The birth of a paradigm: leukemia-initiating cells in acute myeloid leukemia

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TITLE	A cell initiating human acute myeloid leukaemia after transplantation into SCID mice.
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In 1994, Lapidot and colleagues published a groundbreaking paper that provided the first experimental evidence for the existence of acute myeloid leukemia (AML) stem cells,[1] establishing the concept of AML as a hierarchically organized malignancy.

Using transplantation of AML cells into mice with severe combined immunodeficiency (SCID), which lack functional T and B cells, they demonstrated that the ability to initiate leukemia *in vivo* was limited to a small subset of cells with a $CD34^+CD38^-$ immunophenotype (Figure 1). These rare AML cells, at the time referred to as SCID leukemia-initiating cells and later termed leukemic stem cells (LSC), were much less common than colony-forming units, proliferated extensively *ex vivo*, and had the capacity to reconstitute the cell types and specific features present in the clinical sample. The work built on the lab's pioneering work transplanting normal human bone marrow cells into SCID mice[2] and established the SCID mouse model as a robust tool for studying human myeloid leukemia. Although subsequent work identified NSG mice and other strains as even more permissive hosts, the report by Lapidot *et al*. was the first to provide a functional framework "*to understand the processes governing the transformation and progression of leukaemic stem cells and to test new therapeutic strategies*", as the authors presciently stated at the end of their paper.[1]

The most crucial aspect of the work is the notion that AML is organized as a hierarchy, analogous to normal hematopoiesis. This suggested that AML may be maintained by a small population of self-renewing LSC, a hypothesis verified by subsequent work using secondary transplants. The notion of LSC at the top of a hierarchy inspired intense research into the biology of LSC to identify therapeutic vulnerabilities.

As with many seminal discoveries, time and advances in technology have refined the model and identified additional layers of complexity. Genetically distinct AML clones with leukemia-initiating potential can evolve in parallel and may not be trackable to a single cell of origin. Epigenetic mechanisms enable functional diversity even within a genetically identical population of leukemia-initiating cells, suggesting that stemness can represent a state rather than an invariant property. Although much progress has been made since 1994, relapse after an initial response to AML therapy has remained an enormous clinical challenge, reflecting LSC plasticity and the ability of differentiated leukemia cells to acquire LSC properties under therapy pressure. In a disturbing manner, therapy seems to train the AML system, increasing the pool of leukemia-initiating cells with each cycle of response and relapse.

The foundational report by Lapidot and colleagues is a landmark that informed hematology research in a major way, providing the field with a model that captured the complexity of human AML much more comprehensively than is achievable with genetically modified mice. The notion that leukemia-initiating cells reside, for most part, in the $CD34^+CD38^-$ population has stood the test of time and provided a first hint that distinguishing LSC from hematopoietic stem cells will not be easy. Thirty years later, patient-derived xenografts have become the gold standard for therapeutic testing and *in vitro* validation of mechanisms and targets.

