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Humanization of an Antibody Directed Against IgE

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Abstract. IgE antibodies bind to specific high-affinity receptors on mast cells, leading to mast cell degranulation and release of mediators, such as histamine, which produce symptoms associated with allergy. Hence, anti-IgE antibodies that block binding of IgE to its high-affinity receptor are of potential therapeutic value in the treatment of allergy. These antibodies must also not bind to IgE once it is bound to the receptor because this would trigger histamine release. This study describes the humanization of a murine antibody, MaE11, with these characteristics. Variants of the humanized antibody were evaluated to probe the importance of framework residues on antibody binding and to determine which charged residues in the CDR interacted with IgE. We found that only five changes in human framework residues were required to provide for binding comparable to that of the original murine antibody. *Journal of Immunology,* 1993, 151: 2623.

IgE antibodies bind to a specific high-affinity receptor (FcεRI) (1, 2) on mast cells and basophils via their Fc region (constant domains Cε2, Cε3, and Cε4) (3), leading to mast cell degranulation and release of mediators that produce symptoms associated with allergy (4, 5). IgE also binds to a low-affinity receptor (FcεRII and CD23) (6) on B lymphocytes (7, 8) and on cells involved in inflammation, leading to IgE-mediated cytotoxicity and phagocytosis (9). Hence, anti-IgE antibodies that block binding of IgE to its receptors may be of therapeutic value.

Herein we report the humanization of a murine antibody, MaE11, directed against IgE that prevents binding of free IgE to FcεRI on mast cells but does not bind to FcεRI-bound IgE. The latter characteristic is important because this antibody will not trigger histamine release by cross-linking IgE-loaded FcεRI on mast cells. However, as a therapeutic the murine antibody would not be the molecule of choice because clinical use of non-human antibodies has identified three fundamental problems. First, non-human antibodies cause a human immune response that can reduce therapeutic value of the non-human antibody (10–14). Second, therapeutic efficacy is reduced by the relatively rapid clearance of the non-human antibody compared with human ones (15). Finally, non-human antibodies generally show only weak recruitment of effector functions (e.g., antibody-dependent cell-mediated cytolysis), which may be desirable or essential for efficacy (16, 17).

One approach to overcoming these problems involves production of "humanized" antibodies that significantly reduce the amount of non-human sequence in the molecule. This technique, pioneered by Winter et al. (16, 18), involves transplantation of the non-human Ag-binding loops (CDR)[2] onto a human antibody framework. In addition to CDRs, select non-human framework residues must also be incorporated into the humanized antibody to maintain proper CDR conformation (19) or because they interact directly with the antigen (20). The humanized antibody, when properly constructed, will contain approximately 5% non-human residues, most of which will be in the CDRs. Although several humanized antibodies have been reported (21–28), only recently has the clinical efficacy of these

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[2] Abbreviations used in this paper: CDR, complementarity-determining region.

molecules begun to be evaluated (15).

Most humanized antibodies have been designed by comparing the sequence of the murine antibody of interest to a database of human antibody sequences and choosing the human antibody most homologous to that of the murine antibody (23–27). In contrast, we have used a framework derived from consensus sequences of human VL and VH subgroups. This provides for use of the most common framework found among human IgG antibodies and eliminates possible idiosyncracies present in any individual framework, both of which would, hopefully, reduce the chance of an immunogenic response against the humanized antibody. This same framework has been previously used for other humanized antibodies (21, 22).

Thirteen variants of the humanized antibody were evaluated to probe the importance of framework residues on antibody binding. We found that only five changes in human framework residues were required to provide for binding comparable to that of the original murine antibody. We also used an additional 10 variants to ascertain whether any of the charged CDR residues were important IgE-binding determinants.

