Valley Fever Center for Excellence
University of Arizona

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Δcps1 Live, Attenuated Coccidioidomycosis Vaccine

Development Pathway Of A Live, Attenuated Vaccine Against Cocci: From Dogs To People

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A Human Cocci Vaccine is Feasible

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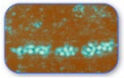
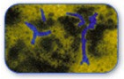
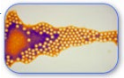
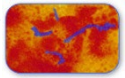
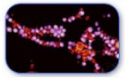
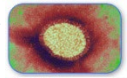
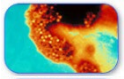
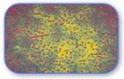
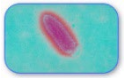
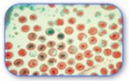
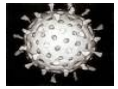
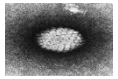
- Natural infection protective against subsequent disease demonstrating that protective immunization is feasible
- Canine vaccine in advanced development by Anivive Lifesciences (Long Beach, CA); favorable expectation of commercial success
- The same vaccine is likely to be safe and effective for humans
- Funding and policy rather than technical risk for human vaccine remains the principal challenge

Δcps1 Vaccine Candidate

- Developed by University of Arizona (Galgiani and colleagues)
- Genetically engineered *C. posadacii*, with deletion of *cps1*, a virulence factor, critical for spherulation and propagation in the parasitic phase
- Multiple antigens expressed, mimicking natural infection

Approved Vaccines Against ~30 Human Diseases

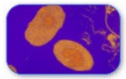
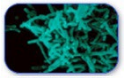
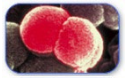
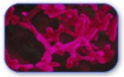
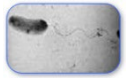
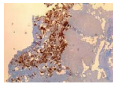
Viral diseases

- ★  Yellow fever
- ★  Mumps
- ★  Poliomyelitis
- ★  Measles
- ★  Rubella
- ★  Influenza
-  Hepatitis A
-  Hepatitis B
-  Rabies
- ★  Japanese encephalitis
- ★  Chickenpox/Zoster
- ★  Rotavirus
-  HPV
- ★  Dengue

- ★  Smallpox (new)
- ★  Ebola
-  Covid-19

★ **Live, attenuated**

Bacterial diseases

-  Pertussis
-  Diphtheria
-  *Haemophilus influenzae* type b
-  Meningococcal meningitis
-  Pneumococcal infections
-  Tetanus
- ★  Tuberculosis
- ★  Typhoid fever
- ★  Cholera
-  Q fever
-  Anthrax

Preclinical Efficacy of *Δcps1*

- 100% survival and reduced fungal burden mouse models[1,2]
- Significant protection in mice with deficiencies in Stat4, Stat3, Ifngr1, Dectin-1 associated with DCM in humans[3]
- Significant reduction in clinical score and fungal burden in dogs[4]
- Adoptive transfer studies indicate immunity dependent on CD4+ T cells and not antibody

1. Narra HP et al Infect Immun 2016;84:3007-16
2. Shibitz LF et al Vaccine 2018;36:3375
3. Powell DA et al. Front Cell Infect Microbiol 2022;11:790488
4. Shubitz LF et al Vaccine 2021;39:6894-6901

Challenges to development of a human Cocci vaccine

Challenge	Risk	Comment
Manufacturing	Low	Spore-former, limited no. CDMOs; downstream purification process required; scale-up; analytical and process validation
Preclinical	Low	Biodistribution and persistence
Immunological marker of protection	*Mod*	*T cell assays, variability of response, antigen for restimulation*
Clinical	Mod	First live eukaryote vaccine, may require larger safety data base; local reactogenicity;
Regulatory	Mod	Traditional pathway
Policy	Mod	Need permissive ACIP recommendation, supportive pharmacoeconomic data

Manufacturing: Arranta Bio

Watertown, MA

- 80,000 ft² (7,432m²) GMP clinical & commercial ready facility operational since Oct 2020
- 13 GMP suites; $120M capital invested
- Process, analytical & formulation development & GMP:
  - Live biotherapeutic products
  - Plasmid DNA
  - mRNA (DS, LNP & DP)
- ~175 employees

Boxborough, MA

- 300,000 ft² (28,000m²) + ability to increase 20k ft² (1,860 m²)
- 8 cGMP suites available with another 4 cGMP suites coming 2023
- LBP, mRNA & oncolytic vaccine platforms with commercial expansion & dedicated capacity available
- Sterile fill and finish capabilities
- Drug substance & Drug Product
- Going to 250 fully staffed

