

Discovery in Vienna brings hope to millions of myeloproliferative neoplasia patients worldwide

Scientists at CeMM and at the Medical University of Vienna decode a genetic mutation responsible for about 15% of myeloproliferative neoplasia (MPN) cases

(Vienna, 13.12.2013) *The discovery of a genetic mutation responsible for around 15% of all cases of the blood production disorder myeloproliferative neoplasia (MPN, a type of blood cancer), attracted the spotlight at the world's most important haematology congress, the annual meeting of the American Society of Hematology (ASH), held between 7-10 December 2013 in New Orleans, USA. The results achieved by the research groups headed by Robert Kralovics at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM) and Heinz Gisslinger at the Medical University of Vienna (MedUni Wien), revolutionise the diagnosis and treatment options for millions of affected patients worldwide.*

These results were published on 10 December 2013 in the prestigious New England Journal of Medicine¹ and presented on 13 December 2013 at a press conference in Vienna. Giulio Superti-Furga, CeMM's Scientific Director, said at the press conference: "The discovery made by Kralovics and Gisslinger is one of the most important findings of Austrian cancer research in the past 20 years. It is all the more significant, as it is directly applicable and millions of patients worldwide can receive more targeted treatment thanks to the new knowledge gained."

MPN is a group of blood diseases characterised by excessive production of blood cells, such as red cells or platelets. Patients with MPN often suffer from thromboses, and in some cases develop difficult-to-treat leukaemia. Although the number of new cases diagnosed each year is small (0.4 cases per 100,000 population per year), the total number of patients affected by long-term chronic illness is still high. The overall number of MPN patients in the EU is estimated to be around 300,000.

Discovery of the modified gene allows accurate diagnosis of MPN patients

MPN first attracted the attention of cancer researchers in 2005, through the decoding of a mutation of the gene Janus kinase 2 (*JAK2*). The discovery of the mutation by Robert Kralovics provided an explanation for the cause of MPN in around 75% of patients. The *JAK2* mutation plays today an important part in diagnosing MPN. Moreover, *JAK2* inhibitors are used as treatment for MPN patients.

The remaining 25% of patients, however, could not benefit from this discovery, since their MPN was not caused by *JAK2* mutations. The research group headed by Robert Kralovics at CeMM has been focusing on this group of patients, who were diagnosed and treated at MedUni Wien by Professor Gisslinger's group. In addition, thanks to collaboration with Mario Cazzola at the University of Pavia in Italy, even more patients have been included in this research project.

¹ T. Klampfl *et al.* Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms.
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The use of next-generation sequencing, a technique that makes it possible to perform high-throughput decoding of the genetic material of affected patients, helped the research team to discover a mutation affecting the gene that encodes the protein calreticulin (*CALR*). This mutation, therefore, contributes crucially to an understanding of molecular MPN pathogenesis. Furthermore, research has shown that MPN patients with a *CALR* mutation have a lower risk of thrombosis and a higher survival rate than patients with a *JAK2* mutation.

Accordingly, MPN patients with a *CALR* mutation have a milder course of the disease than those with a *JAK2* mutation. The publication's co-author Heinz Gisslinger, haematologist at MedUni Wien, says: "MPN patients with a *CALR* mutation can be offered a less aggressive treatment than patients in whom a *JAK2* mutation was detected. This offers great benefits to these patients, since they do not require aggressive therapy."

Patients with a *CALR* mutation will benefit directly from the discovery

The discovery of the *CALR* mutation made it possible to develop a diagnostic test which benefits the affected patients directly. This discovery is an exciting challenge for CeMM. Robert Kralovics, senior author and group director at CeMM, says: "We are currently working to understand the mechanism whereby a *CALR* mutation can lead to MPN, and will focus all our efforts on developing new treatment options. These could be immunological, or rely on small substance doses."

With the new discovery, the scientists at CeMM and at MedUni Wien take on once again a leading role in international cutting-edge research. This is reflected in the interest shown by the scientific community and by advocacy groups, first and foremost the American patients' association of the MPN Research Foundation, which has contributed significantly to financing this research project in Vienna. Its president Barbara Van Husen declares: "Robert Kralovics' discovery of the *CALR* mutation brings hope to many myelofibrosis patients, for whom there have been no treatment options thus far and who had to live with an uncertain long-term prognosis. We at the MPN Research Foundation are proud that we have been able to support Robert Kralovics' research, and welcome the new treatment options that can now be developed for the affected patients."

Where fundamental science meets clinical research and can achieve great things – collaboration between MedUni Wien and CeMM

CeMM and MedUni Wien have been working together for about eight years on finding the molecular causes of important groups of diseases. The objective of this cooperation between fundamental research and the clinical field is to promote personalised medicine and develop targeted treatments matched to genetic causes. Markus Müller, Vice-Rector for Research at MedUni Wien, says: "The ability to interpret the genome has to be reflected in improved diagnosis and treatment options. The discovery made by Kralovics and Gisslinger is a successful example of the new molecular route in medicine."

In view of this discovery, MedUni Wien and CeMM are optimistic about further success stories. "This type of cooperation between systematic medicine and molecular medical

research, between clinical practice and fundamental research, will become even more important in the future,” says Markus Müller, and Giulio Superti-Furga adds: “The result could take the form of discoveries such as this one. We need to remember that following the announcement in December 2013, treatments in haematological outpatient clinics and hospitals worldwide will now be based on a diagnosis found in Vienna. We are talking here about an estimated four million people worldwide who suffer from MPN.”

CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences (CeMM) – brief profile

CeMM is an international, independent and interdisciplinary research institute for molecular medicine. “From the clinic for the clinic” – CeMM is guided by medical needs, and integrates fundamental research with clinical expertise in order to develop innovative diagnostic and therapeutic approaches. Its research projects focus on cancer as well as on inflammatory and immunological disorders. For further information, please visit www.cemm.oeaw.ac.at.

Medical University of Vienna (MedUni Wien) – brief profile

The Medical University of Vienna is one of the longest-established medical training and research institutions in Europe. With almost 7,500 students, it is today the largest medical training body in the German-speaking world. With its 31 university hospitals, 12 medical research centres and many highly specialised laboratories, it is also among the most important cutting-edge biomedical research centres in Europe. It offers over 48,000 m² of clinical research space.

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Graphic:

MPN is a group of blood diseases that can be further classified under various subtypes. In the classic BCR-ABL-negative MPN, around 50% of patients are diagnosed with the subtype polycythaemia vera (PV; characterised by increased production of red blood cells); less common subtypes are essential thrombocythaemia (ET; ca. 25%; patients exhibit an elevated number of platelets) and primary myelofibrosis (PMF; ca. 25%; affected patients have bone marrow fibrosis). The latter, however, is the most aggressive of these three diseases.

The *JAK2* mutation was discovered in 2005. It is present in a large percentage of MPN patients, and since its discovery has been playing an important part in MPN diagnosis. Around 95% of PV patients exhibit a *JAK2* mutation, which is less common in the other two subtypes (around 59% for ET and around 54% for PMF). *MPL* mutations are rarer among ET and PMF patients (around 4% for ET and around 6% for PMF). *CALR* mutations are rarer among ET and PMF patients (around 4% for ET and around 6% for PMF).

The discovery of the *CALR* mutations has made it possible to describe a large group of MPN patients, those who exhibit neither a *JAK2* nor a *MPL* mutation. *CALR* mutations do not occur in PV patients, but they are present in about 25% of ET and about 35% of PMF patients, and thus are an important new component in the diagnosis of MPN.

