

Solving for Speed in Translational CMC

Jesse McCool, Ph.D.

Co-Founder and CEO at Wheeler Bio

May 2023

Drug Development Lifecycle Needs to Improve

Next-gen biologics could address the world's remaining disease but face outdated provider paradigms

The cost to bring a drug candidate from research and discovery to regulatory approval is approximately \$2.6B (capitalized cost, 2013 dollars). Of the \$2.6B figure, \$1.4B represents out-of-pocket cost and \$1.2B is time cost. Studies completed by other researchers have estimated similar figures, with capitalized cost ranging between \$1-\$3B. Typically, total cost to bring monoclonal antibodies and recombinant proteins to market is much lower, averaging around \$1.3B.



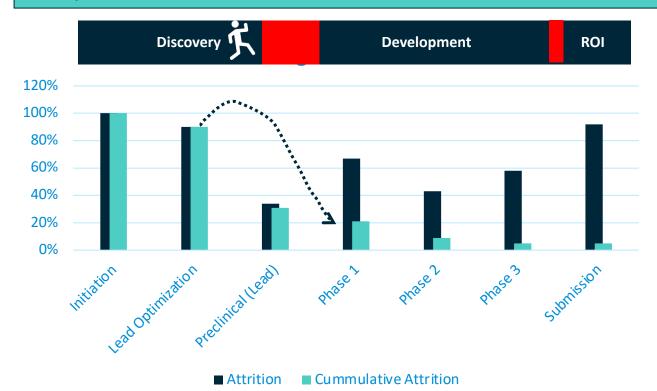
Ref: DeMasi – Tufts Center for Study of Drug Development



Gap in Early-Stage Development Related to CMC

To minimize the risk of later-stage failure, several key CMC areas must be considered in early development

Approximately six out of 100 molecules make it from the discovery stage to phase 3 clinical trials. The attrition of the other 94 molecules represents a gap in early-stage development that could be related to chemistry and manufacturing control (CMC) issues. CMC activities include the establishment of manufacturing processes and product characteristics, as well as defining product testing methods to ensure that the product is safe, effective, and consistent between batches. To minimize the risk of later-stage failure, several key CMC areas mush be considered in early development.



Critical Areas of Risk Consideration for Early-to-Late-Phase Transition Cell Line Performance API CQAs Raw Materials Formulation Manufacturing Process Design Analytical methods Development history

Gap in Early-Stage Development Related to Capital

Seed: Used for the **lead optimization** stage

- Perform in vitro mechanistic validation (POC in animals)
- Generate early *in vivo* data showing therapeutic rationale in a key indication
- The investors need to see that there is a development path and a competitive advantage within the landscape

Series A: Used for **IND enabling studies**

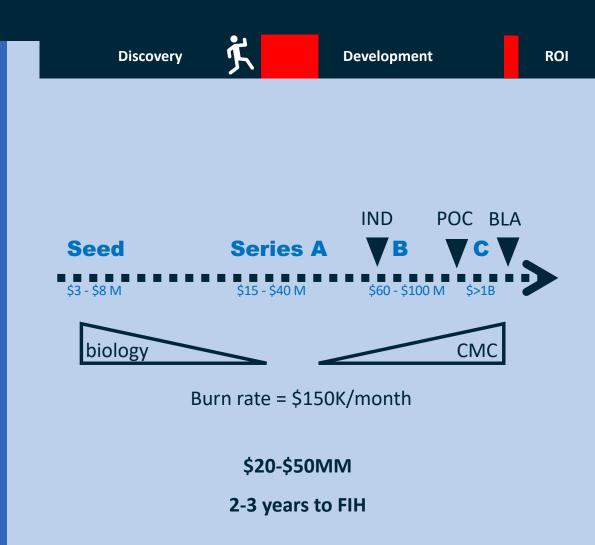
- Demonstrate robust in vivo data that shows a benefit over standard-of-care or competitor with a clear clinical development plan and timelines to human data
- Finish IND enabling studies as the investor wants this round to get close to the clinic and build out a team to execute the plan
- Size of round depends on team and modality/tech

Series B: Used to get to human POC in patients with the disease

- Investor needs to see an exit like IPO or acquisition based on successful clinical data
- Investor needs confidence the money is not just paying for CMC and scale but that POC will be achieved even with some expected delays – so buffer funds needed
- Size of round depends on team and modality/tech and size of buffer

Series C/Crossover : Used to take through to pivotal studies

definitive exit plan



Ref: GSL CMC Consulting – Steve Monks



Developers Take On Most of the Early CMC and Business Risk

Providers typical cannot share risk due to business design which leads to poor customer experience

Figure 1.4-C Benefit- or Risk-Sharing Arrangement Have Arrangement ■ Do Not Have Arrangement 100% Percentage of Respondents 33% 80% 76% 60% 89% 40% 67% 20% 24% 11% 0% All Respondents Commercial Products No Commercial Products

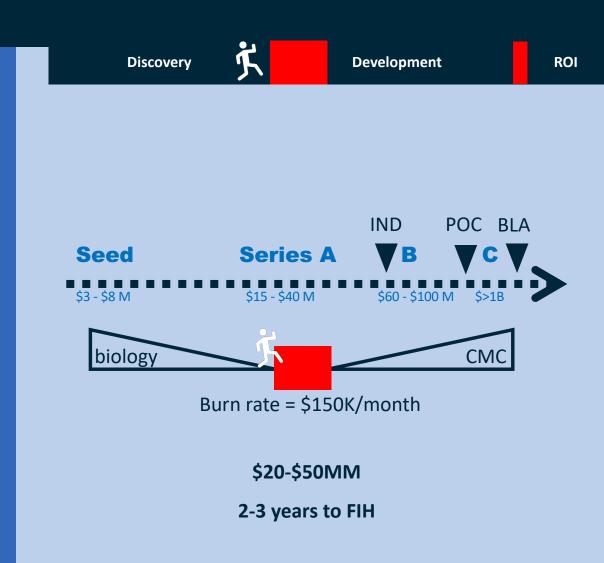


HighTech Business Decisions

How to Solve for Translational Gaps?

