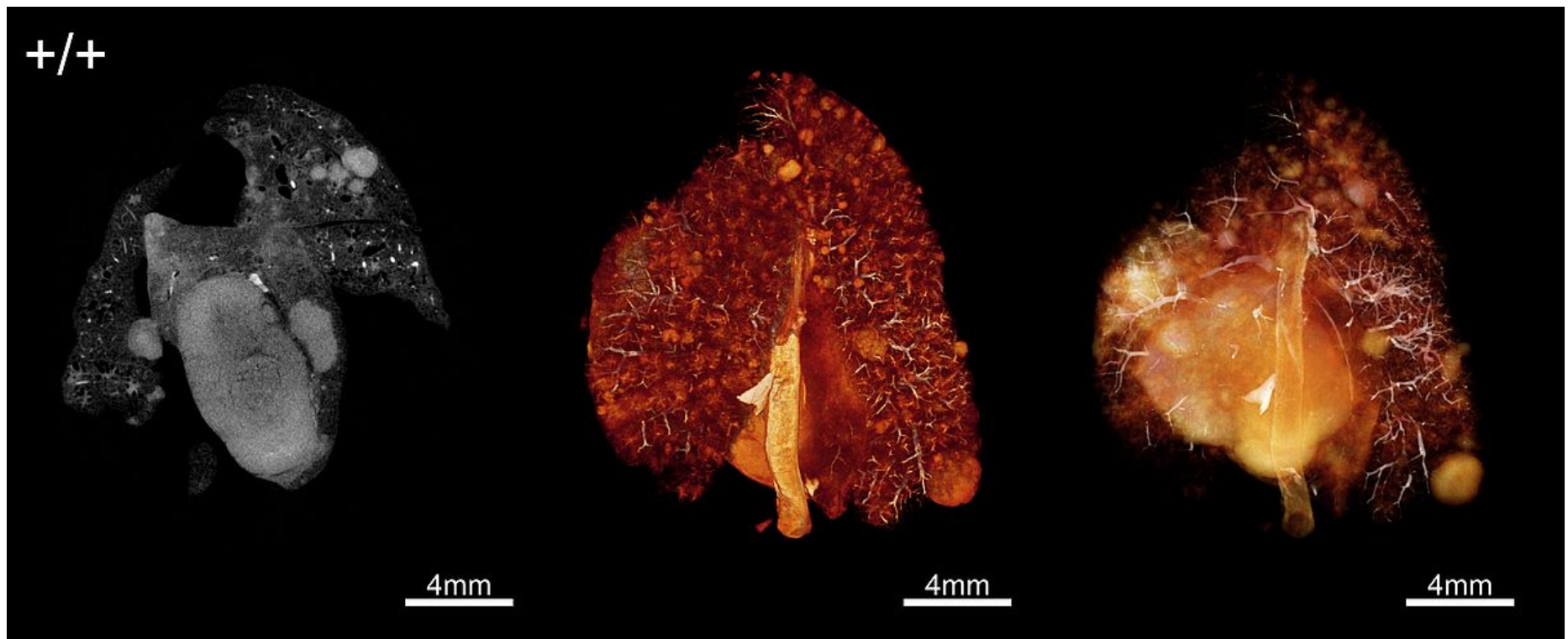


WOMEN AND LUNG CANCER

Long-suspected connection between female sex hormones and development of cancer identified for the first time.

Researchers at the Austrian Academy of Sciences' Institute for Molecular Biotechnology (IMBA) have identified a remarkable connection between sex hormones and primary lung cancer. A medicine that has already been approved for osteoporosis and bone metastasis could now be used to prevent a particularly aggressive form of adenocarcinoma.



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MicroCT image, which shows normal lung tumors in the upper panel. The lower pane...

Every 30 seconds someone in the world dies of lung cancer. Lung cancer metastases that can develop after a primary tumour are particularly unpredictable and aggressive. Just one in ten people survive for more than five years after being diagnosed with advanced lung cancer. In the 1950s it was proven that chemicals found in tobacco smoke can cause the cells in our body to mutate. This breakthrough identified one of the leading causes for a wide variety of cancers. It is primarily the cells in the lungs that are affected by smoking as they are directly exposed to these carcinogenic chemicals. Like all cancers, lung cancer is a very complex disease which is triggered by a combination of different environmental and genetic factors. An international team led by IMBA Scientific Director Josef Penninger has now identified a remarkable connection between sex hormones and lung cancer.

Gender medicine puzzle solved

RANK/RANKL are proteins that help determine the body's bone remodelling and repair function. This bone metabolism mechanism is, in turn, steered by female sex hormones, and plays a role in the normal physiology of the female breast and breast cancer. Until recently, a number of, in many cases, controversial studies proposed that women are more susceptible to lung cancer than men and that lung cancer is more aggressive in women. Until recently, scientists had yet to identify a sex-based trigger for lung cancer.

According to the latest research findings, the RANK/RANKL system plays a significant part in the development of lung cancer, as reported in a new study published in *Genes and Development* by an international team led by Josef Penninger. The good news: a medicine approved for the treatment of osteoporosis and tested in clinical trials studying hormone-related and congenital breast cancer could prove to be an effective weapon in the fight against lung cancer.

Missing link: RANK/RANKL

One common type of lung cancer, adenocarcinoma, which is caused by a mutation of the KRAS gene, is characterised by its particularly aggressive progression. And it was precisely this carcinoma that researchers looked at in the lungs of mice and people. They found that the previously identified RANK/RANKL signal path is active in the cancer cells and promotes rapid tumour growth. “For some time, researchers believed that there was a connection between female sex hormones and this aggressive type of lung cancer. And now we have pinpointed the ‘missing link’. In this carcinoma, RANK/RANKL works like a kind of amplifier, particularly in lung cancer stem cells which can be targeted and switched off,” explained Shuan Rao, primary author of the current publication and postdoctoral research fellow at IMBA. Administering Denosumab, an antibody that has already received regulatory approval, significantly slowed the progression of the disease. With the aggressive KRAS variant of lung cancer, the connection between sex hormones and the development of cancer could open the door to new therapy options. “I am always fascinated by how mysterious and interconnected the body’s signal paths are. To start with, we were able to find the mechanisms behind osteoporosis with the help of RANK/RANKL, then we succeeded in explaining hormone-related breast cancer and now we have landed at lung cancer,” said Josef Penninger, commenting on the huge potential of his discoveries. Based on earlier data, which showed that lung cancer patients participating in a Denosumab clinical trial lived significantly longer, the blockage of RANKL by the antibody will be tested in a phase 3 study of advanced lung cancer (SPLENDOUR trial: survival improvement in lung cancer induced by denosumab therapy). “Nobody knew how it worked. Our data now show for the first time that RANK/RANKL has a direct impact on the development of lung cancer – presumably at a very early stage – and that there is a molecular link to gender and sex hormones. As a result, clinical studies should be conducted in much earlier phases of lung cancer development, with a particular focus on the development of cancer in women,” noted Penninger.

Original publication: Rao et al. „RANK rewires energy homeostasis in lung cancer cells and drives primary lung cancer“, *Genes & Development*, doi/10.1101/gad.304162.117.