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The Blood-Brain Barrier Delivery Company

Opening the door to large molecule biologic therapies for neurological diseases

January 2021

BTI.V (TSX), BIOAF (OTCQB)
www.bioasis.us

Forward Looking Information

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and forward-looking information within the meaning of Canadian securities legislation. This information and these statements, referred to herein as "forward-looking statements", are made as of the date of this presentation or as of the date of the effective date of information described in this presentation, as applicable. The forward-looking statements herein relate to predictions, expectations, beliefs, plans, projections, objectives, assumptions or future events or performance (often, but not always, using words or phrases such as "expects", "anticipates", "plans", "projects", "estimates", "envisages", "assumes", "intends", "strategy", "goals", "objectives" or variations thereof or stating that certain actions, events or results "may", "can", "could", "would", "might" or "will" be taken, occur or be achieved, or the negative of any of these terms and similar expressions).

All forward-looking statements are based on current beliefs as well as various assumptions made by, and information currently available to Bioasis. By their very nature, forward-looking statements involve inherent risks and uncertainties, both general and specific, and risks exist that estimates, forecasts, projections and other forward-looking statements will not be achieved or that assumptions do not reflect future experience. For a description of some of the risks that could cause our actual results to vary from those anticipated by forward-looking statements, please refer to the risk factors described in our filings with Canadian securities regulators, available at www.sedar.com. We caution any person reviewing this presentation not to place undue reliance on these forward-looking statements as a number of important factors could cause the actual outcomes to differ materially from the beliefs, plans, objectives, expectations, anticipations, estimates assumptions and intentions expressed in such forward-looking statements.

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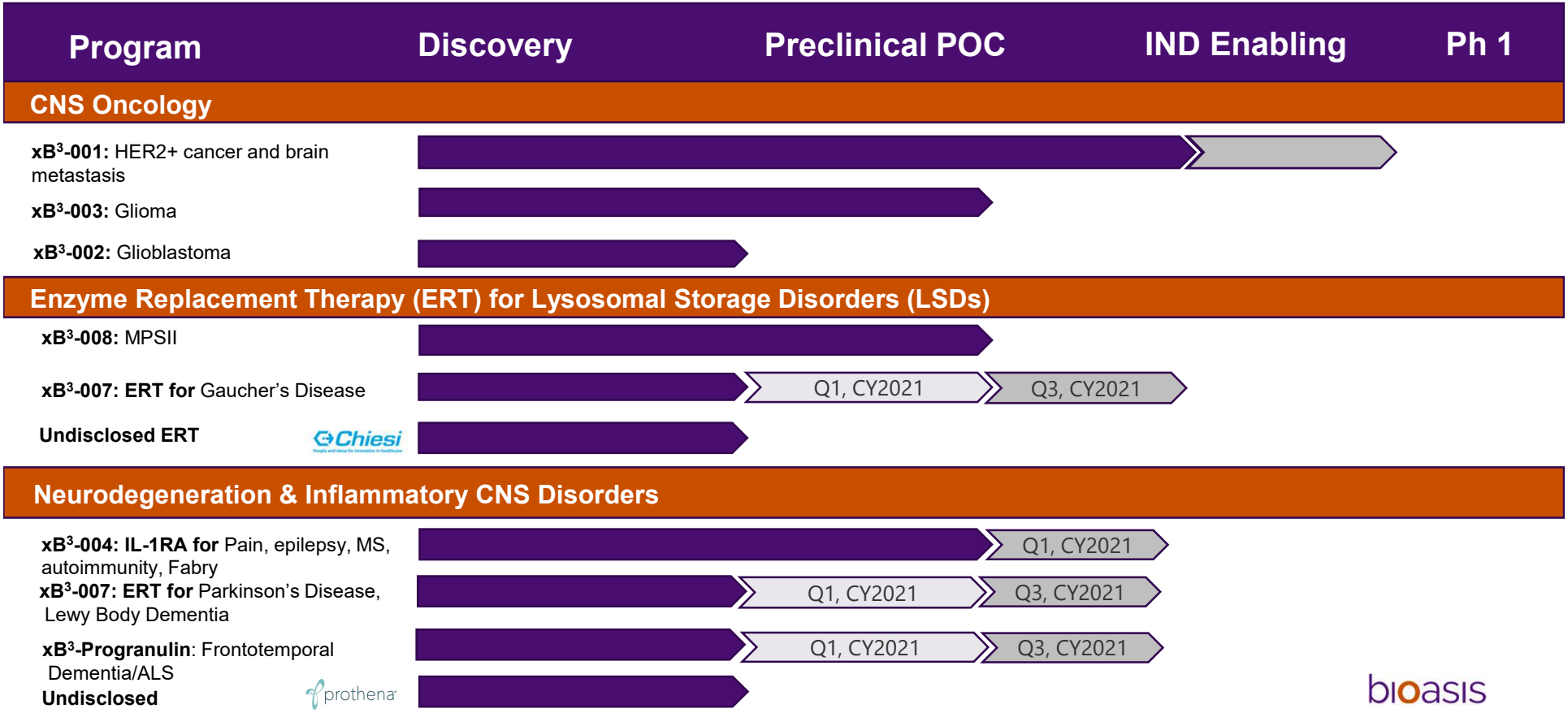
Bioasis Overview

xB³ ™ Platform : Best-in-class technology for BBB drug delivery	**Delivery of Therapeutics Across the BBB Using Our Proprietary xB³ ™ Platform Technology** • Enables delivery of a variety of therapeutics across the BBB, including enzymes, siRNA, antibodies and other biologics and small molecules • Outperforms all other BBB technologies, delivering a greater percentage of injected dose • **120+ patents relating to the xB³ delivery vector**, xB³ fusions and conjugates with active agents and therapies for treating various diseases associated with the central nervous system; **foundation patents through 2034; additional patent term extension up to five years** and ongoing work anticipated to provide further long-term patent protection
Internal pipeline is focused on lower risk, expedited opportunities	**Initial Focus on Orphan Indications & Rare Genetic Diseases with High Unmet Medical Need Where Proof-of-Concept Exists & Where There is also Potential to Benefit a Larger Patient Population** • **xB³-001- xB³ +Herceptin® for HER2+ breast cancer brain metastases** • **xB³-007 - ERT for the treatment of Gaucher's Disease, Parkinson's and Lewy Body Dementia** • **xB³-004 - IL-1RA for pain, epilepsy, MS, autoimmunity, Fabry** • **xB³-Progranulin: Frontotemporal Dementia/ALS**
Strategic partnering broadens uptake of the technology	**Partners are using Bioasis xB³ ™ Platform:** • New licensing agreement with **Chiesi Group**, 4 undisclosed Lysosomal Storage Disease targets • Licensing agreement with **Prothena,** undisclosed neurodegeneration targets • Research agreement with **a major global pharma company**

Bioasis Pipeline

Opening the door to large molecule biologic therapies for neurological diseases



Strategic Approach:

Two Pillar Strategy to Maximize Value and Success

Pipeline Programs: Well-established medicines, fast path to BLA/NDA

- De-risked programs
- Approved drugs, well-established with regulatory agencies, physicians and patients
- Orphan indications, including CNS cancers and rare genetic diseases with fast and cost-effective paths to BLA/NDA submission
- Significant market potential

Business Development: Novel targets & drug candidates

- Higher risk taken on by partner novel targets and new chemical entities
- Strategic partnering with selected Pharma
- Broaden utility and use of technology across multiple CNS disorders and treatment modalities
- Retain upside for Bioasis

=

Maximizing Value and Success of xB³ ™ Platform Generating Multiple Inflection Points

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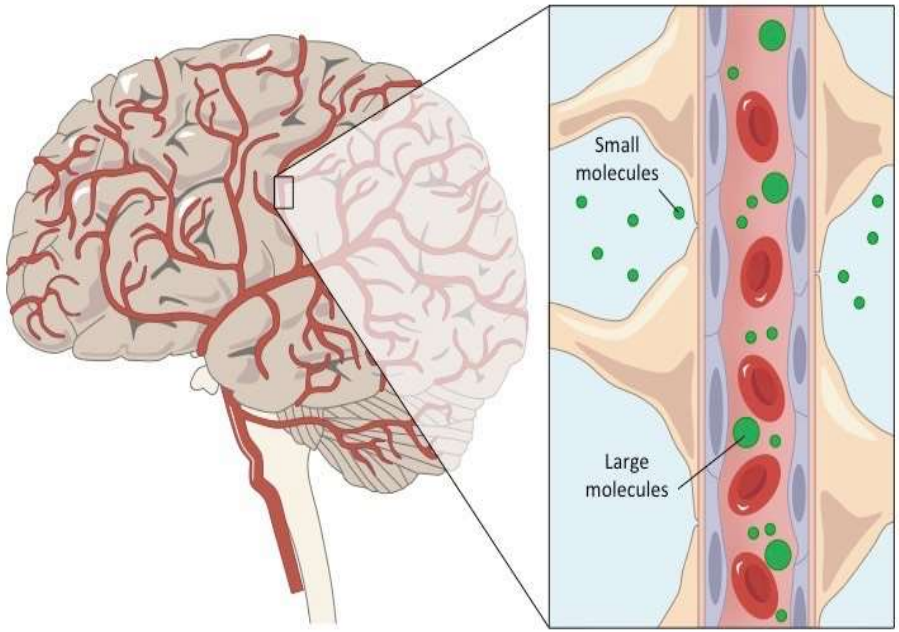
Partnering Provides External Validation of our xB^3 ™ Platform

- Strategic Alliance with Chiesi Group in Lysosomal Storage Diseases
  - Upfront payment of US$3 million, additional potential milestone payments of up to US$138 million and royalties on net sales from licensed products.
- xB^3 ™ Platform Technology Licensing Agreement with Prothena
  - US$1M upfront, up to US$33M in option payments & milestones, additional royalty on product sales
- Agreement With Leading Pharmaceutical Company for Pre-Clinical Research Using the xB^3 ™ Platform Technology
  - US$500,000 upfront, up to US$3M in R&D costs
- Publication of Independent Validation of the Company's xB^3 ™ Platform Technology
  - MedImmune collaboration

The Blood-Brain Barrier

- The blood-brain barrier (BBB) is a highly selective barrier that separates circulating blood from the brain and extracellular fluid in the CNS.
- The BBB functions to prevent the movement of bacteria, large molecules and most small molecules into the brain.
- The purpose of the blood-brain barrier is to protect the brain; however brain diseases are difficult to treat as the BBB significantly hinders the delivery of therapeutics to the brain.
- The ideal method for transporting drugs across the BBB should be controlled and should not damage the barrier in order to maintain its protective effects.



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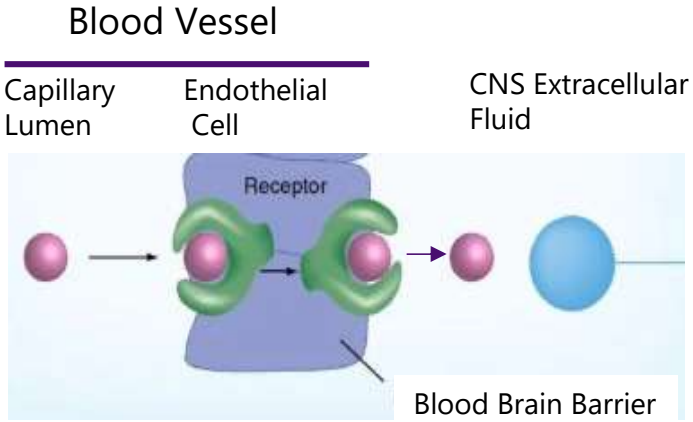
The Bioasis Platform Technology
Active Transport Across the BBB via the LRP1 Receptor



xB^3 Peptide

Derived from an iron-binding human protein found at low concentrations in the blood

- xB^3 has been optimized by Bioasis' scientists to its key constituents (12 amino acids)
- xB^3 has shown improved brain penetration over the full-length protein

Mechanism of Action (MOA)

xB^3 binds to, and moves into cells via receptor-mediated endocytosis/transcytosis involving the Low-Density Lipoprotein Receptor-related protein (LRP1) receptor

- High efficiency receptor with fast endocytosis and recycling
- LRP1 is highly expressed in critical brain regions and across multiple brain cell types
- LRP1 is overexpressed in multiple disease states including brain cancers, Alzheimer's disease and Parkinson's disease

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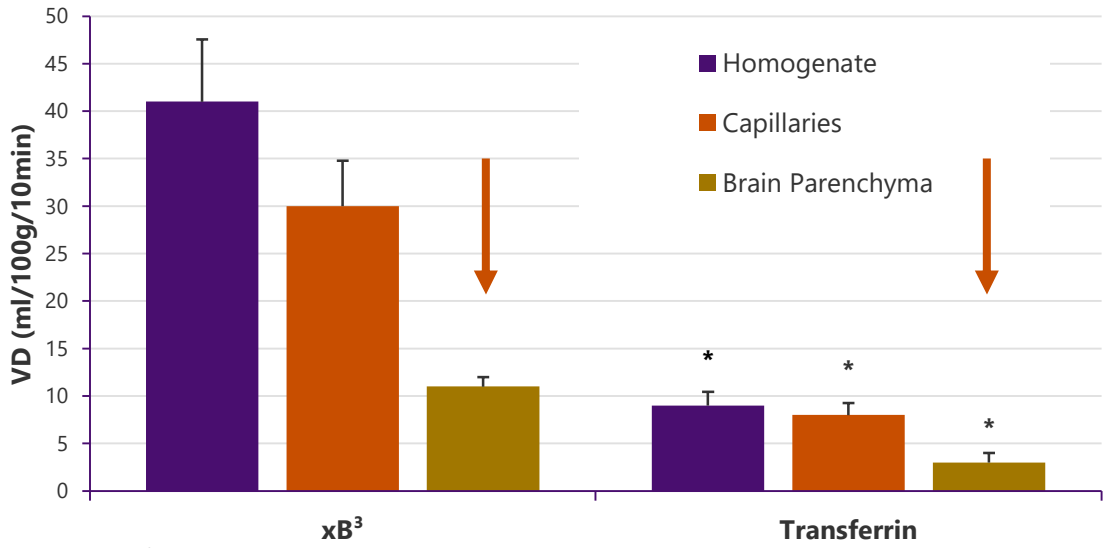
xB^3 TM Platform is Superior to Transferrin

Greater CNS Transport Efficiency demonstrated in vivo

xB^3 platform demonstrates superior volume of distribution in the brain compared to Transferrin as measured by *in situ* brain perfusion



Mean ± SE * p<0.01 Student's t-test (xB^3 to Transferrin comparison)
n=8 for xB^3, n=6 for Transferrin
Mice perfused with 10 nM xB^3 or Transferrin

Mean ± SE ; n=4 for 37C and 4C, n=2 for denatured

Demeule et al. (2002). J. Neurochem. 83, 924-933.

