SELF-ADMINISTERED LONG-ACTING OCTREOTIDE CONJUGATES

Eric L. Schneider, Gary W. Ashley, Ralph Reid, Daniel V. Santi

ProLynx LLC, San Francisco, CA

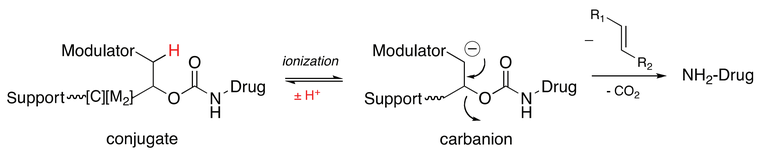
Eric@ProLynxLLC.com

INTRODUCTION

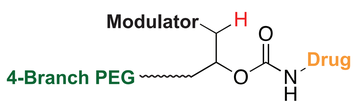
Three synthetic peptidic Somatostatin agonists – Octreotide, Lanreotide and Pasireotide – are approved by the FDA to treat one or more of the following diseases; Gastroenteropancreatic Neuroendocrine Tumors, acromegaly, and Cushing's disease. Because the half-life of the peptidic agonists are short (i.e. hours) and require b.i.d. injections, each has been formulated as a long-acting release (LAR) form that is administered once every 4 weeks. However, the LAR forms suffer certain deficiencies. A) They all require painful intra-gluteal i.m. (Octreotide, Pasireotide) or "deep" s.c. injection (Lanreotide) using a large bore needle, requiring or usually administered by a health professional. b) Octreotide LAR and Pasireotide LAR show a burst-effect that may contribute to certain adverse events; c) in PLGA formulations octreotide drug is extensively *N*-acylated by components of the polymer and d) there is significant "wasted" AUC and consequent over-dosing that could contribute to certain adverse events.

Here, we describe a releasable PEG-Octreotide conjugate using β-eliminative linkers that a) can be self-administered s.c. by the patient once a week; b) administered through a small gauge needle that is less painful, c) shows no burst effect; e) shows a low Cmax and flat C vs T profile with little "wasted" AUC. Simulations indicate that use of an analogous s.c. hydrogel carrier could provide formulations that require q-biweekly or q-monthly administrations. Overall, these conjugates should be more economical and time-saving thus leading to increased compliance and decreased adverse side effects associated with initial burst and high C_{max} effects.

β-ELIMINATION CHEMISTRY UTILIZED BY PROLYNX

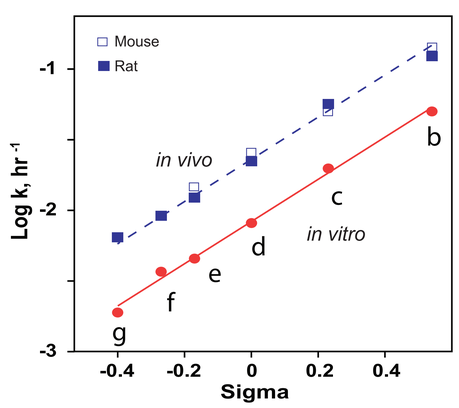


A modulator controls the ionization rate and therefore the rate of elimination and release of drug. *In vitro* and *in vivo* kinetics studies demonstrate that a wide range of release half-lives can be generated by adjusting the electronics of the modulator and show a correlation between the electronics of the modulator and the measured release rates. This correlation indicates the ability to predictably design a linker with any desired half-life.



PEG 40 kDa conjugate, in vitro cleavage

	Modulator	$t_{1/2}$ (hrs)
b	CF_3PhSO_2-	14
c	$ClPhSO_2$-	36
d	$PhSO_2$-	71
e	$MePhSO_2$-	150
f	$MeOPhSO_2$-	160
g	2,4,6-Me_3PhSO_2-	370
	$MeSO_2$-	450
	$O(CH_2CH_2)NSO_2$-	750
	CN-	2,400
	$(Et)_2NSO_2$-	10,500

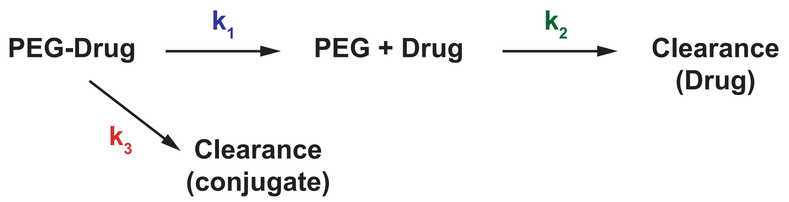


DESIGNING DRUG HALF-LIFE EXTENSION IN VIVO

With knowledge of the *in vitro* release rates of the linkers and known *in vivo* pharmacokinetics of the drug and the macro-molecular carrier, calculation of the *in vivo* half-life extension and drug concentration can be made using the following equations.

1) $k_{DRUG} = k_1 + k_3$

2) $[Drug]_{rel,\ ss} = k_1/k_2\ [PEG\text{-}Drug][V_{conj}/V_{drug}]$



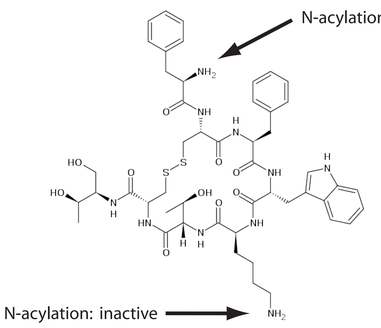
To calculate k_{DRUG} between species, k_3 for the species can be substituted into the equation, with k_1 a constant between species.

