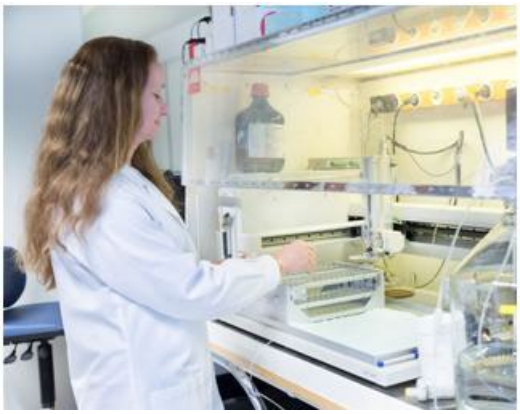
Kanceras drug development projects February 2019

Contents

Important events over the last 12 months – in short

Antagonists of the Fractalkine receptor

The Fractalkine receptor, CX3CR1, controls the immune system and cancer cells. The goal is to prevent cancer- and immune cells from infiltrating healthy tissues.



- Studies on three preclinical disease models have shown cardiovascular protection properties of KAND567.
- Kancera is evaluating KAND567 against primarily cardiovascular inflammation as well as cancer. There is strong scientific support for the idea that KAND567 reduces cardiovascular injury after infarction from

  preclinical animal studies and from major clinical trials conducted by Novartis (CANTOS study in> 10,000 patients) and Freeman Hospital, Newcastle (1,300 heart attack patients). There is currently no effective treatment against this type of problem.

- Kancera AB announced that a new patent application has been submitted describing a new synthesis pathway for KAND567 which provides an improved quality of active substance and the possibility of extended protection for a future drug. In addition, two preparations of KAND567 have been developed which can form the basis for two independent products.
- Kancera AB announced the start of clinical biomarker study in lymphoma patients in collaboration with Karolinska Institutet. This so-called phase 0 study aims to provide information about which patients could benefit clinically from treatment with KAND567.
- Kancera AB announced that unique blockers of the Fractalkine-system have been patented. From the patented blockers, Kancera intends to develop a new drug candidate, which is estimated to take about 12 months. The development of this new drug candidate is not expected to affect the planned clinical phase IIa study of KAND567.
- Kancera AB (publ) hereby reports on project activities and status for the preparation and implementation of a clinical study in cardiovascular inflammation associated with myocardial infarction.
- In the cancer area, Kancerea announced that the research project funded by SWElife has been completed, the final report has been approved by Vinnova.
- Kancera reported that the clinical biomarker study in lymphoma patients is proceeding according to plan
- Within the framework of the EU Research Program Horizon 2020, Kancera has been awarded a research grant of a total of approximately 250,000 Euro for funding a doctoral student in order to explore how the Fractalkine system controls some type of immune cells called macrophages, which are believed to cause pain in, among other things, rheumatism.

Most recent events

- Kancera announced that intermediate goals have been achieved prior to the planned start of clinical trials with the drug candidate KAND567 to demonstrate reduced tissue damage associated with heart attack. In a recent preclinical toxicological study, KAND567 has shown a favorable safety profile, and significant progress has been made in the development of a large-scale production method.
- Kancera announced that the results of a study of lymphoma patients' immune cells show that the Fractalkine system is activated in the cancers of chronic lymphocytic leukemia, diffuse large-cell B cell lymphoma and Hodgkin's lymphoma. In view of this discovery, the company will now deepen the investigations into how drug candidates that interact with the Fractalkine system, such as KAND567, may play a role in future treatments of these diseases.

ROR-inhibitors

Reprogram cancer cells to destroy themselves by apoptosis.

- Research on Kancera's ROR inhibitor has been published by scientists from Karolinska Institutet and Kancera in the reputed scientific journal Leukemia.

- The company's ROR1 inhibitor KAN0441571 penetrates the bone marrow where it achieves an expected pharmacologically active concentration for several hours.

PFKFB3-inhibitors

Strangle supply of glucose to solid tumors and reduces ability of cancer cells to repair their DNA, which together increase the tumor's sensitivity to other cancer therapies.

- Kancera has received prior notice from patent authorities in the EU and the US that patents on the PFKFB3 inhibitor KAN0438757 will be granted.
- The discovery of how Kanceras PFKFB3 inhibitors act against cancer published in Nature Communications.

HDAC6–inhibitors

Aim to kill leukemia cells by preventing the ability of cancer cells to spread, as well as supporting the patient's immune system to recognize and eliminate cancer cells.

- Animal studies show that Kanceras HDAC6 inhibitor KAN0440262 resides in the brain at significantly higher concentrations and for longer than in the blood. This opens up opportunities to exploit the substance against brain diseases, e.g. brain tumors and neuropathic pain.
- A report from EPO (The European Patent Office) enables a faster handling of the patent application, which includes KAN0440262, due to its level of inventiveness.
- Kancera reports that the company has registered a patent application (EP18205819.8) for a third series of novel substances that selectively inhibit the enzyme HDAC6. Kancera has now registered a total of three patent applications in the HDAC6 project, which protect all HDAC6 inhibitors developed by the company so far.

Most recent events

- Kancera AB announced that the company has entered into a Research and Option agreement with Grünenthal, a leading pharmaceutical company in pain research and management. As part of this agreement, Grünenthal will be responsible for all pre-clinical research activities to progress a selected chemical series from Kancera‘s novel HDAC inhibitor portfolio and receives the right to acquire this HDAC series. Through this agreement, Grünenthal will accelerate its ongoing efforts in this area, striving to develop novel and potentially disease modifying treatments for neuropathic pain.

