Coccidioidomycosis (Valley Fever): Considerations for Development of Antifungal Drugs

Nikkomycin Z

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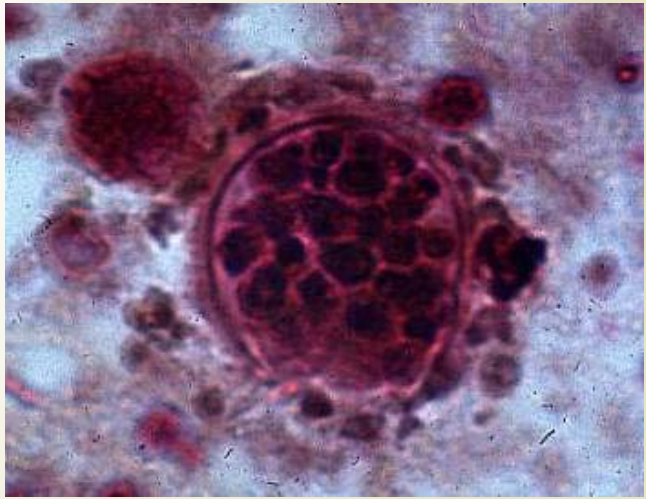
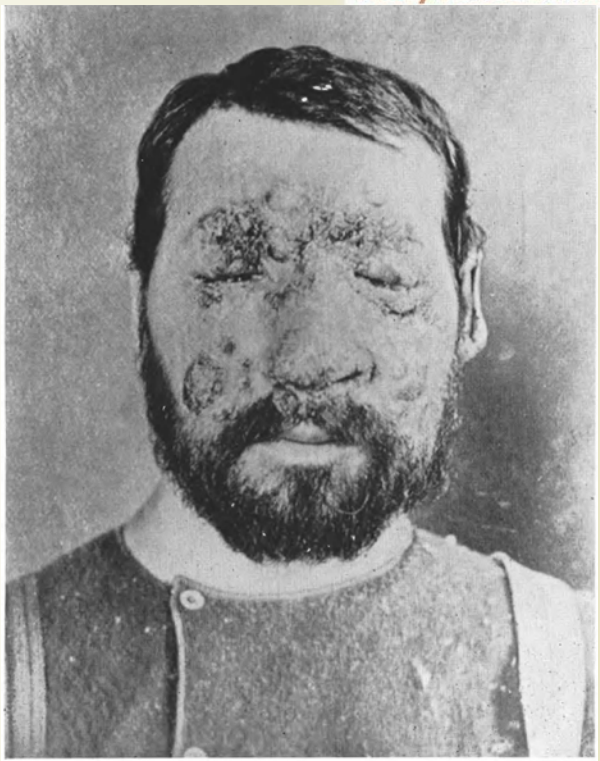
Disclosure: Employee and Shareholder of VFS



Early reported cases

First report: Posada, Argentina, ~1890

Joas Furtado Silverra, an ambitious young man of 33 years, came to the San Joaquin Valley from his home in the Azores in 1886. Within a year or so he noticed a tender spot on the back of his neck, where his collar rubbed the skin. Similar patches appeared on the forehead. Although he was able to work for several years, his fellow laborers were so afraid of his ugly skin lesion that he had to room by himself. In 1893, when his strength had long since failed, he entered the San Francisco City and County Hospital to remain until he died in January, 1895. Fungating skin lesions spread over most of his face and invaded the eyes, destroying his vision. The eruption was so sensitive that the slightest touch caused him to cry out in pain. Regional lymph nodes became swollen and fluctuant. Cough and purulent sputum increased. Rales filled the lungs. Abscesses appeared on the legs and in the testes. Despite frequent surgical



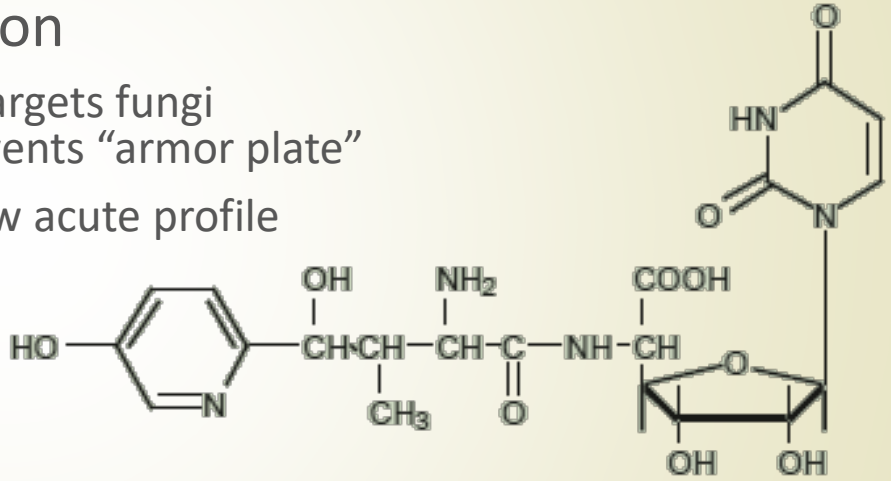
Frontispiece. Photograph of the face from the first known North American case of coccidioidomycosis. (From Rixford and Gilchrist, *Johns Hopkins Hospital Reports*, 1:209-268, 1896.)