- >150 species aerobic, anaerobic, spore-forming bacteria, fungi
- Process, analytical development, manufacturing
- CTM-> commercial scale

Manufacturing Highpoints

- Major elements of GMP manufacturing and analytics already addressed for dog vaccine
- No terminal sterilization-- aseptic processing required
- For human vaccine
  - Conversion to liquid media, closed system (preferred)
  - Additional downstream purification (chromatographic or TFF) step(s)
  - Stable, liquid frozen drug product
  - Development approach discussed with CDMO and no difficulties envisioned

IND Enabling Nonclinical Studies

- Biodistribution and persistence (probably NHPs)
- Repeated dose GLP toxicology CD-1 or Balb/c mouse (with fungal burden lung, liver, spleen, inoculation site)
- Meningitis in rabbits following intracisternal inoculation or in mice following IC inoculation

Phase 1 Clinical Trial Design (N=65)

Safety, preliminary immunogenicity (cocci seronegative)
Randomized, double-blind, placebo-controlled
Ascending dose response, SC vs. IM
1-2 sites
6 mo. Follow-up

1 year

Group	N	Vaccine	Dose (cfu)	Route	Schedule
1	10	Δcps1	3,000	SC	Day 1, 29
2	10	Δcps1	10,000	SC	Day 1, 29
3	10	Δcps1	30,000	SC	Day 1, 29
4	10	Δcps1	100,000	SC	Day 1, 29
5	10	Placebo (0.9% saline)	--	SC	Day 1, 29
6	10	Δcps1	TBD*	IM	Day 1, 29
7	5	Placebo (0.9% saline)	--	IM	Day 1, 29

* Highest tolerated and immunogenic dose, Groups 1-5

Phase 2 Clinical Trial Design (N=500)

- Expanded safety and immunogenicity (cocci seropos. and seroneg.)
- Substantial N for safety to warrant Phase 3
- Randomized, double-blind, placebo-controlled 4:1 ratio
- Dose confirmation, T cell assay endpoints
- 12 mo. follow-up
- 4 sites, CA/AZ

1.5 years

Group	N	Cocci sero	Vaccine	Dose (cfu)*	Route*	Schedule
1	100	Neg	Δcps1	Low	SC or IM	Day 1, 29
2	100	Neg	Δcps1	High	SC or IM	Day 1, 29
3	100	Pos	Δcps1	Low	SC or IM	Day 1, 29
4	100	Pos	Δcps1	High	SC or IM	Day 1, 29
5	50	Neg	Placebo (0.9% saline)	--	SC or IM	Day 1, 29
6	50	Pos	Placebo (0.9% saline)	--	SC or IM	Day 1, 29

* Determined from Phase 1

Regulatory Pathway

Food and Drug Administration (FDA)

- *Traditional approval pathway:* Direct demonstration of efficacy/effectiveness
  - Randomized, controlled trial(s)
- *Accelerated approval pathway:* Bridging human immune responses to immune responses demonstrated to be protective in animals, with effectiveness demonstrated post-licensure
- *Animal rule:* When it is not feasible to establish an immunologic bridge between animals and humans or practically or ethically possible to directly demonstrate clinical benefit in human subjects.

Regulatory Considerations for Pivotal Trials

- Efficiency in collecting clinical data
- Diagnostic precision
- Regulatory requirement for more than 1 trial
  - Unless 1 trial shows very strong evidence, e.g. high lower bound of 95% CI (e.g. COVID vaccine LB requirement of >30%)
  - Sample size feasibility of single study with high LB?
- Eliminate skin test positives to focus on susceptibles
  - Regulatory concern about bias
  - Dogma that no second infections occur supportable?
- Special populations at highest risk
  - Ethnicity, immunocompromised

Is disease incidence sufficiently defined?

	Cases/1000 py	ref
California high incidence counties (Kern, Fresno, Kings, Madera, Tulare)	1.8	1
Military population, San Joaquin Valley	0.6	2
Arizona statewide incidence of lab confirmed	1	3
Metro Phoenix, reported cases, 2007	1-3	4
Maricopa Co., Arizona, 2001	1.6	5
Phase 3 trial, inactivated vaccine	1.7	6

1. Cooksey GLS et al. MMWR 2020;69:1817
2. Ellis GC et al. Emerg Infect Dis 2022;28:1842
3. Tsang CA et al. Emerg Infect Dis 2010;16:1738
4. Centers for Disease Control (unpublished)
5. CDC, MMWR 2003;52:109
6. Pappagianis D Am Rev Rspir Dis 1993;148:656

