

Highly improved metabolic stability and pharmacokinetics of Indium-111-DOTA-gastrin-conjugates for targeting of the gastrin receptor

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Krakow, June 2008

Background

- ^{111}In -DOTA-Minigastrins show good tumor uptake but very high kidney retention.
- Truncated Minigastrins (stepwise removal of Glu) show improved tumor-to-kidney ratios but very low metabolic stability.

Preliminary results of Prof. R. Baum

- ^{68}Ga -DOTA-MG11 (D-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH₂) shows only very faint tumor uptake and little stomach uptake (gastrin receptor positive).
- ^{68}Ga -DOTA-MG9 (D-Glu-Glu-Glu-Ala-Tyr-Hly-Trp-Met-Asp-Phe-NH₂) shows better tumor uptake (in MTC patients) and strong stomach uptake.

Conclusion

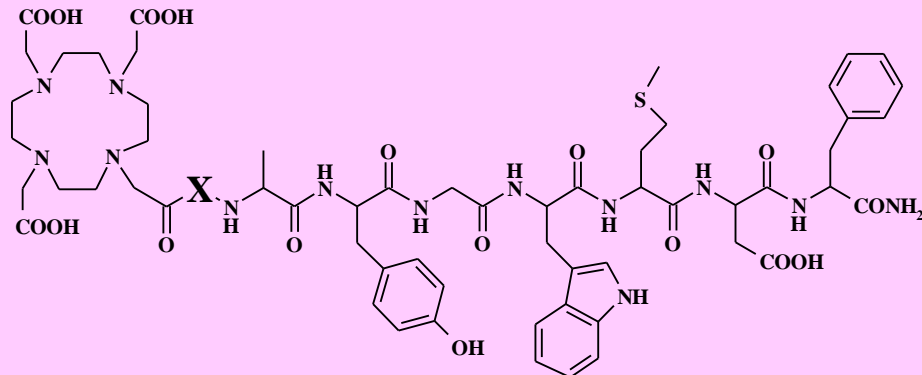
Truncated peptides are metabolically labile.

Our aim

To develop new DOTA-coupled minigastrin analogues with non-ionic spacers which may retain improved tumor-to-kidney ratio and demonstrate higher enzymatic stability in serum.

Characteristics of our gastrin-DOTA-conjugates

DOTA-X-Ala-Tyr-Gly-Trp-Met/**Nle**-Asp-Phe-NH₂



Code	-X-	Binding affinity to CCK/B [nM]	Internalised fraction [%i.D./mio cells]	Serum half-life [h]
PP-F1	PEG4	5,2 ± 0,4	6,6 ± 0,5	1,0 ± 0,2
PP-F2	PEG6	4,1 ± 0,6	7,7 ± 0,7	1,8 ± 0,6
PP-F7	PEG12	6,2 ± 1,8	4,6 ± 0,6	3,1
PP-F3	(D-Ser) ₂	2,7 ± 1,6	11,3 ± 0,3	1,8
PP-F4	(D-Ser) ₃	3,3 ± 1,2	12,5 ± 2,4	2,9 ± 0,5
PP-F5	(D-Gln) ₂	5,0 ± 1,9	9,8 ± 0,2	7,7
PP-F6	(D-Gln) ₃	4,2 ± 2,2	11,9 ± 1,9	25,3 ± 3,8
PP-F8	(D-Gln) ₃ , Nle	4,6 ± 1,9	10,2 ± 3,2	10,8
PP-F9	(D-Gln) ₄	3,9 ± 1,0	13,0 ± 3,6	102
PP-F10	(D-Gln) ₆	7,7 ± 0,4	12,8 ± 3,7	495 ± 104

Biodistribution data of PP-F9 and PP-F10

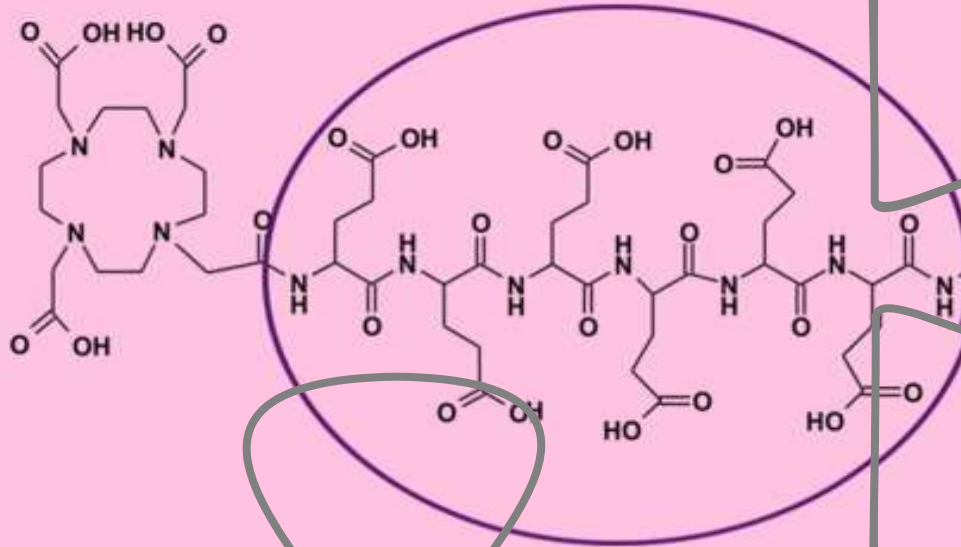
Animal model: Lewis rats with implanted AR4-2J cells
Injection: 0,1nmol of ^{111}In -labelled peptide (1,1MBq)
Blocking: 2000-times excess of cold peptide

