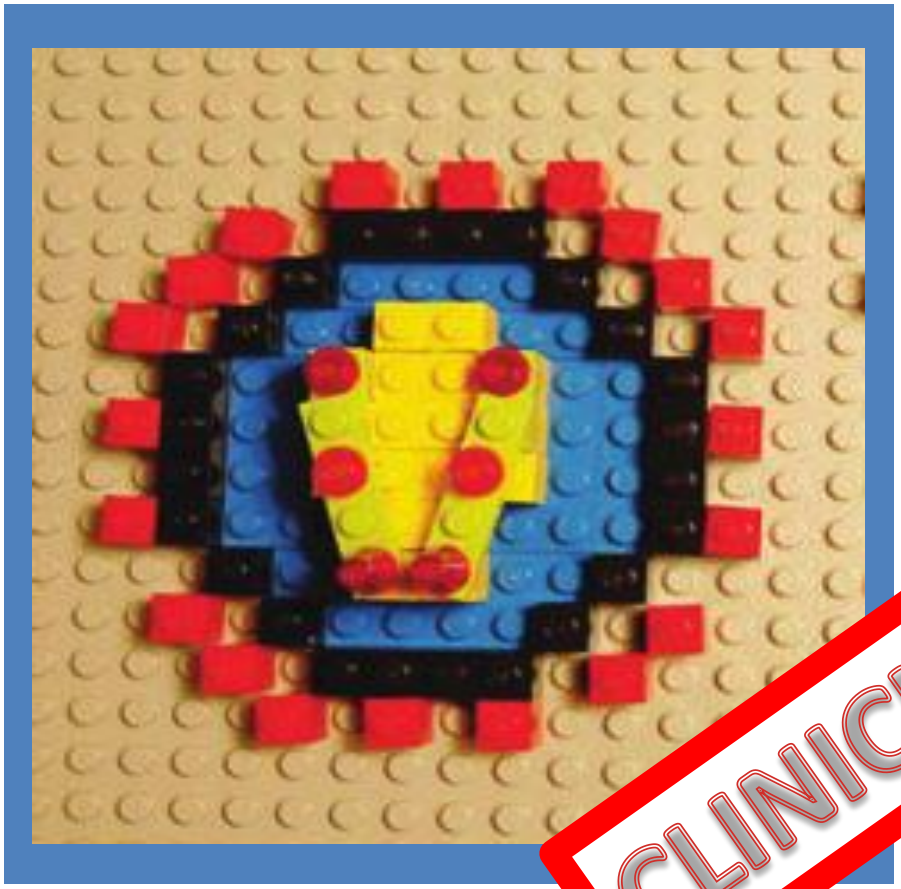
Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za



