

# Targeting Trends

Reporting the latest news in Molecular Surgery



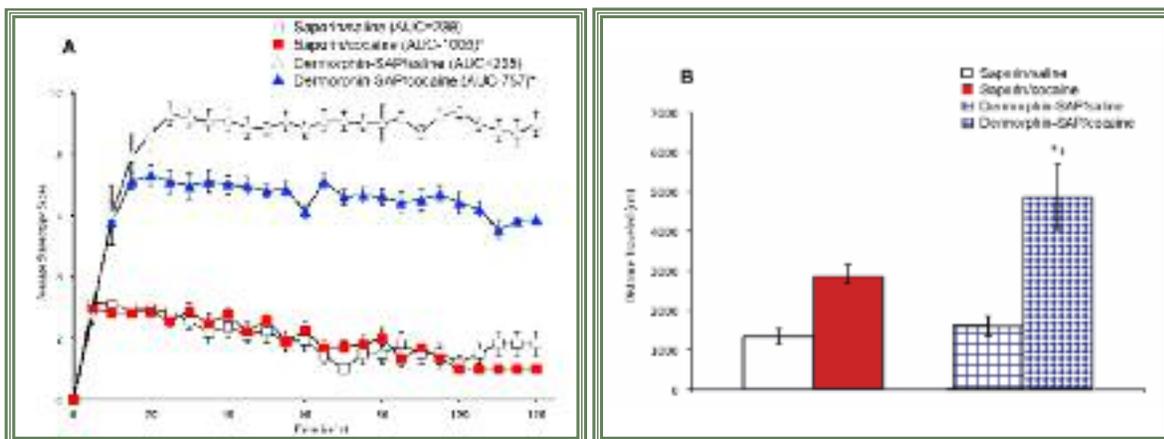
## Striatal patch compartment lesions reduce cocaine-induced repetitive behaviors

by Kristen Ashley Horner and collaborators R. Murray and M.C. Logan

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Repeated exposure to psychostimulants, such as cocaine, can result in patterns of repetitive, inflexible behaviors, known as stereotypy.<sup>1,2</sup> These inflexible behaviors are thought to be similar to the type of behaviors observed with certain psychiatric disorders, such as Tourette syndrome and obsessive-compulsive disorder.<sup>3</sup> Stereotypic behavior has been associated with enhanced activation of the patch compartment of striatum, relative to the surrounding matrix compartment.<sup>1,2</sup> The striatum is a component of the basal ganglia that is important for the initiation of voluntary movement based on the appropriate environmental context. Enhanced activation of the limbic-associated patch compartment within the striatum may result in the perpetuation of behaviors that are driven by internal emotional states. This occurs at the expense of normal adaptive behavioral responses that may be mediated by the matrix compartment which surrounds the patch compartment.<sup>1,3</sup> The functional role of the patch compartment in the development of these types of behaviors has not been previously investigated. Thus, we sought to determine the contribution of the neurons of the patch compartment to the emergence of stereotypy induced by psychostimulant exposure, by lesioning the patch compartment with Dermorphin-SAP (Cat. #IT-12) prior to treatment with repeated, high doses of cocaine.

Mu opioid receptors are densely expressed by the neurons of the patch compartment, while the neurons of the matrix compartment contain relatively few mu opioid receptors.<sup>4,5</sup> Thus, internalization of the Dermorphin-Saporin complex ultimately leads to the destruction of the mu



**Fig. 1:** Effects of intrastratial infusion of Dermorphin-SAP (17 ng/μl) and repeated cocaine treatment (25 mg/kg), twice daily for one week followed by a week-long drug-free period, with a subsequent cocaine challenge (25 mg/kg) on stereotyped behavior (A) and locomotor activity (B). Values are expressed as the mean ± SEM. For stereotyped behavior the area under the curve (AUC values are in parentheses). Locomotor activity is expressed as the total distance traveled for the entire 2-hr observation period in centimeters.

\*Significantly different from respective control group,  $p < 0.005$

+Significantly different from saporin (vehicle)-pretreated cocaine-treated group,  $p < 0.005$ .

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Denise Higgins, Editor



# New Beginnings

Denise Higgins, President



Welcome to Harrison James Russell!  
 Congratulations to proud parents: Candi and Brian Russell  
 Their bundle of joy arrived on December 7.

It's a new year. 2016. Another year passed and a brand new one to look forward to. After more than 21 years of serving the scientific community, Advanced Targeting Systems is making some changes and putting a 'fresh face' on things. Don't worry, we will still provide the same high level of service and expertise to help you move your research and discovery efforts forward.

