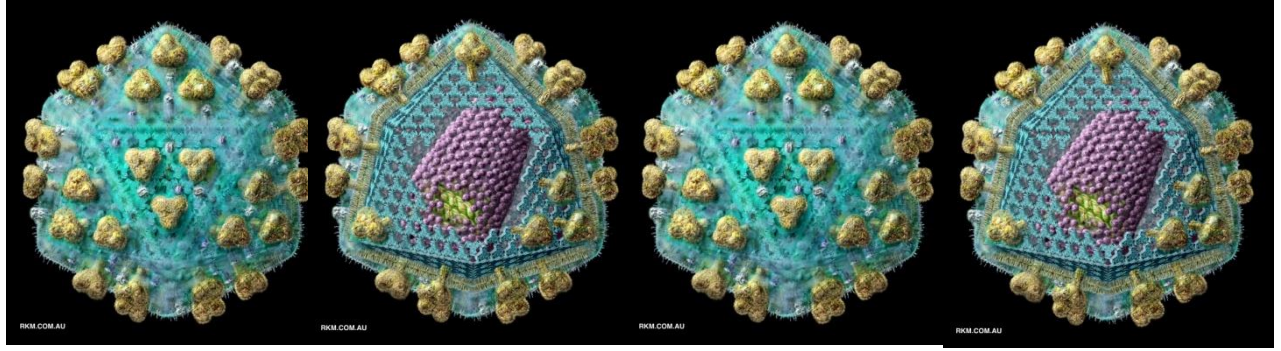


CHALLENGES AND SUCCESSES IN DEVELOPING LOCAL VACCINES

Professor Anna-Lise Williamson
SARChI Chair in Vaccinology

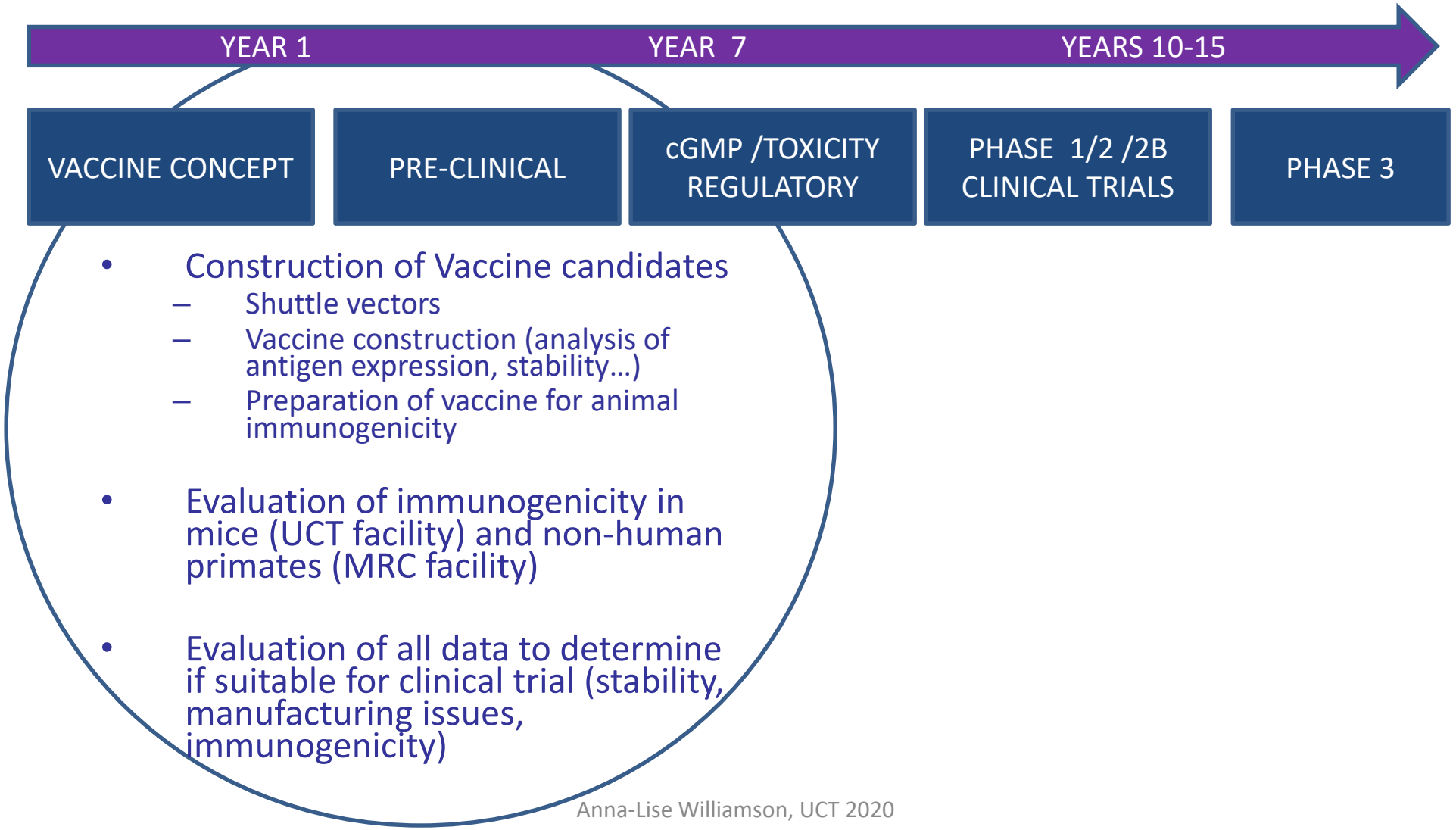
Institute of Infectious Disease and Molecular Medicine,
University of Cape Town

