Aptamers: Cutting Edge Technology to Combat HIV/AIDS

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CSIR

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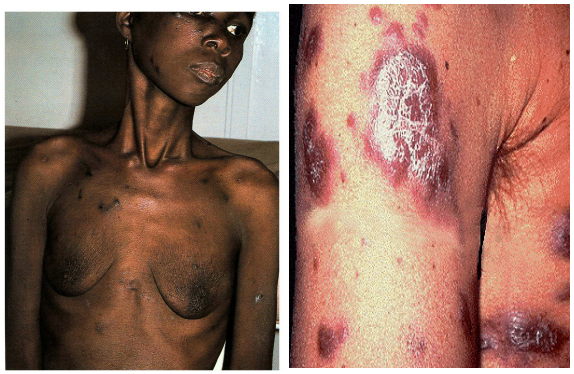
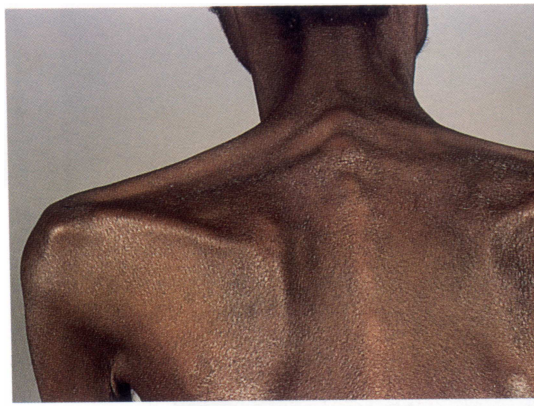
South African Burden of Diseases

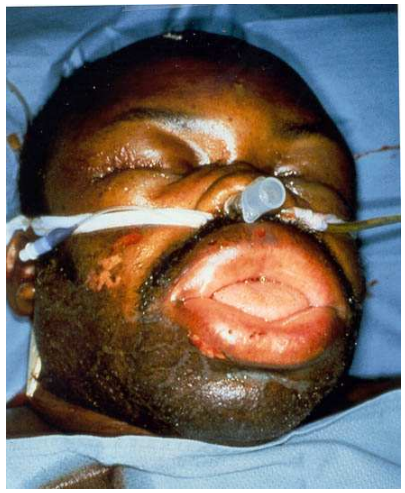


HIV/AIDS **(38% YLLs)**



Diseases of poverty, e.g. TB **(25%YLLs)**

Chronic diseases,
e.g. Heart diseases **(21%YLLs)**



Injuries **(16% YLLs)**

Bradshaw *et al*. 2003. Initial Burden of disease estimates for South Africa. SAMJ. 76(9): 682- 8

Common Denominator in the African burden of disease

- **HIV/AIDS is a common denominator in at least three of the South African quadruple burden of diseases**

  - **HIV/AIDS fuels the TB epidemic (disease of poverty)**

  - **HIV/AIDS one of the underlying cause of some chronic diseases (e.g. cardiomyopathy)**

- **HIV/AIDS is the defining public health problem of our generation.**

- **Greatest challenge facing South Africa and the entire African continent today.**

- **The epidemic has attained a scale at which the impact on the economy and, even more broadly, on our society, is both evident and very serious**

Now that we know the defining public health problem of our generation

What do we do?

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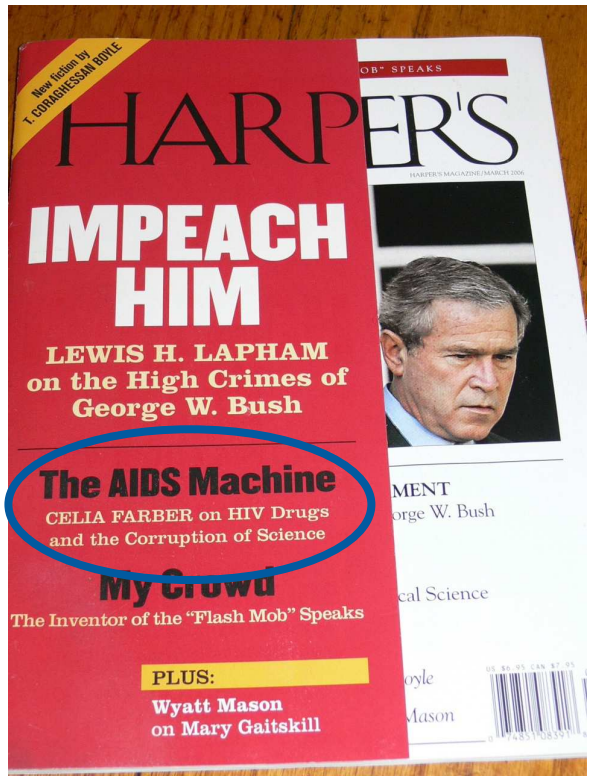
Do We Deny It?

AIDS DENIALISM!