One of the changes we have in store is a facelift for *Targeting Trends*, which Brian Russell (VP of Business Development) will be taking on as the new Editor in the next issue. This was going to happen with this first issue of the year, but as you can see by the beautiful picture here, he has had his hands full with the latest addition to his family. We are all so happy for him and Candi.

Besides his new role as Editor, Brian has also done a tremendous job with a redesign of the website -- executed skillfully and artfully by our webmaster and database guru, Kristen Hartman. We look forward to the exciting new

business development directions Brian will be unfolding.

Those are some of the new things in store for us this year. But before I close, a quick look back. Our illustrious leader, former president, founder, and scientific genius, Doug Lappi, continues to guide our science team and is enjoying a much-deserved 'semi-retirement' with his wife, Darlene. He still comes in every week and meets with the scientists and often gives us a challenge at the ping-pong table! I want to take this opportunity to state very clearly for all to read (old customers, new customers, friends, cat lovers, chronic pain drug development followers -- everyone): Doug Lappi is the Sower of the Saporin seeds that bloomed into a successful company dedicated to providing quality targeting reagents for scientific research and pharmaceutical development. His contributions to science, and the research tools his work has provided, have not only made ATS a successful company, but have advanced the careers of scientists throughout the world. Thank you, Doug.



Douglas Lappi, Ph.D.

American Academy of Pain Medicine,  
 Feb 18-21, 2016  
 Palm Springs, CA



Experimental Biology  
 April 2-6, 2016  
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 Booth #TBA

## Upcoming Events

### Targeting Teaser Solution

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- KNOWLEDGE
- STRIATUM
- DORSOMEDIAL
- VENTRAL

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*Congratulations to the puzzle solvers from last quarter. Each winner will receive a \$100 ATS product credit.*



# Targeting Topics: Recent Scientific References

Reviewed by **Matthew Kohls**

## Endogenous opioid activity in the anterior cingulate cortex is required for relief of pain.

Navratilova E, Xie JY, Meske D, Qu C, Morimura K, Okun A, Arakawa N, Ossipov M, Fields HL, Porreca F

*J Neurosci* 35(18): 7264-7271, 2015.

There are a number of neuronal circuits involved in the processing of pain, including those that control somatosensory, affective, and cognitive aspects of pain perception. Opioid signaling in the anterior cingulate cortex (ACC) plays a part in pain modulation - this area has also been implicated in the encoding of pain aversiveness. In order to examine the neuronal mechanisms of pain relief and the following reward, the authors of this paper administered 48 ng of Dermorphin-SAP (Cat. #IT-12) into the rostral ACC of rats. Saporin (Cat. #PR-01) was used as a control. The results illuminate the opioid pathway during pain treatment, and the dependence of nucleus accumbens dopaminergic transmission on upstream ACC opioid circuits during pain processing.

## proBDNF and p75NTR Control Excitability and Persistent Firing of Cortical Pyramidal Neurons.

Gibon J, Buckley SM, Unsain N, Kaartinen V, Seguela P, Barker PA

*J Neurosci* 35(26): 9741-9753, 2015.

Principal neurons in the entorhinal cortex (EC) display persistent firing (PF) during working-memory tasks. Much of the communication between the hippocampus and the neocortex passes through the EC, and the EC also receives some cholinergic input from the medial septum and diagonal band of Broca. In this work the authors investigated the role of pro-brain-derived neurotrophic factor (proBDNF) and the p75 receptor in excitability and PF in the EC. The authors propose the proBDNF/p75 system as a regulator for pyramidal neuron

excitability and PF in the EC, preventing runaway activity. Some of the western blot and current-clamp data was generated using Anti-p75 (Cat. #AB-N01; no concentration information provided).



## Repeated Mu-Opioid Exposure Induces a Novel Form of the Hyperalgesic Priming Model for Transition to Chronic Pain.

Araldi D, Ferrari LF, Levine JD

*J Neurosci* 35(36): 12502-12517, 2015.

Repeated administration of mu-opioid receptor agonists can lead to persistent mechanical hyperalgesia. One current hypothesis is that a form of hyperalgesic priming is triggered by the repeated activation of these receptors. Classic hyperalgesic priming is associated with signaling via protein kinase C $\epsilon$  (PK $\epsilon$ ), which is mediated by isolectin-B4+ (IB4) nociceptors. In this work the authors eliminated the IB4+ nociceptors with a 3.2  $\mu$ g intrathecal injection of recombinant IB4-SAP (Cat. #IT-10). The authors found that hyperalgesic priming induced through the use of DAMGO was dependent on protein kinase A activation rather than activation of PK $\epsilon$ . This work demonstrates a novel model for hyperalgesic priming transitioning to chronic pain.

