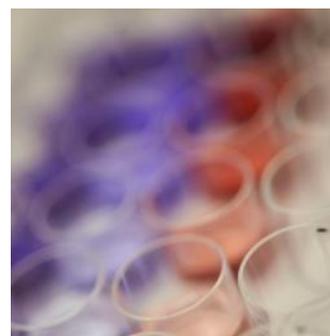
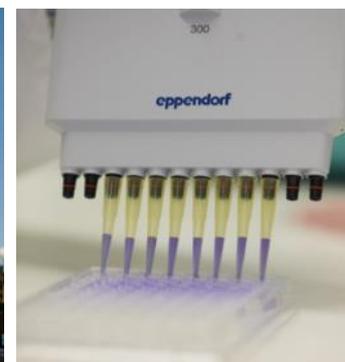




# Nucleic Acid Aptamers: Novel oligonucleotide reagents for disease diagnosis and therapy





## Aptamer Integration

Aptamer Diagnostic is a contract research organisation created to respond to the need for faster, more accurate and more diverse and diagnostic reagents with a longer ...



## Aptamer Development

Aptamer Solutions provides bespoke services to the life sciences sector including the development and manufacture of DNA and RNA aptamers as alternatives to antibodies ...



## Aptamer Therapeutics

Aptamer Therapeutics specialises in the development of nucleic acid aptamers as candidate molecules for therapeutic applications. The ability of aptamers to specifically ...



## Biomarker Discovery

Aptasort have combined a biomarker enrichment process with our aptamer isolation protocols yielding a first-in-kind discovery process. Our proprietary aptamer based ...

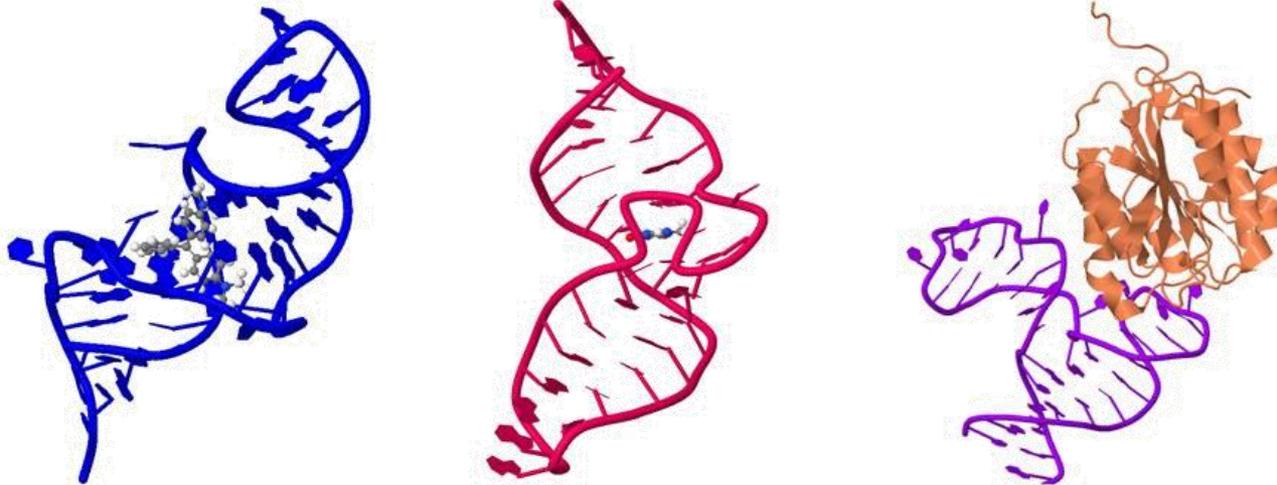


# What is an Aptamer

---

**Aptamer = Nucleic acid sequence selected for its ability to bind specifically to a target ligand**

- Sometimes referred to as 'nucleic acid antibodies'



# What is an Aptamer

---

**Aptamer = Nucleic acid sequence selected for its ability to bind specifically to a target ligand**

- Sometimes referred to as ‘nucleic acid antibodies’

**Aptamers are selected in vitro. No need to use animals**

- Toxic or poorly immunogenic targets
- Not limited to biological conditions
- Tuneable target specificity (or cross-reactivity)

**Aptamers can be raised to any class of target**

- Small molecules
- Peptides, proteins & complexes
- Viruses, cells & tissues
- Whole organisms

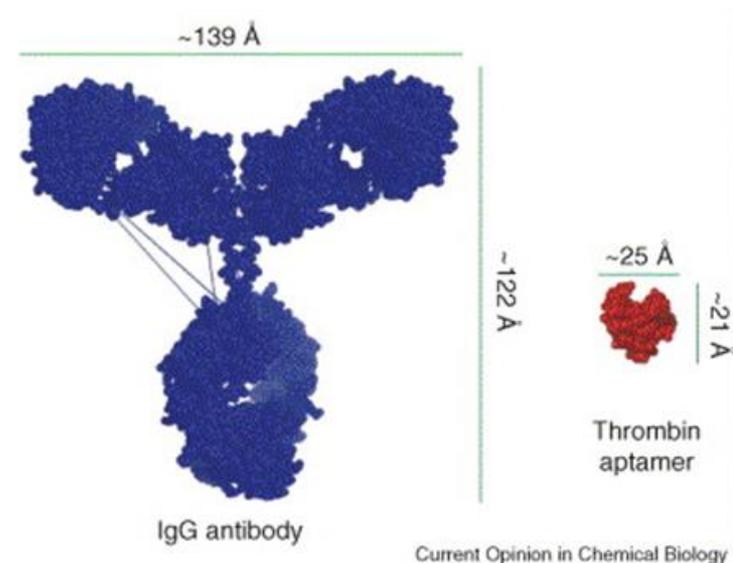
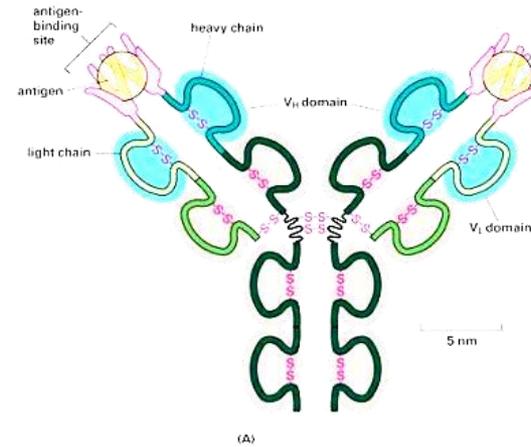
**In vitro manufacture**

- Large scale production & purification
- Strict QC
- Low batch-to-batch variability
- Stored ‘dry’ improving their shelf-life (several years)

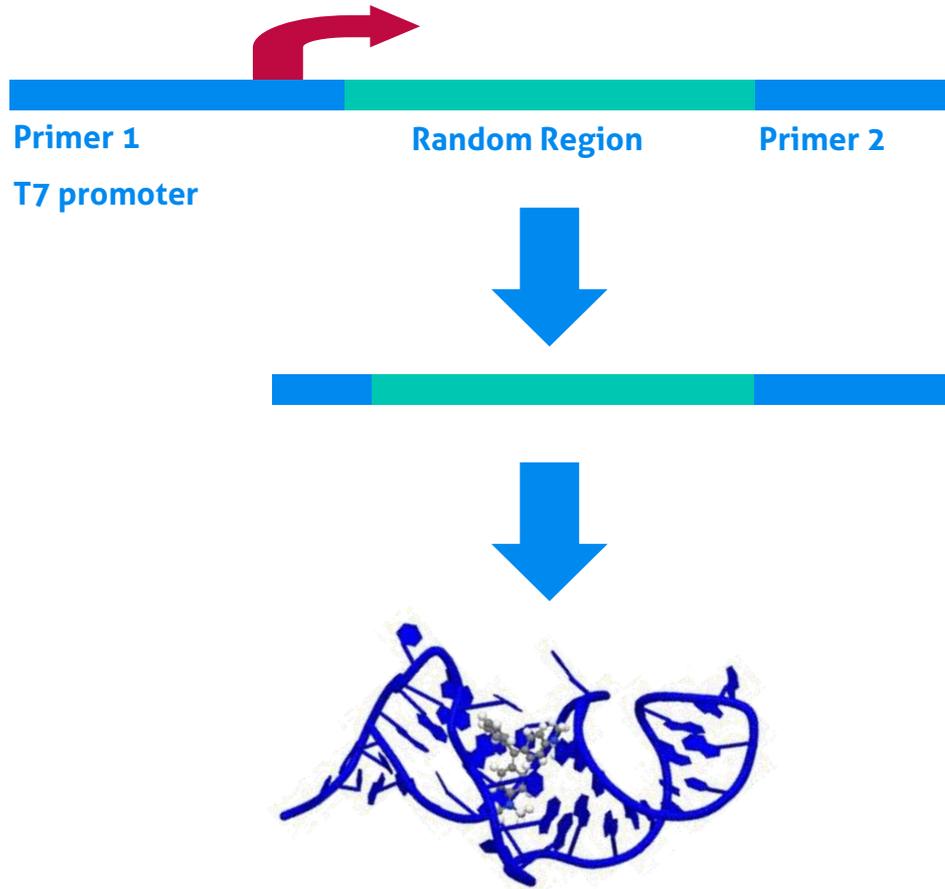


# Aptamers vs Antibodies

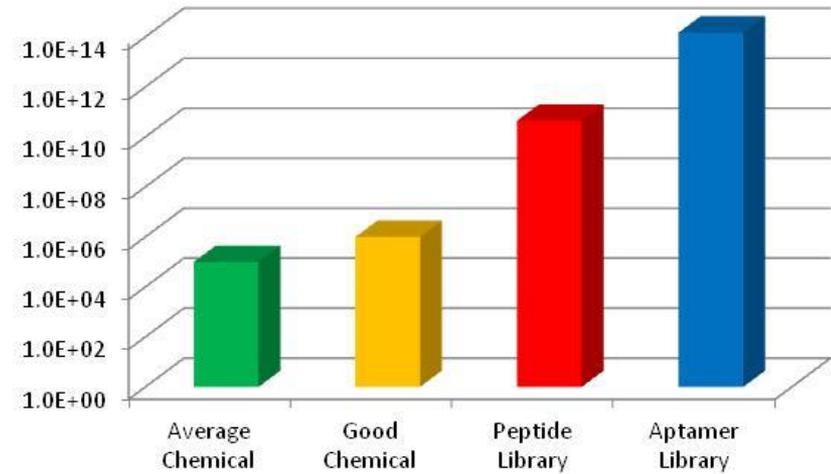
- Antibody structure is comparatively rigid and interactions are only formed with antigen binding domain
- Size makes it difficult for antibodies to access sites which are readily available to aptamers
- Greater potential for ligand contacts = greater specificity & affinity

