A simple solution which has slashed cell line development times at Genmab

From transfection to ambr15 in only 10-13 weeks

The Cell Line Development team at Genmab with VIPS:
From left to right: Jolanda Gerritsen, Regine van Mol and Dorothea Meersma.

The Cell Line Development (CLD) team at Genmab, a large international biotech company working on cutting-edge oncology drugs, decided at the end of 2017 that it wanted to speed up development of the company's growing portfolio of antibody-based therapeutics. Thanks to Solentim's easy-to-implement VIPS™ technology, they have already halved development times with minimal effort and disruption to staff and ongoing projects.

Introduction

Genmab is the largest independent biotechnology company in Europe. Founded in 1999, the company has ambitious goals – to transform cancer treatments with next-generation antibodies.

The company has two products, DARZALEX® and Arzerra®, on the market, with four others in the pipeline. Thanks to two innovative molecular scaffolds, HexaBody® and DuoBody®, Genmab is continuing to design new drugs.

A Need for Optimisation

The Cell Line Development (CLD) team at Genmab is responsible for making high-quality antibody candidates and proteins, which can be tested in animal models for pre-clinical studies and during clinical trials in patients.

In 2017, the team decided to optimise their processes. "As a company, we've been moving far more projects into development very early and need a lot of stable cell lines," explains Jolanda Gerritsen, Technology Expert and Manager of Cell Line Development at Genmab.

A Change in Approach

Choosing the Right Instruments

The CLD team looked for new equipment that could isolate single cells and provide evidence of clonality in one, single cloning round. After review of all the options, they selected the VIPS™ with Cell Metric® CLD imager combination from Solentim.
VIPS is a cell printer that dispenses a single cell in a 30 nanoliter droplet into the bottom of a dry well, of a 96 well plate, and then takes multiple image slices through the droplet to confirm a single cell is present. Cell Metric CLD can then provide subsequent daily whole well imaging for a cassette holding up to 10 x 96-well cloning plates.

Single cell wells – guaranteed:

VIPS dispenses up to 16 (sixteen) droplets into each well ensuring seeding efficiencies of 80-85% (for a 96 WP) – see Figure 1.

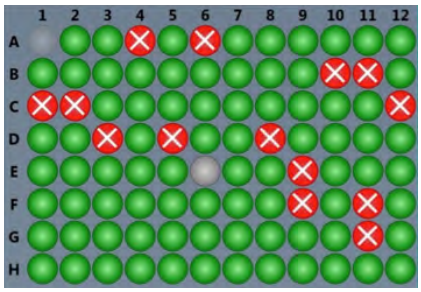


Figure 1. Seeding efficiency for VIPS. Green wells = single cells; Red wells = >1 cell; Grey wells = 0 cells. A1 is a control well.

Plate Number	Single Cell	> 1 Cell	Empty	% monoclonal wells/plate
1	80	14	1	84
2	80	14	1	84
3	83	12	0	87

Each time a droplet is dispensed, the VIPS captures 20 image slices through the droplet as a Z-stack and sophisticated algorithms confirms a cell is present. When a single cell is detected, the well is immediately filled with media.
"There are lots of other cell printers out there that take a picture of a cell on the way to the well, but you don't know if the cell actually arrived there or not," says Gerritsen.

Speed and accuracy:

VIPS can dispense a full 96-well plate within 9-10 minutes. The system also reduces ghost wells and edge effects by printing the cell droplets onto the bottom surface of a dry well (so cells cannot stick to well walls) and in the centre part of the well away from the well edges.

Ensuring clonality:

With whole well imaging, the CLD team can now track a cell colony back to the initial VIPS droplet image, as well as validating the VIPS results for cells dispensed per well.
"We can trace back the data to the single cell, select from our top 48 cell lines, and report all the information – our proof of monoclonality is already in there, and that's really nice," says Gerritsen.

Simple, Fast Validation and Implementation of the New System

The CLD team were keen to choose a single cell printer that fitted seamlessly into their existing processes. Previously, the ClonePix FL instrument had taken a long time to validate before it could be implemented, "We spent 1.5 years with people doing validation experiments and still had a process with two rounds of cloning and a statistical calculation," says Gerritsen.

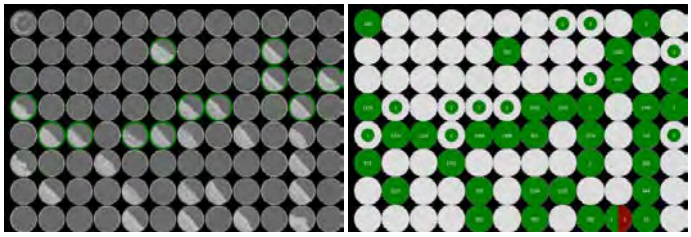
"A machine that just does the job and provides the data within one cloning round would be a significant improvement."

