Disclaimer

This presentation contains forward-looking statements about our plans, objectives, and expectations with respect to the preclinical and clinical development of our products that involve a number of risks and uncertainties including the risk that the clinical development of our products will not necessarily proceed to late stage clinical trial or commercialization. These statements involve language such as “will,” “potential”, “could,” “can,” “believe,” “intends,” “plans,” “expects,” “projects,” or “estimates”.
Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Pain:</strong></td>
<td>An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.</td>
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<td><strong>Neuropathy:</strong></td>
<td>A disturbance of function or pathological change in a nerve. If this occurs in a peripheral nerve it is termed peripheral neuropathy.</td>
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<td><strong>Neuropathic Pain:</strong></td>
<td>Pain due to a primary lesion or dysfunction in the nervous system.</td>
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<td><strong>Neurotransmitter:</strong></td>
<td>Chemicals that act as messengers between cells in the nervous system.</td>
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<td><strong>Dermatome:</strong></td>
<td>An area of skin innervated by a single nerve root from the spinal cord.</td>
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<td><strong>Nociceptor:</strong></td>
<td>A sensory neuron that responds to noxious stimuli and initiates a pain signal.</td>
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<td><strong>Allodynia:</strong></td>
<td>Pain due to a stimulus that does not normally provoke pain.</td>
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<td><strong>Hyperalgesia:</strong></td>
<td>An exaggerated pain response to a stimulus that is normally painful.</td>
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<tr>
<td><strong>Analgesia:</strong></td>
<td>Absence of a pain response to a stimulation that would normally cause pain.</td>
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<tr>
<td><strong>Proprioception:</strong></td>
<td>The sensory perception of body position in space.</td>
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<td><strong>Dysesthesia:</strong></td>
<td>An unpleasant abnormal sensation, whether spontaneous or evoked.</td>
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<tr>
<td><strong>Paresthesia:</strong></td>
<td>A ‘pins and needles’ sensation, usually in the hands and/or feet.</td>
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# Company Snapshot

### Who we are:
A biotherapeutics company developing products that directly target neurons to treat disorders of the nervous system without side effects.

### Target Markets:
Pain and Neuropathy, two neurological problems with substantial unmet medical needs that affect millions.

### Technology:
NEuronal Therapeutics (NET) gene delivery platform for direct treatment of sensory neurons.

### Team:
7 FTE (3 founders + 4 employees)

### Headquarters:
Pittsburgh, PA

### History:
Founded November 2012 via a management buyout of Diamyd, Inc (Founded 2005) by NET technology inventors.
The Problem: Pain and Neuropathy

- The common denominator in disease symptoms of pain and neuropathy are the sensory neurons.

**Nociceptive pain.** Injury to non-neuronal tissue such as muscle, joints, or skin can lead to inflammatory or nociceptive pain. Nociceptive pain is currently treated with anti-inflammatory drugs and narcotics.

**Damage to nervous system structures can lead to neuropathic pain, and/or peripheral neuropathy (numbness, weakness, dysesthesia, paresthesia). Neuropathic pain is currently treated with neuromodulatory drugs.**
Current drugs to treat pain or neuropathy are largely ineffectual and/or have substantial side effects

Because distinct mechanisms can produce a similar pain syndrome, mechanism based therapy may be ineffective in subpopulation of patients presenting with similar symptoms

A relatively limited number of signaling molecules (receptors, ion channels, second messenger systems) are used in the execution of a diverse array of physiological processes, including pain. Consequently, intolerable side effects such as cardiac, respiratory, or CNS depression often limit the systemic use and dose of even the most selective therapeutic interventions
The Solution: Treat Nerves Directly

NET: NEuronal Therapeutics Platform

- Gene delivery vector based on Herpes Simplex Virus type 1
- Targeted expression of therapeutic gene product in nerves
- Local expression = No systemic adverse effects
- Positive safety profile in people. Cannot replicate or cause disease

