

A Global CRO's Perspective to Infectious Disease Prevention and Control

Lessons learned for the next pandemic

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Business Development & Strategy



Cerba Research and Viroclinics-DDL



- A Global Contract Research Organization with more than 50 years of Specialty Diagnostic and Laboratory Services.
- Specialty Services in Virology & Immunology through its specialty BU Viroclinics-DDL.
- One Stop Shop combining Routine and Specialty testing.
- Ranging from pre-clinical testing to support of Phase III studies and Global Logistics.



Our Global Footprint

A Network of Excellence

- Research & Partner labs
- Pre-Processing labs
- Office locations and Technical Platforms

USA:
New York
 Routine, Genetics/NGS, Molecular Biology, IVD, Flow Cytometry, Bioanalytical Lab/PK, Histopathology/IHC, Virology

China:
Shanghai
 Routine, Genetics/NGS, Molecular Biology, Flow Cytometry, Bioanalytical Lab/PK, Histopathology/IHC

France:
Paris & Montpellier
 Genetics/NGS, Molecular Biology, IVD, Flow Cytometry, Histopathology/IHC, Virology, Microbiology, Pre-clinical, Biorepository

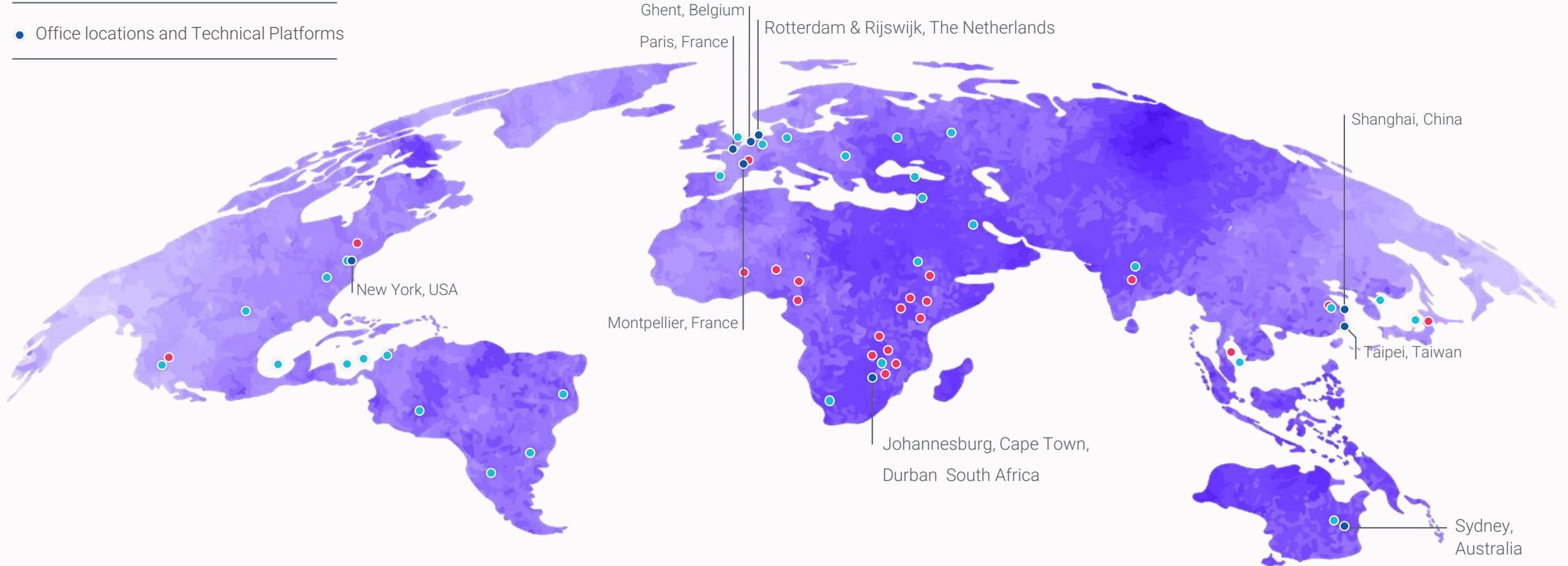
Taiwan:
Taipei
 Routine, Genetics/NGS, Flow Cytometry, Histopathology/IHC Lab/PK, Histopathology/IHC

