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Application of blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, in treating severe systemic sclerosis: A case study

Marion Subklewe [a,b,c,*,1], Giulia Magno [a,1], Christina Gebhardt [d,1], Veit Bücklein [a,b,c], Franziska Szelinski [f], Héctor Julián Rincón Arévalo [f], Gerulf Hänel [b], Thomas Dörner [f], Gerhard Zugmaier [e,2], Michael von Bergwelt-Baildon [a,c,2], Alla Skapenko [d,2], Hendrik Schulze-Koops [d,**,2]

[a] Department of Medicine III – Hematology/Oncology, LMU University Hospital, LMU Munich, Munich, Germany
[b] Laboratory for Translational Cancer Immunology, LMU Gene Center, Munich, Germany
[c] German Cancer Consortium (DKTK), Munich and Berlin sites, and German Cancer Research Center, Heidelberg, Germany
[d] Division of Rheumatology and Clinical Immunology, Department of Medicine IV, LMU University Hospital, LMU Munich, Munich, Germany
[e] Amgen Research (Munich) GmbH, Munich, Germany
[f] Department of Medicine, Rheumatology and Clinical Immunology, Charite University Hospital, Berlin, Germany

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ABSTRACT

Systemic sclerosis, a severe inflammatory autoimmune disease, shares a common thread with cancer through the underlying mechanism of inflammation. This inflammatory milieu not only drives the immune dysregulation characteristic of autoimmune diseases but also plays a pivotal role in the pathogenesis of cancer. Among the cellular components involved, B cells have emerged as key players in hematologic tumor and autoimmune disease, contributing to immune dysregulation and persistent tissue fibrosis in systemic sclerosis, as well as tumor progression and immune evasion in cancer. Consequently, novel therapeutic strategies targeting B cells hold promise in both conditions. Recent exploration of CD19 CAR T cells in severe systemic sclerosis patients has shown great potential, but also introduced possible risks and drawbacks associated with viral vectors, prolonged CAR T cell persistence, lengthy production timelines, high costs, and the necessity of conditioning patients with organotoxic and fertility-damaging chemotherapy. Given these challenges, alternative CD19-depleting approaches are of high interest for managing severe systemic autoimmune diseases. Here, we present the pioneering use of blinatumomab, a bispecific anti-CD3/anti-CD19 T cell engager in a patient with progressive, severe systemic sclerosis, offering a promising alternative for such challenging cases.

The immune system's involvement is pivotal in the pathophysiology of neoplasia. Enhanced comprehension of the processes driving malignant diseases has spurred the development of targeted therapies aimed at addressing chronic inflammatory processes associated with these conditions. One of the forefront realms in targeted tumor therapy lies within immunomodulation, employing therapeutics to obstruct or eradicate pivotal mechanisms driving tumor progression. In recent years, numerous such strategies have been repurposed for diseases driven by chronic, dysregulated immune activation. These adaptations encompass diverse interventions, such as cell therapies for infectious

* Correspondence to: Department of Medicine III, LMU University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany.
** Correspondence to: Division of Rheumatology and Clinical Immunology, Department of Medicine IV, LMU University Hospital, LMU Munich, Pettenkoferstrasse 8a, 80336 Munich, Germany.
E-mail addresses: Marion.Subklewe@med.uni-muenchen.de (M. Subklewe), Giulia.Magno@med.uni-muenchen.de (G. Magno), Christina.Gebhardt@med.uni-muenchen.de (C. Gebhardt), Veit.Buecklein@med.uni-muenchen.de (V. Bücklein), Franziska.Szelinski@charite.de (F. Szelinski), Hector.Rincon@charite.de (H.J.R. Arévalo), haenel@genzentrum.lmu.de (G. Hänel), thomas.doerner@charite.de (T. Dörner), gerhardz@amgen.com (G. Zugmaier), Michael.Bergwelt@med.uni-muenchen.de (M. von Bergwelt-Baildon), Alla.Skapenko@med.uni-muenchen.de (A. Skapenko), Hendrik.Schulze-Koops@med.uni-muenchen.de (H. Schulze-Koops).
[1] These authors contributed equally to the manuscript
[2] These authors contributed equally to the manuscript

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diseases, janus kinase inhibitors for autoimmune disorders or transplant rejection, and CD20-targeting antibodies for B cell depletion across various autoimmune conditions. With the advent of systems biology and systems medicine, the trend of repurposing drugs from one indication to another with overlapping pathophysiological mechanisms is poised to surge, particularly in addressing rare diseases lacking therapeutic options and approval studies. This strategy, known as "drug repurposing," holds promise for rare autoimmune disorders, as it harnesses drugs already proven to selectively target the immune system in oncology. However, it is imperative to meticulously tailor oncological therapies to individual patients with severe autoimmune diseases and closely monitor their safety outcomes under appropriate conditions and precautions.

