

**ANNUAL  
REPORT  
2015**



# CONTENTS

## 2015 ANNUAL REPORT

<b>04</b>	<b>Note from the Chairman and CEO</b>
<b>06</b>	<b>Collectis in brief</b>
<b>07</b>	<b>2015 highlights</b>
<b>08</b>	<b>Therapeutic activities</b>
09	Gene edited CAR T-cells: key concepts
11	Gene editing
12	Therapeutic products
13	Our technologies
14	Working towards a cure
16	Manufacturing
17	Our partners
20	Academic collaborations
<b>21</b>	<b>Calyxt</b>
22	Calyxt: healthier food for a better life
24	From labs to fields
<b>26</b>	<b>Financial statements</b>
27	Tuned in with our shareholders
28	Assets
29	Equity and liabilities
30	Income statement
31	Cash flow statement
32	Share price and capital structure
<b>33</b>	<b>Governance</b>

### Disclaimer

This report and the information contained herein do not constitute an offer to sell or subscribe, or a solicitation of an offer to buy or subscribe, for shares in Collectis in any country. This report contains forward-looking statements that relate to the Company's objectives based on the current expectations and assumptions of the Company's management and involve risk and uncertainties that could cause the Company to fail to achieve the objectives expressed by the forward-looking statements that follow.

# NOTE FROM THE CHAIRMAN AND CEO

## GENE EDITING IS CHANGING OUR LIVES

DEAR  
SHAREHOLDERS,

Collectis has pioneered the field of gene editing for the past 16 years. As a leading company in this arena, we have had the privilege of trying series of nuclease technologies, such as meganucleases, ZFNs, CRISPR-Cas9, TALEN®, Mega-TAL and others. We decided to focus on TALEN® technology for therapeutic and industrial applications because we wanted to work with a technology that, we believe, gathers the required criteria to do gene editing: efficiency, precision, specificity and selectivity. Overall, we are leveraging TALEN®'s transformative potential in two ways: through our T-cell engineering platform to deliver UCART therapeutics and through our wholly owned subsidiary Calyxt, which has built a plant engineering platform to deliver healthier food to consumers. This report lays out our key achievements on both of these fronts.

### UCART THERAPY

The year 2015 was a pivotal year as it led to gene editing now being able to fundamentally transforming our lives. To that end, Collectis made significant strides toward achieving its underlying vision of realizing the therapeutic potential of gene editing.

This progress ultimately culminated in the first-in-man compassionate use of UCART19, Collectis' first gene edited, allogeneic CAR T-cell product. In June 2015, under a special license granted by the Medicines & Healthcare products Regulatory Agency (MHRA) to Great Ormond Street Hospital (GOSH) in London, UCART19, a TALEN® gene-edited, allogeneic CAR T-cell product candidate, was administered to an

infant with an aggressive form of acute lymphoblastic leukemia (ALL) who had exhausted all available treatment options. This first leukemic patient – who could not be saved by any other therapy – was injected with a TALEN®-based gene edited CAR T-cell product candidate at the Great Ormond Street Hospital in the United Kingdom. A poster detailing GOSH's clinical experience in this single patient was presented at the American Society of Hematology (ASH) annual meeting in December 2015.

In the same month, Collectis submitted a clinical trial application (CTA) to the MHRA requesting approval to initiate Phase I clinical trials of UCART19 in leukemia in the United Kingdom.

Prior to this application, in November 2015, Servier exercised its option to license on UCART19 ahead of schedule through an amendment to the initial agreement it had signed with Collectis in February 2014. As a result of this exercise, Servier entered into a global license and collaboration agreement with Pfizer. In consideration for the early exercise of the option, Collectis received an upfront payment of \$38.5 million. We are truly proud of the great teamwork between Servier, Pfizer and Collectis, as it led to a seamless transaction of responsibilities regarding UCART19. The early opt-in by Servier also removed a financial burden from Collectis, as Servier and Pfizer are now responsible for clinical and manufacturing costs related to UCART19. Collectis is eligible to receive up to \$974 million of milestone payments and further exercises of options, plus R&D financing and royalties on sales based on annual net sales of products.

Collectis has made great advances in building a manufacturing process for the first gene-edited living cell product, UCART19. The specificity of Collectis' allogeneic therapies is that T-cells from healthy donors are genetically edited with our proprietary technology TALEN® to seek and eradicate cancer cells. We believe this approach will lead to a drug that would be cost-effective, easily distributed across all geographies, and available to patients who do not have enough T-cells to undergo an autologous CAR-T therapy (based on the patient's own T-cells).

Our focus has now turned to the development of the next product candidate, UCART123. UCART123 is a CD123-targeted, gene-edited, off-the-shelf CAR-T therapeutic product candidate designed for the treatment of acute myeloid leukemia and an orphan form of cancer, blastic plasmacytoid dendritic cell neoplasm.



In 2015, we were thrilled to sign UCART123 clinical collaborations with two world class research institutions. In AML, we are working with Weill Cornell Medical College and in BPDCN, we have partnered with MD Anderson Cancer Center. Working closely together with our excellent investigator partners, we are driving forward UCART123 research and manufacturing efforts to meet the needs of patients. We expect to file an investigational new drug (IND) application with the FDA by the end of 2016 to begin Phase I clinical trial of UCART123 and to bring this therapy to patients as soon as possible.

## CALYXT

Calyxt, our wholly owned subsidiary focused on plant sciences, is a Minnesota-based company that was originally built around Pr. Dan Voytas, its Chief Scientific Officer and one of the key inventors of the TALEN® technology. The growing Calyxt team aims to develop new crops and seeds with health benefits to consumers and with advantages to farmers. For the past 50 years, the majority of plant breeding has been focused on yields that lock farmers into a race toward more productivity, more herbicides and more pesticides. Calyxt is a real game changer in the Ag field in that it has achieved in a very short period what very few agbiotech companies in the world could achieve. Through the power and precision of the TALEN® gene-editing platform, Calyxt has completed field trials for its first products.

Calyxt's lead program is a non-transgenic variety of soybean that has one of the highest oleic acid content in the industry as well as a low linoleic acid content.

When used for frying, Calyxt soybean oil significantly reduces the generation of trans fats, in line with FDA guidance to get rid of all trans fats by 2018. The Calyxt variety has a fatty acid profile similar to olive oil. Calyxt soybeans are already in the field: one ton of beans has been harvested in the U.S. in the fall of 2015. We expect a 30-fold increase for the harvest of Calyxt soybeans by spring 2016 in Argentina.

Calyxt also has a non-transgenic improved quality potato. In these potatoes, the enzyme responsible for sugar conversion in tubers is inactivated. This reduces the sweetening of cold-stored potatoes and decreases the creation of a by product, acrylamide, a carcinogen, when cooked at high temperature. Calyxt cold storable potatoes are already in the field in the U.S. In late 2014 and 2015, the USDA confirmed non-regulated status to four of our lead crop development programs. October harvests last year across the United States were abundant, and we hope that the first gene edited potatoes and soybeans will reach consumer plates within two to three years.

## A BRIGHT HORIZON

In the past two and a half years, we have collectively succeeded in transforming the Collectis Group into a world-leading biotech company. Such a successful radical change in a company is extremely rare, especially in such a short period of time. We are very proud of these achievements, but this is just the start of a great story.

Today, our mission is clear and our financial position strong. We plan to replicate and further develop in 2016 what we have achieved in 2015. We are aiming for another successful UCART rollout with UCART123 while UCART19 data will follow. For Calyxt, 2016 will be a year where new crops will enter the field such as our new gene edited wheat. We are well on the way to increasing our soybean harvests to hundreds of tons, and eager to increase the production yields of our potato breed as well.

We have established ambitious goals: to offer the best products to improve the health and well-being of all while being respectful of nature and code of ethics. Our vision is to make Collectis an even better company, one that contributes to everyone's well-being.

On behalf of the management team and employees of Collectis, we want to thank you for your ongoing support, for believing in Collectis, and for investing in a better future for everyone. ■

Sincerely,

**ANDRÉ CHOULIKA**

# CELLECTIS

## IN BRIEF

Collectis is a biopharmaceutical company focused on developing immunotherapies based on gene edited CAR T-cells (UCART). The Company's mission is to develop a new generation of cancer therapies based on engineered T-cells. Collectis capitalizes on its 16 years of expertise in genome engineering - based on gene editing technologies (such as its flagship TALEN<sup>®</sup> and meganucleases) and pioneering electroporation PulseAgile technology - to create a new generation of immunotherapies. CAR technologies are designed to target surface antigens expressed on cells. Using its life-science-focused, pioneering genome-engineering technologies, Collectis' goal is to create innovative products in multiple fields and with various target markets. Collectis S.A. is listed on the Nasdaq Global market and on the NYSE Alternext market.

Calyxt, Inc., a wholly owned subsidiary based in New Brighton, Minnesota (USA), aims to create healthier crop products such as low trans fat soybean oil, cold storable potato, gluten reduced wheat and low saturated canola oil for the food and agriculture industries. ■

### CONTACT

Collectis, Inc. - 430 East 29th Street - New York, NY 10016 - USA

P.: +1 347 809 5980

Collectis S.A. - 8 rue de la Croix Jarry - 75013 Paris - France

P.: +33 (0)1 81 69 16 00

e-mail: [investors@collectis.com](mailto:investors@collectis.com)

[www.collectis.com](http://www.collectis.com)

Collectis Securities Services:

Société Générale Securities Services (affiliate 042)

Citi - Depository Receipt Services

### INTELLECTUAL PROPERTY:

As of December 31, 2015, the Collectis Group owns 103 patent families (consisting of approximately 66 issued patents and an additional 302 patent applications) and has in-licensed an additional 30 patent families. Our intellectual property portfolio provides significant protections over our product candidates, including protections for the main products we use in the manufacturing process, manufacturing steps, including cell electroporation and genetic modifications, engineered T-cells, single-chain and multi-chain CARs expressed at the surface of T-cells, specific gene inactivation, suicide gene system, and allogeneic as well as autologous treatment strategies using our T-cell products, homologous recombination, nuclease-based gene editing, chimeric nuclease for gene engineering, TAL effector nucleases, meganucleases, and CRISPR-Cas9 nucleases.

We also own trademarks such as Collectis<sup>®</sup>, TALEN<sup>®</sup> and Calyxt<sup>™</sup>.

### MILESTONES

**1999: Collectis is founded**

**2005: Development of a process for the industrial production of nucleases**

**2007: Listing on the Alternext market in Paris**

**2008 – 2010: Acquisition of technologies and establishment of subsidiaries**

**2010: Acquisition of all assets of Cyto Pulse Sciences, Inc. based in Maryland**

The acquisition included Hybrimmune electrofusion technology and PulseAgile technology for RNA transfection by electroporation. PulseAgile is now the standard technology for RNA transfection of T-cells.

