Jan-Feb-Mar 2017 Vol. 18, Iss. 1

Targeting Trends

Reporting the latest news in Molecular Surgery

The locus coeruleus: a potential link between cerebrovascular and neuronal pathology in Alzheimer's disease.

Contributed by S C Kelly, P T Nelson, S E Counts

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that most commonly affects individuals over the age of 65. While of unknown etiology, AD is characterized by a steady decline in cognitive functions including memory, attention, executive functions, and language. There is currently no disease-modifying therapy for the disease, and treatments to date have only yielded modest, short-term symptomatic relief. Recently, the "vascular hypothesis" of AD was proposed, due to the high comorbidity of individuals with cerebrovascular disease (CVD) and AD. These two diseases share similar risk factors and can both lead to dementia, neuronal injury, and neurological dysfunction, suggesting that AD pathogenic mechanisms may involve a dysregulaton of the cerebrovasculature and compromise of neurovascular functioning. However, the potential common mechanisms linking CVD and AD remain unknown.

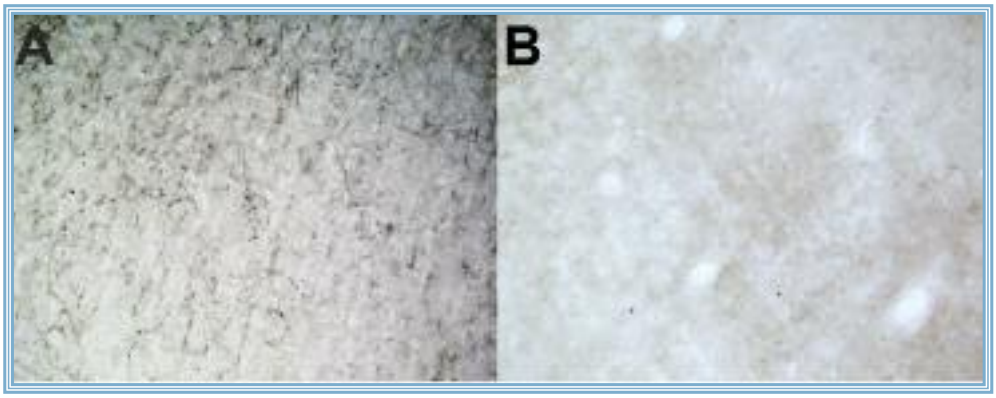

Figure 1: Anti-DBH-SAP lesioned animals are nearly completely depleted of noradrenergic innervation to the PFC. A) Intact innervation of DBH fibers in PFC of control IgG lesioned animal. B) Little to no immunoreactivity for DBH observable in PFC of Anti-DBH-SAP lesioned animal.

In this regard, the locus coeruleus (LC) projection system, which provides the sole source of norepinephrine (NE) to the forebrain, mediates attention, memory, and executive function as well as cerebrovascular function and undergoes severe cell loss in AD.[1] Furthermore, LC-mediated NE signaling is thought to play a role in blood brain barrier maintenance and neurovascular coupling, suggesting that LC degeneration may impact the high comorbidity of CVD and AD. However, the extent to which LC projection system degeneration impacts neurovascular function in AD is unclear.

To model these relationships *in vivo*, we stereotactically lesioned LC projection neurons (Fig. 1; Anti-DBH-SAP Cat. #IT-03) innervating the prefrontal cortex (PFC), a major LC projection zone, in the TgF344-19 rat model of AD (aged 6

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Accelerating Your Research

Denise Higgins - President

As we start a new year, we at Advanced Targeting Systems are more dedicated than ever to providing our customers with the innovate, cutting-edge tools that will accelerate and optimize research. Scientists around the world have published exciting new data to advance our knowledge of how specific cell types affect behavior and disease. With each new discovery, possibilities move closer to realities for unraveling the molecular basis for behavioral abnormalities and cures for devastating diseases.

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CONTROL: p75NTR-positive neurons of rat cholinergic forebrain

TREATED: After icv injection of 192-IgG-SAP (Cat. #IT-01)

Photo provided by C Wrenn & RG Wiley

These are just a few examples of the ATS tools available to accelerate your research. You can browse all products on our website. Use the Search form to find an antibody or other research tool compatible with your interests.

