H2020-SC1-2018-RTD

Grant Agreement Number 815418

Deliverable N°: D16.1

A PowerPoint presentation of the project

Vaccine for Prevention and Treatment of *Trypanosoma cruzi* Infection (CRUZIVAX)

September 2019

Version 1

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EC Project Officer	Patricia Urban Lopez

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1. Introduction

The project presentation will provide the background information to the project and its goals. This can be used by the partners for presenting the project. The presentation will be updated regularly.






CRUZIVAX Project – Horizon2020

Preclinical and clinical validation of a vaccine against Chagas disease

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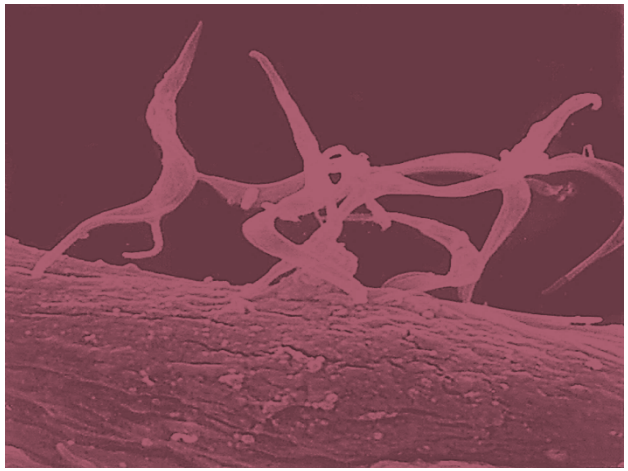
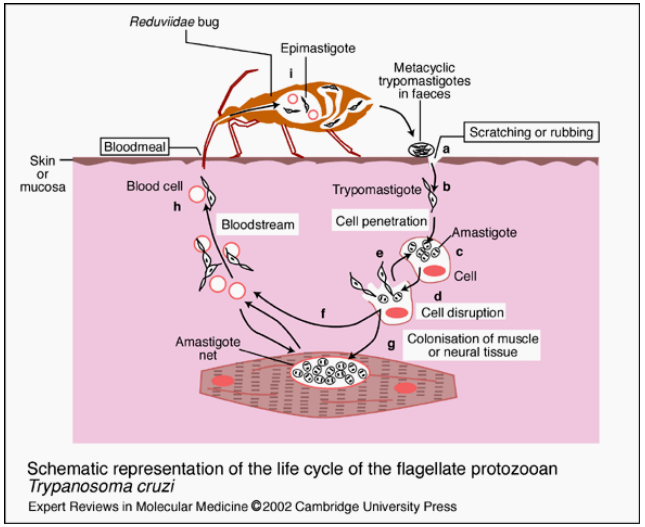
Chagas disease



Trypanosoma cruzi

- Classical transmission
- Organ transplantation
- Transfusion
- Perinatal



Schematic representation of the life cycle of the flagellate protozooan *Trypanosoma cruzi*

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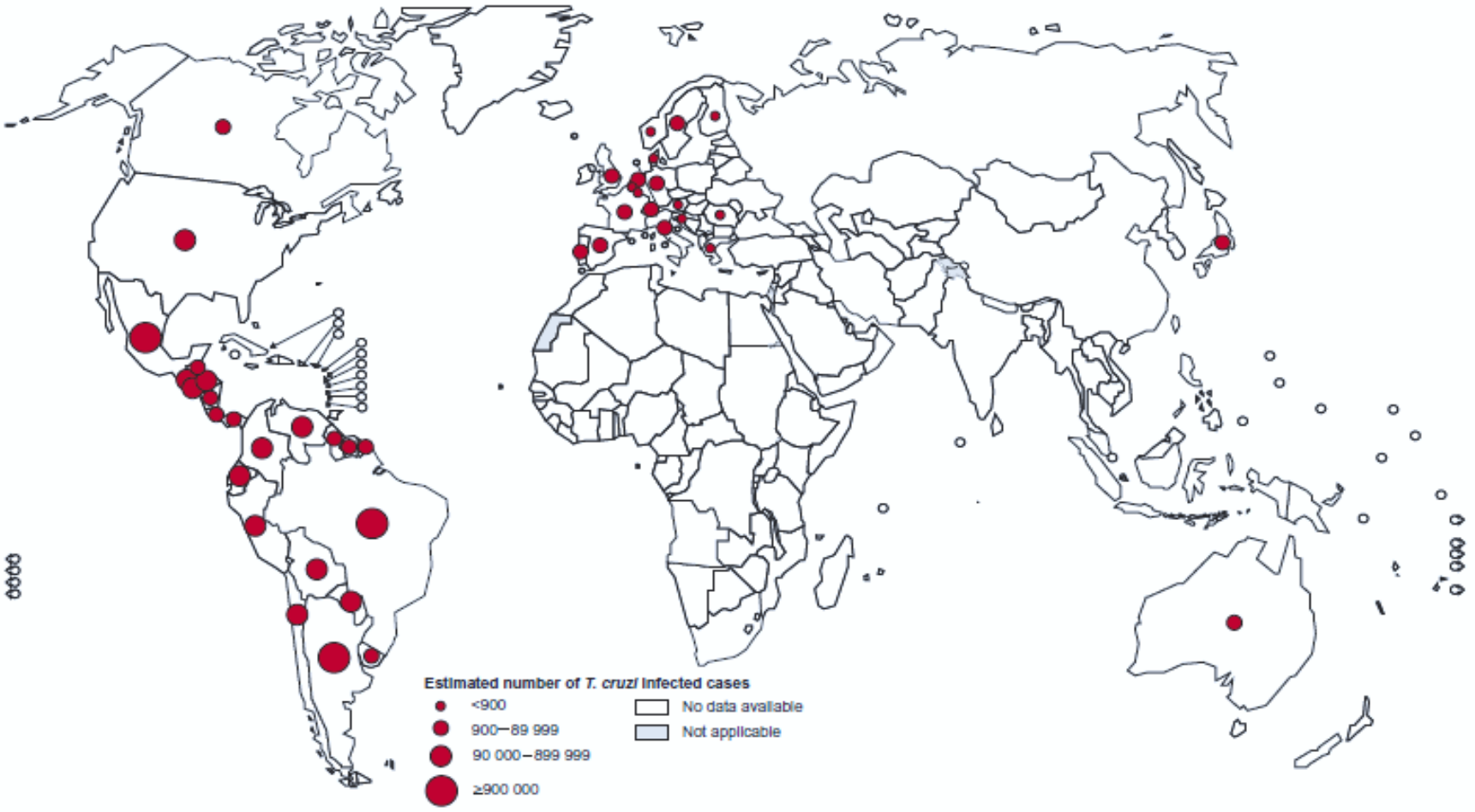
Chagas disease… a global problem



