## Treating myeloid malignancies with Rock inhibitors

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# Overview

Acute myeloid leukemia Â (AML) incidents increases with age and mortality exceeds 90% when it is diagnosed after the age of 65. Specific mutations were shown to exist in pre-leukemic subjects years before the disease breaks. However, currently, there is no preventive therapy available for pre-leukemic individuals. The group of Prof. Liran Shlush showed that treatment with drugs called ROCK inhibitors, typically used for other indications, can inhibit the growth of preâ€‘leukemic mutated cells and prevent disease onset.

# Background and Unmet Need

Once acute myeloid leukemia (AML) is diagnosed, up to 80% of patients will die within 2-5 years. Recent studies identified common mutations among individuals who develop AML, called SRSF2 P95 mutations. These mutations can be detected years before the onset of the disease. It is believed that the hematopoietic stem cell that harbors the mutation gradually expands and accrues additional cytogenetic aberrations, eventually promoting full-blown leukemia. However, although these mutations can be used for early identification of likely future AML patients, there is currently no therapy exists to prevent the disease onset and intervene at the early stage.

# The Solution

The group of Prof. Liran Shlush demonstrates Rho-associated coiled-coil containing protein kinase inhibitors (ROCKi), which can inhibit SRSF2 mutated AML cells in vitro, in vivo, and in primary AML samples. ROCKi enhanced the defective cytoskeleton system, nuclear deformation and segmentation of SRSF2 mutated cells, and caused mitotic catastrophe, eventually leading to cell death.

# Technology Essence

The group of Prof. Shlush designed an in vitro model system of mutated AML cells and used it to screen ~4000 drugs to identify compounds that are toxic specifically to these mutated cells. Among the hits which were identified, several compounds are known to inhibit the Rho-associated protein kinase (ROCK), indicating that targeting different junctions along the rho signaling pathway could inhibit the growth of cells that harbor SRSF2 P95 mutations. Therefore, we suggest ROCK inhibitors can be used as a preventive treatment for pre-leukemic patients. Examples of such drugs include the FDAâ€‘ approved drug Netarsudil and Fasudil, which is approved in Japan and China.

# Applications and Advantages

Treating high-risk subjects at the onset or during early disease progression

## Development Status

The group identified several drug candidates in an in vitro model. Future validation in an in-vivo mice model is ongoing and the development and optimization of novel ROCKi is planned.

### Patent Status

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