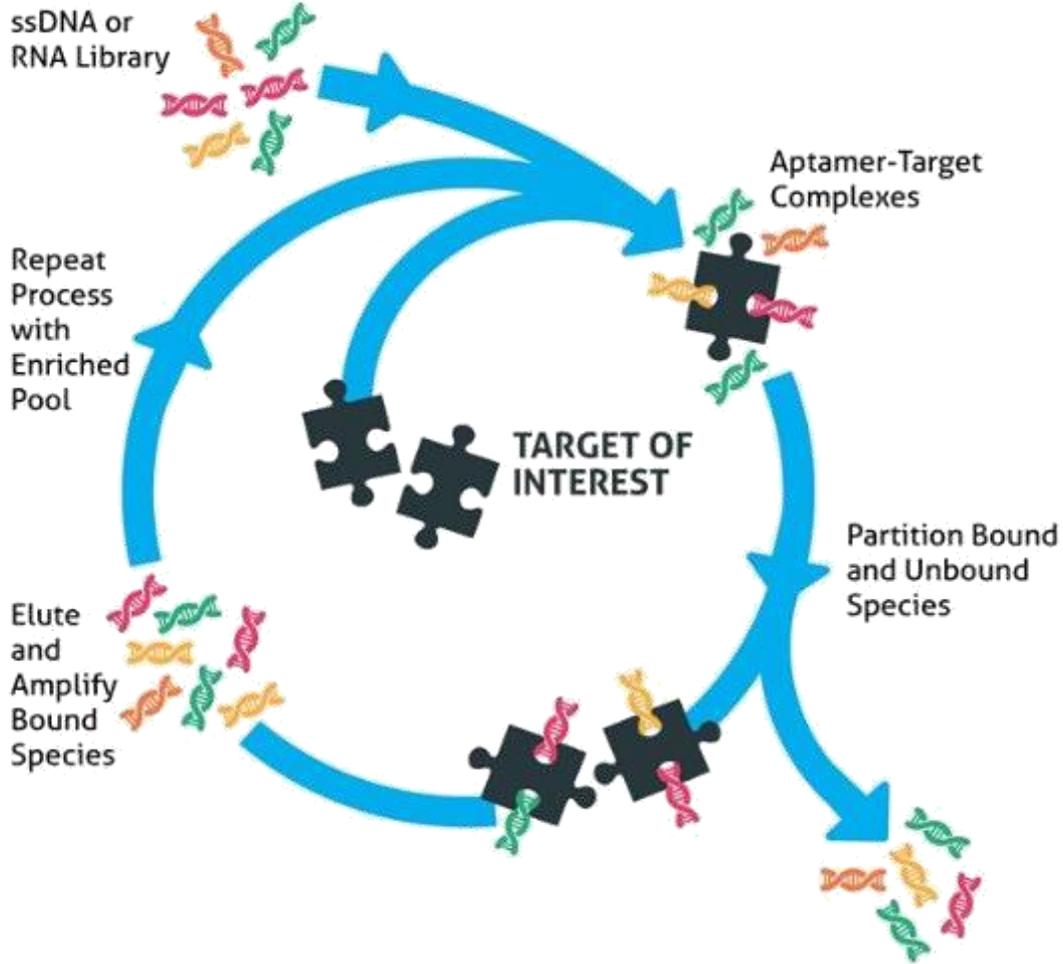


# How We Raise Aptamers - The Starting Library



- Random region = 30 bases =  $4^{30}$  possible sequences

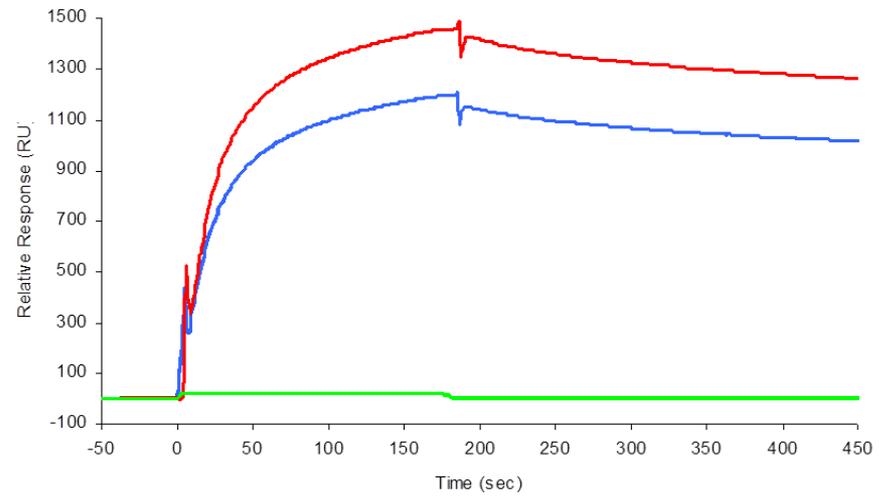
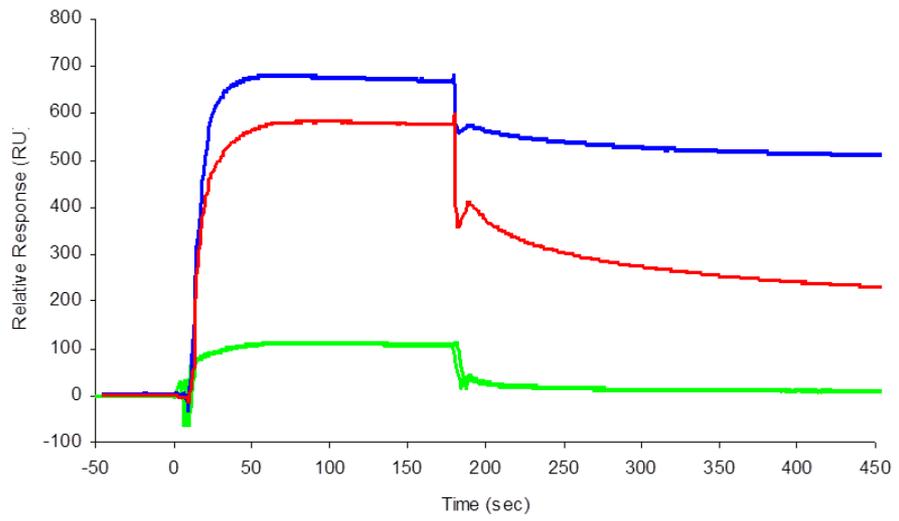




# Aptamer Specificity

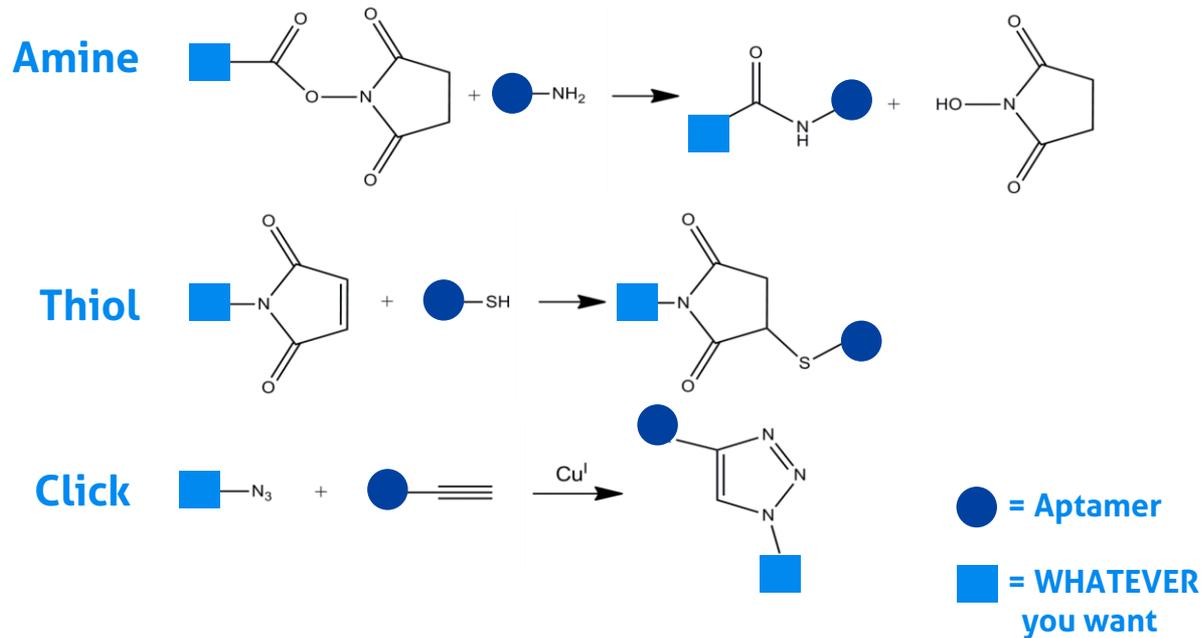


Protein	$K_d^{bFGF}/K_d^{protein}$
bFGF (FGF-2)	1.0
denatured	0.0008
FGF-1	0.0003
FGF-4	0.0006
FGF-5	0.041
FGF-6	0.0005
FGF-7	0.0007
VEGF	0.0008
PDGF AB	0.002
AT III	0.000008
thrombin	0.00003



