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In Silico Evaluation of a Mutant Toxic Shock Syndrome Toxin-1 (TSST-1) of *Staphylococcus aureus* as a Putative Vaccine Candidate

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ABSTRACT

Introduction: The development of a vaccine against *Staphylococcus aureus* has proven to be much more difficult than expected. In this study, we considered and analyzed a mutant Toxic Shock Syndrome Toxin-1 (TSST-1) as a potential vaccine candidate. **Methods**: An NCBI sequence of TSST-1 was analyzed bioinformatically by online tools such as Ensemble and Pubmlst. The protein sequence of TSST-1 was similarly analysed by Expasy ProtParam, Phyre2 and Vaxign databases. The protein functional class was predicted by VICMpred database while the B- and T-cell epitopes were predicted by IEDB and BepiPred tools. The 3D structure was predicted by LOMETS, QMEAN, ProSA-web and ElliPro. The conservation of the epitopes was evaluated by ConSurf tool. **Results:** *In silico* analyses showed that this protein is present in high-prevalence sequence types of circulating clinical strains. It appears that TSST-1 has conserved liner and conformational B-cell epitopes. In addition, there are four potent of T-cell epitopes in this protein. **Conclusion:** This *in silico* data indicated that TSST-1 (and especially amino acid residues 81-221) is a promising vaccine target against *S. aureus*.

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INTRODUCTION

Staphylococcus aureus is among the most important human pathogens responsible for considerable worldwide morbidity and mortality is [1]. This bacterium is known for bloodstream, skin and soft tissue infections as well as endocarditis, pneumonia and toxic shock syndrome (TSS) [2, 3]. Fever, rash, desquamation and hypotension are evident symptoms of *S. aureus* TSST-1 super-antigen (SAg). It has been shown *in vivo* that production of high levels of pro-inflammatory cytokines is associated with TSST-1 as result of a direct crosslink between MHC class II molecules on antigen-presenting cells and T cell receptors (TCRs) with specific Vβ elements [4]. Furthermore, despite the use of new antibiotics and emphasis on disease surveillance and prevention, a high mortality rate of 15-50% remains for *S. aureus* bacteremia. Antibiotic-resistant strains of S. aureus are becoming strikingly common. With the most common one being methicillin-resistant S. aureus, occurring in hospitals and communities around the world [5]. Therefore, the development of new strategies, including vaccine discovery, is needed. Many bacterial infections usually promote robust protective immune responses which is not the case with S. aureus [6]. Because of the individuals who are typically not protected from subsequent *S. aureus* infections, the development of a vaccine against *S. aureus* is urgently needed for public health [7].

Unfortunately, vaccines against *S. aureus* tested in clinical trials have not yet been proven successful in providing protection [8]. The first vaccine named StaphVAX (developed by Nabi and presented by GSK), the second vaccine candidate was V710 (co-developed by Intercell AG and Merck), and the third one is called SA4Ag which contains ClfA adhesion molecule (presented by Pfizer) [6, 9, 10, 11]. For vaccine development, the super antigen (SAg) toxin TSST-1 has been verified as the main virulence factor, as well as rTSST-1 vaccine, a recombinant SAg-based vaccine candidate containing a detoxified double-mutated rTSST-1 antigen. Since October 2016, safety and immunogenicity results have been reported from two additional staphylococcal vaccine trials using a modified recombinant staphylococcal B protein and a single-dose 4-antigen or 3-antigen *S. aureus* vaccine in healthy adults [12-18].

Nowadays, most vaccine design strategies use immunoinformatics tools while the classical vaccinology approaches used before the advent of these tools and before the availability of genomic data were time-consuming and labor-intensive [19]. In this study, we performed an in silico evaluation of mutant TSST-1 of *S. aureus* as a putative vaccine candidate.