Materials and Methods

Construction of humanized antibody

The murine anti-human IgE mAb, MaE11, was generated, cloned, and sequenced at Genentech (unpublished data). To construct the first F(ab) variant of humanized MaE11, F(ab)-1, site-directed mutagenesis (29) was performed on a deoxyuridine-containing template containing a human κ-subgroup I light chain and human subgroup III heavy chain (VH-CH1) in a pUC119-based plasmid, pAK2 (21). F(ab)-2 was then constructed from a F(ab)-1 template. All other humanized F(ab) variants were constructed from a template of F(ab)-2. Plasmids were transformed into *Escherichia coli* strain JM101 (30) for preparation of double- and single-stranded DNA. For each variant both light and heavy chains were completely sequenced using the dideoxynucleotide method. DNA encoding light and heavy chains was then subcloned into a derivative of the *E. coli* F(ab) expression plasmid, pAK19 (31). These derivatives lack the hinge cysteines that form the interheavy chain disulfides in $F(ab')_2$ fragments. F(ab) fragments, as opposed to full-length IgG antibodies, facilitated the analysis of a moderately large number of variants because *E. coli* expression could be used rather than mammalian cell culture techniques. Once the best variant was determined, it was subsequently subcloned into a plasmid encoding a full-length human IgG1 (see below).

The expression plasmids were transformed into *E. coli* strain MM294 (32), and a single colony was grown in 5-ml 2YT-100 μg/ml carbenicillin for 5–8 h at 37°C. The 5-ml culture was added to 100 ml AP5–100 μg/ml carbenicillin and allowed to grow for 16 h in a 500-ml shaker flask at 37°C. The culture was centrifuged at 4,000 × *g* and the supernatant removed. After freezing for 1 h, the pellet was resuspended in 5-ml cold 10 mM Tris-1 mM EDTA; 50 μl 0.1 M benzamidine (Sigma, St. Louis) was added to inhibit proteolysis. After gentle shaking on ice for 1 h, the sample was centrifuged at 10,000 × *g* for 15 min. The supernatant was applied to a protein A-Sepharose CL-4B (Pharmacia) column (0.5 ml bed volume) then washed with 10 ml 3 M KCl-100 mM Tris, pH 8.0, and eluted with 2.5 ml 100 mM acetic acid, pH 2.8, into 0.5 ml 1 M Tris, pH 8.0. The F(ab) was then buffer exchanged into PBS using a Centricon-30 (Amicon) and concentrated to a final volume of 0.5 ml. SDS-PAGE gels of all F(ab)s were run to ascertain purity. F(ab) concentrations were determined using an 0.1% ϵ_{280} of 1.0. The extinction coefficient was determined by using the concentration of protein from an amino acid analysis of purified F(ab)-2 and the A_{280} for this same sample.

Selected F(ab) fragments were analyzed directly by liquid chromatography/mass spectrometry to confirm their molecular weight. Samples were injected into a packed capillary liquid chromatography system (33) and analyzed directly with a Sciex API 3 mass spectrometer. The higher charge states of human growth hormone (m.w. = 22,256.2), acquired using the same instrument parameters as those used for the samples, were used for calibration.

For generation of human IgG1 versions of humanized MaE11, the heavy and light chains were subcloned separately into previously described pRK plasmids (34). Appropriate heavy and light chain plasmids were cotransfected into an adenovirus-transformed human embryonic kidney cell line, 293 (35), using a high efficiency procedure (35, 36). Media was changed to serum free and harvested daily for up to 5 days. Antibodies were purified from the pooled supernatants using protein A-Sepharose CL-4B (Pharmacia). The eluted antibody was buffer exchanged into PBS by G25 gel filtration, concentrated by ultrafiltration using a Centriprep-30 or Centricon-100 (Amicon), sterile filtered using a Millex-GV (Millipore), and stored at 4°C. The concentration of antibody was determined using total Ig-binding ELISA. The concentration of the standard was determined by amino acid composition analysis.