South Africa:
Johannesburg, Durban, Cape Town
 Routine, Genetics/NGS, Molecular Biology, Flow Cytometry, Histopathology/IHC, Virology, Microbiology, BSL3, Biorepository, PBMC

Australia:
Sydney
 Routine, Molecular Biology, Flow Cytometry, Virology

Belgium:
Ghent
 Routine, Molecular Biology, Bioanalytical Lab, Flow Cytometry, Microbiology

The Netherlands:
Rotterdam, Rijswijk & Schaijk
 BSL3, Pre-clinical, Molecular Biology, Genetics/NGS, Pathology, Virology





Outline of the presentation

Preclinical Animal Models

Specialty Testing in Support of Clinical Development

Global Logistics

Lessons Learned for next Pandemic

Preclinical Model Development and Infectious Diseases Expertise

Preclinical Expertise and Capabilities

- 1600 m² preclinical facility in Schaijk, the Netherlands
- SPF, Conventional, BSL2 and BSL3(+)
- Wide Range of different preclinical animal models (including mice, cotton rats, ferrets, hamster, rabbits etc.)
- Solutions for any kind of experimental set up: challenge and transmission studies

Viral Targets

H7N9 A/Influenza
H5N1 A/Influenza
(p)H1N1 A/Influenza
H3N2 A/Influenza
B/Influenza
...and more

RSV (A and B)
hMPV
MERS Coronavirus
SARS-CoV
SARS-CoV-2
Varicella Zoster
Virus
...and more

Measles Virus
Dengue Virus
Monkeypox Virus
Rabies Virus
Polio Viruses
...and more

Type of research

Vaccine Efficacy

Passive Immunization

Immunogenicity

Pharmaco Kinetics

Immunopathology

Pathogenicity

Antiviral Therapy

Antiviral Prophylaxis

Safety

Drug Delivery

Resistance / Mutants

Transmission

...(more)

Read Outs

Virus Titers

Virus Copies

Antibody

CMI

Genomics

Pathology

Histopathology

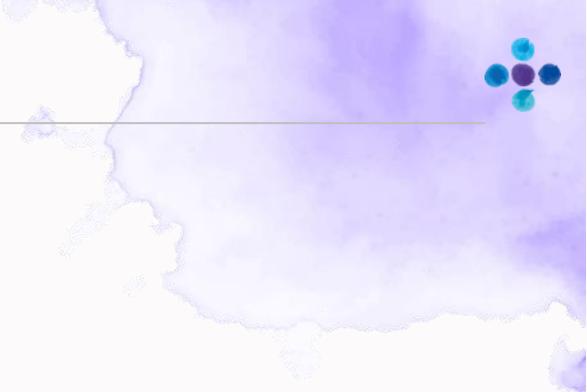
Mortality

Clinical Signs

Imaging

...(more)

SARS-CoV-2 Model Development Timelines



Dec
2019

First case of SARS-CoV-2 in humans

Mar/Apr
2020

Model development
Syrian Golden Hamster

Animal models for COVID-19

Nature 586, 509–515(2020) | [Cite this article](#)

Feb
2020

Stock available for
model development

Apr/May
2020

First efficacy
experiment

Ad26.COV2.S-elicited immunity protects against G614 spike variant SARS-CoV-2 infection in Syrian hamsters and does not enhance respiratory disease in challenged animals with breakthrough infection after sub-optimal vaccine dosing



Matching Each Pathogen to the right Animal Model



SARS-CoV-1 & Avian influenza



MERS



SARS-CoV-2 (VoC)



RSV



Polio - TgPVR21

Cross-Protection against Lethal H5N1 Challenge in Ferrets with an Adjuvanted Pandemic Influenza Vaccine

AS03-adjuvanted H7N9 inactivated split virion vaccines induce cross-reactive and protective responses in ferrets

Supporting Clinical Trials in Infectious Diseases with a One Stop Shop Solution.

