Two Platforms for Next Generation Biomarker Discovery

Enhance genomic data in clinical trials
for better patient outcomes

Cerba Research
in partnership with fulgent

Strong & Sustainable Partnership

Cerba Research

Enhancing genomic data in Clinical Trials for better patient outcomes

Cerba Research

Cerba Research is a global central & specialist laboratory. Our network of specialty labs supports our core therapy expertise in three distinct areas - Oncology, Liver Indications & Infectious Disease.

fulgent

Fulgent Genetics is a CLIA-certified and CAP-accredited NGS laboratory, offering one of the most comprehensive portfolios of clinical genetic tests in the world, as ranked by the Gene Test Registry (NIH) Genetic Testing Registry.

01

Solid Tumor Molecular Profile

Combined DNA & RNA Analysis to maximize clinical care & biomarker discovery

Samuel P. Strom, PhD FACMG
Director of Medical Affairs and
Laboratory Division Director
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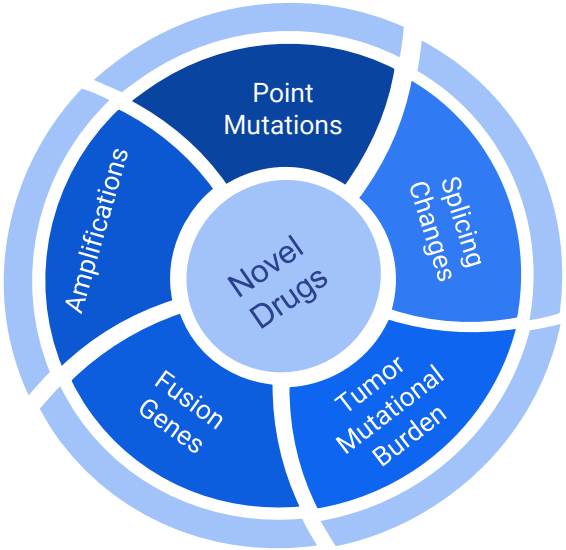
California USA

Molecular Pathology as a Driver

Precision medicine starting to bear fruit



Timeline of key genetic discoveries in oncology

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Molecular pathways in cancer discovered	Oncogenes + Tumor suppressors	Early success	Testing Technology expands	Hybrid of Care + Discovery
Research in the 1980's-2000's leads to identification of key oncogenic pathways: DNA damage repair Growth factor pathways Cellular stress response	Genes such as TP53, BRAF, BRCA1, ATM, and many others are identified functionally by dissecting and branching out from pathways	Herceptin and Gleevec set the stage for precision medicine	Next Generation Sequencing and other technologies become available Novel patterns of mutations and other alterations are discovered Targeted trials ramp up	Second/third wave of targeted drugs Testing tech enables simultaneous clinical evaluation + discovery

HRR as an example

- DNA damage Repair pathway mutations in hereditary cancer
  - Lynch Syndrome
  - HBOC
- Tumor mutations in this pathway cause genomic instability
- “Familiar” genes already included in years-old panels
- HRR assay for PARP Inhibitor Drugs (Breast, Ovarian, Prostate and Pancreatic Cancers)

BRCA1
BRCA2
ATM
BRIP1
PALB2
RAD51C
BARD1
CDK12
CHEK1
CHEK2
FANCL
PPP2R2A
RAD51B
RAD51D
RAD54L

FDA Approves Olaparib for HRR Gene–Mutated Metastatic Castration-Resistant Prostate Cancer