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MATERIALS AND METHODS

Dataset of Sequences

The sequence of 234 amino acids of TSST-1 with accession number WP_103151054 was retrieved from the National Centre for Biotechnological Information (NCBI) database. It has been considered that the mutant H135A is associated with T-cell binding site [20]. This mutant of TSST-1 does not induce a high level of TNF-α expression which plays a role in the development of lethal toxic shock [21].

Detection of TSST-1 among Different Sequence Types (STs)

Ensemble (https://bacteria.ensembl.org/index.html) database, Pubmlst (https://pubmlst.org/), BLAST tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi), was used to detect TSST-1 in the most common clinical sequence types (STs) of *S. aureus.*

Protein Characteristics of TSST-1

The number of amino acids, molecular weight, theoretical pI, Asp + Glu, Arg + Lys, estimated half-life, aliphatic index and instability index were determined using Expasy ProtParam Server (https://web.expasy.org/protparam/) [22]. Alpha helix, beta strand, disordered and helices TM helices were evaluated using the Phyre2 database (http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index) [23]. Adhesion probability was calculated using Vaxign database (http://www.violinet.org/vaxign2) [24]. Protein functional class was predicted using the VICMpred database (http://www.imtech.res.in/raghava/vicmpred/) [25].

Detection of T Cell and Linear B cell Epitopes

Seven human HLA-II supertype alleles were selected for MHC-II epitope prediction (HLA-DRB1:03:01, HLA-DRB1:07:01, HLA-DRB1:15:01, HLA-DRB3:01:01, HLA-DRB3:02:02, HLA-DRB4:01:01, HLA-DRB5:01:01). The T-cell epitope was predicted using tools available in Immune Epitope Database (IEDB) (http://tools.iedb.org/CD4episcore/), which provides a catalog of experimentally characterized T-cell epitopes as well as data on Major Histocompatibility Complex (MHC) binding and MHC ligand elution assays.

B-cell epitopes are antigenic determinants that are recognized by the immune system and represent the specific piece of the antigen to which B lymphocytes bind. These play a vital role in vaccine design. B-cell epitopes were predicted using the BepiPred 2.0 (http://www.cbs.dtu.dk/services/BepiPred/) [26].

Tertiary Structure Determination and Detection of Conformational B Cell Epitopes

The tertiary structures (3D) of the putative vaccine candidates were characterized using LOMETS (https://zhanglab.ccmb.med.umich.edu/LOMETS/). LOMETS is the meta-threading method for template-based prediction of protein structures. Mod Refiner (https://zhanglab.ccmb.med.umich.edu/ModRefiner/) was used to refine the 3D structure of putative vaccine candidates and the quality of these structures was tested using QMEAN (https://swissmodel.expasy.org/qmean/) and ProSA-web (https://prosa.services.came.sbg.ac.at/prosa.php). ElliPro (http://tools.iedb.org/ellipro/) was used to identify discontinuous epitopes (with threshold ≥ 0.6) [27].

Determination of Sequence Conservation

This analysis aims to calculate the degree of conservation of epitopes within a given protein sequence and was performed using ConSurf tool (https://consurf.tau.ac.il/). The threshold for sequence identity was set to 100% and other parameters were set to the default values.

RESULTS

Prevalence of TSST-1 among Different Sequence Types

TSST-1 is a very important SAg of *S. aureus* infection. Through investigation and analysis by Ensemble database and BLAST tool, we found that TSST-1 is the most abundant in ST5 and ST30, which are the most common STs of *S. aureus* (Fig. 1). Information on TSST-1 features and their conservation is presented in Table 1 and Fig. 2.

