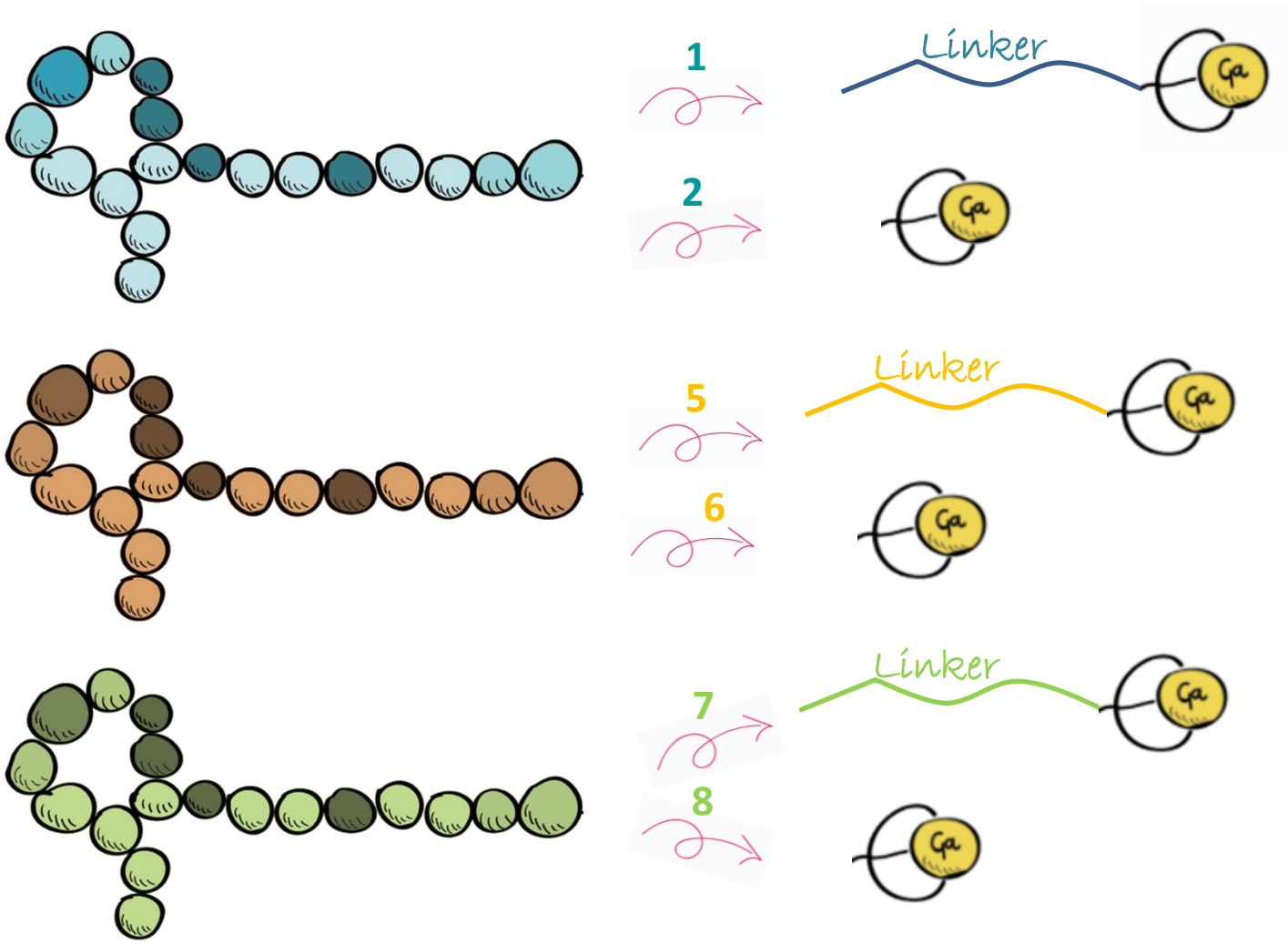
2 Conjugation with THP glutaric

3 Cleavage from the resin

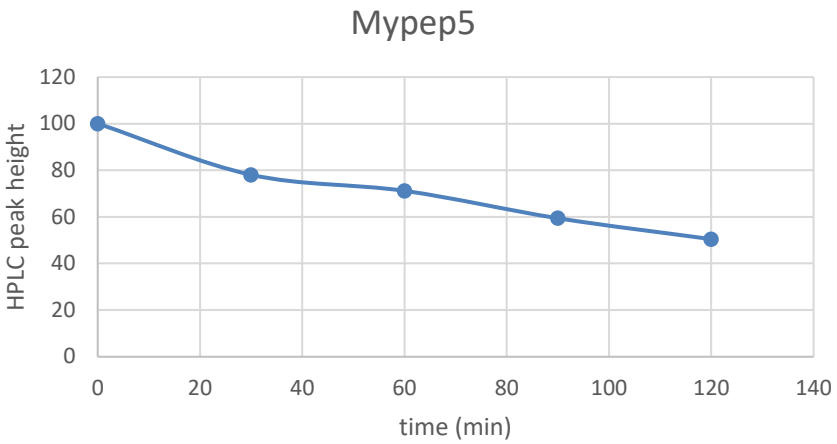


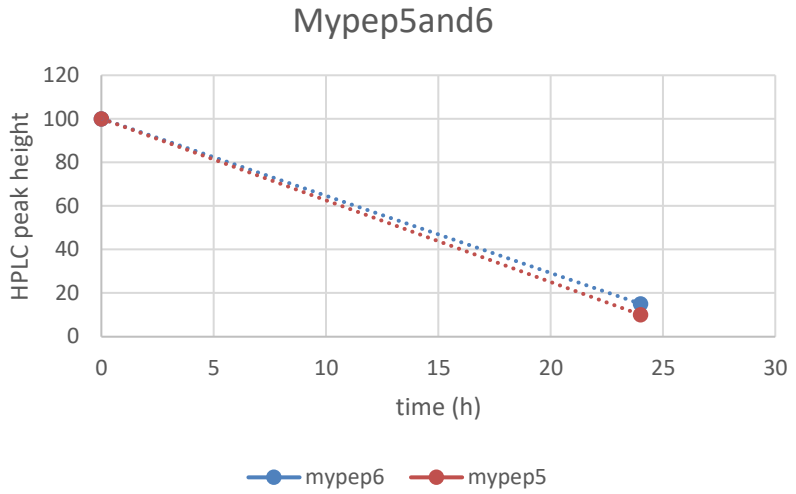
4 → Gallium labelling

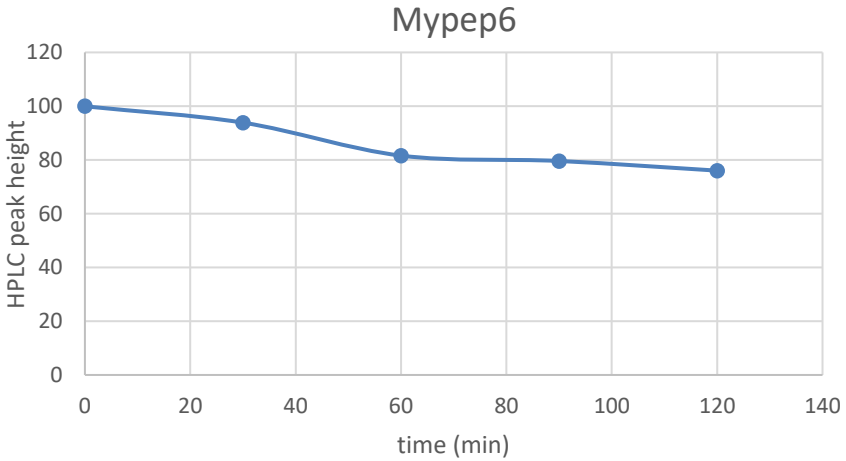
Results and Discussion: Peptide chains



Results and Discussion: LogP and serum stability







LogP					
1	2	5	6	7	8
-1.6	-1.75	-0.8	-0.39	-0.24	-1.37

Conclusions and future perspectives

- ✓ Synthesis of 6 different peptide chains
- ✓ Synthesis of the acid derivative of THP as Gallium chelating moiety
- ✓ Synthesis of the petide-THP conjugates
- ✓ Evaluation of their serum stability, LogP and work in progress for the IC50 values

future objective..

Our future goal will consist in the chelation of ^{68}Ga by all the produced bioconjugates and of the evaluation of their chelating capabilities as well as the c-Met affinity and cell uptake.

and then...

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Developing talents, advancing research

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- ✓ **Dr Giuseppe Floresta**
- ✓ **Dr Vincenzo Abbate**

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