21 **endemic** and 19 **non-endemic** countries

World Health Organization. (2013)
www.who.int/iris/handle/10665/77950

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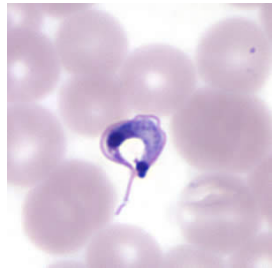
Chagas disease



Source: www.cdc.gov/dpdx

- **~10 million** infected individuals who will progress to chronicity
- **30-40%** chronically infected develop **life-threatening** clinical forms
- Disability adjusted life-year (DALYs): **252,000/year**
- Huge financial burden (annual **costs > EUR 6 billion**)
- Drugs only active in **early infection**, **lengthy** and **highly toxic**
- **No vaccine** available

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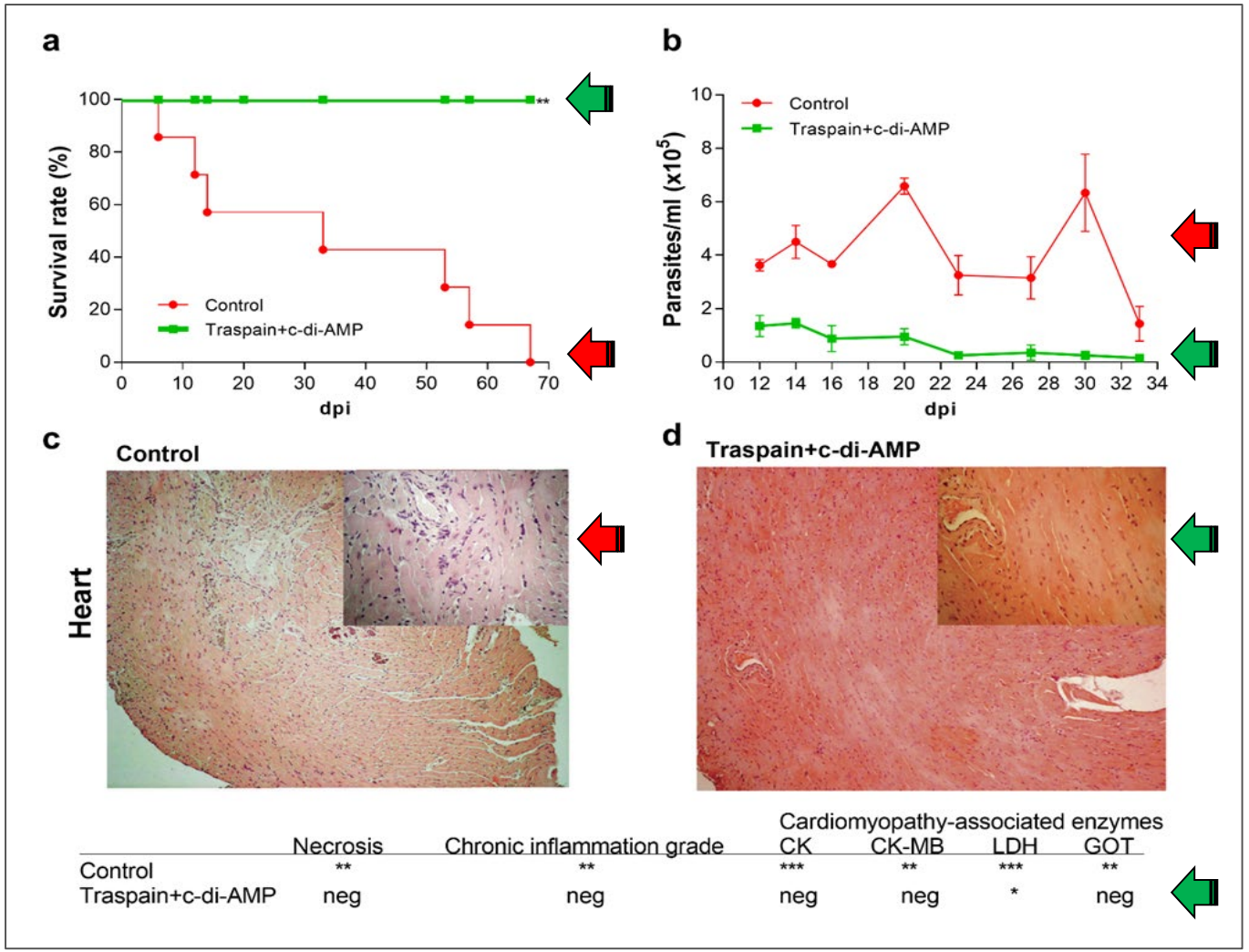
CRUZIVAX Project