	PP-F9			PP-F10		
	4h	4h blocked	24h	4h	4h blocked	24h
kidney	0,397 ± 0,030	0,508 ± 0,053	0,329 ± 0,036	0,354 ± 0,030	0,523 ± 0,053	0,317 ± 0,023
tumor	0,645 ± 0,162	0,141 ± 0,072	0,217 ± 0,040	0,989 ± 0,426	0,159 ± 0,027	0,373 ± 0,081
tumor/kidney	1,6		0,7	2,8		1,2

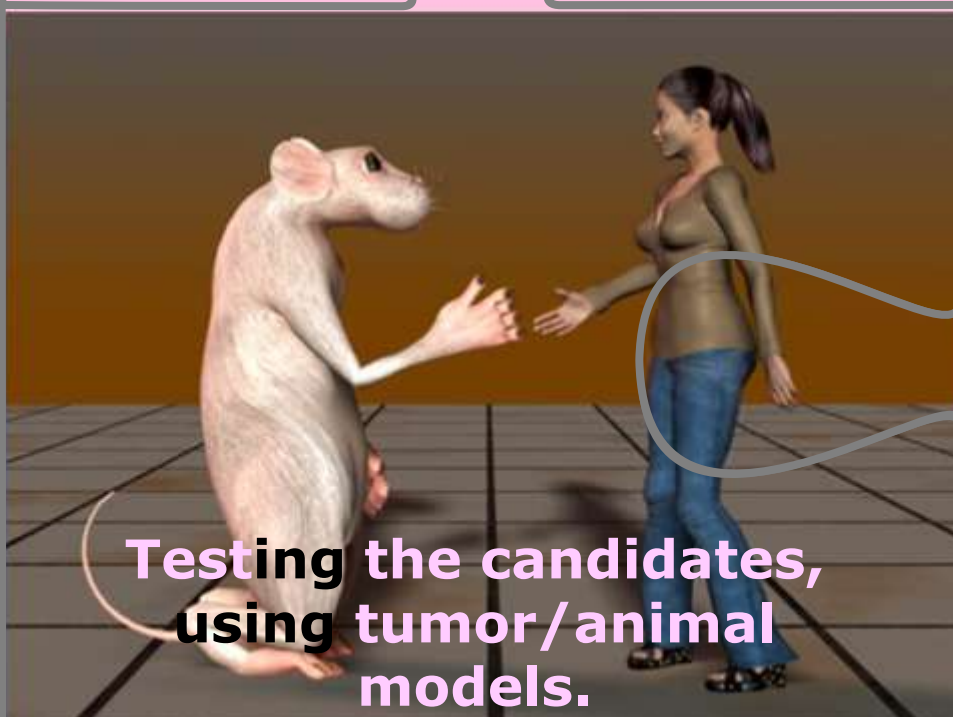
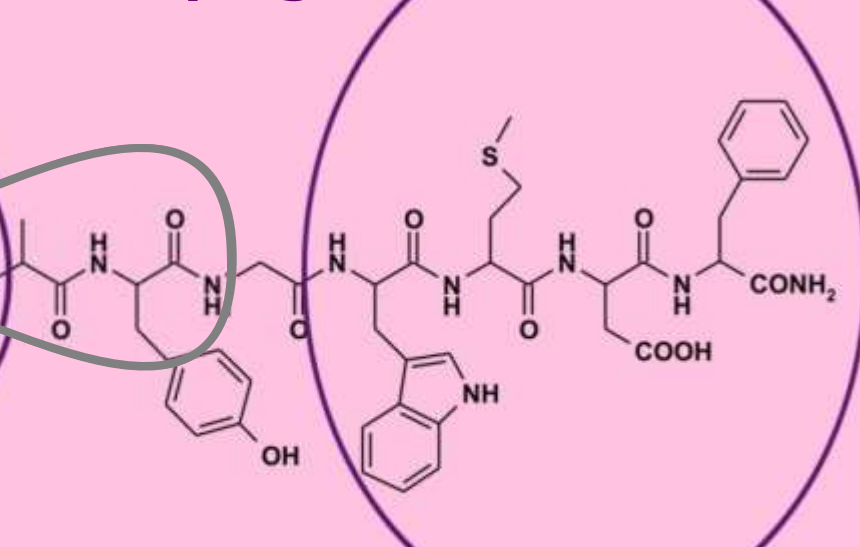
PP-F9 = DOTA-(D-Gln)₄-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH₂

PP-F10 = DOTA-(D-Gln)₆-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH₂

Changing ionic spacer



Keeping C-terminal AA



Testing the candidates,
using tumor/animal
models.



Trying to offer the
best one to the
patient.

Acknowledgement

I thank

- Prof. Maecke for giving me opportunity to start with research work,
 - Basel's group: Rosalba, Abi, Melpo, Maria-Luisa for taking me as part of their group,
 - Ljubljana's group: Tanja, Aljaz, Mare, Ajda, Mojca, Blaz for replacing me in routine work, especially during my stays in Basel.
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- Swiss National Foundation and
 - COST Action BM0607 for financial support.