

How to Transform an Exceptional Case Report Into a Therapy: Following the Frog Out of the Box

Maël Heiblig¹, Vincent Alcazer², Adriana Plesa², H el ene Labussier e-Wallet¹, Pierre Sujobert^{2,3}

Correspondence: Pierre Sujobert (pierre.sujobert@chu-lyon.fr).

Once upon a time in Europe, a 56-year-old man was diagnosed with an acute myeloid leukemia (AML) presenting molecular abnormalities associated with poor outcome (trisomy 8, mutation of *ASXL1*, *SRSF2*, *IDH2*, and *RUNX1*; Figure 1A). According to the knowledge bank approach,¹ his 3-year survival probability was estimated at 11% under intensive chemotherapy regimen (Figure 1B). He refused the proposed therapy (induction chemotherapy with allogeneic hematopoietic stem cell transplantation in case of complete remission). Instead, he decided to test Kamb o, a traditional ritual used by some communities of the southwest Amazon for diverse purposes such as increasing hunting abilities.² The ritual consists in the application on the skin of secretions from the arboreal frog *Phyllomedusa bicolor* after having superficially burned the skin of the recipient with a sharp instrument. The secretions contain a venom, whose effects are rapid and induce various manifestations such as nausea, vomiting, diarrhea, and anaphylactic reactions; some of them are potentially serious, and some fatal cases have been reported.^{3,4} To date, despite the absence of any formal demonstration of the therapeutic effects of Kamb o, this ritual is proposed by New Age therapists all over the world for people suffering from depression, addiction, or various other conditions.⁵ The leukemic patient went through the Kamb o ritual 7 times: after the second time, he became transfusion independent and his blood count was normalized (Figure 1C). A year later, a cytological and cytogenetic complete remission were observed after bone marrow evaluation. He went back to work and was free of disease for four and a half years, when he was diagnosed with AML again. Of note, this AML had a sharply different cytological, immunophenotypical, and cytogenetical profile compared with the first AML diagnosed (Figure 1A), suggesting that it was not a relapse but a new and unrelated AML. At the molecular level, some gene mutations were shared with the first AML (*ASXL1*, *SRSF2*, *IDH2*), whereas additional private mutations

were observed, such as an internal tandem duplication of *FLT3* and another mutation in *RUNX1*, suggesting a phenomenon of evolutionary convergence (Figure 1A). The patient received an induction chemotherapy composed of daunorubicin, aracytine, and midostaurin, but his disease was refractory to treatment, and he died from invasive aspergillosis 2 months later.

One could propose that the Kamb o ritual had no causative role in the remission of the initial AML, which would have occurred anyhow. Indeed, spontaneous remissions are well described for a very specific form of AML occurring in children with trisomy 21,⁶ but have never been described in AML adult patients without trisomy 21. Some rare cases of AML regression have also been documented in patients experiencing severe infection, but the reduction of the tumor burden was generally modest, and relapses invariably occurred in reports ensuring a long-enough follow-up.⁷ Therefore, it may be not so daring to hypothesize that the Kamb o ritual had a causative role in the remission of this patient's AML, the next challenge lies in the analysis of this observation as medical scientists. We can formulate 3 hypotheses regarding the efficacy of Kamb o in this patient:

- The magic bullet hypothesis: Kamb o contains a single component that has strong antileukemic activity against the blast cells of this patient, just as all transretinoic acid or arsenic have an impressive activity on acute promyelocytic leukemia cells.⁸ Dermaseptin B2, a membrane-damaging peptide with demonstrated antitumor properties in *in vitro* and *in vivo* preclinical models,^{9,10} would be a good initial candidate.
- The immunomodulatory hypothesis: Kamb o contains a component that breaks immune tolerance against AML cells, and leads to the clearance of the AML.
- The complexity hypothesis: Kamb o is a very complex mixture of compounds, with a peculiar route of administration, having effects on both tumor cells and immune cells (among other possible targets).

One should be able to demonstrate the magic bullet hypothesis by applying synthetic peptides derived from *Phyllomedusa bicolor* venom on a panel of AML cell lines, or on patient-derived xenograft murine models. Additional explorations using whole genome screens could be useful to determine the pathways involved in AML cell death after exposure to this peptide, or to demonstrate synthetic lethal interactions between genetic events recurrent in AML and sensitivity to this peptide. The pharmacological development would then be straightforward, and usual studies would adapt the formulation, evaluate the pharmacokinetics, and the toxicity profile.

