Engineering a snake toxin as a positron emission tomography agent for diagnosing metastatic renal carcinoma

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=> Mambaquaretin has been identified for its capacity to bind the vasopressin type 2 receptor (V2R, Ciolek, PNAS, 2017)

=> The V2R is expressed in the kidney where it regulates water homeostasis

=> V2R is also ectopically expressed in several cancer cells like the metastatatic form of clear cell renal carcinoma (mccRCC)

=> The MQ232, an optimized form of the mambaquaretin detects mccRCC at early stage (Stanajic, theranostics, 2025)

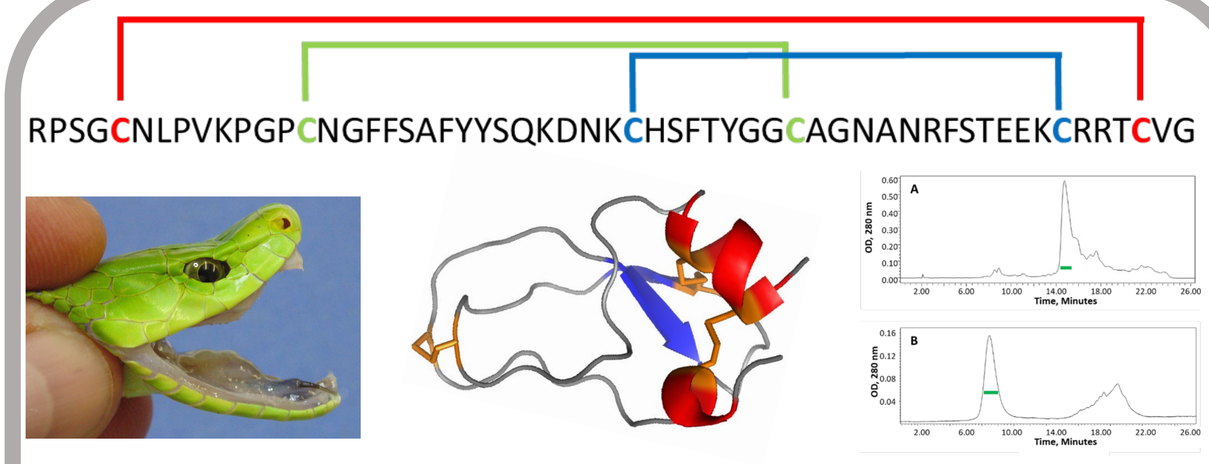
The earlier, The better

Early diagnosis of metastatic clear cell renal cell carcinoma (mccRCC) is of vital importance for patient survival.

Early diagnosis is not possible by lack of specific diagnostic tools.

As snake derived toxin detects early form of mccRCC.

The mambaquaretin



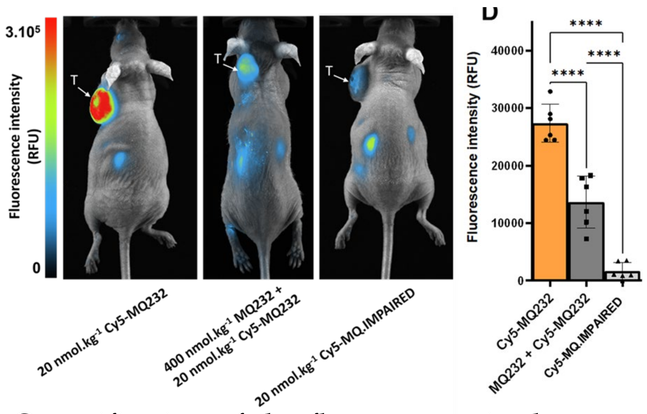
Sequence of the mambaquaretin, 57 residues, 3 disulfide bridges. The African green mamba snake *Dendroaspis angusticeps*. X-ray structure of the mambaquaretin, a Kunitz peptide. The mambaquaretin is produce by one step SPPS. HPLC of the crude peptide before (top) and after (down) of the oxidation of the 3 disulfide bridges.