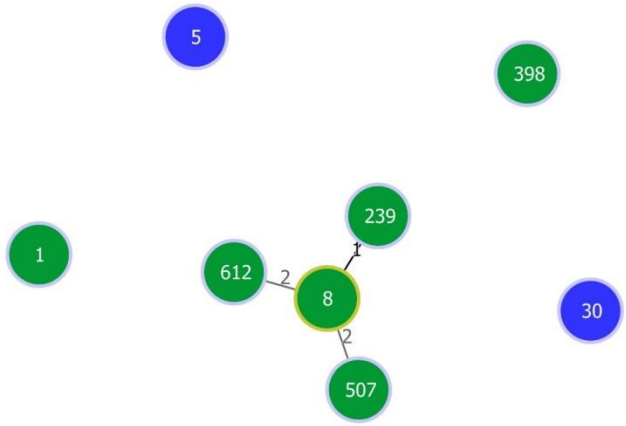


Fig. 1. The minimal spanning tree of different sequence types (STs) in *S. aureus*. These data show that high-prevalent STs, including ST30 and ST5, possess the TSST-1 gene (blue spheres). While other STs do not have the TSST-1 gene (green spheres).

Table 1. Physio-chemical characteristics of mutant TSST-1 protein.

Accession number	WP_103151054
Protein name	Toxic
Number of amino acids	234
Predicted functional class	Virulence
Molecular weight	26.52
Theoretical pI	8.79
The estimated half	>10 h (*E. coli, in vivo*)
Aliphatic index	89.08
Instability index	30.65 (Stable)
Number of disulfide bonds	0
Ag overall prediction	0.84 (Antigen)
Allergenicity	0.33 (Non-allergen)
Homology to host (Human & mouse)	NO
Alpha helix	2%
Beta strand	65%
Disordered	20%
Transmembrane helices	0
TM helices (%)	0%
TM helices (%)	0.369
Adhesion probability score	Extracellular

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T Cell Epitopes and Linear B-cell Epitopes Predictions of TSST-1

T cell epitopes with high scores were predicted for TSST-1, corresponding to the different alleles of MHC-II. Four epitopes with a high binding affinity score of 50 > IC_{50} nM were predicted to be MHC-II binders (Fig. 2). Since B-cell epitopes play a remarkable role in humoral responses, the full-length sequences of TSST-1 were subjected to linear B-cell epitope prediction tool. The linear epitopes with a cutoff value > 0.6 were selected using BepiPred server. The data showed 4 linear B-cell epitopes as indicated in Fig. 2.