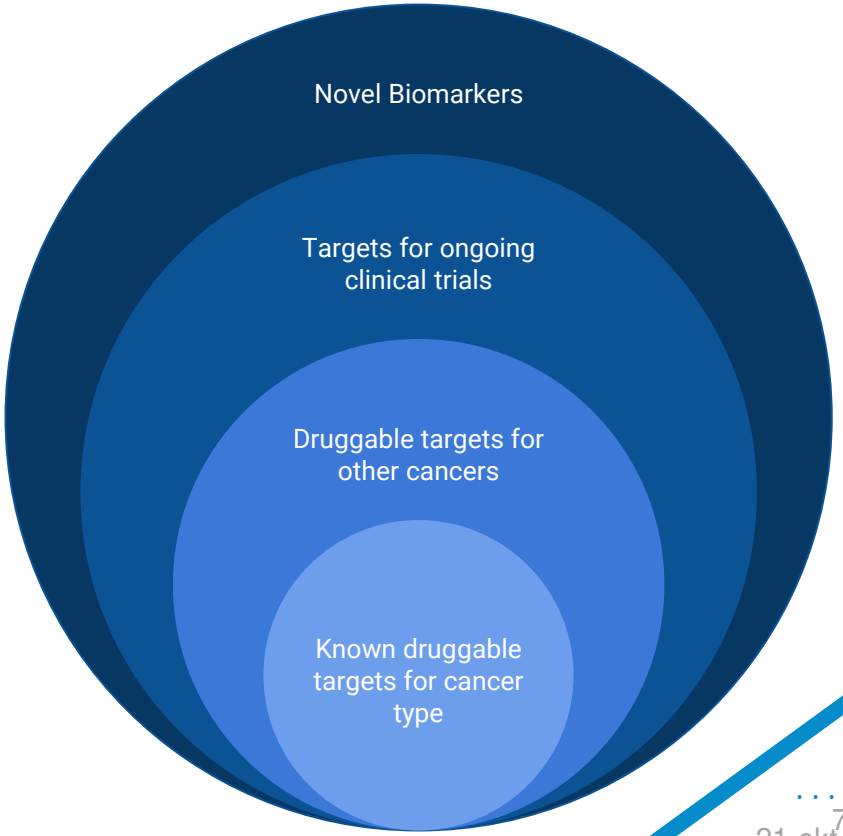
By The ASCO Post Staff

Posted: 5/20/2020 11:30:00 AM

Precision Approach

Focused clinical analysis

Comprehensive raw data



Clinical testing for all major clinical conditions

fulgent
Cerba Research

fulgent

5 **Adult**
- **Cancer / Oncology**
- Cardiology
- Neurology

4 **Pediatric**
- Panels
- Exomes

3 **Newborn**
- Rapid NICU Genome
- NGA

2 **Prenatal**
- Diagnostics Panels
- Exomes

1 **Pre-conception**
- Carrier Screening
- PGT-A

5,700+
Genetic Conditions /Phenotypes

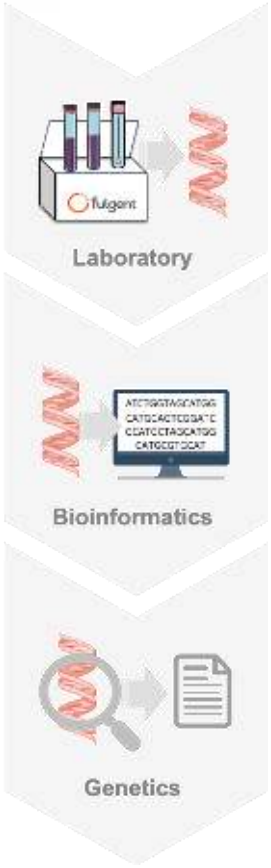
Clinical and Research Molecular services with accredited quality

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

LABORATORY ACCREDITATION CERTIFIED

Fulgent: Infrastructure and Capacity

VERTICAL LABORATORY CONSTRUCTION



Client Services
- Web portal
- Insurance team
- Requisition Intake

Fulgent LIMS
- Specimen Accessioning
- DNA Extraction
- Library Prep & Custom Probes*
- NGS Sequencing*
- Complement Wet Lab*

Bioinformatics
- Multiple Aligners*
- Misalignment and Pseudogene analysis*
- Standard & Custom Variant Callers*
- Variant Filtration*

Annotation
- Public, Commercial, and Private Databases*
- Classification Prediction Algorithms*

Curation
- Multi-Assay Classification Database*
- Multi-Assay Curation Interface*
- Variant Classification

Clinical Reporting
- Reporting Decisions*
- Report Generation*
- Report Delivery
- Clinical Report

- Capacity to sequence over **600** Human Genomes at 30X per week
- Currently processing 100,000+ samples, ~500,000 capacity per year

* Developed or enhanced in-house by Fulgent

Solid Tumor Molecular Profile

illumina TruSight Tumor 170

fulgent Cerba Research

Highlights

- Highly selective gene list (>170)
- Simultaneous analyses of DNA/RNA
  - RNA allows for optimal detection of gene fusions
- Tumor mutation burden analysis
- Competitive detection of a broad range of variants types
  - Single nucleotide variants
  - Small indels
  - Amplifications
  - Splice variants
  - Gene fusions

Test Details

Coverage and Detection:

- ≥5% variant allele frequency
- 99% at ≥ 250x coverage

Gene Count: 170 genes
TAT: 2 weeks

Available now for clinical testing!

Complex Landscape

		DNA Analysis	RNA Analysis	Details
1	Point Mutations	✓		• >=5% Allelic fraction • Hotspots +Novel loss of function • *BRAF, EGFR, BRCA1/2*, etc. • **PARP inhibitors**
2	Amplifications		✓	• >3x copies • Oncogene overexpression • *ERBB2* (HER2), *CCND1* • **Herceptin**
3	Tumor Mutation Burden	✓		• Somatic mutations per megabase • Checkpoint inhibitor drugs • **Pembrolizumab approved for TMB-High (June 2020)**
4	Fusion Genes		✓	• Known partners • Novel partners • **Pralsetinib (GAVRETO) approved for *RET* fusion-positive NSCLC**
5	Splicing Changes		✓	• "Intragenic fusion" • **Tabrecta (capmatinib) approved for *MET* exon 14 in lung cancer (May 2020)**