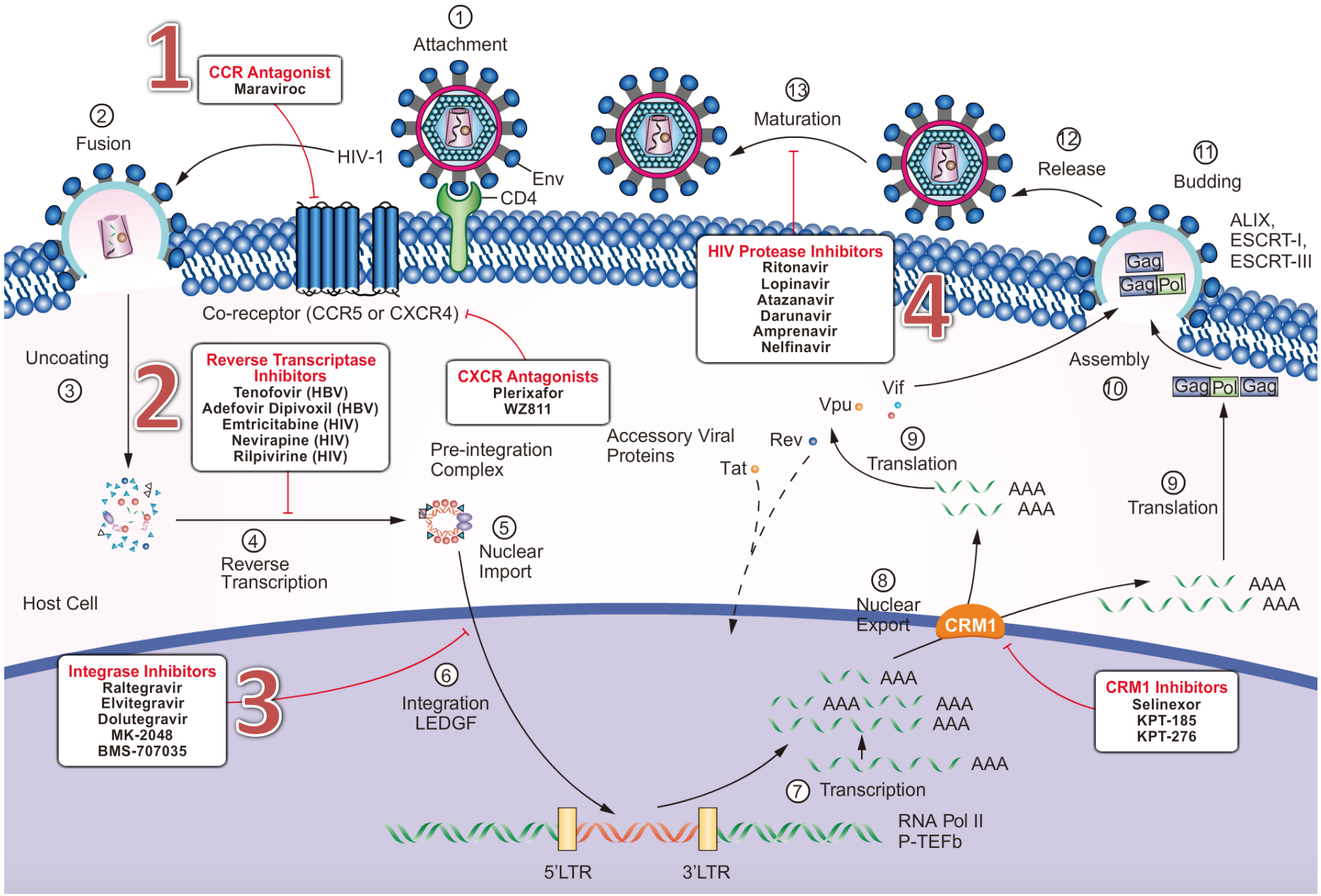
CLINICIAN'S PERSPECTIVE

HIV life cycle revisited: What's new in basic science?

Theresa Rossouw

Outline of the Presentation

- Lifecycle overview
- New drugs & therapies
- Cell entry
  - Co-receptor binding
  - Attachment