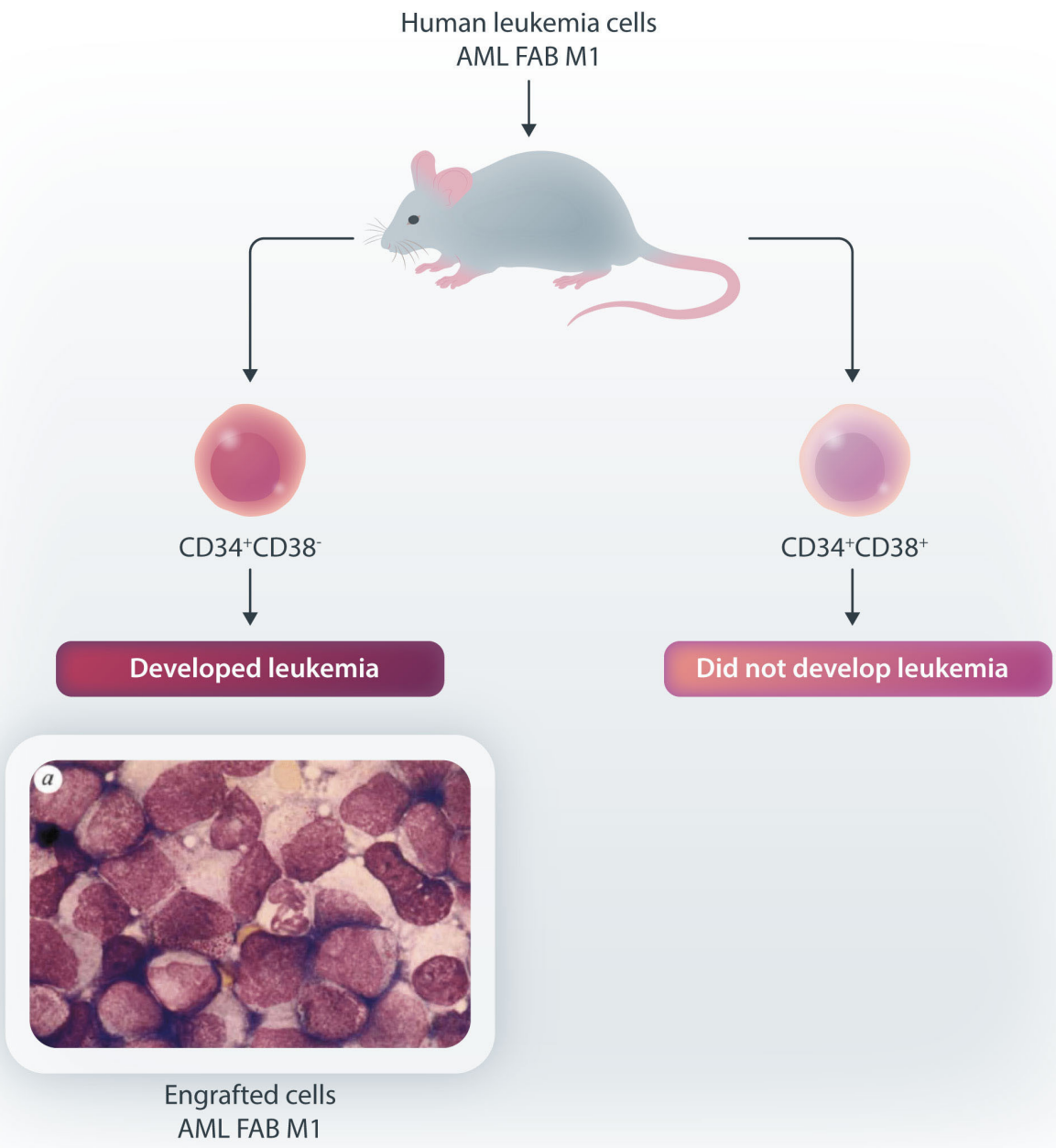

Figure 1. Recapitulation of human acute myeloid leukemia and evidence of a leukemia stem cell hierarchy. Lapidot *et al*. performed transplantation experiments using acute myeloid leukemia (AML) cells introduced into mice with severe combined immunodeficiency (SCID) treated with cytokines. Cytological and DNA analyses revealed significant bone marrow infiltration by AML blast cells, resulting in almost complete replacement of normal murine hematopoiesis. The SCID-leukemia mice faithfully reproduced many morphological and dissemination features characteristic of the donor's disease, providing a robust model of human AML. The study also uncovered a potential hierarchy of leukemia stem cells. Only $CD34^+CD38^-$ cells were capable of initiating leukemia in transplanted mice, while $CD34^+CD38^+$ cells failed to do so. This finding highlights the stem-like properties of the $CD34^+CD38^-$ population in driving leukemogenesis. FAB: French-American-British classification. Figure reproduced, in part, with permission from the original paper by Lapidot *et al.*[1]

Disclosures

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Contributions

NC-R and MWD contributed equally to this paper.

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