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Our Mission

Developing curative genome editing treatments that can positively transform the lives of people living with severe and life-threatening diseases
Modular Platform Drives Diversified Pipeline

FULL-SPECTRUM GENOME EDITING COMPANY

PIPELINE

- **NTLA-2001 for ATTR**: Dosed first patient in global Phase 1 study
- **NTLA-5001 for AML**: Expect to submit IND in 1H 2021 for WT1-directed TCR T cell therapy
- **NTLA-2002 for HAE**: Expect to submit IND in 2H 2021

PLATFORM

- Rapid identification of development candidates
- Precise knockout and/or insertion *in vivo* and *ex vivo*
- Transient Cas9 expression via non-viral delivery

CORPORATE

- Experienced management team
- Well capitalized to drive pipeline forward

**ATTR**: Transthyretin Amyloidosis  
**IND**: Investigational New Drug or IND-equivalent  
**AML**: Acute Myeloid Leukemia  
**HAE**: Hereditary Angioedema  
**WT1**: Wilms’ Tumor 1  
**TCR**: T Cell Receptor
Building a Full-Spectrum Genome Editing Company

**CRISPR is the therapy**

- Genetic diseases

**Modular Platform**

**In Vivo**

**CRISPR is the therapy**

**Ex Vivo**

**CRISPR creates the therapy**

- Immuno-oncology
- Autoimmune diseases

LNP: Lipid Nanoparticle
CRISPR/Cas9 is an Effective Tool for Modifying the Genome

1. **KNOCKOUT**
   - Inactivation/deletion of disease-causing DNA sequence

2. **REPAIR**
   - Correction of “misspelled” disease-driving DNA sequence

3. **INSERT**
   - Insert new DNA sequence to manufacture therapeutic protein
# Development Pipeline Fueled by Robust Research Engine

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<td>NTLA-2001: Transthyretin Amyloidosis</td>
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<td>OTQ923 / HIX763: Sickle Cell Disease</td>
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<td>NTLA-5001: Acute Myeloid Leukemia</td>
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<td>Undisclosed Programs</td>
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<td>Other Novartis Programs</td>
<td>CAR-T, HSC, OSC</td>
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<td>NOVARTIS</td>
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* Lead development and commercial party  ** Rights to certain *in vivo* targets  *** Milestones & royalties  
CAR-T: Chimeric Antigen Receptor T cells  HSC: Hematopoietic Stem Cells  OSC: Ocular Stem Cells
**In Vivo**

**CRISPR is the therapy**

**GENETIC DISEASES**

**Strategic Advantages:**

Systemic non-viral delivery of CRISPR/Cas9 provides transient expression

Potentially curative therapy from single course of treatment

Permanent gain of function with targeted gene insertion
Modular Approach to Unlocking Treatment of Genetic Diseases

PROPRIETARY LNP DELIVERY SYSTEM
- Transient expression
- Large cargo capacity
- Redosing capability

ENABLES MULTIPLE EDITING STRATEGIES

Remove
- KNOCKOUT
  - Knockout toxic or compensatory genes

Insert
- INSERT
  - Introduce functional DNA sequence
  - Any combination of knockout and insertion strategies + AAV

Restore
- Remove / Restore
  - CONSECUTIVE EDITING
    - Any combination of knockout and insertion strategies
Modular *In Vivo* Genome Editing Approach Validated Across Multiple Targets

**Remove**

**KNOCKOUT**
Knockout toxic or compensatory genes

**ATTR:**
>95% reduction of serum TTR sustained for a year in NHPs

**Hem B:**
Circulating human FIX protein in NHPs at or above normal levels

**Restore**

**INSERT**
Introduce functional DNA sequence

**Hem B:**
Circulating human FIX protein in NHPs at or above normal levels

**Remove / Restore**

**CONSECUTIVE EDITING**
Any combination of knockout and insertion strategies

**AATD:**
>98% reduction of disease-causing protein and sustained restoration of wild type AAT in serum to therapeutic levels in mice

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AATD: Alpha-1 Antitrypsin Deficiency  
FIX: Factor IX  
Hem B: Hemophilia B  
NHP: Non-Human Primate
Transthyretin Amyloidosis (ATTR)

Caused by accumulation of misfolded transthyretin (TTR) protein, which affects nerves, heart, kidneys and eyes

- **50,000** hATTR patients worldwide\(^1\)
- **~200-500K** wtATTR patients worldwide\(^2\)

**2-15 years** typical life expectancy from onset of symptoms\(^1\)

**Only chronic treatment options** currently available

**NTLA-2001 in development for ATTR**

- Employs a knockout edit to reduce circulating TTR protein levels
- Aims to address hATTR and wtATTR, both polyneuropathy and cardiomyopathy, with a single course of treatment

