APIS Assay Technologies

Company Overview and Capabilities

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Overview

Precision medicine is the future of disease prevention, diagnosis and treatment

The application of **genomic analysis** and **system biology** are used to study the cause of disease at a **molecular level**, so that **targeted therapies** can be applied to cure the patient's health-related problems.

Predictive

Genetic risks for diseases are identified, signs of illness are recognised, the effects of disease are anticipated.

Preventative

Patients are given tools to recognise early signs of disease when it is most reversible.

Participatory

Patients are empowered to manage their own health and wellbeing.

Personalised

Care is focussed on the individual and how to optimise wellness by predicting disease and tailoring treatment.

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APIS Headquarters are in Manchester (UK)

- The symbol of Manchester is the Worker Bee
- City of industry that is rightly proud of its link with the hard-working insect
- *Apis* is the Latin name for the genus of the Bee (*Apis mellifera* = Honey Bee)

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APIS Global Locations

Manchester, UK

Company HQ
IVD development laboratories, Manufacturing & Compliance teams

Bonn, DE

Clickmer Systems GmbH
Synthetic Antibodies

Belgrade, RS

Bioinformatics, AI/ML & Software Development

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APIS Management Team

Ian Kavanagh
Chief Executive Officer

- PhD in Molecular Biology
- APIS - COO, 12/2018 - 07/2023
- QIAGEN - R&D Director
- Roche Diagnostics - R&D Manager
- Thermo Fisher Scientific - R&D Manager

Helen Fielder
Head of Technology

- DPhil Biochemistry
- QIAGEN - R&D Manager
- QIAGEN - Technical Writer & Applications Specialist

Richard Heath
Head of Marketing

- PhD in Viral Immunology
- Leica Biosystems - Global Product Manager
- Primerdesign, part of Novacyt Group - Head of Marketing
- QIAGEN - Associate Director

Joachim Schorr
Executive Chair of the Board

- PhD in Virology and Immunology
- APIS - CEO, 09/2018 - 07/2023
- QIAGEN - Managing Director
- Caris Life Sciences - CSO
- JS Consulting

Aleksandar Mihajlović
Head of Operations (Bioinformatics)

- MS in Bioinformatics
- Beogenomics - Managing Director
- Seven Bridges - Internal Education Coordinator

Nora Karnowski
Head of Operations (Clickmer Systems GmbH)

- PhD in Molecular Biomedicine
- MBA in Pharma Business Administration
- Co-founder of Clickmer Systems

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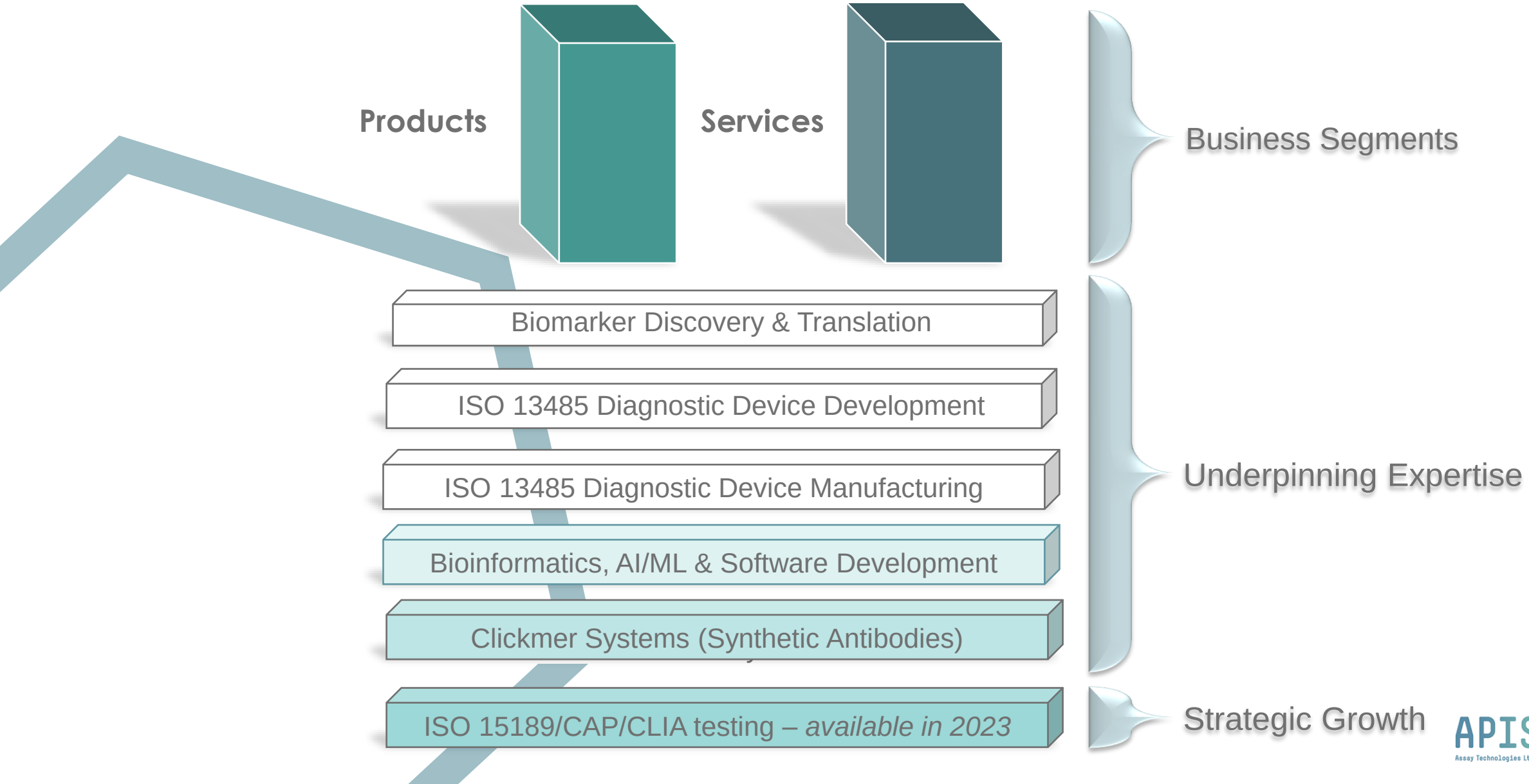
APIS Business Segments