Keeping it Simple

Need for New & Novel Treatment

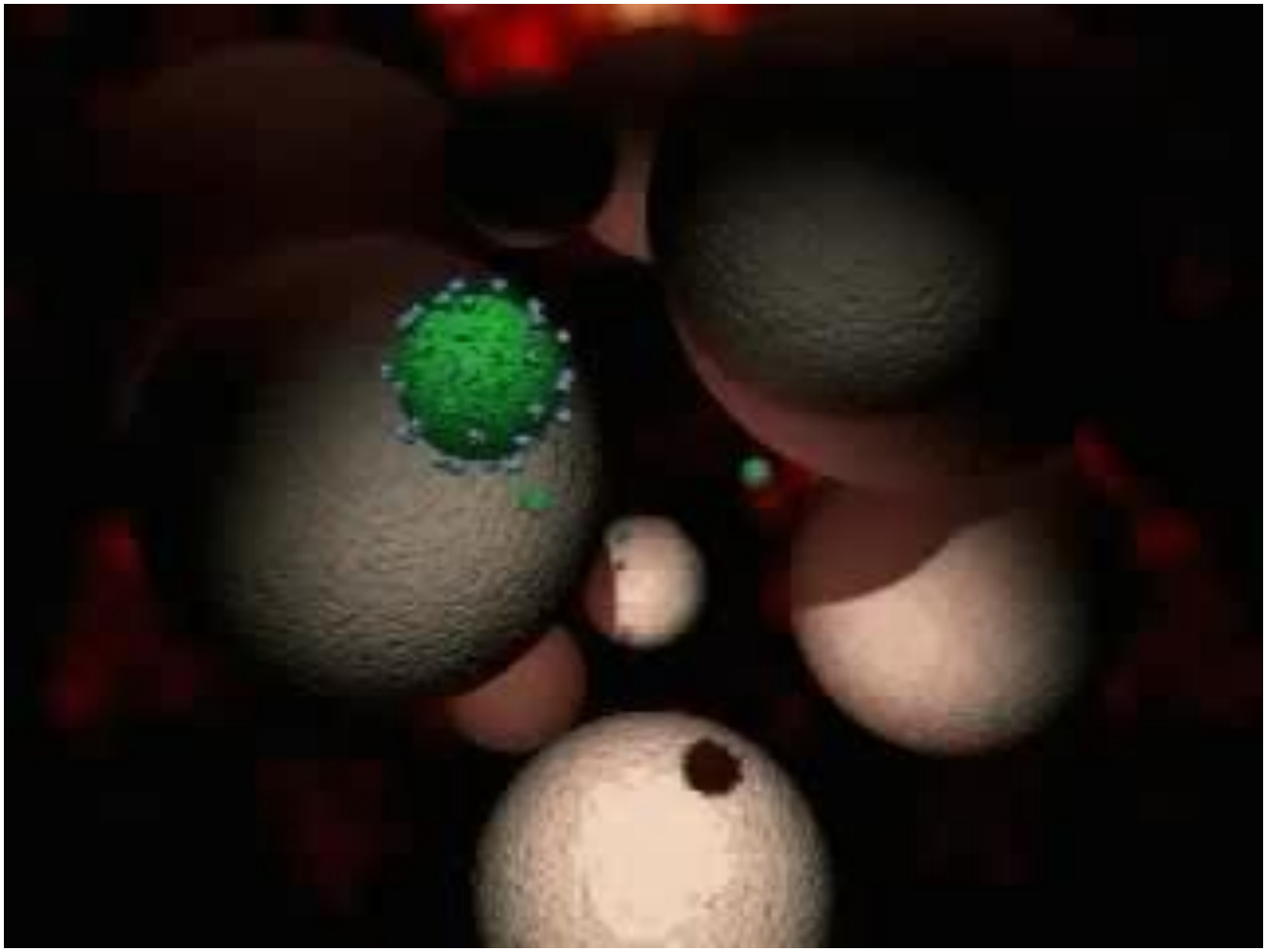
- Class resistance
- Transmission of resistant viruses
- Treatment fatigue
- Serious drug-associated pathology

New Options on the Horizon

NRTIs	NNRTIs
Tenofovir alafenamide (TAF) MK-8591 Apricitabine Elvucitabine Racivir	Doravirine GSK 2248761 (IDX899) RDEA806 Lersivirine
PIs	**INSTIs**
CTP-518 GS-8374 PPL-100	Elvitegravir Dolutegravir Cabotegravir GSK-572

