

# Targeting Trends

*Reporting the latest news in Molecular Surgery*



## SP-SAP Human Clinical Trial for Cancer Pain

### *An Anesthesiologist's Point of View*

by Carl Noe, M.D., Anesthesiology & Pain Management, UT Southwestern Medical Center, Dallas, TX; and Eugene McDermott Center for Pain Management, Dallas, Texas

Dr. Noe is the Principal Investigator in the ongoing trial of SP-SAP

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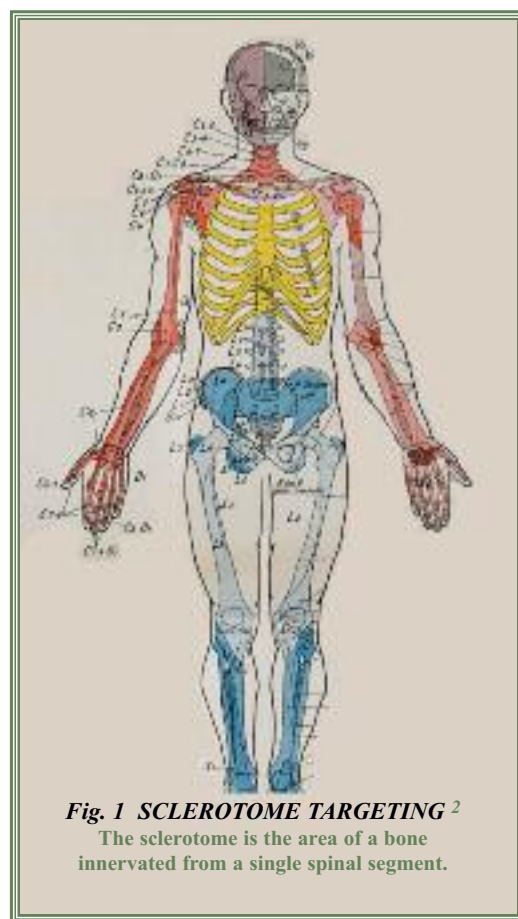
Intrathecal SP-SAP (Substance P attached to the ribosome-inactivating protein, saporin) has been studied in a Phase 1 clinical trial of patients with cancer pain at doses of 1, 2, 4, 8, 16 and 32 mcg. The first patient was treated April 10, 2014. Doses of 64 mcg and 90 mcg remain in Phase 1a of the clinical protocol. Phase 1b will treat multiple patients at the most effective dose. To date, no toxicity has been observed and the study is ongoing to evaluate response, safety, and tolerability. (For information about the trial, please visit: <http://clinicaltrials.gov/show/NCT02036281>).

SP-SAP is administered via an intrathecal catheter placed in the lumbar spine with the use of fluoroscopy and radiopaque contrast injection to ensure accurate delivery of the active drug. So far, the catheter placement has been at L5 vertebral level. The same location was used in the veterinary trial conducted by Dr. Dottie Brown in dogs with osteosarcoma.<sup>1</sup>

The lack of side effects or toxicity have led the clinical trial team to consider possible changes to the protocol that would enhance the effectiveness of SP-SAP in treating chronic pain. A primary endpoint of the trial is: response as defined by a 20% reduction in chronic pain or opioid dose within 4 weeks of treatment. One of the patients has clearly met this endpoint with reduction of pain medication by >20% during a 4-week period, following SP-SAP treatment.

Discussions are ongoing regarding several relevant issues that may affect efficiency of drug delivery and efficacy. 1) Modification of catheter placement may produce more selective responses and reduce required doses.

2) Targeting specific spinal segments using sclerotomes (Fig. 1) may be useful in delivering SP-SAP to a spinal cord location related to the pain origination. Cancer pain may be localized primarily to a bone; in these cases, using a sclerotomal map may help guide therapy to a specific nerve root and spinal cord location.



**Fig. 1 SCLEROTOME TARGETING<sup>2</sup>**

The sclerotome is the area of a bone innervated from a single spinal segment.

Denise Higgins, Editor



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# Product Managers Highlight Their Products



## MATTHEW KOHLS

While recombinant IB4-SAP (rIB4-SAP, Cat. #IT-10) has traditionally been used to eliminate cell populations that display alpha-D-galactose on the cell membrane, such as non-peptidergic c-fiber nociceptor neurons, it has also been found to be a very effective way to create stable transfected cell lines

without the use of drug resistance genes. A recent publication by Sato *et al.* (*J Biotechnology* 10(1):143-153, 2015) demonstrates a new use for this conjugate.



