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SECURITIES & EXCHANGE COMMISSION EDGAR FILING

BIOVIE INC.

Form: 8-K

Date Filed: 2021-05-17

Corporate Issuer CIK: 1580149

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **May 17, 2021**

BioVie Inc.

(Exact name of registrant as specified in its charter)

Nevada	**001-39015**	**46-2510769**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

2120 Colorado Avenue, Suite 230 Santa Monica, California	**90404**
(Address of principal executive offices)	(Zip Code)

(310) 444-4300
(Registrant's Telephone Number, Including Area Code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:
o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class:	Trading Symbol(s):	Name of Each Exchange on Which Registered:
Class A Common Stock, par value $0.0001 per share	**BIVI**	**The NASDAQ Stock Market, LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

Emerging growth company o

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. o

Item 7.01 Regulation FD Disclosure.

Beginning on May 17, 2021, BioVie Inc. (the "Company") plans to make a series of investor presentations (the "Corporate Presentation" and the "R&D Day Presentation") copies of which is attached as Exhibit 99.1 and 99.2, respectively; to this Current Report on Form 8-K and is incorporated herein by reference. The Company also expects to use the Investor Presentation at the BRiley Conference beginning on May 19, 2021 and from time to time thereafter in connection with presentations to potential investors, industry analysts and others. The Investor Presentation is available under the "Events and Presentations" tab in the "Investors" section of the Company's website, located at www.biovie.com.

By filing this Current Report on Form 8-K and furnishing the information contained herein, the Company makes no admission as to the materiality of any information in this report that is required to be disclosed solely by reason of Regulation FD.

The information contained in the Corporate Presentation and the R&D Day Presentation is summary information that is intended to be considered in the context of the Company's Securities and Exchange Commission ("SEC") filings and other public announcements that the Company may make, by press release or otherwise, from time to time. The Company undertakes no duty or obligation to publicly update or revise the information contained in this report, although it may do so from time to time as its management believes is warranted. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases or through other public disclosure.

The information presented in Item 7.01 of this Current Report on Form 8-K and Exhibit 99.1 and 99.2 shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, unless the Company specifically states that the information is to be considered "filed" under the Exchange Act or specifically incorporates it by reference into a filing under the Securities Act of 1933, as amended, or the Exchange Act.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Corporate presentation dated May 2021
99.2	R&D presentation dated May 19, 2021

* Schedules and exhibits have been omitted pursuant to Item 601(a)(5) of Regulation S-K. The Company will furnish the omitted schedules and exhibits to the Securities and Exchange Commission upon request.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: May 17, 2021

BIOVIE INC.

By: /s/ Joanne Wendy Kim
Name: Joanne Wendy Kim
Title: Chief Financial Officer

Forward-looking statements

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This document contains forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 that involve risks, uncertainties and assumptions that could cause BioVie's actual results and experience to differ materially from anticipated results and expectations expressed in these forward-looking statements. BioVie has in some cases identified forward-looking statements by using words such as "anticipates," "believes," "hopes," "estimates," "looks," "expects," "plans," "intends," "goal," "potential," "may," "suggest," and similar expressions. Among other factors that could cause actual results to differ materially from those expressed in forward-looking statements are: successful completion of the acquisition of the biopharmaceutical assets from NeurMedix Inc., BioVie's need for, and the availability of, substantial capital in the future to fund its operations and research and development. Other risks are that BioVie's compounds may not successfully complete pre-clinical or clinical testing, or be granted regulatory approval to be sold and marketed in the United States or elsewhere. BioVie cannot guarantee the effectiveness of its patents or Orphan Drug designations. A more complete description of these risk factors is included in BioVie's filings with the Securities and Exchange Commission. In addition to the risks described above and in BioVie's filings with the Securities and Exchange Commission, other unknown or unpredictable factors also could affect BioVie's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. You should not place undue reliance on any forward-looking statements. BioVie undertakes no obligation to release publicly the results of any revisions to any such forward-looking statements that may be made to reflect events or circumstances after the date of that these slides are posted to BioVie's website or to reflect the occurrence of unanticipated events, except as required by applicable law or regulation.

Investment Highlights

- Multiple shots on goal focused on unmet medical needs: neurodegenerative, advanced liver disease, oncology
- BIV201: Orphan drug in Phase 2b for refractory Ascites; HRS-AKI trials planned. Ascites readout anticipated in early 2022
- NE3107: inhibitor of pathologic inflammation and insulin resistance without toxicity and immunosuppression. Alzheimer's Phase 3 starting mid-2021. Parkinson's, Multiple Myeloma, and Prostate Cancer follow
- Capital efficient development plans with expected near-term data readouts

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Leadership Team

Cuong Do
President & Chief Executive Officer
- 30+ years in biopharma & technology
- President, Samsung Global Strategy Group
- Chief Strategy Officer for Merck
- Senior partner at McKinsey & Company

Jonathan Adams
Liver Cirrhosis Program
- 30+ years in biopharma
- Founded LAT Pharma (BioVie predecessor)
- Mission Pharmacal
- Corbett and other healthcare agencies
- Searle Pharmaceuticals

Clarence Ahlem
Neurodegenerative Disease Program
- 35+ years in biopharma
- Vice President, Product Development Harbor Therapeutics
- Director, Product Development, Hollis-Eden Pharmaceuticals
- SyStemix
- Hybritech
- US San Diego

Chris Reading, PhD
Neurodegenerative Disease Program
- 40+ years in biopharma
- Chief Scientific Officer, Hollis-Eden Pharmaceuticals
- VP of Product and Process Dev. for Systemix
- U Texas Dept. of Tumor Biology
- MD Anderson Cancer Center
- Over 130 peer-reviewed publications

J. Wendy Kim
Chief Financial Officer
- 35 years in finance/ accounting
- As CFO managed corporate finance and operations groups
- Closed M&A transactions and secured financings
- Combined 22 years at KPMG and BDO LLP

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Liver Cirrhosis Program

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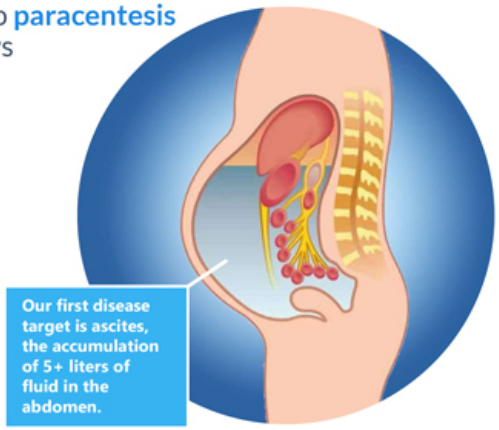
Disease Target: Refractory Ascites

Refractory ascites patients typically undergo **paracentesis** to remove ascites fluid every week to 10 days

Paracentesis:

- Withdrawal of 5–10L of ascites fluid (on average) from abdomen using a large bore needle
- Provides a few days of symptomatic relief
- The kidneys are "burning out" by retaining massive quantities of salt and water
- Patients suffer frequent life-threatening complications
- No remaining options except for TIPS* surgery or liver transplant
- Represents $670 million addressable market with 20,000 targeted US patients
- **No drugs ever approved by FDA** to treat ascites



* TIPS = transjugular intrahepatic portosystemic shunt to channel blood flow around the liver

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BIV201: Continuous Infusion Terlipressin

- Terlipressin was first approved in Germany in 1980s to treat bleeding esophageal varices (BEV)
- Approved for BEV and hepatorenal syndrome (HRS) in European & Asian hospitals (40+ countries)
  - Administered via 1-2 mg bolus injections every 4-6 hours; this dosing method is associated with **serious adverse events**
  - >50,000 patients have been treated with terlipressin[1]
- BioVie is pursuing a novel application: Treating refractory ascites using **continuous infusion terlipressin (BIV201) in the home care setting**
  - Improved safety: continuous infusion shown to reduce SAEs by more than 50% in head-to-head study in HRS[2]
  - Terlipressin has never been approved to treat ascites
  - Not available in the US or Japan

1. Company estimate.
2. HEPATOLOGY 2016;63:983-992

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Novel Prefilled Syringe with Patent-pending Liquid Formulation

- Global PCT filed to protect our novel liquid formulation
- **Improved safety:** Eliminates mixing minute quantities of powder terlipressin that could result in medication errors or sterility loss
- **Enhanced convenience:** Simply inject fluid into the saline bag and attach to pump

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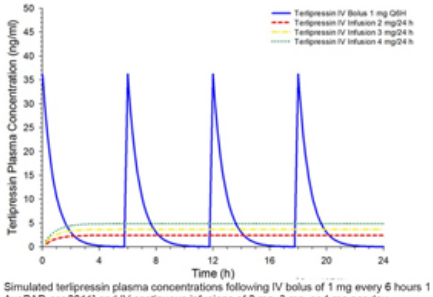
BioVie Phase 2a trial results: BIV201 Pharmacokinetics

Continuous low blood levels of terlipressin versus potentially dangerous spikes with IV-bolus dosing

Source: BioVie poster presentation at AASLD 2019.

Comparison of the PK Profile of Terlipressin Administered by Continuous Infusion or Intermittent IV Boluses.



Simulated terlipressin plasma concentrations following IV bolus of 1 mg every 6 hours 1 [Lucassin, AusPAR-cer 2011] and IV continuous infusions of 2 mg, 3 mg, or 4 mg per day

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Continuous Infusion Terlipressin in 19 Refractory Ascites/HRS Patients (Chapman et al.)

Pre-therapy:

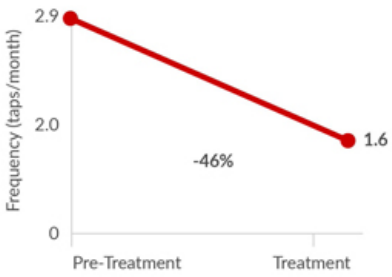
- 70% of patients required weekly large volume paracentesis (LVP)
- 63% poor muscle strength

Results:

- Median duration of CI terlipressin treatment: **51 days**
- 46% average reduction in frequency of paracentesis
- Significantly improved muscle strength and nutritional intake
- No complications directly attributable to terlipressin

Decreased Need for Paracentesis

Change in frequency of paracentesis procedures



Source: JHEP 2019.

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BIV201 Development Plans

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Ascites

- Revised Phase 2 protocol and CMC package covering prefilled syringe cleared by FDA
- 20 to receive BIV201 therapy + standard of care (SOC); 10 to receive SOC only (control group)
  - Primary composite endpoint: Incidence of ascites-related complications over 180 days following randomization
  - Secondary endpoints include ascites fluid removed over 90 days
- Timeframe: Two 28-day cycles of BIV201 therapy within 4 months, then follow patients for additional 60 days
- Currently activating 9 sites and screening patients
  - 3 sites actively screening
  - Patient consenting underway
- Same trial designed expected for single pivotal Phase 3 in mid-2022 with ~120 subjects

HRS-AKI

- Planning a registrational Phase 3 trial in HRS-AKI*
  - Based on changing serum creatinine indicate renal function decline
  - **Expecting better outcomes** because earlier treatment is possible
  - **Expecting improved safety** with continuous infusion dosing compared to Mallinckrodt's CONFIRM study of terlipressin in HRS type 1
    - Mallinckrodt used bolus injections (1 or 2 mg given over approx. 5 min)
    - They achieved the efficacy objective, but safety concerns precluded FDA approval
- Pre-IND package submitted to FDA
  - We will use the same PI's, same sites, and same drug product as our current ascites study
  - Orphan drug designation for HRS (in addition to ascites)

* Hepatorenal syndrome type of acute kidney injury

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Introduction to inflammation and NE3107

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Inflammation

- Inflammation is the result of the body's natural protective processes

Insults	Responders	Master Alarms	Pro-inflammatory factors
• Pathogens • Trauma • Ischemia • Stress • Radiation • Obesity • Cancer	• Blood proteins • Platelets • Granulocytes • Monocytes • Macrophages • Microglia • Endothelial cells	• NFκB transcription factors • Oxidative stress • Reactive oxygen • Reactive nitrogen	• Cytokines • Chemokines • Receptors • Complement factors • Metalloprotinases • Cell adhesion molecules

- If insults and pro-inflammatory cascade eliminated, pathology addressed
- If not, low grade chronic inflammation and associated insulin resistance ensues
- Inflammation and insulin resistance go hand-in-hand

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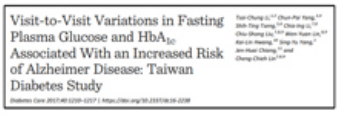
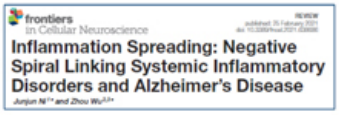
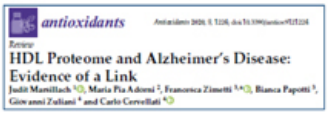
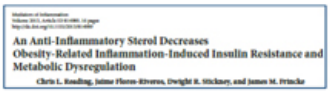
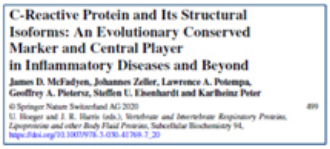
Inflammation and disease pathology well established in many areas











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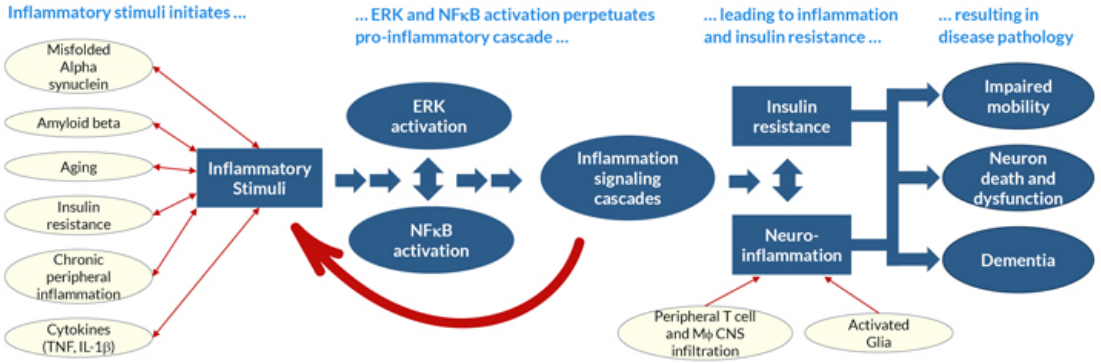
Neuroinflammation drives disease pathology