Novel Treatment Options

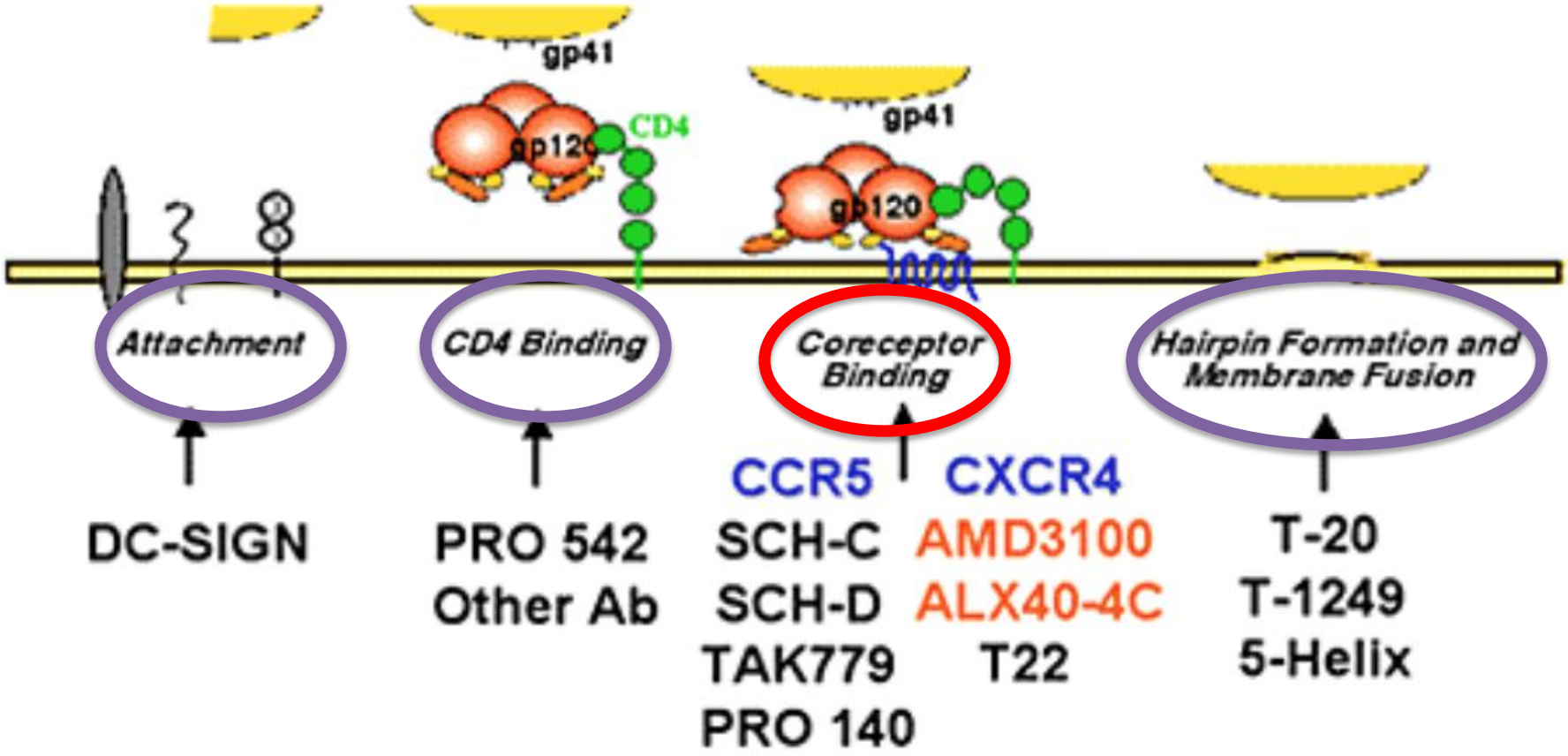
- Maturation inhibitor
  - BMS-955176
  - Vivecon (MP-9055)
- New target: Rev-mediated viral RNA biogenesis
  - ABX464
- Monoclonal antibodies
  - Broadly neutralising antibody VRC01
  - Anti-PD-1 (pembrolizumab)
  - CD4 - TNX-355, TBM-360
- eCD4-Ig
- TLR7 agonist
  - GS9620 – reversal of latency
- Genetic therapy & stem cell research



Entry Inhibition

- Act outside the cell
- No concerns about:
  - Intracellular drug penetration
  - Interactions with drugs metabolized by cytochrome P450
    - PIs and NNRTIs
  - Disruptions of lipid homeostasis

Entry Inhibition



Co-receptors

- Most infections result from virus strains that use CCR5 in addition to CD4 to infect cells
  - R5 virus strains
  - Predominate in first few years
- Mutations may accumulate in Env that enable it to use CXCR4
  - X4 or R5X4 strains
  - Accelerated disease progression
  - In part because CXCR4 is expressed on a much greater fraction of CD41 T cells than CCR5

UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Treatment of HIV and acute myeloid leukemia by allogeneic CCR5-d32 blood stem cell transplantation

Guido Kobbe[1], Rolf Kaiser[2], Elena Knops[2], Nadine Lübke[3], Gabor Dunay[4], Johannes Fischer[5], Falk Hüttig[6], Rainer Haas[1], Dieter Häussinger[6], Björn Jensen[6]

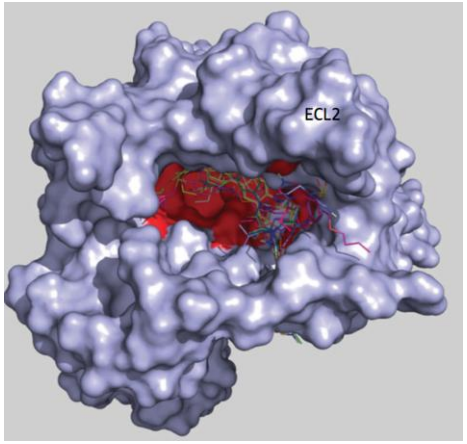
1 Department of Hematology, Oncology and Clinical Immunology, University of Düsseldorf, Germany; 2 Institute of Virology, University of Cologne, Germany; 3 Institute for Virology, University of Düsseldorf, Germany; 4 Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany; 5 Institute of Transplantation Diagnostics and Cell Therapeutics, University of Düsseldorf, Germany; 6 Department of Gastroenterology, Hepatology and Infectious Deseases, University of Düsseldorf, Germany