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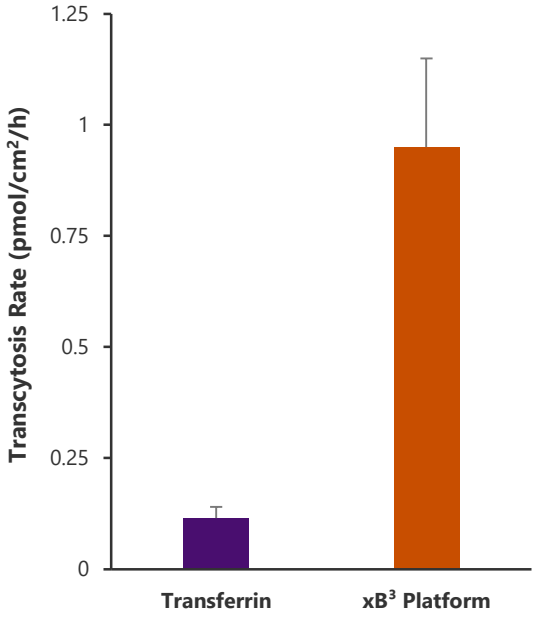
The xB^3 ™ Platform Technology
Outperforms Competing BBB Technologies

xB^3 demonstrates superior transcytosis across *in vitro* BBB model (BBCEC)



** Bioasis internal data **

Features	Bioasis xB^3 Platform	Denali	Genentech	Roche	Armagen	Angiochem
% injected dose in brain	4-6%	1-1.5%	1-1.5%	1-1.5%	1-1.5%	~1.5%
Mode of Action	LRP1	TfR	TfR	TfR	TfR and IR	LRP1
Payload Modalities						
Antibodies	✓	✓	✓	✓	✓	✓
Enzymes	✓	✓			✓	
siRNA	✓					
Small molecules	✓					✓

References: %ID/g brain based on 24 hr timepoint whenever available
[1]Thom G. et al. (2018) J Cereb Blood Flow Metab. ePub May 30, 2018.
[2]Extrapolated from data in Denali therapeutic annual report on form 10-K; Mar 2018
[3]Bien-Ly N, Yu YJ, Bumbaca D, et al. J Exp Med. 2014;211(2):233–244.
[4]Lajoie JM, Shusta EV. Annu Rev Pharmacol Toxicol. 2015;55:613–631.
[5]Weber F. et al., Cell reports. 2018; 22(1): 149-162
[6]Boado R., Pardridge WM., Mol Pharm. 2017 Apr 3; 14(4):1271-1277
[7]Zhou et al., Mol Pharm. 2010 Dec 6; 7(6):2148-2155
[8]Lu F, Pang Z, Zhao J, et al. Int J Nanomedicine. 2017;12:2117–2127
[9]Van Rooy I. et al., Pharm Res. 2011 Mar;28(3):456-471.

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The xB^3 ™ Platform Technology

Key Advantages

Enables the delivery of large molecule therapeutics across the BBB into the CNS

- Improved brain uptake over competing technologies
- Enables targeting of previously unreachable CNS targets

Capable of delivering a broad range of molecules across the BBB

- Antibodies
- siRNA
- Enzymes
- Proteins
- Small molecules

Does not impact either PK, binding, or activity of payload

- Herceptin

Nounou et al. Pharm Res. December 2016, 11 33(12); 2930-2942

- IL1-RA

Thom G. et al. (2018) J Cereb Blood Flow Metab. ePub May 30, 2018

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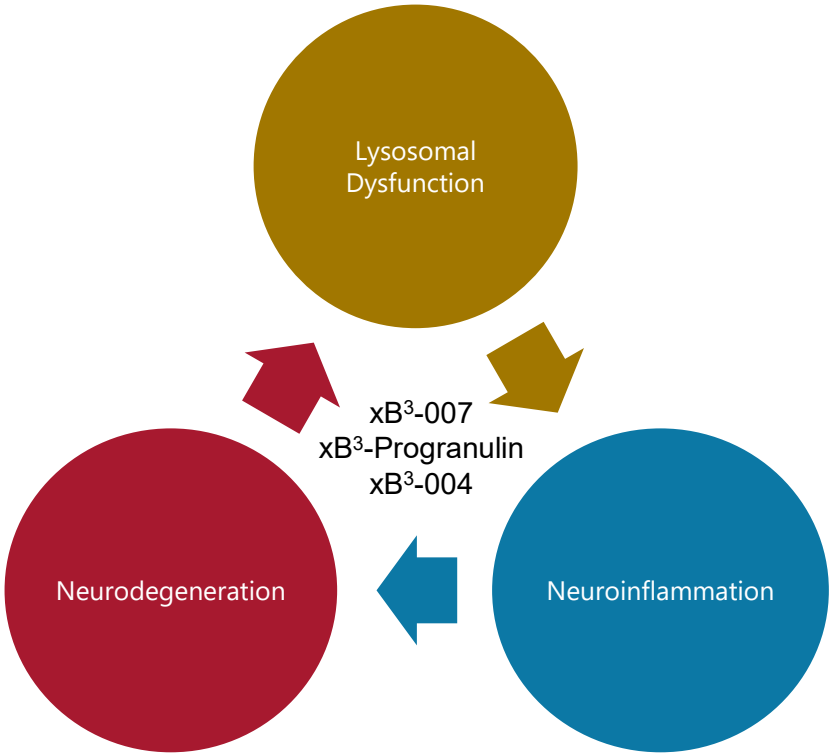
Partnership with Chiesi Group

Bioasis and Chiesi Group Announced Rare Diseases Strategic Alliance on 29 June 2020

- Validates the xB^3 platform.
- Deal provides Chiesi Group with worldwide, exclusive license to use Bioasis' $xB^{3\,TM}$ platform for delivery of undisclosed enzymes for treatment of four lysosomal storage disorders (LSDs).
- Under terms of the agreement, Bioasis will receive an upfront payment of US$3 million, additional potential milestone payments of up to US$138 million and royalties on net sales from licensed products.
- Chiesi Group will be responsible for all costs associated with research, development and commercialization of the four undisclosed LSD programs.
- Giacomo Chiesi, Head of Chiesi Global Rare Diseases, a business unit of Chiesi Group: *"The unique delivery method of their xB^3 platform has the potential to overcome a significant challenge in the treatment of many neurological disorders, which is the ability to cross the blood-brain barrier".*

Disruption of Normal Lysosomal Function Leads to Neuroinflammation and Neurodegeneration



- Neurodegenerative diseases result in a significant burden of mortality and morbidity worldwide
- Disease-modifying therapies are not available for many patients including patients with:
  - Parkinson's disease
  - Lewy Body dementia
  - Frontotemporal dementia
- Improved understanding of genetic basis of LSDs has clarified the role of neuroinflammation and neurodegeneration

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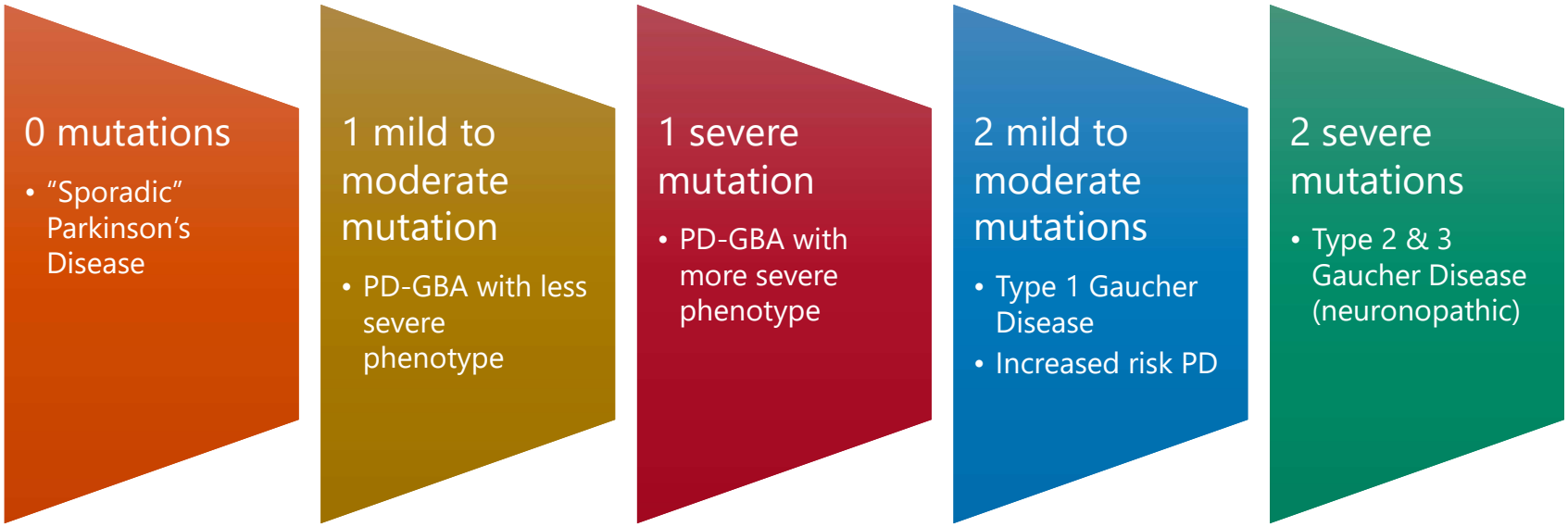
GBA1 Gene Mutations: A Continuum of Pathology from Parkinson's Disease to Neuronopathic Gaucher Disease



- Severity of GBA1 gene mutations are associated with earlier onset Lewy Body Dementia
- Disruption of normal lysosomal function in GD leads to neuroinflammation and release of IL-1b from Inflammasomes
- Our solution: xB^3-007 enzyme replacement therapy for GD, PD and LBD

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GRN Gene Mutations: A Continuum Of Pathology From Frontotemporal Dementia to Neuronal Ceroid Lipofusinosis

Increasing number of GRN mutations = Increasing loss of Progranulin function = Lysosomal dysfunction = neurodegeneration and inflammation

- Progranulin deficiency leads to lysosomal dysfunction
- Lysosomal dysfunction causes neurodegeneration and neuroinflammation
- Inflammasome activation leads to pathogenic IL-β release
- Our solution: xB^3-Progranulin replacement therapy for FTD, NCL, ALS

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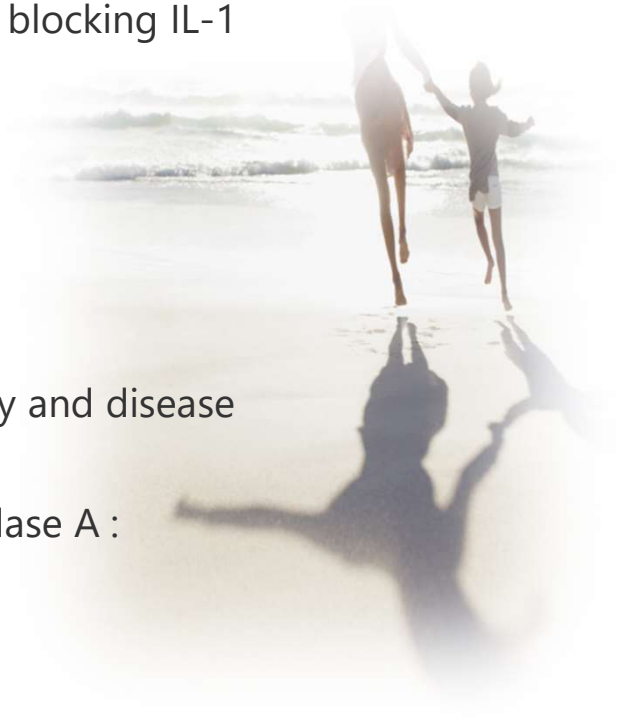
xB^3-004 IL-1 Receptor Antagonist for Multiple Sclerosis and Other Autoinflammatory Disorders

- xB^3-004 inhibits brain and peripheral nerve interleukin 1 (IL-1) by blocking IL-1 receptor binding and reducing neuroinflammation
- Demonstrated efficacy in an animal model of neuropathic pain
- Multiple Sclerosis:
  - IL-1 drives neuroinflammation and white matter disease
  - IL-1 drives synaptic loss (gray matter disease)
  - Cognitive dysfunction and atrophy results, leading to morbidity and disease progression
- Fabry disease, a LSD caused by the deficiency of alpha-galactosidase A :
  - Associated with increased IL-1 production, CNS inflammation
  - May be misdiagnosed as Multiple Sclerosis on MRI
  - Neuropathic pain a common symptom



xB^3-001 is Designed to Improve upon the Efficacy of Herceptin, Preventing Brain Metastases whilst Controlling Cancer in the Rest of the Body

xB^3-001	Product Attribute
✓	Utilizes the most widely used HER2-targeting agent, trastuzumab
✓	Does not impact the PK, binding, or activity of the trastuzumab payload
✓	Localizes in the brain better and shows 10-fold higher concentration of trastuzumab in metastases
✓	Retains peripheral disease control in xenograft models
✓	Safety profile that should allow for use in combination with other agents

- Brain metastases are among the most common form of brain cancer in adults, with an estimated 200,000 patients newly diagnosed each year in the United States.
- Breast cancer is the second most common cause of brain metastases and is associated with increasing mortality rates and poor quality of life.
- **Significant breast cancer market potential for xB^3-001 estimated at US$3.7 billion p.a.**

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Upcoming R&D Milestones

Program	Milestone	Anticipated Timing
xB^3-004 IL-1RA	EAE (Multiple Sclerosis) model read-out	Q1, CY2021
xB^3-007 glucocerebrosidase ERT	BBB data	Q1, CY2021
	Disease model read-out	Q3, CY2021
xB^3-Progranulin	BBB data	Q1, CY2021
	FTD disease model read-out	Q3, CY2021

Value accretive milestones, supportive of additional partnerships and further technology validation

A Strong Patent Portfolio Underpins Bioasis' Platform and Products

Patent portfolio covers Bioasis' platform technologies (their uses and indications)

- Comprises over 120 patents and pending applications (10+ patent families) covering xB^3, p97, fusion proteins of p97 or xB^3 with antibodies, including trastuzumab, bevacizumab, and other payloads
- Key xB^3 patent granted in U.S. (expires in 2034; additional patent term extension up to 5 years)
- Patents have been filed in major geographic markets and have expiration dates in 2034-2035 (plus patent term extensions)

Patent pending for xB^3-trastuzumab (xB^3-001) - and uses/indications

- Patents have been filed in major geographic markets with expiration date in 2035 (plus patent term extensions)
- In June 2019, the European Patent Office issued allowance of a patent application relating to trastuzumab/xB^3 conjugates including xB^3-001, Bioasis' lead product in development for the treatment of HER2+ breast cancer brain metastases.

Additional patents pending for other xB^3-related innovations

- Enzyme Replacement, e.g., Gaucher disease
  - In June 2019, the U.S. Patent Office and Trademark and European Patent Offices issued allowances of patent applications relating to iduronate-2-sulfatase, or IDS, polypeptide/xB^3 conjugates for the treatment of Hunter Syndrome a Lysosomal Storage Disorder.
- Brain transport plus lymphatic engagement
- Innovations in the areas of combination therapies, fusion proteins with various antibodies, CNS-targeted conjugates, treatment of neuropathologies and pain, as well as other innovations. Generally, these patents, when granted, have expiration dates from 2023 to 2037.

Our Management Team

Deborah Rathjen, Ph.D., MAICD, FTSE

Chief Executive Officer & Executive Chair

Previous Chief Executive Officer and Managing Director, Bionomics, Head BD, Peptech (acquired by Cephalon/Teva)

Christine Antalik

Chief Financial Officer

25+ years of experience in accounting & finance, including role of CFO at multiple corporations

Mei Mei Tian, Ph.D.

VP, Head of External Research

15 years of experience in xB^3-related research

Joined Bioasis in 2012

Dr. May Orfali

Consultant Chief Medical Officer

Extensive background in drug and clinical development programs spanning two decades in multiple therapeutic areas, with a focus on rare diseases and oncology.