**2010: Founding of Calyxt, Inc.**

**2011: Collectis acquires exclusive license to TAL effector patents from University of Minnesota**

**2014:**

- Strategic collaboration agreement in allogeneic cell therapy with Servier to develop and commercialize novel product candidates targeting leukemia and solid tumors
- Agreements with Thermo Fisher Scientific covering the uses of TAL nucleases under the brand name TALEN<sup>®</sup>
- Global strategic cancer immunotherapy collaboration with Pfizer to develop immunotherapies against select targets in the field of oncology

**2015:**

- Listing on the Nasdaq Global market in New York
- Research alliance advancing drug discovery and the translation of novel immunotherapies in leukemia with Weill Cornell Medical College
- Broad preclinical and clinical strategic alliance in cancer immunotherapy with MD Anderson Cancer Center
- First-in-man compassionate use of UCART19 for acute lymphoblastic leukemia (ALL)
- Collectis filed first Clinical Trial Application for UCART19, an allogeneic gene edited CAR T-cell product candidate designed for the treatment of hematological malignancies

### LISTING MARKETS

Nasdaq Global market, New York – Ticker: CLLS

NYSE Alternext market, Paris – Ticker: ALCLS.PA

### LEGAL FORM

French *Société Anonyme* with Board of Directors

Number of shares outstanding as of December 31, 2015: 35,178,614

Share capital as of December 31, 2015: €1,758,930.70

Market capitalization as of December 31, 2015: € 982,2 M

# 2015

## HIGHLIGHTS

### CELLECTIS

#### THERAPEUTIC ADVANCES

##### May 7

Presentation of data on Collectis' allogeneic CAR T-cell programs at ASGCT annual meeting

##### May 13

Genome engineering for adoptive immunotherapy at the ASCO annual meeting

##### October 28

Collectis announces successful GMP production process for UCART19

##### December 5

UCART19: First-in-man proof of concept presented at 2015 ASH annual meeting

##### December 23

Collectis files first Clinical Trial Application for UCART19

#### PATENT AND PUBLICATIONS

##### January 6

Issuance by the USPTO of a patent covering a seminal nuclease-based "gene editing" method to Collectis

##### June 10

Publication of an article in *Molecular Therapy* on next generation engineered allogeneic CAR T-cells

##### July 16

Publication of an article in *Cancer Research* on allogeneic CAR T-cell immunotherapies

#### PARTNERSHIPS

##### January 13

Collectis and the Ohio State University, through the Ohio State Innovation Foundation, enter into licensing agreement for Chimeric Antigen Receptor technology targeting multiple myeloma

##### June 2

Weill Cornell Medical College and Collectis enter into research alliance advancing drug discovery and the translation of novel immunotherapies in leukemia

##### July 8

Collectis reaches milestone in Servier collaboration

##### September 3

MD Anderson Cancer Center and Collectis enter into a broad preclinical and clinical strategic alliance in cancer immunotherapy

##### November 19

Servier exercises exclusive worldwide option to license for UCART19

#### FINANCING

##### March 24

Collectis prices Initial Public Offering of American depositary shares

#### CORPORATE

##### April 9

Collectis opens labs and offices in Manhattan, New York

### CALYXT

#### SCIENTIFIC ADVANCES

##### April 14

Calyxt publishes a study demonstrating reduced acrylamide in fried potatoes

##### April 15

Calyxt locks early CRISPR intellectual property uses in plant from the University of Minnesota

##### July 8

Calyxt launches field trials of its cold storable potatoes and high oleic soybean

##### July 16

Calyxt boosts its wheat pipeline

##### July 23

Calyxt announces a publication on *Molecular Plant Journal* demonstrating non-transgenic plant genome editing using protein delivery of nucleases

##### July 28

University of Minnesota grants Calyxt an exclusive license to its homologous recombination technology in plants

##### November 2

Calyxt completes second year of field trials of its cold storable potatoes and high oleic soybean product

#### CORPORATE

##### May 4

Collectis plant sciences becomes Calyxt

#### COLLABORATIONS

##### June 9

S&W Seed Company and Calyxt announce alfalfa seed collaboration

##### December 16

Calyxt announces research collaboration and licensing agreement for trait development in wheat, rice and corn

# THERAPEUTIC ACTIVITIES

## GENE EDITED CAR T-CELLS

### The potential of gene editing

The genome is the fundamental blueprint of life. Research into the function and organization of the genome has revolutionized our understanding of medicine and disease. However, mankind has long sought to go beyond simply understanding the genome and modify it to improve our lives. The first manipulations of the genome occurred in the form of cross-breeding different plants and selecting the best animals for reproduction. The aim of these early efforts was to improve a species by giving them the best possible attributes, such as drought tolerance in plants or increased food output in livestock. With the recent improvements in biotechnology, such as rapid and inexpensive whole-genome sequencing, we are finally starting to realize our goal of effectively editing the genome for scientific discovery, to produce useful proteins, or to treat diseases. These improvements have led to practical “targeted” genome engineering methods that are more predictable, reliable, and effective than earlier techniques, with great potential to improve human health. As a leader in therapeutic genome editing, Collectis stands at the forefront of these efforts.

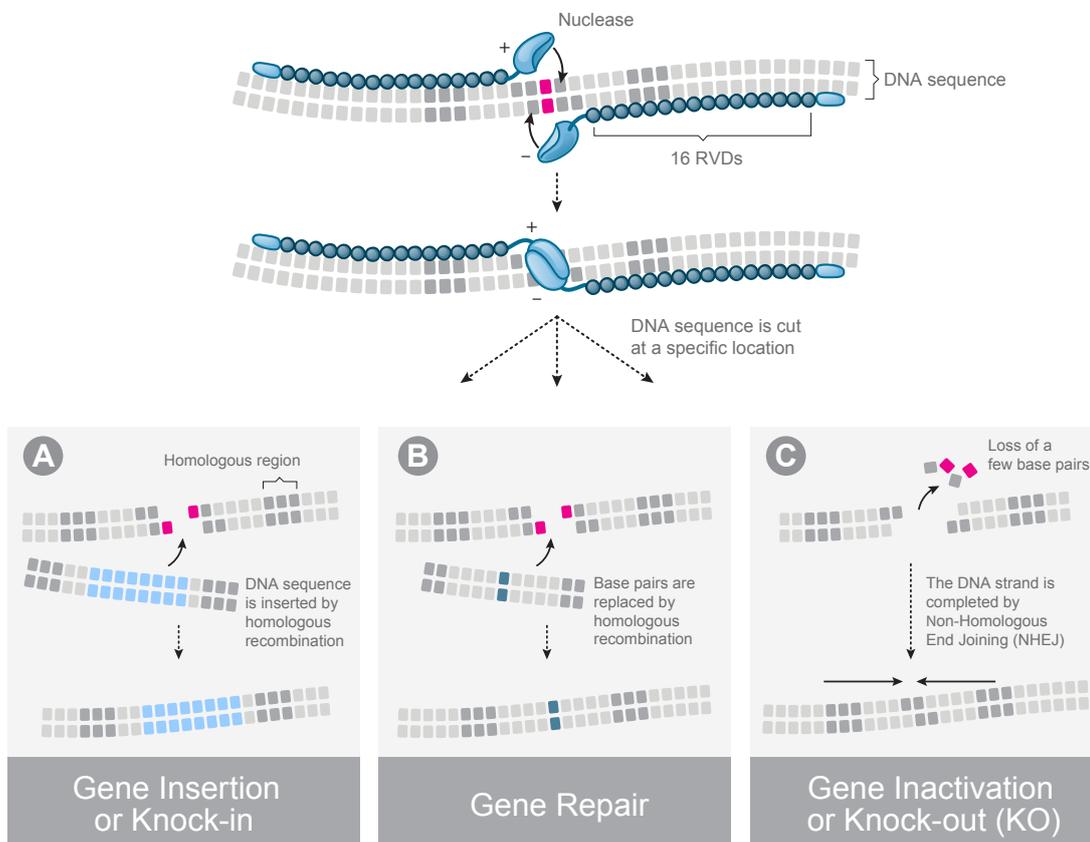
### Application for therapeutic use

Collectis employs core proprietary technologies to develop best-in-class products in the rapidly growing field of immuno-oncology. Our approach takes advantage of genome-edited immune cells that recognize specific targeted antigens on cancer cells to target and eradicate cancers. One key component of this approach is the T-cell, a type of white blood cells that plays an important role in identifying and killing foreign and malignant cells.

### Gene editing approaches

The approaches to genome editing are:

- *Gene insertion*, which is used to add a new attribute to the genome, such as adding in a novel genetic sequence or augmenting the function of a gene by adding additional copies.
- *Gene repair*, which consists of replacing a gene by another one with a functional sequence, similar to correcting a spelling mistake.
- *Gene inactivation*, which is used to prevent or eliminate the function of a gene product. For example, this approach can be used to treat persistent viral infections to disable a gene. ■



## FROM T-CELLS TO UCART PRODUCTS

### T-cells: the soldiers of the immune system

The immune system is tasked with protecting the body from invading pathogens or external harmful materials. To accomplish this, our immune system uses T-cells, which identify and neutralize foreign bodies through the use of "self" and "non-self" antigens, the molecular signatures that all biological entities carry. A central function of the immune system is to discriminate between "self", which is recognized through antigens normally present in the body and borne by cells, proteins, sugars or lipids, and "non-self", which is detected through abnormal or foreign antigens. Cancer cells thrive, in part, because they trick the immune system into treating them as self, even though they express abnormal antigens, and thus immune tolerance occurs when the immune system fails to recognize and attack tumors. Breaking immune tolerance is an important aspect of most immunology based therapeutics because it enables the immune system to recognize and treat tumors as non-self and lead to tumor destruction.

### Chimeric Antigen Receptors (CARs)

CARs are molecules that direct T-cells to recognize specific proteins or antigens present on the surface of other cells. By combining our leading gene editing technologies with the power of CARs, we can engineer T-cells that recognize proteins present on the surface of cancer cells. These anti-cancer CARs target T-cells to specific cancer cells, activating the T-cells and ultimately killing the cancer cells.

CARs are constructed by generating and assembling several modular domains from different proteins. The most common CAR architecture comprises an extracellular domain containing a region that recognizes the targeted antigen and a spacer region that links it to the transmembrane domain, the part of the protein that spans the cellular membrane. This is then followed by an intracellular domain, which is responsible for transmitting an activation signal to the cell upon antigen recognition, causing the CAR engineered cell to attack the tumor cell. This compound structure enables the CAR molecule to carry out all of the functions required to generate a targeted immune response.

Collectis is currently developing a collection of CARs that target antigens on cells from various types of cancer. In addition, we are developing proprietary multi-chain combinations of artificial receptors, which will further increase the efficacy of adoptive cell therapies in the future.



### Universal Chimeric Antigen Receptor T-cells (UCARTs)

Our leading immuno-oncology product candidates are based on CAR technology, and we refer to these as UCARTs (Universal Chimeric Antigen Receptor T-cells). UCARTs are allogeneic "off-the-shelf" therapeutic product candidates, which means they are derived from pre-existing donor cells and not from the patient. As a result of this advantage, the production of UCARTs can be industrialized and thereby standardized over time and from batch to batch with consistent pharmaceutical release criteria.

Each UCART product candidate targets a selected tumor antigen and incorporates specific desirable attributes, such as compatibility with individual chemotherapeutic regimens that cancer patients may undergo. The proprietary UCARTs represent a specific and powerful approach to treating any cancer patient with a given molecular "signature". UCART product candidates developed with our unique gene editing platform, are our first line designed to address unmet medical needs in oncology. ■



CELLECTIS HAS BEEN A PIONEER IN THE USE OF NUCLEASE-BASED GENOME EDITING; WE WERE THE VERY FIRST COMPANY IN THE FIELD, AND WE HAVE BEEN ACTIVE IN IT FOR THE PAST 16 YEARS.