Flurry of New CCR5 Antagonists

First anti-HIV agents that target host proteins rather than viral enzymes or proteins

CCR5 inhibitors				
TAK-652 (TBR-652)	Takeda/Tobira	Phase II	HIV	A potent, orally bioavailable CCR5 antagonist
Aplaviroc	Ono	Terminated (Phase II/III)	HIV	Aplaviroc's development was stopped because of hepatotoxicity
Maraviroc	Pfizer	Approved by US FDA	HIV	The first FDA-approved CCR5 antagonist
PF-232798	Pfizer	Phase II	HIV	A second-generarion Pfizer oral CCR5 antagonist
Vicriviroc	Schering-Plough/Merck	Terminated (Phase III)	HIV	Vicriviroc did not meet the primary efficacy endpoint
INCB9471	Incyte	Phase II	HIV	A new class of oral CCR5 antagonist

CCR5/CCR2 Inhibitor



- Cenicriviroc (formerly TBR-652)
- CCR2 receptor binds to monocyte chemo-attractant protein 1 (MCP-1)
  - Promotes migration of monocytes
  - Role in inflammation
  - Implicated in a range of conditions including liver fibrosis, metabolic syndrome and cardiovascular disease.
- Phase II
  - Lower sCD14
    - High sCD14 independent predictor of all-cause death in SMART
- High drop-out rate because of a complicated dosing

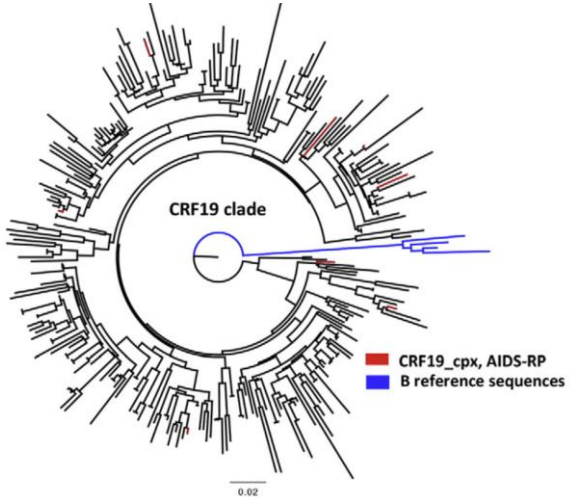
Resistance

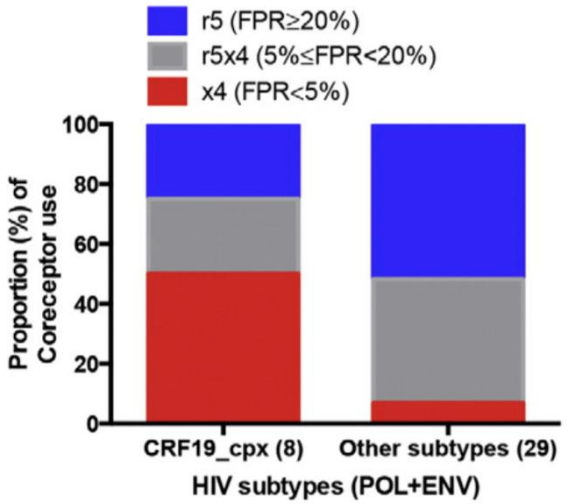
- Two mechanisms
  - Changing the way it uses co-receptors
    - Use the same co-receptor but in a drug-bound form
    - Many mutations in gp120 region of HIV-1 Env, especially in the V2 and V3 regions
  - Switching co-receptor usage
    - CCR5 → CXCR4

Concern with Blocking CCR5

Original Article

CRF19_cpx is an Evolutionary fit HIV-1 Variant Strongly Associated With Rapid Progression to AIDS in Cuba





EBioMedicine 2 (2015) 244–254

Concerns with Blocking CCR5

- Current consensus: CCR5 & CXCR4 are major co-receptors
- Additional chemokine receptors have been reported to act as alternative co-receptors for CD4 when they are over-expressed
  - CCR2b, CCR3, CCR8, CCR9, CXCR6, CXCR1

Safety Concerns

- Normal function of CCR5 & CXCR4 not fully understood
- Might disrupt normal immune function
- CCR5 δ32 mutation
  - No serious or life-threatening immunological impairment
  - But some degree of immune dysfunction
    - Lower risk of organ rejection after transplantation
    - Lower likelihood of clearing hepatitis C virus
    - Higher risk of symptomatic West Nile virus infection
- Genetically engineered CCR5-deficient mice have impaired immune responses to certain OIs

