CDMOs an essential part of the value chain.

www.escoaster.com | www.escovaccixcell.com
Disclaimer

• As Covid-19 is rapidly evolving daily, information presented is accurate as of this date.

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• The presentation provides an overview of the subject and does not intend to be complete in every detail and in all options.

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• Information provided is accurate and updated as of date of presentation. Esco Lifesciences Group has no obligation to update information made in this presentation due to scientific or company progress which content of presentation is incomplete without verbal comments.
Role of CDMOs from CRO, Dx, Vaccines and Therapeutics

Viral isolation
Inoculation of viral isolates from swabs, tissue homogenates, body fluids in host cell lines to enable replication

Bacterial isolation
Inoculation of bacterial isolates into liquid hold media and identification by staining

Real-time PCR
Test for Genetic Material (DNA/RNA) with primers directed against the genome

Identification of bacteria
- Stain and examine under microscope
- Gram -ve (Blue)
- Gram +ve (Red)

Antigen production
Recombinant protein expression and purification
Bacterial, yeast, mammalian systems

Isolation of patient/animal-derived antibodies, screening of Abs with test binding affinity, single clone expansion, MoAB production for therapeutic purposes

Antibody Discovery Lab
- Antigen administration to animals for hybridoma generation
- Positive clone selection and expansion using selective medium
- Harvest of Monoclonal antibodies for screening

“High producers” by ELISA and SPR for binding affinity
Expansion of “high producing hybridomas” - adherent or suspension platform

Vaccine Development in Parallel
- Viral isolation
- Reverse genetics
- Reassorted virus (passaged and rescued from host cells)
- Immunological evaluation in animal models (adjunctive Vaccines)
- Formulation
- CQA/ Correlates of protection

Diagnostics: R&D Clinical Development
Real-time PCR kit (Design Primers and Probes against novel genetic sequence in a rapid screening method)

Diagnostics: Commercial Production and Services
IVD Manufacturing: ISO 13485/EU DIO/LVD 89/98
Diagnostic Testing Services: CAP6015189

Diagnostics: R&D Clinical Development
Microbiology, Paper, Lateral Flow

Storage of Isolates and mAbs
Strains and mAbs are preserved as references for 1-1.5 years

Scale Up Process Development
- GLP/GMP compliant TOX in animal facility
- cGMP compliant phase 1/2
- CGMP certified Phase 3 commercial

Determine Suitable Expression Platform
- MicroFermenter
- MinTide
- Parallel Mini Suspension Bioreactor
- Seed Train/Seed Flask

Sample Collection (Urine, Stool, Blood, Swab, Sputum, Other Fluid, Tissue from Field Specimen)

Microbial identification thru diagnostic techniques
- Sequencing
Detection of novel, divergent species with homology to sequenced organisms

ELISA multiplex
- Confirmatory test against antigens

*The selection and sequencing of appropriate methods for proper identification depend on the sample. The set of tests commonly used for the screening and confirmation of pathogens.
E.G of MDX When to boost. (Beyond vaccine self sufficiency)

Kit Components for imTracker COVID-19

**GEN-Y imTracker COVID-19**

**GEN-Y Biologics**

**Kit Components**
- Wuhan wild type, UK B.1.1.7, South Africa B.1.351, California B.1.427/429, Indian B.1.617.1, Indian B.1.617.2
- RBD variants x 6
- Negative control reagent
- Quality control reagent
- ACE2-Peroxidase (dark vial)

**Generic Lab Consumables for ELISA**
- ELISA coating buffer (PBS)
- ELISA washing buffer (PBS-T)
- ELISA blocking buffer (BSA in PBS-T)
- 96-well microtitre plate
- TMB substrate
- Stop solution

**Generic Lab Equipment for ELISA**
- ELISA plate washer
- ELISA reader

**ELISA Plate Format**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Wuhan</th>
<th>UK</th>
<th>South African</th>
<th>California</th>
<th>Indian 1</th>
<th>Indian 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>A</td>
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<tr>
<td>Sample 2</td>
<td>B</td>
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<td>Sample 3</td>
<td>C</td>
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<td>Sample 4</td>
<td>D</td>
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<td>Sample 5</td>
<td>E</td>
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<tr>
<td>Sample 6</td>
<td>F</td>
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<tr>
<td>QC reagent</td>
<td>G</td>
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<tr>
<td>Negative control</td>
<td>H</td>
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</table>
Colour coding identifies an individual’s personal antibody neutralizing ability versus the most concerning viral variants.