National Research Foundation

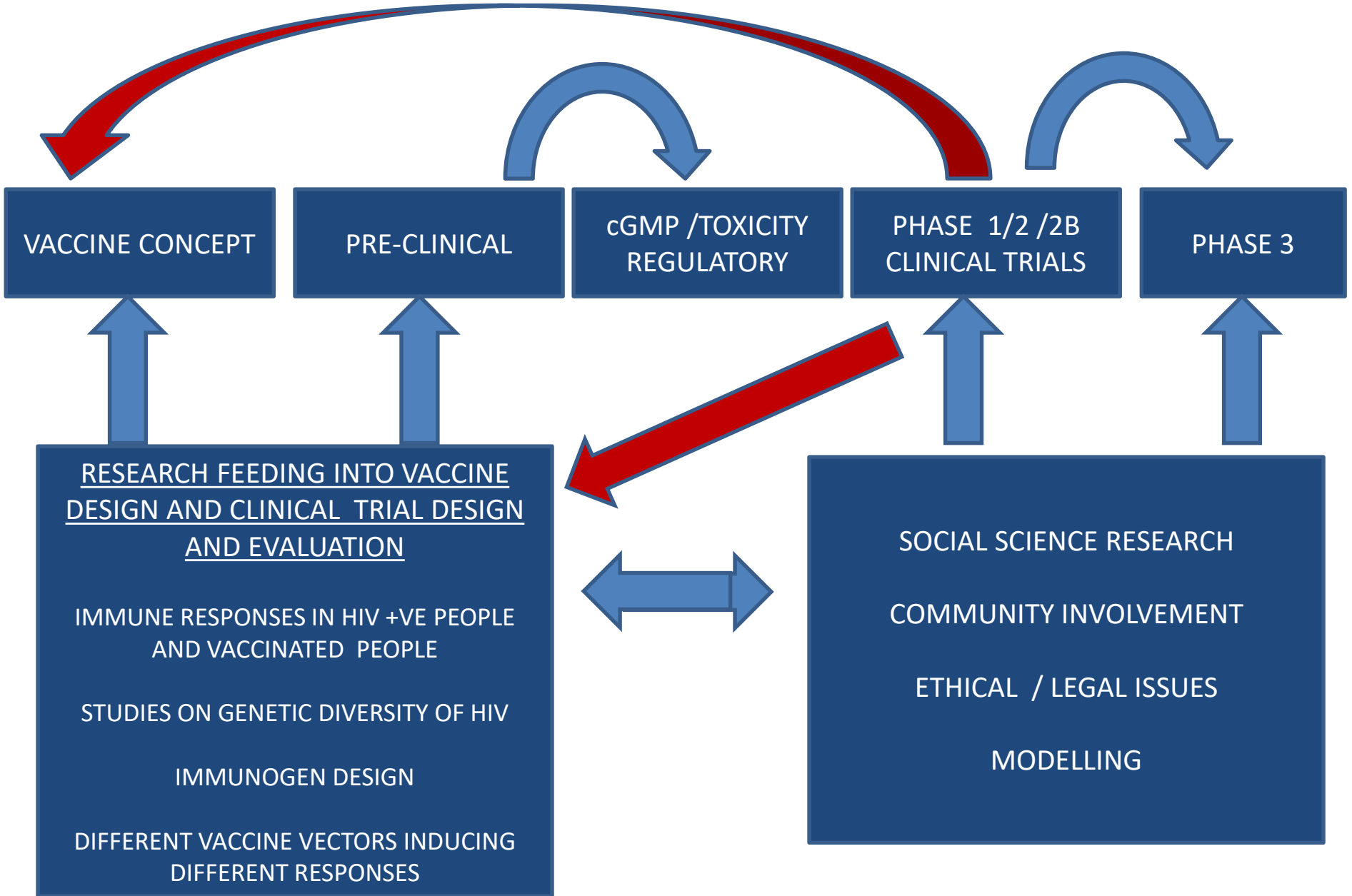
Vaccines are the best way to control infectious disease