Interest in Blocking CXCR4

- Interaction between CXCR4 and its ligand SDF-1 is involved in various disease conditions
  - cancer cell metastasis
  - leukemia cell proliferation
  - rheumatoid arthritis
  - pulmonary fibrosis
  - CXCR4 is expressed in >23 human cancers – breast, ovarian, hepatocellular, hematological, lung, brain, prostate
- CXCR4 inhibitors have potential as novel therapeutics for the treatment of these diseases as well as HIV infection

CXCR4 Antagonists

Compound	Company	Stage of development	Disease	Note
CXCR4 inhibitors				
ALX40-4C	NPS Allelix	Terminated (Phase I/II)	HIV	No apparent effect was observed on viral load
AMD3100	AnorMED	Terminated (Phase I/II)	HIV	Little effect was observed on viral load
AMD3100 (plerixafor)	Genzyme	Approved by US FDA	Stem cell mobilizer	Use in combination with G-CSF
AMD070	Genzyme	Suspended (Phase I/II)	HIV	A derivative of AMD3100 that can be orally administered. Liver histology changes were observed in long-term preclinical toxicity experiments.
T140	Kyoto University	Preclinical	HIV, cancer metastasis, leukemia, rheumatoid arthritis	A downsized analog of T22 peptide that specifically inhibits CXCR4
KRH-3955	Kureha	Preclinical	HIV, cancer metastasis	A highly potent, orally bioavailable CXCR4 antagonist