Rixford, San Francisco, 1896

Nikkomycin Z (NikZ) - Novel Antifungal Fungicidal against Cocci

Valley Fever Solutions

- First in class, NCE (New Chemical Entity), novel Mechanism of Action
  - Novel Mechanism of Action targets fungi
    Blocks chitin-synthase – prevents "armor plate"
  - Strong safety profile helps new acute profile
  - Flexible formulation (oral, IV)



- Good preclinical results
  - Fungicidal in mouse,
    Acute resolution of disseminated disease
  - Positive results in several very sick pet dogs
  - More reports in preparation

Valley Fever Solutions

Fungicidal: cures new infection, (similar with flare-ups, growth)

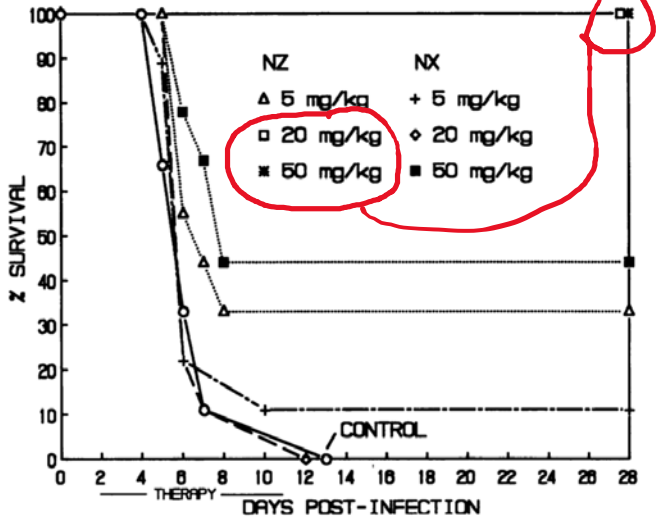


FIG. 2. Survival of mice with pulmonary coccidioidomycosis following intranasal infection with 9×10^3 CFU, comparing untreated controls with mice treated with NX and NZ at three dose levels given b.i.d. (5, 20, and 50 mg/kg). The period of therapy is indicated below the *x* axis.

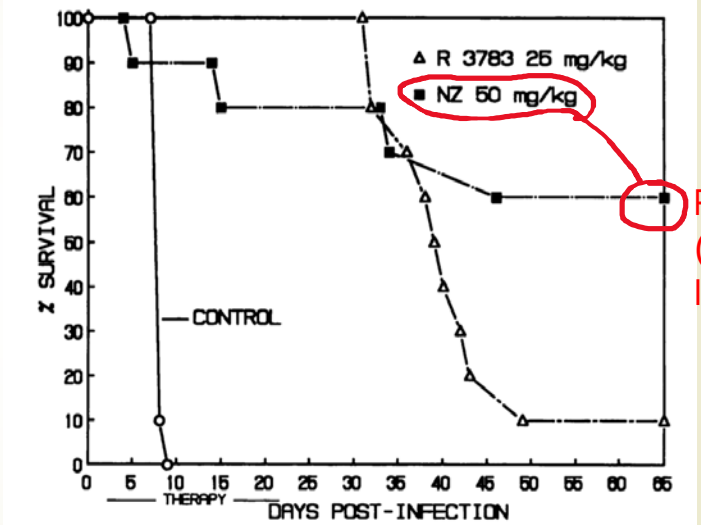


FIG. 3. Survival of mice with meningocerebral coccidioidomycosis infected intracranially with 90 CFU, comparing controls with mice treated with 50 mg of NZ per kg b.i.d. and 25 mg of R 3783 per kg q.d. The period of therapy is indicated below the *x* axis.

Fungicidal (low dose In this study)

Fungistatic

Brain (meningocerebral) very tough,
80% after 300 mg/kg BID (recent studies pending)

VFS_20_0805 FDA

Antimicrob Agents Chemother, 1990:34(4)587-593

Addresses established Disease Fungicidal

Relief of symptoms will be welcome
continuing relief will be apparent,
"Cure" is hard to prove – watch lack of relapse

Short Communications

Efficacy of Nikkomycin Z for respiratory coccidioidomycosis in naturally infected dogs

33% near resolution

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SOC: 3-6 months,
extend if needed
(years, even life)

This trial: NikZ:
2 month,
Limited drug

Nikkomycin Z (NikZ) is a chitin synthase inhibitor with antifungal efficacy against *Coccidioides* spp. and other endemic fungi. Dogs suffer a rate and range of natural coccidioidomycosis similar to humans and were considered an excellent model for initially testing NikZ against naturally acquired disease. Twelve dogs with coccidioidal pneumonia that had been present for an average of three months were treated with 250 mg (5–15 kg) or 500 mg (>15–30 kg) twice daily for 60 days. Nine dogs completed the course of treatment and seven dogs had improvement in disease based on radiographs, clinicopathological parameters, physical examination findings, and subjective assessment by owners; three dogs had resolution or near resolution of disease. Based on this small study, NikZ shows efficacy to treat naturally acquired coccidioidomycosis and merits further development for trials in humans.