Align CMC with Capital

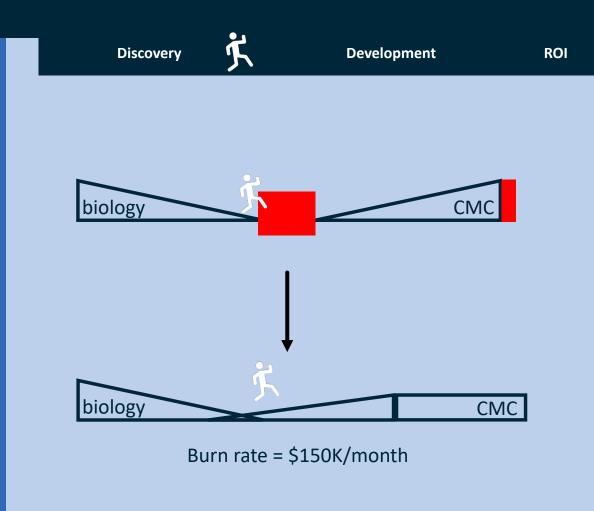
- There is a gap in the drug development process between discovery and early development
- Developers getting stuck with too much technical risk at end of discovery
- Developers experiencing loss of momentum in fundraising between seed and Series A
- CROs have tried to forward integrate but it's too capital intensive to add GMP



Wheeler Shifting the CDMO Paradigm to Fill Gap

CDMO inside venture studio for improved capital and resource alignment

Agility
Ease-of-Access
Speed
Freedom
Innovation



Value Proposition

A new CDMO paradigm built to take on the translational space



Agility

Focused and purpose-built enterprise enables new tier in customer experience



Ease-of-Access

Thoughtful alignment of services to match fundraising process



Speed

Rapid pool-based workflows enable speed-to-clinic



Freedom

Open-source platform for derisking scale-up and tech transfers



Innovation

Tech stacked with integrated digital solutions for derisking the scale-up manufacture



Wheeler Bio:

- ->Agile, Boutique CDMO
- ->Inside Venture Studio
- ->De-risk ROI

Solving for Translation

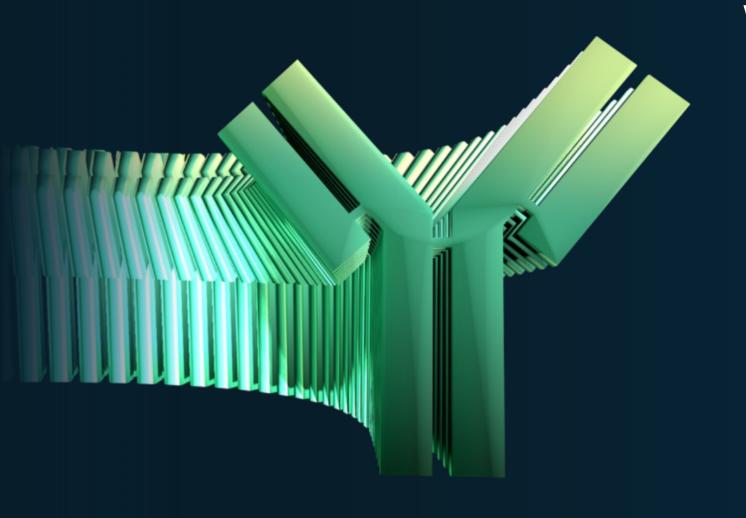
Experienced Leadership

Aligned Culture

Technology Stacked

Compressed Workflow

GMP Go-Live: Q3 2023



Purpose Built

Wheeler Co-Founder Jesse McCool

- Scientist by training with 20+ years in development
- Ph.D. UMASS & Postdoc Dartmouth
- Mascoma | Lonza | Cytovance | Wheeler
- Joined Cytovance in 2013 and helped grow company by 50% in 2 years
- Sold to Shenzhen Hepalink Pharmaceutical Group in 2015 and stayed on to drive growth. Became CEO in 2020 and led HK IPO (\$529MM)
- JV Partner with Alloy Therapeutics (Waltham)

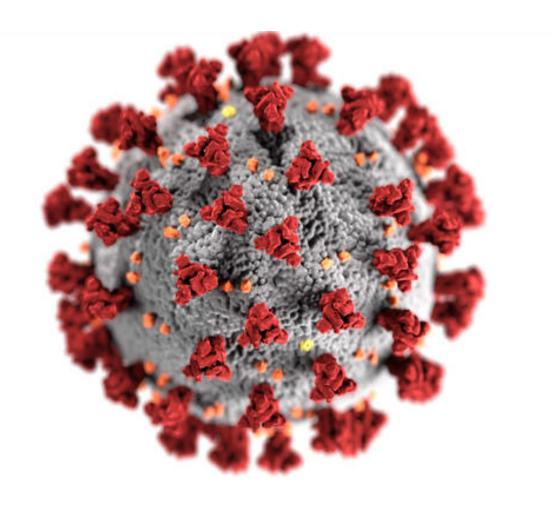


Wheeler Co-Founder Christian Kanady

- Entrepreneur from Oklahoma City and founding partner of Echo with \$1.3B in AUM (PE/VC)
- B.S. University of Oklahoma
- Chesapeake | Echo Energy | Echo | Wheeler
- Investor in life science, technology,
 entertainment, national security, and real estate
- Philanthropist and long-term partner in community development, education, social services, youth athletics, and music, and the Arts
- JV Partner with Alloy Therapeutics (Waltham)



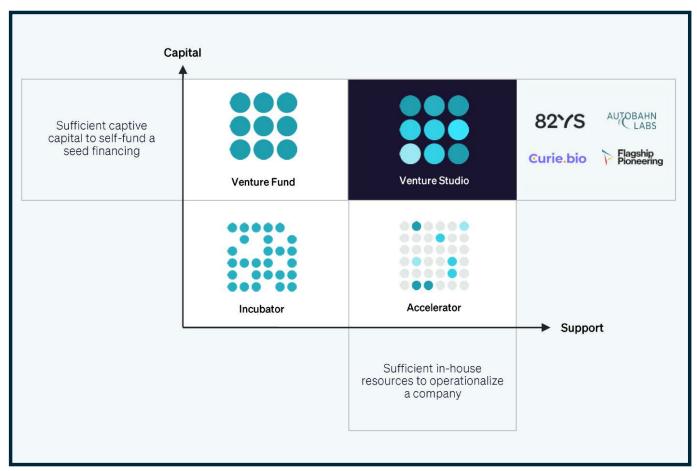
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Echo Is Oklahoma City Based Venture Studio (\$1.3B AUM)

"The Ziggurat"





Echo Building an "Echosystem" - Connective Capital

Connective Capital + Antibodies + Rapid CMC Concepts + Local Clinic + Sick OK = SPEED to Finance, SPEED to Clinic

Day 1 August 17, 2020







Shared Vision: Oklahoma City and its collective stakeholders – including capital- can work together to accelerate the biological drug development process

The First 180 Days of Wheeler

Build Team, Cover Cost with COVID Testing, Plan CDMO

Model CDMO, Pitch Deck, Initiate Seed

Sep 2020

Sep - Nov

October

Oct- Aug

Jan-Mar

May

Welter Nick Mick Mick Corn Muse

Language County of the County of

Training at Phosphorus 9-11 2020

Recruited Team

CLIA License Lab build and validation

Launched product

Wheeler Labs

CDMO Ideation
Colcord Session

Seed Round Start

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Wheeler Bio

Wheeler's Vision, Mission, Core Values

Vision

To transform the CDMO industry for the benefit of patients around the world

Mission

To accelerate the translation of drug discoveries into clinical impact for our clients

Integrity: We strive to be authentic and operate at the highest ethical and quality standards.

Embrace New Ideas: We seek innovative solutions from each other and leverage superior technologies to add value.

Dedication: We wholly commit to a particular course of thought or action and follow through until results are achieved.

Respect for Others: We go out of our way to listen and to be accepting of the experience of others.

