

Cellestia Biotech AG

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# Gene transcription factor inhibitors: a novel class of therapeutics modulating gene expression

Cellestia Biotech AG is developing first-in-class therapies to control pathogenic gene expression by selective inhibition of previously undruggable transcription factors in the cell nucleus. The company's clinical lead, CB-103, has advanced to phase 2 in oncology, followed by a rich R&D pipeline of novel gene transcription factor inhibitors targeting oncology, autoimmune and inflammatory disorders.

Gene transcription is one of the fundamental principles of life, and dysregulation of this process is the core driver of most diseases. Selectively controlling gene expression by directly targeting specific gene transcription factors (GTFs) has been an aim of modern medicine for decades, as it would offer the possibility to modulate a virtually unlimited range of biological processes contributing to disease.

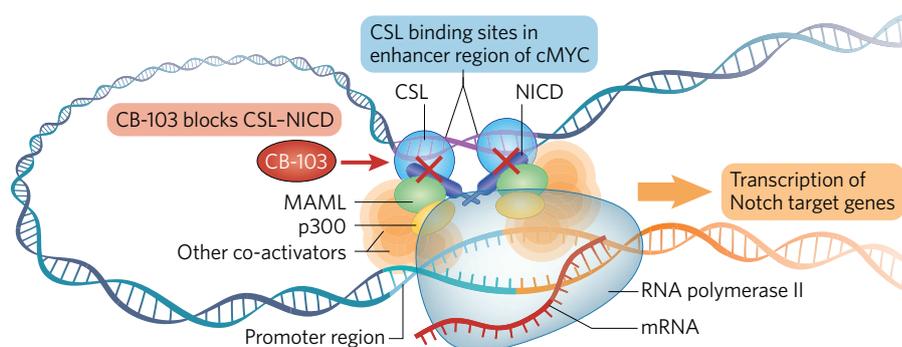
In spite of their enormous therapeutic potential, GTFs have remained undruggable due to lack of small molecule binding pockets and inaccessibility to therapeutic antibodies. However recent advances in structural biology have allowed identification of unique pockets in GTFs amenable to targeting with small molecule drugs. Cellestia Biotech, an integrated clinical stage R&D company has been at the forefront of identifying and targeting GTFs implicated in human disease, and has brought a first-in-class GTF-targeting drug to the clinic.

Based on more than 10 years of academic research led by the company's CSO, Rajwinder Lehal, Cellestia was founded in 2014 as spin-off from the prestigious Swiss Institute for Experimental Cancer Research (ISREC), headed by Doug Hanahan, based at the École Polytechnique Fédérale de Lausanne (EPFL), a world-renowned centre of excellence in Switzerland. Originally incubated at ISREC, today Cellestia has established its independent research facilities in Lausanne and in close proximity to Ludwig Institute for Cancer Research, Swiss Cancer Center Léman, Le Centre hospitalier universitaire vaudois (CHUV), University of Lausanne and EPFL. In addition, multiple international research collaborations have been established, all driving the research pipeline forward.

In 2015, Michael Bauer joined Cellestia as CEO, complementing the academic founder team with industry and development expertise. Headquartered in Basel, Switzerland—one of Europe's most dynamic pharma and drug development hubs—Cellestia has become an integrated R&D company that has attracted a world-class management team, board of directors and has engaged some of the most influential clinical oncologists and researchers supporting the R&D vision of the company.

## Creating a pipeline of selective GTF inhibitors

Cellestia is focused on developing first-in-class therapeutics with novel modes of action in highly relevant and difficult-to-target disease-driving



**Fig. 1 | CSL-NICD binding is essential for assembly and activation of the transcription complex.** CB-103 selectively inhibits CSL-NICD interaction, thereby preventing the assembly of the complex and leading to down-regulation of target gene expression. NICD, notch intracellular domain; MAML, mastermind-like.

biological mechanisms. Cellestia's unique know-how and approach to rational drug design has enabled the company to build a pipeline of novel GTF inhibitors, establishing Cellestia as a leader in this emerging field of innovative drug development.

One key success factor for Cellestia is in its ability to integrate computational power for structure-activity relationship modelling with experience in medicinal chemistry and scientific excellence. These competencies have enabled Cellestia to design, synthesize and evaluate new therapeutics in a very effective rational design process with an outstanding success rate, rapidly creating an attractive portfolio of R&D projects. Cellestia's innovation is backed by a growing portfolio of comprehensive intellectual property coverage to secure exclusivity for the clinical lead as well as novel compound series beyond 2040.