Develop an intranasal needle-free vaccine against *T. cruzi* infection

CRUZIVAX™

- Chimeric trivalent synthetic antigen (Traspain)
- HZI‘s new adjuvant c-di-AMP

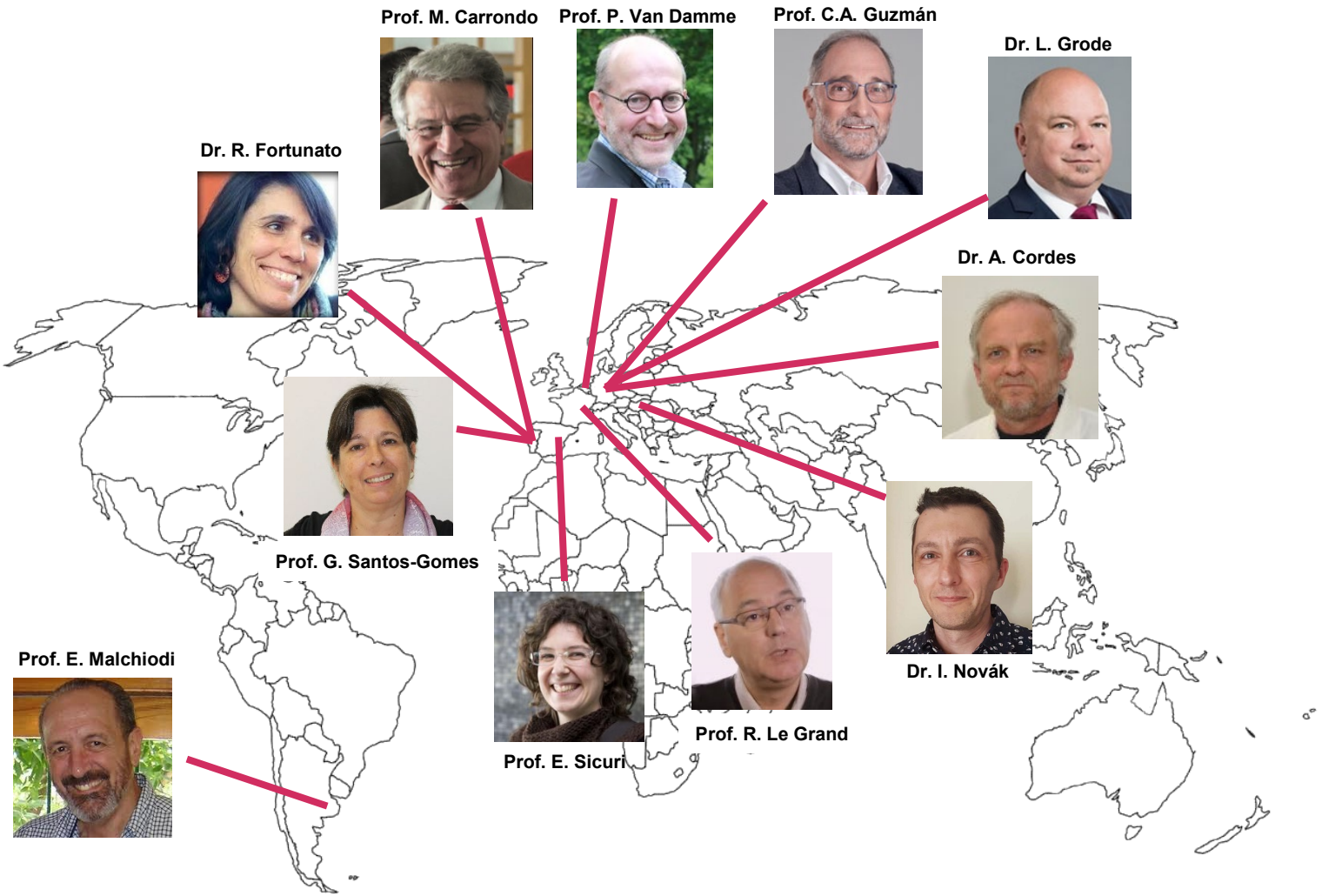
CRUZIVAX™ proof-of-concept



	Necrosis	Chronic inflammation grade	Cardiomyopathy-associated enzymes CK	CK-MB	LDH	GOT
Control	**	**	***	**	***	**
Traspain+c-di-AMP	neg	neg	neg	neg	*	neg

Sanchez Alberti *et al*. (2017) **npj Vaccines**

CRUZIVAX partners



Expertise of the partners

Partner / acronym / type org	Expertise
1 Helmholtz-Zentrum für Infektionsforschung GmbH (HZI) Research Organisation	Immunology, **murine preclinical validation models**, immune monitoring in preclinical models and humans, **vaccinology, adjuvants**, project management, communication, dissemination, exploitation
2 Universidad de Buenos Aires (UBA) University	Immunology, vaccinology, parasitology, **Chagas disease R&D**, communication, dissemination, exploitation
3 Universidade Nova de Lisboa (UNL-IHMT) University	Parasitology, immunology, **dog infection models**, communication, dissemination, exploitation
4 Atomic Energy Commission (CEA-IDMIT) Research organisation	Vaccines, immunology, infectious diseases, **non-human primate models**, communication, dissemination, exploitation
5 Instituto de Biologia Experimental e Tecnológica (iBET) SME	Discovery research, preclinical development, **prophylactic/therapeutic and human/veterinary vaccines**, project management, communication, dissemination, exploitation
6 GenIBET Biopharmaceuticals SA (GenIbet) SME	Scale-up, **technology transfer and GMP manufacturing**, communication, dissemination, exploitation
7 ASA-Spezialenzyme GmbH (ASA) SME	Scale-up, **technology transfer and GMP manufacturing**, enzyme technology, gene technology, communication, dissemination, exploitation
8 Aurigon Toxicological Research Center Ltd (ATRC) SME	GLP-certified testing facility, conduct of immunization studies, **conduct of GLP-compliant toxicity studies in rodent and non-rodent species**, bioanalytical method development and validation, communication, dissemination, exploitation
9 University of Antwerp (CEV) University	Vaccinology, **conduct of clinical trials (phase 1-4)**, immunology, communication, dissemination, exploitation
10 Barcelona Institute for Global Health (ISGlobal) Research organisation	**Health economics of infectious diseases in low- and middle- income countries**, communication, dissemination, exploitation
11 Vakzine Projekt Management GmbH (VPM) SME	**Regulatory consulting**, vaccine development from bench to bedside including technology transfer to GMP manufacturing, non-clinical and clinical development**, clinical trial sponsorship phase 1-3**, **clinical project management**, communication, dissemination, exploitation