If the immunomodulatory hypothesis is correct, the preclinical proof of Kamb o efficacy could be more difficult to obtain,

¹Service d'h ematologie clinique, Hospices Civils de Lyon, H opital Lyon Sud, Pierre B enite, France

²Service d'h ematologie biologique, Hospices Civils de Lyon, H opital Lyon Sud, Pierre B enite, France

³Universit e Claude Bernard Lyon 1, Facult e de m edecine et de maieutique Lyon Sud Charles M erieux, Lymphoma ImmunoBiology Team, Pierre B enite, France

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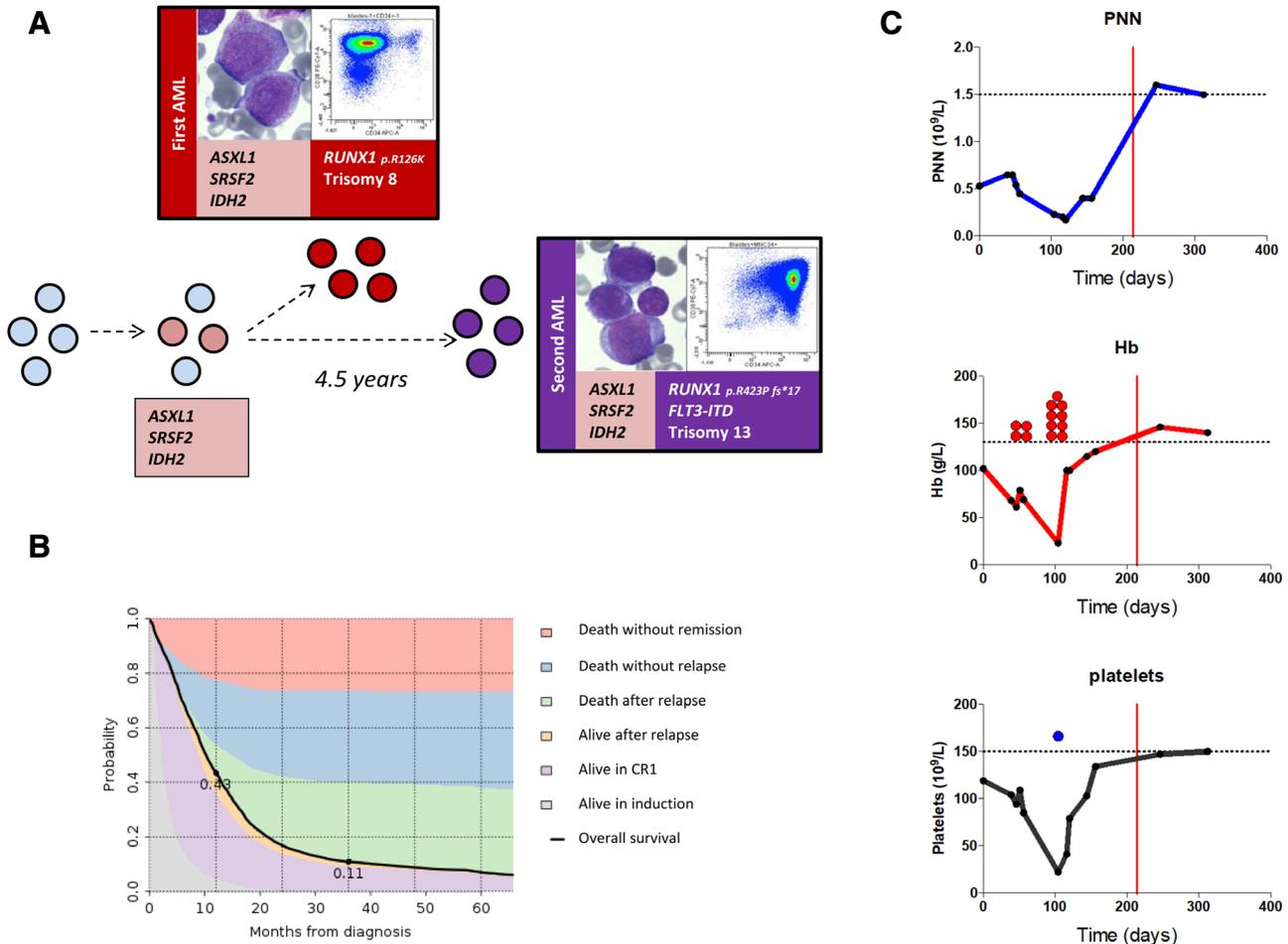


Figure 1. Exceptional response of an AML patient concomitant to Kambô application. (A) Comprehensive analysis of the AML cells at the time of initial diagnosis (first AML) and at the time of AML recurrence (second AML), depicting the cytological and immunological (x-axis, CD34; y-axis, CD38) characteristics of the blast cells. The shared molecular abnormalities are in pink boxes, and the private ones are in red and purple boxes; (B) prognostic estimation according to the knowledge bank approach strategy¹ if the patient was treated with intensive chemotherapy regimen; (C) Progression of the count of polynuclear neutrophils, hemoglobin level, and platelet count (normal value is indicated by the dotted line, red blood cell transfusions are indicated by red dots, and platelet transfusions by blue dot). The time of Kambô initiation is indicated by the red vertical line. AML = acute myeloid leukemia; Hb = hemoglobin; PNN = polynuclear neutrophils.