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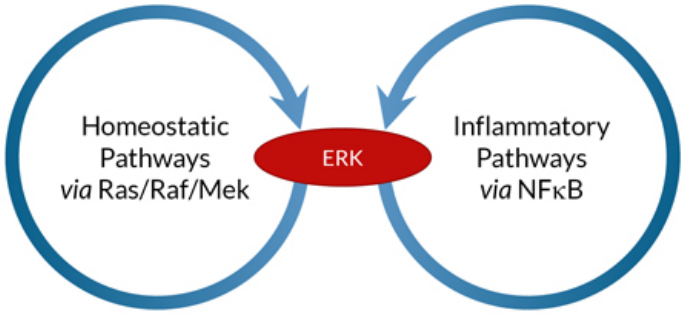
Extracellular Signal-Related Kinase (ERK)



Critical player for both homeostasis and inflammation (and resulting inflammation-induced insulin resistance)

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Forgetting the "Past" So that We Can Remember the "Now" – KOL Panel Excerpts from B. Riley Neuroscience Conference, 2021

"I saw that there was a drug by NeurMedix called NE3107 which was just authorized for a pivotable Alzheimer's Phase 3 trial. What intrigued me about it is because it affects all three mechanism of action that I mentioned: anti-TNF, NFκB, and ERK. What was exciting about some of the early Phase 2 studies is that there's no significant toxicities, it was not immunosuppressive, and because it's an oral drug it was very easy to utilize … "

Professor Alan Mazurek
Icahn School of Medicine at Mount Sinai

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NE3107: A Differentiated Molecule

- First-in-class molecule with desirable characteristics
  - Small molecule
  - Crosses blood-brain barrier
  - Excellent safety profile demonstrated in pre-clinical and clinical trials
- Blocks neuroinflammation and insulin-resistance at the right time/place in pathologic pathway
- Does not inhibit homeostatic activity
- The result of 20+ years of research that started with DHEA leading to identification of the active metabolite that is the inhibitor of pathologic inflammation and insulin resistance. NE3107 resulted from medical chemistry creating the molecule with desired properties

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NE3107 Selectively Inhibits ERK Pathological Inflammatory Cascade (EPIC)

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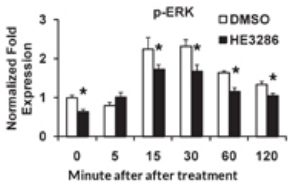
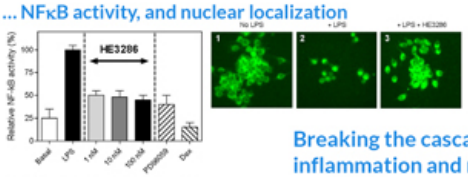
NE3107 reduces ERK activation …

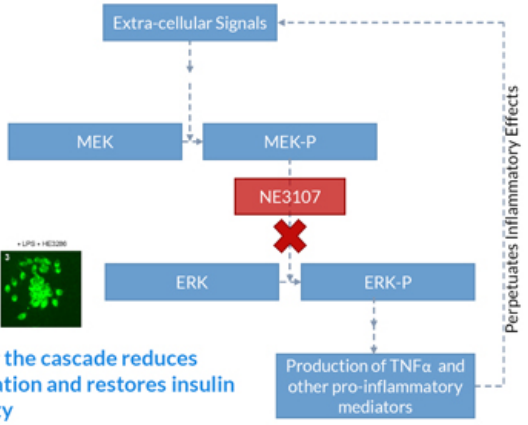


Lu 2010 *Am J Physiol Endocrinol Metab 298 E1036*

… NFκB activity, and nuclear localization



Wang *2010 J Pharmacol Exp Ther 333 70*



Breaking the cascade reduces inflammation and restores insulin sensitivity

Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

By blocking ERK activation, NE3107 prevents downstream impact

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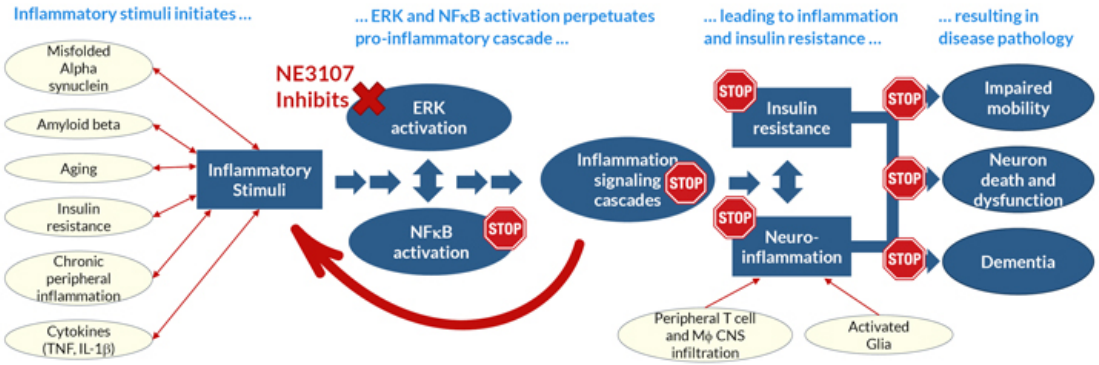

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NE3107 Has Demonstrated Broad Applicability

- NE3107 decreased disease in models of arthritis, insulin resistance, type 1 and 2 diabetes, ulcerative colitis, COPD, pleurisy, multiple sclerosis, optic neuritis, glaucoma and Parkinson's disease
- NE3107 demonstrated broad impact on inflammation
  - Reduced pro-inflammatory biomarkers ceruloplasm, C1q, CRP, IFNγ, IL1β, IL6, IL12, IL17, IL23, MCP1, MMP9, RANTES, iNOS, CCR2 CXCL1, CXCL10, VCAM1 and TNFα, without immunosuppression
  - Decreased LPS- stimulated proinflammatory kinase activity for IKK, JNK, p38, and ERK1/2 in macrophages
  - Increased anti-inflammatory and pro-resolving biomarkers: adiponectin, arachidonic acid, docosahexaenoic acid, HDL and palmitoleate

Sources: Auci, 2007 *Ann N Y Acad Sci 1110* 630, Kosiewicz 2011 *Eur J Pharmacol* 658 257, Offner 2009 *Exp Ther* 329 1100, Lu 2010 *Am J Physiol Endocrinol Metab* 298 E1036, Wang 2010 *J Pharmacol Exp Ther* 333 70, Lambert 2017 *Front Neurosci 11* 45, Nicoletti 2012 *Parkinsons Dis 2012* 969418, Reading 2013 Obesity *2013 21 E343*, Auci 2010 *Int J Mol Med 25* 625, Conrad 2010 *J Inflamm 7* 52, Ahlem 2009 *Ann N Y Acad Sci 1173* 781, Lambert 2017*Front Neurosci 11* 45, Kahn 2014, *Invest Ophthalmol Vis Sci* 55 5744

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Alzheimer's Program

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NE3107's neuroprotective properties

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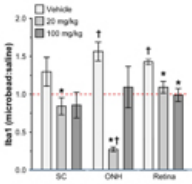
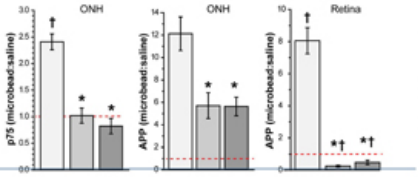
Decreased activated microglia



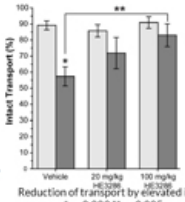
Iba1 is a microglia-specific marker.
† p<0.045 * p<0.037

Decreased neurotrophin receptor (p75) and amyloid precursor protein (APP)



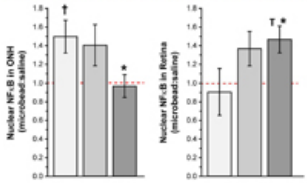
ONH: Optic nerve head. † p<0.047 * p<0.027

Rescued axonal transport

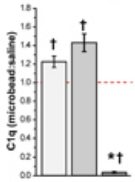


Reduction of transport by elevated intraocular pressure. * p<0.003 ** p<0.025

Decreased Inflammatory NFκB in inflamed optic nerve head; increased homeostatic NFκB in retina



Decreased C1q



Complement component C1q involved with neuronal death. † p<0.037 * p<0.033

Source: Lambert 2017 *Front Neurosci 11 45*

Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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NE3107's ability to enhance insulin sensitization confirmed in Phase 1 trial with impaired glucose tolerance patients

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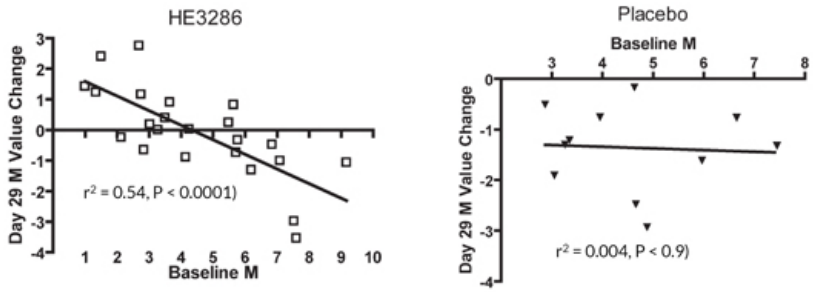
Improved insulin-dependent glucose disposal in 48 obese, inflamed subjects



Day 29 Glucose disposal rate (M, measured in mg/kg/min in glucose clamp studies) value change as a function of baseline M

Reading 2013 *Obesity 21 E343*

Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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NE3107's ability to enhance insulin sensitization confirmed in Phase 2 trial with T2D patients

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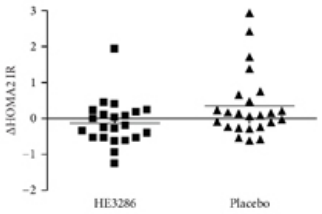
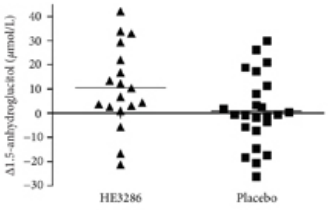
Improved the homeostatic model assessment of insulin resistance ...



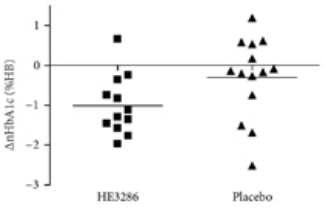
Cohort 1 baseline MCP-1 > 40 pmol/L individual subject changes in homeostatic model assessment of insulin resistance at Day 84

... decreased postprandial glucose ...



Pooled cohorts 1 and 2 changes at Day 84

... decreased HbA1c ...



Day 112 cohort 2 baseline BMI > 31 kg/m²

... decreased insulin resistance in inflamed T2D patients

Effect	Value	Change HE3286	Change Placebo	*P*	Test[a]
ΔHOMA2 IR[c]	Day 84 mean	−0.1	+0.4	0.02	*t*-test

Reading 2013 *Mediators Inflamm 814989*
Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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Insulin sensitizing improvement also brought improvements in AD indicators

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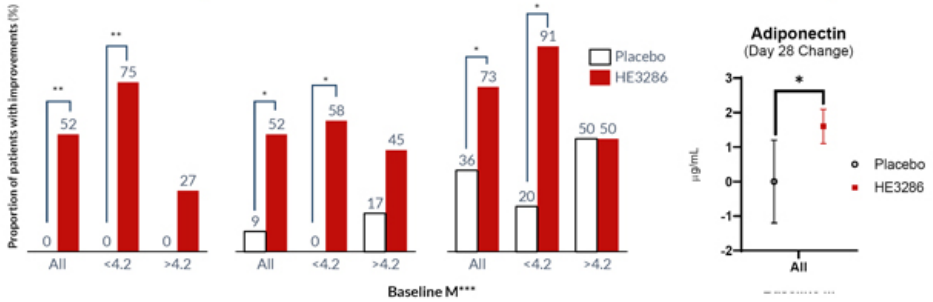
In a Phase 2 study 48 obese subjects with impaired glucose tolerance, NE3107 ...

Increased insulin sensitivity ... ... increased HDL ... ... decreased CRP ... ... and increased adiponectin



* Fischer's exact test p<0.05 **p<0.01
*** Baseline glucose disposal rate (M) measured in mg/kg/min. Median baseline is 4.2
Source: Reading 2013 Obesity *21 E343*
Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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Proceeding Pivotal Phase 3 for Alzheimer's Disease

- NE3107
  - Reduces inflammation and enhances insulin sensitivity, both of which have been shown to reduce AD pathology. NE3107 blocks EPIC, which is upstream from Amyloid beta and phospho-tau, and thus further reduces inflammation
  - Has demonstrated neuroprotection in models of PD, optic neuritis and glaucoma
  - Has absence of toxicity and thus well suited for chronic use
  - Reduces systems deregulation (enhances homeostasis)
  - Crosses BBB
- >80% of AD patients also have (or developing) Type 2 Diabetes
- >3,000 scientific publications support the role insulin signaling and insulin resistance in AD
  - Insulin resistance in AD is caused by a number of factors, including inflammation
- While NE3107 has not been studied directly in AD patient, its impact on inflammation, insulin resistance is expected to directly translate to benefits in AD
  - Decreased inflammation → increased insulin sensitivity → decrease in rate of cognitive decline
  - Potential for enhancement of cognition due to insulin's role in the brain

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NM101: a phase 3 trial in mild to moderate Alzheimer's disease, NCT04669028

A Phase 3, Double-blind, Randomized, Placebo-controlled, Parallel Group, Multicenter Study of NE3107 in Patients who have Mild to Moderate AD

- Pivotal study for Alzheimer's disease. Two weeks each of 5 mg and 10 mg BID dose titration followed by 26 weeks of 20 mg twice daily vs. placebo, approximately 160 subjects in each arm, 80% power
- Diagnosed with AD and without evidence of a vascular contribution. Mild to moderate disease. CDR 1-2. MMSE 14-24.
- 60-85 years old, males and females
- Randomization stratified by MMSE and Homeostatic Model Assessment 2 Insulin Resistance (HOMA2)
- Co-primary endpoints
  - Mean change from Baseline to Week 30 in the eleven-question form of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 12) comparing the NE3107 group to the placebo group
  - Mean change from Baseline to Week 30 in Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) comparing the NE3107 group to the placebo group
- Secondary endpoints
  - ADCS-ADL (functional), ADCOMS (4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating-Sum of Boxes items), NPI-12 (care-giver rating of behavioral changes), MMSE, CDR
  - Glycemic control: HOMA2, Mean Amplitude of Glycemic Excursion (MAGE) using continuous glucose monitoring, fructosamine levels, post-prandial glucose and fasting blood glucose vs time.
  - MRI total hippocampus volume change, baseline to end of treatment in a subset of approximately 50% of active and placebo subjects
  - Target engagement assessed in a small subset of active and placebo subjects using PET to quantify cortical glucose utilization
- CRO cost estimate for the pivotal study is ~$16 million

