

Healthcare industry BW

Methadone – the last step to becoming an anti-cancer drug

It all began several years ago with a surprising discovery in the laboratory. Claudia Friesen, a chemist at Ulm University, discovered that leukaemia cells that were exposed to methadone died within a relatively short period of time. Seven years on and many papers later, what was once a rather exotic substance is now undergoing clinical testing in cancer patients.

Editor's note:

According to a position statement published by the University of Ulm, Ulm University Hospital and the Comprehensive Cancer Center Ulm (CCCU) on 24th August 2016, which BIOPRO's editorial office has had in their possession since 5th December 2016, this article solely concerns basic research findings. Please refer to the comprehensive position statement (see *Downloads* section) of the Comprehensive Cancer Center Ulm (CCCU) for further details. Please also see *Downloads* section for a paper on a retrospective clinical trial on D,L methadone in glioma patients carried out in cooperation with the Charité in Berlin and published in early 2017.

Dr. Claudia Friesen has been extremely interested in anti-cancer drugs ever since she studied chemistry at Heidelberg University. She has been with the University Hospital in Ulm since 1998 and when she joined Professor Erich Miltner's group at the university's Institute of Legal Medicine in September 2007, she started to look more closely at potential drugs for cancer treatment, with a particular focus on drugs with a cytotoxic effect. She made rapid progress and only three months after starting her investigations, Friesen made a groundbreaking discovery that she has been working on ever since.

Surprising death in the test tube





Cancer researcher Claudia Friesen found that methadone is a promising new potential therapy for leukaemia.
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When Friesen and her team tested methadone in leukaemia cells, they were surprised to find that methadone effectively killed leukaemia cells in a comparatively short time; until now methadone has usually only been used for managing severe pain and as an anti-addictive preparation for use in patients with opioid (e.g. heroin) dependence. At the time of Friesen's discovery, little was known about methadone and its mechanism of action. What was known was that it exerts its analgesic effect by binding to opioid receptors and that tumour cells express many opioid receptors on their surface.

Friesen and her team found that methadone induced apoptosis in leukaemia cells, a finding that Friesen was able to deduce from the presence of typical membrane-enclosed vesicles outside the cancer cells. It goes without saying that Friesen was aware that the process of apoptosis is often defective in cancer cells, and is the reason why such cells grow in an uncontrolled manner. The excitement of the hunt had got its hold on her.

In 2008, Friesen published her findings and caused quite a stir in the scientific and non-scientific press, probably because her findings were unusual in the context of mainstream cancer research. The binding of methadone to opioid receptors on cancer cells induces apoptosis, i.e. programmed cell death; the process is triggered by protein-degrading enzymes (caspase 9 and 3), which quickly sweep obstacles such as Bcl-xL and XIAP (X-linked inhibitor of apoptosis protein) out of the way. Moreover, methadone does not have any toxic effects on healthy, non-leukaemic blood cells.

Friesen and her team discovered that the binding of methadone to an opioid receptor leads to the activation of inhibitory G-proteins. These inhibit the enzyme adenylate cyclase, which in turn leads to the downregulation of cyclic adenosine monophosphate (cAMP). This improves the effectiveness of anti-cancer drugs in treating cancer.

Opioid receptors and cell death

Opioid receptors appear to play a key role in the induction of cell death, but little is yet known about them. They are found in the brain and spinal cord of mammals including humans, and bind to endogenous and exogenous opioids such as methadone. They have seven transmembrane-spanning domains and are usually found in areas involved in pain control and regulation of emotional response. Methadone binds to μ receptors.

Cancer cells carry a large number of opioid receptors on their surface. Healthy cells only carry a few. The more opioid receptors a cell has, the easier it is to trigger its death. A cancer cell that has a particularly large number of opioid receptors can be driven to suicide by methadone alone. Unfortunately, as Friesen has found, most tumour cell types do not carry enough opioid receptors for methadone to be effective on its own. However, she has also found that cells with a median density of opioid receptors can be driven to suicide by exposing them simultaneously to methadone and cytostatic drugs, which increases the drugs' cytotoxic potential.