## LEONARDO ANCHETA

Looking for a new way to use our targeted toxins? Let ATS shed a little light on the subject. Researchers have used our targeted toxin technology in conjunction with photochemical internalization (PCI), a light-triggered technique that can help facilitate release of molecules from endocytic vesicles

once inside the cytosol. Researchers are using this method to overcome resistance that develops towards therapeutic agents or intracellular barriers encountered when introducing molecules into cancer cells. Berstad *et al.* (*Biochim Biophys Acta* 1820(12):1849-1858, 2012), Bostad *et al.* (*Mol Pharm* 11(8):2764-2776, 2014), and Berg *et al.* (*Methods Mol Biol* 635:133-145, 2010) demonstrate the use of this pairing with biotinylated antibodies combined with streptavidin-ZAP (Cat. #IT-27).



## LUCAS CHANCE

No, he's not a Product Manager. . . yet!

Welcome to Lucas Ancheta (son to Leonardo and Kate Ancheta), born April 14, 2015, weighing in at 5 lb, 2 oz.



## BRIAN RUSSELL

Opioid receptors are a group of inhibitory G protein-coupled receptors that are heavily involved in analgesia, respiratory depression, GI motility, and addiction. ATS has a comprehensive collection of products that help researchers illuminate the role of opioid receptors. Dermorphin-SAP (Cat. #IT-

12), Deltorphin-SAP (Cat. #BETA-006), Dynorphin-SAP (Cat. #IT-68), and Nociceptin-SAP (Cat. #BETA-001) have been shown to selectively eliminate cells expressing the mu (MOR), delta (DOR), kappa (KOR), or the ORL1 receptor, respectively. With these tools in hand, scientists have continued to discover new ways in which animals, and by extension, humans, respond to exogenous opioid therapy.



## PATRICK SHRAMM

Cannabinoid receptors are involved in a variety of physiological responses including appetite, pain sensation, mood, and memory. We are now offering Anti-CB1-SAP (Cat. #BETA-005) to target and eliminate cells that express the CB1 receptor. Take advantage of this targeted toxin while it's still available as a beta

product. If you're the first to publish data\* you'll receive a \$500 credit for use on ATS products.

*\*Data subject to review.*



## CHELSEA FRIEDMAN

Chlorotoxin, a peptide from the venom of the deathstalker scorpion, has been shown to bind to matrix metalloproteinase-2 (MMP-2) isoforms. These isoforms are upregulated in gliomas and other cancers of neuroectodermal origin, but are not normally expressed in the brain.

Chlorotoxin-SAP (Cat. #BETA-010) is a bonded toxin between chlorotoxin and saporin, and can be a helpful tool in your research by allowing you to specifically target and eliminate cells expressing MMP-2 isoforms without affecting other cells.

***Congratulations to the puzzle solvers from last quarter. Each winner will receive an ATS jigsaw puzzle.***

**Solve this quarter's teaser at  
[www.ATSBio.com/news/15q3\\_teaser.html](http://www.ATSBio.com/news/15q3_teaser.html)**

LAST QUARTER'S WINNERS: Glenn H. Kageyama, Cal Poly Pomona Univ \* Dave Ginsberg, Molecular Innovations \* Judene Bliss, Roswell Park Cancer Institute \* Daniel Pekala, Charles River Laboratories \* Joan Schein, Biochain \* Seto Chice, SUNY HSC at Brooklyn \* Bill Henry, Rhode Island Hospital





# Targeting Topics: Recent Scientific References

**Reviewed by Matthew Kohls**

## **Targeted ablation of cholinergic interneurons in the dorsolateral striatum produces behavioral manifestations of Tourette syndrome.**

Xu M, Kobets A, Du JC, Lenington J, Li L, Banasr M, Duman RS, Vaccarino FM, DiLeone RJ, Pittenger C.

*Proc Natl Acad Sci U S A* 112(3):893-898, 2015.