Unlike more complex cell line development platforms, the VIPS is a simple replacement for the ClonePix FL. "It's plug-and-play, we just needed to do training," says Gerritsen.

In total, the CLD team spent two or three months converting their existing processes to accommodate the VIPS. This was mostly re-adapting their existing cell line development process which had previously been optimised for growing in semi-solid media.

Gerritsen explains that the VIPS combined with Cell Metric CLD gives her confidence that she has complete control over her cell line development, *"unlike fully automated platforms, which are completely different and therefore, it's unkown which cell lines you will select within your CLD process and how the cell lines will behave later in upstream bioreactor fed batch processes."*

"In addition, VIPS and Cell Metric CLD were a fraction of the capital investment compared with some of the new optoelectronic and microfluidic systems on the market, and it's nice for a team like ours that we do not require a dedicated expert user in the team." says Gerritsen.



Cell Metric® (after 21 days)		% outgrowth after VIPS seeding	% outgrowth from Limiting Dilution in the past
31	Wells with Colony growth	33% (still optimising)	10 - 30%
95	Total number of wells seeded		

Figure 2 – Outgrowth example from Cell Metric CLD on Day 21 after seeding on VIPS. Image on the left is a thumbnail summary overview of confluence images for the whole 96 well plate; image on the right is the same plate but presented in an alternative format, based on cell numbers per well.

Going forward, the team hope to optimise their growth media and additives further – to achieve even better outgrowth rates.

"We can demonstrate clonality and it's dropped our timelines dramatically," says Gerritsen. "By adopting VIPS and Cell Metric, the CLD team can cut our timelines for transfection to ambr15 from six months down to 10 -13 weeks." (see Figure 3)

Slashing Project Timelines

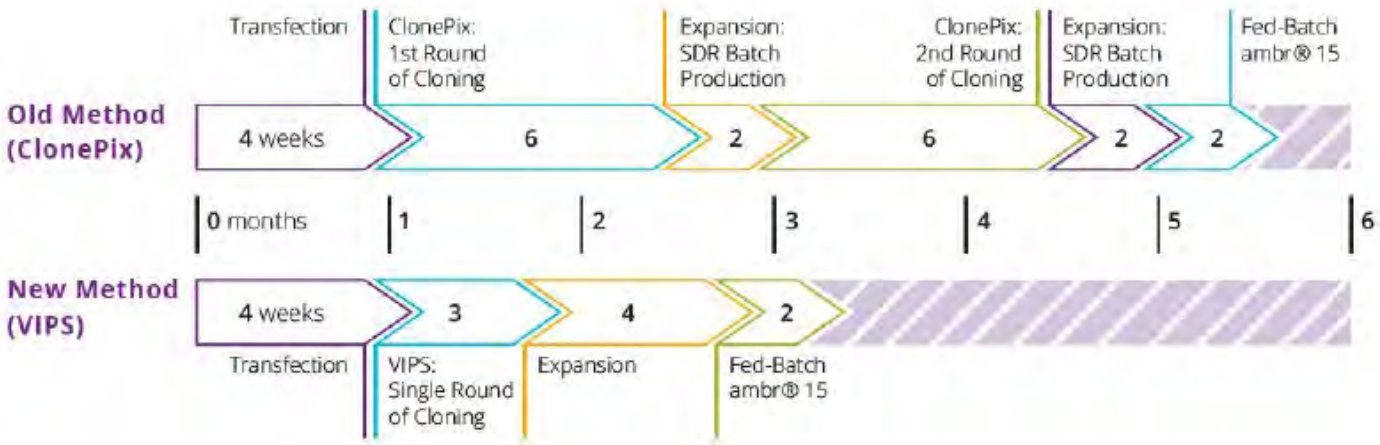


Figure 3 - The Genmab CLD Workflow Timelines: Top is the Old Workflow using ClonePix with 2 rounds of cloning; Bottom is the New Workflow using VIPS and Cell Metric CLD.

Summary

Importantly, from the initial projects run by Genmab, the clones generated using the VIPS process are just as good (titers as measured by fed batch) as the clones selected using the former ClonePix FL method (see Figure 4), but now in less than half the time. Importantly, this has come with complete assurance of clonality, which no longer relies on probabilities, and includes a comprehensive clonality report package which forms part of an IND.

	Process with Clonepix FL	Process with VIPS
Time (months)	5-6	3
Transfections (weeks)	4	4
# clones screened	± 800	± 960
# clones expanded	± 60	48
# sub-cloning rounds	2	1
# clones expanded	± 60	48

Figure 4 - Overview for the changes in the Genmab CLD workflow.

Acknowledgement

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ADVANCED INSTRUMENTS

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