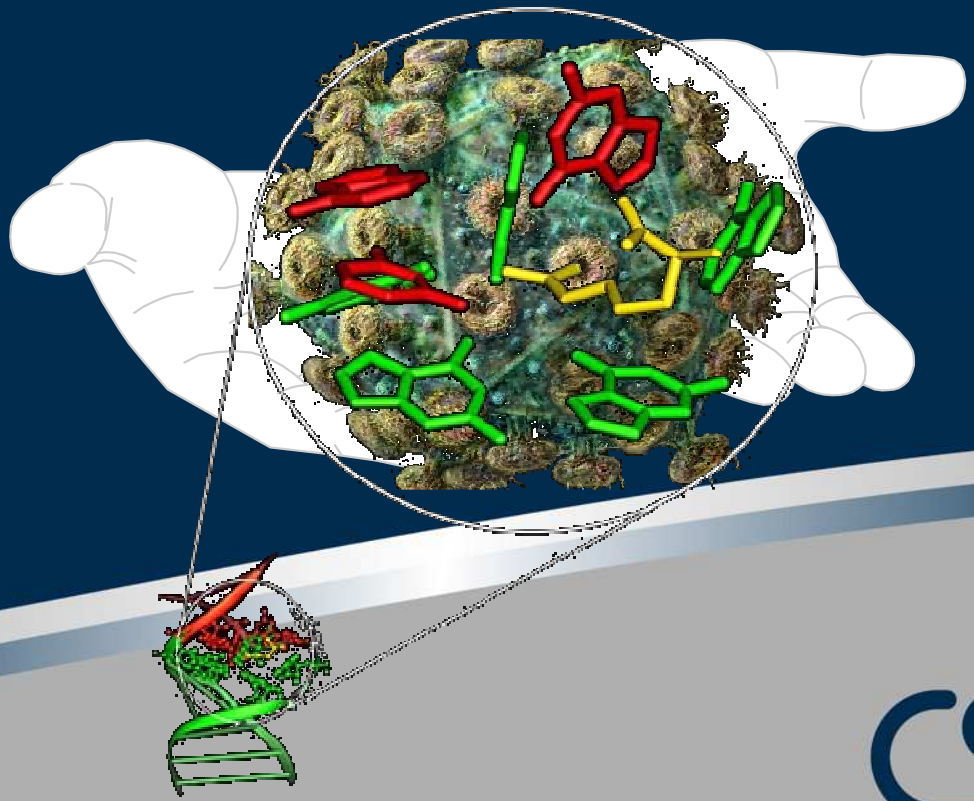
Or…

“Do we accept the diagnosis but defy the verdict”

Norman Cousins, 1989: The Biology of Hope

But How?

Aptamers:
Part of the feasible solution



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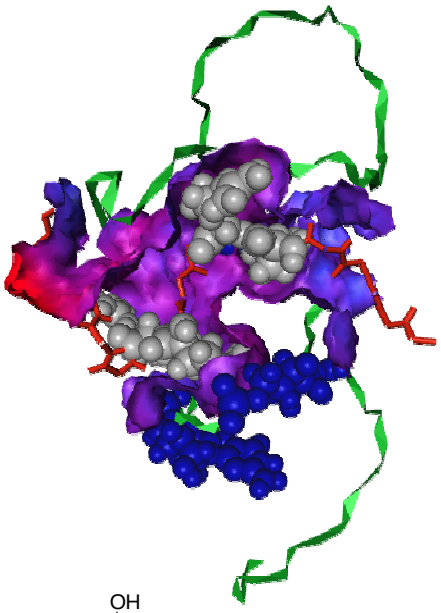
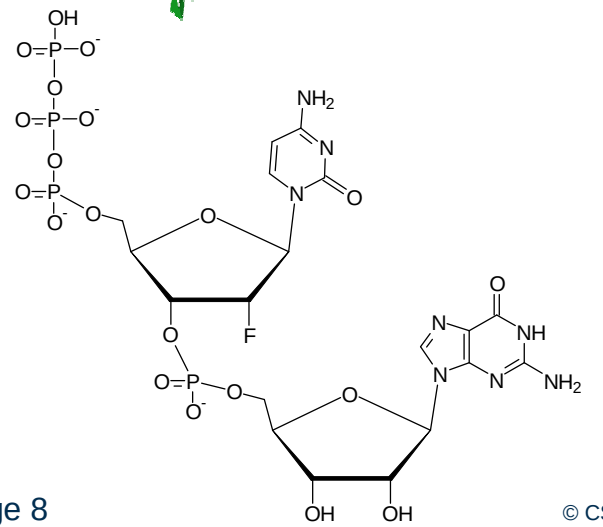
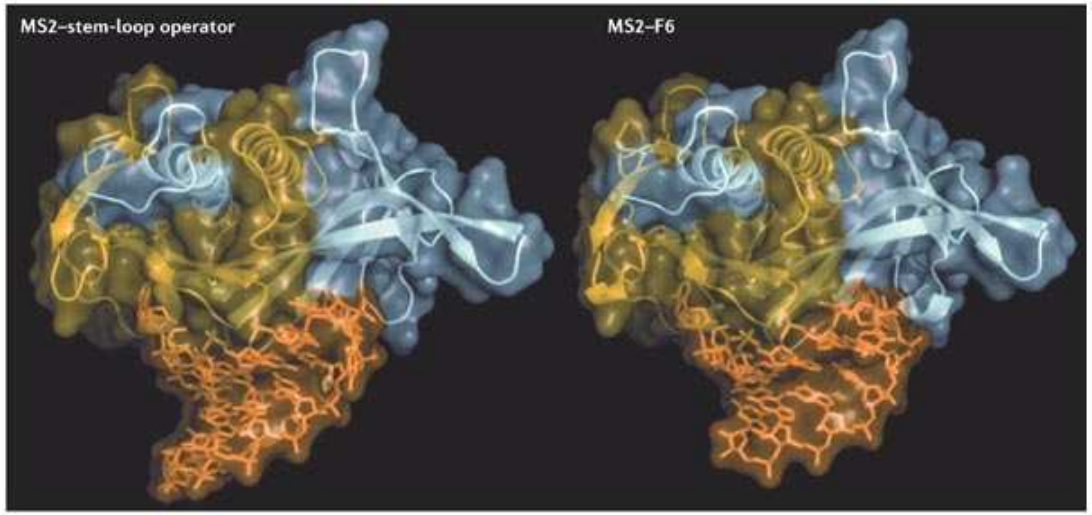
Aptamers: An innovative technology platform





- Artificial nucleic acid ligands (ssRNA) selected *in vitro* for specific binding to a target.
- Form well-defined 3-D shapes, allowing them to bind target molecules in a manner conceptually similar to antibodies (Abs)
- Have molecular recognition properties of Abs
- Small (6 kDa- 40 kDa) to probe protein structure and can penetrate viral defence mechanisms
- Combine optimal characteristics of small molecules and Abs: High affinity & specificity
- Functional products in their own right
- Low immunogenicity
- Resistant to nucleases
- A new approach to drug discovery

Structural lessons from aptamer-protein complexes



- Aptamers are prone to bind to functional domains of the target protein.
  - E.g. substrate binding pockets or allosteric sites
  - Modulate the biological function of the target molecule
- Aptamers are pre-existing molecules that have not been exploited during evolution

Bunka & Stockley 2006. Aptamers come of age–at last. Nature Reviews 4: 588-596

Aptamers: a Paradigm of Darwinian Evolution in a Test Tube

Made to fit?