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Targeting Neuroinflammation in Alzheimer's Disease

- Extensive study data supports reducing neuroinflammation as the key to slowing/reversing cognitive decline
- Other companies focused on this target:

Company	Drug Candidate	Clinical Status	Mechanism of Action	Recent Market Cap (5/14/21)
Denali Therapeutics	DNL788	Early clinical[1]	Impacts TNF mediated neuroinflammation via NFκB pathway	$6.4 billion
Cassava Sciences	Simufilam	Pre-Phase 3[2]	Disrupts neuroinflammatory signaling	$1.6 billion
Athira	ATH-1017	Phase 2/3[3]	Decreases neuroinflammation mediated by TLR4 and via NFκB pathway	$0.7 billion

- NE3107 has significant advantages over competition
  - Ready for Phase 3 start
  - Inhibits proinflammatory pathways without impacting homeostasis
  - Inhibits ***both*** overarching mechanisms of AD pathology: inflammation and insulin resistance

[1] denalitherapeutics.com accessed 5/14/2021
[2] cassavasciences.com accessed 5/14/2021
[3] athira.com accessed 5/14/2021

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Parkinson's Program

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Remarkable similarities between neurodegenerative diseases

- Neuroinflammation and oxidative stress are common features in the major neurodegenerative diseases, Alzheimer's, Parkinson's, frontotemporal lobar dementia and ALS (and TBI)
- Remarkable parallels exist between AD and PD
  - Activated microglia-inflammation
  - Systemic inflammation driven
  - TNF driven
  - Insulin resistance, metabolic dysfunction
  - Mitochondrial dysfunction and Oxidative stress
  - Endoplasmic reticulum stress- unfolded protein response
  - Misfolded protein aggregates (alpha synuclein, Lewy bodies for PD)
  - Controversial etiology, slow progression

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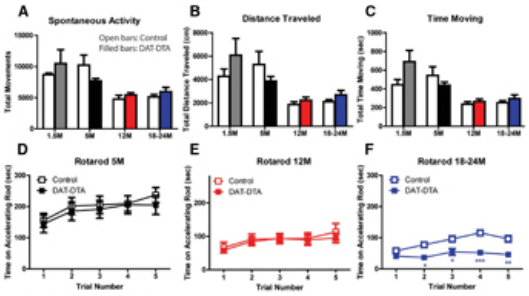
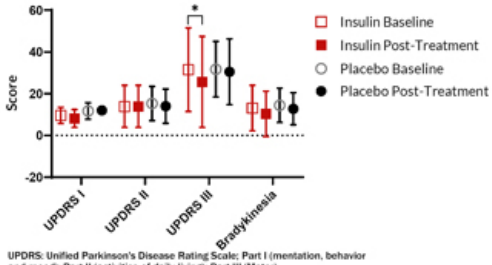
Low dopamine environment *and* inflammation are required to drive parkinsonism

Low dopamine environment alone did not lead to Parkinsonism …



Golden 2013 *J. Neurosci 0890 13*

… but also required inflammation and insulin resistance



UPDRS: Unified Parkinson's Disease Rating Scale: Part I (mentation, behavior and mood); Part II (activities of daily living); Part III (Motor)
From: Novak 2019 *J Pone 0214364*

Reduction of inflammation resulting from insulin-resistance reduced Parkinson's motoric symptoms

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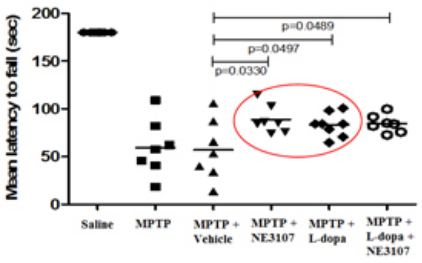
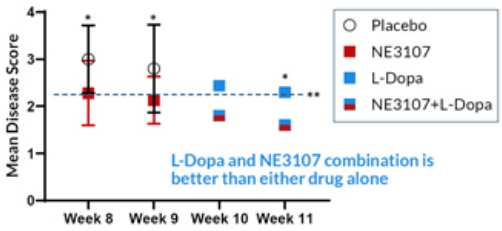
NE3107 has similar promotoric activity to L-dopa in rodent and marmoset models

MPTP Mouse



MPTP Marmoset treated at Week 8



*p<0.001 compared to other treatment arm in time period
** L-Dopa at week 11 not statistically different from NE3107 at weeks 8 and 9

NE3107's promotoric effects observed within 4 days of treatment

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin used to mimic many aspects of PD

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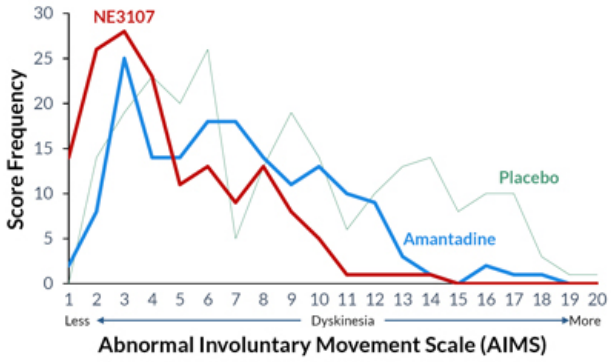
NE3107 decreases L-Dopa-induced dyskinesia (LID)

Distribution of AIMS Scores



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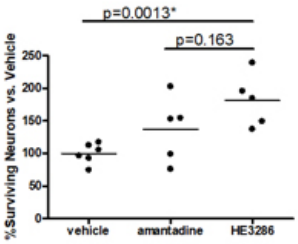
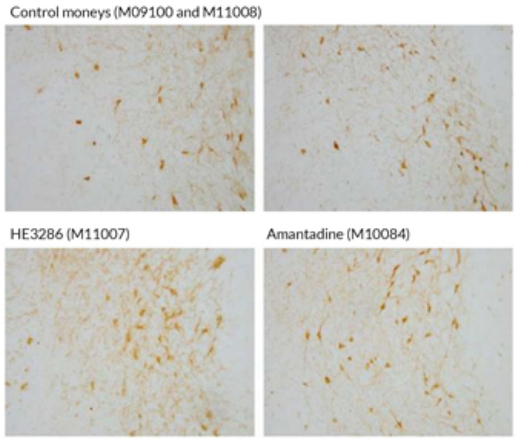
NE3107 preserved TH+ neurons in MPTP marmosets





Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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Proceeding to clinical development for Parkinson's disease

- NE3107 reduces inflammation and enhances insulin sensitivity, both of which has been shown to reduce PD pathology
  - Reduction of inflammation itself may be beneficial since both inflammation and low dopamine environment are required for Parkinsonism
  - NE3107 has been promotoric, reduced LID and preserved dopaminergic neurons in marmosets
- Since NE3107 and L-Dopa combination may be the best therapeutic option, a drug-drug-interaction study in man is needed before proceeding to Phase 2/3
  - No indications of DDI in animal studies have been observed
- Clinical program to test a very clear and plausible hypothesis:
  Decreased inflammation → increased insulin sensitivity →
  - Promotoric activity
  - Reduction in LID

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Parkinson's disease clinical development program

- NM201 Phase 1b: Satisfy FDA requirement for drug-drug interaction study with L-Dopa and assess NE3107 promotoric and anti-LID activity as a go/no-go decision for Phase 2
  - Part A: 30 patients with defined L-Dopa "off state", 2:1 active:placebo, 20 mg BID for 14 days
    - Primary endpoints: Safety, L-Dopa PK and DDI
    - Secondary endpoint: UPDRS* part 1-5
  - Part B: 20 patients with troublesome LID, 1:1 active:placebo, 20 mg BID for 14 days
    - Co-primary endpoints: UPDRS part 1-5 and UDysRS** part 1-4
- NM202 Phase 2/3: Possibly pivotal design. Evaluate NE3107 promotoric activity or ability to delay motor complications, depending on results of NM201 phase 1b
  - 200 patients expected to start L-Dopa therapy within 6 months or 200 patients on L-Dopa for 6-12 months (detail of design pending)
  - Co-primary endpoints: UPDRS pt 1-5 and UDysRS pt 1-4

* Unified Parkinson's Disease Rating
** Unified Dyskinesia Rating Scale (UDysRS)

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Oncology Programs

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Macrophage and MDSC inflammation in cancer

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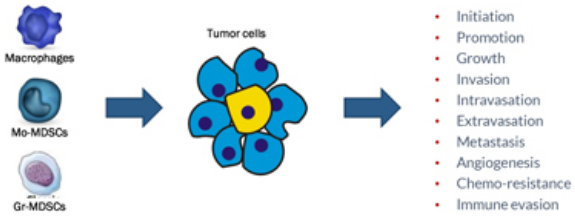
NFκB/ERK signaling is implicated in many cancers

- Acute myeloid leukemias
- Anaplastic large cell lymphoma
- Bile duct
- Bladder
- Breast
- Chronic myeloid leukemia
- Colorectal
- Endometrial
- Hodgkin's disease
- Kidney
- Langerhans cell sarcoma
- Large granular lymphocyte proliferative disorders
- Liver
- Lung
- Melanoma
- **Myeloma**
- Nasopharyngeal
- Ovary
- Pancreas
- **Prostate**
- Skin
- Stomach
- Thyroid
- T-cell lymphomas



- Initiation
- Promotion
- Growth
- Invasion
- Intravasation
- Extravasation
- Metastasis
- Angiogenesis
- Chemo-resistance
- Immune evasion

MDSC: myeloid-derived suppressor cells

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NE3107 in Myeloma

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- NE3107 inhibits:
  - Activation of NFκB/ERK, TNFα and MCP-1
  - IFNα-stimulated IL6 in human myeloma cells
- NE3107 has potential to inhibit proliferation and induce apoptosis in MM
  - Inhibiting cytokine and chemokine production in myeloma-associated macrophages and MDSC
  - Blocking autocrine IL6 production in MM
- Current preclinical study in myeloma looking at NE3107's effects on:
  - Human myeloma cells in culture: 1) Growth; 2 Apoptosis; 3) Combination with proteasome inhibitor
  - Transplanted syngeneic MM cells in mice: 1) Tumor growth; 2) Effects on MM microenvironment; 3) Effects on macrophages and MDSC; 4) Combination with proteasome inhibitor
  - Data in Q2-Q3

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NE3107 in Prostate Cancer

- Macrophages and MDSC secrete IL23 and IL6 in the tumor microenvironment
  - Activates androgen receptor pathways in CRCP (in the absence of androgens)
  - NE3107 inhibits NFκB/ERK signaling that drives IL23 production
- Androgen deprivation leads temporarily ceases growth but stimulates macrophages and MDSC, which secretes IL6 (thereby creating a pro-growth feedback loop)
- NE3107 inhibition of NFκB/ERK signaling blocks IL23 and IL6 may play important role at different stages from early tumorigenesis through metastasis
- Preclinical studies under consideration look at the effects of NE3107 on
  - Spontaneous tumor progression in TRAMP mice (early disease)
  - Syngeneic transplanted androgen-dependent PCa cells(localized disease)
  - ADT induction of chemokines and chemotaxis in vitro
  - Accessory cell-driven IL23 stimulation of PCa androgen receptors in vivo
  - Chemo- and immune-resistance
  - orthotopic PCa model on ADT induction of metastatic disease

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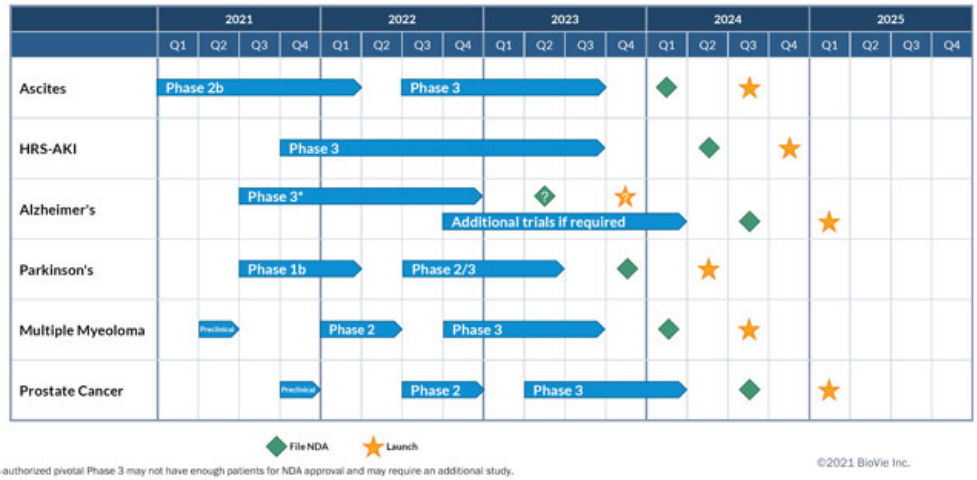
Timeline and Recap

Catalysts & Anticiated Timelines (US)



* The FDA authorized pivotal Phase 3 may not have enough patients for NDA approval and may require an additional study.

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Portfolio Revenue Potential

		Conservative Company Estimates		
	Intellectual Property	US Patient Population	US Peak Sales Potential	Global Sales Potential
BIV201: Refractory Ascites	Orphan Drug; Patent-pending formulation	20,000	$450 million	>$900 million
BIV201: HRS-AKI	Orphan Drug; Patent-pending formulation	17,000	$250 million	>$400 million
NE3107: Alzheimer's	Compound patent thru 2034+	6.1 million	$7 billion	>$10 billion
NE3107: Parkinson's	Compound patent thru 2034+	1.0 million	$1.5 billion	>$3 billion
NE3107: Oncology	Compound patent thru 2034+	TBD	TBD	TBD

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Recap

- Multiple shots on goal focused on unmet medical needs: neurodegenerative, advanced liver disease, oncology
- BIV201: Orphan drug in Phase 2b for refractory Ascites; HRS-AKI trials planned. Ascites readout in early 2022
- NE3107: inhibitor of pathologic inflammation and insulin resistance without toxicity and immunosuppression. Alzheimer's Phase 3 starting mid-2021. Parkinson's, Multiple Myeloma, and Prostate Cancer follow
- Capital efficient development plans with near-term data readouts

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Appendix

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Ascites & HRS Epidemiology Estimates

	Applying for BIV201 Formulation Patent	Company Estimates (000s) Patients Diagnosed with Cirrhosis	Ascites Patients	Refractory & Intractable Ascites[1]	Hepatorenal Syndrome
US	✓	600,000	100	20	17
Japan	✓	270,000[2]	54[1]	11	TBD
Europe	✓	800,000[3]	164	33	TBD
China	✓	2 million[4]	500	100	TBD

Sources/Notes:
1. Estimated at 20% of ascites.
2. D'Amico 2014; Gines 2004.
3. Third party market assessment, published 2015.
4. US Patient Hospital Discharge Data, 2016; BioVie poster presentation at AASLD 2019.