Combining routine and specialty
testing in support of clinical trials



Infectious Diseases Highlights Harmonized With Our Virology Center Of Excellence



~600

ID trials since 2018



~250

COVID-19 trials



90%+

Trials include Specialty Testing



V-DDL

Virology center of excellence

ID Indications Overview

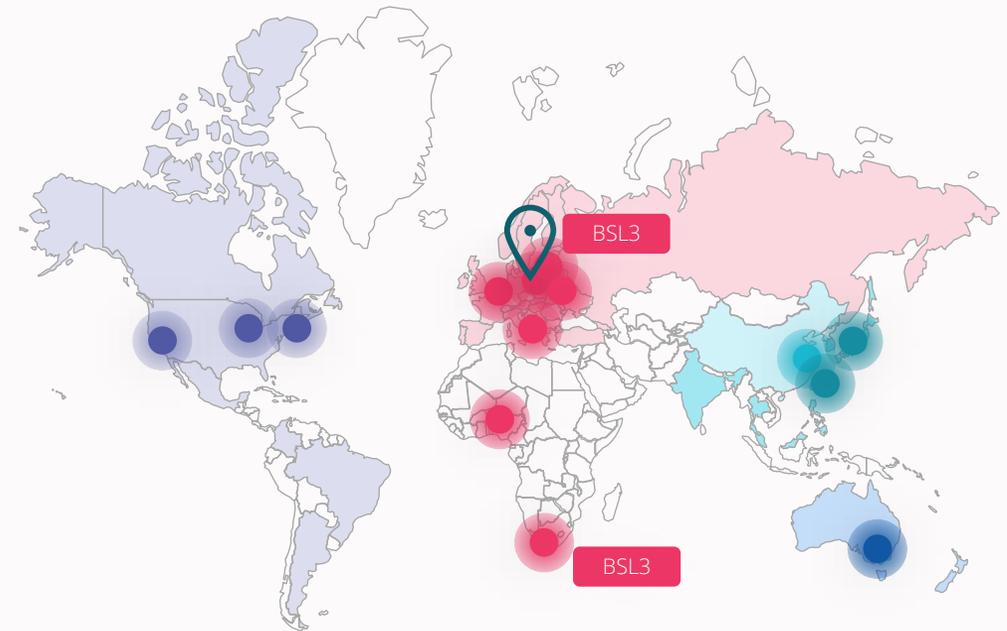
COVID-19

Avian Influenza, HCV, HBV, Influenza, RSV,
Dengue virus, Chikungunya Virus,
Pulmonary aspergillosis
SARS-CoV-1, MERS
C difficile, Tuberculosis. And more...

Interesting Facts

- ✓ Part of operation Warp Speed
- ✓ NIH contract
- ✓ Not for profit organisations & Government
- ✓ Vaccine trials conducted in Africa
- ✓ CEPI Central Lab Network
- ✓ Multiple Phase II and III studies
- ✓ Patient identification supporting clinical research, RWE and Epidemiological studies

Laboratories Overview



Main ID/virology laboratories globally with Viroclinics-DDL, our virology center of excellence



A One-Stop Shop for ID Trial - SARS-CoV-2 example



Genomics

Microbiome
 Metagenome
 TCR / BCR Seq
 qPCR/ddPCR
 Illumina Covid Seq
 SARS-CoV-2 RT-PCR
 NGS/WGS/WES
 RNA-Seq
 Single-cell Seq

Routine/Safety

Serology
 Virology testing
 Sr calprotectin
 Anti-IFN alpha-2
 Hematology
 Biochemistry
 Coagulation
 Urinalysis
 Pregnancy test
 Lipase
 Amylase
 Thyroid function

LBAs /CBAs/ VNAs

ELISA
 ELLA
 MSD
 SARS-CoV-2 specific
 nAb
 Multiplex cytokine
 profiling (37-plex)
 MSD
 50+ ligand binding
 assays

