



ECONOMY

GENOPOLE

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STRUCTURING AND STRENGTHENING AN ECOSYSTEM FOR BIOTHERAPIES AND BIOPRODUCTION

BIOTHERAPIES COMPRISE TREATMENTS DERIVED FROM BIOLOGICAL ENTITIES SUCH AS BACTERIA, VIRUSES OR ANIMAL CELLS THAT ARE GENETICALLY MODIFIED THEN CULTURED IN MASS IN BIOREACTORS. THEY, AND THEIR INDUSTRIAL PRODUCTION, CALLED BIOPRODUCTION, ARE KEY SECTORS FOR THE FUTURE OF THE PHARMACEUTICAL INDUSTRY. BIOTHERAPIES PLAY A ROLE IN THE TECHNOLOGICAL, ECONOMIC AND HEALTHCARE INDEPENDENCE OF FRANCE. PARIS REGION IS A MAJOR ACTOR IN CERTAIN BIOTHERAPIES, PARTICULARLY GENE* AND CELL* THERAPIES. HOWEVER, THE REGION NEEDS TO STRENGTHEN ITS CAPACITIES IN BIOPRODUCTION AND ENSURE THIS LATTER'S FUTURE BY TRAINING TOMORROW'S TALENTS.

revolution is sweeping through the pharmaceutical industry. The term «biotherapies» (also «biopharmaceuticals» or «biodrugs») covers a range of therapeutic entities derived from or developed within living organisms. It contrasts with conventional chemical pharmacology, built upon inert raw materials. The worldwide demand for biotherapies is expected to grow greatly by 2030. Many biotherapies involve large and complex therapeutic molecules for which R&D and manufacturing costs are extraordinarily high. Furthermore, they are not meant for broad use in millions of patients, but rather targeted deployment in specific and relatively uncommon situations (rare diseases, personalized medicine, etc.).

In 2020, France imported 95% of its biotherapies, as it was able to produce locally only five of the 76 biotherapies authorized in Europe¹.

Furthermore, once a market has developed, it becomes nearly impossible for a late-arriving competitor to take a piece of it². Producing these treatments in France is thus of strategic interest to reduce trade deficits, control healthcare system costs and ensure access to stocks.

The pharmaceutical industry, currently confronting decreasing revenue among its flagship products and growing competition from generics, also has a vested interest in committing itself to this new sector.

NATIONAL POLICY ORIENTATIONS

- Sector strategy contract (CSF Santé) Bioproduction project.
- Biopharmaceuticals Major Challenge: improve productivity and lower production costs.
- Biotherapies and bioproduction acceleration strategy within the Innovation Healthcare 2030 plan.

INCUBATORS AND ACCELERATORS: HELPING BIOTHERAPIES TAKE WING IN PARIS REGION

Paris Region count about 15 incubators and accelerators (and projects for several more), many attached to hospital centers, that are helping promising projects and start-ups take flight. Paris Biotech Santé at Cochin Hospital hosts about 12 ecosystem businesses. On the Seine riverside, in Paris' 13th arrondissement, Biopark is home to several up-andcomers such as PathoQuest, a genome sequencing tech provider with roots in Institut Pasteur, or Cellectis, a genome engineering company specialized in the development of immunotherapies. These Parisian structures are highly attractive for businesses, but so are others in Paris Region, starting with Genopole. For example, this latter has been home for 15 years now to Xentech, a contract research organization born of Institut Curie in Paris and specialized in the preclinical evaluation of cancer treatments and the identification of biomarkers and therapeutic targets. The region also counts Villeiuif Bio Park and the Saclay plateau, which will soon play a greater role in start-up creation with the IPHE Paris-Saclay project and the incubator being built by the Servier pharmaceutical group.

NATIONAL AND REGIONAL STRATEGIES

In response to this changing therapeutic landscape, most of the world's large industrial entities are supporting their biotherapy sectors and developing local bioproduction facilities. In Europe, Belgium Switzerland, Italy, Sweden and the United Kingdom have all implemented public support policies³. The high price of biotherapies compared to that of conventional pharmaceuticals is largely due to a lack of industrialization for their manufacturing processes. Thus, national support policies are often focused on finding novel bioproduction procedures. Italy has already achieved this in the field of cell therapies. Now a pharmaceutical production leader in Europe, that country manufactures 12 of the 76 EU-approved biotherapies⁴. Their success is the result of national investments to enable the acquisition of ultra-modern production means and the delivery of high-quality products to the market at competitive prices. Bioproduction is identified in the United Kingdom as a national strategic orientation with the objective of improving bioprocesses to lower costs and become a leader in the sector. France too has set its sights on becoming a manufacturing leader in the fast-growing market of novel proteins and innovative therapies and thus deployed a national policy to achieve that goal (see inset).