## GENE EDITING

### Background on genome editing

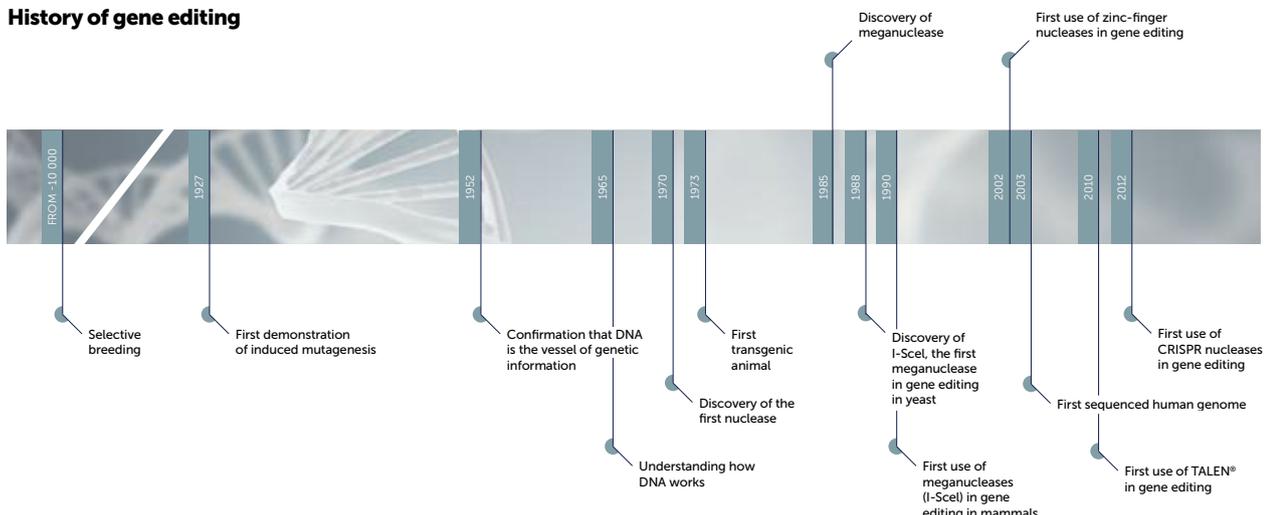
The genome is the blueprint that guides the biological function of every living being. Even before they fully understood what the genome was, humans have tried to modify it. The concept of rewriting the genome to improve human life was in essence born thousands of years ago with the first selective breeding of animals and plants to optimize food production, i.e., to arrive at the most advantageous genetic characteristics. Modern biotechnology arose in the early 1970s with the development of the first methods for transgenesis; for the first time, scientists were able to go beyond selective breeding by inserting external genetic instructions into the genome of a species. These instructions – contained within a recombinant gene – can confer new characteristics.

Breakthroughs in transgenesis ultimately helped enable the precise editing of a genome with controlled DNA modification at a targeted location, which was first developed in the 1980s using a process known as homologous recombination. Gene editing by homologous recombination relies on the delivery of a DNA fragment into the cell. This DNA fragment can be engineered to contain a desired genetic change flanked by matching (“homologous”) sequences. Further discovery that generating DNA breaks at the target location considerably enhances the efficiency of homologous recombination paved the way for gene editing via nucleases.

### Nuclease-based editing technologies

Nucleases are specialized proteins that recognize a specific DNA sequence and cleave it. Nucleases are powerful tools for genome editing, and there are four basic families of nuclease technologies based on different mechanisms of DNA recognition or action. Cellectis has been a pioneer in the use of nuclease-based genome editing; we were the very first company in the field, and we have been active in it for the past 16 years. Our investigators, as well as our co-founder and CEO André Choulika, have been working in genome editing for as much as 28 years and invented the meganuclease technology. At Cellectis, we’ve had

### History of gene editing

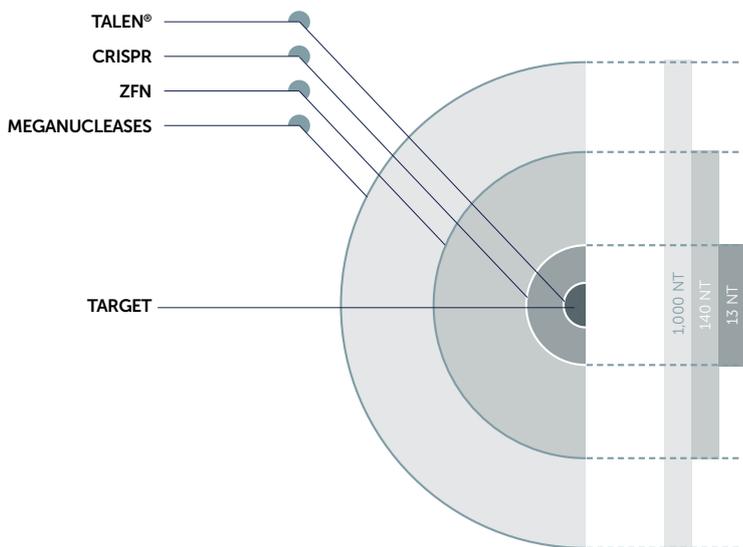


the privilege of trying all of the competing approaches: meganucleases, ZFNs, TALEN® and CRISPR-Cas9. A far cry from early recombination-based approaches, these modern gene editing technologies are targeted, precise and accurate.

The first generation of nucleases – meganucleases and zinc-finger nucleases (ZFN) – were developed over 20 years ago. In terms of efficiency, they represented a vast improvement over gene editing by homologous recombination alone. However, these approaches are costly, and the nuclease constructs themselves are very difficult to engineer, requiring robotic sample handling, expertise and fully dedicated laboratories. These drawbacks prevented meganuclease- and ZFN-based editing technologies from being widely adopted. TALEN® and CRISPR technologies have considerably increased the speed and reduced the cost of genome editing protocols. These two nuclease technologies offer different strengths and weaknesses, requiring the user to select the appropriate technology for a particular use. For research applications, speed and cost are critical factors. For subsequent work, a user must consider how easy it will be to direct a nuclease to cut a specific location in addition to the

ease and convenience of design. For therapeutic and industrial applications, one must consider efficiency and performance. For patient applications, safety is absolutely critical.

Accounting for these different applications, we are confident that TALEN® technology is the most effective tool today for therapeutic gene editing. We routinely achieve 85% to 90% efficiency for a single allele knockout in manufacturing while preserving very high levels of functionality and viability. These values set the standard for therapeutic genome editing and represent the best efficiency and viability in the industry today. Critically, this level of effectiveness is achieved with no measurable toxicity or off-target effects. TALEN® constructs clearly differentiate the desired genome sequence from other, similar sequences to produce high-quality products at competitive costs. For these reasons, we have selected TALEN® as our flagship nuclease structure for gene editing. That is really a standard and probably an industry-best range that can be achieved today without having any significant toxicity or off-target. TALEN®'s activity differentiates clearly to produce high-quality products with competitive cost of goods. ■



Theoretical maximum distance between a target site and the closest sequence recognized by a nuclease given the precision of each family  
 Source: "Rewriting The Book Of Life: A New Era in Precision Gene Editing", Elsy Boglioli and Magali Richard, September 2015

## OUR TECHNOLOGIES

### TALEN®

TALEN® is based on a class of proteins derived from transcription activator-like effectors, or TALEs. TALEs are highly specific DNA-binding proteins that feature an array of 33 or 34-amino acid repeats. Each repeat is highly conserved, with the exception of the so-called repeat variable di-residues (RVDs) at amino acid positions 12 and 13. The RVDs determine the DNA sequence to which the TALE will bind. This simple one-to-one correspondence between the TALE repeats and the corresponding DNA sequence makes the process of assembling repeat arrays to recognize novel DNA sequences straightforward. These TALEs can be fused to the catalytic domain from a DNA nuclease, FokI, to generate a transcription activator-like effector nuclease (TALEN®). The resulting TALEN® constructs combine high specificity and activity, effectively generating engineered sequence-specific nucleases that bind and cleave DNA sequences only at pre-selected sites.

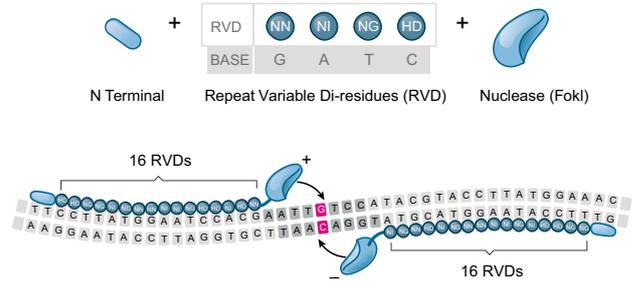
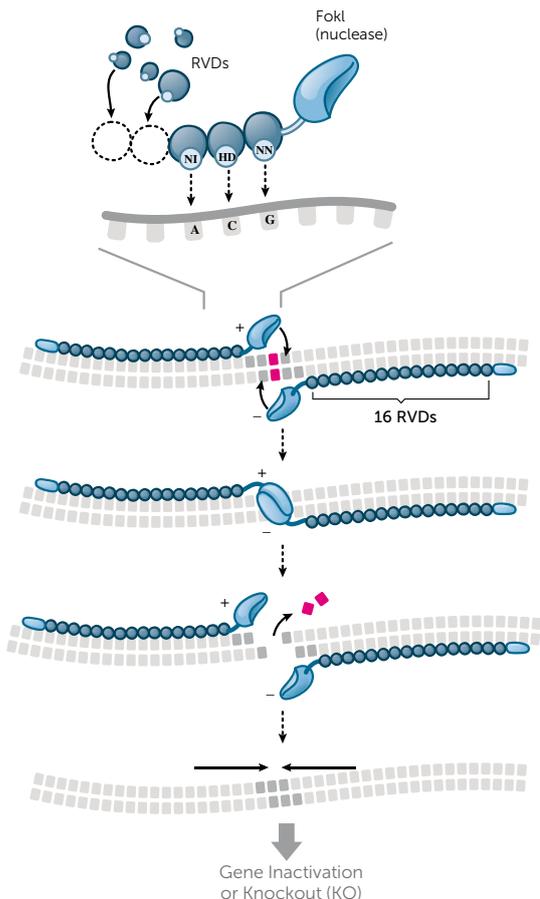
A custom TALEN® is created to target the precise gene sequence

TALEN® binds to its target sequence

FokI nuclease heads clip the DNA at the target sequence

The DNA is degraded at the cleavage site and bases are lost

DNA ends are rejoined resulting in a mutation, leading to the knockout of the target gene



Our approach aims to deliver an off-the-shelf product with the following benefits:

- Market Access. Enable products to be shipped globally, thereby reducing deployment obstacles and providing accessibility to a broad patients population;
- Cost-effectiveness. Streamlined manufacturing process has the potential to reduce costs;
- Novel Features. Develop products with specific safety and control properties;
- Compatibility. Develop products taking into consideration the current standards of cancer care;
- Consistency. Qualify and develop cancer products that are designed for optimal dosage, while reducing batch-to-batch variability.

In addition, vectorization of TALEN® is simple and easy. Due to these factors, TALEN® constructs have many applications in genome engineering and represent the best available technology for therapeutic applications.

### PulseAgile

In 2010, Collectis acquired the assets of Cyto Pulse Sciences Inc., a Maryland-based company specializing in technology and equipment related to electroporation, which is the process of delivering messenger RNA (mRNA) or DNA molecules into cells using highly controlled electric fields. Cyto Pulse's leading PulseAgile electroporation technology uses a unique electrical field wave-form that, in combination with a proprietary buffer solution, enables molecules, such as nucleases, to enter efficiently into the cell while maintaining a high percentage of viable cells. PulseAgile uses a particularly effective combination of high voltage peaks, which are optimized to create transient holes in the cell membrane, followed by lower voltage pulses that help mRNA migrate into the cells. Critically, PulseAgile is optimized to preserve high cell viability and thus suited for large-scale manufacturing. For example, T-cells that undergo TALEN® encoding mRNA electroporation maintain cell viability of approximately 90%.

