SPERO THERAPEUTICS

NTM Drug Development: An Industry Perspective

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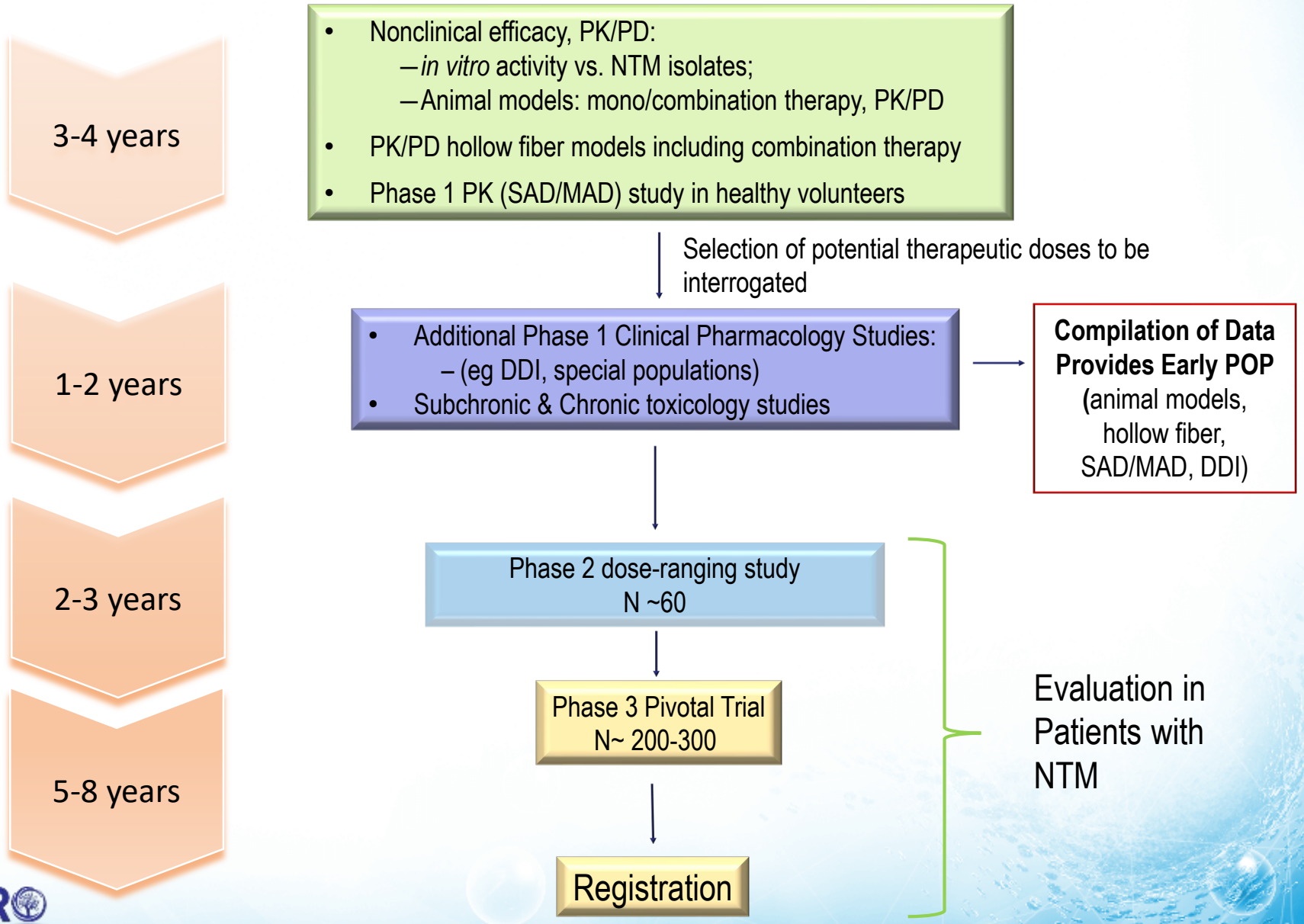
Conflict of Interest Disclosure

- Angela Talley is a full time employee of Spero Therapeutics, Inc.