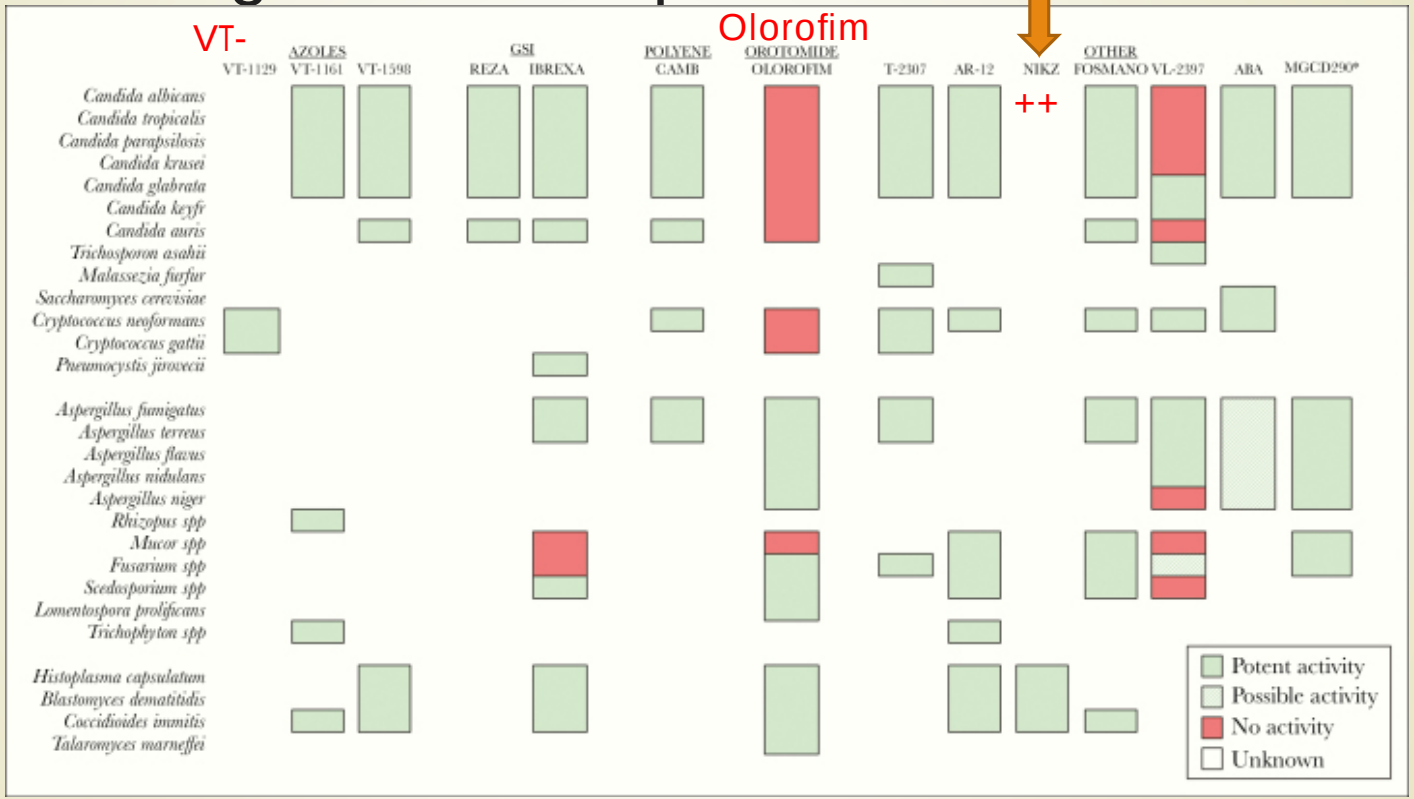
Medical Mycology, 2013, S1, 747-754

Valley Fever Solutions

Trial Strategy Considerations

- Target Indication (strategy around drug candidate choice)
  - Indication of interest (intractable, rare)
  - Trial Design opportunities (clinical, regulatory)
  - Superior endpoints? (such as biomarker)
  - Enrollment candidates
  - Impact against large indication is a benefit
- Drug Attributes
  - Safety (Side effects, DDI)
  - Tolerability (Mode – oral/IV, frequency, dosage format)
  - Drug supply limitations
    - Manufacturability, stability