In creating this pipeline, Cellestia has shown that targeting GTFs is not just an attractive concept in principle, but one that works in practice. Cellestia's most advanced program in oncology, with its lead compound CB-103, is in phase 2 clinical trials for treatment of patients with multi-drug resistant cancers. In addition, the company has a rich pipeline of pre-clinical assets, with in vivo proof of concept in relevant animal models, covering a wide range of indications such as oncology, virus-induced cancers, and autoimmune and inflammatory disorders. These achievements put Cellestia on an excellent track to bring first-in-class innovative therapies to patients, addressing currently unmet medical needs across a wide range of indications.

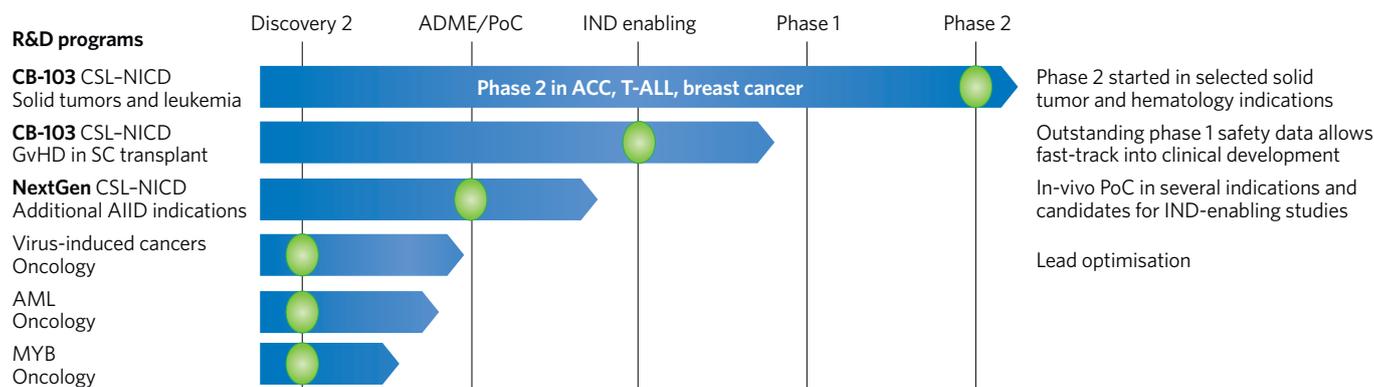
## A breakthrough in cancer research

Despite decades of progress in cancer research and emerging novel therapeutics, cancer remains the leading cause of death worldwide. Effective treatments have to overcome the extraordinary complexity of cancer biology, especially the ability of cancer to escape established therapies by activating resistance mechanisms or using alternative pathways promoting metastasis and growth. The emergence of multi-drug resistance remains a challenge in the development of successful cancer therapies.

Recent successes have been achieved with targeted therapeutics and immuno-oncology approaches, and some drugs have shown striking efficacy, particularly in biologically simple, early-stage cancers or those driven by rare and dominant oncogenic mutations. However, as these therapies eventually fail, the mortality rate remains high due to advanced metastatic cancers. While most therapies today are combination and/or sequential therapies, only few are specifically addressing the issue of targeting resistance and disease-escape mechanisms.

The importance and oncogenic contribution of the Notch signaling pathway is well recognized, making it a clinically relevant therapeutic target in cancer. In most cancers, oncogenic aberrations of the Notch pathway emerges as the disease evolves into a genetically complex disease, with simultaneous activation of multiple oncogenic pathways.

As one of the pivotal embryonic cell signaling pathways, this mechanism is tightly controlled in the adult organism. In healthy tissues, it leads to production of proteins mediating important functions such as tissue renewal, repair, hematopoiesis



**Fig. 2 | Cellestia's pipeline of gene transcription factor inhibitors: a novel class of therapeutics modulating gene expression.** ACC, Adenoid Cystic Carcinoma; ADME, absorption, distribution, metabolism and excretion; AIID, autoimmune and inflammatory disorders; AML, acute myeloid leukemia; GvHD, graft-versus-host disease; IND, investigational new drug; NICD, notch intracellular domain; PoC, proof-of-concept; T-ALL, T-cell acute lymphoblastic leukemia.

and stem cell differentiation, while, in the case of oncogenic hyperactivation, the overshooting production of these proteins can lead to cancer.

Being a cell-to-cell communication mechanism of physically adjacent cells, the upstream part of Notch signaling involves five different activating ligands, proteins displayed on the surface of signal-sending cells. These ligands can interact with four different receptors on the surface of signal-receiving cells. These receptors are composed of a receptor domain exposed to the cell surface, a transmembrane domain reaching across the cell membrane and an intracellular part called the Notch intracellular domain (NICD).