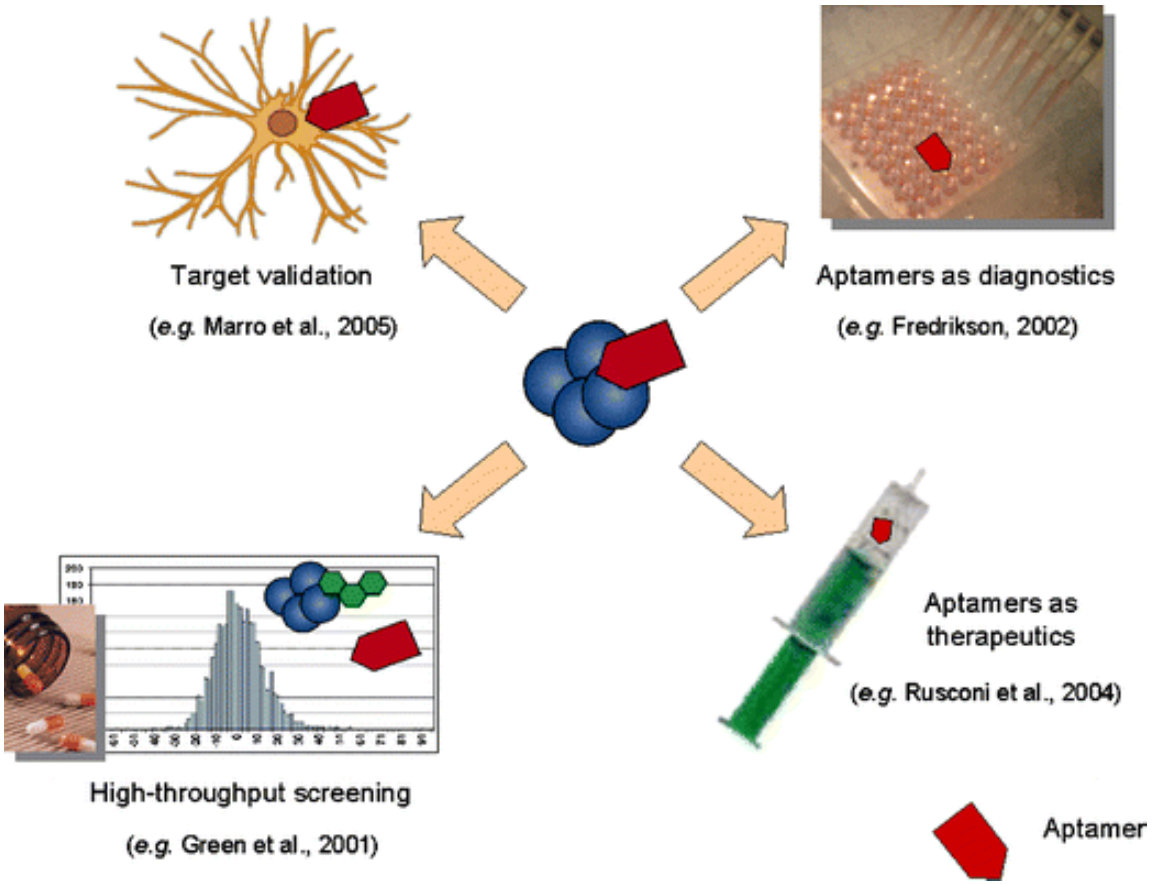
X

or

Off the peg?

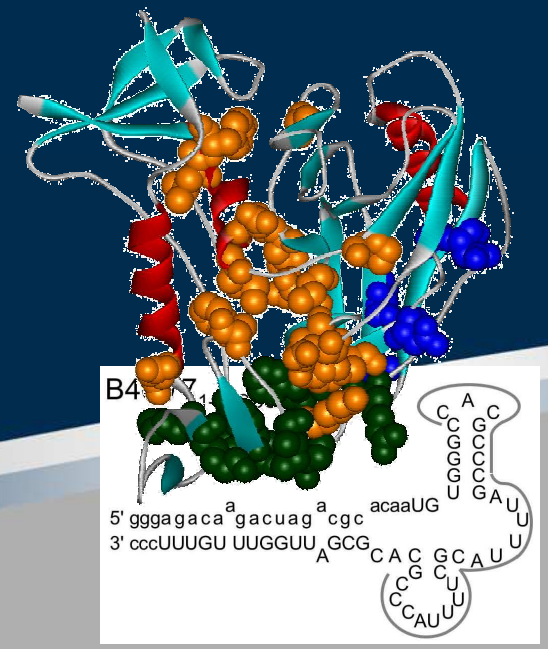
✓

Aptamers as therapeutics & multifunctional tools



Proske *et al.* 2005. Aptamers –basic research, drug development, and clinical applications. Appl Micr Biotech 69:367-74

