

## Colored nuclei reveal cellular key genes

Bonn researchers show how disease-relevant genes can be identified more easily

**The identification of genes involved in diseases is one of the major challenges of biomedical research. Researchers at the University of Bonn and the University Hospital Bonn (UKB) have developed a method that makes their identification much easier and faster: they light up genome sequences in the cell nucleus. In contrast to complex screenings using established methods, the NIS-Seq method can be used to investigate the genetic determinants of almost any biological process in human cells. The study has now been published in Nature Biotechnology.**

Humans have around 20,000 genes. They determine how our body functions, how we develop and how cells multiply. "Certain genes are responsible for vital immune responses, for example, but are also involved in life-threatening inflammatory processes," says Prof. Dr. Jonathan Schmid-Burgk, research group leader at the Institute of Clinical Chemistry and Clinical Pharmacology at the UKB and member of the Immunosenescence<sup>2</sup> Cluster of Excellence at the University of Bonn. "Our research interest is to identify these genes in order to better treat diseases."

### Conventional methods: high effort and limited spectrum

CRISPR screening methods can be used to systematically examine genes for their function in cells. "CRISPR is used to switch off a random gene in each cell," explains Schmid-Burgk. "We then enrich the cells in which a specific biological process is altered, and identify the genes switched off." This procedure is quite complex: for each process studied, a method to enrich relevant cells has to be established, e.g., using cell sorting machines. Another weak point: CRISPR screening does not work well in every cell type - human immune cells in particular often do not survive the multi-stage process.

### New method: simple detection of colored cell nuclei with a microscope

The researchers from Bonn have now developed an optical CRISPR screening method that allows to identify important genes much more easily and quickly: Nuclear In-Situ Sequencing, or NIS-Seq for short. "CRISPR is also used here," explains Caroline Fandrey, a doctoral student in Prof. Schmid-Burgk's research group and first author of the study. "However, we can observe almost any biological process in cells while they are still alive in order to identify the key genes involved." The researchers use a trick to do this: in addition to the CRISPR sequence, they introduce a so-called phage promoter into the cellular genome, which amplifies the CRISPR sequences and makes them visible by different colors. Colorful confetti can be detected in each nucleus using conventional fluorescence microscopes to reveal which gene has been switched off.

### Less than one hundred cells uncover a relevant gene

“With NIS-Seq, we currently need around a week to identify a relevant gene,” says Marius Jentzsch, also a doctoral student of Prof. Schmid-Burgk and first author of the paper. “For a conventional CRISPR screen, it often takes months to precisely separate the cells according to their function.” Another advantage of the new method is that it works in almost all cells, even in particularly small or inactive cells - provided they have a cell nucleus. In the study, the researchers successfully analyzed eight cell types from two species. Schmid-Burgk: “We are convinced that our method will become a standard tool for the identification of genetic key players in cellular processes.”

## Participating institutions and funding

In addition to the University of Bonn and the UKB, the University of Melbourne, the German Rheumatism Research Centre Berlin (DRFZ) and the Polish company Appilson were involved in the study. The project was funded by the Cluster of Excellence ImmunoSensation<sup>2</sup> and the Transdisciplinary Research Area (TRA) Life & Health at the University of Bonn as well as the DFG Collaborative Research Center 1454: Metaflammation and Cellular Programming.

## Publication (Open Access)

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## Photo:

Showing how the genes relevant to diseases can be identified more easily (clockwise from top left): Alexander Hoch, Katja Blumenstock, Marius Jentzsch, Caroline Fandrey und Prof. Jonathan Schmid-Burgk.  
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