Editorial

Michel Lussier

— CHAIRMAN OF THE BOARD

Dear Shareholders,

In 2015, Celyad set solid foundations to support its growth in 2016 and beyond. Thanks to its latest technological acquisition and its introduction on Nasdaq, Celyad moved from a Belgian cell therapy company specialized in ischemic heart failure to a global player which has the means and competency to develop clinical programs both in cardiovascular disease and in immuno-oncology, across Europe, U.S. and Asia.

This year will be a very important for the Company since the results of CHART-1 Phase III European trial as well as the results of our first Phase I/IIa study in immuno-oncology are expected mid-2016. Our hope is that the Phase III results will demonstrate the clinical benefits millions of people have been waiting for, the patients in particular, who may experience a major improvement in their quality of life.

The potential of our NKR-T program is also very significant and Celyad is just at the beginning of this adventure. We still have many opportunities to explore clinical trial assessing NKR-2 both in liquid and solid tumors through the autologous approach and the development of our allogeneic platform which is now protected by a strong IP. The U.S. patent we received has potential indeed a broad applicability for the development of TCR deficient CAR-T therapies. This could radically change the dynamics of the immuno-oncology industry, making Celyad an unavoidable leader at time of commercialization.

I take this opportunity to thank the Celyad team for the great commitment its shows everyday to deliver first-in-class treatments to patients and make of Celyad a successful company. I also thank you all for your support and trust in our Company.

2015 key highlights

JANUARY - Celyad enters into the immune-oncology field with the **acquisition of Oncyte CAR T-Cell portfolio from Celdara Medical**.

Portfolio includes three autologous CAR T-Cell cell therapy products and an allogeneic T-Cell platform, targeting a broad range of cancer indications.

MARCH - Completion of a **EUR 32 million private placement** of ordinary shares to dedicated life sciences European and US investors.

Paediatric Investigation Plan waiver obtained from EMA on C-Cure® market registration.

APRIL - Enrolment of the first patient in Phase I/IIa clinical trial to assess the safety and feasibility of NKG2D CAR T-cells in cancer patients with hemaetological indications.

MAY - **Cardio 3 BioSciences becomes Celyad**

JUNE - Celyad raises **USD 100,1 million** gross proceeds with **Nasdaq Initial Public Offering**

JULY - **Dosing of the last CHART-1** (Congestive Heart failure Cardiopoietic Regenerative Therapy) **patient of the European Phase III clinical trial**, triggering the 9-month follow-up period. Full data **readout expected in mid-2016.**

AUGUST - New collaboration and distribution agreement with Hong-Kong based partner, Medisun International Limited ("Medisun"). This license agreement confirms Celyad's intention to expand the global footprint of its lead cardiac disease cell therapy candidate for the treatment of ischemic heart failure, C-Cure®.

NOVEMBER - Issuance of United States Patent No. 9,181,527 relating to allogeneic human primary T-Cells that are engineered to be T-Cell Receptor (TCR)-deficient and express a Chimeric Antigen Receptor (CAR).

Initiation of the certification by the EMA of the non-clinical data of C-Cure® aimed to prepare the submission of a marketing-authorization application.

Celyad renames its CAR T-Cell program into NKR-T program (NKG2D CAR-T becoming NKR-2).

Completion of a 30-day safety follow-up of **first patient** cohort in **NKR-2 Phase I/IIa trial** demonstrating the **absence of toxic response** in the first dose tested ever in human.

DECEMBER - Treatment of the first patient of the second cohort in NKR-2 Phase I/IIa trial

Publication of the CHART-1 trial design methods paper in the European Journal of Heart Failure.

U.S. Food and Drug Administration (FDA) authorized the Company's Investigational New Drug (IND) application to proceed thus allowing the **use of C-Cath$_{ez}$™ in CHART-2.**

ALL OVER 2015

Reinforcement of the Group management bodies with the recruitment of seasoned and highly experienced directors and senior managers.

"We have received a lot of questions from our shareholders about our platform in immuno-oncology. This technology is complex. This is why we have decided to explain, more simply, the potential of our NKR-T program and the assets that make it unique and different in particular."

— DR. CHRISTIAN HOMSY, CEO.

