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Sommario	Acute myeloid leukaemia (AML) is a group of aggressive haematopoietic malignancies associated with adverse outcome. Fms-like tyrosine kinase 3 (FLT3) receptor mutations confer a particularly poor prognosis to AML patients. There is no satisfactory treatment against this disease, especially for the cases harbouring FLT3 mutations, and the quest for novel therapeutic options continues. Drug repurposing represents a powerful strategy to single out existing agents active in novel therapeutic contexts. We performed a high-throughput drug screening, designed to search for agents that inhibit the growth of AML cell lines with mutated FLT3 within libraries of FDA-approved compounds or molecules in advanced phases of clinical trials. Auranofin, an antirheumatic drug, and pyrvinium pamoate, an anthelmintic agent, were identified and chosen from the list of 290 hits for in vitro and in vivo validation. We confirmed that in vitro treatment with auranofin and pyrvinium pamoate reduces AML cell growth through a cytotoxic and cytostatic effect, respectively. We identified the synergies/additivities of the two molecules with standard anti-AML drugs (e.g., cytarabine, doxorubicine) and a specific FLT3 inhibitor (quizartinib). Auranofin synergised with cytarabine and its effect was additive when combined with quizartinib; pyrvinium pamoate showed an additive effect when used

	with doxorubicin and quizartinib. Next, we determined that both auranofin and pyrvinium pamoate act through their described mechanism of action, i.e., inhibit thioredoxin reductase (auranofin) and Wnt signalling (pyrvinium pamoate). In addition, we identified a novel mechanism of action for the two agents: the induction of the endoplasmic reticulum stress and the unfolded protein response that follows. Our results support the potential of auranofin (less so in the case of pyrvinium pamoate) for the treatment of AML patients, including those with FLT3 mutations, provided that the ongoing in vivo validation is successful.
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