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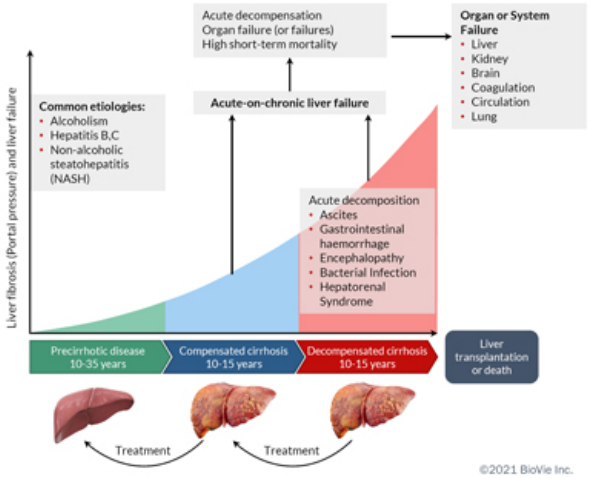
Liver Cirrhosis Progression[1] and Onset of Ascites

Typical patient experience:

- Liver cirrhosis worsens over decades
- Ascites (detected by ultrasound) is the most common first major complication[2]
  - Initial treatment is off-label diuretics
- Signals liver decompensation and patients at risk of:
  - GI/variceal bleed, encephalopathy, infection, hepatorenal syndrome (HRS), other deadly complications
- Patients become refractory to diuretics and ~50% will die within 12 months[3] unless receive liver transplant

[1] Adapted from Arroyo et al. 2016
[2] Ge and Runyon 2016
[3] Bureau et al. 2017



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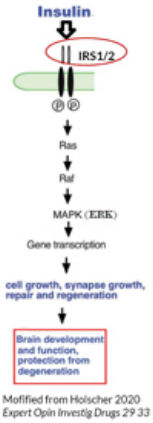
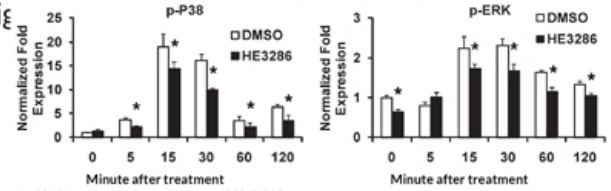
NE3107 blocks inflammatory, but not homeostatic ERK signaling



Mofified from Holscher 2020 *Expert Opin Investig Drugs 29 33*

- Insulin Receptor Substrate (IRS) IRS1/2 can be activated by insulin *via* tyrosine phosphorylation, requires homeostatic ERK
- IRS1/2 also phosphorylated by proinflammatory serine kinases p38 and JNK, requires inflammatory ERK
  - When this happens, insulin signaling is blocked
- NE3107 blocks NFκB, p38 and JNK activation ➔ prevent ERK activation by serine phosphorylation ➔ restores insulin sig



Lu 2010 *Am J Physiol Endocrinol Metab 298 E1036*

Note: NE3107 was originally known as HE3286 from Hollis-Eden Pharmaceuticals

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NE3107 vs. Others

Company	Approach	NE3107 Benefits
AC Immune	• Semorinemab (ACI-3024) promotes clearance of tau • Does not address inflammatory stimuli other than tau	• Small molecule • Broader anti-inflammatory activity
Alector	• AL002 is an antibody that stimulates microglial phagocytosis optimally targeting amyloid or bacteria • The antibody could have a large impact on neuroinflammation	• Oral small molecule with CNS access
Annovis Bio	• Posiphen (ANVS401) mechanism decreases APP and tau, but does not impact systemic inflammatory stimuli and insulin resistance in Alzheimer's Disease • Posiphen mechanism inhibits production of alpha synuclein, which has a central role in Parkinson's Disease pathophysiology	NE3107 may be superior with • Blocking inflammation-driven factors in AD • Blocking non-alpha synuclein inflammatory factors in PD
Athira Pharma	• ATH-1017 decreases inflammation mediated by TLR4 among other activities • By disrupting TLR4, ATH-1017 reduces inflammation via the NFκB pathway	NE3107 may • Act more selectively downstream in the pathway • Inhibit insulin resistance and inflammation initiated by other cytokines and chemokines
AZTherapies	• ALZT-OP1 is a combination of cromolyn and ibuprophen • Does not distinguish between inflammatory and homeostatic activities	• More selective • Downstream in pathway
Biogen and Eli Lilly	• Biogen's Aducanumab and Lilly's donanemab remove amyloid plagues • Do not address inflammatory stimuli other than amyloid beta	• Small molecule • Broader anti-inflammatory activity
Cassava Sciences	• Simufilam (PTI-125) disrupts inflammatory signaling meditated by the α7-nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4) • By disrupting TLR4, Simufilam reduces inflammation via the NFκB pathway	NE3107 may • Act more selectively downstream in the pathway • Inhibit insulin resistance and inflammation initiated by other cytokines and chemokines
Cortexyme	• Atuzaginstat (COR388) decreases inflammation by Porphyromonas gingivalis bacterial infection that potentially decreases amyloid beta and p-tau inflammatory stimuli • Role of bacterial infection to the total inflammatory in AD is unknown	• Broadly applicable to all AD patients – not just with bacterial infection
Denali Therapeutics	• DNL788 for AD is a small molecule impacting TNF mediated inflammation and cell death • Very similar role to NE3107 in inhibiting TNF perpetuation of NFkB pathway • DNL151 for PD is a small molecule impacting LLRK2 focused on disease progression	• Approved for phase 3 start in AD • Broader inhibitor of insulin resistance and inflammation with promotoric and anti-LID activity, in addition to neuroprotection in NHP models in PD
Immune Bio	• XPRO1595 is a large molecule that inhibits TNF; Phase 1 • Very similar role to NE3107 in inhibiting TNF perpetuation of NFkB pathway	• Oral small molecule with CNS access; inhibits pro-inflammatory activation of TNF/TNFR1/2 without impacting homeostatic role of TNFR1; Phase 3
vTv Therapeutics	• Azeliragon (TTP488) is an inhibitor of RAGE cell surface receptors • Since RAGE has homeostatic functions, chronic RAGE inhibition may have adverse effects	• More selective • Downstream in pathway

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NeurMedix Transaction

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NE3107 and Related Molecules

- First-in-class potent & safe inhibitors of the pathological inflammatory cascade
- Compelling animal and clinical data
- FDA authorization to initiate pivotal Phase 3 trial for Alzheimer's Disease
- Result of 20+ years of research

Research Expertise

- Clarence Ahlem, COO
- Chris Reading, PhD., CSO
- Leading experts on the molecules and pathways
- Deep experience working with the assets
- Both scientists expected to join BioVie post-closing

Investor Friendly Terms

- Modest upfront payment
- Milestones contingent on positive progress weighted to approval and commercialization
  - Clinical trial endpoints
  - NDA Acceptance
  - FDA Approval
  - Commercialization

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Deal Overview

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Upfront Considerations

- At closing
  - 8,361,308 newly issued shares
  - Approximately $3.0 million in cash
- Additional $7.3 million cash payment payable after:
  - Pivotal Phase clinical trial for Alzheimer's drug candidate has met its primary endpoint; ***and***
  - Company raised at least $50 million capital

Contingent Milestones

- Payable in shares; capped at 87.5% ownership
  - 4.5 million shares upon hitting endpoints in pivotal trials
  - 4.5 million shares upon FDA acceptance of NDA filing
  - 4.5 million shares upon FDA approval of NDA
  - 4.5 million shares upon achieving $1.0 billion trailing 12-month net sales

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Developing Transformative Therapies to Overcome Chronic Debilitating Diseases

R&D Day • May 19, 2021

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Forward-looking statements

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This document contains forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 that involve risks, uncertainties and assumptions that could cause BioVie's actual results and experience to differ materially from anticipated results and expectations expressed in these forward-looking statements. BioVie has in some cases identified forward-looking statements by using words such as "anticipates," "believes," "hopes," "estimates," "looks," "expects," "plans," "intends," "goal," "potential," "may," "suggest," and similar expressions. Among other factors that could cause actual results to differ materially from those expressed in forward-looking statements are: successful completion of the acquisition of the biopharmaceutical assets from NeurMedix Inc., BioVie's need for, and the availability of, substantial capital in the future to fund its operations and research and development. Other risks are that BioVie's compounds may not successfully complete pre-clinical or clinical testing, or be granted regulatory approval to be sold and marketed in the United States or elsewhere. BioVie cannot guarantee the effectiveness of its patents or Orphan Drug designations. A more complete description of these risk factors is included in BioVie's filings with the Securities and Exchange Commission. In addition to the risks described above and in BioVie's filings with the Securities and Exchange Commission, other unknown or unpredictable factors also could affect BioVie's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. You should not place undue reliance on any forward-looking statements. BioVie undertakes no obligation to release publicly the results of any revisions to any such forward-looking statements that may be made to reflect events or circumstances after the date of that these slides are posted to BioVie's website or to reflect the occurrence of unanticipated events, except as required by applicable law or regulation.

Agenda

- Welcome & Overview
- Liver Cirrhosis Programs
- Inflammation & NE3107
- Alzheimer's Disease Program
- Parkinson's Disease Program
- Oncology Programs
- Timeline & Recap

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Core themes for today

Advanced Liver Disease Program

- No FDA-approved product for Ascites. BIV201 is a safe and efficacious orphan drug with high PTRS* and near-term readout

Neurodegeneration Programs

- Inflammation → insulin resistance → disease pathology
- NE3107 selective inhibits ERK activation and disrupts the proinflammatory cascade
  - Reduced inflammation → increased insulin sensitivity → decreased disease pathology
- Directly applicable for Alzheimer's and Parkinson's

Oncology Programs

- Inflammation also implicated in many cancers. NE3107 likely to have a role in Myeloma and Prostate Cancer due to same MOA shown for neurodegeneration programs

* Probability of Technical and Regulatory Success

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Liver Cirrhosis Program

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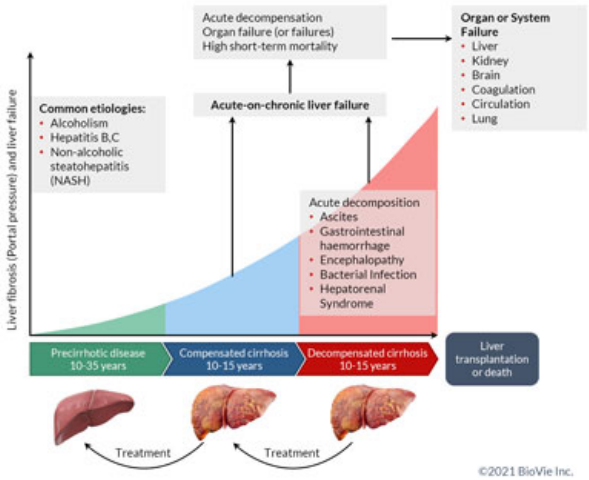
Liver Cirrhosis Progression[1] and Onset of Ascites

Typical patient experience:

- Liver cirrhosis worsens over decades
- **Ascites** (detected by ultrasound) is the most common first major complication[2]
  - Initial treatment is off-label diuretics
- Signals **liver decompensation** and patients at risk of:
  - GI/variceal bleed, encephalopathy, infection, hepatorenal syndrome (HRS), other deadly complications
- Patients become **refractory to diuretics** and **~50% will die within 12 months**[3] unless receive liver transplant



[1] Adapted from Arroyo et al. 2016
[2] Ge and Runyon 2016
[3] Bureau et al. 2017

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Ascites & HRS Epidemiology Estimates

		Company Estimates (000s)			
	Applying for BIV201 Formulation Patent	Patients Diagnosed with Cirrhosis	Ascites Patients	Refractory & Intractable Ascites[1]	Hepatorenal Syndrome
US	✓	600,000	100	20	17
Japan	✓	270,000[2]	54[1]	11	TBD
Europe	✓	800,000[3]	164	33	TBD
China	✓	2 million[4]	500	100	TBD

Sources/Notes:
1. Estimated at 20% of ascites.
2. D'Amico 2014; Gines 2004.
3. Third party market assessment, published 2015.
4. US Patient Hospital Discharge Data, 2016; BioVie poster presentation at AASLD 2019.

