



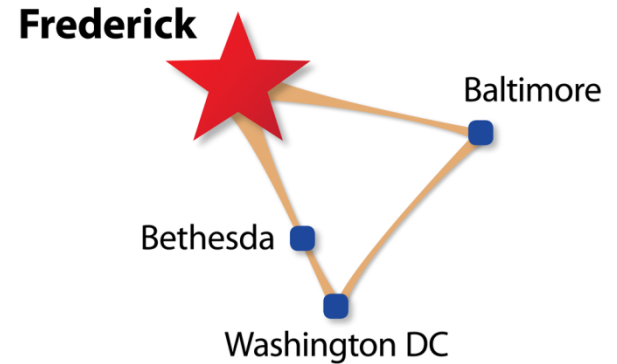
# **A Novel Approach to BSL-4 Research:** *Establishing a Clinical Core Services Group in High Containment*

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# The NIAID Integrated Research Facility (IRF) at Fort Detrick, Frederick, MD



# Clinical Core Services – Scope



## Facility Support

- BSL-3 Training
- BSL-4 Training
- Robust Protocols
- Automation

## Laboratory Support

- Clinical Pathology
- Immunology
- Molecular Biology
- Viral Repository
- Virology

# Hands-on BSL-3 Training

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# Training Requirements – BSL-3

- Biosurety Program under auspices of:
  - National Agency Check and Inquiries, Department of Justice
  - Centers for Disease Control and Prevention
  - Occupational Medical Service
  - Division of Occupational Health and Safety
- BSL-3 pretraining
  - Complete NIH lab safety and blood-borne pathogens course
  - Complete BSL-2 training
  - BSL-3 Practice in BSL-2 suite
- BSL-3 training in BSL-3 suite
- Select agent training

# Hands-on BSL-4 Training

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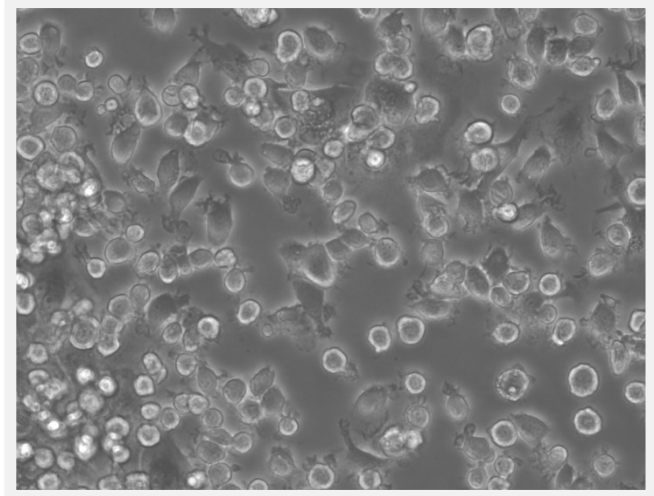


# BSL-4 Training

- BSL-4 pretraining
  - Complete BSL-3 hands-on training
  - Approved by minimum of 2 mentors
- NIH BSL4 training on main campus
- IRF BSL-4 facilities training
- To work unsupervised:
  - First 5 visits one-on-one in BSL-4 suite under mentor
  - Complete a minimum of 100 hours/40 visits supervised in BSL-4 suite

# Standardized Protocols

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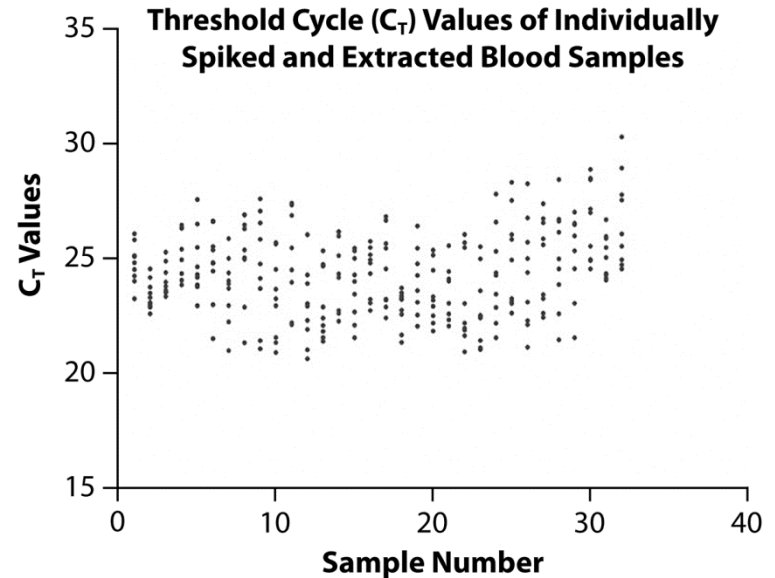