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Our Board of Directors

Deborah Rathjen, Ph.D., MAICD, FTSE

Executive Chair

Previous Chief Executive Officer and Managing Director, Bionomics, Head BD, Peptech (acquired by Cephalon)

Mario Saltarelli, M.D., Ph.D.

Director

Former Executive Vice President and Chief Medical Officer, Syntimmune

John E. Curran, CPA

Director

Former Partner, Deloitte & Touche LLP

David M. Wurzer, CPA

Lead Director

Executive Vice President and Chief Investment Officer, Connecticut Innovations

Medical Advisory Board

Dr. May Orfali, Chairperson of the Advisory Board in her role of consultant Chief Medical Officer, has an extensive background in drug and clinical development programs spanning two decades in multiple therapeutic areas, with a focus on rare diseases and oncology. Her career includes senior positions at Oncology and Rare Disease Consulting, CANbridge , Pfizer, Wyeth, Artisan Pharma, Aeris, Cubist and Boston Scientific Corporation.

Dr. Hope S. Rugo is Professor of Medicine at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, where she is also the director of Breast Oncology and Clinical Trials Education.

Dr Javier Cortés is Head of Breast Cancer and Gynecological Tumors at Ramon y Cajal University Hospital in Madrid and Clinical Investigator of the Breast Cancer Research Program at Vall d'Hebron Institute of Oncology, Barcelona.

Dr. John de Groot is a Professor, and Chairman ad interim, in the Department of Neuro-Oncology at The University of Texas MD Anderson Cancer Center.

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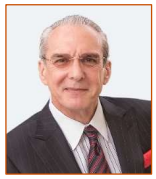
Scientific Advisory Board

Prof. John H. Krystal, M.D.
Chair
Yale University School of Medicine
Yale-New Haven Hospital

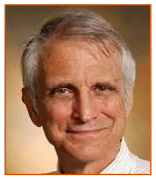


Jeffery L. Cummings, M.D.
Member
Cleveland Clinic, Center for Neurodegeneration and Translational Neuroscience

Mario Saltarelli, M.D., Ph.D.
Member
Former Chief Medical Officer, Syntimmune

Jack Hoppin, Ph.D.
Member
Co-founder and Chief Executive Officer, Invicro

Sue O'Connor, B.Sc. (Hons), Ph.D.
Member
Vice President, Innovation & Strategic Initiatives
Bionomics Ltd.



John P. Wikswo, Jr., Ph.D.
Member
Vanderbilt University, Vanderbilt Institute for Integrative Biosystems Research and Education

Investment Highlights

- Bioasis' xB^3 Platform validated through deal with Chiesi in LSDs
- *Deal propelled Bioasis into a leadership position in new therapies that restore lysosomal function, reduce brain inflammation and provide disease modifying potential for neurodegenerative conditions and enabled investment in core preclinical programs:*
  - xB^3-007: Gaucher disease, PD, Lewy Body Dementia
  - xB^3- Progranulin: neuronal ceroid lipofusinosis, FTD, ALS
  - xB^3-004: Multiple Sclerosis, Epilepsy, Autoinflammatory diseases
- Multiple upcoming preclinical milestones from these programs in 2021
- Lead asset xB^3-001 in neuro-oncology:
  - Targets HER2+ breast and gastric cancer and brain metastases
  - Worldwide peak revenue potential for the treatment of HER2+ breast cancer estimated at US$3.7 billion
  - Potential for accelerated approval
- Partnering anticipated to deliver meaningful near-term catalysts

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January 2021

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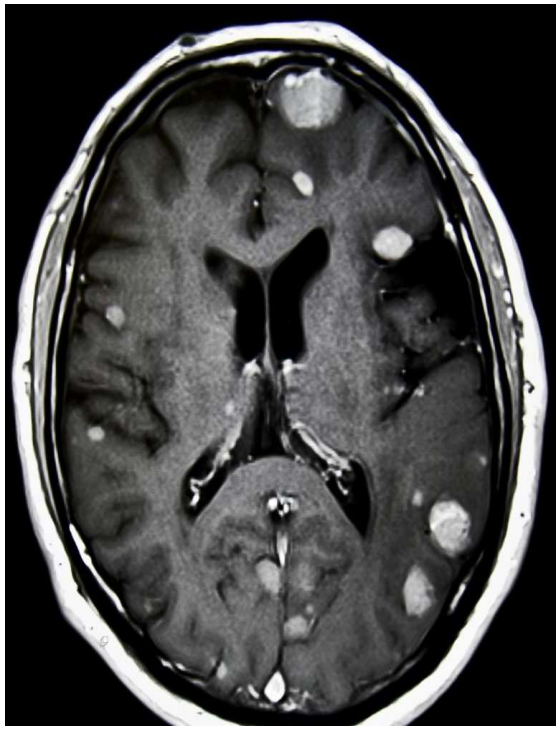
Breast Cancer Brain Metastases: Unmet Clinical Need

- Brain metastases are among the most common form of brain cancer in adults, with an estimated 200,000 patients newly diagnosed each year in the United States.
- Breast cancer is the second most common cause of brain metastases and is associated with increasing mortality rates and poor quality of life.
- HER2(+) breast cancers often show faster growth and metastasis compared to HER2 (-) breast cancers, with up to 50% of HER2+ patients developing brain metastases over time.
- ***Most systemic treatments do not penetrate the BBB***
- ***Current treatment options are limited***
- ***Safer and more effective treatment for brain metastases are needed***



xB^3-001 is Designed to Improve upon the Efficacy of Herceptin, Improving upon CNS Disease Control and Potentially Development of CNS Metastases

xB^3-001 in HER2+ mBC

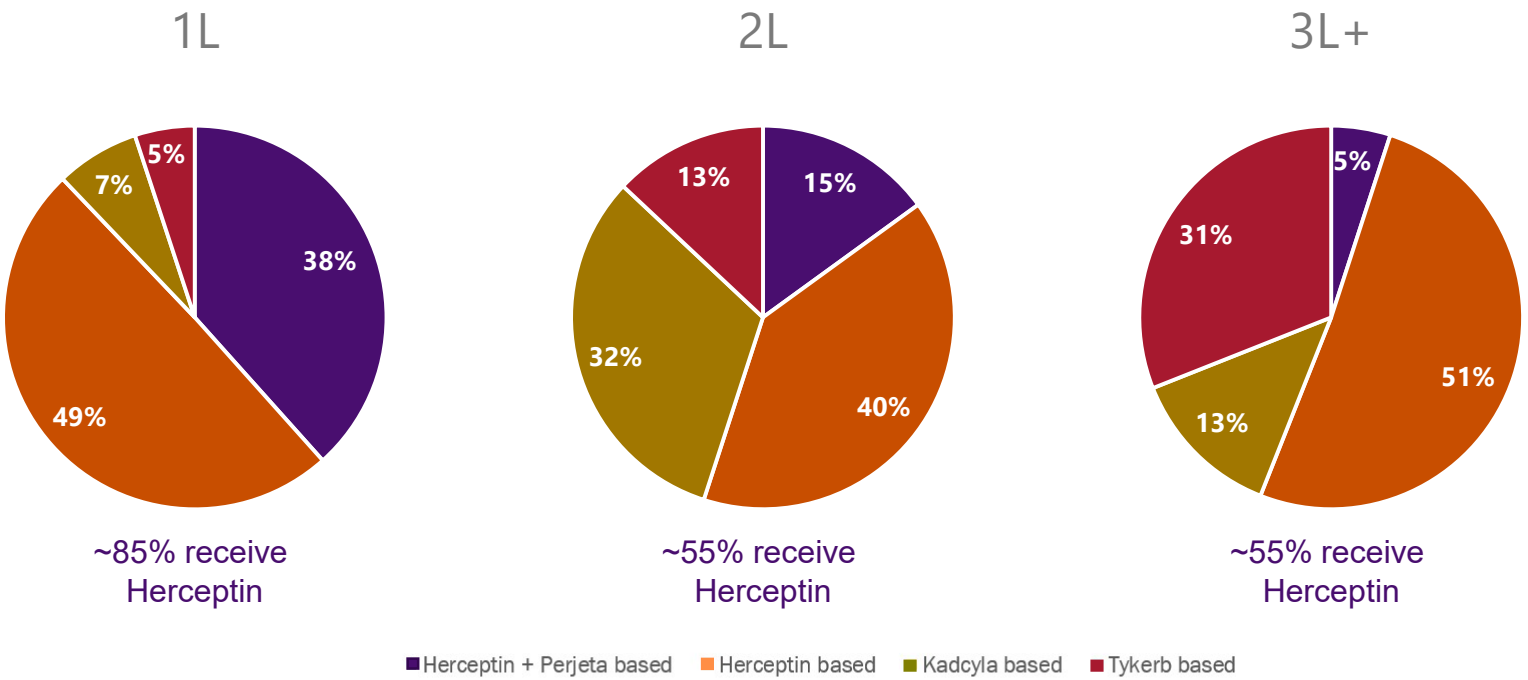
xB^3-001	Product Attribute
✓	Utilizes the most widely used HER2-targeting agent, trastuzumab
✓	Does not impact the PK, binding, or activity of the trastuzumab payload
✓	Localizes in the brain better and shows 10-fold higher concentration of trastuzumab in metastases
✓	Retains peripheral disease control in xenograft models
✓	Safety profile that should allow for use in combination with other agents

xB^3-001 could launch as HER2-targeted therapy of choice in 2L+ patients with CNS metastases

Demonstrating superiority to Herceptin in CNS disease prevention would position for broad use

The Majority of HER2+ mBC Patients Receive Herceptin in all Lines of Therapy

Market Share for HER2-Targeting Agents by Line of Therapy



Source: Kantar Treatment Architecture

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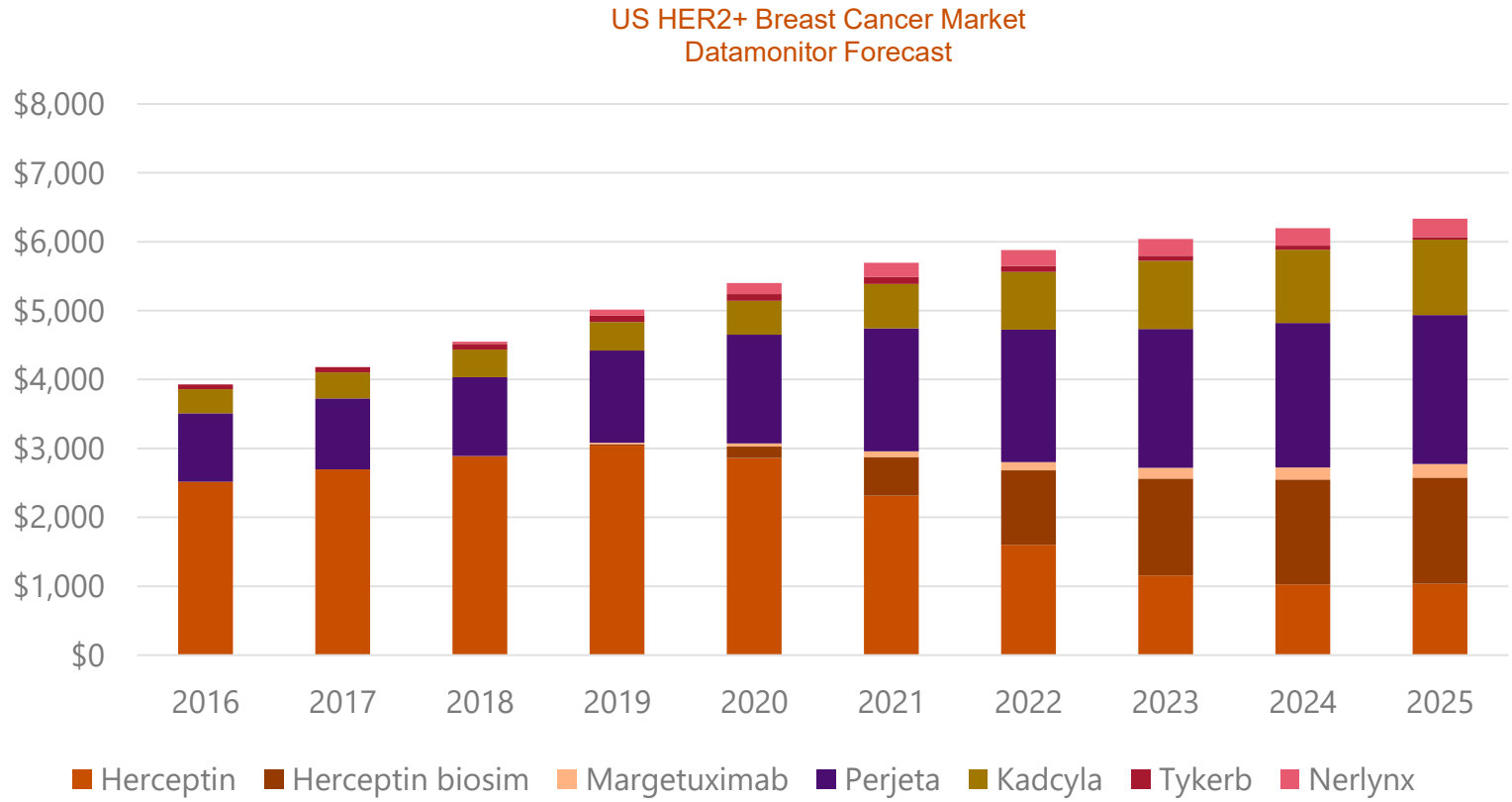
Datamonitor Expects Continued Growth of the US HER2+ Breast Cancer Market, Reaching >$6B by 2025



Source: Datamonitor

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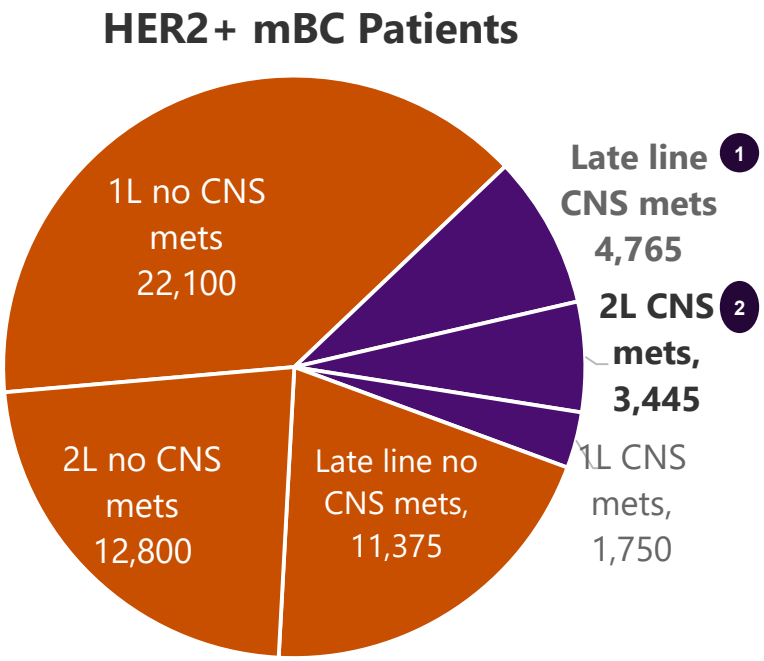
xB³-001 Revenue Potential for 2L+ Patients with CNS Metastases is ~US$440M Worldwide