Postmortem studies of Tourette syndrome patients has revealed a reduction in the number of specific striatal interneurons. The authors explored the hypothesis that this neuronal deficit is enough to produce the symptoms of Tourette syndrome in mice. Animals received 90-ng injections of Anti-ChAT-SAP (Cat. #IT-42) into the striatum. Rabbit IgG-SAP (Cat. #IT-35) was used as a control. The data suggest that loss of the striatal interneurons is enough to produce some, but not all, of the symptoms caused by Tourette syndrome.

## **Role of striatal cholinergic interneurons in set-shifting in the rat.**

Aoki S, Liu AW, Zucca A, Zucca S, Wickens JR.

*J Neurosci* 35(25):9424-9431, 2015.

The authors examined the role that cholinergic interneurons in the striatum play in a process called strategy set-shifting, where an attentional shift is required. Rats received bilateral injections of Anti-ChAT-SAP (Cat. #IT-42) into either the dorsomedial striatum or ventral striatum (500 ng total). Initial task learning was unaffected by either lesion. Lesioned animals displayed set-shifting deficits, and the deficit characteristics depended on the location of the lesion.

## **A central role for spinal dorsal horn neurons that express neurokinin-1 receptors in chronic itch.**

Akiyama T, Nguyen T, Curtis E, Nishida K, Devireddy J, Delahanty J, Carstens MI, Carstens E.

*Pain* 156(7):1240-1246, 2015.

Chronic itch is caused by increased sensitivity of itch-signaling pathways. It can be generated by normally itchy stimuli (hyperknesis) and by normally non-itchy light touch (alloknesis). The authors used an

ovalbumin-induced atopic dermatitis model to study chronic itch in mice. The mice received 400-ng intrathecal injections of Bombesin-SAP (Cat. #IT-40), SSP-SAP (Cat. #IT-11), or the control Blank-SAP (Cat. #IT-21). While Bombesin-SAP significantly attenuated hyperknesis, it had no effect on spontaneous scratching or alloknesis. SP-SAP reduced all behavioral signs of chronic itch.



## **Neurokinin 3 Receptor-Expressing Neurons in the Median Preoptic Nucleus Modulate Heat-Dissipation Effectors in the Female Rat.**

Mittelman-Smith MA, Krajewski-Hall SJ, McMullen NT, Rance NE.

*Endocrinology* 156(7):2552-2562, 2015.

Kisspeptin and Neurokinin B (NKB) expression in the infundibular, or arcuate, nucleus is increased after menopause. Here the authors investigate whether KNDy (kisspeptin, NKB, and dynorphin expressing) neurons are able to influence cutaneous vasodilation through Neurokinin 3 (NK3)-expressing projections from the median preoptic nucleus (MnPO). Rats received two 10-ng injections of NK3-SAP (Cat. #IT-63) into the MnPO. Blank-SAP (Cat. #IT-21) was used as a control. The data indicate that NK3-expressing neurons in the MnPO facilitate vasodilation.

## **Hindbrain catecholamine neurons activate orexin neurons during systemic glucoprivation in male rats.**

Li AJ, Wang Q, Elsarelli MM, Brown RL, Ritter S.

*Endocrinology* Epub2015.

Norepinephrine and epinephrine-secreting catecholamine neurons are strong stimulators of food intake. The authors investigated the interaction between these catecholamine neurons and orexin neurons in the perifornical lateral hypothalamus (PeFLH), which are known to be involved with the

stimulation of food intake, increased arousal, and behavioral activation. Rats received 82-ng injections of Anti-DBH-SAP (Cat. #IT-03) into the PeFLH terminal field in order to lesion catecholamine neurons. Saporin (Cat. #PR-01) was used as a control. Assessment of food intake in response to 2-deoxy-D-glucose, as well as selective catecholamine activation, indicated that orexin neuron activation may be involved in glucoprivic appetite responses.

## **Orexin-A Enhances Feeding in Male Rats by Activating Hindbrain Catecholamine Neurons.**

Li AJ, Wang Q, Davis H, Wang R, Ritter S.

*Am J Physiol Regul Integr Comp Physiol* Epub2015.

Although administration of orexin, norepinephrine, and epinephrine all induce significantly increased food intake, the potential interaction between the networks affected by these molecules has not been studied. In this work, the authors investigate the hypothesis that orexin neurons may stimulate feeding through the activation of catecholamine neurons. Rats received 82-ng injections of Anti-DBH-SAP (Cat. #IT-03) into the hypothalamus in order to lesion hypothalamically-projecting catecholamine neurons. Saporin (Cat. #PR-01) was used as a control. While the normal response to orexin A is increased food intake, lesioned animals did not display this response, indicating that catecholamine neurons are necessary for orexin modulation of food intake.

