Leishmaniasis: Challenges for Vaccine Development

Steven G. Reed

Infectious Disease Research Institute

Seattle

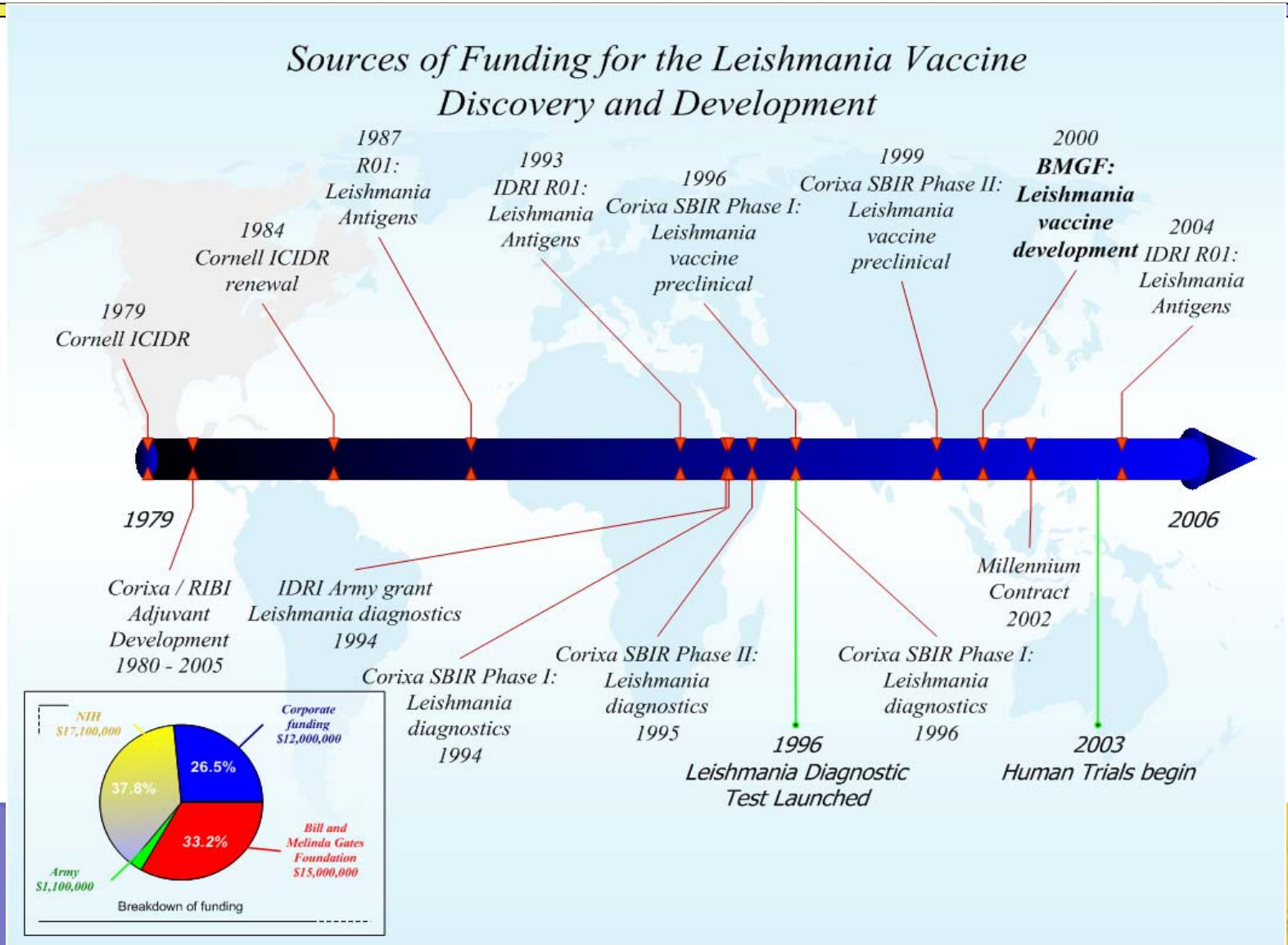
IDRI Goals: Leishmaniasis

- To improve existing vaccines for use in therapy and prevention.
  - Antigen Discovery
  - Vaccine Development
  - Manufacturing Process
  - Clinical Testing
- To improve existing diagnostics for VL and PKDL and develop a test(s) to demonstrate cure