Biomarker Products

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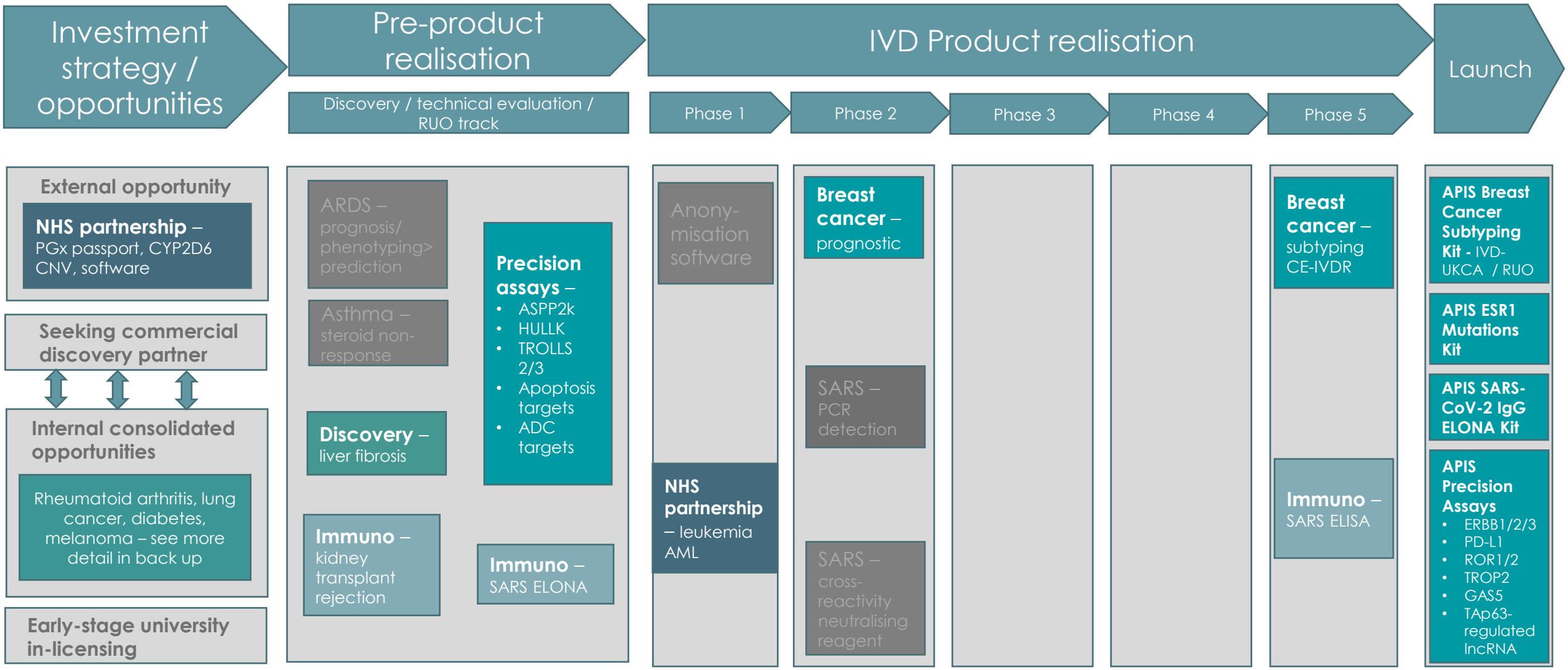
APIS Workstream

Biomarker Products

Biomarker Research and Development

- Internally funded R&D that is technology and disease area agnostic
- Our biomarker roadmap strategy is generated using our proprietary internal assessment procedure
- In-licensing of IP from academic and other research institutes
- Internal development towards commercial stage, applying our expertise in product development and realization
- Revenues recognized via out-licensing of biomarker assets emerging from Industrial Feasibility
- Potential clients for this workstream will include diagnostic and pharmaceutical companies

Biomarker Development Pipeline



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APIS Breast Cancer Subtyping Kit

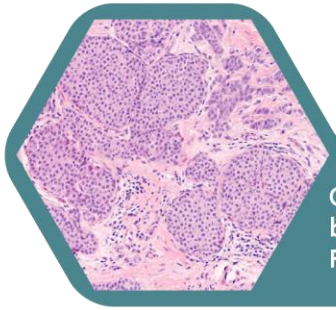
The APIS Breast Cancer Subtyping Kit is a highly reproducible, RNA-based diagnostic workflow for detecting mRNA expression of standard biomarkers (ER, PR, HER2, Ki67) and novel proliferative biomarkers from pre-operative CNB or resected FFPE breast tumour tissue.

APIS Solution

APIS Breast Cancer Subtyping Kit

The APIS Breast Cancer Subtyping Kit:

1. Delivers highly repeatable and reproducible results for the same patient sample, tested in different laboratories
2. Provides a single high-resolution method for determining HER2 amplification
3. Utilises a novel four-gene proliferative signature to improve the use of Ki67 alone for measuring proliferation
4. Is accompanied by validated software that enables automatic results interpretation



CNB or resected breast tissue FFPE sections

Nucleic acid extraction

Apis Breast Cancer Subtyping Kit

Real-time PCR

Apis Reporting Software

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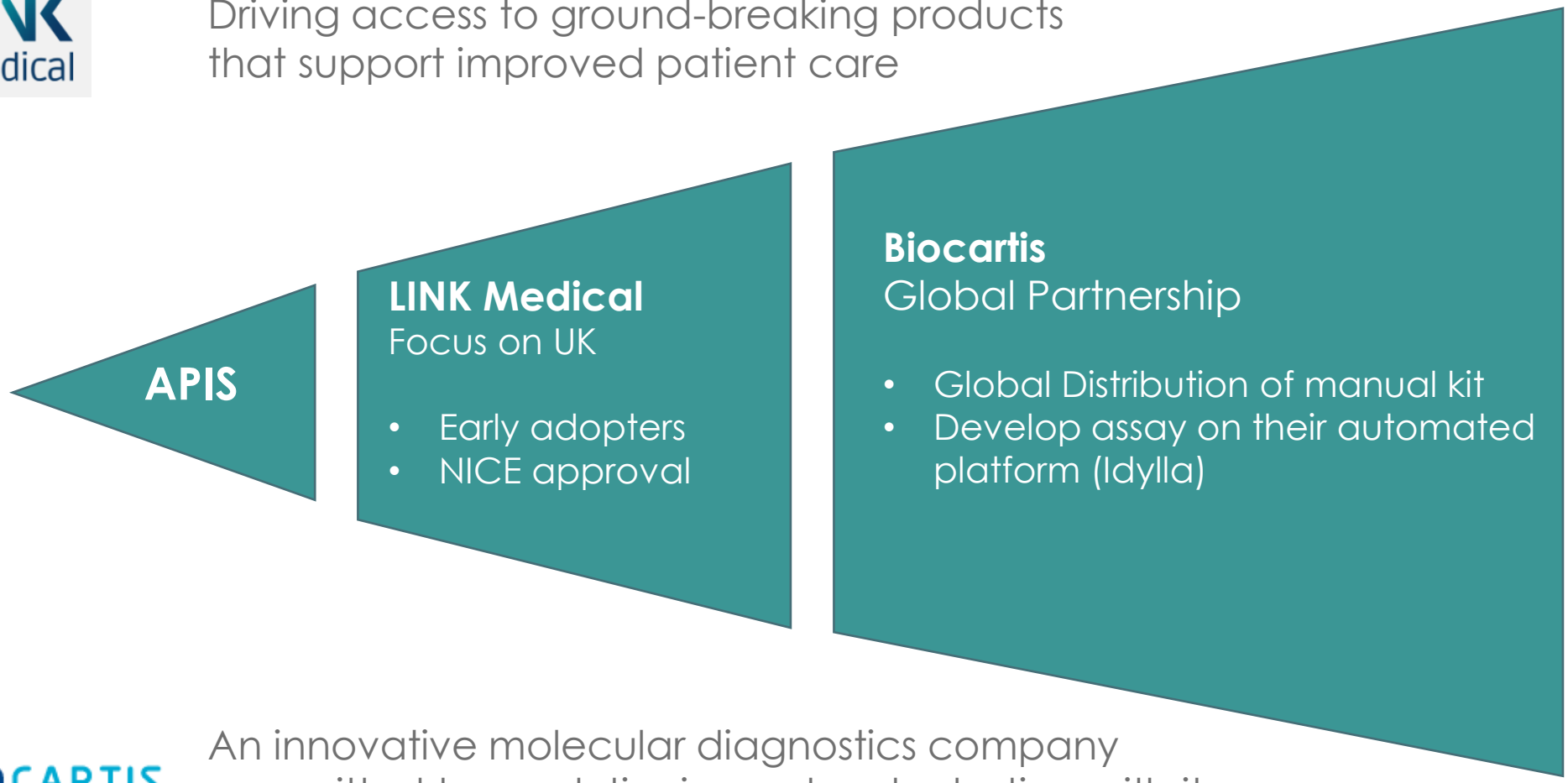
APIS Breast Cancer Subtyping Kit

Commercialisation

Driving access to ground-breaking products that support improved patient care



An innovative molecular diagnostics company committed to revolutionize molecular testing with its unique proprietary Idylla™ platform.

