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INDUSTRY FOCUS

Biotechnology

An exclusive collection featuring top-tier articles, visionary experts, and essential industry insights

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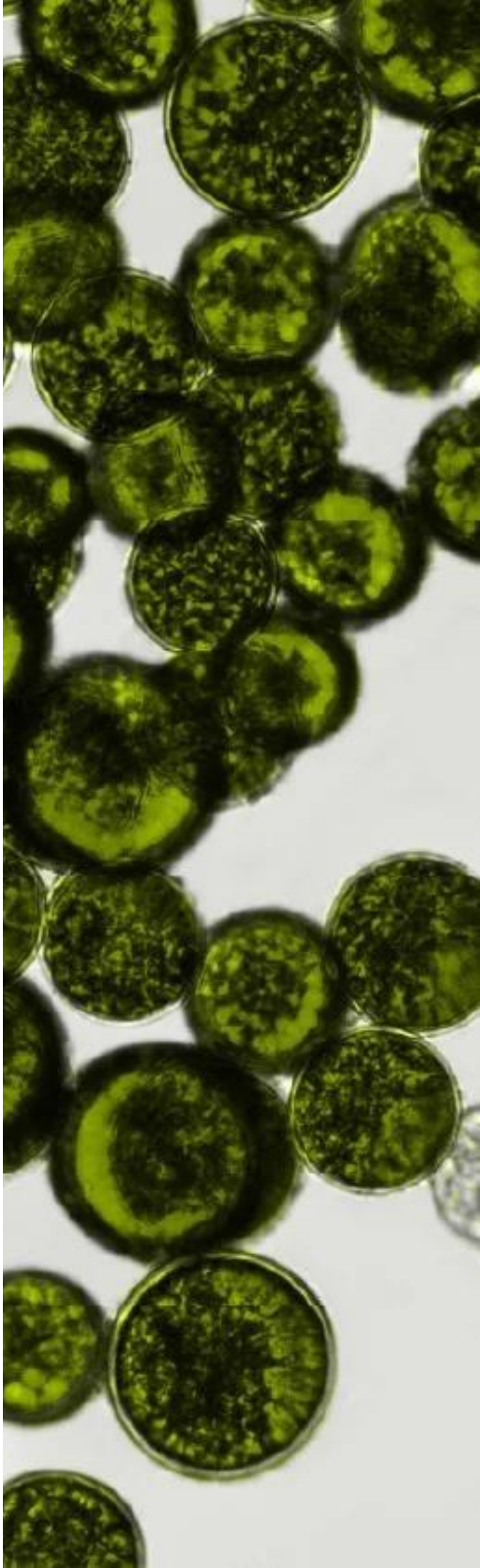

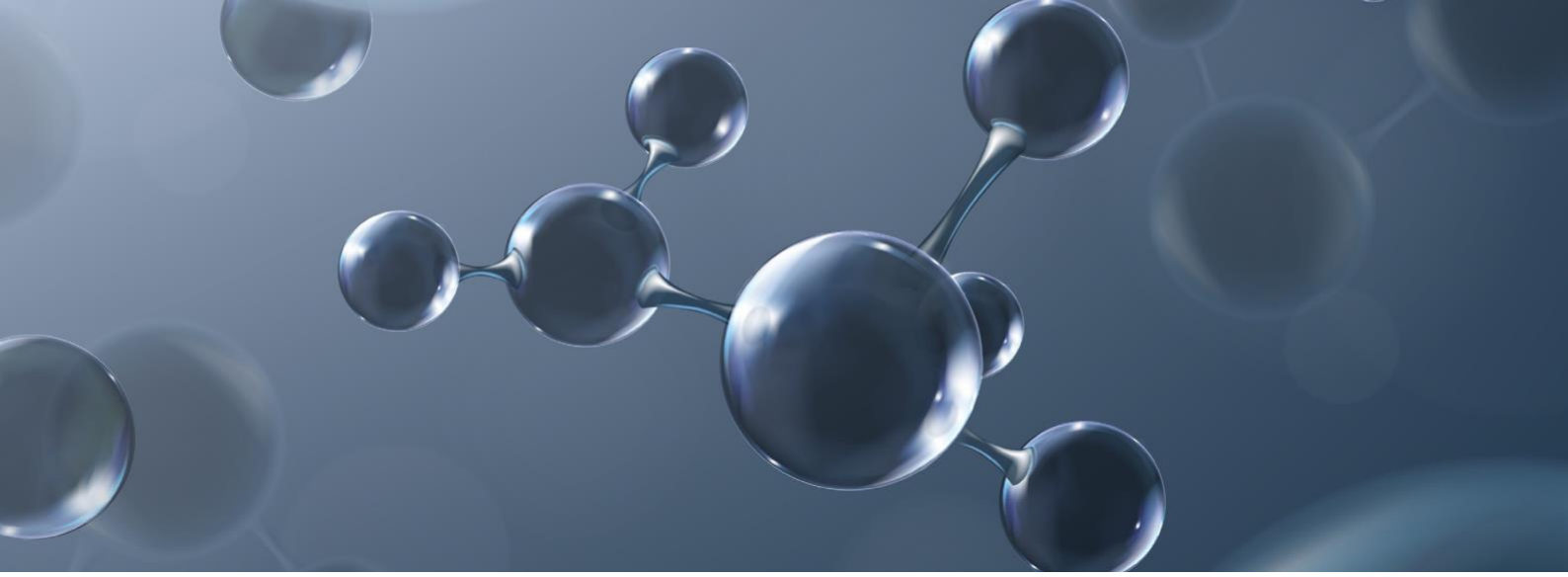

Foreword

Welcome to the latest edition of our Industry Focus eBook, where we explore the dynamic and fast-evolving world of biotechnology. As scientific discovery continues to accelerate, biotechnology remains at the forefront of innovation, transforming healthcare, pharmaceuticals, materials science, and environmental sustainability in remarkable ways.

From advanced bioprocessing systems to revolutionary gene-editing technologies, the biotechnology sector is driving solutions that have the potential to reshape modern medicine and improve lives on a global scale. Automation and precision are becoming increasingly central to research and manufacturing, enabling scientists to streamline workflows, optimize cultivation strategies, and generate high-quality analytical data with greater efficiency than ever before.

This edition also highlights the growing influence of nanotechnology in biopharma, where lipid nanoparticles, exosomes, and smart nanocarriers are opening new pathways for targeted drug delivery and personalized treatment approaches. Alongside these advances, emerging sensor technologies are helping to create more responsive and individualized therapeutic strategies, supporting the continued shift toward precision medicine.

Breakthroughs in genetic engineering continue to capture global attention, particularly with innovations in CRISPR technology that are expanding possibilities in cancer treatment and tackling one of healthcare's most pressing challenges: antibiotic resistance. At the same time, biotechnology is extending beyond traditional medical applications through the development of biomaterials that support tissue regeneration, postoperative care, and even sustainable photonic technologies derived entirely from natural materials.

The importance of sustainability and efficiency also remains a key theme throughout this collection. Advances in fermentation and oxygen transfer technologies are improving industrial bioprocesses, while eco-friendly biomaterial innovations demonstrate how biotechnology can contribute to a more sustainable future without compromising performance or scientific ambition.

Together, the articles in this eBook showcase the extraordinary breadth of biotechnology today. They reflect the creativity, collaboration, and ingenuity driving progress across academia and industry alike.

As you explore these pages, we hope you are inspired by the discoveries, technologies, and ideas shaping the future of biotechnology and the many possibilities that lie ahead.

Building an automated platform for bioprocess development and downstream analytics with the BioXplorer 100

Modern bioprocess development strategies are calling for increased automation and high-throughput experimentation, in turn placing a greater demand on the technology. To match the ongoing progress being made in genetic engineering, a diverse range of microbial hosts have been developed as the foundations for creating a great number of natural products.

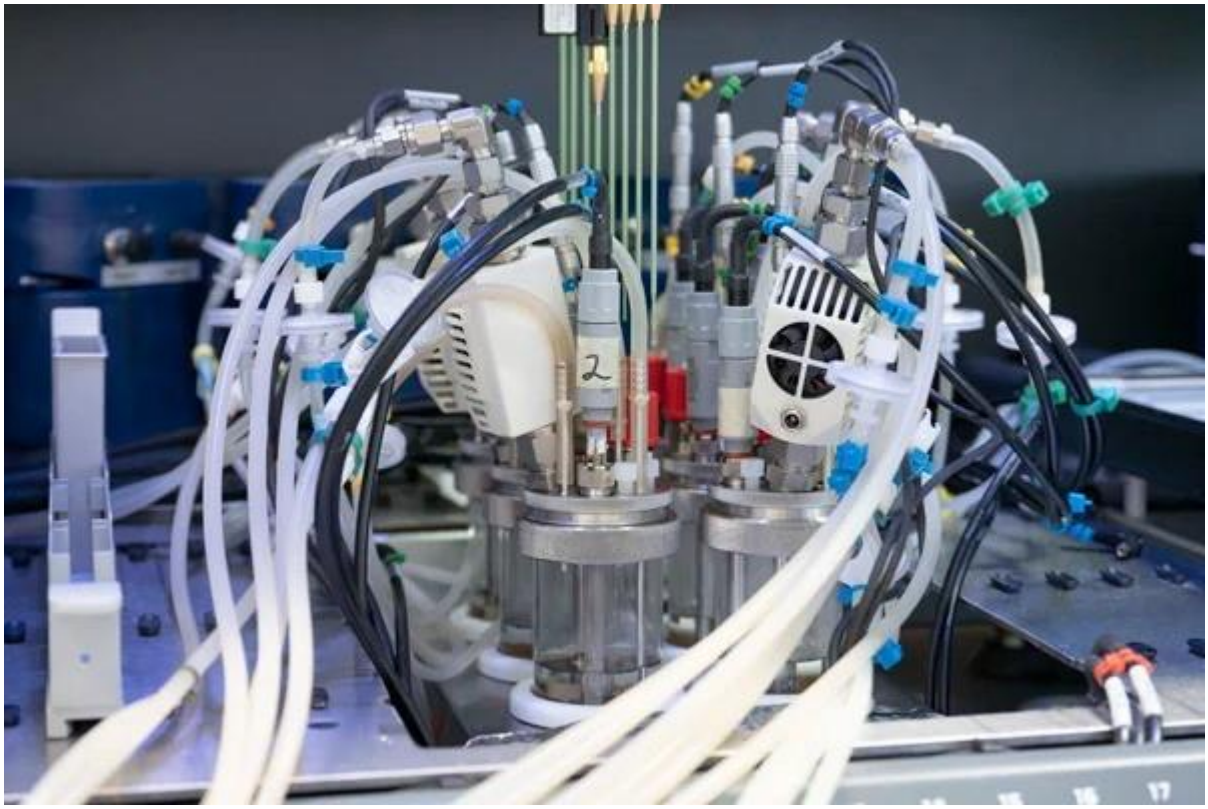

Image Credit: H.E.L Group

However, developments can be time-intensive, taking several days to complete, as these microbial hosts are pushed to their metabolic limits in batch, fed-batch, or continuous fermentations (chemostats, turbidostats, perfusion, or auxostats). Production strategies respond by limiting human interference through automation, maximizing rates, and minimizing working time as a result.