\(^1\) Ann Med. 2015; 47(8): 625–638.  \(^2\) Compiled from various sources

\(\text{hATTR: Hereditary ATTR} \quad \text{wtATTR: Wild-Type ATTR}\)
**ATTR:** Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs

![Graph showing sustained reduction of TTR protein after a single dose](image)

- **Control**
- **Lead LNP: Dose Level #1 (n=3)**
- **Lead LNP: Dose Level #2 (n=3)**

Therapeutically relevant serum TTR knockdown

**Single Dose**
First Patient Dosed in Landmark CRISPR/Cas9 Clinical Trial

**NTLA-2001 Global Phase 1 Study Design:** Two-part, open-label, multi-center study of NTLA-2001 in adults with hATTR with polyneuropathy

**Total Enrollment:**
Up to 38 patients, age 18 to 80 years

**Intervention:**
Single dose administered via an intravenous (IV) infusion

**PART I**
Single-Ascending Dose

- N= Up to 30 subjects*
- Up to 4 dose-escalation cohorts

**PART II**
Single Dose Expansion Cohort

- N = 8 subjects
- Administer optimal dose selected from Part I

**PRIMARY OBJECTIVES**
Evaluate safety, tolerability, PK and PD
- Measure serum TTR levels

**SECONDARY OBJECTIVES**
Evaluate efficacy on clinical measures of neurologic function
- Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)

*Minimum of 3 subjects per cohort
NIS: Neuropathy Impairment Score
mNIS+7: modified NIS+7
PK: Pharmacokinetics
PD: Pharmacodynamics

Clinicaltrials.gov ID: NCT04601051
Hereditary Angioedema (HAE)

Genetic disease characterized by overproduction of bradykinin, which leads to **recurring, severe and unpredictable swelling** in various parts of the body.

<table>
<thead>
<tr>
<th>1 in 50,000 HAE patients(^1)</th>
<th>Attacks can occur every <strong>7-14 days</strong> on average for untreated patients(^1)</th>
<th>NTLA-2002 in development for HAE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway obstruction is particularly dangerous because it can cause death by asphyxiation</td>
<td>Only <strong>chronic treatment options</strong> currently available</td>
<td>• Employs a knockout edit of <em>KLKB1</em> gene in hepatocytes</td>
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<tr>
<td></td>
<td></td>
<td>• Aims to reduce plasma kallikrein activity to prevent excess bradykinin production leading to HAE attacks after a single course of treatment</td>
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</table>

Knockout of KLKB1 Aims to Reduce Bradykinin Activity in People with HAE

- Kallikrein inhibitors are **clinically validated** in preventing HAE attacks.
- **KLKB1** knockout is **expected to be safe**, as human nulls show no associated pathology*

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Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs

*K Banerji et al., NEJM, 2017

![Graph showing Kallikrein Activity Reduction](image)
HAE: Rapid Path to NTLA-2002 Development Candidate Nomination

**LNP Delivery System:**
*gRNA Reprograms Genetic Target*

- Cas9 mRNA
- AAAA
- **KLKB1 gRNA**
- **TTR gRNA**
- Target-specific gRNA

**HAE Program:**

Builds on ATTR program’s infrastructure, including modular LNP delivery system

Applies insights gained from ATTR and other research programs to liver knockout target

Platform advances expedite progression to NHP proof-of-concept

Expect to submit IND or IND-equivalent in 2H 2021
**Ex Vivo**

**CRISPR creates the therapy**

**IMMUNO-ONCOLOGY / AUTOIMMUNE DISEASES**

**Strategic Advantages:**

CRISPR/Cas9 enables precise genome engineering for creating cell therapies to treat IO and AI diseases

Pursuing modalities, such as TCR, with broad potential in multiple indications

Focused on recapitulating natural cell physiology
TCR T Cell Modality Broadens Opportunity to Address Most Tumors

Selecting naturally-occurring, high-affinity TCRs

- TCRs efficiently detect tumor antigens
- Physiological signaling minimizes T cell exhaustion and immune toxicity
- Healthy donor TCRs avoid reactivity against normal tissues
- High-affinity TCRs can activate both cytotoxic and helper T cells

Total Addressable Tumor Targets

CAR-T: Limited to surface antigens

TCRs: Recognizes both surface and intracellular antigens

Intracellular Tumor Antigens

CRISPR Engineering Overcomes Key Challenges of Traditional Approaches

**Key Challenges**

- Mutagenesis risk from random lentiviral insertion
- Mixed expression of endogenous and tgTCR
- Mispaired TCRs have unpredictable specificities and pose GvHD risk
- Lower tgTCR expression per T cell leads to reduced efficacy

