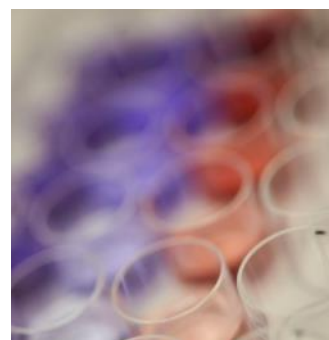




Nucleic Acid Aptamers: Novel oligonucleotide reagents for disease diagnosis and therapy





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

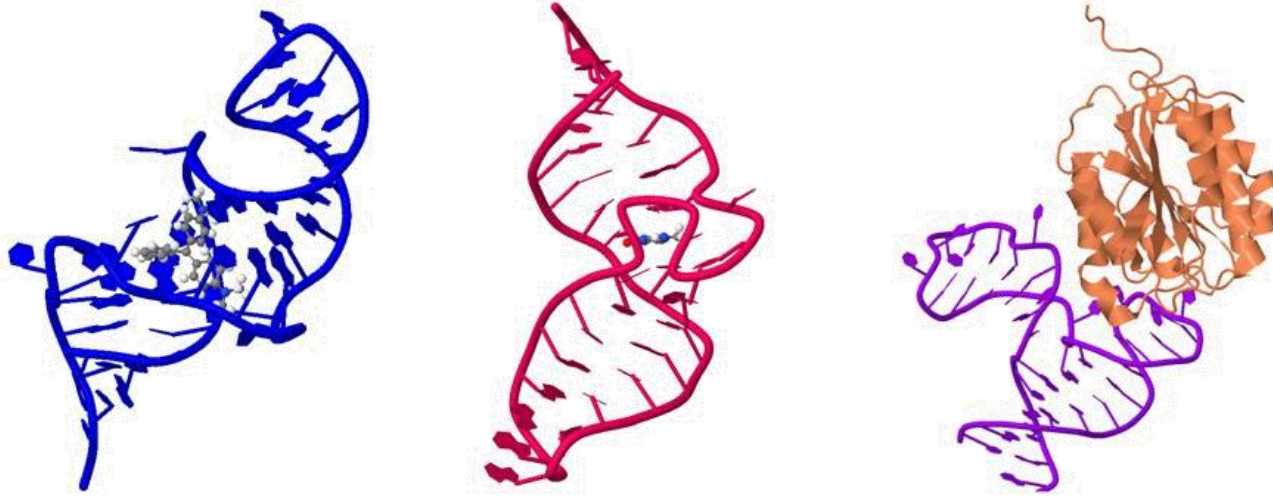
Aptasort have combined a biomarker enrichment process with our aptamer isolation protocols yielding a first-in-kind discovery process. Our proprietary aptamer based ...



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

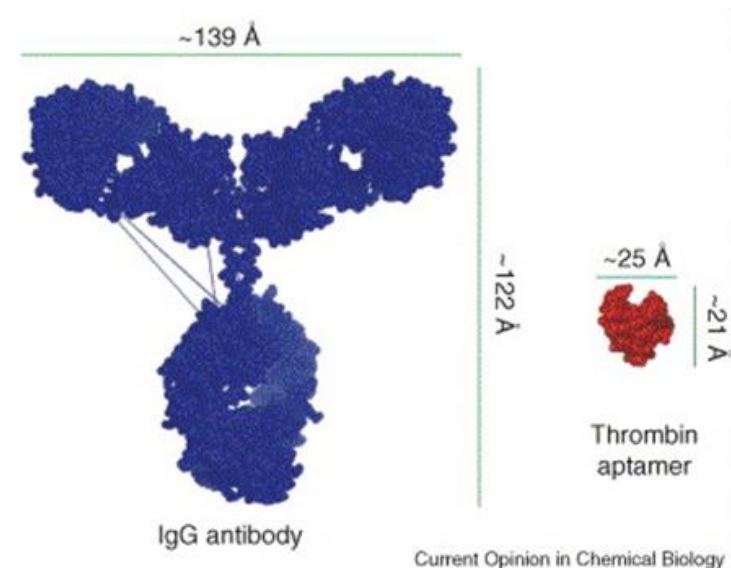
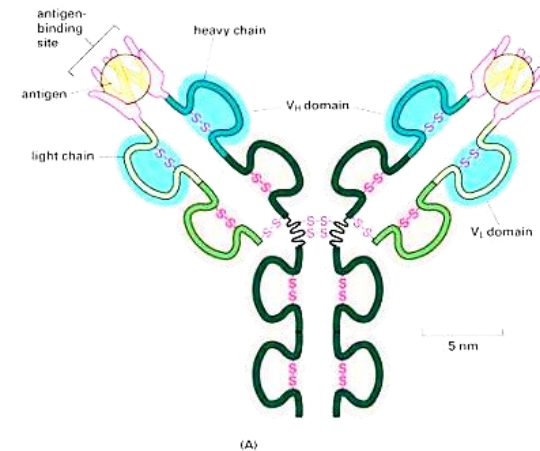
In vitro manufacture

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

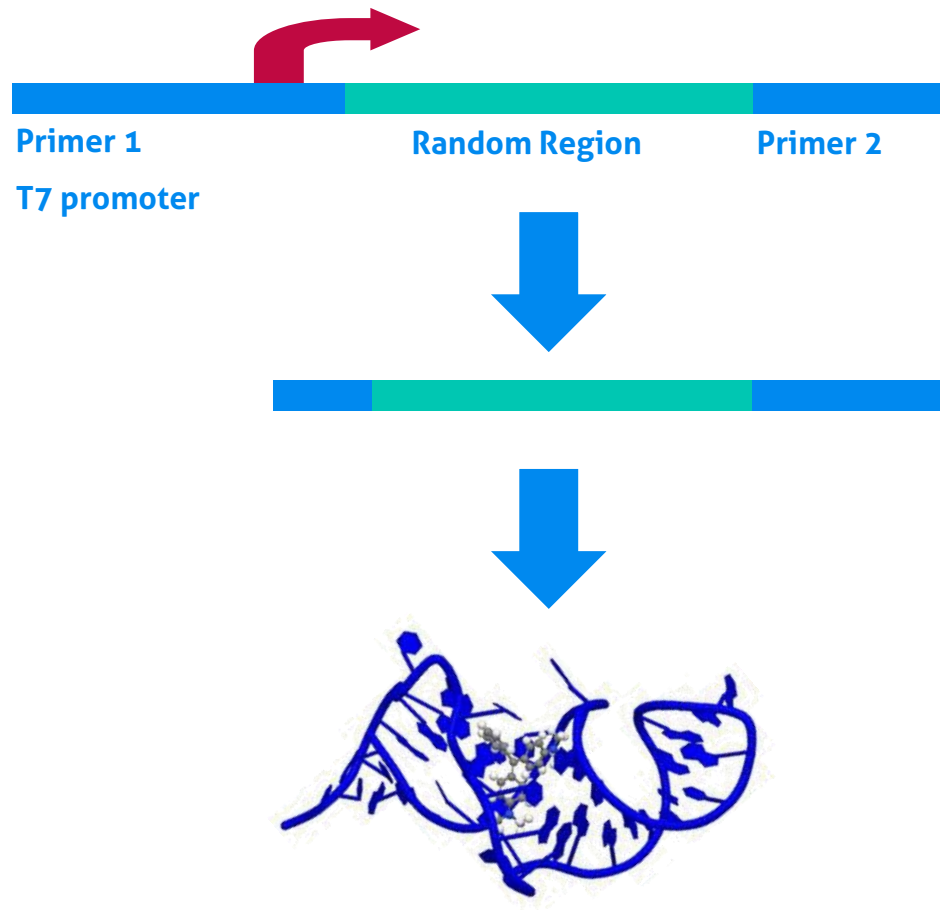


Aptamers vs Antibodies

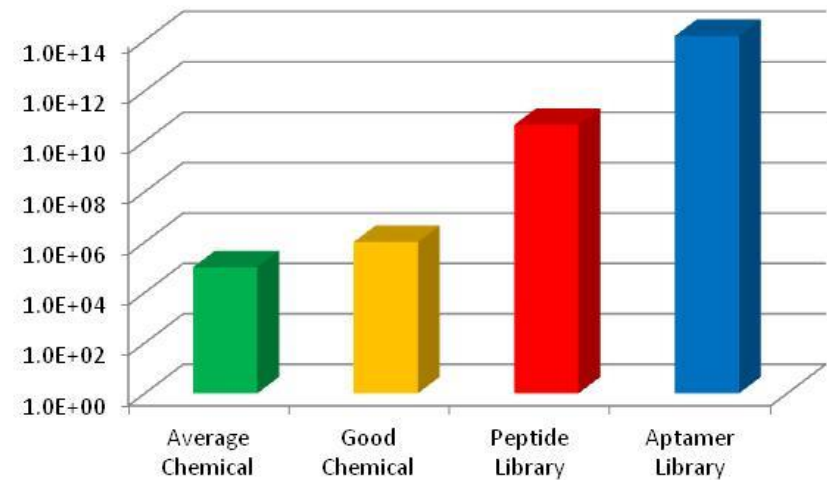
- Antibody structure is comparatively rigid and interactions are only formed with antigen binding domain
- Size makes it difficult for antibodies to access sites which are readily available to aptamers
- Greater potential for ligand contacts = greater specificity & affinity