## **Selective optogenetic stimulation of the retrotrapezoid nucleus in sleeping rats activates breathing without changing blood pressure or causing arousal or sighs.**

Burke PG, Kanbar R, Viar KE, Stornetta RL, Guyenet PG.

*J Appl Physiol* (1985) 118(12):1491-1501, 2015.

Hypoxia and hypercapnia both play roles in the activation of normal breathing. If either one is severe enough, arousal will also occur. The authors looked to better define the CNS pathways utilized by hypoxia and hypercapnia, as well as the pathways responsible for activation of arousal due to these conditions. The authors used optogenetic activation of the retrotrapezoid nucleus and C1 and A5 catecholaminergic

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# Targeting Topics: Recent Scientific References

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neurons, as well as selective C1 neuron stimulation in rats. Some rats also received bilateral injections of Anti-DBH-SAP (Cat. #IT-03) totaling 0.88 µg into the region of the lateral horn of the second thoracic segment.

## Role of cerebrospinal fluid-contacting nucleus in sodium sensing and sodium appetite.

Xing D, Wu Y, Li G, Song S, Liu Y, Liu H, Wang X, Fei Y, Zhang C, Li Y, Zhang L. *Physiol Behav* 147:291-299, 2015.

Sodium concentration in the cerebrospinal fluid (CSF) is tightly regulated, and this regulation requires numerous sensors spread throughout the brain. Here the authors injected 900 ng CTB-SAP (Cat. #IT-14) into the lateral ventricles. Investigation of spontaneous and induced sodium intake indicates the CSF-contacting nucleus is an important link in the sodium sensing network, and interacts with the lateral parabrachial nucleus.

## Inflammatory Macrophages Promotes Development of Diabetic Encephalopathy.

Wang B, Miao Y, Zhao Z, Zhong Y. *Cell Physiol Biochem* 36(3):1142-1150, 2015.

Diabetes can cause neuroinflammation leading to dementia. Diabetes was induced in mice by injection of streptozotocin (STZ). In order to investigate the role of inflammatory macrophages in the development of diabetic encephalopathy, the authors used twice weekly 20-µg IP injections of Mac-1-SAP (Cat. #IT-06). Mice receiving Mac-1-SAP had significantly reduced numbers of inflammatory macrophages in the brain, and also reduced responses to STZ injection.

## Striatal patch compartment lesions reduce stereotypy following repeated cocaine administration.

Murray RC, Logan MC, Horner KA. *Brain Res* Epub2015.

Stereotypy is defined as abnormally repetitive motor movements accompanied by an inability to initiate normal adaptive responses. Psychostimulants such as cocaine will often produce these movements. It is thought that stereotypy is related to

activation of the patch compartment of the striatum. In order to better understand the function of the patch compartment in stereotypy due to repeated exposure to cocaine, the authors administered bilateral injections of Dermorphin-SAP (Cat. #IT-12) into the rostral striatum. Saporin (Cat. #PR-01) was used as a control.



## Role of adrenomedullin in the cerebrospinal fluid-contacting nucleus in the modulation of immobilization stress.

Wu YH, Song SY, Liu H, Xing D, Wang X, Fei Y, Li GL, Zhang C, Li Y, Zhang LC. *Neuropeptides* 51:43-54, 2015.

The CSF-contacting nucleus (CSF-CN) is a brain structure containing neurons that can bidirectionally transmit signals between the brain parenchyma and the CSF. In order to better understand what regulatory peptides modulate this organ, the authors eliminated the CSF-CN of rats with a 500-ng icv injection of CTB-SAP (Cat. #IT-14). Saporin (Cat. #PR-01) was used as a control. The elimination of the CSF-CN worsened the response to chronic immobilization stress; with other data this information suggests that the CSF-CN uses adrenomedullin as a stress-related peptide.

## Treatment Considerations for Cancer Pain: A Global Perspective.

Pergolizzi JV, Gharibo C, Ho KY. *Pain Pract* Epub2014.