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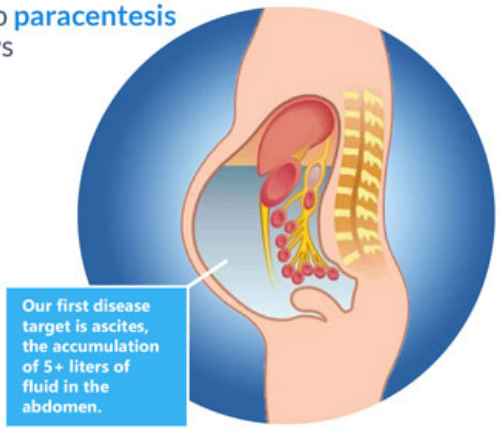
Disease Target: Refractory Ascites

Refractory ascites patients typically undergo **paracentesis** to remove ascites fluid every week to 10 days

Paracentesis:

- Withdrawal of 5–10L of ascites fluid (on average) from abdomen using a large bore needle
- Provides a few days of symptomatic relief
- The kidneys are "burning out" by retaining massive quantities of salt and water
- Patients suffer frequent life-threatening complications
- No remaining options except for TIPS* surgery or liver transplant
- Represents $670 million addressable market with 20,000 targeted US patients
- **No drugs ever approved by FDA** to treat ascites



* TIPS = transjugular intrahepatic portosystemic shunt to channel blood flow around the liver

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BIV201: Continuous Infusion Terlipressin

- Terlipressin was first approved in Germany in 1980s to treat bleeding esophageal varices (BEV)
- Approved for BEV and hepatorenal syndrome (HRS) in European & Asian hospitals (40+ countries)
  - Administered via 1-2 mg bolus injections every 4-6 hours; this dosing method is associated with **serious adverse events**
  - >50,000 patients have been treated with terlipressin[1]
- BioVie is pursuing a novel application: Treating refractory ascites using **continuous infusion terlipressin (BIV201) in the home care setting**
  - Improved safety: continuous infusion shown to reduce SAEs by more than 50% in head-to-head study in HRS[2]
  - Terlipressin has never been approved to treat ascites
  - Not available in the US or Japan

1. Company estimate.
2. HEPATOLOGY 2016;63:983-992

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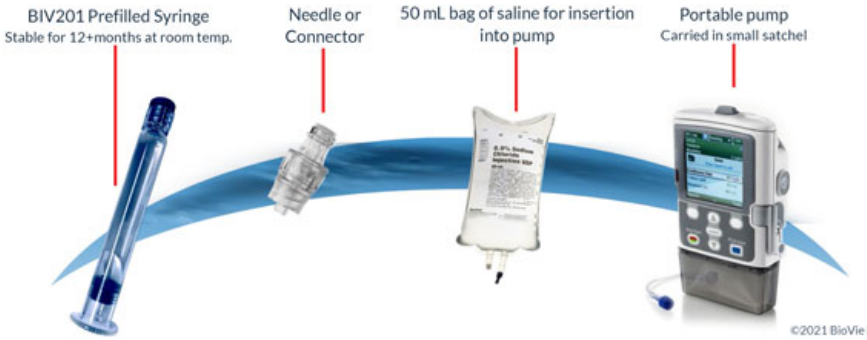
Novel Prefilled Syringe with Patent-pending Liquid Formulation

- Global PCT filed to protect our novel liquid formulation
- **Improved safety:** Eliminates mixing minute quantities of powder terlipressin that could result in medication errors or sterility loss
- **Enhanced convenience:** Simply inject fluid into the saline bag and attach to pump



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BioVie Phase 2a trial results: BIV201 Pharmacokinetics

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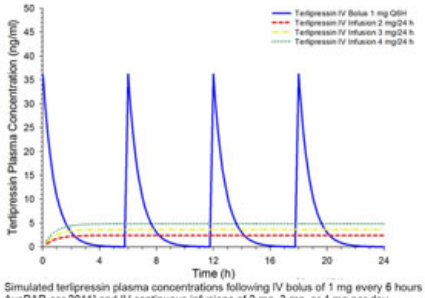
Continuous low blood levels of terlipressin versus potentially dangerous spikes with IV-bolus dosing

Source: BioVie poster presentation at AASLD 2019.

Comparison of the PK Profile of Terlipressin Administered by Continuous Infusion or Intermittent IV Boluses.



Simulated terlipressin plasma concentrations following IV bolus of 1 mg every 6 hours 1 [Lucassin, AusPAR-cer 2011] and IV continuous infusions of 2 mg, 3 mg, or 4 mg per day

BIV201 is an investigational therapy

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Continuous Infusion Terlipressin in 6 Refractory Ascites/HRS Patients

(Data licensed from Dr. P. Angeli)

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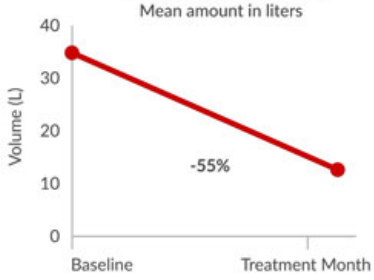
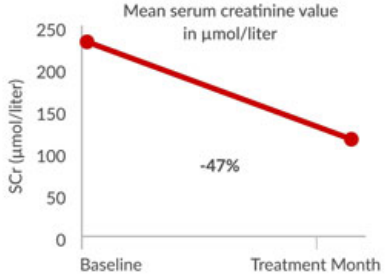
Decreased ascites fluid

Mean amount in liters



Improved renal function

Mean serum creatinine value in µmol/liter



Source: Adapted from BioVie US Patent application 16/379,446 Angeli et al.

No drug-related side effects were reported in this study.

Terlipressin is not available in the US

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Continuous Infusion Terlipressin in 19 Refractory Ascites/HRS Patients (Chapman et al.)

Pre-therapy:

- 70% of patients required weekly large volume paracentesis (LVP)
- 63% poor muscle strength

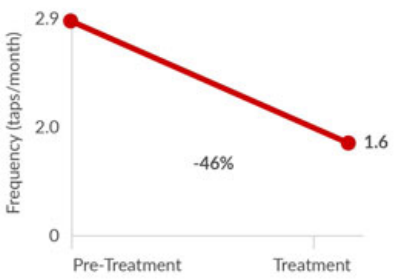
Results:

- Median duration of CI terlipressin treatment: **51 days**
- 46% average reduction in frequency of paracentesis
- Significantly improved muscle strength and nutritional intake
- No complications directly attributable to terlipressin

Source: JHEP 2019.

Decreased Need for Paracentesis

Change in frequency of paracentesis procedures



Terlipressin is not available in the US

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BIV201 Ascites Development Plan

- **US Phase 2 trial with 30 refractory ascites patients**
  - 20 to receive BIV201 therapy + standard of care (SOC); 10 to receive SOC only (control group)
    - Primary composite endpoint: Incidence of ascites-related complications over 180 days following randomization
    - Secondary endpoints include ascites fluid removed over 90 days
  - Plan to enroll an average of 3 subjects each at 10 study sites
  - Timeframe: Two 28-day cycles of BIV201 therapy within 4 months, then follow patients for additional 60 days
  - Patients treated at home using visiting nurses
  - Will test a unique quality-of-life assessment tool developed by BioVie
- Currently activating 9 sites and screening patients
  - 3 sites actively screening
  - First patient consented and entered trial
- Expecting a **single pivotal US Phase 3 clinical trial** for the NDA submission
  - Design similar to Phase 2 study with ~120 patients at ~20 study sites*

* Trial size to be determined based on Phase 2 results

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BIV201 HRS-AKI Development Plan
(Hepatorenal Syndrome – Acute Kidney Injury)

- Planning a registrational Phase 3 trial for BIV201 in HRS-AKI
- Mallinckrodt recently completed the CONFIRM Phase 3 trial of terlipressin in type-1 HRS:
  - **Efficacy objective was achieved**, but safety concerns precluded FDA approval
  - Mallinckrodt used bolus injections (1 or 2 mg given over ~5 min) which were associated with severe side effects
- BioVie will use BIV201 continuous infusion administration (eg, 2 mg terlipressin over 24 hours) – **much safer based on European studies**
  - Reduced SAEs by >50% in head-to-head study vs. IV bolus dosing
- We will target HRS-AKI patients, less severely ill than HRS type 1, expected to further improve BIV201 efficacy and safety results
- Submitted a pre-IND meeting package to FDA in May
- We plan to use the same PI's and same sites as our current ascites study, and additional sites to treat an estimated ~250 subjects

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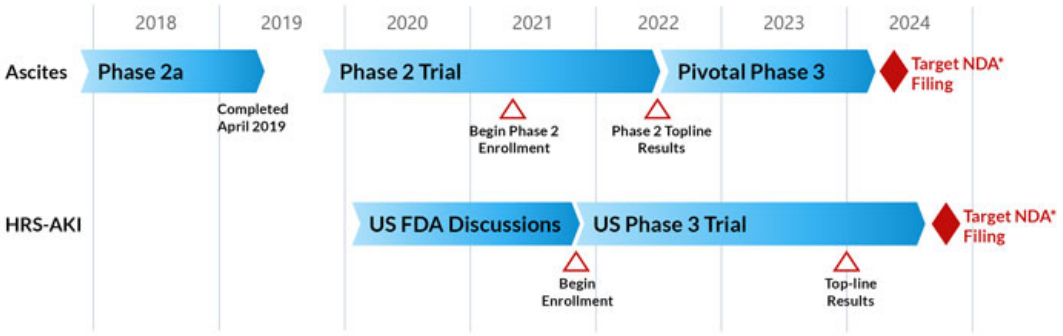
BIV201 Projected US Clinical Timeline



* New Drug Application

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Inflammation & NE3107

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Inflammation

- Inflammation is the result of the body's natural protective processes

Insults	Responders	Master Alarms	Pro-inflammatory factors
• Pathogens	• Blood proteins	• NFκB transcription factors	• Cytokines
• Trauma	• Platelets	• Oxidative stress	• Chemokines
• Ischemia	• Granulocytes	• Reactive oxygen	• Receptors
• Stress	• Monocytes	• Reactive nitrogen	• Complement factors
• Radiation	• Macrophages		• Metalloprotinases
• Obesity	• Microglia		• Cell adhesion molecules
• Cancer	• Endothelial cells		

- If insults and pro-inflammatory cascade eliminated, pathology addressed
- If not, low grade chronic inflammation and associated insulin resistance ensues
- Inflammation and insulin resistance go hand-in-hand

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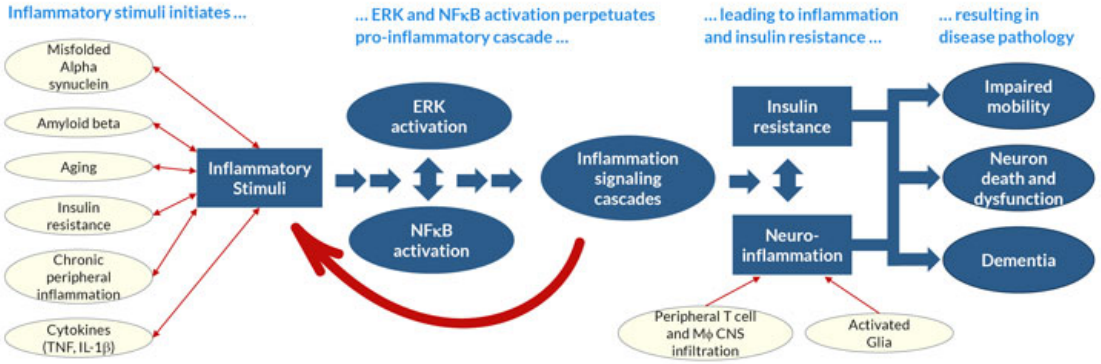
Neuroinflammation drives disease pathology



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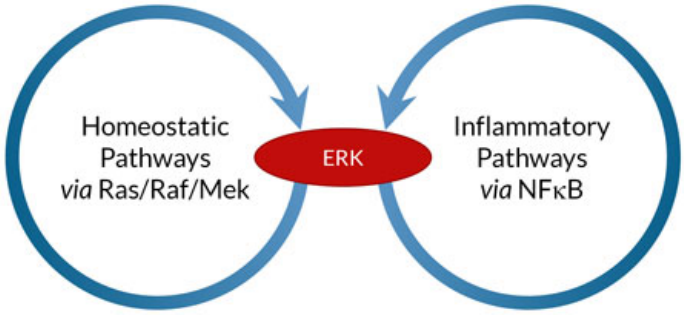
Extracellular Signal-Related Kinase (ERK)



Critical player for both homeostasis and inflammation (and resulting inflammation-induced insulin resistance)

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NE3107: A Differentiated Molecule

- First-in-class molecule with desirable characteristics
  - Small molecule
  - Crosses blood-brain barrier
  - Excellent safety profile demonstrated in pre-clinical and clinical trials
- Blocks neuroinflammation and insulin-resistance at the right time/place in pathologic pathway
- Does not inhibit homeostatic activity
- The result of 20+ years of research that started with DHEA leading to identification of the active metabolite that is the inhibitor of pathologic inflammation and insulin resistance. NE3107 resulted from medical chemistry creating the molecule with desired properties

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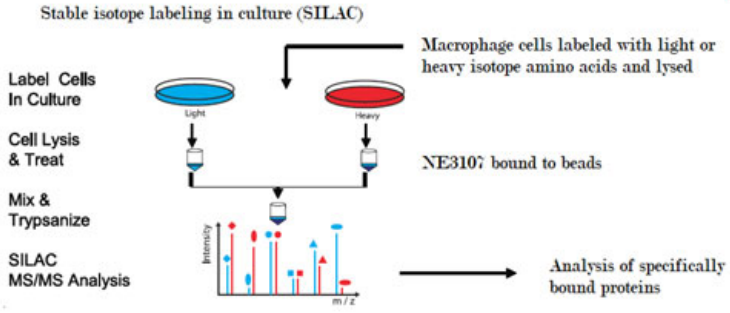
NE3107 binds ERK



Gene ID	IPI number	Gene	Product	
26413	IPI00119663	Mapk1	mitogen-activated protein kinase 1	ERK2
26417	IPI00230277	Mapk3	mitogen-activated protein kinase 3	ERK1

Binding to ERK was confirmed *in silico* using molecular modeling

Reading 2012 *PLoS One* 7 e32147

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NE3107 Selectively Inhibits ERK Pathological Inflammatory Cascade (EPIC)

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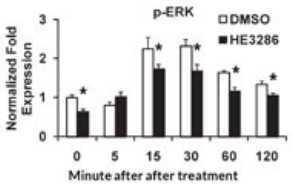
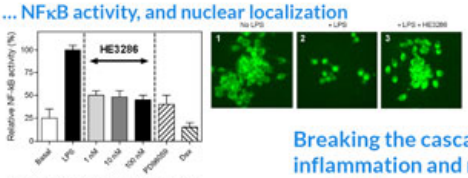
NE3107 reduces ERK activation …