These demands are well documented at the Chair of Bioprocess Engineering at Technical University of Berlin (TU Berlin), and resulted in the development of a completely automated platform for microbial bioprocesses in the KIWI-biolab, in which H.E.L's BioXplorer 100 serves as the operational core.

Integration of the BioXplorer 100 into a fully automated lab environment

The KIWI-biolab research focuses on establishing the model-based automation of bioprocesses and analytics: intelligently linking hardware with automation plays a central role in achieving this goal.

The pursuit of these aims led the KIWI-biolab to construct its BioXplorer Facility, an automated platform where H.E.L's BioXplorer 100 serves as the central component. This system is capable of running continuous fermentations for up to seven days.

This platform considerably reduces manual intervention, enhances reproducibility, and delivers high-resolution data across a diverse range of experimental conditions, while cultivating diverse microbial strains, predominantly Pichia pastoris and *Escherichia coli* (*E. coli*).

The BioXplorer Facility's abilities have been used across a wide range of projects, including cultivations for targeting vaccine antigens and antibody production, as well as enzyme synthesis, such as glucose oxidase.

To meet these objectives, the fed-batch fermentation strategies used at the KIWI-biolab demand stringent controls of liquid additions. This is where the BioXplorer 100's liquid-feed module has been instrumental, as continuous and pulse-based feeding plans supply an assortment of solutions (acid and base for pH control, glucose or glycerol-based media, methanol, etc.) during fermentations, which can last for up to 50 hours.

Similarly, many of these bioprocesses include steps in which the temperature fluctuates, typically between 20 and 37 °C. Achieving control of cultivation conditions at temperatures lower than room temperature is easy, thanks to the BioXplorer 100's compatibility with Huber Minichiller. Moreover, the parallel reactor platform incorporates off-gas analysis via BlueSens sensors.

The KIWI-biolab has also integrated the BioXplorer 100 into a robotic laboratory environment that supports dynamic fermentation and analytical workflows. To facilitate automated liquid sampling, a Tecan Freedom Evo 150 liquid-handling station was used. This allowed for the addition of supplementary pulses, among other solutions, such as IPTG to introduce plasmids and induce gene expression in engineered strains, or magnesium supplements to the cultures.

Image Credit: H.E.L Group

Image Credit: H.E.L Group

Integration with advanced and high-throughput analytical technologies

Image Credit: H.E.L Group

Reliable analytical data is just as important as fermentation automation in achieving high-quality bioprocesses. At KIWI-biolab, the mobile robotic lab assistant, MiLA, supports sample transfers to high-throughput analytic platforms. The liquid samples collected during the cultivation phase, using the Tecan Freedom Evo 150 liquid-handling station, are analyzed using sophisticated analytical techniques.

For instance, the Cedex Bio HT measures process-relevant parameters such as glucose, glycerol, acetate, magnesium, and ammonia, while the two-dimensional HPLC QTOF determines concentrations of other substrates and metabolites in the culture medium.

KIWI-biolab researchers are better equipped thanks to this automated infrastructure and tightly integrated workflow, which can produce high-resolution data. This allows for a better understanding of strain metabolism and related bioprocesses, supporting systematic process optimization centered on data interpretation rather than conventional manual sampling and offline measurements.

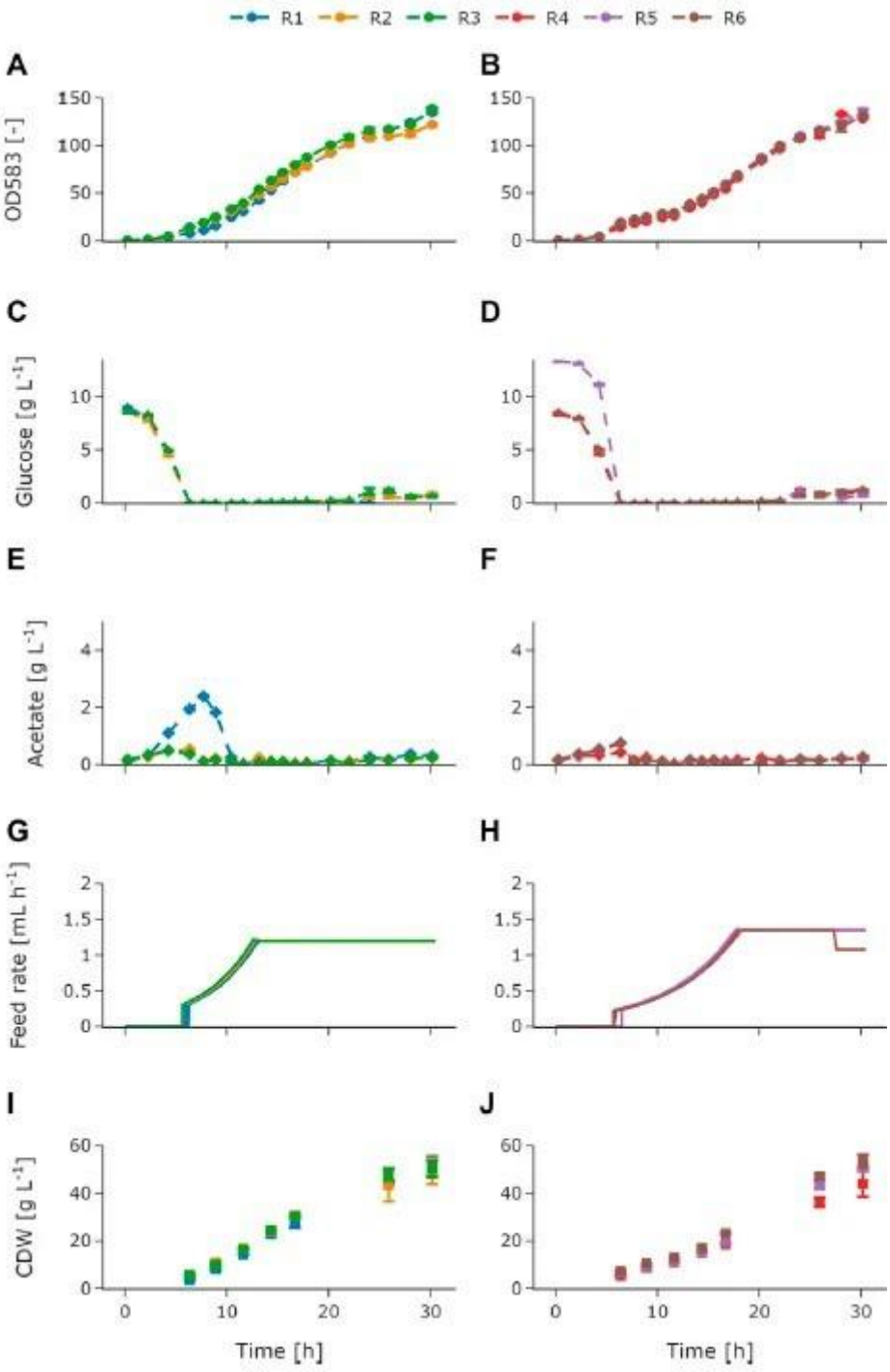

Image Credit: H.E.L Group

Adaptive platform development through technical support and customization

The H.E.L Group's experience with automated systems was a key driver for the KIWI-biolab during platform development. The BioXplorer 100 was easily integrated into the existing laboratory infrastructure, while seamlessly delivering a complete solution.

By integrating H.E.L's high-throughput automated fermentation system, with its automated liquid-handling station and high-throughput analytics equipment, members of the KIWI-biolab team have considerably extended the platform's functionality. This, in turn, has boosted screening eficiency across a diverse range of experimental conditions for microbial bioprocesses.

The support the H.E.L Group technical team provides during and after commissioning, along with bespoke software development and customized function extensions, enables the platform to adapt to the challenges posed by evolving research methodologies. The system can therefore evolve alongside the lab's research goals.

As bioprocess research continues its transition toward automation and data-driven decision making, the KIWI-biolab's case study demonstrates how a well-managed, blended experimental platform can advance and accelerate microbial process development and facilitate scalable, eficient research operations.

About H.E.L Group

H.E.L develops and manufactures innovative scientiic instruments and software designed to optimize the eficiency, safety, and productivity of key processes in chemistry and biology applications.

The H.E.L team of 70 includes highly skilled process and software engineers, based at their extensive research and manufacturing facilities in the UK, as well as sales and support ofices around the world.

H.E.L has a long history of solving complex challenges for customers. Since 1987, the Company has worked with businesses and laboratories globally, providing proprietary automated solutions for the pharma, biotechnology, chemical, battery, and petrochemical sectors.

We continue to expand the reach of our products and services to further support and enable R&D and process optimization across Europe, the US, China, and India.

H.E.L is accredited with ISO 9001: 2015

Our mission

To help create a healthier, sustainable, safer world for everyone.

Our vision

We equip scientists with the right tools and knowledge to develop safe, eficient new processes and molecules that beneit the world and its population.

Our values

Insightful through experience. With over 30 years of in-house expertise and experience, we know how to overcome a challenge

Collaborative by design. Dedicated to listening, learning, and working closely with industry experts, we empower others to fulill potential

Tenacious in spirit. Always looking for new and innovative solutions, we don’t stand still; instead, we are focused on reaching the next success

Proud of progress. Fueled by our ability to make a real difference, while celebrating the achievements of others

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New CRISPR tool selectively cuts tumor DNA while sparing healthy cells

Cancer cells excel at evading detection, but subtle chemical differences set them apart from healthy cells. Now, a team of scientists from Wageningen University & Research and Van Andel Institute has identiied a way to exploit this distinction. Using a variant of CRISPR, a modern tool for editing DNA, they distinguished tumor DNA from healthy DNA and selectively cut only the former. The study, published today in *Nature*, is an early but promising step toward a cancer therapy that targets and destroys tumor cells with high precision.

The new method relies on methyl groups, small chemical tags attached to DNA that regulate whether genes are on or off. This process, called DNA methylation, is altered in cancer cells and can act as a molecular "ingerprint" that differentiates malignant cells from healthy ones.

Precision gene editing with ThermoCas9

The team conducted the study using ThermoCas9, a CRISPR variant discovered in bacteria several years ago by Wageningen's John van der Oost, Ph.D. Like other CRISPR systems, researchers can program ThermoCas9 to locate and cut speciic sections of DNA within a cell. VAI's Hong Li, Ph.D., and her lab analyzed ThermoCas9's structure and found that it can distinguish between unmethylated and methylated genes.