Market Potential – xB³-001 CNS Metastases Treatment



CNS Metastases Treatment

Late Line

Improved CNS disease control in 3L+ patients
~4,765 candidates [1]
8 mos median duration of therapy

Market Potential
$380M US/$760M WW

xB³-001 Potential (@ 30% share)
$115M US/$230M WW

2L+

Superior to Kadcyla in 2L+ patients with CNS mets
~8,210 candidates [1] [2]
10 mos median duration of therapy

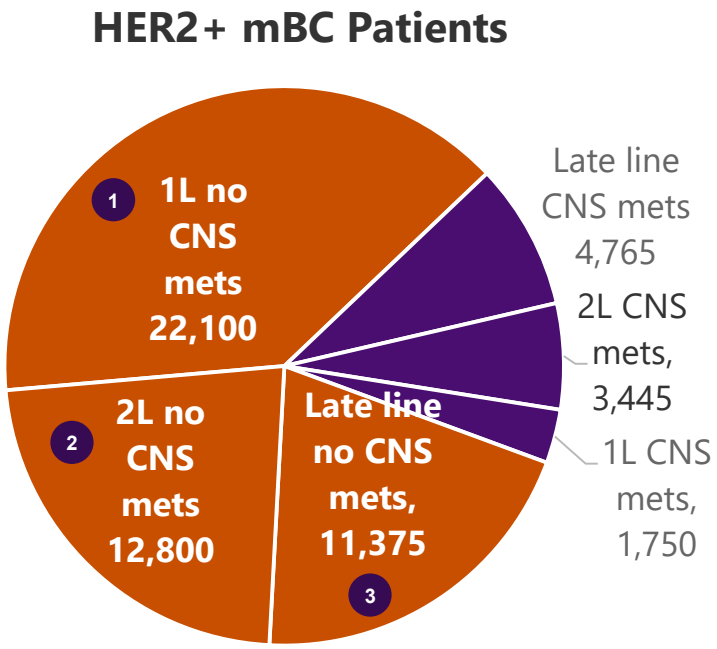
Market Potential
$725M US/$1.45B WW

xB³-001 Potential (@ 30% share)
$220M US/$440M WW

Source: NCI SEER; Kantar Patient Metrics and Treatment Architecture; Datamonitor

Assumptions: Price of $10,000 per month, in between Herceptin and Kadcyla; US accounts for 50% of WW sales

Market Potential – xB^3-001 CNS Metastases Prevention



CNS Metastases Prevention

2L+ Patients without CNS Metastases

~24,000 candidates [2] [3]

8-10 mos median duration of therapy

Market Potential

$2.2B US/$4.4B WW

xB^3-001 Potential (@ 30% share)

$660M US/$1.32B WW

1L+ Patients without CNS Metastases

~46,000 candidates [1] [2] [3]

8-18 mos median duration of therapy

Market Potential

$6.2B US/$12.4B WW

xB^3-001 Potential (@ 30% share)

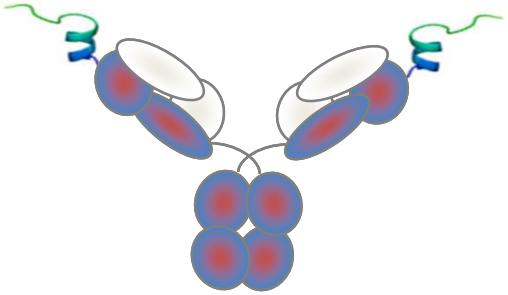
$1.85B US/$3.7B WW

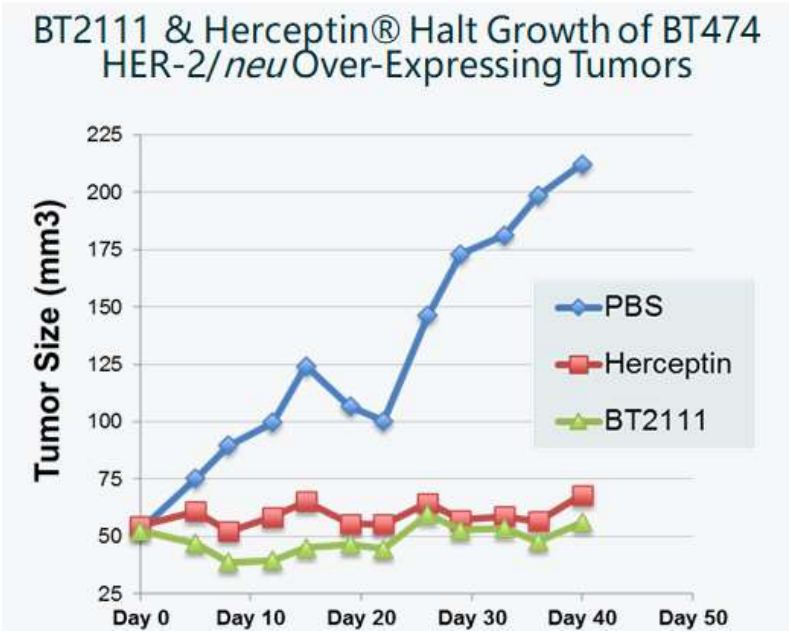
Source: NCI SEER; Kantar Patient Metrics and Treatment Architecture; Datamonitor

Assumptions: Price of $10,000 per month, in between Herceptin and Kadcyla; US accounts for 50% of WW sales

xB^3-Herceptin Retains Peripheral Anti-Tumor Efficacy in the BT474 Xenograft Model

xB^3 can be added to a therapeutic through chemical conjugation or fusion





BT2111 = xB^3-001 (xB^3-Herceptin)
Ip injection 2x/wk for 5 weeks; 10mg/kg molar equivalent; n=10

Work performed at Biopharmaceutical Research Inc.

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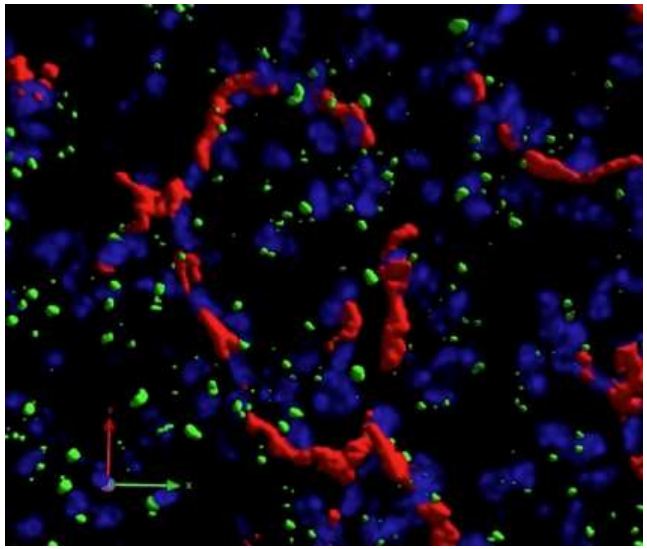
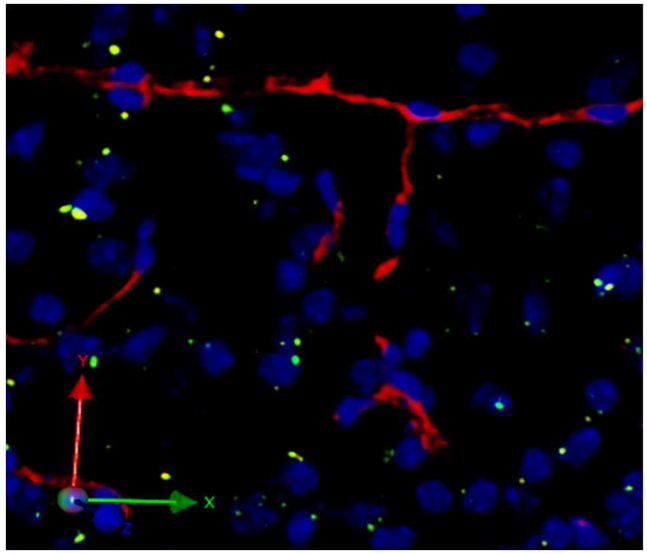
xB^3- 001 Demonstrates Significantly Increased Localization in Brain Parenchyma Compared to Herceptin®

Confocal Images Two Hours Post IV Administration (10mg/kg) in mouse brain



xB^3-Herceptin

Red: Brain capillaries
Blue: Brain Nuclei
Green: xB^3-Herceptin in brain



Herceptin

Red: Brain capillaries
Blue: Nuclei
Green: Herceptin in brain

Work performed at National Research Council of Canada – Research Facility

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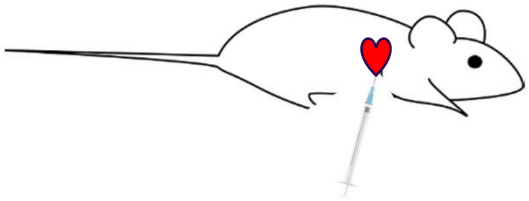
HER2+ Human Breast Cancer Brain Metastasis Mouse Model

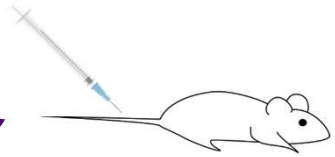
5 weeks post breast cancer cell administration

Intracardiac injection



MDA-MB-231-BR$^{HER2/eGFP}$ (Brain targeting HER2+ human breast cancer cells

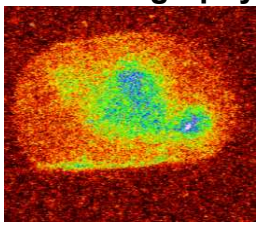
5 weeks



Following establishment of brain metastases single IV injection of ^{125}I labeled test articles (10 mg/kg molar equivalent; n=3)

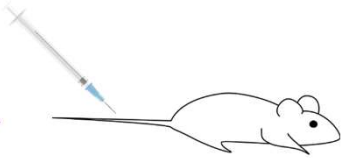
2h

Autoradiography



Quantification of brain radioactivity via microcomputer image device

3 weeks



Following establishment of brain metastases biweekly IV injection of test articles (10 mg/kg molar equivalent; n=8-9)

2 weeks

Efficacy assessment

- Tumor number
- Tumor size

Nounou, MI, et al. Pharm Res. 2016 Dec;33(12):2930-2942. Epub 2016 Aug 15

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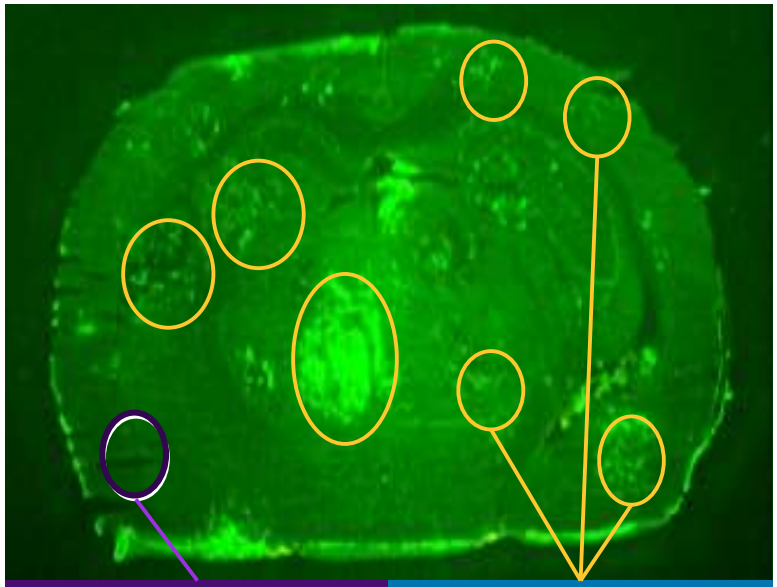
xB^3-001 in Human HER2+ Brain Metastasis Mouse Model

Target Engagement and Biological Effects

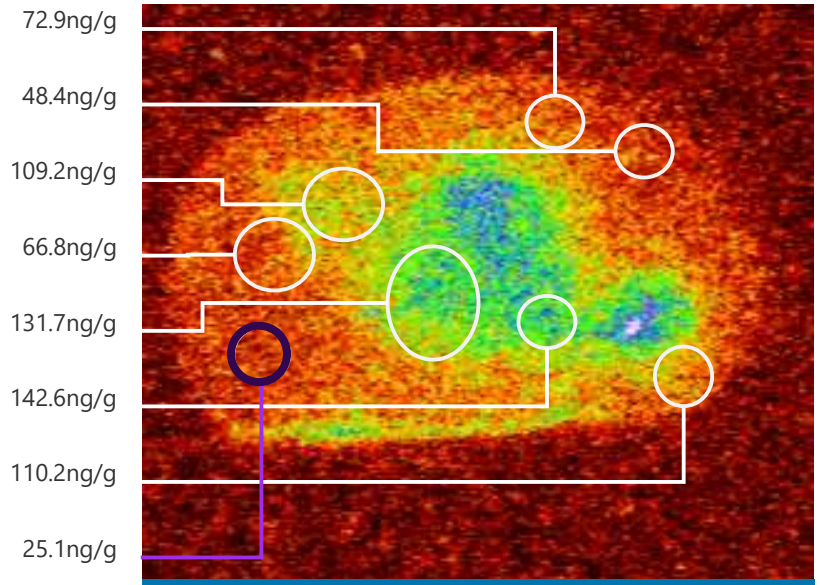
Metastases localization 5 weeks Post Inoculation



Brain tissue distal to tumors (BDT) | **Breast cancer metastasis distributed throughout the brain**

MDA-MB-231-$BR^{HER2/eGFP}$ breast cancer cell line injected in the left cardiac ventricle of mice.

Concentrations of xB^3 -001 within Brain Regions at 2hrs post dose



Preferential uptake of radio-labeled xB^3-001 conjugate into tumors compared with BDT

Single injection of ^{125}I-xB^3 -001 administered 5 weeks after initial intracardiac injection of cells and establishment of brain metastases.