Phase 3 Clinical Trial Design (N=716) Very high-risk population

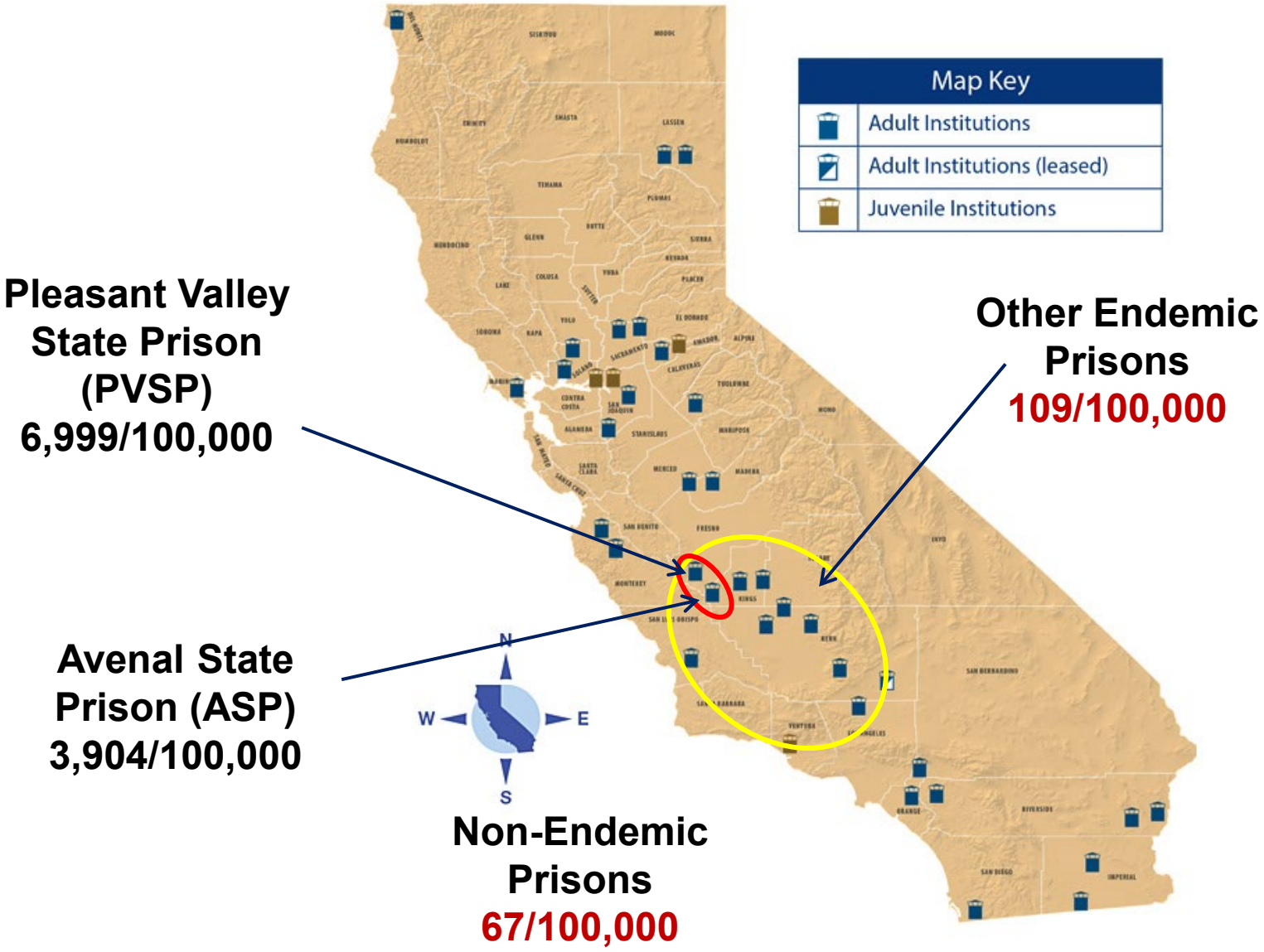
- Objective: efficacy signal
- High risk population, California State Prisons
- Skin test negative selection
- Assumed incidence 4%
- 80% efficacy, α=.05, β=80%
- Randomized, double-blind, placebo-controlled 1:1 ratio
- 12 mo. follow-up
- 2 sites California State Prisons

1.5 years

Group	N	Cocci sero	Vaccine	Dose (cfu)*	Route*	Schedule
1	358	Neg	Δcps1	TBD	SC or IM	Day 1, 29
1	358	Pos	Placebo (0.9% saline)	--	SC or IM	Day 1, 29