The team then introduced ThermoCas9 into human cells grown in culture dishes: healthy cells in one set of dishes and tumor cells in another set. This approach worked: ThermoCas9 cut DNA in tumor cells while leaving healthy DNA intact. The system therefore proved capable of detecting the subtle chemical differences between healthy and tumor cells and acting on them.

> *"ThermoCas9 is the irst CRISPR-associated enzyme to respond to differences in the most abundant type of DNA methylation in human and other eukaryotic cells. This means we now have a system that we can target speciically toward tumor cells."*
>
> *John van der Oost, Ph.D., Wageningen University & Research*

The study represents the irst time a CRISPR-based method has relied on methylation to target human cancer cells.

"ThermoCas9 uses methylation like an address to precisely target cancer cells while leaving

healthy cells untouched," Li said. "The indings could be a game changer."

A precise molecular it

The explanation for ThermoCas9's selective behavior lies in the way it binds to DNA. Before a CRISPR system cuts DNA, it must irst attach to a short recognition sequence next to its target, known as the PAM (Protospacer Adjacent Motif). ThermoCas9 is unique in that its PAM sequence includes a human methylation site, meaning it can contain a methyl group.

"The CRISPR system binds very precisely to this recognition code," Van der Oost explained.

Compare it to a screwdriver that its perfectly into a matching screw head. If there is a protrusion inside the groove, the screwdriver no longer its, nor is it capable of performing its job. In the same way, a methyl group disrupts the it between ThermoCas9 and the DNA, preventing binding and leaving the DNA sequence untouched.

"ThermoCas9 is a perfect example of the value of fundamental research; you have to know how these individual pieces work together," Li said. "We used biochemistry and structural biology to discover a mechanism that we one day hope will lead to more precise, effective cancer treatment."

Steps toward clinical research

There is still a long way to go before the technology can be translated into a potential cancer treatment. The new study demonstrates selective DNA cleavage but does not yet show that this effect can kill tumor cells. The next step focuses on damaging tumor DNA su ciently to trigger cell death.

Aberrant methylation patterns also play a role in many other diseases, including childhood cancers such as neuroblastoma and autoimmune disorders. In the future, ThermoCas9 or a similar CRISPR tool may evolve into a versatile molecular strategy that recognizes diseased cells by their chemical "signature" and selectively disables them.

Source:

Van Andel Institute (VAI)

Journal reference:

Roth, M. O., *et al.* (2026). Molecular basis for methylation-sensitive editing by Cas9. *Nature*. DOI: 10.1038/s41586-026-10384-z. https://www.nature.com/articles/s41586-026-10384-z

Emerging Nanoplatforms in Biopharma: LNPs, Exosomes, Smart Nanocarriers

Nanoplatforms have the capacity to turn biologics into real medicines by protecting payloads, steering them to the right cells, and making advanced therapies manufacturable.

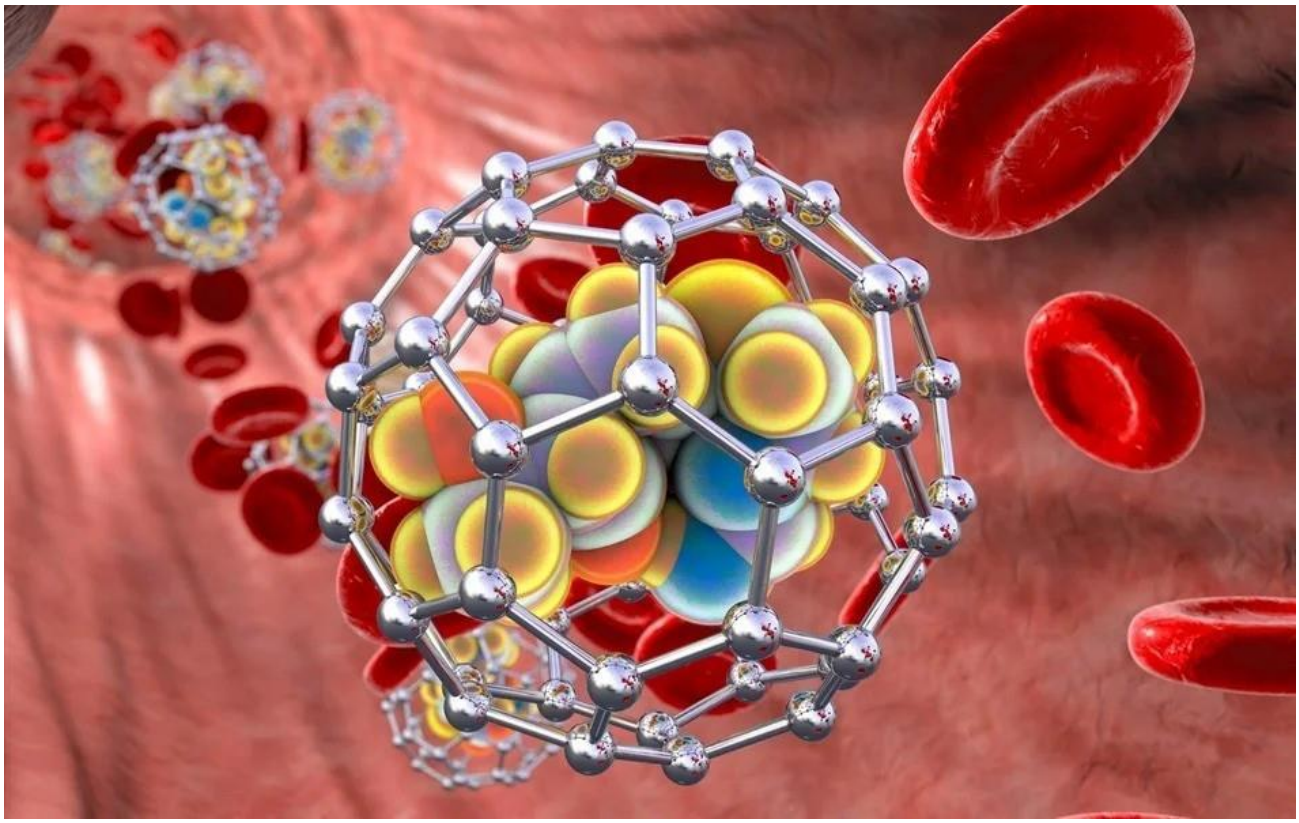

Image Credit: Kateryna Kon/Shutterstock.com

At the same time, only a small fraction of nanomedicines successfully translate to the clinic, making it essential to understand which platforms matter now, where they are being applied, and what it takes to move from benchtop innovation to scaled manufacturing.[1]

Biopharmaceutical pipelines are increasingly dominated by monoclonal antibodies, RNA therapeutics, viral vectors, and gene-editing systems, which are potent but often fragile and hard to deliver eficiently.[2]

Nanoplatforms address this by protecting labile cargos, improving pharmacokinetics, and enabling targeted delivery to tissues or cell subsets, thereby expanding the therapeutic index of advanced biologics.[2]

Several converging trends make this especially important now.

Post-pandemic momentum in lipid nanoparticle (LNP) and mRNA vaccines has validated

nanoscale carriers at a global scale and accelerated regulatory familiarity.

Growing interest in gene editing, cell reprogramming, and immuno-oncology requires tools that can safely deliver nucleic acids and proteins into speciic cells *in vivo*.

Pressure to improve manufacturability and cost of goods for complex biologics is pushing the ield toward modular, scalable nanoformulation strategies that can be reused across programs.[2]

Types of Emerging Nanoplatforms

Nanoplatforms can be thought of as a small number of families with distinct strengths and constraints.

- LNPs are the most clinically mature nanocarrier family for nucleic acids.
- Polymeric systems excel in controlled-release and long-acting formulations - but can face heterogeneity challenges.
- Inorganic/hybrid carriers enable theranostics but must prove clearance and long-term safety.

Lipid-Based Nanoplatforms

Lipid-based systems, including classic liposomes, solid lipid nanoparticles, and modern LNPs, are now the most clinically mature nanoplatforms for biopharmaceutical delivery.

They form self-assembled structures that can encapsulate small molecules, peptides, proteins, and nucleic acids, offering biocompatibility, tunable size, and well-characterized manufacturing routes.[3]

Key applications of lipid-based nanoplatforms include mRNA vaccines and RNA therapeutics, where ionizable LNPs protect RNA and promote endosomal escape for eficient cytosolic delivery, as well as delivery of siRNA and antisense oligonucleotides to the liver and other tissues using tailored lipid compositions and targeting ligands.[3]

They also enable improved formulations of protein biologics and small molecules through liposomes and lipid-like nanocages that control release, reduce immunogenicity, and enhance tumor accumulation.[3]

Polymeric and Inorganic Nanoplatforms

Polymeric nanoparticles, micelles, dendrimers, and nanogels are a more flexible platform for design. They can incorporate responsive chemistries that change conformation, solubility, or

degradation rates in speciic microenvironments. They are used in cancer and autoimmune diseases for controlled release, combination delivery, and to evade e▮ux-mediated drug resistance.

They also support oral and mucosal delivery of biologics using mucoadhesive or pH-responsive polymers that protect cargos through harsh barriers and release them at deined sites. In addition, they enable long-acting injectables for peptides and proteins by using slow polymer erosion to maintain therapeutic levels over extended periods.

Inorganic and hybrid platforms, such as mesoporous silica, magnetic nanoparticles, and metal-organic frameworks, provide structurally deined frameworks with high surface areas. They can integrate imaging or theranostic functions.

These systems show promise in precision oncology, enabling targeted hyperthermia and image-guided delivery with magnetic nanoparticles.

They are also useful for combination therapies, where mesoporous silica can load multiple agents and release them in response to pH or redox cues.

For both polymeric and inorganic systems, successful translation requires simpliied chemistries to reduce heterogeneity, careful assessment of long-term biodistribution and clearance, and reliable standardized assays for corona formation, immunogenicity, and off-target accumulation.

