CHILDREN'S MEDICAL RESEARCH INSTITUTE

Jeans for Genes®

Overcoming Chemotherapy-Resistant Leukemia

The Problem

Intensive chemotherapy regimens for T-cell acute lymphoblastic leukemia (T-ALL), including standard-of-care VXL treatment, have reasonable patient response rates and outcomes, with 50% survival across 5 years. However, for adult patients who relapse, a more alarming picture presents itself: less than 10% of patients survive long term[1]. It has been demonstrated recently that a failure to eradicate leukemia stem cells (LSCs) during chemotherapy is responsible for patient relapse. These LSCs are maintained and protected by the tumour microenvironment, and often evade commonly used oncology drugs.

The development of pharmacological agents that inhibit key signalling pathways involved in LSC physiology (e.g. interleukin-7, Notch1 and Kit) have been pursued as a therapeutic strategy for chemotherapy-resistant leukemia. Despite demonstrating significant promise in pre-clinical models, clinical studies reveal that long-term exposure to these small molecules result in significant toxicity and therapeutic resistance (due to LSC plasticity and activation of alternative signalling pathways).

The Solution

Our approach involves the pharmacological targeting of the dynamin enzyme, which is common to multiple signalling pathways, using a novel class of compounds known as Dynoles®. Dynamins are a family of large GTPases required for the final scission step during clathrin-mediated endocytosis, a physiological process fundamental to downstream signal transduction. Therefore, reversible inhibition of dynamin with Dynoles® results in the distortion of multiple oncogenic signalling cascades, restricting LSC plasticity and propensity for therapeutic resistance **(Figure 1)**[2,3]. Combination therapy of standard-of-care VXL and a Dynole® therefore displays promise in effectively combating T-ALL and preventing relapse.

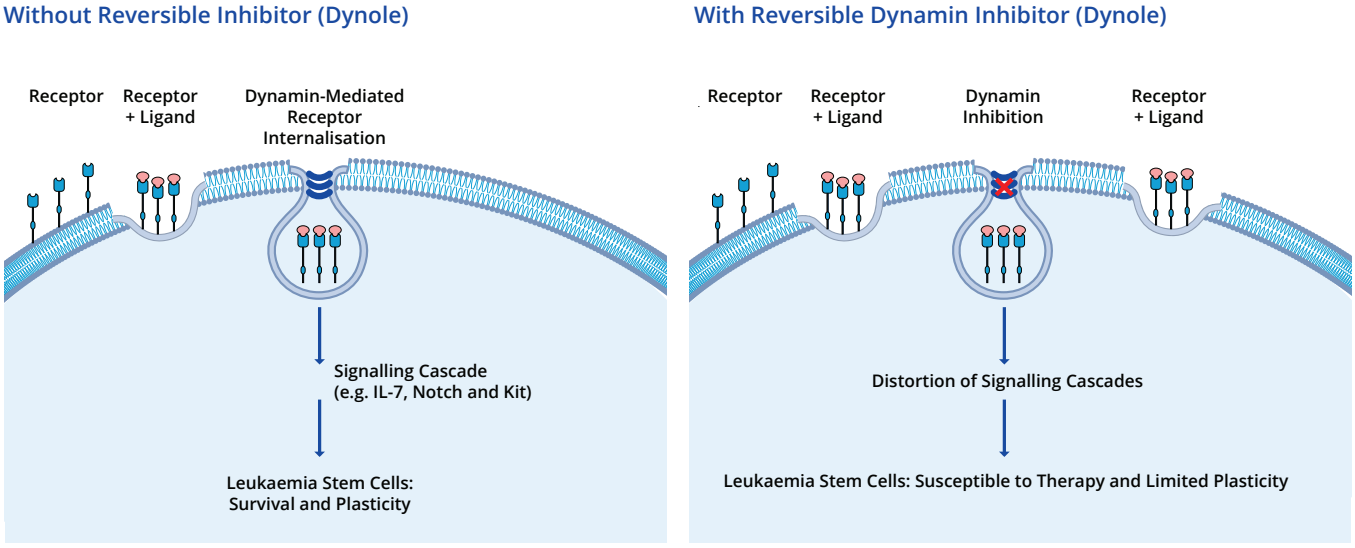

Figure 1: *Overview of how dynamin-mediated receptor internalisation facilitates signalling cascades (e.g. interleukin-7, Notch1 and Kit) that ultimately contribute to LSC survival and plasticity, and how inhibition by Dynoles® distort signalling cascades to overcome this.*

Our Results

Combination therapy, using a Dynole® with the standard-of-care VXL treatment, has demonstrated remarkable efficacy in pre-clinical models, with over 50% of both mouse populations exhibiting leukemia-free survival for the duration of the study (compared to 0% for VXL alone) **(Figure 2)**[4].