No effect

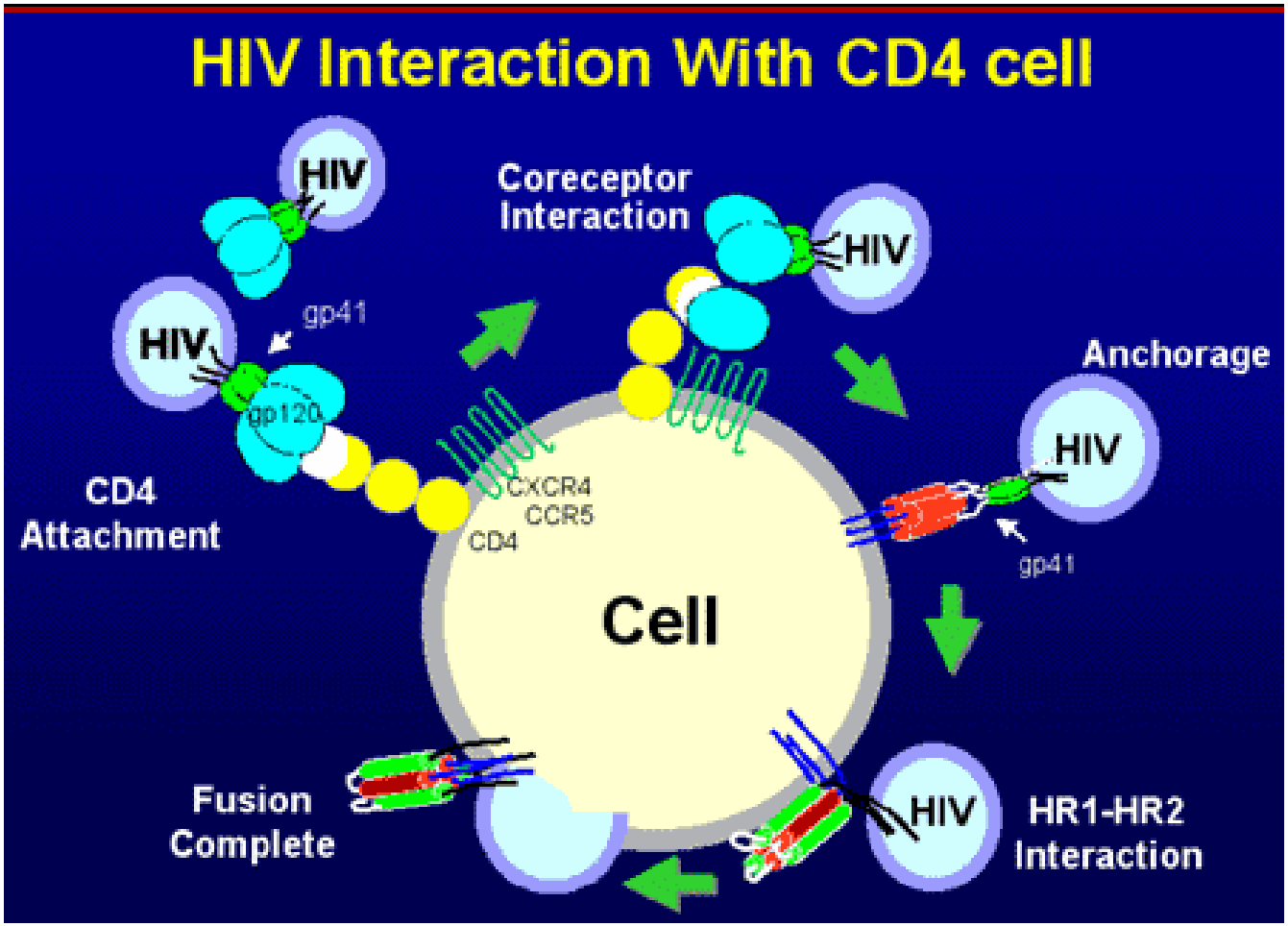
Cardiotoxicity

Liver toxicity

Safety Concerns

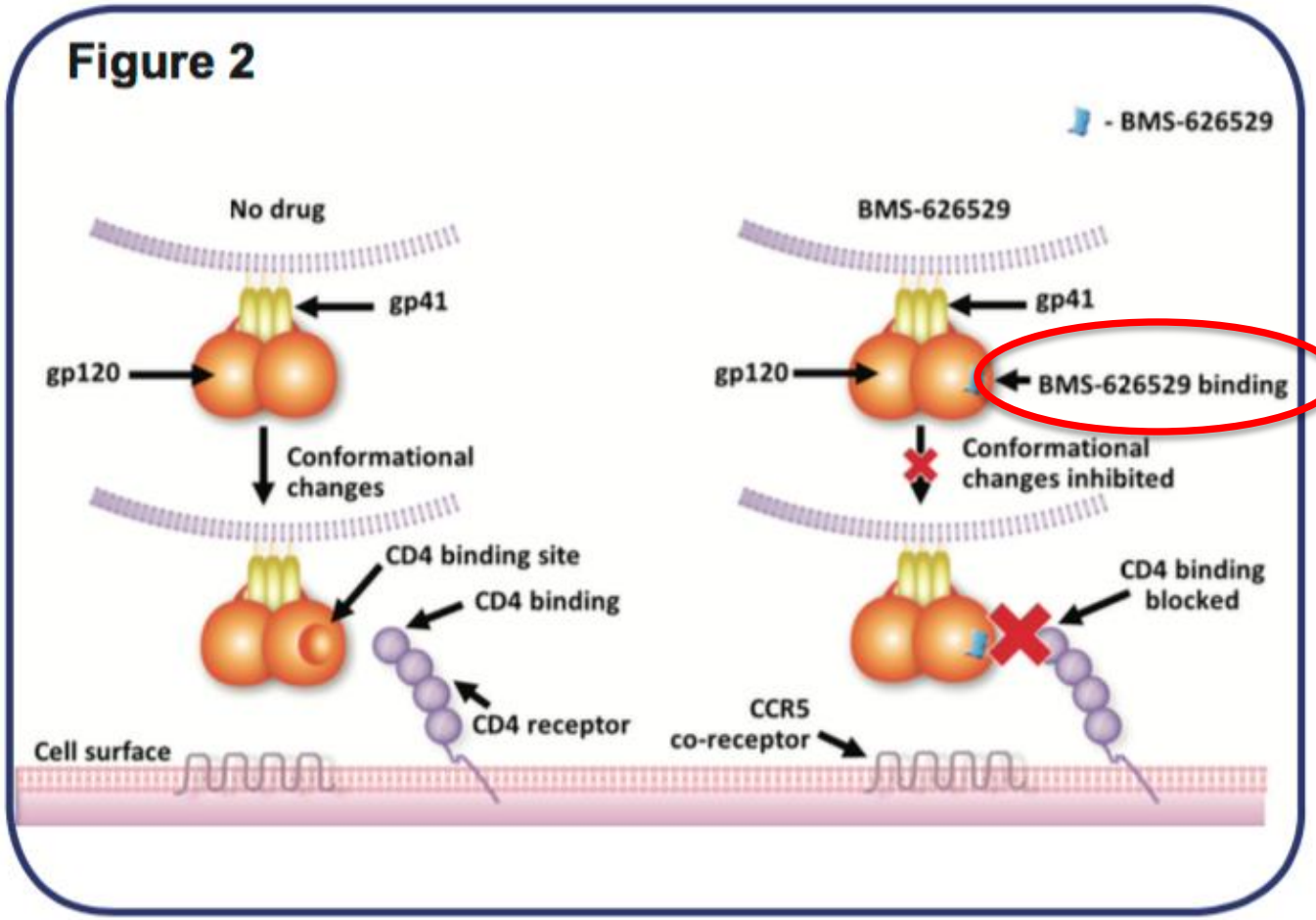
- Even less is known blocking CXCR4
- CXCR4 is expressed in a wide variety of normal tissues
  - lymphoid tissues, thymus, brain, spleen, stomach & small intestine
- Mice lacking CXCR4 have abnormal hematopoiesis, cardiogenesis & vascularization
- SDF-1/CXCR4 interaction is critical for:
  - retention of hematopoietic stem cells in BM
  - foetal hematopoiesis