Nounou, MI, et al. Pharm Res. 2016 Dec;33(12):2930-2942. Epub 2016 Aug 15

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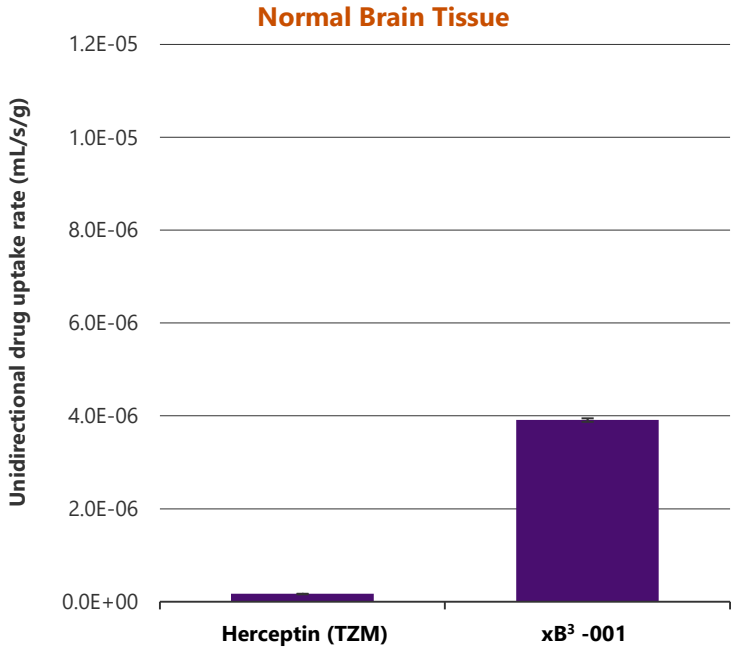
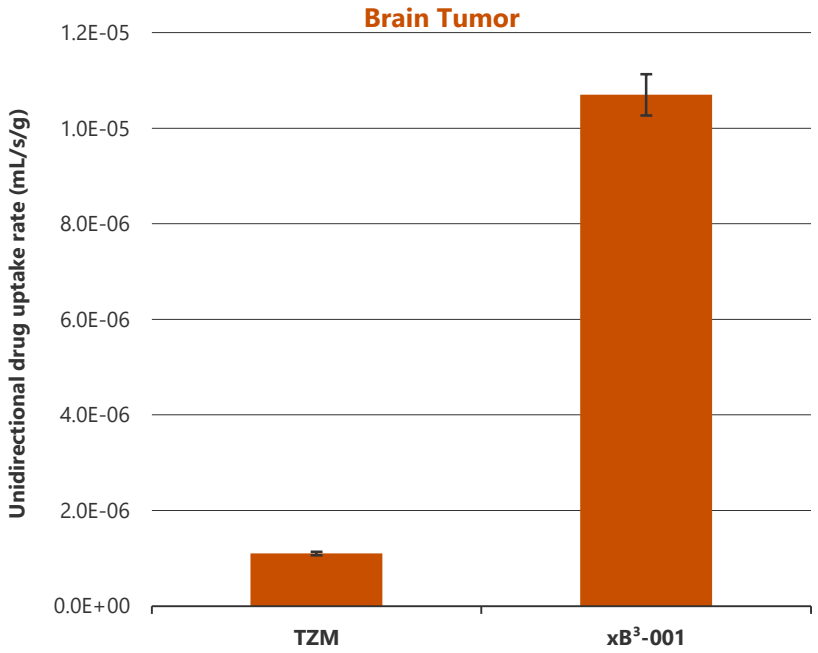
xB^3 ™ Platform Delivers 10-Fold Higher Herceptin® to Brain Metastases



Mean ± SD; n = 61 (TZM), n = 77 (xB^3 -001); single dose; up to 8 hrs post dose.



Mean ± SD; n = 336 (TZM), n = 213 (xB^3 -001); single dose; up to 8 hrs post dose

Nounou, MI, et al. Pharm Res. 2016 Dec;33(12):2930-2942. Epub 2016 Aug 15

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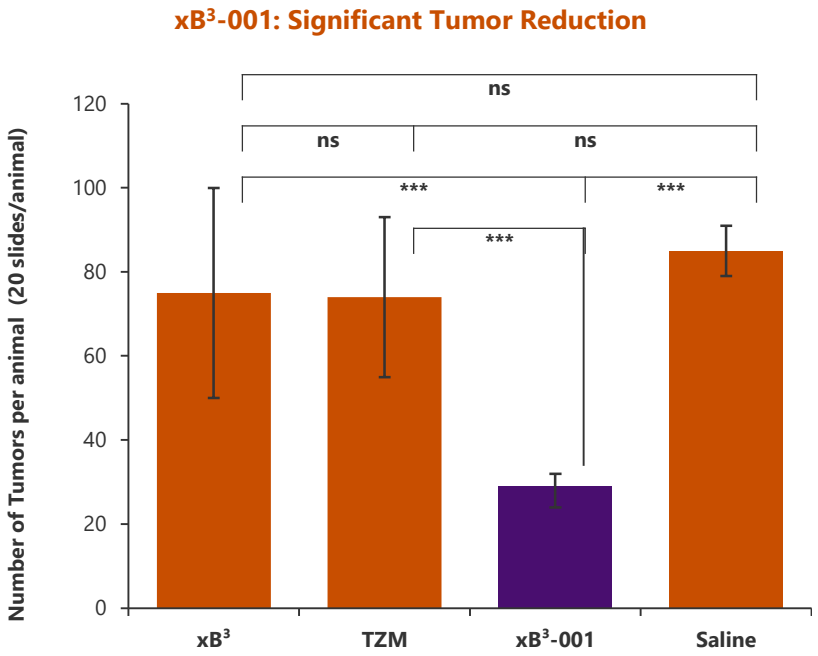
xB^3 TM Platform Delivers Herceptin® (Trastuzumab, TZM) to Brain Metastases and Reduces Both Tumor Number and Size



TZM: Trastuzumab; n= 13 for xB^3, TZM groups; n=8-9 for xB^3 -001, Saline groups. Biweekly IV treatment for 2 weeks. 10mg/kg molar equivalent. One-way ANOVA **P<0.001, ***P<0.001, ***P<0.0001 Mean+/-SEM

Group	Tumor size based on pooled data from all individual values in group	
	# of tumor	Tumor size (mm^2) Mean ± STDEV
Saline control (n=9)	765	1.654 ± 1.673
xB^3 -001 (n=8)	223	0.710 ± 0.727[1]
TZM (n=13)	962	1.402 ± 1.217

[1]. xB^3 -001 group vs. TZM group *P*<0.001

xB^3 -001 vs. TZM Treatment

- Reduced tumor number by 68%
- Tumors that remained after treatment were 46% smaller
- TZM treatment show no effect on reducing number of metastases with negligible reduction in tumor size

Nounou, MI, et al. Pharm Res. 2016 Dec;33(12):2930-2942. Epub 2016 Aug 15

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xB^3 – 001 Path to Market

- **If clinically active, xB^3-001 has the potential to be a candidate for accelerated approval:**
  - Addresses a serious or life-threatening condition.
  - Must demonstrate an effect on an intermediate clinical endpoint or surrogate endpoint, for example tumor shrinkage, in a way that is reasonably likely to predict clinical long-term benefit and can be measured earlier than that benefit. **As brain metastases determine the prognosis of HER2+ MBC patients they are a good surrogate for clinical benefit (survival).**
- **A non-inferiority study is not required as Herceptin is not effective in treating HER2+ brain metastases**
- **xB^3 – 001 accelerated approval study:**
  - The FDA have indicated that Bioasis should seek a meeting at the end of the Phase 1 component of the currently planned trial. At this time the company may have an opportunity to discuss an accelerated approval strategy and study design.

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xB³ ™ Platform Technology

MedImmune - Bioasis Collaboration

MedImmune

Original Article

JCBFM
Journal of Cerebral Blood Flow & Metabolism
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journals.sagepub.com/home/jcbfm
SAGE

A peptide derived from melanotransferrin delivers a protein-based interleukin 1 receptor antagonist across the BBB and ameliorates neuropathic pain in a preclinical model

George Thom[1], Mei-Mei Tian[2], Jon P Hatcher[3], Natalia Rodrigo[1], Matthew Burrell[1], Ian Gurrell[3], Timothy Z Vitalis[4], Thomas Abraham[5], Wilfred A Jefferies[6], Carl I Webster[1] and Reinhard Gabathuler[4]

Abstract

Delivery of biologic drugs across the blood–brain barrier is becoming a reality. However, the solutions often involve the assembly of complex multi-specific antibody molecules. Here we utilize a simple 12 amino-acid peptide originating from the melanotransferrin (MTf) protein that has shown improved brain delivery properties. 3D confocal fluorescence microscopic analysis demonstrated brain parenchymal localisation of a fluorescently labelled antibody (NIP228) when chemically conjugated to either the MTf peptide or full-length MTf protein. Measurement of plasma kinetics demonstrated the MTf peptide fusions had very similar kinetics to an unmodified NIP228 control antibody, whereas the fusion to MTf protein had significantly reduced plasma exposure most likely due to a higher tissue distribution in the periphery. Brain exposure for the MTf peptide fusions was significantly increased for the duration of the study, exceeding that of the fusions to full length MTf protein. Using a neuropathic pain model, we have demonstrated that fusions to interleukin-1 receptor antagonist (IL-1RA) are able to induce significant and durable analgesia following peripheral administration. These data demonstrate that recombinant and chemically conjugated MTf-based brain delivery vectors can deliver therapeutic levels of drug to the central nervous system.

Keywords

Blood–brain barrier, central nervous system, interleukin-1 receptor antagonist, melanotransferrin peptide, pharmacokinetic

Received 31 July 2017; Revised 23 March 2018; Accepted 26 March 2018

Introduction

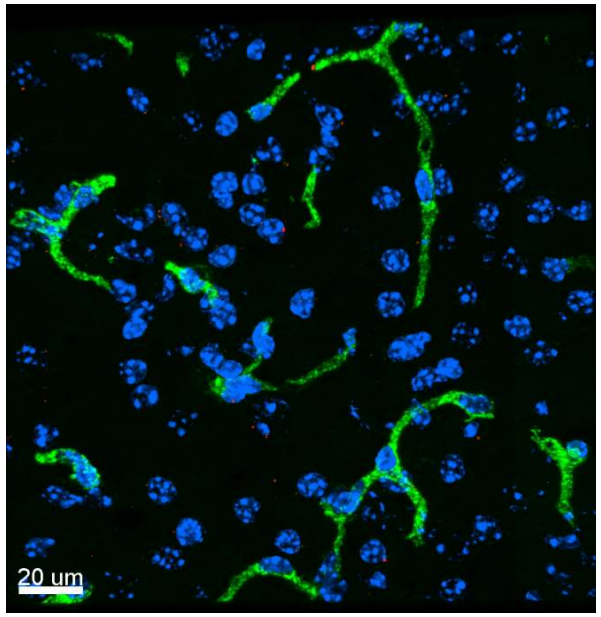
Although protective in design, the blood–brain barrier (BBB) presents a constant challenge to effectively deliver therapeutic drugs directed at the treatment of brain diseases. Efficient drug delivery across the BBB is most important in the treatment of neurophysiological disorders (including neuropathic pain, Alzheimer's disease

[1]MedImmune, Cambridge, UK
[2]Bioasis Biosciences Corp., Guilford, CT, USA
[3]Neuroscience IMED Biotech Unit, AstraZeneca, AKB, Cambridge, UK
[4]Bioasis Technologies Inc., Richmond, BC, Canada
[5]Neural and Behavioural Sciences & Microscopy Imaging Core Lab, College of Medicine, The Pennsylvania State University, Hershey, PA, USA
[6]The Michael Smith Laboratories, University of British Columbia, Vancouver, BC, Canada; The Vancouver Prostate Centre, Vancouver General Hospital, Vancouver, BC, Canada; The Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada; Centre for Blood Research and Departments of Microbiology and Immunology, Medical Genetics, and Zoology University of British Columbia, Vancouver, BC, Canada

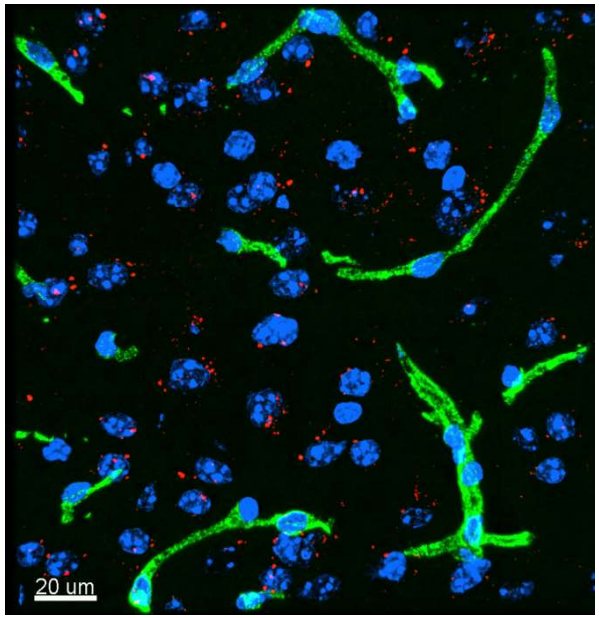
Corresponding author:
Mei-Mei Tian, Bioasis Biosciences Corp., 14 Water Street, Guilford, CT 06437, USA.
Email: meimei@bioasis.us

xB^3 Facilitated the Penetration and Preferential Localization of IL-1RA Antibodies in the Brain Parenchyma

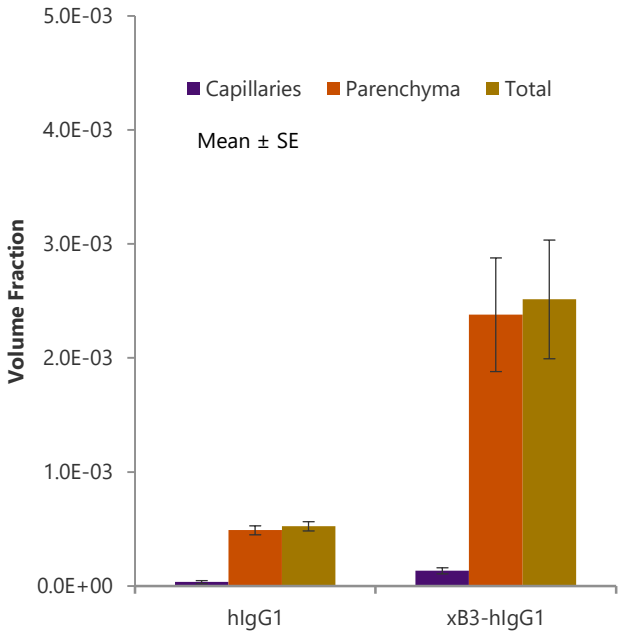
Confocal Images Two Hours Post Single IV Administration (10mg/kg) in Wild-type Mice



hIgG 1
Capillary
Nucleus



xB^3-hIgG1
Capillary
Nucleus



Mean ± SEM; n=3 mice/ molecule; single IV injection

Thom G. et al. (2018) J Cereb Blood Flow Metab. ePub May 30, 2018.