because no effect will be observed in cell line models. All experiments should be performed in immunocompetent mice genetically modified to develop AML, which would be technically challenging. As with vaccines, the whole administration strategy, including administration route and interval between administrations, is also of major importance for efficient immunization.¹¹ The high number of dendritic cells in the skin associated with the burn-induced local release of potential damage associated molecular patterns could play a role in the immune effects (if any) of the Kambô ritual, and an intravenous injection may not yield similar effects. The significant biological differences between mice and humans (eg, the thalidomide story¹²) might also prevent the observation of therapeutic effects in a rodent model.

Things get even more complicated if the third hypothesis is true, because it will be hardly impossible to reproduce in a preclinical model the correct dosing of the different active molecules, administered via an appropriate route, and following an appropriate schedule. In this case, even if Kambô turns out to be a potent remedy for AML, a formal demonstration using preclinical models and the clinical development might be (nearly) impossible.

To build on this frustration, one has to consider what barriers limit the ability to develop new therapies. The conceptual framework of evidence-based medicine has been elaborated to generate proof of efficacy (so-called evidence) based on a statistical

correlation between a medical intervention and a modification of patient health.¹³ This theory is the dominant paradigm in medicine, and is accounted by the impressive progresses it has allowed over the past 70 years. However, one should keep in mind that alternative strategies have also been successfully applied in Western tradition medical sciences (eg, the invention of vaccination), as well as in medical sciences developed elsewhere such as Chinese medicine. Obviously, we will not argue that evidence-based medicine should no longer be used to produce medical knowledge, but instead propose to additionally consider pragmatic complementary approaches to develop therapeutic strategies.

In evidence-based medicine, case report is considered as the lowest level of evidence. When describing the disease course of a single patient after a therapeutic intervention, several uncontrolled confounding factors might be the actual cause of health improvement, thus majoring the risk to inappropriately conclude that the therapeutic intervention is effective. Moreover, induction (generalization of an observation based on a single case) is not possible given the heterogeneity of diseases (even in a narrow nosological category) and the stochastic nature of some adverse events. However, the description of single case reports is regaining interest, especially in the context of cancer treatment, with the observation of exceptional responders.¹⁴ In

this context, the value of single observations is the only way to cope with the huge amount of data collected at the genomic level, and it is increasingly admitted that one can learn unexpected lessons from exceptional responders. Consequently, the heuristic value of case reports is getting more and more recognized, as long as pharmacological agents are considered. In the case of the Kambô ritual, the absence of controlled and standardized way of administration and the absence of large scale studies of toxicity compromise the credibility of such reports.

Another major difference between exceptional responders and the case reported here is the absence of mechanistic explanation for the clinical effects (if any) of the Kambô ritual. Following the principles of experimental medicine exposed by Claude Bernard, successes have been achieved by translating fundamental knowledge into medical technology. Based on this tradition, most scientific efforts aim at understanding the pathophysiology, to design intelligent strategies to “translate” this knowledge into medical practice. The heuristic value of this approach is beyond doubt, but other strategies might also bring a lot of impressive results for patients. Indeed, some major achievements in medicine have followed another route, starting with empirical observation of efficacy in patients, and ending with the discovery of unsuspected biological mechanisms (eg, the use of imatinib for hypereosinophilic syndromes with FIP1L1-PDGFR α fusion transcript¹⁵). Following these examples, we could pragmatically propose the use of Kambô in medical institutions for patients with relapsing or refractory AML without alternative options, in the setting of a phase 1 trial. However, is there any regulatory agency that will allow and fund such a protocol? The answer is probably not, because most scientists are reticent to imagine a clinical trial for a treatment that is not supported by a biological rationale. Whereas a high level of risk is not an obstacle to the development of innovative strategies (such as allogeneic hematopoietic stem cell transplantation or chimeric antigen receptor T cells for example), the absence of a conceptual framework to justify a clinical test seems to be a definitive barrier far more difficult to overcome.

Can we add to the paradigm of translational medicine a pragmatic strategy that could be supported by single observations, such as the one reported here? This would obviously require a strong shift in the modern conception of medicine that is not reducible to a hard science based on strong causality and mechanistic explanations. Of course, a set of preclinical experiments should be attempted first, to understand as much as possible the mechanisms underlying such intriguing case reports, but should these experiments fail in providing any explanation, would it be unethical to propose such a therapy to patients with no alternative solution? The goal of this article is definitively not to claim that Kambô should be proposed to AML patients, at least not with the level of evidence accumulated so far, but to propose to use this example as an illustration of the need to diversify the methodology for the development of new therapeutic approaches, that is, to follow the frog and jump out of the box.

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