Solid Tumor Molecular Profile

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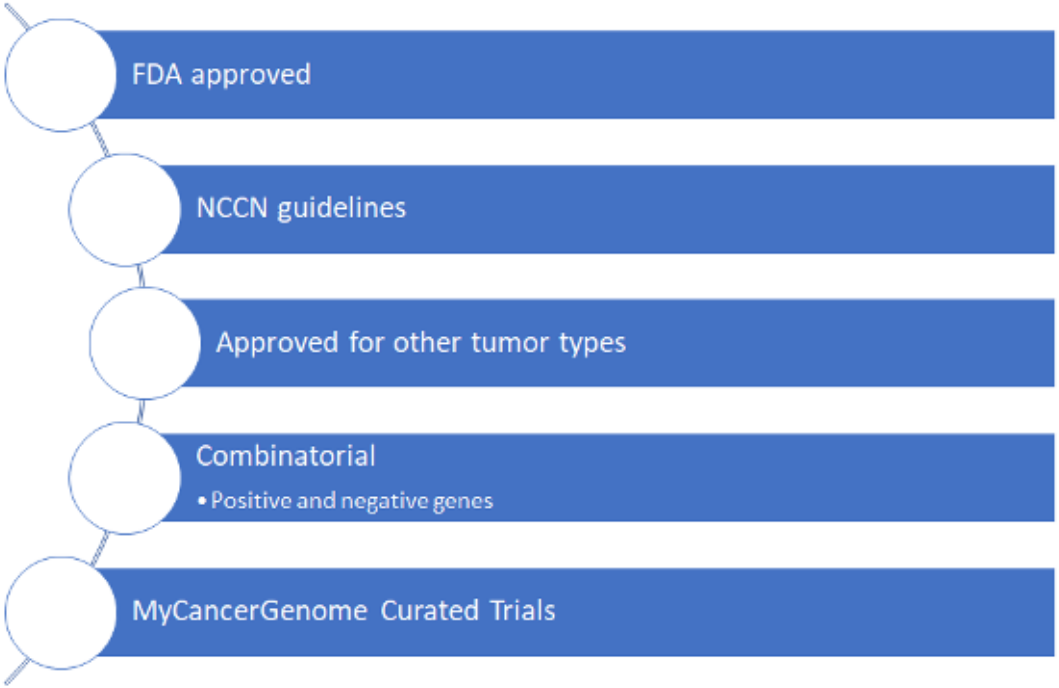
Cerba Research

Approach to Reporting



Solid Tumor Molecular Profile

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FINAL RESULTS

Melanoma

170 Gene Panel
Gene sequencing, amplification, and fusion gene analysis

Clinically significant mutations: NRAS Q61L c.182A>T
Tumor Mutation Burden: 86.49 (TMB-High)
Variants of Unknown Significance: 5
BRAF, CTNNB1, GNA11, GNAQ, KIT,
Negative Genes: MAP2K1, NF1, and 162 others.

Actionability Summary	Result based on Molecular Profile
Recommended approved therapies:	None
Other potential therapies:	None
Counter-indicated therapies:	None
Clinical Trials:	8

Notes and Recommendations:

- These results are dependent on specimen quality.
- More information about these mutations and your cancer type can be found at MyCancerGenome.org
- Guidelines for the treatment and management are based upon recommendations from the National Comprehensive Cancer Network (NCCN.org) and the US Food and Drug Administration (FDA.gov).
- Clinical Trials information is based on a regularly updated information provided by ClinicalTrials.gov. Eligibility for clinical trials is predicted based on the detected mutations, but actual eligibility and acceptance into trials is not guaranteed. Only trials currently accepting new enrollees and located within 100 miles if the provided home zip code of the patient are listed on this report. Additional trial at greater or different distances are available upon request.

Solid Tumor & Liquid Biopsy Molecular Profiles

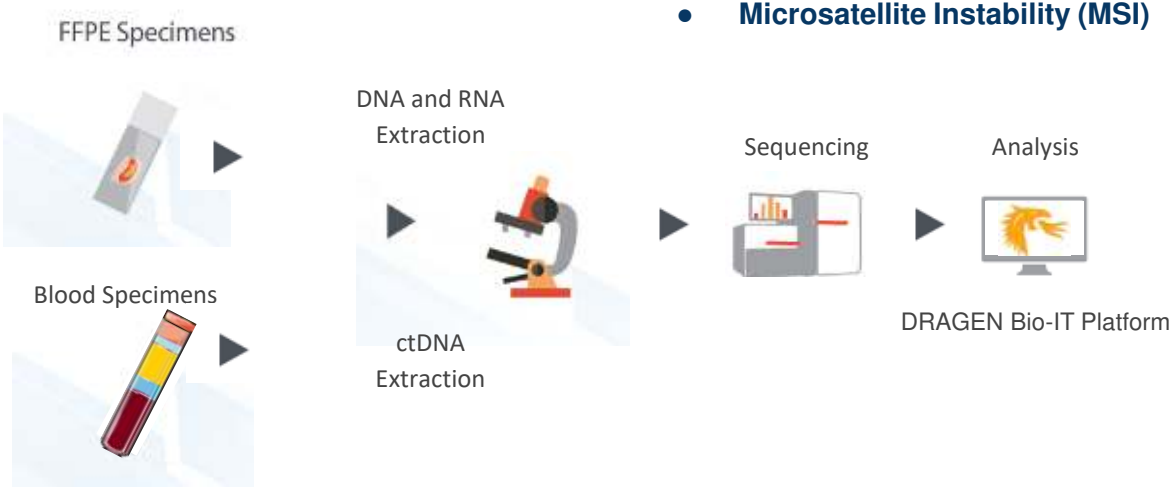
illumina TruSight Oncology 500

fulgent Cerba Research

Highlights

- Highly selective gene list (>500)
- Simultaneous analyses of DNA/RNA
  - RNA allows for optimal detection of gene fusions
- Circulating tumor DNA (ctDNA) analyses
- Competitive detection of a broad range of variants types
  - small variants (SNV, Indel, MNV)
  - CNA
  - gene fusions
- **Tumor mutation burden analysis (TMB)**
- **Microsatellite Instability (MSI)**

Biomarkers for checkpoint inhibitors



Available now for clinical trials!

