Leukaemia, or blood cancer, occurs when the precursors of white blood cells in the bone marrow turn into cancerous cells. Unlike other cancers, leukaemia is not a single tumour but instead consists of cancer cells in the bloodstream and bone marrow. In children, leukaemia treatments are so effective that the prognosis for recovery is as high as 90 per cent. Heinäniemi points out that the disease may recur, however.

“Even if leukaemia is treatable after a relapse, it still means that chemotherapy, a long course of cytostatic drugs, takes several years. Therefore, more effective treatments are important, and for some patients the treatments could be reduced. There are patients for whom it is difficult to find treatments, but on the other hand, treatments for childhood leukaemias last long.”

A professor of computational biomedicine, Heinäniemi studies how defects in gene regulations influence the development of cancer cells.

“Blood cancers include various types of leukaemias, acute and chronic leukaemias. Of these, myeloid leukaemias are mainly adult diseases, whereas lymphoblastic leukaemias are children’s diseases,” Heinäniemi explains.

In acute leukaemia, the blood stem cell genome in the bone marrow is altered and white blood cell precursors begin to divide uncontrollably. In children, the commonest form of leukaemia develops from a precursor of B- and T-cells of the immune defence system, and is called acute lymphoblastic leukaemia.

**New drug candidates discovered through data analysis**

Heinäniemi’s research group has carried out gene expression profiling analyses related to cancer. Gene expression refers to a sequence of events in the cell in which the code in DNA is copied into RNA and then into a protein under the control of this messenger molecule. The gene that promotes cancer development can be activated or inactivated. Regulatory regions that affect gene function also play a role in the development of DNA damage in childhood leukaemia and more mature cancer of the lymphoid tissue.

In 2019, Heinäniemi and other researchers collected a large dataset of more than 10,000 patient samples. This data on haematological malignancies (HEMAP) will continue to be shared with researchers through the Finnish ELIXIR node CSC – IT Center for Science. They were able to deduce more than 30 types of cancer from this dataset by computational methods. In addition, new disease biomarkers and new drug candidates were discovered when the data was combined with drug target databases.

For example, subtypes of childhood leukaemia were found that behave differently at the molecular level.
We can already see from the data clustering that even subtypes of the disease have unique genetic profiles and can be identified from the data. The combined data revealed to us, at the molecular level, the heterogeneity of the disease, and the similarities between different diseases.”

Heinäniemi has used the data to look for patients for whom treatment could be less rigorous. Cytostatic drugs are medicines used to destroy cancer cells. However, they can cause many side effects. Patients with a poor treatment response also tend to have an increased risk of relapse.

Single-cell analysis helps find effective drug treatment

Together with Olli Lohi from Tampere University, Heinäniemi’s team mapped the entire human genome to see how different genes could act as predictors of childhood leukaemia.

“Potential biomarker genes for childhood leukaemias were identified in the HEMAP data. We initially set out to identify poor drug response, but in the follow-up genomic study we discovered the traits of leukaemia patients who respond well to drug treatments.”

One such sign of a good response is cells in the cell cycle. Cell life usually follows a rhythm – the cell cycle – in which cell division, i.e. mitosis, alternates with an intermediate phase, or interphase. The goal of the cell cycle is usually to produce two identical cells by cell division.

“By mapping individual cells, we determined the number of cells in the cycle. We were able to separate the different cells into phases, and the number of cells in the cycle seemed to be an important marker of a good response. Single-cell analysis is a good way to study how a cancer cell behaves. From there, the rarer surviving cells are revealed among the rest of the mass. It is important to study how drug treatment affects the cancer cell behaviour,” Heinäniemi says.

Single-cell RNA sequencing (scRNA-seq) measures the activities of all genes in each cell separately, giving a more accurate view of cellular differences. This is important information, because cancer cells try to escape from immune cells by mutating.

“In cancer research, it is important to obtain data at the level of a single cell. The fact is that cancer cells change all the time, meaning that each cell begins to be different.”

Now, single-cell technology for studying leukaemia can measure the profile of up to 10,000 cells in a single bone marrow sample. As single-cell technology becomes more common in cancer research, it will be easy to measure even millions of cells.

Preventing cancer cells from escaping during treatment

Heinäniemi’s group in the research project found that leukaemia treatment rapidly triggers different kinds of escape pathways in cells by altering gene reading. This enables the cancer cell to evade the treatment given. The RNA molecular profiles that are read affect the construction of the functional part of the cell. In a way, this indicates the current state of the cell and what it is trying to do.

“A leukaemia cell is a type of bone marrow stem cell that still has the potential to change its phenotype. It can take on different phenotypes to try to hide from the treatment. For example, making the cell not divide so wildly is one escape route. During initial treatments, the cell can also switch between differentiation states and find a drug-resistant state.”

In Heinäniemi’s group, a broad molecular profile measured from cells can be grouped using computational methods. This makes it possible to distinguish normal bone marrow cells from leukaemia cell profiles, and to identify different leukaemia cell phenotypes based on measurements. Models can also be trained to learn the relationship between different measurements collected from the same sample.

“The diagnostic stage does not fully reveal what kind of escape mechanisms
those cancer cells may have. This is where single-cell technology has helped, because now we can measure those rare, resistant cell types during treatment. So we get new information, and we can then think about how we can prevent the cell from escaping, or find out where it is hiding.

Combining data from multiple sources

Now Heinäniemi’s team has started to use the neural network models they have developed. Data is collected from different studies for this model.

“Our leukaemia project focuses on childhood cancers. It’s a very rare type of cancer: if we don’t get the data combined, the data sets will be very small. The aim is to use CSC’s infrastructure for these projects. This would allow the data to be processed and made available to the scientific community.”

It is not possible to conduct a study using Finnish data only.

“We have a long history of Nordic collaboration. Now other European countries have also joined in. The aim would be to enable data provision for researchers who cannot process the data themselves. We bring together profiles that have already been collected and measured, because collecting them from public databases is laborious. The aim is to bring the single-cell data together in one place and in an accessible format. When we can bring the results of different research groups around the world together in one place, we can quickly compare which drug candidates might work.”

Sharing data requires building trust. In practice, this means working with the patients involved in the projects.

“It’s really important that they are involved and that their data is stored securely, and that researchers are able to do their work with the data. This is what CSC is enabling at national and EU level through its involvement in the ELIXIR infrastructure.”

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