Our Application of the Aptamer Technology to Combat HIV/AIDS



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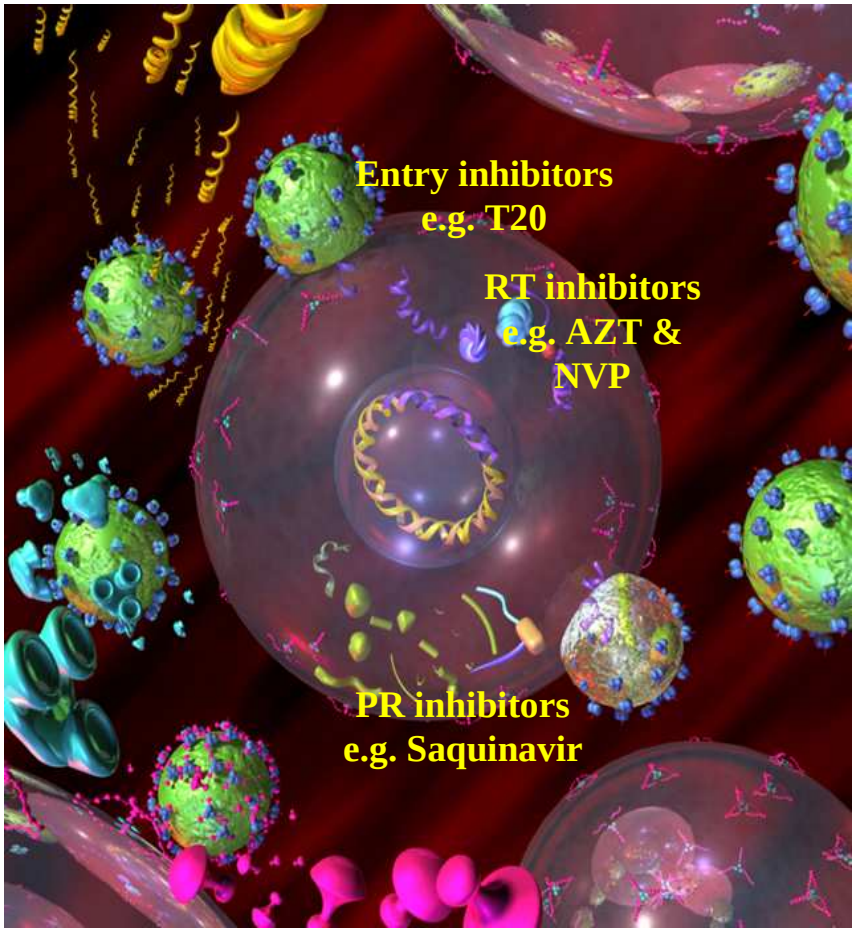
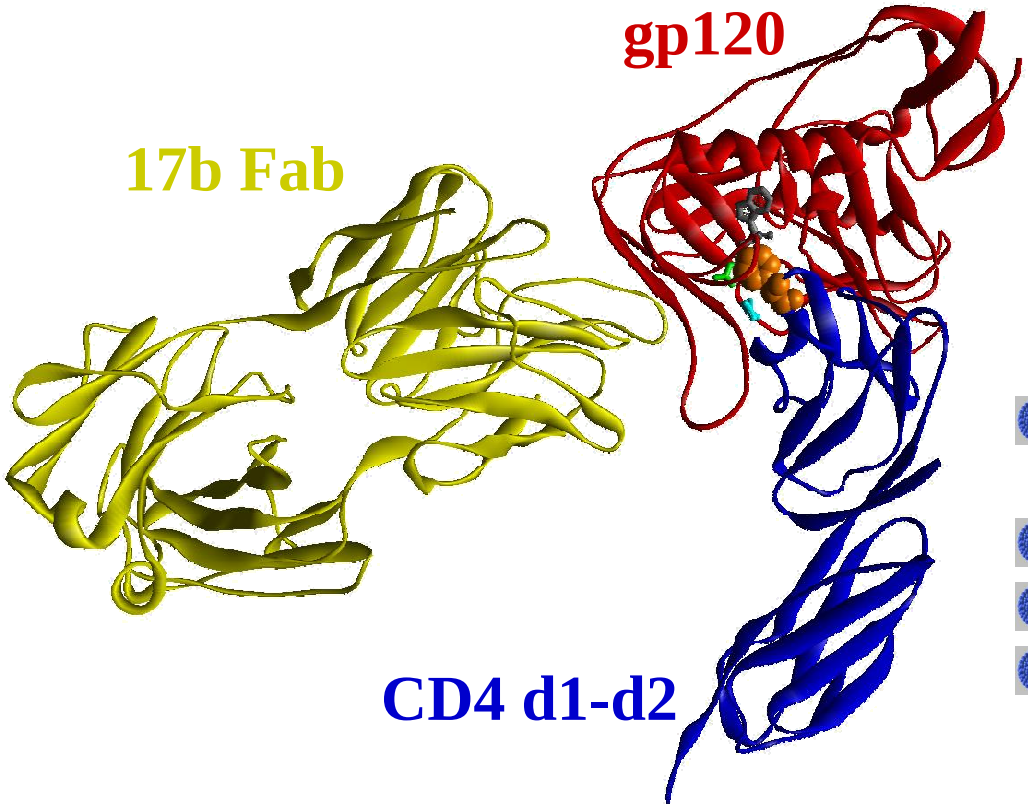
Problem Identified!



- Almost all of the ARV drugs currently in clinical use only act on the virus after it has infected target cells
- Treatment of infected individuals is costly to our health service.
- Drug resistance compounds problem