Importantly, PulseAgile provides a high-quality platform for delivering DNA encoding nucleases to target T-cells, where it can be translated to generate an active nuclease protein that can access and specifically cut the cell's genomic DNA. The mRNA molecules are rapidly degraded by the cell, which means that the nuclease is only expressed for a short time, reducing the long-term risks of genomic modification. ■

# WORKING TOWARDS A CURE

## PRODUCT CANDIDATES

### Pipeline

#### Our lead immuno-oncology product candidates

Product name Targeted Indication	Product development	In Vitro Studies	In Vivo Studies	Manufacturing	CTA/IND filing	Alliance
<b>UCART19</b> Acute Lymphoblastic Leukemia (ALL) Chronic Lymphocytic Leukemia (CLL)						Servier
<b>UCART123</b> Acute Myeloid Leukemia (AML) / Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)						Wholly-Owned
<b>UCARTCS1</b> Multiple Myeloma (MM)						Wholly-Owned
<b>UCART38</b> Multiple Myeloma (MM) / T-cell Acute Lymphoblastic Leukemia (T-ALL)						Wholly-Owned
<b>UCART22</b> Acute Lymphoblastic Leukemia (ALL)						Wholly-Owned

#### UCART123

Our first wholly-owned product candidate, UCART123, is an engineered T-cell product candidate that targets CD123, an antigen located on CD123 expressing leukemia such as on cancer cells in acute myeloid leukemia, or AML, and blastic plasmacytoid dendritic cell neoplasm, or BPDCN. UCART123 is at a preclinical stage of development. We have initiated the manufacturing process transfer of UCART123 to CELLforCURE, to whom we subcontract the manufacturing of the clinical supplies of UCART123, and we will start manufacturing clinical grade UCART123 in large scale according to GMP in 2016, for purposes of conducting clinical investigations. Preclinical and translational activities on UCART123 in AML will be performed in collaboration with Weill Cornell Medical College. The research at Weill Cornell is led by co-principal investigators Dr. Gail J. Roboz, Director of the leukemia program and an Associate Professor of medicine, and Dr. Monica Guzman, an Assistant Professor of pharmacology in medicine. In addition, we collaborate with the MD Anderson Cancer Center on the preclinical development of UCART123 in BPDCN in view of a potential clinical trial. The studies on UCART123 led at MD Anderson are under the direction of Pr. Hagop Kantarjian, MD, Chair, Department of leukemia.

#### UCARTCS1 and UCART38

UCARTCS1 and UCART38 are allogeneic engineered T-cell product candidates designed for the treatment of CS1-expressing or CD38-expressing hematologic malignancies which develop in multiple myeloma (MM). UCARTCS1 is at a preclinical stage of development. We intend to initiate manufacturing of UCARTCS1 according to GMP in 2016, for purposes of conducting clinical trials. Preclinical and translational activities for UCARTCS1 in MM will be performed in collaboration with the MD Anderson Cancer Center. UCART38 is at an early preclinical stage. Preclinical and translational activities on UCART38 in T-cell ALL are to be performed in collaboration with the MD Anderson Cancer Center.

#### UCART22

Like CD19, CD22 is a cell surface antigen expressed from the pre B-cell stage of development through mature B-cells. UCART22 is an allogeneic engineered T-cell product candidate designed for the treatment of acute lymphoblastic leukemia.

UCART22 is at an early preclinical stage of development. Preclinical and translational activities on UCART22 in ALL will be performed in collaboration with the MD Anderson Cancer Center in view of a potential clinical trial.

#### UCART19: FIRST-IN-HUMAN PROOF OF CONCEPT

During the 57<sup>th</sup> American Society of Hematology (ASH) Annual Meeting on December 5, 2015, Great Ormond Street Hospital (GOSH) at University College London (UCL) presented encouraging data from a first-in-man use of UCART19 product candidate. This first-in-human application of our TALEN<sup>®</sup> engineered T-cell product candidate represents a landmark in the use of new gene engineering technology and provides early encouraging data for a ready-made T-cell strategy that will be further tested in clinical investigations.

GOSH has treated in June 2015 a young leukemia patient under a special license from the Medicines & Healthcare products Regulatory Agency (MHRA) with Cellectis' TALEN<sup>®</sup> gene edited allogeneic UCART19 product candidate because no other therapies were available for refractory relapsed acute lymphoblastic leukemia (ALL) following mismatched allogeneic stem cell transplantation.

In response to an unsolicited request from Professor Waseem Qasim, Consultant Immunologist at GOSH and Professor of Cell and Gene Therapy at University College London (UCL) Institute of Child Health, Cellectis gave its approval for the use of its UCART19

product candidate and technologies under GOSH's "Specials" license and responsibility, for the particular clinical needs of that individual patient.

Professor Qasim said: "The successful treatment of a patient with UCART19 cells represents a landmark in the use of new gene engineering technology. If replicated in other patients, it could represent a huge step forward in treating leukaemia and other cancers."

On November 18, 2015, we signed with Servier an amendment to our collaboration agreement whereby notably Servier exercised its option to acquire the exclusive worldwide rights to further develop and commercialize UCART19, which was about to enter into Phase I clinical development for chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL).

## DEVELOPMENT OF A PRODUCT CANDIDATE TAKES PLACE IN SEVERAL STAGES:

### Discovery

Identification of a new potential target which could lead to a future product candidate.

### Product development

Engineering of "Chimeric Antigen Receptor" (CAR) T-cell is the technology developed by Cellectis to construct new potential products. This approach allows Cellectis to develop allogeneic products through a gene-editing mechanism of T-cells derived from healthy donors. Gene editing is performed using TALEN®, which allows very precise and targeted gene modification and provides new attributes to the product such as compatibility with the standard of care.

### Preclinical development

*In vitro* and *in vivo* studies are performed on cell lines, primary samples and using animal models in order to demonstrate the activity of a product candidate, assess its potential toxicity and support the clinical development.

### CTA/IND filing

The Clinical Trial Application (CTA) is the regulatory step consisting on the submission of the required study documentation package to the health authority to obtain the authorization to perform clinical investigation.

### Clinical studies

Testing of the candidate medication in humans.



## FROM A PRECLINICAL TO A CLINICAL STAGE

### Preclinical development

The goals of preclinical studies are to demonstrate the anti-tumor activity of the UCART product candidates, to study their mechanism of action and to assess their potential toxicity following administration to patients. Those studies are conducted both *in vitro* and *in vivo* in animal models in association with a risk-benefit analysis performed in the context of the particular clinical indication under study. Preclinical studies are part of the Clinical Trial Authorization application and the Marketing Authorization Application (AMM, or *Autorisation de Mise sur le Marché* in French).

## PHASES OF CLINICAL TRIALS

Clinical trials take place in several phases:

**Phase I:** First time an experimental drug or treatment is tested in humans to examine how well the drug is tolerated.

**Phase II:** Trials designed to examine if the drug or treatment has a clinical activity.

**Phase III:** Trials designed to assess the treatment effect on a clinically meaningful endpoint.

**Phase IV:** Post-marketing studies to gain additional information regarding the safety of the drug or treatment. ■

# MANUFACTURING

## GMP Manufacturing & Solutions

GMP, or Good Manufacturing Practices, are a set of regulations applicable to the manufacturing of health products, especially medicines intended for human use, such as UCART products for example. A company is required to comply with GMP regulations, in order to be granted from governmental regulatory agencies, its license to manufacture pharmaceutical products. The GMP Manufacturing & Solutions department takes manufacturing processes established at R&D level, converts them to GMP, and ensures their deployment with GMP compliant raw materials and environments. The department is responsible for the manufacturing of clinical trial material ("CTM"), making it available for clinical studies and afterwards, and also for the manufacturing of final GMP commercial cellular gene therapy products. The team interacts internally with different departments ranging from development, planning, to regulatory and legal, as well as externally with raw materials contractors or GMP manufacturing contract organizations.

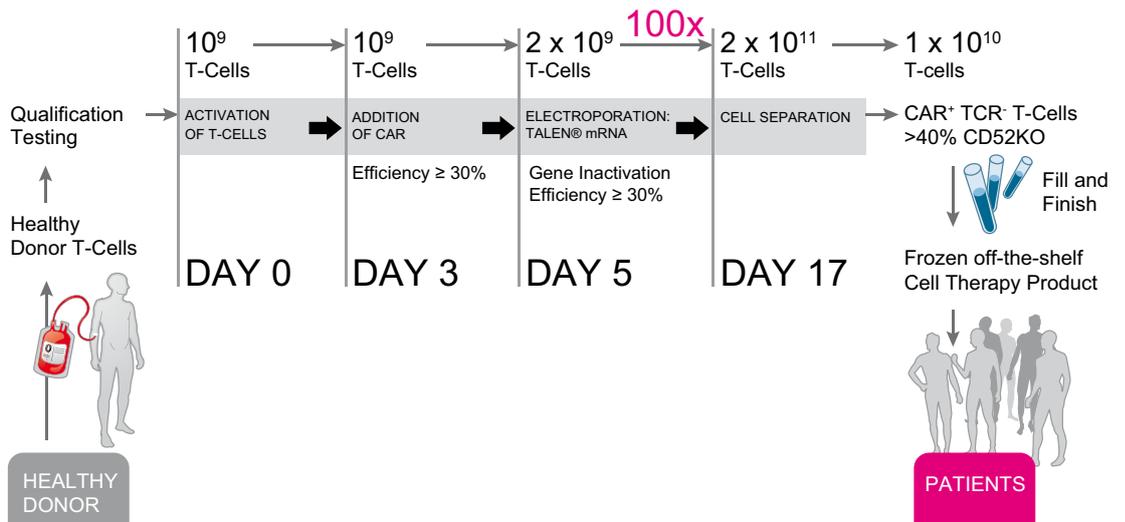
## Our manufacturing process

Through our manufacturing process, we obtain therapeutic UCART product candidates from healthy, tested and qualified donor T-cells, rather than from patient samples. This "off-the-shelf" approach leads to lower production costs. In addition, our process – powered by TALEN® and our proprietary PulseAgile electroporation technologies – inactivates genes in a highly efficient manner that avoids harming T-cells during processing. As a result, we can manufacture

quality UCART products with high yields and potentially in bulk. This could enable us to manufacture in bulk, and we expect that T-cells from one healthy donor, and one manufacturing run of UCART, could be used to create hundreds of doses of product and more when scaling up the process. These efficiencies may not only reduce costs to patients but also lead to competitive gross profit margins. In 2015, the manufacturing process of our first UCART product candidate, UCART19, was further developed, pursuant to GMP quality standards, and was deployed in a GMP environment. Production was started to meet the needs of the first phase clinical trials, as part of the clinical development of UCART19 in adult and pediatric acute lymphoblastic leukemia as well as in adult chronic lymphocytic leukemia. For that production campaign, we relied on external GMP capacity at CELLforCURE, a contract manufacturing organization. On October 28, 2015, we announced that we completed a series of three production runs of UCART19.

On January 19, 2016, we announced that, pursuant to a second agreement, CELLforCURE will also produce clinical batches of UCART123, our first wholly owned UCART product candidate, to meet the needs of the first phase clinical trial, as part of the development of UCART123 in malignancies, such as acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN). ■

## Manufacturing process platform : designed for cGMP compatibility



# OUR PARTNERS

The way our portfolio is structured is that we have a category of Collectis self-owned product candidates that we are developing, all of them in liquid tumors. Then we have a number of product candidates that we are working on for Pfizer and Servier.



## SERVIER

In February 2014, Collectis entered into a strategic collaboration agreement with Servier, the first independent French pharmaceutical research company, to develop and commercialize novel product candidates.