Project portfolio

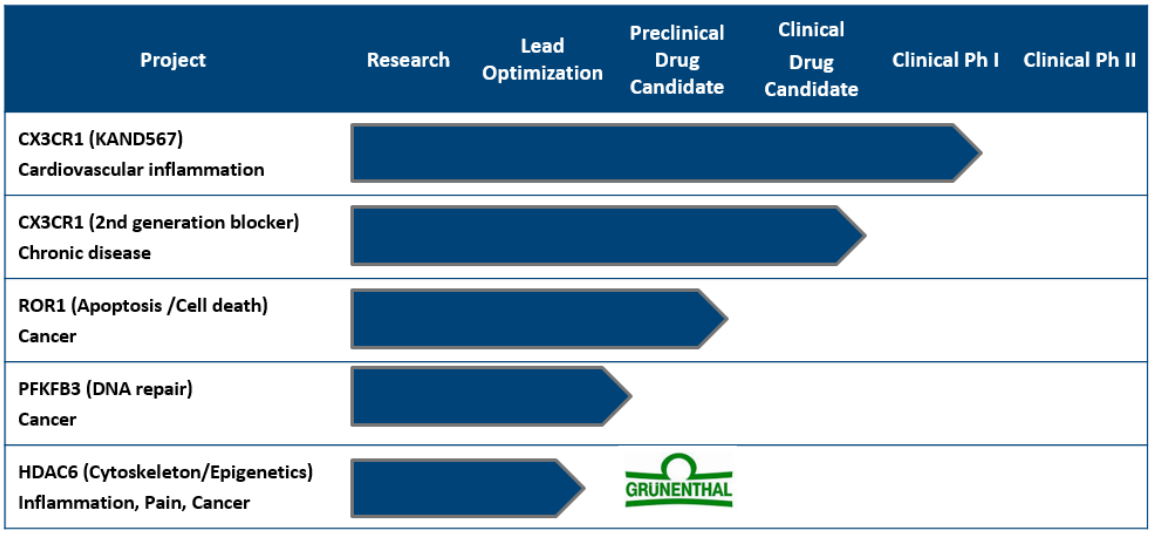
Kancera is engaged in the development of four drugs for cancer and autoimmune diseases that begin in a new treatment concept and end with a patented drug candidate offered for sale to major pharmaceutical and biotech companies in late pre-clinical or early clinical development.

The goal of completing the phase 1 study for KAND567 in the Fractalkine project before the end of Q4 2017 has been achieved. Kancera AB is now continuing the clinical development of KAND567 against inflammatory cardiovascular injuries, e.g. in connection with infarction. As Kancera has previously announced that the company's primary internal resources will be focused on Fractalkine projects targeted at inflammation and cancer, the main resources available in 2017 and 2018 were placed on the Fractalkine project. Hence the development of other projects has become more dependent on external collaborations.

The company has four drug development projects in the portfolio.

- **Antagonists of the Fractalkine Receptor CX3CR1 for the treatment of heart damage after an infarct and the most aggressive form of blood cancer.** Blocking the CX3CR1 receptor counteracts inflammation and metastasis by preventing cancer and immune cells from infiltrating healthy tissues.
- **ROR inhibitors for treatment of cancer.** Inhibitors of ROR reprogram the cancer cells so that they destroy themselves. In the laboratory, the ROR technology has been shown to work in both solid tumors and leukemia cells.
- **Inhibitors of PFKFB3 for treatment of cancer.** Inhibitors of PFKFB3 strangle the energy supply from glucose to tumor cells and decrease the ability of the cancer cells to repair their DNA. The combined effect may increase the tumor's sensitivity to other cancer treatments such as radiation therapy.
- **HDAC6 inhibitors for treatment of cancer.** HDAC6 inhibitors primarily aim at increasing the patient's immune system's capacity to recognize and eliminate cancer cells, as well as to prevent the ability of cancer cells to spread.

Figure 1. Kancera AB's project portfolio



Fractalkine project

– controls the immune system against cancer and inflammation

Product profile – Fractalkine inhibitor

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Heart and renal injuries after myocardial infarction
Secondary indication	Cancer, chronic inflammation
Administration	Myocardial infarction: IV , Cancer and inflammation: per oral
Product differentiation	*Effect:* a) Selective modulation of inflammation b) Cancer: increased time to disease progression. *Safety:* Low level of mechanism-related side effects is expected. *New mechanism of action:* Expected to be the first small molecule antagonist of the Fractalkine receptor.

Kancera AB has entered into an agreement with Acturum Life Science AB for the purpose of evaluating and further developing the unique blocker of the Fractalkine-signalling KAND567 (AZD8797, for example, KAN0440567). The agreement with Acturum Life Science gave Kancera AB the right to evaluate KAND567 in preclinical studies and then acquire the project. In view of the effects shown in disease models that are relevant for the treatment of cancer pain, Kancera AB announced in April 2016 the decision to acquire the Fractalkine project after successful transfer of know-how and data from AstraZeneca and Acturum. Payment for the Fractalkine project is made through a three-stage offset issue with a total of 6 million shares in Kancera AB. Part payments are made as the project progresses successfully until the first clinical study has been completed. This payment model means that the two companies share the risk of product development until the first study has been conducted in humans. Kancera AB intends to strengthen the protection of the Fractalkine blocker by applying for Orphan drug designation with the aim of ensuring at least 10 years of market exclusivity in Europe and 7 years in the United States.

KAND567 is an orally available small molecule that blocks CX3CR1, the Fractalkine receptor. Fractalkine is an immune-modulating factor, called a chemokine, which transmits signals via the CX3CR1 receptor, thereby controlling the function of immune cells and cancer cells. The amount of Fractalkine and its receptor CX3CR1 has been shown to be elevated in several inflammatory diseases, in cancer and in chronic pain conditions.

Kancera's drug candidate KAND567 is the most advanced drug candidate against CX3CR1 and has been shown to be effective against inflammation and pain in multiple preclinical disease models.

In the healthy individual, Fractalkine and its receptor, CX3CR1, control the migration of immune cells from the blood across the vessel wall to areas where the immune system is needed. However, animal studies show that the Fractalkine receptor is not essential for survival and that important immune functions are retained intact despite the absence of the receptor. Effectively combatting local inflammation while maintaining a well-functioning immune system is expected to be the basis for successful development of KAND567.

Autoimmune diseases and cancer can both be caused and aggravated by a dysfunctional immune system. The human immune system consists essentially of a specific immune system that is taught to attack foreign structures in the body, and a non-specific immune system that can quickly, and without learning, attack foreign structures. The Fractalkine system belongs to the latter.