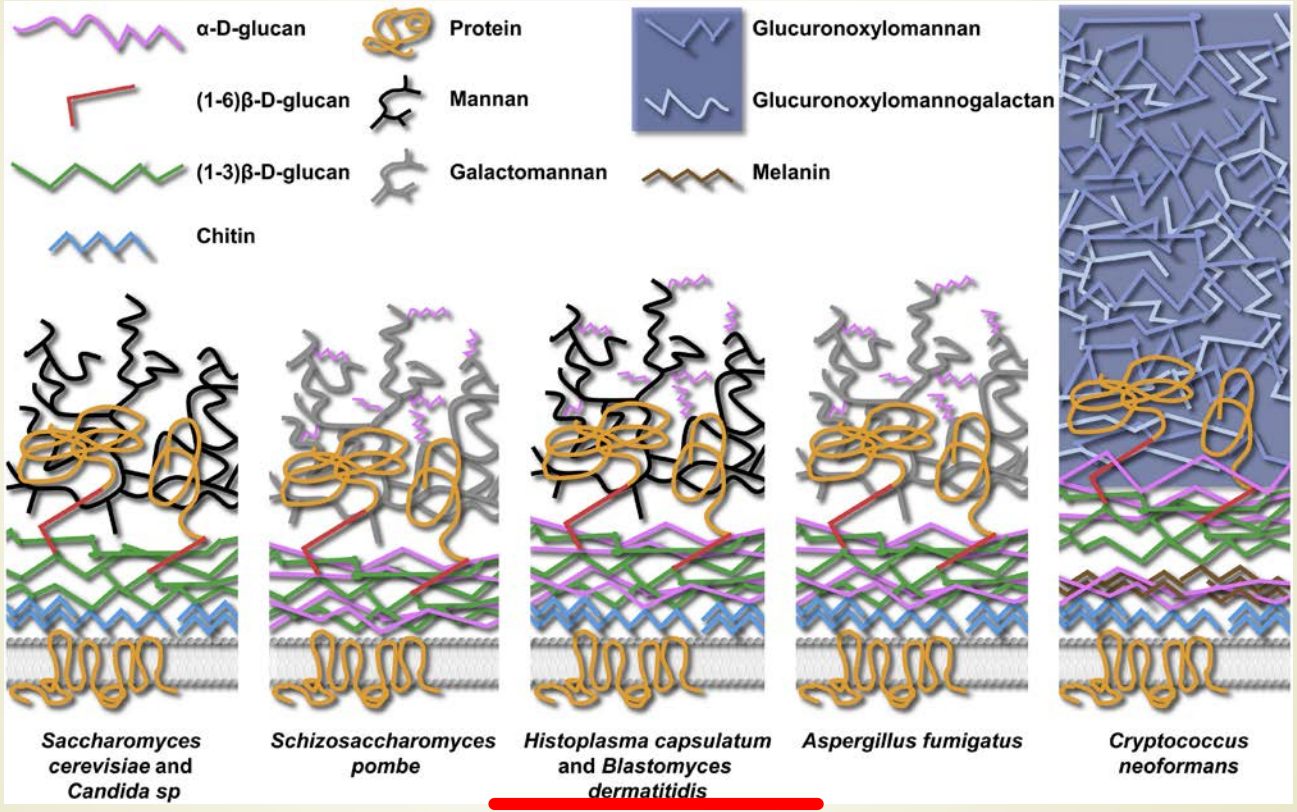
Drugs in Development



VFS_20_0805 FDA

Rauseo AM et al., Open Forum Infect. Dis., 2020:7(2):ofaa016

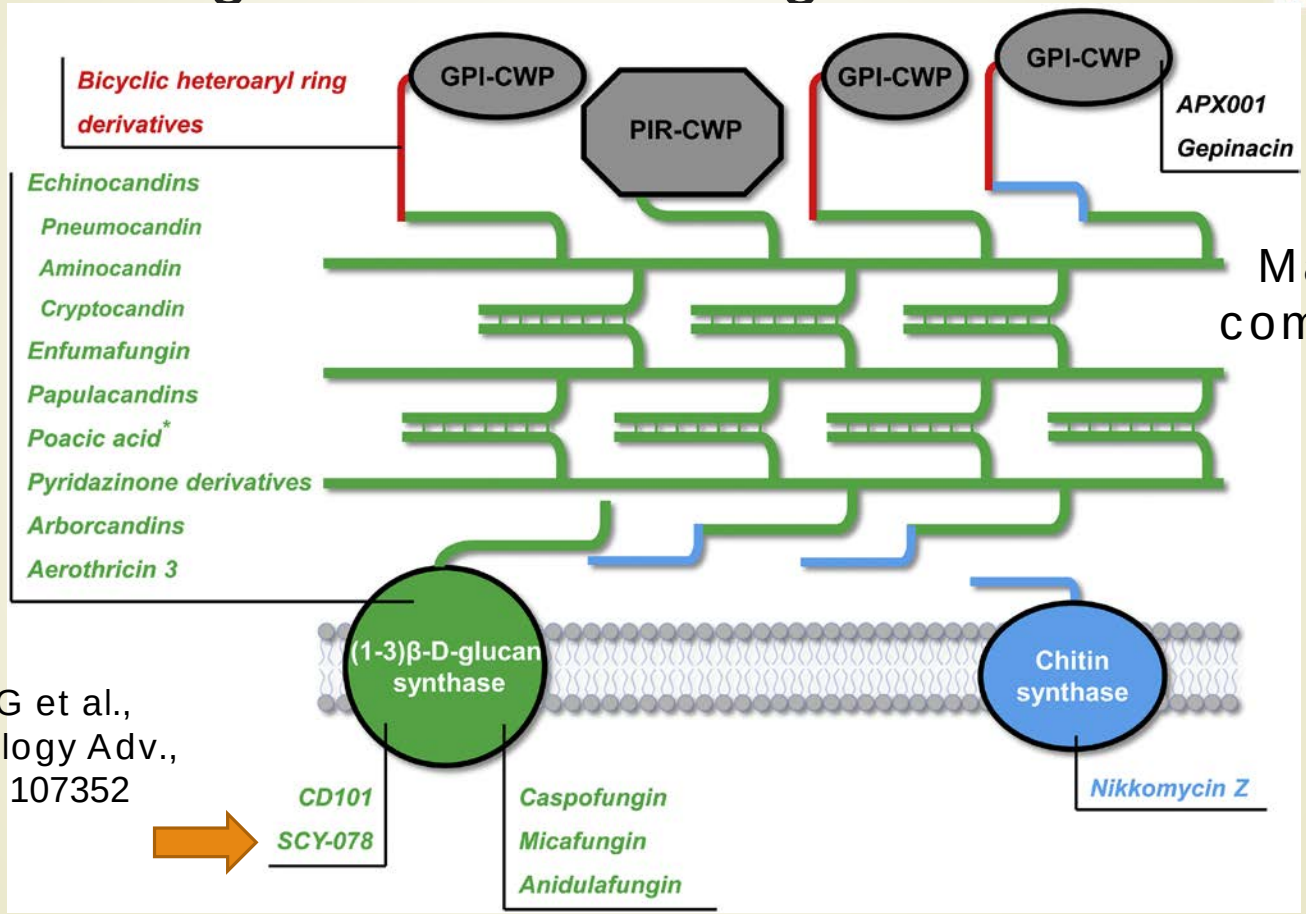
Fungal Cell Wall Components



VFS_20_0805 FDA

Cortés JCG et al., Biotechnology Adv., 2019:37(6) 107352

Fungal Cell Wall Drug Action



Many useful combinations

Inhibit chitin synthase

NikZ

Cortés JCG et al., Biotechnology Adv., 2019:37(6) 107352

Market / Business Considerations

- Business motivation
  - 3T's: Team, Technology, Target (addressable market)
    - Team can be reinforced/replaced
    - Technology (drug) may have formulation opportunities (AmB)
    - Target has to be credible and attractive to investor
  - Market size, time to revenue, duration of revenue
  - Competing / alternative opportunities

Anti-infectives Success Rates

Phase 1>2
69.5% (18%)
Phase 2>3
42.7% (26%)
Phase 3>NDA
72.7% (60%)
NDA > Approve
88.7% (89%)

Step (all)