**Our Solution**

- Precise replacement of endogenous TCR with tgTCR
- No insertional mutagenesis risk
- Reduced risk of unwanted reactivity against normal tissues
- High tgTCR expression per T cell leads to a more efficacious cell product
Our Approach for TCR Replacement with Elimination of Endogenous TCRs Creates a Homogenous T Cell Product

Intellia’s Approach (TRAC and TRBC KO + Insertion)

TRAC KO only + Insertion

High and Uniform Expression of tgTCR per T cell

Removal of Endogenous TCR Prevents Mispairing

Normalized tgTCR Expression (%)

% Cells with mispaired TCRs

TCR A TCR B TCR C TCR D

TCR A TCR B TCR C TCR D

Based on FACs analysis
Proprietary Process Enables Multiple Sequential Edits With Minimal Translocations

Efficient multiplexed editing

- Standard Process: Cas9/sgRNA RNP electroporation based on manufacturer’s instructions

Higher T cell expansion

Reduced translocations

- Intellia Process

Gene 1
Gene 2
Gene 3

% Editing

Fold Expansion

Cumulative Translocation Events per 200 Cells

- Translocations to other chromosomes
- Reciprocal Translocations
- Complex Translocations
Acute Myeloid Leukemia (AML)

Cancer of the blood and bone marrow that is rapidly fatal without immediate treatment, and is the most common type of acute leukemia in adults.\(^1\)

\(\geq 21K\) new cases in the U.S. in 2019\(^1\)

\(\geq 40K\) new cases in the 7MM\(^2\) in 2018\(^1\)

\(<30\%\) 5-year overall survival\(^1\)

NTLA-5001 in development for AML

- Engineer WT1-directed T cells capable of specifically killing AML blasts

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\(^1\) NIH SEER Cancer Stat Facts: Leukemia – Acute Myeloid Leukemia (AML)

\(^2\) GlobalData EpiCast Report: Acute Myeloid Leukemia July 2017, 7MM: Seven Major Markets (includes U.S.)
Wilms’ Tumor 1 (WT1) is an Attractive Tumor Target

WT1 is Overexpressed in >90% of AML Blasts
- Independent of mutational status
- Low normal tissue expression

WT1 is Overexpressed in Variety of Solid Tumors
- AML program provides foundation for expansion into solid tumors

Sugiyama et al., Jap J Clin Oncol, 2010
Cilloni et al., J Clin Oncol, 2009
Engineered T Cells Capable of Specific and Potent Killing of WT1-Positive AML Blasts

Lead WT1-Specific TCR Profile:

• Sourced from healthy donor T cells
• *HLA-A*02:01 restricted TCR
• Displays high avidity for VLD* epitope
  – VLD epitope is efficiently processed by tumor proteasome, and presented by AML blasts

Proprietary T Cell Engineering Process Yields:

• Consistent high-level editing efficacy
• High and homogeneous tgTCR expression
• Cytotoxic and helper T cell response
• No detectable bone marrow cell toxicity

*VLD is the WT1(37-45) epitope VLDFAPPGA
In collaboration with IRCCS Ospedale San Raffaele
Achievements and Next Steps

- Engineered WT1-specific T cells capable of specifically killing patient-derived AML blasts
- Nominated NTLA-5001 as development candidate
- Submit IND or IND-equivalent in 1H 2021
Multiple Workstreams to Advance Cell Therapy Efficacy in Solid Tumors

Allogeneic Cell Source
• Knock out MHC-I and MHC-II complexes
• Address multiple surface protein signals
• Achieve persistence in presence of natural killer cells

Functional Modulation
• Knock out and/or knock-in of key receptors, including checkpoint inhibitors, to modulate T cell functionality in multiple microenvironments

Solid Tumor Efficacy
• CRISPR screening to unravel targetable key regulators of T cell fitness in the tumor microenvironment
## Upcoming Milestones: Driving Forward *In Vivo* and *Ex Vivo* Programs in 2020

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<th><strong>NTLA-2001</strong></th>
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<td><em>In Vivo</em></td>
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<td><strong>ATTR</strong></td>
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<td><strong>HAE</strong></td>
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<tr>
<td>✔ Received regulatory authorization to initiate Phase 1 study ✔ Dosed first patient in global Phase 1 study by YE 2020</td>
<td>✔ Presented preclinical data at scientific conference in 1Q 2020 ○ Submit IND or IND-equivalent for NTLA-5001 in 1H 2021</td>
<td>✔ Presented preclinical data at scientific conference in 1Q 2020 ✔ Nominated NTLA-2002 as development candidate in 1H 2020 ○ Submit IND or IND-equivalent for NTLA-2002 in 2H 2021</td>
<td>○ Present preclinical data at upcoming scientific conferences in 2020</td>
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*Intellia Therapeutics*
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