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## OUR PURPOSE: DEFEAT DEGENERATION

<table>
<thead>
<tr>
<th>RARE NEURODEGENERATIVE DISEASES</th>
<th>AMYOTROPHIC LATERAL SCLEROSIS</th>
<th>PARKINSON’S</th>
<th>ALZHEIMER’S</th>
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<tr>
<td>Orphan</td>
<td>20,000+ (US)</td>
<td>1,000,000+ (US)</td>
<td>5,500,000+ (US)</td>
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<td>&gt;30 lysosomal storage diseases</td>
<td>&gt;45 known genetic associations</td>
<td>&gt;95 known genetic associations</td>
<td>&gt;35 known genetic associations</td>
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</table>

Significant unmet medical need with no disease-modifying medicines
OUR JOURNEY: CLINICAL MILESTONES AND KEY PARTNERSHIPS

FILINGS
- RIPK1
  - DNL104 P1
- LRRK2
  - DNL201 P1
- RIPK1
  - LRRK2
  - DNL151 P1
- RIPK1
  - LRRK2
  - DNL201 P1b
- LRRK2
  - pRIPK1
  - DNL758 P1
  - ETV:IDS
  - DNL310 P1/2
- EIF2B
  - DNL747 P1b (ALS+AD)
  - DNL151 P1b
  - DNL343 P1

CLINICAL DATA
- DNL747
  - Phase 1
- DNL104
  - Phase 1
- DNL201
  - Phase 1
- DNL201
  - Phase 1b

2015
- 2016
- 2017
- 2018
- 2019
- 2020

ENABLING STRATEGIC PARTNERSHIPS

- HARVARD UNIVERSITY
- Genentech
- A Member of the Roche Group
- DZNE
- F-star
- VIB
- Lonza
- CENTOGENE
- THE RARE DISEASE COMPANY
- AbCellera
- SI RION BIOTECH
- Takeda
- SANOFI
- THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
- UCSD
OUR APPROACH: TWO PLATFORMS

DEGENOGENE BIOLOGY

- Lysosomal function
- Glial biology
- Cellular homeostasis

Deep biology and drug discovery expertise in three focus areas

BLOOD-BRAIN BARRIER (BBB) TECHNOLOGY

Proprietary drug delivery technology to ensure access to the brain
## OUR PORTFOLIO

<table>
<thead>
<tr>
<th>PROGRAM TARGET</th>
<th>DRUG CANDIDATE</th>
<th>DISEASE INDICATION</th>
<th>DRUG DEVELOPMENT</th>
<th>PARTNER</th>
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<tr>
<td></td>
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<td>Drug Discovery</td>
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<td>LYSOSOMAL FUNCTION PATHWAY</td>
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<td>IND-Enabling</td>
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<td>LRRK2</td>
<td>DNL201</td>
<td>Parkinson’s</td>
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<tr>
<td></td>
<td>DNL151</td>
<td>Parkinson’s</td>
<td></td>
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<tr>
<td>Iduronate 2-sulfatase</td>
<td>DNL310</td>
<td>MPS II (Hunter Syndrome)</td>
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<td>PGRN</td>
<td>DNL593</td>
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<td>Alpha-Synuclein</td>
<td>ATV:aSyn</td>
<td>Parkinson’s, DLB, MSA</td>
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<td>Sulfamidase</td>
<td>ETV:SGSH</td>
<td>MPS IIA (Sanfilippo Syndrome)</td>
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<td>ETV:LF1</td>
<td>LSD with Neurodegeneration</td>
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<td>GLIAL BIOLOGY PATHWAY</td>
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<td>RIPK1 (CNS)</td>
<td>DNL747</td>
<td>Alzheimer’s, ALS, MS</td>
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<td>Sanofi</td>
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<td>TREM2</td>
<td>ATV:TREM2</td>
<td>Alzheimer’s</td>
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<td>Takeda</td>
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<td>CELLULAR HOMEOSTASIS</td>
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<td>EIF2B</td>
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<td>Takeda</td>
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<td>Tau</td>
<td>ATV:Tau</td>
<td>Alzheimer’s</td>
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<td>Undisclosed</td>
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<td>OTHER</td>
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<tr>
<td>RIPK1 (Peripheral)</td>
<td>DNL758</td>
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<td>Sanofi</td>
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<td>LRRK2</td>
<td>Crohn’s Disease</td>
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<tr>
<td>Undisclosed</td>
<td>OT1</td>
<td>Other</td>
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</table>
## OUR PROGRESS AND PLANS

### 2019 Progress

<table>
<thead>
<tr>
<th>Program</th>
<th>Overview</th>
</tr>
</thead>
</table>
| **LRRK2**<br>Parkinson’s | ✓ Completed DNL201 Phase 1b  
✓ Initiated DNL151 Phase 1b  
✓ DNL151 Phase 1 in HV results |
| **ETV:IDS**<br>Hunter Syndrome | ✓ Initiated observational biomarker study  
✓ Submitted IND for DNL310 |
| **EIF2B**<br>ALS | ✓ CTA approved for DNL343 |
| **RIPK1**<br>ALS, Alzheimer’s | ✓ Completed enrollment of DNL747 Phase 1b  
✓ Initiated Open-Label Extension in ALS  
✓ Initiated DNL758 Phase 1 in HV (Sanofi) |
| **BBB Platform** | ✓ Submitted IND for first Transport Vehicle (TV) biotherapeutic  
✓ Progressed PTV:PGRN to IND-enabling studies |