A prototypic, rare autoimmune disease is systemic sclerosis (SSc). SSc is a debilitating multi-organ autoimmune disease characterized by increasing fibrosis of the skin, connective tissue and internal organs, which leads to continuous loss of function of the affected organs and to premature death. A truly effective therapy for the disease is not known. One reason for this is that the exact mechanisms of the underlying pathophysiology of SSc are still largely unknown. However, there is plenty of evidence that dysregulation of the immune system plays an important role in the disease [1,2]. Here, B cells are of particular interest: autoantibodies against certain nuclear antigens are a hallmark of organ involvement in SSc [3], B cell-stimulating factors are increased in the serum and in fibrosing tissue [4], B cell homeostasis is disturbed, showing an increased number of expanded naïve B cells as well as a reduced memory B cell pool [5,6], and in animal models B cell-depleting approaches can lead to inhibition of fibrosis [7,8]. In the absence of effective, especially targeted therapies, attempts have therefore been made to treat SSc by B cell depletion. Rituximab (RTX), a monoclonal antibody against the B cell surface molecule CD20, has shown positive clinical effects in several small observational studies, particularly on fibrosis of the skin and lungs [9,10]. While the effect on the skin was confirmed in randomized studies [11], the effect on the lungs was not greater than in the comparator arm cyclophosphamide [12]. Whether this is because RTX does not cause sufficient B cell depletion in the tissue or because those B cells that are fundamental for the disease are not reached by anti-CD20 therapy (such as the CD20 negative, autoantibody-producing plasmablasts or the expanding, precursor B cells) is not clear. The significance of CD20-targeting therapies in SSc has therefore not been conclusively evaluated. Based on these findings and considerations, however, attempts have recently been made to treat rapidly progressive severe SSc with the aid of CD19 chimeric antigen receptor (CAR) T cells [13,14]. Administration of CD19 CAR T cells led to rapid clinical improvement, paralleled by seroconversion. While the effect of the extensive conditioning therapy required as part of CAR T cell therapy cannot be ruled out for the short-term effects described in one study [13], in the other, a dramatic reduction in pulmonary fibrosis could be documented eleven months after the administration of the CAR T cells [14]. B cells therefore appear not only to be of paramount importance in the immunopathogenesis of SSc but also to actively maintain fibrosing processes in SSc. A therapy of SSc with the aim of depleting CD19-positive B cells therefore seems justified.

CD19 CAR T cells have impressively demonstrated the importance of CD19-positive B cells in the pathogenesis and progression of several rheumatic autoimmune diseases [13–17]. However, CAR T cells are associated with a number of potentially significant problems: They require specific, individualized production, which costs both time and considerable money; they are generated by transfection with viral vectors, which recently led to a class-wide boxed warning by the FDA following the occurrence of T cell malignancies in CAR T cell-treated patients [18,19]; they require extensive conditioning of patients prior to administration, e.g. with cyclophosphamide and fludarabine, which can lead to toxic effects in particular in the case of cardiac and/or renal organ involvement of the underlying autoimmune disease; and as observed in patients with oncological disease, they may persist in the recipients years after administration, which may result in uncontrolled target, i.e. B cell depletion.

This provides the rationale to deplete CD19-positive B cells with an alternative approach as a therapy of SSc. Blinatumomab is a bispecific antibody construct that engages T cells with B cells by binding CD3, a chain of the T cell receptor and CD19, leading to destruction of the latter cell population by the former. Blinatumomab has been demonstrated to lead to B cell depletion and decrease in immunoglobulin levels in patients with hematologic tumors [20,21]. We reasoned that the administration of blinatumomab should achieve deep B cell depletion that would be similar in magnitude to the one following CD19 CAR T cell therapy but without the concerns associated with CAR T cell therapy mentioned above.