Soluble receptor assay

A 96-well assay plate (Nunc) was coated with 0.05 ml 1 μg/ml FcεRI α-chain IgG chimeric receptor (Genentech; unpublished data) in coating buffer (50 mM carbonate/bicarbonate, pH 9.6) for 12 h at 4–8°C. The wells were aspirated and 250 μl blocking buffer (PBS, 1% BSA, pH 7.2) was added and incubated for 1 h at 4°C. In a separate assay plate the samples and reference murine MaE11 were titered from 200 to 0.001 μg/ml by 1:4 dilutions with assay

buffer (0.5% BSA and 0.05% Tween 20, PBS, pH 7.2) and an equal volume of 10 ng/ml biotinylated IgE (37) was added and the plate incubated for 2–3 h at 25°C. The FcεRI-coated wells were washed three times with PBS and 0.05% Tween 20 (Sigma) and 50 μl from the sample wells were transferred and incubated with agitation for 30 min at 25°C. Fifty μl/well of 500 μg/ml Streptavidin-HRP (Sigma), diluted 1:5000 in assay buffer, was incubated for 15 min with agitation and then the plate was washed as before. Fifty μl/well of Microwell Peroxidase Substrate (Kirkgaard & Perry Laboratories) was added and color was developed for 30 min. The reaction was stopped by adding an equal volume of 1 N HCl, and the absorbance measured at 450 nm. The concentration at 50% inhibition was calculated by plotting percentage of inhibition versus concentration of blocking antibody with a nonlinear four-parameter curve fit using the Kaleidagraph data analysis application (Synergy Software).

FACS-based binding assays

The ability of the antibody to inhibit FITC-conjugated (38) IgE binding to the α-chain of the high-affinity FcεRI receptor expressed on CHO 3D10 cells (39) was determined by flow cytometry. FITC-conjugated IgE (40 nM) was preincubated with the antibody ($0.3–1 \times 10^{-6}$ M) at 37°C for 30 min in FACS buffer (PBS, 0.1% BSA, and 10 mM sodium azide, pH 7.4). The complex was then incubated with 5×10^5 CHO 3D10 cells at 4°C for 30 min. The cells were washed three times with FACS buffer and mean channel fluorescence at 475 nm measured on an FACScan flow cytometer (Becton Dickinson). MaE1 (Genentech), a murine anti-human IgE mAb that does not block IgE binding to the FcεRI α-chain, was used as a positive control and MOPC21 (Cappel), a murine monoclonal that does not recognize IgE, was used as a negative control.

Binding of antibodies to IgE-loaded FcεRI

Antibody binding to human IgE associated with the α-subunit of FcεRI expressed on CHO 3D10 cells (39) was determined by preincubating 5×10^5 CHO 3D10 cells with 10 μg/ml human IgE for 30 min at 4°C. Cells were washed three times followed by a 30-min incubation with varying concentrations of either murine anti-human IgE mAbs MaE1 or MaE11 or the humanized mAb variant 12. MOPC21 (murine IgG1) was used as a control for the murine mAbs, whereas humanized 4D5 mAb (21) (human IgG1) was used as a control for humanized variant 12. Binding of murine mAbs was detected with a FITC-conjugated $F(ab')_2$ goat anti-mouse IgG (10 μg/ml). Humanized mAb binding was detected with a FITC-conjugated $F(ab')_2$ goat anti-human IgG (50 μg/ml), which had been affinity purified on an IgE column to minimize cross-reactivity to IgE.

VH domain

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MaE11     DVQLQESGPGLVKPSQSLSLACSVTGYSITS[GYSWN]WIRQF
F(ab)-2   EVQLVESGGGLVQPGGSLRLSCAVSGYSITS[GYSWN]WIRQA
humIII    EVQLVESGGGLVQPGGSLRLSCAASGFTF-S[DYAMS]WVRQA
          1        10        20        30          40

MaE11     PGNKLEWMG[SITYDGSSNYNPSLKN]RISVTRDTSQNQFFL
F(ab)-2   PGKGLEWVA[SITYDGSTNYADSVKG]RFTISRDDSKNTFYL
humIII    PGKGLEWVA[VISNGSDTYYADSVKG]RFTISRDDSKNTLYL
                   50        60        70        80

