Press release

How to save lives: Caroline Hutter maps a rare childhood cancer entity

(Vienna, 29.09.2020) **Caroline Hutter, MD, PhD, loves to solve tricky puzzles. One of them is Langerhans cell histiocytosis – a disease of which almost nothing was known until a few years ago. Hutter not only heads the Biology of Langerhans cell histiocytosis group at St. Anna Children's Cancer Research Institute, she is also a passionate pediatrician. This combination helps her to ask the right research questions. As Hutter also prefers reading *Nature* rather than *Time Magazine* at home, she even sometimes has an inspiration while sleeping.**

What are you currently working on?
In my research group, we are investigating Langerhans cell histiocytosis (LCH), a very rare disease for which the first treatment protocol was developed in Vienna, together with an American research group. Prof. Gadner initiated this at the beginning of the 1980s, making Vienna the worldwide study center. Children with LCH all over the world who need a therapy, were and still are registered at our institute and are treated according to a protocol that was developed here. When I started my work, LCH was an uncharted field. That was what attracted my attention.
When I started working at St. Anna Children's Hospital, we had a patient with LCH and the attending senior physician told me: Nobody knows about this disease. I thought that, with the right approach, it could be easy to find out. That was 15 years ago. It was not known then, whether to classify LCH as cancer or as an autoimmune disease.
Besides, it was not clear which cells were involved. In case of leukemia, we know knew that the disease originates from B or T lymphocytes. Referring to LCH we had no idea.

How would you describe LCH today?
It is a cancer, but a very unusual one. Because, unlike most other cancers, in LCH there is usually only one mutation present, BRAF-V600E. Moreover, the immune system seems to play an important role. If you find a cell harboring this mutation, it does not necessarily mean that the disease occurs, but there is an interaction with the immune system as well. LCH is a hybrid between immunological and cancer disease.
It may be possible to use LCH as a model for more complex diseases. Since there is only one mutation, it might be easier to separate between cancer and healthy tissue.
In general, little is known about the development of cancer. Probably it is not only due to mutations, but many other factors why a person develops cancer.

Which progress has there been in therapy?
Small children often develop a very severe form of LCH, which can cause death. In order to be cured, they often need a rather intensive therapy. A very similar form of the disease is often completely harmless for a child who is ten years old, for example. It could even heal by itself, at least in part. Such a form of cancer that heals on its own is very unusual.
Patients only receive chemotherapy if several locations or very specific regions are affected. Children who have a tumor in their arm, for example, do not receive treatment at first because it sometimes disappears by itself. But why is this so?
When the BRAF V600 mutation has been discovered, it became possible to use drugs that inhibit the signaling pathway inside the LCH cell that is over activated because of this mutation. Such BRAF inhibitors were already used in melanoma before their application to LCH.

How well does this therapy work?
In case of LCH, we have saved the lives of children in a very serious state of the disease. Using a method established in our laboratory, we soon succeeded in reliably identifying LCH, and thus were able to use this inhibitor very early on. This enabled us to stabilize these children and within a few days they were clinically fit enough to be transferred from intensive care to a standard care unit.
We also once received a blood sample from a boy from abroad and recommended to the colleagues to use a BRAF inhibitor in a certain dosage. The boy was in intensive care with multiple organ failure and after one week with the inhibitor back in the standard ward. That was years ago and he is still doing very well.

With the discovery of this mutation and the associated inhibitor, the disease has lost its fright. It is still not curable, but due to the BRAF inhibitor, but it is now kept in check.

What are the next steps?
We want to know how exactly BRAF inhibitors work on LCH cells. This understanding would allow us to develop a protocol on a rational basis and to study worldwide how to combine the inhibitor with chemotherapy.
Some experts believe that therapy with the inhibitor alone is sufficient. However, I am convinced that it must be combined with chemotherapy to achieve long-term healing. When the inhibitor is removed, LCH often returns after a short time in most patients. However, I do not consider it a good idea to administer a long-term therapy without knowing the consequences to a growing organism yet.
Our goal would be to develop a reasonable protocol depending on the severity of the disease, together with all other pediatric centers.

Which other research projects are you working on?
At St. Anna Children's Cancer Research Institute I am doing research on the pathogenesis of LCH. We want to find out from which cells this disease originates and why it sometimes heals on its own, and in other times it does not. Which biological program of the body is running that explains these different clinical courses of the disease?
The heterogeneity of tumors can be elucidated on a molecular level by single cell analyses. Therefore together with my colleague Florian Halbritter from the Department of Integrative Analysis, Developmental Biology & Cancer Genomics, with the CeMM Research Center for Molecular Medicine, and colleagues from MedUni Vienna, we analyzed single cell data of LCH patients. This was the first time that such a tumor was fully disassembled, and we could identify several subgroups of tumor cells in the same tumor (https://bit.ly/3kH1MDR). Certain subgroups of cells seem to be more relevant for the tumor development, being more aggressive. But we still know far too little. Is there an intrinsic developmental program running, just as, for example, an embryo develops because this process is induced by a certain program or does the tumor adopt such programs? Probably external factors also play a role, i.e. immune cells, the microenvironment of the tumor, etc. This is an ecosystem that we are now picking apart step by step.

What problems are you facing?
Often the challenge is that the more you research, the more complex the subject becomes. A new chamber opens, you go into the next room and there are another twenty doors.

How do you not lose focus?
I have a hypothesis, a relatively precise idea of how this disease might work. I then go to the door that most likely confirms my hypothesis. Scientists nowadays could look into countless data generated, but without a precise focus, it is a waste of time and and doesn't get us anywhere.

