Investigator-Initiated Development of Nikkomycin Z The Lesson Learned

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FDA Valley Fever Workshop

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Impact: Polio vs Valley Fever

	Rates per 100,000	
	Polio (1955)	Coccidioides
Domain		
All Reported	18	20
Paralytic	1	
Disseminated		1

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Impact: Polio vs Valley Fever

	Rates per 100,000	
	Polio (1955)	Coccidioides
Domain	World (2.7 billion)	AZ & CA only (0.042 billion)
All Reported	18	20
Paralytic	1	
Disseminated		1

Galgiani, J. Infect. Dis., 2008

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Reframing Drug Development for Coccidioidomycosis

- Like polio, *Coccidioides* spp. is a biohazard, albeit only for an endemic population and its visitors.
- Where endemic, illness is anything but trivial.
- Economic impact is ~$1.5 Billion, justifying the development of better therapies or vaccines.
- However, the business models for developing Valley fever drugs (and vaccines) compete poorly against other investment opportunities.

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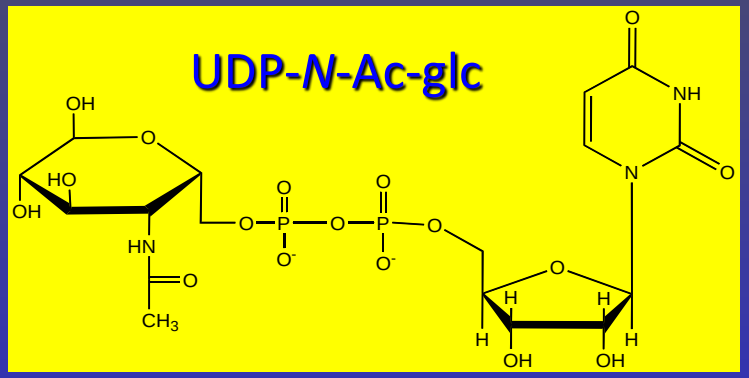
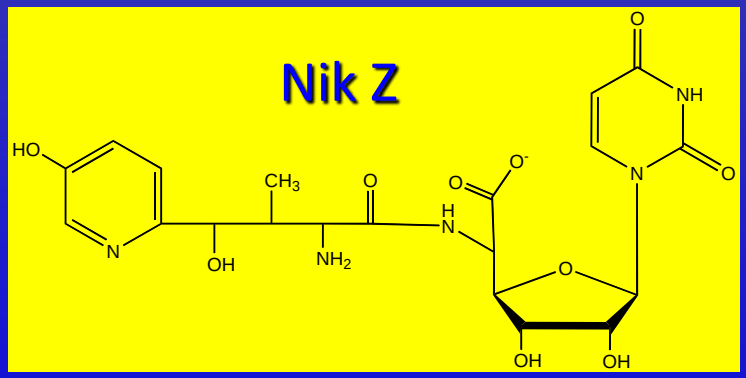
Nikkomycins resemble UDP-*N*-acetylglucosamine

- UDP-*N*-acetylglucosamine is a precursor to chitin
- Nikkomycin Z is a competitive inhibitor of chitin synthase





MIC of Diverse Fungi to NikZ

Organism	No. Strains	Geometric Mean MIC_{100} (μg/ml)
Coccidioides posadasii	1	0.0625
Blastomyces dermatitidis	10	0.25
Histoplasma capsulatum	9	2.47
Sporothrix schenkii	10	0.407
Candida albicans	59	5.56
Candida parapsilosis	10	4.29
Candida rugosa	1	7.8
Candida tropicalis	7	>500
Candida krusei	5	445
Candida lusitaniae	1	>500
Cryptococcus neoformans	30	144
Torulopsis glabrata	21	>500
Aspergillus flavus	2	500
Aspergillus fumigatus	2	500

Bayer, on file 1990

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Nikkomycin Z:
A Possible Cure for Valley Fever

New paradigm: Complications might be prevented by curing the infection with early treatment.

Infection remaining in lungs of mice treated with	# with Growth	# with no Growth
No Drug	8	0
or		
Nikkomycin Z	1	7

Hector et al, 1990

Nikkomycin Z

- 1970s: Discovered by Bayer
- 1980s: Cured mice with Valley Fever
- 1990s: Development started by Shaman Pharmaceuticals
  - Company went out of business in 2000
- Development stalled because it lacked a new pharmaceutical sponsor