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CRUZIVAX Project

C.A. Guzmán

M. Carrondo

C.A. Guzmán G. Santos-Gomes

I. Novák

L. Grode

E. Sicuri

Development of vaccine components

GLP & GMP production of the vaccine components

Preclinical validation of the vaccine in different animal models

Toxicology

Preparation and implementation of a clinical phase I trial

Health economics studies and demand assessment

E. Malchiodi

A. Cordes

E. Malchiodi

R. Le Grand

C.A. Guzmán

P. Van Damme

Project objectives

- **preclinical identification** of the best vaccine formulation and vaccination strategy in prophylactic and therapeutic settings **in mice**
- assess the **immunogenicity** and the prophylactic and therapeutic **efficacy** of the best vaccine formulation and vaccination strategy **in dogs and non-human primates** (NHP)
- establish the production processes of good laboratory practice (**GLP**) and good manufacturing practice (**GMP**) grade antigen and adjuvant
- provide **non-toxicology data and safety assessment** of the vaccine candidate
- assess the safety and immunogenicity of the vaccine candidate through a **clinical phase 1 study** in healthy volunteers
- determine the potential demand and supply for the Traspain vaccine, as well as critical field implementation parameters by performing a flanking **health economic analysis**

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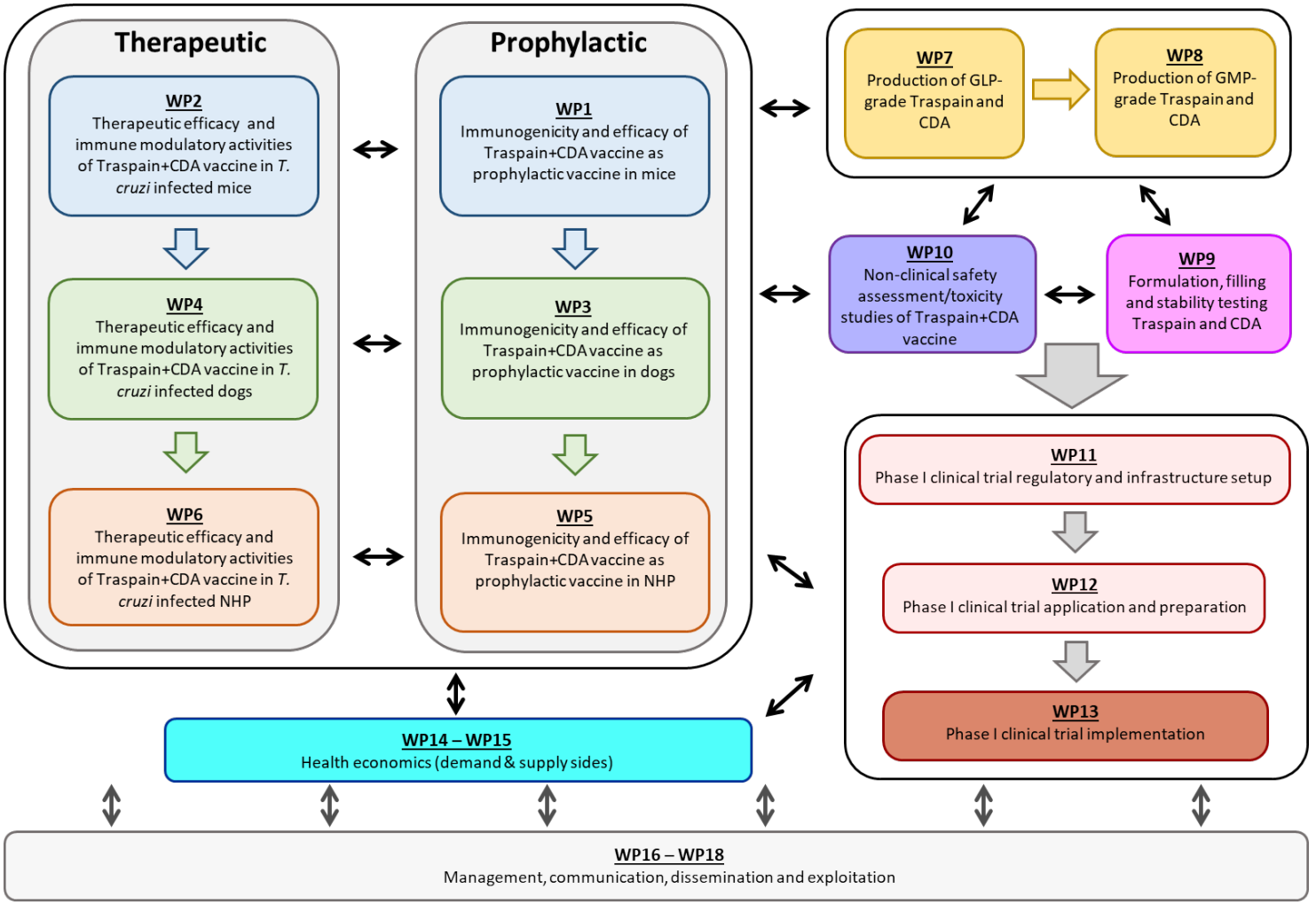
CRUZIVAX – Project Structure