This review discusses the treatment of cancer pain, addressing various aspects of the overall picture, such as early pain treatment

to reduce central sensitization and chronic pain, pain assessment tools, and guidelines for treating specific populations of patients. Some of the current tools for pain management are discussed, including SP-SAP, which is currently in clinical trials as a cancer pain therapeutic (see cover article).

## Novel Mechanisms of Spinal Cord Plasticity in a Mouse Model of Motoneuron Disease.

Gulino R, Parenti R, Gulisano M. *Biomed Res Int* 2015:654637, 2015.

Here the authors investigate spinal plasticity mechanisms involving a number of different proteins, including BDNF, Shh, Notch-1, Numb, and Noggin. The model used is a mouse motoneuron depletion strategy, where the animals receive 3 µg of CTB-SAP (Cat. #IT-14) into each of the medial and lateral gastrocnemius muscles. The results indicate that TDP-43, a nuclear DNA/RNA binding protein, may be an important regulator of synaptic plasticity.

## Effects of immunotoxic and electrolytic lesions of medial septal area on spatial short-term memory in rats.

Dashniani M, Kruashvili L, Rusadze Kh, Mataradze S, Beselia G. *Georgian Med News* (239):98-103, 2015.

In this work the authors investigated how essential septohippocampal projections are in a spatial working memory model. Rats received bilateral injections of 192-IgG-SAP (Cat. #IT-01, 600 ng total) or GAT-1-SAP (Cat. #IT-32, 195 ng total) into the medial septum. Saporin (Cat. #PR-01) was used as a control.

## Selective lesion of gaba-ergic neurons in the medial septum by gat1-saporin impairs spatial learning in a water-maze.

Burjanadze M, Mataradze S, Rusadze K, Chkhikvishvili N, Dashniani M. *Georgian Med News* (240):59-64, 2015.

The authors investigated the role of GABAergic neurons in the medial septum on spatial learning using a Morris water maze test. Rats received bilateral injections totaling 162 ng of GAT-1-SAP (Cat. #IT-32) into the medial septum. Saporin (Cat. #PR-01) was used as a control. The lesioned animals

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# Targeting Talk: Product Q&A

**Q:** For *in vitro* cytotoxicity assays, could you tell me:

- 1) whether you incubate primary with your Saporin secondary for a specific amount of time prior to cell addition, and
- 2) do you use a single concentration of secondary per well or a primary:secondary ratio -- like 1:2 or 1:4?

**A:** The primary antibody should be incubated with the ZAP product for 20 min prior to addition to the cells. Internalization often happens so quickly that you would lose some efficacy due to the antibody being bound and internalized prior to the ZAP product complexing with the primary.

We do recommend maintaining a constant 5 nM (~ 45 ng/well) concentration of the ZAP product in the well and titrating your primary only. This way the EC<sub>50</sub> you generate will be the EC<sub>50</sub> of the primary antibody with all else held constant. The best starting concentration for your primary antibody is 10-100 nM in the well.

**Q:** Your targeted toxin kits come with different controls. I'm not sure of the best way to use them; there is included unconjugated antibody, unconjugated saporin, and a control conjugate, mouse IgG-SAP. Should I use them all in the same experiment or for different purposes?

**A:** For mouse IgG-containing conjugates, the ideal control is Mouse IgG-SAP (Cat. # IT-18). Mouse IgG-SAP — that is, saporin conjugated to mouse IgG — that has no specific antigen for targeting is the best control. Unconjugated saporin is still considered a second good control, useful in cases where down-regulation by the antibody is a concern.

**Q:** Which control is best to use with Octreotide-SAP?

**A:** The best control to use with Octreotide-SAP is Blank-SAP (Cat. #IT-21). Blank-SAP serves as a control for all our peptide-targeted SAP conjugates. Listed below are the appropriate controls to use with our primary saporin conjugates.

Send a message on our website to get answers to your targeting questions.

(continued from page 3)

displayed significant deficits during the water maze task, indicating that GABAergic neurons in the medial septum are intrinsic to organization of spatial map-driven behavior.

## Exploratory behavior and recognition memory in medial septal electrolytic, neuro- and immunotoxic lesioned rats.

Dashniani MG, Burjanadze MA, Naneishvili TL, Chkhikvishvili NC, Beselia GV, Kruashvili LB, Pochkhidze NO, Chighladze MR.

*Physiol Res* Epub2015.