The majority of today's powerful anti-inflammatory drugs block either major parts of the immune system (e.g. cortisone,

anti-TNF, cyclosporin, anti-VLA4) or target the specific immune system (e.g. JAK inhibitor, PD1 / L1 inhibitor). These drugs are successful, but in a significant proportion of patients they are not effective enough. In addition, a strong inhibition of the immune system involves an increased risk of serious infections and cancer.

New drugs, such as blockers of the Fractalkine signal, are now being sought to effectively and selectively target the non-specific immune system in humans to achieve better therapeutic effects and lower side effects risk. The immune system, through immune cells called macrophages, has been linked to several severe diseases including cancer and chronic inflammatory diseases of the gastrointestinal tract, joints, nerves and blood vessels.

Blocking of the Fractalkine system has been shown in clinical trials to produce the desired effect against autoimmune diseases such as Crohn's disease and rheumatoid arthritis in hard-to-treat patients. These positive studies have been conducted by the drug company Eisai with a monoclonal antibody (E6011) directed against the ligand Fractalkine, preventing it from binding to receptor CX3CR1. The results of the studies increase the likelihood for Kancera's drug candidate KAND567 to achieve clinical and commercial success as the first small molecule drug acting through the Fractalkine system.

The two drug candidates against the Fractalkine system, the E6011 and KAND567 antibody, behave as two sides of the same coin, i.e. one affects the Fractalkine system transmitter and the other affects the receiver of the signal. Both the antibody and KAND567 are expected to act in the bloodstream to prevent immune cells from penetrating tissues and creating or maintaining inflammation. The antibody is given via injections while KAND567 can be given both as an injection or as a tablet or capsule orally. KAND567 is expected to have an advantage over the antibody since, being a small molecule, it can more easily penetrate into tissues outside the blood vessels to exert its effect. Blockage of the Fractalkine system may prove to be the basis for a whole new class of drugs for the treatment of multiple common diseases.

Previous results in a multiple sclerosis disease model (PNAS, 2014, Vol. 111, pp. 5409-5414) also indicate that Kanceras KAND567 treatment produces the desired effect against autoimmune disease. This research study further supports the idea that desired effects against the disease can be achieved without significant side effects on the specific immune system. If this can be repeated in humans, it represents a competitive advantage over other drugs acting through the immune system.

Kancera's studies have also shown that KAND567 can reduce nerve damage associated with chemotherapy, which may enable more effective treatment for cancer by counteracting dose-limiting side effects. Today there is no effective treatment for this type of nerve damage.

In addition, there is reason to test whether Fractalkine-blocking drugs can directly attack cancer cells. The reason for this is that several types of cancer cells have acquired abilities possessed by the unspecific immune system. One of these abilities is to use the Fractalkine system to spread, like the immune system, into the body. If KAND567 can block this ability in cancer cells, the possibility exists for preventing or reducing metastasis.

Independent research groups have studied Fractalkine signaling and its biological and clinical role have reported data supporting that an antagonist of the Fractalkine-receptor may:

- facilitate the immune system’s attack on cancer
- prevent cancer cells from spreading to nerves and bone marrow
- reduce cancer pain caused by the tumor itself and side effects of chemotherapy

Although the drug candidate KAND567 was originally developed by AstraZeneca more than 10 years ago, the compound is still the leading small molecule antagonist of the Fractalkine receptor CX3CR1. There are other projects that develop small molecule drug candidates against CX3CR1. Kerberos Biopharma (USA) develops small molecule antagonists of the CX3CR1 and their candidate JMS-17-2 has shown interesting effects against breast cancer metastasis in animal models (AACR; Cancer Res 2015; 75 (15 Suppl): Abstract No.4116. doi: 10.1158/1538-7445. AM2015-4116). However, public information indicates that JMS 17-2 does not have the desired pharmaceutical properties, which is supported by the fact that the compound was administered to the animal model by injection in the abdomen. As mentioned above, the pharmaceutical company Eisai Co. Ltd. develops a monoclonal antibody that captures Fractalkine and makes Fractalkine unavailable to its receptor CX3CR1. In the fall of 2017, Eisai Co. Ltd published a small molecule CX3CR1 modulator called E6130 which has shown effect in two mouse models of colitis

(Wakita et al., Mol Pharmacol. 2017 Nov; 92 (5): 502-509). During 2017, a single-ascending dose (SAD) phase 1 clinical study of E6130 was completed in healthy volunteers, see: (https://www.clinicaltrials.gov/ct2/show/NCT02902978?term=E6130&rank=1).

Our assessment is that a small molecule antagonist of the Fractalkine receptor CX3CR1 has the potential to be a significantly better anti-cancer drug compared to an antibody that captures Fractalkine. This assessment is based on the fact that it is more difficult for antibodies to penetrate and affect a solid tumor compared to a small molecule and that CX3CR1 may affect cancer and immune cells independently of the presence of the Fractalkine ligand. A third aspect is that a small molecule is usually cheaper to produce than an antibody, which may lead to more extensive use of the small molecule than the antibody, if it otherwise meets the requirements for efficacy and safety.

KAND567 is a drug candidate that has undergone toxicological evaluation according to GLP and with a production method that has been proven in kg scale.

According to plan, Kancera's Fractalkine project was taken into clinical Phase Ia study in May 2017 and completed in December 2017. In the study, drug characteristics, safety and tolerability have been documented for KAND567 in healthy subjects. The results show that KAND567 is safe and well tolerated up to plasma concentrations that are five to ten times higher than the calculated effective level for therapeutic effect in humans. The results also showed that KAND567 blocks the Fractalkine system not only by direct interaction with the Fractalkine receptor but also by reducing the number of Fractalkine receptors on the surface of immune cells. Kancera is evaluating KAND567 primarily against cardiovascular inflammation, but also for cancer.

