Targeting Talk: *Agonist Effects*

by Dr. Douglas Lappi

Q: Do conjugated toxins (Dermorphin-saporin in particular) exhibit agonist effects? I've generated behavioral and tissue time course effects but have not established agonist effects for this conjugated toxin.

A: The peptide ligand toxins should exhibit agonist effects. They are constructed purposely to retain complete agonist activity, including for us the most important: internalization. So, for instance, SP-SAP (Cat. #IT-07) causes receptor internalization similar to SP, as reported in Mantyh *et al*. (Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor. *Science* 278:275-279, 1997).

As to dermorphin-SAP (Cat. #IT-12) specifically, it has agonist activity very much like dermorphin. This is reported in Porreca *et al*. (Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. *J Neurosci* 21:5281-5288, 2001) in which it's stated:

The bilateral microinjection of 3 pmol of dermorphin or of dermorphin-saporin directly into the RVM produced a robust antinociceptive effect in the 52°C hot-water tail-flick test. The peak antinociceptive effect of dermorphin, 78 ± 13.2% MPE, was not significantly different from that of the dermorphin-saporin conjugate, which was 59 ± 4.7% MPE ($p > 0.5$, Student's t test).

Usually the amount needed to give a response is lower than the amount needed to kill a cell. Depending on what your system is; it may be a peculiarity of that system, but I would be a little concerned about not seeing an agonist effect. On the other hand, if you have demonstration of specific toxicity, it may not be all that crucial.

SP-SAP Research Replacement

SP-SAP (formerly Cat. #IT-07) is being replaced by SSP-SAP (Cat. #IT-11). Scientific advisors have given counsel for this replacement because SSP-SAP is a superior lesioning agent in many situations, due to its targeting vehicle, a protease-resistant form of substance P. An excellent example is the paper by Martin and Sloviter, *J Comp Neurol* 436:127-152 (2001), in which after ineffective intraparenchymal injection of SP-SAP in the hippocampus, SSP-SAP was used with tremendous efficacy. In almost all applications we expect SSP-SAP will be used at a lower dose than SP-SAP.

We will not compromise the work of those that are midstream in experiments with SP-SAP. Orders from those who wish to continue with SP-SAP will be honored. This will be a gradual phase-out since SP-SAP is being developed as a chronic pain therapeutic (see update on Page 2). Please rest assured that your work is the backbone of our company and all questions or comments will be carefully considered.

Questions about an ATS product or Molecular Surgery technique? Write to us at ats@ATSbio.com