APIS ESR1 Mutations Kit

- An advanced qPCR assay for the sensitive and precise detection of mutations within the oestrogen receptor gene
- A qualitative test, detecting eleven ESR1 mutations across three exons: exon 5 (E380Q), exon 7 (S463P) and exon 8 (P535H, L536R, L536Q, L536H, L536P, Y537C, Y537S, Y537N and D538G)
- Mutation-specific probes to enable highly sensitive detection of the target mutations
- Utilises PCR clamp and blocker technology, which ensures specific amplification of the mutant sequence, even in the presence of a high wild-type background

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APIS ESR1 Mutations Kit - Key Benefits

- Wide target coverage - the kit has been designed to cover 11 different ESR1 mutations
- High specificity - includes clamp and blocking technology to ensure no wild-type detection
- High sensitivity - all mutations are detected at ≤ 1% MAF (Mutant Allele Frequency)
- Easy to use - our assays are designed to be user-friendly, with a simple protocol. The reagents have been optimised for precise and sensitive detection in human DNA.

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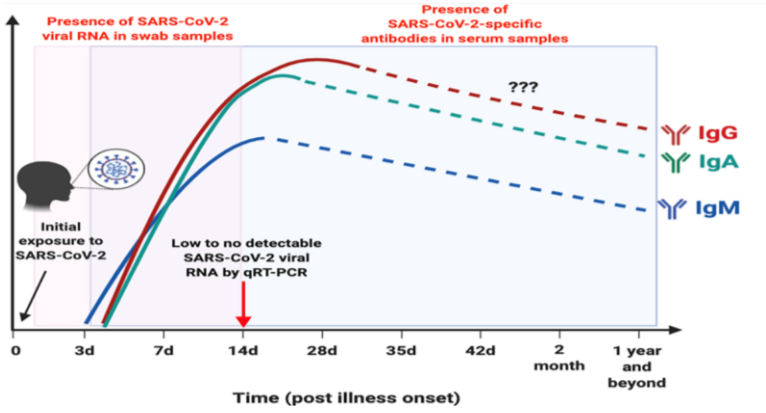
SARS-CoV2 Immunity

Background

- A highly accurate, quantitative immunoassay is needed for evaluation of immunity status (post-infection and post-vaccination) to aid vaccine development/booster dosing, disease prevention, and research studies
- For maximum impact on clinical decision making, there is a need to link antibody levels to level of protection against infection



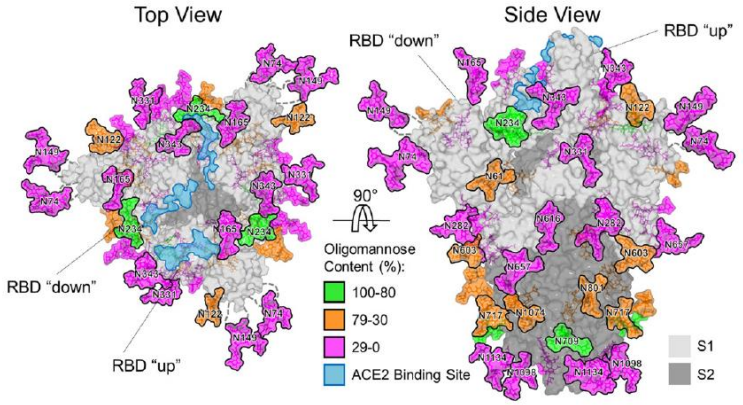
https://www.frontiersin.org/articles/10.3389/fimmu.2020.00879/full

Technical Challenges

- Demonstrating accuracy of quantitation for significant variants of concern pre- and post-launch
- Finalising a control/cut-off concept, with large-scale vaccine roll out negative serum/plasma will become increasingly rare

Product Description

- Quantitative ELISA to detect IgG antibodies against SARS-CoV2 Spike protein in human venous serum/capillary fingerprick serum
- Report correlation to neutralizing antibodies
- Option to protect against human common coronavirus cross-reactivity that may emerge using cross-reactivity neutralizing reagent (UKRI grant)



Structure-based mapping of S protein glycan shield – stabilized prefusion trimer (HEK 293-expressed)

Collaborations

- Clickmer Systems, Bonn
- University of Virginia

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APIS SARS-CoV-2 IgG ELONA Kit

- An *in vitro* enzyme-linked oligonucleotide assay (ELONA) intended for the quantitative detection of IgG antibodies to SARS-CoV-2 spike protein in human serum

- This kit demonstrates the capabilities and advantages of Clickmer 'modified aptamers' and offers improvements over the traditional ELISA antibody-only based approaches

- Key Benefits
  - Delivers highly repeatable and reproducible results
  - Clickmers synthetic synthesis ensures batch-to-batch continuity, reproducibility and reliability
  - High throughput testing, up to 88 individual samples per plate
  - Reports SARS-CoV-2 IgG levels according to NIBSC working reagent (21/234)
  - Accompanied by a validated APIS analysis template that enables automated results calling