KAND567 has shown, in three preclinical animal models, cardiovascular-protective anti-inflammatory properties by significantly reducing infarct size, stabilizing vessel plaques that can cause infarction and counteracting reocclusion (restenosis) after expansion of the coronary artery with so-called vascular stents. These studies were carried out when the project was owned by AstraZeneca. Clinical evidence from Novartis CANTOS study in 2017 showed that anti-inflammatory treatment reduces the risk of complications following myocardial infarction. In addition, follow-up analyzes showed a strong and dose-dependent reduction of lung cancer in patients treated with anti-inflammatory drugs. Publications of independent research groups also support blocking of the Fractalkine system to protect the heart in conjunction with myocardial infarction (in animal models), and the Fractalkine system is an independent risk marker and driving factor behind the inflammation of the blood vessel and the heart muscle after myocardial infarction (shown in a study of a total of 1300 patients). Inflammatory cells from the blood infiltrate the heart after the infarction and cause complications in the aftermath. Among these disease-causing immune cells, are those identified as responsible, together with an active Fractalkine system, for complications following myocardial infarction. Together, these results provide support for KAND567 as a drug candidate for the treatment of cardiovascular disease. The results also provide information on appropriate biomarkers for the identification of patients who could benefit from such treatment.

In 2017, results were published that support the idea that the Fractalkine system in immune cells is correlated with an aggressive disease in lymphoma and suggests that a blockade of the Fractalkine system could inhibit the disease. In view of these findings, as well as the results from Kancera's clinical phase I study that demonstrate that KAND567 works against the identified immune cells, Kancera AB has initiated a collaboration with the Karolinska Institutet. The collaboration aims to prepare for a clinical study by evaluating biomarkers for the Fractalkine system in blood and cancer tissue and the effect of KAND567 on these biomarkers (in isolated blood from the patients), which may provide information on which patients could benefit clinically from treatment with KAND567.

Events during 2018 and 2019 up to the date of this report

Kancera reports results from clinical Phase I study and strategy for continued development of KAND567
On February 19th 2018, Kancera AB reported results from a Phase I study in healthy subjects with the immunoregulating drug candidate KAND567. The study has shown that KAND567 is safe and well tolerated up to plasma concentrations that were five to ten times higher than the calculated effective level for therapeutic effect in humans. Upon further increase of the dose, a reversible increase in markers for liver effect was noted. The results also showed that KAND567 blocks the Fractalkine system by reducing the number of Fractalkine receptors on the surface of immune cells.

Kancera has also reported results from three preclinical disease models showing cardiovascular protection

properties of KAND567. Kancera evaluates KAND567 primarily against cardiovascular inflammation but also against cancer.

Kancera informs about the patent application for extended product protection and new product formulation for KAND567
Kancera AB announced that a new patent application has been submitted describing a new synthesis pathway for KAND567 which provides an improved quality of active substance and the possibility of extended protection for a future drug. In addition, two preparations of KAND567 have been developed which can provide the basis for two independent products that can be targeted at various diseases and buyers.

Kancera AB announces the start of clinical biomarker study within the fractalkine project
Kancera AB announced the start of a clinical biomarker study in lymphoma patients in collaboration with Karolinska Institutet. This so-called phase 0 study aims to prepare for a clinical study by evaluating biomarkers for the Fractalkine system in blood and cancer tissue and the effect of KAND567 on these biomarkers (in isolated blood from the patients), which can provide information about which patients should be able to benefit clinically from treatment with KAND567.

A new patent application from Kancera lays the foundation for the development of additional drug candidates in the Fractalkine project
Kancera AB announced that unique blockers of the Fractalkine System have been patented. From the patented blockers, Kancera intends to further develop a new drug candidate, which is estimated to take about 12 months. The development of this new drug candidate is not expected to affect the planned clinical phase IIa study of KAND567. With two independent products (KAND567 and a future new drug candidate), which are protected by separate patent applications, Kancera's opportunities are further strengthened to commercialize the Fractalkine project in several disease areas, such as cardiovascular disease, inflammation and cancer.

Planning for clinical study in patients with myocardial infarction
Kancera reported on project activities and status for the preparation and implementation of a clinical study in cardiovascular inflammation associated with myocardial infarction. In the cancer area, it is announced that the research project funded by SWElife has been completed, the final report has been approved and that the clinical biomarker study in lymphoma patients is proceeding according to plan.

Furthermore, Kancera reported from internal and independent researchers that a blockade of the Fractalkine system in the context of acute myocardial infarction is expected to positively affect the healing and function of the heart, protect renal function and reduce the risk of recurrent vessel complications. The planning of the Phase IIa study is thus broadened to include biomarkers for all three effects, which in turn indicates that the probability increases for the study to demonstrate an attractive opportunity for further development of KAND567.

Development and production of pharmaceutical product for intravenous (IV) administration, toxicology studies and complementary preclinical efficacy studies are proceeding according to plan and will continue during the autumn. In parallel, completion of clinical study protocols and the establishment of a consortium for the implementation of the Phase IIa study are ongoing.

Vinnova funded project completed
Within the cancer indication Kancera's Fractalkine project was awarded SEK 1 million last year in funding from the Swedish Innovation Innovation Agency Vinnova Strategic Innovation Program (SWElife). The appropriation is aimed at projects "having a very high level of innovation and commercialization potential". The one-year project has now been completed and Vinnova has approved the final report.

Development of pharmaceutical product for oral administration
In the project, the first step in developing a drug product of KAND567 for oral administration has been conducted which includes the development of a solid formulation of KAND567 for rapid release from capsules, which is required for phase II studies in cancer. Furthermore, in collaboration with Per Kogner's research team at Karolinska Institutet, a study has been carried out in an animal model of the childhood cancer neuroblastoma. The treatment with KAND567 did not show a statistically significant decrease in tumor growth in this study, which may be due to the unexpected rapid growth of the tumors and delayed start of treatment. However, laboratory studies have shown that the KAND567 and Fractalkine system can inhibit repair enzymes necessary to protect the cancer cells DNA. Against this background, Kancera continues to study how KAND567 can be combined with treatments (cytostatics or radiation) that cause breaks in the cancer cells DNA.

