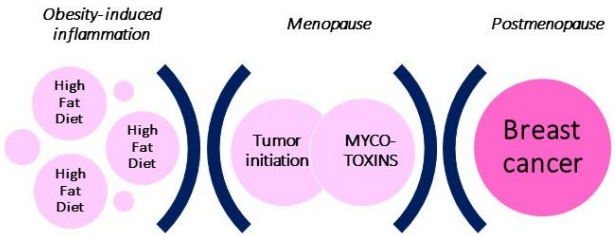
ESTROGENIC MYCOTOXINS (ZEA, A-ZOL) AND TUMOR PROGRESSION - AN IN VITRO MODEL OF OBESITY AND BREAST CANCER

Over the past few decades, the worldwide incidence of **overweightness and obesity** has been rising at an alarming rate. The prevalence of obesity has increased substantially in almost all countries of the world and a further increase is expected. Since years cancer has been viewed as a disorder of the proliferation of cells, but today is also considered as a metabolic disease. This suggestion primarily erased from the observation of cancer-associated metabolic changes on a tumour level. In recent years **obesity** has been identified as a risk factor for the development of **breast cancer (BC)** in postmenopausal women and has been associated with a poor outcome.

BC is the most common cancer in women and is one of the main causes of cancer-associated globally. Based on the Global Cancer Observatory (GLOBOCAN) in 2020 approximately 2.26 million new BC cases were diagnosed and 0.68 million BC-associated deaths occurred worldwide Especially in **BC**, obesity is associated with higher morbidity rates- women who gained between 0.5 and 2 kg/m2 after having a breast tumour diagnosed have an elevated risk of death as compared with women who maintained their weight. The connection between obesity and **BC** is, in part given to low-grade chronic systemic inflammation initiated by the accumulation of fat, which attracts inflammatory cells that secrete cytokines, chemokines, and growth factors with pro-tumorigenic potential which might participate in tumour initiation and progression. Malignant cells exhibit a high proliferation, which in turn might be enhanced by inflammation. The inflammatory molecules in the tumor microenvironment are mainly secreted by tumor cells themselves and/or other stromal cells.



There is a convincing epidemiological evidence showing that exposure to **endocrine disrupting chemicals** such as polychlorinated biphenyls (PCBs), DES and mycoestrogens is linked to increased BC risks. **Endocrine disrupting chemicals** acting through different pathways can act together with endogenous estrogens to provide combinatorial effects and raise the total estrogenic burden. Due to the fact that **zearalenone (ZEA) is endocrine disruptor** interrupting the estrogenic pathway, there might be a connection between exposure to this mycotoxins and **BC**. **ZEA** as one of the most prevalent estrogenic mycotoxin is mainly produced by ***Fusarium* fungi**. These fungi contaminate cereal grains, including maize, wheat, sorghum, barley, and oats, and produce **ZEA** in the farm and field or during the period of harvesting and storage at a low temperature and high humidity. ZEA is metabolized in the liver t to metabolites, such as α-zearalenol (α-ZOL).The presence of α-ZOL was reported to contaminate crops like corn stems or rice, but it occurs in the corn-by product, corn silage and soy meal. The studies showed that α-ZOL is 3-100 times higher estrogenic activity than ZEA.

ZEA is one of endocrine disrupting chemicals which modulates the production of progesterone, testosterone, cortisol and estradiol in human an animals. Tolerable daily intake of ZEA was established by **European Food Safety Authority** in 2014 as 0.25μg/kg/body weight. It is believed that the **chronic exposure to Zearalenone in different population groups might reach almost 83%.** According to **EFSA** reports, ZEA is not established as carcinogenic in human and animals, although increase in the incidence in food, lack of monitoring of its active metabolites and co-exposure with other mycotoxins, triggered EFSA postulation to monitor ZEA and its metabolites - αZOL as being **possibly harmful to humans** and animals. ZEA and αZOL has for long been recognized as a non-steroidal estrogenic compound that causes hypoestrogenism and anabolic activity in reproductive organs of animals. It can bind to and activate estrogen receptors with an efficacy similar to 17-βestradiol (E2). This observations suggested that endocrine-disrupting mycotoxins that co-occur in human food might interact and influence human health. To the best of our knowledge, **it has not been proven yet whether the consumption of mycotoxin and a high-fat diet can result in chronic inflammation which stimulates the development of breast cancer.**

Thus, the **objective of this project is to investigate a potential role of mycotoxin in chronic systemic inflammation induced by obesity and associated with it tumor progression with *in vitro* as well as *in vivo* preclinical mouse model of obesity and postmenopausal breast cancer**. In detail, we will evaluate the role of estrogenic mycotoxin ZEA, αZOL and high intake of a dietary fat in the proliferation and invasion of breast cells with the focus on molecular pathways linking inflammation and cancer: protein kinase B /phosphatidylinositol 3-kinase (Akt/PI3K), mitogen-activated kinases (MAPKs), forkhead box protein A1 (FOXA1), G protein-coupled estrogen receptor (GPER), JAK/STAT and epithelial-to-mesenchymal transition (EMT). Moreover, we will evaluate if ZEA and αZOL might influence the propagation of postmenopausal breast cancer with coexisting obesity in vitro.