CRUZIVAX – Timing of WPs

WP	Title	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	Immunogenicity and efficacy of Traspain+CDA in mice																				
2	Therapeutic efficacy of Traspain+CDA in infected mice																				
3	Immunogenicity and efficacy of Traspain+CDA in dogs																				
4	Therapeutic efficacy of Traspain+CDA in infected dogs																				
5	Immunogenicity and efficacy of Traspain+CDA in NHP																				
6	Therapeutic efficacy of the Traspain+CDA in infected NHP																				
7	Production of GLP-grade Traspain and CDA																				
8	Production of GMP-grade Traspain and CDA																				
9	Formulation, filling and stability of Traspain and CDA																				
10	Non-clinical safety assessment studies of Traspain+CDA																				
11	Phase 1 clinical trial regulatory and infrastructure setup																				
12	Phase 1 clinical trial preparation, application and management																				
13	Phase 1 clinical trial implementation																				
14	Demand side: Quality of life and demand for Traspain+CDA																				
15	Life-long use of resources and associated costs for Chagas disease																				
16	Management, communication, dissemination and exploitation 1																				
17	Management, communication, dissemination and exploitation 2																				
18	Management, communication, dissemination and exploitation 3																				
19	Ethics requirements																				

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CRUZIVAX – Timing of WPs

WP	Title	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	**Immunogenicity and efficacy of Traspain+CDA in mice**						M1.1		M1.2												
	Task 1.1: Production of research grade recombinant Traspain																				
	Task 1.2: Harmonization of the immune response monitoring																				
	Task 1.3: Safety and Tolerability of Traspain and Traspain+CDA			D1.1																	
	Task 1.4: Traspain+CDA immunogenicity in young female mice																				
	Task 1.5: Traspain+CDA immunogenicity in young male mice					D1.2															
	Task 1.6: Validation of the best vaccination strategy in adult mice																				
	Task 1.7: Traspain+CDA vaccine efficacy against *T. cruzi*							D1.3													
	Task 1.8: Traspain+CDA capacity to prevent *T. cruzi* persistence																				
2	**Therapeutic efficacy of Traspain+CDA in infected mice**									M2.1		M2.2									
	Task 2.1: Mice infection and treatment protocols																				
	Task 2.2: Treatment efficacy analysis											D2.1									
	Task 2.3: Antigen and pathogen-specific immune response											D2.2									
3	**Immunogenicity and efficacy of Traspain+CDA in dogs**					M3.1		M3.2				M3.3									
	Task 3.1: Accommodation of Beagle dogs																				
	Task 3.2: Dogs immunization							D3.1													
	Task 3.3: Immunogenicity of Traspain+CDA in dogs								D3.2												
	Task 3.4: *T. cruzi* inoculum for challenge studies																				
	Task 3.5: Vaccine efficacy against *T. cruzi* challenge in dogs											D3.3									
4	**Therapeutic efficacy of Traspain+CDA in infected dogs**											M4.1		M4.2							
	Task 4.1: Treatment of *T. cruzi* chronic infected dogs																				
	Task 4.2: Vaccine therapeutic efficacy in *T.cruzi* infected dogs											D4.1		D4.3							
	Task 4.3: Traspain+CDA responses in chronically infected dogs													D4.2							

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CRUZIVAX – Timing of WPs

WP	Title	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
5	**Immunogenicity and efficacy of Traspain+CDA in NHP**						♦M5.1/2/3		♦M5.4			♦M5.5/M5.6									
	Task 5.1: Establishing the *T. cruzi* infection model in macaques						♦D5.1														
	Task 5.2: Assess vaccine immunogenicity and safety in NHP						♦D5.2/D5.3														
	Task 5.3: Assess vaccine efficacy in NHP											♦D5.4/D5.5									
6	**Therapeutic efficacy of the Traspain+CDA in infected NHP**																		♦M6.1/M6.2/M6.3		
	Task 6.1: Vaccine immunogenicity in *T. cruzi* infected NHP													♦D6.1					♦D6.2		
	Task 6.2: Evaluate vaccine efficacy in *T. cruzi* infected NHP																		♦D6.3/D6.4		
7	**Production of GLP-grade Traspain and CDA**							♦M7.1													
	Task 7.1: Establishment of supporting analytical techniques				♦D7.2																
	Task 7.2: Establishment of Master Cell Bank under cGMP conditions			♦D7.1																	
	Task 7.3: Traspain for preclinical studies				♦D7.3																
	Task 7.4: Traspain production for GLP-toxicology							♦D7.4													
	Task 7.5: CDA for preclinical and GLP-toxicology studies																				
8	**Production of GMP-grade Traspain and CDA**											M8.1/M8.2♦			♦M8.3						
	Task 8.1: Traspain cGMP production for phase 1																				
	Task 8.2: CDA cGMP production for phase 1														♦D8.1						
	Task 8.3: Preparation of all documents																				
9	**Formulation, filling and stability of Traspain and CDA**														M9.1♦		♦M9.2				
	Task 9.1: Biological activity and stability of CDA and Traspain				♦D9.1																
	Task 9.2: Formulation, filling and quality control																				
	Task 9.3: Stability testing																♦D9.2				D9.3♦
10	**Non-clinical safety assessment studies of Traspain+CDA**						♦M10.1								♦M10.2						
	Task 10.1: GLP-toxicity studies														♦D10.1						