Here we report the course of the world's first administration of blinatumomab in a patient with a rapidly progressive severe course of SSc. The 35-year-old female presented for the first time to a rheumatologist in October 2022 with typical Raynaud's phenomenon of the hands, that had been present for four months, puffy fingers and purulent ulcerations on several fingertips. Capillary microscopy revealed a typical SSc pattern with rarified capillary density, megacapillaries and capillary hemorrhages. Serologically, she had antinuclear antibodies (titer of 1:6400) with a fine granular pattern and highly elevated antibodies against Scl70. A cardiac echo was without pathological findings, but there were pronounced ventricular extrasystoles. There were no pathological findings on pulmonary function. Initially and prior to the presentation to rheumatology, a total of 40 iloprost infusions had been administered. In December 2022, bosentan was started. Beta-blockers proposed for the treatment of the extrasystoles were contraindicated due to the pronounced acral perfusion disorder, and calcium antagonists were not tolerated. Due to the patient's urgent desire to have children, only a few alternatives were available for immunomodulatory therapy, but an existing therapy with hydroxychloroquine and oral glucocorticoids up to 20 mg/d was discontinued or slowly reduced, respectively, because of questionable indications. The disease was relatively stable until July 2023, when the patient first presented to our department. Digital ulcerations had not occurred since the start of bosentan, but the Raynaud's symptoms had worsened despite the warm weather to up to three episodes lasting up to two hours each per day and increasingly affecting the feet as well as the hands, so that treatment with azathioprine 3 x 50 mg/d and another cycle of 14 days with daily 20 μg iloprost was started. This, however, did not result in any change in the acral symptoms. In the fall of 2023, the patient started to complain of pronounced joint pain in the small joints of the hands and feet, the wrists and the knees. In addition, stiffness of the skin on both hands and feet and on the forearms increased rapidly. Cervical immobility and, for the first time, difficulty swallowing on reclination of the head developed as an expression of fibrosis of the ventral cervical skin. In November 2023, azathioprine was changed to mycophenolate, knowing that this therapy was not compatible with the patient's desire to have children (Fig. 1A). At the end of December 2023, the patient was no longer able to put on a shirt because the stiffness of the skin on her neck and upper chest severely restricted her ability to move her arms. At this point, the skin on both arms was completely fixed up to the middle third of the upper arm, and on the lower legs up to above the ankles (resulting in a modified rodman skin score (mRSS) of 21 [22]). There was a striking hypersensitivity of the skin to touch, which was perceived as "like a sunburn". A cardiac MRI revealed myocardial fibrosis predominantly in the left ventricle and an increased tracer uptake in both peroneal sinuses, indicating fibroblast activation, was detected by ^{68}Ga-FAPI-74 positron emission tomography CT examination.

Under the impression of the rapidly progressive disease, the options were discussed intensively with the patient. Not least due to the patient's continued desire to have children, an option was sought that would not involve any measures with a potentially negative effect on fertility in the 35-year-old patient, such as the administration of cyclophosphamide.