### **July 8: Achievement of a significant milestone under the Company's collaboration agreement**

On July 8, 2015, Collectis announced the achievement of a significant milestone under its collaboration agreement with Servier, in the preclinical development of two next-generation product candidates in solid tumors. Under the terms of the collaboration agreement, Collectis received an undisclosed payment. "We are very pleased with the productivity of this alliance enabling us to accelerate our development in the field of solid tumors", commented Mathieu Simon, MD, EVP Chief Operating Officer of Collectis.

"We believe that immunotherapy will dramatically change the management of metastatic cancers. Our goal at Servier is to make these new technologies available for the largest number of cancer patients", commented Jean-Pierre Abastado, Ph.D., Director Oncology Innovation Therapeutic Pole of Servier.

### **November 18: Servier early exercises its option to acquire the exclusive worldwide rights to further develop and commercialize UCART19**

On November 18, 2015, Collectis and Servier signed an amendment to their existing collaboration agreement from February 2014 especially for UCART19, a TALEN® gene-edited allogeneic Chimeric Antigen Receptor T-cell (CAR-T) immunotherapy. Under this amendment, Servier early exercised its option to acquire the exclusive worldwide rights to further develop and commercialize UCART19, which was about to enter Phase I development for chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). ■

"WE BELIEVE THAT IMMUNOTHERAPY WILL DRAMATICALLY CHANGE THE MANAGEMENT OF METASTATIC CANCERS. OUR GOAL AT SERVIER IS TO MAKE THESE NEW TECHNOLOGIES AVAILABLE FOR THE LARGEST NUMBER OF CANCER PATIENTS" **JEAN-PIERRE ABASTADO, PH.D., DIRECTOR ONCOLOGY INNOVATION THERAPEUTIC POLE OF SERVIER**



## PFIZER

In June 2014, Cellectis and Pfizer entered into a global strategic collaboration to develop Chimeric Antigen Receptor T-cell (CAR-T) immunotherapies in the field of oncology directed at select targets. Cellectis' CAR-T platform technology provides a proprietary, allogeneic approach (utilizing engineered T-cells from a single donor for use in multiple patients) to develop CAR-T therapies that is distinct from other autologous approaches (engineering a patient's own T-cells to target tumor cells). Under the terms of the agreement, Pfizer has exclusive rights to pursue development and commercialization of CAR-T therapies, in the field of oncology, directed at a total of fifteen targets selected by Pfizer.

On November 18, 2015, we announced that we signed with Servier an amendment to our collaboration agreement whereby notably Servier exercised its option to acquire the exclusive worldwide rights to further develop and commercialize UCART19, which was about to enter into Phase I development for chronic

lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). **Pfizer and Servier announced they entered into an exclusive license and collaboration agreement to further develop and commercialize UCART19.** As we were developing UCART19, there has been a lot of interest from different partners in acquiring the rights in the U.S. for this gene-edited product candidate. They announced that under the terms of their agreement, Pfizer and Servier will work together on a joint clinical development program for UCART19 and share development costs. **Pfizer will be responsible for potential commercialization of UCART19 in the United States,** and Servier will retain marketing rights in countries outside the United States. ■

## ACADEMIC COLLABORATIONS

### The Ohio State University

On January 13, Cellectis announced that it has entered into an exclusive license agreement with The Ohio State University, through the Ohio State Innovation Foundation, to develop and commercialize chimeric antigen receptor (CAR) technology targeting multiple myeloma cells. The CAR technology licensed to Cellectis is related to CS1, an antigen that is over-expressed in multiple myeloma cells. Cellectis intends to pursue the development of a CS1 CAR T-cell program for this targeted indication.

Multiple myeloma is the second most common type of blood cancer with a five-year survival rate of 45%. This cancer represents a major unmet medical need.

### Weill Cornell Medical College

On June 2, Weill Cornell Medical College and Cellectis have entered into a strategic translational research alliance to accelerate the development of a targeted immunotherapy for patients with acute myeloid leukemia (AML), a deadly blood cancer. Under this alliance, Weill Cornell Medical College (WCMC) and Cellectis are conducting research and develop clinical strategies with the objective of implementing and conducting one or more clinical trials at WCMC on UCART123 and potentially other product candidates in AML. Cellectis funds the research program and WCMC and Cellectis work together to develop and implement improvements to the research plans. The objectives of the collaboration are to demonstrate functionalities and specificity of UCART123 *in vitro* and *in vivo*, define the preclinical package required for the clinical trial application, prepare the clinical trial protocol, the regulatory and other study-specific documents, and discovery research for the identification of novel targets in AML patients potentially enabling the development of additional CARs for AML.

Cellectis is responsible for generating and manufacturing UCART123 and performing *in vitro* and *in vivo* preclinical activities on tumor cell lines and in animal models. WCMC is responsible for evaluating UCART123 activity against primary AML samples and in animal models, as well as toxicity against HSCs in animal models. WCMC also works on the development and implementation of correlative studies. In addition, WCMC and Cellectis collaborate on the preparation of clinical trial protocols. Finally, Cellectis and WCMC are working on target discovery in the AML area, in order to identify new potential targets for AML and generate new potential candidate products for AML patients.

### MD Anderson Cancer Center

On September 3, Cellectis and the University of Texas MD Anderson Cancer Center (MDACC) have entered into a research and development alliance to bring novel cellular immunotherapies to patients suffering from different types of liquid tumors. The alliance is aimed at developing novel cancer immunotherapies based on Cellectis' allogeneic chimeric antigen receptor (CAR) platform. MD Anderson Cancer Center's leukemia and myeloma teams are working with Cellectis to bring better treatments to patients suffering from cancers with high unmet medical needs, particularly multiple myeloma (MM), acute lymphocytic leukemia (ALL), T-cell acute lymphocytic leukemia (T ALL) and blastic plasmacytoid dendritic cell neoplasm (BPDCN).

The alliance is built on MD Anderson's outstanding translational and state-of-the-art preclinical and clinical teams in leukemia and myeloma, coupled with Cellectis' first-in-class allogeneic CAR T-cell therapy approach and manufacturing capabilities, to pursue the development of Cellectis' product candidates UCARTCS1, UCART22, UCART38 in T-cell ALL and UCART123 in a rare non curable disease BPDCN. Under this strategic alliance, the MDACC and Cellectis collaboratively conduct several preclinical studies on product candidates: UCART123 in BPDCN, UCARTCS1 for MM, UCART38 for T-ALL and UCART22 for ALL. Cellectis provides funding and support for these studies. The objective of the studies is to build on complementary expertise from MDACC and Cellectis for the development of the product candidates. ■



# calyxt



*Our high-oleic soybean crops growing  
in Argentina, February 2016*

# CALYXT:

"HEALTHIER FOOD FOR A BETTER LIFE"

## LEVERAGING GENE EDITING TRANSFORMATIVE POTENTIAL THROUGH COLLECTIS' WHOLLY OWNED SUBSIDIARY CALYXT, TO DELIVER HEALTHIER FOOD TO CONSUMERS.

Founded in 2010, Calyxt (previously Collectis plant sciences), based in the Minneapolis-St. Paul area, Minnesota, is an agricultural biotechnology company focused on developing healthier food products to benefit both consumers and growers.

Capitalizing on its team and new technologies, the company aims to create healthier crop products such as high-oleic/low trans fat soybean oil, cold storable potato, gluten reduced wheat and low saturated canola oil for the food and agriculture industries.

Our business philosophy is to focus on developing products and maximizing value through partnerships. Calyxt is developing a network of partnerships in order to secure accessibility of its food products to consumers. ■

### CONTACT

Calyxt, Inc.  
600 County Road D W.  
Suite 8  
New Brighton, MN 55112  
P.: +1 (651) 683-2807  
contact@calyxt.com  
[www.calyxt.com](http://www.calyxt.com)

### LEGAL FORM:

Calyxt, Inc. is a U.S. incorporated company wholly owned by Collectis S.A.



### MILESTONES

**2010: Collectis plant sciences (now Calyxt) is founded**

**2011: Collectis acquires exclusive license to TAL effector patents from University of Minnesota**

**2012:**

- Calyxt and Bayer CropScience strengthen gene editing partnership
- Medicago and Collectis enter into research agreement to improve therapeutic proteins using nuclease technology
- Calyxt announces the signature of a strategic partnership with SESVanderHave in sugar beet

**2013:**

- TAL-effector nuclease: issuance by the USPTO of two new patents
- Collectis has successfully engineered the genome of photosynthetic algae with a view to biofuel production

**2014:**

- Calyxt and Bayer CropScience extend their partnership to improve crops by gene editing
- Calyxt reports generation of high oleic soybean in Journal of Plant Biotechnology
- Calyxt reports improvement of oil content in algae
- Calyxt and Two Blades Foundation announce the execution of a cross-license agreement on TAL effector nuclease technologies

**2015:**

- Calyxt locks early CRISPR intellectual property uses in plants from University of Minnesota
- Collectis Plant Sciences becomes Calyxt
- S&W Seed Company and Calyxt, Inc. announce alfalfa seed collaboration
- Calyxt launches field trials of its cold storable potato and high oleic soybean
- University of Minnesota grants Calyxt an exclusive license under the patents family "Gene Targeting Using Replicating DNA Molecules"
- Calyxt announces research collaboration and licensing agreement with Plant Bioscience Limited for the development of new traits in wheat, rice and corn

## PRODUCTS

Calyxt applies customized techniques at a cutting edge facility to develop products using diverse technologies that could apply to a broad range of horticultural and agronomic plant species. The platform utilizes technical expertise in many facets of plant tissue culture and horticultural science. Platform scientists are well versed in various technologies including protoplast isolation/regeneration, biolistic and T-DNA-mediated techniques.

### High Oleic Soybean

Soybean oil is low in monounsaturated fatty acids compared to canola and olive oils. Consumption of oils high in monounsaturated fats is considered healthier, and such oils typically have a longer shelf life and enhanced oxidative stability. Partial hydrogenation is often undertaken to improve soybean oil's fatty acid profile. However, a negative consequence of hydrogenation is the production of trans-fatty acids, which when consumed, raises low-density lipoprotein, or LDL, cholesterol levels and contributes to cardiovascular diseases.

We are developing a new variety of soybean with a high oleic acid and low linolenic acid content, which eliminates the need for hydrogenation and the creation of trans fat. This new variety has a fatty acid profile very similar to olive oil, with the added benefit of a decrease of approximately 20% in saturated fatty acids compared to standard soybean oil. In mid-2015, we received two letters from the USDA confirming that our high oleic and low linolenic varieties were deemed non-regulated. In November 2015, we announced that Calyxt completed the second year of multi-location field trials in Minnesota and South Dakota of its high oleic/no trans fat soybean variety.

### Cold Storable Potato

During the cold storage of potatoes, starch is converted into reducing sugars through a process known as "cold-induced sweetening". Once these cold-stored potatoes are cooked at temperatures above 250°F, the free amino acids and reducing sugars interact to form browning and acrylamide. The National Toxicology Program has reported that acrylamide is "reasonably anticipated to be a human carcinogen". The International Agency for Research on Cancer similarly considers acrylamide to be a "probable human carcinogen" based on studies in laboratory animals.

Companies operating in the potato market lose a portion of raw material potatoes that are stored. This loss, which is estimated to be approximately 10%, results from a combination of sprouting and browning, both of which can be avoided by colder storage. However, cold storage traditionally has been limited by the cold-induced sweetening that results from this type of storage. A cold storable potato, like the one developed by Calyxt, can address sprouting and browning as well as the traditional storage limitations. We have developed a potato that can be cold stored but does not produce acrylamide during cooking. In November 2015, we announced the completion of the first field trials of cold storable potatoes.