«We have world-class researchers, universities, hospitals, industrial integrators, leading bioclusters like Genopole, major industrial groups and a cornucopia of SMEs including innovative biotechs and deeptechs* ready and able to help us unlock industrial bioproduction: the foundation has been laid!» Medicen President Christian Deleuze

Paris Region is also looking to become a European leader in biotherapies and bioproduction. Several calls for proposals enable the passage from innovation to industrialization, and more generally, a number of actions and programs are underway to support and strengthen the Île-de-France ecosystem. Medicen President Christian Deleuze underlined the territory's potential at the Regional Conference for Biotherapies and Bioproduction, held 12 May 2021. There remained however the task of mapping the Paris Region ecosystem, i.e., the principal objective of the present analysis.

A RICH ECOSYSTEM, BUT LIMITED BIOPRODUCTION CAPACITIES

Our analysis of the Île-de-France biotherapies and bioproduction ecosystem is built upon the identification of companies, business launch and means facilities (incubators, accelerators, office+lab facilities; abbreviated IPHE hereafter), and academic research centers. For the purposes of our analysis, «biotherapies» are defined mainly as gene therapies, cell therapies, immunotherapies, vaccines and extracellular vesicles.

Renowned actors and a medical world's first

Our evaluation performed with input from the innovation strategy firm D&Consultant showed a limited but rich ecosystem comprising about 140 businesses roughly equally divided between the biotherapy and tech-provider fields. About 60 biotherapy businesses are involved in R&D, half of them in biotechnologies and more than a quarter in other physical and natural sciences⁵. Many of these companies are SMEs, although Paris Region also counts major French and international laboratories that contribute to the ecosystem's visibility. Most of these latter are commercial entities with no bioproduction or biotherapy research staff in Paris Region, but there are exceptions. For example, Sanofi has its global R&D and manufacturing center for immunotherapies at Vitry-sur-Seine. Servier has immunotherapy R&D teams at Suresnes and intends to open an incubator and research center in Gif-sur-Yvette (within the Saclay plateau) in 2022. Finally, Novartis boasts a bioproduction facility in the Courtabœuf Paris-Saclay Park in Les Ulis. That facility, since Novartis' acquisition of CellforCure, is Europe's leading platform for the large-scale production of advanced therapy medicinal products within the setting of cell therapy projects.

Nonetheless, the veritable potential of the Île-de-France ecosystem is to be found in the presence of promising start-ups and SMEs born of institutional research. Ipsirius, an Inserm spin off, illustrates this well. That company is developing an induced pluripotent* stem cell (iPSC) bioengineering platform for immunotherapies and a nextgeneration, allogeneic iPSC-based polyvalent cancer vaccine.

Ipsirius and the other companies active in biotherapy development or production need products and services provided by tech providers, the activities of which are highly diverse in Paris Region. Most of them provide R&D activities but there are about 10 tech providers working in informatics⁶.

Along with its numerous start-ups and SMEs, the Île-de-France biotherapies ecosystem also benefits from the direct implication of three major groups: Dassault Systèmes, Capgemini Engineering (ex Altran Technologies) and Thermo Fischer Scientific. The first two have teams in Vélizy-Villacoublay working on manufacturing and quality in the fields of vaccines and biotechnologies, and the third unites several affiliates at the Courtabœuf Paris-Saclay Park in Les Ulis, as well as in Ivry-sur-Seine following its acquisition of PPD France.

There are also close to 60 world-renowned academic research centers that contribute to the expansion of biotherapies and often give birth to start-ups in Paris Region. Their work holds great promise. The biotherapies ecosystem in Paris Region recently achieved a world's first. In May, a Franco-Swiss team led by Professor José-Alain Sahel, founder of the Institut de la Vision in Paris, partially restored the eyesight of a patient with a degenerative disease of the retina. The Île-de-France company GenSight Biologics, a leader in gene therapies for blindness, was also involved in that success.

GLOSSARY

Gene therapies treat genetic diseases by repairing or replacing defective genes: functional genes are inserted in the genomes of affected cells to compensate for the dysfunctioning gene. The introduced gene is, itself, the active pharmaceutical ingredient of the therapy. The «gene drug» is delivered to the target tissue and ultimately the cell itself by a transport mechanism called a vector.

