TOLREMO therapeutics AG
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Eradicating the seed of cancer drug resistance

TOLREMO therapeutics AG aims to fundamentally change the way modern cancer drugs are used. The company's resistance-breaking add-on therapies boost the long-term efficacy of existing cancer drugs by inhibiting nongenetic mechanisms of cancer drug resistance.

The lack of a durable response to many cancer drugs is an ongoing challenge that limits the survival of patients with cancer. During treatment with cancer drugs, tumors become more complex as different subpopulations of cancer cells acquire different resistance-causing mutations. These mutations are hardwired into the genome of the tumor, leading to irreversible genetic drug resistance.

TOLREMO therapeutics AG, a privately held Swiss biotechnology company, develops resistance-breaking add-on therapies designed to eliminate the most treatment-resilient cancer cells in a tumor. The company's research shows that alongside the intended effects of cancer drugs, such as targeting an oncogene or the vasculature of a tumor, these drugs also induce 'transcriptional escape programs', which precede the development of genetic drug resistance.

By preventing broad transcriptional reprogramming early in the course of a cancer therapy, it is possible to stop cancer cells from escaping drug treatment, which in turn boosts the long-term efficacy of cancer drugs.

"We have developed a technology platform that allows us to detect and eliminate those cancer cells that would otherwise go on to seed drug-resistant tumors," said Stefanie Flückiger-Mangual, CEO and one of the scientific founders of TOLREMO. "This has enabled us to screen thousands of potential resistance-breaking molecules, establish industry-standard validation cascades, and develop two resistance-breaking lead series that contain several hundred structural variants, all within a short period of time."

Founded in 2017 as a spin-off from ETH Zürich (a Swiss Federal Institute of Technology), Switzerland, TOLREMO is making rapid progress under the leadership of an experienced team with strong credentials in the scientific and pharmaceutical industries. This helped the company to raise $2.4 million in seed funding in 2017, followed by another $9.0 million in series A financing in 2018, which was led by the Swiss venture capital firm BioMedPartners and supported by Redalpine Venture Partners and Altos Venture. The financial backing has enabled TOLREMO to swiftly progress two preclinical development programs that target different escape mechanisms.

Adaptive drug resistance

In one program, TOLREMO is developing a new class of chemicals designed to prevent the development of resistance to oncogene-targeting cancer drugs, such as epidermal growth factor receptor inhibitors (EGFRis) and BRAF inhibitors (BRAFis).

TOLREMO has found that drugs such as EGFRis and BRAFis not only block downstream oncogenic MAP kinase signaling, as intended, but also induce broad phenotypic and transcriptional reprogramming events. This adaptive reprogramming of some cancer cells is a method of coping with exposure to the cancer drugs, and occurs at the start of a therapy. The findings have been confirmed in clinical biopsies.

"Transcriptional escape mechanisms are induced with the very first dose of cancer drug, so our add-ons are designed to prevent this from happening when they are given in combination with a cancer drug," said Flückiger-Mangual. "Our results so far show that our lead molecule can really boost the long-term efficacy of several oncogene-targeting drugs that are used to treat different kinds of cancer. It's amazing to see the effect that preventing those early reprogramming events can have on the long-term outcome of a therapy (**Fig. 1**)."

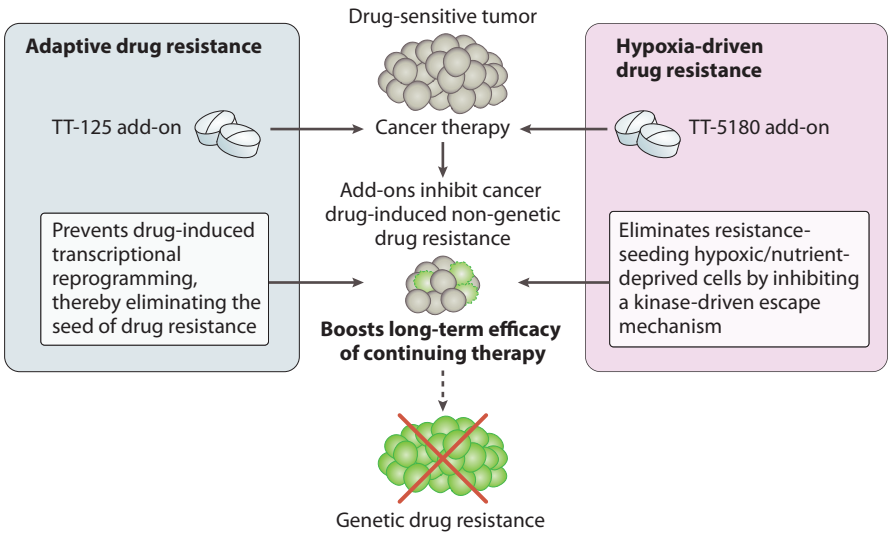

Fig. 1 | Resistance-breaking therapies. Add-ons inhibit cancer drug-induced non-genetic drug resistance.

Hypoxia-driven drug resistance

In a second program, TOLREMO is developing add-on compounds designed to prevent the development of resistance to antiangiogenic cancer therapies or radiotherapy. Antiangiogenic drugs work by targeting the tumor vasculature, but this also leads to nutrient- and oxygen-starved (hypoxic) areas in the tumor, which harbor extremely aggressive cancer cells.

TOLREMO has identified a novel kinase vulnerability in hypoxic and nutrient-starved cancer cells with its proprietary 3D cancer microtissue-based screening platform, and has validated the target in a range of different preclinical proof-of-concept studies. TOLREMO's compounds inhibit the kinase and downstream escape mechanisms that play a vital role in the survival of resistance-driving cancer cells (**Fig. 1**).

"Hypoxic, nutrient-starved cancer cells are notoriously resistant to different treatment modalities, such as antiangiogenic therapies or radiotherapy," said Flückiger-Mangual. "Our add-on compounds offer an entirely new therapeutic entry point to tackle this problem, which could fundamentally change the way we approach the treatment of many cancers."

Increasing the value of existing cancer drugs

TOLREMO's proprietary drug discovery and development platform has the potential to catalyze a new wave of resistance-breaking therapies that will meaningfully extend the lives of cancer patients.

The company's lead assets can be combined with various cancer drugs used for different indications, and could therefore substantially increase the value of existing cancer drug portfolios. Not only could they help to increase sales and market share, TOLREMO's add-ons could also be valuable tools for cancer drug life-cycle management, as combination therapies can extend the patent protection of already marketed cancer therapies.

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