* Determined from Phase 1

Cocci Cases per 100,000 Inmates in Endemic Prisons, 2011



Wheeler C et al. Emerg Infect Dis 2015;21:70

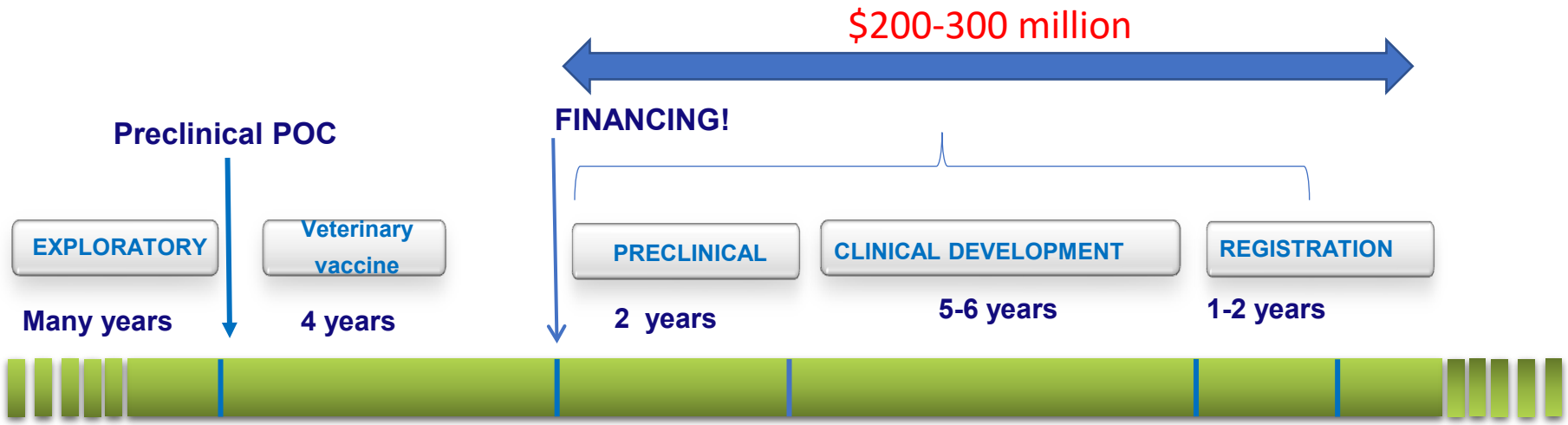
Phase 3 Clinical Trial Design (N=5,866) General population

- Pivotal safety, efficacy (cocci skin test neg)
- Randomized, double-blind, placebo-controlled (parallel)
- Lot consistency
- Multiple sites, selected for high incidence CA/AZ
- Skin test negative selection
- Assumed attack rate 0.25%/year over 2 years
- 80% Power to detect VE 70% ($p<0.05$)

2 years

Group	N	Vaccine	Lot	Dose (cfu)	Route	Schedule
1	2933	Δcps1	A, B, C (n= ~ 1000/lot)	TBD	SC or IM	Day 1, 29
3	2933	Placebo (0.9% saline)		--	SC or IM	Day 1, 29

Δcps1 Vaccine Development



- ΔCps1 vaccine candidate
- Characterization
- Animal model

- Process development
- Vaccine production
- Characterization
- Assay development
- Dog model validation
- Safety, efficacy

- Contracts w/ CDMOs
- Process development
- Vaccine production
- Characterization
- Assay validation
- Toxicology, biodistribution
- Human T cell Immunol assays
- Pre-IND

- IND
- Phase 1-3 trials
- Mfg scale up, validation
- Pediatric plan

- BLA
- Launch inventory
- Pre-approval site inspection

Univ Arizona

Anivive

Dog efficacy data are IND-enabling

USDA registration

Crozet

Conclusions

- *The time has come to address a neglected infectious disease and public health problem in the world's richest economy*
- Live, attenuated, self-adjuvanting vaccine most likely to elicit immune responses resembling natural infection
- Relatively low technical risk, mitigated by dog vaccine
- CMC and clinical development pathway feasible
- Small, regional but potentially profitable market
- Public funding and incentives required (e.g. Priority Review Voucher*)
- Private investments are expected to follow with the advance of clinical development

*The US FDA **Priority Review Voucher** program grants a voucher for priority review to a drug developer as an economic incentive to develop treatments for disease indications with limited profitability.