June 6, 2012

Kai Kaila, Ph.D.
Professor
Department of Biosciences
P.O. Box 65 (Viikinkaari 1)
00014 University of Helsinki
Finland

FedEx Delivery address:
University of Helsinki
Department of Biosciences
Viikinkaari 1
00790 Helsinki, Finland
Attention: Katri Wegelius

By FedEx: 7984-7713-8886

Dear Kai:

In response to your emails of May 28, 2012 and June 3, 2012 and as promised in my email of June 1, 2013 are samples of the following two peptides.

Selective AVP V_{1a}/V_2 Antagonist

$d(CH_2)_5[Tyr(Me)^2,Ala\text{-}NH_2{}^9]AVP$[a,b,c,d,,g]

CL-14-88

M.W. 1165.4 ~ 5 mg

Please note that this material is synthetic. It is non-toxic, non-infectious and non-hazardous.

[a]Original synthesis and some pharmacological properties in rat bioassays are reported in:

M. Manning, S. Stoev, K. Bankowski, A. Misicka, B. Lammek, N.C. Wo and W.H. Sawyer. Synthesis and Some Pharmacological Properties of Potent and Selective Antagonists of the Vasopressor (V_1-receptor) Response to Arginine Vasopressin. *J. Med. Chem.* **35**:382-388, 1992.

[b]Its pharmacological properties in rat bioassays are given in Table 9 (peptide 4) on page 484 in the review entitled: **"Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin V_{1a}, V_{1b}, V_2 and OT receptors: research tools and potential therapeutic agents"**, Maurice Manning, Stoytcho Stoev, Bice Chini, Thierry Durroux, Bernard Mouillac, and Gilles Guillon in: Advances in Vasopressin and

Oxytocin – from Genes to Behaviour and Diseases (eds. Inga Neumann and Rainer Landgraf), *Progress in Brain Research* **170**:473-512, 2008. **(A pdf of this review is attached)**.

[c]This V_{1a} antagonist is slightly more potent than the more widely used $d(CH_2)_5[Tyr(Me)^2]AVP$ (Manning Compound) (Table 9 (peptide 1) in review). In contrast to $d(CH_2)_5[Tyr(Me)_2]AVP$, which is a weak V_2 agonist, this peptide is a weak V_2 antagonist.

Its Antivasopressor $pA_2 = 8.75$

Its Antiantidiuretic $pA_2 = \sim 6.0$

ED Ratio = ~590

Its oxytocic properties and V_{1b} properties have not been evaluated.

[d]This peptide has been used in a number of published studies carried out in the laboratory of Ewa Szczepańska-Sadowska. See for example:

Cudnoch-Jedrzejewska A, Dobruch J, Puchalska L, Szczepańska-Sadowska E. Interaction of AT1 receptors and V_{1a} receptors-mediated effects in the central cardiovascular control during the post-infarct state. Regul Pept. 2007 Aug 16; 142(3):86-94. Epub 2007 Feb. 15. Erratum in: Regul Pept. 2007 Dec 4; 144(1-3):131.

Potent and Selective AVP V_2/V1a Antagonist

$d(CH_2)_5[D\text{-}Ile^2,Ile^4,Ala\text{-}NH_2{}^9]AVP$[e,g]

ST-12-73

M.W. 1086.4 ~ 3.0 mg

[e]Its pharmacological properties in rat bioassays are reported in: W.H. Sawyer, K. Bankowski, A. Misicka, E. Nawrocka, M. Kruszynski, S. Stoev, W.A. Klis, J.P. Przybylski and M. Manning. Potent V_2 vasopressin antagonists with structural changes at their C-terminals. *Peptides* **9**:157-163, 1988.

[f]See also Peptide 5, Table 7, page 613 in recent review entitled **"Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics"**. *Journal of Neuroendocrinology* **24**:609-628, 2012. **(Attached here as a pdf)**.

As reported in these references this peptide has the following antiantidiuretic (anti-V_2) and antivasopressor (anti-V_{1a}) potencies. Its antioxytocic potencies have not been determined.

Anti V_2 pA_2 = 8.16 (ED = 0.46 nMole/Kg)

Anti V_{1a} pA_2 = 6.25 (ED = 38 nmole/Kg)

It is 83 times more potent as a V_2 antagonist than as a V_{1a} antagonist.

You can find citations to the use of this V_2 antagonist through the ISI Web of Science or Pub Med.

gWith regard to the storage of these peptides, I hope the following is helpful. In the powder form, they are stable for months when stored at room temperature and for years when stored in the refrigerator. Sterile aqueous solutions are stable at room temperature for two to three weeks and for many months when stored in the refrigerator at +4 degree C.

I hope that these peptides will be useful in your studies on the role of the V_{1a} receptor in the regulation of the BBB Na/H exchanger in postnatal rats.

Best regards,

Maurice Manning, Ph.D., D.Sc.
Professor
Biochemistry and Cancer Biology
Mail Stop #1010
The University of Toledo Health Science Campus
3000 Arlington Avenue
Toledo, OH 43614-2598
Phone: (419) 383-4143
FAX: (419): 383-6228
email: maurice.manning@utoledo.edu
Website: HYPERLINK "http://www.utoledo.edu/med/depts/biochem/faculty/manning.html" http://www.utoledo.edu/med/depts/biochem/faculty/manning.html

MM/amc

By email: HYPERLINK "mailto:kai.kaila@helsinki.fi" kai.kaila@helsinki.fi
HYPERLINK "mailto:katri.wegelius@helsinki.fi" katri.wegelius@helsinki.fi

Sent by Fedex: Wednesday, June 6, 2012

Expected Date of Delivery: Friday, June 8, 2012

College of Medicine
Dept. of Biochemistry & Cancer Biology, Mail Stop #1010, Health Science Campus
3000 Arlington Ave., Toledo, OH 43614-2598
Phone: 419-383-4143 Fax: 419-383-6228 email: maurice.manning@utoledo.edu