It is an honor to have served the scientific community for almost 23 years. Thank you for the opportunity. Let me know if there is anything more we can do to help keep your research on target.

Have a great 2017!

The latest addition to the Ancheta family!

Leonardo Ancheta has been an important part of ATS since 2003. He started out in laboratory research, quickly excelled in flow cytometry, and then took on product management responsibilities. Leonardo is now not only a Product Manager for ATS, but is also Director of CytoLogistics, an ATS partner providing contract laboratory services and flow cytometry.

Congratulations are in order for Leonardo and his wife, Kate, on the birth of their second child, Lila. She made her first appearance on February 18.

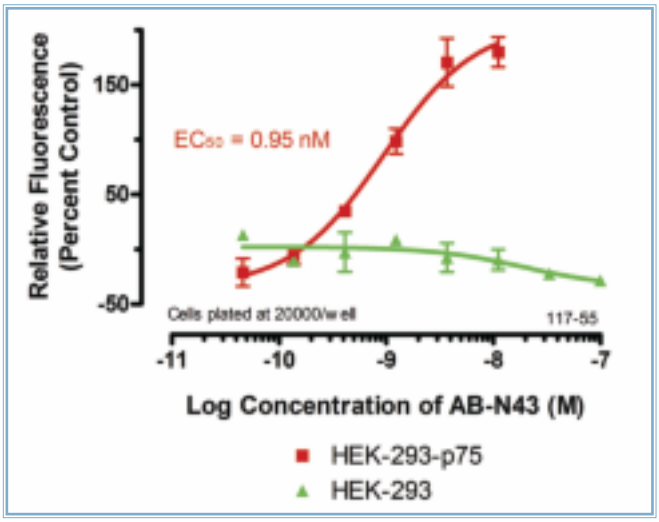
Welcome Princess Lila!

Proud Parents: Leonardo and Kate Ancheta
Proud Brother: Lucas

Fab-pHAST: The newest targeting tool

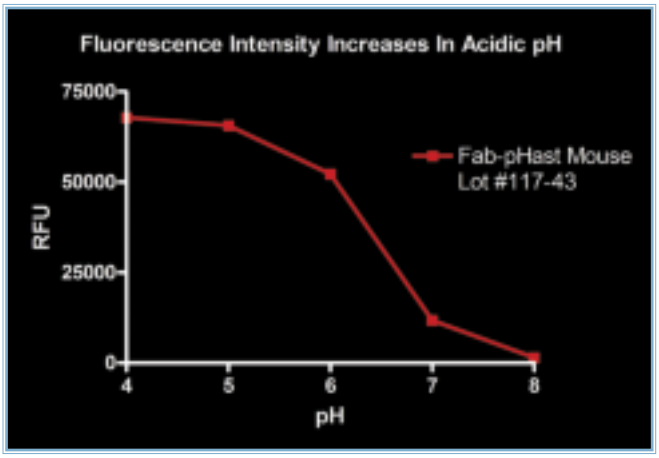
Contributed by Patrick Shramm, Product Manager for Fab-pHast

We are pleased to announce a new set of tools to rapidly screen antibodies, Fab-pHast conjugates. The ATS pHAST product line provides the FASTEST results in quantitative testing of your antibody's specific-binding and internalization. Fab-pHast contains a pH-dependent fluorescent reporter that increases intensity in acidic surroundings, such as the environment inside a cell. You just mix the Fab-pHast with your antibody, add to cells, and in less than 24 hours you have illuminated your lead antibody candidates!



