

# Selecting a Rapid Point-of-Care Test Kit to Monitor Cytokine Levels in Patients Undergoing Dose Escalation in Immunotherapy

Kagen Quiballo<sup>1</sup>, Didier Lefebvre<sup>2</sup>

<sup>1</sup>University of Illinois Urbana-Champaign, Illinois, United States; <sup>2</sup>CPD-AbbVie Inc., North Chicago, Illinois, United States

Presented at the AbbVie DEV-SCI DPD & ARD Summer Intern / Researcher Poster Session, August 1, 2019

### ABSTRACT

A patient's immune system response to immunotherapy treatment can be so rapid as to present a risk of adverse events ranging from flu-like symptoms to even death as a result of Cytokine Release Syndrome (CRS).

To avoid CRS, clinicians conduct dose escalation studies and monitor cytokine levels in a patient's blood. If the samples are sent to central lab, getting back cytokine readings can take 12-24 hours. This is not fast enough to manage CRS. Rapid point-of-care test kits are needed to get results on site in less than 90 minutes.

The goal of the project is to select a rapid point-of-care test kit from multiple suppliers already on the market so as to begin dose escalation studies by first Quarter 2020.

Among the many options considered, the Ella platform from Bio-Techne ranked highly according to the stakeholder's needs and is the best of the top 5 options analyzed.

### OBJECTIVE

AbbVie needs to select a point-of-care test kit to rapidly titrate a subset of cytokine biomarkers to monitor patients at risk of Cytokine Release Syndrome (CRS) at the onset of tumor treatment with immunotherapy during phase 1 dose escalation studies.

- Beginning with user needs and analytical product requirements, to comb through data sheets and web-sites from multiple suppliers to determine the closest matches to the desired test kit requirements.
- Using a Pugh Matrix, to reduce the number of vendor options.
- To analyze the top options to present the pros and cons to the stakeholders in order to help them make the final choice.

### METHODS

#### USER/STAKEHOLDER NEEDS

SCORE	ANALYTES	ASSAY TIME (minutes)	VALIDATED	AVAILABILITY	SPECIFICITY	DYNAMIC RANGE (logs)	SENSITIVITY (LLOD   pg/mL)
5	IL-6 & IFN-γ	< 60	medical	1 <sup>st</sup> Q 2020	no interaction	4-5	< 1
3	IL-6 only	60-90	scientific			3-4	1 – 2
1	*no IL-6*	* > 90 *	*not validated*	*not available*	no mention	< 3	> 2

SCORE	IMPRECISION (% CV)	ACCURACY (% spike recovery)	(Dilution) LINEARITY (R <sup>2</sup> )	PREDICATE ASSAYS (R <sup>2</sup> )	SITE-TO-SITE	COST (\$)	LIFECYCLE
5	≤ 10	90 – 110%	90 – 110%	≥ 0.95	robustness & ruggedness	affordability	consider large scale use
3	≤ 20	80 – 120%	80 – 120%	0.90 – 0.95			
1	> 20	70 – 130%	70 – 130%	≤ 0.90			

#### WEIGHTING FACTORS

ATTRIBUTE	WEIGHT
ANALYTES	5
ASSAY TIME	
VALIDATED	
AVAILABILITY	
SPECIFICITY	
DYNAMIC RANGE	
SENSITIVITY	3
IMPRECISION	
ACCURACY	
LINEARITY	
PREDICATE ASSAYS	1
SITE-TO-SITE	0
COST	
LIFECYCLE	

### IMMUNO-ONCOLOGY

Cancer can survive unchecked because the immune system does not recognize it as an intruder, but immunotherapy (IO) can help the immune system detect the cancer and attack it.

### CYTOKINE RELEASE SYNDROME

When a patient responds to IO, the response can be so rapid as to present a risk of adverse events if the dose is not carefully fine tuned to avoid Cytokine Release Syndrome. CRS is a runaway inflammatory response, also called cytokine storm.

### SYMPTOMS

Symptoms include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, and loss of coordination.

### CRS PREVENTION: DOSE ESCALATION STUDIES

Determine if dose range achieves both efficacy and safety requirements

### RESULTS

#### TECHNOLOGY LANDSCAPE

30+ INSTRUMENT OPTIONS → 30 OPTIONS → < 10 OPTIONS

**NO RELEVANT TECHNOLOGY**

- Minifab
- Abreos Biosciences
- Microdermics

**NO IL-6 OR IFN-γ**

- Alere: AFINION
- Sekisui Diagnostics: FastPack
- True Diagnostics: TrueDX Assays
- Buhlmann: Quantum Blue CRP
- Abbott: i-STAT Handheld
- Abbott: Piccolo Xpress
- Nanomedical Diagnostics: Agile

**ASSAY TIME > 90 MIN.**

- Eve Technologies: Discovery & Multiplex Assays
- BioLegend: Legend MAX Kit
- Bio-Rad: Bio-Plex MAGPIX/200/3D
- ACD: RNAscope
- Novus Biological: IL-6 ELISA Kit
- R&D Systems: Quantikine ELISA Kit
- Quanterix: Simoa HD-1 Analyzer
- \*\*Thermo Fisher Scientific: Luminex 200 & ProcartaPlex Simplex (industry standard)