Bio-Derived Nanoplatforms

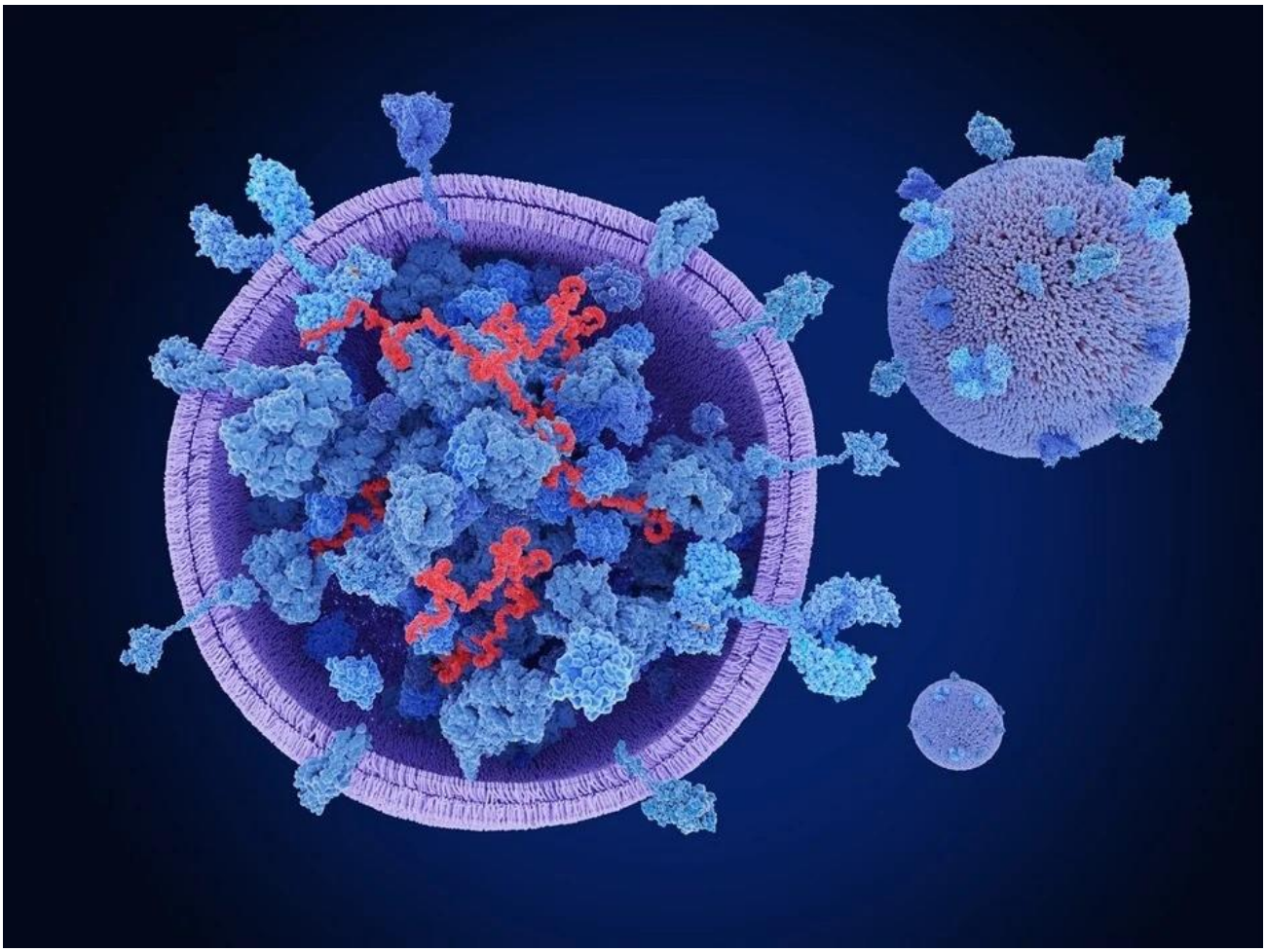

Image Credit: Juan Gaertner/Shutterstock.com

- Bio-derived carriers (exosomes/protein nanoparticles) offer biocompatibility but face more challenging CMC/regulatory paths.
- Translation depends on analytics, QbD manufacturing, and early regulatory alignment

Bio-derived nanocarriers harness or mimic the body's own transport systems, offering superior biocompatibility and natural biodistribution patterns. Exosomes are nanoscale vesicles secreted by cells.

Often called nature's LNPs, they provide intrinsic stability and low immunogenicity. Exosomes enable excellent membrane penetration for proteins, RNAs, and small molecules.

On top of this, they have built-in targeting via surface proteins and lipids. These targeting effects can be engineered using ligands or PEG to improve circulation and speciicity. They also serve dual therapeutic and diagnostic roles, such as in liquid biopsies.

Protein-based nanoparticles, such as albumin, ferritin, and silk ibroin, work similarly. They provide biocompatible, biodegradable scaffolds. These can load drugs or biologics and add

targeting decorations.

However, clinical and manufacturing translation demands solutions for scalable sourcing and puriication with consistent composition, standardized loading methods ensuring high encapsulation without aggregation or dysfunction, and clear regulatory deinitions of identity, potency, and release criteria for these complex biological nanosystems.

Smart, Stimuli-Responsive and Precision Nanoparticles

Smart nanocarriers are increasingly being designed across all nanoplatform families to respond to speciic stimuli such as pH, redox state, enzymes, temperature, or external ields, thereby controlling when and where a therapeutic is released.

These systems aim to align pharmacology with disease biology, concentrating active drug at sites of pathology while limiting systemic exposure.

Emerging examples include environment-responsive micelles and nanogels that disassemble in acidic tumors or inflamed tissues. Multifunctional theranostic nanoparticles combine imaging agents, targeting ligands, and therapeutic payloads for real-time tracking and adaptive dosing.

However, these conceptually powerful platforms increase the complexity of synthesis and quality control, demanding close integration between materials design, preclinical modeling, and manufacturing science.

What's Needed for Translation and Scalable Manufacturing?

Translation to the clinic and reliable commercial manufacturing across nanoplatforms face common challenges organized into four interlocking domains: design, evidence, manufacturing, and regulation/business.

Rational design emphasizes modular, reusable nanocarrier chassis for multiple drug candidates with minimal tuning, incorporating translational constraints like available excipients, scalable operations, and established analytics early rather than prioritizing preclinical eficacy alone.

Robust preclinical evidence addresses gaps between animal models and human outcomes. It uses better modeling of physiology, immunity, and microenvironments. It also includes systematic checks of biodistribution, protein corona, and long-term safety. These deine biomarkers for dosing and patient stratiication.

Industrialization needs quality-by-design frameworks. These deine CMAs, CPPs, and CQAs. They rely on high-resolution analytics and simple synthetic routes. Formulation complexity often conflicts with GMP standards.

Regulatory and business alignment involves early regulator engagement on classiication and analytics, plus models accounting for costs, cold-chain, and reimbursement, particularly for personalized or exosome products, while DELIVER-style frameworks link design, evidence, manufacturing, regulation, and risk mitigation to de-risk development and accelerate clinical impact.

Platform Family	Best For	Strengths	Bottlenecks
Lipid-based (LNPs, liposomes)	mRNA/siRNA/AZOs; some small molecules	Clinically proven; scalable; tunable; can enable endosomal escape	Targeting beyond liver, stability, and immune effects
Polymeric (micelles, dendrimers, nanogels)	Controlled release; combo delivery; long-acting	Highly designable; responsive chemistries; depot formats	Heterogeneity, reproducibility, an degradation safet
Inorganic/hybrid (silica, magnetic, hybrids)	Theranostics; multi-drug loading	Deined structure; imaging integration	Clearance, biodistribution persistence, safet
Bio-derived (exosomes, protein NPs)	Biologics needing biocompatibility/uptake	Natural traficking; low immunogenicity potential	Sourcing/Puriica identity/potency, regulatory clarity

Platform Family	Best For	Strengths	Bottlenecks
Stimuli-responsive (cross-family)	Site-speciic release	Precision + reduced systemic exposure	Synthesis/QC complexity, GMP analytics burden

Emerging nanoplatforms now map a distinct, functional landscape. Lipid-based systems remain (for now) the clinical workhorses, proven at scale and validated in patients. Polymeric and inorganic hybrid carriers power inely tuned, controlled delivery. Bio-derived vesicles and protein particles point toward a new class of highly biocompatible vectors.

Across all categories, stimuli-responsive designs are pushing precision from lab to practice. To move these platforms forward, developers must weigh manufacturability and regulatory readiness as heavily as biological performance.

Integrated science–engineering–policy thinking is no longer optional. Such thinking is a prerequisite for biopharmaceutical success in the coming decade.

The next wave of progress is predicted to converge on hybrid architectures, AI-accelerated design workflows, and standardized CMC frameworks that further close the gap between the research lab and the clinic.

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The BioXplorer range:
Customizable, scalable automated bioreactors

Early Screening → Pre-Pilot Scale

High throughput Screening

BioXplorer 100

- Discovery & optimization of bioprocesses
- Strain optimization development

8 zones | 200 mL

Focused Screening

BioXplorer 400

- Multiple feed/gas lines + sensor options
- Optimization of aerobic & anaerobic fermentations

4 zones | 500 mL

High- Pressure Screening

BioXplorer 400P

- Achieve high OTR via pressure control
- Synthesis of high-value organic chemicals

4 zones | 500 mL | *p*

Pre-pilot Validation

BioXplorer 5000P

- Optimization closer to production conditions
- Validation of strain engineering

1 zone | 1 - 10 L

Example applications

- (Syn)gas fermentation
- Gut microbiome
- Pressure fermentation
- Aerobic & anaerobic fermentation
- Biofuel production
- Cultivated meat

Operating the BioXplorer 100 as a turbidostat to maximize high-density E. coli cultivation

The ability to precisely control microbial growth is crucial in bioprocess development, continuous manufacturing, and microbial physiology studies. Using a turbidostat helps ensure cultures maintain a constant cell density, as it can react to turbidity feedback in real time and adjust the inlow of fresh medium, enabling exceptionally stable and reproducible culture conditions.

Figure 1. *H.E.L BioXplorer 100, bench-top parallel 8 bioreactor platform. Image Credit: H.E.L Group*

The BioXplorer 100 (Figure 1) delivers turbidostat capabilities through its integrated BioVIS probe (Figure 2) and WinISO software-controlled pumping system. This article discusses how to optimize high-density *Escherichia coli* cultivation using this parallel bioreactor system.

To establish an accurate correlation between probe output and cell density at high biomass, where optical scattering effects cause non-linearity, a non-linear calibration curve was formulated to facilitate the process.

Once calibrated accordingly, the BioXplorer 100 can successfully maintain a stable *E. coli* cell concentration at a speciied point under continuous growth conditions. This offers better control, consistency, and productivity across experimental evolution, process development, and physiological states.

Figure 2. *BioVIS probe for online monitoring of total cell growth and biomass within a bioreactor. Image Credit: H.E.L Group*

Key benefits

- Consistent cell physiology for long-duration or comparative experiments
- Parallel cultivation capability for screening and optimization workflows
- Automated dilution control for stable high-density operation
- No need for external optical monitoring equipment

Using the BioXplorer 100 as a turbidostat

1. **Initial growth phase (circa 0–155 minutes):** From the moment of inoculation, the culture enters the growth phase (~55 mins). After a lag phase, an increase in OD is observed alongside a decrease in DO as cells consume oxygen.
2. **Exponential phase (circa 155–300 min):** A rapid increase in biomass with continued DO decline reflects high metabolic activity. At around 275 mins, the DO exhibits a sharp increase, likely due to media exhaustion.
3. **Turbidostat control activated (~300 min):** Once the OD setpoint is reached, the system automatically enters the dilution phases.
    - Fresh medium is added as the feed pump flow increases

- OD stabilizes at the set target.