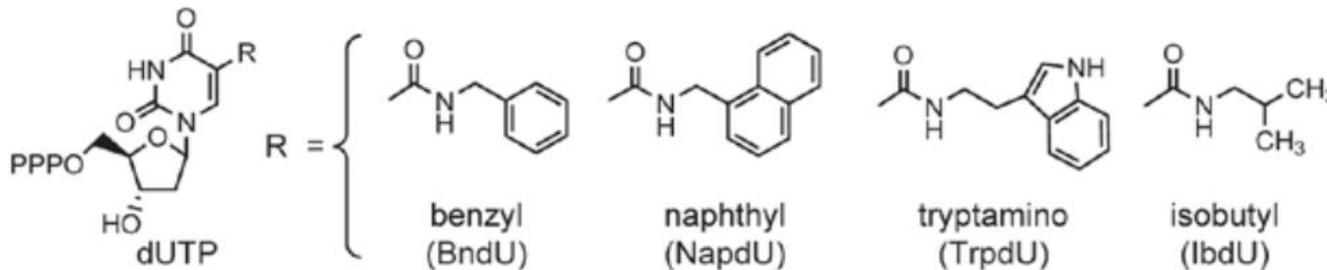
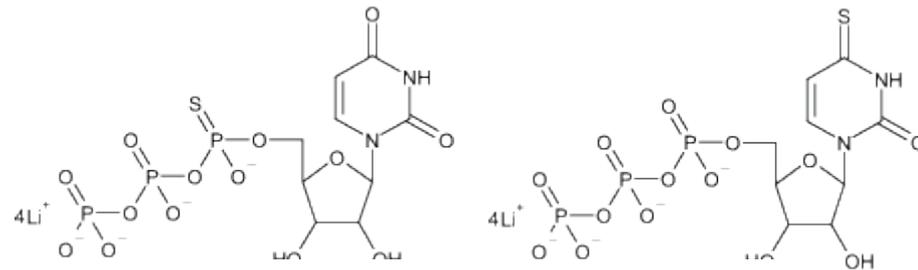
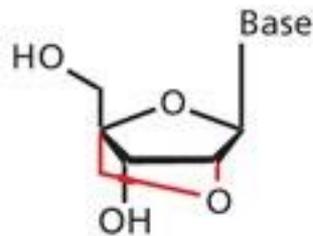
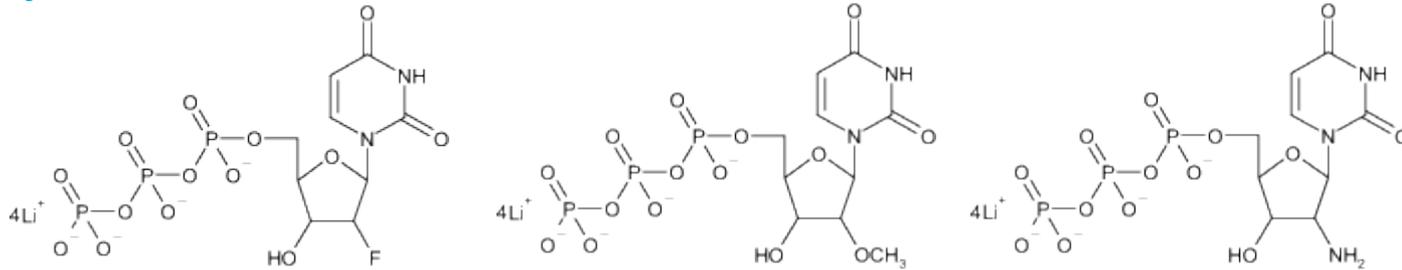
# Labelling Aptamers

- Aptamers can be produced by chemical synthesis incorporating simple chemical groups
- These can be used to attach a variety of functional moieties to suit the end application



# Nucleotide Modifications

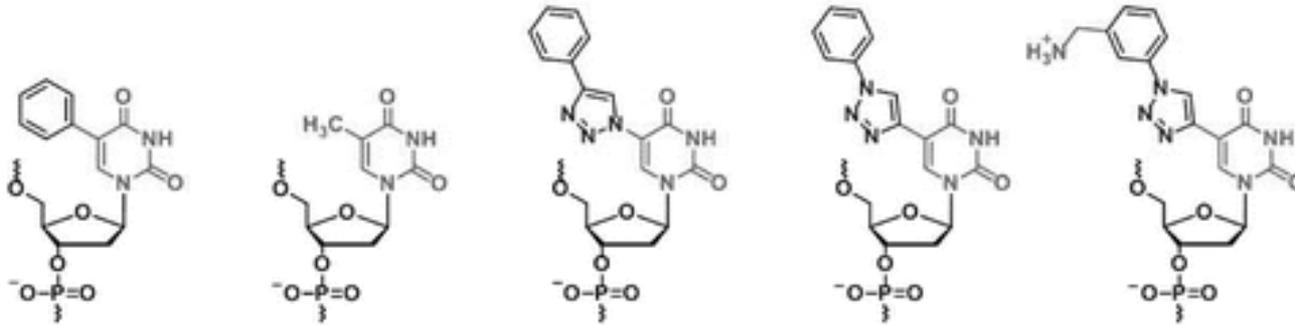
- RNA molecules are often preferred in aptamer selection for diversity of 3D structures
- Stability is still an issue for unmodified RNA



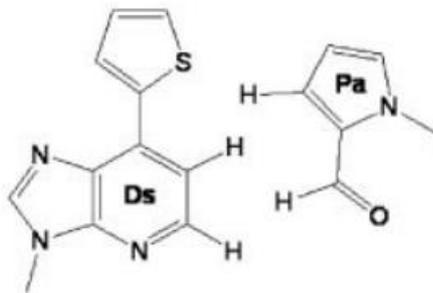
SomaLogic



# Nucleotide Modifications



Pofahl, Wengel, and Mayer. (2014) Multifunctional Nucleic Acids for Tumor Cell Treatment *Nucleic Acid Therapeutics*. 24(2): 171-177.



Hirao I, Kimoto M. (2012) Unnatural base pair systems toward the expansion of the genetic alphabet in the central dogma *Proc Jpn Acad Ser B Phys Biol Sci*. 88(7):345-67.



He W, et al. (2012) X-aptamers: a bead-based selection method for random incorporation of drug like moieties onto next-generation aptamers for enhanced binding. *Biochemistry*. Oct 23;51(42):8321-3.



# Key Advantages to Industry

---

## Security of supply

- Many potential manufacturers or in-house production
- Standard, well established manufacture processes
- Large batch production
- Chemically synthesised = Excellent QC
- Low batch-to-batch variability

## Stability

- Cold storage not required
- Indefinite shelf-life

## Improved properties

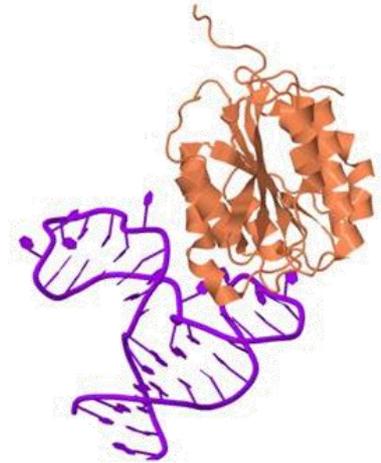
- Simpler modifications and conjugates = higher proportion of functional molecules
- Readily soluble at high concentrations
- Non-immunogenic property
- Small size

## Portfolio Expansion

- Possibility of addressing targets not amenable to antibodies

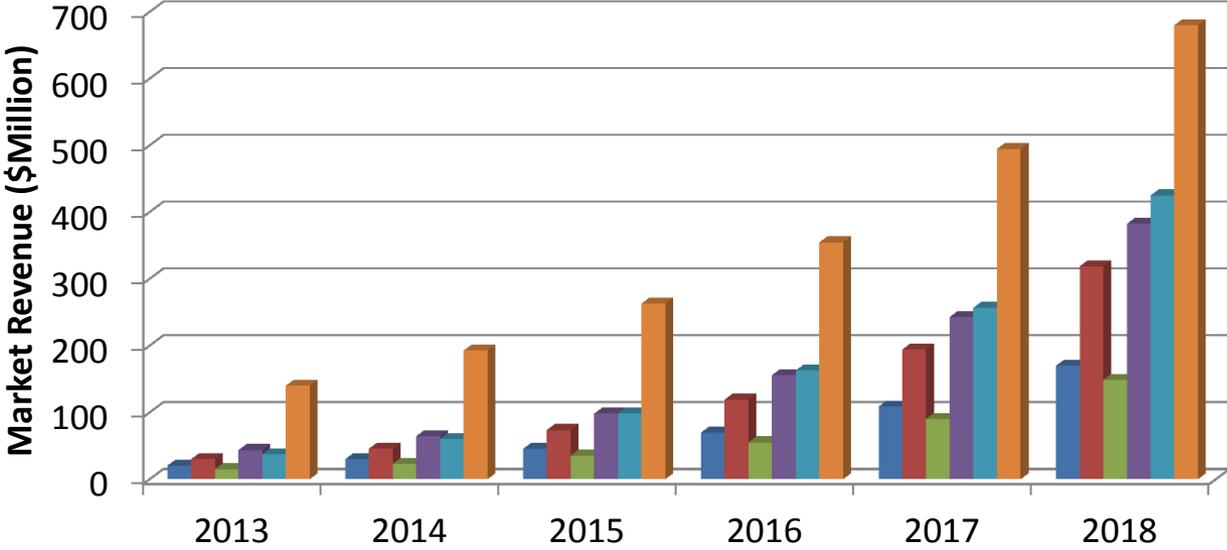
## Corporate responsibility (3Rs)

- Replacement - use of non-animal methods
- Reduction - methods which reduce the number of animals used
- Refinement - methods which improve animal welfare



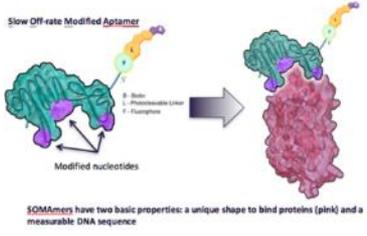
National Centre  
for the Replacement  
Refinement & Reduction  
of Animals in Research