Clinical Development Success Rates 2006-2015 – BIO, Biomedtracker, Amplion 2016

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%

Likelihood of Approval	Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Hematology	283	26.1%	197	35.7%	114	63.0%	50	84.0%
Infectious disease	916	19.1%	569	27.5%	283	64.5%	133	88.7%
Ophthalmology	267	17.1%	201	20.1%	100	45.2%	40	77.5%
Other	301	16.3%	205	24.4%	89	61.5%	43	88.4%
Metabolic	241	15.3%	146	25.1%	62	55.6%	27	77.8%
Gastroenterology*	156	15.1%	115	20.0%	59	55.9%	26	92.3%
Allergy	107	14.7%	70	21.8%	30	67.0%	16	93.8%
Endocrine	791	13.2%	492	22.4%	250	55.9%	107	86.0%
Respiratory	428	12.8%	278	19.6%	82	67.3%	37	94.6%
Urology	108	11.4%	87	20.0%	35	61.2%	14	85.7%
Autoimmune	837	11.1%	540	17.0%	221	53.5%	86	86.0%
All Indications	9985	9.6%	6403	15.3%	2541	49.6%	1050	85.3%
Neurology	1304	8.4%	842	14.2%	377	47.8%	161	83.2%
Cardiovascular	632	6.6%	423	11.2%	186	46.7%	76	84.2%
Psychiatry	451	6.2%	297	11.6%	128	49.0%	58	87.9%
Oncology	3163	5.1%	1941	8.1%	525	33.0%	176	82.4%