Efficiency: We strive to continuously improve our processes, facilities, services, and systems by challenging status quo and eliminating waste.

Play to Win: We give our all to help ensure victory for our clients and to give the patients they serve hope.

Wheeler's Vision, Mission, Core Values

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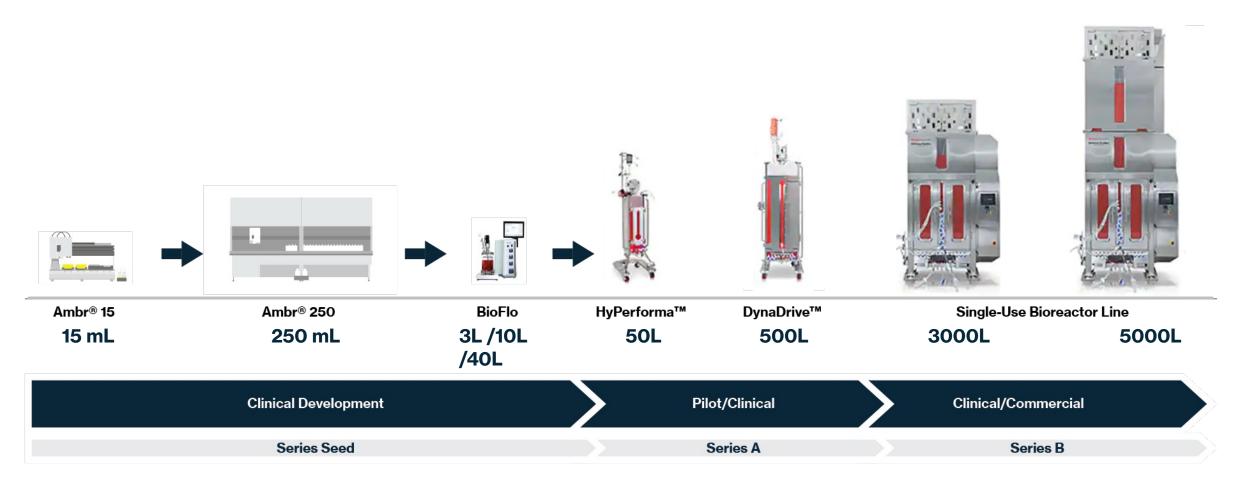
Novel Operating Model

Hub-and-spoke concept to better connect cost-advantaged Oklahoma with drug developers



Scalable Equipment Plan

From benchtop to FIH to pivotal studies, reliably and predictably





Platform Process - Portable CMC™ - Late Phase Process for FIH

Enhances the baseline process, product and CMC knowledge and understanding **Process Validation Bioburden and Endotoxin Controls Developing Analytical Methods Qualified Analytical Methods Validated Methods** Portable CMC™ **Calibrated Equipment Qualified Equipment Knowledge and Understanding** Pre-CGMP **Increasing CGMP Expectations Baseline CMC Knowledge and Understanding** Clinical Development **Preclinical Development Preclinical (Toxicology Studies)** Phase II Phase L Phase III Commercial Discovery **Fully Validated Processes Apply GLPs Apply GDPs Start Applying Start Process Validation** and Facilities **CGMP** Lifecycle Approach

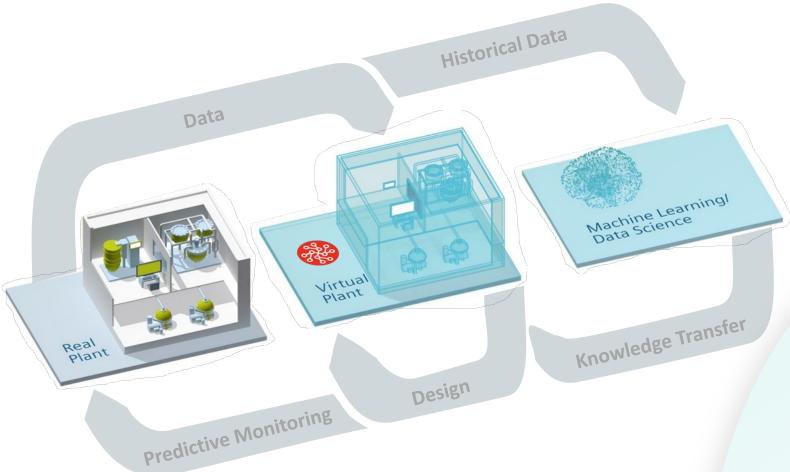


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Digital Twins

Support better manufacturing processes in faster timelines





Michael Sokolov

DataHow

Digital Twins to

- Improve predictability
- Improve insights
- Support better manufacturing processes in faster timelines

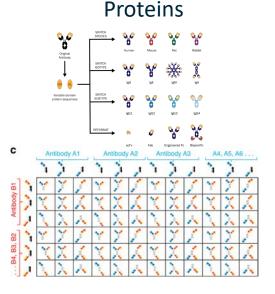
Challenges In Standard Processing, Digitalization, and Prediction

Biology is difficult to model and data points are few (too expensive)

- Lack of N's at scale
- Huge complexities with biological based systems need a variety of tools to solve technical issues
- Process scientists are good practitioners of equipment/process but lack data science expertise
- Expensive data points

Thousands of interactions

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Hundreds of interactions

Process Development



Manufacturing



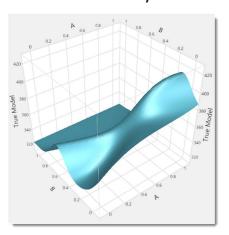
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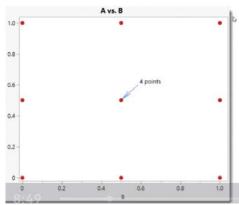
The Prediction Problem

Data is Expensive- Each Experimental Run Costs FTEs

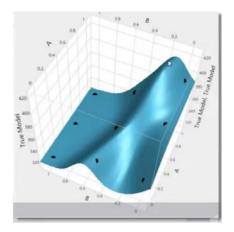
The Actual Response Surface of System



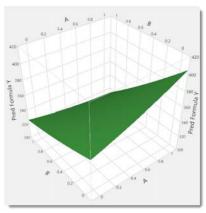
12-run DoE for Full Quadratic Model



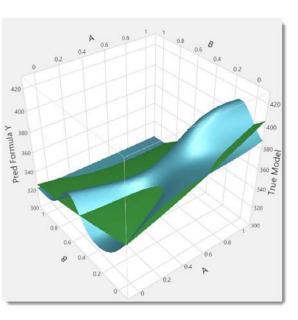
True Response Surface Overlay



Full quadratic fit

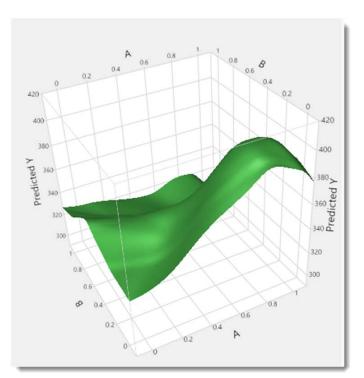


Poor fit

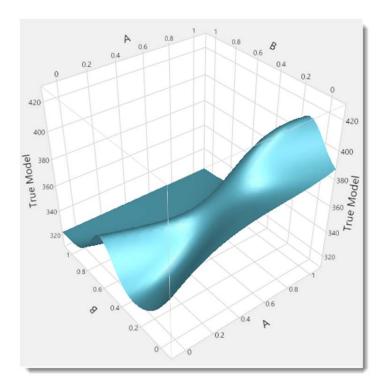


Can Solve Some of The Prediction Problem With Space-Filling Designs & Bootstrapping Models like (SVEM)