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CRUZIVAX – Timing of WPs

WP	Title	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
11	**Phase 1 clinical trial regulatory and infrastructure setup**			♦M11.1								♦M11.2									
	Task 11.1: First scientific advice meeting with Belgian regulators			♦D11.1																	
	Task 11.2: Second scientific advice meeting											♦D11.2									
	Task 11.3: Qualification audits to set-up infrastructure											♦D11.3									
12	**Phase 1 clinical trial preparation, application and management**											♦M12.1			♦M12.2						
	Task 12.1: Trial management, logistics and engagement of required subcontractors																				D12.4♦
	Task 12.2: CTA to ethics committee and national authority														♦D12.1						
	Task 12.3: Clinical trial preparation															♦D12.2/D12.3					
13	**Phase 1 clinical trial implementation**														M13.1♦		♦M13.2			♦M13.3	
	Task 13.1: Phase 1 clinical trial of the vaccine candidate																D13.1♦				
	Task 13.2: Exploratory endpoints vaccine immunogenicity																				D13.2/D13.3/D13.4♦
	Task 13.3: Comparison of the efficacy and immunogenicity data of the various species																				D13.5/D13.6♦
14	**Demand side: Quality of life and demand for Traspain+CDA**		♦M14.1									♦M14.2									
	Task 14.1: Defining attributes and modalities for DCE.																				
	Task 14.2: Preparation of DCEs following best practices.																				
	Task 14.3: REDCap/ODK for DCEs to policy makers & patients																				
	Task 14.4: DCEs piloting, data collection and monitoring																				
	Task 14.5 Data management, cleaning and analysis											♦D14.3									
	Task 14.6: Obtaining EQ-5Q from Euroqol																				
	Task 14.7: Incorporate the EQ-5Q questionnaire into tablets			♦D14.1/14.2																	
	Task 14.8: Piloting, Data collection, data monitoring																				
	Task 14.9: Data analysis											♦D14.4									

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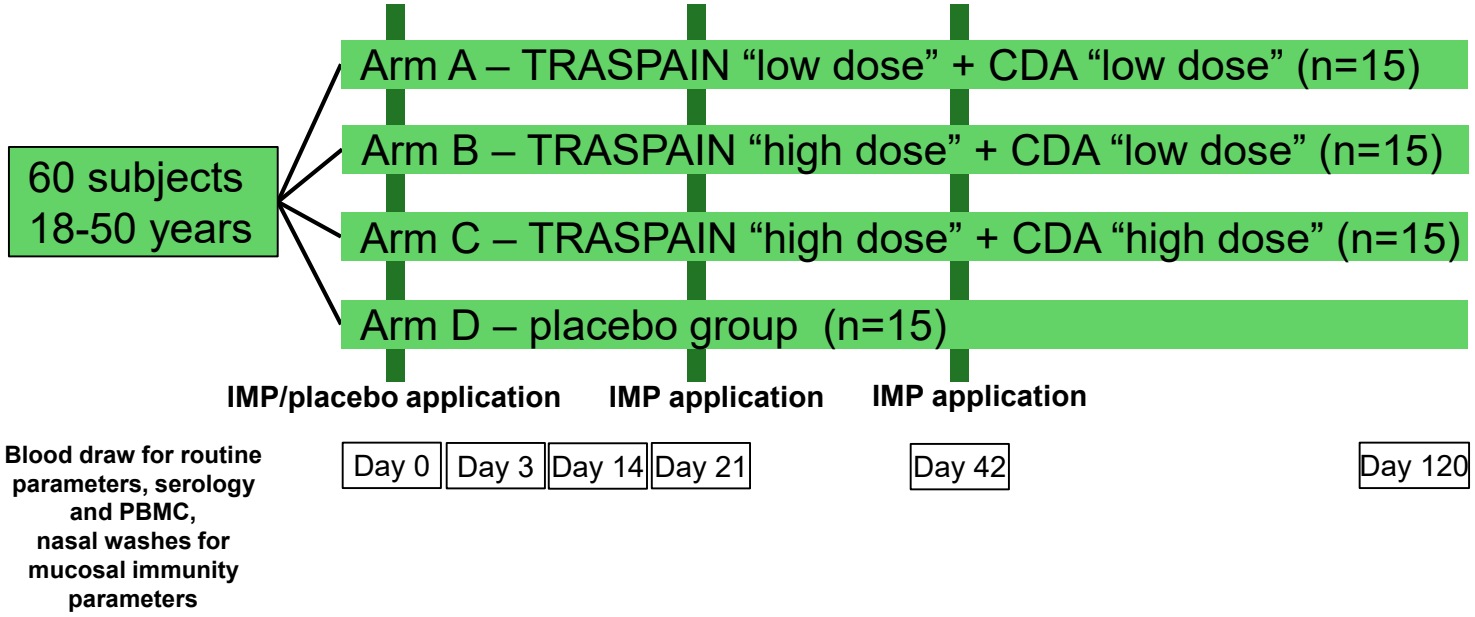
CRUZIVAX – Timing of WPs

WP	Title	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
15	**Life-long use of resources and associated costs for Chagas disease**												♦M15.1								
	Task 15.1: Data mining			♦D15.1																	
	Task 15.2: Estimate of life-long costs for Chagas disease												♦D15.2								
16	**Management, communication, dissemination and exploitation 1**		♦M16.1																		
	Task 16.1: Project management and coordination								♦D16.5/D16.6												
	Task 16.2: Communication, dissemination and exploitation		♦D16.1/2/		♦D16.4																
17	**Management, communication, dissemination and exploitation 2**																				
	Task 17.1: Project management and coordination													♦D17.2/D17.3							
	Task 17.2: Communication, dissemination and exploitation												♦D17.1								
18	**Management, communication, dissemination and exploitation 3**																				
	Task 18.1: Project management and coordination																				D18.2/D18.3♦
	Task 18.2: Communication, dissemination and exploitation																				D18.1/D18.4♦
19	**Ethics requirements**	9.1♦		♦D19.2					♦D19.3												

CRUZIVAX – First in human study

Clinical trial scheme



CRUZIVAX – Clinical Trial

First-in-human subject and evaluator blinded, placebo-controlled

- **Safety, reactogenicity, tolerability and immunogenicity** of two different intranasal dose levels of a Traspain-based vaccine (CRUZIVAX™) with a cyclic-di-AMP (CDA) adjuvant in healthy subjects aged 18-50 years
- **60 subjects** will be enrolled into the study
- Subjects will receive **3 doses at days 0, 21 and 42**
- CRUZIVAX™ / CDA will be investigated at three dose levels: low/low, high/low and high/high
- Each of the 4 arms (including placebo) will include 15 subjects
- Subjects will be followed-up until **120 days** post-prime vaccination

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CRUZIVAX – Objectives of the Clinical Trial