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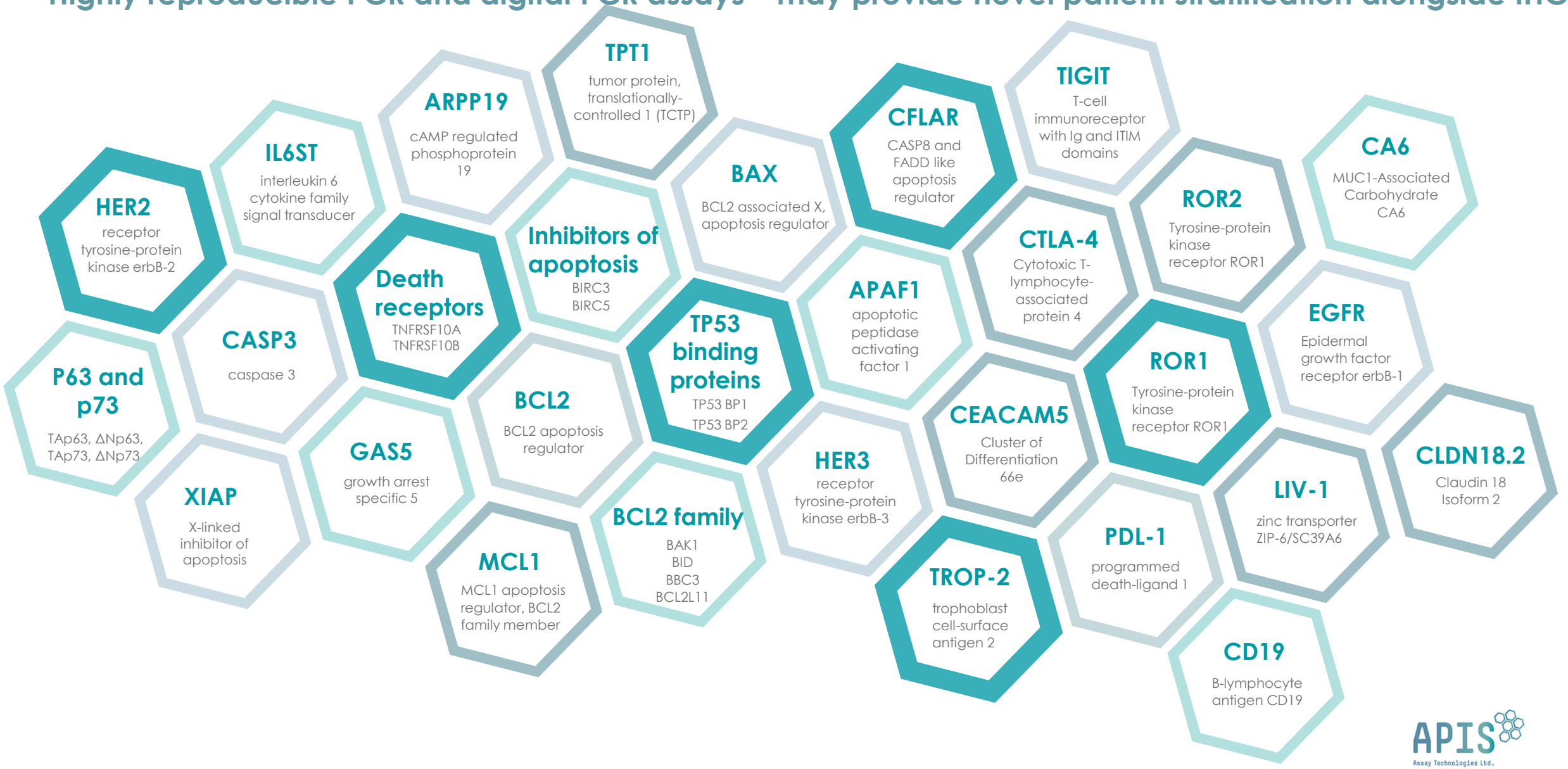
APIS Precision Assays for CDx Development

Highly reproducible PCR and digital PCR assays – may provide novel patient stratification alongside IHC



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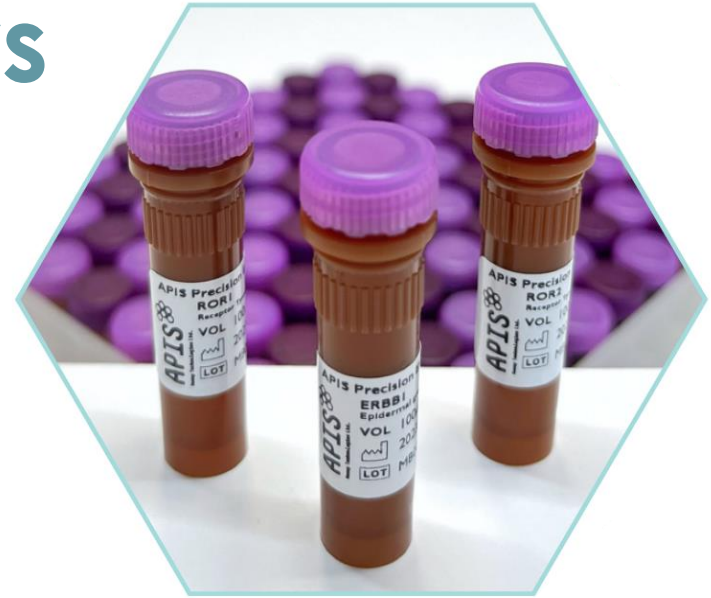
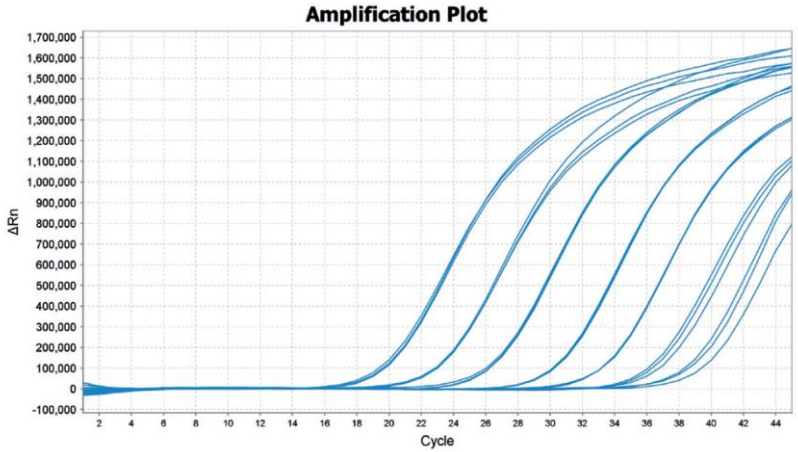
APIS Precision Expression Assays



- For the quantitative expression analysis of human biomarkers using one-step RT-qPCR

- Key Benefits
  - High specificity - extensive in silico analysis and wet-lab testing
  - High efficiency - assays have >90% PCR efficiency guaranteed
  - Easy to use - no requirement for melt curve analysis post-run
  - Reagent flexibility - tested with a variety of PCR master mixes

- New kits available for
  - ERBB1
  - ERBB2
  - ERBB3
  - GAS5
  - PD-L1
  - ROR1
  - ROR2
  - TROP2
  - TAp63-regulated lncRNAs



Demonstrated assay performance and linearity down to a low copy number. HULLK Precision Expression Assay: Efficiency: 104%; R2: >0.99.