Opportunity

- Multiple candidate agents in existing and novel classes
  - Gyrase inhibitors, macrolides, rifamycins, ethambutol, oxazolidinones, aminoglycosides, tetracyclines, BL-BLIs, others
- Increasing recognition of NTM as a chronic debilitating disease state
- Current SOC is inadequate, poorly tolerated
- Effective regimen(s) are urgently needed (can't wait 10 years)
- Unique opportunity to catalyze new development approach to get these agents to patients in need faster

Drug X: Clinical Development Path



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Drug X: NTM Clinical Development

- Current status/understanding:
  - The definitive efficacy endpoint(s) for NTM clinical trials are unclear
  - Sputum culture conversion as a surrogate endpoint may not be predictive of clinical benefit
  - Important to demonstrate a benefit to the patient via a clinically meaningful endpoint
  - Patient reported outcomes could be one method to evaluate clinical benefit, but the specific elements of the tool need to be defined
  - Need for placebo in order to understand safety

→ Development of clinical endpoints that reflect the early objectives of therapy may be more appropriate primary efficacy measures or part of a composite endpoint

Drug X Clinical Development: Key Questions

What are the objectives of treatment of pulmonary NTM?

Cure?	• Is durable microbiological response at 12, 18, 24 months an appropriate objective of therapy?
Symptomatic improvement on therapy?	Which symptoms? How to measure? • daily QoL: patient reported (PRO assessment tool) which one?, objective assessments • functional status: FEVI/ 6MWT, other objective assessment?
Improvement or delay of disease progression?	• Is the duration of progression-free survival as compared with SOC a reasonable endpoint? If so, what is the appropriate measurement?
What is the appropriate timing for assessment of response?	• Should the primary endpoint reflect the early objectives of treatment on or at completion of therapy rather than durable response?

Drug X Clinical Development: Key Questions

- **Whom should we study?**
  - Salvage therapy in treatment-refractory patients or treatment-naïve/inexperienced patients at the cusp of starting therapy?
  - Pulmonary MAC or Pulmonary NTM? Subtypes?
  - Are different populations appropriate for early (Phase 2) vs. pivotal trials?

- **Which endpoints are appropriate to assess benefit?**
  - What are the clinical outcome measures to assess "objective improvement of symptoms" (per consensus definition)?
  - Which outcomes (clinical or microbiologic) are most appropriate as a primary efficacy endpoint?
  - Are there population/patient-specific differences in endpoints?
  - How do we evaluate a new NME vs. a new regimen?