Challenges to Leishmania Vaccine Development

- **PROBLEM: How to finance?**
  - Making a vaccine requires industry–type effort, But
  - Activity generally carried out in academic organizations
  - Solution requires creative leveraging of public/private funds
- **IDRI Solution:** Create PPP, including "Non-Profit Biotech" collaborating with industry

Funding Development of a Leishmaniasis Vaccine



Challenges to Leishmania Vaccine Development

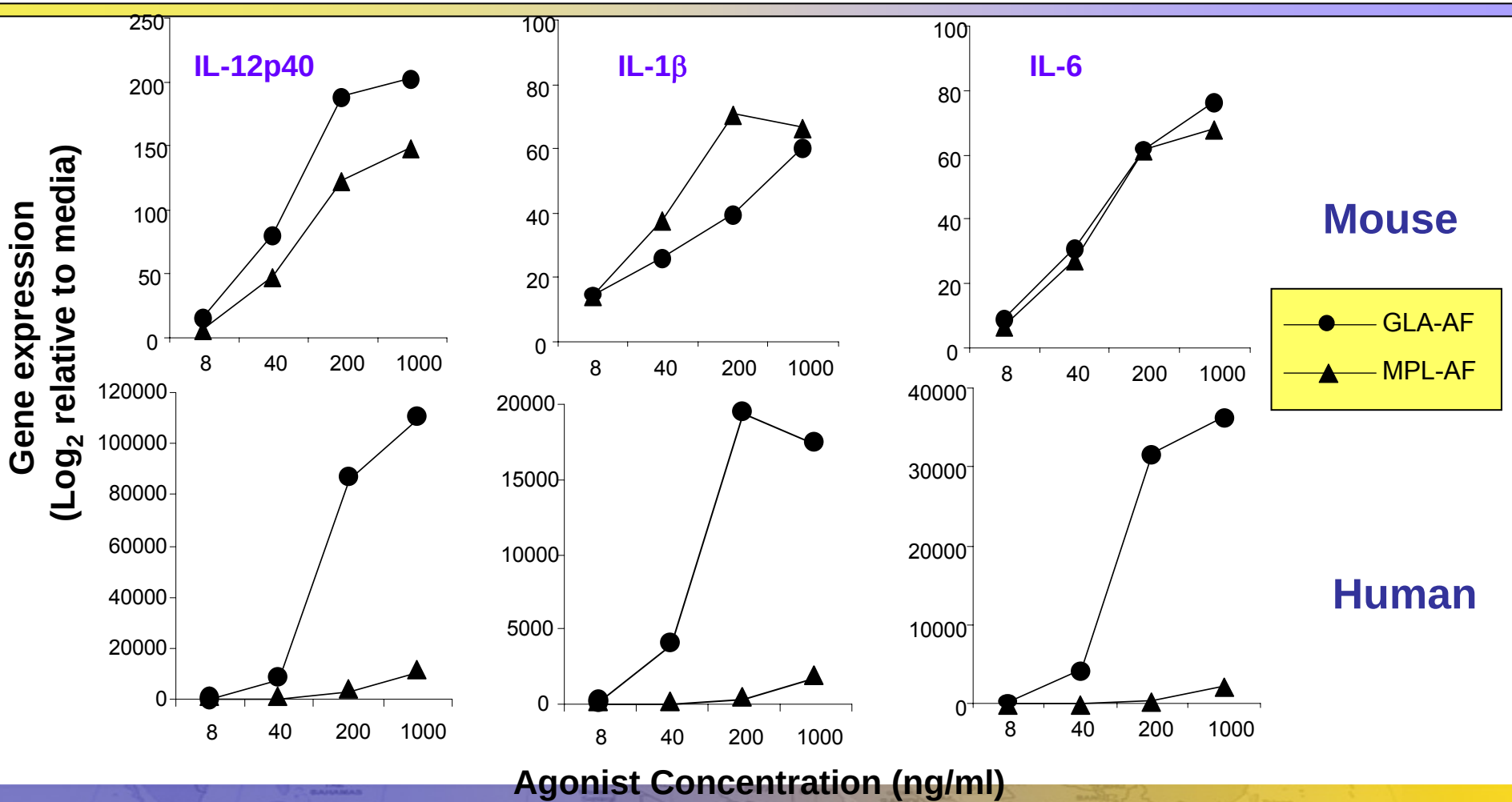
- **Problem: How to Access Adjuvant?**
  - Academic adjuvants not practical (IL12, P. acnes- IFN)
  - Most new clinical adjuvants are in hands of industry
  - Available clinical adjuvants promote too much Th2 (alum, AS02)
  - Mouse data misleading (i.e. CpG)

