SPERO THERAPEUTICS

SPR720: Novel Oral Therapy for Non-tuberculous Mycobacterial (NTM) Infections

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Non-Tuberculous Mycobacteria (NTM): A Rare Chronic Infectious Disease

Progressive lung disease

Infection caused by environmental pathogen

Common in COPD, bronchiectasis, asthma, and CF

Increasing Prevalence

50,000-100,000 patients in U.S. suffer from NTM

8% annual increase in prevalence predicted year-over-year in the U.S.

Significant Unmet Need

5-yr mortality rate of 35%

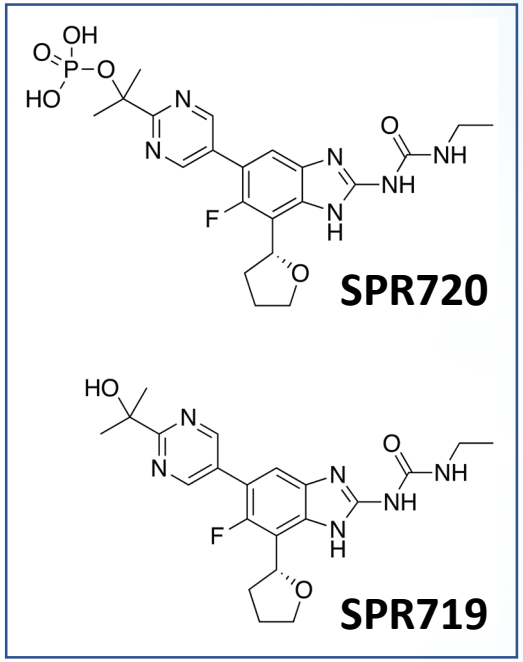
No currently approved oral agents for NTM

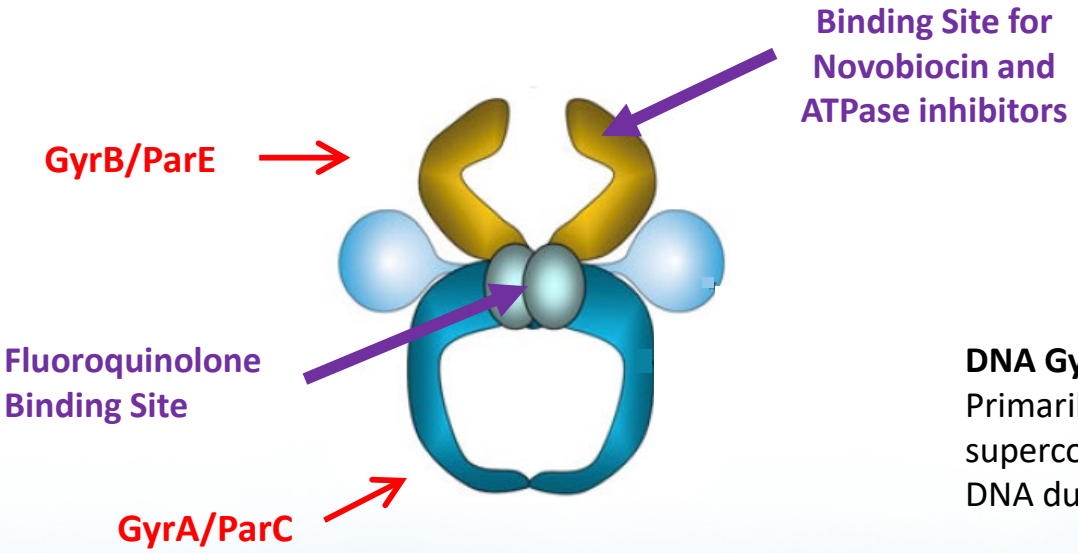
SOC has limited efficacy, high toxicity

- Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med.* **2012**; *185*(8): 881-886.
- Strollo SE, Adjemian J, Adjemian MK, Prevots DR. The burden of pulmonary nontuberculous mycobacterial disease in the United States. *Ann Am Thorac Soc.* **2015**; *12*(10): 1458-1464.
- NTMfacts.com