Cell

FCM
 NGF Cytex Aurora is here
 Intracellular cytokine
 detection by FCM
 Immunophenotyping
 Collection & processing of
 PBMCs
 ELISpot assays

Tissue

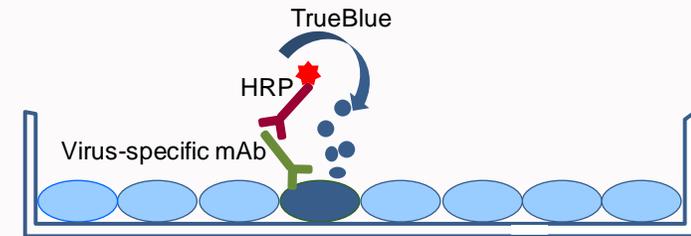
Biomarker analysis &
 immune profiling
 Multiplex/Simplex IHC
 250+
 biomarkers/protocols
 Full histopath service
 NanoString®, FISH, ISH

Specialty testing SARS-CoV-2 Serology and Virology



ViroSpot-based assays for measuring virus titer, virus neutralization, and inhibition of virus replication

- Cell-based assays for enumerating virus-infected cells: Infected cells are detected via a virus specific mAb



- Automated detection and counting of virus-infected cells using CTL ELISpot reader (GLP and 21CFR part 11 compliant software)

Major advantage:

This type of assays use the wild type viruses → golden standard; no virus pseudoparticles or other surrogate systems needed



ViroSpot-based assays for SARS-CoV-2

- **Virus titration** (titer: TCID50/mL)
 - Validated for nasopharyngeal (NP) swabs
 - Validated range: Virus titer 1.5 – 5.9 Log₁₀ TCID50/mL
- **Neutralization assay** (titer: MNA50/80) for testing serum and mAbs
 - Validated for SARS-CoV-2 Wuhan and all VoC
 - Validated range: MNA80 titer 21 – 3,972
 - **Capacity: currently 1000 samples/week, scalable if needed**
- **Antiviral assays** (IC₅₀)
 - SARS-CoV-2 Wuhan, VoC
 - **Capacity: high (depending on assay design)**

Other assays for SARS-CoV-2

- **ELISA** (titer or Elisa Unit (EU)/mL)
- **MesoScaleDiagnostics (MSD)** platform
 - several V-plex and S-plex SARS-CoV-2 Panels and V-plex Respiratory Panel 1 (for the detection of 6 respiratory disease antigens)
- **Cytotoxicity assays** (LDH release, WST-8, Cell Titer-Glow)

Specialty testing SARS-CoV-2 CMI (ELISPOT and FCS)



ELISpot On Demand

- The ELISpot assay is a highly sensitive immunoassay for the quantification of antigen-specific B and T cells secreting signature molecules (e.g. cytokines and antibodies) at single cell level.
- ELISpot can be used for defining the quality of the immune responses (e.g., Th1/Th2/Th17; Ig isotypes)
- To measure circulating ASCs and antigen-specific B cell memory
- Enzymatic- or fluorescence-based ELISpot
- Automated High-throughput analysis
- Assays are qualified for phase 1 and 2 clinical studies

Spots represent the ‘footprints’ of secreting cells



Cytokine secreting cells
(T cells)



Antibody secreting cells
(B cells)

ELISPOT / FLUOROSPOT Assay

Based on the commercial kits from CTL (Cellular Technology Limited).

Read-out by CTL UV X Analyzer and ImmunoSpot® software.

Assays have been qualified for phase 1 and phase 2 studies.