Update of the clinical biomarker study
The clinical biomarker study in lymphoma patients conducted in collaboration with Karolinska Institutet is proceeding as planned and, so far, samples from approximately 50 patients have been analyzed. The study is expected to be completed in the fourth quarter of 2018. In this so-called phase 0 study, biomarkers for an activated Fractalkine system and the effect of KAND567 on these biomarkers in isolated blood from the patients are evaluated. An activated Fractalkine system has been proposed by independent academic researchers to accelerate the progression of lymphoma by increasing blood flow into the tumor and/or counteracting an attack from the patient's immune system. The study aims to provide information on which patients could benefit clinically from treatment with KAND567 and thus how a possible Phase IIa clinical study could be conducted.

Kancera has been awarded EU funding for research on the Fractal System in inflammatory diseases
Within the framework of EU research program Horizon 2020, Kancera has been awarded a research grant of a total of approximately 250,000 Euro for funding a doctoral student in order to explore the role of the Fractalkine system in the development of pain in arthritis. Kancera is part of a consortium together with 11 internationally recognized research groups to investigate new approaches to neurodegenerative pain and chronic pain syndrome.

Within the framework of Horizon 2020, the EU has allocated Kancera AB and its partners a total of approximately 2 800 000 Euro for a research program called TOBeATPAIN. Kancera's part of the grant of approximately 250,000 Euro provides funding for research for a PhD student for three years, after which partners at Karolinska Institutet fund the fourth and final research year. The PhD student's research will be done in close cooperation with Professor Camilla Svensson at Karolinska Institutet.

The aim of the doctoral research project is to explore how the Fractalkine system controls a type of immune cell called macrophages which are thought to cause pain in rheumatism. Appointment of the service will be via Karolinska Institutet.

The research program is coordinated by Professor Marzia Malcangio at King's College in London. Marcia is a distinguished researcher in the field of nervous system diseases.

Within the consortium, Kancera, together with the University of Würzburg, is responsible for how discoveries within the consortium can be transformed into new therapies and to benefit health care. The work will be done with the support of consortium members Eli Lilly in the UK and Bionorica Research GmbH in Austria.

In connection with the Q3 finacial report Kancera provided a status update for the Fractalkine project:

- New effect study in animal model of myocardial infarction showed that lower doses than expected give a significant cardiovascular effect
- Preliminary results from the GLP toxicology study showed that the calculated effective dose of KAND567 was safe (final results from this study are expected in January).
- Phase 0 study in lymphoma patients will be completed in December and the analyzes are expected to be completed in January 2019.

Kancera has achieved important intermediate goals prior to the planned start of clinical studies with the drug candidate KAND567
Kancera AB announced that intermediate goals have been achieved prior to the planned start of clinical trials with the drug candidate KAND567 to demonstrate reduced tissue damage associated with heart attack. In a recent preclinical toxicological study, KAND567 has shown a favorable safety profile, and significant progress has been made in the development of a large-scale production method.

Kancera reports results from analyses of the Fractalkine system in lymphoma patients' immune cells
Kancera AB (Nasdaq First North: KAN) today announces that the results of a study of lymphoma patients' immune cells show that the Fractalkine system is activated in the cancers of chronic lymphocytic leukemia, diffuse large-cell B cell lymphoma and Hodgkin's lymphoma. In view of this discovery, the company will now deepen the investigations into how drug candidates that interact with the Fractalkine system, such as KAND567, may play a role in future treatments of these diseases.

ROR-project
– reprograms cancer to self-destruct

Product profile – ROR1 inhibitors

Property	Summary of "Target Product Profile" (TPP)
Primary indication	B cell lymphoma
Secondary indication	Lung, pancreatic, breast, and ovarian cancer
Administration	Peroral with other drugs
Product differentiation	*Effect:* Induction of tumor-selective cell death in blood, bone marrow and lymph in blood cancer as well as in solid tumors provides opportunities for complete remission. *Safety:* ROR1 is mainly found in cancer cells, which is why a ROR1 targeted treatment should give a lower level of side effects compared to broad-acting drugs. *New mechanism of action:* Adds effect to existing drugs.

When healthy cells suffer genetic damage that is not repaired, a cellular suicide is normally initiated in order to eliminate the threat that these injuries constitute for the surrounding healthy parts of the body. Cancer cells, in contrast, have developed a resistance to signals that should lead to cellular suicide when serious injuries occur in the genome. In fact, the genomic errors in the cancer cells are a prerequisite for the aggressive and life-threatening characteristics of the cancer.

Kancera has shown that if the growth factor receptor ROR1 is present in the tumor then anti-ROR drugs can be developed that reprogram cancer cells to destroy themselves through cellular suicide. This fact is the basis for the development of Kancera's drug candidate.

Kanceras first drug candidate in the ROR project is directed against lymphocytic leukemia. After decades of stagnation in the development of drugs against this disease, several new drugs have been approved such as Imbruvica from Pharmacyclics/J&J/Abbvie and Zydelig from Gilead. The introduction of these drugs has brought great progress especially in the treatment of patients with advanced and refractory disease. For these patients, the disease can now be stabilized for an additional two to three years, compared with the traditional treatment. Clinical experience shows that significant medical need persists despite these advances.

There is still a lack of a drug against chronic lymphatic leukemia (CLL), which causes a long-term control of the disease (give complete remission) without posing a threat to the patient's organs that are function normally. Kancera's inhibitors of the cancer-selective growth factor receptor ROR1 has the potential to become such a drug since the company and independent researchers have demonstrated that blocking of ROR1 leads cancer cells, even the most treatment-refractory, to destroy themselves. Also, ROR1 is selectively found in cancer cells and not in the surrounding healthy tissue and a drug that acts with a high selectivity against ROR1 has the potential to give the patient possibilities to live a normal life with limited side effects of the treatment.

About 15% of patients with CLL develop a very hard-treated form of lymphoma called Richter's syndrome. Neither the standard treatments nor the newest drugs against CLS have the desired effect against Richter's syndrome which is why there is a great medical need for new drugs against this disease. Studies have shown that tumor cells in Richter's syndrome carry ROR1 in a majority of subjects studied. Kancera has also shown that the company's ROR1 inhibitor kills cancer cells that represent Richter's syndrome and expresses ROR-1.