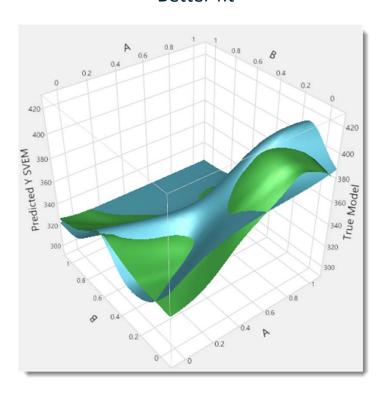
SVEM fit with SFD



True response surface



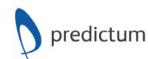
Better fit



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Self-Validating Ensemble Models

P. Ramsey, M. Gaurdard, Predictum Inc

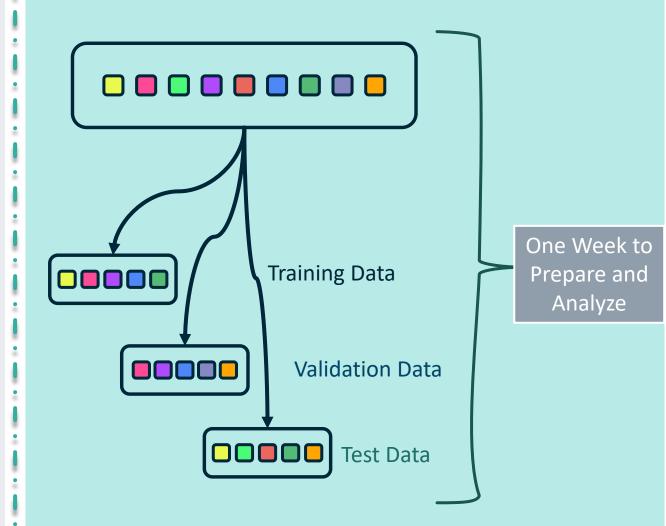




Traditional ML Approach



SVEM-ML Approach



Digital Lab

More data, better insights, efficiency for scientists and clients







Protocols designed in the cloud, from anywhere

e.g. HT cell culture and Protein Purification



Data Integrated from multiple sources

on-line and off-line data, structured, with metadata

Data Served to Modelling Tools at Data Synapses





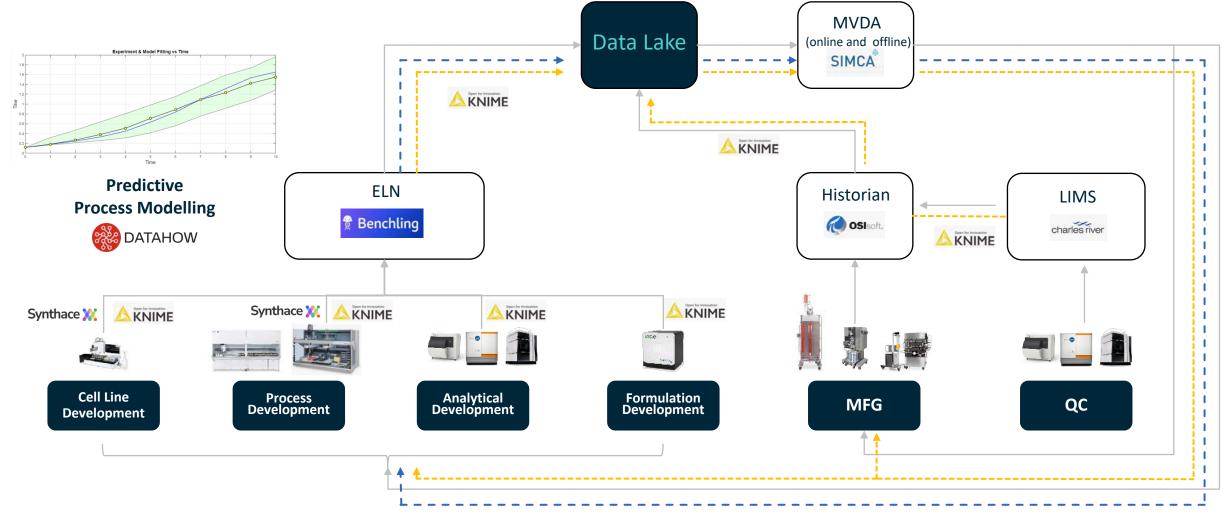
Markus Gershater Synthace





Digital Foundation for CGMP Control Strategy

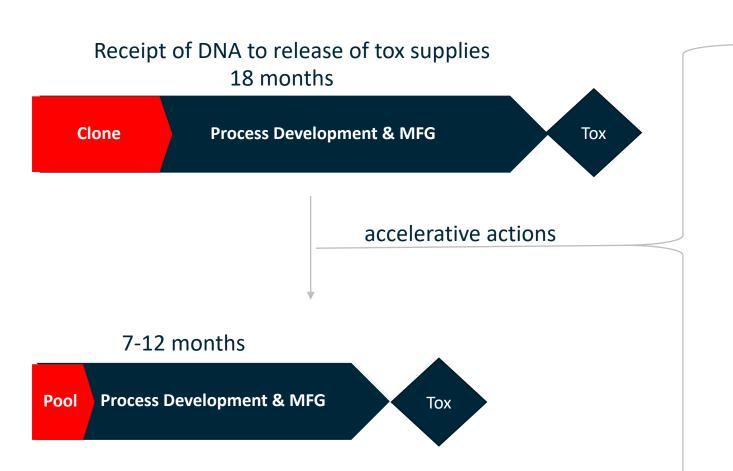
From Vectors to Drug Substance



Transposons for Cell Line Development

Oren Beske ATUM





Mounting Support in 2010s for a Disruptive CMC Concept

AICHE

Accelerating Patient Access to Novel Biologics Using Stable Pool-Derived Product for Non-Clinical Studies and Single Clone-Derived Product for Clinical Studies

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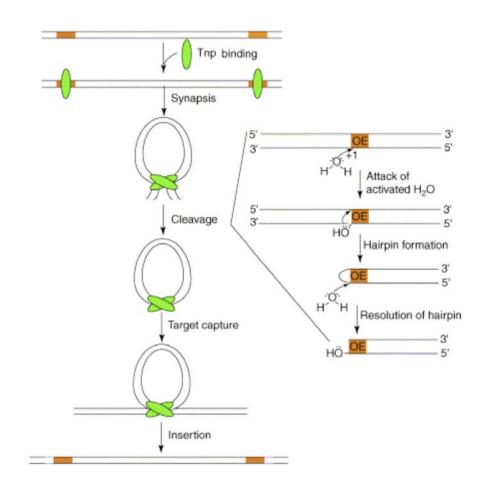
Beyond preclinical research: production of CHO-derived biotherapeutics for toxicology and early-phase trials by transient gene expression or stable pools