02

Flow Cytometry in Immuno-Oncology

Biomarker Assessment in

Global Clinical Trials

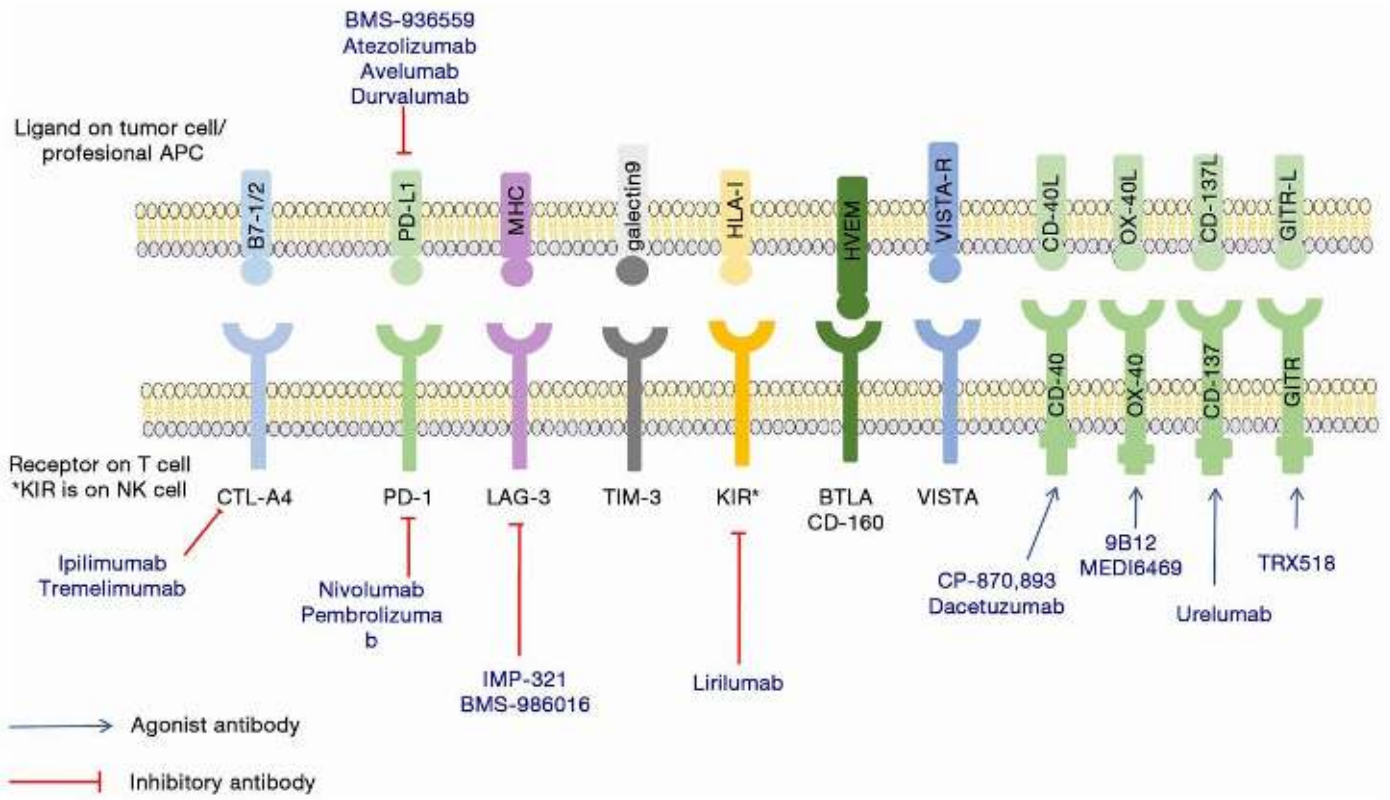
Advances in Flow Cytometry

- Flow cytometry is a powerful tool to analyze thousands of single cells to obtain multiple cellular parameters.
- Advances in Flow cytometry allows the identification of biomarkers quickly and with relatively high sensitivity.
- Flow cytometry-based assays to detect intracellular antigens such as cytokines and phosphorylated signaling proteins, allows functional analysis and helps with therapeutic strategies and predict therapeutic response.