- **IDRI Solution:**
  - License MPL
  - Optimize MPL formulation
  - Develop synthetic MPL substitute to lower COG

Next Generation of TLR-4 Agonists

Gluco-pyranosylphospho-Lipid A Molecules; Enhance Potency Over MPL

DC: 4h in vitro activation



Human
PBMC
IL-1β

MPL

Sample	Wells	Values	R	Result	MeanResult	Std.Dev.	CV%	Dilution	Adj.Result
01	A5	0.616		0.955	1.012	0.080	7.9	10.0	10.123
	A6	0.716		1.069					
02	B5	0.387		0.698	0.696	0.002	0.2	50.0	34.817
	B6	0.385		0.695					
03	C5	0.004	R	0.266	0.271	0.007	2.6	250.0	67.747
	C6	0.013		0.276					
04	D5	0.003	R	0.265	0.264	0.001	0.5	1250.0	329.714
	D6	0.001	R	0.263					
05	E5	0.004	R	0.266	0.267	0.002	0.7	6250.0	1669.709
	E6	0.006	R	0.269					
06	F5	-0.002	R	0.259	0.260	0.001	0.6	31250.0	8119.517
	F6	-0.000	R	0.261					
07	G5	-0.004	R	0.257	0.258	0.000	0.2	156250.0	40236.425
	G6	-0.003	R	0.258					

R - Outside standard range
Mean Adjusted Result: 7209.72

GLA

Sample	Wells	Values	R	Result	MeanResult	Std.Dev.	CV%	Dilution	Adj.Result
01	A7	3.335	R	4.022	3.994	0.040	1.0	10.0	39.936
	A8	3.285	R	3.966					
02	B7	3.247	R	3.922	3.906	0.024	0.6	50.0	195.276
	B8	3.217	R	3.889					
03	C7	3.192	R	3.861	3.856	0.006	0.2	250.0	964.106
	C8	3.185	R	3.852					
04	D7	1.459		1.906	1.962	0.079	4.0	1250.0	2453.067
	D8	1.558		2.019					
05	E7	0.650		0.995	1.015	0.029	2.8	6250.0	6342.622
	E8	0.686		1.035					
06	F7	0.178		0.462	0.462	0.001	0.2	31250.0	14431.931
	F8	0.177		0.461					
07	G7	0.005	R	0.266	0.272	0.007	2.8	156250.0	42465.061
	G8	0.014		0.277					