## Roles of isolectin B4-binding afferents in colorectal mechanical nociception.

La JH, Feng B, Kaji K, Schwartz ES, Gebhart GF

*Pain*. 2015 Oct 5. [Epub ahead of print]

Primary afferent neurons are often classified as peptidergic or non-peptidergic. One characteristic of the non-peptidergic neurons is that they bind isolectin-B4. In the spinal cord these neurons terminate mainly in inner lamina II. Non-peptidergic neurons in the spinal cord have been found to be involved in various aspects of pain response. In this work the authors examined the role of non-

peptidergic neurons in the viscerosensory system. Rats received 1.5  $\mu$ g of intrathecal recombinant IB4-SAP (Cat. #IT-10) between the L5 and L6 vertebrae. Saporin (Cat. #PR-01) was used as a control. While IHC demonstrated that a majority of viscerosensory L6 colon DRG neurons are IB4+, they do not play a significant role in colorectal mechano-nociception.

## Phenotypic and functional characterization of Bst+/- mouse retina.

Riazifar H, Sun G, Wang X, Rupp A, Vemaraju S, Ross-Cisneros FN, Lang RA, Sadun AA, Hattar S, Guan MX, Huang T

*Dis Model Mech* 8(8): 969-976, 2015.

The belly spot and tail mutant mouse strain was first reported on in 1976. Among other phenotypic changes, it carries ocular mutations including retinal colobomas, reduced retinal ganglion cells (RGCs), and axon misrouting. In order to assess the use of this strain as a murine model for stem cell therapies of retinal degenerative diseases the authors performed a number of characterization experiments including electron microscopy, immunohistochemistry, testing of circadian rhythms, and morphological studies. Some of the immunohistochemistry was done using Anti-Melanopsin (Cat. #AB-N38) at a 1:5000 dilution.

## Disrupting spinal noradrenergic activation delays recovery of acute incision induced hypersensitivity and increases spinal glial activation in the rat.

Arora V, Morado-Urbina CE, Aschenbrenner CA, Hayashida KI, Wang F, Martin TJ, Eisenach JC, Peters CM

*J Pain*. 2015 Nov 3. pii: S1526-5900(15)00924-4 [Epub ahead of print]

A significant percentage of patients who undergo surgery experience prolonged clinically impactful pain, reducing the quality of life and physical function. Disruption of the descending noradrenergic input has been hypothesized to be important to the generation of this type of pain state. Using an acute incision model, the authors administered 5  $\mu$ g of Anti-DBH-SAP (Cat. #IT-03) to the L5-L6 interspace of rats. Mouse IgG-SAP (Cat. #IT-18) was used as a control. Lesioned animals demonstrated a

(continued on page 4)

**New versions of Orexin-SAP are now in development and production. If you are interested in testing Orexin-SAP and/or orexin receptor antibodies, please contact us.**

# Targeting Topics: Recent Scientific References

(continued from page 3)

significant increase in mechanical hypersensitivity, and a smaller increase in thermal hypersensitivity. This and other results suggest that spinally projecting noradrenergic pathways are necessary for normal recovery from surgical incision, and possibly other types of pain.

## Denervation of the Lacrimal Gland Leads to Corneal Hypoalgesia in a Novel Rat Model of Aqueous Dry Eye Disease.

Aicher SA, Hermes SM, Hegarty DM

*Invest Ophthalmol Vis Sci* 56(11): 6981-6989, 2015.

One result of functional disruption of the tear gland is dry eye disease (DED), which represents a group of disorders rather than a singular one. DED manifests itself in altered responses to noxious corneal stimulation, but many of these patients do not actually have dry eyes or tear gland dysfunction. In order to investigate what circuits are involved in DED the authors created two models, one of which used the ablation of p75 receptor-expressing neurons innervating the extraorbital lacrimal gland. Rats received 2.5 µg of 192-IgG-SAP (Cat. #IT-01) directly into the left extraorbital lacrimal gland. Tear production in the lesioned animals was normal, and responses to noxious cold stimuli were impaired. This accompanied by unchanged fiber density indicates that the nociceptive signaling was affected on a molecular level.

## Cholinergic deafferentation of the hippocampus causes non-temporally graded retrograde amnesia in an odor discrimination task.