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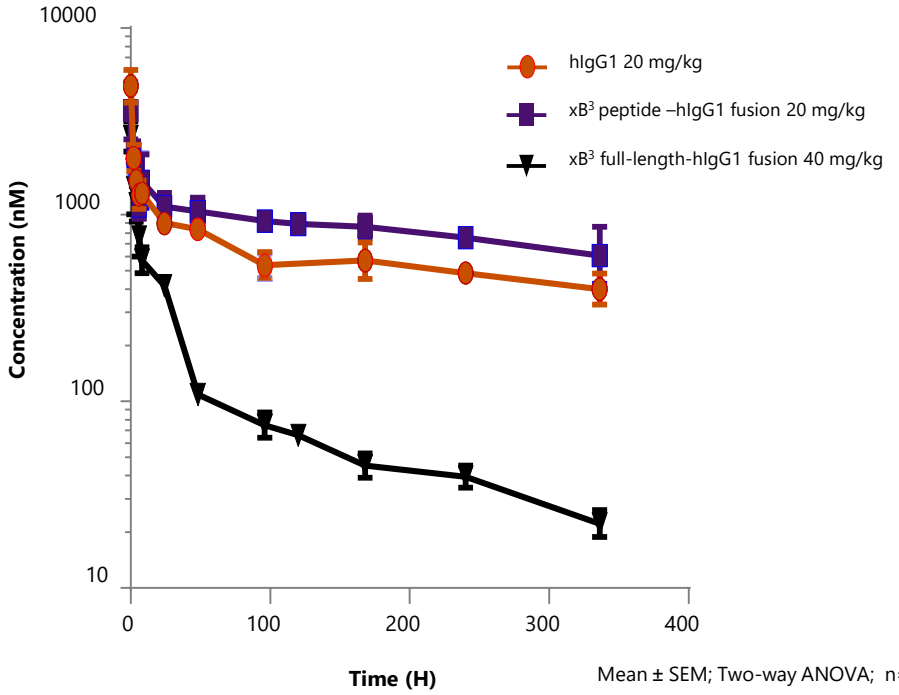
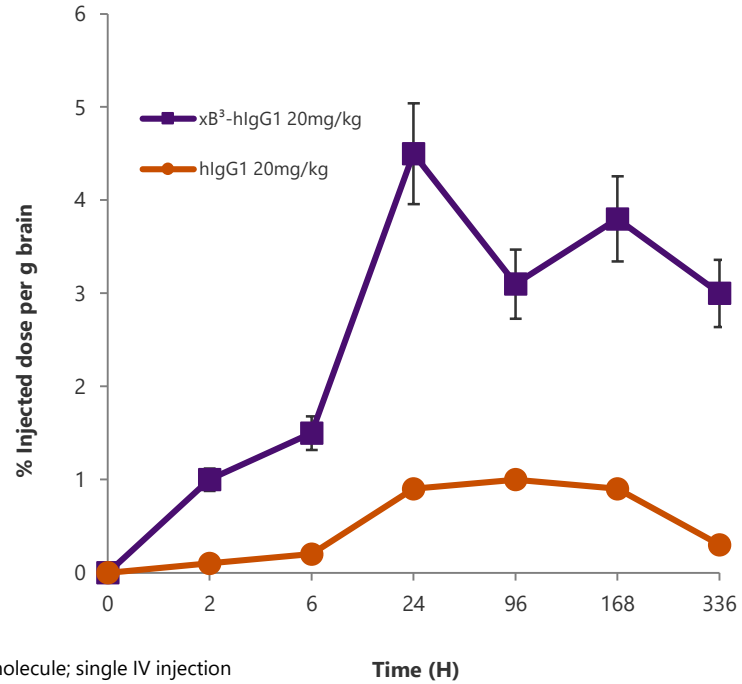
xB³ Resulted in Significant Exposure in the Brain Without Negative Impact on Plasma PK

xB³ peptide-Ab Fusion show improved Plasma PK compared to xB³ full length-Ab fusion



xB³-Ab Fusion significantly increased Brain Exposure over Ab alone



Mean ± SEM; Two-way ANOVA; n=6 mice/ molecule; single IV injection

Thom G. et al. (2018) J Cereb Blood Flow Metab. ePub May 30, 2018.

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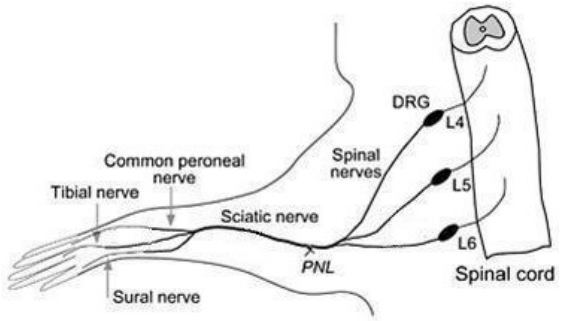
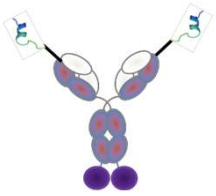
Efficacy Model: Neuropathic Pain Mouse Model

- Neuropathic pain model (Seltzer et al, 1990)
  - Sciatic nerve of one limb partially ligated
  - Results in mechanical hyperalgesia
- Neuropathic pain centrally mediated
  - Drug must reach CNS to relieve pain
- Analgesic drug will reduce pain if it reaches the CNS
  - IL-1 receptor antagonism has been implicated in relieving the symptoms of neuropathic pain (Gabay et al, 2011)
    - IL1RA (Kineret) can induce analgesia **only** when delivered intrathecally
    - Peripheral delivery of IL1RA or control IgG-IL1RA do not induce analgesia



hIgG1-IL1RA



xB^3-NH-hIgG1-IL1RA

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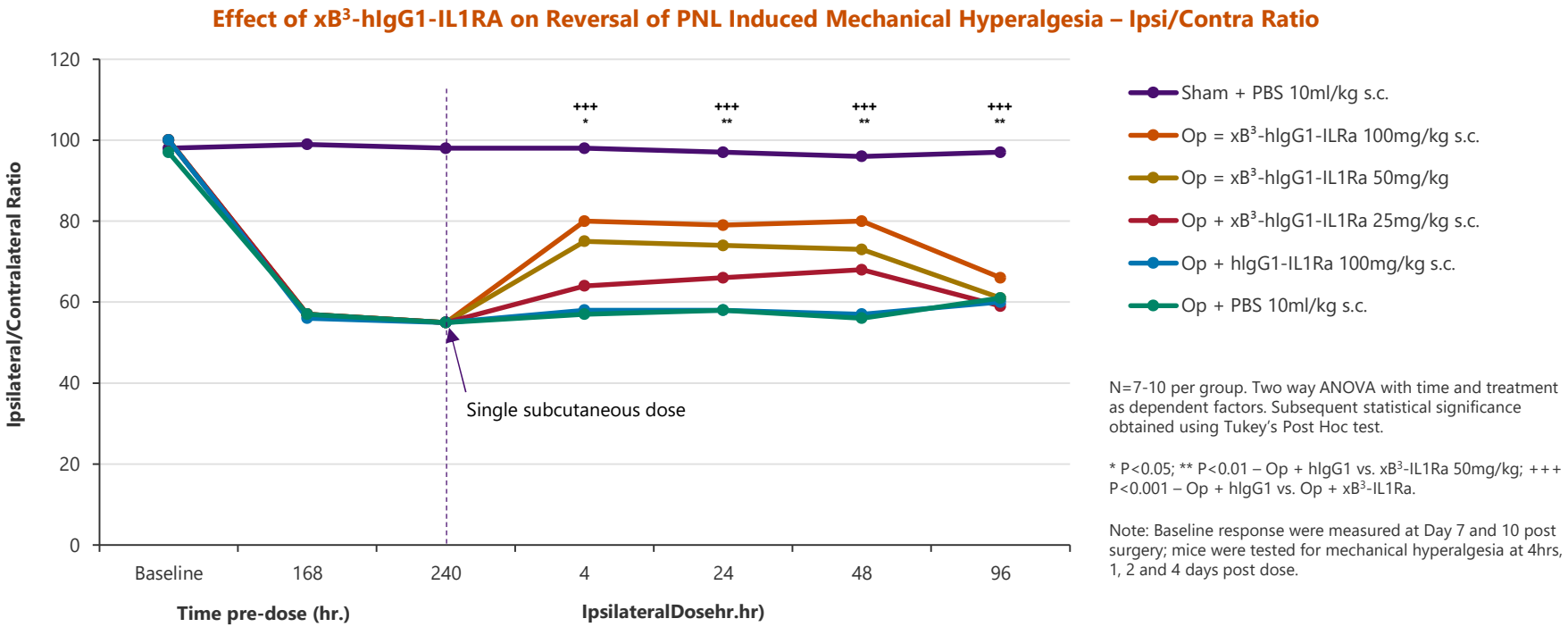
Systemic administration of xB^3 – 004 (IL1RA Fusion): Dose Dependent PD Effects in Neuropathic Pain Model



N=7-10 per group. Two way ANOVA with time and treatment as dependent factors. Subsequent statistical significance obtained using Tukey's Post Hoc test.

* P<0.05; ** P<0.01 – Op + hIgG1 vs. xB^3-IL1Ra 50mg/kg; +++ P<0.001 – Op + hIgG1 vs. Op + xB^3-IL1Ra.

Note: Baseline response were measured at Day 7 and 10 post surgery; mice were tested for mechanical hyperalgesia at 4hrs, 1, 2 and 4 days post dose.

Thom G. et al. (2018) J Cereb Blood Flow Metab. ePub May 30, 2018.

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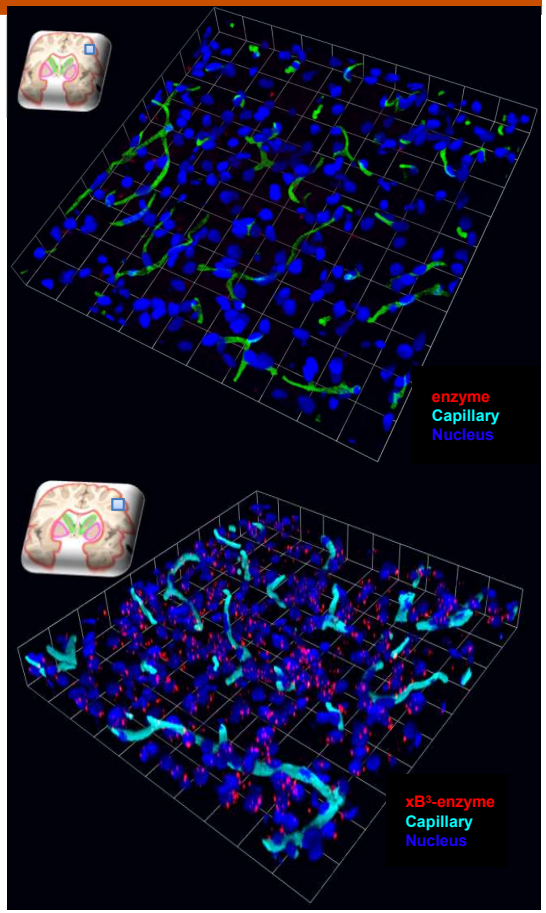
xB^3 can Effectively Deliver Enzymes to Treat Lysosomal Storage Disorders

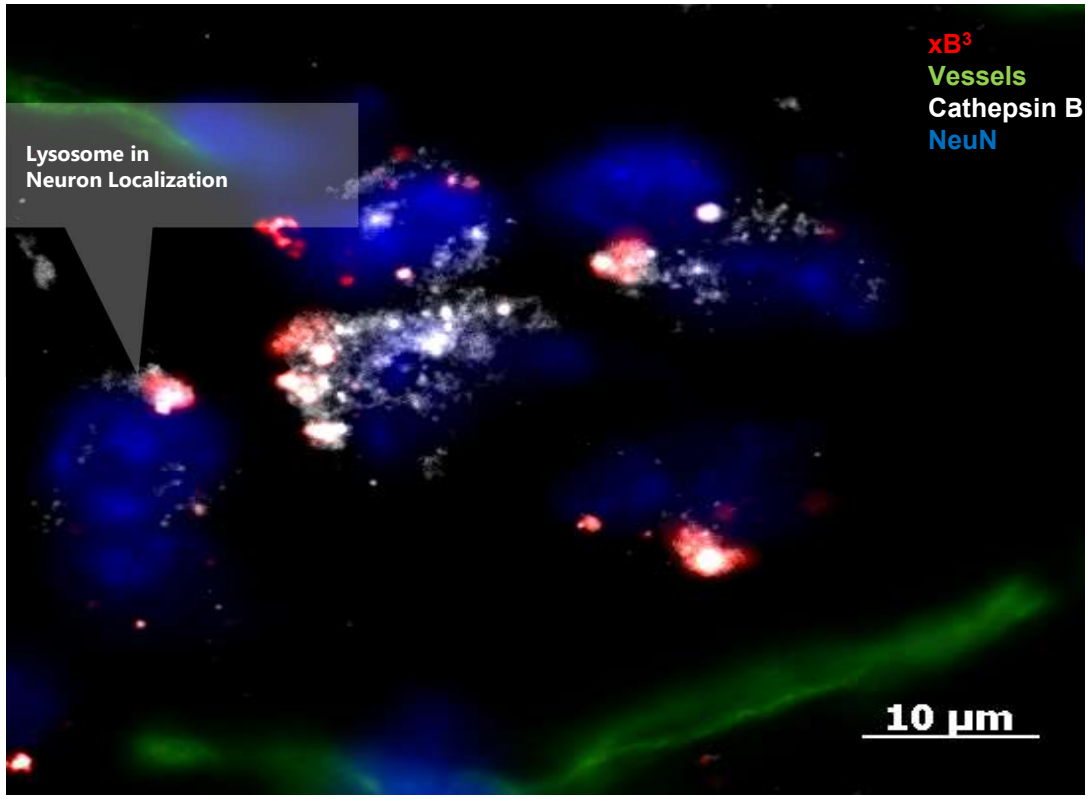
Hunter Syndrome (MPS II)

- Lysosomal Storage disease, MPS II is caused by an iduronate 2-sulfatase (I2S) enzyme deficiency
- Currently CNS effects are untreatable

Bioasis' xB^3 peptide-I2S fusion molecule increased I2S uptake into the brain and was accompanied by cellular and biochemical changes characteristic of enzyme activity.



Localization of xB^3 in lysosomes of brain neurons



- Localizes in Brain Neuron Lysosomes (2h Post IV Injection)
- Associated with a lysosomal compartment in neurons as shown with co-staining of NeuN and cathepsin B

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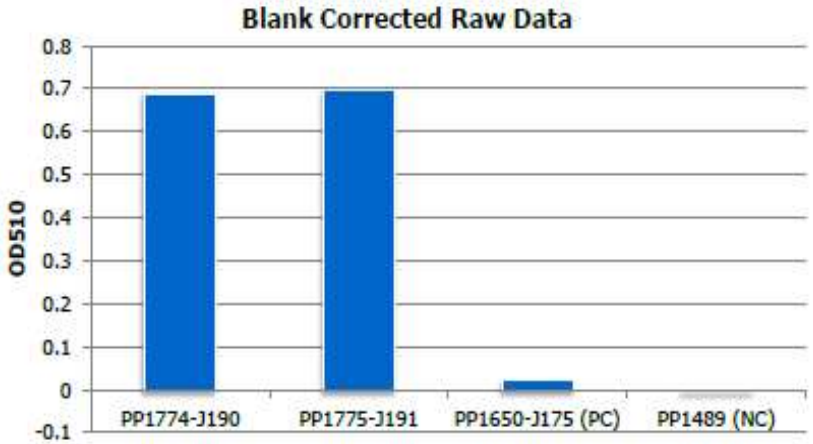
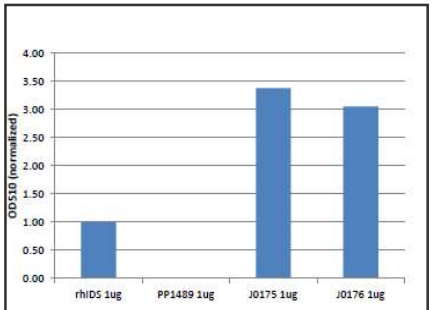
xB^3-I2S Fusion Molecule Show Greater Enzymatic Activity Compared to Commercially Available rhI2S

SDS, reducing condition



Assay Buffer: 50mM Sodium Acetate, 100mM NaCl, pH5.0
Stop solution: 0.2M NaOH
Substrate: 4-PNCS, 2mM in assay buffer
Positive control: PP1650-J175 (I2S-MTf)
Negative control: PP1489 (TZM-MTf homodimer)
Incubation: 24hr @ 37C
PP1774-J190: xB^3-I2S*
PP1775-J191: xB^3-I2S*

* (J190 and J191 are different lots of xB^3-I2S)



Assay Buffer: 50mM Sodium Acetate, 100mM NaCl, pH5.0
Stop solution: 0.2M NaOH
Substrate: 4-PNCS, 2mM in assay buffer
Positive control: rhI2S (R&D systems, cat# 2449-SU)
Negative control: PP1489 (TZM-MTf homodimer)
Incubation: 24hr @ 37C