Rare Disease Success Rates

(Anti-Infectives)
Phase 1>2
69.5% (18%)
Phase 2>3
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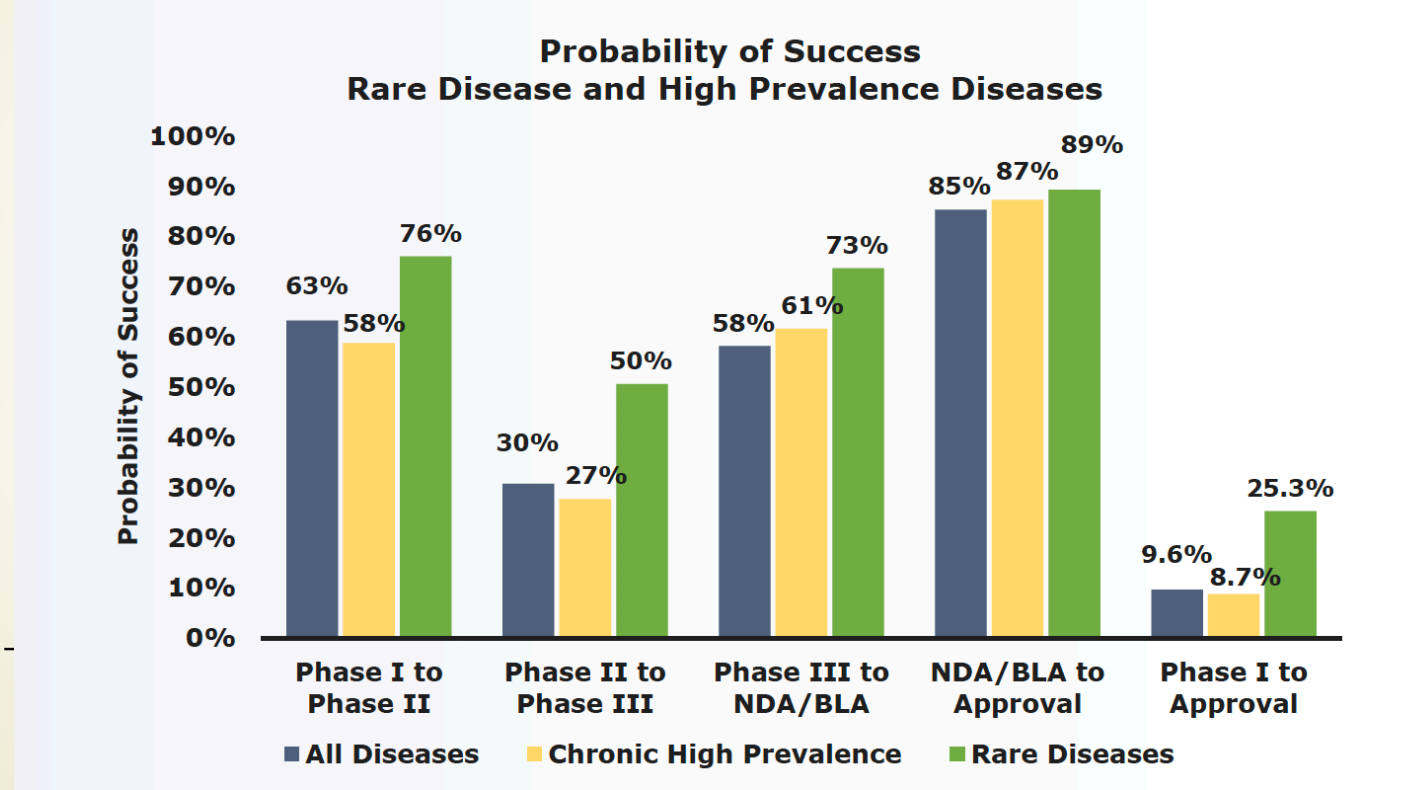
Clinical Development Success Rates 2006-2015 - BIO, Biomedtracker, Amplion 2016