Seeking an industry partner for preclinical and clinical development of Dynoles® as adjuvant therapy for chemotherapy-resistant leukemia.

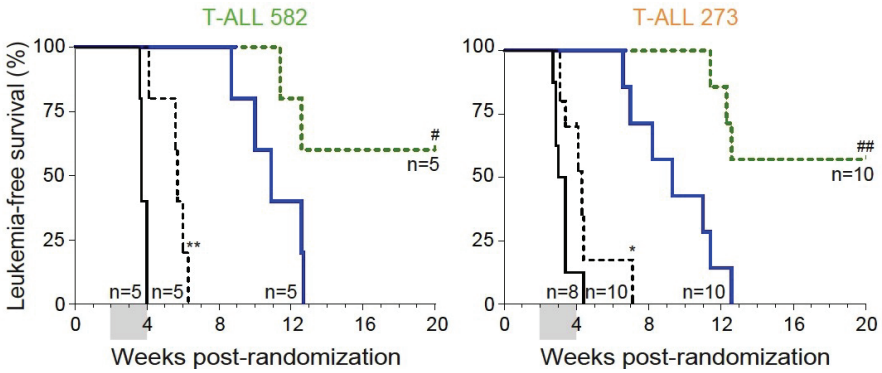

Figure 2: *Kaplan-Meier curves of mice injected with two patient-derived T-ALL cells (T-ALL 582 and T-ALL 273), treated with vehicle (–), Dynole®-34-2 alone (--), VXL alone (–) or combination (--). This highlights the anticipated initial survival with VXL alone followed by relapse and death, while combination therapy demonstrates prolonged survival of mice[4].*

In a separate study, transient endocytosis inhibition has been shown to be safe in humans and a valid oncology therapeutic strategy[5]. This clinical trial, carried out with collaborators, used a repurposed dynamin inhibitor and immunotherapy on a cohort of human patients.

Our long-standing partnership with University of Newcastle has allowed for the development of bespoke pharmacology centred around the Dynole® scaffold, with a unique allosteric binding site identified and fifth-generation compounds (exhibiting enhanced solubility and potency) synthesised **(Figure 3)**. Our intention is to seek an industry partner to facilitate the preclinical and clinical development of Dynoles® as adjuvant therapy for chemotherapy-resistant leukemia and ultimately improve patient outcomes.

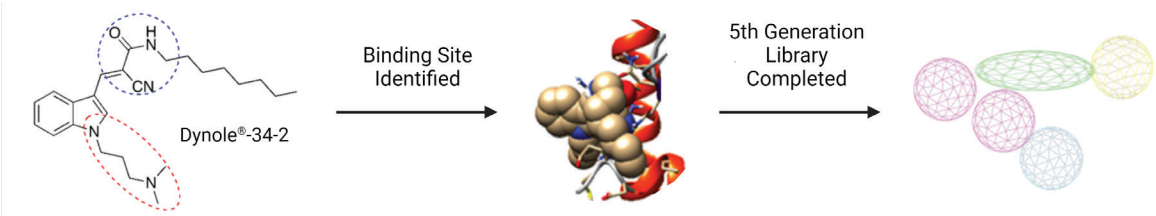

Figure 3: *Overview of recent developments in the Dynole® pharmacology program.*

Our Competitive Advantages

Focused library development – new knowledge of the binding site has enabled targeted approaches to new analogues

Fifth-generation Dynoles® synthesised with clear intellectual property potential

Extensive dynamin enzyme biology, molecular modelling, and pharmacology know-how and capabilities

Extensive understanding of survival signalling pathways maintaining LSC survival and experience with animal models of leukemia.

Combination therapy has broad applicability to other cancer types where stem cells allow for relapse

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References

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[2] Tremblay, C.S. et al. (2016). "Loss-of-function mutations of dynamin 2 promote T-ALL by enhancing IL-7 signalling." **Leukemia**. 30: 1993–2001.

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[4] Tremblay, C.S. et al. (2020). "Small molecule inhibition of Dynamin-dependent endocytosis targets multiple niche signals and impairs leukemia stem cells." **Nature Communications**. 11(1): 6211.

[5] Chew, H.Y. et al. (2020). "Endocytosis inhibition in humans to improve responses to ADCC-mediating antibodies." **Cell**. 180: 895–914, e27.