Ex vivo experiments with patient cancer cells and human cancer cell lines confirmed the apoptotic effect of methadone ("the speed with which cell death occurs depends on the type of tumour"), and animal models were used to confirm the results in vivo. The scientists tested the effect of methadone in combination with a chemotherapeutic drug in mice bred to have human leukaemia and found that the tumour stopped growing, and did in fact shrink and disappear completely.

Mutual increase in cytotoxic potential makes the clinical application of methadone more likely

But this was not the only thing Friesen and her team discovered. They also observed a phenomenon that has brought their findings closer to clinical application (Friesen 2013). When methadone binds to opioid receptors, cancer cells not only take up greater amounts of the anti-cancer drug than without methadone, they also reduce the efflux of the drug. In addition, the anti-cancer drug used leads to an increase in the number of opioid receptors that are expressed on the cancer cell surface, with the result that more methadone can bind. In other words, methadone and the anti-cancer drug mutually increase their cytotoxic potential.

Friesen has already shown this “dual synergism” for several substance classes with a cytotoxic effect (e.g. platinum complexes, anthrocyclines).

Friesen strongly believes that the mutual increase of the agents’ cytotoxic potential improves the therapeutic outcome: significantly lower amounts of cytostatic drugs would be required, which in turn would reduce the number of adverse drug effects. Methadone also has the potential to sensitise resistant cancer cells to anti-cancer drugs and give ‘untreatable’ patients another chance of treatment with a better outcome.

Even cancer stem cells capitulate in vitro



Glioblastoma cells survive treatment with an anti-cancer drug.
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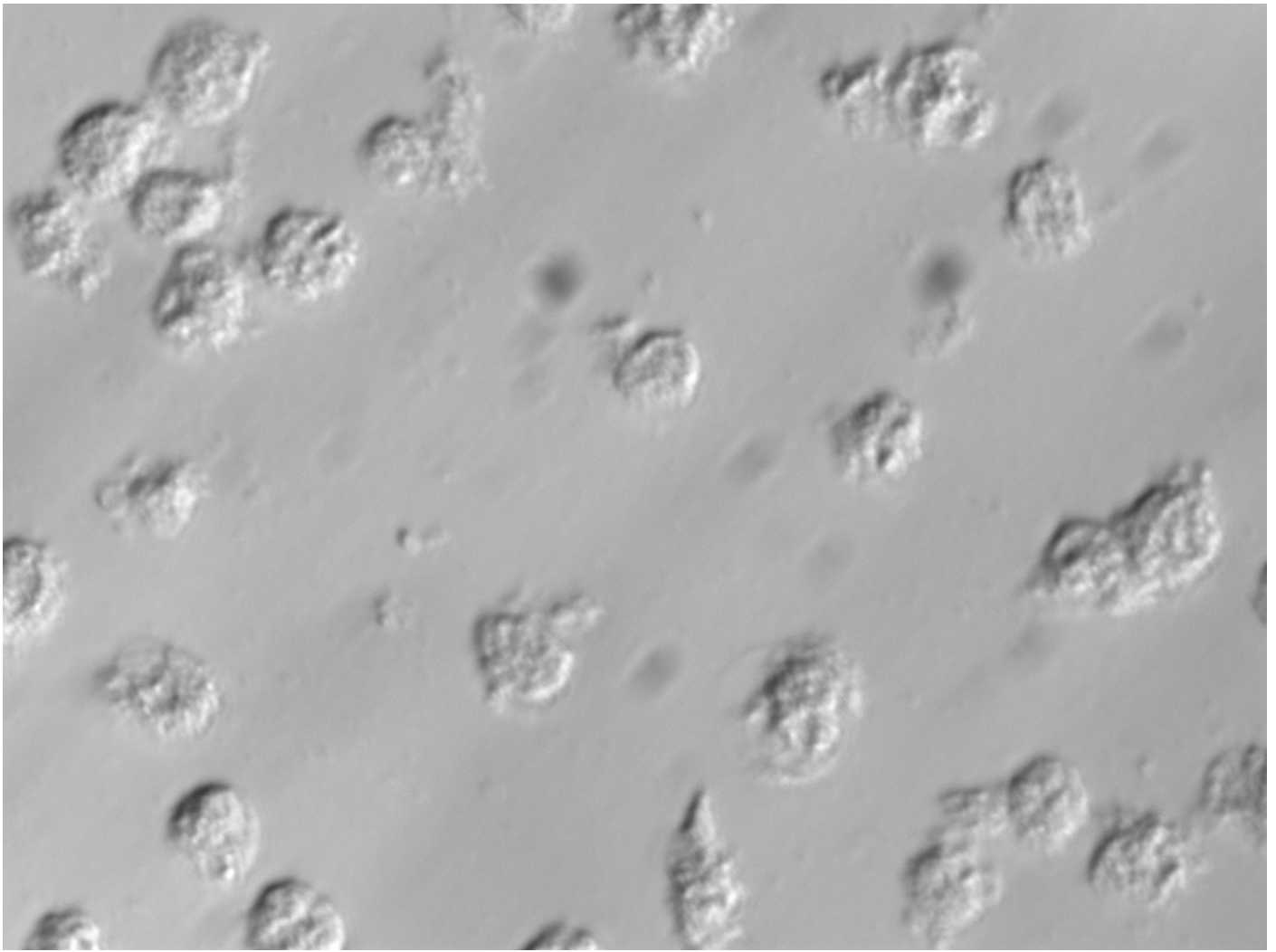
Recently, Friesen’s research group (Friesen 2014) has once again come up with findings that highlight the positive effect of methadone in the treatment of cancer. The researchers found that methadone breaks chemo- and radioresistance in leukaemia cells expressing opioid receptors and sensitises leukaemia cells for doxorubicin treatment, and hence apoptosis.