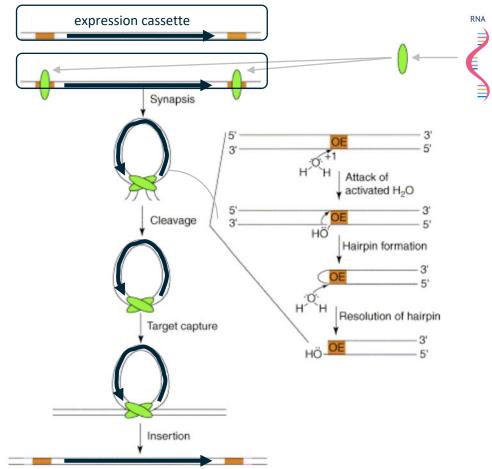
Matthew Stuible¹, Frank van Lier¹, Matthew S Croughan² and Yves Durocher¹



Leap-In Transposase® Platform (ATUM)

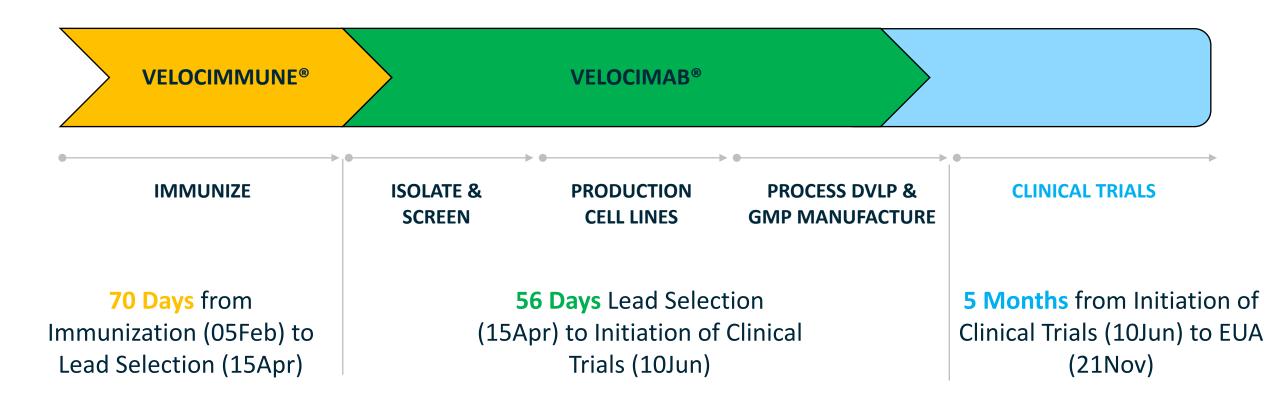
Reliable, Reproducible, and Representative Cell Substrate (pools and clones)





What Has Changed? Pandemic Allowed for Speed-to-FIH Concepts

REGEN-COV™ Rapid response platform at pandemic speed from REGENERON





More Coming Towards "Max Acceleration"

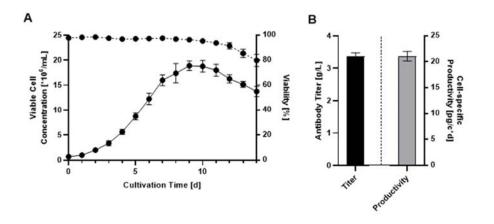
BI platform for two tiered CLD strategy

8 x 2,000 L Batches with Pool



Towards maximum acceleration of monoclonal antibody development: Leveraging transposase-mediated cell line generation to enable GMP manufacturing within 3 months using a stable pool

Valerie Schmieder ^a, Juergen Fieder ^a, Raphael Drerup ^b, Erik Arango Gutierrez ^b, Carina Guelch ^c, Jessica Stolzenberger ^d, Mihaela Stumbaum ^e, Volker Steffen Mueller ^f, Fabian Higel ^f, Martin Bergbauer ^g, Kim Bornhoefft ^h, Manuel Wittner ⁱ, Petra Gronemeyer ^j, Christian Braig ^k, Michaela Huber ^l, Anita Reisenauer-Schaupp ^m, Markus Michael Mueller ⁿ, Mark Schuette ^o, Sebastian Puengel ^a, Benjamin Lindner ^a, Moritz Schmidt ^a, Patrick Schulz ^a, Simon Fischer ^a, ^e



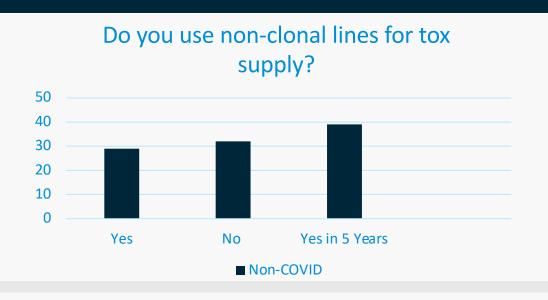
Large-scale manufacturing of mAb1 in the 2000 L scale using a stable CHO pool cell line generated via transposase-mediated STI. Viable cell concentration, viability, productivity of 8 x 2000 L scale batches.

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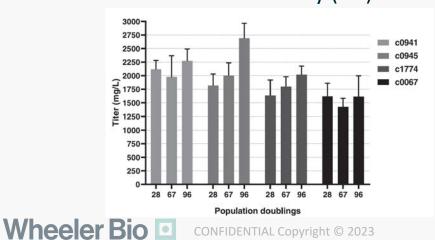




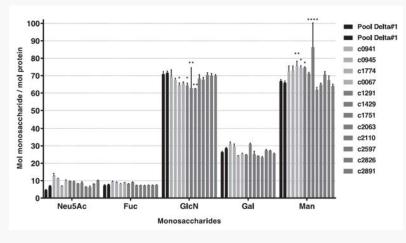
Stable Bulk Pools Are Gaining Momentum

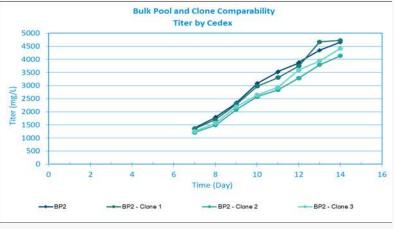


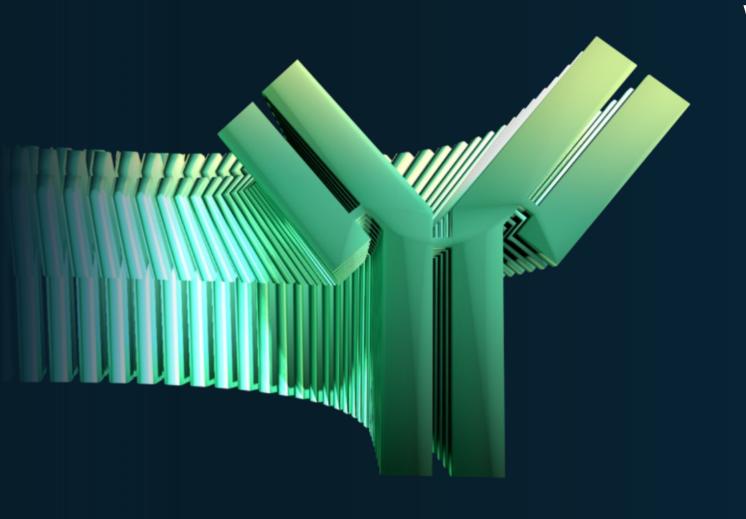
Genetic Stability (ref)



Consistent PQs across stable cell line pools stable cell lines (ref)







Capabilities

Wheeler Bio Facilities

Research, development, and clinical manufacture*



Boston Research Center

1,200 sq. ft.