Multicolor flow cytometric analyses of SARS-CoV-2 specific T lymphocytes

Phenotype

- T cells subsets (e.g., CD4+, CD8+ T cells, Tregs, T follicular helper cells)
- Differentiation subsets (e.g., Naïve vs memory subsets)
- Activation markers (to identify antigen-specific responding cells)

Effector functions (Intracellular cytokine staining)

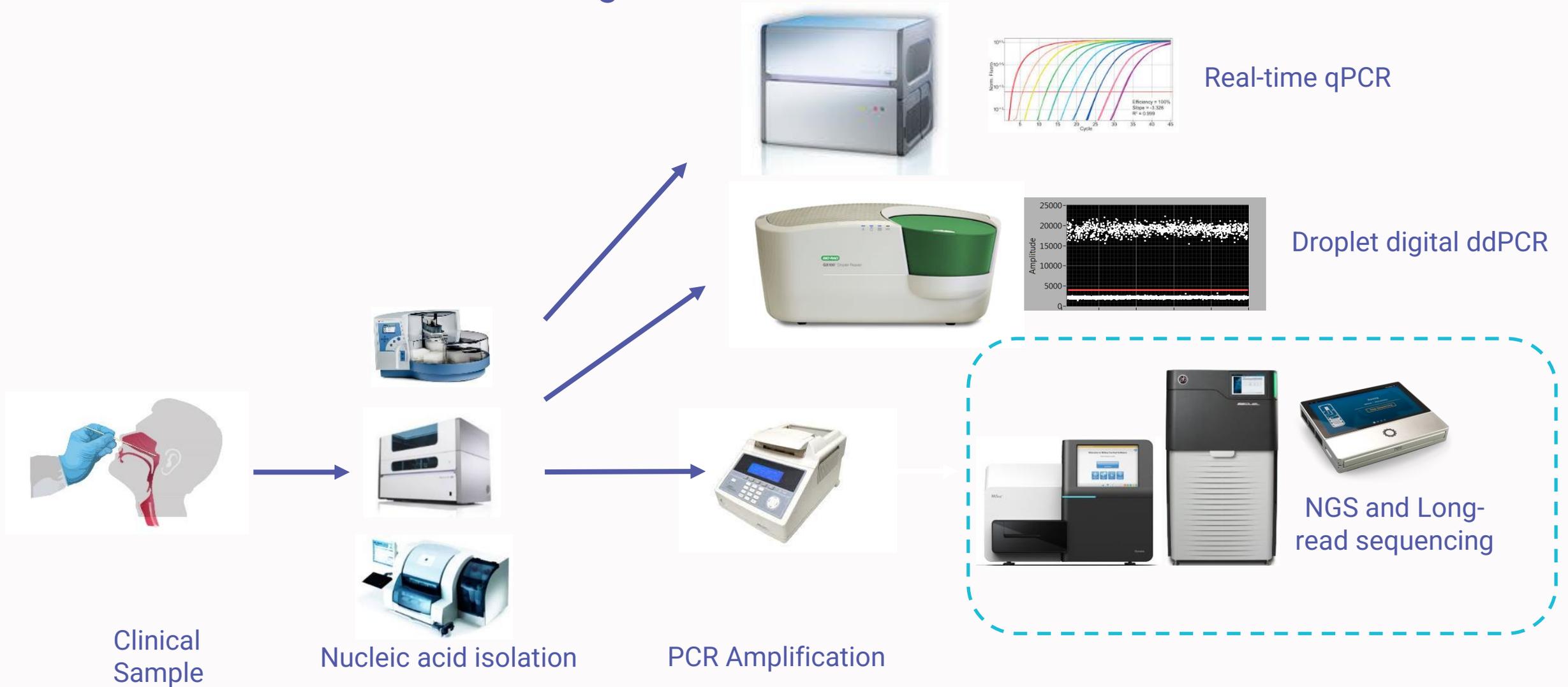
- Cytokines (IL-4/IL-6/IL-2/TNF- α /IFN- γ)
- Chemokines
- Cytotoxicity (e.g., Granzyme B)