SPR720: Key Differentiating Factors

- **Novel chemical class**: aminobenzimidazole
  - SPR720 is phosphate prodrug of the active parent SPR719
- **Mechanism-of-Action**: Gyrase inhibitor, not a fluoroquinolone
  - Inhibits ATPase subunits in Gyrase (GyrB) and Topoisomerase IV (ParE)
  - Target in mycobacteria is GyrB
- **No cross-resistance** with marketed antibiotics





DNA Gyrase
Primarily responsible for introducing negative supercoils into conformationally constrained DNA during bacterial DNA replication

In vitro Activity Against a Range of NTM Species

NTM Species	N	SPR719 MIC_{50}	SPR719 MIC_{90}	MIC ranges: standard of care agents				
				AMK	CIP	CLR	MINO	FOX
M. abscessus subsp. *abscessus*	30	2	4	2 - 64	2 - >4	≤2 - >8	>16	16 - 64
M. abscessus subsp. *massiliense*	10	2	2	4 - 16	≥4	≤2	4 - >8	32 - 64
M. chelonae	10	4	4	16 - 32	2 - >4	≤2	≤1 - >8	>128
M. immunogenum	10	4	8	8 - 16	2 - 8	≤2	>8	>128
M. fortuitum group	10	0.25	1	≤1	≤0.12	≤0.06 - >16	≤1 - >8	32 - 64
M. avium complex	41	0.5	2	8 - >64	ND	0.25 - >64	ND	ND
M. simiae	10	1	2	8 - 32	4 - >16	8 - >64	ND	ND

Barbara Brown-Elliott at UT-Tyler, Texas, USA 2018; MIC values in µg/mL; ND = not determined

NTM Species	N	MIC_{50}	MIC_{90}	MBC
M. abscessus subsp. abscessus	29	2	8	>32 (static)
M. avium complex	12	1	2	>32 (static for *M. avium*)
M. kansasii	10	<0.03	0.06	<0.03

