SPECIAL EDITION 2022

BIOPROCESSWATCH

MABDESIGN
THE IMMUNOTHERAPY NETWORK

ABOUT **MABDESIGN**

MabDesign, the French Association of the Biotherapy Industry

MabDesign, the French biotherapy industrial association, aims to support, federate and increase the visibility of the biopharmaceutical industry, foster exchanges, promote the development and competitiveness of companies, and stimulate innovation by encouraging the emergence of start-ups from academic research.

In order to carry out its development strategy and to adapt to changes in the industrial ecosystem, MabDesign's governance has evolved to meet the specific needs of the various companies working in the biotherapy industrial sector. Therefore, the Board of Directors of MabDesign already composed of DBV Technologies, Lyonbiopole, Pierre Fabre and Sanofi, has been strengthened with the arrival of ABL Europe, bioMérieux, Institut Pasteur, Thermo Fisher Scientific and TreeFrog Therapeutics as well as four Qualified Persons with Nicola Beltramineli (Innate Pharma), Hervé Broly (Merck), Philippe Germanaud (SANOFI), and Stéphane Legastelois (33 California). Their arrival to the Board of Directors reinforces MabDesign global vision of the current challenges and opportunities of the biopharmaceutical industry.

Moreover, to achieve its goals MabDesign sets up a coherent set of actions promoting exchanges, collaborations and skills development. In this dynamic MabDesign has developed a **national directory** that brings together industrial and academic players in biotherapy and allows to identify online the know-how available in France. MabDesign organizes high-level **international scientific events**, in collaboration with key ecosystem players, to highlight innovation and stimulate exchanges between companies in the sector. With the help of its Scientific Committee (**COSSF**), MabDesign writes summary reports (**ImmunoWatch**) for the biotherapy industry. MabDesign offers specialized and **innovative continuous professional training** solutions to enable companies to adapt their skills to the market evolution and maintain their competitiveness. Finally, MabDesign offers its members a **wide range of services** to help companies of all sizes to optimize their positioning, protect and enhance their innovations, conquer new markets and raise public funds.

Operational since September 2015, MabDesign currently has over **220 member companies** and its diversity is its strength. MabDesign's dynamic network includes pharmaceutical and biotech companies, service providers (eg. CROs, CDMOs, etc), professional training actors, high-tech equipment suppliers and specialized consultants.

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INTRODUCTION

According to our latest information, France is currently at the fourth place behind United Kingdom, Switzerland and Germany in Europe as biologic developer with a pipeline of 540 biopharmaceutical drug candidates being developed by French companies. Importantly, these candidates include therapeutic antibodies, recombinant proteins, vaccines, cellular therapies, gene therapies and advanced therapy medicinal products[1]. In more recent news, the French government has announced its 20-by-30 objective for the national biopharmaceutical industry to bring 20 new biopharmaceutical therapeutic or prophylactic drug to market by 2030. The need for adequate and timely bioprocessing capabilities for both clinical and commercial batches is thus undeniable.

For several years now, MabDesign has been actively participating in national and regional programmes and organising scientific events and gatherings focusing on bioprocessing. Indeed, since 2016, our annual Bioproduction Congress has gathered so far more than 1000 participants, 137 Speakers and 103 Sponsors and Exhibitors and has allowed for more than 1050 B2B meetings. As such, this event is considered as a major French scientific event where stakeholders from Europe gather together to showcase and exchange the latest innovations in bioprocessing. In parallel, we have also been providing strategic consultancy services together with various training opportunities to key actors of this field, including academia, public bodies, SMEs and biotech and pharmaceutical companies.

BioprocessWatch marks our organisation's latest endeavour and commitment to support the different academic and industrial French stakeholders involved in the field with the hope that through the latter and combined with our various past, current and future services, actions and training opportunities, MabDesign has been making a contribution, however humble it might be, in supporting and promoting the national biopharmaceutical and bioprocessing industry.

In 2021, the 6th edition of the Bioproduction Congress organized by MabDesign was also the comeback to face-to-face meetings after a previous edition in digital format due to the pandemic. What better topic to address this year than the Bioproduction Challenges & Opportunities for Biotherapies created by the COVID-19 pandemic, and the lessons learned from this unique situation. With 260 experts on the bioprocessing field from 9 different countries, including 42 high profile speakers and 4 workshops, gathered togehter to discuss how to advance the field of Bioproduction both in France and worldwide. In a dynamic and stimulating event of 1 and half days, 35 companies showcased their latest technologies and more than 200 B2B Meetings have taken place promoting collaborations and generating new commercial leads.

[1] Source : GlobalData

The scientific program of this edition was set-up by a **Scientific Advisory Board** composed of **LFB Manufacturing** : Roland BELIARD, **Pierre Fabre** : Alain BECK, **Quality Assistance** : Arnaud DELOBEL, **UCB Pharma** : Annick GERVAIS, **CELONIC** : Laszlo PARTA, **Novartis** : Francisca GOUVEIA, **Yposkesi** : Sophie BLONDEL, **Merck Serono** : Hervé BROLY, **SANOFI** : Elodie GUIDAT, **Debiopharm** : Olivier COCHET, **EverZom** : Nicolas ROUSSEAU, **TreeFrog** : Maxime FEYEUX, **Xenothera** : Bernard VANHOVE, **SANOFI PASTEUR** : Cédric CHARRETIER, **EFS** : Sophie DERENNE. We would like to thank them for their efforts for bringing together the experts on the frontline of the development in a unique event to exchange on the future of bioproduction, the current challenges and the new solutions being presented by French companies as well as international stakeholders. Moreover, the success of the congress also comes from the support from our 37 sponsors/exhibitors and our 12 partners of this event.

Due to the importance of the topics being addressed during the meeting, we have decided to include them in a special edition of the **BioprocessWatch** so that all actors can benefit from it. We would like to thank all the speakers that participated on the event and have contributed to this edition of the BioprocessWatch. Due to confidentiality and intellectual property reasons, some presentations from the congress have not been made available here.

We hope you will enjoy reading this special edition of the BioprocessWatch and we will be more than happy to see you this year at the **7th edition of the Bioproduction Congress, September 29-30, 2022 in Lyon.** Check the website at **http://www.biopcongress.com.**

Franck Mercier
Siemens

SIEMENS

Covid 19 : Supporting BioNTech and winning the race against time

BioNTech manufactures one of the leading COVID-19 vaccine, BNT162b2 in collaboration with US pharmaceutical specialist Pfizer. The company started manufacturing in Marburg, Germany in April 2021 in the German state of Hesse. In the fall of 2020, it took over a production facility from Novartis for this purpose. The relevant expertise was already available, since BioNTech also acquired a highly qualified employee base along with the production facility, all of whom were experienced in developing new technologies. Siemens provided support with the switchover to vaccine production. There are two reasons for this: Siemens already knew the Marburg facility very well, and had worked with it previously on activities including automation of vaccine production development. The two companies could also look back on a number of projects they had already completed together in the previous years.

Everyone involved in the project knew how important it was: The sooner production could start, the sooner more vaccine doses will be available. The hopes of society therefore depended on this project. A project of this magnitude normally takes about a year, but in this case the participants completed the conversion in just five months. They all worked overtime and took no leave in order to advance the project as fast as possible. Things that would normally be done by working together on-site were instead performed largely by a decentralized team based in separate home offices. The project was a complete success.

During the project to switch the Marburg plant over to production of mRNA-based vaccines, Siemens focused on future viability. All the improvements are Industrie 4.0-compatible. One of the challenges with the conversion was the fact that it involved switching from rigid to mobile production with many single-use components. At the same time, working with mRNA meant a higher clean room class than was previously required in the facility and a lot of manual stages that require operator guidance. Paper is now an avoidable “contamination factor” that doesn’t arise with digital production. That was the basis for opting for a MES, which was ready to use in just 2½ months. This solution enables complete paperless manufacturing and full electronic batch recording. Seamlessly integrating automation solutions makes it possible to develop, optimize, and manage production processes automatically. The individuals

in charge can easily monitor, observe and, if necessary, record every stage of production and every base material. Batch release is based on the principle of “review by exception” – in other words, deviations are dealt with when the system recognizes them based on exception rules. That makes the process less labor-intensive and much faster, since otherwise the individuals in charge would have to check several thousand pages on paper. As a result, digital production is a significant factor in making the process faster and improving quality.

To ensure a smooth start to production, Siemens is also supporting the implementation of the system at BioNTech with Hypercare and a 24/7 project-based standby arrangement. That means the employees in production can request help with operating the system from the manufacturer at any time of the day or night. The project is a complete success for both parties and production was able to start before the end of February with the production of the drug substance: the mRNA. “We want to thank Siemens for their excellent collaboration on this project and the huge effort they put in, often exceeding 100 percent,” says Valeska Schilling, Head of Production Department at BioNTech Marburg.

Pierre Monsan
Cell-Easy

Cell-Easy: GMP grade ASC production at affordable cost for academic clinical trials

Cell-Easy is implementing the industrial scale GMP production of adipose tissue mesenchymal stem cells (ASC) for clinical trials. The aim is to reach an affordable cost for this kind of cell therapy products.
The process starts from the Stromal Vascular Fraction extraction from liposuction samples and consists in a four-step amplification of the cells, which are then frozen and stored under gazeous nitrogen atmosphere, and delivered for clinical trials.
Cell-Easy holds a joint framework agreement with Toulouse Hospitals (CHU) and has signed a MoU with AP-HP (Hôpital St-Louis, Paris). Initial targets are Alzheimer disease, Crohn's disease anal fistula, lower limb ischemia and autoimmune diseases. In parallel, Cell-Easy is developing a Contract Development and Manufacturing Organisation activity (CDMO) to give access to its state-of-the-art production platform to industrial partners interested in the GMP production of adherent cells (stem cells, Master Cell Banks, Working Cell Banks) and of their secretome (exosomes, nano-vesicles).

SESSION 1
FAST-TRACK BIOPRODUCTION : WHAT WE HAVE LEARNED FROM COVID-19 OUTBREAK

Cell Culture Media Supply for Europe and Beyond

New manufacturing site opens in December

The new FUJIFILM Irvine Scientific facility in Tilburg, Netherlands, is your local supply chain solution for cell culture media. Now our expertise, flexibility, industry-leading turnaround times, robust raw materials program, and best-in-class Quality System will be delivered locally in December 2021.

Collaborative partnership with best-in-class manufacturing

We become an extension of your supply chain to provide you with advanced cell culture solutions including media products, services, and technologies for bioprocessing and cell and gene therapy. Our capabilities, expertise, and support help your life-saving medicines and therapies get to market.

Exceptional customer service and faster response times

FUJIFILM Irvine Scientific is your trusted and responsive local advisor. We are here when you need us with a dedicated team of media manufacturing experts ready to support you.