THE HUMAN VACCINE PIPELINE

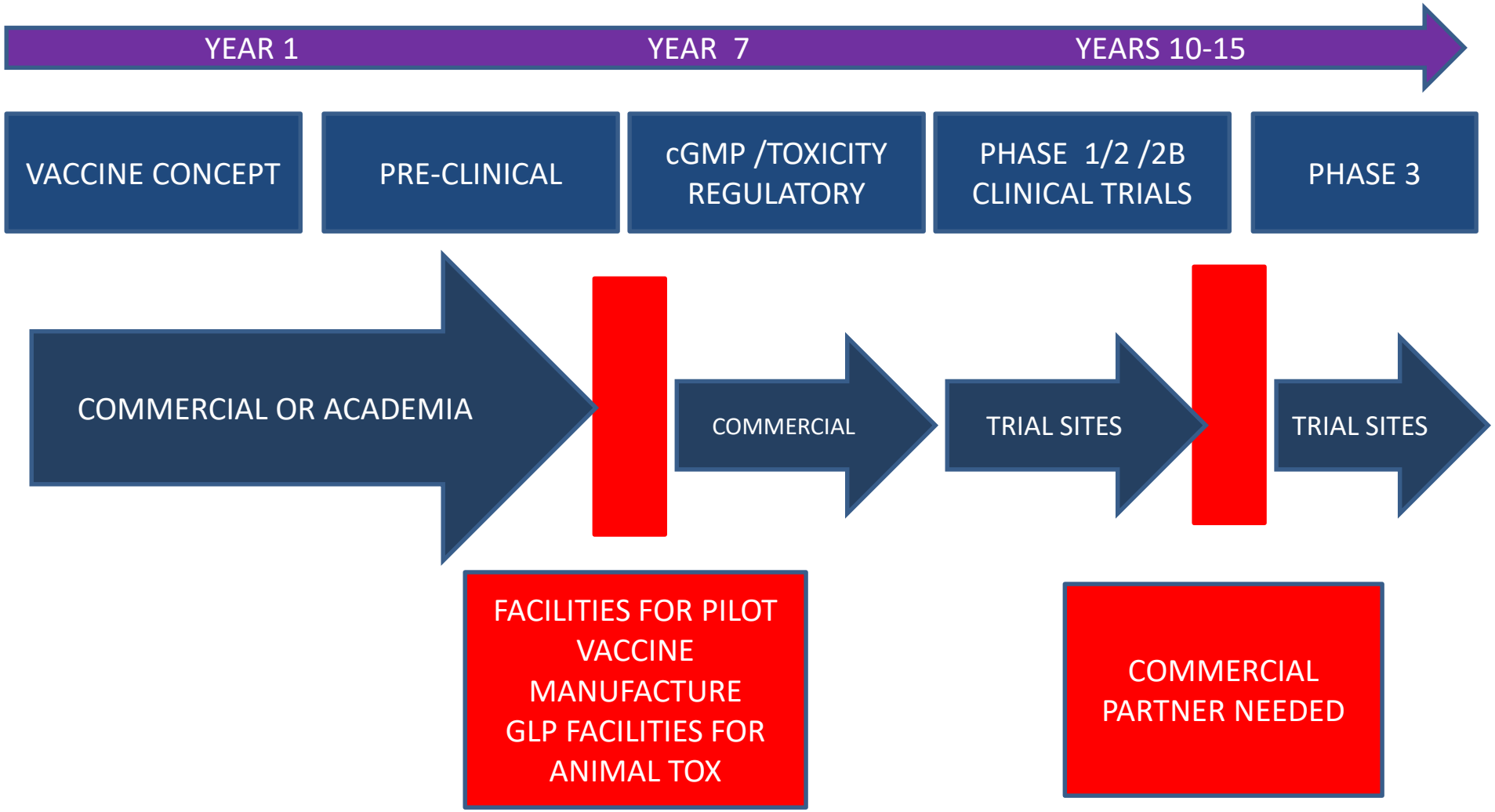
THE HUMAN VACCINE PIPELINE



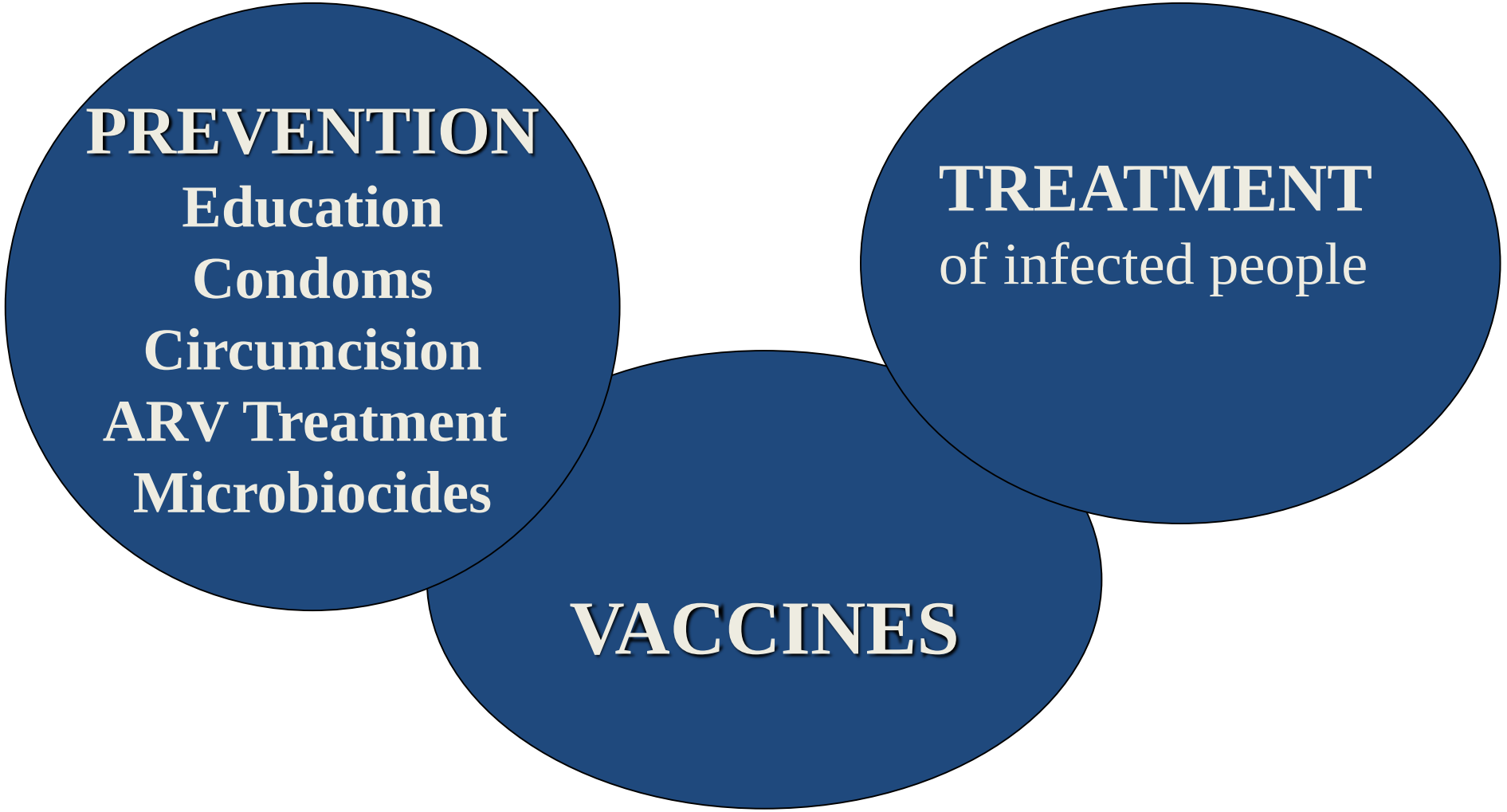
NETWORKS TO ENABLE THE VACCINE PIPELINE



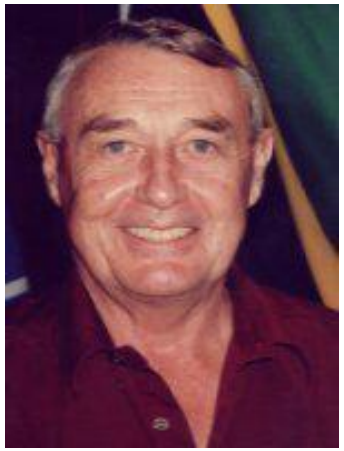
CHALLENGES IN THE VACCINE PIPELINE



INTEGRATED PLAN TO CONTROL HIV/AIDS



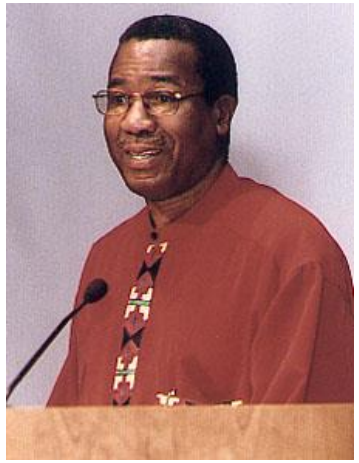
Vision for South African AIDS Vaccine Initiative SAAVI



Walter Prozesky

Health-e News 2000 – “We believe and there is a firm scientific conviction that a vaccine against AIDS will be developed.”