On demand panel design

Specialty testing SARS-CoV-2 Genomics



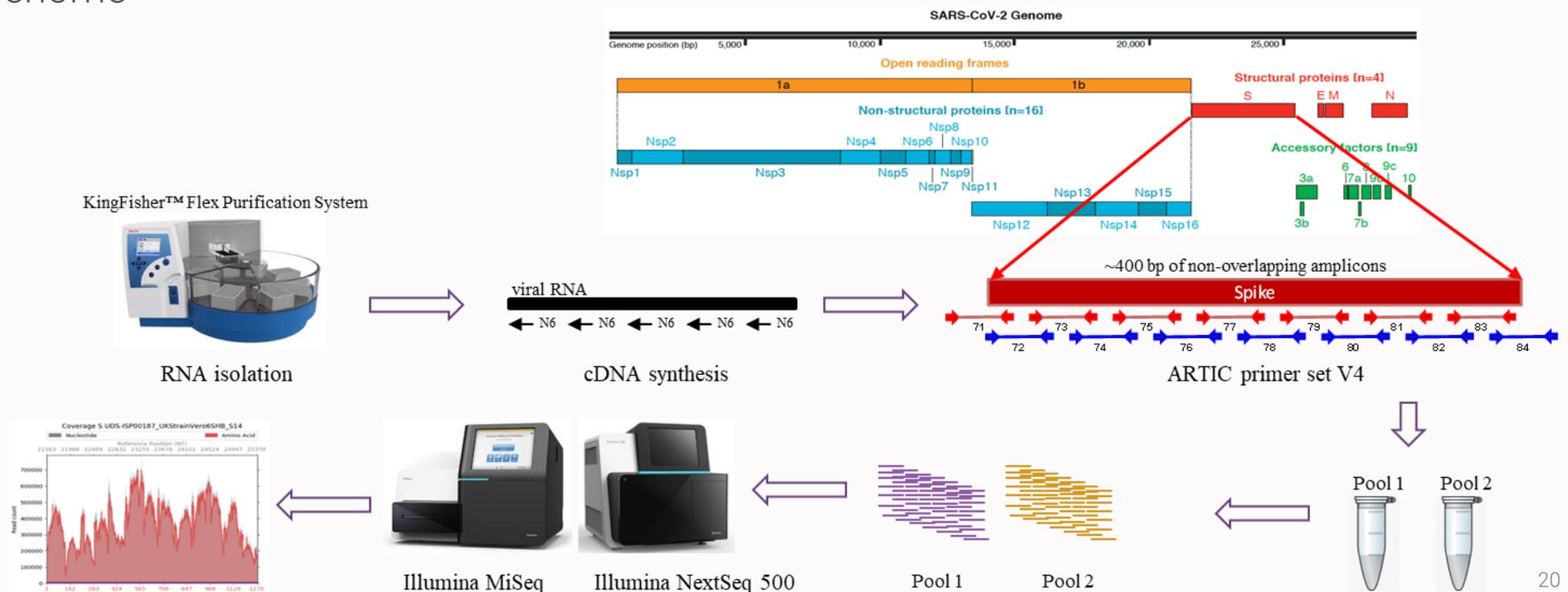
SARS-CoV-2 Molecular Testing





SARS-CoV-2 sequencing

- Sequencing of SARS-CoV-2 has been used to monitor circulating strains (lineage analysis), detect resistant variants for antiviral therapy and characterize breakthrough infections in vaccine studies
- Targets developed at the beginning of the pandemic:
 - Whole genome
 - Spike
 - RdRP
 - Nsp12





NGS Sequencing Data Flow: From Big Data To FDA Submission

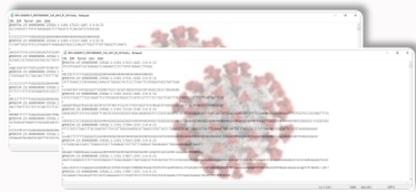


FASTQ files

Reference seq

Variant table

Coverage graph (# nt per genomic position)



```

>Wuhan-Hu-1
ATTAAAGGTTT
ATACCTTCCCA
GGTACAAACCA
...

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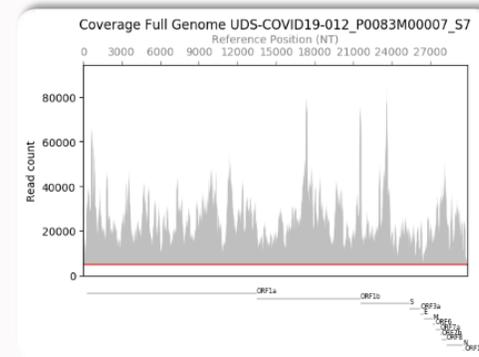