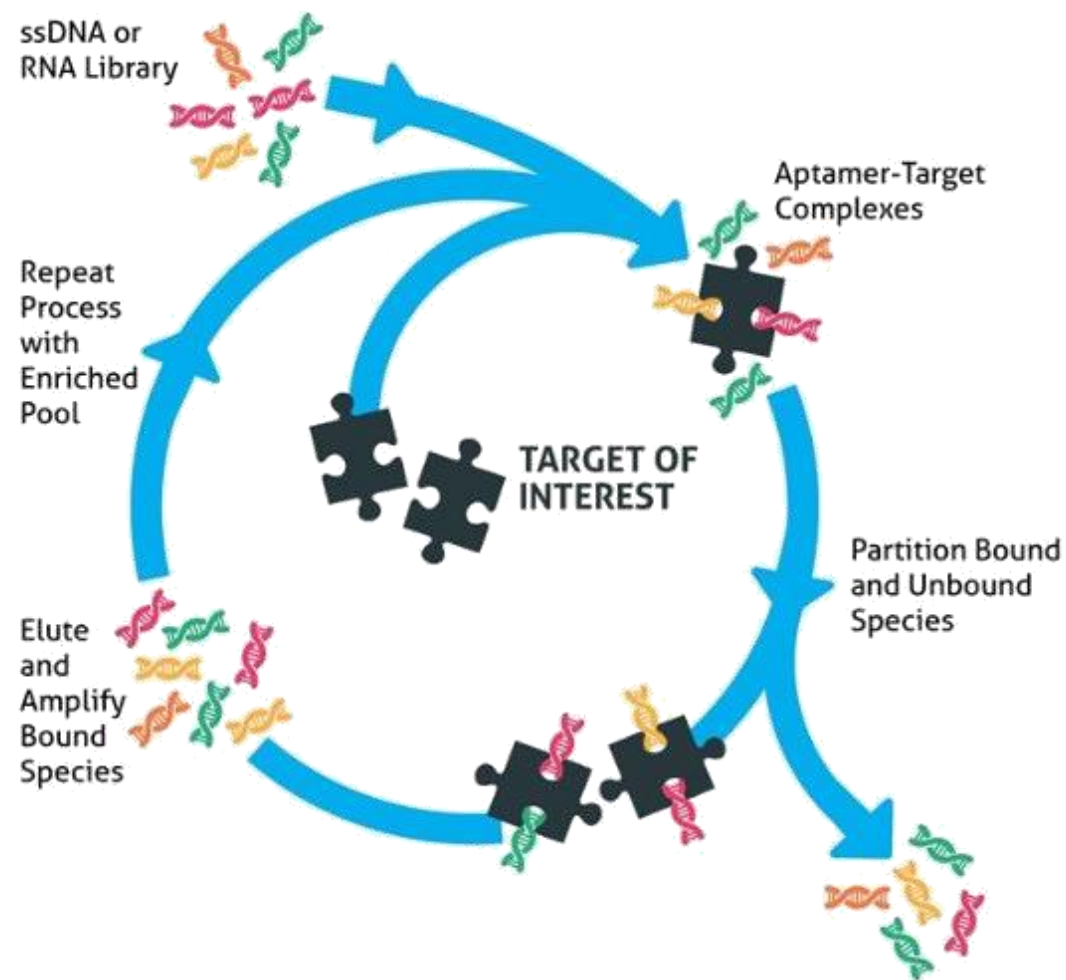


How We Raise Aptamers - The Starting Library

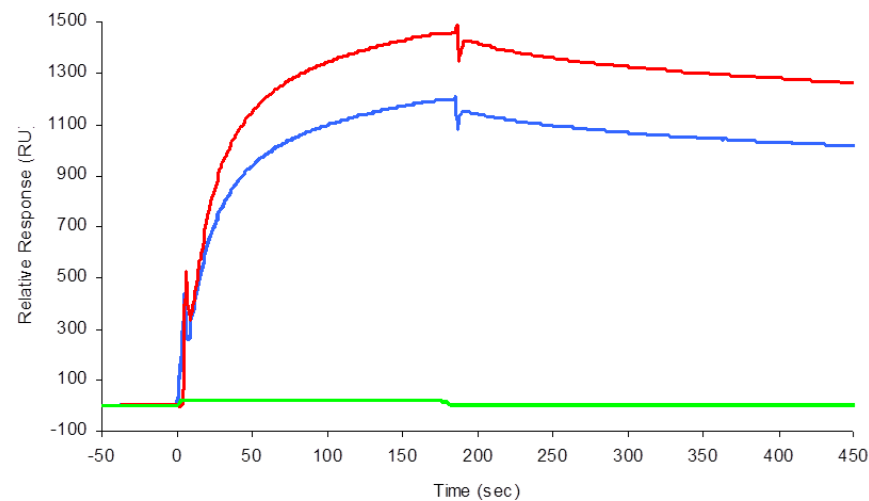
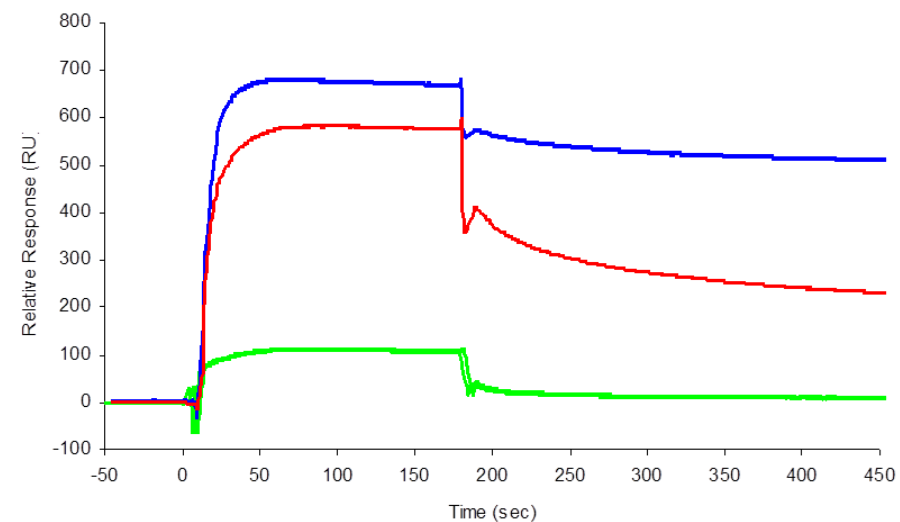


- Random region = 30 bases = 4^{30} possible sequences



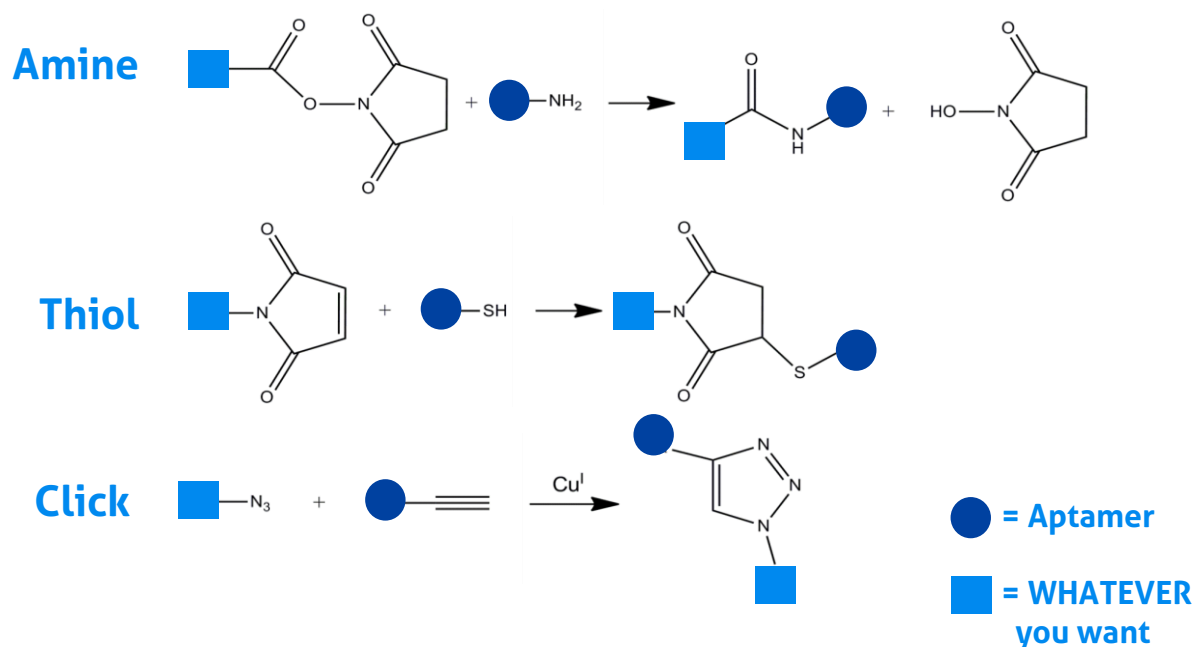


Protein	$K_d^{bFGF}/K_d^{protein}$
bFGF (FGF-2)	1.0
denatured	0.0008
FGF-1	0.0003
FGF-4	0.0006
FGF-5	0.041
FGF-6	0.0005
FGF-7	0.0007
VEGF	0.0008
PDGF AB	0.002
AT III	0.000008
thrombin	0.00003