Dr Walter Prozesky, the driving force behind South Africa’s effort to find an AIDS vaccine, speaks this with “firm conviction”.



Malegapuru William Makgoba

Nature 1999 “ There is no guarantee, predestination or monopoly of scientific discoveries. The only certainty is that countries that invest in the effort will ultimately find the vaccine. South Africa is now ready to participate fully in this international effort to find an effective and affordable vaccine from our own vantagepoint.”

SAAVI - History (http://www.saavi.org.za/)

- The South African AIDS Vaccine Initiative (SAAVI) was established in 1999 as an initiative of the South African government and managed as a lead programme of the **South African Medical Research Council** (SAMRC). SAAVI's role was to co-ordinate and support the development and testing of HIV vaccines in South Africa with the aim of finding an affordable, effective and locally relevant HIV vaccine.

- SAAVI was initially funded through grants from the South African Departments of Health and Science & Technology, ESKOM, the Impala Platinum Community Development Trust, Transnet and the European Commission.

SAAVI Achievements

(http://www.saavi.org.za/)

- Establishment of a network of expertise in HIV vaccine development, testing, community engagement, socio-behavioural and ethical issues- capacitation of 5 HIV vaccine clinical trial sites
- Improved understanding of HIV diversity, immunology and prevalence in relation to the South African epidemic
- The development, preclinical and clinical (phase 1) testing of 2 HIV subtype C vaccine candidates
- The establishment and accreditation of a GLP laboratory for potency testing of vaccine candidates
- Capacity development of researchers and technicians in HIV vaccine development, testing, community engagement, socio-behavioural and ethical issues.

Some Reasons for Success of SAAVI

- Bring everyone together in the same forum including a high level scientific advisory committee with political support.

- Members of the SAC were advocates for SAAVI – they gave direction for the projects and facilitated funding for the projects.

PRINCIPAL INVESTIGATORS:

UCT HIV VACCINE DEVELOPMENT TEAM 2000-2008

Anna-Lise Williamson
DIRECTOR

BCG AND POXVIRUS BASED VACCINES

IMMUNOLOGY

Enid Shephard

SUBUNIT AND “NOVEL” VACCINES

Ed Rybicki

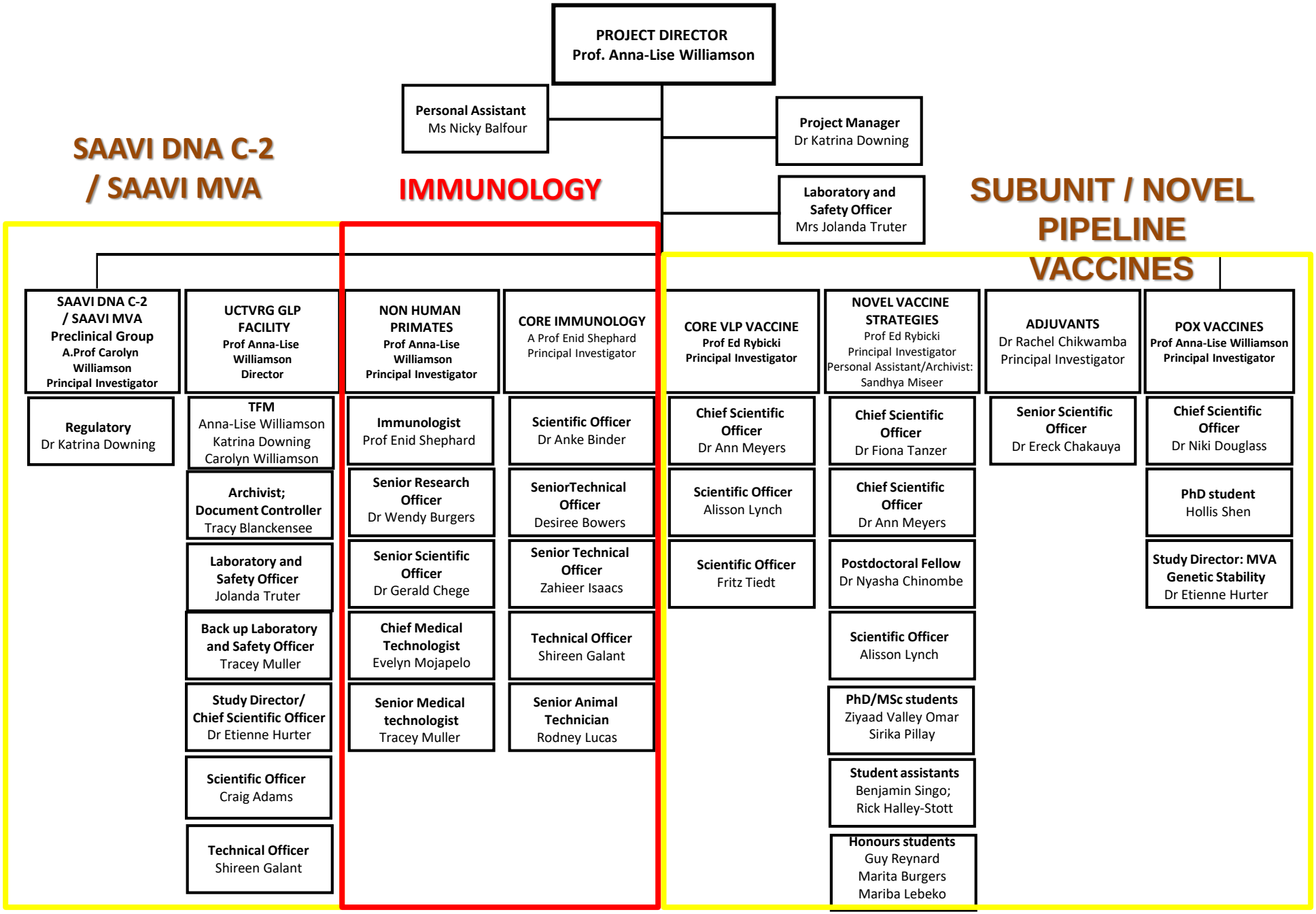
DNA VACCINES – PRECLINICAL PROGRAMME

Carolyn Williamson

SAAVI FUNDED HIV VACCINE PIPELINE AT UCT

PLATFORMS	SHUTTLE VECTOR	VACCINE MADE	VACCINE READY FOR TESTING IN ANIMALS	Mice	Macaques Baboons	Clinical Trial
VACCINES FOR CLINICAL TRIAL- FUNDING NIH AND SAAVI						
SAAVI-DNA C2						
SAAVI-MVA-C						
LATE PIPELINE – FUNDED BY SAAVI AND NIH						
BCG-GAG						
VLP GAG						
EARLY PIPELINE-DISCOVERY PROJECTS- - FUNDED BY SAAVI AND NRF						
VLP MULTIGENE						
NOVEL DNA						
NOVEL POXVIRUS- LSDV, PPV					LSDV	
PLANT VLP AND ZERA TECH						

SAAVI HIV VACCINE DEVELOPMENT GROUP- 2008



GLP GROUP

UCTVRG GLP FACILITY
Prof Anna-Lise Williamson
Director

TFM
Anna-Lise Williamson
Katrina Downing
Carolyn Williamson

Archivist; Document Controller
Debbie Stewart

Laboratory and Safety Officer
Dr Janice Ogden

Study Director/ Chief Scientific Officer
Dr Etienne Hurter

Scientific Officer
Craig Adams

Technical Officer
Shireen Galant

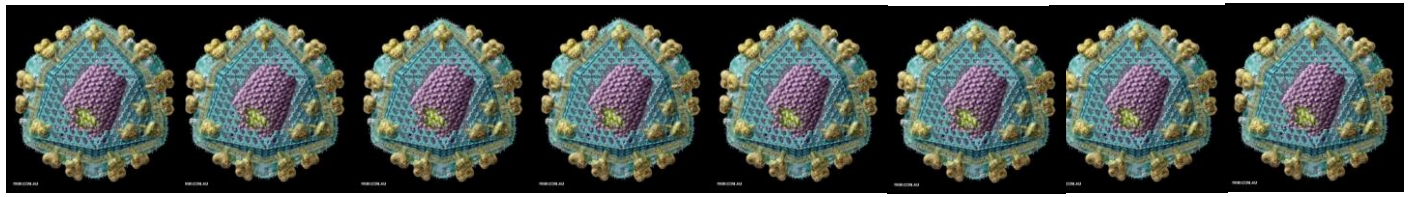
SAAVI FUNDING FOR PRODUCT DEVELOPMENT ENDED IN 2008

GLP FACILITY FUNDED TO TEST VACCINE POTENCY

Time-Line for SAAVI DNA C2 and SAAVI MVA C Vaccines

- Late **1990s** Carolyn Williamson (UCT) & collaborators characterised recently transmitted HIV subtypes and selected virus sequences for candidate vaccines.
- **2000** SAAVI started funding UCT group to make candidate HIV vaccines.
- **2001** SAAVI Scientific Advisory Committee gave **instructions to "fast-track" vaccines** for clinical trial.
- **11/ 2001** Vaccines Developmental Resources Group (Division of AIDS, NIAID, NIH) **agreed to fund the manufacturing, safety testing and regulatory documentation** costs for two SAAVI vaccines.
- **2002-2006** preclinical results, **manufacture and remanufacture of both vaccines**, tox studies done, trial designed and regulatory documentation written.
- **2007** the Food and Drug Administration (USA) approved phase 1 trial
- **2008** trial approved by South African MCC and GMO EC
- **2009** Phase one clinical testing started in Boston (USA) in February 2009 and South Africa in July 2009.
- **2010** immunogenicity results of trial showed positive results and that vaccines were safe
- **2011** further trials planned in combination with protein boost.

HIV VACCINE TRIALS NETWORK



NATIONAL INSTITUTES OF HEALTH

LOCALLY DEVELOPED CANDIDATE HIV-1 SUBTYPE C VACCINES FOR SOUTH AFRICA

THREE CLINICAL TRIALS

- HVTN 073 / SAAVI-102-
- HVTN 073E / SAAVI-102E
- HVTN 086 / SAAVI 103

Funding from SAAVI, NRF and DAIDS (NIH, USA)
Part of the HIV Vaccine Trials Network (USA)

SAAVI
SOUTH AFRICAN AIDS VACCINE INITIATIVE

HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 073 / SAAVI 102

A phase 1 placebo-controlled clinical trial to evaluate the safety and immunogenicity of SAAVI DNA-C2 vaccine boosted by SAAVI MVA-C vaccine, with or without Novartis Sub C gp140 vaccine with MF59 adjuvant, in HIV uninfected healthy vaccinia naïve adult participants in South Africa and the United States

DAIDS DOCUMENT ID 10520

BB IND 13525 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

Glenda Gray- Chair and L-G Bekker – Cape Town Site

HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 086 / SAAVI 103

A phase 1 placebo-controlled clinical trial to evaluate the safety and immunogenicity of SAAVI DNA-C2, SAAVI MVA-C and Novartis subtype C gp140 with MF59 adjuvant in various vaccination schedules in HIV-uninfected healthy vaccinia-naïve adult participants in South Africa

DAIDS DOCUMENT ID 11688

CLINICAL TRIAL SPONSORED BY

South African AIDS Vaccine Initiative (SAAVI),
Medical Research Council of South Africa (MRC-SA)
Cape Town, Republic of South Africa

Gavin Churchyard – Chair
Koleka Mlisana – Co Chair

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical and Vaccine Immunology

Subtype C gp140 Vaccine Boosts Immune Responses Primed by the South African AIDS Vaccine Initiative DNA-C2 and MVA-C HIV Vaccines after More than a 2-Year Gap