### 2020 Plans

<table>
<thead>
<tr>
<th>Program</th>
<th>Overview</th>
</tr>
</thead>
</table>
| **LRRK2**<br>Parkinson’s | Complete DNL151 Phase 1 HV and Phase 1b  
Select molecule and prepare for Phase 2/3 |
| **ETV:IDS**<br>Hunter Syndrome | Initiate Phase 1/2 for DNL310 in patients  
Establish biomarker PoC in patients |
| **EIF2B**<br>ALS | DNL343 Phase 1 in HV results to enable patient study |
| **RIPK1**<br>ALS, Alzheimer’s | Results from DNL747 ALS and Alzheimer’s studies |
| **BBB Platform** | Establish TV Platform PoC in humans (ETV:IDS)  
Initiate IND-enabling studies for additional programs |
LRRK2 PROGRAM
LRRK2 inhibition is a potential therapeutic approach in both LRRK2-mutant PD and sporadic PD


PARALLEL EARLY CLINICAL DEVELOPMENT WITH TWO LRRK2 INHIBITORS (DNL201 AND DNL151)

- Most advanced LRRK2 program in clinical development
- Advanced two chemically distinct molecules through extensive Phase 1 and Phase 1b program (n >300)
  - DNL201 completed Phase 1 and Phase 1b
  - DNL151 has interim Phase 1 data; Phase 1b data expected in mid 2020
- Goal is to select the best molecule for Phase 2/3 program in mid 2020 based on all clinical data
  - Safety, PK properties, target engagement, improvement in lysosomal biomarkers

* Protocol amended to add higher dose cohorts for both DNL151 Ph 1 and Ph 1b studies

Select DNL201 or DNL151 for Phase 2/3 program in mid 2020
**DNL201 PHASE 1B IN PATIENTS MET ALL BIOMARKER GOALS**

**Target Engagement**
Reduction of pS935 LRRK2 (Whole blood)

**Pathway Engagement**
Reduction of pRAB10 (PBMCs)

**Lysosomal Function**
Reduction of BMP (Urine)

**DNL201 TID**

- Placebo (PBO)
- Low Dose
- High Dose

**BL = Baseline**

**Pre = Pre-dose**

DNL201 demonstrates strong LRRK2 inhibition and improvement in lysosomal biomarkers
DNL201 PHASE 1B: POTENTIAL CORRECTION OF ELEVATED LYSOSOMAL BIOMARKERS DRIVEN BY LRRK2 MUTATION

Metabolic Profiling Shows Lysosomal Biomarker Accumulation in LRRK2 Carrier CSF

LRRK2 Inhibition Reduces Lysosomal Biomarkers in LRRK2 G2019S Carriers

Lysosomal Biomarker 1

Lysosomal Biomarker 2

Lysosomal Biomarker 3
DNL151 PHASE 1 IN HV MET ALL BIOMARKER GOALS

DNL151 demonstrates strong LRRK2 inhibition and modulation of lysosomal biomarkers

% inhibition measured for the 28 Day safety cohort (Group H, not shown) was similar to the equivalent 10-day dose group (group F)
SAFETY SUMMARY TO DATE

DNL201

Phase 1
• Generally well tolerated, data presented (MJFF Oct 2018)

Phase 1b
• Low dose generally well tolerated
  • Most common AEs (all mild except one) were headache and nausea
  • One SAE, Legionella pneumonia, considered unrelated to study drug
• High dose had a higher incidence of moderate adverse events
  • One severe headache leading to dose reduction
  • One early withdrawal preceded by nausea and headache
• Across study, all treatment-related AEs were manageable and reversible
• No dose dependent effects on pulmonary function
• No dose dependent effects on supine or standing vital signs, except for increase in standing HR in 2 subject in HD
• Trend toward mild increase in creatinine (within normal range)

DNL151

Phase 1 (Ongoing)
• Generally well tolerated
• Majority of AEs were mild, no SAEs, no discontinuations related to active drug, no severe AEs
• Protocol amended to explore safety profile in higher dose cohorts

Phase 1b (Ongoing)
• No SAEs to date
• Protocol amended to add higher dose cohort

Both molecules show acceptable safety profiles to advance to Phase 2/3
LRRK2 CLINICAL PROGRAM: SUMMARY AND NEXT STEPS

SUMMARY

- Achieved target engagement and biomarker goals supporting the hypothesis that LRRK2 inhibition modulates and improves lysosomal function in Parkinson’s disease
- Both molecules to date show acceptable safety profiles to advance to Phase 2/3