To investigate recognition memory that incorporates a spatial or temporal component, the authors lesioned the medial septum of rats using several techniques. For specific lesioning of cholinergic neurons rats received bilateral injections of 192-IgG-SAP (Cat. #IT-01, 500 ng total) into the medial septum. Saporin (Cat. #PR-01) was used as a control. While electrolytic lesions produced disruptions of spatial recognition memory, immunotoxin lesions did not, indicating that the cholinergic neurons of the septohippocampal pathway are not essential to processing this type of learning.

## Appropriate Controls for Conjugates

Blank-CTA (IT-61)	peptide-targeted CTA conjugates	SP-CTA and Neurotensin-CTA
Blank-SAP (IT-21)	peptide-targeted SAP conjugates	SSP-SAP, MOR-SAP, CRF-SAP, NPY-SAP, CCK-SAP, Galanin-SAP, Bombesin-SAP, Oxytocin-SAP, Neurotensin-SAP, NK3-SAP, Dyno-SAP and NMB-SAP
Fab IgG-SAP (IT-67)	goat IgG Fab-ZAP secondary conjugates	Fab-ZAP mouse, Fab-ZAP human, Fab-ZAP rat, Fab-ZAP rabbit and FabFc-ZAP human
Goat IgG-SAP (IT-19)	goat IgG-containing targeted toxins	Mab-ZAP, Rab-ZAP, Hum-ZAP, Rat-ZAP, Anti-M-ZAP, Hug-M-ZAP and gPIG-ZAP
Human IgG-SAP (IT-49)	human IgG-containing targeted toxins	Custom Conjugates
Mouse IgG-SAP (IT-18)	mouse IgG-containing targeted toxins	192-IgG-SAP, OX7-SAP, Anti-DBH-SAP, ME20.4-SAP, Anti-SERT-SAP, Anti-CD25-SAP human, Mac-1-SAP rat, Anti-CD22-SAP, Anti-6 His-ZAP, Anti-GFP-ZAP, Anti-Basigin2-SAP, Anti-V5-ZAP, and Anti-FLAG (M5)-ZAP
Mouse IgM-SAP (IT-41)	mouse IgM-containing targeted toxins	Anti-M-ZAP
Rabbit IgG-SAP (IT-35)	rabbit IgG-containing targeted toxins	mu p75-SAP, GAT1-SAP, Goat-ZAP, Anti-ChAT-SAP, Melanopsin-SAP and Chick-ZAP
Rat IgG-SAP (IT-17)	rat IgG-containing targeted toxins	Mac-1-SAP, Anti-DAT-SAP, Anti-CD25-SAP mouse and Anti-CD103-SAP



# SP-SAP Human Clinical Trial for Cancer Pain

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3) Targeting specific myotomes (Fig. 2). Patients with sarcomas may have pain in a soft tissue that can be localized to a myotome and the nerve root(s) that innervate the area. Using information from the patient, physical examination, imaging and myotomal charts may help target treatment. For example, suppose a patient has a sarcoma arising from myotome-derived skeletal muscle that is predominantly innervated by the left L2 nerve root. Theoretically, a catheter could be placed posterior to where the left L2 nerve root enters the cord so that the injected SP-SAP would be close to the dorsal horn (which is the target).

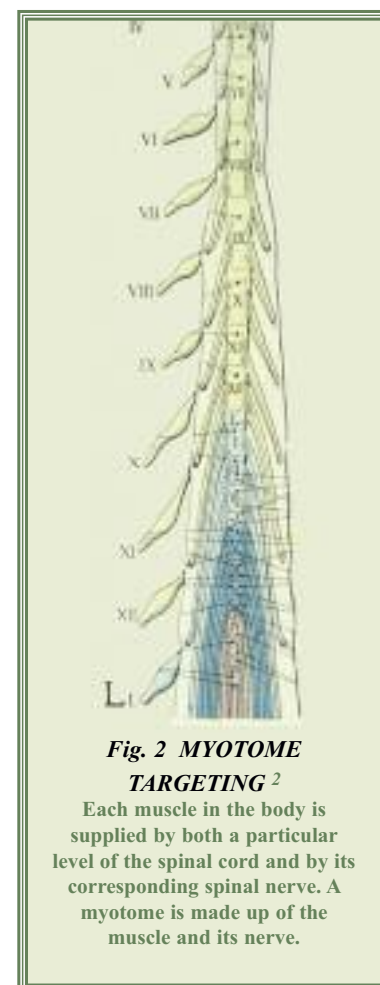
4) Consideration of the baricity of SP-SAP may also be useful to more efficiently direct the placement of the drug in the spinal fluid.