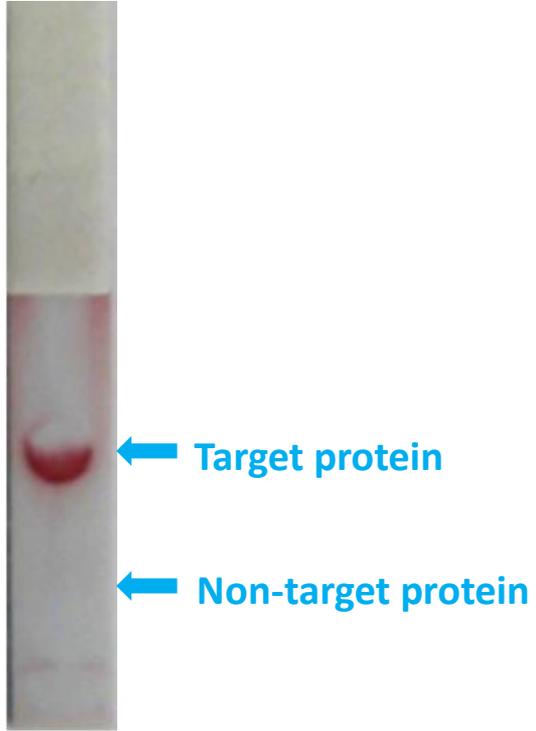
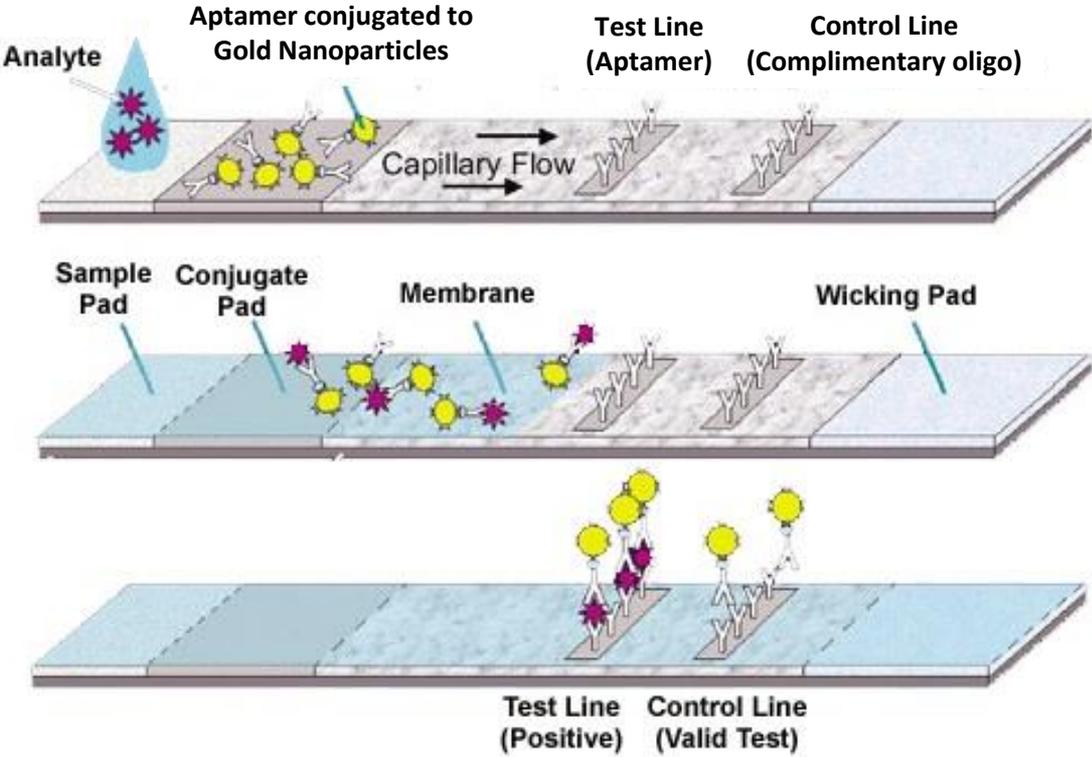


**Therapeutics**  
**Diagnostics**  
**Biosensors**  
**Drug Discovery**  
**Biomarker Discovery**  
**Research Applications**

- Growth in other areas is currently lower due to progression through developmental stages to commercialization.
- Novel aptamer based tools and services are entering the market

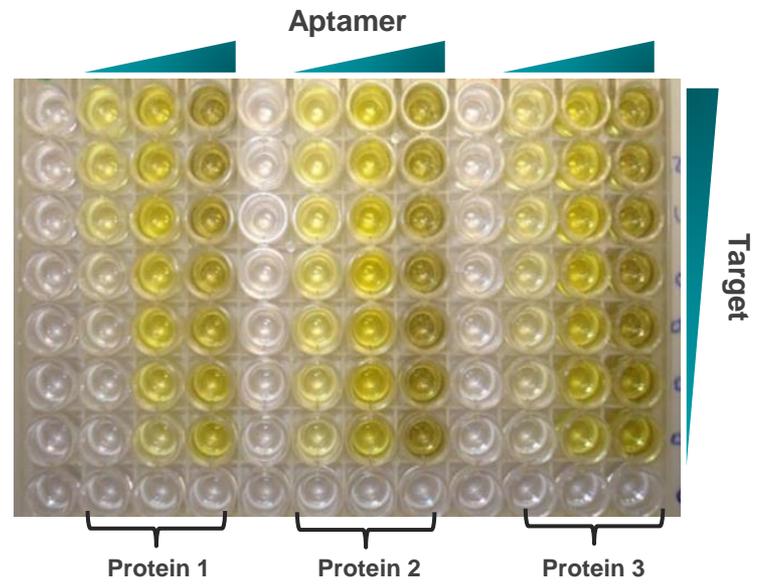
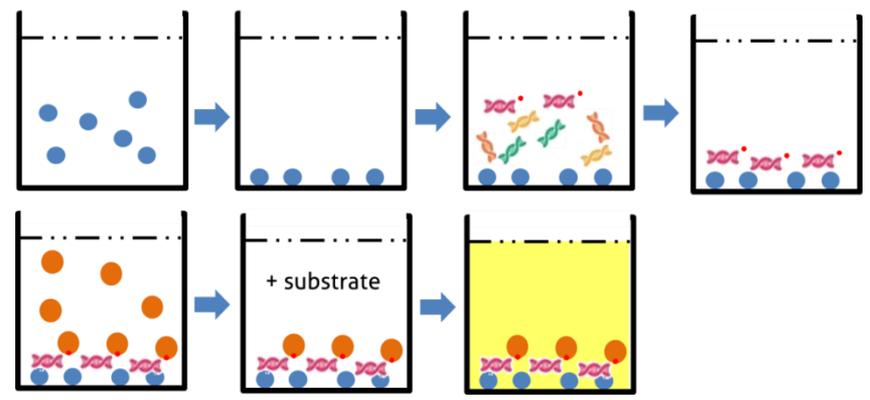


