Company Overview

Yale Innovation Summit
May 18, 2021

MITOTHERAPEUTIX

Using siMCJ to treat MCJ based metabolic disorders
Mitotherapeutix established in 2014

- **Focus**: Development of drugs to treat metabolic disorders
- **Drug Target**: MCJ-mitochondrial regulator of metabolism - eliminate and increase energy
  - MCJ/DNAJC15 is resident in Liver, Kidney and Heart and is elevated in disease states: Fatty Liver/NASH; cirrhosis; acute and chronic kidney disease, heart failure.
- **Therapeutic Impact**: Modulation of this protein increases metabolism and has an impact in treating disease
  - Six murine models of liver disease- KO of MCJ has beneficial therapeutic effects
- **Approach**: Using siRNA based MCJ suppression to treat disease
  - Utilizing siRNA drug discovery and delivery program
  - Patented GalNAc liver delivery technology discovered and developed internally
- **Status**: Completed initial in vivo testing of lead candidate in:
  - Non-human primates and demonstrated significant MCJ suppression
Pipeline: Multiple potential indications- “Platform in a drug”

Therapeutic Program | Candidate | Exploratory Research and PoC | DC* Optimization | IND Enabling | Phase I
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Liver | MT-001 | Nonalcoholic Steatohepatitis (NASH), (NAFLD) |  |  |  
Kidney | MT-002 | Acute liver injury (e.g. APAP-induced) |  |  |  
Cancer | MT-003 | AKI, CKD |  |  |  
Cardiovascular | MT-004 | CD8 CAR-T |  |  |  
TBD |  | Heart Failure |  |  |  

IND filing planned in Q4 2022

* DC – Development Candidate

Each disease candidate has its own delivery approach, nucleotide sequence or chemical modifications and therefore would be considered a unique drug.
Mito- SiMCJ drug discovery process

Bioinformatics → Sequence selection and siMCJ synthesis → In vitro screening in both human and mouse cell lines

In vitro screening in primary human hepatocyte for on and off target activity → In vivo screening in wildtype mouse for MCJ KD in liver

Exploratory tox study in rat, then in monkey → In vivo testing in Cyno monkey for MCJ KD in liver

In vivo optimization in wildtype mouse with selected sequences → Development candidate selection

Company Overview
Summary:

- Unique MCJ target identified and patented
- Ability to enhance mitochondrial respiration and ATP generation without ROS production
- Drug discovery platform to treat multiple metabolic diseases
- GalNAc liver delivery technology discovered, developed and patented
Summary:

✓ NASH drug leads identified; excellent in vivo activity in mice and non-human primates

✓ Seeking $5-10 million funding/partnership to advance the NASH program to IND filing and Phase 1 clinical trial

✓ Expecting approval of $2.2MM NIH SBIR grant for NASH program that will accelerate IND enabling process

➢ Looking for potential commercial partners and institutional investors
MCJ (DnaJC15) is a “mitochondrial brake”

- MCJ localizes at the inner membrane of the mitochondria
- MCJ associates with Complex I of the electron transport chain (ETC)
- MCJ is a negative regulator of Complex I and mitochondrial respiration
- Loss of MCJ increases Complex I activity and mitochondrial ATP levels without increasing oxidative stress.
- Disrupting MCJ expression is a therapeutic strategy to enhance mitochondria metabolism and fitness of the cells.

Champagne et al. Immunity 2016;
Barber et al. Nat. Communications 2017;
Barber et al. Nat Communications 2020
Non-Alcoholic Fatty Liver Disease (NAFLD)

- Fatty liver diseases have been estimated to affect 25-30% of world population.
- NAFLD
  - healthy liver
  - reversible

- Steatosis
  - simple fat accumulation
  - reversible

- NASH
  - non-alcoholic steatohepatitis
  - irreversible

- Cirrhosis
  - cirrhosis
  - irreversible

Targeting MCJ

Fatty liver diseases have been estimated to affect 25-30% of world population.
MCJ is preferentially expressed in metabolically active tissues (liver, kidney, heart)