R - Outside standard range
Mean Adjusted Result: 9556.00

92.3 nanomolar GLA is equivalent in potency to 57 micromolar MPL

Challenges to Leishmania Vaccine Development

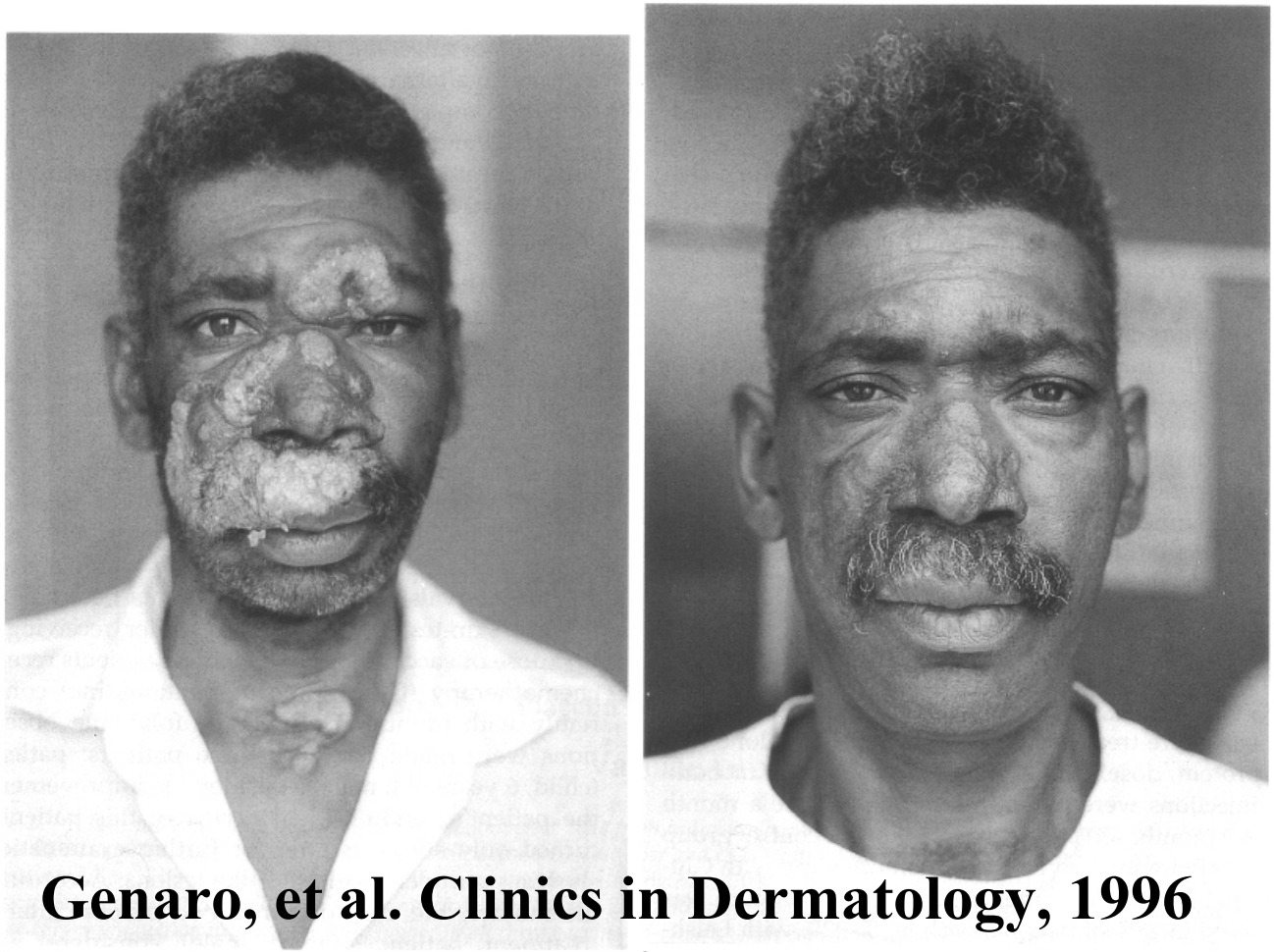
- **Problem: How to demonstrate POC**

- **Solution:**
  - Perform clinical trials in multiple indications
  - Prophylactic/Therapeutic approaches