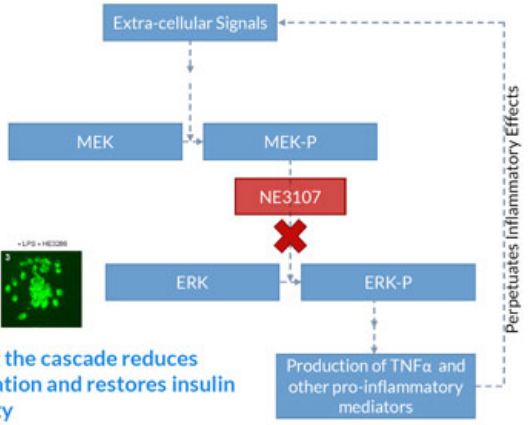


Lu 2010 *Am J Physiol Endocrinol Metab 298 E1036*

… NFκB activity, and nuclear localization



Wang 2010 *J Pharmacol Exp Ther 333 70*



Breaking the cascade reduces inflammation and restores insulin sensitivity

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

NE3107 inhibits systemic inflammation across different disease models

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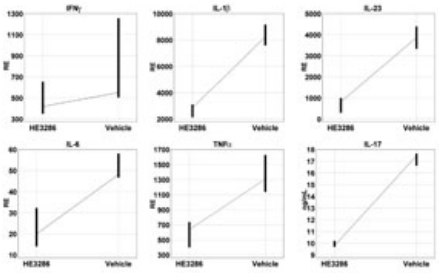
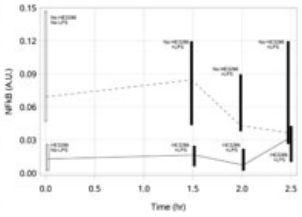
Decreased IFNγ, IL-1β, IL23, IL-4, TNFα and IL-17 expression in an RA model …

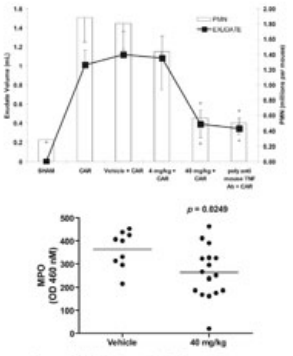


Offner 2009 *J Pharmacol Exp Ther 329 1100*

…NFκB in an endotoxin shock model …



… and inflammatory cell infiltrates and myeloperoxidase in COPD models



Conrad 2010 *J Inflammation 7 52*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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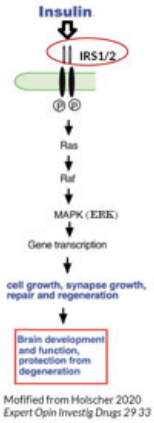
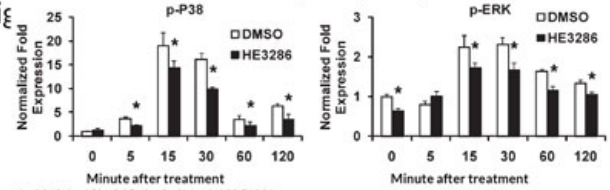
NE3107 blocks inflammatory, but not homeostatic ERK signaling



Modified from Holscher 2020 *Expert Opin Investig Drugs 29 33*

- Insulin Receptor Substrate (IRS) IRS1/2 can be activated by insulin *via* tyrosine phosphorylation, requires homeostatic ERK
- IRS1/2 also phosphorylated by proinflammatory serine kinases p38 and JNK, requires inflammatory ERK
  - When this happens, insulin signaling is blocked
- NE3107 blocks NFκB, p38 and JNK activation ➔ prevent ERK activation by serine phosphorylation ➔ restores insulin sig



Lu 2010 *Am J Physiol Endocrinol Metab 298 E1036*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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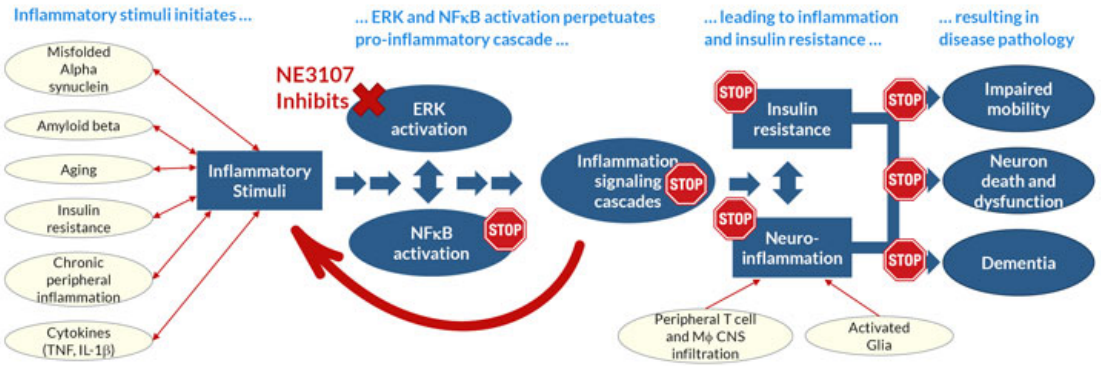
By blocking ERK activation, NE3107 prevents downstream impact



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Alzheimer's Disease Program

Forgetting the "Past" So that We Can Remember the "Now" – KOL Panel Excerpts from B. Riley Neuroscience Conference, 2021

"I saw that there was a drug by NeurMedix called NE3107 which was just authorized for a pivotable Alzheimer's Phase 3 trial. What intrigued me about it is because it affects all three mechanism of action that I mentioned: anti-TNF, NFκB, and ERK. What was exciting about some of the early Phase 2 studies is that there's no significant toxicities, it was not immunosuppressive, and because it's an oral drug it was very easy to utilize … "

Professor Alan Mazurek
Icahn School of Medicine at Mount Sinai

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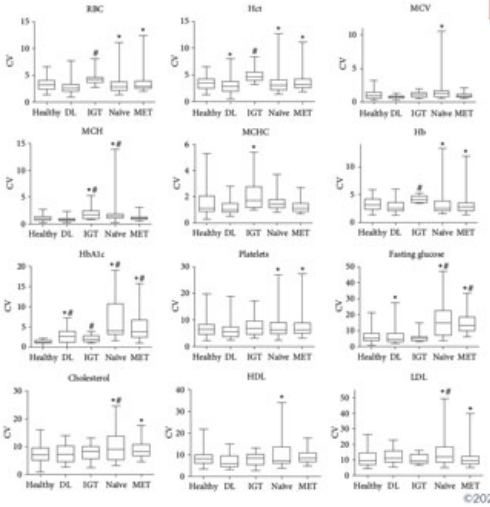
Inflammation drives systems dysregulation

- Patients with increasing metabolic disease show greater variability for individual hematology, metabolic and chemistry values
- Indicates increasing dysregulation



DL: dyslipidemic placebo group, IGT: impaired glucose tolerant placebo group, Naïve: treatment-naïve uncontrolled T2DM placebo group, MET: uncontrolled T2DM placebo group on a stable dose of metformin

Hb: hemoglobin, Hct: hematocrit, RBC: red blood cell count, MCV: mean cell volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, HbA1c: hemoglobin A1c, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol.

#Statistically Significant Welch ANOVA). •Statistically significant 2-sided *FF* test.

Reading 2013 *Mediators Inflamm 814989*

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NE3107 decreased systems dysregulation in advanced T2D patients

- Heteroscedasticity* investigated by analyzing data distributions for normality (Shapiro-Wilks *W* test)
  - Deviations from normal distribution represents dysregulation
- Placebo patients had significantly abnormal data distributions after 84 days of treatment whereas NE3107 subjects did not
  - Placebo patients had many parameters that significantly deviated from normal distribution (i.e., dysregulated)
  - NE3107 treatment reduced systems dysregulation

Group	Day	Parameter	HE3286 *W* test *P*	Placebo *W* test *P*
Cohort 1	84	Δlnsulin[a]	>0.1	**<0.0001**
		ΔC-peptide	>0.1	**<0.0001**
		ΔFasting glucose	>0.1	**0.02**
		ΔHOMA2 %B	>0.1	**<0.0001**
		ΔHOMA2 IR	>0.1	**0.002**
		Δleptin	>0.1	**0.005**
	84	ΔHbA1c	>0.1	**0.006**
Cohort 1 MCP-1 > 40[b]		ΔFasting glucose	>0.1	**0.02**
		ΔHOMA2 %B	>0.1	**<0.0001**
Cohort 2	84	ΔnHbA1c	>0.1	**0.04**
		Δlnsulin	>0.1	>0.1
		ΔFasting glucose	>0.1	**0.03**
		ΔHOMA2 %B	>0.1	>0.1
		ΔMCP-1	>0.1	**0.005**
		ΔTriglycerides	>0.1	**<0.0001**
	112	ΔnHbA1c	>0.1	**0.0007**
		Δlnsulin	>0.1	>0.1
		ΔFructosamine	>0.1	**0.002**
		ΔHOMA2 %B	>0.1	**<0.0001**
Cohort 2 BMI > 31[c]	84	ΔHOMA2 %B	>0.1	**0.007**
		ΔMCP-1	>0.1	>0.1
		ΔTriglycerides	>0.1	>0.1
	112	Δlnsulin	>0.1	**<0.0001**
		ΔC-peptide	>0.1	**<0.0001**
		ΔHOMA2 %B	>0.1	**<0.0001**
		ΔHOMA2 IR	>0.1	**<0.0001**

* Heteroscedasticity describes differences in variances between groups.

Reading 2013 *Mediators Inflamm 814989*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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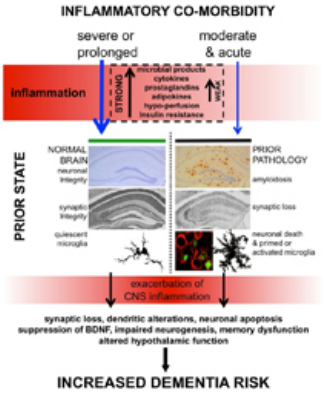
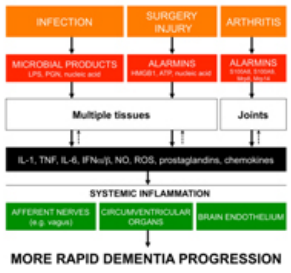
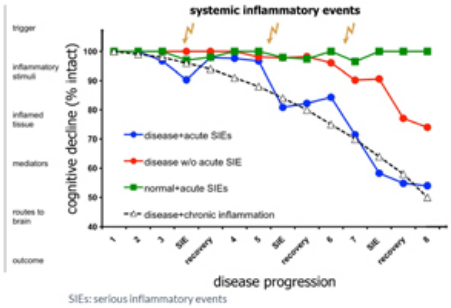
Systemic inflammation and co-morbidity as drivers of cognitive decline







SIEs: serious inflammatory events

Cunningham 2015 *Alzheimers Res Ther 7 33*

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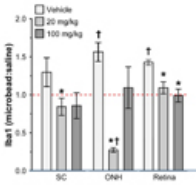
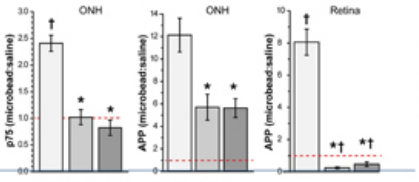
NE3107's neuroprotective properties

Decreased activated microglia



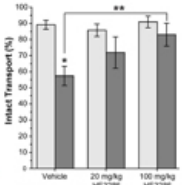
Iba1 is a microglia-specific marker.
† p<0.045 * p<0.037

Decreased neurotrophin receptor (p75) and amyloid precursor protein (APP)



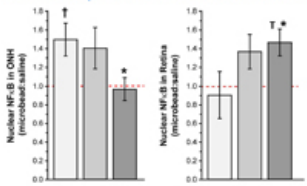
ONH: Optic nerve head. † p<0.047 * p<0.027

Rescued axonal transport

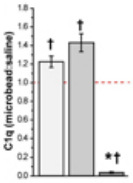


Reduction of transport by elevated intraocular pressure. * p<0.003 ** p<0.025

Decreased Inflammatory NFκB in inflamed optic nerve head; increased homeostatic NFκB in retina



Decreased inflammatory C1q



Complement component C1q involved with neuronal death. † p<0.037 * p<0.033

Source: Lambert 2017 *Front Neurosci 11 45*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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NE3107 preserves ganglion cell function in Optic Neuritis

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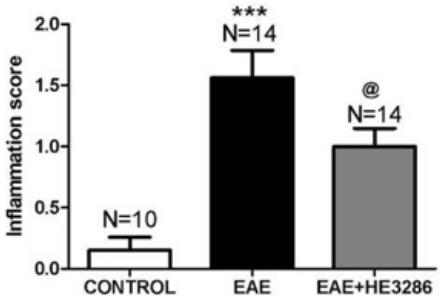
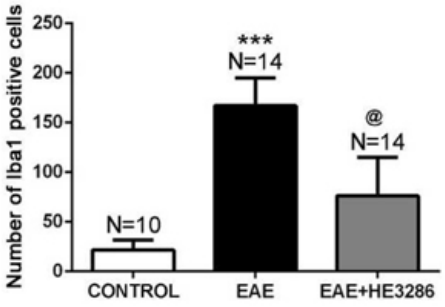
Decreases optic nerve head inflammation …



… and reduced activated microglia in optic nerves



Kahn 2014 *Invest Opthalmol Vis Sci 55 5744*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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NE3107 enhances insulin sensitization in animal models

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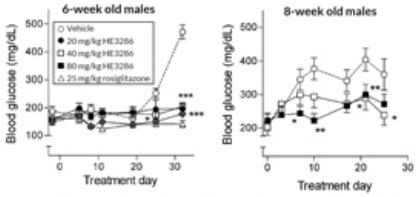
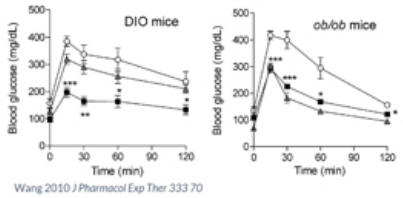
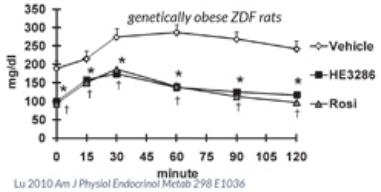
HE3286 suppresses development of hyperglycemia in diabetic db/db mice …



… and the levels of insulin and glucose in oral tolerance tests



Wang 2010 *J Pharmacol Exp Ther 333 70*



Lu 2010 *Am J Physiol Endocrinol Metab 298 E1036*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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NE3107's ability to enhance insulin sensitization confirmed in Phase 1 trial with impaired glucose tolerance patients

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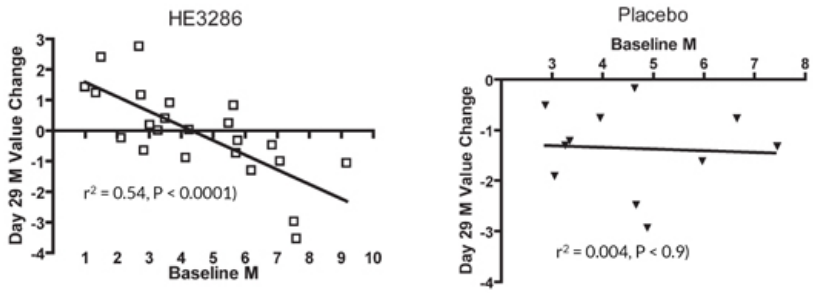
Improved insulin-dependent glucose disposal in 48 obese, inflamed subjects