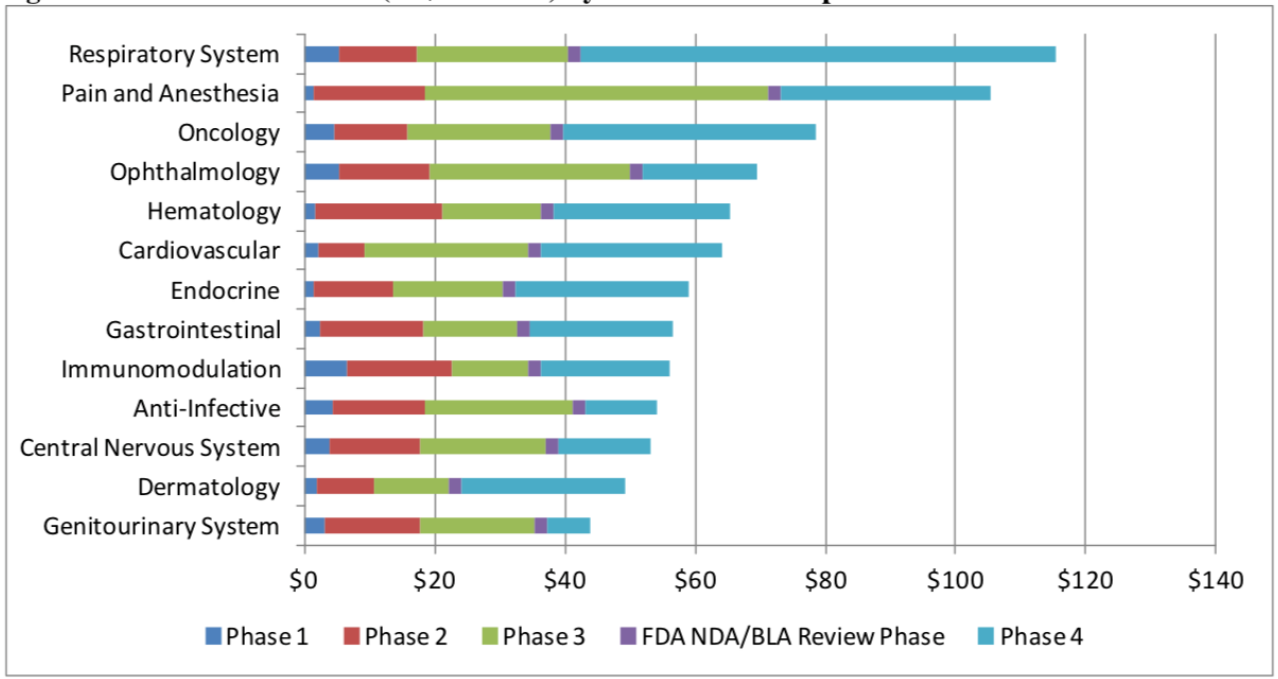
Valley Fever Solutions

Development Costs

- Capitalized cost $1.3-1.8 B ($2.3B, $5.5B for large pharma, Phase IV)
- Out of Pocket costs $870 M ($350M for single drug company) (Tufts, see Wikipedia)

EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT
ERG, July 25, 2014

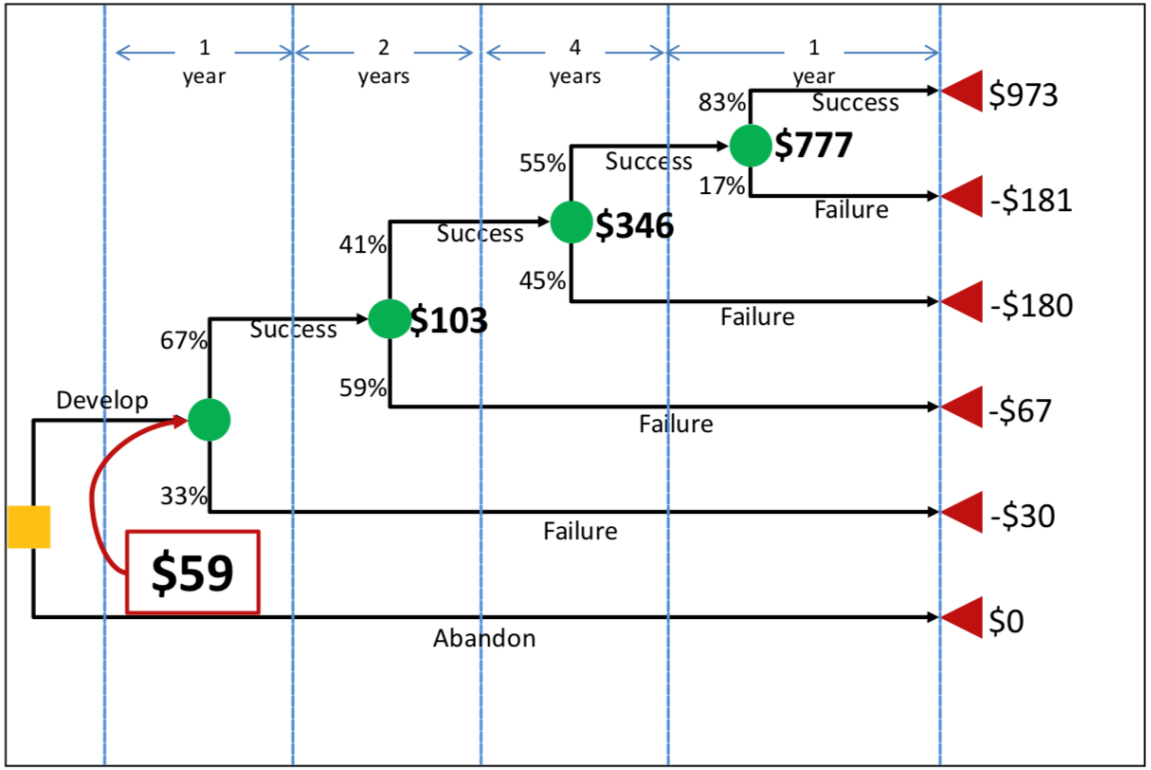
Figure 3: Clinical Trial Costs (in $ Millions) by Phase and Therapeutic Area