FUJIFILM
Value from Innovation

www.irvinesci.com/europe

IrvineScientific

Eric Olmos
LRGP - CNRS UMR7274

Large-scale human cell cultures: some key (multi-disciplinary) engineering aspects

Pr. Eric OLMOS
Université de Lorraine, Laboratoire Réactions et Génie des Procédés UMR CNRS, Nancy, France / Intégrateur Industriel MTInov

Today, the cultivation of human cells at a larger scale (namely a few dozen liters), especially mesenchymal stem cells (MSC), pluripotent stem cells or CAR-T cells faces engineering challenges that concern, among others, culture system technologies, scale-up criteria pertinence, couplings between physical and biochemical phenomena (such as agitation / aeration vs cell stemness and functionality) or culture medium composition. One way to deal with these scientific and technical questions is to develop an integrative multi-disciplinary approach that simultaneously consider each aspect of large-scale stem cell culture. For instance, for adherent-dependent cell culture, mathematical models predicting the just-suspended agitation rate of microcarriers are useful to determine adapted agitations at each bioreactor scale (Loubière C et al.,2019). The choice of smart small-scale bioreactors is also necessary to determine improved culture conditions during early phases of process development (Loubière, C. et al., 20192-II). These preliminary phases should also be based on Quality By Design approaches to determine the Critical Quality Attributes of the culture process, then to focus industrialization on specific bottlenecks and thus finally to reduce the development duration and costs (Maillot, C. et al., 2021).

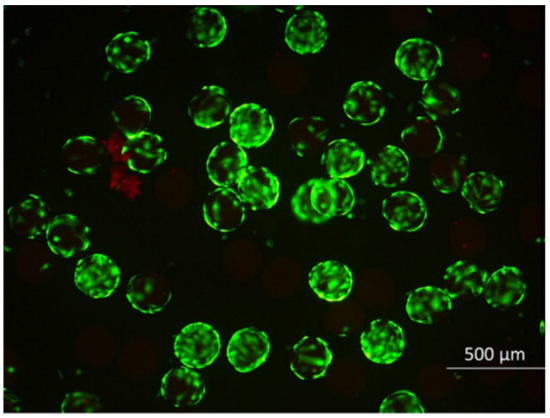

Figure 1. Pictures of fluorescent staining of Wharton's Jelly-MSCs cultivated on dissolvable microcarriers in perfused-continuous STR (Sion et al., 2021)[4]

During scale-up phase, innovations should be looked for (i) to propose new strategies of culture, such as modified perfused modes of culture for adherent cell cultures (see Figure 1), (ii) to study kinetics of cell culture by using on-line in-situ probes such as dielectric probe to monitor cell growth(Maillot, C. et al., 2021). The use of Design of Experiments should be recommended to determine local optimal set of culture conditions.

Lastly, the transposition of best culture conditions at larger scale should be based on a more physical description of the microenvironments encountered by the cells in the bioreactors by intensively using Computational Fluid Dynamics coupled with kinetic and / or metabolic models (Loubière C et al.,2019).

In the near future, the development of Artificial Intelligence use for human cell cultures (especially

for human cell cultures (especially Machine Learning or Artificial Neural Networks) should drastically decrease the time needed to reach culture optimal conditions at production scale. The integration of metabolic and physical modelling but also of advanced online monitoring in such approaches is also expected to strengthen the global engineering strategies.

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Thibaut Fourniols
EverZom

Selection of the optimal cell source for extracellular vesicles production in regenerative medicine or drug delivery

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Extracellular vesicles (EVs) are vesicles secreted by cells from several biogenesis pathways. EVs are currently developed for therapies mainly in regenerative medicine to replace stem cell therapy (Nagelkerke A et al., 2021; Lee JY et al., 2021), and in the drug delivery field as nanocarriers (Meng W et al., 2020). They gather the multiple nomenclatures of exosomes, microvesicles, apoptotic bodies, and other natural "-osomes" products. They are ubiquitous, present in all biological fluids from all species (humans, animals, plants, microorganisms). They have attracted a lot of interest because they contain biomolecules, such as phospholipids, intraluminal and membrane-bound proteins, and different types of RNAs. One intrinsic characteristic of EVs is their heterogeneity. Cells produce different populations of EVs, and each particle contains its proper combination of biomolecules.

To produce EVs at a large scale, they must be collected from cell culture conditioned medium, or directly from a biological fluid such as milk or blood. The selection criteria for the EV cell source can be divided in two categories: i) the EV intrinsic properties, in line with their therapeutic activity, and ii) the cell line characteristics associated to their robustness for large production (Kim J, et al., 2021).

Each EV type is associated to endogenous biological properties, that will drive their pharmaceutical effect. It is related to their biomolecular content, and their physical properties. Two academic studies have compared several cell sources for EV bioactivity: Wiklander & al. have followed the biodistribution of EVs in a mouse with 6 various cell lines from human, rat, or mouse. For each organ, the amplitude of EV proportion at 24h varied significantly, with between 45 and 75 % in the liver, or between 4 and 18 % in the Gastro-intestinal tract for instance (Wiklander OPB et al., 2015). Furthermore, Barile & al. have compared EVs from cardiomyocytes progenitor cells (CPC), bone-marrow derived mesenchymal stem cells, and dermal fibroblasts, for their cardiac regenerative properties. Only CPC-EVs showed a significant cardiac function improvement in two different pathological models (Barile L, et al., 2018). These 2 examples show that cell source has a direct impact on EVs properties.

Then, the cell source directly influences the ability to produce a large EV quantity, which is important in terms of collected doses. Different cells secrete very different quantities of EVs in the same culture conditions. In any cases, cells must be expanded widely, over multiple passages. It means that their availability, together with their stability during the scale-up is essential. Finally, using stably transfected cells can allow to engineer produced EVs, and the ability to be transfected is variable among cell lines, HEK293 being the most famous.

Clinical trials using EVs provide an overview of current EV sourcing. All except one phase II trials have used mesenchymal stem cells (MSC). This MSC proportion remains important at all stages but the diversity increases a lot with preliminary studies (Silva AKA, et al., 2021).

Once the type of cell sourcing for EVs has been selected, it remains to decide to work with primary cell line, which will be closer to the physiological properties but available only during a limited time, or with immortalized cells, with some safety risks and a potential derivation of the cell line. But immortalization allows a phenotypic and genotypic stability, increases the amplification potential, and batch consistency. At the same time, it will reduce costs associated to multiple master cell bank validations. Immortalization was not possible for cell therapy due to safety concerns, but with EVs it becomes straightforward.

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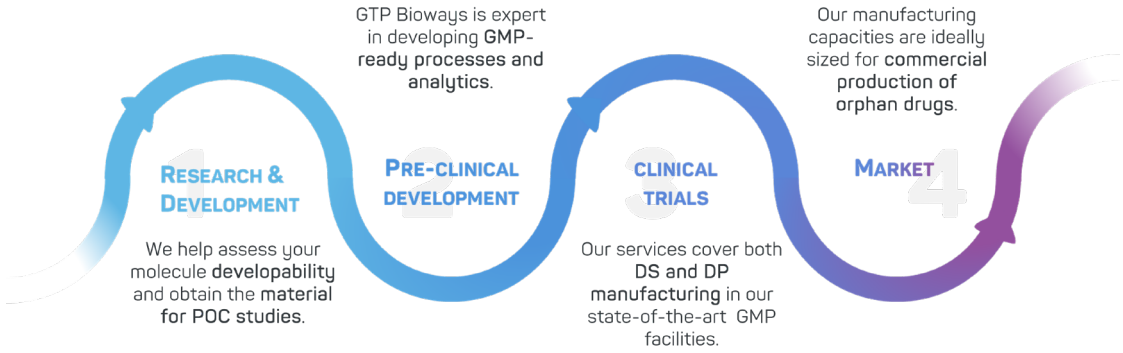
7. Silva AKA, Morille M, Piffoux M, et al. Development of extracellular vesicle-based medicinal products: A position paper of the group "Extracellular Vesicle translatiOn to clinicaL perspectiVEs – EVOLVE France." Advanced Drug Delivery Reviews. 2021;179:114001. doi:10.1016/j.addr.2021.114001

GTP Bioways

GTP Bioways CDMO
Continuum for biologics

GTP Bioways is a CDMO (Contract Development and Manufacturing Organization), offering a unique service in developing production processes and manufacturing biotherapies, antibody-drug conjugates and nanomedicines. With its development and production sites based in France, GTP Bioways supports biopharma companies aiming to develop innovative molecules, from R&D through to clinical trials.



Our CDMO services include:

- **R&D services:** GTP Bioways offers custom production services with all prominent expression systems to provide proteins and antibodies for your R&D studies. With experience spanning over 800 different proteins, our team has acquired the agility to express and purify even the most challenging proteins.
- **Process development:** Our team has over 20 years' experience in developing processes for the production of challenging molecules, including proteins, antibodies and nanodrugs. We know that the energy spent in process development is an investment into the future success of your programme and we will always focus on developing the most efficient, robust and high-quality manufacturing process for your specific molecule.
- **GMP manufacturing:** GTP Bioways operates state-of the-art manufacturing facilities for the production of biologics, bioconjugates and nanodrugs. We are sized to address your needs for clinical studies and small-batch commercial supply. Our QA team is strongly involved at each step of the project and can provide IND/IMPD support.
- **Fill & Finish:** GTP Bioways is one of the few CDMOs covering the whole value chain thanks to our in-house aseptic fill-&-finish for a wide range of active pharmaceutical ingredients including biologics, small molecules and cytotoxics. With our unique state-of-the-art filling line with single-use isolators, we offer flexible manufacturing of your drug product with the highest quality standards.