For example, from the read out:

- Yellow color means there is good neutralizing antibody protection whereas dark blue indicates levels that may be below the threshold of protection or have no protection leading to reinfection with that variant.

- The evolution of the neutralizing antibody capability in these patients can be tracked further with repeated tests—say 3/6/9 months following the 2nd vaccine dose.

- By understanding the current status of an individual’s neutralizing antibodies against multiple viral variants, this will enable the ability to:
  - Track Travel Appropriateness
  - Track Vaccine Effectiveness
  - Track Booster Requirement
  - Track Vaccination Status at Border for Entry
  - Track Data on Immunity against Multiple Variants
  - Track Data Differences in Groups; by gender, blood type, ethnicity, age …
Gen-Y imTracker MULTI for Covid-19 – Sample Test Result

Virus Strain | Wuhan | alpha | beta | delta | epsilon | kappa
---|---|---|---|---|---|---
Neutralization % | 84.3 | 59.2 | 46.4 | 82.5 | 85.0 | 82.1

Over 40% = Good neutralization  20-40% = Weak Neutralization  Under 20% = No Neutralization
Population Cohort Studies.

ACE2 inhibition ELISA (Wuhan-Hu-1 RBD) by Age

pVNT by Age

Please note that this is only a preliminary result. Some data are affected by outliers in triplicates so there will be some changes. Some samples became very neutralizing at v4. Suspected infection after v3. Need to check anti-NC antibody titer at v4.
CDMOs Enabling Companies to Overcome Valley of Death in Commercialization

Highest Yield
Affordable Cost
Linearly Scalable
Quality by Design
FTO

Preclinical Development
Final Animal Model
File IND with CMC

Translational Research
Final Animal Model
GLP Tox Non Human Primate or Large animals (Rabbit, Pig) GLP Material.

Basic Research
PDC in Mice

Early Stage Discovery

Phase 1
Safety Clinical Cohort small number

Phase 2
Safety, Efficacy Clinical Cohort larger number

Phase 3
Safety, Efficacy Clinical Cohort largest number / Challenge study (if applicable e.g. Flu Vaccine). Process locked in and will not change.

Phase 4
Also known as post market surveillance, e.g. Safety for up to 10 years post gene therapy.

Process Valley of Death 1
Lab-GLP/GMP
- Identify Critical Quality attributes
- Process Analytical Technique
- Identify cGMP Assays and Analytical Methods to guide and inform cGMP PD

Process Valley of Death 2
Lab-GLP/GMP
- GMP to full cGMP
- In some instances processes that work in phase 2 are not repeatable or consistent when scaling up into Phase 3 / Commercial

Process Valley of Death 3
Commercialization roll out
- Lack of reimbursement
- Anti-movements (e.g. Anti Vaccines)
- Lack of public awareness
- Slow introduction into NHIP or approval by regulatory (e.g. biosimilars)
- Lack of infrastructure (e.g. Central Diagnostic Labs or ICUs for Car T, autologous facilities), viral vector shortage globally, etc.
Current Landscape and use cases of Covid-19 Therapies

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<th>Proposed Disease Pathogenesis</th>
<th>Viral Replication</th>
<th>Inflammation</th>
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<th>Asymptomatic or presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
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<tr>
<td>Positive SARS-COV-2 test; no symptoms</td>
<td>Mild symptoms (e.g. fever, cough or change in taste or smell no dyspnea)</td>
<td>Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%</td>
<td>Oxygen Saturation&lt;94% respiratory rate ≥30 breathes / min lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, and multiorgan dysfunction of failure</td>
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</tr>
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Management Considerations

- **Monitoring for symptoms**
  - Home based monitoring tele-medicine.
  - Palliative care.
  - Prophylactic usage if staying with at risk individuals
  - Clinical monitoring: if patient is hospitalized and at high risk for deterioration suggest EUA
  - Hospitalization, oxygen therapy and specific therapy e.g. exosomes.
  - Critical care and specific EUA therapy e.g. exosomes.
## Current Landscape and use cases of Covid-19 Therapies including stage of clinical trials

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### Antiviral Therapy

**III/EU: Merck Molnupiravir**

*Do not require supplemental oxygen, but are at risk of progression to severe forms of the disease.*

