Michael Bauer – CEO & Board Member, Cellestia

Cellestia has established itself as one of the leading companies in the discovery, research and development of innovative, first-in-class therapeutics targeting gene transcription factors for the treatment of cancer and AIID

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Dr Michael Bauer, a Novartis early development veteran, now serves as CEO of Basel-based Cellestia. Here, Bauer explains why Cellestia's unique transcription factor targeting molecule potentially represents a breakthrough in cancer research, the ways in which the firm's funding strategy has evolved, and how its future growth trajectory might look.

Can you begin by introducing your career trajectory prior to joining Cellestia?

Over the last 25 years, I have had senior leadership positions in clinical and preclinical drug development, project & portfolio management, regulatory affairs, and metabolism research. My academic background is a chemistry master's degree from the University of Hamburg, Germany, and a PhD in Biotechnology from the Technical University of Hamburg-Harburg, Germany

Having worked in life sciences product development with Novartis Oncology (Switzerland), Polyphor (Switzerland), Arpida (Switzerland), Syngenta (Switzerland) and Zeneca (United Kingdom), I have gained in-depth experience in early and late-stage drug development, lifecycle management, design and implementation of both regulatory and development strategies, negotiations with regulatory authorities, licensing, and portfolio restructuring and divestments. In most of these roles, I have been working at the interface between research, development, and business with both an operational and strategic perspective.

How did you come to be CEO of Celestia back in 2015?

Having previously worked in larger corporations, I really enjoyed the biotech environment during my time at Arpida. Then, while at Novartis and Polyphor the idea to join a biotech company's founder team further grew and led to setting up a virtual search team evaluating emerging opportunities to join innovative start-up companies as co-founder.

Through a friend and senior business mentor I was introduced to Cellestia, led at the time by its scientific founder Rajwinder Lehal. At the end of 2015, I joined as CEO and co-founder, bringing drug development and business expertise to the academic founder team. Starting from a single-compound post-doc project, we have now built Cellestia into an integrated R&D company with the clinical stage lead compound in Phase 2 and a rich R&D pipeline of novel, first-in-class gene transcription factor inhibitors.

What attracted you to the company initially and how does Cellestia's approach differ from that of other companies in the crowded oncology field?

I found the company's scientific innovation very intriguing, as targeting disease promoting biological mechanisms at the level of gene transcription was an area that had been considered difficult, if not impossible. However, Raj had found a way to prove it worked, mastering a problem that had challenged generations of scientists. As by 2015 the project had reached the point of candidate selection for starting drug development and personal relationships with the team were well established, I decided to join as co-founder and CEO.

Back in 2015, there was one set of data that really convinced me to join the company, as it opened the potential to develop a curative therapy in relapsed refractory multi-drug resistant T-Cell Acute Lymphoblastic Leukemia (T-ALL):

From a cooperation with Children's Hospital Zurich, Cellestia had access to blood samples of children who died at the age of approximately five years. Their disease could not be controlled by any therapy, neither established standard of care nor any new experimental multi-drug chemotherapy. In essence, all possible approaches had failed for these patients who ultimately died at a very young age.

Knowing that the mode of action controlled by CB-103 was a key driver of this fatal outcome of T-ALL, the efficacy of CB-103 in blood cultures from these patients was investigated, showing a very strong single agent activity in the blood samples; CB-103 has shown a highly potent and selective cytotoxic effect just on the leukemic cells, without affecting any other cell type. Furthermore, there was a potent synergy in combination with a wide range of established anti-cancer drugs.

In essence, this data suggested that with CB-103 we could overcome multi-drug resistance in these patients with a good chance of a curative outcome for patients with currently no hope for effective treatment today – patients that typically die rapidly despite all efforts.

Now, six years later, we have seen the first case in the clinic confirming this initial hope could indeed become true: Cellestia has recently been asked to provide CB-103 as emergency rescue treatment for a young man suffering from multi-drug resistant relapsed refractory T-ALL. Several high-dose multi-drug combinations did not get the disease under control and the patient's prospects of surviving the next few weeks were dismal. As he was confirmed to have a NOTCH-positive disease, CB-103 was added to the failing therapies and within a few days, the leukemic blasts could be eradicated to the point that the patient could then proceed to Stem Cell Transplantation (SCT) procedures. Speaking to the treating physician, he indicated that he had not expected the patient to survive the next few weeks, not to even think of getting the patient into SCT. The patient is now recovering well after successful SCT.

Taking together the outstanding safety profile demonstrated in Phase 1, clear signs of clinical efficacy, and strong biomarker data confirming target engagement and down-regulation of cancer-promoting target genes, we feel that our clinical program is on a very good track. We have now started Phase 2 clinical development in a range of different indications.