## Standardized Protocols

- As a core service group, we provide data from a variety of procedures such as study-specific assays and viral stock information to scientists
- We develop rugged protocols to ensure reproducible data from different technicians
- Protocol development is complete when 3 technicians produce reproducible results

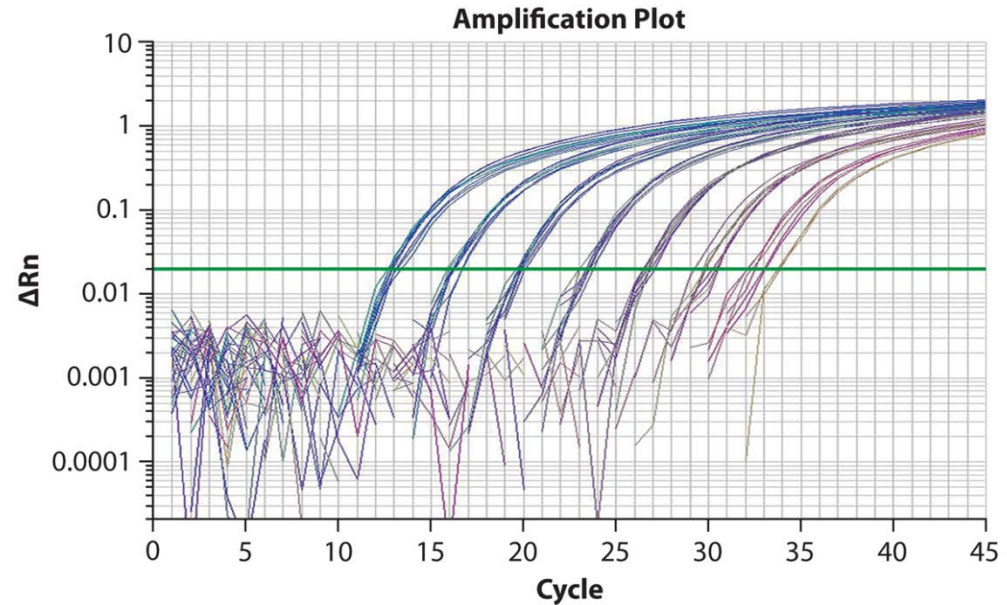
# Standardized Protocols – Initiation

- At initiation of DNA extraction protocol development, replicate results of cycle threshold ( $C_T$ ) values are between 20 and 30 cycles
- Acceptable results by clinical laboratory standards, but not by quantitative PCR guidelines
- Goal:  $C_T$  values should replicate within  $0.5 C_T$  on either side of the mean (here just under 25)



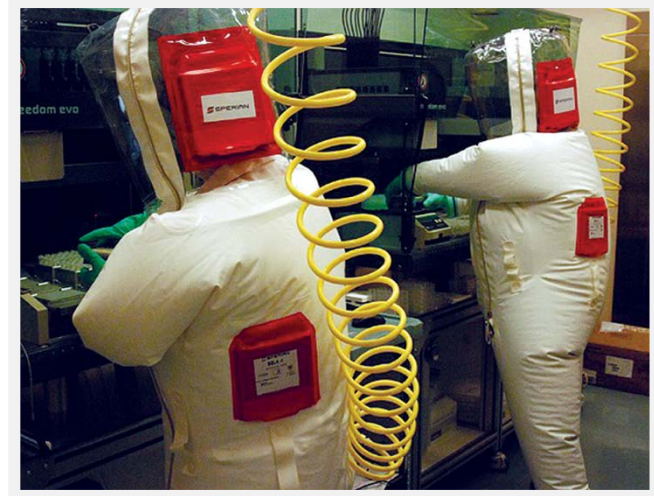
# Standardized Protocols – Completion

- Through optimization of reagent and cycling conditions, the assay was further “ruggedized”
- Standard curves of Quantitative Polymerase Chain Reaction from 3 technicians running three replicates using completed rugged protocol



## Automation in the BSL-4

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# Automation and Robotics

- To provide timely data with the highest degree of accuracy, we installed liquid-handling robots into high containment for high-throughput processing
- All of our clinical diagnostics are run with automated instruments instead of manual instruments, allowing us to present real-time data instead of running assays on banked samples at study end.