Leishmaniasis: Rationale for a Therapeutic Vaccine

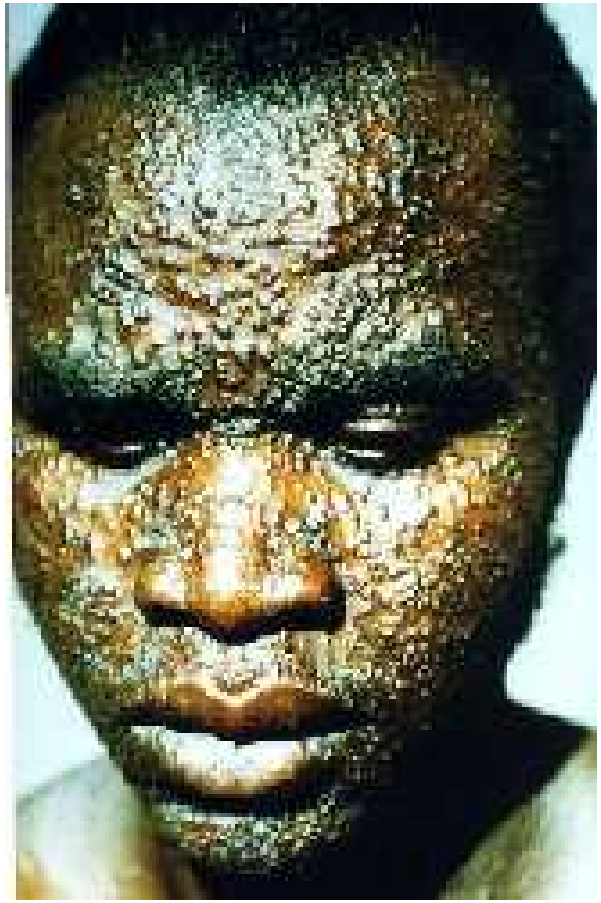
- Animal Models
  - *L. major* in mice
  - *L. infantum* in dogs
- Success of immuno-chemotherapy VL trials in Brazil, India
- Clinical experience with ML/CL in Brazil and Venezuela
- PKDL studies in Sudan