4. **Steady-state metabolic response:** By introducing fresh medium, the cell concentration is diluted to the setpoint level. This causes DO to spike before returning to a steady level.

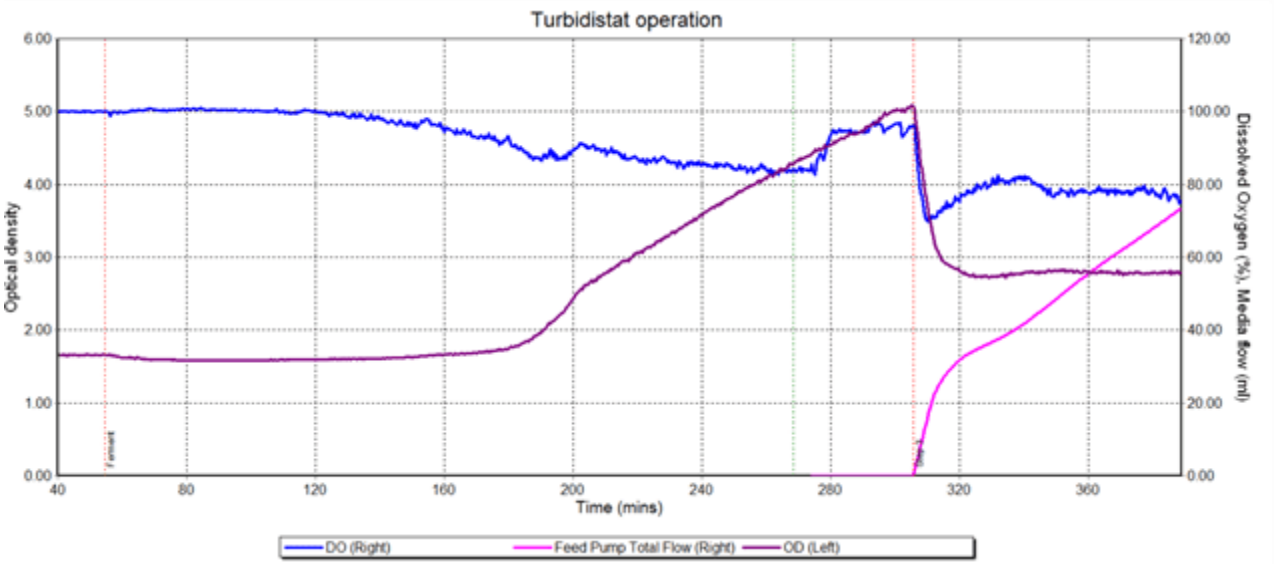

Figure 3. *Turbidostat control proile of BioXplorer 100. Image Credit: H.E.L Group*

Controlling microbial growth in liquid cultures is a requirement across biotechnology research and industrial bioprocessing. Conventional batch cultures are less suited to processes that require consistency and reproducibility, as they typically exhibit dynamic shifts in nutrient availability and metabolic state.

Turbidostats counter this by offering continuous cultivation under steady, controlled growth conditions. This is achieved by automatically diluting the culture when turbidity exceeds a predetermined threshold, thereby maintaining a constant biomass. This enables:

- Improved productivity for biosynthesis and protein expression
- Increased reproducibility between experiments
- Long cultivation times without manual intervention
- Microbial physiology and strain development research promotion
- Steady-state physiology and metabolism

As a parallel, small-scale bioreactor system, the BioXplorer 100 is well-suited for developing dynamic bioprocesses. Its built-in BioVIS probe delivers a constant, *in situ* optical attenuation measurement with real-time automated growth regulation capabilities that can be conigured using WinISO to return calibrated OD-equivalent values as needed.

However, ensuring accuracy during turbidostat operation is paramount, and this requires careful calibration of the probe signal to optical density (OD600), especially at high cell densities, where turbidity and OD are not linearly correlated.

Materials and methods

Microbial culture growth conditions

- Organism: *Escherichia coli*
- Culture volume: 50 mL in BioXplorer 100 vessel*
- Temperature: 37 °C
- Agitation: 200 and 400 rpm
- Biomass Set Point: 2.75 g/L
- Control software: WinISO

Equipped with the BioVIS probe, the BioXplorer 100 was inoculated with an *E. coli* culture, which was allowed to grow until a predetermined biomass setpoint was reached. Upon reaching the setpoint, WinISO automatically activated dilution control, introducing a fresh medium and flushing out effluent to maintain a constant culture volume and biomass.

**50–150 mL culture volume can be used with the BioXplorer 100 and 120-400 mL culture volume with the BioXplorer 400.*

Turbidity was continuously monitored, and the system adjusted the medium feed in real time. This maintains target cell density without manual interference.

For each vessel, the surplus culture volume was automatically drawn out through a dip tube, controlled by an independent peristaltic pump, under the guidance of the WinISO software.

Results and discussion

Calibration performance

Dilution is typically conducted when preparing diluted samples for OD_{600} measurement by UV–Vis spectrophotometry. It cannot be achieved when using an *in situ* optical probe. Therefore, to ensure an accurate correlation between the BioVIS attenuation signal and true cell density at high biomass, a non-linear calibration model was required.

This calibration makes the BioVIS signal reliable when used as a feedback input to maintain steady, constant control over the culture.

Non-linear calibration of BioVIS probe

To generate a calibration curve, samples were collected at incremental culture densities and measured o▮ine at OD600 using a spectrophotometer. These OD values were compared against the raw probe signal (transmitted light intensity).

The resulting calibration curve (Figure 1) exhibits the relationship between the BioVIS probe output and the o▮ine-measured OD_{600} of the *E. coli* culture. The absorbance signal and OD_{600} are approximately proportional at low cell densities, indicating that the BioVIS output can be taken when OD_{600} is below ~1.0.

The probe response at low OD_{600} was nearly linear. Increased light scattering at higher densities (OD_{600} of 1.5) led to nonlinearity, indicating a non-linear calibration model is required for accurate biomass interpretation.

With increasing cell density, a non-linear relationship is observed. Above ~OD_{600} ≈ 1.5, there is a slower increase in the BioVIS signal when compared to the true OD_{600}. This appears to occur as the dense cultures induce multiple scattering, limiting the fraction of transmitted light detected and breaking the simple proportionality assumed by the Beer-Lambert law in dilute solutions.

By applying a non-linear calibration model, the BioXplorer 100 can accurately determine biomass across the entire operating range. This enhances turbidostat control at high cell densities.

Conclusion

The BioXplorer 100 offers excellent turbidostat capabilities when supported by a non-linear turbidity calibration, providing controlled, stable, and reproducible high-density cultivation.

The system facilitates reproducible steady-state operation with minimal manual intervention by maintaining a high-density *E. coli* culture in continuous growth conditions.

The BioXplorer 100 combines real-time biomass monitoring, automated dilution control, and dynamic parallel bioreactor coniguration, making it the ideal solution for applications such as adaptive evolution studies, strain development, process optimization, and high-value biomolecule production.

For researchers and process developers seeking a reliable solution, the BioXplorer 100 offers a

scalable platform capable of delivering robust continuous microbial cultivation.

The system's performance enables long-duration, reproducible continuous culture, supporting process optimization, strain development, and high-value biomolecule production with minimal manual intervention, thereby boosting experimental conidence.

Summary

H.E.L's BioXplorer 100 and BioXplorer 400 parallel bioreactor systems can operate as robust turbidostat systems, enabling real-time control of culture density across diverse media and high-density microbial applications.

Both platforms can maintain a stable biomass setpoint under continuous cultivation when paired with the *in situ* BioVIS optical attenuation probe and WinISO-controlled automated dilution, making them ideal for long-running, steady-state processes.

Overall, the BioXplorer platform delivers consistent cell physiology, reliable operations over long durations, and true parallel cultivation. When it comes to process development, strain optimization, screening studies, and high-value biomolecule production, this system is second to none.

The BioXplorer 400P extends the range by offering another robust, scalable option for advanced pressurized bioprocessing applications. Together, the BioXplorer family can be considered a complete solution for continuous microbial cultivation with built-in optical monitoring and dynamic control strategies.

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Our mission

To help create a healthier, more sustainable, safer world for everyone.

Our vision

We equip scientists with the right tools and knowledge to develop safe, e cient new processes and molecules that beneit the world and its population.

Our values

Insightful through experience. With over 30 years of in-house expertise and experience, we know how to overcome a challenge

Collaborative by design. Dedicated to listening, learning, and working closely with industry experts, we empower others to fulill potential

Tenacious in spirit. Always looking for new and innovative solutions, we don't stand still; instead, we are focused on reaching the next success

Proud of progress. Fueled by our ability to make a real difference, while celebrating the achievements of others

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Sensor Technologies in Personalized Biopharma

In personalized biopharma, sensor technologies are advanced tools that capture *biological signals*, *biomarkers*, and *treatment responses* in real time, helping turn medicine from a standardized intervention into something far more adaptive and precise.

In practice, they give researchers and clinicians a clearer view of how therapies are working, supporting better decisions, stronger outcomes, and fewer adverse effects.[1-3]

Image Credit: Oksana Klymenko/Shutterstock.com

Why do We Need Personalized Biopharma?

The push toward personalized therapy is creating demand for tools that can track how patients respond outside the clinic, not only in occasional appointments.

Sensor technologies in personalized biopharma help close this gap by generating continuous, patient-speciic data on biomarkers, drug activity, and physiological change. They can support faster intervention, more precise dosing, and a model of care increasingly guided by real-time feedback rather than periodic snapshots.

How Sensor Tech is Expanding Personalized Biopharma

Non-Contact Biomonitoring and Drug Tracking

Wearable non-contact sensing technology continuously monitors drugs without direct contact with biofluids, reducing issues like sweat evaporation and contamination. It can analyze diverse physical parameters, including spectra, morphology, and heat distribution, and allows simultaneous detection of multiple drug molecules.

Its user-friendly design and ease of operation make it highly suitable for patients taking several medications. Non-contact sensing methods include optical and electromagnetic approaches, which detect optical signal/electromagnetic ield changes while interacting with biological materials.[3]

Optical and Electromagnetic Sensing

Non-contact optical sensing is highly accurate, sensitive, and resistant to electromagnetic interference. It monitors physiological signals like respiration, blood pressure, heart rate, and blood glucose. Incident light interacts with target molecules, producing reflected/refracted light whose intensity and wavelength differences reveal characteristic absorption peaks.