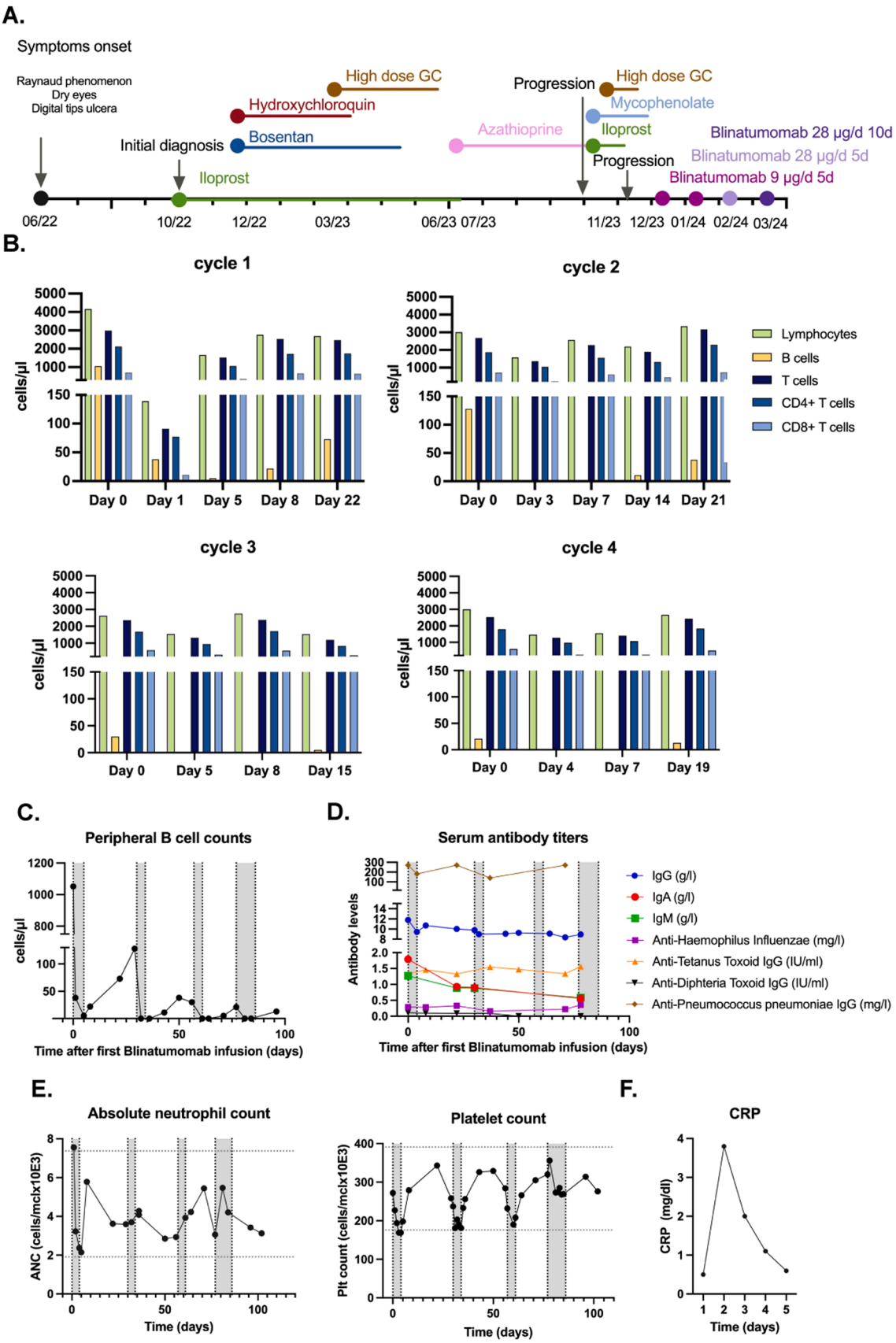

Fig. 1. A) Graphical representation of patient's history and treatment. B) Lymphocyte subpopulations over the course of treatment. C) Peripheral B cell count over time. Days of blinatumomab administration are displayed in grey. B cell count rapidly decreased upon blinatumomab infusion in cycle 1, 2, 3 and 4. D) Effects of treatment with blinatumomab on serum antibody levels. Days of blinatumomab administration are displayed in grey. E) Absolute neutrophil count and platelet count over the course of treatment. Days of blinatumomab administration are displayed in grey. F) Serum CRP levels during the first five days of cycle 1.

Blinatumomab was administered for the first time at the end of December 2023 at a dose of 9 μg/d as continuous intravenous infusion for five days. The therapy was excellently tolerated. Apart from a temporary increase of CRP (Fig. 1F) and an episode of a self-limiting skin rash on day two, there were no signs of acute or delayed toxicity, in particular no fever or signs of cytokine release syndrome, so that the administration of an IL-6R antagonist could be dispensed. Also, no signs of neurotoxicity developed during or after treatment.

Peripheral B cell depletion occurred rapidly, starting at day one of treatment, and, at the end of the five-day treatment cycle, less than 10 B cells/μl were detected (Fig. 1B, C). The number of peripheral T cells was also significantly reduced on day one (< 100/μl), particularly affecting the CD8 T cell subset, but recovered promptly to normal values. At the end of the cycle, T cell numbers were within normal limits and they have remained stable since. The absolute neutrophile count (ANC) dropped remarkably from 7.22 G/l to 1.68 G/l at day three of the cycle and recovered to pre-treatment values by day nine (Fig. 1E). The counts stayed within normal range during further blinatumomab application. Of note, there were no signs of infection during treatment. Platelets dropped during the cycle from 272 G/l to 169 G/l, slightly below the lower limit of normal, at day four, and recovered to pretreatment values by day nine (Fig. 1E).

Two days after starting the blinatumomab infusion, the patient reported a general improvement in symptoms (reduced swelling of the fingers, increased mobility of the neck, decreased sensitivity of the skin to touch). The clinical examination three weeks after the initiation of therapy revealed increased mobility of the hands and fingers and significantly softer skin on the forearms (mRSS = 12).