The binding of an activating ligand to one of these receptors leads to a conformational change, which in turn leads to proteolytic cleavage by the enzyme  $\gamma$ -secretase, releasing NICD into the cell cytosol. NICD then translocates to the cell nucleus, where it associates with other proteins to form the CSL-NICD-MAML transcription complex, which binds to DNA and triggers highly specific gene transcription (Fig. 1).

This signaling is tightly regulated and highly dependent on biological context in different tissues and organs. It is controlled by the concerted action of tissue-specific regulatory proteins and co-factors, which are also involved in the assembly of the transcription complex. The pivotal initiating step in the assembly of the transcription factor complex, however, is the sequential assembly of CSL, NICD and MAML, which together constitute the core of the GTF that binds to DNA and drives pathway-related gene expression.

A wide range of activating events can lead to oncogenic activation of this signaling cascade, including gain-of-function mutations in receptor genes, constitutive activation by chromosomal translocation, upregulation by pathway crosstalk, as well as mutations in regulatory genes. Cellestia's CB-103 controls dysregulation of this signaling cascade, irrespective of the activating event, by interfering with CSL-NICD-MAML interactions and preventing assembly of the GTF, thereby blocking oncogenic gene expression. In targeting this pathway at the level of gene transcription, Cellestia is the first company to safely and effectively control Notch-related oncogenic signaling in any patient, regardless of molecular cause of pathway hyperactivation. Cellestia has fully validated CB-103's novel

mode of action, confirming the exquisitely selective and highly potent control of gene transcription.

The superior potency and safety of CB-103 has been confirmed in a phase 1 clinical trial, showing strong target engagement and downregulation of key target genes such as those encoding cyclin D1, cMyc and members of the HES family. CB-103 has also demonstrated clinical benefit for patients with cancers driven by CSL-NICD-MAML activation, leading to eradication of pathway-related circulating tumor DNA and outstanding progression-free survival. With the validity of the approach confirmed, Cellestia has now initiated phase 2 clinical trials of CB-103.

## Cellestia is the first company to safely and effectively control Notch-related oncogenic signaling in any patient, regardless of molecular cause of pathway hyperactivation

With this unique approach, Cellestia has been able to close an important gap in the quest to break multi-drug resistance in cancer, as CB-103 can effectively take out the Notch/CSL-NICD-MAML component of any human cancer. Thanks to this innovative approach, CB-103 overcomes the issues related to the first generation of Notch pathway-targeting drugs, the  $\gamma$ -secretase inhibitors, which are very toxic, and the second-generation receptor/ligand-targeting monoclonal antibodies, which had a narrow efficacy spectrum and also monoclonal antibody-specific toxicities.

### Biomarkers and diagnostics: the right drug for the right patient

As a highly selective targeted therapy, CB-103 is being developed for cancer patients in which aberrant signaling of this mode of action contributes to tumor growth, metastatic spread and eventually multi-drug resistance. Identifying these patients is essential both for running informative clinical trials of CB-103, and, in the future, ensuring that this therapy is only given to patients who will benefit from it.

To meet this goal, Cellestia has developed a comprehensive biomarker and diagnostic program that will be used for identification of patients requiring such targeted therapy as well as evaluating pharmacodynamic responses to treatment. This program will finally serve as the basis for companion diagnostic development guiding the use of CB-103 to identify patients who most benefit.

### Building an R&D company and unlocking the potential of GTF-targeting drugs

Based on the experience gained in discovery and development of CB-103, Cellestia has been able to build in-house capabilities to design and develop drugs selectively targeting GTFs across a wide range of indications (Fig. 2).

The next series of compounds to enter IND-enabling studies in 2021 are geared towards oncology and indications in autoimmune and inflammatory disorders, based on preclinical work showing that they simultaneously downregulate expression of pro-inflammatory cytokines and promote immune tolerance by expanding regulatory T cells.

Finally, a number of early-stage programs addressing relevant oncology targets such as MYB, and other novel GTF targets relevant in virus-induced cancers and acute myeloid leukemia, are advancing well.

Since the company was founded, Cellestia has raised \$50 million in private equity and won several non-dilutive research grants to build a proprietary R&D platform yielding a rich pipeline of clinical and preclinical programs, which are validating the approach and potential of this new class of therapeutic targets. As a rapidly growing integrated R&D company, having achieved major milestones such as confirmed safety, target engagement and entering phase 2 for the clinical lead, and in vivo proof of concept across multiple indications for the pipeline programs, the company is preparing for a Series C financing in 2021.

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