# Automation

## Automated instruments:

- Clinical chemistry and special proteins (COBAS Integra400 Plus)
- Coagulation (STACompact) and hematologic analysis (Sysmex 2000VT)
- Flow cytometry (BD Fortessa with HTS)
- Multiplex genomic and proteomic biomarker analysis (Luminex FlexMap 3D)
- Microbial detection (BacT/ALERT)

# Automation – Biosafety

*Class I biosafety cabinet for all clinical instruments*

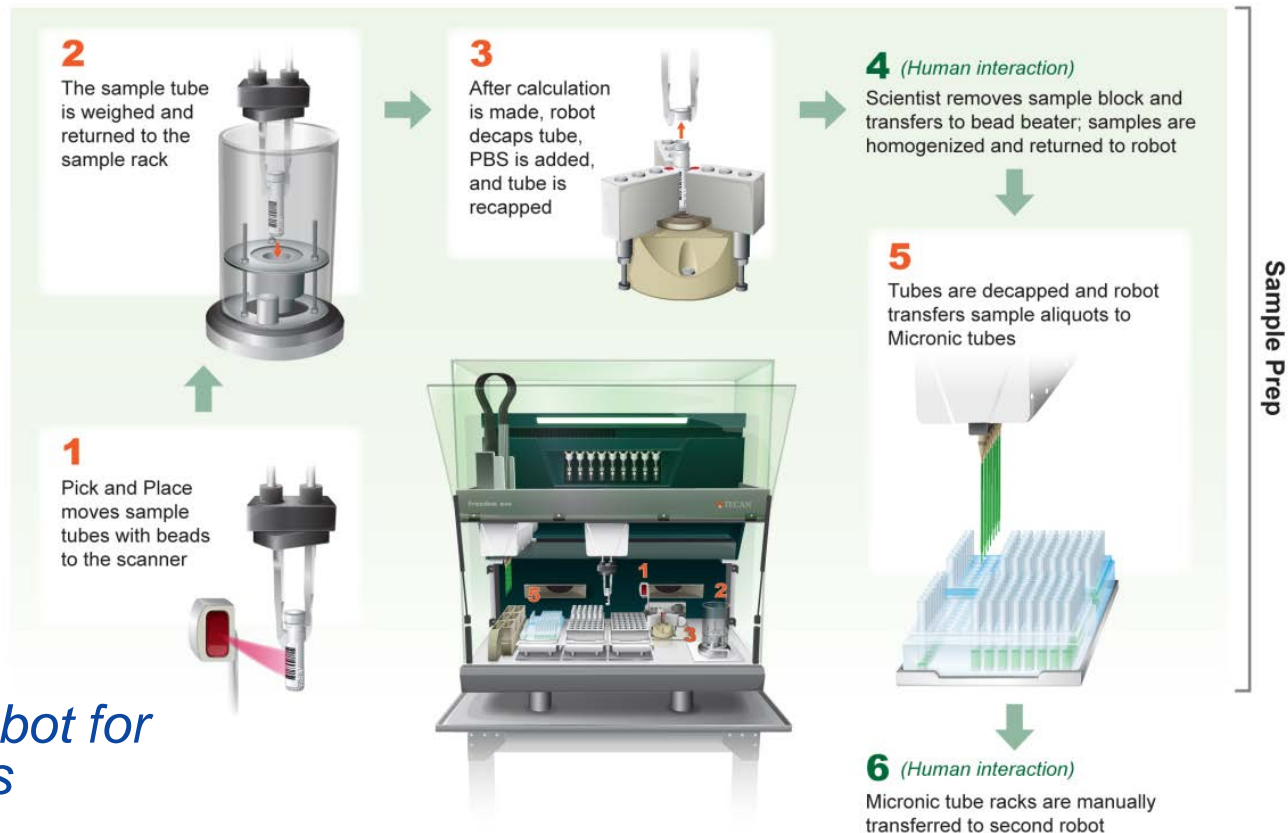


# Robotics

- We designed three liquid handlers using Tecan EVOware platforms for:
  - Extracting DNA and RNA from tissues
  - Performing plaque assays, titrations, and staining
  - Capping and decapping tubes, weighing, and liquid handling
- The robotic workstations are Class I biosafety cabinet enclosures