Immunotherapy for Leishmaniasis



Genaro, et al. Clinics in Dermatology, 1996

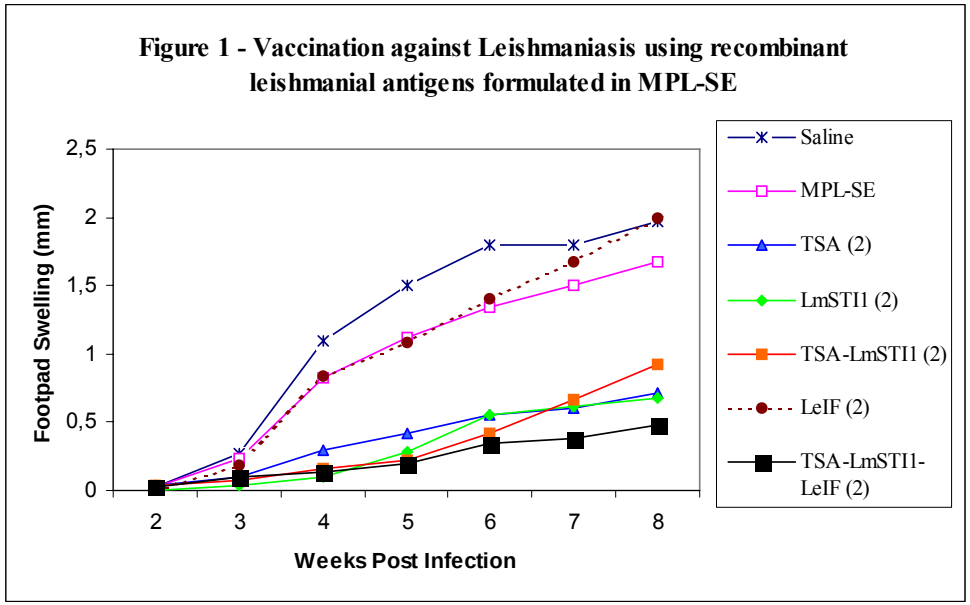
PKDL in Sudan



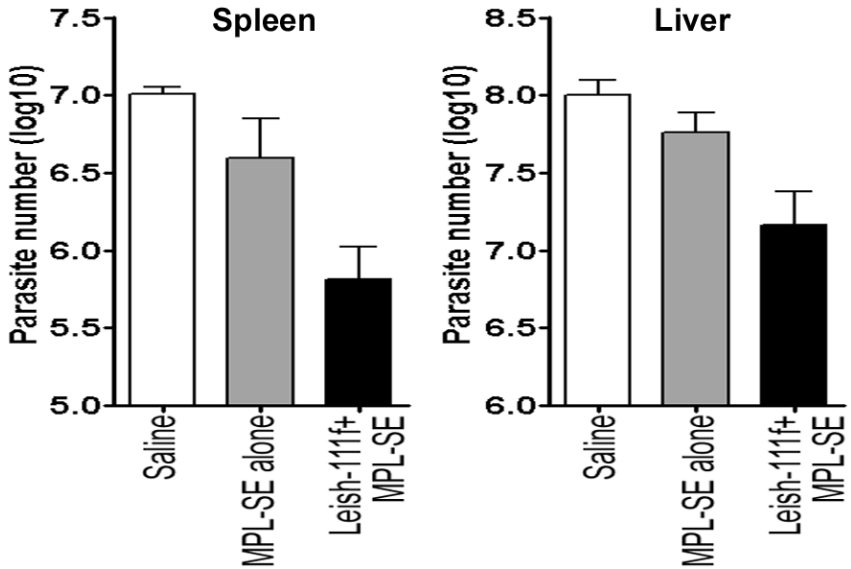
Leish-111f + MPL-SE
Clinical Development

Leish-111f: Recombinant Antigen Comprised of 3 Linked Subunits

Leish-111f (TSA-LmSTI1-LeIF)



BALB/c - *L. major*



C57BL/6 - *L. infantum*

Leish-111f + MPL-SE Vaccine

Leish-111f

Antigen

MPL-SE

Adjuvant

Complete Vaccine

Leish-111f + MPL-SE Vaccine Therapeutic Indications (In Progress)

- Combine vaccine with chemotherapy for treating:
  - VL
  - PKDL
  - CL
  - ML

Leish-111f + MPL-SE Vaccine Prophylactic Indications (Planned)

- Cutaneous leishmaniasis
- Visceral leishmaniasis (prevent VL, prevent PKDL)