### Low Gluten Wheat

In 2013, wheat was the second-most produced cereal grain globally. A key component of wheat is gluten. Gluten gives elasticity to dough, helping it rise and keep its shape and often gives texture to the final product. However, gluten found in wheat can also be responsible for adverse immune system reactions. People sensitive to gluten generally feel better on a diet with less gluten.

We are working to remove the components of gluten responsible for that harmful immune reaction. The gluten-reduced wheat program is at an early stage of development.

### Improved Fat Profile Canola

We are also developing a new breed of canola with high oleic acid, low linoleic acid and linolenic oil, similar to our soybean product. ■

### Pipeline

Product	Trait	Discovery	Estimated Field Trial
Soybean	High oleic	Done	
	High oleic/low linolenic oil stack	Ongoing	2016
	Protein content	Ongoing	2017
Potato	Cold storage	Done	
	Browning reduction	Ongoing	2017
	Cold storage/browning reduction stack (fries variety)	Ongoing	2018
	Cold storage/browning reduction stack (chips variety)	Ongoing	2018
Canola	Improved oil	Ongoing	2018
	Herbicide tolerance	Ongoing	2018
Wheat	High dietary fiber	Ongoing	2017
	Powdery mildew disease resistance	Done	2016

## FROM LABS TO FIELDS

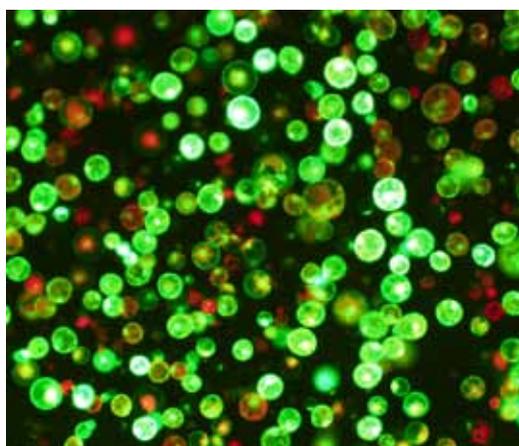
### Gene Editing in Agricultural Biotechnology

The underlying process of targeted gene editing using plant nucleases is no different than the process we apply to human organisms and cells. We seek to create a sequence-specific DNA break in the gene-of-interest and allow the cell's natural repair mechanisms to create a stable change at that location in the genome. The resulting changes can precisely alter certain genes to remove potentially harmful proteins or to confer specific traits.

Plant breeders have been crossbreeding varieties and selecting advantageous traits for thousands of years. The aim of targeted gene editing is to simply speed up that process by incorporating changes into elite germplasm known from wild ancestors or from other species altogether, to produce the best possible attributes faster and more cheaply. This gene-editing approach is more predictable, more reliable, and more effective than current techniques. Calyxt is applying our plant gene-editing platform to a broad range of horticultural and agronomic plant species. Calyxt performs transient expression of nucleases into a single-cell protoplast system by proprietary transformation technologies to allow precise gene editing, while avoiding the presence of foreign DNA in the final product. Following the completion of this gene-editing step, the modified plant single cell is re-grown into a fully functional plant and multiplied. The creation of these new varieties is already applicable to a wide range of crop families.

### Technologies

Scientists at Calyxt engineer and utilize customized nucleases (for example, TALEN®) to create valuable traits through precise modification of plant genomes. We have built a world-class team of plant geneticists and molecular biologists, creating the premier nuclease-mediated genome-editing platform in plants. We edit genes naturally present in the plant genomes through temporary expression of TALEN® products to knock out genes, which creates engineered plants that bear mutated endogenous, and that are not transgenic.



### The Power of Plant Protoplasts

A plant protoplast is simply a plant cell that no longer has its rigid cell wall (it has been removed either enzymatically or mechanically). Millions of protoplast can be isolated from a single plant leaf. The protoplast isolation and regeneration knowledge developed at Calyxt allows for a single, modified cell to develop into a whole plant, forging a new path for the creation of improved plant varieties. Transient expression of a TALEN® into the single-cell protoplast system allows for precise gene editing, while eliminating the risk of foreign DNA integration. The creation of these new varieties using the protoplast system is already applicable to a wide range of crop families. Calyxt scientists are continually developing new handling techniques in plants for which there is little known about the protoplast system.

### Product Development

Our goal is to quickly develop a large number of traits in key crops, obtain regulatory clearance and field validation data, and become a new leader in the agricultural biotechnology landscape.

Based on the USDA letter dated August 28, 2014, confirming that Calyxt's potato products fall outside of the scope of plant regulation, we seek to enter the U.S. agricultural biotechnology market by using our proprietary TALEN® technology, which we believe will enable us to expedite the trait development process to 6 years and significantly lower the cost associated with development. In addition, our gene-editing approach results in transgene-free food products. We believe this will result in a simpler, shorter and cheaper regulatory pathway because our products may avoid the significant expenses and long process associated with plant deregulation. We thus believe Calyxt will have the ability to commercialize its products quickly without incurring major regulatory costs or going through time-consuming deregulation studies.

In order to accelerate the adoption of our healthier food products by farmers, Calyxt combines them with traits that we have also developed with our technology for improved agricultural efficiency. We believe we have the unique opportunity to develop products at a much lower cost than currently developed transgenic plants and to do so within a shorter timeline. ■

*Potato protoplasts expressing green fluorescence to demonstrate high transformation efficiency*

## MANAGEMENT TEAM

### Dr. Luc Mathis, Chief Executive Officer

Luc Mathis earned his Ph.D. in Paris (Institut Pasteur) and completed a post-doctoral fellowship at the California Institute of Technology. He began his career as group leader on the developmental biology and genetics of neural stem cells at the Institut Pasteur with a tenure-track position. He joined Collectis in 2006 in business development for various R&D markets before joining Calyxt.

### Dr. Dan Voytas, Chief Science Officer

Dan Voytas graduated from Harvard College in 1984 and received his Ph.D. in genetics from Harvard Medical School in 1990. He conducted post-doctoral research at Johns Hopkins University School of Medicine where he was a fellow of the Life Science Research Foundation. In 1992, Dr. Voytas joined the faculty at Iowa State University. He was promoted to Associate Professor in 1997 and to Professor in 2001. In 2008, he joined the faculty in the Department of Genetics, Cell Biology and Development at the University of Minnesota (UMN) and he is Director of the UMN's Center for gene editing. He is a co-founder of Calyxt.

### Dr. Feng Zhang, Chief Operations Officer

Feng Zhang obtained his Ph.D. from Iowa State University working on maize genetics and received post-doctoral training at the University of Georgia with Dr. Sue Wessler. He is the co-inventor of more than 10 patents and patent applications. Before joining Calyxt, he co-invented TALEN® technology with Dr. Dan Voytas at the University of Minnesota and Dr. Adam Bogdanove at Iowa State University. Dr. Zhang joined Calyxt in 2010 to develop and lead the trait development programs for crops and vegetables.

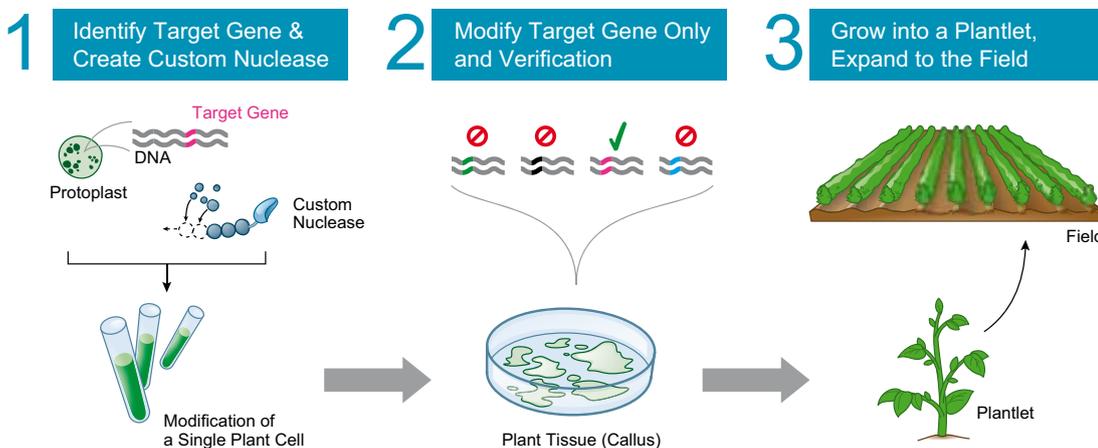
### Dr. William Haun, Director of Product Development

William Haun earned a B.S. and M.S. in Agronomy, Plant Breeding and Plant Genetics from the University of Wisconsin-Madison and a Ph.D. and post-doctoral training in Plant Biology and Genetics from the University of Minnesota. He joined Calyxt in May 2010, setting up the transformation platform and launching some of the Company's first projects. He moved into a business development role in January 2013, and now focuses on commercializing the Company's first products and building relationships with partners for product development. ■



*Soybean crops at full flower, Argentina, January 2016*

### Calyxt Platform



# FINANCIAL STATEMENTS

## TUNED IN WITH OUR SHAREHOLDERS

In March 2015, Collectis raised \$228 million of gross proceeds in a U.S. IPO on the Nasdaq, listing 5,5 million American Depositary Receipts. The proceeds from this listing, as well as our partnership revenue stream, put Collectis in a strong financial position to fund operations through 2018, with a 2015 year-end cash position of \$342 million.

Our stock price has performed positively over the last two years, reflecting the metamorphosis of Collectis into a product candidate platform company focusing on oncology; we finished 2014 with a plus of over 430% and in 2015 with a plus of over 120% in our share price, peaking at €41.95, its highest level ever on the Alternext market. The daily average volume of shares traded was 245,742 on the Alternext market and 263,234 on the Nasdaq market, representing 2-3 times the average recorded in 2014.

During the second half of 2015, the biotech sector has been hit hard, following a drug-pricing debate that was kicked off in the U.S. by contenders of the current U.S. presidential race. This debate was concurrent with a global risk-off attitude that was spurred by global economic growth concerns.

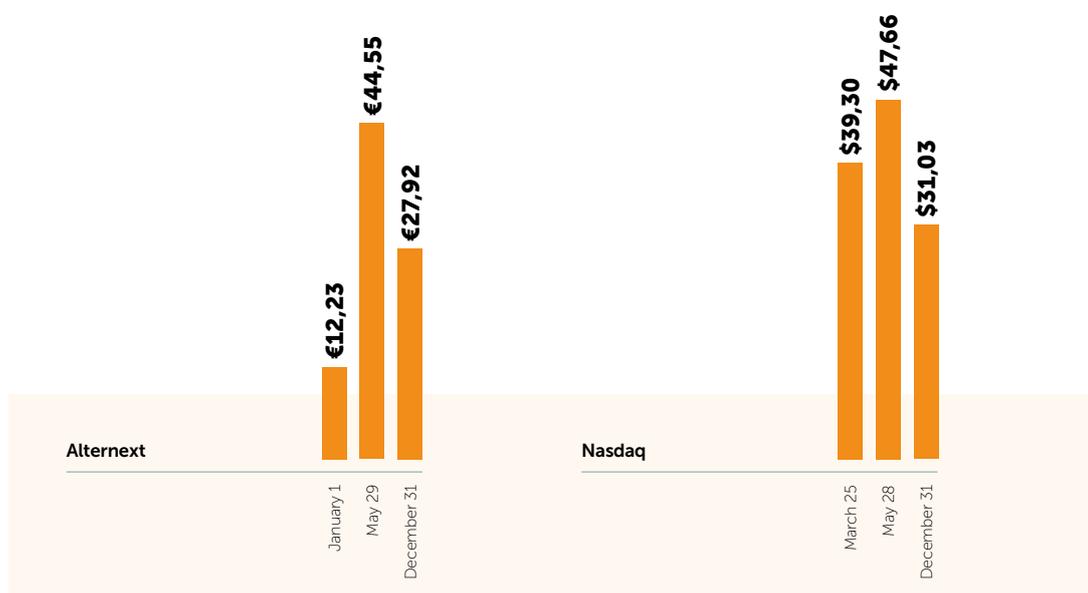
The strong outperformance of the biotech sector, which had raised valuation concerns and fear of a new Nasdaq bubble, has cooled down. Biotech stocks grew faster than any other sector in the U.S., with the capitalization of shares in the Nasdaq Biotechnology Index (NBI) up about 240 percent since the beginning of 2012, the Wall Street Journal reported. This trend is now in correction, with the NBI down 25% year-to-date in 2016.