BD symphony

BD FACS Canto

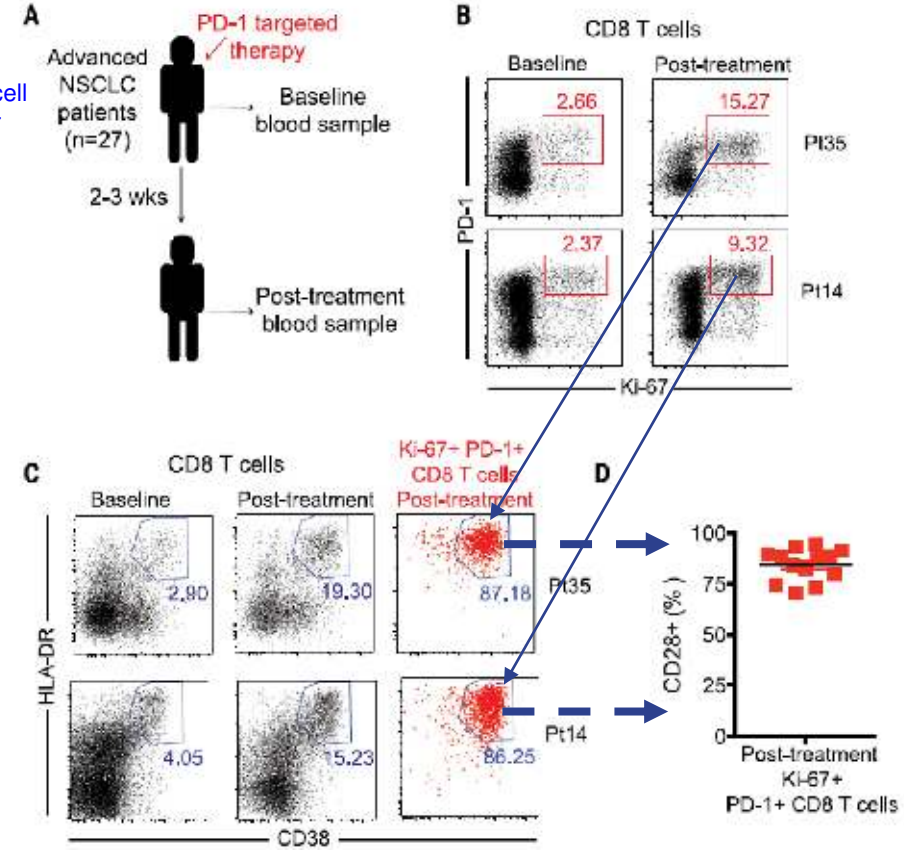
Immune Checkpoints



Márquez-Rodas et al., Ann Transl Med (2015)

Biomarker assessment with Flow Cytometry

Non-small cell lung cancer



Kamphorst, A., et.al. Science, March 2017.

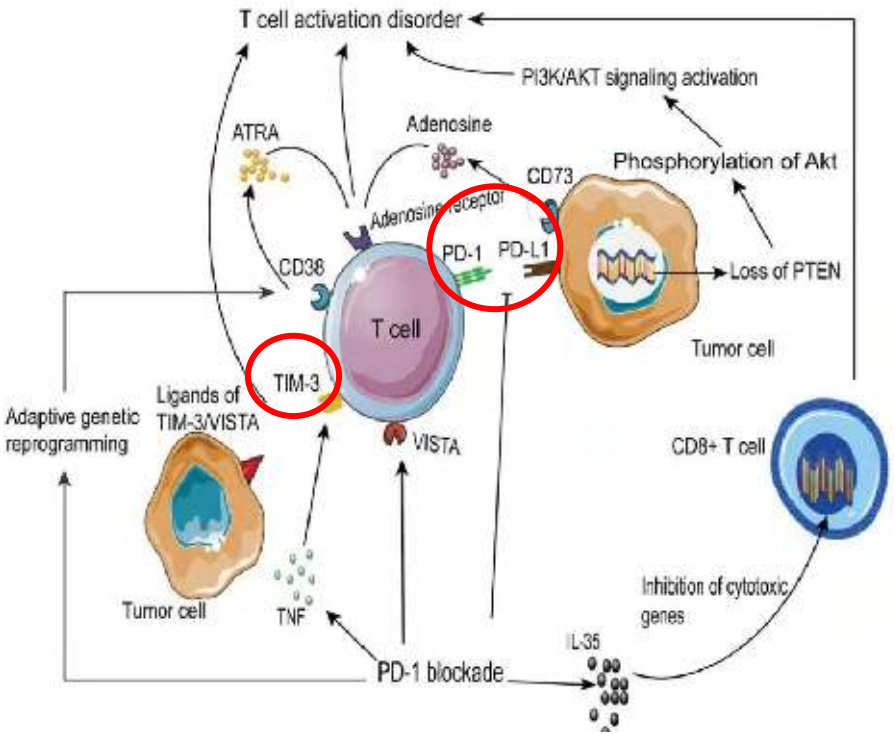
- Role of CD28/B7 pathway for rescue of exhausted CD8 T cell after PD-1 therapy.
- Mouse studies showed CD28/B7 block prevented rescue of CD8 T cell responses mediated by PD-1 blockade.
- Samples from advanced lung cancer patients receiving PD1 therapy:

These data suggest that CD28 signals may also be important for proliferation of PD-1+ CD8 T cells during PD-1 therapy in cancer patients.