Day 29 Glucose disposal rate (M, measured in mg/kg/min in glucose clamp studies) value change as a function of baseline M

Reading 2013 *Obesity 21 E343*
Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

NE3107's ability to enhance insulin sensitization confirmed in Phase 2 trial with T2D patients

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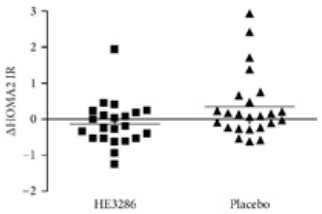
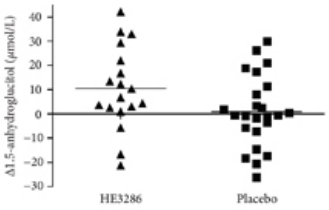
Improved the homeostatic model assessment of insulin resistance …



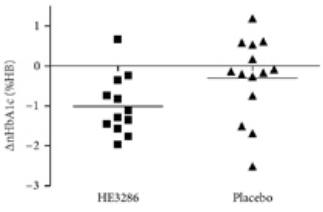
Cohort 1 baseline MCP-1 > 40 pmol/L individual subject changes in homeostatic model assessment of insulin resistance at Day 84

… decreased postprandial glucose …



Pooled cohorts 1 and 2 changes at Day 84

… decreased HbA1c …



Day 112 cohort 2 baseline BMI > 31 kg/m²

… decreased insulin resistance in inflamed T2D patients

Effect	Value	Change HE3286	Change Placebo	*P*	Test[a]
ΔHOMA2 IR[c]	Day 84 mean	−0.1	+0.4	0.02	*t*-test

Reading 2013 *Mediators Inflamm 814989*
Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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Insulin sensitizing improvement also brought improvements in AD indicators

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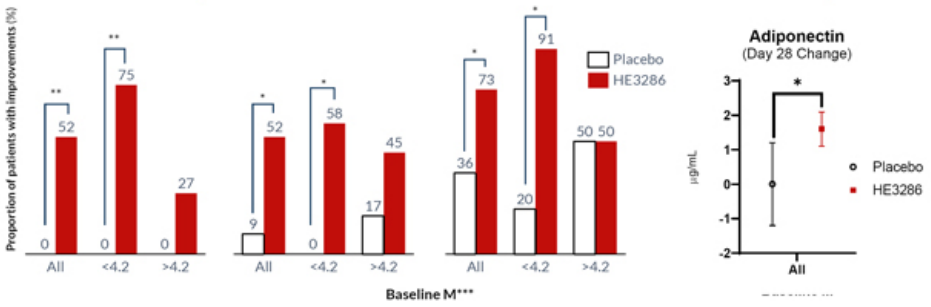
In a Phase 2 study 48 obese subjects with impaired glucose tolerance, NE3107 …

Increased insulin sensitivity … … increased HDL … … decreased CRP … … and increased adiponectin



* Fischer's exact test p<0.05 **p<0.01
*** Baseline glucose disposal rate (M) measured in mg/kg/min. Median baseline is 4.2
Source: Reading 2013 Obesity 21 E343
Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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Proceeding Pivotal Phase 3 for Alzheimer's Disease

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- NE3107
  - Reduces inflammation and enhances insulin sensitivity, both of which have been shown to reduce AD pathology. NE3107 blocks EPIC, which is upstream from Amyloid beta and phospho-tau, and thus further reduces inflammation
  - Has demonstrated neuroprotection in models of PD, optic neuritis and glaucoma
  - Has absence of toxicity and thus well suited for chronic use
  - Reduces systems deregulation (enhances homeostasis)
  - Crosses BBB
- >80% of AD patients also have (or developing) Type 2 Diabetes
- >3,000 scientific publications support the role insulin signaling and insulin resistance in AD
  - Insulin resistance in AD is caused by a number of factors, including inflammation
- While NE3107 has not been studied directly in AD patient, its impact on inflammation, insulin resistance is expected to directly translate to benefits in AD
  - Decreased inflammation → increased insulin sensitivity → decrease in rate of cognitive decline
  - Potential for enhancement of cognition due to insulin's role in the brain

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NM101: a phase 3 trial in mild to moderate Alzheimer's disease, NCT04669028

A Phase 3, Double-blind, Randomized, Placebo-controlled, Parallel Group, Multicenter Study of NE3107 in Patients who have Mild to Moderate AD

- Pivotal study for Alzheimer's disease. Two weeks each of 5 mg and 10 mg BID dose titration followed by 26 weeks of 20 mg twice daily vs. placebo, approximately 160 subjects in each arm, 80% power
- Diagnosed with AD and without evidence of a vascular contribution. Mild to moderate disease. CDR 1-2. MMSE 14-24.
- 60-85 years old, males and females
- Randomization stratified by MMSE and Homeostatic Model Assessment 2 Insulin Resistance (HOMA2)
- Co-primary endpoints
  - Mean change from Baseline to Week 30 in the eleven-question form of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 12) comparing the NE3107 group to the placebo group
  - Mean change from Baseline to Week 30 in Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) comparing the NE3107 group to the placebo group
- Secondary endpoints
  - ADCS-ADL (functional), ADCOMS (4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating-Sum of Boxes items), NPI-12 (care-giver rating of behavioral changes), MMSE, CDR
  - Glycemic control: HOMA2, Mean Amplitude of Glycemic Excursion (MAGE) using continuous glucose monitoring, fructosamine levels, post-prandial glucose and fasting blood glucose vs time.
  - MRI total hippocampus volume change, baseline to end of treatment in a subset of approximately 50% of active and placebo subjects
  - Target engagement assessed in a small subset of active and placebo subjects using PET to quantify cortical glucose utilization
- CRO cost estimate for the pivotal study is ~$16 million

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Parkinson's Disease Program

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Remarkable similarities between neurodegenerative diseases

- Neuroinflammation and oxidative stress are common features in the major neurodegenerative diseases, Alzheimer's, Parkinson's, frontotemporal lobar dementia and ALS (and TBI)
- Remarkable parallels exist between AD and PD
  - Activated microglia-inflammation
  - Systemic inflammation driven
  - TNF driven
  - Insulin resistance, metabolic dysfunction
  - Mitochondrial dysfunction and Oxidative stress
  - Endoplasmic reticulum stress- unfolded protein response
  - Misfolded protein aggregates (alpha synuclein, Lewy bodies for PD)
  - Controversial etiology, slow progression

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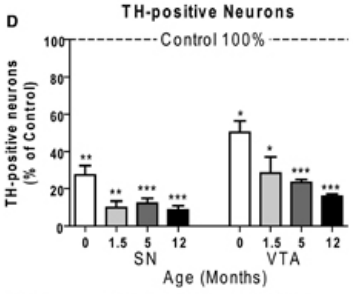
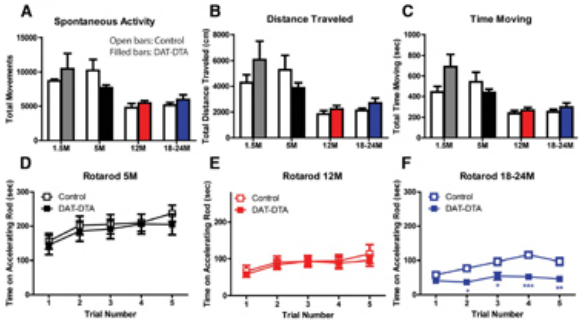
A low dopamine environment alone does not drive parkinsonism…

PD mice had dramatic loss of dopaminergic neurons …



Intracellular expression of diphtheria toxin A used to deplete SNc

… but did not show motor behavior deficits compared with control mice



SN: dopaminergic neurons in the substantia nigra pars compacta; VTA: ventral tegmental area; DAT-DTA: PD model mice
Golden 2013 *J. Neurosci* 0890 13

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… Low Dopamine *and* inflammation required for parkinsonism in patients

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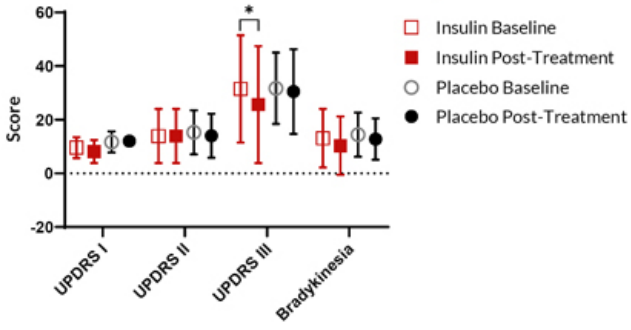
Intranasal Insulin treatment reduced inflammation and improved motor activity



UPDRS: Unified Parkinson's Disease Rating Scale; Part I (mentation, behavior and mood); Part II (activities of daily living); Part III (Motor)
From: Novak 2019 *J Pone 0214364*

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NE3107 impact in mice models of Parkinson's …

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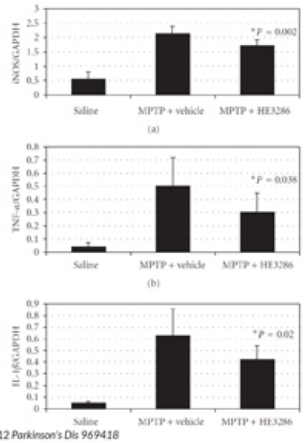
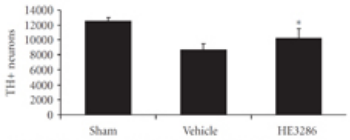
Reduced iNOS, TNFα, and IL1β …



… and preserved dopaminergic neurons



HE3286 attenuated TH-positive neuron loss in mice after MPTP injections.

Nicoletti 2012 *Parkinson's Dis 969418*

Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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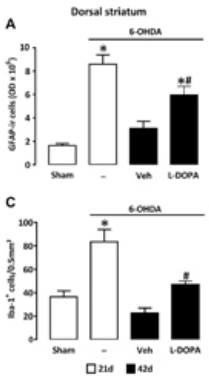
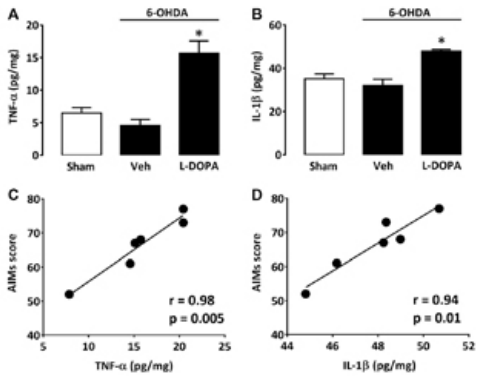
Striatal inflammation drives LID

L-Dopa drives striatal inflammation…



… resulting in L-Dopa induced dyskinesia (LID)



6-OHDA: 6-hydroxydopamine-lesioned mice rendered dyskinetic
Pereira 2021 *F Phar 617085*

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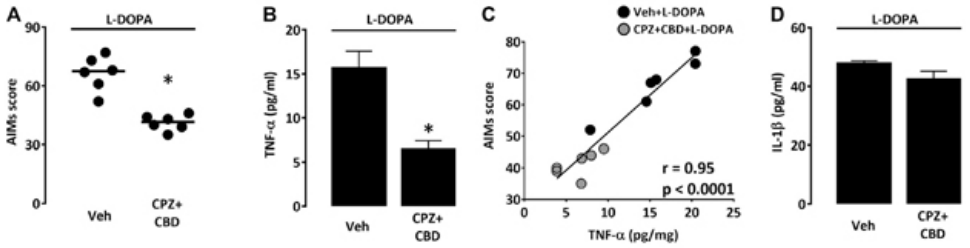
Reduction of TNF-induced inflammation reduces LID



6-OHDA: 6-hydroxydopamine-lesioned mice rendered dyskinetic; AIM: Abnormal Involuntary Movement Scale (lower is better); CPZ-CBD: capsazepine (CPZ) with cannabidiol (CBD), anti-inflammatory agents
Pereira 2021 *F Phar 617085*

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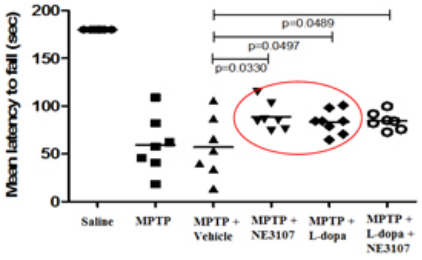
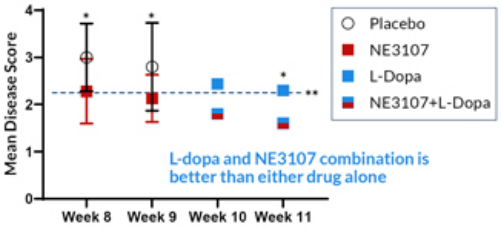
NE3107 has similar promotoric activity to L-dopa in rodent and marmoset models

MPTP Mouse



MPTP Marmoset treated at Week 8



*p<0.001 compared to other treatment arm in time period
** L-Dopa at week 11 not statistically different from NE3107 at weeks 8 and 9

NE3107's promotoric effects observed within 4 days of treatment

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin used to mimic many aspects of PD

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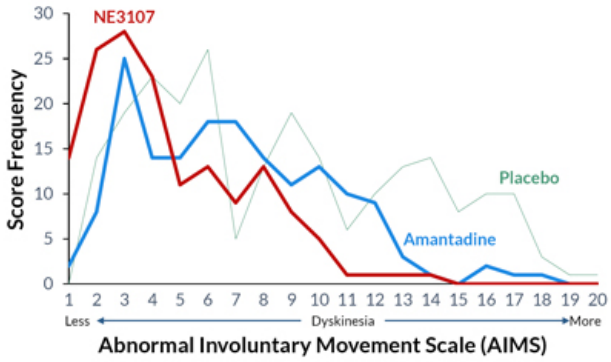
NE3107 decreases L-Dopa-induced dyskinesia (LID)