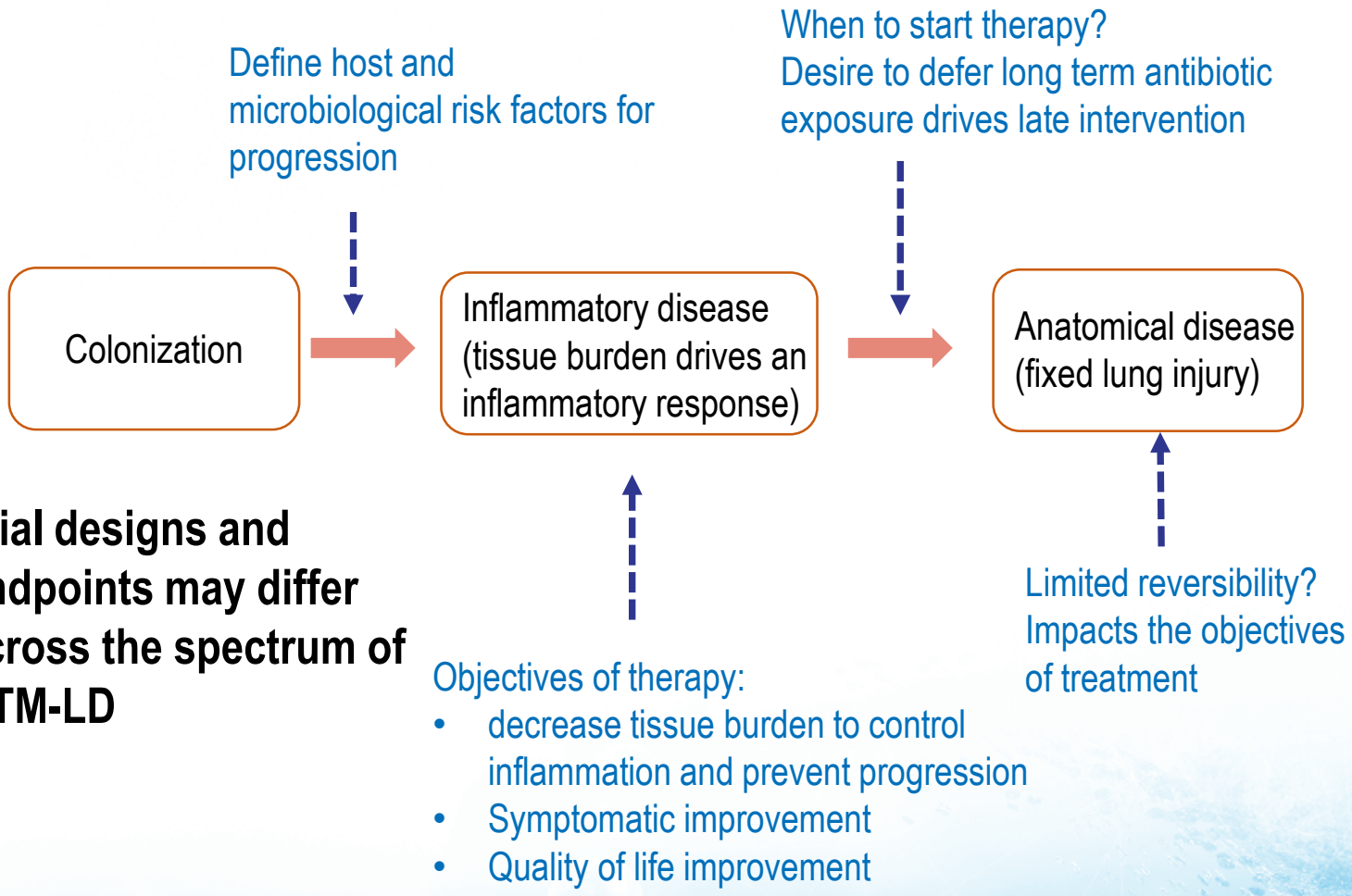
- **Timing/Feasibility:** What is minimum treatment duration for a specific clinical or micro endpoint (or population) at which we might detect a meaningful difference?

Drug X: Efficacy vs. Comparators

- How do you standardize a background regimen in a treatment-refractory population particularly in an early efficacy assessment?
- Is it appropriate to add a single agent to a potentially failing SOC regimen?
- In what settings is a monotherapy vs. placebo trial design appropriate?
- Given the recruitment and feasibility challenges, are there the opportunities for platform trial collaboration to increase efficiency?
- What lessons can we learn from the MDR-TB experience? From regimen-building in HIV? Oncology?

More questions than answers…

The heterogeneity in the patterns of disease and the response to therapy may reflect our limited understanding of the pathophysiology of NTM-LD



NTM Drug Development: Addressing Barriers and Challenges

- Better understanding of pathophysiology of NTM lung disease and factors associated with disease progression/treatment response
  - Collaboration to optimize the utility of existing data
- Better translation of preclinical data to clinically effective new combination regimens
  - Technology to identify promising compounds based on preclinical data (e.g. validation of hollow fiber)
  - Early identification of combination partners
- Feasible trial designs with earlier definitive primary endpoints
- Feasible development path for accelerated approval
- Development of validated Patient Reported Outcome measures
- Pathway for regimen-based development (MDR-TB parallels)