# Aptamer Lateral Flow Devices (LFDs)



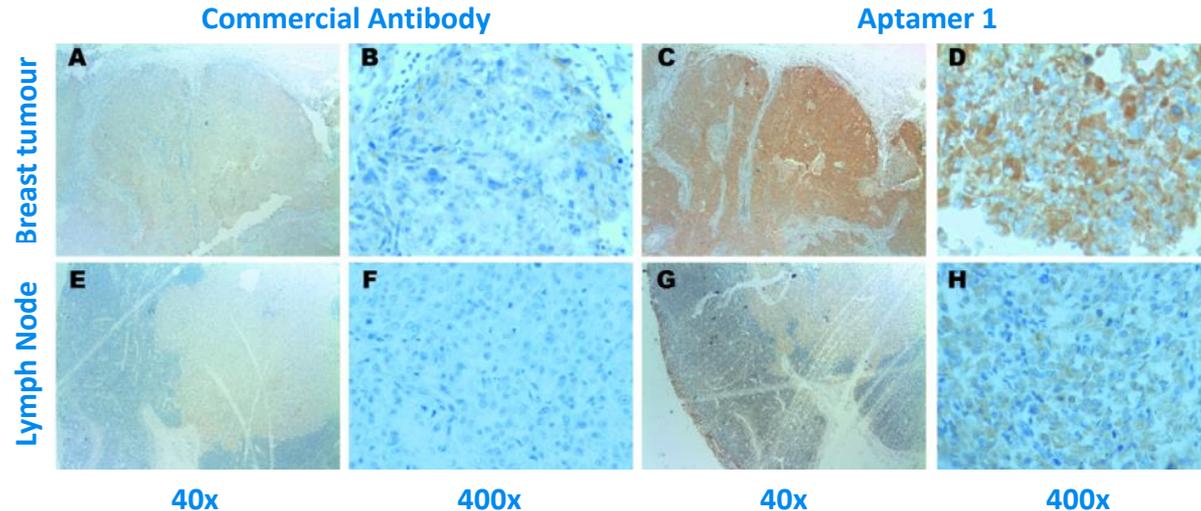
## ELONA

Enzyme Linked OligoNucleotide Assay

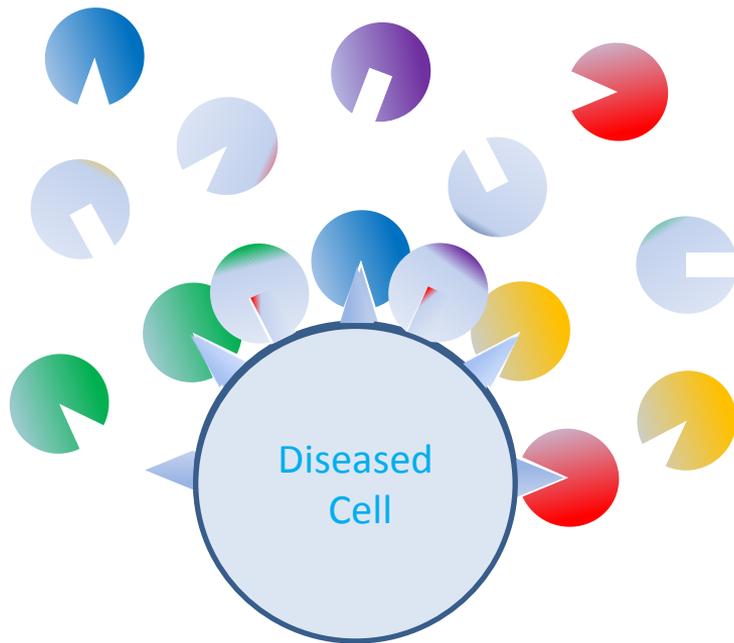


# FFPE sections

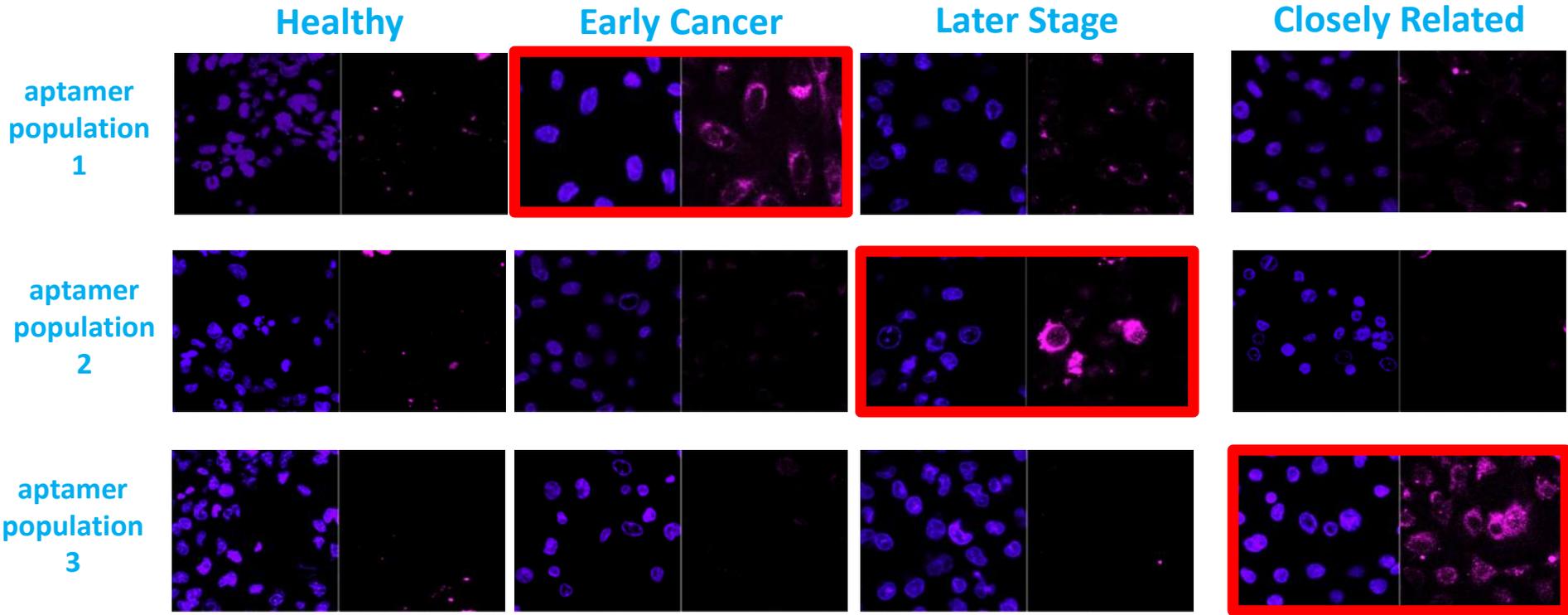
- Formalin-Fixed Paraffin Embedded FFPE samples can be problematic
- Formaldehyde is used to inactivate, stabilize or immobilize proteins for long term storage.
- Aptamers against purified proteins have also been used in conventional FFPE staining



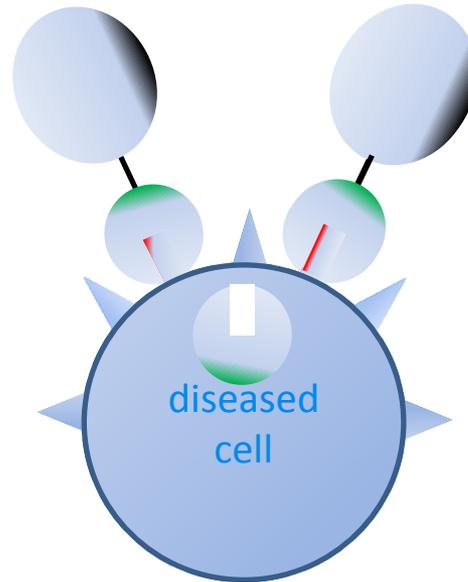
- Aptamers can be selected directly against FFPE sections
- Novel reagents compatible with commercial IHC systems

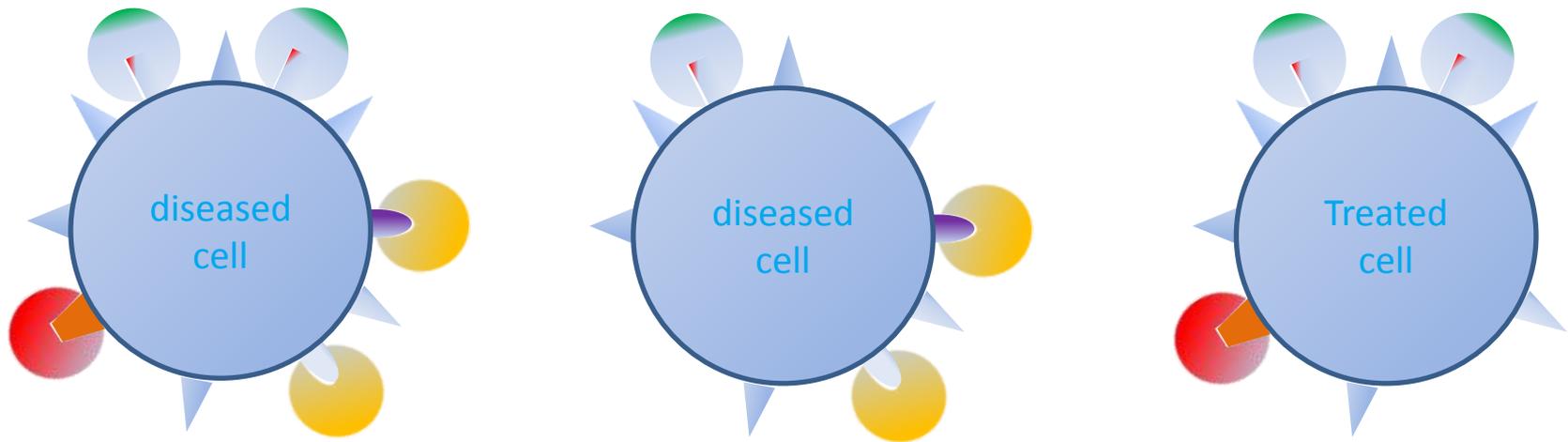


# Aptamer Based Biomarker Discovery

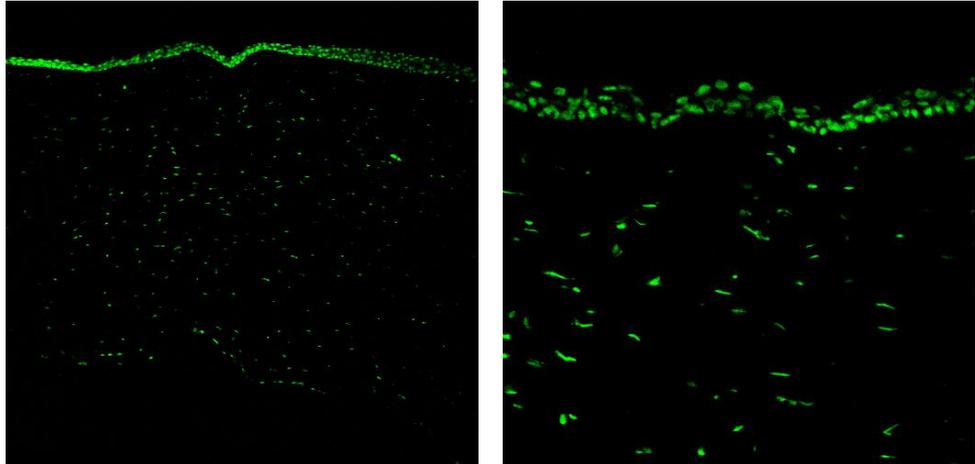


our process was used to identify aptamers against unknown biomarkers in 3 months where 10 man-years of research failed