Unexpectedly, Friesen and her team also succeeded in doing the same with glioblastoma stem cells. This project was supported with funds from German Cancer Aid. Glioblastoma is the most common malignant brain tumour in adults and has a bad prognosis. It cannot currently be cured.

There have already been a few clinical cases that substantiate Friesen’s findings. For example, Friesen knows of a cancer patient who was no longer responding to conventional chemotherapies and was given palliative chemotherapy in combination with methadone. The combined administration of methadone and anti-cancer drug led to a strong reduction in tumour volume. The administration of methadone therefore appears to have led to the sensitisation of tumours cells. Some of the patient’s tumours even disappeared completely. It goes without saying that methadone has dramatically increased the patient’s quality of life.

Despite undergoing several chemotherapies, another cancer patient nevertheless developed liver metastases. Eventually, the combined administration of anti-cancer drug and methadone led to the destruction of the metastases. A patient from Florida, USA, with small-cell lung cancer contacted Friesen to tell her that he was given methadone to relieve cancer pain and has survived for 12 years instead of the predicted six months. Friesen has also received reports of successes from Westphalia-Lippe where palliative doctors prescribe methadone as standard for the treatment of peritoneal carcinomatosis.

A new helper for conventional cancer therapy?



Methadone can break the resistance of glioblastoma cells to anti-cancer drugs and induce apoptosis. Apoptosis leads to a typical granular cell shape.
© Friesen/University Hospital of Ulm

Despite all positive results achieved so far, Claudia Friesen knows that the use of methadone in the treatment of cancer patients has its limits. The effect of methadone will depend on the dose used and on the condition of the patient treated. Nevertheless, it would be considered successful from the patient's perspective if methadone was shown to improve upon conventional cancer treatment.

Although the use of methadone as an anti-cancer drug has already reached the clinical trial stage, Claudia Friesen will continue to have plenty of work to do and she is planning to focus specifically on the molecular processes that are ignited in tumour cells when methadone binds to opioid receptors. Understanding these processes might help scientists to elucidate how methadone is able to effectively trigger cellular apoptosis.

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