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Contract IVD Development and Manufacturing

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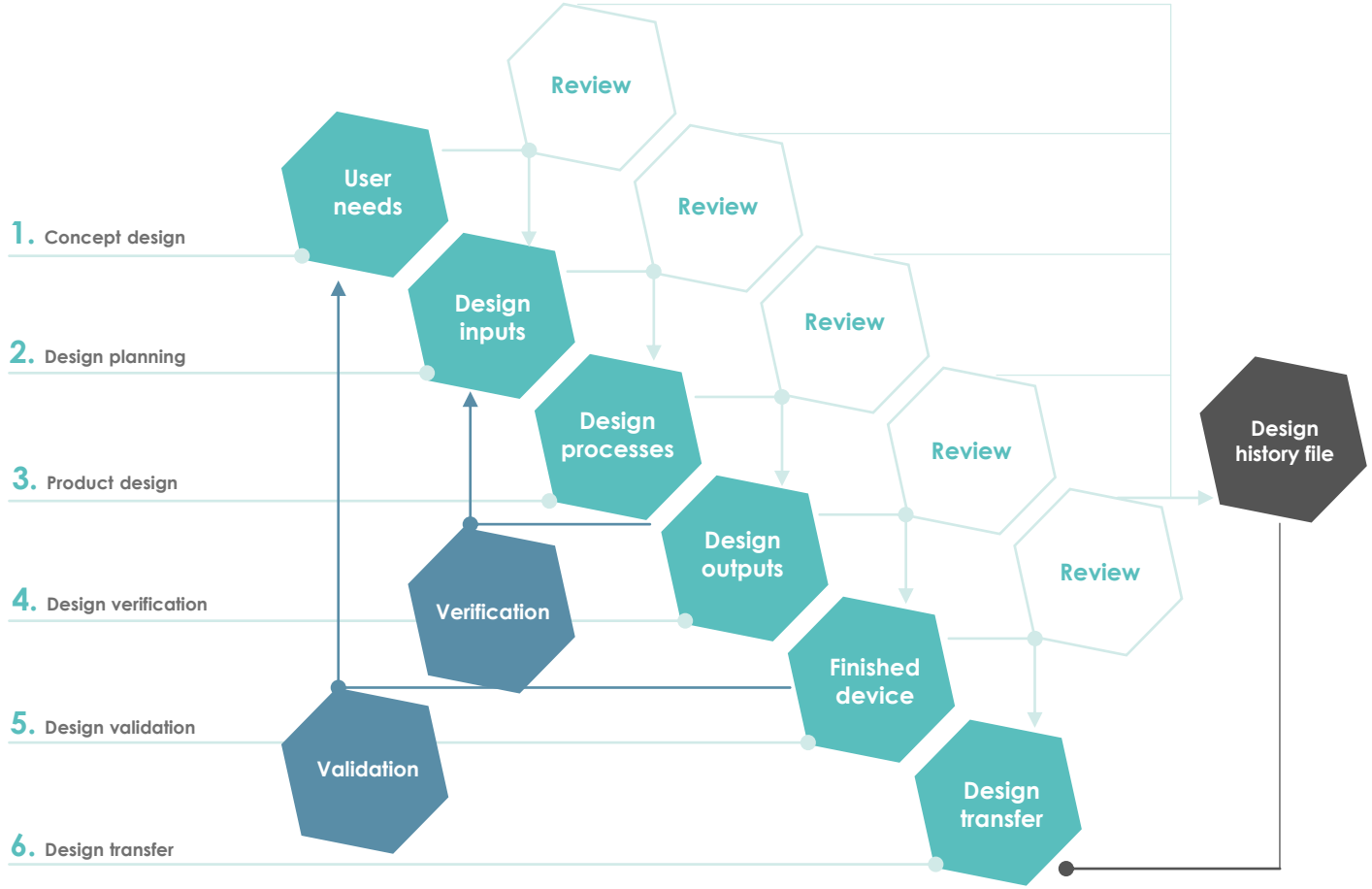
APIS Workstream - Services

Contract IVD Development

IVD Research and Development

- Externally funded service provision for molecular diagnostics product development
- Fully ISO 13485 Quality Management System
- Revenues generated via milestone payments defined in underpinning Contract Development agreements
- 3-year master development agreement in place with major MDx Company



APIS MDx Capabilities

Expertise

Technology:

- PCR: (*qPCR, RT-qPCR, dPCR)*
- NGS
- Immunoassay: *ELISA/ELONA, IHC*
- *Antibody analogue selection (Clickmers)*
- Sample preparation
  RNA, DNA, protein & direct
- Sample matrix
  FFPE, blood, swab, stool, sputum, saliva, urine, BAL, CSF
- Microbiology
  Culture, blood culture
- Cell culture

Bioinformatics and Software:

- Customised pipeline development
- Data analysis & software development
- AI/ML algorithms
- Biostatistics

Manufacturing:

- Design Transfer Capabilities
- Prototyping – Early phase kit configurations
- Pilot line – Final configuration for V&V
- Commercial

Clinical Affairs:

- Clinical study strategy & design
- Set up & management of clinical sites
- Clinical site monitoring
- Study report writing

Quality Management:

- ISO 13485 certification
- FDA 21 CFR 820 compliant
- Product Realisation SOP to CE-IVDR 2017/746

Regulatory Affairs:

- Preparation of regulatory strategies
- Pre-submission and communication
  Notified Bodies (BSI), Competent Authorities (FDA, MHRA, etc)
- Preparation of technical files

Over 250 years of combined IVD development experience

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APIS MDx Capabilities

End-to-End Competency: Assay Definition to Product Registration

Assay Definition

- Selection of the technology and the biomarker(s)

Assay Design

- Assay component selection & development

IVD Common Technical Specification

- Assay verification & validation

Customised Development and Production

- Assay fabrication

Commercial Presentation

- Packaging & documentation

Registration

- Registration of the product for its use as an IVD

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APIS MDx Capabilities

ISO 13485 MDx Development & Manufacturing

Assay & Software Development

Design Inputs and planning

Feasibility
- Assay design
- Component assessment
- Multiplex design & selection
- Sample handling & input assessment
- Optimisation
- Assay controls assessment
- Feasibility performance

Development
- Develop Control concept
- QC spec setting
- Design transfer
- Stability studies
- Risk mitigation studies
- Software and documentation
- Guardband

Verification
- LOD/LOB/LLOQ
- Quant studies (Linearity)
- Accuracy
- In use studies
- Cross contamination
- R&R studies
- Interfering substances/specificity

Validation
- Validate design meets the user's needs
- Clinical performance studies
- Finalise the instructions for use
- Finalise technical files for regulatory submission

Technical Documentation

Customer requirements
Regs &Clinical strategy
Feasibility plan

Product Risk Management File
Technical Feasibility Report
Product Requirements
Manufacturing Feasibility Assessment

Design Transfer Plan
Development study reports
IP landscape assessment
Verification and Validation Plans