```

A100T @ 10%
C105T @ 2%
G137A @ 87%
C223DEL @ 43%
...

```

- Substitutions (A23403G)
- Insertions (21990.1T)
- Deletions (A21766DEL)



Consensus seq

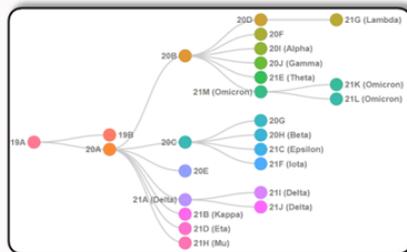
```

>Sample14
ATTACCGGTTT
ATACCTTCCCA
GGTACAATCC
A...

```

SARS-CoV-2 Classification

- Pangolin (Lineages)
- Nextclade (Clades)



GUIDANCE DOCUMENT

Submitting Next Generation Sequencing Data to the Division of Antiviral Products Guidance for Industry Technical Specifications Document

JULY 2019

Download the Final Guidance Document

Home | User's Guidance

Facebook | Twitter | LinkedIn | YouTube | Email

Decklet Number: FDA-2017-D-0421

Issued by: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health

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INFORMANTICS (OPENING)

Communicating regulatory high-throughput sequencing data using BioCompute Objects

Charles Hadley S. King IV^{a,b}, Jonathon Keeney^a, Nuria Guimera^c, Souvik Das^c, Michiel Weber^c, Brian Fochtman^a, Mark O. Walderhaug^d, Sneh Talwar^a, Janisha A. Patel^a, Raja Mazumder^{a,b}, Eric F. Donaldson^{d,1,*}

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^dUS Food and Drug Administration, Silver Spring, MD 20993, USA

Global Capabilities in CTO PBMC Isolation & Processing



Global and expertised Capabilities In Clinical Trial Operations

Local, Regional,
National, International



Global / International
Shipment



Spacial Conditions,
Incl. Dry Ice



Multiple Couriers
Worldwide



IATA / ADR



Support of global studies

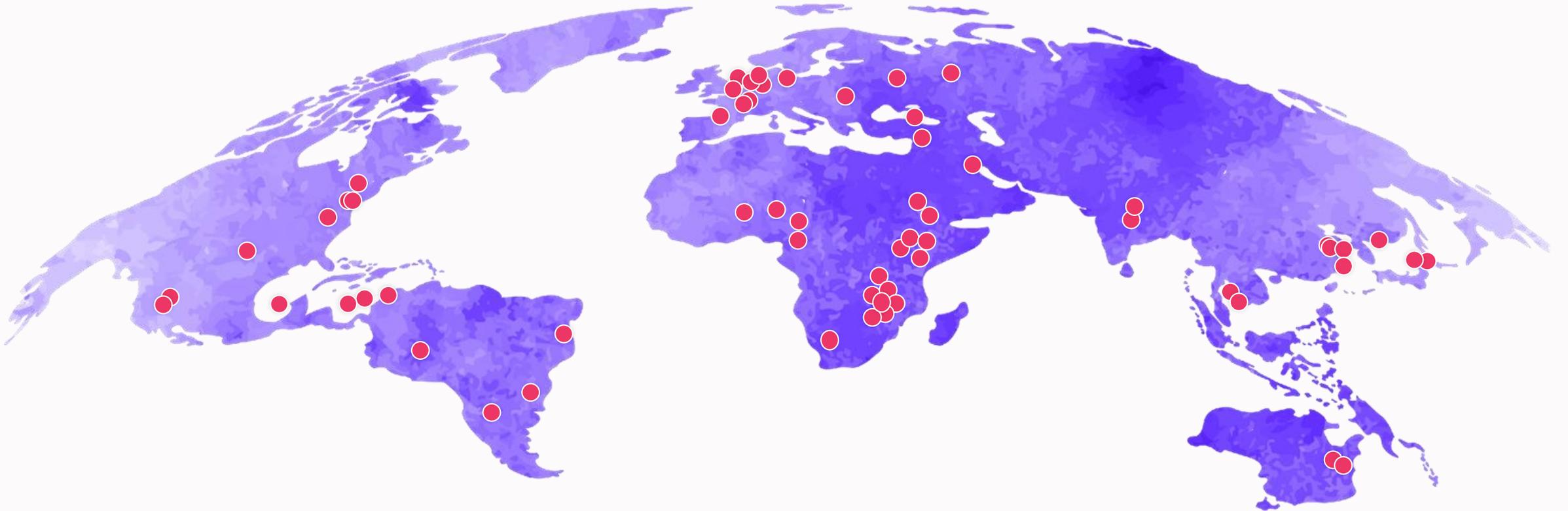
- Global logistic planning & support
- Customized design of sample kits per study and visits
- Building sample kit and (translating) lab manuals
- Pro-active and prospective reconciliation
- Contingency planning
- In-house biomedical products department
- Sample storage / Biobank
- [PBMC isolation & processing](#)
- Database management with QA and QC
- 24/7 helpdesk



PBMC Processing Capability & Expertise