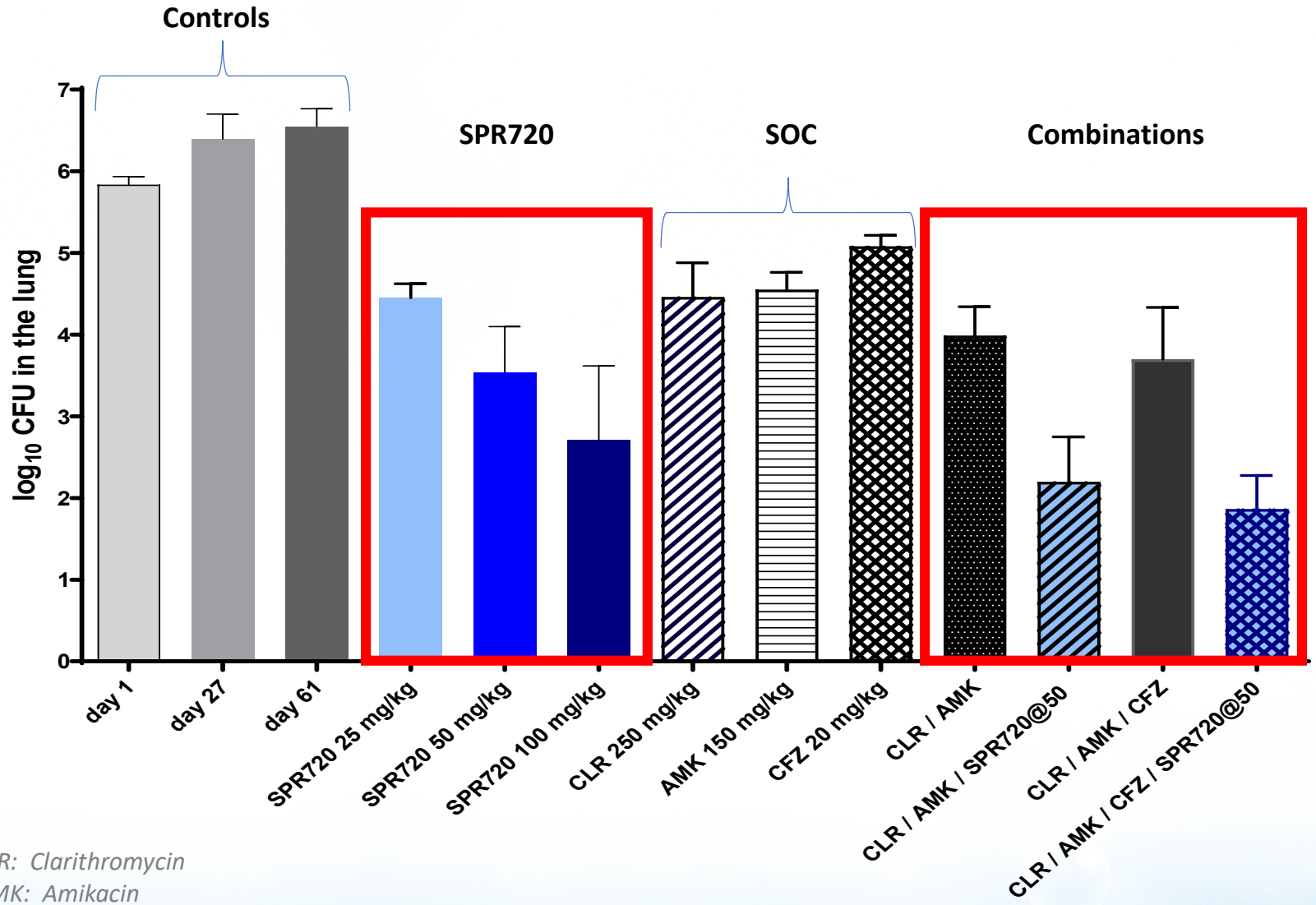
Jakko van Ingen at Radboud University, Nijmegen, Netherlands 2018; MIC/MBC values in µg/mL

AMK: Amikacin
CIP: Ciprofloxacin
CLR: Clarithromycin
MINO: Minocycline
FOX: Cefoxitin

**SPR719 is the active parent of SPR720 and is used for in vitro testing*

Brown-Elliott, B.A., *et. al*. *Antimicrob Agents Chemother*. **2018**; *62 (11)*: e01503-18.

SPR720: Effective as Monotherapy & Combination Therapy in *M. abscessus* Murine Model of Infection



- *M. abscessus* 1513
- SCID mice treated daily starting on day 28 for a total of 28 days (chronic model)

Test Article	MIC (μg/mL)
SPR719	1
Amikacin	2
Clarithromycin	>8

CLR: Clarithromycin
AMK: Amikacin
CFZ: Clofazimine

Data from the lab of Diane Ordway (CSU).

SPR720: Non-Clinical Data Supports Clinical Evaluation

- SPR720 converts rapidly to SPR719
- CYP inhibition IC_{50}s >40 μM; no time or concentration dependent inhibition

- *In vitro* safety assessments predict no major issues
- hERG IC_{50} > 30 μM; non-cytotoxic; non-genotoxic: *in silico*, Ames, chromosome aberration, *in vivo* micronucleus negative

- Repeat dose GLP 28-day rat and NHP toxicity studies completed
- Rat NOAEL = 100 mg/kg/day; NHP NOAEL = 300 mg/kg/day