When the carrier is a non circulating hydrogel, $k_3 = 0$ and the drug elimination rate is the linker cleavage rate:

$$k_{DRUG} = k_1$$

OCTREOTIDE BACKGROUND

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-L-Thr-ol



Octreotide: 2 hr half-life in humans, necessitates bid s.c injections.

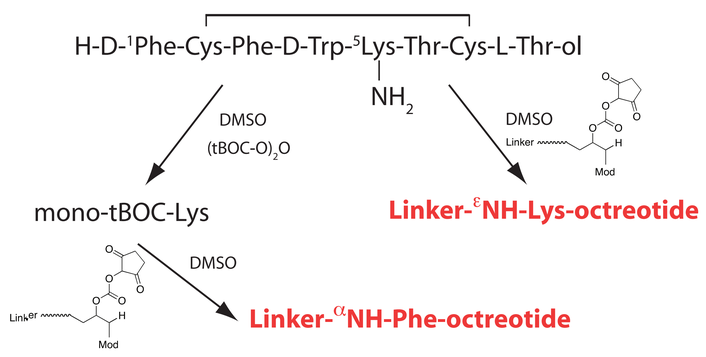
Sandostatin LAR: PLGA encapsulation of octreotide for once a month i.m. injection.

Pro: once a month

Cons: Painful injection, health care professional administered, inital burst from PLGA, ~50% modification from PLGA

CAM2029: Fluid Crystal nanoparticle encapsulated octreotide for once a month s.c injection, in Phase 1.

ATTACHMENT OF PROLYNX LINKER TO OCTREOTIDE



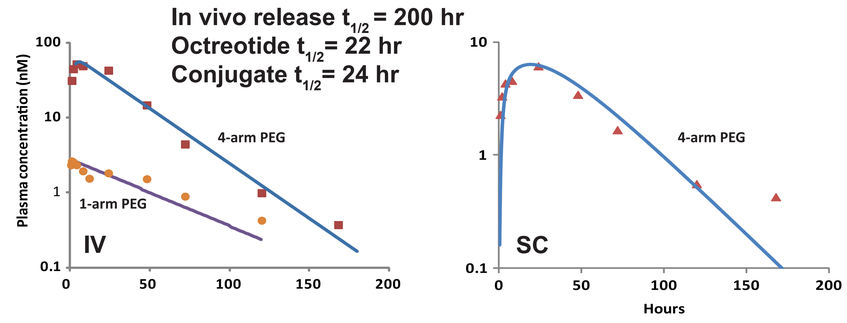
RELEASABLE PEG_{40kDa}-OCTREOTIDE KINETICS AND RAT PK

$^{\varepsilon}N$-acylated octreotide was prepared with linkers containing the $PhSO_2$ and $MePhSO_2$ modulators and attached to 1-arm and 4-arm PEG_{40kDa}.

In vitro release kinetics

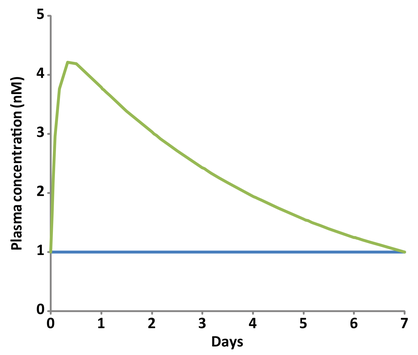
	$t_{1/2}$ (hours)
$PhSO_2$	185
$MePhSO_2$	360

PEG_{40kDa}-octreotide was injected IV and SC into rats for pharmacokinetics and the plasma samples were analyzed by MS-MS for released octreotide content.



Simulation in humans :

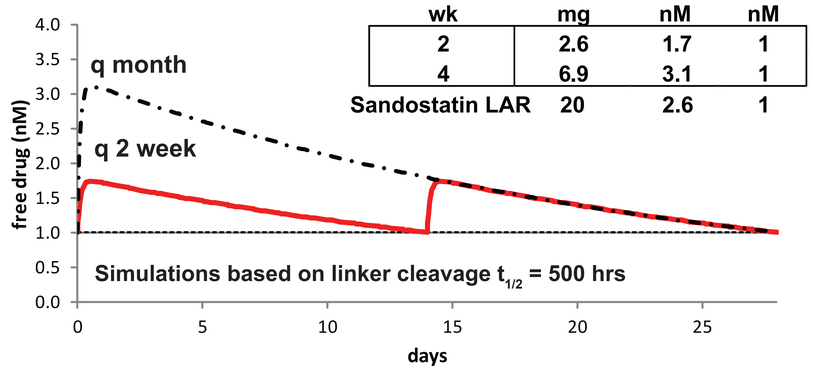
Cleavage $t_{1/2}$ = 200 hr
Octreotide $t_{1/2}$ = 75 hr
Dose = 5.3 mg octreotide
C_{max} = 4 nM
C_{min} = 1 nM



HYDROGEL-OCTREOTIDE SIMULATIONS

By utilizing our injectable hydrogel formulation, the octreotide can be attached via the β-eliminative linkers for q 2 week and q monthly sc injections.

Dose interval wk	octreotide mg	Cmax nM	nM
2	2.6	1.7	1
4	6.9	3.1	1
Sandostatin LAR	20	2.6	1



SUMMARY

- **ProLynx has soluble PEG conjugates that achieve once-weekly dosing.**
- **Translation to hydrogel should allow for once-a-month delivery.**
- **Both formulations:**
  - **SC injection for self administration and decreased pain.**
  - **Show no burst effect or modification compared to sandostatin LAR (i.e. PLGA)**