Techniques like *surface-enhanced Raman spectroscopy* and *infrared spectroscopy* have been used *in vivo* to analyze metabolites. Electromagnetic sensing measures target molecules based on dielectric permittivity.

Resonant methods evaluate the interaction strength between the target and electromagnetic waves, while non-resonant methods depend on wave transmission characteristics. Terahertz (THz) waves (0.1-10 THz) provide unique ingerprint spectra with high transmission and low energy.

Case Study: Lactate Monitoring

One study in *Biosensors* has demonstrated non-invasive lactate monitoring in interstitial fluid using a chip-less tag resonator system, with resonant frequency changes proportional to lactate concentration, accurately measuring levels from 1 to 10 mM and enabling evaluation of aerobic exercise.[3]

Direct Sensing Technologies: Bioluids, Interstitial Fluid, and More

Image Credit: ProShine Studio/Shutterstock.com

Invasive sensing technology directly monitors biofluids like blood and interstitial fluid, detecting target molecule changes in real-time.

Penetration depth varies: interstitial fluid requires more than 2.3 μm of invasion, which corresponds to the stratum corneum thickness, while blood sampling requires insertion into supericial veins, which is a deeper invasion level. Initially used for glucose monitoring, wearable invasive sensors now track drug metabolism and integrate with drug delivery systems, advancing personalized medicine.[3]

Microneedles and Electrochemical Sensing

Contact and invasive sensing technologies detect target molecules through either electrochemical or optical methods. To monitor interstitial fluids using electrochemical sensing, microneedles serve as solid supports, with sensitive elements such as antibodies/aptamers/enzymes at their tips.

Typically 100-600 μm long and 50-200 μm wide, microneedles penetrate the stratum corneum and epidermis to access the dermis, avoiding nerves to minimize irritation and promote rapid healing. Microneedle fabrication methods include soft lithography, three-dimensional (3D) printing, and template modeling, producing single and arrayed structures from

silicon/metals/conducting polymers.

Functionalizing microneedles with sensitive elements before using them in target molecular assays is an essential step. Enabling β-lactamase immobilization on microneedles in the previous *Biosensor* study, for example, allowed penicillin detection in interstitial fluids.[3]

Implantable Optical Sensors and Blood-Based Monitoring

Optical sensing implants sensitive elements in the body for constant drug monitoring.

Single-walled carbon nanotubes functionalized using deoxyribonucleic acid (DNA) measure changes in the chemotherapy drug doxorubicin concentration in interstitial fluid by red-shifting carbon nanotube photoluminescence's emission and excitation wavelengths.

When blood is the test sample, flexible electrodes are delivered using catheters (<0.6 mm diameter) into blood vessels to contact drug molecules. However, the sensor implantation in the vein triggers inflammatory responses, which can be mitigated by anti-inflammatory materials, chemical surface modiications, and flexible materials that reduce the mismatch between the soft living tissue and the rigid implantable surface.

Blood's complex composition, including sugars, lipids, and proteins, can introduce further interference, complicating accurate detection.[3]

Epidermal Sensing Technology and Wearable Monitoring

Image Credit: Guillermo Spelucin R/Shutterstock.com

Bodily fluids such as tears, sweat, and saliva can provide key health data and show linear correlations with blood levels. Epidermal sensing technologies detect target molecules by integrating sensitive elements on the skin/mucosal surfaces. Electrochemical and optical sensors are most common for their high sensitivity and accuracy.

Wearable sensor forms, including skin patches, gloves, and clothing, allow direct, convenient monitoring of secreted fluids without additional preparation. As a result, they enable fast and noninvasive health assessment.[3]

Optical Wearables: Colorimetric and Fluorescent Sensing

Wearable optical sensors rely on color change mechanisms between fluorophores/chromophores and target molecules in biofluids, enabling direct quantitative analysis via image analysis software. Colorimetric sensing relies on enzyme-substrate redox reactions.

For instance, glucose measurement uses enzymatic cascade reactions, turning o-dianisidine blue/iodine brown, while creatinine reacts with peroxidase-catalyzed creatinine acid to form a purple-red complex with 4-aminophenanthrene-4-aminophenazone. Fluorescence-based wearable sensors offer higher sensitivity and lower detection limits than colorimetric

methods.

Unlike enzyme-dependent colorimetric reactions, fluorescent sensors covalently attached to biomarkers directly detect diverse molecules and ions in biofluids such as sweat and tears, improving accuracy and versatility in noninvasive monitoring.[3]

Electrochemical Wearables and Ion-Selective Detection

Electrochemical technology is a leading wearable sensing method due to its high sensitivity, rapid response, and excellent linearity, making it widely used across various applications.

In wearable monitoring, biosensors like aptamers, enzymes, and antibodies are immobilized on a transducer, and changes in current/potential are analyzed to quantify target molecule concentrations.

This technology offers accurate, reliable, and skin-compatible monitoring, demonstrating huge potential for diverse health and biochemical applications. Ion-selective electrodes (ISEs) measure the activity/concentration of speciic ions by detecting the membrane potential, which is calculated using the Nernst equation. They are fabricated using ion-exchange carriers like carbon-based materials, conductive polymers, and nanomaterials.

Current research focuses on health-relevant ions, including potassium ions (K^+), sodium ions (Na^+), and lead ions (Pb^{2+}).

For instance, a study developed sodium ion-selective electrodes using potassium tetrakis(p-chlorophenyl)borate (KTClPB) and sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl] borate (NaTFPB) with a 6.5-11.8 mM detection range. Lithium ions have also been successfully monitored for bipolar disorder treatment.[3,4]

Enzyme-based Electrochemical Sensing

Enzyme-based electrochemical sensing detects target molecules by immobilizing speciic enzymes on working electrodes, generating electrical signals upon recognition. Sensitivity depends on immobilization eficiency, enzyme stability, and electron transfer rates. Amperometric and potentiometric enzyme sensors have been developed for diverse metabolites, with glucose oxidase technology being the most advanced and commercialized.

Other enzymes include uricase for uric acid, lactate oxidase for lactate, and β-hydroxybutyrate dehydrogenase for ketones. β-lactamase and tyrosinase enzymes track β-lactam antibiotics and L-DOPA, respectively, for continuous drug monitoring.

Organophosphorus hydrolase is used to assay organophosphorus pesticides, preventing irreversible damage from high exposure.[3]

Where Sensor Technologies in Personalized Biopharma are Heading

Sensor technologies may revolutionize personalized biopharma. By enabling real-time, accurate detection of drugs, biomarkers, and physiological signals, these devices improve treatment precision, minimize side effects, and support patient-speciic therapeutic strategies.

As these platforms become smaller, smarter, and easier to integrate into both care delivery and biopharmaceutical workflows, they are likely to play a larger role in making personalized therapy continuous, rather than episodic.

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Scientists Create Eco-Friendly Laser Entirely from Biomaterials

A laser constructed from peanut tissue and carbon dots demonstrates that nature's imperfections can rival precision-engineered devices in performance and utility.

Study: Biomaterial-based random lasers achieved from peanut kernel doped with birch leaf–derived carbon dots. Image Credit: New Africa/Shutterstock.com

Umeå University physicists collaborated with Chinese researchers to produce a laser manufactured entirely from biomaterials, including birch leaves and peanut kernels. The environmentally friendly laser could become a low-cost and widely available tool for medical diagnosis and imaging.

The indings demonstrate how a so-called 'random laser' may be created completely of biological components.

> *Our study shows that it is possible to create advanced optical technology in a simple way using only local, renewable materials.*
>
> *Jia Wang, Study Author and Associate Professor, Department of Physics, Umeå University*

A random laser is one in which light scatters many times inside a disordered material before forming a concentrated beam. It offers enormous promise for applications such as medical imaging and early disease detection, hence it has received a lot of scientiic interest. Traditional random laser materials, on the other hand, are either hazardous or costly and dificult to produce.

Jia Wang and her colleagues built the laser from two common natural materials: birch leaves and peanut seeds. They created nanometer-scale carbon dots from birch leaves to act as the gain medium, and then sliced peanut kernels into little cubes with rough and uneven surfaces that help trap and scatter light.

The laser is still driven by an external light source, but the functional components that scatter and magnify the light are entirely composed of biomaterials.

> *The synthesis of the carbon dots is simple and straightforward, essentially a one-step pressure-cooking process. Instead of relying on complex technology, the natural microstructure of the peanut kernel does the job on its own.*
>
> *Jia Wang, Study Author and Associate Professor, Department of Physics, Umeå University*

The researchers determined how much energy was necessary to make the laser produce light, and the results revealed that it works similarly to artiicially engineered lasers.

In addition, the laser's emission pattern is influenced by the unique microstructure of each peanut, which could serve as a kind of spectral ingerprint. This makes it extremely dificult to repliicate, an attractive feature for security applications.

> *The potential of this biomaterial-based random laser extends beyond bioimaging and diagnostics. Given its low cost, renewability, and safety, it could also be developed into an optical tag for authenticating high-value documents, luxury goods, and electronic devices.*
>
> *Jia Wang, Study Author and Associate Professor, Department of Physics, Umeå University*

Jia Wang's research group has long been focused on using local, renewable resources to power innovative technology. Two years ago, they released a study demonstrating how birch leaves harvested on Umeå University's campus can be utilized to produce organic semiconductors. These materials are found in thin TV and mobile phone screens.

Journal Reference:

Huang, Z. *et.al.* (2025) Biomaterial-based random lasers achieved from peanut kernel doped with birch leaf–derived carbon dots. *Nanophotonics*. doi.org/10.1515/nanoph-2025-0312

Source:

- https://www.degruyterbrill.com/document/doi/10.1515/nanoph-2025-0312/html

Pressure-enhanced oxygen transfer in aerobic fermentation

Oxygen transfer is a key limitation in aerobic fermentations that directly impacts cell growth, productivity, and bioprocess eiciency.