In vivo selectivity of Cy5-MQ232 probe

The CHO-304 genetically modified cell line express the hV2R (Droctové et al. Theranostics. 2020. PMID: 33052234). 5 millions of cell implanted in NMRI-*Foxn1*$^{nu/nu}$ mice.



The Vilber camera to image live mice



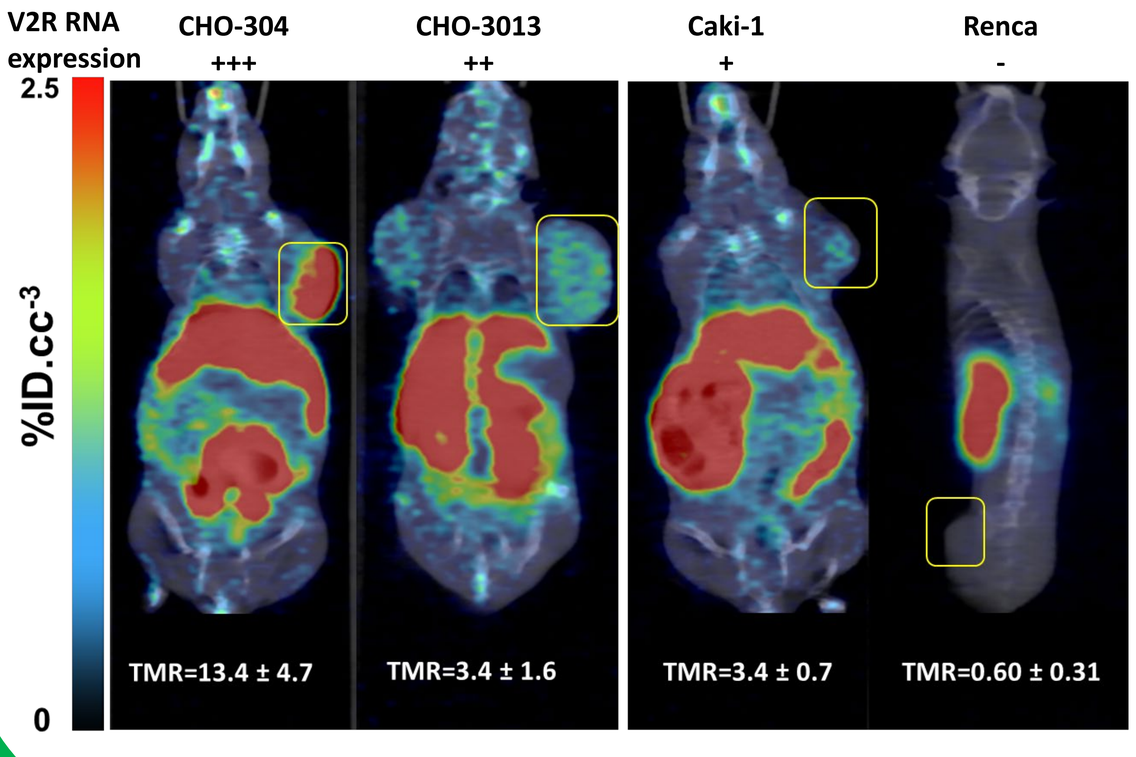
Quantification of the fluorescence in the organs of interest obtained from CHO-304 xenografted NMRI-Foxn1nu/nu mice euthanized at t+4 h after i.v. injection

In vivo visualization of V2R^{+} tumors in mccRCC representative mice model using [^{18}F]F-MQ232

The Caki-1 cell line, derived from human mccRCC express the V2R (Brodaczewska, et al . *Molecular Cancer* 2016). The Renca cell line, derived from a mice renal cancer, neither expressed the V2R.
5 millions of cell implanted in NMRI-*Foxn1*$^{nu/nu}$ mice for 3-4 weeks before imaging
PET imaging 4h after i.v. injection of [^{18}F]F-MQ232 (3.0 ± 0.7 MBq) per mice.