Years of High Risk, expense

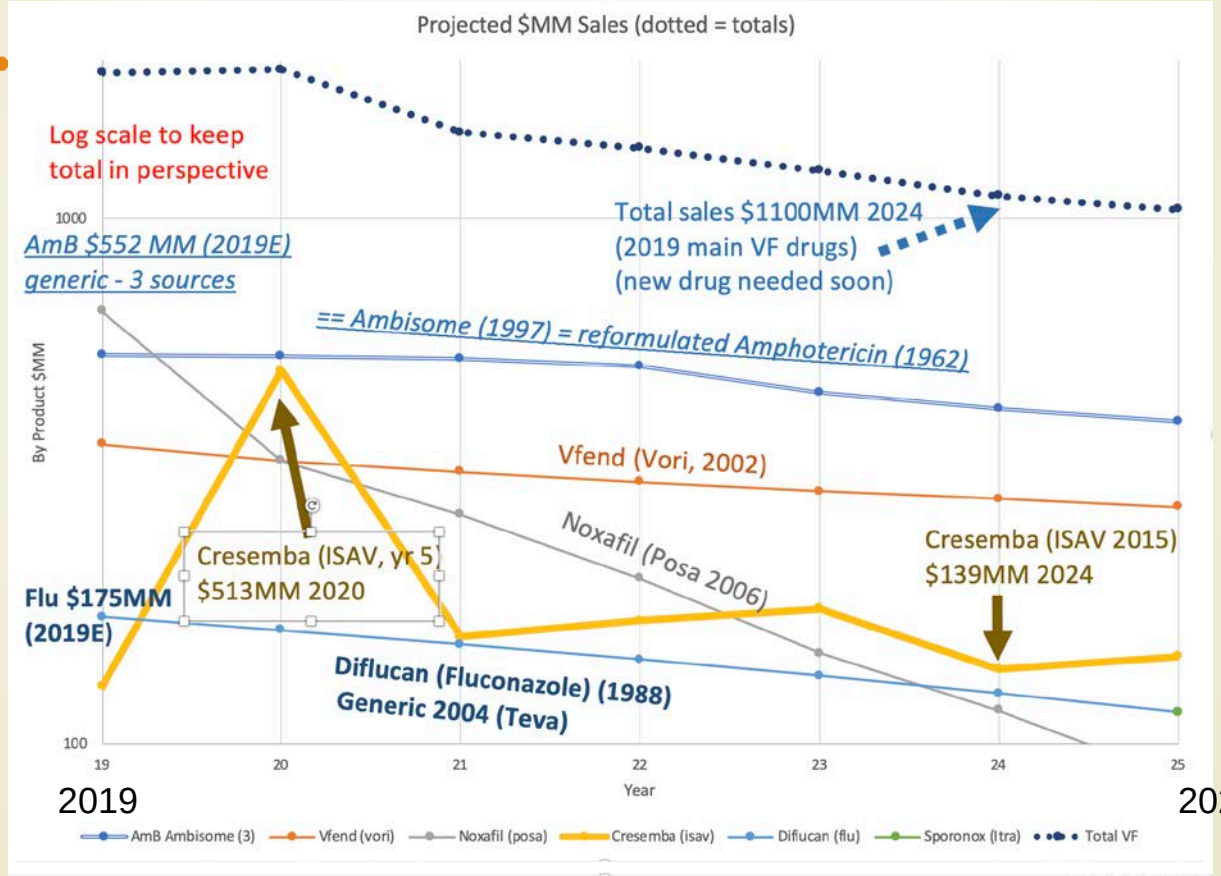
EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT
ERG, July 25, 2014

Figure 2: Drug Development Decision Tree Depicting Net Present Value (NPV) of Returns at Each Node

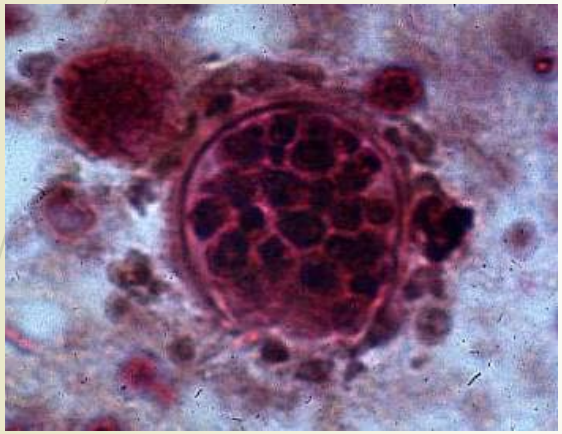


Valley Fever Solutions

2019E: New drugs: $500-800K in 5 year peak
Main drugs used for VF: $1.8B (to $2.8B)



Thank You!
Valley Fever Solutions: Nikkomycin-Z



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