What have you learned during Cellestia's journey through the clinical trials process that will help you to make a more robust case when it comes to eventually bringing a treatment to market?

The Phase I trial for CB-103, for budgetary reasons, started off small and local in Spain and Switzerland with just a handful of clinics. We limited the indications to those which are known to be driven by NOTCH, with a focus on adenoid cystic carcinoma (ACC), a very rare cancer of the salivary gland. In this sense, it was not a typical Phase I trial as it was, from the start, accompanied with an intense sample collection and biomarker program.

Now, having confirmed the outstanding safety of our drug and demonstrated clinical efficacy, we have expanded clinical development globally: To the original sites in Switzerland and Spain, we added additional clinics in Germany, France, the USA, China, South Korea, and Taiwan. With this global approach, we have access to an international patient population, which is critical for rapid recruitment as well as confirming safety and efficacy in patients with different ethnic backgrounds.

As expected, based on pre-clinical research, we could already demonstrate efficacy and outstanding safety CB-103 in Phase 1. This not only gives us the confidence going into Phase 2 clinical development, but also represents a major breakthrough in cancer research.

Cellestia is the first company to control NOTCH oncogenic signalling safely and potently in any cancer patient. Due to the novel mode of action, we have been able to overcome the issues and limitations of first- and second-generation drugs, the gamma-secretase inhibitors (GSIs) and monoclonal antibodies (mABs) targeting the pathway further upstream, at the periphery.

Additionally, as well as being extraordinarily efficacious on the target mode of action, CB-103 is one of the safest cancer drugs I have ever come across. It has a very benign side effect profile at doses which show a clear disease control and down-regulation of cancer promoting target genes. The outstanding safety profile of CB-103 also opens the doors to another set of indications in Auto-Immune and Inflammatory Disorders (AIID):

NOTCH is well documented as being involved in many inflammatory processes and blocking this mechanism could have a dual anti-inflammatory effect: Down-regulation of specific pro-inflammatory cytokines, and up-regulation of immune-protective regulatory T-Cells and related anti-inflammatory cytokines.

While pre-clinical research has confirmed this possibility with GSIs and mABs, clinical use of these drugs had always been an issue due to safety concerns, a problem we do not have with CB-103, because of the novel mode of action, controlling the pathway very selectively at the level of gene transcription.

Having done cytokine profiling in some of our patients, it is very exciting for us to know, that also this works in patients: We already have achieved clinical proof of concept, having seen the desired immune modulation in absence of severe side effects in blood samples from our trial patients. We could also observe that this effect is selective on active inflammation and very specific, contrary to cyclosporine and corticosteroids delivering a more un-specific general immunosuppressive effect, which has again undesirable side-effects.

One very promising indication, related to oncology, is the treatment of GvHD (Graft versus Host Disease), where NOTCH related signalling is known to be a cause and driver of GvHD. We are therefore planning to also initiate a proof-of-concept study in GvHD.

Beyond GvHD, there are many other indications that can and should be treated with a drug targeting NICD-CSL/NOTCH pathway and for that, we are advancing the first next-generation compounds to start IND-enabling studies as we plan to position another compound in these indications, outside of oncology. We expect to conclude the pre-clinical development and enter Phase 1 clinical development within the next year.

Can you outline the scope of Cellestia's clinical development program?

Having finished Phase 1, Cellestia is now pursuing Phase 2 single agent trials in orphan indications like ACC, T-ALL and other rare diseases in a so-called "basket trial" which includes a defined number of patients with different cancers. We have been able to set up a very flexible adaptive design study, which opens several strategic options towards pivotal trials, depending on the results of the next study phase.

Importantly, in Phase 2 we will begin selecting patients based on our biomarker programs. As we developed the drug, we also developed our own biomarker panels to select patients based on genetic mutations and upregulation of oncogenic pathways which we monitor with next-generation sequencing, gene expression profiling or immunochemistry. We have a full panel of biomarker activities developed and in place for patient selection and pharmacodynamic monitoring.

Another area is the development of CB-103 in combinations. As the mechanism of action is implicated in driving resistance to established cancer medicines, we are advancing our approach also in combination with standard of care therapies, which all eventually fail, because of NICD-CSL/NOTCH pathway activation. We know from our own research, that CB-103 is synergistic with several such drugs and well-tolerated in combination, so the development of combination regimens to break multi-drug resistance will be an essential part of our clinical program.