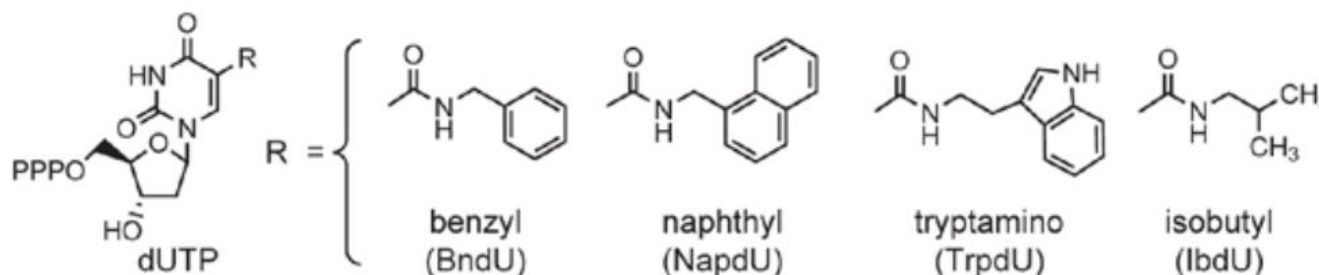
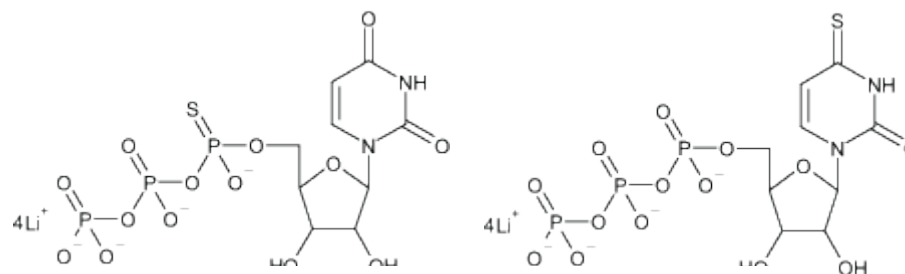
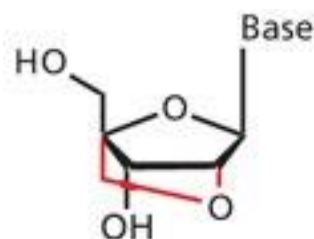
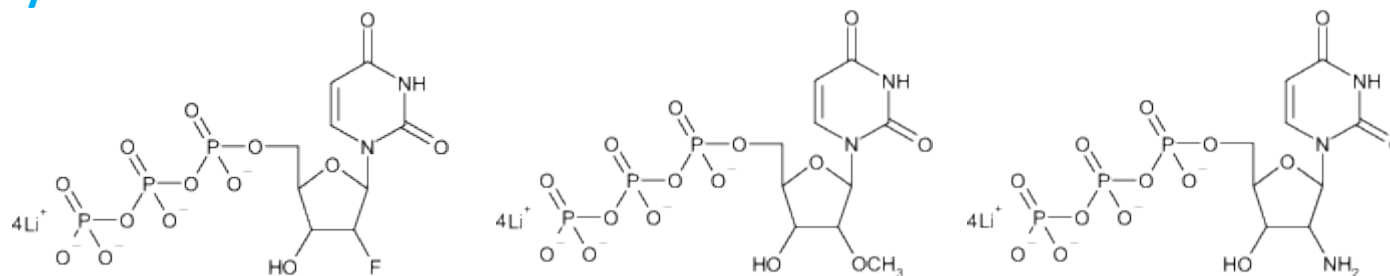
Labelling Aptamers

- 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

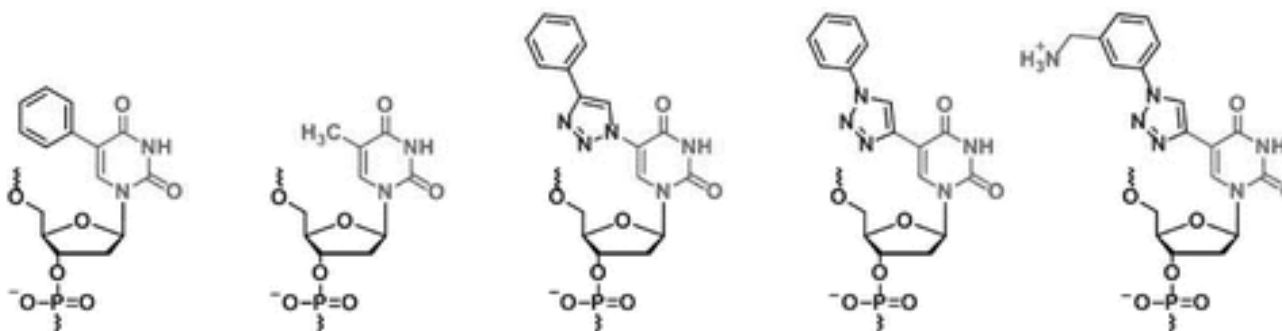
- RNA molecules are often preferred in aptamer selection for diversity of 3D structures
- Stability is still an issue for unmodified RNA



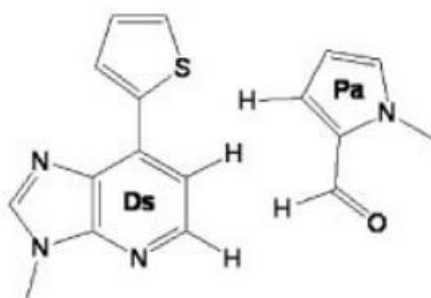
SomaLogic



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

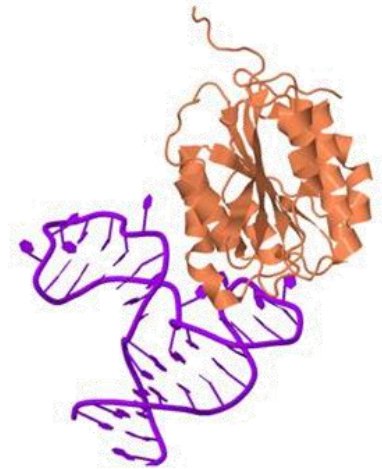
- Simpler modifications and conjugates = higher proportion of functional molecules
- Readily soluble at high concentrations
- Non-immunogenic property
- Small size

Portfolio Expansion

- Possibility of addressing targets not amenable to antibodies

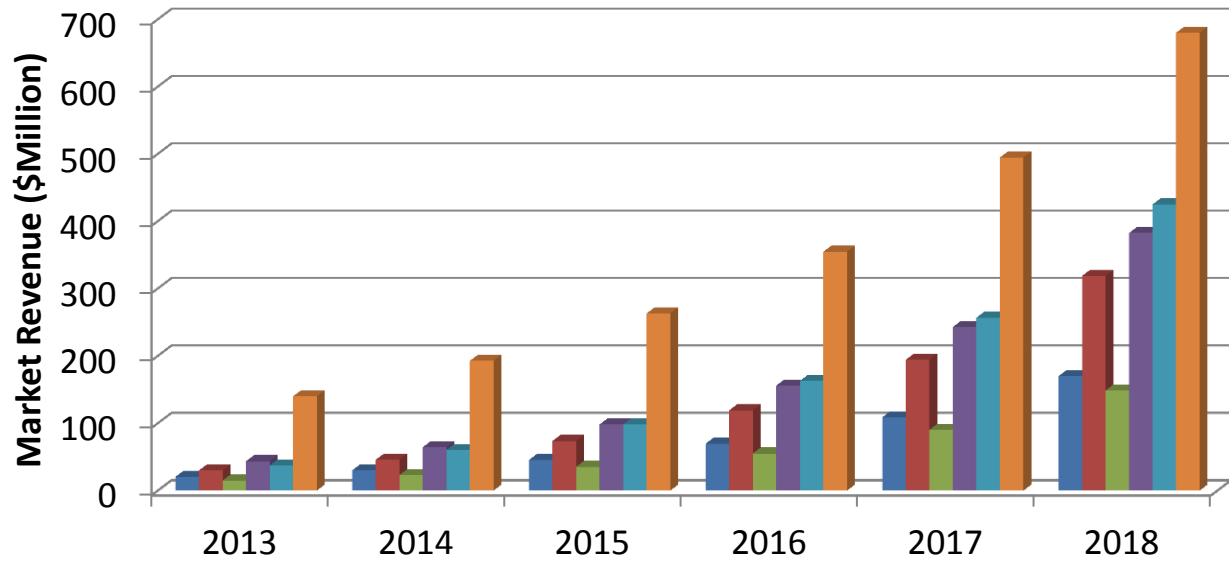
Corporate responsibility (3Rs)

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



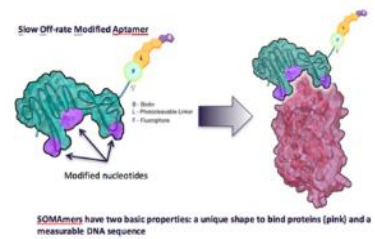
National Centre
for the Replacement
Refinement & Reduction
of Animals in Research