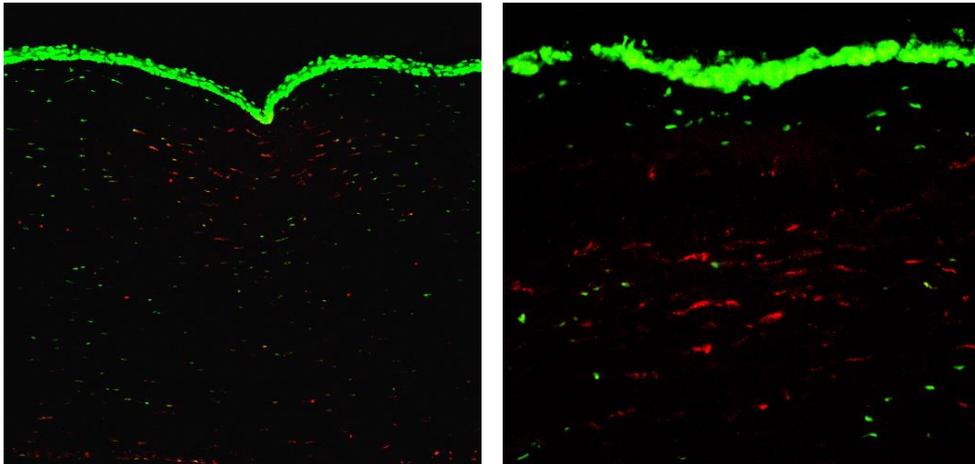


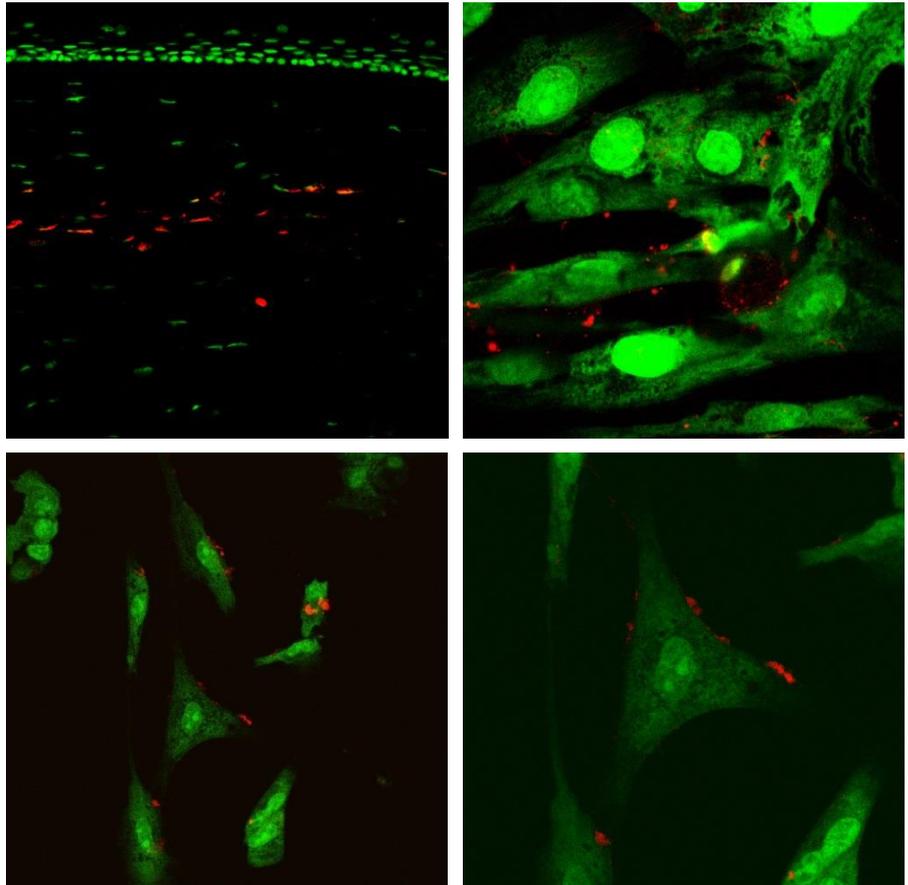


Unselected population



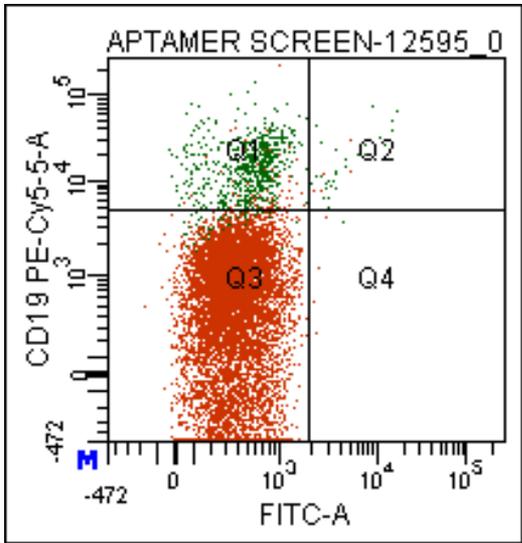
Aptamer population



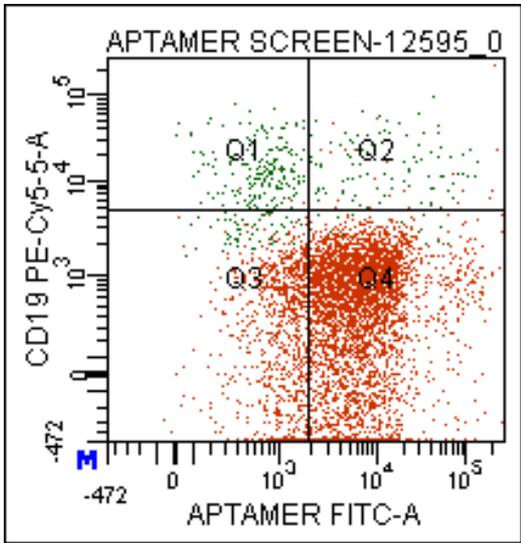


**GREEN = Healthy plasma cells**

**RED = Neoplastic plasma cells**

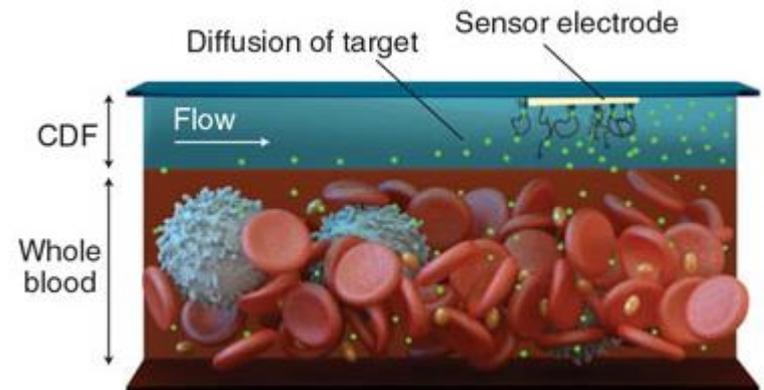
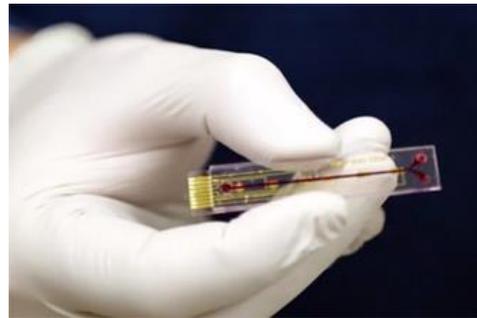
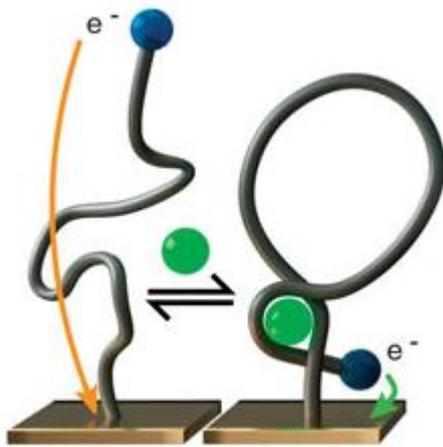


Naïve pool



Aptamer pool

## Microfluidic Electrochemical Detector for In vivo Continuous monitoring - MEDIC



*Sci Transl Med* 27 November 2013:  
Vol. 5, Issue 213, p. 213ra165  
Sci. Transl. Med. DOI: 10.1126/scitranslmed.3007095

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### RESEARCH ARTICLE

#### BIOENGINEERING

#### Real-Time, Aptamer-Based Tracking of Circulating Therapeutic Agents in Living Animals

Brian Scott Ferguson<sup>1,2</sup>, David A. Hoggarth<sup>1</sup>, Dan Maliniak<sup>3</sup>, Kyle Ploense<sup>3</sup>, Ryan J. White<sup>4</sup>,

Nick Woodward<sup>3</sup>, Kuangwen Hsieh<sup>2</sup>, Andrew J. Bonham<sup>5</sup>, Michael Eisenstein<sup>2,6</sup>, Tod E. Kippin<sup>1,3</sup>,

Kevin W. Plaxco<sup>7,8</sup> and Hyongsok Tom Soh<sup>1,2,6,8,\*</sup>





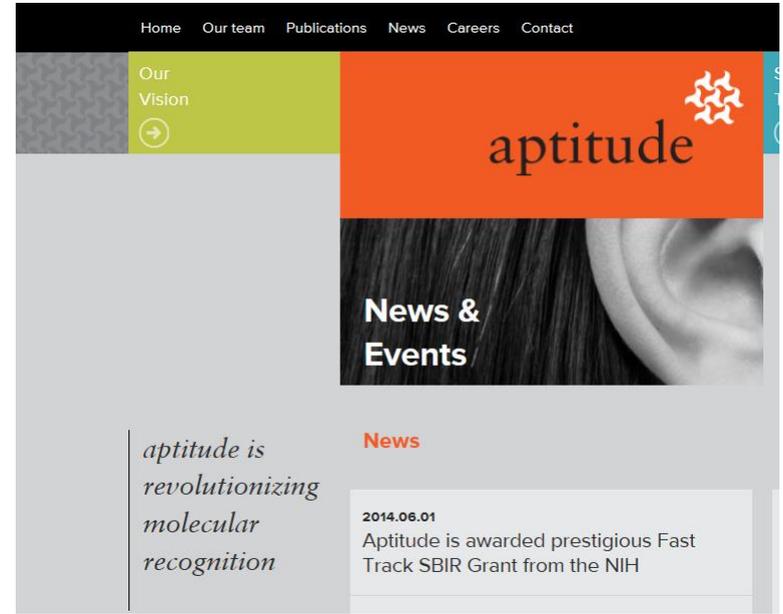
Proudly serving Ventura, Santa Barbara and San Luis Obispo counties

## Getting a grip on diabetes: Aptitude device gets fast track status for clinical trials

By Erika Martin / Friday, October 24th, 2014 / Comments Off

Aptitude creates a special type of molecule called an aptamer, which it is using to develop a first-of-its-kind hand-held device that measures insulin concentrations in real-time and can diagnose pre-diabetes. The government's interest in furthering such research is unsurprising as diabetes affects more than 9 percent of Americans.