Instructions for Use
Design Transfer Report
Verification Reports

Design Validation Reports
Instructions for Use
Regulatory technical files

Manufacturing

Prototype lots

Pilot lots

Commercial lots

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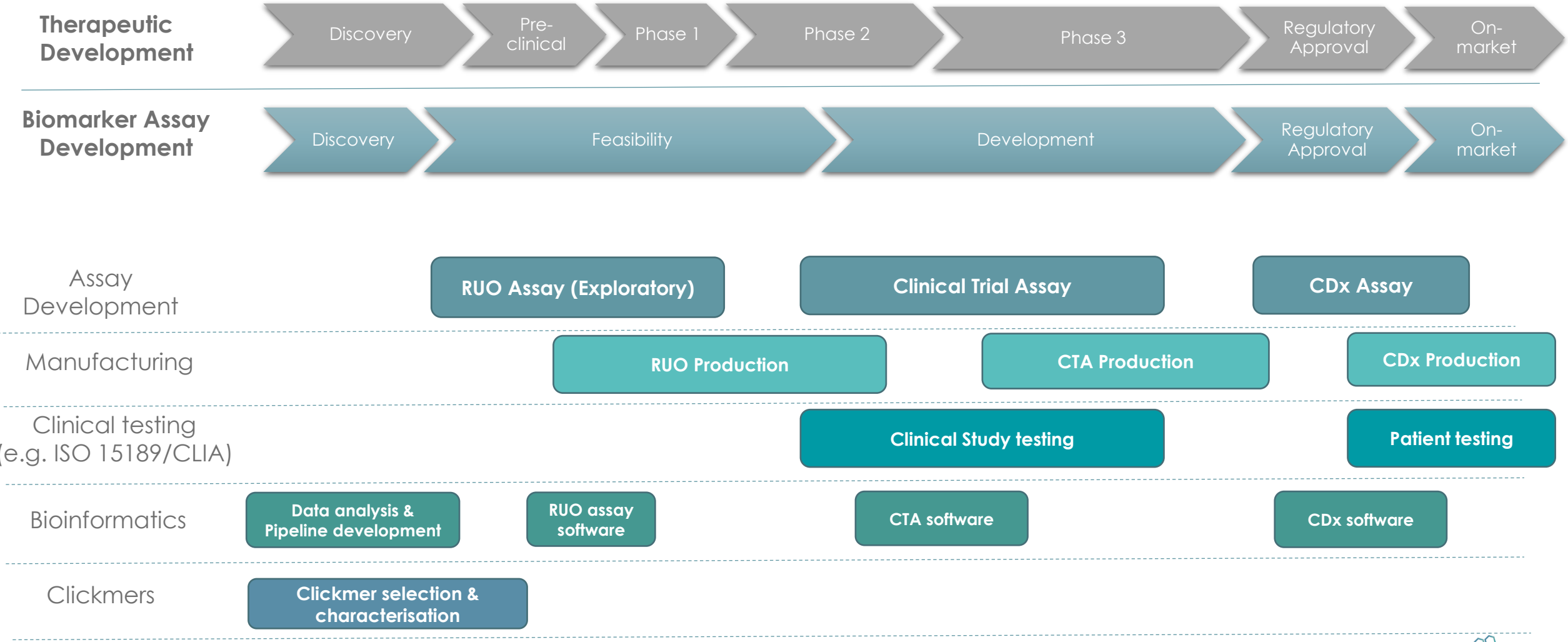
APIS CDx Capabilities

Biomarker Discovery to Assay Development



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Services - Contract IVD Development

Case Study

- Master Service Agreement signed with large Global Diagnostic company. >£30 million volume of work over 5 years
- APIS are responsible for the technical assay development and Clinical Performance Assessment for CE-IVDR and FDA 510 (k), bringing new content onto the client's Syndromic Sample-to-result MDx platform
- Highly complex assay development involving detection of between 30-60 bacteria, virus or fungal targets and associated resistance markers on the different panels
- Project activities
  - Panel A: US Claim extension verification campaign (currently under review by FDA)
  - Panel B: full assay development – in Verification and Validation phase
  - Panel C: CE-IVD panel verification campaign complete (launched Q1 2022)
  - Panel D: full assay development – in Development phase
  - Panel E: full assay development – in Development phase

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Manufacturing at APIS

- Production of prototype, pilot lots and commercial batches within APIS Manchester under ISO 13485:2016 to provide kits to internal and external projects throughout phases of development and commercialisation
- Priorities managed in-house to enable fast turnaround for projects. Not relying on a CMO that may have other priorities
- Expertise
  - Design Transfer Capabilities
  - Prototyping – Early phase kit configurations
  - Pilot/Commercial manufacturing
  - Process validation
  - Raw material sourcing
  - Commercial manufacturing
  - Distribution
  - Stability studies
  - APIS has manufacture 2x IVD kits in 2022

Cold Storage

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Clinical Services

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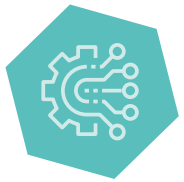
Clinical Capabilities

Clinical Performance Study strategy, design and planning:

- Devise strategy to meet device-specific regulatory and product requirements
- Advise on schedule and budget
- Provide Clinical Strategy Document



Clinical site selection, management, and monitoring:

- Strong relationships with testing sites (EU, UK and US)
- Identify sites based on population, facilities, expertise, etc.
- Project management, oversight and monitoring

Submissions and notifications:

- Ethics committee submissions/renewals
- Notifications to regulatory bodies
- Annex XIV applications

Sample procurement and logistics:

- Import permits
- Sample and material transport
- Sample randomisation/anonymisation

Study protocol and report writing:

- Clinical Performance Study Plan
- Statistical analysis/ data management/ monitoring plans
- Clinical Performance Study Report

Performance evaluation plan and report writing:

- Performance Evaluation Plan
- Performance Evaluation Report
  - Scientific Validity Report
  - Analytical Performance Report
  - Clinical Performance Report

Post-market surveillance and post-market performance follow-up:

- Post-market surveillance planning and reporting
- Post-market performance and claim extension study design, execution and documentation

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Quality, Regulatory & Clinical Compliance Services

- To help navigate the IVD regulatory environment across different regions (including CE-IVDR, UKCA and FDA)

- Our dedicated Quality, Regulatory and Clinical Affairs teams will work closely with you to ensure compliance, providing cost effective and efficient support wherever necessary

- Key Benefits
  - Clinical Performance Study design and management (ISO 20916:2019 and ICH E6)
  - Clinical site selection, management, and monitoring, including sample procurement
  - Clinical Evidence documentation (e.g. Performance Evaluation Plans/Reports and Scientific Validity)
  - Technical file generation for submission to regulatory bodies (e.g. CE-IVDR)
  - Supporting the IVDD to IVDR CE-marking transition

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Bioinformatics

Competencies & expertise in bioinformatics, AI/ML & software development

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in silico Solutions

Bioinformatics NGS Pipeline Development

- Bespoke NGS & multi-OMICs data analysis
- Pipeline development & deployment for internal and/or customer use
- WGS, WES, RNAseq, scRNAseq, proteomic & metagenomic data
- Nextflow expertise
- Visualisation tools & software
- Novel tool development
- Scalable cloud- & HPC- infrastructure setup

Discovery Research

- *in silico* genomic biomarker discovery
- *in silico* Molecular Diagnostics (MDx)
- Protein interaction network discovery
- Aptamer and small molecule drug analog discovery
- Neoantigen discovery
- *in-silico* applied machine learning and artificial intelligence

Real-World Data/Evidence Exploration

- *in silico* retrospective Clinical Trial simulations
- Longitudinal data analysis
- Novel biomarker signature discovery
- Clinical phenotype-genotype associations
- Novel cohort identification & stratification

Gene & Cell Therapy: Vector Integration Site Analysis

- CAR T-cell Discovery Pipelines
- Post-therapy efficacy WGS/WES diagnostic tool
- WGS Lentiviral integration identification
- *in silico* CRISPR applications

Pharmacogenomics

- NGS-based PGx pipeline development
- Bespoke PGx-driven patient solutions based on PharmGKB and CPIC dosing guidelines
- *in silico* longitudinal studies on therapeutic efficacy and unmet patient needs