MaE11     KLNSATAEDTATYYCAR[GSHYFGHWHFAV]WGAGTTVTVSS
F(ab)-2   QMNSLRAEDTAVYYCAR[GSHYFGHWHFAV]WGQGTLVTVSS
humIII    QMNSLRAEDTAVYYCAR[DSRFF-----DV]WGQGTLVTVSS
            abc       90        100abcd         110
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VL domain

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MaE11     DIQLTQSPASLAVSLGQRATISC[KASQSVDYDGDSYMN]WYQQKP
F(ab)-2   DIQLTQSPSSLSASVGDRVTITC[RASQSVDYDGDSYMN]WYQQKP
humκI     DIQMTQSPSSLSASVGDRVTITC[RASQSVDIS--SYLN]WYQQKP
          1        10        20        30  abcd        40

MaE11     GQPPILLIY[AASYLGS]EIPARFSGSGSGTDFTLNIHPVEE
F(ab)-2   GKAPKLLIY[AASYLES]GVPSRFSGSGSGTDFTLTISSLQP
humκI     GKAPKLLIY[AASSLES]GVPSRFSGSGSGTDFTLTISSLQP
                   50        60        70        80

MaE11     EDAATFYC[QQSHEDPYT]FGAGTKLEIK
F(ab)-2   EDFATYYC[QQSHEDPYT]FGQGTKVEIK
humκI     EDFATYYC[QQYNSLPYT]FGQGTKVEIK
                   90        100
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FIGURE 1. Amino acid sequences of murine MaE11, humanized MaE11 variant 2 [F(ab)-2], and human consensus sequences of heavy chain subgroup III (humIII) and light chain κ subgroup I (humκI) (42). Murine residues are italicized. The definition of CDR residues of Kabat et al. (42) are included within brackets; the definition by Chothia et al. (19) are in boldface. Kabat et al. (42) numbering used with insertions shown as a, b, c.

Computer graphics models of murine and humanized F(ab)s

Sequences of the VL and VH domains (Fig. 1) were used to construct a computer graphics model of the murine MaE11 VL-VH domains; this model was used to determine which framework residues should be incorporated into the humanized antibody. Models of the humanized variants were also constructed to verify correct selection of murine framework residues. Construction of the models was performed as described previously (21, 40).

Results

Expression and purification of humanized MaE11 F(ab)s and antibodies

Shaker flask expression levels of F(ab)s were usually 0.5–1 mg/L of culture. Full-length antibody recoveries ranged

Table I
Humanized MaE11 F(ab) variants

Variant	Changes from F(ab)-2[a]		Purpose	Concentration at 50% inh. (ng/ml)		F(ab)-X	F(ab)-X
	VL	VH		Mean	SD[b]	F(ab)-2	MaE11
F(ab)-1	*Leu* 4 Met Arg 24 *Lys* Glu 55 *Gly* Gly 57 *Glu*	*Val* 24 Ala *Ile* 37 Val Thr 57 *Ser* Ala 60 *Asn* Asp 61 *Pro* Val 63 *Leu* Gly 65 *Asn* *Phe* 78 Leu	Straight CDR swap	>100,000		>16.0[c]	>560
F(ab)-1B[d]		Leu 78 *Phe*		98,000		16.0	547
F(ab)-2				6083	1279	1.0	34
F(ab)-3	*Leu* 4 Met *Met* 33 Leu		Packing; CDR-L1	9439	508	1.6	53
F(ab)-4	*Leu* 4 Met		Packing; CDR-L1	6770	349	1.1	38
F(ab)-5		*Val* 24 Ala	Packing; CDR-H1	9387	733	1.6	52
F(ab)-6		*Phe* 78 Leu	Packing; CDR-H1, H2	17,537	4372	2.9	24
F(ab)-7		*Ile* 37 Val	VL-VH interface	8622	107	1.4	48
F(ab)-8	Glu 55 *Gly* Gly 57 *Glu*		Unusual Gly 55-X-Glu 57 MaE11 sequence	5799	523	1.0	32
F(ab)-9		Ala 60 *Asn* Asp 61 *Pro*	CDR-H2; Ala 60 *Asn* at VL-VH interface	1224	102	0.20	6.8
F(ab)-10	Ala 13 *Val* Val 19 *Ala* Val 58 *Ile* Leu 78 *Val* Val 104 *Leu*	Val 48 *Met* Ala 49 *Gly* Ala 60 *Asn* Val 63 *Leu* Phe 67 *Ile* Ile 69 *Val* Met 82 *Leu* Leu 82c *Ala*	Repack F(ab)-2 interior as in murine MaE11	842	130	0.14	4.7
F(ab)-11		Ala 60 *Asn* Asp 61 *Pro* Val 63 *Leu* Phe 67 *Ile*	CDR-H2; packing of *Leu* 63 and *Ile* 67	416	66	0.07	2.3
F(ab)-12		Ala 60 *Asn* Asp 61 *Pro* Phe 67 *Ile*	CDR-H2; packing of Val 63 and *Ile* 67	501	84	0.08	2.8
MaE11				179	63	0.03	1.0