**Real-time Point of Care Insulin Monitoring Device for Improved Diabetes Management**  
Ferguson, Brian Scott  
Aptitude Medical Systems, Inc., Santa Barbara, CA, United States



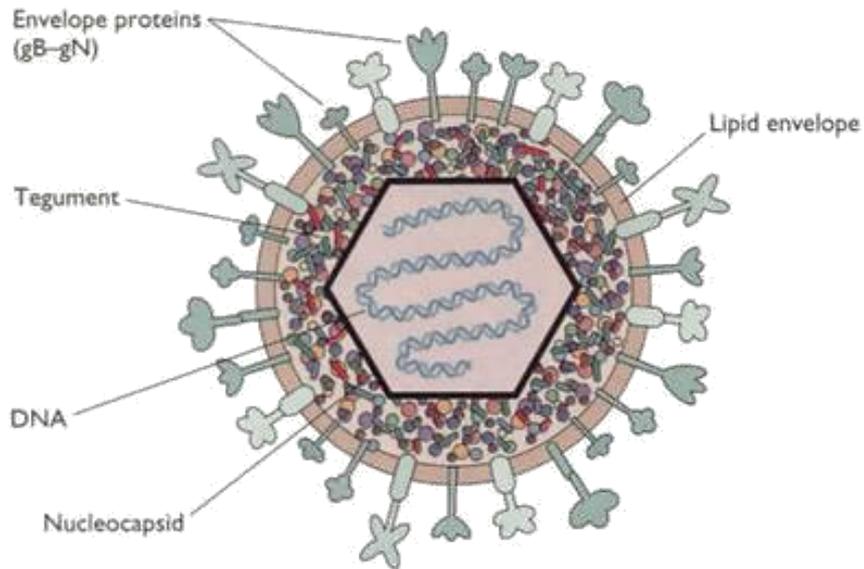
[www.apitudemedical.com](http://www.apitudemedical.com)



- A lot of previous work on oligonucleotide based therapies
- Aptamers are finding uses as direct therapeutics
- Modulators of other therapeutic agents
  - Slow release
  - Inactivate / antidotes
- Therapeutic chimera's
  - Aptamer-siRNA
- Aptamer based delivery vehicles for drug conjugates



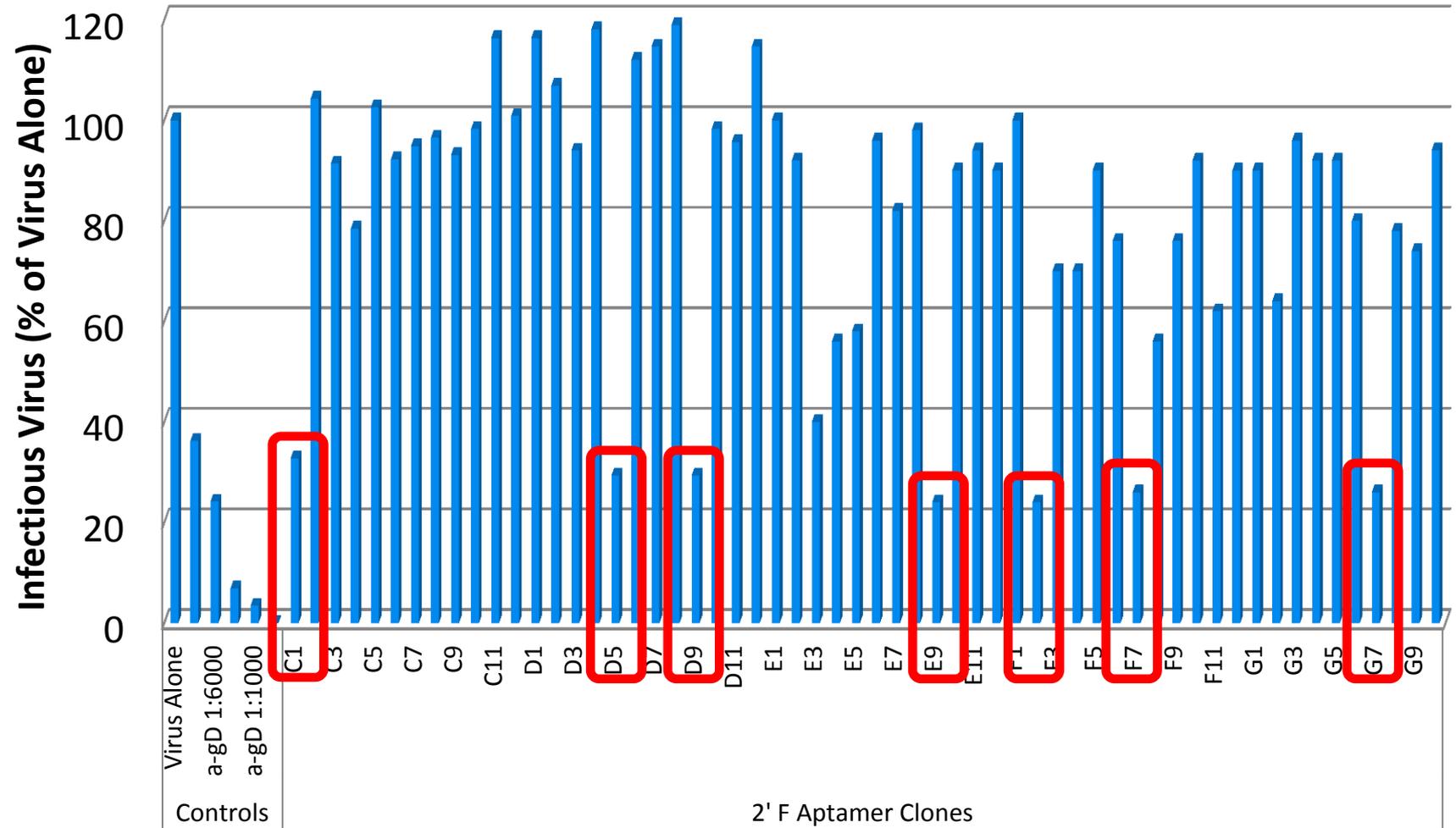
# Virus Specific Aptamers



- RNA aptamers bind to the gD protein of HSV-2
- Aptamers inhibit viral entry (IC50 of 20-50nM)
- Block both major entry receptors, Nectin1 and HVEM
- No interaction with HSV-1



# Aptamers Inhibit Viral Infection

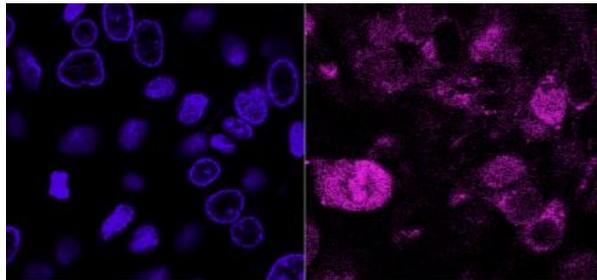


# Aptamer Targeting Agents

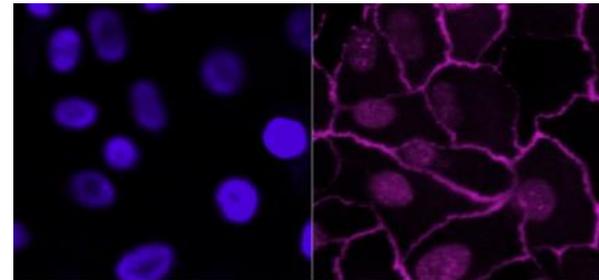
Careful application of different binding parameters can lead to aptamers with different properties on the same cell line.

Selections carried out to isolate aptamers which 'do' or 'do not' get internalised.

Aptamers serve as cell specific targeting agents for therapeutic conjugates



Aptamers get internalised



Aptamers stay on cell surface

Chemistry & Biology

Previews



## A Trojan Horse for Human Immunodeficiency Virus

Silvia Catuogno,<sup>1,2</sup> Carla Lucia Esposito,<sup>1,2</sup> and Vittorio de Franciscis<sup>1,\*</sup>

<sup>1</sup>Istituto di Endocrinologia ed Oncologia Sperimentale, CNR, 80145 Naples, Italy