Oklahoma City Development Center

10,000 sq. ft.



Oklahoma City Manufacturing Center

35,000 sq. ft.

Molecular Biology:	Vector Design, Engineering, and Validation
Transient Expression:	ExpiCHO and Expi293
Stable Cell Line Generation:	Horizon CHOSOURCE™ with TNT Transposon Technology & ATUM Leap-In® Transposon Technology with miCHO™ Cell Line
HTP Protein Sciences:	HTP Protein Expression, Purification, and Analytics
Advanced Expression Systems	Proprietary

Transient Expression:	ExpiCHO and Expi293	
Stable Cell	ATUM Leap-In® Transposon Technology with	
Line	miCHO™ or Horizon CHOSOURCE™ Cell Lines	
Development:	Stable Bulk Cultures (SBC) and Clone Isolation	
Process Development:	High Throughput Upstream Cell Culture (optimization, intensification, characterization) & Downstream Purification, Process Dev., Scale-up, and Tech. Transfer	
Analytical Development:	High Throughput Protein Analytics supporting PD, Analytical Test Method Dev., Qualification, and Tech. Transfer	
Formulation Development:	5 51	
Preclinical Material Supply:	Standardized Wheeler Process, Analytical, and CoT. From SBCs or Clones. Lead Candidate Selection through Tox	

Master Cell Banking:	Two (2) Grade C MCB Suites with Automated Vialing Capabilities
Solution Preparation:	Grade C Solution Prep. Suite with Singleuse Mixers for Media and Buffers
Clinical Production Suites	Two (2) Grade D Ballroom Suites with : Fully Closed SUT Process Equipment
QC Testing and Release:	RightSource sM - For Raw Materials, DS/DP Testing, Stability, and Environment Monitoring

Engineering:

Custom Development Services

State-of-the-art CMC development laboratory with well integrated digital solutions



Cell Line
Development



Process

Development



Analytical Method Development



Formulation Development



Preclinical Material Supply



Clinical Material Supply



Reliable, reproducible, & representative materials from standard process supporting four (4) lead molecules

Module	WP	Purpose	Description
Lead	WP 1	Platform access point	DNA to SBC Bank + CQA Test on 4 Lead Molecules
Selection	WP 2	Formulations & Manufacturability	SBC to CPP Test at 10 L on 4 Leads Molecules (Manufacturability)
	WP 3	Single-cell cloning	SBC to SBC-DCB (non-CGMP)
Clone Selection	WP 4	MCB prep from clone	DCB to MCB (CGMP)
	WP 5	Clone stability	MCB to 60+ GEN (Cell Substrate Stability per ICH Q5D)
	WP 6	Rapid tox materials	SBC/MCB to TOX (40L) (SBC is an accelerated option)
СОМО	WP 7	Clinical materials	MCB to RDS (released CGMP drug substance)
Selection	WP 8	Drug product	Managed Outsourcing
	WP 9	Prep for scale-up and TT	RFP and Tech Transfer for Pivotal Trial Material Supply





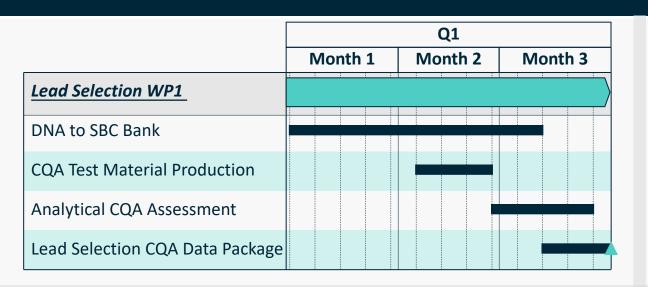


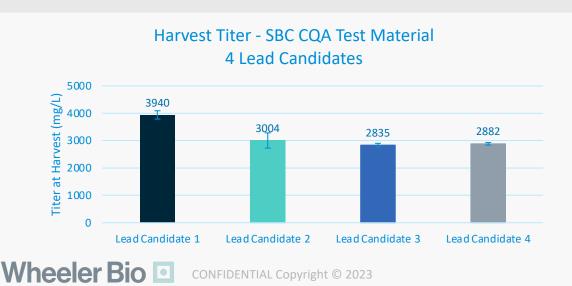
Portable CMC™ - Lead Selection Module

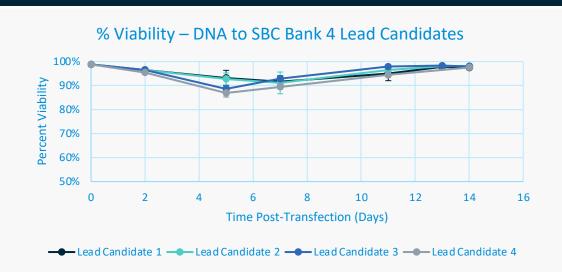
Module	WP	Purpose	Description
Lead	WP 1	Platform access point	DNA to SBC Bank + CQA Test on 4 Lead Molecules
Selection	WP 2	Formulations & Manufacturability	SBC to CPP Test at 10 L on 4 Leads Molecules (Manufacturability)



Prepare Stable Bulk Cultures & Representative Materials With Supporting Analytics For Lead Candidate Selection



