SEXTON BIOTECHNOLOGIES

Improved COGs with nLIVEN PR™

BioDefined Media supports reduced cytokine supplementation for T Cell Expansion

THE CHALLENGE

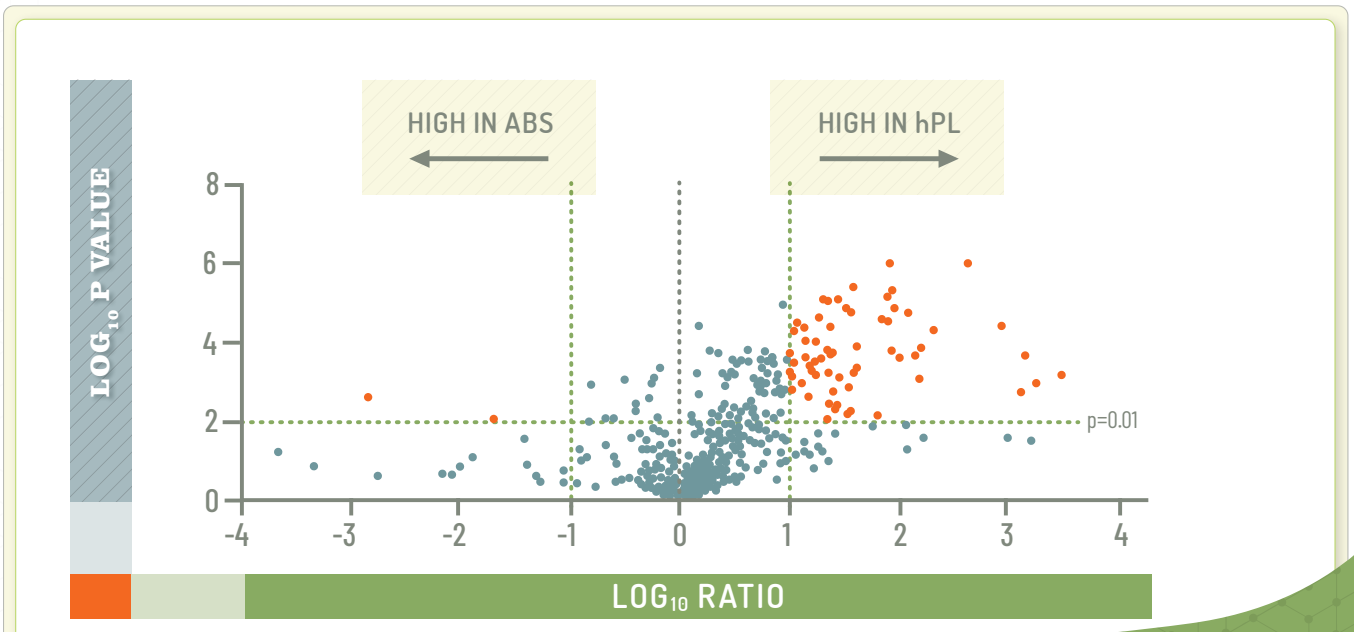
Chimeric Antigen Receptor T cell (carT) Therapies have shown incredible efficacy against multiple hematological cancers. At present, the majority of both commercially available products and those in clinical trials are autologous by nature. Given the inherent variability of these starting materials, manufacturing processes strive to limit variability from other process inputs such as cell culture reagents. We have previously described how BioDefined Media can provide a more standardized alternative to AB Serum,[1,2] whilst also inferring a preferential Tn/Tcm phenotype with improved efficacy in vivo[3]. Herein, we would like to describe how the composition of BioDefined Media allows for reduction in cytokine supplementation and reduced overall cost of goods.

Under the conditions of our study, replacement of AB Serum with nLiven PR results in a reduced need for IL2 in a carT manufacturing process with a projected cost improvement of ~$3M over 10,000 patient doses. These savings could potentially allow for employment of an additional 40FTEs dedicated to manufacturing. Combined with the positive impact of nLiven on T cell expansion and phenotype, nLiven is quickly establishing itself as the gold standard supplement for carT manufacturing.