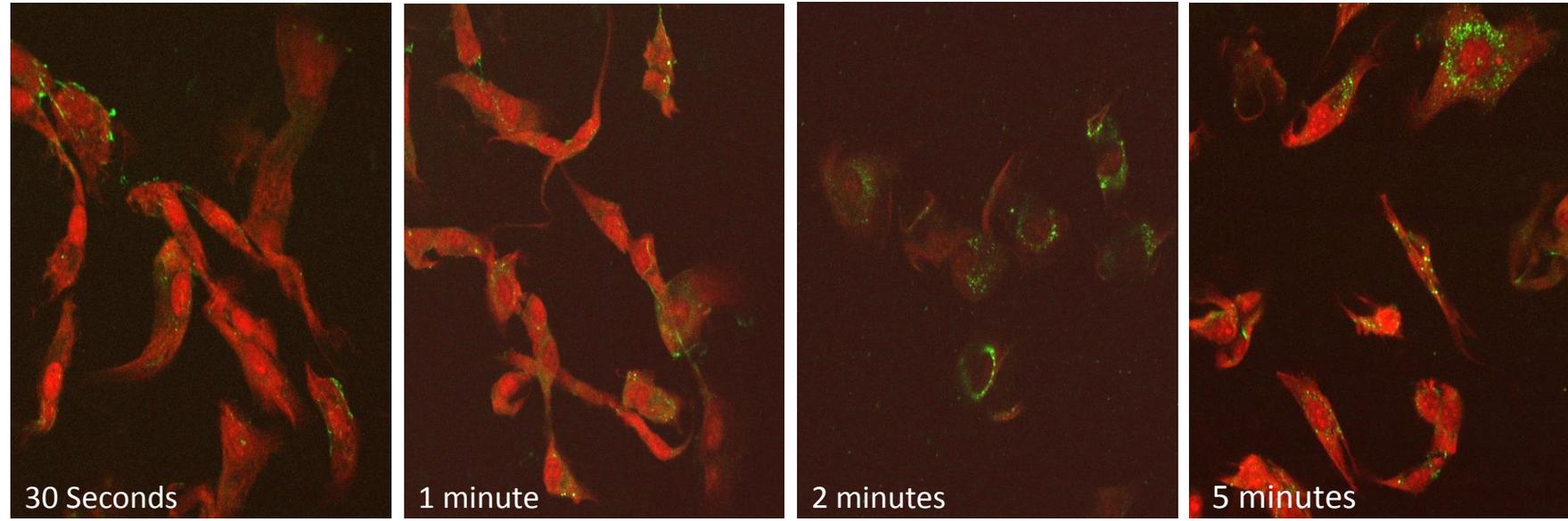
<sup>2</sup>Co-first author

\*Correspondence: defranci@unina.it

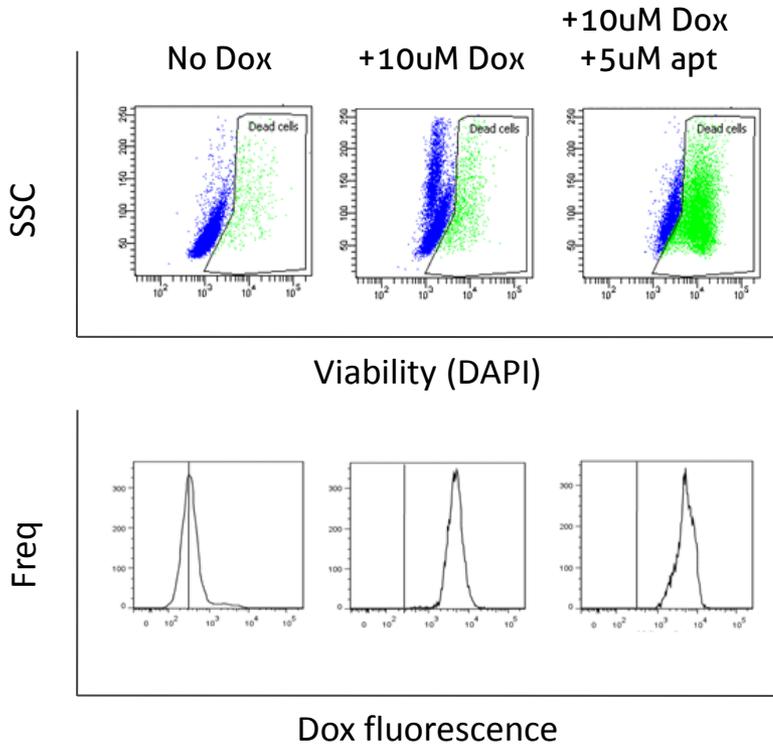
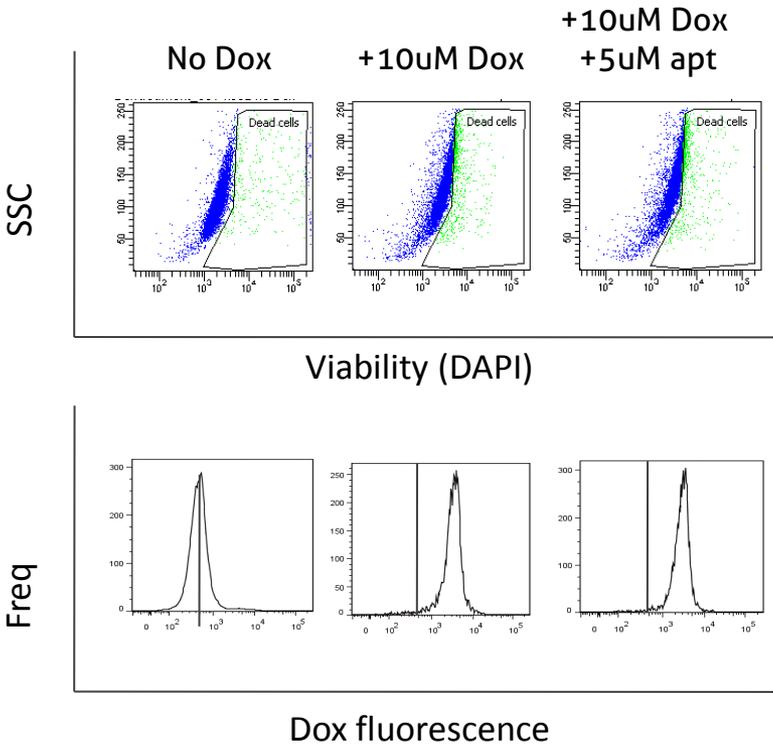
<http://dx.doi.org/10.1016/j.chembiol.2015.03.002>



# Aptamer 'delivery vehicles'



# Aptamer Delivery of Cytotoxic Compounds





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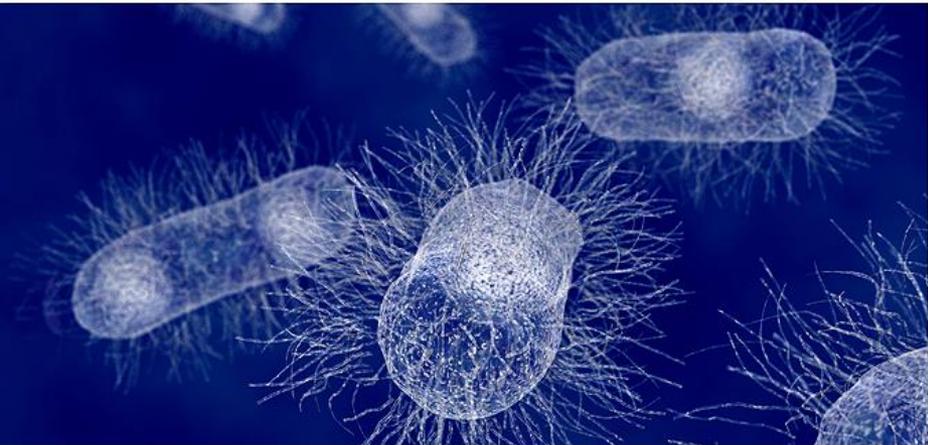
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altermune technologies  
redirecting the human body's  
own natural and potent  
immunity to fight infection...



- **Altermune is a novel therapeutics company with an innovative aptamer based technology, Alphamers**
- **Alphamers are the latest brainchild of Nobel Laureate Dr. Kary Mullis**
- **Alphamers harness a potent component of the immune system and incorporate aptamers to specifically target pathogen**



## Clinical efficacy of oligonucleotides reported in multiple tissues

### Eye (local injection)

Macugen

### Lung (inhalation)

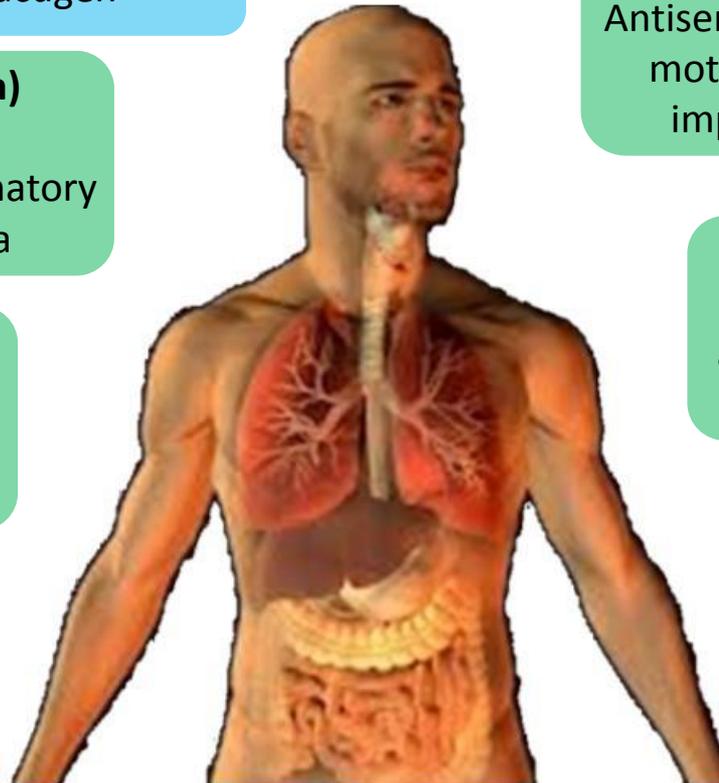
Pharmaxis  
inhaled anti-inflammatory  
oligo for asthma

### Kidney (systemic)

Isis  
Knockdown of SGLT2 to  
promote glucose excretion

### Skin (local injection)

Pfizer  
CTGF is a growth factor  
associated with scar severity



### CNS (injection)

Isis  
Antisense oligo increases survival  
motor neuron protein levels  
improves motor function.

### Muscle (systemic)

Prosensa  
antisense oligo induces exon  
skipping in dystrophin gene

### Oncology (Systemic)

Isis  
Antisense oligo to clusterin  
targets apoptotic pathway in  
prostate cancer

**No target is 'undruggable'**



## Coagulation

NU172; Thrombin inhibiting DNA aptamer  
Arc1779 von Willebrand factor inhibition

## Angiogenesis

Macugen; Vascular endothelial growth factor (VEGF)  
ARC1905; Compliment component 5 (C5)  
E10030; platelet derived growth factor (PDGF)

## Cancer

AS1411; Nucleolin  
NOX-A12; CXC chemokine ligand 12 /  
Stromal Cell-Derived Factor-1  
(CXCL12/SDF-1)

## Diabetes

NOX-E36; Chemokine Ligand 2

## Anaemia

NOX-H94; Hepcidin



# Therapeutic Aptamers – Development

## Cancer

PSMA  
Substance P  
HER3, E2F, EGFR, GRH  
Cytohesin 2, Mucin 1

## Neurological Disorders

BACE-1  
prion protein PrP  
amyloid beta-protein

## Viral Targets

HIV: RTase, Integrase, Rev,  
gp120, gp140  
HCV:  
Influenza

## Thrombosis

Thrombin  
Factor IXa  
Activated Protein C

## Angiogenesis

Fibroblast Growth Factors  
Angiopoietins

## Inflammation

Chemokines  
Neutrophil Elastase  
Interferons

Staphylococcus

Sepsis

Migraine

Lupus

Prevent Infection

Prevent Metastasis

Pain management

Allergy prevention

Modulate immune responses

Prevent metastasis





start with the end in mind



next generation diagnostics

Thank you for your attention

Any questions?



enabling drug discovery



follow the facts, find the truth



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@AptamerGroup