Four weeks after the first infusion, the second five-day cycle of 9 μg/d blinatumomab was started. This cycle was also excellently tolerated with no signs of toxicity, no rash and no CRP elevation. Similar to the first cycle, clinical symptoms improved already during therapy. B cells, which amounted to 128 cells/μl at the beginning of the second cycle, rapidly depleted. In contrast to the first cycle, the number of peripheral T cells and the peripheral ANC remained constant in the second cycle, while platelets again dropped during the cycle, but remained within normal limits, and increased to pretreatment values shortly after the end of the infusion. Four weeks after the start of the second cycle, a third five-day treatment cycle was initiated, however, as the peripheral B cell pool had started to recover after the first two cycles already after two weeks and treatment was well tolerated, the daily dose of blinatumomab was increased to 28 μg/d. The increase in dose had no effect on the tolerability which again was excellent. The B cell count, initially at 30 cells/μl, rapidly depleted. Like during cycle two, no significant changes in T cell numbers or ANC occurred and the platelets temporarily dropped in numbers, but remained within the normal limits. Three weeks later, a fourth cycle with 28 μg/d blinatumomab was started with continuous treatment for ten days. There was again no sign of toxicity and no infection. Like in the previous cycles, B cell depletion occurred rapidly while no significant changes in T cells, T cell subsets, ANC or thrombocytes were noted. After the fourth cycle, the pronounced Raynaud's phenomenon in the hands was significantly reduced in frequency and length of the individual episodes, and it was no longer present in the feet. The mRSS three weeks after the completion of the fourth cycle was ten and the patient had no joint complaints, no burning sensation on skin contact, no feeling of tension in the thoracic skin, no restriction of movement in the arms, no restriction of cervical mobility and no difficulty swallowing.

In summary, we present the first case worldwide in which blinatumomab was used as a B cell-depleting therapy in a non-malignant disease. The case shows that blinatumomab is safe and effective and can be used in patients with rapidly progressing severe systemic sclerosis. The treatment was well tolerated at all doses and resulted in profound B cell depletion. This did not lead to an increased susceptibility to infection. Of note, serum IgG levels and specific antibody titers against infectious agents (haemophilus influenzae, pneumococcus) or toxins (tetanus and diphtheria) were not affected by the therapy (Fig. 1D). T cells and leukocytes were only depleted during the first two days of the first therapy cycle and remained in the normal range between and during consecutive treatment cycles. Clinically, the therapy led to a rapid improvement in symptoms. This may indicate that B cell depletion also had an immediate effect on the inflammatory component of the active disease and that lymphocytic infiltration at the beginning of therapy may have contributed to feelings of tightness and stiffness of the skin. However, in addition to the improvement in mRSS, the amelioration in acral perfusion may indicate that B cell depletion leads to an improvement in fibrosis in SSc, in line with previous suggestions [9,10,11,23]. The long-term success of the therapy described here will be monitored and further studies will need to follow to determine the value of B cell-depleting therapy with blinatumomab in SSc.

Ethics approval

This study was approved by the ethics committee of the university hospital of the LMU Munich (24-0328).

Patient consent for publication

Consent obtained directly from the patient.

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CRediT authorship contribution statement

Gerulf Hänel: Writing – original draft, Writing – review & editing. **Thomas Dörner:** Writing – original draft, Writing – review & editing. **Michael von Bergwelt-Baildon:** Writing – original draft, Writing – review & editing. **Alla Skapenko:** Writing – original draft, Writing – review & editing. **Hendrik Schulze-Koops:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Marion Subklewe:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Giulia Magno:** Writing – original draft, Data curation. **Christina Gebhardt:** Writing – original draft. **Gerhard Zugmaier:** Conceptualization, Data curation, Writing – original draft. **Veit Bücklein:** Writing – original draft, Writing – review & editing. **Franziska Szelinski:** Writing – original draft, Writing – review & editing. **Héctor Julián Rincón Arévalo:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Veit Bücklein: AMGEN: Honoraria; Celgene: Research Funding; Pfizer: Honoraria; Kite/Gilead: Research Funding, Honoraria; Novaritis: Honoraria. Consultancy/Advisory, BMS: Consultancy/ Advisory, Takeda: Consultancy/Advisory. **Marion Subklewe:** receives industry research support from Amgen, BMS/Celgene, Gilead, Janssen, Miltenyi Biotec, Novartis, Roche, Seattle Genetics and Takeda and serves as a consultant/advisor to AvenCell, CDR-Life, Ichnos Sciences, Incyte Biosciences, Janssen, Miltenyi Biotec, Molecular Partners, Novartis, Pfizer and Takeda. She serves on the speakers' bureau at Amgen, AstraZeneca, BMS/Celgene, Gilead, GSK, Janssen, Novartis, Pfizer, Roche and Takeda. Gerhard Zugmaier is an employee from Amgen. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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