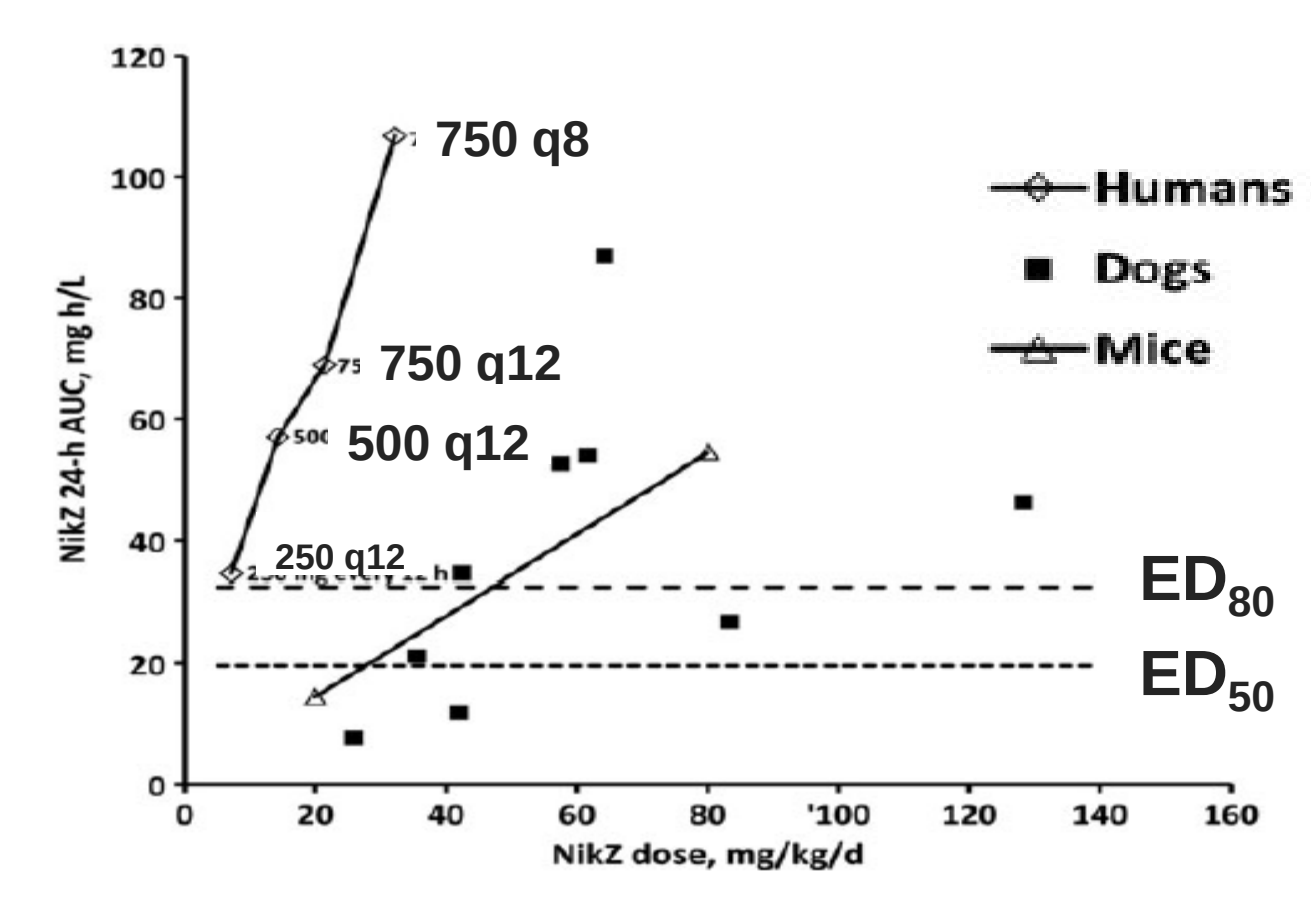
Until….

- Acquired by the University of Arizona in 2005

Milestones by U Arizona & Valley Fever Solutions

- 2006; Orphan Drug desig. (7 yrs excl.)
- 2007: IND reactivated; VFS incorporated
- 2014: Q.I.D.P. desig. (5 yrs excl.)
- 2015: Phase I 2-week (n=32 subjects)
- 2019: Pre-Phase II Type C meeting
- Ongoing: Improved manufacturing Process