Immunotherapy - a new targeted approach **to fight cancer**

Immunotherapy for cancer treatment

Immunotherapy is based on the premise that our immune system is capable to destroy abnormal cells such as cancer cells, but in some instances, the cancer cells develop mechanisms that allow them to evade the detection or the activity of our immune defenses. The therapies developed in immune-oncology attempt to restore and to activate the immune system ability to detect and destroy cancers.

Chimeric antigen receptor T-cells (CAR T-cells)

A central player in cancer immunotherapy is a type of white blood cell known as the T-cell which is equipped with cell killing mechanisms. In healthy subjects, T-cells identify and kill infected or abnormal cells, including cancer cells.

A Chimeric Antigen Receptor (CAR) is engineered by inserting, in the DNA of a T-cell, a sequence that will push the T-cell to express an antibody designed to recognize and bind an antigen present on the cancer cell.

To make this construction effective in killing cancer cells, another protein must be added inside the T-cell that will act as a signal that triggers cell killing once antibody/antigen binding has occurred. A T-cell combining the antibody that allows the recognition of the cancer cell and the signaling that allows it to destroy is a CAR-T cell.

In an attempt to render that CAR-T cell more potent, researchers have added other proteins, called co-stimulatory molecules, which are in charge of helping CAR-T cells survive for a longer period of time after they have been injected in the body, and/or push them to multiply.

The CAR manufacturing technology modifies T-cells outside the body. The steps are the following :

- Harvest cancer patient's white blood cells from a normal blood draw in a process called leukapheresis.
- Select T-cells from the white blood cells.

- Transfer of the genes that code for the CAR in the DNA of the T Cells
- Multiply the CAR to reach a therapeutic dose (iv) infuse these CAR-T cells back into the patient.

Natural Killer Cells and the Innate Immunity

Natural Killer Cells (NK cells) are yet another type of white blood cells. They constitute the first line of defense against external aggression (viruses or bacteria) and against cancer. NK cells primary role seems to be surveillance, early detection and essentially to hold the line until T-cells and other immune cells can come to the rescue.

In order to recognize their targets, NK cells use receptors (proteins) present on their surface that recognize specific targets, called ligands, and expressed by cells under stress. NK cells have both activating receptors, such as NKG2D, or NKp30, and inhibit

Celyad's NKR-T-cell platform

The Celyad T-cell immunotherapy approach is unique and builds on work conducted by Professor Charles Sentman and his team at Dartmouth College (Hanover, NH).

Sentman had the idea of copying the NK activating receptors (for example NKG2D or NkP30) and insert them on a T-cell very much like other CAR approaches. Instead of inserting a gene that codes for an antibody, Sentman inserted genes that coded for the NKG2D or the NkP30 receptors.

In order to provide the intracellular signaling from killing the attacked cell once the receptor binds to its ligands, Sentman used the same intracellular signaling construct as what is used in other CARs (a portion of the CD3 protein). Hence, a new CAR platform was invented, named NKR-T, meaning NK Receptor T-cell.

NKR-T uses also a co-stimulatory domain to increase the potency of the cell, but instead of inserting a gene coding for CD28 or 4-1-BB like other CAR-T, NK receptor naturally use a co-stimulatory molecule already present in T-Cell, called DAP 10 making the overall CAR construct much simpler.

Clinical development of NKR-2

Autologous NKR-2 is currently being evaluated clinically in a first-in-human Phase I/IIa dose-escalation study (ClinicalTrials.gov NCT02203825) at the Dana-Farber Cancer Institute (Boston, MA), to assess safety and feasibility in relapsed or refractory Acute Myeloid Leukemia (AML) and Multiple Myeloma (MM) patients (two blood related cancers, together constituting more than 50% of all blood cancers). No safety issues have

been observed so far and trial results are expected throughout 2016. The broad reach of this technology allows Celyad to plan for a large clinical program testing the activity of this compound in many different cancer indications.

Differentiation and advantages of NKR-2 T-cells :

- The NKG2D receptor binds to 8 different ligands that are generically expressed by a vast majority of cancer cells, both hemaetological and solid malignancies (around 80% of cancer types).
- NKR-2 targets and kills tumors as well as the blood vessels that feed them and also express the ligands of the NKG2D receptor.
- NKR-2 also targets and kills the inhibitory cells that are present in the tumor environment preventing the tumor from evading the immune system.
- Last but not least, what is unique is that NKR-2 induces adaptive auto-immune response thanks to the creation of a long term cell memory against the tar¬geted tumor.