A schematic of the NET biotherapeutics platform. The HSV-1 virus contains unique long and unique short sequences bounded by inverted repeat sequences. NET vectors are missing two essential immediate early viral genes, ICP4 and ICP27, and deleted for the promoters of two other genes, ICP22 and ICP47. A therapeutic gene is engineered into the NET vector, driven by a promoter of choice, to produce a NET drug candidate. NET vectors are propagated in specially engineered cell lines that provide the missing gene products.
The Solution: Treat Nerves Directly

**NET: NEuronal Therapeutics Platform**

1. Simple intradermal application
2. NET vectors are delivered to dorsal root ganglion by retrograde transport
   The transgene is expressed directly in transduced neurons
3. The resultant protein can have a therapeutic effect directly in the neuron and/or be released within the spinal cord to have a local therapeutic effect
The Solution: Treat Nerves Directly

NET Platform Advantages

1. Directing therapeutic gene expression to a specific region of the neuraxis achieves a level of precise drug delivery unmatched by any other method
   - Ensures our active substance (i.e. gene product) has greater access to its site of action and virtually eliminates any systemic adverse effects

2. Precise delivery lowers the efficacious dose of active substance orders of magnitude compared to systemic or intrathecal drugs
   - This also substantially decreases the opportunity for systemic and central adverse effects
The Solution: Treat Nerves Directly

**NET Platform Advantages**

3. Expression of gene products that the body already produces and uses reduces concern about off-target effects
   - Unlike many traditional small molecule pharmaceuticals we know exactly where and how our NET drug candidates achieve their therapeutic effects

4. Broadly applicable to most neurological problems
   - Aside from pain and neuropathy other indications include neurodegenerative disorders (e.g. PD), motor neuron diseases (e.g. ALS), and nerve regeneration

5. Can express therapeutic proteins or agents that affect gene expression (interfering RNA, transcription factors, etc...)
Our Markets

• Indications where direct treatment of sensory neurons would lead to improved efficacy and safety
  • Neuropathic Pain
  • Prevention of Neuropathy
  • Chronic Nociceptive Pain – not responsive to current treatments
  • Acute Nociceptive Pain – an alternative to oral opiate use

• All are large potential markets
  • 100 million people with chronic nociceptive pain in US
  • 2-8% of US population suffer from neuropathic pain
  • 2.75 million people are treated with chemotherapy per year (est)
Neuropathic Pain – Diabetes

• Neuropathic pain is a complication of diabetes.
  • 25 million Americans have diabetes and the number is rising rapidly
  • 20% of people with diabetes will develop Painful Diabetic Neuropathy
  • US market alone is approximately 5 million people

• Current drugs have limited efficacy and substantial side effects
  • <20% of patients respond adequately
  • Localized delivery of a known analgesic peptide to the synapse between the primary nociceptor and second order transmission neuron could overcome these problems
Drug Candidate PGN-305

PGN-305 for Painful Diabetic Neuropathy (PDN)

- Expresses Glutamic Acid Decarboxylase (GAD) gene
- The GAD enzyme produces GABA, an inhibitory neurotransmitter
- GABA is released into the spinal cord where it inhibits pain signaling to the brain
- More efficacious than current treatment in preclinical models

The threshold (in grams) at which a rat responds in a pain-like behavior to a mechanical stimulus is decreased following induction of diabetes (Normal vs. Placebo). A single subcutaneous injection of PGN-305 into the hind paw normalizes this mechanical hyperalgesia substantially more than does Gabapentin. *p<0.05, paired T-test.
Prevention of Neuropathy

• Neuropathy is a side effect of chemotherapy induced nerve damage
  • Estimated 2.75 million chemotherapy patients per year (cisplatin 250-500K)
  • Up to 95% of patients who undergo platin-based chemotherapy develop Chemotherapy Induced Peripheral Neuropathy (CIPN)
  • Major dose-limiting side effect of chemotherapy
  • Reduced course of chemotherapy = reduced survival rates

