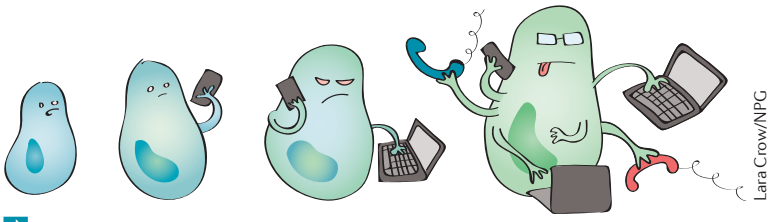
Nature Reviews Cancer | Published online 14 Oct 2016; doi:10.1038/nrc.2016.110



Lara Crow/NPG

CELL DIFFERENTIATION

Pushing differentiation

> This is why recent results [...] showing that cell differentiation blockade in the early stages of AML can be overcome are exciting and hopeful

Although great efforts in understanding the mechanisms underlying acute myeloid leukaemia (AML) have resulted in better diagnosis of the disease, attempts to improve its current treatment — a regimen combining cytarabine and anthracycline, that has been standard of care for the past 40 years — have been unsuccessful. This is why recent results from David Scadden, David Sykes and collaborators showing that cell differentiation blockade in the early stages of AML can be overcome are exciting and hopeful.

Strategies to overcome myeloid differentiation blockade had been tried before, achieving cellular differentiation in patients with mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2. However, these patients represent only a small subset (15%), whereas the remainder of AML cases involve complex and heterogeneous combinations of gene mutations. Sykes *et al.* searched for differentiation pathways shared across a range of genetic subtypes of AML and observed that homeobox transcription factor HoxA9 — which is normally repressed upon myeloid differentiation — was upregulated in 70% of patients with AML. The authors generated a model of differentiation using an oestrogen receptor (ER)–HoxA9 fusion protein transduced in murine bone marrow cells. The presence of oestradiol (E2) activates ER–HoxA9 and cells proliferate indefinitely as immature myeloblasts, whereas withdrawal of E2 causes the cells to undergo synchronous and terminal neutrophil differentiation over 5 days. The authors also derived an ER–HoxA9 GFP cell line from mice in which GFP had been inserted in the lysozyme locus. Because lysozyme is expressed only in differentiated cells, GFP expression would identify those components that had triggered differentiation in the presence of active HoxA9.

Sykes *et al.* evaluated the differentiation potential of 330,000 small molecules, of which 12 showed the ability to induce myeloid differentiation. Two compounds, C03 and C07, were then shortlisted based on their documented activity in murine and human AML models. To identify the protein targets of these two compounds, the authors generated cell lines resistant to each drug and elucidated the mechanism of drug resistance by analysing upregulated genes across the two cell lines (one per compound) by RNA sequencing. Only eight genes were shared across the cell lines, one of which encoded dihydroorotate dehydrogenase (DHODH), an enzyme involved in the intracellular *de novo* synthesis of pyrimidines. Both C03 and C07 were confirmed as inhibitors of DHODH.

Finally, the authors checked the ability to induce differentiation *in vitro* by treating mouse and human AML cells with brequinar sodium (BRQ), an inhibitor of DHODH. BRQ led to induction of myeloid differentiation and significant reduction in leukaemic burden in several mouse models of AML, including human cell line xenografts, patient-derived xenografts and syngeneic mouse models.

As differentiation therapy has proved successful in the treatment of patients with acute promyelocytic leukaemia with all-*trans* retinoic acid (ATRA) and arsenic trioxide, this study provides yet another therapeutic target for induction of AML differentiation.

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ORIGINAL ARTICLE Sykes, D. B. *et al.* Inhibition of dihydroorotate dehydrogenase overcomes differentiation blockade in acute myeloid leukemia. *Cell* **167,** 171–186 (2016)