Cell therapy, also called regenerative medicine, uses stem-cell-derived cell grafts to restore the function of tissues and organs damaged by disease, age or trauma. The stem cells underlying cell therapies are cultured in laboratories and selectively differentiated into the different types of cells that constitute tissues and organs. **Deeptechs** are start-ups proposing products or services built upon disruptive technologies.

Immunotherapies are

treatments designed to enhance (and sometimes diminish) immune response. This may involve the administration of immunomodulators or the directed use of specific immune system proteins such as immunoglobulins.

Extracellular vesicles are

nanovesicles derived from the cell membrane and secreted into the extracellular space. Interest in extracellular vesicles is increasing because of their patient-tailorable ability to transfer biological contents (e.g., gene/drug combinations in certain cancers) between cells. **Industrial integrator** is a label designating a technological platform able to accelerate the development of technological solutions and innovative therapies.

Pluripotent stem cells are cells able to multiply indefinitely and differentiate into any type of cell in the organism

Induced pluripotent stem cells, abbreviated as iPSCs, are created by genetically reprogramming differentiated adult cells, skin cells for example, back to the pluripotency of embryonic stem cells.

Greater Paris, Genopole and Paris Saclay

Counting close to three-quarters of its businesses, the majority of the regional biotherapies ecosystem is located in the Greater Paris Metropolis (MGP). Paris alone represents half of it, with about 40 biotherapy establishments and 30 tech providers. Beyond the MGP, about a fourth of the remaining ecosystem is located in the north of the Essonne administrative department, either at Genopole (about 20 establishments) in Évry or on the Saclay plateau (about 15)—particularly the Courtabœuf Paris-Saclay Park in the collectivities of Villebonsur-Yvette and Les Ulis. A number of major entities are to be found there, such as LFB Biomédicaments, Cellforcure (acquired by Novartis) Thermo Fischer Scientific, and now Regen Lab, a world leader in the development and production of autologous platelet rich plasma for cell therapies, which recently transferred its activities from Switzerland to France.

Still little bioproduction in Paris Region

Despite its essential nature for the ecosystem and the boost given by the arrival of Regen Lab, the bioproduction potential in Paris Region remains low, represented mainly by only two small caps, Yposkesi and Cellforcure, and one pharmaceutical group, Sanofi in Vitry-sur-Seine. LFB Biomédicaments also merits mention in this setting⁷.

Being vastly insufficient in comparison to the richness and momentum of the ecosystem in general, the development of bioproduction in Paris Region is a vital issue, all the more so in that two of the three main actors given above manufacture products only on their own behalf. The rarity of local subcontracted bioproduction capacities may result in companies turning to foreign services for their clinical batches and most likely their commercial batches too. Structuring bioproduction in France and in Europe is thus imperative. To place itself within this structuration, Paris Region is actioning two primary levers: an industrial integrator strategy and bioproduction specialist training.

TOMORROW'S ECOSYSTEM: INDUSTRIAL INTEGRATORS AND EXPERT TRAINING

Magenta: an industrial integrator* at Genopole

Magenta is an industrial integrator providing expertise in cell & gene therapies and biotherapy production. It seeks to address needs in frequent pathologies, primarily cancers and infectious diseases, via autologous therapies for personalized medicine or allogeneic therapies for «off the shelf» therapeutic needs.

Within a fruitful environment for innovation in technologies and the development of novel products, Magenta proposes cell or combinatory gene and cell therapy approaches responding to specific clinical indications. The integrator is developing solutions with immense industrial potential by mining the therapeutic potential of umbilical cord blood or bioengineered iPSCs, among other technologies. Magenta enables a quicker move to clinical trials