Glenda E. Gray,[a,b] Kenneth H. Mayer,[c] Marnie L. Elizaga,[d] Linda-Gail Bekker,[a] Mary Allen,[f] Lynn Morris,[g] David Montefiori,[h] Stephen C. De Rosa,[d] Alicia Sato,[d] Niya Gu,[d] Georgia D. Tomaras,[h] Timothy Tucker,[b] Susan W. Barnett,[i] Nonhlanhla N. Mkhize,[g] Xiaoying Shen,[h] Katrina Downing,[a] Carolyn Williamson,[a,j] Michael Pensiero,[f] Lawrence Corey,[d] Anna-Lise Williamson,[a,j] for the NIAID-funded HIV Vaccine Trials Network

June 2016 Volume 23 Number 6

PLOS ONE

RESEARCH ARTICLE

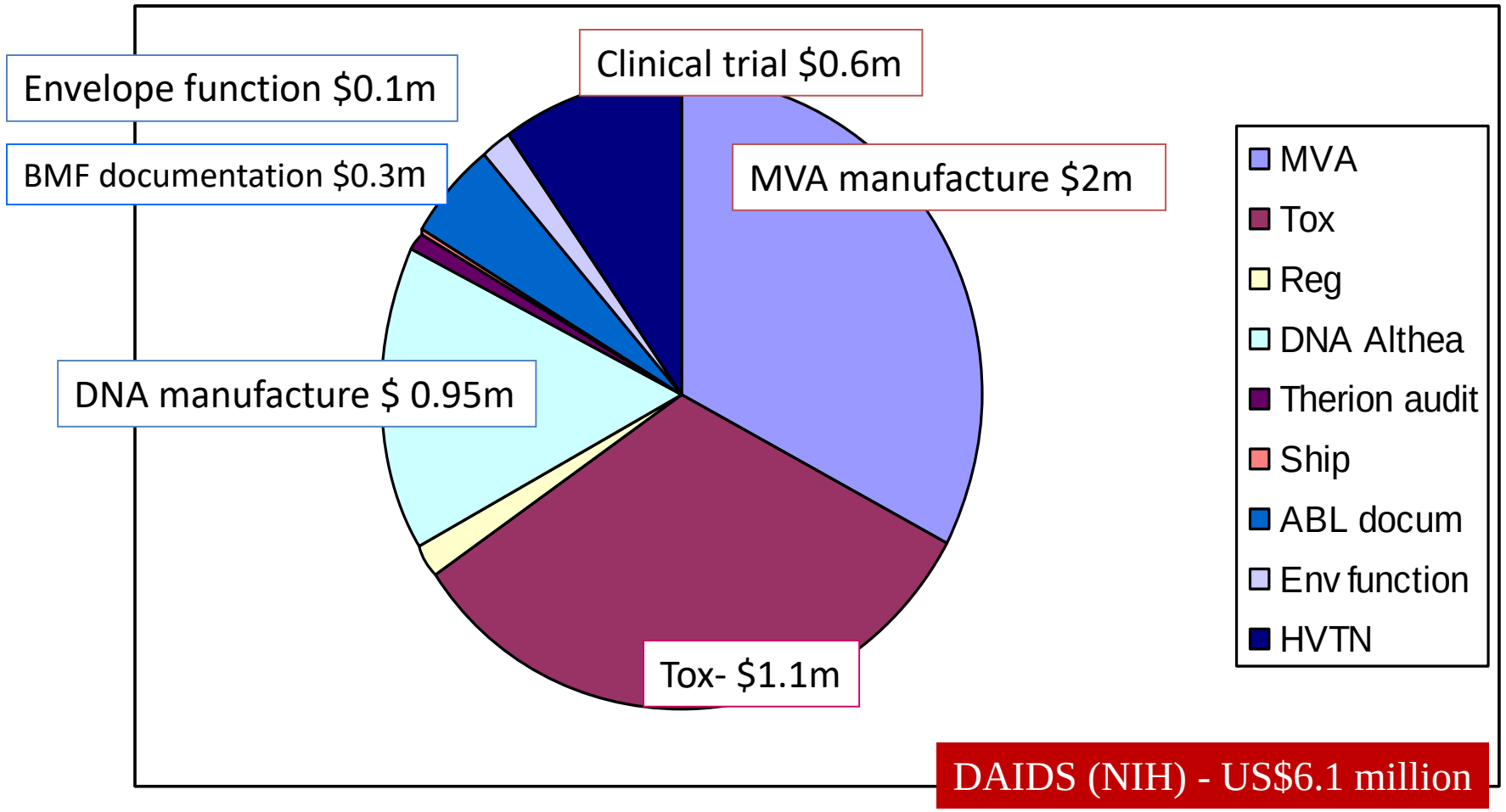
Sequential Immunization with gp140 Boosts Immune Responses Primed by Modified Vaccinia Ankara or DNA in HIV-Uninfected South African Participants

Gavin Churchyard[1,2,3]*, Koleka Mlisana[4], Shelly Karuna[5], Anna-Lise Williamson[6], Carolyn Williamson[6], Lynn Morris[7], Georgia D. Tomaras[8], Stephen C. De Rosa[5,9], Peter B. Gilbert[5], Niya Gu[5], Chenchen Yu[5], Nonhlanhla N. Mkhize[7], Tandile Hermanus[7], Mary Allen[10], Michael Pensiero[10], Susan W. Barnett[11], Glenda Gray[12,13], Linda-Gail Bekker[14], David C. Montefiori[15], James Kublin[5], Lawrence Corey[5,9]

September 1, 2016

UCT HIV VACCINE DEVELOPMENT PROGRAMME PART OF THE GLOBAL INITIATIVE AND NOT WORKING IN ISOLATION

PARTNERSHIP WITH DIVISION OF AIDS , NIH
APPROXIMATE COSTS NIH CONTRIBUTION TO SAAVI DNA/MVA PROGRAMME



DAIDS (NIH) - US$6.1 million

Closure of SAAVI Offices

"On 31 December 2012, as part of the revitalization of the SAMRC, the SAAVI Office and the Masikhulisane Community Engagement Programme at the SAMRC were closed.