You only get lost?
Yes, exactly. That's why for me the crucial question before every project is whether it will benefit the patients. Or whether it helps us to better understand the biology of the disease. That's what I also tell my staff when it comes to what we focus on next. Because our research is mainly made possible by donations and grants. We get the money to help the children.

How did you come to oncology?
On the one hand, biological interest played a role for me: What happens inside the body that makes our own cells turn against us? In addition, you can achieve a lot. Many children died of leukemia in the 1960s. Nowadays, around 90 percent of children with, for example, acute lymphocytic leukemia are cured.
Of course I also had my doubts, because I am also confronted with the incredible suffering of families. Nevertheless, in my opinion there is no other subject where you can achieve so much. You really do not have to ask yourself for one single day why to go to work. The great thing about clinical work in oncology with children is that you build a relationship and you can do a lot, not only medically, to make families feel that they are well looked after.

Why did you choose science?
I deliberately looked for a position where you could work scientifically and clinically. I did not just want to operate and implement what already exists, but I wanted to actively advance the field by myself. St. Anna Children's Cancer Research Institute has a

unique position due to the combination of basic research and clinical work. You obtain a different view of the disease when you know the patient and see the different courses of the disease.

In some cases, all treatment options have been exhausted and nothing more can be done for the child, despite intensive research. How do you deal with such a situation?
When a child dies that has been cared for over many years, it is still terrible. But I think you develop a different perspective. You accept much more that death is a part of life. You are grateful for the time that is given to you to spend with your own children. For myself and for the families it is important that you have tried everything that is possible. We have an excellent hospital and research institute here. If there is anything that we cannot offer, we send the child to a place where he or she gets the appropriate treatment. Years ago, before we had CAR-T cells in Vienna, we sent a child with leukemia to Philadelphia. The child was cured and is still doing well today. Now children from all over Europe come to us for the CAR-T cell therapy. If I had any doubts that we are not doing everything in our power to cure child with cancer, then I could not move on with my job.

What motivates you?
For me, research is a passion. I love to read papers. I find that totally exciting and interesting, but also relaxing. At home, I prefer to read *Nature* over *Time Magazine*, for example – although that's not bad either.
You can only do science if you are passionate about it. That means, for example, lying in bed at night, thinking about a problem and even liking it.

What do you particularly like about your job?
In the clinic, I love working with the children. Children are fantastic. At the research institute I like the tricky part of research: solving puzzles.

What is the biggest challenge?
Bringing it all together: Clinic, research, family in just 24 hours a day.

What do you need to be successful in science?
Like music, doing research is a creative process for which you have to do a lot of homework. You must know the field, you have to stay on the cutting edge of science, you have to think *out of the box*. You must have all the tools at your disposal - and beyond that, you have to develop a breakthrough concept.

Quotes:
"For me, the crucial question before every project is: Does it benefit the patients?"

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All other research portraits that were created during the Childhood Cancer Awareness Month can be found here
https://science.ccri.at/category/news-press-events/
https://kinderkrebsforschung.at//

Caroline Hutter, MD, PhD
Caroline Hutter, MD, PhD, has been principal investigator of the Langerhans cell histiocytosis research group at St. Anna Children's Cancer Research Institute since 2017 and consultant in pediatric oncology at the hematology and oncology department of St. Anna Children's Hospital. In addition to clinical and research activities, the scientist teaches at the Medical University of Vienna.
Hutter studied medicine at the Medical University of Vienna and biochemistry at the Imperial Cancer Research Fund and University College London, where she also received her PhD. This was followed by a post-doc position at the Research Institute of Molecular Pathology in Vienna. After her specialist training in pediatrics and adolescent medicine, Hutter also completed the additive specialist training in Pediatric Hematology and Oncology in 2015.

Hutter has been researching Langerhans cell histiocytosis for over ten years. She is national coordinator of the clinical study INdividualized Therapy FOr Relapsed Malignancies in Childhood, INFORM, and the Registry for Rare Histiocytosis. In addition, Hutter is the national deputy leader of the LCH-IV, International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis.
Hutter is a member of various professional societies, including the Austrian Society for Pediatric Hematology and Oncology, the Histiocyte Society and the American Association for Cancer Research. She is reviewer of renowned journals such as *Blood* and *Cancer Immunology Research*. Hutter has received various grants and awards, such as the Jon Pritchard Award 2012 at the Nikolas Symposium or the PhD Fellowship of the Imperial Research Fund and the Austrian Federal Ministry of Education, Science and Culture.

Langerhans cell histiocytosis
Langerhans cell histiocytosis (LCH) is a cancer disease often caused by an activating mutation in the BRAF gene. It also has features of an autoimmune disease, as LCH lesions attract immune cells and exhibit characteristic inflammation of the tissue. Fundamental questions about this disease are still being discussed. LCH is not easy to study – it is a rare disease for which no suitable preclinical models exist. Nevertheless, revolutionary discoveries have been made in recent years that have led to the classification of LCH as a neoplasia and provided new strategies for targeted treatment of LCH.
The history of LCH is closely linked to St. Anna Children's Hospital and St. Anna Children's Cancer Research Institute. - From 1983, St. Anna Children's Hospital acted as a study center for one of the first international studies on the treatment of LCH in children and adolescents (the DAL-HX studies). More than 22 countries worldwide are participating in the current study (LCH-IV). These collaborations have resulted in a significant improvement in survival and a significant decrease in recurrences in children with LCH.

About St. Anna Children's Cancer Research Institute, CCRI
The CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, we combine basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.
https://science.ccri.at/
#ChildhoodCancerAwarenessMonth #awareness #missioncancer #ccri #kinderkrebsforschung #stanna #gemeinsamstarkgegenkrebs #ccam

Photo: Caroline Hutter, MD, PhD
Gold Ribbon Sujet

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