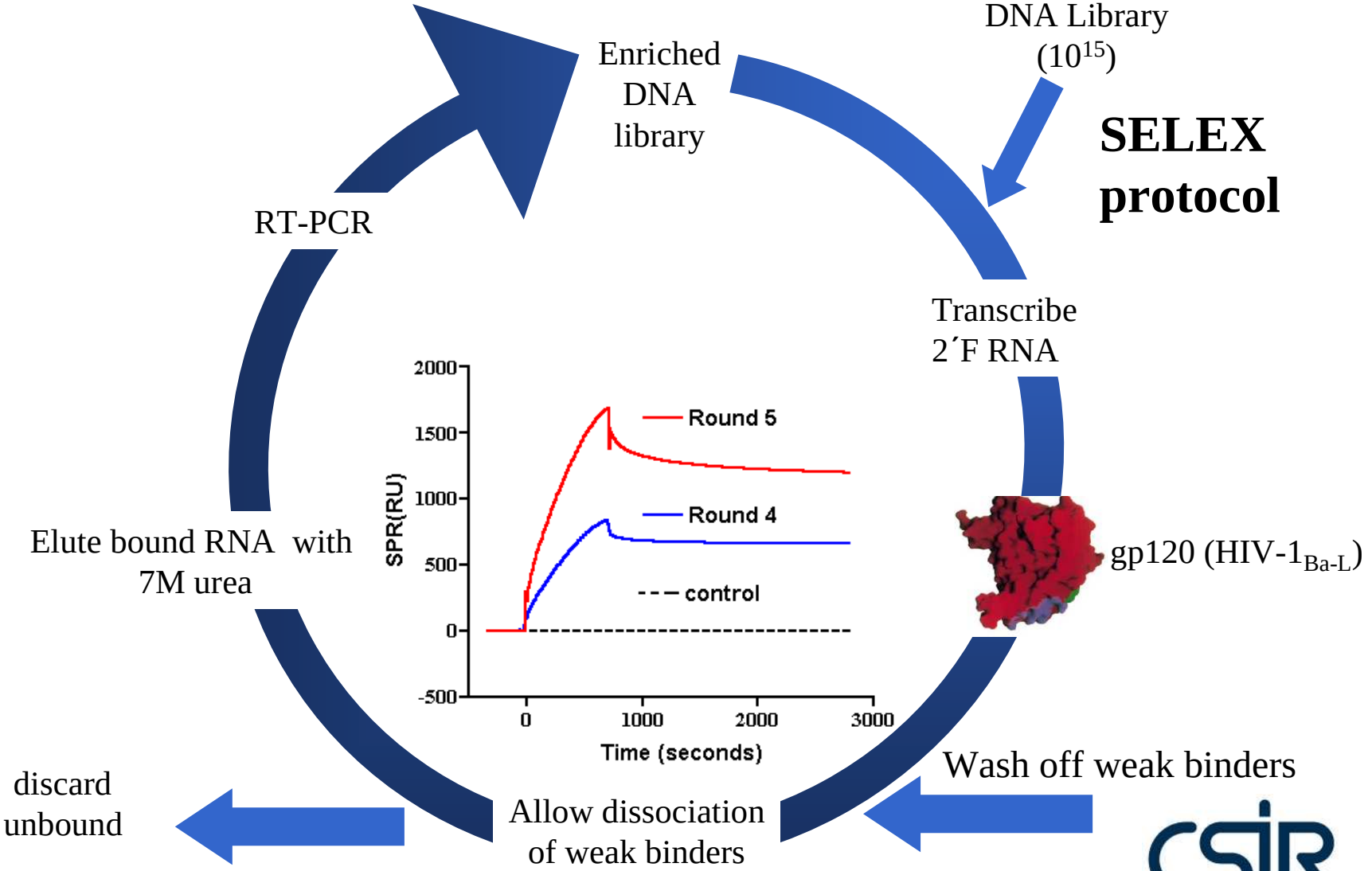
More Problem



- HIV cunningly shield itself from the immune system attack:
  - Occlusion of receptor binding sites
  - Hypervariable loops
  - Conformational shifts
  - Extensive glycosylation
- Su gp120 is both a multiple lock system and the master key
- Lynchpin and Achilles' heel
- Strong and weak point
- Desirable target for therapeutic intervention

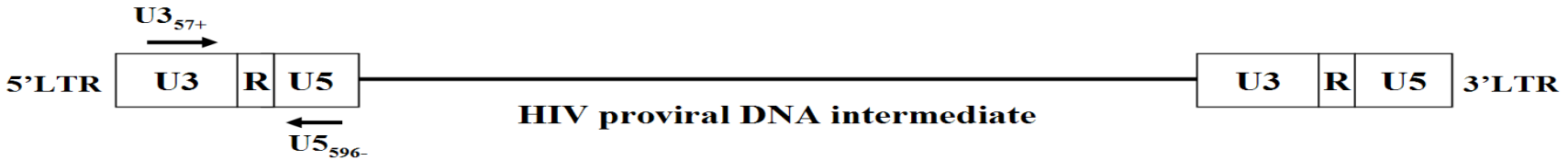
Kwong *et al.*, 1998. Nature 393:648-59

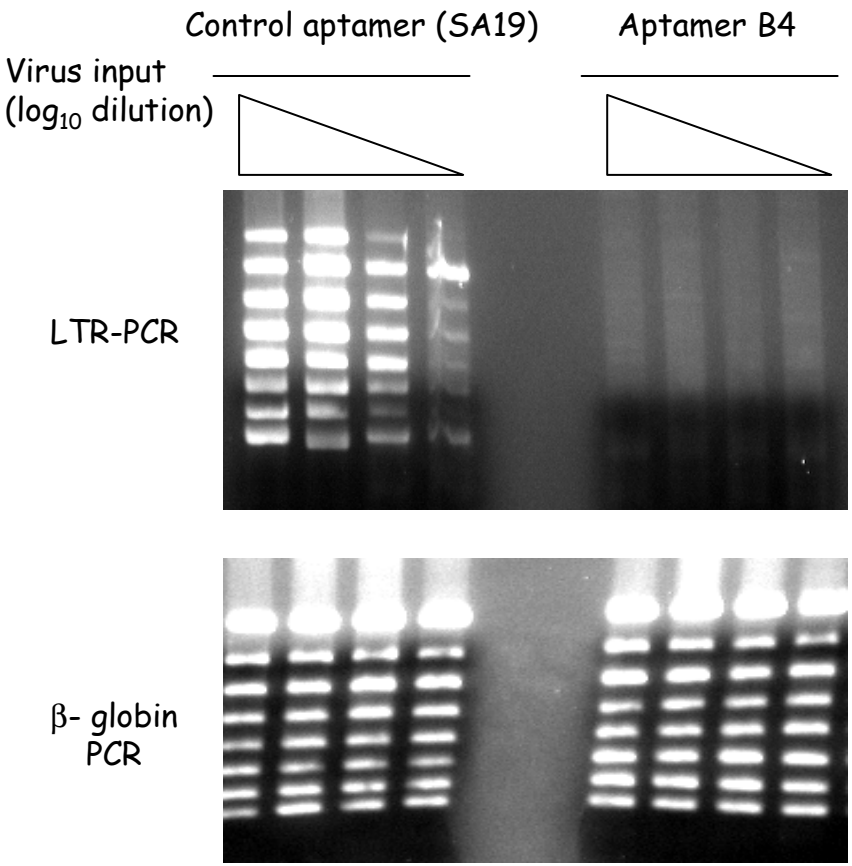
BIASelection: Isolation of anti-gp120 aptamers