Key figures

- > 3,500 sqm facilities
- Up to 1000 L for biologics and up to 60 kg for nanodrugs
- Up to 10 000 units/batch (syringes or vials)

SESSION 2

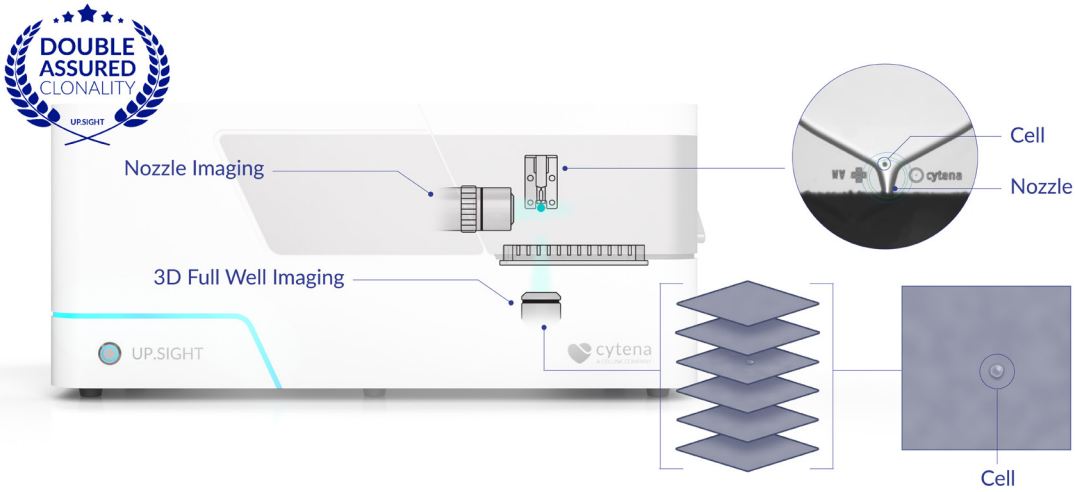
HOW TO ACCELERATE THE FIRST IN MAN : CELL LINE & NON CLONAL CELL LINE

Adrian Zambrano
CYTENA

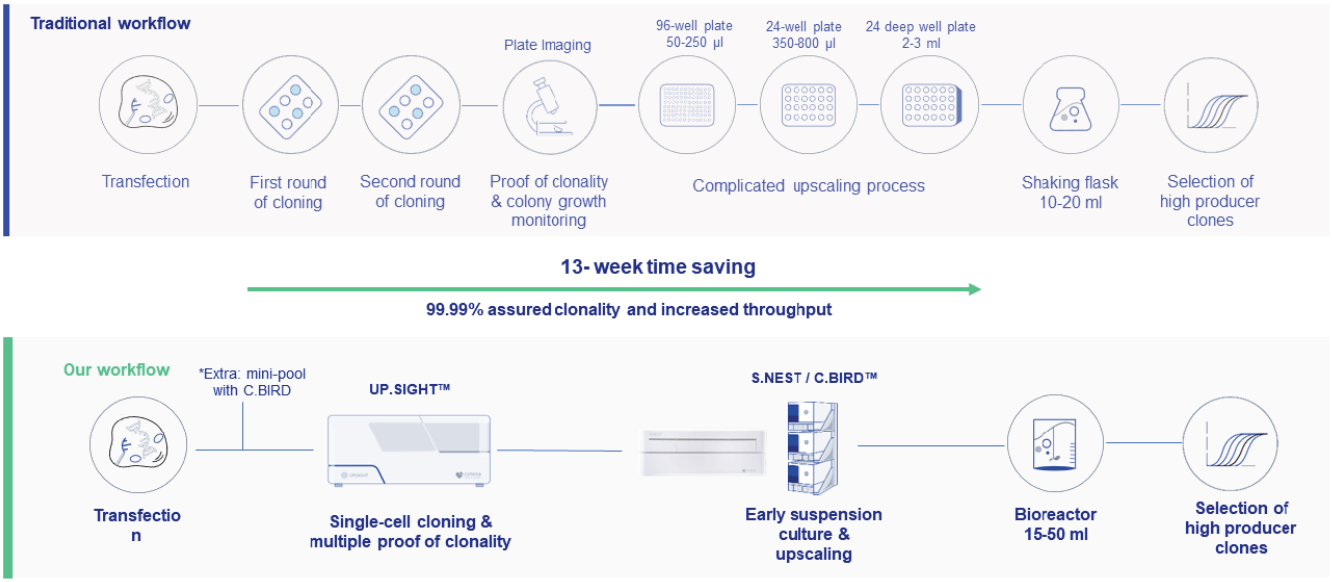
CYTENA
A BICO COMPANY

UP.SIGHT: The ultimate upgrade to your cell line development workflow

The UP.SIGHT™, developed by CYTENA, uses optics- and microfluidics-based single-cell dispensing technology. Clonality of dispensed cells is doubly assured by nozzle imaging and 3D Full Well Imaging for >99.99% probability of monoclonality. Faster processing speeds enable the isolation and imaging of hundreds of clones in under 30 minutes, significantly minimizing the hands-on time typically required.



The instrument's onboard software analyzes cell morphology to isolate single cells according to set parameters such as size, roundness and even fluorescence intensity; it is also compatible with a wide range of cells. Disposable dispensing cartridges eliminate the risk of cross contamination and improve the viability of cells. Colony tracking from day 0 is made easy with an integrated imager.



The UP.SIGHT arrives automation ready, and CYTENA's expert application specialists offer full application support, ensuring the ultimate upgrade to your cell line development workflows. To learn more, visit www.cytena.com

Félix A. Montero-Julian
bioMérieux

1 hour testing for Mycoplasma contamination in bioproduction samples using the BIOFIRE® FILMARRAY® 2.0 Industry system

Félix A. MONTERO-JULIAN PhD | Scientific Director Healthcare Business | bioMérieux Industry

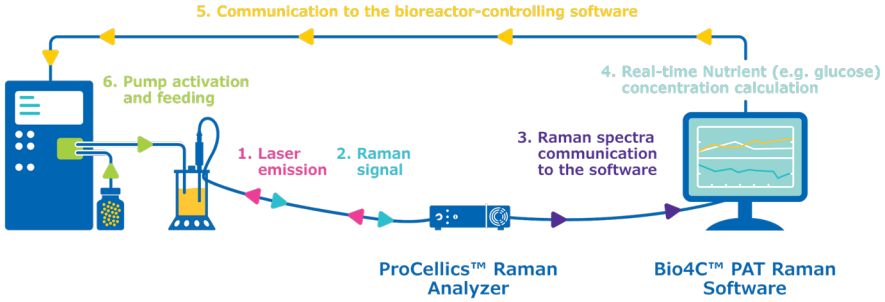
The prevention and monitoring of mycoplasma contamination is an ever-present challenge in the biopharmaceutical industry. Compendial mycoplasma screening requires up to 28 days and often must be performed off-site. For faster time-to-results, Nucleic Acid Tests (NAT) have been developed as alternative methods. However, NATs require highly-skilled technicians to extract nucleic acid, set-up PCR plates, and interpret data. In contrast, the newly developed BIOFIRE® MYCOPLASMA FILMARRAY® 2.0 Industry system combines nucleic acid purification and nested multiplex PCR for detection of mycoplasmas in under an hour using a closed, fully automated sample-to-answer system requiring little technical training and with less than 2 minutes of hands-on-time. Internal validation data indicate suitable specificity and limit of detection to be used as both an in-process control and release test. Evaluations performed by bioproduction manufacturers confirm suitability of the BIOFIRE® MYCOPLASMA in the presence of high density monoclonal antibody producing Chinese hamster ovary (CHO) cells as a rapid mycoplasma test for in-process control or release at harvest.

Taken together, the highly sensitive and specific analytical performance, rapid automated results and compact system design of the BIOFIRE® MYCOPLASMA solution presents a unique potential for at-line in-process mycoplasma testing with near real-time results, the system simplifies the implementation of in-house mycoplasma testing to eliminate a common manufacturing bottleneck and improve mycoplasma surveillance throughout the manufacturing process.

Célia Sanchez
Merck Life Science

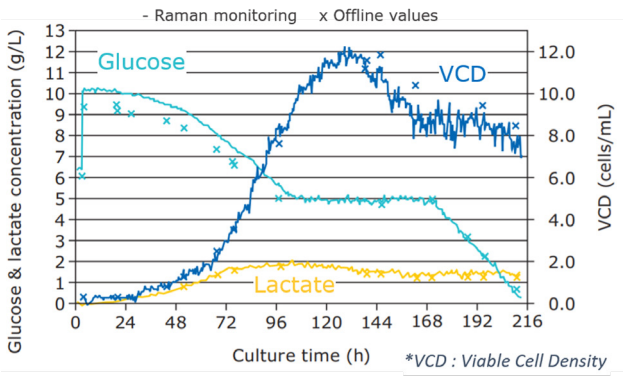
Bioprocess monitoring and control: a use case of Raman spectroscopy

The bioprocessing industry is moving towards automation and monitoring of bioproduction. To achieve this goal, new analytical instruments and tools are needed. For example: Raman spectroscopy has shown good performances in the real-time monitoring of cell culture parameters which allows automation of feeding strategy.
The Raman effect consists of the exchange of energy between the optical wave and the vibrations of the material. In simple words, it means that when light interacts with a chemical bond, the colour of the light is changed and we collect a Raman spectrum. This change of colour is different for every chemical bond: a Raman spectrum is a molecular fingerprint.



How does it work for bioprocesses? A laser is emitting light from the analyser to the end of the probe through an optical cable. The Raman effect occurs in the media, the spectra are collected by the probe and go back to the analyser through the optical cable. The spectra are then sent to the software where the calculation using chemometric model are performed and result in concentration value for the main nutrients and cell densities. The cell culture parameters determined in real-time can be sent to the bioreactor systems to trigger some event such as the activation of feeding pumps.

In this use case, a CHO-S cell culture was carried out in a bench-top glass bioreactor in fed-batch mode. The Raman parameters were chosen so that the cell culture parameters were measured every half an hour. In this experiment, the glucose concentration value is used to trigger the pump of a complete feed containing glucose so that the glucose concentration remained stable around 5g/L.
The glucose concentration was precisely maintained at 5g/L for three days by the programmed feedback loop. The feeding was stopped when maximum vessel volume was reached. The glucose continued to be consumed by the cells.



This automation and monitoring can take place simultaneously for several process parameters (glucose, lactate, cell densities (total and viable), ammonium, glutamate, glutamine, other amino acids) and quality attributes (protein titer, IgG, glycosylation, by-products, protein structure, others). Three criteria are required to monitor a parameter or an attribute:

- It is a molecule or related to a set of molecules
- In a sufficient concentration (% rather than ppm)
- There is a reference measurement available

Fabien Chauchard
Chauvin Arnoux

Real-time analysis of freeze-dried products as an answer of today's challenges in vaccine production

Dr. F. Chauchard and Dr D. Brouckaert, INDATECH - Chauvin Arnoux, France

Biotechnological production is continuously growing as it provides the ability to produce strong active compounds. The Covid-19 crisis has even shown the power of new approaches such as RNA vaccines or antibody medicines but also the need of fast process development. Even more important are the challenges in manufacturing, aiming at fast and high volume production but still keeping maximum requirements on safety and quality.

Most biopharmaceutical products are difficult to store due to formulation instability. Therefore, freeze-drying is the most commonly process used to increase the stability of those products, increasing their shelf-life and facilitating handling and transport. Due to the increasing demand for such lyophilized biotechnological formulations, the size of the industrial freeze-driers continue to increase. The lyocake validation requires more and more samples and increases the pressure on QC laboratory.

SAM-Spec is an innovative non-destructive multipoint NIR technology able to analyze in few ms the most Critical Quality Attributes (such as residual moisture content, cake density, cracks and melt) directly through the vials in-line and in real-time. In order to provide a complete analysis of production, this 100% inspection solution can be combined with an automated unloading system. This new solution on the market presents several advantages that will be discussed during the presentation.

Ilaria Scarfone
Thermo Fisher Scientific

Applied Biosystems SEQ Rapid Analytical Methods

Applied Biosystems™ SEQ analytical testing products are rapid molecular methods designed for pharmaceutical manufacturing to help ensure quality and safety of your pharmaceutical products. Our methods offer fully integrated solutions, utilizing highly sensitive molecular technologies. Sensitivity, accuracy, specificity and time to results are critical in the detection of contaminants and quantitation of impurities.