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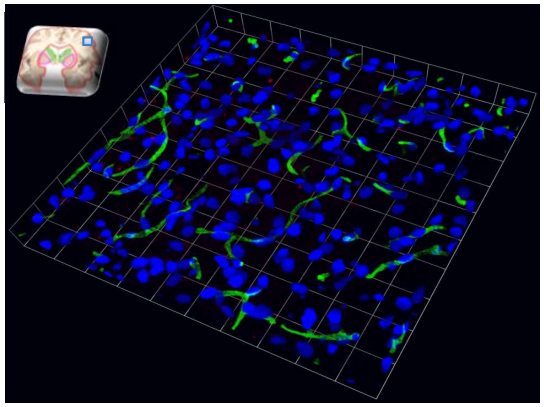
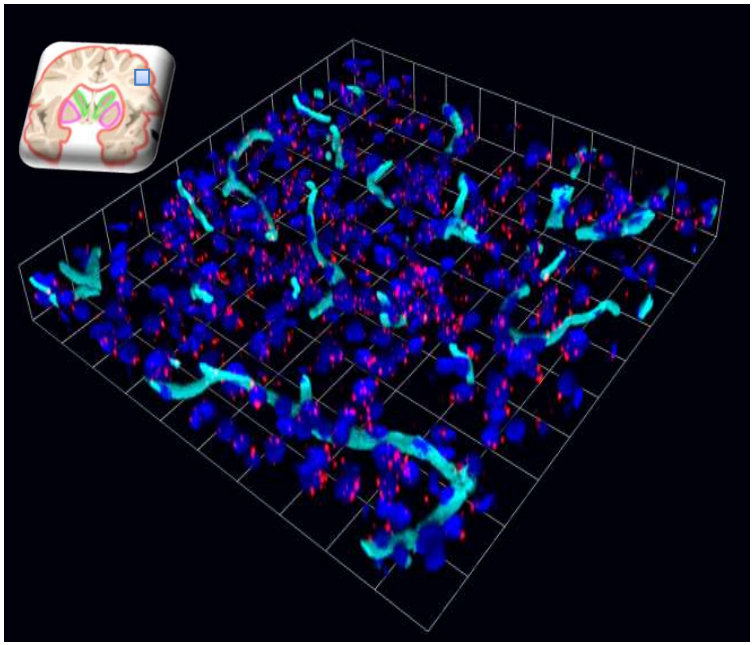
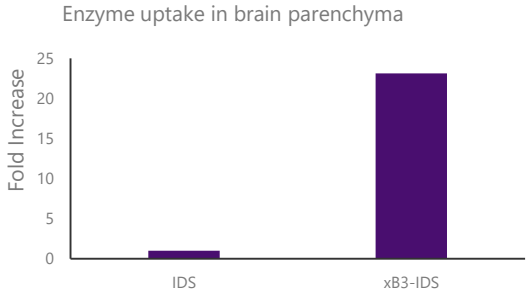
Enzyme Delivery: Over 20-Fold Superior Delivery of I2S Enzyme by xB^3 to the Brain Parenchyma Compared to Native I2S Enzyme

Native Enzyme does not enter the brain tissue



xB^3 + I2S Enzyme enters the brain tissue





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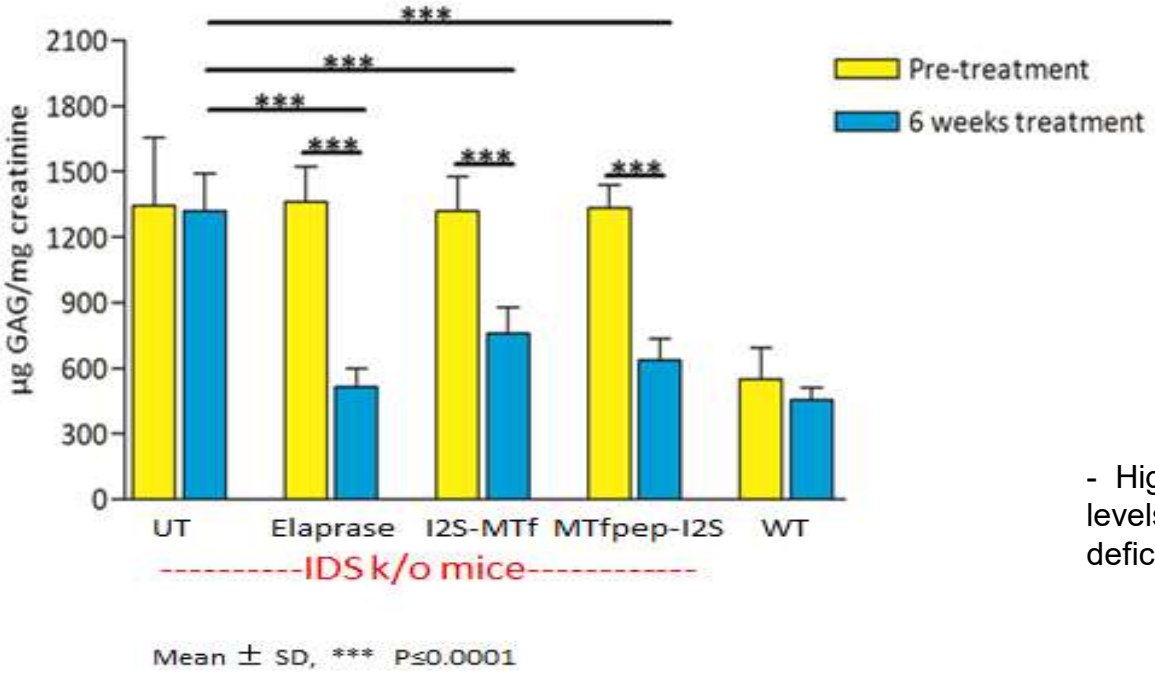
I2S-MTf and xB^3-I2S Fusion Proteins are Fully Active and Effective Against Targets in the Periphery



Mean ± SD, *** P≤0.0001

- High GAGs (GlycoAminoGlycans) levels in urine is an indication of the deficiency of IDS enzyme

Study Conducted at University of Padua

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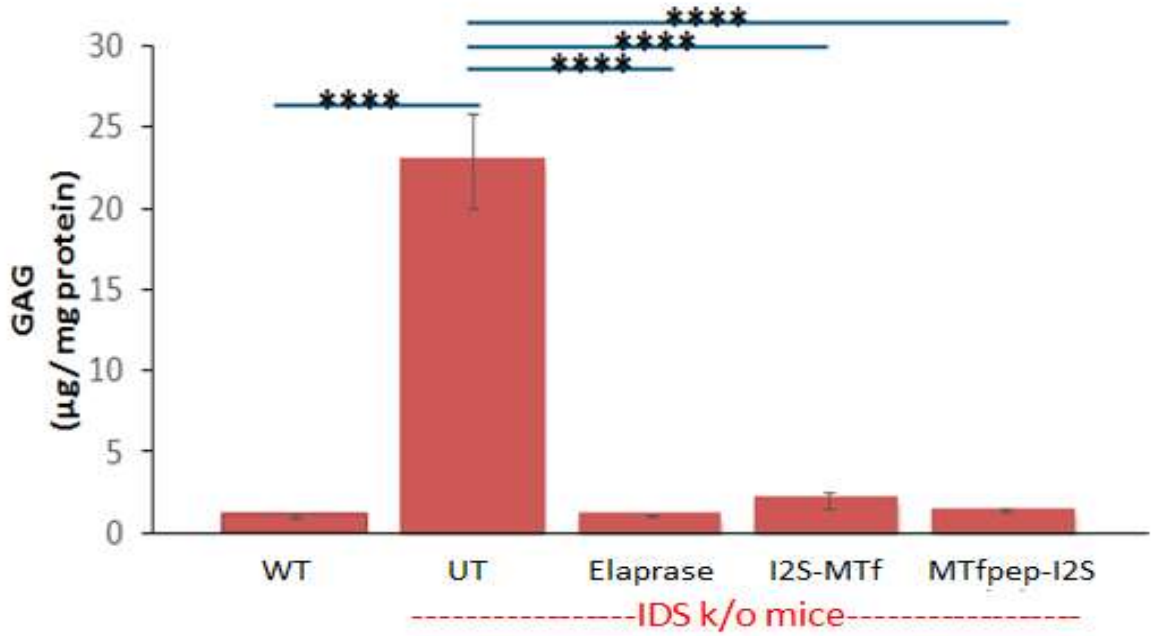
xB^3-I2S Fusion treatment of IDS k/o Mice Significantly Reduced Liver GAG Levels Similar to that Found in WT Mice.



**** P≤0.00001, 1-way ANOVA

GAG content was measured by using Bjornsson's protocol (Bjornsson, 1993), with modifications previously described by our group (Friso et al., 2008).
(MTfpep = xB3)

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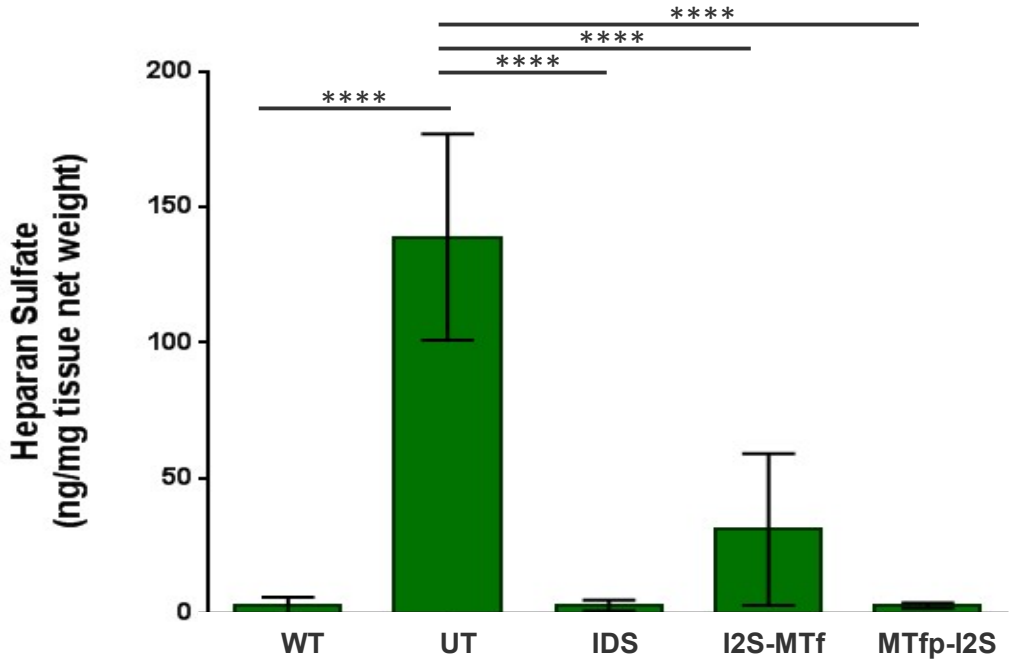
xB^3-I2S Fusion Treatment of IDS k/o Mice Significantly Reduced Liver HS Levels Similar to that Found in WT Mice.



----------IDS k/o mice----------

**** P≤0.00001, 1-way ANOVA

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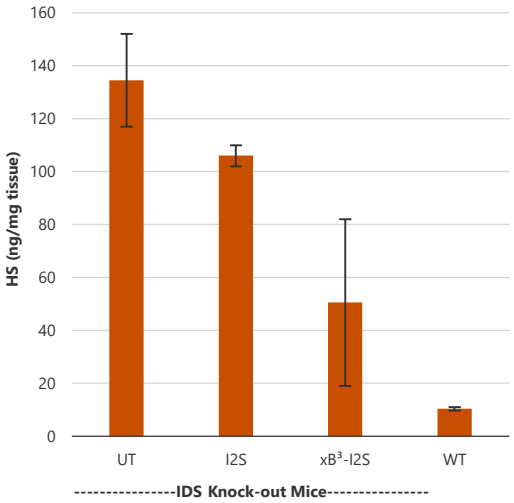
xB^3-I2S Treatment Facilitated the Reduction of Heparan Sulfate Levels, Reduced Number of Storage Cell Vacuoles & Reduction in Number of Lysosome Vesicles in the Brain

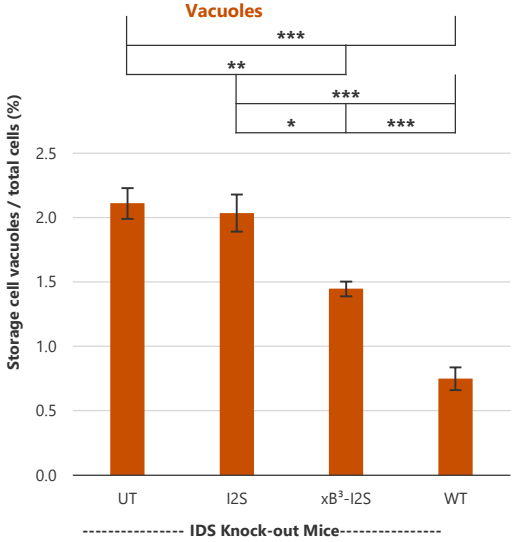
- Significant reduction in brain heparan sulfate accumulation, cell vacuolation and lysosome vesicles in a Hunter Syndrome mouse model
- Increase in brain heparan sulfate accumulation, cell vacuolation and lysosome numbers are hallmarks of Hunter Syndrome

Reduction in Heparan Sulfate Accumulation



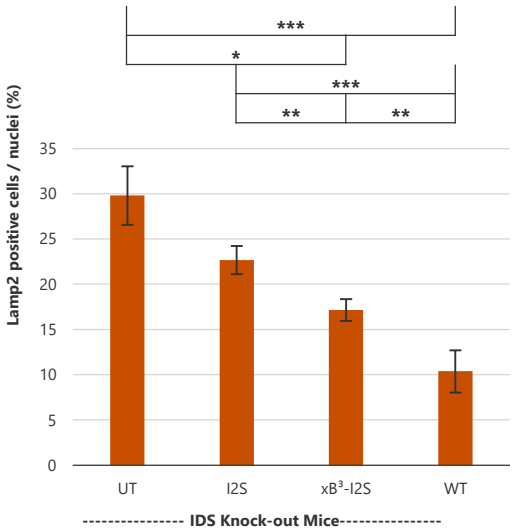
Mean ± SEM; n= 2-3

Reduction in Number of Storage Cell Vacuoles



Mean ± SEM (***P≤0.0001, **P≤0.001, *P≤0.01, One-way ANOVA); n=4-5

Reduction in Number of Lysosome Vesicles



Mean ± SEM (***P≤0.005, **P≤0.05, *P≤0.01, One-way ANOVA); n=5

Work performed at University of Padova, Italy

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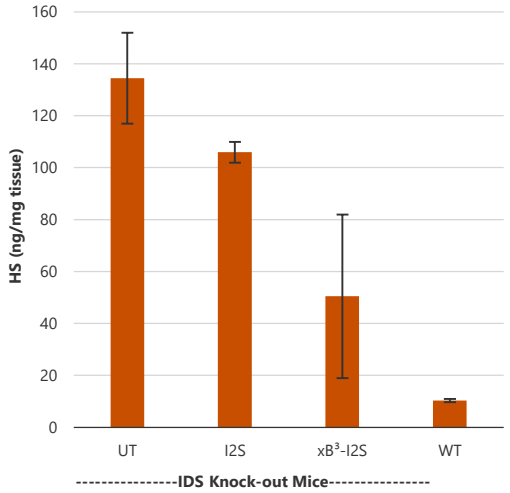
xB^3-007: Glucocerebrosidase
Gaucher's Disease, Parkinson's Disease & Lewy Body Dementia