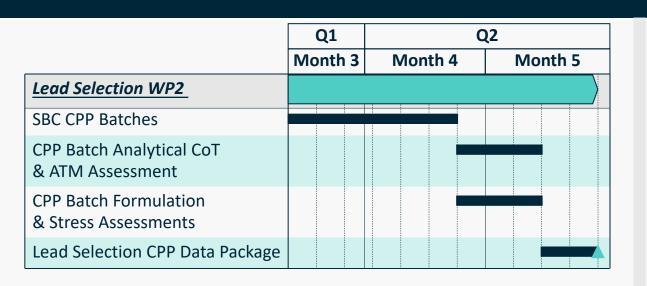


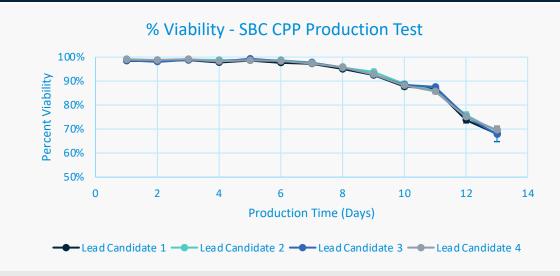


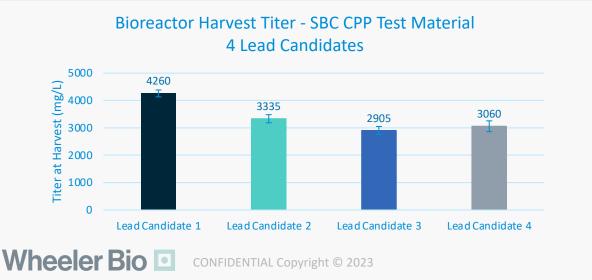
Quality Attribute	Product/Process Characteristic	Assay Type
Quantity/Strength	Amount/Concentration	Absorbance at 280 nm (A280)
Activity/Identity	Target Antigen Binding	Bio-layer Interferometry (BLI)
Quality	Purity - Size Variants	Capillary Electrophoresis-SDS (non-reduced/reduced) & Size Exclusion Chromatography (SE-UPLC)
Quality	Purity - Size Variants	CE-SDS (reduced)
Quality/ Characterization	Purity - Charge Heterogeneity	Capillary Isoelectric Focusing (cIEF)
Characterization	PTM - N- Glycans	Labelled, Released N-Glycan Profile by UPLC
Characterization/ Identity	Primary Structure/ Molecular Weight	Intact Mass by LC/MS (Non-reduced Glycosylated, Non-reduced De-Glycosylated, Reduced Glycosylated, Reduced De-glycosylated)
Characterization/ Identity	Primary Structure PTMs	Peptide Mapping by LC-MS/MS
Stability	Melting Temperature	Dynamic Light Scattering (DLS), Static Light Scattering (SLS), Intrinsic Fluorescence
Stability	Aggregation Temperature	DLS, SLS, Intrinsic Fluorescence
Safety	Endotoxin	Limulus Amebocyte Lysate (LAL)



Verify Process Control & Generate Representative Materials for Preclinical Testing







	Upstream In-Process Analytical Titer pCO2		Downstream In-Process Analytical	Analytical Certificate of Test	
			Amount/Concentration	Strength – Amount/Concentration	Safety – Residual DNA
	Viable Cell Density pO ₂		Purity - Size Variants	Potency – Target Antigen Binding	Safety – Residual HCP
	Viability	Sodium	Purity - Residual DNA	Purity – Size Variants	Safety – Residual Protein A
	Glucose	Potassium	Purity - Residual HCP	Purity – Charge Heterogeneity	Safety – Endotoxin
	Lactate	Calcium	Purity - Residual Protein A	Characterization – Primary Structure/N- Glycans	рН
	Glutamine	Osmolarity	Unit Operation Recoveries (Step Yields)	Characterization – Primary Structure PTMs	Conductivity
	Glutamate	Bicarbonate	Process Recovery (Overall Yield)	Identity – Primary Structure/Molecular Weight	Appearance
	Ammonium	CO ₂ Saturation		Identity – Peptide Map Fingerprint	
	рН	O ₂ Saturation			





Portable CMC™ Clone Selection Module

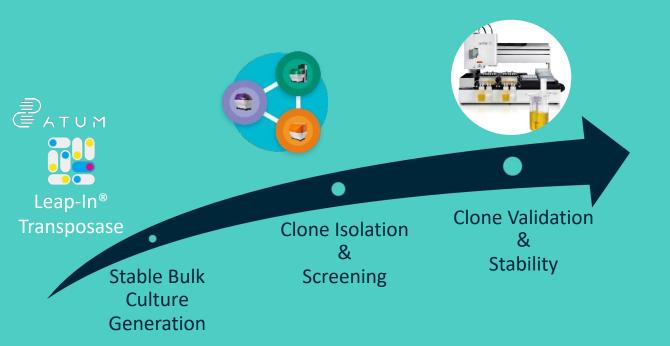
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	WP 3	Single-cell cloning	SBC to SBC-DCB (non-CGMP)	
Clone Selection	WP 4	MCB prep from clone	DCB to MCB (CGMP)	
	WP 5	Clone stability	MCB to 60+ GEN (Cell Substrate Stability per ICH Q5D)	





WP 3 Single-Cell Cloning

Transposon-based systems drive optimal lead selection & enables reliable, reproducible, representative stable bulk cultures



Cell Sorting, Transfection, and Imaging Technologies

- Wolf® Cell Sorter
- Neon™ Transfection System
- Echo Revolve 4 Upright and Inverted Microscope

Solentim Cell Line Development Ecosystem:

- VIPS™ high efficiency multi-tasking single cell seeder
- Cell Metric[®] high contrast whole-cell imager
- ICON™ productivity analyzer
- STUIDIUS™ data management system

High-Throughput

- Ambr[®]15 and Ambr[®]250
- BioFLO 320 (3cc 50cc BioBLU vessels)

Process Analytics

- Vi-Cell™ XR Cell Viability Analyzer
- Cedex Bio Analyzer
- Integrated and Standalone BioProfile® FLEX2
- Octet® RH16







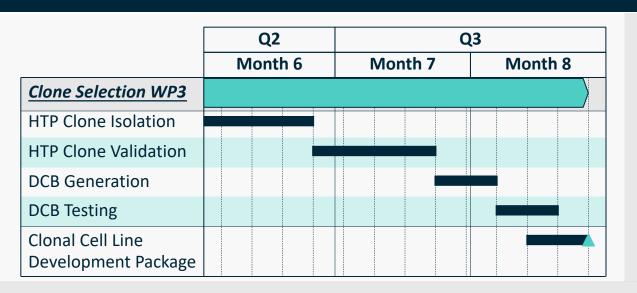


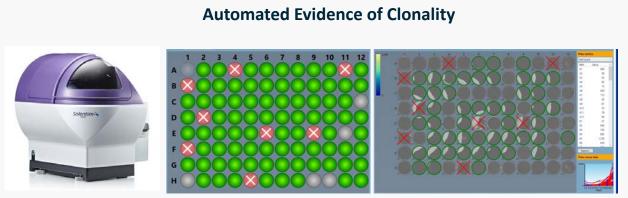






Automated Single Cell Isolation, Evidence of Clonality, Titer, Viability, and Productivity Ranking to Select Top Clones







