Modulation of the $F_1F_0$-ATPase Induces Apoptosis of Mouse and Human Lamina Propria T Cells and is Efficacious in Models of IBD

Luigi Franchi, Lycera Corp
Acknowledgements

Lycera Corp.
Anthony W. Opipari
Rod Morgan
Mark Spahr
Brian Sanchez
Charles Lesch
Corrin Hepburn
Alexander Hurd
Clarke Taylor
Chad Van Huis
Don Skalitzky
Peter Toogood
Laura Carter
Gary Glick

University of Rome “Tor Vergata”
Giovanni Monteleone
Ivan Monteleone
Davide di Fusco
Francesca Zorzi
Irene Marafini
Francesco Pallone

University of Michigan
Peter D.R. Higgins
Kelli Porzondek

Northwestern University
Kelan Hlavaty
Background: Targeting the $F_1F_0$-ATPase

- Large, 16-subunit complex embedded in mitochondrial inner membrane
- Final enzyme in the electron transport chain, (aka respiratory complex V)
- During oxidative phosphorylation, proton flow drives rotating motor function catalyzing the generation of ATP
- Lycera has discovered small molecules modulators of the $F_1F_0$ ATPase which induce apoptosis of susceptible cells by increasing intracellular superoxide levels
Induction of Apoptosis by ATPase Modulators (LYC-51194)

Apoptosis is triggered by indirect effect on the mitochondrial respiratory chain

Modulation of the F$_1$F$_0$-ATPase leads to hyperpolarization of the mitochondrial membrane potential and an increase in the production of superoxide by complex III

Sundberg et al. (2009)
ATPase Modulators Act Selectively on Chronically Activated Lymphocytes

Bioenergetic and redox abnormalities sensitize chronically-activated lymphocytes to $F_1F_0$-ATPase modulation resulting in selective apoptosis

Normal Lymphocytes
- Generate ATP by aerobic glycolysis
- High anti-oxidant stores (glutathione) and low superoxide levels

Chronically Activated Lymphocytes
- Generate ATP by oxidative phosphorylation
- Depleted anti-oxidant stores and elevated basal superoxide level
- ATPase Modulator induced increases in superoxide not detoxified $\rightarrow$ apoptosis

Science Translational Medicine, 2011, 3: 67ra8
ATPase Modulators are Effective in Different Murine Model of Autoimmune Disease

- Selective apoptosis of chronically activated lymphocytes translates to broad efficacy profile
- No effect on T-dependent antibody production

The ATPase Modulator LYC-51194 Reduces Severity of TNBS-Induced Chronic Colitis

Body Weight Change (% of Day 0)

- Control (n=6)
- LYC-51194 (n=8)
  - * p<0.001
- Vehicle (n=8)

LYC-51194 Dosing (30 (mg/kg))
The ATPase Modulator LYC-51194 Reduces Severity of Adoptive Transfer-Induced Colitis

LYC-51194 (n=6)  
Vehicle (n=6)

p< 0.05
The ATPase Modulator LYC-51194 Dosed Therapeutically *in vivo* Improves Inflammatory Bowel Disease (IBD) in Murine Models

Histology scores following therapeutic administration of LYC-51194

Chronic TNBS

Adoptive Transfer

Histology scores following therapeutic administration of LYC-51194
The ATPase Modulator LYC-51194 Induces Death of Lamina Propria T Cells

- **Chronic TNBS**
  - % survival of lamina propria T lymphocytes
  - Vehicle vs. LYC-51194
  - *p < 0.005

- **Adoptive transfer**
  - % survival of lamina propria T lymphocytes
  - Vehicle vs. LYC-51194
  - *p < 0.005
ATPase Modulator LYC-51194 Induces Death of LP T Cells from CD Patient Biopsies

Isolated lamina propria T cells from CD biopsies treated with LYC-51194 ex vivo
ATPase Modulator LYC-51194 Selectively Induces Death of CCR9+ Gut-tropic T cells in PBMC from CD Patients
Conclusions

• ATPase Modulators are efficacious in several rodent models of IBD

• ATPase Modulators induce cell death in lamina propria T cells from CD subjects

• Taken together these data suggests that ATPase Modulator compounds may be a promising approach for treating IBD