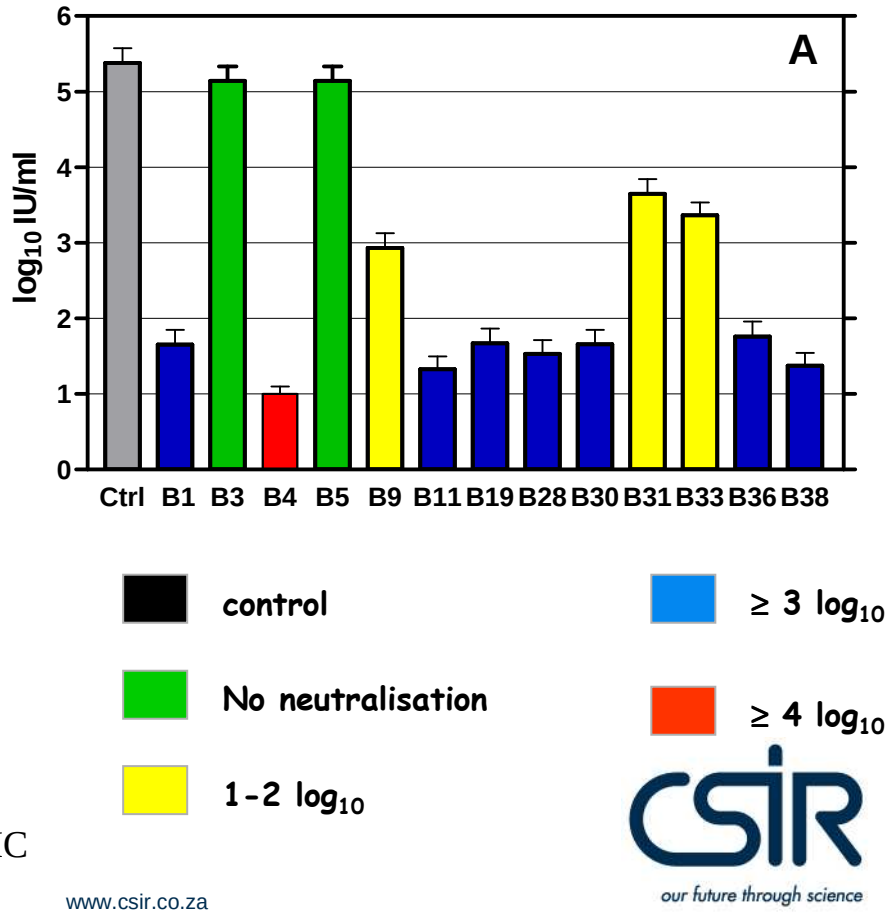


Khati *et al*. 2003. J. Virol. 77(23): 12692-98

Neutralization of HIV-1_{Ba-L} by aptamers







Limiting-dilution infectivity assay in human PBMC

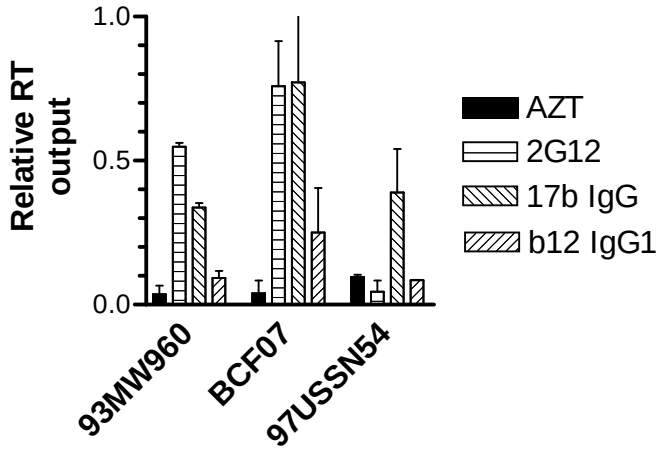
Khati *et al*. 2003. J. Virol. 77(23): 12692-98

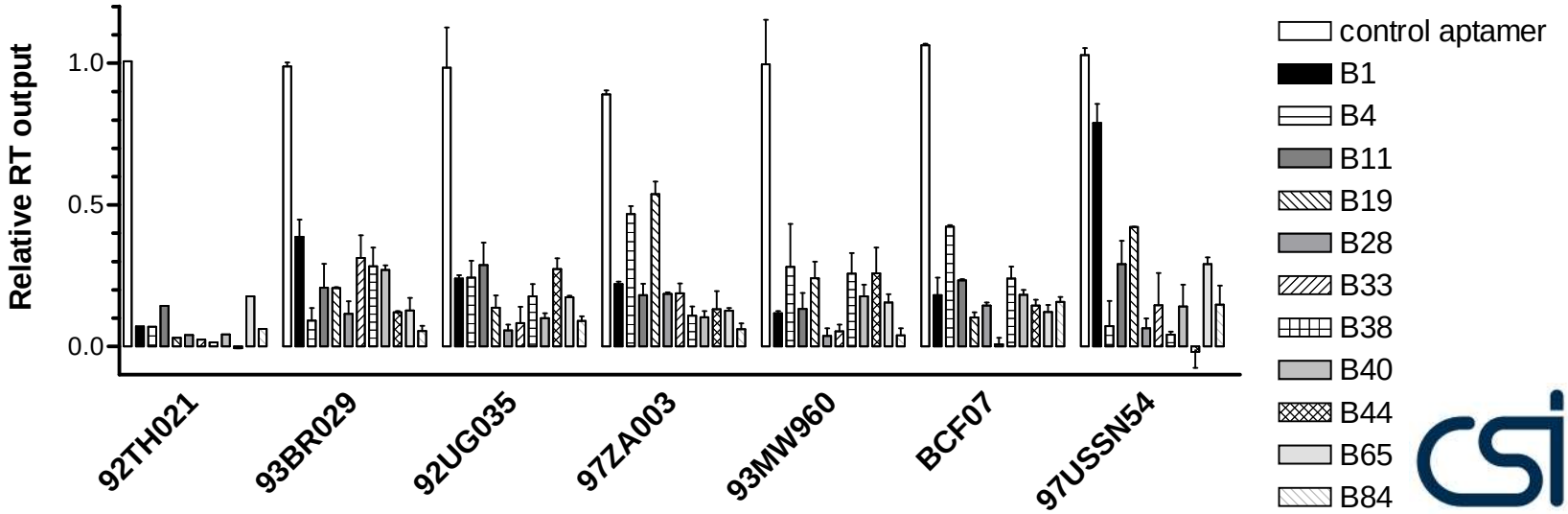
Utility of aptamers against clinically relevant HIV PIs