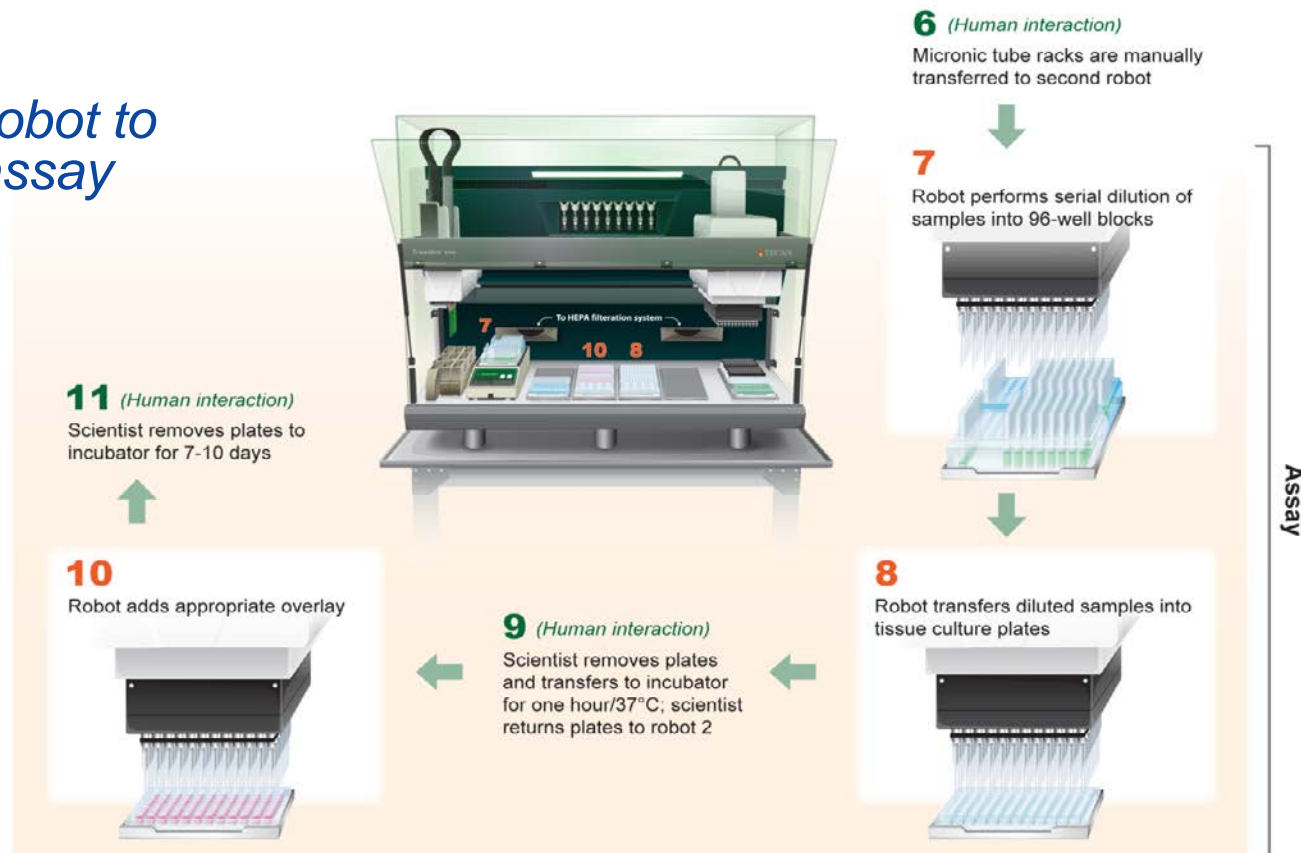
# Robotics



*Workflow using robot for preparing samples*

# Robotics

## Workflow using robot to perform plaque assay



## Automation – Results

- Capacity to process samples from 4 studies concurrently – all aliquots individually tracked
- Daily processing includes: clinical chemistries, complete blood cell counts with differentials, coagulation profiles, and flow cytometry
- Post study processing includes: antibody concentration, viral plaque assays, quantitative polymerase chain reaction, ELISA's, and cytokines

# Conclusions



- Rigorous hands-on training programming is an important safety measure for BSL-4 operations.
- With rugged protocols, scientific staff can be rotated.
- Using automated platforms, we provide study scientists and veterinarians with in-life information for animal health monitoring.
- Using robotic platforms is an accepted method for improving assay reproducibility, and lessening risk to staff by decreasing exposure to potentially infectious material.

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