UNIQUE PROTEIN PROFILE OF HPL

Cytokines represent a significant component in the COGs model of cell therapies due to both the high cost of GMP reagents and the cost of qualifying new materials due to variability. Simplifying the manufacturing process by removing variable and expensive components will result in not only lower overall costs, but also reduced risks in manufacturing a reproducible product. We previously introduced the concept of BioDefined media[1] and referenced some of the work undertaken to characterize the composition of our nLiven PR, an irradiated Human Platelet Lysate, compared with AB Serum. While a component of platelet lysate is certainly similar to serum, there is a very distinct composition, as demonstrated by analyzing the distribution of proteins.

••• FIGURE 1 ••• ***Proteomic volcano plot of proteins in nLiven PR™ and AB Serum***



Improved COGs with nLIVEN PR™

In addition to the data presented in that paper, the proteomic data revealed significantly higher values of T cell expansion-associated cytokines IL-2, IL-7 and IL-15 (Table 1). This observation suggested that the composition of nLiven PR could reduce the need for additive interleukin addition.

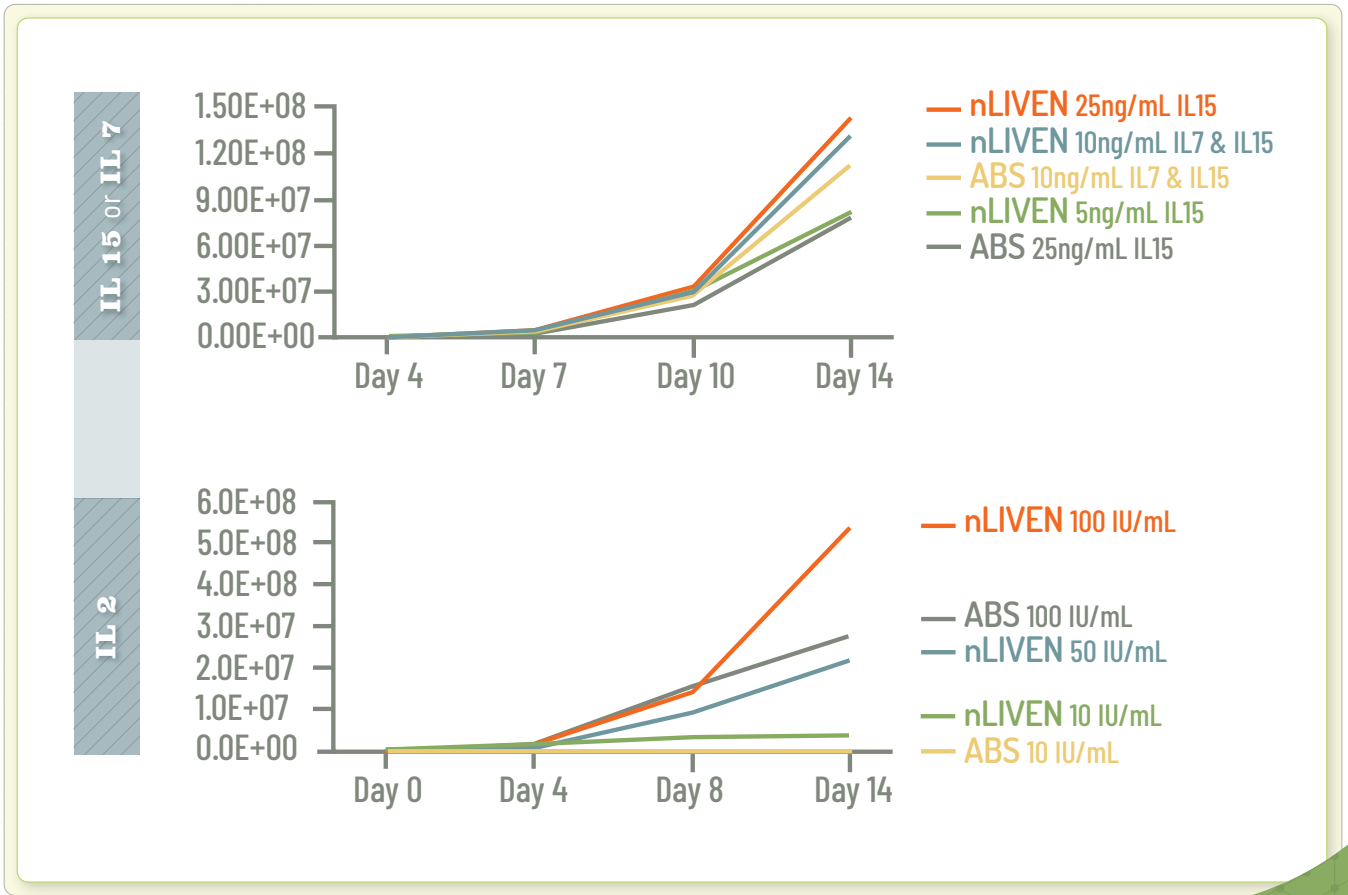
	nLIVEN PR™ pg/ml (SD)	AB SERUM pg/ml (SD)
IL 2	67 (9)	1 (1)
IL 7	322 (24)	4 (7)
IL 15	44 (9)	18 (17)

