Cell Line Qualifying Attributes for Prediction of Good Producers

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ABSTRACT

Early stage titer of IgG-expressing cell lines is not predictive of final titer in production fed-batch for several reasons

- Adaptation process from static to suspension culture affects cellular dynamics and mechanics.
- Static titer is used as only decision driving criteria.
- Challenges in measuring growth in small vessels at the early stage.
- Scarcity of *big data analysis* tools for the study of qualifying attributes defining a good cell line.

APPROACH

In order to investigate the patterns that define the best candidate cell line, an analysis of the progression of growth and titer data has been conducted:

- *Early stage specific productivity* **96WP[cQp]** variation is positively correlated (covariance) with *late stage titer* **FB[t]** attribute and is a more powerful prediction tool than early stage titer 96WP[t].
- Multivariate analysis tools could explain relationships between cell line attributes in a big-data format.
- Early stage growth measurements was derived from a corrected confluence analysis.

SIGNIFICANCE

Early stage selection based on 96WP[cQp] captures more final top performers than 96WP[t].
This method might optimize the cell line screening process and therefore accelerate the generation of bio-therapeutics:

- An increase in selection efficiency of ~20-50% was achieved.
- A consequent 20-50% workload and reagent saving was also observed

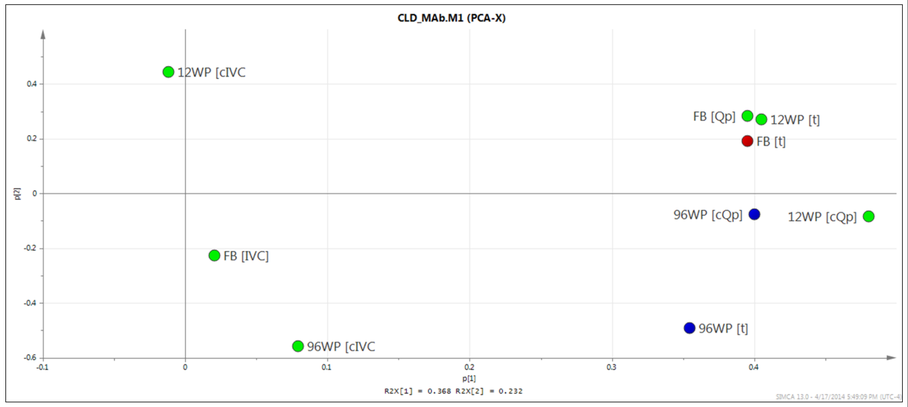
RESEARCH

	Titer [t]	Growth [IVC]	Productivity [Qp] (titer/growth)
96WP	96WP[t]	96WP[IVC]	96WP[Qp]
12WP	12WP[t]	12WP[IVC]	12WP[Qp]
96DWP fed-batch [FB]	FB[t]	FB[IVC]	FB[Qp]

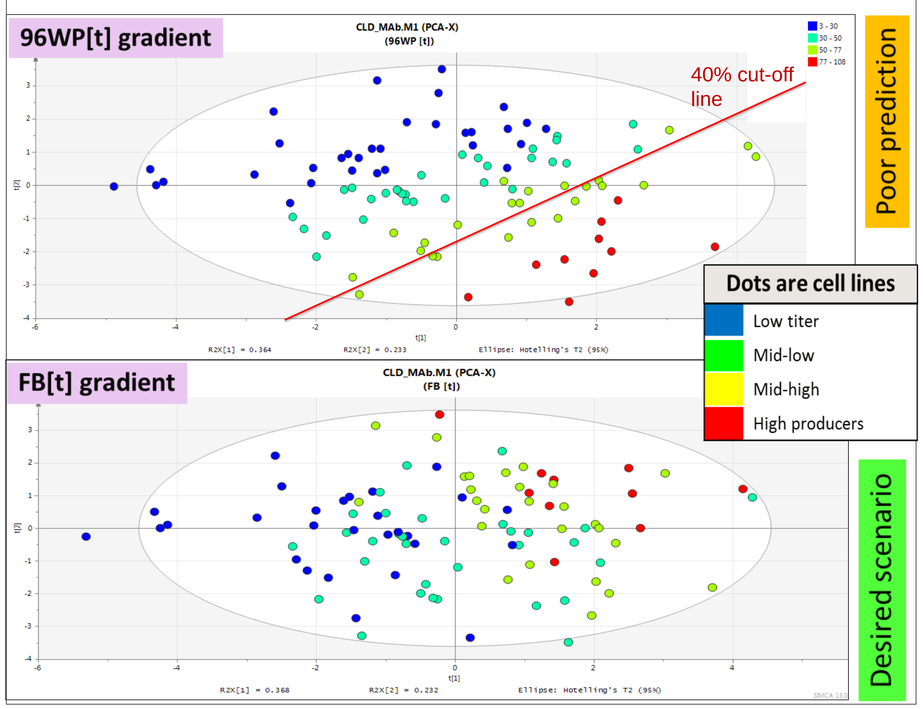
Attributes to be evaluated in this study including titer, growth and productivity across different vessels from stationary to suspension condition.