Tracking Top Performing Clones During Outgrowth

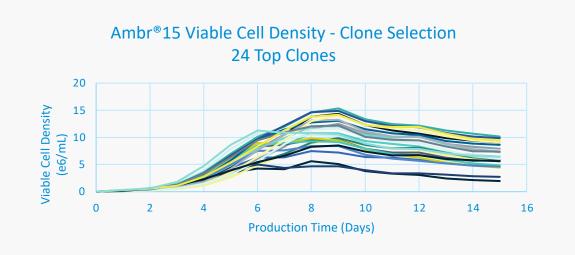


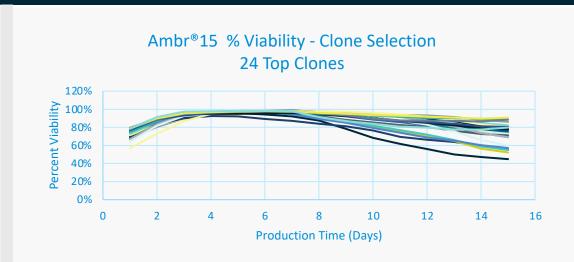


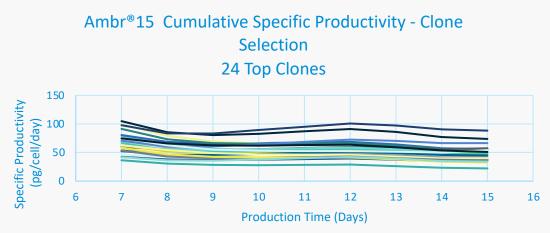


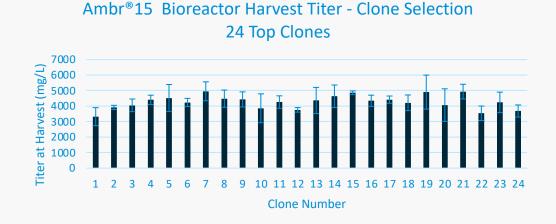


High Throughput Clone Validation with Bioreactor Process Analytical Monitoring and Productivity Assessment



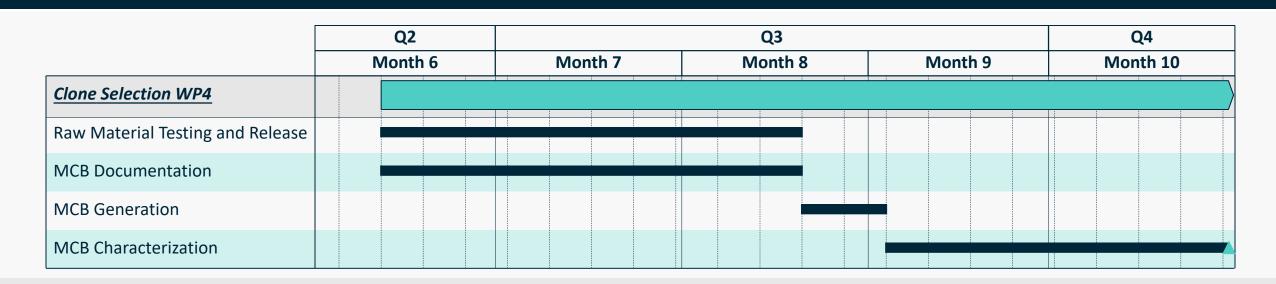








Master Cell Bank (CGMP) Generation, Characterization, and Release

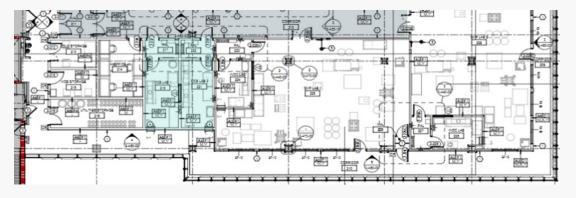


Automated Master Cell Bank Vialing





Two (2) Grade C Master Cell Banking Suites





Master Cell Bank (CGMP) Cell Substrate Stability 60 Generations per ICH Q5D

	Q3	Q	4
	Month 9	Month 10	Month 11
Clone Selection WP5			
Cione Selection WPS			
MCB Cell Substrate Stability			
Wieb cell substrate stability			



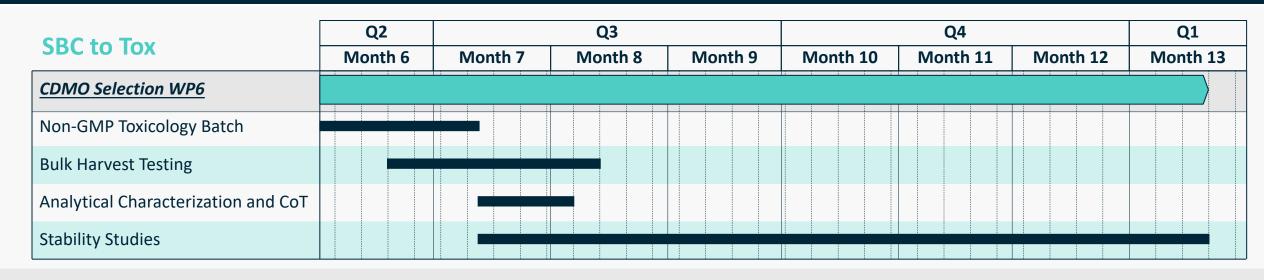


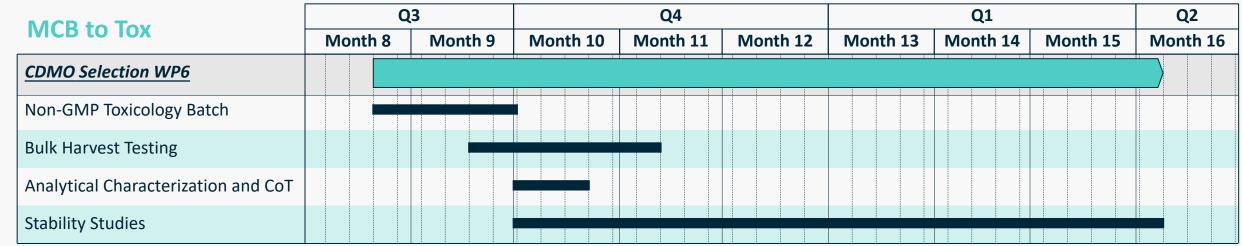


Portable CMC™ CDMO Selection Module

Module	WP	Purpose	Description	
	WP 6	Rapid tox materials	SBC/MCB to TOX (40L) (SBC is an accelerated option)	
СОМО	WP 7	Clinical materials	MCB to RDS (released CGMP drug substance)	
Selection	WP 8	Drug product	Outsourcing partner	
	WP 9	Prep for scale-up and TT	RFP and Tech Transfer for Pivotal Trial Material Supply	

Use of Stable Bulk Cultures Accelerates the Timeline to Initiate Toxicology Studies By 3 Months







Summary of Wheeler Bio

Solving for Translation	Agile, boutique CMC development business embedded in venture studio	
Experienced Leadership	Seasoned development team with CMC and regulatory experience	
Aligned Culture	 Every employee is a shareholder with shared vision, mission, and core values Purpose-built business to solve for customer experience 	
Technology Stacked	 Leap-In Transposase® CLD Platform Synthace® Experiment Platform Ambr® 250 Digital Twin (DataHowLab) DynaDrive Single-Use Bioreactors (ThermoFisher) 	
Compressed Workflow	 CRO Integration Portable CMC™ Platform RightSource™ Insourcing QC Solution 	



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Wheeler Bio

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Thank you!