IMMUNOTHERAPY

Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent

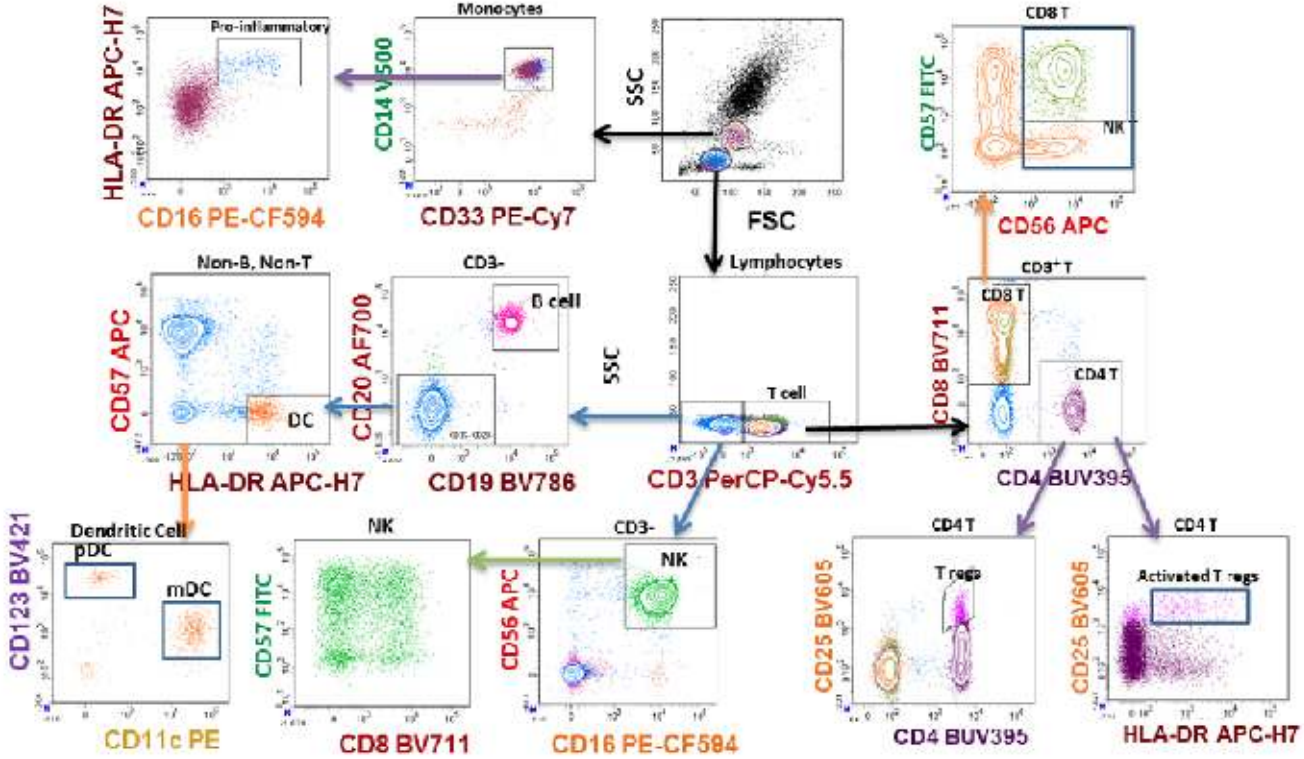
Predictive Biomarkers



Flow cytometry-based assays can provide data for patient specific treatment plan

Ren et.al., Molecular Cancer. 19:19 (2020)

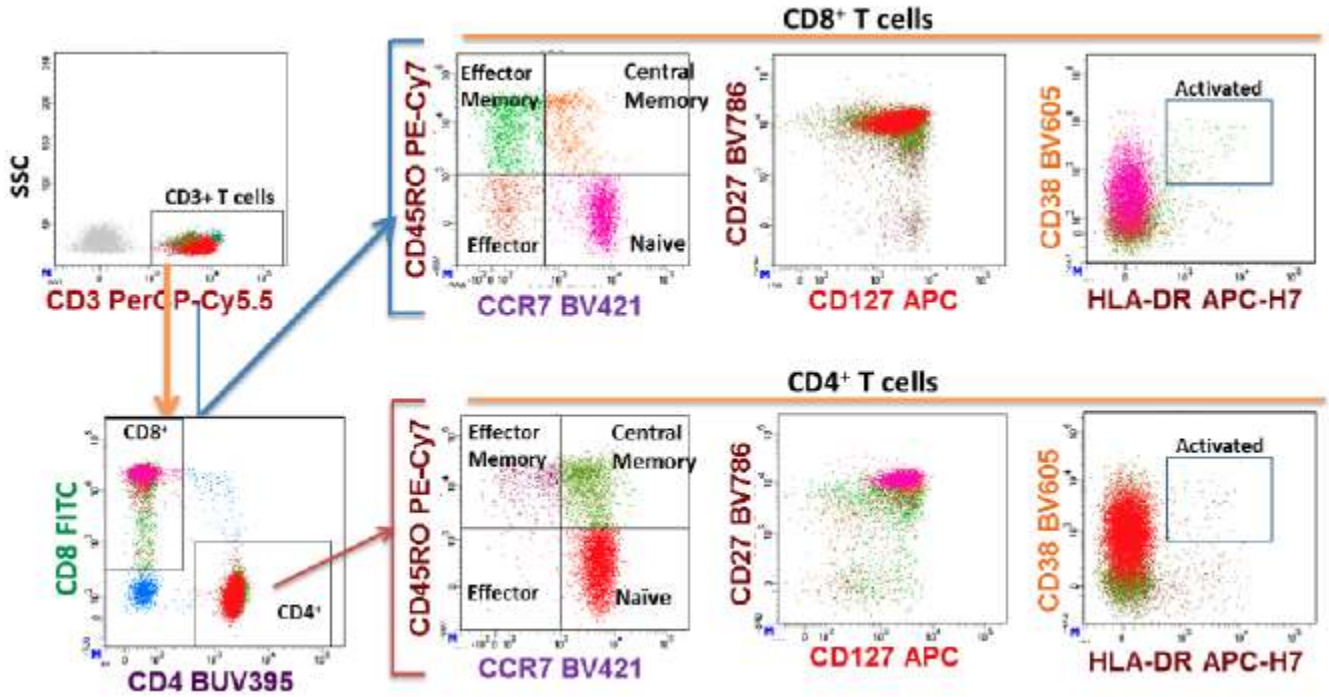
Power of Flow Cytometry
Immune Profiling – Lymphocytes and Subsets