Koppen JR, Stuebing SL, Sieg ML, Blackwell AA, Blankenship PA, Cheatwood JL, Wallace DG

*Behav Brain Res* 299: 97-104, 2015.

The memory impairments experienced in neurodegenerative disorders such as Alzheimer's disease have been well documented. One theory attributes these impairments to the loss of cholinergic basal forebrain neurons, a hallmark of Alzheimer's disease. Some patients experience a retrograde amnesia, in which older memories are relatively stable and more recent memories are frequently lost. The temporal relationship of memories to disease onset



has not been definitively established. In this work the authors administered either 150 ng or 200 ng of 192-IgG-SAP (Cat. #IT-01) into the medial septum of rats. Using a string-pulling task, a model for temporal learning was established. The results indicate that cholinergic projections originating in the medial septum are involved in long-term memory retrieval, and that loss of these neurons does not create a temporal type of amnesia.

## Selective inhibition of dopamine-beta-hydroxylase enhances dopamine release from noradrenergic terminals in the medial prefrontal cortex.

Devoto P, Flore G, Saba P, Frau R, Gessa GL  
*Brain Behav* 5(10): e00393, 2015.

Dopamine-beta-hydroxylase (DBH) is a neuronal enzyme that is a potential target for the treatment of cocaine abuse, alcohol dependence, and eating disorders. Here the authors administered 5 µg of icv Anti-DBH-SAP (Cat. #IT-03) to rats, and assessed the effect of the dopaminergic lesion on levels of extracellular dopamine. Mouse IgG-SAP (Cat. #IT-18) and saporin (Cat. #PR-01) were used as controls. Extracellular levels of dopamine were significantly increased in both lesioned animals and those treated with the DBH inhibitor nopicastat. Clonidine could reverse the nopicastat effect, but not the effect of Anti-DBH-SAP treatment. The data demonstrate a mechanism for the synergistic effect of cocaine on nopicastat-induced dopamine release.

## Treatment Efficacy of NGF Nanoparticles Combining Neural Stem Cell Transplantation on Alzheimer's Disease Model Rats.

Chen Y, Pan C, Xuan A, Xu L, Bao G, Liu F, Fang J, Long D

*Med Sci Monit* 21: 3608-3615, 2015.

NSC (neural stem cell) transplants into animals have been shown to compensate for the loss of cholinergic cells in the basal

forebrain, a hallmark of Alzheimer's disease. One hurdle to overcome is the actuation of NSC differentiation into the specific replacement cells needed. In this work the authors administered 5 µL of icv 192-IgG-SAP (Cat. #IT-01) to rats, followed by a graft of NSCs in the presence of NGF nanoparticles with a polymer coating. Rats receiving both NSCs and NGF nanoparticles showed significantly improved memory and learning functions as compared to control animals.

## Basal Forebrain Cholinergic Deficits Reduce Glucose Metabolism and Function of Cholinergic and GABAergic Systems in the Cingulate Cortex.

Jeong da U, Oh JH, Lee JE, Lee J, Cho ZH, Chang JW, Chang WS

*Yonsei Med J* Jan;57(1):165-72, 2016.

A common result of cholinergic neuron loss in the hippocampus and cortical regions due to Alzheimer's disease is a reduction in glucose metabolism. The authors examine the interaction between the cell loss and metabolic changes. Rats received 5-µg bilateral cortical injections of 192-IgG-SAP (Cat. #IT-01), were subject to water maze testing, and analyzed by 18F-2-fluoro-2-deoxyglucose positron emission tomography. Lesioned animals displayed decreased learning performance and reduced metabolic activity in the cingulate cortex.

## Method for Confirming Cytoplasmic Delivery of RNA Aptamers.

Dickey DD, Thomas GS, Dassic JP, Giangrande PH

*Methods Mol Biol* 1364: 209-217, 2016.

In this work the authors describe a protocol involving combining biotinylated aptamers and Streptavidin-ZAP (Cat. #IT-27) at a 4:1 molar ratio, then testing the conjugates in an *in vitro* cytotoxicity assay. FGF-SAP (Cat. IT-38) was used as a control. This is a method to confirm delivery of a payload by RNA aptamers to the cytoplasm of cells.

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## Targeting Talk: Product Q&A

**Q:** Our QA group wants to know about the safety of the toxin in your conjugates? What precautions should we take in handling saporin products?