In a troublesome time, a company has to be well financed. Collectis has a strong balance sheet and is well positioned to continue its progress into the years ahead. In an industry where large investments are needed to develop potentially life-saving therapies, it is important to be well capitalized in order to successfully navigate through a challenging market environment.

At Collectis, we are extremely proud of our achievements throughout 2015 and we maintained a proactive communication approach with our shareholders. Our management team participated in more than 400 investors meetings both in the U.S. and in Europe during the year.

Two General Shareholders Meetings were held on February 16 and May 18, giving occasion to our management team to explain the Company's positioning in the field of immuno-oncology, our corporate strategy and to answer our shareholders' questions. In 2015, the Collectis Group issued 47 press releases, or an average of one every 8 days.

Collectis also held a meeting dedicated to individual shareholders at our head office on October 5. Approximately 60 people attended this meeting, during which the management team presented the Company and more specifically the therapeutic programs in development, Calyxt and the interim financial statements at June 30, 2015. This meeting permitted questions from shareholders present and those sent by e-mail to be answered. ■



## BALANCE SHEET – ASSETS

In thousands of euros, except per share data	December 31, 2014	December 31, 2015
<b>Assets</b>		
<b>Non-current assets</b>		
Goodwill	-	-
Intangible assets	1 026	956
Property, plant, and equipment	2 610	5 043
Other non-current financial assets	1 977	845
<b>Total non-current assets</b>	<b>5 613</b>	<b>6 844</b>
<b>Current assets</b>		
Inventories and accumulated costs on orders in process	135	158
Trade receivables	5 881	6 035
Subsidies receivables	8 170	9 102
Other current assets	5 468	4 685
Cash and cash equivalents	112 347	314 238
<b>Total current assets</b>	<b>132 001</b>	<b>334 218</b>
<b>TOTAL ASSETS</b>	<b>137 614</b>	<b>341 062</b>

## BALANCE SHEET – EQUITY AND LIABILITIES

In thousands of euros, except per share data	December 31, 2014	December 31, 2015
<b>Shareholders' equity</b>		
Share capital	1 472	1 759
Premiums related to the share capital	192 842	420 682
Treasury share reserve	(251)	(184)
Currency translation adjustment	(762)	(1 631)
Retained earnings	(132 536)	(137 188)
Net income (loss)	20	(20 544)
<b>Total shareholders' equity - Group Share</b>	<b>60 786</b>	<b>262 894</b>
Non-controlling interests	(1 259)	725
<b>Total shareholders' equity</b>	<b>59 527</b>	<b>263 619</b>
<b>Non-current liabilities</b>		
Non-current financial debt	2 824	66
Non-current provisions	398	437
<b>Total non-current liabilities</b>	<b>3 222</b>	<b>503</b>
<b>Current liabilities</b>		
Current financial debt	862	1 921
Trade payables	9 802	6 611
Deferred revenues and deferred income	59 492	54 758
Redundancy plan	715	32
Current provisions	700	921
Other current liabilities	3 294	12 697
<b>Total current liabilities</b>	<b>74 865</b>	<b>76 940</b>
<b>TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY</b>	<b>137 614</b>	<b>341 062</b>

## INCOME STATEMENT

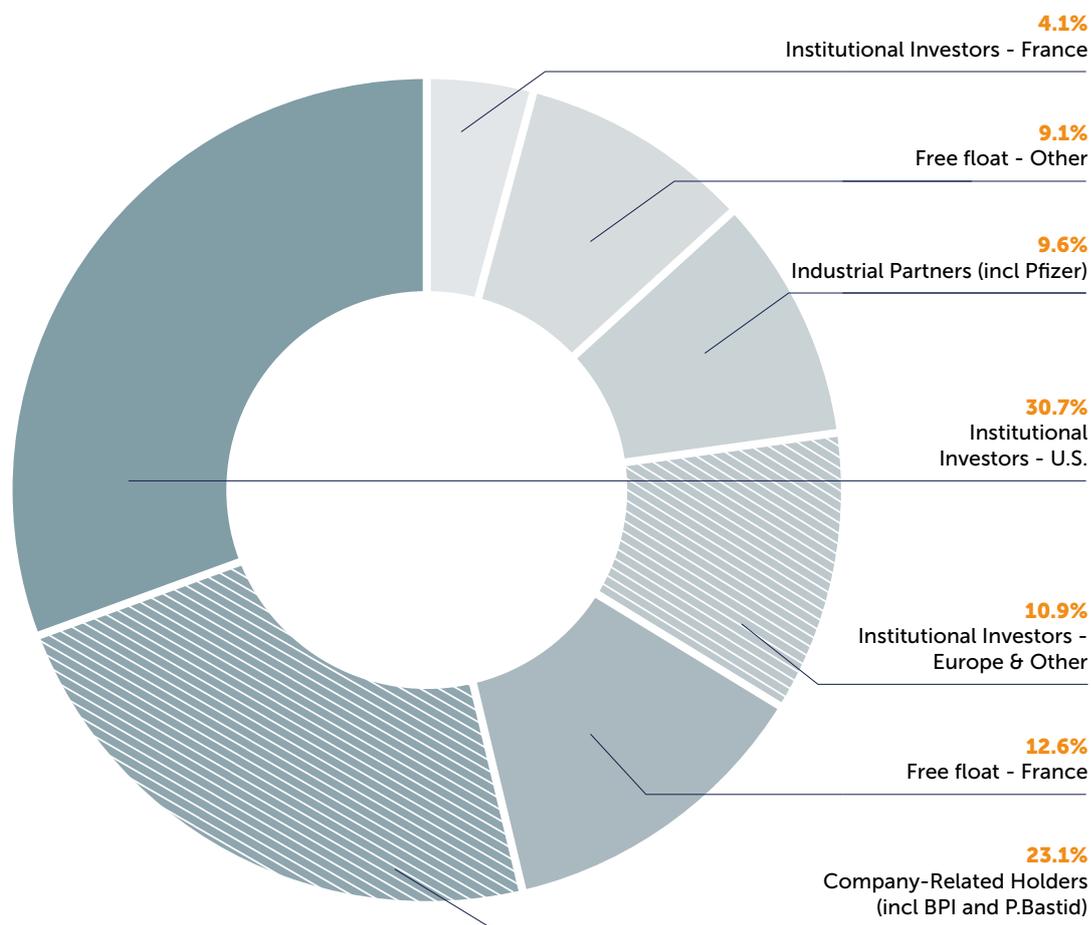
In thousands of euros, except per share data	For the three-month period ended December 31, 2015	For the year ended December 31, 2015
<b>Revenues and other income</b>		
Revenues	26 991	50 346
Other income	2 194	6 039
<b>Total revenues and other income</b>	<b>29 184</b>	<b>56 385</b>
<b>Operating expenses and other operating income (expenses)</b>		
Royalty expenses	(1 322)	(2 475)
Research and development expenses	(16 036)	(52 410)
Selling, general and administrative expenses	(8 093)	(27 238)
Other operating income	297	812
Redundancy plan	(10)	249
Other operating expenses	(2 814)	(3 246)
<b>Total operating expenses and other operating income (expenses)</b>	<b>(27 978)</b>	<b>(84 309)</b>
<b>Operating income (loss)</b>	<b>1 207</b>	<b>(27 924)</b>
<b>Financial gain (loss)</b>	<b>7 036</b>	<b>7 550</b>
Income tax	-	-
Income (loss) from continuing operations	8 242	(20 373)
Loss from discontinued operations	-	-
<b>Net income (loss)</b>	<b>8 242</b>	<b>(20 373)</b>
Attributable to shareholders of Collectis	8 242	(20 544)
Attributable to non-controlling interests	-	171

## CASH FLOW STATEMENT

In thousands of euros, except per share data	December 31, 2014	December 31, 2015
<b>Net (loss) income for the period of continuing operations</b>	<b>1 850</b>	<b>(20 373)</b>
Adjustments for :		
- Expenses related to share-based payments	548	30 103
- Net finance expenses / revenue	(7 095)	(7 550)
- Amortization and depreciation	1 372	1 745
- Other items	(981)	703
<b>Operating cash flows before change in working capital</b>	<b>(4 306)</b>	<b>4 628</b>
Decrease (increase) in current assets	(6 873)	1 120
Decrease (increase) in subsidies receivables	(2 317)	(612)
(Decrease) increase in current liabilities	55 969	(1 900)
<b>Change in the working capital</b>	<b>46 779</b>	<b>(1 392)</b>
<b>Net cash flows provided by (used in) operating activities of continuing operations</b>	<b>42 473</b>	<b>3 236</b>
Sale (Acquisition) of subsidiaries net of cash disposed of	505	(2 850)
Acquisition of property, plant and equipment	(347)	(3 890)
Net change in non-current financial assets	(1 542)	(238)
Other	31	13
<b>Net cash flows provided by (used in) investing activities of continuing operations</b>	<b>(1 353)</b>	<b>(6 965)</b>
Increase in share capital net of transaction costs	58 775	199 299
Decrease in borrowings	(1 032)	(564)
Treasury shares	161	67
<b>Net cash flows provided by financing activities of continuing operations</b>	<b>57 904</b>	<b>198 802</b>
<b>Cash and cash equivalents at the beginning of the year</b>	<b>7 559</b>	<b>112 347</b>
(Decrease) increase in cash of continuing operations	99 024	195 073
(Decrease) increase in cash of discontinued operations	(748)	-
Effect of exchange rate changes on cash	6 511	6 818
<b>Cash and cash equivalents at the end of the year</b>	<b>112 347</b>	<b>314 238</b>

## STOCK PRICE EVOLUTION & SHAREHOLDING STRUCTURE AS OF DECEMBER 31, 2015

Amid still challenging and volatile market conditions, the share price varied between €12.23 on January 1 and €44.55 on May 29 on the Alternext market; between \$47.66 on May 28 and \$31.03 on December 31 on the Nasdaq market. The stock price reached its highest level ever with €44.55 on May 29 on the Alternext market. The daily average volume of shares traded was 245,742 on Alternext and 263,234 on Nasdaq, 2,3 times the average recorded in 2014. ■



# GOVERNANCE

## EXECUTIVE COMMITTEE

### **Dr. André Choulika, Chief Executive Officer**

André Choulika, Ph.D., is one of the founders of Collectis and has been Chairman of the Board and Chief Executive Officer since 2000. He has also been President of Calyxt since August 2010. From 1997 to 1999, Dr. Choulika worked as a post-doctoral fellow in the Division of Molecular Medicine at Boston Children's Hospital, where he was a pioneer in the analysis and use of meganucleases to modify complex genomes. After receiving his Ph.D. in molecular virology from the University of Paris VI (Pierre et Marie Curie), he completed a research fellowship in the Harvard Medical School Department of Genetics. André Choulika also has management training from the HEC (Challenge +).