Completed Clinical Trials

US Healthy Subjects
Phase 1

Colombia Healthy Subjects

Phase 1 MST+/ Phase 2 MST-

Brazil CL Patients Phase 1

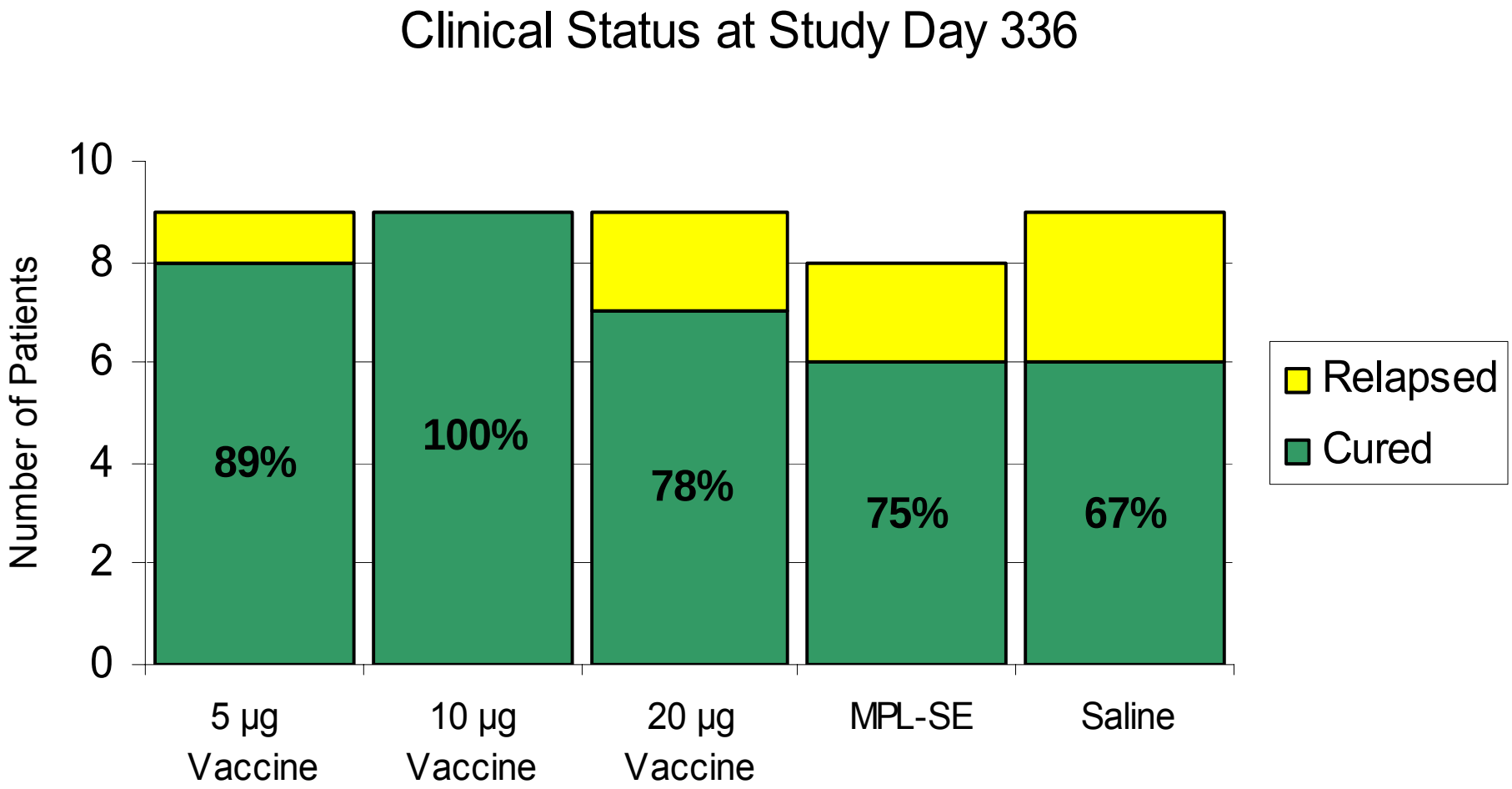
Peru ML Patients Phase 1

2003 2004 2005 2006 2007

Brazil/Peru Trial - Design

	Brazil Phase 1	Peru Phase 1
Population	CL	ML
Vaccine Dose *(n)* __ Leish -111f + 25 μg MPL-SE	5 μg *(9)* 10 μg *(9)* 20 μg *(9)*	5 μg *(12)* 10 μg *(12)* 20 μg *(12)*
Control *(n)*	MPL-SE *(8)* Saline *(9)*	Saline *(12)*
Chemotherapy	Antimonial	Antimonial
Endpoints	Safety and Tolerability Immunogenicity Clinical Evolution	

Brazil CL Therapeutic Trial Results



Summary

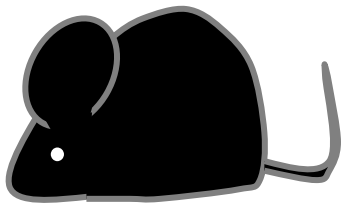
The Leish-111f + MPL-SE vaccine:

- Safe and well tolerated
- Immunogenic
- Does not exacerbate disease when given with chemotherapy to CL and ML patients