**A:** Saporin is a Type 1 ribosome-inactivating protein (RIP), due to its N-glycosidase activity, from the seeds of *Saponaria officinalis*. It was first described by Fiorenzo Stirpe and his colleagues in 1983 in an article that illustrated the unusual stability of the protein.<sup>1</sup> Among the RIPs are some of the most toxic molecules known, including ricin and abrin (the latter is the poison preferred by the characters in movie *The Blue Lagoon*). These toxins contain a second protein strand that inserts the RIP into a cell, making it able to enzymatically inactivate the ribosomes, shutting down protein synthesis and resulting in cell death, and eventually causing death of the victim.

Saporin does not possess a cell-binding chain<sup>2</sup> and has no method of internalization without a targeting agent to escort it into a cell. It is this fact that also adds to the safety of its use in the lab. Autoclaving or exposure to 0.2 M NaOH is sufficient to decontaminate material that has been in contact with

Saporin and its conjugates. The LD<sub>50</sub> for Saporin in mice is 4-8 mg/kg;<sup>3</sup> this dosage amount would be insignificant in humans. Hundreds of articles in the scientific literature (search "Saporin" in Pub Med) have demonstrated tremendous specificity in targeting neuronal cells with many different Saporin conjugates and by many different scientists.

### REFERENCES

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2. Barthelemy I, Martineau D, Ong M, Matsunami R, Ling N, Benatti L, Cavallaro U, Soria M, Lappi DA. The expression of saporin, a ribosome-inactivating protein from the plant *Saponaria officinalis*, in *Escherichia coli*. *J Biol Chem.* 1993;268(9):6541-8. PMID: 8454624.
3. Stirpe F, Derenzini M, Barbieri L, Farabegoli F, Brown AN, Knowles PP, Thorpe PE. Hepatotoxicity of immunotoxins made with saporin, a ribosome-inactivating protein from *Saponaria officinalis*. *Virchows Arch B Cell Pathol Incl Mol Pathol.* 1987;53(5):259-71. PMID: 2889289.

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## Striatal patch compartment lesions reduce cocaine-induced repetitive behaviors

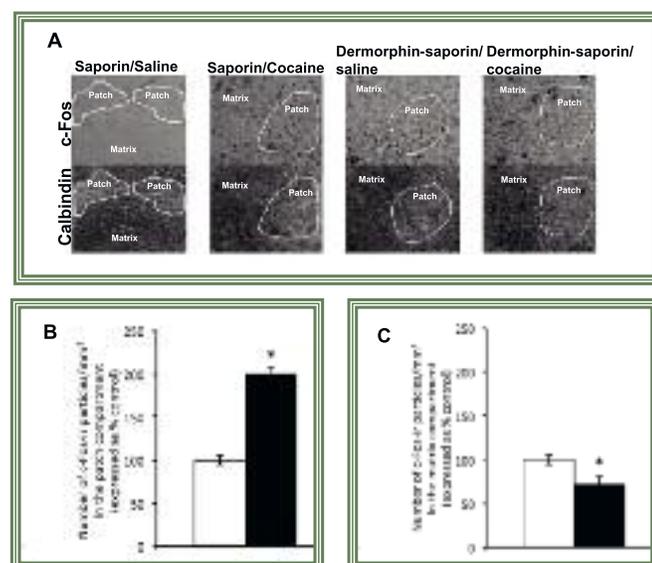
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opioid receptor-containing neurons of the patch compartment of striatum, while leaving non-mu opioid receptor-expressing neurons surrounding the patch compartment intact (Fig. 2). Animals were bilaterally-infused in the striatum with Dermorphin-SAP (17 ng/ $\mu$ l<sup>6</sup>) and allowed to recover for eight days. The animals were given daily injections of cocaine (25 mg/kg) or saline for one week, followed by a weeklong drug-free period.<sup>7</sup> Rats were then given a challenge dose of cocaine (25 mg/kg), placed in plexiglass chambers and the locomotor behavior was observed for 2h, followed by sacrifice. Stereotypic behaviors were rated on a scale from 1-10, with 10 representing the highest degree of the response 7-9. Stereotypy scores were generated by averaging the scores from four behavioral dimensions: repetitiveness/flexibility (the number of alternative motor responses emitted), frequency (the number of responses per unit time), duration [the percentage of time spent performing the most dominant response(s)] and the spatial distribution of the motor response.<sup>7,9</sup> Horizontal activity was defined as the number of quadrants the animal crossed on a 4 x 4 grid, using AnyMaze software (Stoelting, Wood Dale, IL, USA) and converted into centimeters.<sup>9</sup> The degree of activation in the patch and matrix compartments was determined using c-Fos immunohistochemistry, which is considered a ubiquitous indicator of neuronal activation, and was coupled with calbindin immunohistochemistry to delineate the patch and matrix compartments.