ResDNASEQ Residual DNA Quantitation System

The removal of host cell and vector impurities is a critical step in the purification of biopharmaceutical products. A major challenge is the accurate and sensitive quantitation of host cell and vector DNA impurities in drug substance samples. The Applied Biosystems™ ResDNASEQ™ Residual DNA Quantitation System is a fully integrated real-time qPCR system for quantitation of residual host cell DNA and residual plasmid DNA, including a highly characterized DNA reference standard.

- **Assays for commonly used cell lines**— CHO, HEK293, human, *E. coli*, Vero, MDCK, *Pichia pastoris*, NS0 and Sf9/Baculovirus
- **Assays for residual plasmid DNA**— targeting kanamycin resistance genes
- **Rapid testing and streamlined workflow**— time-to-results typically under 5 hours
- **Ultrahigh sensitivity and specificity**— no cross-reactivity to unrelated DNA
- **Optimized sample prep**— quantitative DNA recovery with manual or automated extraction
- **Worldwide support network**— expert training, technical support, validation and regulatory guidance

MycoSEQ Mycoplasma Detection System

Mycoplasmas are relatively common bacterial contaminants of mammalian cell cultures. Regulatory guidance requires that all products derived from mammalian cell culture be tested for the presence of mycoplasmas.
The Applied Biosystems™ MycoSEQ™ Mycoplasma Detection System is a fully integrated solution for real-time PCR–based mycoplasma detection. Following validation, regulatory review, and acceptance, the MycoSEQ assay is now used by many global manufacturers of different biotherapeutics modalities.

- **Proven, regulatory accepted method**— following validation, has been accepted by world wide regulatory authorities for over 42 on-market products
- **Rapid testing and streamlined workflow**— time-to-results typically in under 5 hours
- **Proven specificity**— detection of over 90 Mycoplasma species with no known cross-reactivity with closely related non-mycoplasma species
- **Demonstrated sensitivity**— detects less than 10 copies/reaction
- **Discriminatory positive/extraction control**— minimize risk of false-positive results
- **Dependable**— rapid analysis with Applied Biosystems™AccuSEQ™ Real-Time PCR Detection Software

MicroSEQ Microbial Identification System

Bacterial and fungal contamination of raw materials and production facilities negatively impact product quality and safety. The use of a genetic approach for microbial detection based on the 16S ribosomal DNA (rDNA) gene for bacteria or a specific genomic region of the large-subunit rDNA gene for fungi can help prevent delayed product releases, back orders, and even recalls. Identify bacterial and fungal species typically in under 5 hours with the Applied Biosystems™ MicroSEQ™ Microbial Identification System.

- **Comparative gene sequence analysis of rDNA**— considered the gold standard for microbial identification and is the method of preference in the USP guidance

CAMPUS BIOTECH DIGITAL

As part of its contract, the French biomanufacturing sector is launching an ambitious training platform: the Campus Biotech Digital. This platform is ambitious and differentiating in this field, both in its ability to bring together a group of players in the sector and in the training program on offer. It will enable the development of skills to meet the new technological challenges. Covering the entire bioproduction chain, the Campus Biotech Digital will use various innovative digital solutions to promote the understanding of processes and the appropriation of professional practices. The members of the consortium decided to work hand in hand in a collaborative approach to serve a higher interest.

The Campus Biotech Digital aims to pool different biotechnology and digital skills and expertise by stepping up cooperation within the sector and building an expanded ecosystem of innovative educational content design spaces in line with the needs of industry. This unique alliance embodies the commitment of the stakeholders to work together to organize and support the development of health biotechnology skills.

An outstanding collective intelligent project

Led by an industrial consortium

Training organisations

IT and Digital Partners

Equipment OEM Partners

Startups SMEs

Public Private Partnership

Regional support

Institutional Partners

The training modules will replicate steps in the bioproduction value chain, offering an immersive experience - like the simulators used to train airline pilots - through the use of digital twins, virtual reality, augmented reality, optimized control rooms and machine learning supported by artificial intelligence. There are numerous expected benefits. For example, the training modules will be tailored to the learner and the equipment, thus matching the needs of industry as closely as possible.

13 first curriculums over 3 years

The Campus is financed by an exceptional public/private partnership**, including €11.75 million under the "Engineering of vocational and on-the-job training and innovative offers" scheme run by the Caisse des Dépôts (Deposit and Consignment Office) on behalf of the government. In addition, it receives funds from the Opérateur de Compétences Interindustriel (inter-industry skills operator) and the Île-de-France region, and manufacturers in the sector have come together in a consortium to invest more than €30 million.

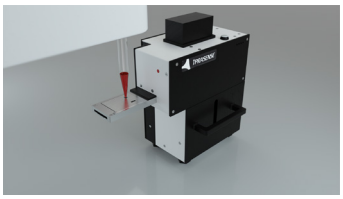
Iprasense

IPRASENSE, specialist in cell culture monitoring instruments

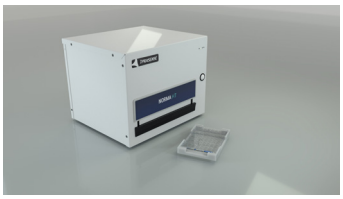
IPRASENSE is a start-up company located in Montpellier (France) specialized in cell culture monitoring instruments. Its automatic cell counters and viability analyzers (NORMA product range) is now present in many pharmaceutical industries.

In a few seconds, and from only a few microliters of cell culture, the cell counting and viability analysis are obtained with precision. The sample preparation is no longer necessary (no dilution and no labeling) allowing considerable time saving. The NORMA range, based on the new lensless imaging technology, is declined in several products: simple counters for easy and fast benchtop cell counting (NORMA XS) as well as high-throughput cell counters with the possibility of integration to micro-bioreactors in parallel for a full automation of the process (NORMA 4S). Cell counting in multi-well plates is also possible with integration to robotic pipettors (NORMA HT). The NORMA automatic cell counter answers the current problems encountered by the traditional Trypan Blue method, such as the intensification of the cell culture conditions tested with smaller volume required. These instruments successfully respond to these challenges and some of them are already installed in GMP environments!

NORMA XS



NORMA 4S

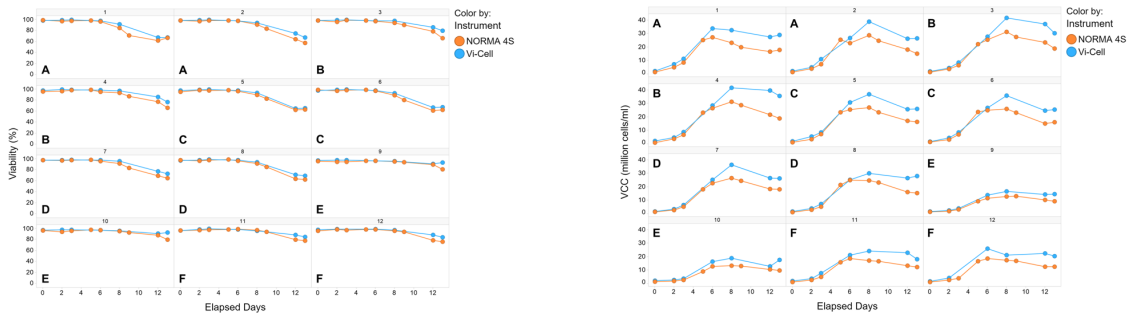


NORMA HT

iConcensus project

This project will develop innovative analytical, hardware, software and high-throughput tools to achieve a faster, safer and more cost-effective process for the development and manufacture of biopharmaceuticals, vaccines and advanced therapies.

In this context, the NORMA technology has been tested and evaluated in comparison with one of the reference cell counter based on the trypan blue method. These data revealed that the NORMA technology correlates well with the Trypan Blue reference method ! The NORMA 4S has also been successfully tested and integrated into the high-throughput parallel micro-bioreactors Sartorius Ambr15 and is now in operation in several companies.

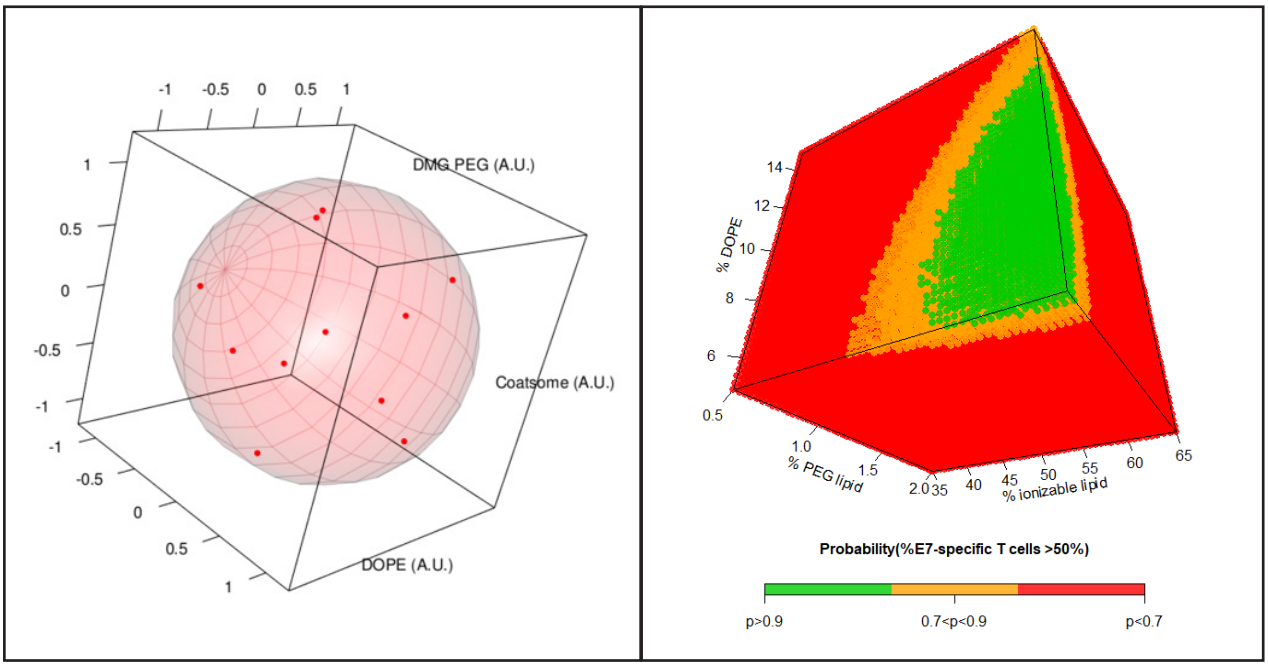


Cell viability and Viable cell count correlation between the NORMA 4S and the Vi-Cell XR on Ambr15 48-way. The six feed conditions vere performed in duplicate on CHO cells. (Data courtesy of GSK)

easyQBD: a Quality by Design SaaS Platform. Application to the development of lipid nanoparticles for mRNA delivery