- Gaucher's disease (GD) results in the deficiency in an enzyme, causing a portion of old cells to be stored in areas such as the liver, spleen, lungs, lymph system, and bones instead of being expelled from the body. It is caused by mutations in GBA1 gene that encodes glucocerebrosidase enzyme
  - **Type II is an acute, infantile, neuropathic form of the disease, associated with severe brain damage: No effective treatments are currently available**
    - **Early onset (3-6 months), severe, rapidly progressing, fatal within two years**
    - **Pathologies: seizures, spasticity, enlarged spleen & liver, poor development**
- Cerezyme® (glucocerebrosidase) is used as an **enzyme replacement therapy** for patients with Gaucher's Disease Type I. Cerezyme robustly treats the peripheral symptoms of Type I (non-neuropathic), however, is not able to cross the BBB and is not effective in Types II and III
  - Bioasis scientists have preliminary data demonstrating the ability of an enzyme to cross the BBB with an associated decrease in heparin sulfate as well as glycosaminoglycans in the central nervous system

Reduction in Heparan Sulfate Accumulation



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Delivery of siRNA based treatment to brain in an induced ischemic stroke

Why

- Utility of siRNA therapeutic approaches for CNS diseases has been limited by their distribution *in vivo*
  - Preferentially localize to the kidney and liver, unable to cross the BBB

Aim

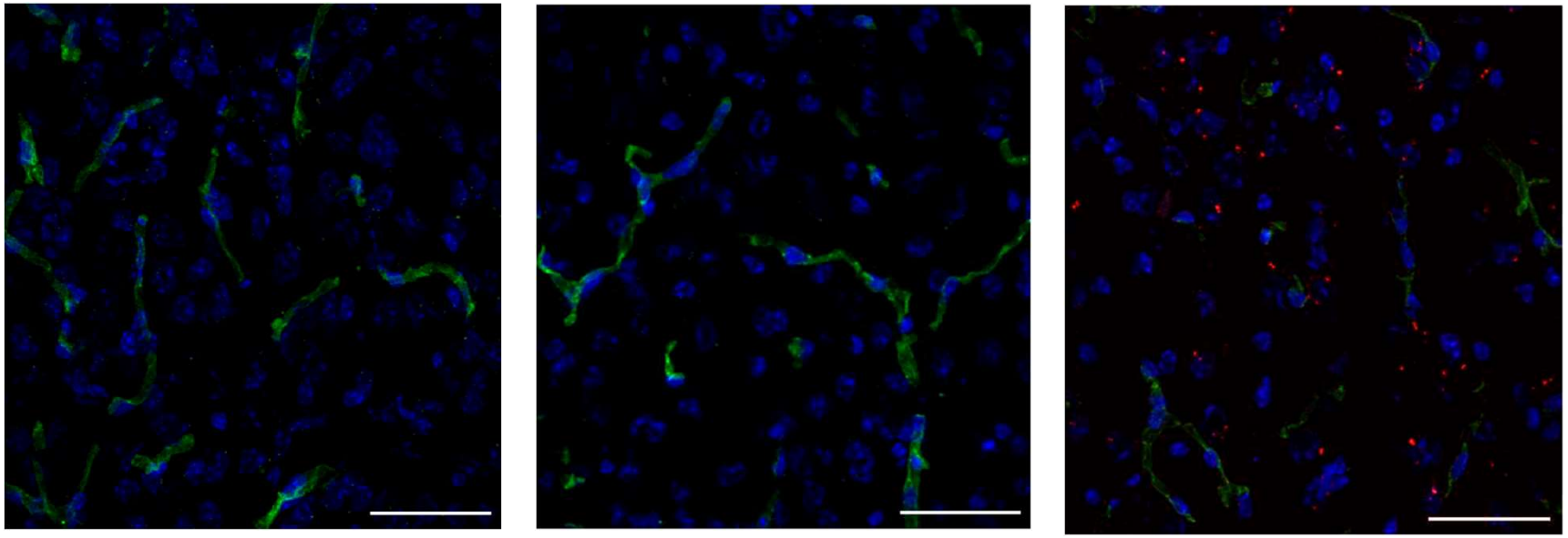
- Delivery of siRNA to brain to knock down gene targets associated with specific CNS disease / condition

Target

- NADPH oxidase (NOX) enzyme gene in ischemic stroke
  - Stroke is one of the leading causes of death in North America, with majority result from blockage of blood vessels in the brain (ischemic stroke)
  - NOX4 has been identified in neurons, astrocytes and microglia
  - NOX4 is thought to be responsible for majority of oxidative stress observed in acute traumatic brain injury[1]
  - Animal deficient in NOX4 are strongly protected from ischemic stroke[2,3]

Conjugation to xB^3 Facilitated the Transport of siRNA Across the BBB into Brain Parenchyma of Wild Type Mice

Confocal Images One Hour Post Single IV Administration (10mg/kg) in Wild-type Mice



siRNA / xB^3-siRNA
Capillary
Nucleus

PBS | siRNA | xB^3-siRNA

Work performed at National Research Council of Canada – Research Facility

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Stroke Induction Via Middle Cerebral Artery Occlusion

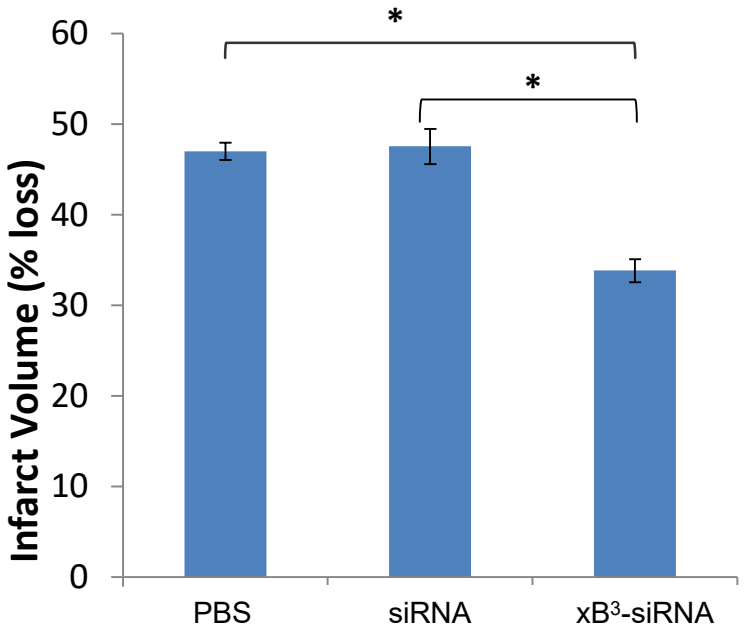
Model:

- Middle cerebral artery occlusion via filament
- Duration of occlusion: 60 min
- Animal sacrificed 24 hrs post reperfusion
- Dose: 30 mg/kg
- Administration: i.v. prior to stroke induction

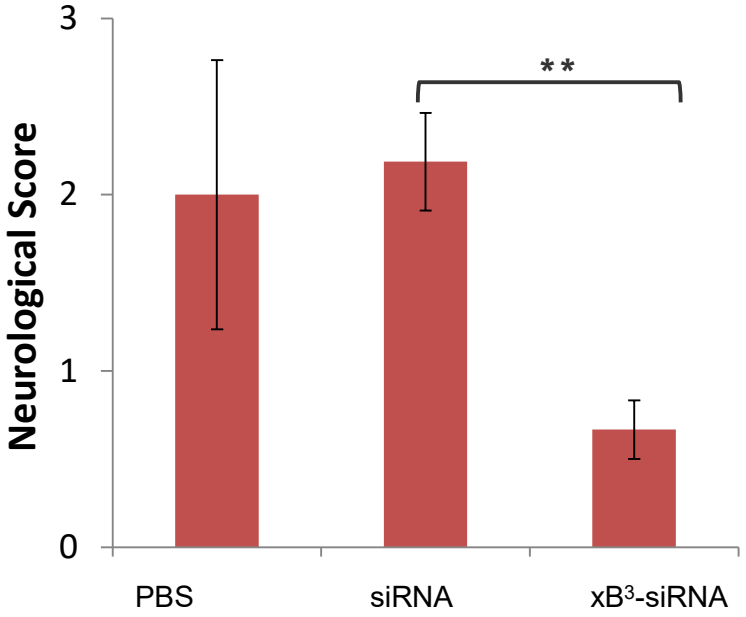
Analysis>

- Cerebral infarction – via 2,3,5-triphenyltetrazolium chloride colorimetric staining
- Neurological deficit – blinded behavioral assessment base on scale of 0 (best) - 5 (worst)
- Knock-down quantification (mRNA level) – Quantitative PCR

Pretreatment with xB^3-siRNA Conjugates Significantly Reduced the Infarct Volume and Improved Neurological Deficit



* P ≤ 0.05 (1 way Anova); n=4



** P ≤ 0.01 (1 way Anova); n=4

Work performed at National Research Council of Canada – Research Facility

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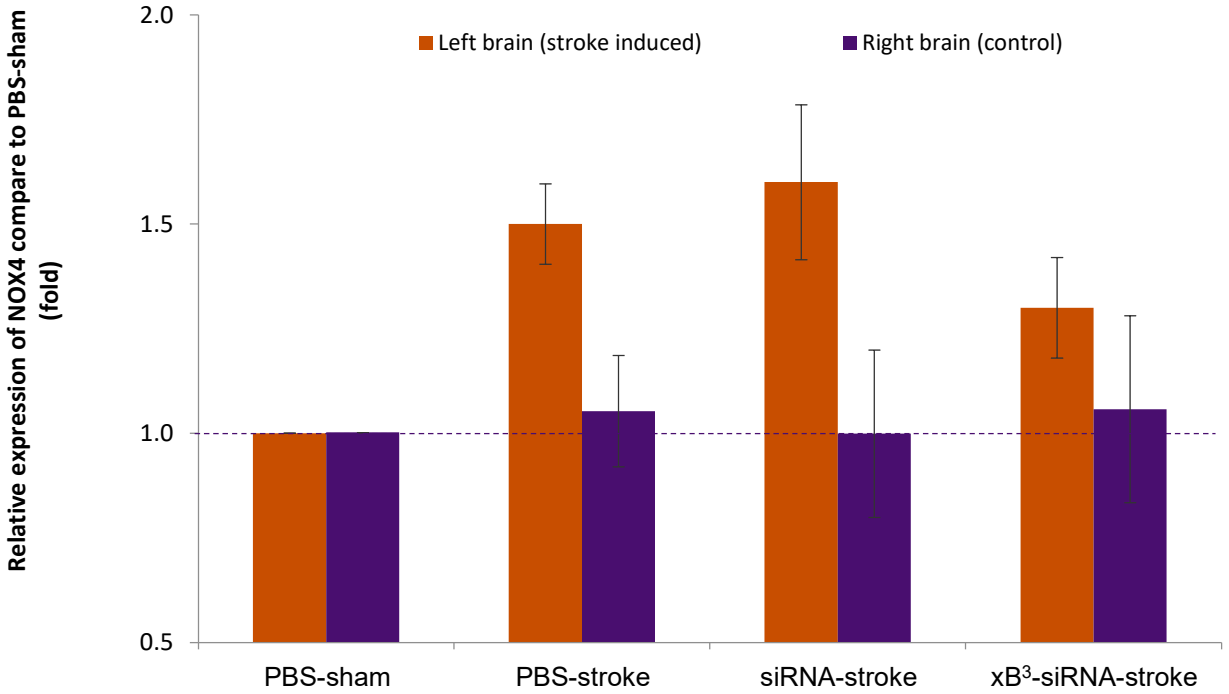
xB^3-siRNA Pretreatment Reduced NOX4 Expression Compared to siRNA or PBS in Stroke Induced Brain at mRNA Level



Mean ± SEM; n=4; data obtained from a separate set of animal as those used for the analysis of infarct volume/neurodeficit

Work performed at National Research Council of Canada – Research Facility

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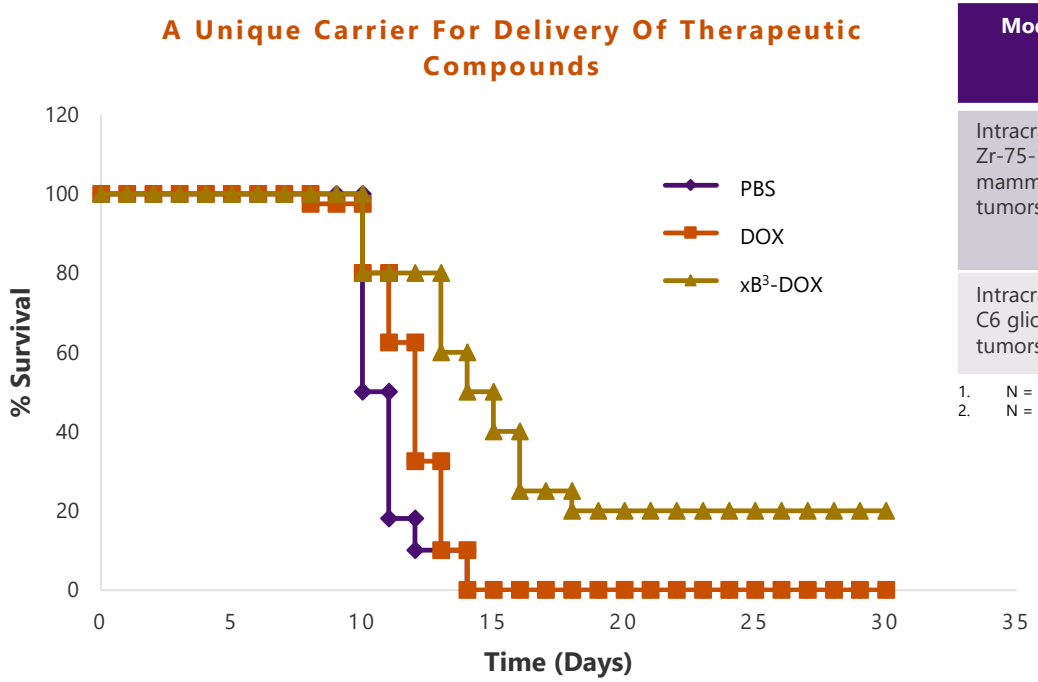
Small Molecule: Doxorubicin Conjugate Achieves Significant Increase in Survival in Intracranial Tumor Mouse Models



N = 10; total in DOX group = 20mg/kg, total ADR in xB^3-DOX group = 5.5mg/kg; dosing schedule D3,4,5,6,7,10,11,12,13,14

Model	Compound (Total ADR dosed)	Mean survival (Days)	% change in mean survival	Significance
Intracranial Zr-75-1 mammary tumors[1]	PBS	10	-	-
	DOX (20mg/kg)	9.24	-7.6	P<0.05
	xB^3-DOX (5.5 mg/kg)	17.7	77	P<0.005
Intracranial C6 glioma tumors[2]	PBS	20.2	-	-
	xB^3-DOX (0.49 mg/kg)	28.3	40	P<0.001

1. N = 10; dosing schedule D3,4,5,6,7,10,11,12,13,14;
2. N = 10; dosing schedule D1,3,7,10,14

- Treatment with xB^3-DOX raised the mean and median survival to 77% and 40% respectively
- 2/10 mice in xB^3-DOX treatment group survived to over 50 days and were tumor-free at autopsy

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