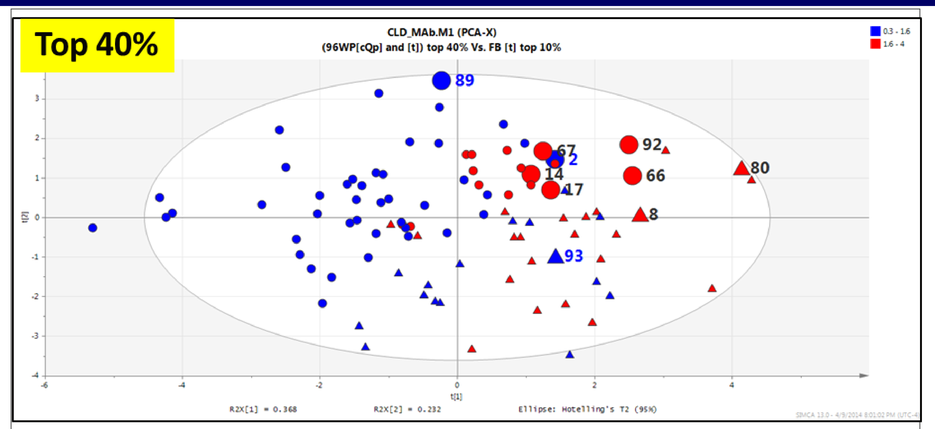
	Same transfection experiment		DOE approach	
Parental	23		61	Genomic
Cell line	23-14	23-16	61-12	Phenomic
Sub-lines #	81	96	96	

DOE included 3 different genetic sets in order to evaluate genomic and phenomic characteristics.



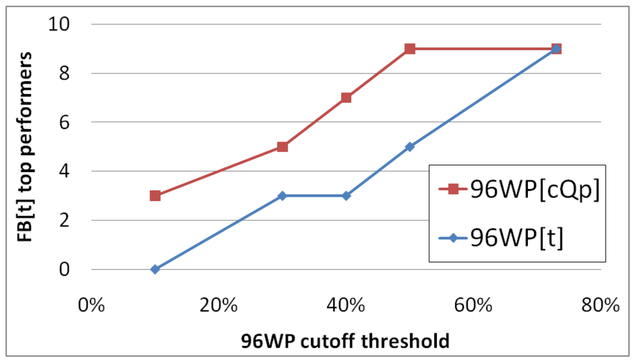
Multivariate Analysis explains relationships among all the attributes studied.
1. Attributes closely located behave similar (positive covariance).
2. Attributes far away from the origin drive the *"best cell line"* model.





Magnified shapes are final top performers in fed-batch and a 40% cut-off early screening is here used. 96WP[cQP] in red captures more top fed-batch performers than 96WP[t] in blue.

	[t] high	[t] low
[cQp] high	▲	●
[cQp] low	▲	●



96WP[cQp] is consistently more powerful than 96WP[t] in predicting final fed-batch performers, across different cutoff thresholds.

Multivariate analysis by SIMCA

Titer data by Octet
Growth data by corrected confluence

CONCLUSIONS

- Current 96-well plate screening aims to identify the top fed-batch producers at the early stage of development.
- Titer **96WP[t]** (standard screening attribute nowadays) doesn't completely predict top producers in the final fed-batch.
- Productivity **96WP[cQp]** shows a good predictive power combining existing 96WP[t] with new developed 96WP[IVC] attribute.
- 96WP[cQp] can be considered an enhanced prediction tool and it would save at least 20% initial workload in cell line development or maximize effectiveness by a 20% factor.
- Taken together, these observations suggest that it is possible to study cell line at a multivariate analysis level in order to simplify the current development therefore impacting the delivery of bio-therapeuticals.