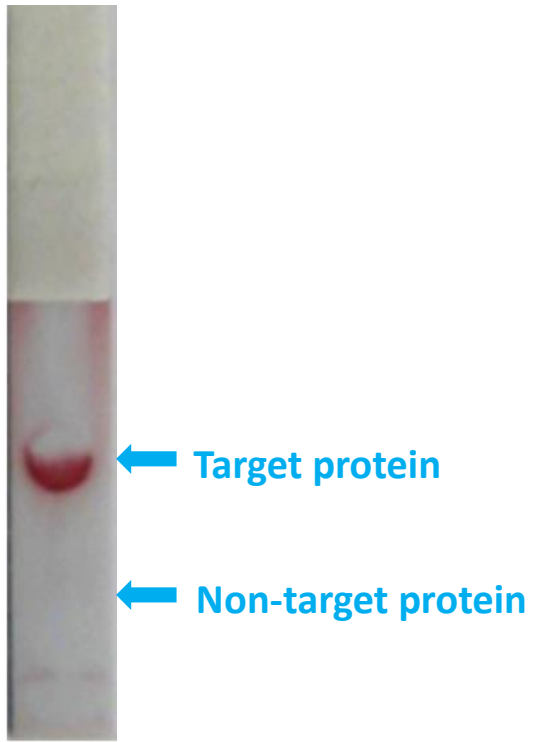
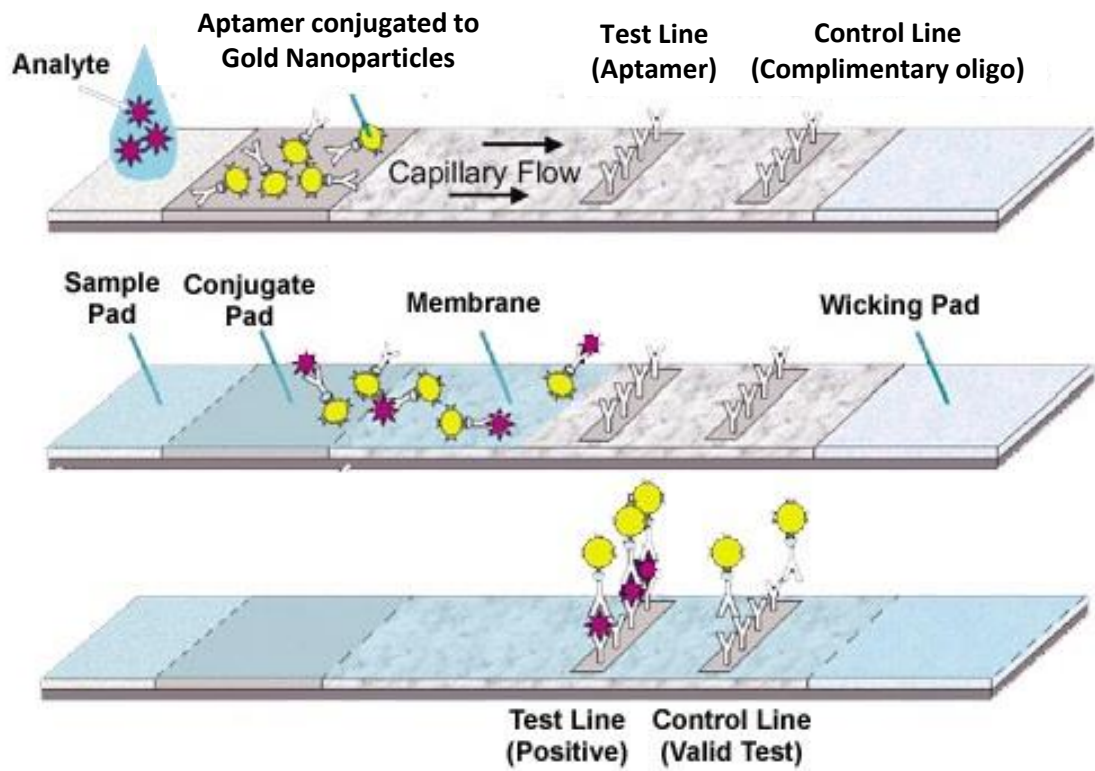


Therapeutics
Diagnostics
Biosensors
Drug Discovery
Biomarker Discovery
Research Applications

- 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

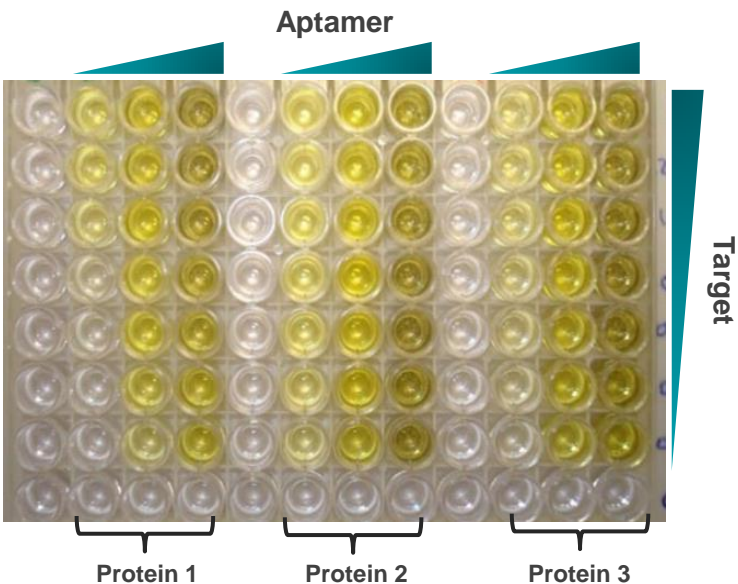
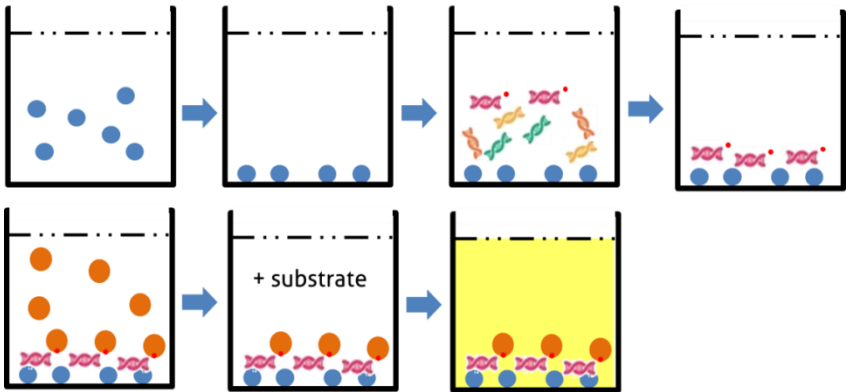


Aptamer Lateral Flow Devices (LFDs)