Thierry Bastogne, tbastogne@cybernano.eu, (Université de Lorraine, CYBERNANO),
Sanne Bevers (eTheRNA, Belgium), Sander A.A. Kooijmans (UMCU, The Netherlands),
Lucie Hassler (CYBERNANO, France), Samir El Andaloussi (Karolinska Institutet, Sweden),
Raymond M. Schiffelers (UMCU, The Netherlands), Stefaan De Koker (eTheRNA, Belgium)

The transfer of mRNA by lipid nanoparticles has become an important issue in recent years not only for anti-COVID-19 applications but also for the development of new treatments against cancer. eTheRNA, UMCU, Karolinska Institutet and CYBERNANO are collaborating on this subject and in particular on the optimization of the formulation of a lipid nanocarrier capable of inducing an acceptable immune response. The question is to determine the values of three Critical Material Attributes making it possible to obtain an acceptable probability of an immune response (Criticial Quality Attribute) of at least 50%. For this purpose, the easyQBD service platform was used to implement the good development practice: Quality by Design (ICHQ8-Q11) and to respond effectively to this problem while reducing experimental costs. A Roquemore's Hybrid design composed of 11 different experiments was applied in triplicate to a panel of mice. All the statistical analysis was performed in a Bayesian framework both for the selection of relevant variables, the model identification and the validation of the model predictions. A quality region (in green in Figure below) has been identified in which the corresponding formulations have more than 90% chance of satisfying the expected performance on the immune response. Validation tests on a formulation selected in this area corroborated the model's predictions. In addition to this result, this study also demonstrates the effectiveness of the Quality by Design easyQBD platform to support the development of innovative pharmaceuticals.



«This work was carried out as part of the EXPERT, which received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 825828»

MGA Technologies

Biopharma 4.0, when technologies accelerate biotech processes

We are designing and building tailormade machines and production lines integrating all 4.0 technologies mostly with premium clients. Solutions we propose include collaborative and mobile robotics, connected and communicating machines, bigdata mining, machine learning, AI, digital twins, smart HMI, … in a nutshell : we foresee an IT & OT merger at the service of performance and flexibility of bioproduction. Applications include upstream processing, downstream processing and fill & finish operations. Technologies and innovations are accelerating and allow now for new concepts and design of machines and facilities. During Covid-19 situation, we have seen how fast our certitudes can be jeopardized. We anticipate this situation will remain, therefore speed, agility, flexibility, modularity are the new drivers and the new key success factors for our factories. These new drivers can be and will be integrated in machines 4.0 the best Biopharma Factories will run in the Future. We will overview the new key technologies coming up and how to anticipate rapid changes and integrate them in the Facility of the Future of Biopharma 4.0.

Nexbiome Therapeutics

Nexbiome Therapeutics is the first private incubator of microbiome biotech companies

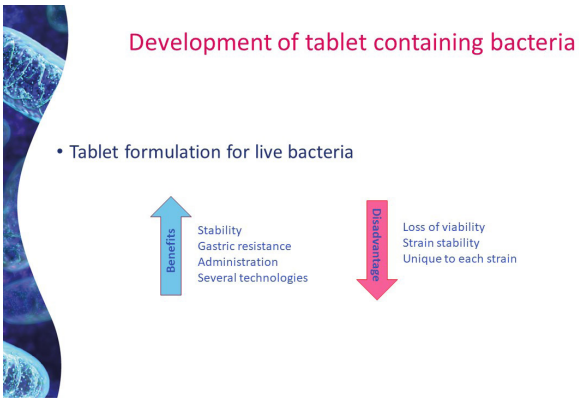
We define the microbiome as an ecosystem of microorganisms, the composition of which predisposes to health or to illness. Consequently, we are convinced that the microbiome represents the reservoir of therapeutic solutions for the future of human health.

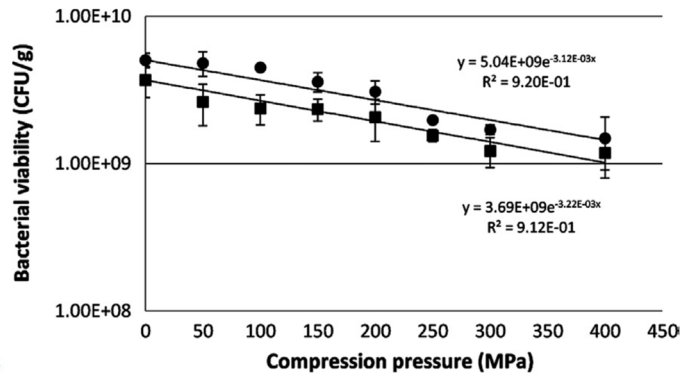
Our mission is to identify the best research projects and turn them into biotech companies that will bring innovative health solutions to the market. Our ambition is to contribute to the emergence of global champions in every therapeutic segment for which health through the microbiome makes sense.

One of our project, called Ladybiome, was to develop a tablet containing live bacteria for the treatment of vaginal infections.

Indeed, the beneficial effects of probiotic bacteria on woman health are now widely acknowledged, and this has prompted growing interest in research and development in the pharmaceutical field. However, to be viable when they reach their target, the bacteria must be able to survive during the manufacturing process and the biological pathway.

Tablet form best meets the requirements for protecting acid labile drugs, but the tableting process could be an additional stress for the bacteria.





This study evaluated the initial effect of compression pressure on the Lcr35® strain. A stability study was also performed on the tablets and revealed a beneficial effect of this form. A new mathematical model was developed combining compression and temperature parameters to predict the bacterial viability at any pressure and time.

Moreover, the genetic profile of Lcr35® (Rep-PCR, microarrays), its resistance to acidity and its ability to inhibit *Candida albicans* growth, after compression, were determined to evaluate the target product profile (TPP) in a Quality by Design (QbD) approach.

As a dosage form, tablets containing probiotic can guarantee that an adequate amount of bacteria reaches the therapeutic target (intestinal or vaginal) and that the product remains stable until the time of consumption.

InnoBioVir

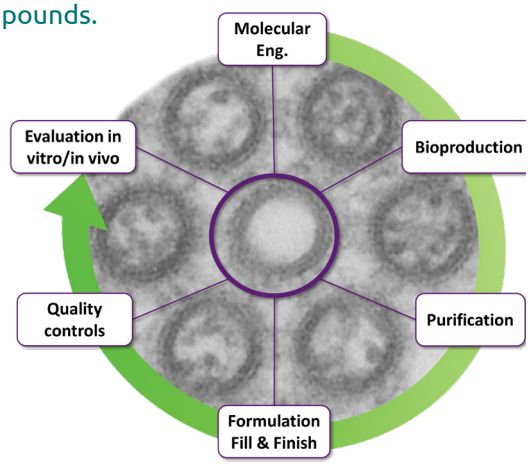
Service, R&D and training for production, formulation and evaluation of viral antigens and bio-compounds

https://www.innobiovir.univ-lyon1.fr

InnoBioVir (IBV) is the synergetic alliance between two cutting-edge academic laboratories (LAGEPP, VirPath) and two training centres (IPIL, IUT Lyon 1), aiming to propose cross-competencies expertise in the field of bioproduction, formulation and evaluation of viral antigens and bio-compounds.

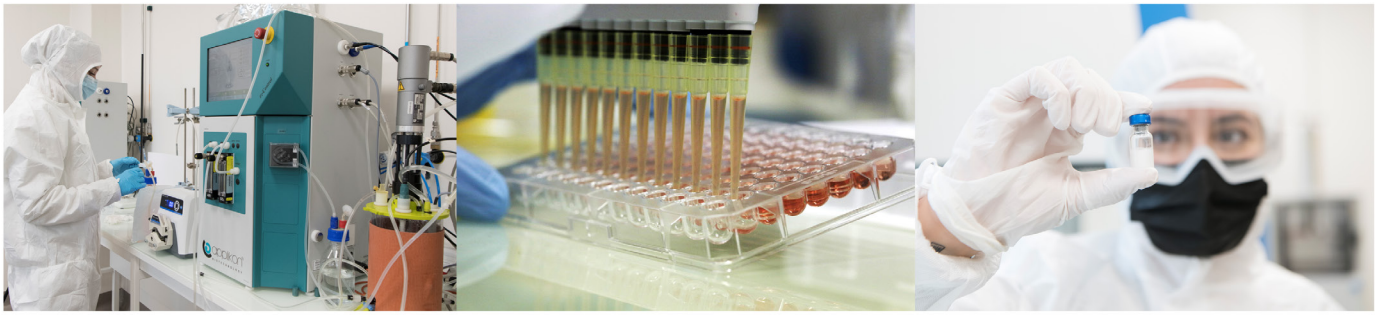
Tailor-made services

Addressed to both public and private innovators in the field of public health, IBV combines competencies all along the value chain of product and process development, with a particular focus on viral production and galenic methods.
Depending on the level of development and expertise needed, IBV can offer URS-based batch production services (non-GMP) or perform scientific developments either as service or as collaborative project.



From R&D batches to scalable process development

Using standard production methods, InnoBioVir can quickly generate small batches (1 to 10L) of biological material for formulation and *in vitro/in vivo* evaluation tests. IBV also proposes innovative and scalable technologies (suspension cell culture in bioreactor, chromatography, TFF) to perform a complete process development in the view of manufacturing industrialization.
InnoBioVir deploys its capabilities over more than 500 m^2 of technical floors, including BioSafety Level 2 and 3 facilities.



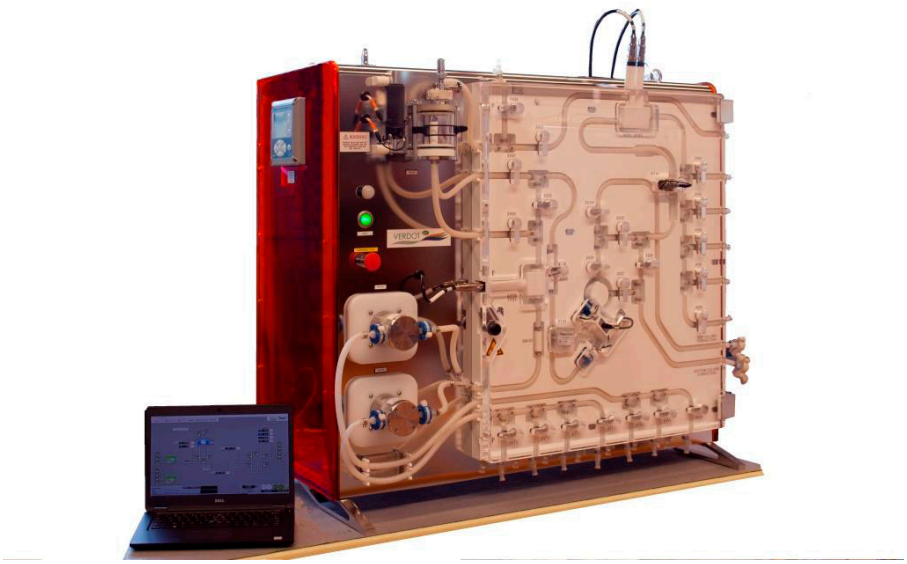
Industry-oriented trainings

Relying on deep knowledge of pharmaceutical field, InnoBioVir proposes advanced training programs designed to meet biopharma industry needs of today and tomorrow. Technicians and Engineers will be trained in a GMP-like environment on viral production, purification, quantification, as well as formulation and fill & finish methods.
Supported by AURA region (IRICE program), InnoBioVir brings innovative solutions to current and future challenges in the bioproduction industry.