Primary objectives:

- Assess unsolicited and solicited **serious adverse events (SAEs)** of CRUZIVAX™ / CDA from Day 1 to the end of the trial
- Assess unsolicited and solicited **reactogenicity** (local and systemic) events of CRUZIVAX™ / CDA from Day 1 to Day 7 post vaccination
- Assess unsolicited and solicited **severe adverse events (AEs)** of CRUZIVAX™ / CDA from Day 1 to Day 7 post vaccination

Secondary objectives:

- Assess **immunogenicity** of CRUZIVAX™ / CDA: measurement of antibody response by ELISA (antigen-specific IgG titre and analyses for seroconversion), collected from baseline until Day 120 post-prime

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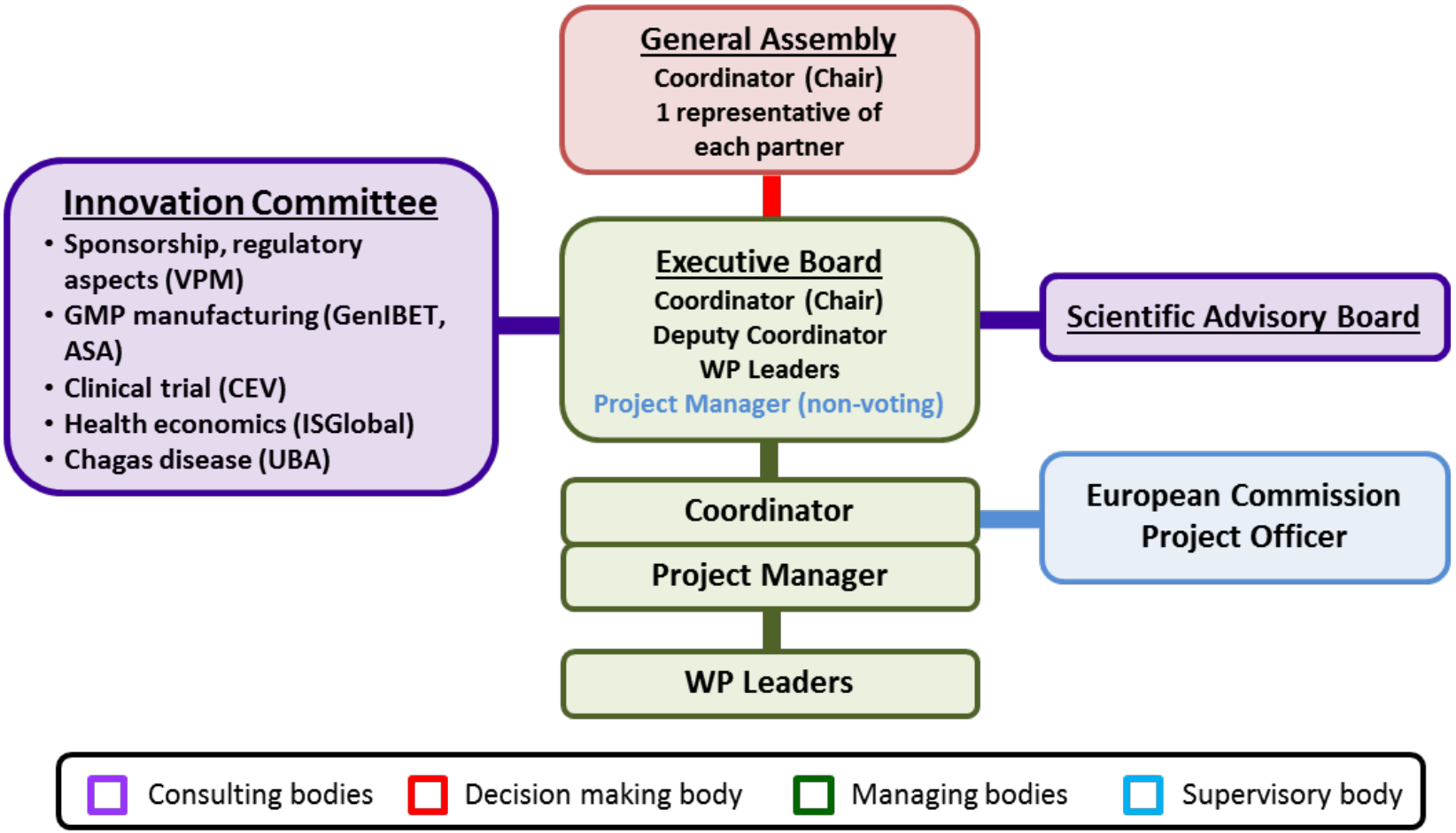
CRUZIVAX – Management Structure



CRUZIVAX – Executive Board

Proposed Executive Board members	Partner	Gender
C. A. Guzmán - Coordinator (Chair); (WP1&16-18 leader)	P1-HZI	M
E. Malchiodi - Deputy Coordinator (WP2 leader)	P2-UBA	M
G. Santos-Gomes (WP3&4 leader)	P3-UNL-IHMT	F
R. Le Grand (WP5&6 leader)	P4-CEA-IDMIT	M
M. Carrondo (WP7 leader)	P5-iBET	M
A. Cordes (WP8&9 leader)	P7-ASA	M
I. Novak (WP10 leader)	P8-ATRC	M
L. Grode (WP11 leader)	P11-VPM	M
P. Van Damme (WP12&13 leader)	P9-CEV	M
E. Sicuri (WP14&15 leader)	P10-ISGlobal	F
Project Manager **B. Prochnow** (nv*)	P1-HZI	M