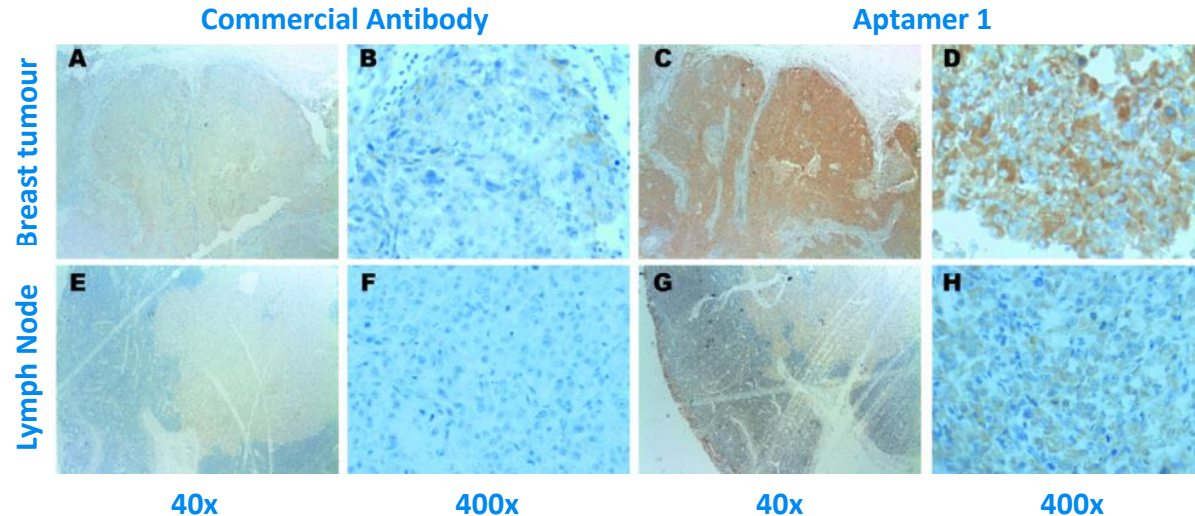
ELONA

Enzyme Linked OligoNucleotide Assay



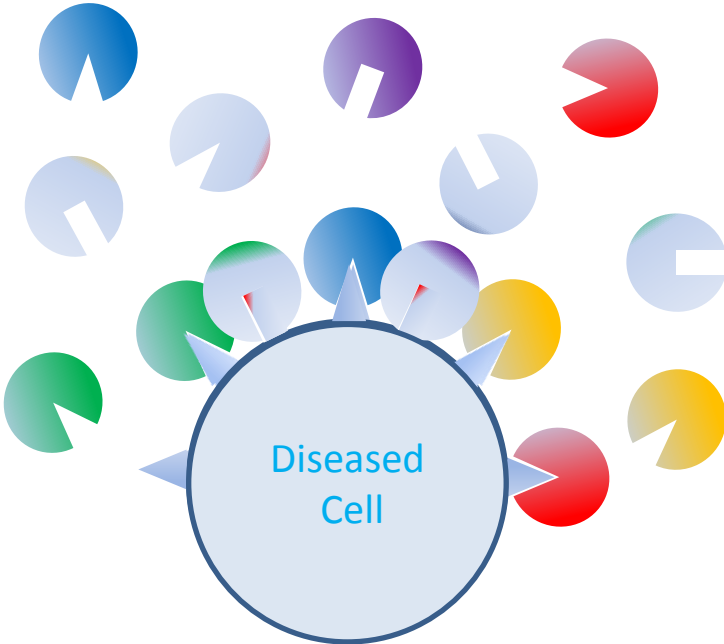
FFPE sections

- 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

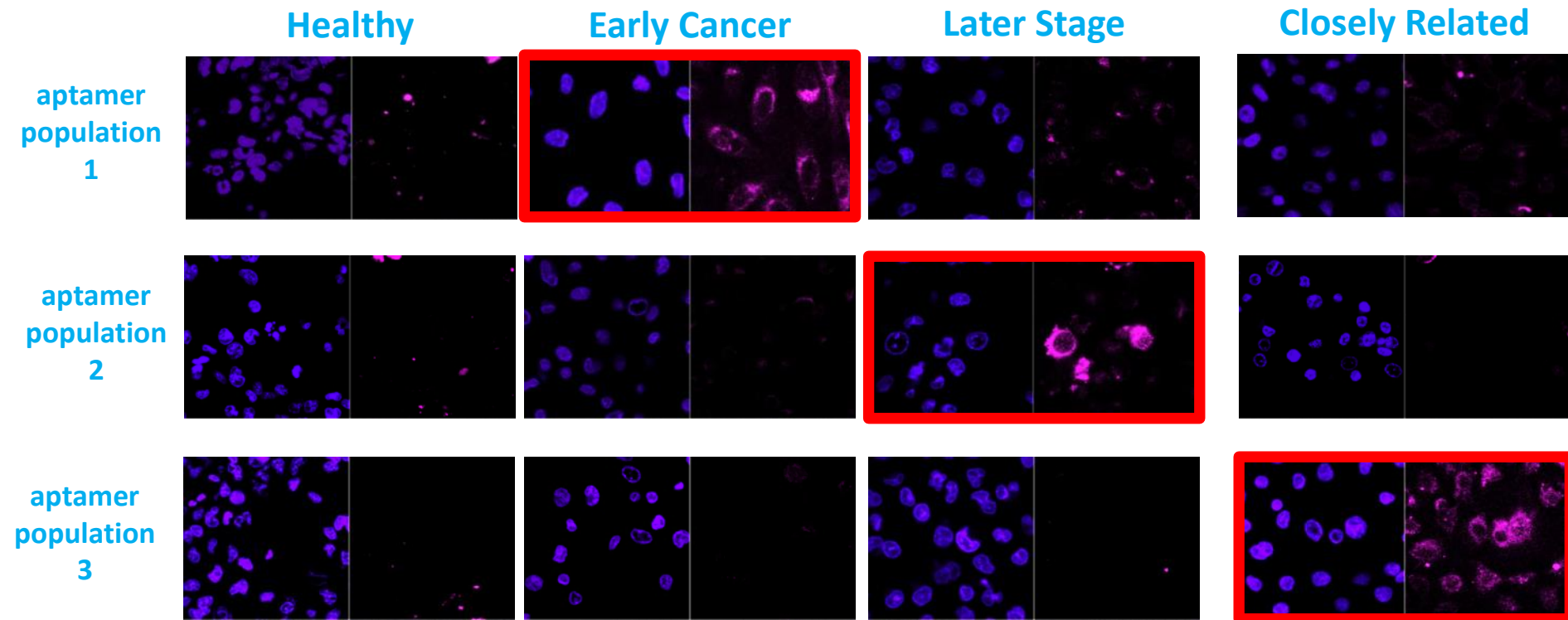


- Aptamers can be selected directly against FFPE sections
- Novel reagents compatible with commercial IHC systems



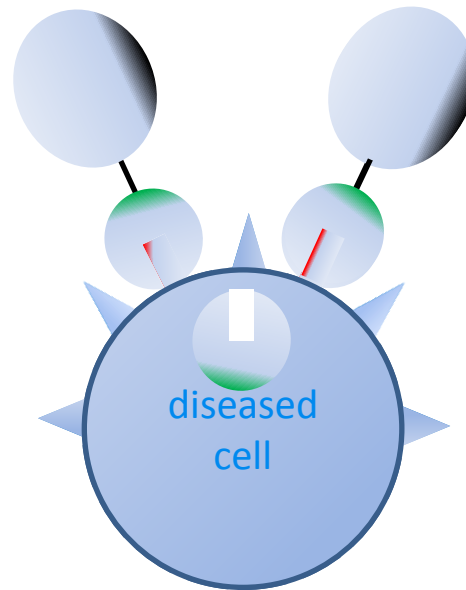


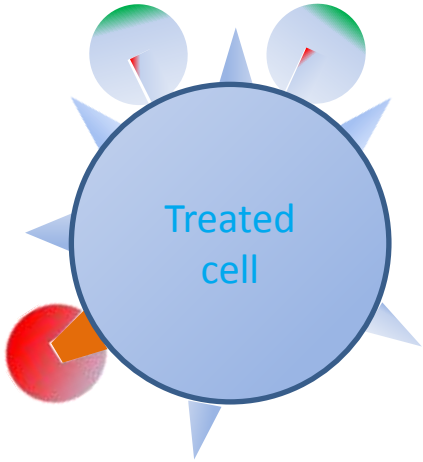
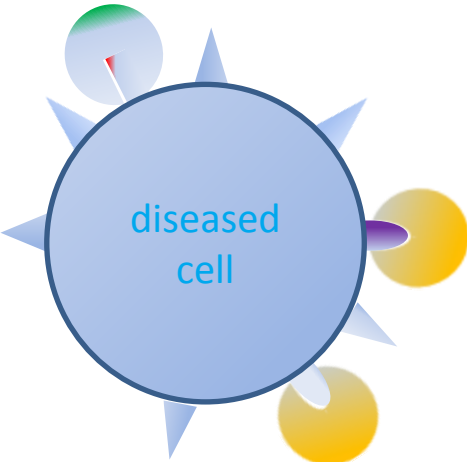
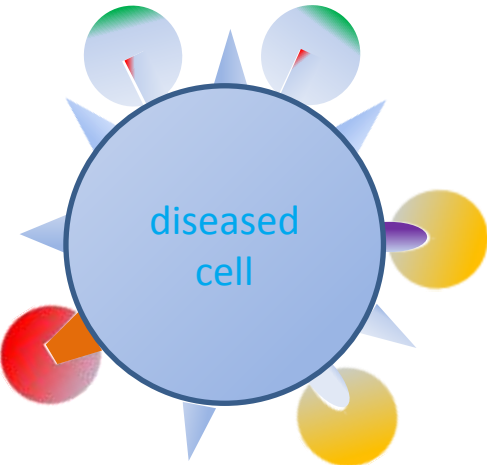
Aptamer Based Biomarker Discovery



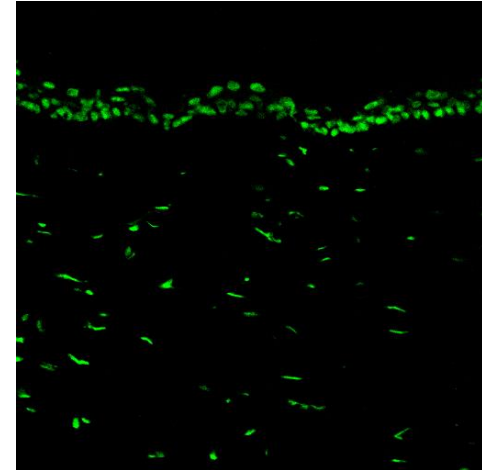
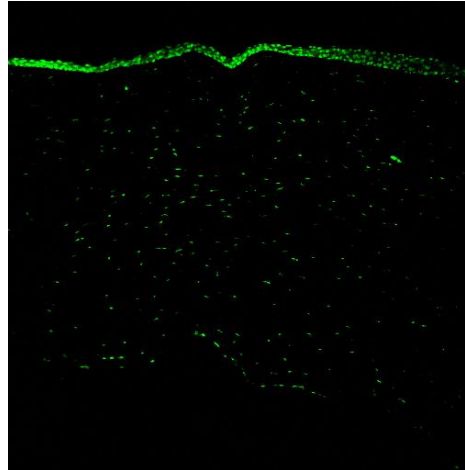
our process was used to identify aptamers against unknown biomarkers in 3 months
where 10 man-years of research failed



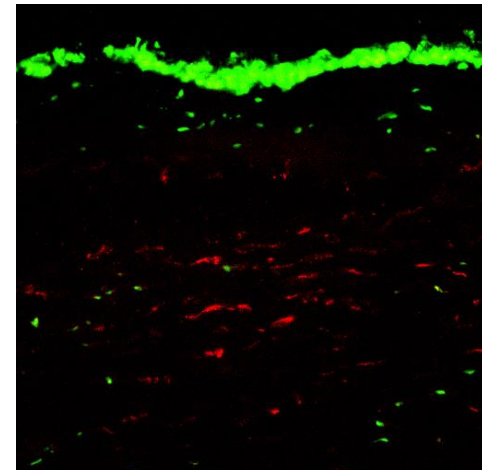
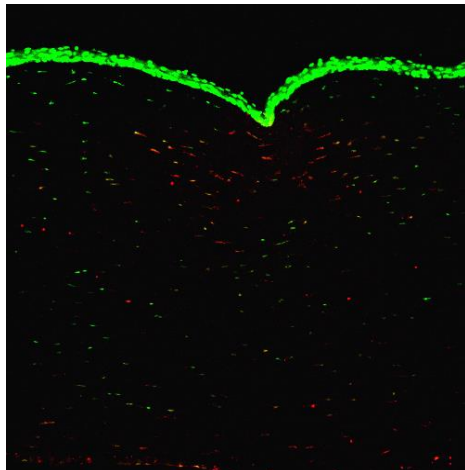