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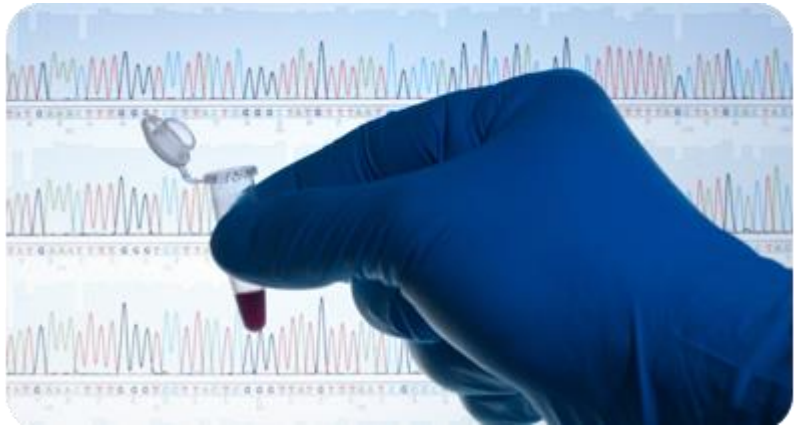
in silico Solutions

Clinical Genetic Variant Diagnostics

- Pipeline development for Whole Genome/Exome Sequencing (WGS/WES) alignment, annotation, re-annotation and data analysis services
- Consensus output of multiple variant and copy number variant callers
- Clinical genotype-phenotype associations
- Bespoke visualisation tool development
- GCP/CLIA/FDA/IVDR Variant Report generating software
- Diagnostic genomics panel/assay design

Drug/Enzyme Discovery & Optimisation

- Molecular docking and binding affinity studies
- *in silico* molecular evolution of proteins/enzymes
- Protein-Protein interaction networks and 3D molecular interaction modelling



Software Development & Data Stewardship

- Data modelling
  - Augmentation of clinical and multi-OMICS data
- Platform development
- *in silico* applied ML/AI
- The development of cloud, on-prem and HPC-based solutions
- Clinical data storage, management and curation solutions
- *in silico* clinical diagnostics/decision support tools
- Visualization and reporting tools
- Distributed, and secure web applications for health industry
- ISO 27001 accredited
- Best practice Software Architecture

Consultancy Support

- Bioinformatics training & on-boarding
- Project initialisation, planning & design
- Project management & reporting
  -Agile & SCRUM methodologies
- Technical documentation writing

Clinical Trial Management Software

- GCP & CLIA software validation
- Experimental study design & biostatistics

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Clickmers

APIS Assay Technologies proprietary technology as alternative detection reagents

Utilises Nobel Prize winning ‘Click’ chemistry – October 2022

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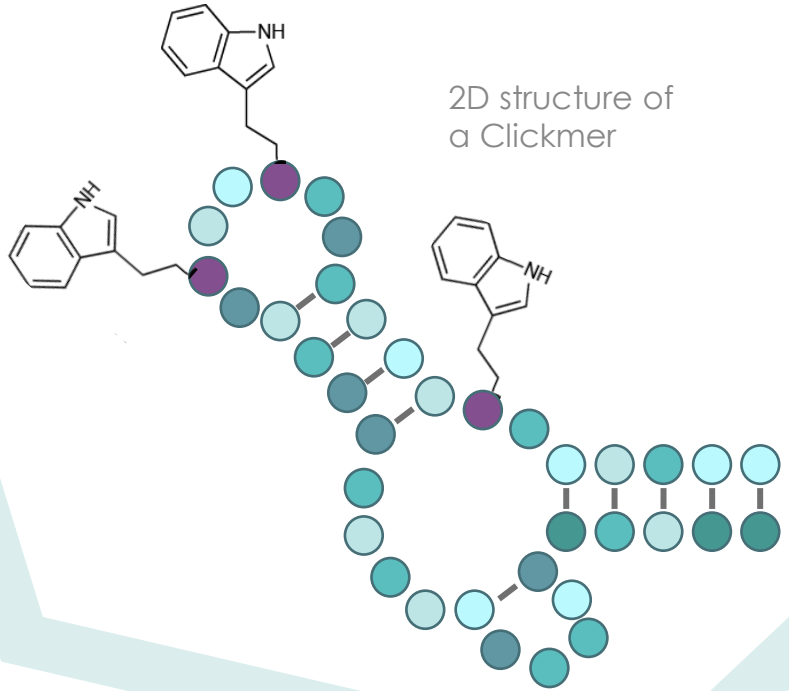
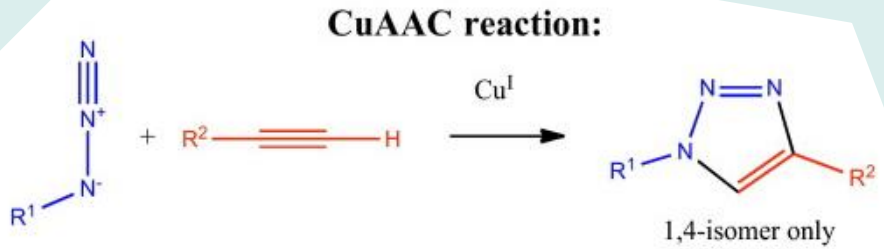
What are Clickmers?

- Chemically modified ssDNA oligonucleotides
- They adaptively bind targets based on variations in sequence and modifications
- Three dimensional structures bind to targets with high affinity and specificity



2D structure of a Clickmer



R1 = chemical structure that is used as the modification

R2 = deoxyuridine inside the DNA strand

- Naïve DNA contains 4 nucleobases
  - Limits target interaction possibilities
- Nobel Prize winning Click chemistry for introduction of side-chains / modifications increases probability of developing excellent binders

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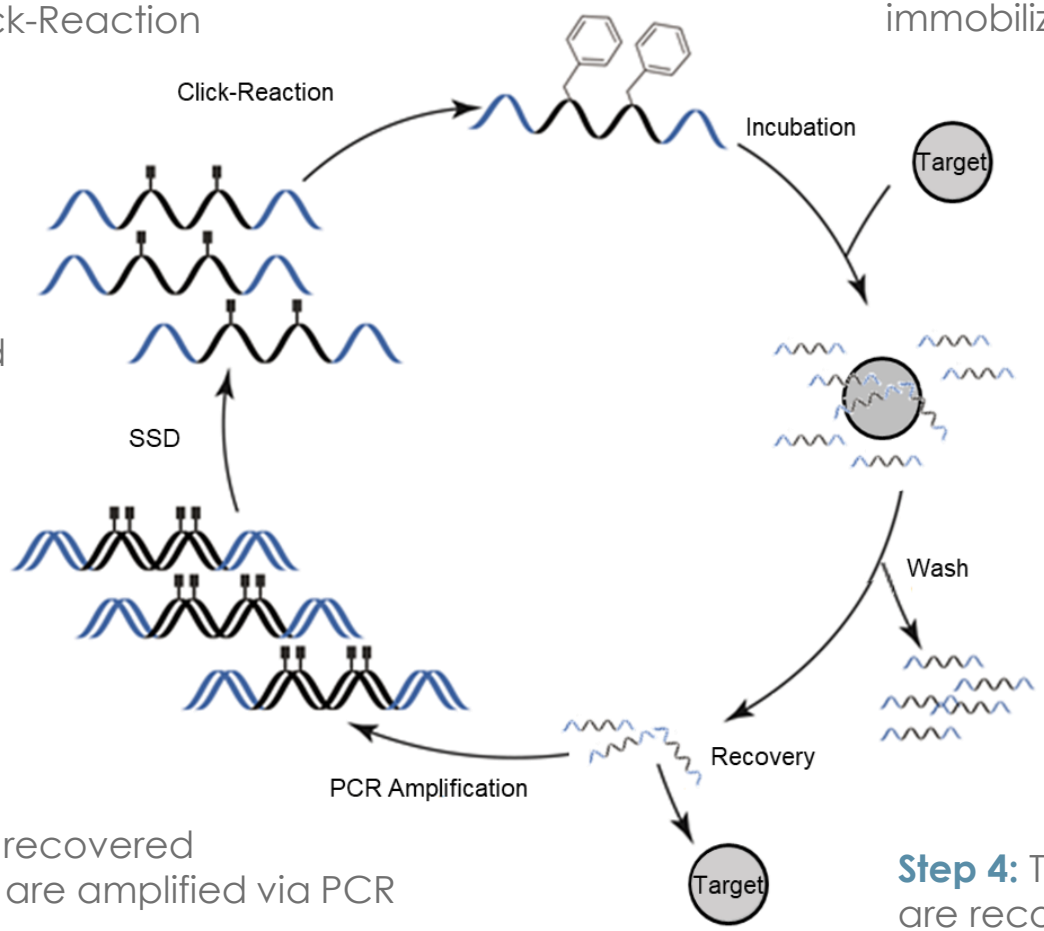
How are Clickmers Developed?