**NOT AVAILABLE BY 2020**

- \*\*Proxim Diagnostics: Handheld Analyzer (lifecycle)
- Bioporto: NGAL ELISA Kit
- Dakotari Diagnostics: Agile
- Zomedica Pharmaceuticals Corp: TRUFORMA
- Qorvo Biotechnologies: ZM-024
- Milenia Biotech: QuickLine IL-6 ELISA

#### LIFECYCLE OPTIONS UNDER REVIEW

- \*\*Protein Simple: Ella
- Protein Fluidics: PuMA (contact with supplier initiated)
- Vista Therapeutics: NanoBioSensor (contact initiated)
- Gyros Protein Technologies: Gyrolab xPlore (contact initiated)
- \*\*Meso Scale Diagnostics: V-PLEX (assay time to be clarified)
- Singulex: Erena SMC Instrument (assay time to be clarified)
- Singulex: Clarity System (analytes to be clarified)
- Xip Diagnostics: Molecular Counting: (analytes to be clarified)

### PUGH MATRIX

ATTRIBUTE	Thermo Fisher Scientific: Luminex 200 & ProcartaPlex Simplex	Meso Scale Diagnostics: MESO SECTOR S 600 & V-PLEX	Protein Simple: Ella	Proxim Diagnostics: Handheld Analyzer v2.1	Protein Fluidics: Pu•MA	Vista Therapeutics: NanoBioSensor	Gyros Protein Tech: Gyrolab xPlore
ANALYTES	IL-6 & IFN-γ	IL-6 & IFN-γ	IL-6 & IFN-γ	IL-6 only	IL-6	IL-6	IL-6
ASSAY TIME	run: 3-5 hrs read: ~45 min	turn around: <4.5 hrs smp prep: 2 hrs read: 1-3 min	assay prep: 10-15 min smp prep: 0-45 min read: 1 hr	smp-to-result: <15 min	< 90 min	< 90 min	< 90 min
VALIDATED		RUO			RUO	RUO	RUO
AVAILABILITY	available	available	available	unavailable	available	available	available
SPECIFICITY	tested	tested	tested				
DYNAMIC RANGE	3.6 logs	3.9 logs	4.0 logs	4.0 logs	5	5	5
SENSITIVITY	0.038 pg/mL	0.06 pg/mL	0.26 pg/mL	1.5 pg/mL	3	3	3
IMPRECISION	inter: 4.5% intra: 6.2%	inter: 7.3-5.2% intra: 4.5-3.6%	inter: 8.3-7.1% intra: 2.4-3.9%	< 10% CV	5	5	5
ACCURACY	94-97%	87-92%	88-99%				
LINEARITY	102-115%	105-110%	110-120%	3			
PREDICATE ASSAYS	0.9733		> 0.9	0.953	5		
SITE-TO-SITE			7.5% CV				
*COST (does not represent large scale)	plate: \$200 - \$300 reader: \$62,500	plate: \$300 - \$400 reader: \$190,000	plate: \$750-\$1,200 reader: \$63,000	plate: \$1500 reader: \$1700			
EASE OF USE	CRO only	CRO only	POC + error mitigation	TBD	TBD	TBD	TBD
SCORE	160	170	182	99	70		

### TURN AROUND TIME

NOW: 12 – 24 HRS  
GOAL: < 90 MIN

### CLINICAL BACKGROUND INFORMATION

The first patient is scheduled to be enrolled in a phase 1 dose escalation study by first quarter 2020. Patient failed to respond to standard of care therapy prior to being referred to immuno-oncology clinic. This means that time is quickly running out to try cutting edge immunotherapy available at a limited number of treatment centers.

### REFERENCES

- "Ella." ProteinSimple, [www.proteinsimple.com/ella.html](http://www.proteinsimple.com/ella.html)
- "Luminex Technology Multiplex Assays." Thermo Fisher Scientific - US, [www.thermofisher.com/us/en/home/life-science/antibodies/immunoassays/procarta-plex-assays-luminex.html](http://www.thermofisher.com/us/en/home/life-science/antibodies/immunoassays/procarta-plex-assays-luminex.html)
- "SECTOR S 600." Meso Scale Discovery, [www.mesoscale.com/en/products\\_and\\_services/instrumentation/sector\\_s\\_600](http://www.mesoscale.com/en/products_and_services/instrumentation/sector_s_600)
- Shimabukuro-Vornhagen, Alexander, et al. "Cytokine Release Syndrome." *Journal for Immunotherapy of Cancer*, BioMed Central, 15 June 2018,

### ACKNOWLEDGEMENTS

This project was made possible by Catherine Tribouley / AbbVie Early Oncology Discovery, Didier Lefebvre / CPD and Masha Trenhaile / Abbvie Innovation Center at UIUC

The authors also thank Rubin Vitaly / Analytical Sciences at AbbVie for providing valuable advice

### CONCLUSIONS

The Ella platform satisfies all main inclusion criteria and a promising performance compared to the industry standard. It is the best option that we have the most information on currently.

### DISCLOSURES

All authors are employees of AbbVie. Didier Lefebvre may own AbbVie stock or options.

Both Luminex and the Meso Sector S 600 perform highly for all technical attributes, but have long assay times.

Handheld Analyzer v2.1 has a promising performance, but is not available 1Q 2020.

Pu•MA, NanoBioSensor, and Gyrolab xPlore satisfy the main inclusion criteria. Suppliers are in contact with for additional information on instrument performance.

Both Singulex and Xip were contacted in July 2019 with no response.