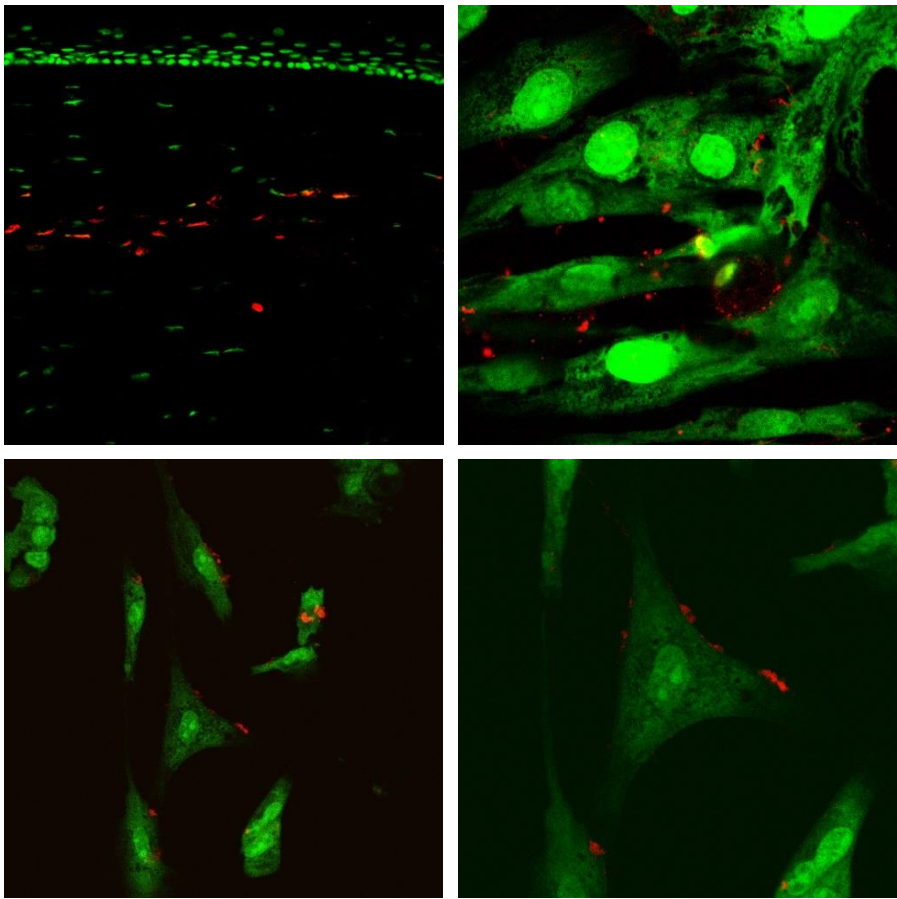


Unselected population



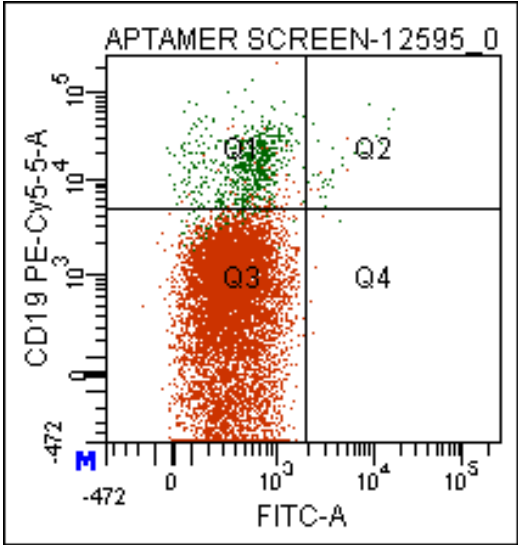
Aptamer population



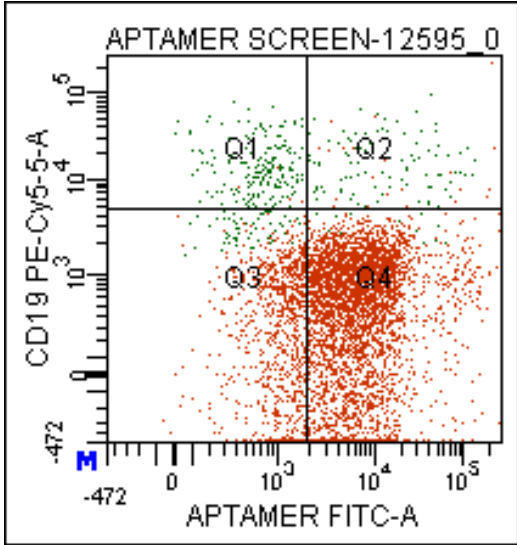


**GREEN = Healthy
plasma cells**

**RED = Neoplastic
plasma cells**



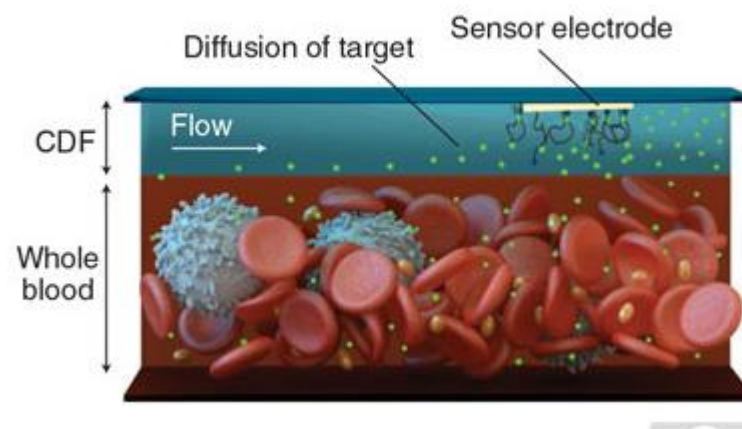
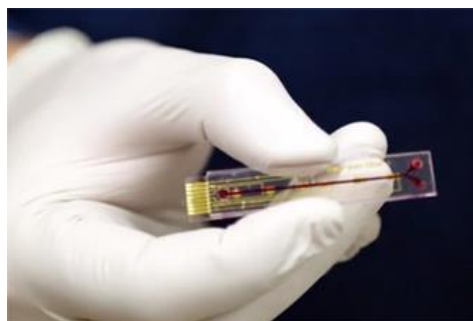
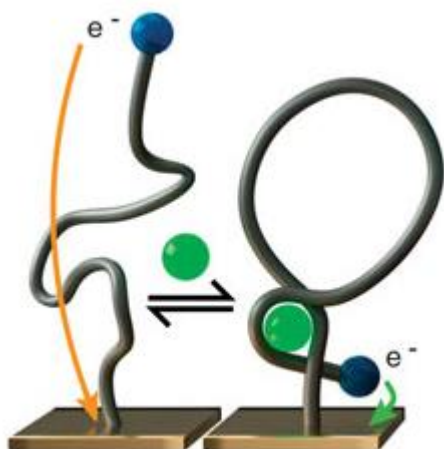
Naïve pool



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^{1,2}, David A. Hoggarth¹, Dan Maliniak³, Kyle Ploense³, Ryan J. White⁴,
Nick Woodward³, Kuangwen Hsieh², Andrew J. Bonham⁵, Michael Eisenstein^{2,6}, Tod E. Kippin^{1,3},
Kevin W. Plaxco^{7,8} and Hyongsok Tom Soh^{1,2,6,8,*}



Aptamer Diagnostics in Clinical Trial

PACIFIC COAST BUSINESS TIMES

Proudly serving Ventura, Santa Barbara and San Luis Obispo counties

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

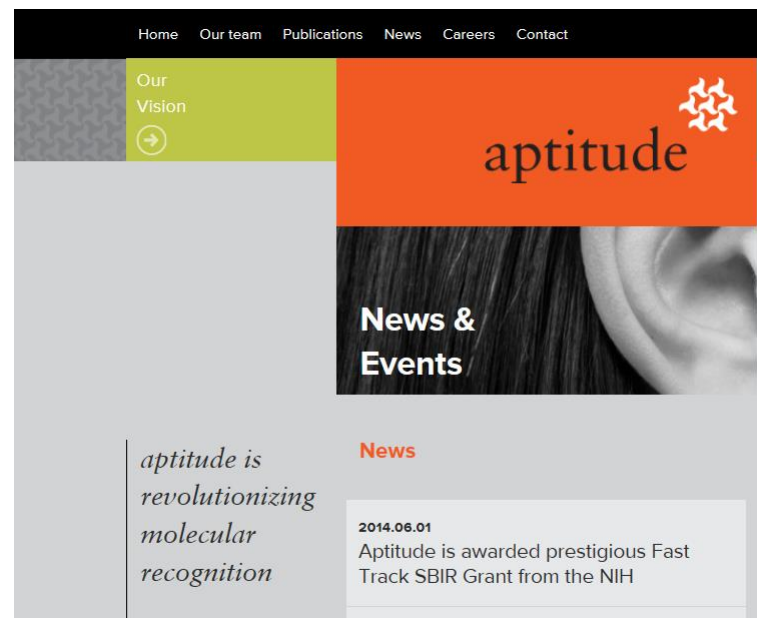
By [Erika Martin](#) / Friday, October 24th, 2014 / Comments Off