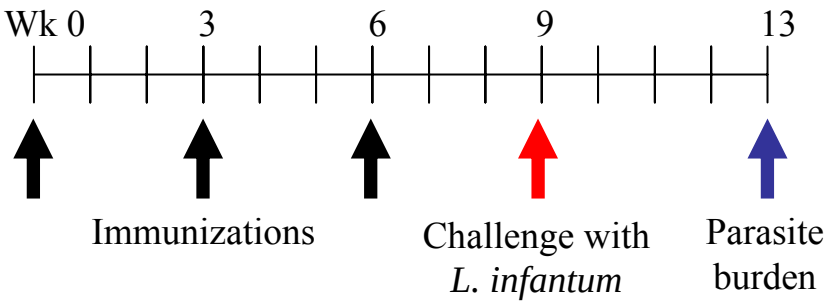
Vaccine Development; Sub-unit vaccines

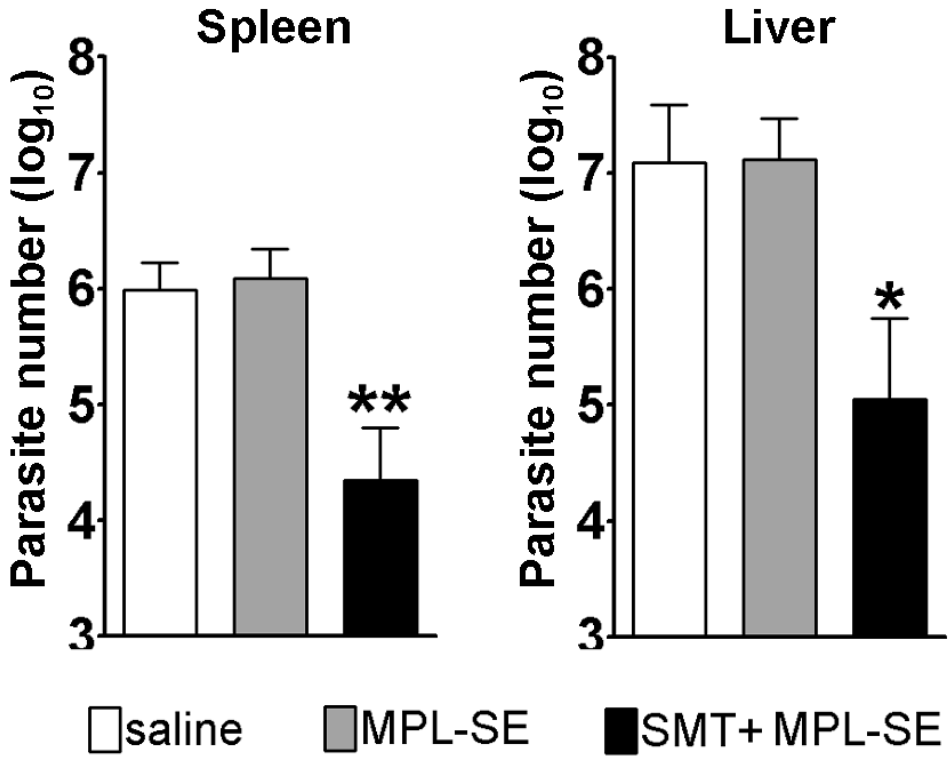
- Selective:
  - Use only relevant antigens
  - Use adjuvants with desired qualities
- Versatile: Antigens can be used alone, in combination, as fusions
- **Manufacturing options greatly increased**

Next Generation Vaccine: SMT plus MPL-SE



C57BL/6 mice





Sterol 24-c-methyltransferase (SMT): A Potent Leishmaniasis Vaccine Candidate

SMT is involved in the biosynthesis of ergosterol; target of amphotericin B

Leishmania SMT is highly conserved among species (>96%), and is homologous to those of *Trypanosoma* (66%) and *Candida* (39%), but no homologous protein found in humans.

Challenges to Leishmania Vaccine Development

- **PROBLEM: Who will manufacture the vaccine?**

- **Solution:**
  - Reduce risk for Pharma (keep cost low, finalize POC studies, define market potential
  - Leverage canine market

Challenges to Leishmania Vaccine Development

- **PROBLEM: Sustainability**

- **Solution:**
  - Incentives for Pharma
  - Exclusive vs. Non-Exclusive (include diligence requirements)
  - Multiple Indications
  - Vaccine registration in Europe, U.S., etc.

Summary: The Ideal Leishmania Vaccine

- Safe
- Induces effective T cell response against appropriate antigens
- Induces long-term immunity
- Prophylactic and therapeutic activity
- Effective against more than one form of leishmaniasis
- Cost-effective
- Reproducible, transferable manufacturing process

Leishmaniasis Vaccine Development:Future Directions

- Finalize Antigen Selection
- BUT Antigen ≠Vaccine
- MPL-SE is Effective, but, COG is an Issue
- Animal Studies, Mice, Hamsters, Dogs (combine with rabies)
- Obtain POC in Clinic

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