VERDOT IPS²

The FlexiPro system, the LPLC system with disposable fluid path capable to drive small scale AAV purification and large scale proteins separation

Low pressure liquid chromatography is a key application in GMP single-use processes across a large spectrum of applications: from 8ml-scale AAV purification to much larger scale purification of proteins, monoclonal antibodies, and vaccines. VERDOT's FlexiPro Single-Use Chromatography system spans this broad range on a single benchtop equipment by the means of its four overlapping flow ranges from Ultra Low Flow (10 to 110mL/min), to High Flow (20 to 600L/h). This has made it the ideal choice for Biopharmaceutical Companies and Contract Development and Manufacturing Organizations. The session presented The FlexiPro system, performance, and examples of applications.

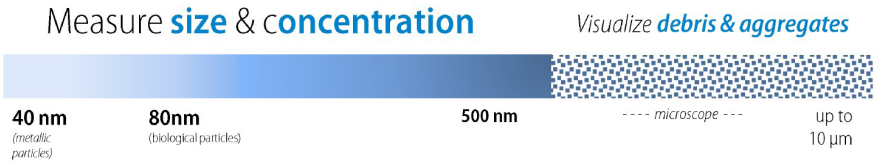


Myriade

Videodrop, a new tool for fast in-process controls and the measurement of the size and concentration of viruses in 40s

Today, Gene and Cell therapies are booming. However, due to the lack of solutions allowing rapid & continuous monitoring throughout the bioproduction process, Biotech' companies are working "almost blind". They often have to wait several hours or even days to get some results (ex:P24 Elisa tests). Therefore, there is a major need for new «in-process» quality control tools.

Myriade, a 100% French company, developed VIDEODROP: an innovative nanoscale imaging technology. VIDEODROP makes it possible to **measure the size & concentration of biological nanoparticles** in real time (40s),



in a single drop (5µL) without labeling & no purification in the range of 80 nm - 500nm & a concentration of 1E8 to 1E10 particles/ml.

During the bioproduction process, VIDEODROP is used for the quantification of the physical titer. Thanks to its rapidity of measurement, it allows to **continuously monitor processes, directly perform yield calculation** after Harvesting, Clarification, Purification, Concentration, or Diafiltration, and thus enhance process optimization and formulation screening being able to **work directly on real samples in a non-denaturant way at any stage of the process.**

Thereby, Videodrop is a promising **tool for fast in-process controls**, continuous monitoring, and final product characterization of complex viral vector solutions of **Lentiviruses, adenoviruses, retrovirus & extracellular vesicles.**

Claire Durand
Lionnel Lueginbuehl
Elodie Ly
Pall Corporation

Successful Fill-in & Finish: Insights & Best Practices

Pall Corporation provides critical filtration, separation and purification solutions to meet the demanding needs of a broad spectrum of life sciences and industrial customers around the globe. Across 80 locations and 10,000 people worldwide, we are unified by a singular drive: to solve our customers' biggest fluid management challenges. And in doing so advance health, safety and environmentally responsible technologies.
Final fill is arguably the most quality sensitive section of the biopharmaceutical process. Often, it involves a close working relationship between the producer, the hardware supplier of the final fill apparatus and the single-use supplier.
It is crucial that a trusted relationship is present, and that the product contact apparatus have quality built in and documented assurance of process suitability. This means, the right materials, the right documentation, and the right design, including formulation, filtration, fluid management, storage, and final fill.

During this workshop we have reviewed the following:

- Pall capabilities for fill and finish operations, including single-use technologies
- Defining and implementing single-use assemblies for fill and finish operations
- Implementing practical solutions for safe Pre-Use Post-Sterilization Integrity Testing (PUPSIT) in different filtration configurations

After a very interactive plenary presentation, participants were able to discuss during a hands-on session about the relevance of standardized arrangements (shadowboard) to make single-use system installation, leak testing, PUPSIT and operating a safer, simpler, and faster final filtration process.
A case study on this topic was recently published in collaboration with Swissfillon. Click on the following link to learn more how this CMO company implemented single-use technologies for formulation and filling operations: https://www.pall.com/en/biotech/webinars/swissfillons-approach-to-single-use-formulation-filling.html

Contact person: Elodie Ly, elodie_ly@pall.com

Philippe Béchaud
Félix Montero-Julian
Arnaud Paris
bioMérieux

Charaterization and Analytical Tools for Cell and Gene Therapies

Although cell and gene therapy products are reshaping how diseases are cured, manufacturing these products can be challenging. C&GT products are using living cells, therefore stability can be an issue for both source materials and final products. Moreover, these products often have a short shelf life and are manufactured at low volume. Regarding QC testing, analytical methods and technologies play an important role for the control and monitoring of these products. Some release tests, like sterility testing, require 14 days with traditional method to get results, which is not acceptable for patients in therapeutic emergency.

The goal of the workshop was to explore the main challenges for analytical development in the field of C&GT, discuss what is the best timing for a C&GT developer to think about the implementation of QC methods (what step in product development?) and where those tests are performed (CDMO, external or internal lab)? What is a reasonable TIME TO RESULT for the « sterility » testing ? why? How will QC be performed in 2025 for C&GT products? What is the most critical analytical technology we should focus on ?

The main outcomes of the discussion were:

- Quality attributes testing is critical and should be initiated very early, at R&D/preclinical stages. In house testing is usually preferred
- It is important to discuss early analytical methods for safety testing as will need to be validated early clinical (Ph1). Those tests are often outsourced at the beginning to CRO and/or CDMOs.
- The sterility testing is still the bottleneck.
- Release testing: improved Time To Result required but with a LOD equivalent to compendial methods
- It's very important to test Raw materials, especially when using closed systems
- New technologies like Next Gene Sequencing and PCR techniques will be very powerful.
- Being involved in discussion with industry players, regulatory bodies is key as everybody is still learning

Vous trouverez ci-dessous les réflexions à la suite de l'échange lors de la table ronde «Public and Private funds for bioproduction industry» concernant les financements des innovations des sociétés DeepTech en France (*texte en français*).

Sociétés technologiques / DeepTech : Financer son innovation

par MabDesign

Le secteur de la Santé est aujourd'hui un axe stratégique de développement de la France, grandement soutenu par le gouvernement et les différentes instances gouvernementales.

Ainsi, au travers notamment du Plan Santé 2030, l'objectif est de se repositionner comme un leader de l'innovation en Santé et d'accélérer sur le territoire le développement des technologies. En matière de technologies de bio-production, l'enjeu est clair : redevenir une terre de bioproduction de médicaments et retrouver sa souveraineté sanitaire.

Les promesses des innovations de ruptures, aussi bien au niveau des thérapies que des technologies de développement et de production, renforcent l'attractivité du marché de la Santé pour les différents investisseurs.

Il est important de noter que les outils de financements et les indicateurs clés de performance (ou KPIs, Key Points Indicators,) peuvent être différents selon la nature de l'innovation développée (société développant un produit thérapeutique ou une société développant une technologie).

L'Etat a lancé en 2019 un grand plan DeepTech, opéré par BPI France, afin de soutenir le développement des sociétés dites de DeepTech. En Mars 2021 (deux ans après le lancement du programme), le plan DeepTech avait généré la création de 200 start-ups, investi 870 millions d'euros (sur les 2,5 milliards d'euros initialement prévus) et mobilisé plus de 10 000 personnes autour du « DeepTech Tour » en France.

La startup Deeptech peut se définir comme une startup qui propose des produits ou des services sur la base d'innovations de rupture qui transformeront durablement nos modes de vie. Les projets Deeptech se caractérise par trois critères distinctifs :

- Ils proposent un produit qui apporte une forte valeur ajoutée sur son marché.
- Ils utilisent une technologie de rupture protégée par la Propriété Intellectuelle.
- Ils se développent en lien étroit avec des équipes de recherche publique ou privée.

Par ailleurs, la vague du numérique a fait des startups des acteurs centraux de l'innovation, permettant de constituer un écosystème solide et performant. Après la révolution du numérique, la deeptech est le deuxième étage de la fusée, pour faire de la France un leader de l'innovation de rupture.

Démarrer et développer un projet innovant nécessite d'avoir accès à des financements à chaque étape de la vie de l'entreprise. Il existe ainsi de nombreux types de financements, publics ou privés, activables en fonction de la typologie de la société, des technologies développées et des étapes de développement du produit ou du type de technologie portée par l'entreprise.

L'origine des financements (privés, publics, gouvernementaux…) et leurs typologies (subventions, prêts, prises de participation…) présentent tous des critères d'éligibilité. Ces critères prennent en compte un ensemble de facteurs internes et externes à l'entreprise tels que :

- L'équipe (ressources humaines, savoir-faire) et équipements…
- Le produit / la technologie (type, complexité …)
- Marchés (indication, compétition…)
- L'innovation (brevets…)
- …

L'ensemble de ces critères d'évaluation sont autant de verrous à lever pour accéder aux financements associés. Les sociétés, tout au long de leurs développement, doivent répondre aux attentes des différents acteurs du financement et s'assurer d'une structuration solide de leur plan de développement.

Il est à noter que les financements sont classés en deux grandes catégories :

- **Financements non dilutifs** : les aides publiques, les concours, les prêts, les subventions… Ce sont des financements qui interviennent en phase de création ou en phase dites « early » de la société. Ils permettent de générer du capital en augmentant les fonds propres de la société.

- **Financements dilutifs** : le Capital-Investissement, le Venture Capital, les Family Offices et Business Angels… Ce sont des financements qui interviennent en phase d'amorçage et d'accélération. Ils correspondent à l'entrée de nouvelles parties dans le capital social, se traduisant par une détention d'un pourcentage de l'entreprise.

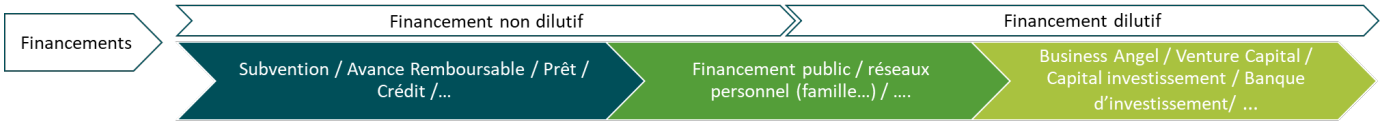


Fig. 1 : Les deux grands types de financements : non dilutifs ou dilutifs.