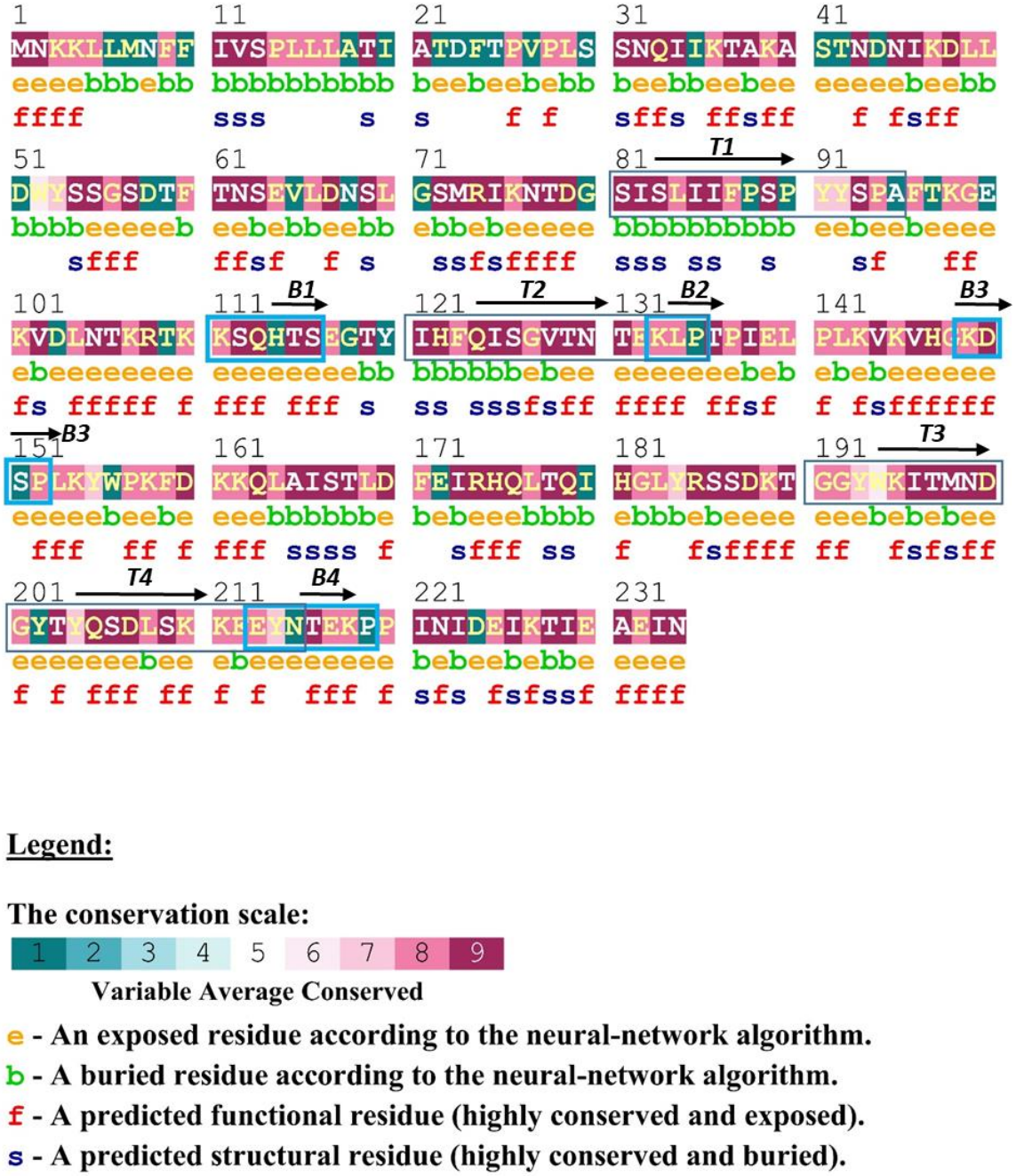


Fig. 2. Conservation analysis of TSST-1 protein and epitope location. The location of B-cell epitopes (blue rectangles) and 15-mer of T-cell epitopes (black rectangles) were characterized on the sequence. These data show 4 B-cell epitopes (B1 to B4) and 4 MHC-II T-cell epitopes (T1 to T4). T3 and T4 are two overlapped T-cell epitopes.

Prediction of 3D Structure and Conformational B Cell Epitopes

Given the importance of conformation of the epitopes for the humoral response, conformational B-cell epitopes of the designed sequence were predicted based on protein-antibody interactions. Discontinuous peptides were selected that had surface protein atoms responsible for binding to antibodies with threshold of ≥ 0.6. The compositions, number and sequence position of the amino acids, and score values are summarized in Table 2.

The 3D representation of the three predicted discontinuous epitopes of the final protein is given in Fig. 3.

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Table 2. Conformational epitopes of TSST-1 protein as predicted by ElliPro.

No.	Residues	Number of residues	Score
1	_:K36, _:T37, _:A38, _:K39, _:A40, _:S41, _:T42, _:N43, _:D44, _:N45, _:I46, _:K47, _:K143, _:K145, _:V146, _:H147, _:G148, _:K149, _:D150, _:S151, _:P152, _:L153, _:K154, _:I180, _:H181, _:G182, _:L183, _:Y184, _:S186, _:S187, _:D188, _:K189, _:T190, _:G191, _:N234	35	0.721
2	_:N62, _:E64, _:V65, _:L66, _:D67, _:N68, _:S69, _:L70, _:G71, _:S72, _:R74, _:K76, _:N77, _:T78, _:D79, _:G80, _:S81, _:I82, _:F87, _:Y92, _:S93, _:P94, _:A95, _:F96, _:T97, _:K98, _:G99, _:E100, _:K101, _:K110, _:K111, _:S112, _:Q113, _:H114, _:T115, _:S116, _:E117, _:G118, _:T119, _:Y120, _:I121	41	0.7
3	_:T131, _:E132, _:K133, _:L134, _:P135, _:T136, _:P137, _:I138, _:E139, _:L140, _:P141, _:W156, _:P157, _:K158, _:F159, _:D160, _:K161, _:K162, _:Q163, _:T197, _:M198, _:N199, _:D200, _:G201, _:Y202, _:T203, _:N222, _:D224, _:E225, _:K227, _:T228	31	0.611