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



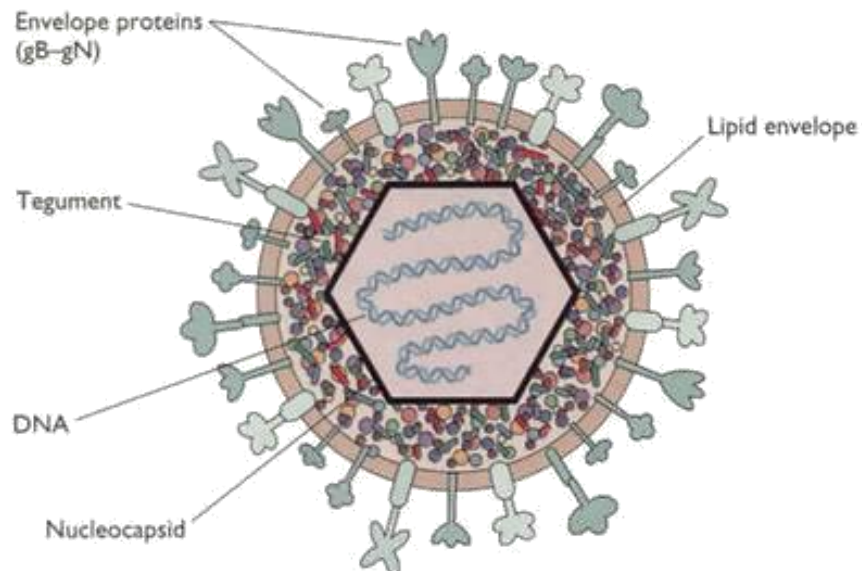
www.apitudemedical.com



Aptamer Therapeutics

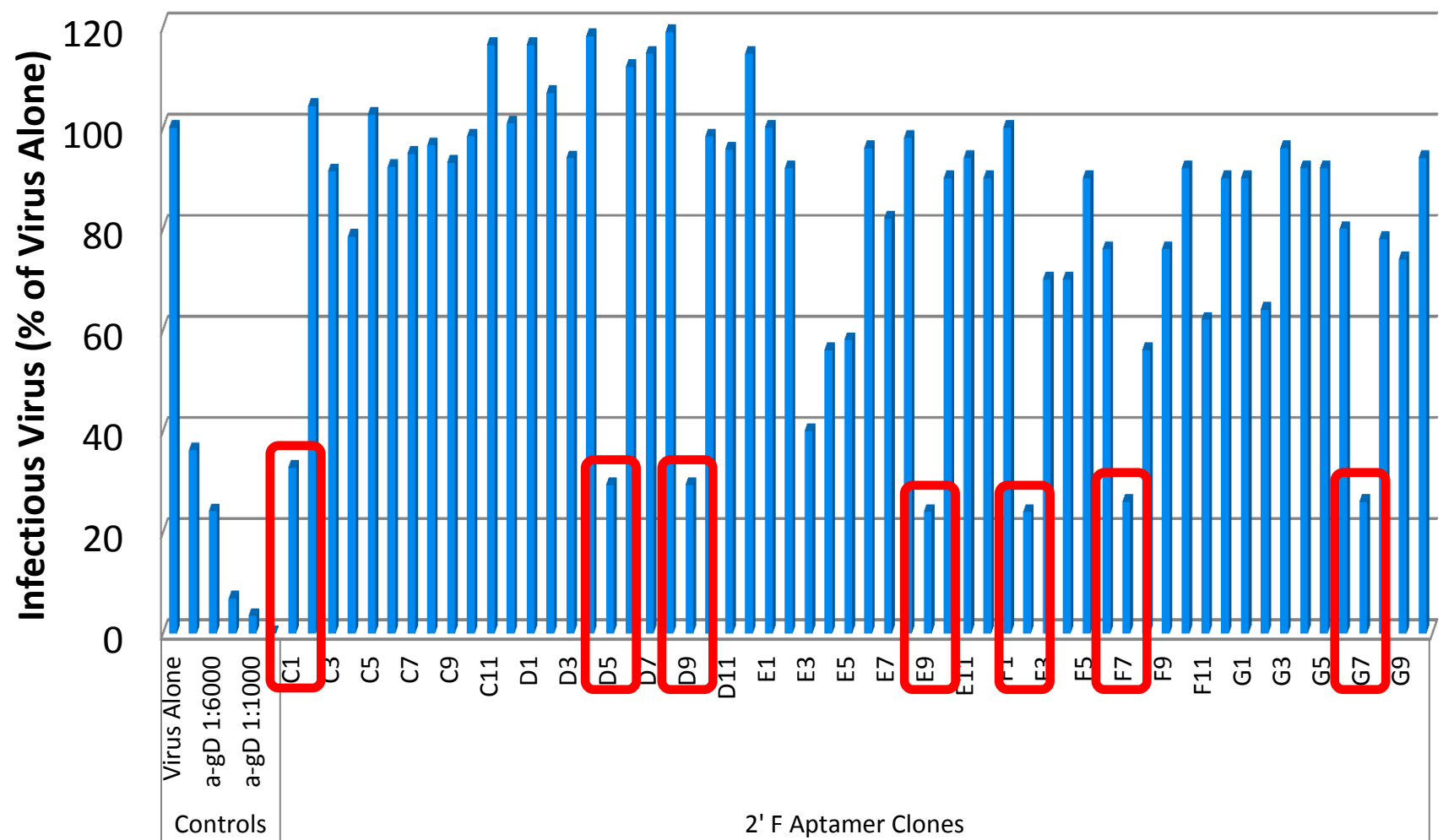
- A lot of previous work on oligonucleotide based therapies
- Aptamers are finding uses as direct therapeutics
- Modulators of other therapeutic agents
 - Slow release
 - Inactivate / antidotes
- Therapeutic chimera's
 - Aptamer-siRNA
- Aptamer based delivery vehicles for drug conjugates





- 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



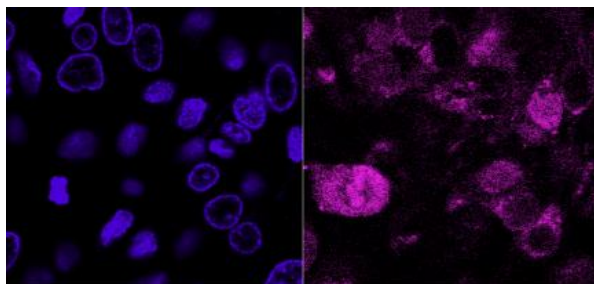


Aptamer Targeting Agents

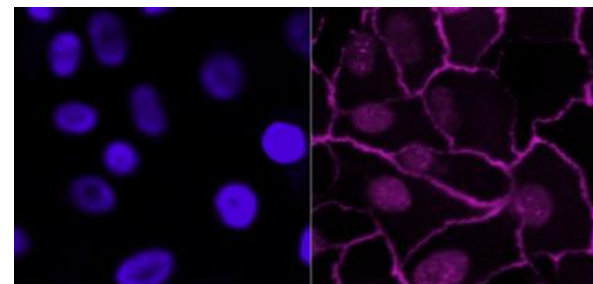
Careful application of different binding parameters can lead to aptamers with different properties on the same cell line.

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,^{1,2} Carla Lucia Esposito,^{1,2} and Vittorio de Francisci^{1,*}