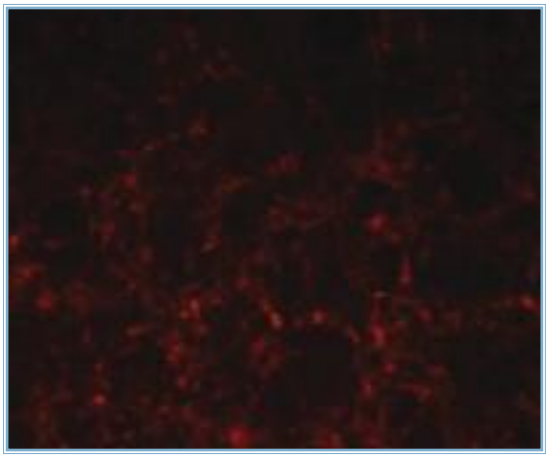
pHast Ab Internalization Assay: Parental HEK-293 cells, and HEK-293 cells transfected with the p75 receptor, were plated in a 96-well plate overnight. Titrated 192-IgG antibody (Cat. AB-N43) was incubated at RT with 50 nM of Fab-pHast Mouse (Cat. PH-02) for 20 minutes prior to addition to cells. Plates were incubated overnight to allow maximum internalization, but a few hours is sufficient for detection. Plates were read on a Spectra Max Gemini EM (Ex: 532nm/Em: 560nm). Data analysis was done by PRISM (GraphPad, San Diego).

When ordering, be sure to choose the appropriate species for your primary antibody. These products are designed to provide an EC_{50} by way of a fluorescence-detecting plate reader. Your best candidates reach maximum intensity overnight, but you can make quantitative decisions in just a few hours. Other applications include qualitative visualization under a fluorescent microscope or analysis via flow cytometry.



Fluorescence (RFU) is shown as a function of pH for Fab-pHast Mouse (Cat. PH -02).

The more acidic pH shows a large amount of fluorescence, while the basic pH shows almost no fluorescence. Plates read on a Spectra Max Gemini EM (Ex: 532nm/Em: 560nm).



ICC image of Anti-NGFr (192-IgG, Cat. AB-N43) illuminated with Fab-pHast Mouse (Cat. PH-02). Cells were plated at 20,000 cells/well in a 96-well plate and allowed to adhere overnight. 10 nM of primary antibody was incubated at RT with 30 nM of Fab-pHast. Cells were incubated overnight to allow maximum internalization, although internalization can be detected in a few hours. Cells were analyzed on a Leica microscope under 20X magnification using a Y3 filter cube.

Recent Publications & References

Photoentrainment and Pupillary Light Reflex Are Mediated By Distinct Populations of Iprgcs.

Chen SK, Badea TC, Hattar S.

Nature 476(7358):92-95, 2011. PMID: 21765429

Intinsically photosensitive retinal ganglion cells (ipRGCs) express the photopigment melanopsin and regulate a wide array of light-dependent physiological processes. Genetic ablation of ipRGCs eliminates circadian photoentrainment and severely disrupts the pupillary light reflex (PLR). Molecularly distinct subpopulations of M1 ipRGCs innervate different brain regions to execute light-induced functions. A dilution of 1:1000 of Anti-Melanopsin (Cat. #AB-N38) was used for immunohistochemical analysis of retina sections.

Gate Control of Mechanical Itch By a Subpopulation of Spinal Cord Interneurons.

Bourane S, *et al.*

Science 350(6260):550-54, 2015. PMID: 26516282

Light mechanical stimulation of the hairy skin can induce a form of itch known as mechanical itch, normally suppressed by inputs from mechanoreceptors. However, in many forms of chronic itch this gating mechanism is lost. This study reveals a dedicated spinal cord inhibitory pathway that gates the transmission of mechanical itch. Mice were given an intrathecal injection of 400 ng Bombesin-SAP (Cat. #IT-40) in 10 ml of sterile saline to ablate GRPR-expressing neurons.

Different Immune Cells Mediate Mechanical Pain Hypersensitivity in Male and Female Mice.

Sorge RE, *et al.*

Nat Neurosci 18(8):1081-83, 2015. PMID: 26120961

A large and rapidly increasing body of evidence indicates that microglia-to-neuron signaling is essential for chronic pain hypersensitivity. Using multiple approaches, the authors found that microglia are not required for mechanical pain hypersensitivity in female mice; female mice achieved similar levels of pain hypersensitivity using adaptive immune cells, likely T lymphocytes. This sexual dimorphism suggests that male mice cannot be used as proxies for females in pain research. Mac-1-SAP mouse/human toxin (Cat. #IT-06, 15 µg in 8.8 µl) and Saporin control (Cat. #PR-01, 8.8 µg in 8.8 µl) were administered via i.t. injection.