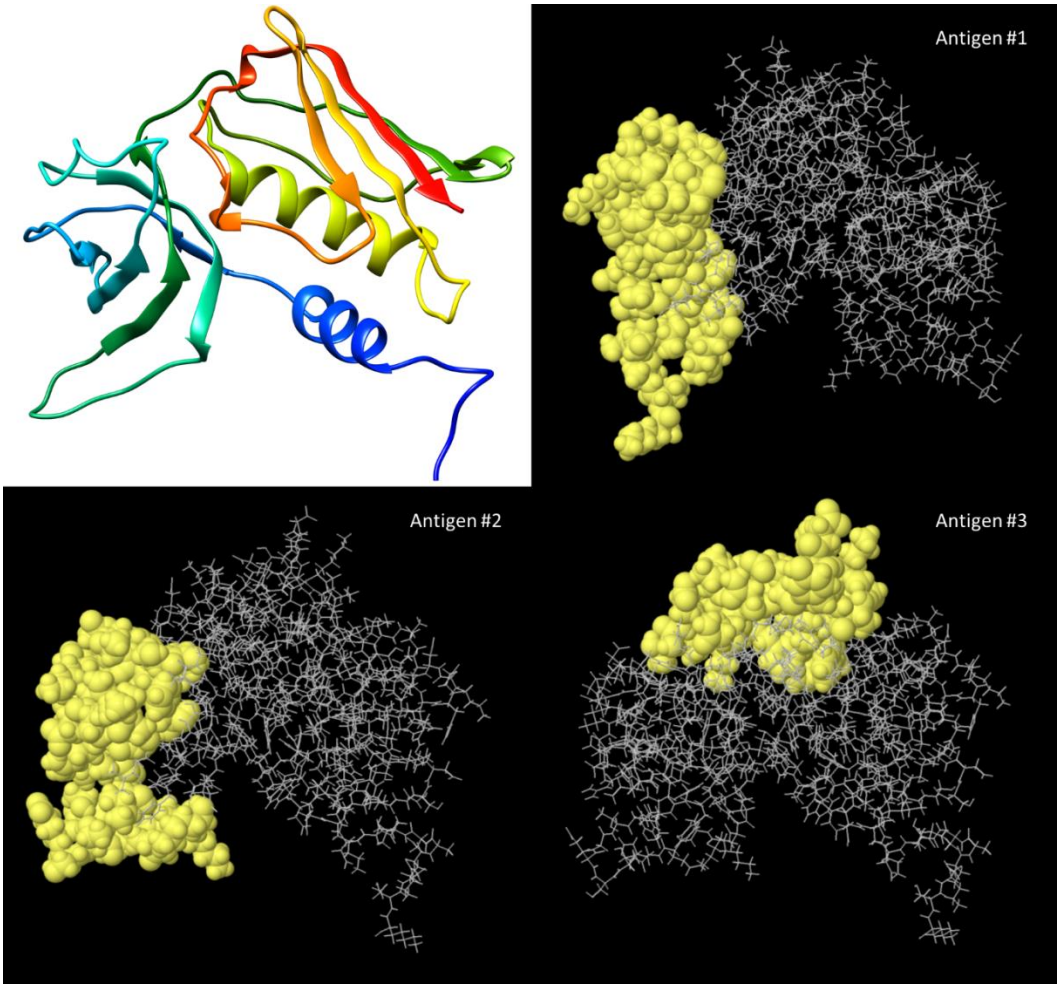


Fig. 3. The 3D structure of TSST-1 protein and the location of conformational B-cell epitopes on TSST-1. This Figure shows that there are 3 main conformational B-cell epitopes (yellow color) on the tertiary structure of TSST-1.