### **Dr. Julia Berretta, VP Business Development and Strategic Planning**

Julia Berretta, Ph.D., joined Collectis in 2010 in the scientific alliance and business development department. She has served as VP Business Development and Strategic Planning since 2014. Prior to joining Collectis, she worked as a researcher at the CNRS in Gif-sur-Yvette. Julia Berretta received her Ph.D. in molecular biology from the Université Paris XI, and holds a specialized Master's Degree in innovation management from Neoma Business School.

### **Dr. Philippe Duchateau, Chief Scientific Officer**

Philippe Duchateau, Ph.D., joined Collectis in 2001 to pioneer the field of gene editing and he has served as Chief Scientific Officer since 2012. After receiving his Ph.D. in 1993 in biochemistry and molecular biology at the Institut Pasteur (Lille, France), he completed a research fellowship from 1993 to 2001 at the University of California, San Francisco, within the Cardiovascular Research Institute. As head of Collectis' Research department since 2004, he helped to the development of Collectis' technologies.

### **Eric Dutang, Chief Financial Officer**

Eric Dutang, Certified Public Accountant in France, joined Collectis as Deputy Chief Financial Officer in May 2015. Eric began his career as financial auditor with KPMG, first in Paris for five years and then in New York for two years. He worked for listed companies in France and the U.S. such as Vivendi, Veolia Environnement or Cablevision. He then became a member of the transactions and advisory teams in Paris for seven years where he carried out acquisitions/

disposals for listed companies and private equity funds. After serving at KPMG, he worked on international business developments for French public listed groups, including Air Liquide and Thales. Eric holds a Master of Finance and Executive MBA from HEC Paris (France)/ Babson Massachusetts (USA).

### **Dr. Mathieu Simon, Executive Vice President, Chief Operating Officer**

Mathieu Simon, MD, has served as Executive Vice-President Chief Executive Officer of Collectis Therapeutics since 2012 and as Chief Operating Officer since 2013. Dr. Mathieu Simon is also Member of Collectis Board of Directors since 2013. Prior to joining Collectis, Dr. Simon was Senior Vice President Head of Global Pharmaceutical Operations at Pierre Fabre S.A. From 1994 to 2010, Dr. Simon has served at Wyeth Pharmaceuticals in both senior corporate and regional roles (Head of International Marketing and Medical Affairs and managing Director of several Wyeth Affiliates). Dr. Simon today is an advisor at the European Commission D.G. Research and Innovation with a special expertise in Market Access and pricing initiation. In addition to his Collectis role, Dr. Simon is also Senior Strategic Advisor at Messier Maris Partners, an international investment-banking boutique located in New York and Paris.

### **Dr. David Sourdive, Executive Vice President Corporate Development**

David Sourdive, Ph.D., is a co-founder of Collectis and has held the position of Executive Vice President, Corporate Development since 2008. Dr. Sourdive has also been a member of Collectis' Board of Directors since 2000. Since 2014, Dr. Sourdive has also served on the board of directors of Mediterranean Institute for Life Sciences. David Sourdive graduated from the École Polytechnique and received his Ph.D. in molecular virology at the Institut Pasteur. He also has management training from the HEC (Challenge +).

### **Marie-Bleuenn Terrier, General Counsel**

Marie-Bleuenn Terrier joined Collectis as Legal Counsel in 2008, and was appointed General Counsel in 2013. Prior to joining Collectis, she worked as Legal Counsel for Pfizer from 2004 to 2006, and for Boehringer Ingelheim from 2006 to 2008. Marie-Bleuenn Terrier also serves as Secretary of the Board of Directors since 2015. She holds a Master's degree in Law from the Panthéon La Sorbonne University in Paris.

## BOARD OF DIRECTORS

### **Dr. André Choulika, Ph.D., Chairman**

#### **Laurent Arthaud, Independent Director**

Laurent Arthaud has served as a member of Collectis' Board of Directors since 2011. Mr. Arthaud has been the Managing Director of Life Sciences and Ecotechnologies for Bpifrance Investissement (formerly CDC Enterprises, a subsidiary of Caisse des Dépôts) since 2012. From 2006 to 2012, Mr. Arthaud held the position of Deputy CEO at CDC Entreprises. Mr. Arthaud is a graduate of the École Polytechnique and the l'École Nationale de Statistique et d'Administration Économique.

#### **Pierre Bastid, Independent Director**

Pierre Bastid has served as a member of Collectis' Board of Directors since 2011. He has been a member of the Board of Directors of HOUGOU S.A. since 2011. He also currently serves on the Boards of Directors of HOUGOU Développement S.A., Louise 342-344 S.A., Crystal Sunrise S.A., Shango S.A., Hebioso S.A., Les Bastidons S.A., Nepteam S.A.S., Krishna S.C. and La Chartreuse B S.C.

#### **Alain Godard, Independent Director**

Mr. Godard is a graduate of the École Nationale Supérieure Agronomique de Toulouse. He began his agronomy career in 1967 in Africa as a researcher at the l'Institut de Recherche pour les Huiles et Oléagineux (institute for research on oils and oleaginous plants). He has served as a member of Collectis' Board of Directors since October 2007. He has been the Chief Executive Officer of SARL Godard & Co. since June 2009, and he also serves on the Board of Directors of Fermentalg SA.

#### **Jean-Marie Messier, Independent Director**

Jean-Marie Messier has served as a member of our Board of Directors since May 2015. He is co-founder and head of Messier Maris & Associés, an international investment banking firm. Mr. Messier has served on the Board of Directors of Rentabiliweb Group since May 2011. After graduating from the French university, Ecole Polytechnique, Mr. Messier attended the Ecole Nationale d'Administration. He became Managing Partner at Lazard Frères in 1988, a position he held for six years. Prior to this, he was responsible for the French Government's Privatization plan. Mr. Messier served as President of Vivendi Universal from 1994 to 2002. During these years, he founded the mobile firm Cegetel and turned Vivendi into a conglomerate focused on two core activities: utilities and communications, selling off assets in other areas.

### **Dr. Annick Schwebig, Independent Director**

Annick Schwebig, MD, has served as a member of Collectis' Board of Directors since 2011. In 2000, she founded the French subsidiary of Actelion, of which she is the General Manager. Actelion is a biopharmaceuticals company specializing in innovative treatments to serve unmet medical needs. A graduate of the University of Paris medical school, Dr. Schwebig worked as a senior manager at the biopharmaceuticals company Bristol-Myers Squibb for 17 years from 1983 to 2000.

### **Dr. Mathieu Simon, MD, Director**

### **Dr. David Sourdivé, Ph.D., Director**

## COMMITTEES OF THE BOARD OF DIRECTORS

### **Audit and Finance committee**

Laurent Arthaud, Independent Director  
Pierre Bastid, Independent Director  
Jean-Marie Messier, Independent Director

### **Compensation Committee**

Alain Godard, Independent Director  
Dr. Annick Schwebig, Independent Director

### **External Auditors**

Statutory Auditors  
Ernst & Young  
JMH Conseils

® Collectis

Collectis

Collectis S.A., 8 rue de la Croix Jarry - 75013 Paris - France  
Collectis, Inc., 430 East 29th Street - New York, NY 10016 - USA  
e-mail: [media@collectis.com](mailto:media@collectis.com)  
website: [www.collectis.com](http://www.collectis.com)

Calyxt

600 County Road D W. Suite 8 - New Brighton, MN 55112 - USA  
e-mail: [contact@calyxt.com](mailto:contact@calyxt.com)  
website: [www.calyxt.com](http://www.calyxt.com)

Photo credits

The Collectis Group

Graphic designers

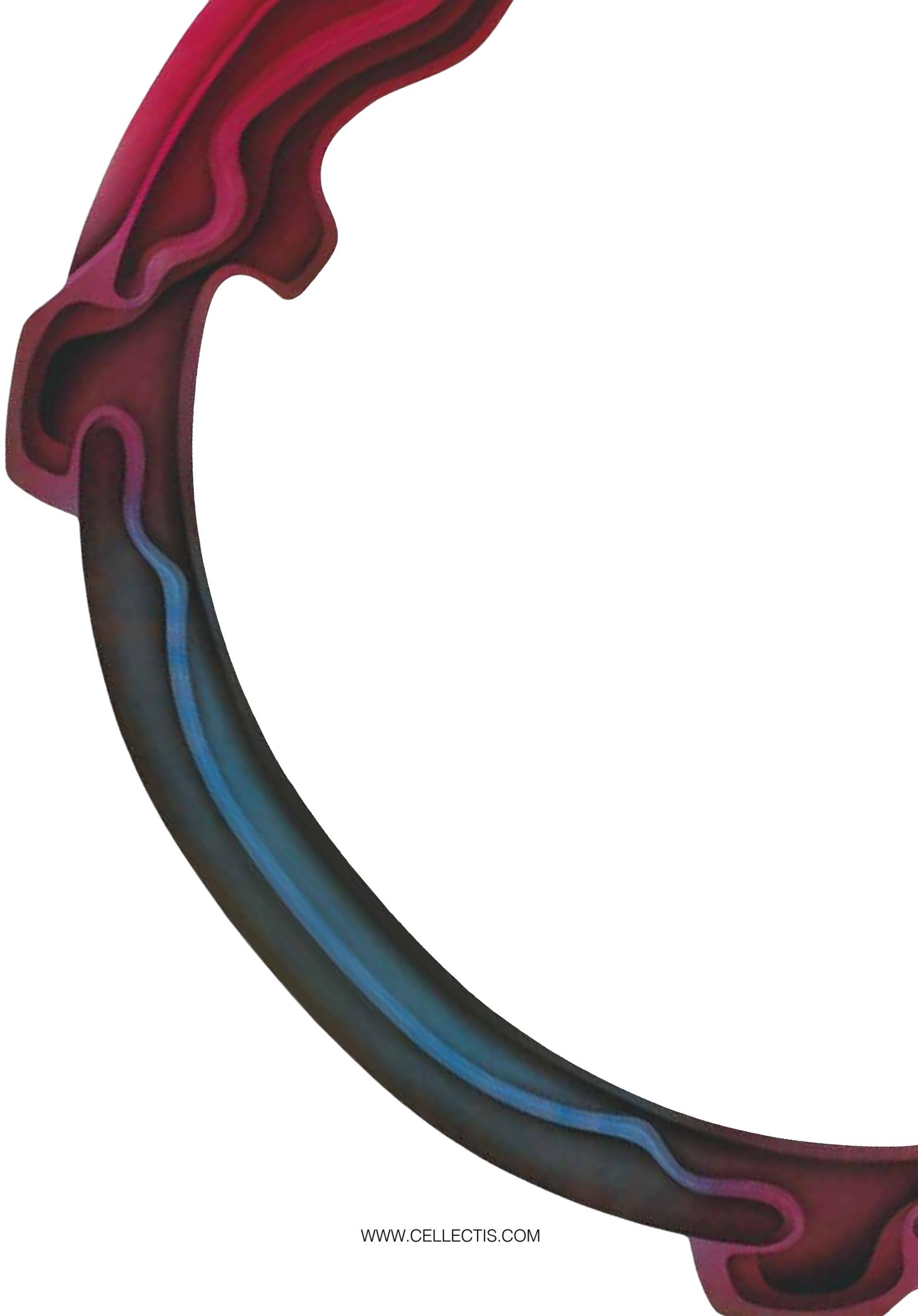
Avantmidi.fr agency

Cover: Valentina Herrmann

Painting by Guy Dessauges - Untitled

Oil on panel, 1982

With the courtesy of Mr. Hans Demarmels



[WWW.CELLECTIS.COM](http://WWW.CELLECTIS.COM)