Along with discussions to improve drug delivery and efficacy are considerations of the patient population being treated now (end-stage cancer patients unresponsive to opioid treatment) and future populations that could benefit from treatment with SP-SAP. In the current trial, several patients had previous spine surgery that complicated the catheter placement for intrathecal treatment. Also, patients have had heterogeneous and progressive disease and worsening pain during the study, complicating the interpretation of responses. For example, several patients reported a reduction in opioid requirements and transient pain relief. In a population where pain continues to spread along with the cancer, it is difficult to determine if the transience is due to the dose level of SP-SAP (too little) or the establishment of 'new' pain.

End-stage cancer patients are a needy population that desperately need relief from chronic pain. The early signs of efficacy for SP-SAP are encouraging and the next doses (64 mcg and 90 mcg) may bring the long-term pain relief needed.

## References

1. Brown DC, Agnello K. (2013) Intrathecal substance p-saporin in the dog: efficacy in bone cancer pain. *Anesthesiology* 119(5):1178-1185.
2. *Sémiologie du système nerveux* by Dejerine, J. (Joseph Jules), 1849-1917, Published 1901.



**Fig. 2 MYOTOME  
TARGETING <sup>2</sup>**

Each muscle in the body is supplied by both a particular level of the spinal cord and by its corresponding spinal nerve. A myotome is made up of the muscle and its nerve.

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## Upcoming Events

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- Bovine IgG quantification kit (Cat. #RDB-05)
- Protein A quantification kit (Cat. #RDB-06)

# Targeting Tools: Beta Products

*Beta Products. Great Opportunity for Discovery at a Very Low Price.*



Saporin conjugates specifically eliminate cells identified by an extracellular marker. Each week we release new products for beta testing, so check out the website frequently (<http://atsbio.com/catalog/beta.php>). There are two conjugate configurations for Beta products. The first is a **direct conjugate** of the targeting agent to saporin; the second is a **bonded toxin** between the targeting agent and the secondary conjugate Streptavidin-ZAP (Cat. #IT-27; saporin attached to streptavidin).

## Each of the Beta products has:

- Saporin activity confirmed
- Peptide sequences and/or Antibody binding specificity published/confirmed

### *Nociceptin-SAP (Cat. #BETA-001)*

bonded toxin • targeting agent: nociceptin

### *Octreotide-SAP (Cat. #BETA-002)*

bonded toxin • targeting agent: octreotide peptide

### *Azido-ZAP (Cat. #BETA-003)*

direct conjugate • targeting agent: terminal azide group

### *Anti-CB1-SAP (Cat. #BETA-005)*

bonded toxin • targeting agent: Ab to hum/rat cannabinoid receptor 1

### *Deltorphin-SAP (Cat. #BETA-006)*

direct conjugate • targeting agent: deltorphin

### *Anti-OX1r-SAP (Cat. #BETA-007)*

bonded toxin • targeting agent: antibody to mouse, rat, guinea pig orexin 1 receptor

### *Anti-OX2r-SAP (Cat. #BETA-008)*

bonded toxin • targeting agent: antibody to rat orexin 2 receptor

### *Exenatide-4-SAP (GLP-1-SAP; Cat. #BETA-009)*

bonded toxin • targeting agent: exendin-4 peptide, a glucagon-like peptide-1 agonist