C-Terminal Phosphorylation Regulates the Kinetics of a Subset of Melanopsin-Mediated Behaviors in Mice.

Somasundaram P, *et al.*

Proc Natl Acad Sci U S A 2017. PMID: 28223508

The authors show that the melanopsin photoresponse shutoff due to C-terminal phosphorylation determines the kinetics of the intrinsic light response in ipRGCs, the PLR, and reentrainment, but not masking and phase angle of entrainment. Immunofluorescence was performed using rabbit Anti-Melanopsin (1:1,000, Cat.# AB-N38) as the primary antibody with a 2-d incubation period, followed by goat anti-rabbit IgG 488 as the secondary antibody.

Rehabilitation Drives Enhancement of Neuronal Structure in Functionally Relevant Neuronal Subsets.

Wang L, *et al.*

Proc Natl Acad Sci U S A 113(10):2750-55, 2016. PMID: 26903653

In this study, the authors show that intense rehabilitation training after focal brain injury drives significant structural changes in brain cells located adjacent to the injury. Importantly, the basal forebrain cholinergic system is required for enabling rehabilitation to impact brain structure. Rats underwent cholinergic ablations by injecting 192-IgG-SAP (Cat. #IT-01) into the nucleus basalis (0.2-0.25 mcl of 0.375 mg/ml solution in artificial CSF).

Antibody Therapy Targeting Cd47 and Cd271 Effectively Suppresses Melanoma Metastasis in Patient-Derived Xenografts.

Ngo M, *et al.*

Cell Rep 16(6):1701-16, 2016. PMID: 27477289

This study involved antibody-mediated blockade of CD47 coupled with targeting of CD271+ melanoma cells by way of ME20.4-SAP (Cat. #IT-15). Mice bearing human melanoma tumor were randomized into four treatment groups with one group treated with ME20.4-SAP (1 mcg/50 mcl) injected directly into the center mass of the tumor once every 2 days. A therapeutic effect was observed.

Targeting Cd73 in the Tumor Microenvironment With Medi9447.

Hay CM, *et al.*

Oncoimmunology 5(8):e1208875, 2016. PMID: 27622077

Administration of MEDI9447 results in relief from adenosine monophosphate (AMP)-mediated lymphocyte suppression *in vitro* and inhibition of mouse syngeneic tumor growth *in vivo*. *In vitro* experiments validating the internalization of antibodies into cell lines MDA-MB-231 and 4T1 were measured using the Fab-ZAP human antibody internalization kit (Cat. #KIT-51-Z). Based on these data, a Phase I study to test the safety, tolerability, and clinical activity of MEDI9447 in cancer patients was initiated (NCT02503774).

Impact of Altered Cholinergic Tones on the Neurovascular Coupling Response to Whisker Stimulation.

Lecrux C, *et al.*

J Neurosci 37(6):1518-31, 2017. PMID: 28069927

The authors assessed the effects of varying ACh tone on whisker-evoked NVC responses in rat barrel cortex. ACh depletion was achieved via unilateral icv injection (4 mcg/2 mcl) with 192 IgG-SAP (Cat# IT-01) or saline. They conclude that ACh is not only a facilitator, but also a prerequisite for the full expression of sensory-evoked NVC responses

A Non-Inheritable Maternal Cas9-Based Multiple-Gene Editing System in Mice.

Sakurai T, *et al.*

Sci Rep 6:20011, 2016. PMID: 26817415

Yhe authors generated transgenic mice with systemic Cas9 overexpression to simplify generation of genetically-modified animals using the CRISPR/Cas9 system. Primary fibroblasts from Cas9 mice transiently transfected with Ggta1 gRNA

Recent Publications & References

(continued from page 4)

and then treated the fibroblasts with rIB4-SAP (Cat. #IT-10). Ggta1 +/+ and KO/+ cells were killed, while biallelic Ggta1 KO cells survived as they did not synthesize the α-Gal epitope. This method has potential to generate other genetically-modified animals.

Acute Hypoxia Activates Hypothalamic Paraventricular Nucleus-Projecting Catecholaminergic Neurons in the C1 Region.

Silva TM, Takakura AC, Moreira TS.