45 processing labs in America, Europe, Africa, Asia, and Australia

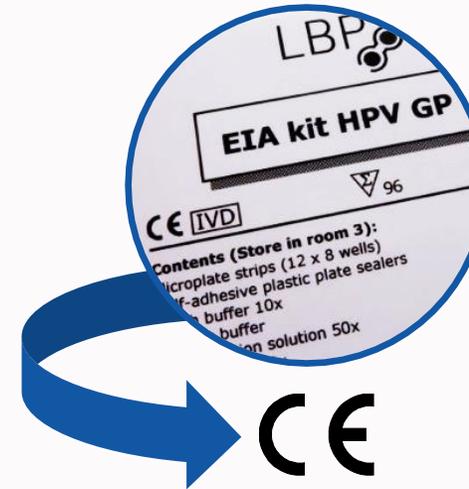
- > Premium Logistics
- > High Quality Standards
- > Extensive Network
- > Standardized SOP



- Diagnostic kits
- Clinical trial kits
- IVD directive 97/78/CE
- All classes
- Annex IIa and IIb (high risk, Notified Body-involvement)
- Annex III (self-certifying)
- Prepared for the new IVD directive
- Customized kits
- Pre-labeled kits & Forms

Our Services

Production of **135.000** Kits Annually



CE



FDA
compliant



Cerba Research and Viroclinics-DDL

A Global One stop Shop Solution Combining
Routine and Specialty testing in ID



Lessons learned and preparation for the next Pandemic

We deploy an expert global team who can utilise their experience, their knowledge and the best technologies available to accelerate clinical trials to ultimately reduce the burden of infectious disease

Technology & Infrastructure

BSL3 & BSL2 facilities

Largest global PBMC & processing lab network across 5 continents

Expertise in building bespoke virology test kits

Certified and qualified labs for animal studies and sample analyses

Science and knowhow

Certifications and permits in place – Coronavirus Animal models permits (SARS-1, MERS).

Readily available platforms and (animal) models -HPAI

Virospot assay broadly applicable, same primary Ab for CovS. Suited for (HP)AI

One stop shop: Same assay platforms preclinical and clinical studies if opportune

People & network

Scientist to scientist communication

Trained and certified team

Access to newest clinical isolates

Access to university insights (susceptibility SARS-2 VoC in animal models)

Access to serum (low-mid-high responders)

A Global CRO's Perspective to Infectious Disease Prevention and Control

Prepared for the next pandemic

Thank you!

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Cerba Research



Viroclinics-DDL

A Cerba Research Company