### *Chlorotoxin-SAP (Cat. #BETA-010)*

bonded toxin • targeting agent: chlorotoxin

### *CGRP-SAP (Cat. #BETA-011)*

bonded toxin • targeting agent: a-CGRP

### *Methotrexate-SAP (Cat. #BETA-012)*

direct conjugate • targeting agent: Methotrexate

### *MOA-SAP (Cat. # BETA-013)*

bonded toxin • targeting agent: blood group B lectin from Marasmius Oreades

### *Anti-PD-L1-SAP (Cat. #BETA-014)*

bonded toxin • targeting agent: antibody to human PD-L1

### *Anti-CD105-SAP (Cat. #BETA-015)*

bonded toxin • targeting agent: antibody to human CD105

### *Anti-CD38-SAP (Cat. #BETA-016)*

bonded toxin • targeting agent: antibody to mouse CD38

### *Anti-Cripto-SAP (Cat. #BETA-017)*

bonded toxin • targeting agent: antibody to mouse/human Cripto-1

### *Anti-CXCR4-SAP (Cat. #BETA-018)*

bonded toxin • targeting agent: antibody to human CXCR4

### *Anti-MC4R-SAP (Cat. #BETA-020)*

bonded toxin • targeting agent: antibody to human MC4R

### *ACTH-SAP (Cat. #BETA-021)*

bonded toxin • targeting agent: ACTH peptide

### *αMSH-SAP (Cat. #BETA-022)*

bonded toxin • targeting agent: αMSH peptide

### *Vasopressin-SAP (Cat. #BETA-023)*

bonded toxin • targeting agent: vasopressin peptide

### *Anti-CD15-SAP (Cat. #BETA-024)*

bonded toxin • targeting agent: antibody to CD15

### *Anti-CD24-SAP (Cat. #BETA-025)*

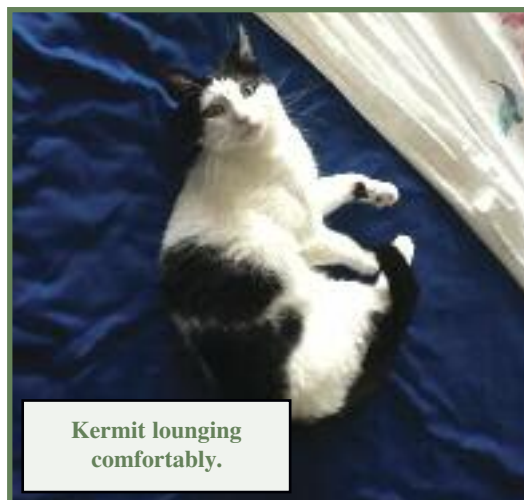
bonded toxin • targeting agent: antibody to human CD24

### *VIP-SAP (Cat. #BETA-027)*

bonded toxin • targeting agent: Vasoactive intestinal peptide

### *GnRH-SAP (Cat. #BETA-028)*

bonded toxin • targeting agent: GnRH peptide



Kermit lounging comfortably.

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## Targeting Technology

Advanced Targeting Systems' technology - Molecular Neurosurgery - is a modification of one of the most widely used techniques: surgical lesioning of a region and observation of the effect.

Choose an ANTIBODY<sup>§</sup> specific to your cell type.



SAPORIN is a potent cytotoxin. Safe in the lab. Lethal in the cell.

ATS binds SAPORIN with your ANTIBODY to make a powerful targeting agent.

§ or anything recognized on the cell surface and internalized.

The targeting agent is administered to the cells (*in vivo* or *in vitro*).

The antibody seeks out its target receptor on the cell surface.



Cells that do not have the receptor will not be affected.

The conjugate is internalized and SAPORIN breaks away from the antibody.



SAPORIN inactivates the ribosomes.

The result is **CELL DEATH**.

## Targeting Teaser

Unscramble these five Jumbles **taken from this issue's cover story**, one letter to each block, to solve the puzzle.

MOLESCROTE



CHEATTER



BRUMAL



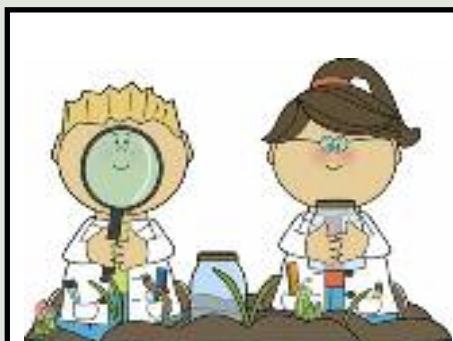
DULIF



VACATINING



ANSWER: THEY STUDIED THE ...



What the students did when school was out for the summer.

Arrange the circled letters to form the answer, as suggested by the above clue.

WIN!



**SOLVE** the puzzle online with the correct solution by September 30, 2015.

**WIN** a \$100 product credit!

[www.atsbio.com/news/15q3\\_teaser.html](http://www.atsbio.com/news/15q3_teaser.html)