AUC for Humans, Dogs & Mice with Mouse ED_{50} and ED_{80}



Shubitz et al 2014

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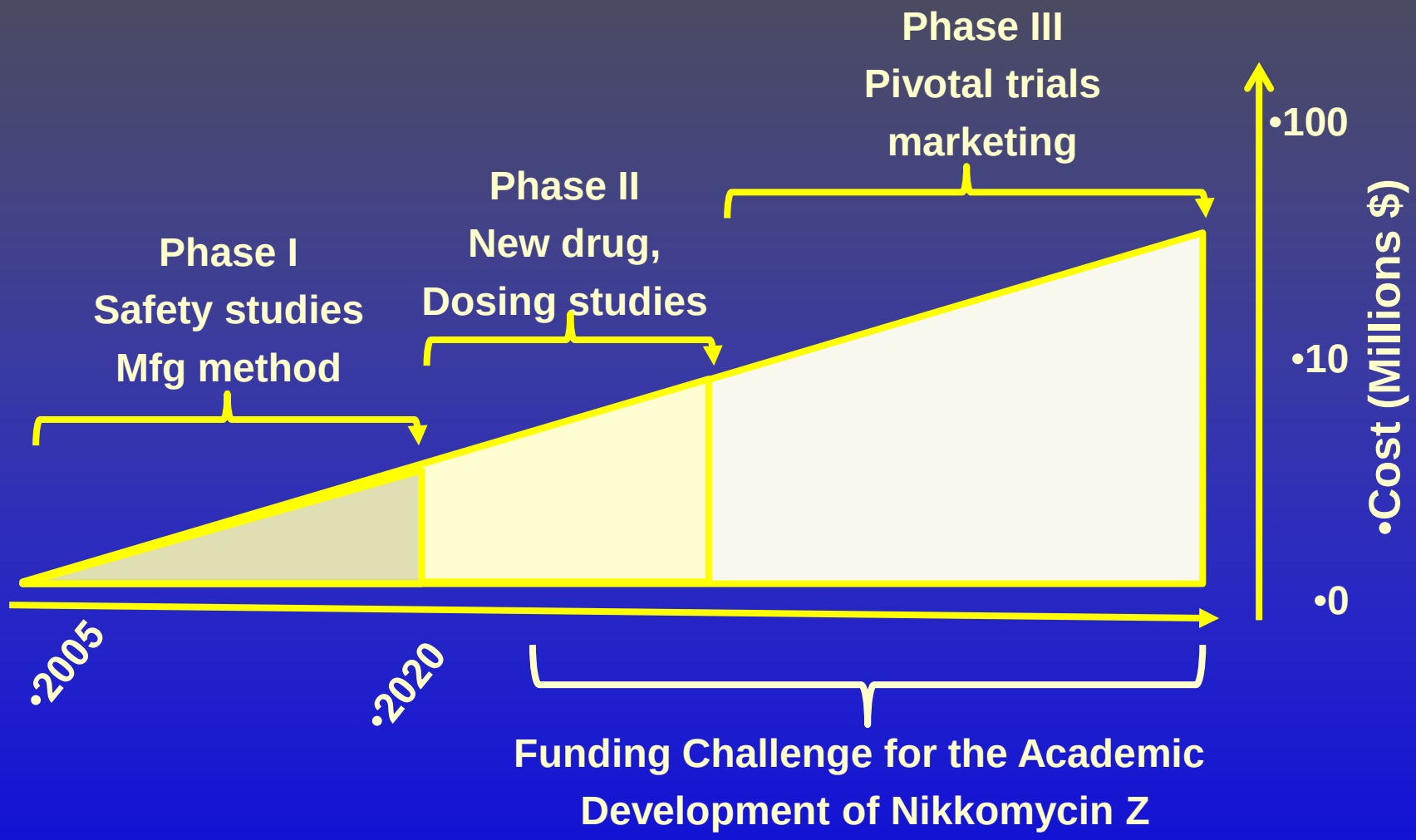
15 years - $12 million

	to	from	
NIH			
‘06 Planning	UA	NIH	$0.2 M
‘07 Analytic services	UA	NIH	~$0.4 M
‘08 Pre-clinical PK/PD	VFS	NIH	$0.9 M
‘09 Manufacturing	VFS	NIH	$3.0 M
‘13 Prod. Services	VFS	NIH	~$1.5 M
‘15 Manufacturing	VFS	NIH	$1.7 M
FDA			
‘07 Clinical trial	UA	FDA	$1.0 M
Philanthropic			
Tai Fnd; VFAF	UA		$3.5 M

NikZ Project cost/timeline



Summary

- Therapy for coccidioidomycosis is clearly an unmet need.
  - ~$1.5 Billion public health impact
- Nikkomycin Z
  - Novel mechanism of action.
  - Excellent pharmacologic profile.
  - Potentially curative.
- Development is limited only by finances.

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The Lesson Learned

- The business models for new Valley Fever therapies compete very poorly against other investment opportunities.
- Future paths forward likely will require a government response to the public health need.

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Federal Support of Valley Fever Therapies or Vaccines

- FDA: Tropical Medicine PRV program

  July: Declined inclusion of coccidioidomycosis because there is a “potential significant market” for a vaccine. **REALLY?**

- NIH: Support clinical trials.
  - SAnds-PPC study; Mycoses Study Group
- BARDA:
  - Expand CARB-X to include fungi. (?)

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Thank-you

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