Finally, we will investigate CB-103 in the prophylaxis of GvHD in patients after stem-cell transplantation following high-dose chemotherapy for treatment of various leukaemia indications.

Additionally, the global expansion of the program is critical for our clinical development strategy and value generation.

How has Cellestia's corporate strategy developed?

Initially, Cellestia was focused on one mode of action and had a single asset: CB-103 with a promising novel mode of action. In other words, it was more a project than a company.

Developing CB-103 and gaining a deeper understanding of the mode of action, we discovered the power of this novel approach targeting disease-promoting gene transcription more generally.

In the meantime, while we have successfully advanced our lead compound to Phase 2, we also have developed Cellestia into an integrated R&D company and established ourselves as a leader in targeting gene transcription factors for use in different therapeutic areas such as oncology and AIID.

While this is our focus, in principle this approach is valid for any biological target of therapeutic interest, in any indication. In this sense, we are delivering a breakthrough in biomedical research and we successfully demonstrate this with a growing pipeline of new discovery projects.

Our discovery engine is driven by integrating decades of deep know-how in targeting transcription factors using and combining state-of-the-art tools such as artificial intelligence, machine learning and sophisticated structural biology which drive very effective and targeted high-end medicinal chemistry and rational molecular design programs generating new lead structures which are then produced, tested and confirmed in our laboratories to deliver the desired therapeutic benefit.

With this approach, we have been able to build up a growing pipeline of highly attractive pre-clinical assets following our clinical lead program.

Cellestia has both Swiss and international investors on board; how has it approached financing up to this point and what are its investment needs today?

Cellestia has successfully built a highly qualified global private investor base. We started off with private investors, predominantly experienced pharma executives who privately invest in biotech start-ups, and who were able to critically analyse our data and develop their own opinion on our work. Having this kind of shareholder base has been considered in a way as a "built-in" due diligence creating trust with local family offices and successful biotech entrepreneurs who privately make larger investments. We conducted a series of seed financings, starting with CHF 500,000 in early 2016 and reaching CHF nine million over the course of two and a half years. At the end of the

seed financing rounds, our first institutional investor, PPF Group, a European investment fund, engaged and former Novartis CEO David Epstein came on board as an advisor and investor.

After securing European investments, we started to reach out to the dynamic capital markets in Asia, including China, an important geography in both market size and patient access terms. China has a huge patient pool and the legislation put in place over the last ten years has raised the country's clinical research and development to Western standards. Additionally, because of the nature of the Chinese healthcare system, there is a high degree of centralisation and specialisation in the country, which is very helpful for clinical development. This means that for rare diseases only a handful of clinics are needed to access a large patient pool, making patient access much easier than in some European countries.

In its Series A and B financing rounds, Cellestia enjoyed the strong support of existing shareholders and won two major investments from Asian funds: FC Capital from Shanghai, China and Partners from Seoul, South Korea. Both funds are highly sophisticated and globally active healthcare investment funds.

Cellestia has raised CHF 50 million building an integrated R&D company with a highly attractive clinical-stage and preclinical pipeline, we are now targeting an additional CHF 40-60 million from larger US and European funds. This capital will finance our Phase 2 programs for CB-103, move our next generation compound development into the clinical stage, and allow us to further advance our preclinical research pipeline.

What business model will Cellestia take in the future? Will the company look to out-license its programs or bring them through to market itself?

Cellestia has established itself as one of the leading companies in the discovery, research and development of innovative, first-in-class therapeutics targeting gene transcription factors for the treatment of cancer and AIID.

The successful development of CB-103 in cancer therapies and our growing pipeline, as well as our ambition to further exploit and deepen our ability to target additional transcription factors for the treatment of currently untreatable diseases will require significant financial resources. For this, we anticipate taking the company to IPO on NASDAQ and we are also looking into strategic partnerships for late-stage development and commercialization of our drugs.

What would you like PharmaBoardroom's international executive audience to take away about Cellestia?

Cellestia has achieved a breakthrough in biomedical research in successfully controlling a major cancer and inflammation-promoting mode of action with CB-103. For our lead compound we have demonstrated evidence of outstanding safety and efficacy and now advance into Phase 2 in oncology and GvHD. Furthermore, we have established our company as a leader in targeting gene transcription factors, controlling disease at the transcription level, opening access to an un-exploited universe of novel disease-promoting molecular targets, that were thus far not possible to treat. With this, we expect to significantly expand our activities in areas of currently un-med medical need with innovative first-in-class therapeutics.

Having established a successful track record in achieving our goals since its foundation in 2014, we feel that we are on a good track to establish Cellestia as a trusted partner in the development of novel, ground-breaking medicines.

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