Activities funded through the NDOH SAAVI allocation are now managed under the HIV Programme of the **Grants Innovation and Product Development (GIPD) Division** of the SAMRC. The NDOH funds are used to support basic laboratory science, capacity building, community engagement and clinical research in HIV. "

SHIP FUNDING (2014-2020)

- Improved DNA and MVA based HIV vaccines.
- Improved design of proteins vaccines
- Production of protein vaccines in tissue culture and plants
- Considerable improvement in immunogenicity including Tier 2 neutralisation
- Development of lumpy skin disease virus as an HIV vaccine vector
- Patent applications (N=4)

Result of Present Strategies for HIV Vaccines

- Promising HIV candidates will be a challenge to get to clinical trial
- No managed pipeline or capacity to respond to modifying vaccines based on data generated in clinical trials
- Lack of sufficient local funds takes away the bargaining power we had as South Africans when meeting and defining relationships with international partners
- Lost opportunities because organisations have more bargaining power than individuals

South African Capacity Needed

Improved Non- Human Primate Facility

+

Infrastructure for better transition between product development and application

+

Pilot Vaccine Manufacturing Plant

=

SA capacity to make HIV and OTHER candidate vaccines

SPECIAL REPORT SWINE FLU

SA wants own H1N1 flu vaccine

2009-08-26 22:29

"South Africa has arrived at a situation where we have no option but to start developing our own vaccine capacity, not only for H1N1, but generally," Minister Motsoaledi told parliament in 2009.

• H1N1 contagious period 'longer'

their own population first before thinking about the developing world," Motsoaledi said.

South Africa does have a growing vaccine industry, but is considered by experts to be unlikely to be able to produce a swine flu vaccine any time soon.

The World Health Organisation (WHO) declared swine flu a pandemic in June. It has killed about 1 800 people after spreading to nearly 180 countries, 25 of them in Africa.

Director-General of the World Health Organization warns of a global pandemic

- “As coronavirus spreads around the world, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization says the window for containment is narrowing, and warns of a global pandemic.”

https://www.cnbcafrica.com/international-video/2020/03/01/prepare-for-a-coronavirus-pandemic-who-chief-says-full-interview2020

South Africa will not be first in line for drugs or vaccines against Coronavirus

– we need to be more self sufficient

Veterinary Vaccines

INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

Lumpy Skin Disease Virus as a Recombinant Vaccine Vector

Niki Douglass, Ros Chapman and Anna-Lise Williamson

science & innovation
Department:
Science and Innovation
REPUBLIC OF SOUTH AFRICA

NRF
National Research Foundation

technology innovation AGENCY

ELSEVIER

Vaccine 20 (2002) 2693–2701

Vaccine

www.elsevier.com/locate/vaccine

Immunogenicity of a recombinant lumpy skin disease virus (neethling vaccine strain) expressing the rabies virus glycoprotein in cattle

Kate Aspden [a], Alberdina A van Dijk [b,1], John Bingham [b,2], Dermot Cox [a], Jo-Ann Passmore [a], Anna-Lise Williamson [a,*]

[a] *Division of Medical Virology, Department Clinical Laboratory Sciences, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town 7925, South Africa*

[b] *Onderstepoort Veterinary Institute, Private Bag X05, Onderstepoort 0110, South Africa*

Received 4 September 2001; received in revised form 10 December 2001; accepted 14 March 2002

1 × 10e6 ffu/ml given IM at day 0

Rabies virus neutralising antibodies levels in international units (IU) per millilitre in the cattle sera

Day	Calf 9L34	Calf 9L47	Calf 9L48	Calf 9L49
0	0.0	0.0	0.0	0.0
28[a]	27.0[c]	186.2	15.5	15.5

[c] A value of 0.5 IU/ml is the value taken by the World Health Organisation as the minimum antibody titre required to elicit protection against rabies.

Next Generation of LSDV-Rabies Vaccine being made at UCT:

- Insertion site is now intergenic compared to ribonucleotide reductase gene
- Positive selection marker, ECOGPT, removed
- Fluorescent marker used instead of Beta-galactodisase
- Better promoters selected.

HISTORIC RECOMBINANT LSDVs MADE AT UCT

- LSDV- Bovine ephemeral Fever Virus – did not give conclusive results as challenge was not virulent (D.Cox, A. Cohen, A van Dijk)

- LSDV- Rift Valley Fever Virus gave partial protections from virulent challenge in sheep (A. Cohen, A van Dijk, R. Swanepoel)

Cohen A., D. Cox, A. A. Van Dijk, A. Korber, K. R. Dumbell and A-L Williamson (1999) Lumpy Skin Disease Virus as a Recombinant Vaccine Vector for Rift Valley Fever Virus and Bovine Ephemeral Fever Virus. European Society for Veterinary Virology. 4th International Congress on Veterinary Virology. "Virus survival and Vaccination" Edinburgh, Scotland 24-27 August 1997. Conference Proceedings. Moredun Research Institute, Reprographics Section. ISBN 0-70840-613-0

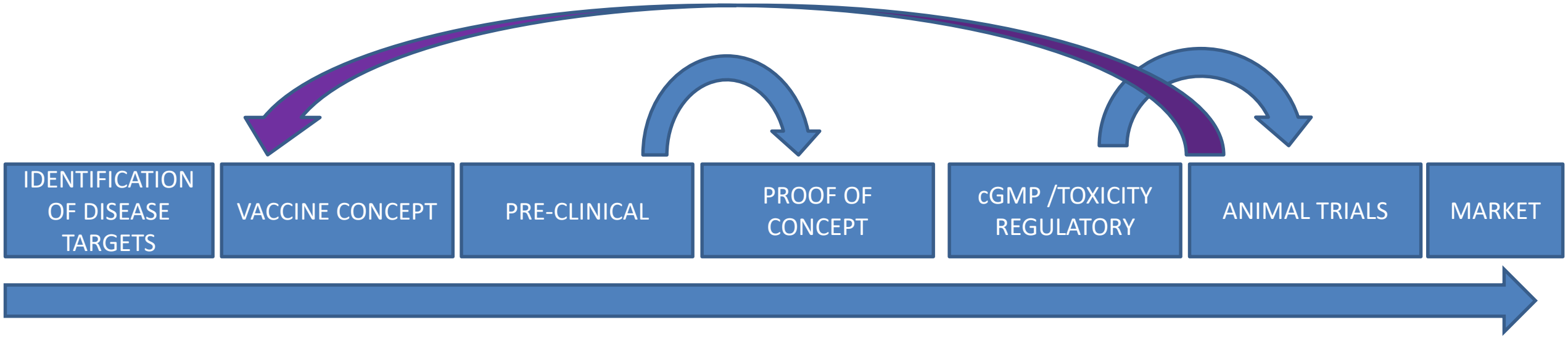
Next Generation of LSDV-BEFV Vaccine being made at UCT – funded by TIA:

- Novel LSDV backbone and cloning sites
- Neutralising antibodies in rabbits
- Cattle experiments planned
- Partnership with Onderstepoort Biological Products

Need to bring together all stakeholders to develop the veterinary vaccine pipeline for Africa

- Epidemiologists identifying disease priorities in Africa
- Research scientists providing an understanding of vaccine targets and potential correlates of protection
- Laboratories with expertise in the development of vaccines
- Experts in the regulatory requirements
- Commercial manufacturers with the capacity to assess and develop new products

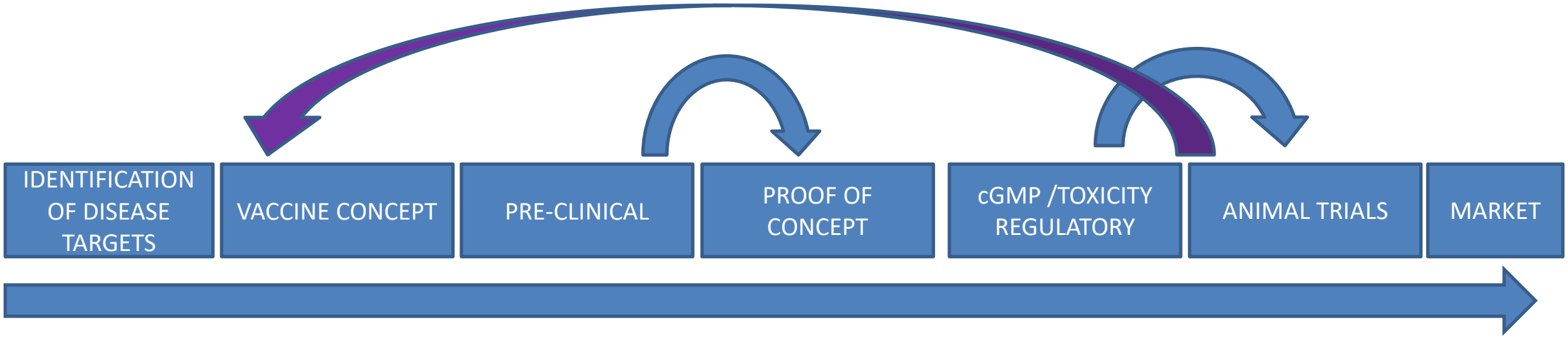
NETWORKS TO ENABLE THE VACCINE PIPELINE



STUDIES ON GENETIC DIVERSITY OF PATHOGENS

DIFFERENT VACCINE VECTORS INDUCING DIFFERENT RESPONSES

NETWORKS TO ENABLE THE VACCINE PIPELINE



STUDIES ON GENETIC DIVERSITY OF PATHOGENS

DIFFERENT VACCINE VECTORS INDUCING DIFFERENT RESPONSES

Major block is animal testing in target animals

Veterinary Vaccine Conclusions

- We have considerable expertise in making poxvirus recombinants.
- Our goal is to develop products based on LSDV so that we have a common platform for multiple vaccines.
- At UCT we can test vaccines in small animals but cannot do the large animal testing need for veterinary products.
- We need partnerships to enable our products to get to market – this included facilities and expertise to do the large animal testing as well as commercialisation.

Vaccines For Africa Initiative

- **Need major coordination, strong leadership, relevant experience, respected scientific advisors and vision.**

- **Resources are important but will not impact on vaccine development without overall vision and support of that vision from all role players**
- Financial commitment is needed in the long term with short and long term outputs.
- We will struggle to get future South African vaccines to market if individual researchers are funded without overall coordination of the goals and ensuring that the resources are in place.

Conclusion

South Africa has the ability to construct candidate vaccines and to test them –

we should participate in the whole vaccine pipeline and not just test other people's products!!!

Key Role Players in SAAVI-DNA C2 and SAAVI- MVA C Development	
Characterization and Selection of HIV-1 Subtype C Isolates for Use in Vaccine Development – before SAAVI	Carolyn Williamson (UCT), L. Morris (NICD), Gita Ramjee (MRC), S. A. Karim (KZN), M. F. Maughan (Alphavax) , R. Johnston (UNC) R. Swanstrom (UNC, USA)
Invitation for A-L Williamson to present to NIH to obtain funding for manufacture, toxicity, trials	Tim Tucker- previous director of SAAVI
SAAVI DNA-C construction, SAAVI MVA-C design, safety testing of HIV genes, potency , genetic stability, mouse immunogenicity, non-human primate immunogenicity, preparation of IB, Participation in protocol development, documents for MCC, IND and GMO	UCT group headed by Anna-Lise Williamson
Quality Assurance for SAAVI-DNAC2 GLP compliant potency assay	Maureen Lambrick and team (NHLS, GSH)
Macaque and Baboons	Delft MRC non- human primate facility
Neutralizations	L. Morris (NICD, NHLS, JOHANNESBURG)
T cell data, provision of peptides, training and QC T cell assays for non-human primate work	C. Gray (NICD, NHLS, JOHANNESBURG)
Manufacture of SAAVI vaccines	Althea and Therion (USA)
Phase 1 trial protocol	Glenda Gray (Wits) protocol chair HVTN Linda-Gail Bekker (Cape Town site)
Regulatory documentation (MCC, FDA, GMO)	ABL, NIH, SRI,UCT, Wits

FUNDING ACKNOWLEDGEMENTS

DoH

DST