DISCUSSION

Immunotherapy is the most effective approach to prevent infections affecting bloodstream, skin, and soft tissues, as well as diseases such as endocarditis, pneumonia, and toxic shock syndrome (TSS), caused by clinical strains of *S. aureus*. It appears that promoting immunogenicity and induction of protective immunity against *S. aureus* are ideal criteria to formulate an effective and safe vaccine against *S. aureus* [4]. In order to determine the immunodominant B- and T-cell epitopes of antigens that play a substantial role in pathogenicity and induction of immune responses, bioinformatics is an effective tool [28]. The aim of the present study was to evaluate the immunogenicity of TSST-1 protein based on in silico methods.

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Given the importance of T cell-mediated immunity along with B-cell responses to protect against *S. aureus* infection [29], we decided to also evaluate MHC-II epitopes. Although, the best linear B- and T-cell epitopes of TSST-1 were located in amino acids 81-221, the results of defining conformational epitopes showed that amino acids 36-121 of TSST-1 were high score discontinuous epitopes.

An ideal vaccine against *S. aureus* should be distributed across different pathogenic strains and should contain conserved epitopes among clinical strains. We found that TSST-1 is widely expressed in many *S. aureus* strains. By producing a vaccine against this antigen, immunity against various sequence-type infections could be established. According to STRING database, this protein has interactions with some virulence factors, such as Polyglutamate capsule, a main virulence factor in *Bacillus anthracis* and Staphylococcal exotoxin 7 [30, 31]. The mutation of a histidine to an alanine residue at position 135 (H135A) has significantly reduced the super-antigenic activity and toxicity of TSST-1 [32]. Based on *in silico* analyses, the amino acids 81-221 of TSST-1 can potentially activate B and T cells. Because all B- and T-cell epitopes are available in this exposed region and superantigenic reactivity is associated with several amino acids localized in this segment.

Following the vaccines which have failed against *S. aureus*, a successful strategy will require a multicomponent approach that may include candidate immunogens. In addition, a more predictive animal model, and utilization of a Th1/Th17 adjuvant can enhance the immune responses [33]. Developing a vaccine against *S. aureus* has proved far more difficult than expected. The failed vaccine candidates from Merck, Pfizer and Nabi have common themes: a limited number of surface antigens, lack of immunological candidates, omission of adjuvants with failure to induce a CD4+ Th1/Th17 immune response, and an unrepresentative mice model. Essentials for macrophage and neutrophil activation and recruitment are Th1 (IFN-γ) and Th17 (IL-17) responses [34]. Genetic deficits in phagocytic, Th17 and IL-17 functions predispose the subjects to staphylococcal infections and confirm the mechanisms described above [35, 36]. An experimental study has shown that H135A mutant vaccination of TSST-1 is able to provide IL-17A-dependent host defense against S. aureus infection which promotes chemokine-mediated infiltration of phagocytes into sites of the infection [37].

Moreover, induction of IL-17 production incorporated with T cell-activating epitopes, causes the immune pathway to produce memory Th17 [38]. When the immune system encounters TSST-1 again, it initiates memory-Th17 activation that has a remarkable role in eliminating extracellular bacteria such as *S. aureus*. It would be conceivable to utilize mutant TSST-1 peptide as a vaccine subunit against *S. aureus*. In this case, we need Monophosphoryl lipid A (MPL®) plus aluminum adjuvants to enable a Th1/Th17 priming response in subunit vaccines [39]. In this direction, BioMed Co. has recently used detoxified double mutant TSST-1 with aluminum adjuvant as a proposed vaccine formulation [40]. Further, in vitro and in vivo studies including immunological assays in animal models are needed to confirm the immunogenicity and protection of amino acid residues 81-221 of TSST-1 peptide as a putative subunit vaccine against clinical cases of *S. aureus* infections.

CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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