A first generation of Kancera's ROR inhibitors has been shown to work rapidly and efficiently against CLL cells from patients, even against treatment-resistant cells from patients with treatment-resistant CLL. This has been

demonstrated in the lab against isolated cancer cells and in animal studies where human disease has been recreated in mice. A first drug candidate, KAN0439834, was selected against CLL, but the substance disappears relatively quickly from blood circulation and does not provide sufficient effect against solid cancer.

Kancera's development of a second generation of ROR inhibitors has extended the retention time in the blood, which is expected to provide efficacy against several cancers. Independent research groups have demonstrated that ROR1 is involved in blood cancer forms such as acute myeloid leukemia (AML) and multiple myeloma (MM) as well as certain refractory solid cancers like pancreatic cancer, ovarian cancer and triple negative breast cancer (an especially intractable form of breast cancer that lacks three common targets of cancer drugs, hence "triple negative").

A first goal in this work has been achieved since a second generation of ROR inhibitors have been developed that exhibit an improved effect against cancer cells (lower dose required to achieve the same killing effect). In addition, these ROR inhibitors are retained in the blood circulation for a time long enough to have the potential to be efficient against lymphoma and solid tumors. This second generation of ROR inhibitors have been shown to be effective in solid tumors in a disease model in which triple negative breast cancer in humans has been implanted and studied in zebra fish and have also been shown to eliminate ROR1-carrying leukemia cells in a mouse model of human CLL.

The assessment is that Kancera is a world leader in the development of small molecule drugs against the cancer-specific growth factor ROR. If ROR1 is blocked, then e.g. leukemia cells are reprogrammed to destroy themselves. There are competing groups that develop antibodies and modified immune cells directed against ROR1. In contrast to these, Kancera's ROR inhibitors have the ability to penetrate into cancer cells and kill these even if ROR1 is not present on the surface of the cancer cells. Neither antibodies nor modified immune cells are able to do this.

Events during 2018 and 2019 up to the date of this report

Research on Kancera's ROR inhibitor published in a reputed international scientific journal
Kancera announced that an article entitled "First-in-class oral small molecule inhibitor of the tyrosine kinase ROR1 (KAN0439834) induced significant apoptosis of chronic lymphocytic leukemia cells" has been published by researchers from Karolinska Institutet and Kancera in Leukemia (Leukemia, 2018) doi: 10.1038 / s41375-018-0113-1 March 27 (E-publ. ahead)). The article documents the molecular mechanisms that cause the small molecule KAN0439834 to produce a potent anti-tumour effect in preclinical models of chronic lymphocytic leukemia (KLL). The basic structure of the drug candidate was identified from the Kancera chemical library from which a set of 110,000 substances were screened against ROR1 and further developed with tests against CLL cells from patients to KAN0439834.

Kancera reports that KAN0441571 penetrates the bone marrow
Kancera reported that KAN0441571 penetrates the bone marrow where it achieves an expected pharmacologically active concentration for several hours. This property may be of significant importance for the treatment of blood cancers that originate from the bone marrow and in the treatment of ROR-dependent bone metastases.

PFKFB3-project
- blocks cancer cells' ability to repair themselves

Product profile – PFKFB3-inhibitors

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Solid tumors treated with DNA-damaging therapy such as ovarian and lung cancer
Secondary indication	Inflammation
Administration	Peroral/Intravenous
Product differentiation	*Effect:* Synergistic effect with PARP-inhibitors, radiation or chemotherapy. *Safety:* PFKFB3 is mainly found in hypoxic tissue and in cancer cells which is why a PFKFB3 selective drug can be expected to give a low level of side effects. *New mechanism of action:* Adds effect to existing drugs.

The project aims to develop PFKFB3 enzyme inhibitors to strangle the energy metabolism in cancer cells, thereby rendering the cancer cells more sensitive to chemotherapy and radiotherapy. Kancera has, together with Professor Thomas Helleday and his research group at Karolinska Institutet, made a surprising discovery that shows how Kancera's PFKFB3 inhibitor enters the cancer cell's nucleus and enhances the effect of a recently given radiation dose. This discovery has been claimed in a US patent application owned by Kancera.

The background to this invention is the unique metabolism of cancer. Cancer cells consume *e.g.* up to 200 times more sugar compared to healthy cells. In recent years, both academic researchers and pharmaceutical companies have paid attention to that the altered metabolism contributes to that cancer cells can survive with very little oxygen available, creating an environment where aggressive cancer cells develop. By strangulating the special metabolism that cancer cells need to resist both chemotherapy and radiation, the tumor becomes weakened. Healthy cells, on the other hand, are not affected by the treatment in the same way since they have a different metabolism than the cancer cells. Thus, a new strategy for fighting cancer has emerged.

PFKFB3 is an enzyme that acts as a gas pedal in the metabolism of sugar to energy. Kancera has developed a compound that inhibits PFKFB3 and shown that this slows the growth of pancreatic cancer in an animal study. Although this cancer is very difficult to treat, the assessment was that the effect of the PFKFB3 inhibitor was not strong enough to proceed with the selected compound as a mono-therapy. Instead Kancera started a collaboration with Professor Thomas Helleday's group at Karolinska Institutet to better understand how PFKFB3 inhibitors are to be used to achieve maximum effect against cancer.

The collaboration with Professor Helleday and Karolinska Institutet has now led to the discovery that PFKFB3 not only regulates the metabolism of sugar to energy but also migrates into the cancer cell's nucleus where PFKFB3 contributes to the cell's ability to repair genetic material (DNA). As can be expected from this discovery, Kancera's patent pending compound KAN0438757 increases the damage that radiation causes cancer cells. These results support the continuation of the work by Kancera to develop a drug candidate against PFKFB3 and test it in combination with radiation treatment to combat resistant cancers.