• There are no current treatment options for CIPN
  • Neurotrophic factors are small proteins that have been shown to protect against the development of CIPN in animals
  • The effective systemic dose of neurotrophic factors in animals is 100x – 1000x greater than the maximum human tolerable dose
  • Localized delivery of small amounts of neurotrophic factors could overcome this problem
Drug Candidate PGN-703

PGN-703 for Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Expresses Neurotrophin-3 (NT-3) gene
- Produces NT-3 protein, a neurotrophic factor
- NT-3 Protects neurons from chemical and metabolic damage
- Prophylactic treatment proven successful in preclinical models

Rats treated with 3 mg/kg cisplatin twice per week for 6 weeks develop peripheral neuropathy characterized by loss of proprioception, assessed by timing how long they can stay on a rotating drum (Normal vs. Placebo). Rats subcutaneously injected into both hind paws with PGN-703 three days prior to cisplatin treatment do not develop peripheral neuropathy. *p<0.05, paired T-test.
Nociceptive Pain

- Most common form of pain
  - 100 million people in US estimated to suffer from chronic nociceptive pain
  - Response to inflammation associated with tissue damage or chronic disease
  - NSAIDs provide efficacy for less severe nociceptive pain

- Opioids are used to treat moderate to severe pain
  - Consistent use of opioids will lead to tolerance
  - Oral opioid use can have off target effects including changes in cognition, constipation, and respiration
  - Abuse is a major medical and social problem
  - Localized delivery of small amounts of endogenous opioids could overcome these problems
Drug Candidate PGN-202

PGN-202 for Cancer Pain

- Expresses Preproenkephalin (PENK) gene
- Processed into endogenous opioid peptides leu- and met-enkephalin
- Phase I and II studies completed in cancer pain
- Excellent NET platform safety profile

Pain response in Phase I clinical trial subjects with severe, intractable, terminal cancer pain given PGN-202. Subject cohorts demonstrated dose-response like decrease in reported pain. Values represent average numeric rating scale (NRS) of pain intensity (+/- standard error of the mean) for each cohort over the 4 weeks following dosing of PGN-202.
## Competition

### PDN
- FDA approved drugs
  - Duloxetine (Cymbalta®)
  - Pregabalin (Lyrica®)
  - Tapentadol ER (Nucynta ER®)
- Several off-label drugs
- <10 Phase II or later
- No New Chemical Entities in late stage trials

### CIPN
- No FDA approved drugs
- Minor efficacy in Phase II or later
  - Acetyl-L-carnitine
  - Vitamin E
  - Glutathione
  - Ca²⁺/Mg²⁺ infusion

### Nociceptive Pain
- NSAIDS for mild to moderate pain
- Opioids for moderate to severe pain
  - Oxycodone
  - Morphine
  - Fentanyl
  - Hydrocodone
Corporate Development Plan

We pursue a corporate development strategy based on the following key components:

- Secure corporate partnerships for the developmental support and commercialization or co-marketing of specific products
- Continue research and development to enhance core technology and product value
- Secure VC and federal grant funding as well as support through sponsored research and university or government collaborations for efficient early stage and clinical product development

A continuous cycle of product development is envisioned where corporate partnering/outlicensing of one product following a Phase II proof-of-concept clinical trial would fund the preclinical and clinical development of the next product.
Corporate Development Plan

Months

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<th>6</th>
<th>12</th>
<th>18</th>
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<th>36</th>
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PGN-305

- cGMP Mfg
- Phase I/II Study

PGN-703

- cGMP Mfg
- Phase I/II Study

PGN-202

- Proposed Investigator Initiated Phase II Study
Our Team

Darren Wolfe, Ph.D.
President, CEO

James Wechuck, Ph.D.
Vice President, CSO

David Krisky, M.D., Ph.D.
Vice President, CMO

James Goss, Ph.D.
Senior Dir. Preclinical Dev.

Amy Shireman, B.S.
Financial Controller, H.R. Dir.