Distribution of AIMS Scores



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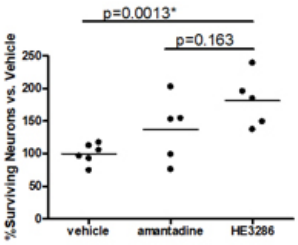
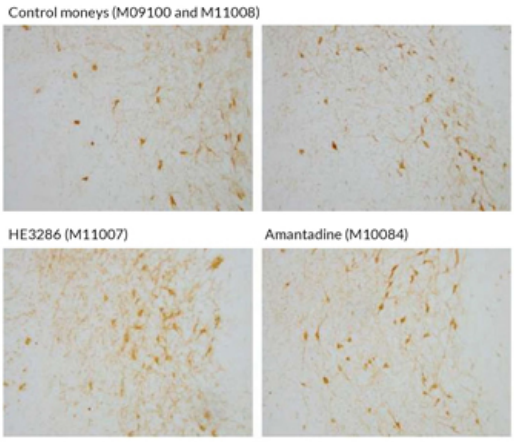
NE3107 preserved TH+ neurons in MPTP marmosets





Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

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Proceeding to clinical development for Parkinson's disease

- NE3107 reduces inflammation and enhances insulin sensitivity, both of which has been shown to reduce PD pathology
  - Reduction of inflammation itself may be beneficial since both inflammation and low dopamine environment are required for Parkinsonism
  - NE3107 has been promotoric, reduced LID and preserved dopaminergic neurons in marmosets
- Since NE3107 and L-Dopa combination may be the best therapeutic option, a drug-drug-interaction study in man is needed before proceeding to Phase 2/3
  - No indications of DDI in animal studies have been observed
- Clinical program to test a very clear and plausible hypothesis:
  Decreased inflammation → increased insulin sensitivity →
  - Promotoric activity
  - Reduction in LID

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Parkinson's disease clinical development program

- NM201 Phase 1b: Satisfy FDA requirement for drug-drug interaction study with L-Dopa and assess NE3107 promotoric and anti-LID activity as a go/no-go decision for Phase 2
  - Part A: 30 patients with defined L-Dopa "off state", 2:1 active:placebo, 20 mg BID for 14 days
    - Primary endpoints: Safety, L-Dopa PK and DDI
    - Secondary endpoint: UPDRS* part 1-5
  - Part B: 20 patients with troublesome LID, 1:1 active:placebo, 20 mg BID for 14 days
    - Co-primary endpoints: UPDRS part 1-5 and UDysRS** part 1-4
- NM202 Phase 2/3: Possibly pivotal design. Evaluate NE3107 promotoric activity or ability to delay motor complications, depending on results of NM201 phase 1b
  - 200 patients expected to start L-Dopa therapy within 6 months or 200 patients on L-Dopa for 6-12 months (detail of design pending)
  - Co-primary endpoints: UPDRS pt 1-5 and UDysRS pt 1-4

* Unified Parkinson's Disease Rating
** Unified Dyskinesia Rating Scale (UDysRS)

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Oncology Programs

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Inflammation drives cancer progression

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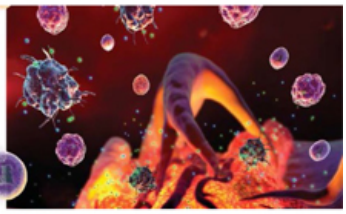
Understanding chronic inflammation, which contributes to heart disease, Alzheimer's and a variety of other ailments, may be a key to unlocking the mysteries of cancer

A Malignant FLAME

BY GARY STIX



Stix, 2006 *Sci Am July 60*

Inflammatory cell signaling is at the heart of cancer progression

- Tumor cells
- Hematopoietic
- Immune
- Vascular
- Stromal cells

Modified from Colotta 2009 *Carcinogenesis 30 1073*

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Macrophage and MDSC inflammation in cancer

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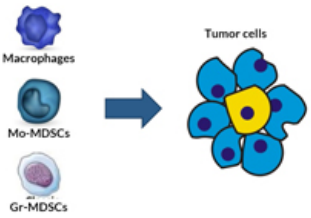
NFκB/ERK signaling is implicated in many cancers

- Acute myeloid leukemias
- Anaplastic large cell lymphoma
- Bile duct
- Bladder
- Breast
- Chronic myeloid leukemia
- Colorectal
- Endometrial
- Hodgkin's disease
- Kidney
- Langerhans cell sarcoma
- Large granular lymphocyte proliferative disorders
- Liver
- Lung
- Melanoma
- **Myeloma**
- Nasopharyngeal
- Ovary
- Pancreas
- **Prostate**
- Skin
- Stomach
- Thyroid
- T-cell lymphomas



- Initiation
- Promotion
- Growth
- Invasion
- Intravasation
- Extravasation
- Metastasis
- Angiogenesis
- Chemo-resistance
- Immune evasion

MDSC: myeloid-derived suppressor cells

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Myeloma and Prostate Cancer (PCa)

- Stem cell diseases
  - Myeloma initiated in CD34+ hematopoietic stem cells and have a clonal Ig rearrangement. Initial indolent course with MGUS. Plasma cells are the result of myeloma stem cell maturation.
  - Prostate cancer initiated in prostatic epithelial stem cells; they lack androgen receptor expression: androgen independent.
- Growth factor-driven
  - IL6 is "B cell growth factor"; it is both an autocrine and a paracrine driver of MM
  - Androgens are the principal growth factor for PCa
- Both tumors produce inflammatory factors that recruit and activate accessory cells in the tumor microenvironment

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NE3107 in Myeloma

- NE3107 inhibits activation of NFκB/ERK, TNFα and MCP-1.
- NE3107 inhibits IFNα-stimulated IL6 in human myeloma cells.
- NE3107 has potential to inhibit proliferation and induce apoptosis in MM by two mechanisms:
  - Inhibiting cytokine and chemokine production in myeloma-associated macrophages and MDSC
  - Blocking autocrine IL6 production in MM

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Current preclinical study in myeloma

- Studying effects of NE3107 on human myeloma cells in culture
  - Growth
  - Apoptosis
  - Combination with proteasome inhibitor
- Studying effects of NE3107 on transplanted syngeneic MM cells in mice
  - Tumor growth
  - Effects on MM microenvironment
  - Effects on macrophages and MDSC
  - Combination with proteasome inhibitor
- Data expected in Q2-Q3

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Prostate Cancer

- The progression of PCa is also critically dependent on accessory cells in their microenvironment
- NFκB/ERK activation promotes initial tumors in the prostatic epithelium, drives their progression, and is critical in their transition to castrate-resistant prostate cancer (CRCP)
- NFκB/ERK primes epithelial-mesenchymal transition and stemness of CRCP
- In the PCa microenvironment, Macrophages and MDSC secrete IL23, which has been shown to activate androgen receptor pathways in CRCP (in the absence of androgens)
- NE3107 inhibits NFκB/ERK signaling that drives IL23 production

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Androgen deprivation therapy (ADT)

- PCa is treated by starving the tumor of androgens, leading to temporary cessation of growth
- We now know that the action of ADT stimulates inflammation in the tumor microenvironment. ADT activates macrophages and MDSC
- PCa release "alarmins" that activate inflammation and stimulate IL6 secretion by accessory cells in the tumor
- The secreted IL6 binds to its receptor on PCa, and activates STAT3, stimulating a positive feedback loop between PCa and macrophages and MDSC
- Blocking this feedback can inhibit metastasis of CRCP

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NE3107 in PCa: several ways to win

- Early (rising PSA)
  - NE3107 has been shown to decrease prostate inflammation in mice, and may block the progression of PCa
  - Delaying the initiation of ADT prolongs life in PCa
- Localized disease
  - Decreasing the inflammatory milieu in the PCa microenvironment is expected to decrease tumor growth, and increase anti-tumor immune responses
- CRCP
  - NE3107 has been shown to inhibit IL23 production, and is expected to inhibit the formation of CRCP
  - NE3107 is expected to decrease chemotherapy resistance and increase apoptosis
- Metastasis
  - In addition, NE3107 inhibits NFκB/ERK/chemokines responsible for CRCP metastasis.

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Preclinical studies in PCa

- Developing protocols and reviewing investigators for preclinical studies
- Early
  - Effects of NE3107 on spontaneous tumor progression in TRAMP mice
- Localized disease
  - Effects of NE3107 on syngeneic transplanted androgen-dependent PCa cells
- CRCP
  - Effects of NE3107 in vitro on ADT induction of chemokines and chemotaxis
  - Effects of NE3107 in vivo on accessory cell-driven IL23 stimulation of PCa androgen receptor
  - Effects of NE3107 on chemo- and immune resistance
- Metastasis
  - Effects of NE3107 in an orthotopic PCa model on ADT induction of metastatic disease.

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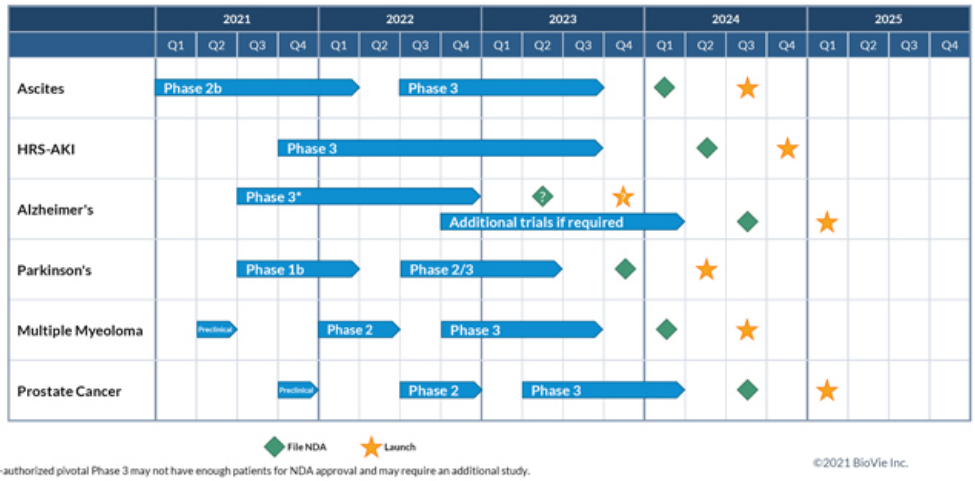
Catalysts & Anticipated Timelines (US)



* The FDA-authorized pivotal Phase 3 may not have enough patients for NDA approval and may require an additional study.

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Portfolio Revenue Potential

		Conservative Company Estimates		
	Intellectual Property	US Patient Population	US Peak Sales Potential	Global Sales Potential
BIV201: Refractory Ascites	Orphan Drug; Patent-pending formulation	20,000	$450 million	>$900 million
BIV201: HRS-AKI	Orphan Drug; Patent-pending formulation	17,000	$250 million	>$400 million
NE3107: Alzheimer's	Compound patent thru 2034+	6.1 million	$7 billion	>$10 billion
NE3107: Parkinson's	Compound patent thru 2034+	1.0 million	$1.5 billion	>$3 billion
NE3107: Oncology	Compound patent thru 2034+	TBD	TBD	TBD

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Recap

- Multiple shots on goal focused on unmet medical needs: neurodegenerative, advanced liver disease, oncology
- BIV201: Orphan drug in Phase 2b for refractory Ascites; HRS-AKI trials planned. Ascites readout anticipated in early 2022
- NE3107: inhibitor of pathologic inflammation and insulin resistance without toxicity and immunosuppression. Alzheimer's Phase 3 starting mid-2021. Parkinson's, Multiple Myeloma, and Prostate Cancer follow
- Capital efficient development plans with expected near-term data readouts

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Appendix

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NE3107 vs. Others

Company	Approach	NE3107 Benefits
AC Immune	• Semorinemab (ACI-3024) promotes clearance of tau • Does not address inflammatory stimuli other than tau	• Small molecule • Broader anti-inflammatory activity
Alector	• AL002 is an antibody that stimulates microglial phagocytosis optimally targeting amyloid or bacteria • The antibody could have a large impact on neuroinflammation	• Oral small molecule with CNS access
Annovis Bio	• Posiphen (ANVS401) mechanism decreases APP and tau, but does not impact systemic inflammatory stimuli and insulin resistance in Alzheimer's Disease • Posiphen mechanism inhibits production of alpha synuclein, which has a central role in Parkinson's Disease pathophysiology	NE3107 may be superior with • Blocking inflammation-driven factors in AD • Blocking non-alpha synuclein inflammatory factors in PD
Athira Pharma	• ATH-1017 decreases inflammation mediated by TLR4 among other activities • By disrupting TLR4, ATH-1017 reduces inflammation via the NFkB pathway	NE3107 may • Act more selectively downstream in the pathway • Inhibit insulin resistance and inflammation initiated by other cytokines and chemokines
AZTherapies	• ALZT-OP1 is a combination of cromolyn and ibuprophen • Does not distinguish between inflammatory and homeostatic activities	• More selective • Downstream in pathway
Biogen and Eli Lilly	• Biogen's Aducanumab and Lilly's donanemab remove amyloid plagues • Do not address inflammatory stimuli other than amyloid beta	• Small molecule • Broader anti-inflammatory activity
Cassava Sciences	• Simufilam (PTI-125) disrupts inflammatory signaling meditated by the α7-nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4) • By disrupting TLR4, Simufilam reduces inflammation via the NFkB pathway	NE3107 may • Act more selectively downstream in the pathway • Inhibit insulin resistance and inflammation initiated by other cytokines and chemokines
Cortexyme	• Atuzaginstat (COR388) decreases inflammation by Porphyromonas gingivalis bacterial infection that potentially decreases amyloid beta and p-tau inflammatory stimuli • Role of bacterial infection to the total inflammatory in AD is unknown	• Broadly applicable to all AD patients – not just with bacterial infection
Denali Therapeutics	• DNL788 for AD is a small molecule impacting TNF mediated inflammation and cell death • Very similar role to NE3107 in inhibiting TNF perpetuation of NFkB pathway • DNL151 for PD is a small molecule impacting LLRK2 focused on disease progression	• Approved for phase 3 start in AD • Broader inhibitor of insulin resistance and inflammation with promotoric and anti-LID activity, in addition to neuroprotection in NHP models in PD
Immune Bio	• XPRO1595 is a large molecule that inhibits TNF; Phase 1 • Very similar role to NE3107 in inhibiting TNF perpetuation of NFkB pathway	• Oral small molecule with CNS access; inhibits pro-inflammatory activation of TNF/TNFR1/2 without impacting homeostatic role of TNFR1; Phase 3
vTv Therapeutics	• Azeliragon (TTP488) is an inhibitor of RAGE cell surface receptors • Since RAGE has homeostatic functions, chronic RAGE inhibition may have adverse effects	• More selective • Downstream in pathway

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