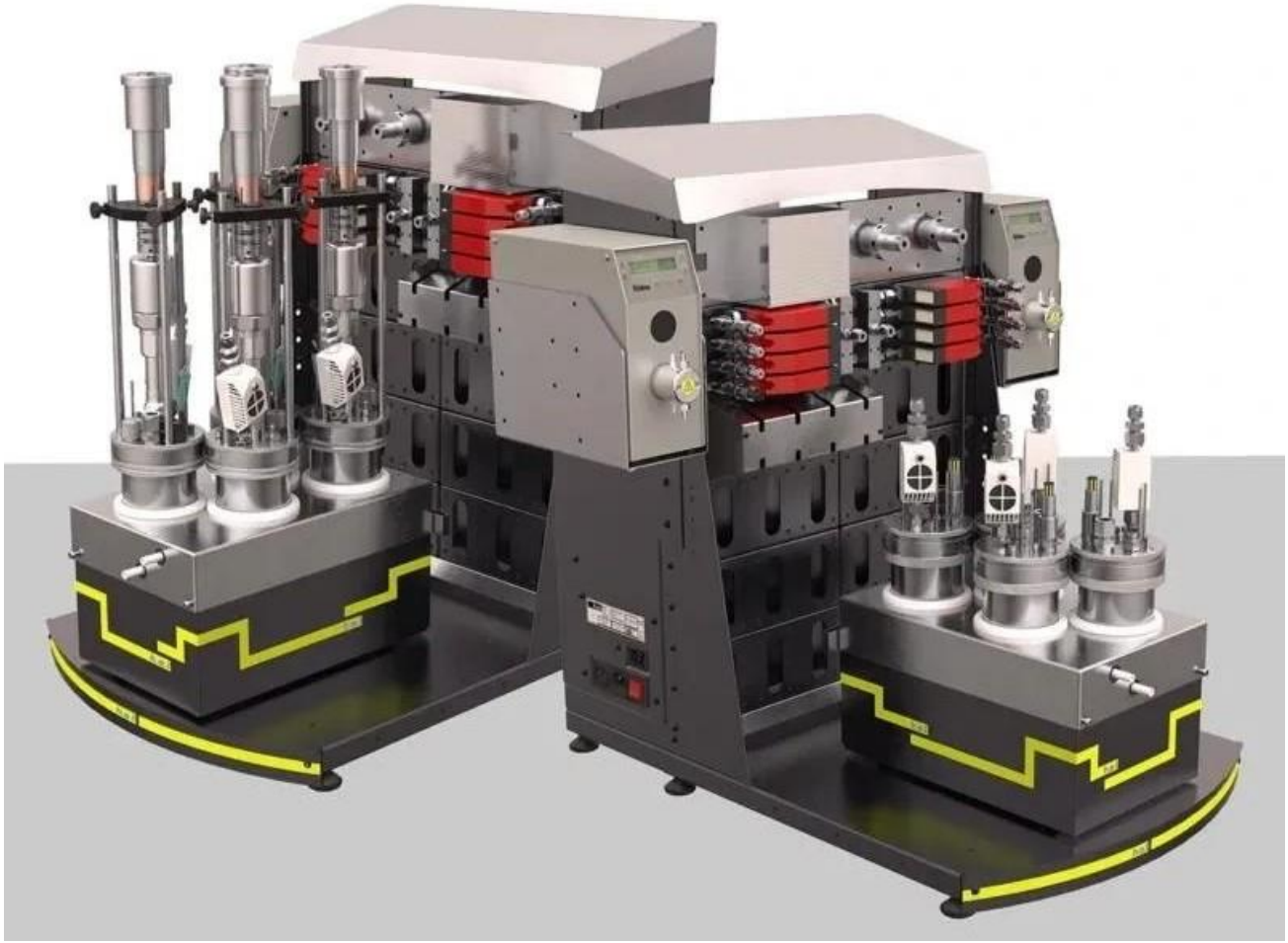

Figure 1. H.E.L Group's BioXplorer 400P. Image Credit: H.E.L Group

Introducing more pressure to a bioreactor facilitates an increase in the Oxygen Transfer Rate (OTR), which in turn improves gas solubility in the fermentation broth. More bioprocess scientists are switching to pressurized systems to improve the availability of dissolved gases and expedite gas-dependent bioprocesses.

This article discusses how operating at increased pressure has a considerable impact on the availability of dissolved oxygen and OTR (k_La), using the Bioxplorer 400P high-pressure parallel bioreactor system.

There is an improvement in oxygen solubility in the fermentation broth with an increase in

pressure, facilitating faster and more eficient bioprocesses. The Bioxplorer 400P enables precision control of dissolved oxygen by pressure, as it provides a powerful alternative to conventional agitation-based strategies.

Key benefits

- **Accelerates fermentation** by enhancing oxygen availability
- **Enables higher productivity** without influencing shear stress
- **Provides a scalable route** for the optimization of oxygen transfer
- **Allows precise dissolved oxygen control via pressure**
- **Reduces reliance on agitation for oxygen transfer,** reducing shear stress and protecting sensitive cultures

What is k_La: Why is it important in fermentations?

k_La refers to the volumetric oxygen mass transfer coeficient and is used to measure the eficiency of oxygen transfer from bubbles to liquid in the bioreactor.

Effectively, k_La clariies the speed at which oxygen is made available to cells, making it a key parameter for aerobic fermentation performance, productivity, and scale-up. Greater operating pressures raise oxygen solubility in the fermentation broth, which can improve oxygen transfer and boost process eficiency all round.

Previous studies conducted with the H.E.L bench-top bioreactor systems (BioXplorer 100 & 400) have demonstrated that a constant k_La can be leveraged as a basis for scale-up, as the values acquired from the instrument can be reproduced accurately in traditional-scale bioreactors (Gill *et al*., 2008).

In these studies, k_La is used as a measure of how effective the oxygen transfer is for liquid under pressure.

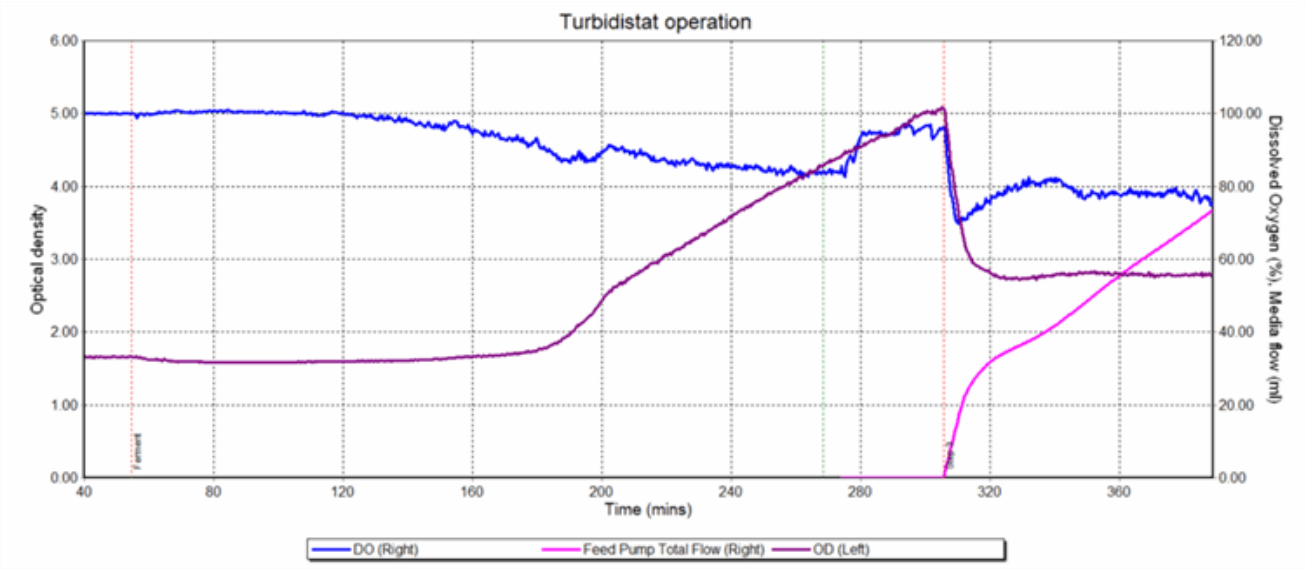

Figure 2. *Turbidostat control proile of BioXplorer 100. Image Credit: H.E.L Group*

The BioXplorer 400P

The BioXplorer 400P is an automated four-zone parallel pressure bioreactor system developed for the discovery and optimization of novel bioprocesses.

Designed for applications ranging from syngas fermentation to cell-free enzymatically catalyzed processes, the BioXplorer 400P leverages pressure capabilities in combination with precise gas feed control to accelerate bioprocesses that are dependent on the availability of dissolved gases.

Materials and methods

Experiments were designed to assess the influence that pressure has on oxygen transfer under controlled conditions:

- Reactor: 500 mL stainless steel reactor
- Working volume: 300 mL w/v dilute solution of sodium sulphite.
- Gas: 1 vvm (300 sccm) air gas blend containing H_2.
- Temperature: 37 °C.
- Stirring: 1500 rpm.

The BioXplorer 400P stainless steel pressure vessel was equipped with a gas sparger, pH probe, DO probe, overhead motor, and magnetic drive with Ruston impeller (Figure 2). The system was subjected to increased pressure cycling between gassing with air and scrubbing

with nitrogen.

Results and discussion

Figure 3 exhibits the dissolved oxygen (DO) proile of a reactor as it is cycled between gassing with air and nitrogen. As pressure increases, the DO in the liquid increases within the reactor.

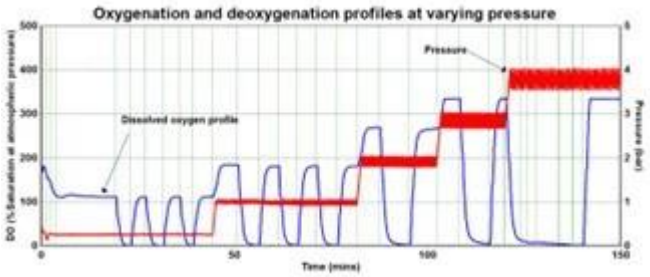

Figure 3. *Oxygenation and deoxygenation proile at various pressures over time. Image Credit: H.E.L Group*

As displayed in Figure 4, the gradient of the DO proile depicts the rate of change of oxygen concentration, which is a measure of oxygen flux. Applying the fact that 100 % saturation aligns with an oxygen concentration of ~9 mg/L (at room temperature), the analogous oxygen flux proile (in grams per liter per minute) can be generated.

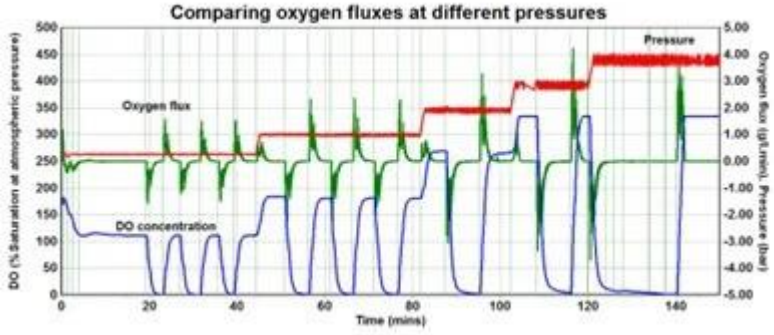

Figure 4. *Comparison of O_2 lux at different pressures. Image Credit: H.E.L Group*

Pressure can be used to manipulate the oxygenation level. This would typically be achieved through a manipulation of the stirrer speed. However, this is not possible when handling more fragile organisms such as algae and amoeba due to the negative influence of shear forces on cell integrity.