••• TABLE 1 ••• *RayBioTech Assay data for nLiven PR (3 lots) and AB Serum (3 lots)*

OUR GOAL

We therefore looked as to whether supplementing T cell cultures with nLiven in place of AB Serum could allow for lower concentrations of cytokines to be added. The results of the study showed that nLiven PR does support the reduction of supplemental cytokine addition. In fact, when using IL 7 and IL 15, complete removal of IL 7 still results in robust cell expansion. In the case of IL 2, use of nLiven PR and IL 2 at 50 IU/ml resulted in the same expansion as AB Serum and 100 IU/ml IL 2.

••• FIGURE 2 ••• *T Cells growth in nLiven or AB Serum with varying concentrations of IL7/IL15 or IL2*



IMPACT

To understand how these data could benefit in a scaled GMP manufacturing setting, we created a simple cost model representative of a carT expansion process (Table 2). The model serves to understand the cost impact of reducing IL-2 concentrations at a high level, and incorporates only costs of media supplementation (nLiven/AB Serum) and varying IL-2 concentrations. It does not take into account other direct reagent costs, material qualification, labor or facility costs.

MANUFACTURING PROCESS	14 days	GRex100M
MEDIA VOLUME/ MEDIA CHANGE	1000 mL	N/A
NUMBER OF MEDIA CHANGES	5	Day 0,3,6,9,12
NLIVEN (5%) COST/ TX DOSE	$1204.50	Sexton Biotechnologies – PL-PR-500
AB SERUM (5%)/ TX DOSE	$837.50	Sigma Aldrich - H6914
IL-2 100IU/ML COST/ TX DOSE	$1362.50	Miltenyi Biotec – 170-076-147
IL-2 50IU/ML COST/ TX DOSE	$681.25	Miltenyi Biotec – 170-076-147

••• TABLE 2 ••• *(Above) COGS model design*

••• TABLE 3 ••• *(Below) COGS per Therapeutic dose*

DOSES	nLIVEN 50IU/mL	AB SERUM 100IU/mL
1	$1885.75	$2200.00
10	$18,857.50	$22,000.00
100	$188,575.00	$220,000.00
1000	$1,885,750.00	$2,200,000.00
10000	$18,857,500.00	$22,000,000.00

Table 3 clearly demonstrates the significant cost savings associated with reducing IL-2 concentration in the presence of nLiven. Furthermore, this model does not take into account the significant time and cost of requalifying new lots of IL-2, thus potentially inferring further cost savings by reducing the number of lots needed for manufacture.
The impact of the cost savings can be applied in multiple ways, an example being manufacturing headcount. Assume an annual manufacturing technician salary of $75,000 – the $3.2M reduction of costs at 10000 doses could be applied for an additional ~40FTEs, thereby further expanding capacity for manufacture of additional doses.

References

[1] Sexton Biotechnologies, Phacilitate – Redefining Cell Culture Supplementation (2021)
[2] Thompson, Improving the Quality Cell Yield of T-Cell Immunotherapies through selective pressures imparted by culture media supplements (2020)
[3] Watanabe - Expanding CAR-T Cells in hPL renders T Cells with in vivo longevity (2019)

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