CRUZIVAX – WP Leaders

WP	Leader (gender)	Partner	Country
1	C. A. Guzmán (M)	P1-HZI	Germany
2	E. Malchiodi (M)	P2-UBA	Argentina
3 & 4	G. Santos-Gomes (F)	P3-UNL-IHMT	Portugal
5 & 6	R. Le Grand (M)	P4-CEA-IDMIT	France
7	M. Carrondo (M)	P5-iBET	Portugal
8 & 9	A. Cordes (M)	P7-ASA	Germany
10	I. Novak (M)	P8-ATRC	Hungary
11	L. Grode (M)	P11-VPM	Germany
12 & 13	P. Van Damme (M)	P9-CEV	Belgium
14 & 15	E. Sicuri (F)	P10-ISGlobal	Spain
16-18	C. A. Guzmán (M)	P1-HZI	Germany

CRUZIVAX – Exploitation

- **Implementation of proactive IP rights strategy** for protection and targeted exploitation of results
- Installation of an **Innovation Committee** to maximize impact and optimal exploitation of data
- Close interaction with the relevant regulatory authorities aiming at **a rapid market authorization** of the vaccine after a successful phase I trial
- **Providing research data** to the scientific community by **open access** publications

CRUZIVAX – Dissemination

- Implementation of **a strategic plan to integrate science and technology in the society**
- Establishment of a project **corporate identity image** for CRUZIVAX
- Establishment and further development of an **external website** (www.cruzivax.eu)
- Development and implementation of a **communication plan**
- Regular project internal **information exchange** for knowledge, data and experience sharing
- Workshop for young scientists leading to interdisciplinary understanding and **knowledge transfer**

Expected outcome

- First-in-human studies of CRUZIVAX™ as prophylactic vaccine candidate against Chagas disease
- Evaluation of CRUZIVAX™ efficacy as therapeutic vaccine alone and in combination with anti-parasitic drugs in 3 animal species
- Evaluation of the efficacy of CRUZIVAX™ as prophylactic veterinary vaccine in relevant animal species
- Identification of potential biomarkers and/or correlates of protection for future studies
- Health economic analysis in endemic (under-resourced) and non-endemic areas

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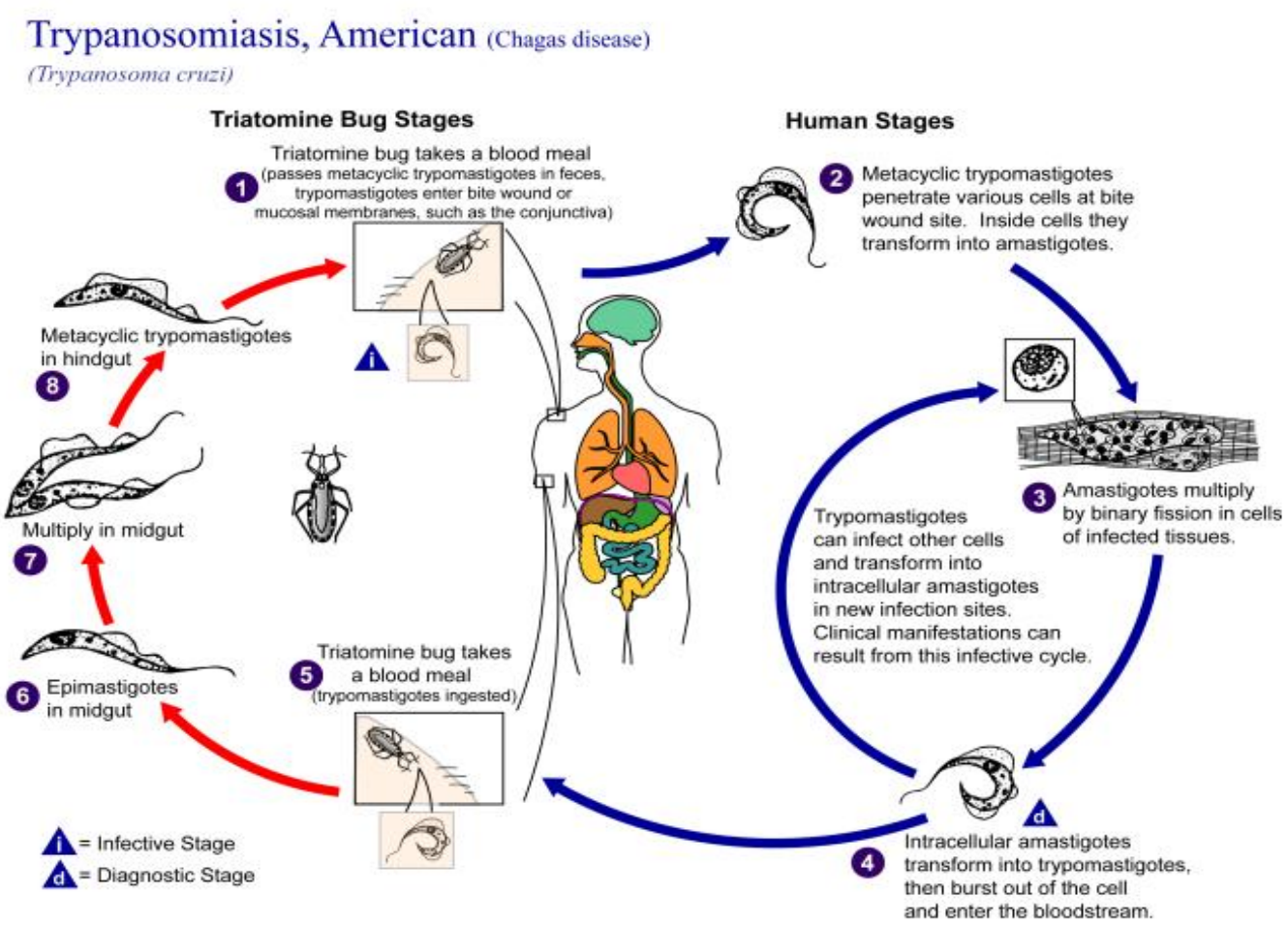

https://phil.cdc.gov/

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CRUZIVAX Project – Horizon2020

Preclinical and clinical validation of a vaccine against Chagas disease

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 815418.