Exp Neurol 285(Pt A):1-11, 2016. PMID: 27569537

This study suggests that catecholaminergic C1-PVH projection is hypoxia-sensitive and the pathway between these two important brain areas can be one more piece in the complex puzzle of neural control of autonomic regulation during hypoxia. Rats were injected with Anti-DβH-SAP (Cat. #IT-03), 21 ng/100 nl unilaterally into the PVH.

Targeted Ablation of Cardiac Sympathetic Neurons: A Promising Approach to Prevent Sudden Cardiac Death.

Xia W, Liu Y.

Int J Cardiol 202:425-26, 2016. PMID: 26433164

The authors demonstrate that targeted ablation of cardiac sympathetic neurons by bilateral stellate ganglia injection of CTB-SAP (Cat. #IT-14) is a novel method for sympathetic blockade. CTB-SAP is retrogradely transported to the plasma membranse of sympathetic preganglionic neurons (SPNs) and bind to the GM1 gangliosides and subsequently ablate these neurons.

Cholinergic Basal Forebrain Lesion Decreases Neurotrophin Signaling Without Affecting Tau Hyperphosphorylation in Genetically Susceptible Mice.

Turnbull MT, Coulson EJ.

J Alzheimers Dis 55(3):1141-54, 2017. PMID: 27767994

The authors investigated whether degeneration of basal forebrain cholinergic neurons (BFCNs) and/or resultant decrease in neurotrophin signaling cause aberrant tau hyperphosphorylation. Mice were infused with mu p75-SAP (Cat. #IT-16) at a concentration of 0.4 mg/ml or control Rabbit IgG-SAP (Cat. #IT-35).

Characterization of the First Fully Human Anti-Tem1 Scfv in Models of Solid Tumor Imaging and Immunotoxin-Based Therapy.

Yuan X, *et al.*

Cancer Immunol Immunother 2016. PMID: 27933426

MS1 and MS1-hTEM1 cells were treated with site-specific biotinylated scFv78 conjugated with Streptavidin-ZAP (Cat. #IT-27) at a molar ratio of 4:1 (scFv78:ZAP) starting from 40 nM serially diluted down to 0.04 nM. The scFv78-saporin immunoconjugate exerted dose-dependent cytotoxicity with high specificity to TEM1-positive cell *in vitro*.

Differential Roles for Cortical Versus Sub-Cortical Noradrenaline and Modulation of Impulsivity in the Rat.

Benn A, Robinson ES.

Psychopharmacology (Berl) 234(2):255-66, 2017. PMID: 27744551

Rats received bilateral injections of Anti-DβH-SAP (Cat. #IT-03), 0.02 mcg in 0.5 mcl into the PFC and 0.004 mcg.0/.2 mcl for NAcSh lesions. Data suggest that noradrenaline in the nucleus accumbens shell plays an important role in the effects of atomoxetine.

Neuroprotective Effects of Testosterone Metabolites and Dependency on Receptor Action on the Morphology of Somatic Motoneurons Following the Death of Neighboring Motoneurons.

Cai Y, Chew C, Muñoz F, Sengelaub DR.

Dev Neurobiol 2016. PMID: 27569375

This study examined whether the protective effects of testosterone could be mediated via its androgenic or estrogenic metabolites and if these neuroprotective effects were mediated through steroid hormone receptors. These motoneurons were lesioned by intramuscular injection of CTB-SAP (2 ul, 0.1%l Cat. #IT-14).

Transcriptomic Analysis of Mouse Cochlear Supporting Cell Maturation Reveals Large-Scale Changes in Notch Responsiveness Prior to the Onset of Hearing.

Maass JC, *et al.*

PLoS One 11(12):e0167286, 2016. PMID: 27918591

The authors examined the regenerative potential of supporting cells in production of hair cells in response to a blockade of the Notch signaling pathway at the time of birth, but a complete lack of response just a few days later. Analysis included IHC on frozen sections of paraformaldehyde-fixed temporal bones of LfngEGFP mice. Anti-NGFr (mup75; Cat. #AB-N01AP)

Lack of Phenotypical and Morphological Evidences of Endothelial to Hematopoietic Transition in the Murine Embryonic Head During Hematopoietic Stem Cell Emergence.