¹Istituto di Endocrinologia ed Oncologia Sperimentale, CNR, 80145 Naples, Italy

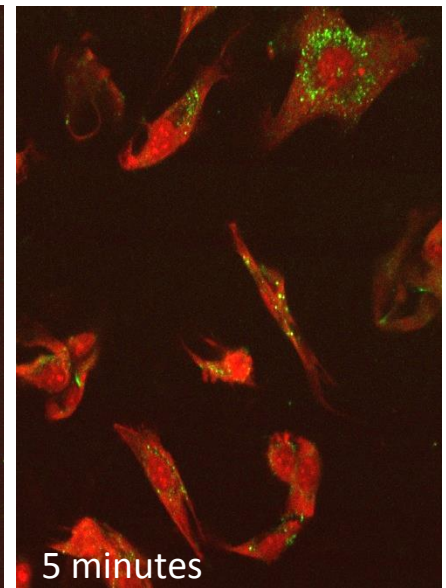
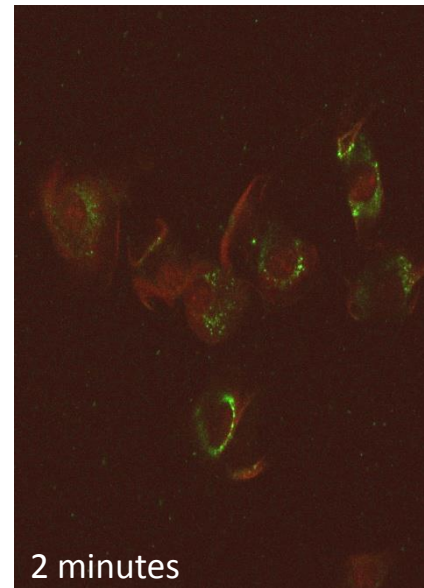
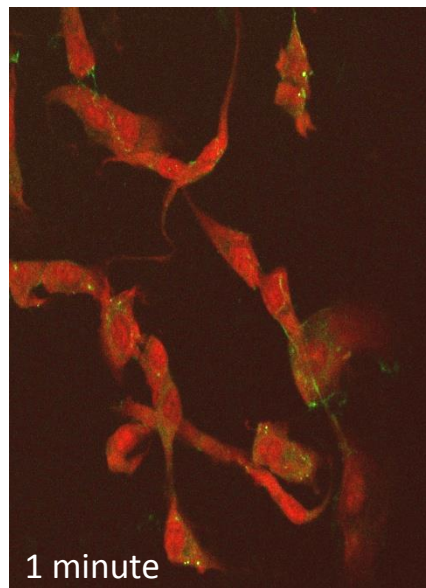
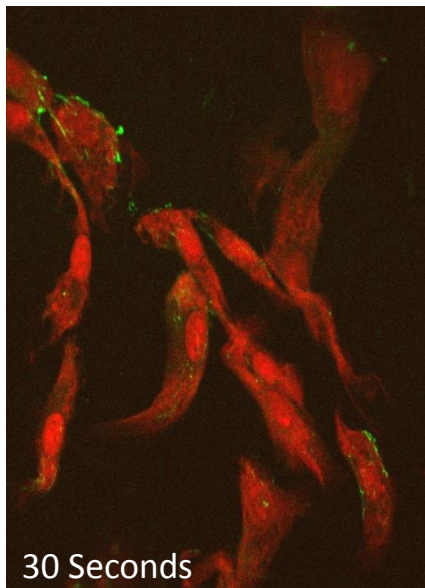
²Co-first author

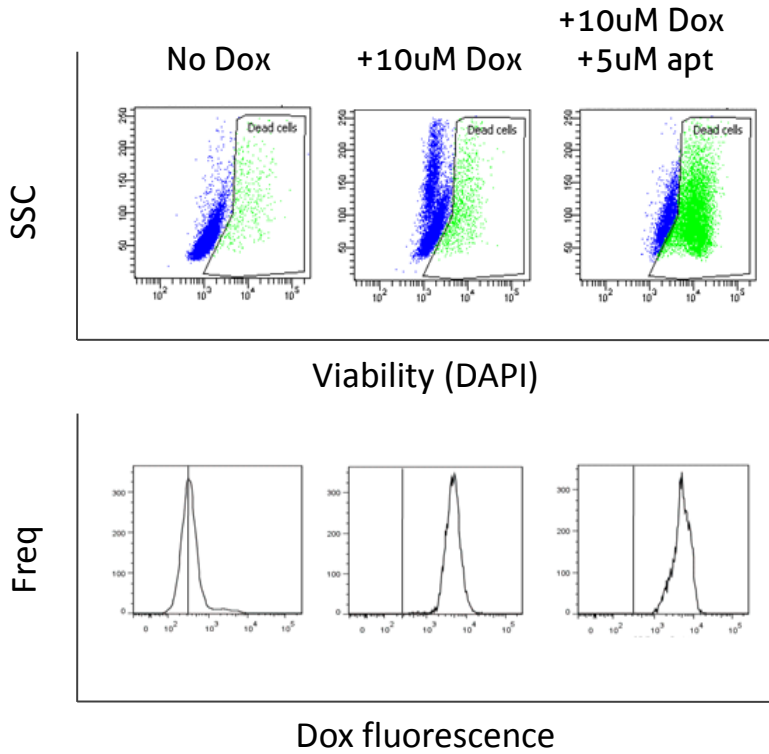
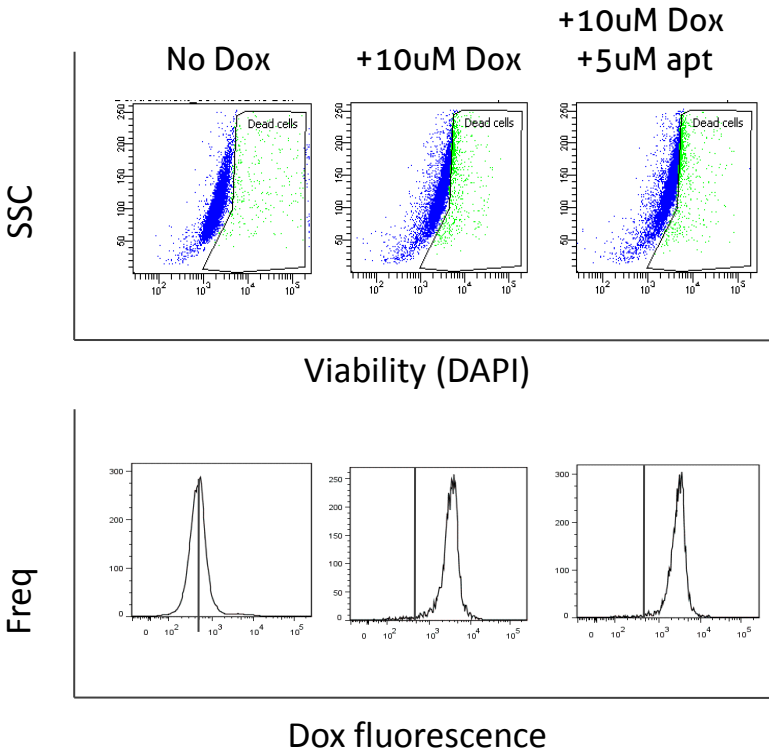
*Correspondence: defranci@unina.it

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



Aptamer 'delivery vehicles'





Aptamer Targeting Agents



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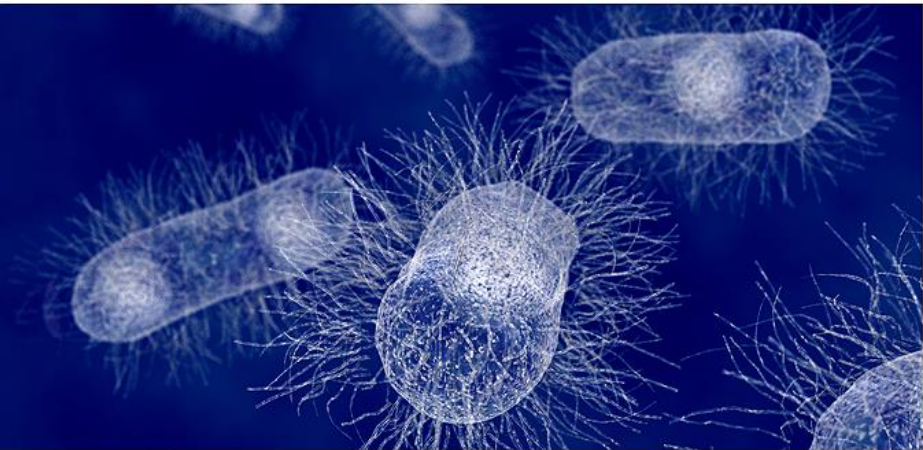
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altermune technologies
redirecting the human body's
own natural and potent
immunity to fight infection...



- **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**



Therapeutic Oligonucleotides

Clinical efficacy of oligonucleotides reported in multiple tissues

Eye (local injection)

Macugen

Lung (inhalation)

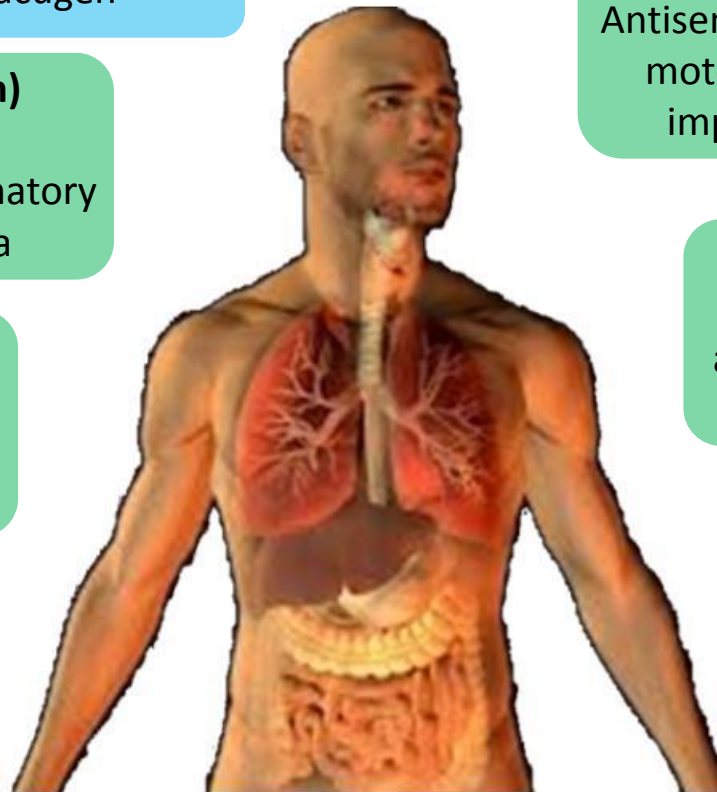
Pharmaxis
inhaled anti-inflammatory
oligo for asthma

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