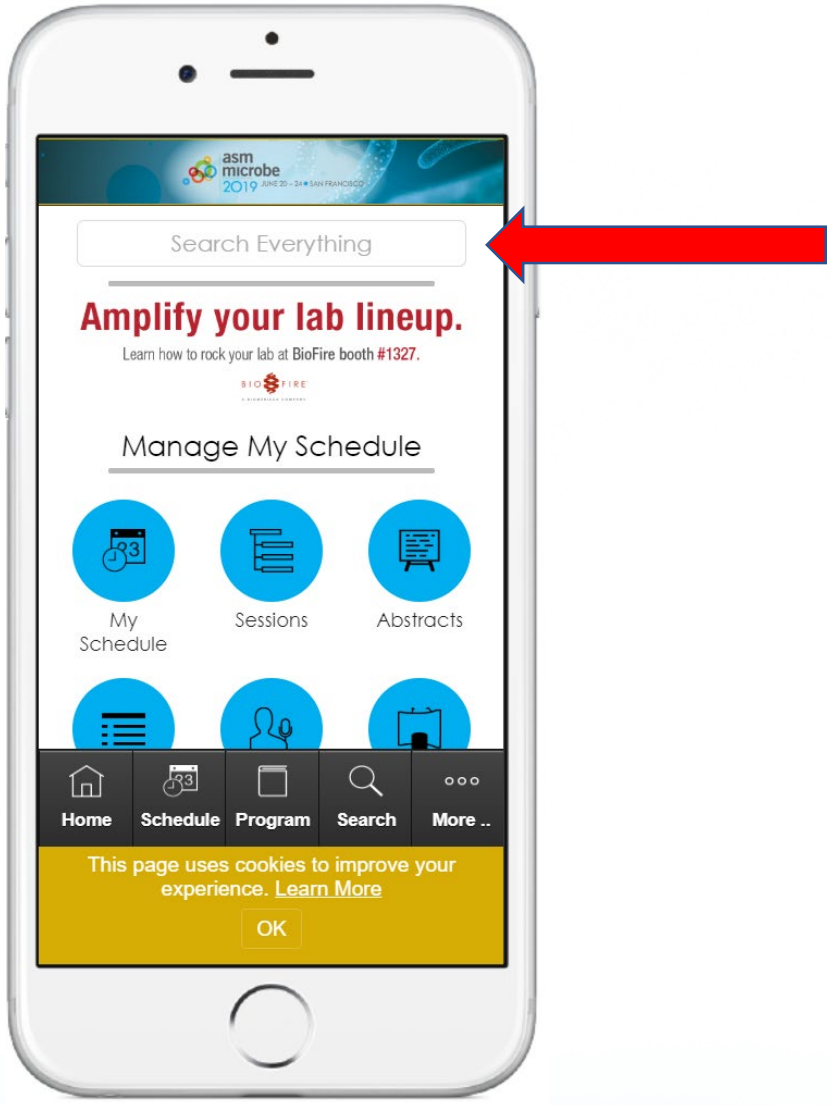
- Exposures at the NOAEL provide a therapeutic index relative to the efficacious exposure using *M. abscessus* murine models

SPR720-101: Phase 1 SAD/MAD Study (Ongoing)

A Two-part, Randomized, Double-blind, Placebo-controlled, Phase I Study of the Safety, Tolerability and Pharmacokinetics of SPR720 Following Administration of Single and Multiple Ascending Oral Doses in Healthy Volunteers

- Objectives: Safety, Tolerability, PK (including Food Effect), TQT
- Single Center (Simbec, UK)
- Healthy volunteers, male and female (non-childbearing): 18-55 yo
- 8 Single Ascending Dose (SAD) Cohorts including 1 Food Effect Cohort
- 3 Multiple Ascending Dose (MAD) Cohorts (7-days duration)
- 88 subjects (planned); 3:1 randomization (n = 8/cohort: 6 SPR720, 2 placebo)
- Continuous Holter monitoring incorporated for downstream TQT analysis

Learn more about the Spero pipeline



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