The polymerase chain reaction, so simple, so clever: the discovery that made minimal residual disease come true

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Today, every child with acute lymphoblastic leukemia (ALL) can benefit from minimal residual disease (MRD) monitoring, which enables therapy to be tailored according to the patient's individual response to treatment. Before MRD monitoring become possible, hematologists already suspected that residual cells persisted in children in cytological remission from their leukemia. But how can you detect what you cannot see? The answer came with the polymerase chain reaction (PCR).[1]

The first goal of Kary Mullis, a self-described 'generalist with a chemical prejudice' was to develop a prenatal diagnostic test for the β-globin mutation in sickle cell di-

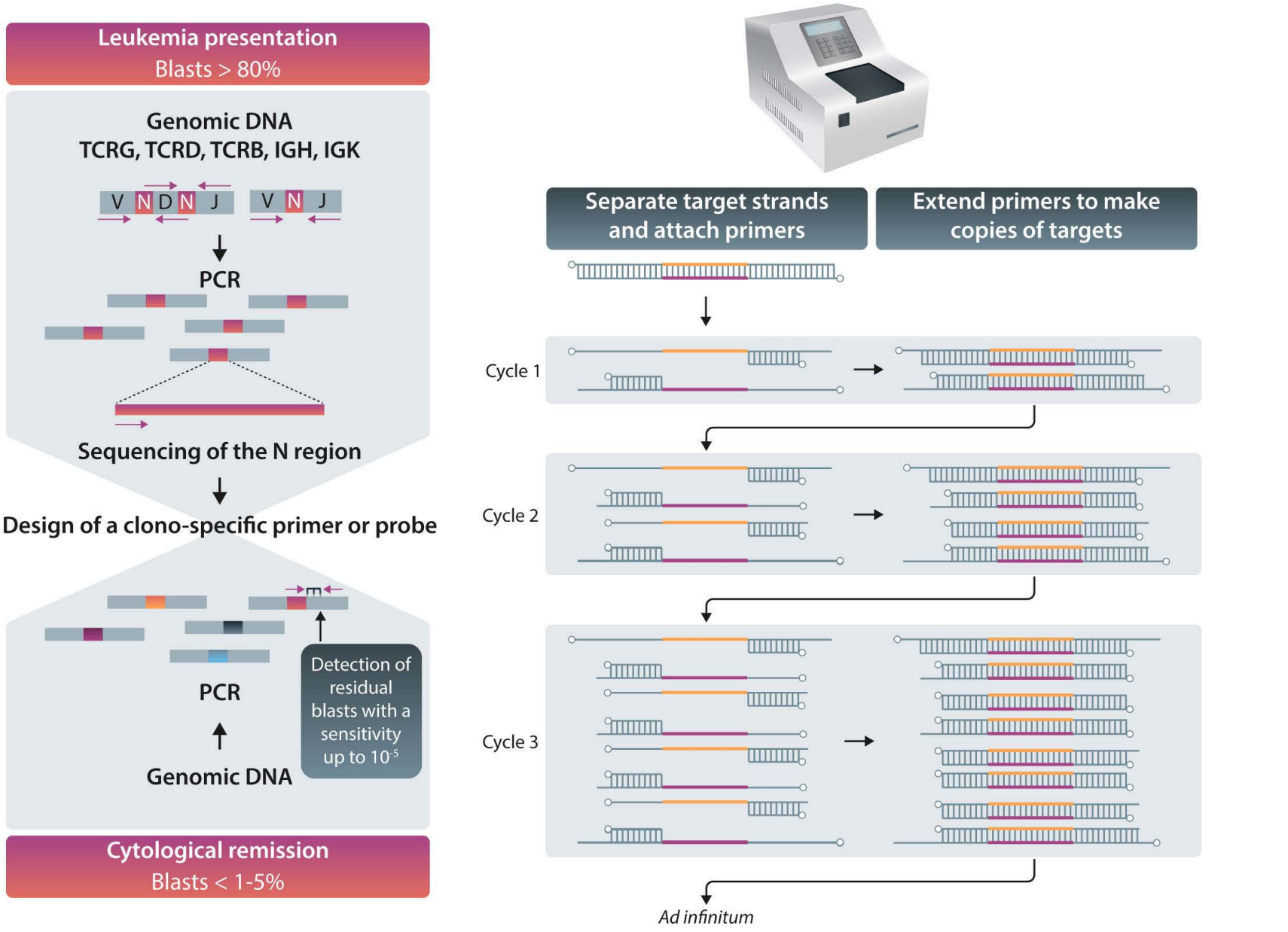

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Figure 1. Polymerase chain reaction analysis for minimal residual disease assessment. Left: principle of minimal residual disease (MRD) detection based on clono-specific immunoglobulin (IG) and T-cell receptor (TCR) gene rearrangements. Characterization of *IG/TCR* rearrangements present in acute lymphoblastic leukemia (ALL) blasts at diagnosis enables a clono-specific probe or primer to be designed. At remission, this probe or primer can be used to detect patient's residual blasts using either allele-specific polymerase chain reaction (PCR) or hybridization of PCR products with the allele-specific probe. Right: the Perkin-Elmer Cetus DNA Thermal Cycler, first commercial system automating the thermal cycling required in the PCR, introduced in 1987, and the principle of PCR as first reported by K Mullis.[3]

sease. Southern blot was cumbersome, with limited sensitivity. Kary Mullis began to think about how to make DNA-based diagnosis more practical. There were two possibilities: amplify the signal by improving the probing system or amplify the target. The latter option turned out to be the right one. This was the birth of the concept of PCR, which consists of the exponential amplification of a specific target DNA delimited by the position of two primers on a template DNA molecule.[1] By 'extracting' the fragment of interest from the source DNA and amplifying it, PCR provides unlimited amounts of precise genetic material for diagnosis.

Thanks to its principle of exponential amplification, PCR not only enabled genetic screening for sickle cell disease, but also provided a tool for detecting nucleic targets with an unprecedented level of sensitivity. The idea soon arose that it could make the detection of residual disease possible. But what PCR target should be used? What PCR target is specific to leukemia cells? Fusion genes had still only been identified in a minority of cases of ALL. Why not use T-cell receptor and immunoglobulin rearrangements? Such rearrangements, which are inherent to lymphocyte physiology, are found in virtually all ALL thus making it possible to track down the leukemic clones (Figure 1).

A sensitive technique, a specific marker, the first assay for monitoring MRD in leukemia was born.[2] This enabled the detection of one leukemia cell among hundreds of thousands of normal cells. It would soon be shown that residual disease is still present in patients in cytological remission and is one of the most powerful prognostic factors in ALL. Is the invention of PCR a revolution? Probably not. Although considered one of the most important inventions of the late 20th century, it did not lead to a new paradigm. Actually, PCR emerged from a surprisingly simple conceptual idea. Let's bet with Kary Mullis that many molecular biologists have since asked themselves with a tinge of regret, 'Why didn't I think of that?'[3] PCR is a fine illustration of a breakthrough made possible by a lot of ingenuity and multidisciplinarity, not forgetting... a moonlit walk in the mountains of California.[3] Beyond MRD monitoring, PCR has certainly revolutionized diagnostic practice in hematology in many ways. It is for this reason, and because we must always remember the fruitful importance of multidisciplinarity, that the discovery of PCR deserves to be given the status of "landmark in hematology".

Disclosures

No conflicts of interest to disclose.

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