**RESULTS:** Dermorphin-SAP pretreatment significantly reduced the intensity of cocaine-induced stereotypy. Stereotypic behavior is also accompanied by a reduction in locomotor activity, and increased locomotor activity was seen in cocaine-treated animals that were pretreated with Dermorphin-SAP (Fig. 1). This pretreatment attenuated cocaine-induced c-Fos expression in the patch compartment, while enhancing cocaine-induced c-Fos expression in the matrix compartment (Fig. 2). The patch compartment is thought to mediate emotional and motivational aspects of behavior while the surrounding matrix compartment is important for processing externally-based sensorimotor information.<sup>7</sup> The current data show that animals that underwent patch compartment lesions prior to repeated cocaine exposure exhibited increased locomotor activity and diminished stereotypy and enhanced relative activation of matrix compartment. When the patch compartment is fully intact, a subsequent dose of cocaine may result in relatively greater activation of the patch-based circuits thereby masking the effects of the activation of matrix-based pathways, leading to greater levels of stereotypy as compared to locomotor activity. On the other hand, when the patch compartment is not fully functional, a subsequent dose of cocaine may tip the balance of activity in favor of the matrix compartment, leading to a greater degree of activation of the direct pathway, and increased locomotor activity, as compared to stereotypy. Together, these data indicate that the patch compartment of striatum is necessary for repetitive behavior and is an important component of the basal ganglia circuitry that mediates repetitive behaviors, and suggest that when the activity of this region is enhanced as a result of repeated psychostimulant exposure, internally-driven motivational states may overrule ongoing adaptive behaviors, leading to focused stereotypy and perhaps, maladaptive habitual behaviors.

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**Fig. 2:** Effects of Dermorphin-SAP pretreatment on cocaine-induced immunoreactivity in the patch and matrix compartments of striatum. Photomicrographs showing calbindin immunoreactivity and c-Fos immunoreactivity in adjacent sections of the striatum, superimposed over the calbindin-labeled sections (A). Quantitative analysis of c-Fos immunoreactivity in the patch (B) and matrix (C) compartments of rats intrastratially-infused with Saporin alone or Dermorphin-SAP (17 ng/ $\mu$ l), prior to repeated treatment with cocaine. Data are presented as the percent control of the number of c-Fos immunoreactive particles/mm<sup>2</sup> in the patch and matrix compartments.

\* $p < 0.05$  vs. saporin-pretreated control animals  
+ $p < 0.05$  vs. saporin-pretreated cocaine-treated animals.

# Targeting Tools: Featured Products

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

§ or anything recognized on the cell surface and internalized.

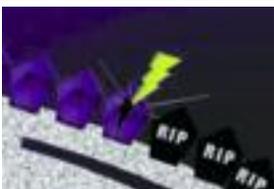
The targeting agent is administered to the cells (*in vivo* or *in vitro*).

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**.

### Daily Promotions on Targeting Tools

- Check our website daily
- Follow us on Twitter or LinkedIn
- Don't miss out on the savings!

#### January Specials from each of our Product Managers



#### 10% Discount

Orders placed directly through the website receive 10% off throughout January by clicking on **My Account**, registering, and entering Promo Code: **WEB2016**. *Brian Russell*

#### Save 10% on IB4 products

We created a better version of **isolectin B4!** This recombinant version has all the binding properties of the native protein, but no contamination from other lectins. Use Discount Code **IB4Tools0116**. *Matt Kohls*



#### Targeting p75 – 10% off

Mouse, rat and various mammalian species like humans, primates and rabbits; that's what you can **target with our low affinity nerve growth factor receptor** (p75NTR) saporin-conjugates. Use Discount Code **p75ntr0116**. *Leonardo Ancheta*

#### Discounts on Antibodies to Small Molecules

Order any of our **AB-T antibodies**, receive 10% the total price if you also order the corresponding antigen. Small molecules can be a part of radical processes, vitamins, neurotransmitters, bacteria strains, and even 2nd generation antibodies. Use Discount Code **abt0116**. *Patrick Shramm*



#### FGF Targeting

I've got a great promo for all of you FGF researchers! We're offering a **10% discount** on **50 FGF products** including ligands, receptors, antibodies and even our targeted toxin! Enter coupon code **FGF0116** at checkout. *Chelsea Friedman*