Step 1: An ssDNA library with a diversity of up to 10^{16} is chemically modified with the Click-Reaction

Step 2: The modified ssDNA library is incubated with the immobilized target of interest



Step 6: The double-stranded PCR product is digested by λ-Exonuclease => ready for Step 1 cycle 2

Step 3: The non-binding sequences are removed from the target with increasing stringency

Step 5: The recovered sequences are amplified via PCR

Step 4: The binding sequences are recovered from the target

Click-SELEX is an *in vitro* evolutionary process of iterative cycles

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Why choose Clickmers?

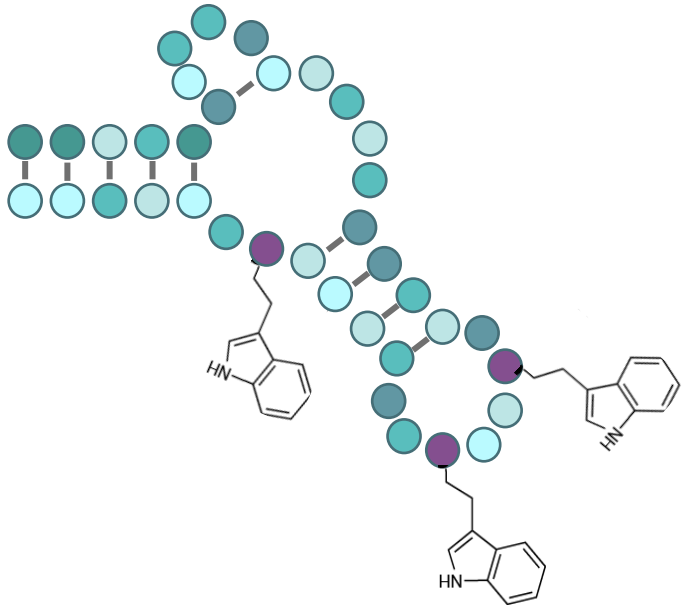
- **Variable modifications** expand the chemical space and interaction properties

- **Mode of action is similar to Antibodies, with alternative physiological properties, such as:**
  - Low immunogenicity
  - Biodistribution and tumor penetration
  - Different clearance pathway from the body

- **Wide range of conditional activation properties** (e.g. salt/ion/pH responsiveness)

- **Versatile application throughout assay formats** (direct/indirect ELONA, LFA, determination of antibody titers) and indications

- Superb **batch-to-batch reproducibility**



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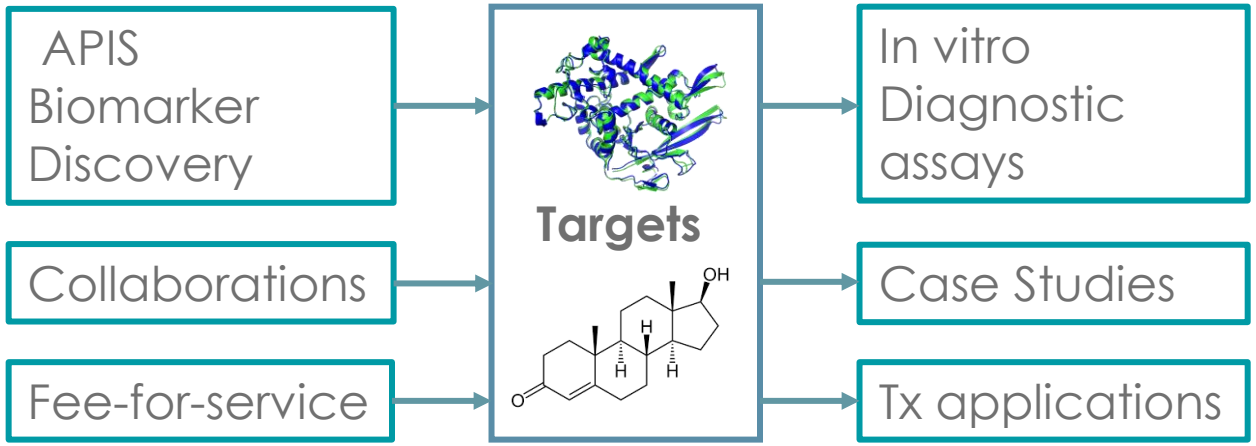
SELEX pipeline

The value of the SELEX output depends on the quality of the biomarker pipeline



IVD
Epcam
Ebola s-GP
Steroids
Liver Fibrosis signature
Complement components

Therapeutic applications
Neuroblastoma TME targets
Rare renal disease targets
Insulin-like growth factor receptor
Calcitonin Gene Related Peptide
CD79-b
CD22

Case Studies
a-synuclein oligomers
β-amyloid oligomers
Staph Aureus oligopeptide autoinducer
Strep pneum oligopeptide autoinducer
Staph Aureus secreted protease
4,5-dihydroxy-2,3-pentanedione

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Portfolio

Target	Clickmer selection/characterization = assay component development				Assay development				
Assay requirements →	SELEX	Modification analysis	Specificity and Sensitivity	Sequence Optimization →	Tech evaluation	Feasibility	Development	Validation & Verification	Regulatory approval / launch
SARS CoV2 Spike hIgG									
TBEV* NS1									
CXCL9									
West Nile Virus NS1									
Yellow Fever NS1									
Mouse IgG									
Annexin A1									
Trop2									
Her2									
IL4-receptor a									
Streptavidin									

* Tickborne encephalitis Virus

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Custom Clickmer Development

Clickmer development is available to integrate into our customer's platform, or to integrate as part of our Contract Assay Development service

- **Clickmers provide next-generation antibody-analog tools** that are enabling researchers and diagnostic developers to overcome the limitations of antibody-based technology and batch-to-batch variability.

- Our **Clickmer Systems Development Service** offers a structured milestone-defined development pipeline that is focused on understanding customer requirements and project aims.

- **Contact one of our experts today**, to start the conversation of how we are using Nobel Prize winning chemistry in our proprietary technology.

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Thanks!

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