HIV-1 Isolate	Subtype	Characteristic
93BR029	F	Isolated from seropositive individual in Brazil
92TH021	E	Derived from asymptomatic individual in Thailand
92UG035	D	Isolated from seropositive individual in Uganda
97ZA003	C	Isolated from seropositive individual in South Africa
93MW960	C	Isolated from seropositive individual in Malawi
97USSN54	A	Isolated from a Senegalese woman living in the USA with full blown AIDS
BCF07	Group O	Isolated from a 29 year old woman from Cameroon

Khati *et al*. 2003. J. Virol. 77(23): 12692-98

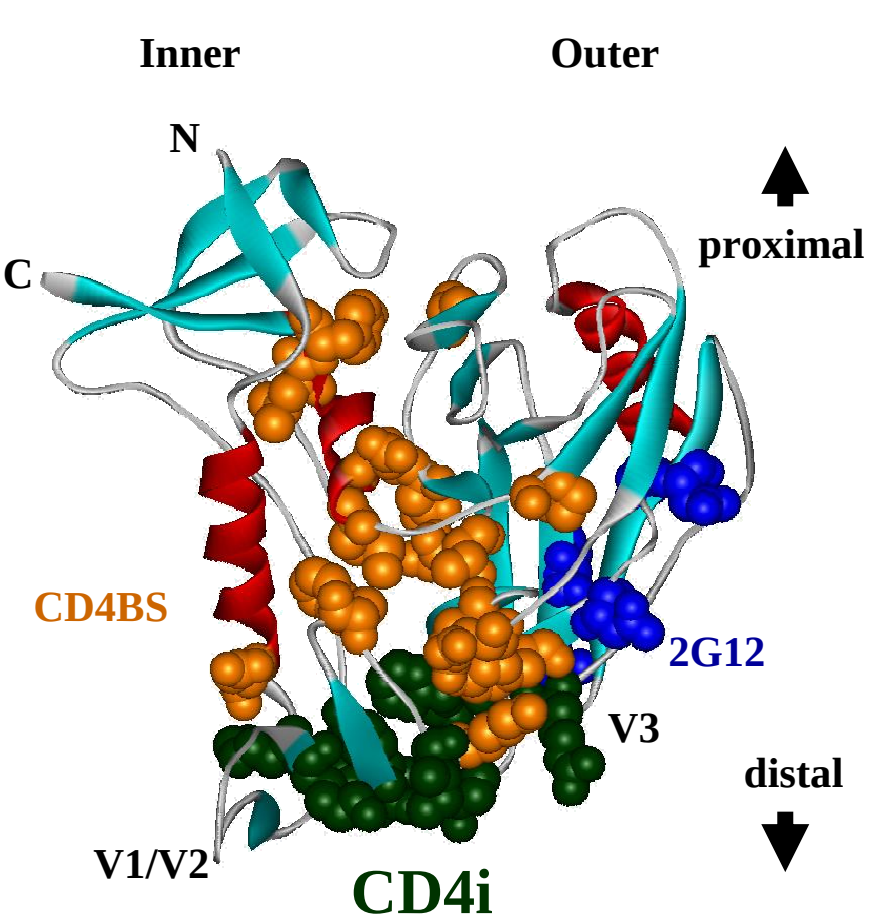
Pan-clade neutralization of HIV-1 clinical isolates by aptamers

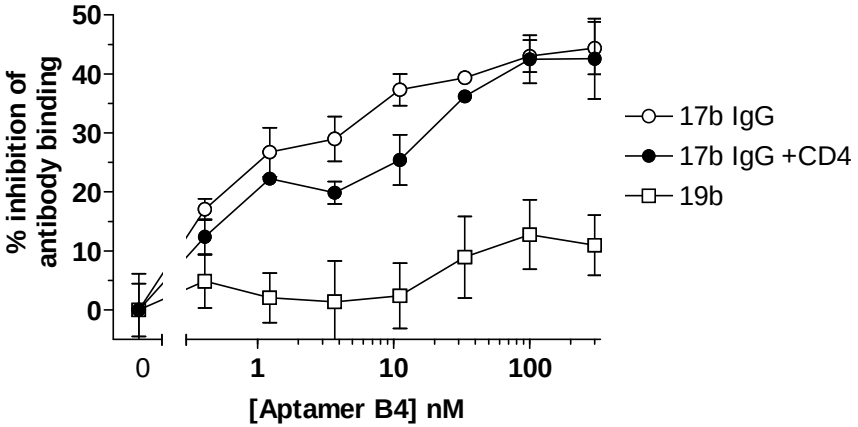


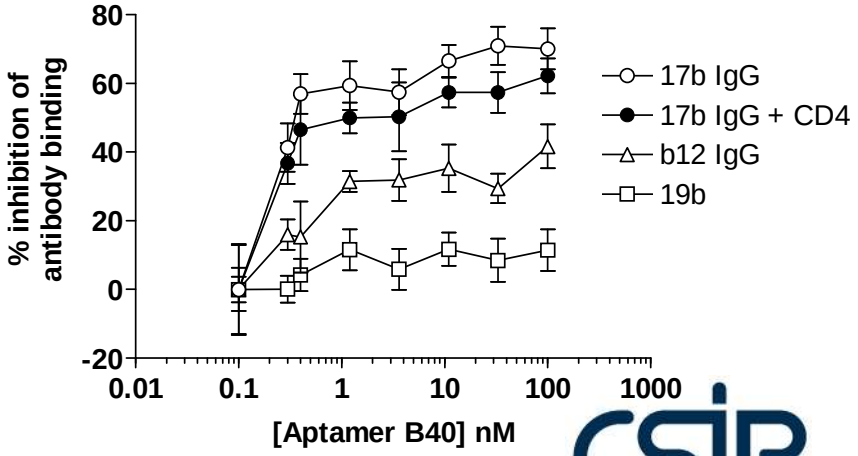


Khati *et al*. 2003. J. Virol. 77(23): 12692-98

Mechanism of neutralization: Competition of aptamers with NAbs for binding to gp120