Interactive version of the map: https://bit.ly/biotech-idf

LARGE PHARMACEUTICAL LABORATORIES, BUSINESSES, EQUIPMENT PROVIDERS, SPECIALIZED BUSINESS PREMISES AND ACADEMIC RESEARCH Paris-Charles de Gaulle Sarcelles VAL-D'OISE Aenitis Technologies Paris Le Bourget SEINE-ET-MARNE 5 Argenteuil Saint-Denis SEINE-SAINT-DENIS Bobigny Biogen H. Bichat Madecell Acticor D Nanterre Pherecydes Mitologics Lilly Novartis Le Raincy Lynceus -Oroxcell T Parexe AstraZeneca Novo Nordisk H. Saint-Louis Biocitech Lysogene PARIS MEARY Entreprise MEARY -0 H. 15-20 I. de la Vision Biofacet 17 Foresight 15 Paris santé 4Dcell Karcinolis BioLabs Hôtel-Dieu Servier npus Elvesys 2 H. Necker Imagine Agoranov_ 513 Hybridenics Torcy HAUIS-DF-SFINE 714 Tech Care Paris Sarepta 12 11 -* Millidrop Amgen 3 eur : C du Cerveau Nogent-sur-Marne Boulogne-Billancour Bio Rad - Biopark I. Roche PatoQuest $\mathbf{\star}$ - Evevensys Institut du Cerveau I. de Myologie HEGP Janssen Gilead H. Pitié Salpétrière Paris Biotech Santé H. Bicêtre 🛧 Telomium Script I. Cochin BIO&D EFS Core Biogenesis Encefa Ixaka Everimmune Genomic Vision vax r Life Sc 9 2 Abbelight Dassault Systèmes Villejuif Bio Park Í 🖈 L'Haÿ-les-Rose Sanofi **Capgemini Engineering** Créteil 1. François Jacob H. Henri-Mondor MIRCen I. Gustave Roussy Archimmed efs IMRB Cancer Campus VAL-DE-MARNE **NeuroSpin** I. Sc du Vivant FJ Evora Bio \mathbf{t} Paris-Orly Servier Incubateur IPHE Paris-Saclay U. Paris-Saclay Abcell Bio Europio Scientific Palaiseau Core Biogenesis urofins Pharma Diagen Eukarys IncubAlliance 🗘 Genosafe Thermo Fisher Genosplice Technology Genex ntegrägen New England Biolabs France LFB CNRS Cellforcure Polytheragene Synchrotron Soleil Synsight Yposkesi Whitelab Genomics I. François Jacob LGRK/IRCM IDMIT CNRGH lentech Yubsis ESSONNE Genoscope * Généthon U. d'Évry 🗙 Synhelix 200 Évry-Courcouronnes Inatherys Pharming Inatherys 5 km 0 Genopole Généthon © L'INSTITUT PARIS REGION 2021 Genopole I-Stem ART-TG CITHERA Sources: Institut Paris Region and D&Consultants Vaxon Vaxea

THE BIOTHERAPIES AND BIOPRODUCTION SECTOR IN PARIS REGION



thanks to its industrial transfer capacities. It provides specific analytics to guarantee the safety and efficacy of treatments and contributes to the validation of new international standards. Magenta was founded by and unites two internationally renowned laboratories: Cithera and the Genomic Therapy Technology Research Accelerator (ART-TG, see inset).

The Magenta industrial integrator synergizes the conceptualization of disruptive technologies, the development of products and the standardization of bioproduction processes. It is both a catalyst for the national bioproduction ecosystem and a generator of future immunotherapies. Magenta is revolutionizing research for and the management of patients suffering from serious cancers or infectious diseases.

Meary: an industrial integrator and an essential link in the French biotherapies ecosystem

The Meary Center for Cell and Gene Therapies within the Paris network of public hospitals (AP-HP) is another industrial integrator of the Biopharmaceuticals Major Challenge (see inset page 2). It offers all state of the art services and competencies needed for manufacturing advanced therapy medicinal products (ATMPs), i.e., gene & cell therapies and tissue engineering. Working in close proximity with both patients and researchers, the Meary Center functions on a dynamic of innovation for the sector's academic and industrial actors.

The center's activities include: manufacturing, controlling and releasing experimental clinical batches of ATMPs; optimizing and industrializing production processes; and providing process development accompaniment to research teams, start-ups and industrials. Projects benefit from expert teams and cutting-edge equipment specifically conceived for bioproduction.

The projects currently underway are supported by institutional financing or industrial partnerships and focused on the deployment of clinical trials or the development of bioproduction technologies. The Meary Center is involved in several clinical trials evaluating the efficacy and tolerability of innovative therapeutic approaches in numerous indications, including cancer and neurological disorders, among others. Additionally, the center has the means for creating cell banks.

The Meary Center has established partnerships with a number of biotherapy actors in Paris Region (Astraveus, Honing Biosciences, Mnemo Therapeutics, MadeCell, Everzom, Evora, etc.) and across France (bioMérieux, TreeFrog Therapeutics, Emercell). With its operational means able to support the development of today's and tomorrow's disruptive innovations, the Meary Center is an essential link in the French bioproduction ecosystem.