NEXT STEPS

- Make selection between DNL151 or DNL201 for next stage of clinical development based on full data sets from both molecules (safety, target engagement, improvement of lysosomal biomarkers)

DNL201: Complete biomarker analysis of Ph 1b; Develop slow release formulation to support BID dosing and complete biomarker analysis

DNL151: Evaluate DNL151 at higher doses in the Ph 1 HV study and Ph 1b Parkinson’s disease studies

- Actively establishing a global network for patient enrollment:
TRANSPORT VEHICLE PLATFORM TECHNOLOGY
THE BLOOD-BRAIN BARRIER IS AN OBSTACLE FOR TREATING NEURODEGENERATIVE DISEASES

Engineered Transport Vehicle (TV) technology to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)
Denali’s **TV Technology** enables multiple modality-based platforms to deliver a wide range of large-molecule therapeutics across the **Blood-Brain Barrier**.

- Enzyme Transport Vehicle (ETV)
- Antibody Transport Vehicle (ATV)
- Protein Transport Vehicle (PTV)
- Oligonucleotide Transport Vehicle (OTV)
ETV: IDS FOR HUNTER SYNDROME

Existing enzyme replacement therapies do not effectively cross the BBB
Neurodegeneration in many patients progresses, even after treatment
ETV:IDS CORRECTS GAGS AND LIPID STORAGE IN THE BRAIN AFTER SYSTEMIC ADMINISTRATION

Iduronate-2-sulfatase (IDS) Architectures

**Liver GAGs**

- Total sGAG levels (ng/µg protein)

**Brain GAGs**

- Total sGAG levels (ng/µg protein)

**Brain BMP**

- di-22:6-BMP levels (ng/mg protein)

n=8 per IDS KO; TIR\textsuperscript{mu/hu} group or 5 per TIR\textsuperscript{mu/hu} group, data shown as mean ± s.e.m.; *** p < 0.001, **** p < 0.0001, ns = not significant

ETV:IDS reduces liver and brain GAGs and reverses BMP accumulation in the brain in preclinical models.
SYSTEMIC ADMINISTRATION OF ETV:IDS BLOCKS NEURODEGENERATION IN HUNTER SYNDROME MICE

ETV:IDS corrects GAGs and prevents neuroaxonal injury upon chronic dosing at therapeutically-relevant doses

**NfL IS A MARKER OF NEUROAXONAL INJURY**

![Axonal Degeneration](image)

---

**GAGs in Brain**

![Graph showing GAGs in Brain](image)

**NfL in CSF**

![Graph showing NfL in CSF](image)

---

**n=9-10 per IDS KO; TIR^mu/hu group or 10 per TIR^mu/hu group, data shown as mean ± s.e.m.; * p < 0.05, *** p < 0.001, **** p < 0.0001**

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OBJECTIVE: BIOMARKER PROOF OF CONCEPT IN HUNTER SYNDROME AND ENABLE TV PLATFORM

- Phase 1/2 multicenter, open-label study in pediatric subjects with Hunter syndrome
- 6 month study to evaluate safety, PK, and pharmacodynamic and define clinical dose
- Interim PoC readout expected late 2020

SUCCESS CRITERIA

- Safety: Well tolerated and safe in doses tested
- Biomarker: >50% reduction in CSF GAGs from baseline
Denali’s **TV Technology** enables multiple modality-based platforms to deliver a wide range of large-molecule therapeutics across the **Blood-Brain Barrier**.
ATV:TREM2 IMPROVES MICROGLIAL FUNCTION

TV technology can be applied to antibodies to enhance brain uptake and function.
Denali’s **TV Technology** enables multiple modality-based platforms to deliver a wide range of large-molecule therapeutics across the **Blood-Brain Barrier**.
PTV: PGRN IMPROVES LYSOSOMAL FUNCTION IN BRAIN

Progranulin (PGRN) Architectures

PTV: PGRN

**TV technology can effectively deliver other proteins to brain**

**Brain BMP**

**Liver BMP**

Data shown as mean ± s.e.m.; **** p < 0.0001

One-way ANOVA, Sidak's multiple comparison correction
Denali’s **TV Technology** enables multiple modality-based platforms to deliver a wide range of large-molecule therapeutics across the **Blood-Brain Barrier**.
OUR PLANS

2020 Plans

LRRK2
Parkinson’s
- Complete DNL151 Phase 1 HV and Phase 1b
- Select molecule and prepare for Phase 2/3

ETV:IDS
Hunter Syndrome
- Initiate Phase 1/2 for DNL310 in patients
- Establish biomarker PoC in patients

EIF2B
ALS
- DNL343 Phase 1 in HV results to enable patient study

RIPK1
ALS, Alzheimer’s
- Results from DNL747 ALS and Alzheimer’s studies to enable progression

BBB
Platform
- Establish TV Platform PoC in humans (ETV:IDS)
- Initiate IND-enabling studies for additional programs

Timing
- Mid 2020
- Mid 2020
- First half 2020
- Late 2020
- Late 2020
- Mid 2020
- Late 2020
THANK YOU