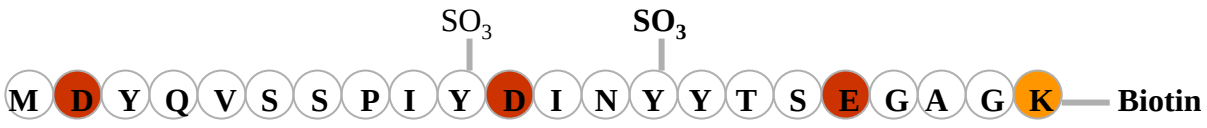


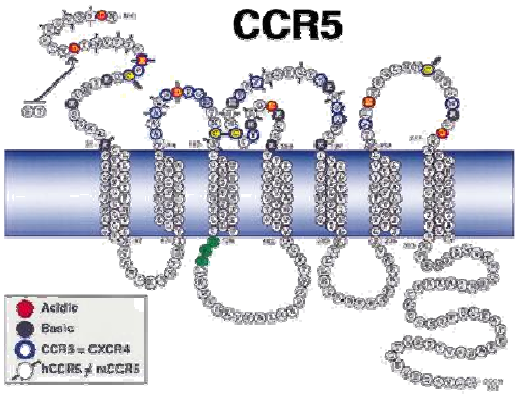


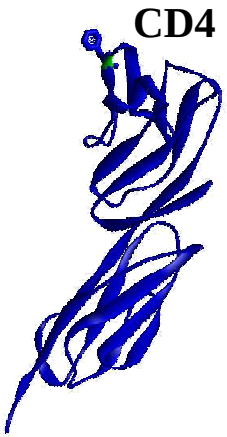


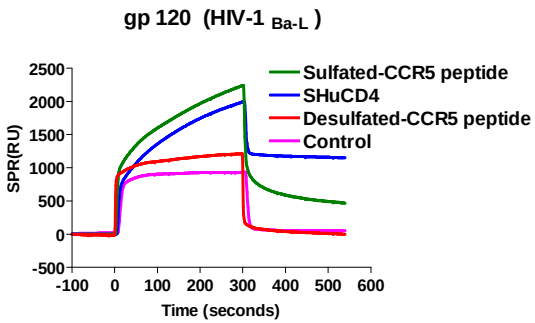
Khati *et al*. 2003. J. Virol. 77(23): 12692-98

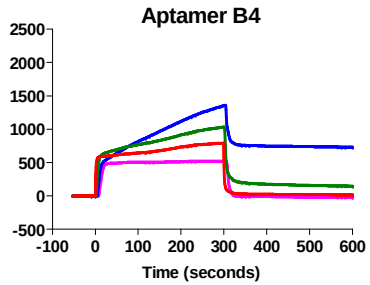
Aptamers interfere with gp120 binding to its natural receptors

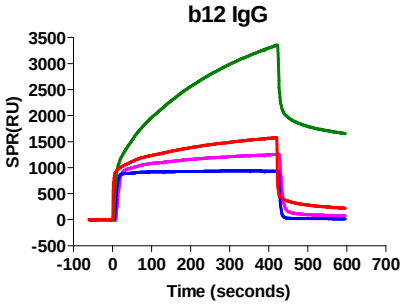


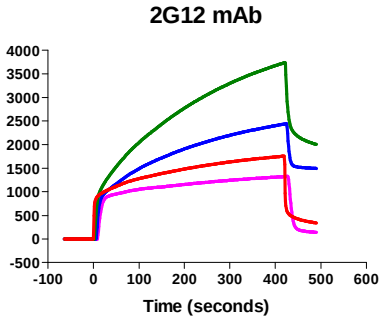


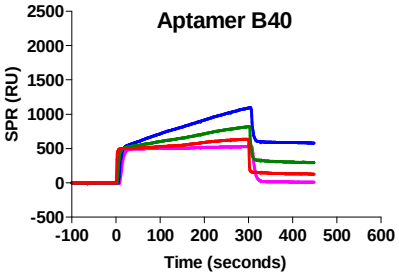


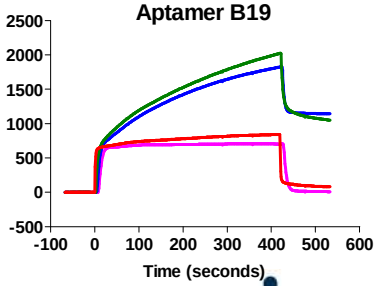












Dey, Khati et al. (Nov 2005) J. Virol. 79 (21)

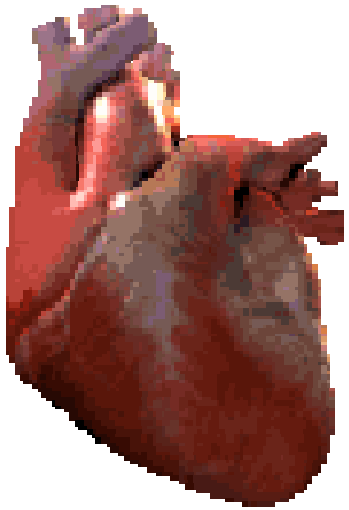
Bio2Biz: Bench to Bedside (Current Focus)

- Use aptamers for analysis and neutralization of endemic, South African strains of HIV-1 from adult and pediatric patients at various stages of disease.

- Exploit aptamers to provide structural leads for the development of potent and even smaller molecules that can mimic their HIV neutralizing properties.

- Determine if the structural mimetic would provide hope for salvage therapy for patients failing current ARV's including HAART, as well as alternatives for initial therapy for newly infected individuals.

Bio2Biz: Bench to Bedside (Future Focus)



- Exploit aptamers to elucidate and treat HIV associated cardiomyopathy

- Isolate aptamers against early markers of active TB and develop rapid and reliable diagnostics

In the face of adversity
It is not all gloom!