Ainsi dans ce document nous vous proposons dans un premier temps, une présentation des types de financements publics, puis dans un deuxième temps, un aperçu des étapes clefs et obstacles que doit surmonter une société lors d'une levée de fonds auprès d'investisseurs privés.

I. Les financements publics Français et Européens

La Banque Publique d'Investissement (BPI) est l'acteur incontournable du financement de l'innovation en France. La BPI peut accompagner les structures depuis les premières étapes de création de la société jusqu'à la commercialisation de son produit (thérapeutique ou technologique). Véritable « guichet de financement », et opérateur clé pour l'état, la BPI soutient la création et l'amorçage des sociétés de biotechnologie via différentes offres, comme des bourses et des crédits, ou intervient en tant que garant et en fonds propres.

Fig. 2 : Implantation de BPI France : 42 sites différentes répartis dans les différentes régions de France.

a. Aides à la création de l'entreprise

Pour financer cette première étape du projet, plusieurs solutions s'offrent aux acteurs :

- **Concours I-Lab** permettant d'accompagner la création de son entreprise.
- **Bourse French Tech** à destination des entreprises de moins de 1 an et/ou à des entrepreneurs individuels (personne physique).
- **Bourse French Tech Emergence** à destination des entreprises de moins de 1 an et/ou à des entrepreneurs individuels (personne physique) sur des projets dit DeepTech.
- **I-PhD** permettant de valoriser les travaux de recherche de thèse via la création d'une entreprise.

b. Aides en recherche & développement : valider une preuve de concept

La société est créée, au stade de TPE/PME, et en croissance. Elle doit consolider ses projets avec des études de faisabilité et des preuves de concepts :

- **Subvention Innovation** à destination des projets d'innovations technologiques.
- **Prêt d'amorçage avec le FEI (Fonds Européens d'Investissement)** permettant de renforcer sa trésorerie et de générer des conditions favorables à l'arrivée d'investisseurs.
- **Concours d'innovation i-Nov**, permet de financer un projet à haute valeur ajoutée afin de favoriser l'émergence d'une entreprise leader dans son domaine d'expertise.
- **Aide au développement Deeptech** réservée aux projets Deeptech et permettant de financer les dépenses de Recherche & Développement d'innovation de rupture avant leurs industrialisation et/ou commercialisation.

c. Aides au développement industriel

La société a développé un projet et entre dans une phase d'industrialisation, elle recherche des partenaires nationaux et internationaux :

- **Aide pour le développement de l'innovation** à destination des recherches industrielles (faisabilité du projet).
- P**rêt d'amorçage investissement avec le FEI** pour renforcer sa trésorerie après une levée de fonds.
- **La French Tech Seed - Obligations Convertibles** pour amplifier une levée de fonds (I-lab / PIA…).

d. Aides à la commercialisation

Phase finale du projet, la société est établie et commercialise son innovation :

- **Prêt Innovation FEI** pour financer le lancement sur le marché de l'innovation (service ou produit).

Ces financements publics sont divers et complémentaires. Ils assurent un accompagnement de la société depuis les étapes les plus précoces jusqu'à la commercialisation du produit et/ou de la technologie.

Il existe aussi des possibilités de financement pour des projets collaboratifs de grandes ampleurs au travers du **PIA** (Programme d'Investissement d'Avenir). La stratégie d'accélération lancée en janvier 2021 représente une enveloppe de 20 milliards d'euros sur cinq ans, dont 800 millions d'euros pour les seules biothérapies. Ce fonds est réparti entre divers axes de soutien au développement (Plan de Relance, Loi de Programmation de la Recherche…), sous la forme de subvention et d'avance remboursable.

II. Les investissements publics et privés

En parallèle des divers soutiens cités plus haut, un levier majeur du financement des biotech et des start-ups est l'investissement (Capital-Risque) par des fonds publics et/ou privés. Ces fonds proviennent de particuliers, de banques d'affaires, d'assureurs, de grands groupes pharmaceutiques et des gouvernements.

Ces investissements, souvent importants (pouvant être de plusieurs millions à plusieurs dizaines de millions d'euros), sont soumis à une analyse fine et poussée des sociétés.

Il intervient alors une notion cruciale pour la biotech : la science (et donc l'innovation) ne suffit plus à elle seule à justifier l'intérêt des investisseurs. En effet, c'est toute la société (projet, équipe, technologie, outils…) et son environnement (concurrence, marché, indication…) qui sont étudiés lors d'une étape déterminante pour l'investisseur, la **Due Diligence** dont les étapes seront détaillées ultérieurement.

a. Les investissement BPI

La BPI propose dans son pôle « Biotech » quatre fonds d'investissements ciblant des entreprises, à un stade « early-stage », développant des produits thérapeutiques ou des technologies médicales innovantes, répondant à des besoins médicaux importants et non satisfaits.

Les fonds d'investissement sont :

- **Fonds InnoBio2** de 143 millions favorisant les nouvelles thérapies, les technologies de la santé (dispositifs médicaux, diagnostic, les technologies de développement et de production et enfin le domaine de la santé numérique).
- **Fonds Biothérapies Innovantes et Maladies Rares** de 50 millions d'euros, mis en place pour développer les solutions thérapeutiques sur les indications de maladie rares.
- **Fonds Accélération Biotechnologies Santé** de 340 millions d'euros pour l'accélération des sociétés innovantes dans la Santé.
- **Fonds Patient Autonome** de 50 millions d'euros.

La BPI dispose aussi d'un fonds d'investissement majeur pour des financements plus importants, le fonds **Large Venture** (1.75 Milliard d'euros). A contrario du fonds Biotech, le fonds Large Venture n'est pas dédié au secteur de la Santé mais cible les technologies au sens large (Tech/Digital, Ecotechnologies…). Ils ont pour objectifs de financer l'hyper-croissance avec des tickets de l'ordre de plusieurs millions d'euros (entre 10 - 20 millions d'euros) par projet.

b. Les investissements privés

Les sociétés de capital-risque (ou Venture Capital (VC)) capitalisent sur des fonds issus de partenariats dits limités. Ces partenaires (grands groupes pharmas, banques d'investissement, fonds …) investissent dans une Venture Capital pour une durée définie (de 6 à 10 ans) après laquelle ils obtiennent un remboursement avec intérêts.

Les Venture Capital offrent des investissements pour des jeunes structures type start-up qui présentent un fort potentiel de développement. Les investissements sont risqués mais évoluent dans des secteurs attractifs normalement à croissance exponentielle. Les montants des investissements sont généralement de l'ordre de 5-15 millions d'euros, mais ils peuvent être occasionnellement plus important.

Les VC gèrent un portefeuille de plusieurs sociétés de produits thérapeutiques ou de technologies. La gestion de ce portefeuille est complexe et le fonds dérisque son capital en diversifiant ses investissements en termes de types

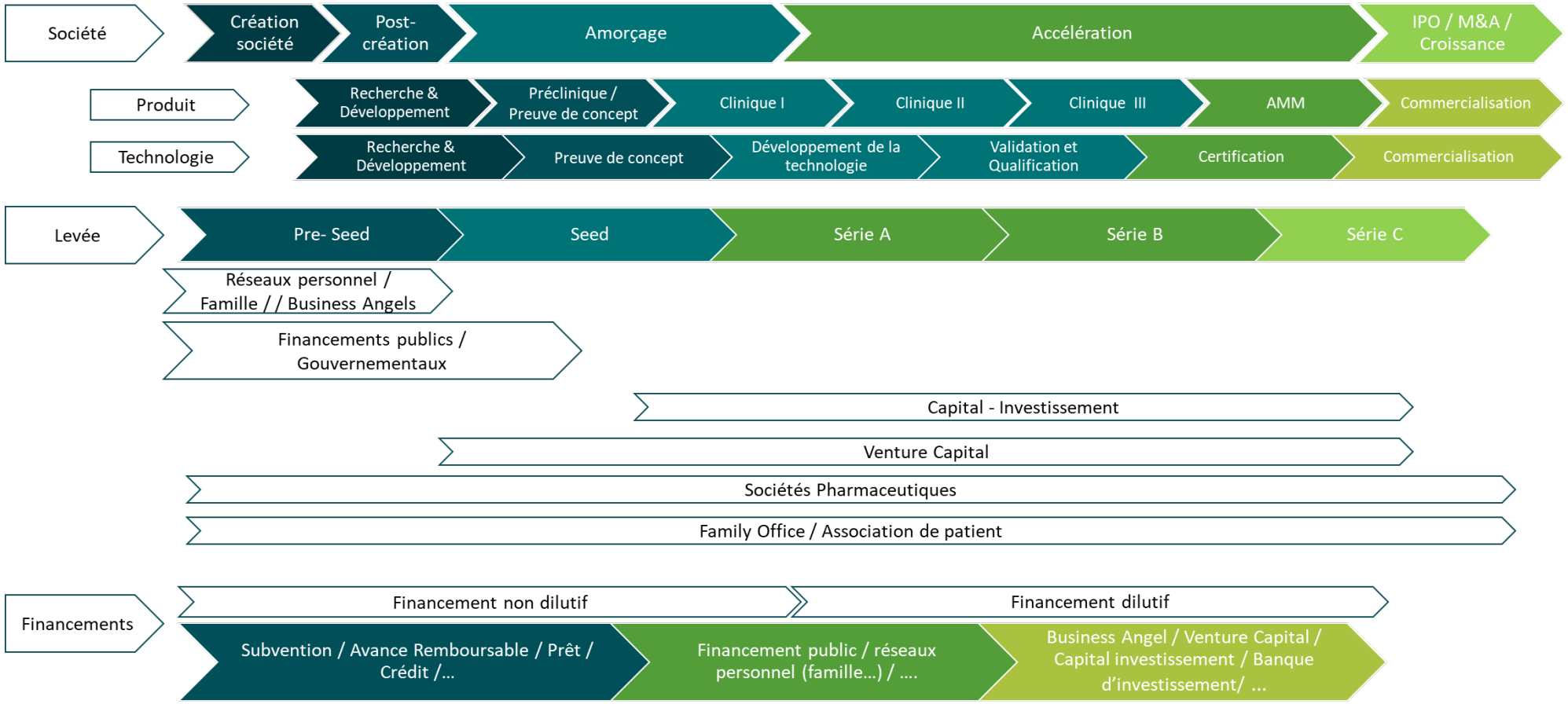


Fig. 3 : Stades de développement d'une société et financements associés.
Il est à noter que la segmentation des étapes et des financements est donnée à titre indicatif et que certains acteurs peuvent avoir une action plus transverse (initier un financement plus tôt ou plus tard dans la chaine de développement de la société).

de projets (médicaments chimiques, biomédicaments…), types de technologies (dispositif médical, outils d'intelligence artificielle…) et stades de développement (R&D et produits plus avancés dans le pipeline). Ces investissements assurent au Venture Capital des parts dans l'entreprise ciblée, parts qui seront à l'origine du remboursement lors de la « Sortie » de la société.