Radiation therapy is an effective method to treat cancer but it is challenged by the fact that cancer cells exhibit resistance and by the adverse side effects of the radiation itself. To improve the therapeutic effect and reduce the side effects it is desirable to make cancer cells more sensitive to radiation. One of the most attractive ways to achieve this is to make it difficult for cancer cells to repair the genetic damage produced by radiation preferably without hindering healthy cells to repair their DNA. Healthy cells are exposed to external factors that cause single-strand DNA breaks, e.g. by sunlight. However, gamma radiation is stronger and causes, in addition to single-strand breaks, also double-strand breaks in the DNA. A drug that blocks repair of double-strand breaks but allows the repair of single-strand breaks could thus do more damage to cancer cells exposed to gamma radiation (and chemotherapy) compared to the healthy cell that has been exposed to sunlight. The discovery by Kancera together with Prof. Thomas Helleday's research group points to that Kancera's PFKFB3 inhibitor meets these requirements.

There are various possibilities to attack the metabolism of the cancer, and inhibition of PFKFB3 has attracted several pharmaceutical companies. However, the development of drugs against PFKFB3 is technically challenging, which is likely to have contributed to that no drug against this enzyme has been tested in clinical efficacy studies (Phase 2) yet. This also means that the area is not yet dominated by any company. Examples of companies working with PFKFB3 are AstraZeneca and the American biotech company Advanced Cancer Therapeutics. In comparison with AstraZeneca's compounds, Kancera's PFKFB3 inhibitors may have the advantage to be more cancer-selective due to a mechanism of action different from that of the compounds that AstraZeneca have published. Regarding the PFKFB3 inhibitors from Advanced Cancers Therapeutics, Kancera has not been able to demonstrate that they have the desired effect on DNA repair that Kancera's PFKFB3 inhibitor shows.

Kancera has three patent applications (one granted in the US) in the PFKFB3 project. Two of these cover new PFKFB3 inhibitors (registered in 2010 and 2012) and one of these (registered in 2016) covers the combination therapy with PFKFB3 inhibitors and radiation.

Events during 2018 and 2019 up to the date of this report

Discovery of how Kancera's PFKFB3 inhibitor acts against cancer published in a reputable scientific journal
Kancera AB today announced that the article entitled "Targeting PFKFB3 radiosensitizes cancer cells and suppresses homologous recombination" has been published by researchers from Karolinska Institutet and Kancera AB in the journal Nature Communications(1).

The article documents the molecular mechanisms that give the small molecule KAN0438757 a potent anti-tumor effect in preclinical models. In the current study, researchers discovered that the enzyme PFKFB3 helps cancer cells resist radiation therapy. The discovery shows that PFKFB3 binds to the cancer cell's damaged DNA (genome) where the enzyme contributes to a repair that leads to continued growth.

This new knowledge thus supports the fact that a drug that blocks PFKFB3 could change a resistant cancer to one that is sensitive to radiation therapy. This hypothesis was tested by evaluating Kanceras PFKFB3 inhibitor KAN0438757 against cancer cells in combination with radiation. The researchers could show in the laboratory that the cancer cells' ability to repair their genetic material and to survive was prevented by this combination, while healthy cells were not affected by KAN0438757.
The research has been funded by Kancera, Swedish Society for Medical Research, Marie Sklodowska-Curie Appropriation No. 722729, which is part of the EU Horizon 2020 program, as well as Torsten Söderberg and Ragnar Söderberg Foundation and others
(1)http://www.nature.com/ncomms.
DIO:10.1038/s41467-018-06287-x

HDAC6-project
– acts against cancer by controlling the cancer cells' ability to spread

Product profile – HDAC6-inhibitors

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Glioblastoma
Secondary indication	Pain
Administration	Peroral
Product differentiation	*Effect:* a) new mechanism of action that in combination with other drugs may give an increased effect on the ability of the cancer cell to divide, b) under investigation: immuno-stimulating effect against cancer by small molecule. *Safety:* Due to high selectivity for HDAC6, a lower degree of gastro-intestinal effects is expected compared to the less selective HDAC inhibitors that are currently in clinical development. *New mechanism of action:* Combination of effect on HDAC6 and Kancera's "Target 2".

HDAC6 is an enzyme that controls the interior cell fibers, a type of cell skeleton, functions and thereby how cells can move in the body. Active HDAC6 affects the tumor's ability to invade surrounding healthy tissue and form metastases. HDAC6 has also been shown to be a useful marker providing an indication on how difficult the cancer is to treat. Taken together, these observations point to that HDAC6 contributes to cell changes that lead to tumor formation and invasion of tumor cells into healthy tissue making HDAC6 an attractive target for the development of new effective drugs against cancer.

Recent research also shows that HDAC6 inhibitors can help the patient's immune system to recognize and attack cancer cells. The HDAC6 inhibitors relieve a molecular brake, called PD-L1, which is applied on the immune cells by the cancer. Thus, HDAC6 inhibitors may constitute an effective small molecule replacement of the new PD-L1 antibodies which are in clinical use today, with the advantages that the small molecule drug can be taken in pill form instead of via syringe and will be cheaper to produce, which can make the drug available to more patients.
It remains for Kancera to show how effectively the company's compounds can counteract the ability of the cancer to slow down the patient's immune system.

There are currently five HDAC inhibitors on the market for the treatment of various forms of T-cell lymphomas, AML and multiple myeloma. These inhibitors are active against several members of the HDAC family of enzymes leading to severe side effects on e.g. the gastrointestinal tract. Also, the risk of significant negative impact on cardiac function is high. Kancera's discovery of selective HDAC6 inhibitors may provide a solution to how the healthcare system can take advantage of the HDAC inhibitor's effect on cancer without causing the patient severe side effects.

Kancera's HDAC6 inhibitors are covered by two patent applications submitted in 2015 and 2016. These compounds are more potent and selective in vitro against cancer cells from multiple myeloma than the furthest developed competing HDAC6 inhibitor ACY-1215.

