

## Epigenetic diversity in childhood cancer

**Cancer is caused by genetic programs running astray. Tumors of the elderly carry many DNA mutations that can influence disease course. In contrast, much fewer genetic variants exist in childhood cancers, leaving their clinical diversity unexplained. This conundrum has now been addressed for Ewing sarcoma, one of the most aggressive childhood cancers. Researchers at the St. Anna Children's Cancer Research Institute (CCRI) and the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences observed unexpected variety in the epigenome of these tumors. This finding, published in *Nature Medicine*, supports the importance of epigenetics in childhood cancers and provides new perspectives for developing personalized therapies.**

(Vienna, 30 January 2017) Tumors of the elderly, such as breast cancer and colon cancer, accumulate thousands of DNA mutations. These genetic defects contribute to cancer-specific properties including uncontrolled growth, invasion in neighboring tissues, and evasion from the immune system. Similar properties are also found in childhood cancers, although those tumors carry much fewer genetic defects, making it difficult to explain their clinical heterogeneity.

This is particularly true for Ewing sarcoma, an aggressive bone cancer in children and adolescents. A single genetic defect – the EWS-ETS fusion – is present in all tumors, initiating cancer development and defining Ewing sarcoma as a disease. But the tumors carry very few DNA mutations that could explain the observed differences in the disease course of Ewing sarcoma patients. Tackling this question, a team of scientists from Austria, France, Germany and Spain led by Eleni Tomazou from the St. Anna Children's Cancer Research Institute in Vienna profiled many Ewing tumors. They found that the disease's clinical diversity is reflected by widespread epigenetic heterogeneity.

Using novel bioinformatic methods developed by Nathan Sheffield at CeMM, the team studied the tumors' DNA methylation patterns – one of the most important facets of the human epigenome. Ewing sarcoma showed unique characteristics that differ markedly from others cancers, and the DNA methylation patterns also varied between patients. Moreover, the researchers found that Ewing sarcoma tumors appear to retain part of the characteristic DNA methylation patterns of their cell-of-origin.

Thus, the diverse clinical courses observed among Ewing sarcoma patients may be explained epigenetically: As DNA methylation influences gene activity, the combination of Ewing sarcoma specific and cell-of-origin specific patterns can lead to different outcomes. The

epigenetic diversity also appears to correlate with the tumors' aggressiveness and metastatic state.

Regarding the future of Ewing sarcoma treatment, Heinrich Kovar, Scientific Director of St. Anna Children's Cancer Research Institute, optimistically stated: "These new insights into the biology of Ewing sarcoma provide the basis for developing epigenetic biomarkers that can reliably predict disease course and therapy response. After two decades of stagnation in the therapy for patients with Ewing sarcoma, we expect new impulses for personalized therapy of this aggressive cancer".

"Our findings in Ewing sarcoma also provide an interesting concept for other cancer with low genetic complexity", Christoph Bock, Principal Investigator at CeMM, adds. "In the era of precision medicine, understanding the causes and consequences of tumor heterogeneity will be crucial to develop personalized therapies. Only with precise knowledge of the molecular mechanisms underlying each tumor, we can hope to treat in a targeted way and with far fewer side effects."

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**Attached pictures:** 1. Scientists at the Laboratory of Heinrich Kovar (© CCRI) 2. Artistic rendering of a methylated DNA molecule (© Christoph Bock/CeMM)

**The study** "*DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma*" is published in *Nature Medicine* on 30 January 2017. DOI:10.1038/nm.4273

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**Heinrich Kovar** is a molecular biologist and the Scientific Director of St. Anna Children's Cancer Research Institute. He has been studying the molecular basis of bone cancer in children and adolescents for many years.

<http://science.ccri.at/research/research-areas/solid-tumours/molecular-biology-of-solid-tumours/>

**Eleni Tomazou** is a senior Postdoc at the Lab of Heinrich Kovar at the St. Anna Children's Cancer Research Institute. She established epigenetic research at St. Anna and recently received a FWF Elise Richter grant for career development of female scientists in Austria.

**Christoph Bock** is a genome researcher and Principal Investigator at CeMM. His research focuses on the role of epigenetics in the development of disease. He also leads the joint Biomedical Sequencing Facility of CeMM and the Medical University Vienna.

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The **St. Anna Children's Cancer Research Institute (CCRI)** advances diagnostic, prognostic and treatment strategies for children and adolescents suffering from cancer by supporting basic, translational and clinical research into the specific features of different pediatric cancers, with the aim to make the most innovative treatment options available to young patients. <http://science.ccri.at>

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna.

[www.cemm.at](http://www.cemm.at)

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