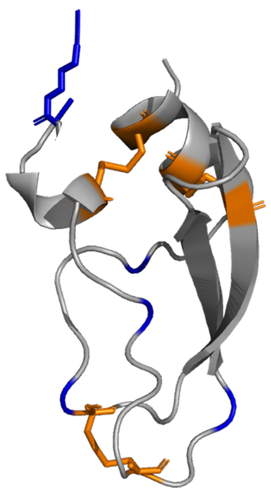
Micro-PET apparatus



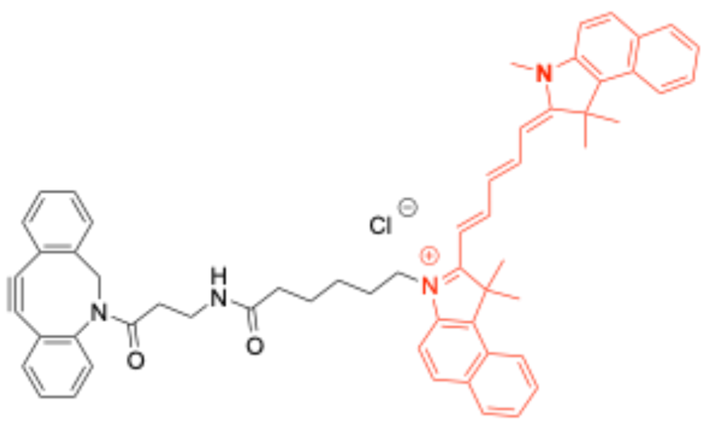
MQ232-derived probes are able to image the V2R ectopically expressed in tumors.

[^{18}F]F-MQ232 is the starting point for the development of a diagnostic tool that could enable early detection of mccRCC.

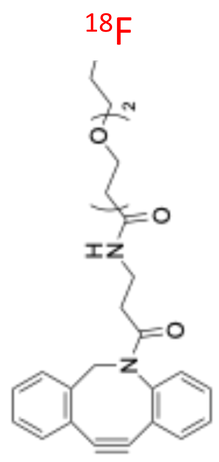
MQ232 derived in diagnostic tools



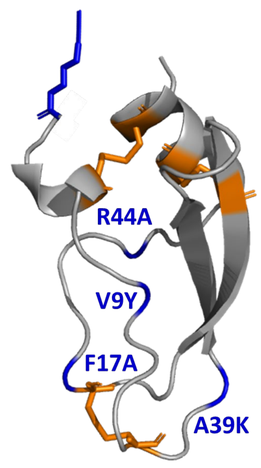
MQ232 with an azido moiety



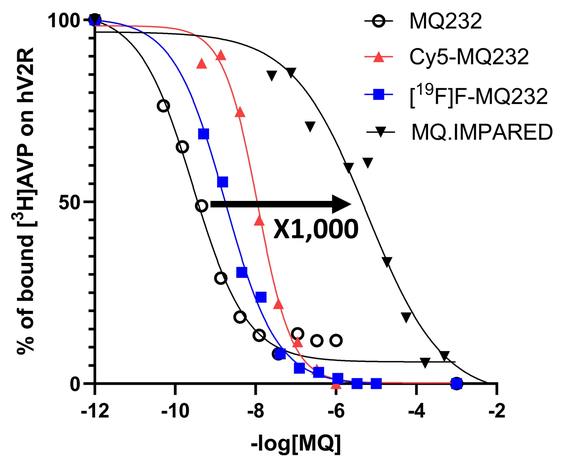
Cy5-dibenzocyclooctyne molecule for fluorescence imaging



[^{18}F]F-dibenzocyclooctyne molecule for PET imaging



The MQ-IMPAIRED, an inactive form of the MQ232



MQ232 and derivate display nM affinities. MQ-IMPAIRED displays µM affinity