Iizuka K, *et al.*

PLoS One 11(5):e0156427, 2016. PMID: 27227884

The authors analyzed both c-Kit hematopoietic cluster and Runx1 hemogenic endothelium in the whole-head vasculature. Alexa488 labeled anti-NGFr (Cat. #FL-N01AP) was used in flow cytometry.

The P75 Neurotrophin Receptor Augments Survival Signaling in the Striatum of Pre-Symptomatic Q175(wt/hd) Mice.

Wehner AB, *et al.*

Neuroscience 324:297-306, 2016. PMID: 26947127

The authors investigated the role of p75 in the Q175 knock-in mouse model of Huntington's Disease by examining levels of activation of downstream signaling molecules to determine if p75 represents a promising therapeutic target. Anti-NGFr (mup75; Cat. #AB-N01AP) was used at a 1:2000 dilution in immunoblotting.

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The locus coeruleus: a potential link in Alzheimer's disease.

(continued from page 1)

months old) using the noradrenergic immunotoxin, dopamine-β-hydroxylase (DBH)-saporin or a control Mouse IgG-Saporin (Mouse IgG-SAP Cat. #IT-18; n = 7-9/group). Prior to sacrifice, at 1-month post-op, the rats were tested behaviorally on the Barnes maze task—a special learning and memory paradigm. Rats that received the Anti-DBH-SAP lesion were significantly slower to find the escape cage in the maze (Fig. 2). Additionally, the lesioned rats continued to investigate incorrect holes multiple times showing a deficit in working memory. This behavioral deficit in particular is indicative of LC dysfunction in the PFC. These rats showed no locomotor differences as determined by the open field test (not shown). To continue this study, postmortem PFC will be analyzed for LC fiber innervation, NE levels, and cerebrovascular (cerebral amyloid angiopathy, micro-hemorrhage, cerebral artery endothelial remodeling) and AD-like pathology (amyloid load, tau epitopes, inflammation). We will determine the extent to which CVD and AD pathologic variables correlate with noradrenergic innervation and behavioral outcomes. We hope these studies will elucidate noradrenergic pathways contributing to neurovascular pathology and cognitive decline during the onset of AD and provide therapeutic rationale for targeting LC neuroprotection to modify disease progression.

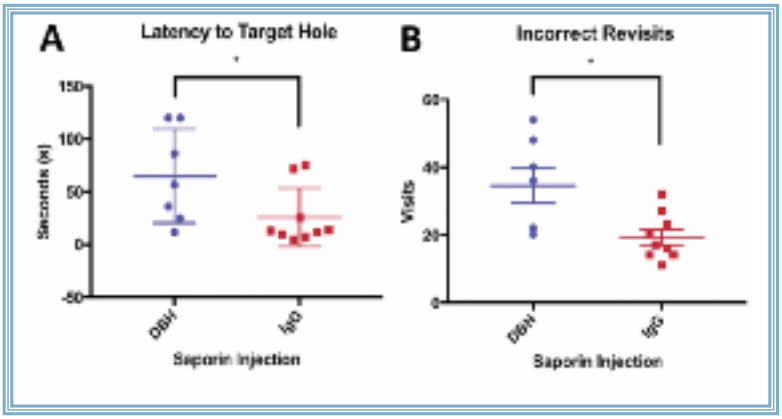

Figure 2: Anti-DBH-SAP lesioned animals are significantly impaired on the Barnes Maze task compared to performance of control saporin (IgG) injected animals

A) IgG Animals were significantly faster to find target hole than Anti-DBH-SAP lesioned animals on the probe trial (P= 0.476)

B) Anti-DBH-SAP lesioned animals revisited more holes that they had already investigated indicating a deficit in working memory (P=0.0110)

Reference

1. Bondareff W, Mountjoy CQ, and Roth M (1981) Selective loss of neurones of origin of adrenergic projection to cerebral cortex (nucleus locus coeruleus) in senile dementia. *Lancet* 1(8223):783-4.

(continued from page 5)

Immunohistochemical Detection of Corticotropin-Releasing Hormone (Crh) in the Brain and Pituitary of the Hagfish, Eptatretus Burgeri.