Campus Biotech Digital: developing the competencies needed to empower bioproduction

Campus Biotech Digital saw the day in 2020 to address an inescapable fact: bioproduction needs professional talents to develop. Accelerating training is critical for energizing the transformation of this sector, which is expected to create thousands of new jobs over the next ten years.

The primary objective is to deploy training and competency development in novel industrial processes, particularly as concerns the qualitative demands of sterile facilities and the role of data analysis in biotechnologies, both of which affect the entirety of value chain processes.

«It's about developing an economy of biotechnology and bioproduction knowledge in France via the construction of a competencies hub to ultimately serve patients and the sector overall, while also ensuring that innovative therapeutic solutions are accessible to all.» Campus Biotech Digital Director Karim Vissandjee

Campus Biotech Digital is an unprecedented initiative piloted by an industrial consortium uniting bioMérieux, Novasep, Sanofi and Servier. It comprises an array of national entities including biotechnology schools and training institutions, Left: Institut de la Vision. Right: Genopole.

MAGENTA'S FOUNDING LABORATORIES

- Cithera (Center for iPSC Therapies, Inserm) coordinates the national infrastructure for stem cell and tissue engineering (Ingestem) and provides its expertise in the bioengineering of clinicalgrade induced pluripotent stem cells (iPSC)* and their derivatives.
- ART-TG (Inserm) is a specialist in ex vivo gene therapies. Their process involves taking diseased or dysfunctional cells from a patient, correcting or activating them via gene therapy tools, and regrafting them in the patient. ART-TG thus aims to replace defective cells or eliminate tumor cells. The laboratory's use of novel genome editing technologies for targeted therapeutics brings innovation to the field of immunotherapy.

€30 MILLION IN PUBLIC-PRIVATE FINANCING

Campus Biotech Digital receives funding from an exceptional public-private partnership within the framework of the «Professional and Continuing-Training Engineering for Innovative Offers» program piloted for the French State by the Caisse des dépôts, and benefits additionally from the support of OPCO2i (operator of interindustrial competencies), the Île-de-France Administrative Region and finally the strong mobilization of its nonprofit alumni association for total investments of more than €30 million.

major computer and informatics groups (strategic partnership agreements with Atos, IBM and Microsoft), equipment providers, and SMEs & start-ups specialized in bioproduction or digital sciences.

The project involves territorial relays and a design and expertise center located at the Sanofi site in Vitry-sur-Seine.

Campus Biotech Digital's initial and continuing training are complementary to academic learning. They cover all aspects of the bioproduction chain in an immersive and personalized manner. Similar to flight simulator training for pilots, Campus Biotech Digital uses a variety of digital tools to reproduce the essential elements of production, up to and including the delivery of a product to a patient. It also employs AI-supported cognitive approaches to enable the appropriation of the professional practices needed in industry, in a way that reflects «real life» as closely as possible. The program creates a virtuous circle wherein the continuous training of employees, young graduates and experts alike injects ever-increasing competencies into the bioproduction sector, augmenting both its performance and attractiveness.

Bioproduction is a strategic sector for the coming years. Research alone is insufficient; France must also produce. It is nothing less than a question of technological, economic and healthcare sovereignty for the country. Paris Region has numerous advantages, but to ensure its place in the years to come, disruptive technologies and expert training need to take center stage today.■

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- 5. French economic activity nomenclature (NAF) codes 7211Z and 7219Z.
- 6. Programing, systems and programs counselling, specific-purpose programs (NAF codes 6201Z, 6202A, 5829C).
- LFB Biomédicaments' activities in Les Ulis are focused on therapeutics derived from blood plasma, which are not part of the biotherapies considered here. The company's site in Paris Region comprises its head office and R&D and production activities. In Toulouse, the company produces monoclonal antibodies, and in Arras, it is opening a large facility that will most notably produce antibodies for use in immunotherapies.

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RESOURCES

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Map: www.bit.ly/biotech-idf



^{1.} CSF-ITS - Initiative technologie de rupture pour la bioproduction, rapport détaillé [Initiative for bioproduction disruptive technologies] D&Consultant, November 2020.

^{2.} The «winner takes all» principle.

^{3.} CSF-ITS – Initiative technologie de rupture pour la bioproduction, rapport détaillé [Initiative for bioproduction disruptive technologies] D&Consultant, November 2020.

^{4.} Ibid.