Reference: BD Biosciences webinar

14-color immunophenotyping

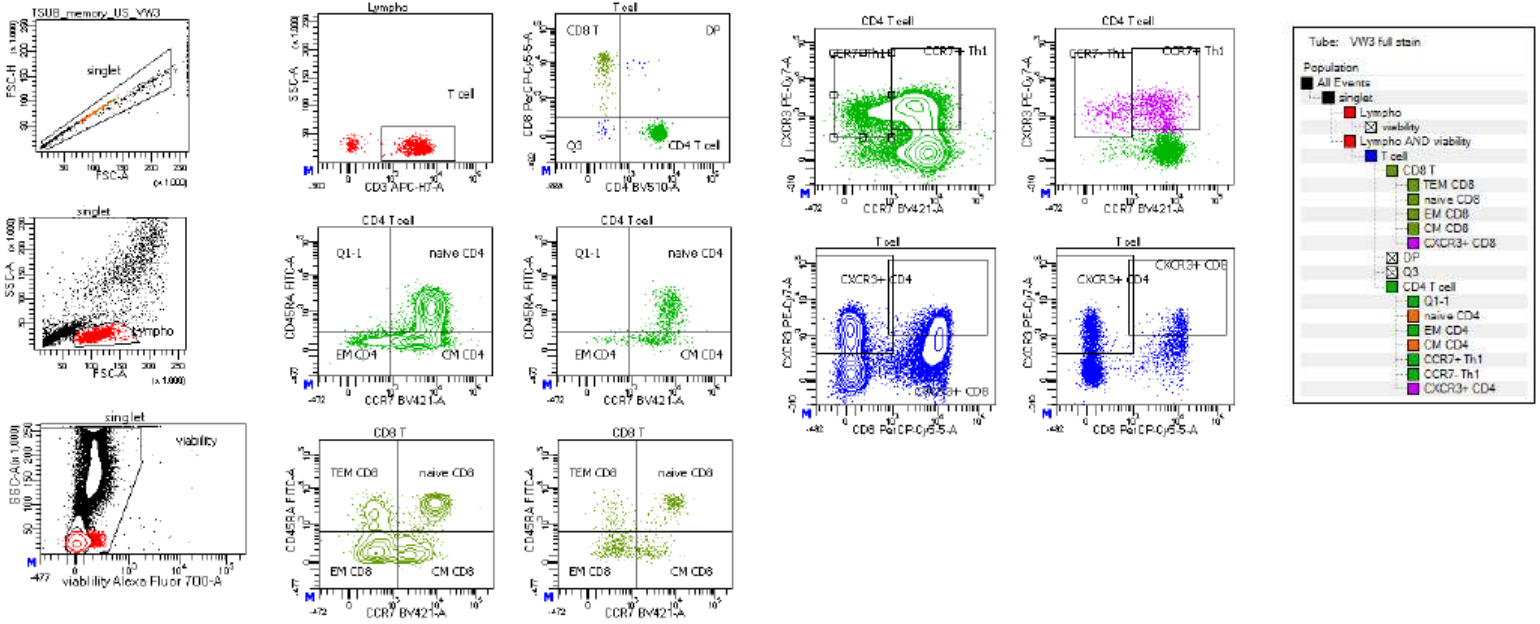
Power of Flow Cytometry
Immune Profiling – T cell memory subsets



Reference: BD Biosciences webinar

Flow Case Study

Tube	BV421	BV501	BV605	FITC	PE	PerCP-Cy5.5	PE-Cy7	APC	AF700	APC-H7
1	CCR7	CD4		CD45RA		CD8	CXCR3		Viability	CD3
2	CCR7	CD4		CD45RA		CD8			Viability	CD3