La « stratégie de sortie » représente les options potentielles qui s'offrent au VC pour rentabiliser son investissement. La « sortie » peut se faire à différentes étapes du développement de la structure et sous différents formats :

- IPO : une introduction en bourse permettant l'arrivée de nouveaux acteurs dans le capital;
- M&A : une méthode de croissance qui passe par l'acquisition et la fusion avec d'autres acteurs;
- Le licensing du produit ou de la technologie;
- …

Les Venture Capital sont donc des leviers majeurs du financement et de la croissance des sociétés. Un investissement d'une ou de plusieurs de ces structures nécessite donc une analyse et une évaluation fine et poussée des sociétés. Afin d'obtenir un bénéfice lors de l'exécution de la stratégie de sortie de la biotech, le financeur doit s'assurer de la solidité de la société (équipe, savoir-faire...), de la valeur ajoutée de l'innovation (propriété Intellectuelle, « first in class ») et de la réalisation du projet (faisabilité, technique de production, partenaire…).

Ainsi un audit approfondi de la société sera effectué permettant d'évaluer au mieux ses capacités de croissance et de prises de valeur.

III. Préparer sa levée de fonds

Bien qu'indispensable à toute croissance, la levée de fonds d'une société est un exercice complexe, chronophage et qui nécessite de l'expérience. Ce processus aussi bien dans sa préparation en amont que dans son déroulement occupera la totalité du temps du porteur de projet et d'une partie de son équipe.

C'est donc une étape cruciale qui nécessite préparation, anticipation, sans qu'aucune garantie de succès ne soit assurée.

Nous vous proposons ci-dessous une ébauche des différentes étapes qui constituent une levée de fonds. Ces étapes mènent à la Due Diligence, une analyse complète de la viabilité d'une société sur tous les aspects (financier, scientifique, réglementaire…).

a. La « Pré-Due Diligence »

1. Pitch Deck

Bien que certaines structures d'investissement fassent du scouting et évaluent des biotech, il est fort à parier que la première approche sera à l'initiative de la société. Une approche pro-active est fortement conseillée. Ce premier contact se fait par l'intermédiaire d'un « Pitch Deck » (ou Slide Deck, start-up Deck) de 15 à 25 slides.

Ce support est crucial, il doit être suffisamment intéressant pour retenir l'intérêt du financeur et donc conduire à un entretien oral. L'objectif de ce Deck n'est pas la levée de fonds mais de provoquer une rencontre.

Le sujet du Deck doit couvrir les points clés du plan d'affaires, les produits et/ou services fournis, les projections financières et les besoins de financement. C'est un support visuel que doit présenter la société.

Le contenu du Deck doit présenter la proposition de valeur, le problème à résoudre (technologique, impasse thérapeutique…), le marché ciblé et l'opportunité qu'il représente et enfin la solution apportée par l'innovation. Une fois le cadre posé, le pitch deck doit permettre au financeur de comprendre comment cette solution va être génératrice

de revenu (le client final peut être différent de l'utilisateur final) dans un contexte compétitif. Derrière ce business model doit aussi être mis en exergue les analyses et projections financières ainsi que l'utilisation des fonds levés.

Enfin le Deck devra présenter l'équipe, les partenariats éventuels et si possible les stratégies de sortie possible de la société.

Une fois construit, ce Pitch Deck est à faire parvenir aux différents fonds identifiés.

2. Sélection du pitch par un fonds

Les Deck sont donc lus par des analystes qui réalisent une première sélection des dossiers pour une présentation officielle aux fonds. Les critères de sélection varient en fonction des fonds et de leurs portefeuilles. En effet, les fonds gèrent des portefeuilles complexes de plusieurs sociétés de produits thérapeutiques ou de technologies et dérisquent leurs investissements en diversifiant les types de projets (médicaments chimiques, biomédicaments…), types de technologies (dispositif médical, outils d'intelligence artificielle…) et stades de développement.

Ainsi, malgré l'intérêt d'un projet, ce dernier peut ne pas être retenu par des fonds en raison de leurs stratégies à l'instant t.

3. Présentation aux fonds d'investissement

Une fois sélectionné, « le vrai travail » commence. La présentation ici doit être plus dense et détaillée, on parle alors de 30 à 40 slides. L'exercice est laborieux et le taux d'échec élevé. Il ne faut pas s'attendre à un engagement du fonds à l'issue de cette étape, il s'agit d'une prise de connaissance et d'information pour valider l'intérêt initial. La rencontre pourra se faire avec un « Partner » (décideur) du fonds mais de manière générale, la société rencontrera l'analyste à l'origine de la sélection du Pitch.

La présentation plus complète est à travailler et à challenger auprès d'entrepreneurs et de partenaires, car malgré le temps passé, les retours de ces phases tests permettront de mettre en évidence les points d'amélioration du support et des explications associées.

Cette étape nécessite donc humilité et remise en question afin de tendre vers la présentation « parfaite » construite sur les échecs des présentations tests avec les fonds, et il faudra faire preuve de résilience.

Ce premier échange doit rassurer le fonds sur la capacité des parties prenantes à travailler ensemble.

Le fonds doit croire en l'Homme (l'équipe) et avoir envie d'aller plus loin dans les échanges. C'est un rendez vous qui posera les bases des relations et une prise d'informations sur les besoins et attentes des deux parties.

4. Sélection du dossier par les Partners du fonds

Les analystes font un reporting à fréquence régulière (hebdomadaire, bimensuelle…) des sociétés rencontrées. Présentation des sociétés, feedback des entretiens et remplissage ou non des critères d'éligibilité définis par le fonds d'investissement selon sa grille d'évaluation. A partir de ce point, si la société est sélectionnée par le fonds pour continuer le processus, elle interagira alors avec des décideurs. Le fonds va entrer dans une phase d'analyse complète et extrêmement poussée de la société sur tous ses aspects.

5. Etapes du Deep Dive : Challenge de la biotech

Cette étape représente 2 à 6 meetings, selon les processus des fonds, au cours desquels seront évalués l'équipe, la technologie, le Business Plan…

De nombreuses questions seront posées pour comprendre et challenger la biotech. Le fonds d'investissement veut

dérisquer son potentiel investissement et cherchera donc tous les éléments susceptibles d'être un problème. Les investigateurs seront des experts du fonds ainsi que des experts externes réunis en équipe projets. C'est une enquête approfondie qui doit garantir au fonds la viabilité de son investissement en termes d'un ratio bénéfice/risque favorable.

Ce travail comprend donc la préparation en amont des réunions de l'ensemble des données demandées par le fonds, la présentation et la défense des informations transmises ainsi qu'une forte anticipation des potentielles faiblesses qui seront identifiées et soulevées par les investigateurs. Des membres de l'équipe de la biotech seront sollicités en fonction des sujets et des expertises.

D'un point de vue global, ces cinq premières étapes représentent plusieurs centaines d'heures de travail en équipe, étalées sur 1 à 3 mois. Si plusieurs fonds d'investissements sont contactés en parallèles (ce qui est conseillé), c'est donc 100% du temps du porteur de projet qui est bloqué et ce, sept jours sur sept.

6. Term sheet : les conditions du financement

L'étape finale de la levée de fonds est l'établissement d'une « Term Sheet » (protocole d'accord), document établissant les conditions du financement. C'est le comité de Fonds qui participe à la rédaction de ce document. Il est à noter que cette étape peut prendre du temps car c'est un élément crucial pour les investisseurs.

Ce document décrit ainsi le montant du financement, la typologie et structuration de l'investissement et, étant donné la nature dilutive de l'investissement, la répartition des pourcentages de parts de la société. Toutes les conditions ou termes pouvant venir amender l'offre sont aussi inclus dans ce document. Certaines négociations peuvent avoir lieu entre les parties prenantes avant que la Term Sheet ne soit acceptée. Lors de la négociation, le rôle du porteur du projet est clef, sa préparation à cette étape est donc absolument nécessaire pour assurer la signature d'une Term Sheet équitable et juste entre toutes les parties. Avoir le sens des affaires (« business acumen ») sera élémentaire et déterminant pour réussir cette étape.

Note : bien que la Term Sheet arrive en fin de processus, son succès est soumis aux différentes étapes décrites en amont. En effet, chaque étape doit être perçue comme une négociation à part entière sur laquelle seront basées les discussions des étapes suivantes.
Les règles du financement sont variables d'un fonds à un autre, rien n'est donc à prendre pour acquis et le porteur du projet devra faire preuve d'agilité et d'adaptabilité à chaque étape pour chaque fonds. La réflexion et la préparation en amont de la prise de contact des fonds d'investissements sont déterminantes pour « affronter » leurs processus et les négociations.

b. La « Due Diligence légale »

C'est une étape qui voit l'arrivée des avocats de chaque partie prenante contenue dans la Term Sheet. Tous les points de cette dernière sont analysés et validés du point de vue légal. Tous les échanges ayant eu lieu sont revus et étudiés afin d'éviter tout éventuel désaccord sur la signature du document.

Les avocats rédigent aussi le « Pacte d'Associés », car le financement conduit par définition à l'entrée de nouveaux associés au capital de la société. Cette étape peut induire de nouvelles phases de négociation.

Cette étape longue et fastidieuse peut représenter à elle seule 2 à 3 mois de travail et de discussion.

c. Phase de libération des fonds

Etape dite de « Closing » ou une assemblée générale des associés (historiques et nouveaux) permet de libérer les fonds selon les conditions préalablement établies (sur objectifs, échelonnement des versements en fonction des indicateurs d'avancement…).

En conclusion, la levée de fonds est un process de 6 mois à 9 mois qui impliquera toute l'équipe de la société cherchant à être financée. Le processus nécessitera une dévotion totale et une motivation absolue du porteur de projet pour assurer toutes les chances possibles.

Pour qu'un deal soit un succès, les différentes parties doivent faire preuve de transparence et d'équité dans la négociation et l'établissement de leur accord.

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Upcoming Events

7TH BIOPRODUCTION CONGRESS

29-30 September 2022 - Lyon

CMC READINESS TO ACCELERATE BIOTHERAPEUTICS FOR PATIENTS

http://www.biopcongress.com

24 May 2022
LYON

MABDESIGN THE IMMUNOTHERAPY NETWORK

PARTNERING DAY

https://mabdesign-partnering-day.mabdesign.b2match.io/

10TH AIS Antibody Industrial 2022 Symposium

JUNE 28-29, 2022
MONTPELLIER, FRANCE

MAbImprove LabEx Tours Montpellier

MABDESIGN THE IMMUNOTHERAPY NETWORK

https://aiscongress.com/

Immunotherapies & innovations for Infectious Diseases

6th Congress 2022 – November 2022 – LYON, FRANCE

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LYONBIOPOLE AUVERGNE-RHÔNE-ALPES

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