- III: GlaxoSmithKline (GSK) and Vir Biotechnology, sotrovimab
- III: Casirivimab-imdevimab, made by Roche-Regeneron
- EU: Hospitalized, Repurposed Tocilizumab

### Antibody Therapy

*Do not require supplemental oxygen, but are at risk of progression to severe forms of the disease.*

- III: GlaxoSmithKline (GSK) and Vir Biotechnology, sotrovimab
- III: Casirivimab-imdevimab, made by Roche-Regeneron
- EU: Hospitalized, Repurposed Tocilizumab

### Anti-inflammatory Therapy

- Phase 2: OBCTCD24 EXO-CD24 Treat CRS (occurs in 5-19 Patients)
- Repurposed: Corticosteroids (Dexamethasone)

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Esco Aster Microbial Process for LMIC Open-Source Vaccines e.g. RBD219-N1C1

New operational paradigm from traditional CDMO to DBOT?
Esco Aster Single Use Suspension Mabs Generic Production

Cryovial Hek 293 or CHO MCB/WCB (Thermo or Merck or Canada)

T-75 (TBC)

Seed Train

Filtration

Suspension Bioreactor perfusion single use up to 6,000L

Harvest+Filtration

TFDF or Single Use continuous centrifuge

3 step Chromatography

Final Filtration, Formulation & Filling in DS Bag.

Freeze -60 TBD if CRF or BF.
Esco Aster Single Use Adherent Vero Virus/Oncolytic Virus/Viral Vector Production

Cryovial Adherent Vero Cells: MCB/WCB.

T-175

CelCradle X Vero Seed Cell with automated harvesting

TideXcell Vero+Infection

Harvest Virus

TFDF/TFF or Single Use continuous centrifuge

DNA Digest Benzonase

One step ion exchange Chromatography SO3 or Precipitation

Formulation 0.2µ Filtration & Filling in Glass or COP vial.

Freeze -60 or thermostable TBD if CRF or BF.
mRNA/LNP Vaccines

**Plasmid DNA production**
Typically done by CDMO

**mRNA production and purification**
Typically done by Biotech company up to final DS

**Formulation into LNP**
LNP Formulation PD and CTM typically done by CDMO
DP Typically done by CDMO
Preparing for future COVID-19 variants and the need for booster shots against these variants

- Developing novel mRNA vaccine
- Fraction of the cost of current vaccines, less than US$10 per dose
- Planned deployment 2023
- Optimized for wide range of variants
Provaxus Vaccine Advantages: High-Tech Low-Cost

- mRNA vaccines are proven to be highly effective
- Lower price point compared to other mRNA vaccines
- Improves safety
- Removal of ultra-low temperature cold chain
- Local Manufacturing
Cost-enabled Provaxus vaccines are designed with the intent to provide access to superior vaccine technology to the world’s most vulnerable and underserved populations.
Overall Exosome Manufacturing Workflow

1. Culture in Bioreactor
   - Continuous propagation and harvest of secreted product done through perfusion process mode.

2. (A) Concentration and Buffer Exchange
   - Continuous recirculation using TFF for product concentration and media exchange.
   - (B) Clarification
     - Filtration to remove cell debris and media components.

3. Chromatography
   - Purification of EV from impurities like non-EV content, DNA, viruses, and endotoxins that can be performed in continuous and batch mode.

4. EV loading
   - Loading the EV with cargo of interest using appropriate methods.

5. Chromatography
   - Purification of the loaded EVs from the unloaded EVs performed in batch mode.

6. Sterile Filtration

7. Filling

Drug Product

Continuous mode

Batch mode

Concentrated EV in desired media

Purified EV

4. Sterile Filtration

5. Formulation and Filling (Medical Novel EV Product)
CDMOs play an important role in vaccine self sufficiency.

- Esco Aster has variety of mfg platforms and partners to help in early stage development and tech transfer from CDMO model to DBOT model.
  - Fermentation of sub-unit vaccines (Gen-Y)
  - Adherent VERO for LAIV/LAV (Vivaldi Biosciences)
  - Suspension for Covid-19 Mabs for Dx Antigens and Therapeutics (Gen-Y)
  - mRNA-LNP platform (Provaxus)

- Esco Aster is the only life sciences company that is neutral and operates within African continent for African from our base in South Africa.

- We are here to support you in your vaccine self sufficiency journey from tools, technologies, platforms, human resources, training.

- Contact us to collaborate!