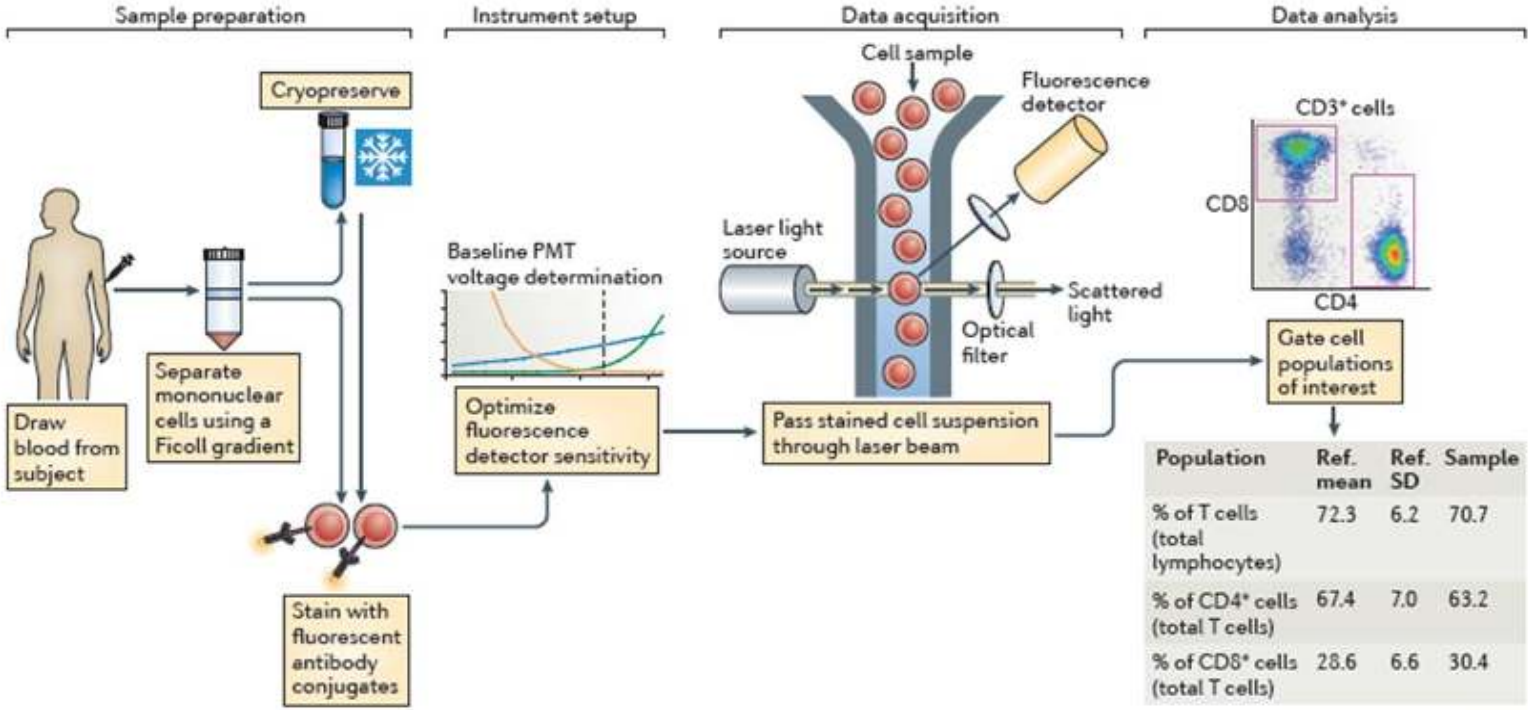


Flow Cytometry-based Assay in Clinical Trials

- Fit-for-purpose assay validation
  - **Fit**
    - Biomarker data must be reliable
  - **Purpose**
    - Decision making during drug development
  - **Fit-for-Purpose**
    - Analytical validation requirements
      - Specific to the **stage of drug development**
      - Specific to the **intended use** of the biomarker data
      - Specific to the **regulatory requirements** associated with that use
  - Practical, iterative approach
- Global implementation

Lee JW, et.al., Fit-for-purpose method development and validation for successful biomarker measurement. Pharm Res 2006;23:312.

Standardizing Global Clinical Trial



Population	Ref. mean	Ref. SD	Sample
% of T cells (total lymphocytes)	72.3	6.2	70.7
% of CD4+ cells (total T cells)	67.4	7.0	63.2
% of CD8+ cells (total T cells)	28.6	6.6	30.4

Maecker et al, Nature Immunology 12: 191 (2012)

Flow Cytometry at Cerba Research

Client-specific

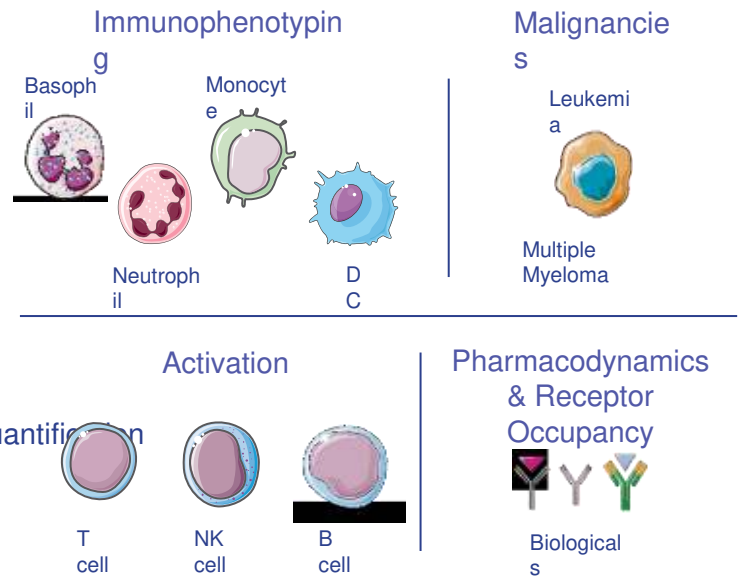
- Tailor-made building of proprietary/drug-specific panels
- In-house method development and validation
- Using disease-specific specimens where relevant
- Method transfer to other Cerba Research labs

Centralized analysis and review for Global trials

Specimens: Blood & Bone Marrow Aspirate

Harmonized Flow Cytometry Labs in 3 continents

- Harmonized for immunophenotyping and fluorescence quantification
- Standardized application set-up
- Global instrument/assay standardization procedures
- Global acceptance criteria
- Centralized expert review



Flow Cytometry at Cerba Research - Global Footprint

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USA

Instruments
2 FACS Canto II (10 colors)
2 FACSLyric (12 colors IVD)

Scientific Staff
Global Head of Flow Cytometry
1 Principal Scientist
1 Scientist
2 Associate Scientists
1 Principal Scientist to be hired
in Q4, 2020

Europe

Instruments
1 FACS Canto II (8 colosr)
2 FACS Canto (10 colors)
2 FACSLyric (12 colors, IVD)

Scientific Staff
3 Senior/Principal Scientists
2 Scientists
1 Associate Scientist
1 Associate Scientist to be hired in Q4, 2020

Australia

Instruments
2 Navios Beckman Coulter
2 FACSLyric (12 colors, IVD)

Scientific Staff
1 Senior Scientist

China

Instruments
3 FACS Canto (8 colors)
1 DXFLEX 3 lasers (13 colors)
2 Calibur
3 Mindray Bricyte E6 2 lasers (4 colors)

Scientific Staff
1 Senior Scientist

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