The data in Figure 5 shows a control loop that was created in this experiment to link a requested DO set point with the control output to a back-pressure regulator (BPR).

The system's pressure will change periodically as a result of automatic regulation dictated by BPR, which is not, however, manipulated explicitly.

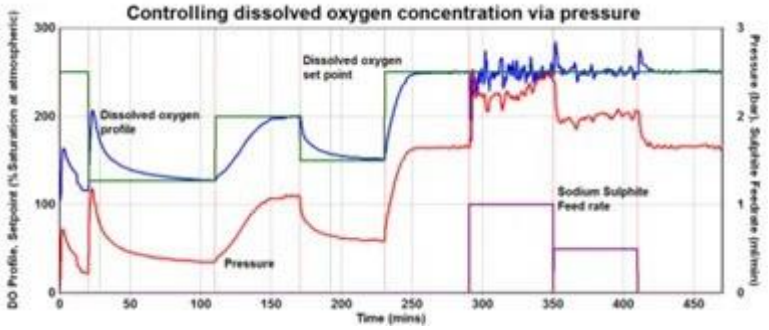

Figure 5. *Control of dissolved oxygen via pressure over time using an automatically controlled BPR. Oxygen concentration increases stepwise with pressure showing clear correlation between pressure and oxygen transfer rate. Image Credit: H.E.L Group*

Data was processed using H.E.L analysis tools. Each of the colored sections represent a separate curve-itting region, and the markers represent measured data points.

Each itted curve yields a different k_La estimate. The k_La values demonstrate a high level of reproducibility, with k_La = 2.0 min -1 +/- 10 %, i.e., independent of pressure.

During the irst 250 minutes of the experiment, the DO set point fluctuated at a range between 120 and 250 %. The reactor DO intervals were easily attained and automatically maintained using a BPR assist, which regulated pressures between 0.4 and 2.5 bar.

The set point of the DO was stabilized at around 250 minutes, and the DO stability was evaluated by introducing sodium sulphite, which extracts oxygen from the liquid in an oxygen scavenging reaction.

After sodium sulphite has been nourished, the BPR demonstrated a notable rise in the reactor's pressure to ensure the DO remained at the set point until the experiment concluded.

Conclusion

In agreement with Henry's Law, the DO concentration (but not k_La) scales approximately linearly with oxygen partial pressure. In these high-pressure experiments, the DO value underwent a signiicant improvement and demonstrated a near-proportional relationship with applied pressure.

Operating bioprocesses at elevated pressures (e.g., up to 10 bar) using the BioXplorer 400P can lead to signiicant improvements in oxygen transfer. Achieving comparable gains via k_La optimization alone would present a considerable challenge, due to additional factors such as gas–liquid interfacial area, bubble size, and agitation.

By leveraging pressure rather than increased agitation, the risk of shear stress is minimized, preserving and maintaining sensitive cultures.

The results show that applying pressure in the BioXplorer 400P bioreactors boosts DO levels and improves gas transfer rates. This makes pressure-enhanced transfer a power tool to improve yield, productivity, and biomass growth across complex bioprocesses.

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Bifunctional biomaterials for postoperative management of osteosarcoma

Background

Osteosarcoma is the most prevalent primary malignant bone tumor in children and adolescents. The current standard treatment involves a combination of chemotherapy and radical surgical resection. This approach, however, confronts two major clinical challenges: a high risk of postoperative recurrence and metastasis, and the creation of extensive bone defects that severely impair functional recovery and long-term quality of life.

The advancement of biomaterials technology offers a promising strategy to address these dual challenges concurrently. These materials can function as localized drug delivery systems that enhance antitumor e ▮ cacy while minimizing systemic toxicity. Moreover, they have facilitated the application of novel therapeutic modalities, such as photothermal, magnetic hyperthermia, microwave thermal, chemodynamic, and sonodynamic therapies. Crucially, these biomaterials are also designed to provide structural support and biological cues for bone regeneration, thereby fulilling the goal of bifunctional integration.

This review presents a systematic and innovative classiication of these cutting-edge bifunctional biomaterials. It provides a critical analysis of their design principles, therapeutic e ▮ cacy, and clinical translation potential, with the aim of establishing a new theoretical framework and proposing future research directions for the comprehensive postoperative management of osteosarcoma.

Research progress

This review innovatively categorizes bifunctional biomaterials for post-osteosarcoma repair into three distinct strategic paradigms:

The traditional bifunctional strategy achieves initial functional integration by co-loading antitumor components and osteogenic components within a single carrier. Some studies further endow these systems with auxiliary capabilities such as temperature monitoring and reactive oxygen species scavenging. However, due to the simultaneous release and action of both active components, this approach still presents inherent limitations in functional synergy: the hostile microenvironment created during antitumor therapy (e.g., hyperthermia, ROS) may inhibit bone regeneration, while prematurely initiated tissue repair could potentially compromise complete tumor eradication.

The enhanced antitumor bifunctional strategy aims to further improve therapeutic e ▮ cacy on

the basis of dual-function integration. Through sophisticated material design, this approach enhances tumor-killing effectiveness via two main pathways: optimizing unitary therapies (such as inhibiting heat shock proteins to enhance photothermal e ̄ cacy, or supplementing substrates for chemodynamic therapy), or constructing multimodal synergistic treatment systems (e.g., chemo-photothermal combination, photothermal-chemodynamic synergy). These advancements enable more thorough tumor clearance, thereby creating favorable conditions for subsequent bone regeneration.

The temporally regulated bifunctional strategy, as a more intelligent research direction, focuses on resolving the temporal conflict between functions. By designing differential release kinetics, constructing core-shell structures, or incorporating external stimulus-responsive mechanisms, this strategy achieves precise control over the therapeutic sequence of "thorough tumor elimination irst, followed by bone regeneration activation." This effectively decouples the two functions in temporal and spatial dimensions, ultimately maximizing therapeutic beneits.

These three strategic paradigms clearly outline the ield's evolutionary trajectory from simple functional superposition, to e ̄ cacy enhancement, and inally to temporal intelligence control.

Future prospects

Although bifunctional biomaterials demonstrate signiicant potential in postoperative osteosarcoma management, they still face challenges such as discrepancies between experimental models and clinical reality, insu ̄ cient long-term safety validation, and complexities in scaled-up production processes. Future development will place greater emphasis on holistic, personalized, and intelligent material designs, while establishing comprehensive safety evaluation systems and standardized production protocols. With advancing interdisciplinary collaboration, these innovative solutions are expected to successfully transition into clinical practice, ultimately providing osteosarcoma patients with safer and more effective comprehensive treatment options.

Source:

Research journal

Journal reference:

Dong, H., *et al*. (2025). Dual-Function Biomaterials for Postoperative Osteosarcoma: Tumor Suppression and Bone Regeneration. *Research*. doi: 10.34133/research.0978. https://spj.science.org/doi/10.34133/research.0978

CRISPR gene-drive technology reverses antibiotic resistance in bacteria

Antibiotic resistance (AR) has steadily accelerated in recent years to become a global health crisis. As deadly bacteria evolve new ways to elude drug treatments for a variety of illnesses, a growing number of "superbugs" have emerged, ramping up estimates of more than 10 million worldwide deaths per year by 2050.

Scientists are looking to recently developed technologies to address the pressing threat of antibiotic-resistant bacteria, which are known to flourish in hospital settings, sewage treatment areas, animal husbandry locations and ish farms. University of California San Diego scientists have now applied cutting-edge genetics tools to counteract antibiotic resistance.

The laboratories of UC San Diego School of Biological Sciences Professors Ethan Bier and Justin Meyer have collaborated on a novel method of removing antibiotic-resistant elements from populations of bacteria. The researchers developed a new CRISPR-based technology similar to gene drives, which are being applied in insect populations to disrupt the spread of harmful properties, such as parasites that cause malaria. The new Pro-Active Genetics (Pro-AG) tool called pPro-MobV is a second-generation technology that uses a similar approach to disable drug resistance in populations of bacteria.

"With pPro-MobV we have brought gene-drive thinking from insects to bacteria as a population engineering tool," said Bier, a faculty member in the Department of Cell and Developmental Biology. "With this new CRISPR-based technology we can take a few cells and let them go to neutralize AR in a large target population."

In 2019 Bier's lab collaborated with Professor Victor Nizet's group (UC San Diego School of Medicine) to develop the initial Pro-AG concept, in which a genetic cassette is introduced and copied between the genomes of bacteria to inactivate their antibiotic-resistant components. The cassette launches itself into an AR gene carried on plasmids, circular types of DNA that replicate within cells, thereby restoring sensitivity of the bacteria to antibiotic treatments.

Building upon this idea, Bier and his colleagues developed a follow-on system that spreads the antibiotic CRISPR cassette components via conjugal transfer, which is similar to mating in bacteria. As they described in the *Nature* journal *npj Antimicrobials and Resistance*, the researchers showed that this next-generation pPro-MobV system can exploit a naturally created bacterial mating tunnel between cells to spread the key disabling elements. They demonstrated the process working within bacterial bioilms, which are communities of microorganisms that contaminate various surfaces and can be extremely dificult to remove

under conventional cleaning methods. Bioilms also contribute to the spread of disease and are created in the majority of infections that lead to serious disease, in part because bioilms help combat antibiotics by creating a protective layer of cells that is dificult for antibiotics to diffuse through. The new technology therefore carries potential in health care settings, environmental remediation and microbiome engineering.

> *The bioilm context for combatting antibiotic resistance is particularly important since this is one of the most challenging forms of bacterial growth to overcome in the clinic or in enclosed environments such as aquafarm ponds and sewage treatment plants. If you could reduce the spread from animals to humans you could have a signiicant impact on the antibiotic resistance problem since roughly half of it is estimated to come from the environment."*
>
> *Ethan Bier, Professor, UC San Diego School of Biological Sciences*

The researchers also found that components of the active genetic system could be carried and delivered by bacteriophage, or phage, which are viruses that are natural evolutionary competitors of bacteria. Phage are being specially engineered to combat antibiotic resistance by evading bacterial defenses and inserting disruptive factors inside cells. pPro-MobV elements, the researchers envision, would work in conjunction with such engineered phage viruses. This active genetic platform also can incorporate a highly eficient process known as homology-based deletion as a safety measure to remove the gene cassette if desired.

"This technology is one of the few ways that I'm aware of that can actively reverse the spread of antibiotic-resistant genes, rather than just slowing or coping with their spread," said Meyer, a professor in the Department of Ecology, Behavior and Evolution, who studies the evolutionary adaptations of bacteria and viruses.

Source:

University of California - San Diego

Journal reference:

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