Kancera has also discovered that the company's HDAC6 inhibitors can be designed to operate also through an additional mechanism, which has not been described publicly for competitive reasons. Kancera's results show that a combined effect against HDAC6 and Target 2 in a more efficient manner stops the cancer cell's ability to proliferate.

Kancera AB has developed a selective HDAC6 inhibitor that combines good killing effect on cancer cells in the laboratory with significantly improved uptake and stability in blood circulation in mice on oral administration compared

with the furthest-developed, competing HDAC6 inhibitor ACY-1215. Kanceras HDAC6 inhibitor is now being evaluated in disease models.

New animal studies show that KAN0440262 effectively passes through the blood-brain barrier and resides in the brain at significantly higher concentrations and for longer than in the bloodstream. This combination of properties allows Kancera to exploit the substance against multiple brain disorders, including brain tumor (glioblastoma) and neuropathic pain. Kancera has also been able to demonstrate that treatment that has given relevant exposures in the brain of KAN0440262 does not lead to notable effects on animal behavior or general health. The so-far positive safety profile of KAN0440262 is further supported by studies conducted without a remark on 44 safety markers in vitro. However, before clinical trials can take place, extended toxicological studies are required.

Events during 2018 and 2019 up to the date of this report

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The EPO (The European Patent Office) has, in a report (International Preliminary Report on Patentability), assessed that the patent application comprising KAN0440262 is both innovative and has sufficient inventiveness
Following such a positive report, several countries also offer the possibility of a faster handling of patent applications, a so-called "Patent Prosecution Highway". This patent application, which includes KAN0440262, enters the national registration phase in June 2018.

Kancera AB applies for a patent for a third series of HDAC6 inhibitors
Kancera reported that the company has registered a patent application (EP18205819.8) for a third series of novel substances that selectively inhibit the enzyme HDAC6. Kancera has now registered a total of three patent applications in the HDAC6 project, which protect all HDAC6 inhibitors developed by the company so far.

Kancera gains a strong partner for the further development of their HDAC inhibitors
Kancera AB announced today that the company has entered into an Research and Option agreement with Grünenthal, a leading pharmaceutical company in pain research and management. As part of this agreement, Grünenthal will be responsible for all pre-clinical research activities to progress a selected chemical series from Kancera‘s novel HDAC inhibitor portfolio and receives the right to acquire this HDAC series. Through this agreement, Grünenthal will accelerate its ongoing efforts in this area, striving to develop novel and potentially disease modifying treatments for neuropathic pain.

Patent portfolio and intellectual property rights

The basis for the commercial potential of new drugs is a broad patent protection. Patent work is an important and integral part of Kancera’s operations, especially in the early preclinical phases. Kancera’s management has extensive experience in establishing patent strategies and build competitive patent portfolios even in highly competitive fields. For Kancera’s projects, patent strategies and patent portfolios are developed together with internationally established patent law firms. Timelines for the first patent application is determined from case to case depending on competitor activity. When Kancera sells drug candidates, there is a negotiation on whether the Company's patents or patent applications are to be licensed or sold, directly or through option.

Kancera AB currently has 11 patent families for small molecules: four for Fractalkine blockers, two for ROR inhibitors, three for PFKFB3 inhibitors and three for HDAC6 inhibitors. In addition, Kancera AB has two patent families covering antibodies to ROR1. However, these are not being developed commercially at the current time.

Project/ Patent-family	Desciption	Status	Application/ Patent number	Applica-tion date	Patent agency
Fractalkine	Substans patent 1	**Granted patent in:** China Germany France UK Italy Japan Sweden USA	US 7947693	2006-04-03	Swea IP Law
Fractalkine	Substans patent 2	**Granted patent i:** China Germany France UK Italy Japan Sweden USA	US 7960395	2007-09-27	Swea IP Law
Fractalkine	Process patent	**Patent application** UK, international application in next step.	GB1807898.0	2018-05-15	Potter Clarkson
Fractalkine	Substans patent 3	**Patent application** UK, international application in next step.	P66314GB	2018-07-06	Potter Clarkson
ROR1	Substans patent 1	**Patent application:** Australia Brasil Europe Hongkong India Israel Japan Canada China Mexico New Zeeland South Africa South Korea USA	PCT/EP2016/052091	2016-02-01	Brann
ROR1	Substans patent 2	**Patent application:** Europe* USA* HongKong* India* Japan* China* South Korea*	PCT/EP2017/067262	2017-07-10	Brann
ROR1	Mouse AB	**Granted patent in:** Europe China USA **Patent application:** India	PCT/EP2010/007524	2010-12-10	Novitas Patent

ROR1	Human Ab	**Granted patent in:** Europe China USA **Patent application:** India	PCT/EP2011/072490	2011-12-12	Novitas Patent
PFKFB3	Patent family"Sulfonamide compounds"	**Granted patent in:** Europe USA **Patent application:** Hongkong India	PCT/EP2011/066250	2011-09-19	Brann
PFKFB3	Patentfamily ”Bisarylsulfonamides "	**Granted patent in:** Australia Europe Hongkong Japan China Mexico New Zeeland South Africa USA **Patent application:** Brasilien Indien Israel Sydkorea	PCT/EP2012/076836	2012-12-21	Brann
PFKFB3	Patentfamily "Biarylsulfonamides in combination with radiation therapy".	**Patent application:** USA (Continuation-in - Part)	PCT/EP2012/076836	2012-12-21	Brann
HDAD6	Substans patent 1	**Patent application:** Australia Europe Canada New Zeeland USA	PCT/EP2015/060329 3	2015-05-11	Brann
HDAC6	Substans patent 2	**Patent application:** Australia Europe India Japan Canada Kina New Zeeland South Africa USA Russia South Korea	PCT/EP2016/077914	2016-11-16	Brann
HDAC6	Substans patent 3	**Patent application:** Europa	18205819.8.	2018-11-13	Brann

*in progress

Market outlook for Kancera's products

To be updated

For more information, contact:

Thomas Olin, CEO: +46 73 520 40 01

Kancera AB (publ)

Karolinska Institutet Science Park

Banvaktsvägen 22

SE 171 48 Solna

Visit our home page at: www.kancera.se