New Strategies



HIV Entry -- From Molecular Insights to Specific Inhibitors. http://www.medscape.org/viewarticle/418682

CD4 Attachment Inhibitor – BMS-663068 (fostemsavir)



Thompson M et al. CROI 2015. Poster 545

Combinectin (BMS-986197)

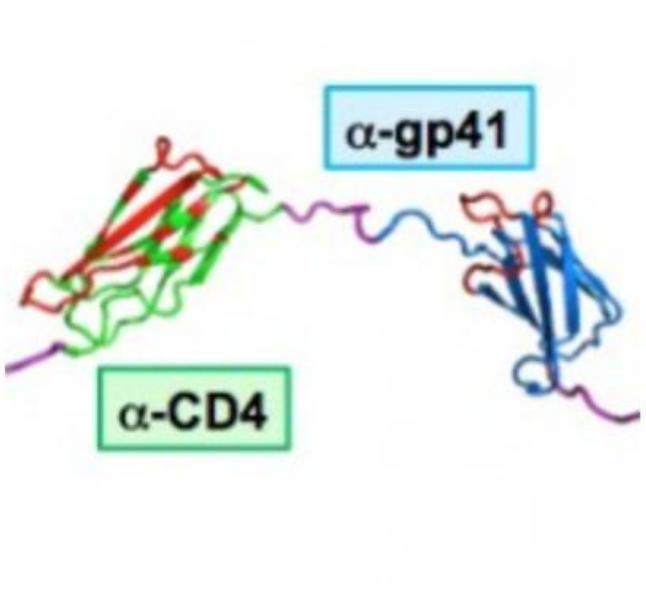
- Novel recombinant biologic molecule
- 3 independent & synergistic modes of blocking HIV entry
- Potential as single long-acting regimen for HIV-1 as a self-administered s/c weekly injection
- Adnectins are small proteins
  - Derived from human fibronectin protein
  - Modifiable binding loops resembling certain antibody regions

Combinectin

1. Anti-CD4 adnectin: allows binding to the receptor, but prevents conformational changes needed for binding to co-receptors
2. Anti-gp41 adnectin: attacks the N17 sequence of the HIV gp41 envelope protein subunit
3. Alpha-helical peptide fusion inhibitor: works similarly to enfuvirtide

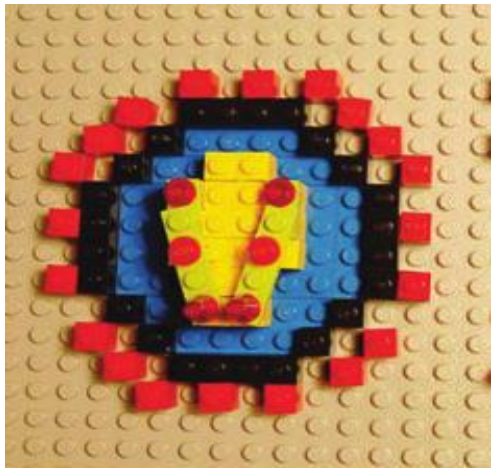
Human serum albumin (HSA) molecule: optimize in vivo PK

Early laboratory and animal studies



Part of combinectin BMS-986197 (from Krystal et al, CROI 2016, abstract 97)

Conclusion



- New options on the horizon
  - Less toxic
  - Less frequent dosing
  - Possibly even self-administered injections
- More options for patients with drug-resistant virus

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Thank You

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

2016