Amano M, *et al.*

Gen Comp Endocrinol 236:174-80, 2016. PMID: 27444128

Anti-CRH (Cat. #AB-02) was used to better understand the neuroendocrine system of hagfish. A standard curve was obtained from 0.78 ng/ml to 50 ng/ml.

Participation of D-Serine in the Development and Reproduction of the Silkworm Bombyx Mori.

Tanigawa M, Suzuki C, Niwano K, Kanekatsu R, Tanaka H, Horiike K, Hamase K, Nagata Y.

J Insect Physiol 87:20-29, 2016. PMID: 26828952

The authors used rabbit antibody against glutaraldehyde-conjugated D-alanine (Cat. #AB-T049) to examine the distribution of D-alanine throughout the silkworms.

Differentiation Defect in Neural Crest-Derived Smooth Muscle Cells in Patients With Aortopathy Associated With Bicuspid Aortic Valves.

Jiao J, Xiong W, Wang L, Yang J, Qiu P, Hirai H, Shao L, Milewicz D, Chen YE, Yang B.

EBioMedicine 10:282-90, 2016. PMID: 27394642

Anti-NGFr (ME20.4, p75, Cat. #AB-N07) was used for the immunofluorescence staining and flow cytometry of NCSCs.

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If so, please send a PDF of your publication to admin@atsbio.com so we can feature your research in our next issue!

Talking about Targeting

Advanced Targeting Systems offers a full line of antibodies to neurotransmitters; everything from serotonin and L-DOPA, to noradrenaline and dopamine. These antibodies are an excellent choice for immunohistochemistry applications as they are ideally primed for use in tissues that have been perfused with a mixture of paraformaldehyde and gluteraldehyde.

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Q: Could you confirm if Anti-Conjugated Caprylic Acid (Cat. #AB-T084) can detect free Caprylic acid or only when conjugated with BSA or another carrier protein?

A: This antibody does not recognize BSA or need Caprylic acid to be conjugated to BSA in order for it to bind. However, it DOES need to be used in the presence of gluteraldehyde in order to create the proper epitope for the antibody to recognize the Caprylic acid.

Q: I was wondering whether it could be possible to receive more information about the Gibberellic acid antibody (Cat. #AB-T130)? Is it possible to use this antibody to recognize free gibberellic acid by a direct ELISA system?

A: The most common use for this product is immunohistochemistry. ELISA is used to test cross-reactivity and is not a recommended application for these antibodies. On its own, gibberellic acid is too small a molecule to provide a complete effective epitope, so for IHC the tissue is perfused with a gluteraldehyde component which provides the epitope complement needed for the antibody to recognize gibberellic acid.

Q: For your conjugated neurotransmitter antibodies, what concentrations and sizes do you provide?

A: All of these antibodies are sold in 50-mcl volumes. No concentrations are needed for these products as they all have recommended dilutions for use listed on the data sheets.

Q: What protocol should I use for these antibodies?

A: We recommend using the protocols available on our website. Some have specific protocol recommendations which you can link to from the product page.

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Washington, DC USA
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Booth #2554

Amer Assoc Immunologists
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May 12-16
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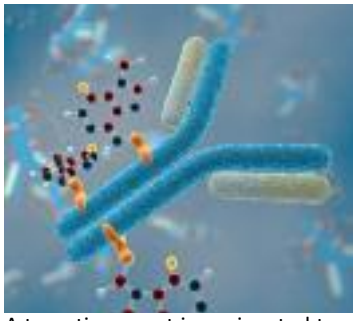
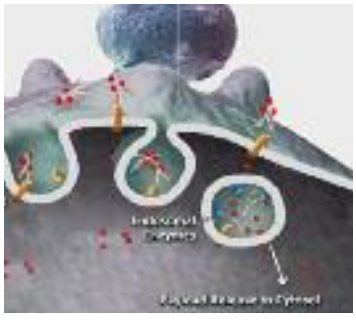


A targeting agent is conjugated to a payload. Here the conjugate is an antibody linked to a small molecule.

The targeted conjugate binds only the cells that are specific to the antibody causing the receptor to internalize.



The internalized conjugate is digested by enzymes releasing the payload into the cytosol. The payload is then free to alter the cell.

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The Eyes Have it! Melanopsin Offer
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