[a] Murine residues are italicized; residue numbers are according to Kabat et al. (42).
[b] Mean and SD of three soluble receptor assays.
[c] A F(ab)-X/F(ab)-2 ratio >16 means that this variant exhibited no binding even at the highest F(ab) concentrations used.
[d] Changes from F(ab)-1.

from 30 to 50 μg/L based on ELISA. As noted previously (31, 41), the human consensus sequence used allows purification of F(ab) fragments from *E. coli* periplasmic extracts on protein A. F(ab) was always present primarily in the periplasmic extract but detectable at a low level in the media. Mass spectrometry was performed on selected F(ab)s to confirm their m.w.: F(ab)-2, expected M_r 48,303, measured M_r 48,306; F(ab)-9 expected M_r 48,329, measured M_r 48,332; F(ab)-10 expected M_r 48,285, measured M_r 48,286. These values are within the expected error limit of the system (0.01%).

Design of humanized MaE11 antibodies

In contrast to other investigations that have used human sequences closest to the murine Ig of interest (23–27), our humanized antibodies use a human consensus sequence. This consensus sequence consists of a framework based on human VH subgroup III and VLκ subgroup I (42).

CDRs, as defined by Kabat et al. (42), were grafted onto the human framework—all framework residues were retained as human. This variant is best described as a straight CDR swap. F(ab)-1 showed no detectable inhibition of IgE binding to its receptor (Table I). Even when one framework residue (H67), subsequently found to be important for maintenance of binding, was replaced with the corresponding murine framework residue, IgE binding was still not restored (F(ab)-1B; Table I). The failure of such "CDR swap" variants to bind their antigens has been reported previously (21, 25).

F(ab)-2 was the first variant based on modeling. In addition to the six murine CDRs, several murine framework residues were incorporated into the human framework (Fig. 1). The definition of CDRs provided by Kabat et al. (42), i.e., based on sequence variability, were used except for CDR-H1 and CDR-H2. CDR-H1 definitions based on sequence variability (42) and on crystallographic studies of

1). We therefore redefined CDR-H1 to include both definitions, i.e., residues H26–H35. The definition of CDR-H2 based on sequence variability contains more residues than that based on antibody-antigen crystal structures (Fig. 1). Because none of the crystal structures reported to date show antibody-antigen contacts for antibody residues H60–H65, we used the CDR-H2 definition provided by Chothia et al. (19). Hence, in F(ab)-2 a shorter version of CDR-H2 (residues H50–H58) was used compared with F(ab)-1.

In F(ab)-2 VH, 28 human consensus residues were altered to murine, including only three murine framework residues: *Val* H24, *Ile* H37, and *Phe* H78 (murine residues in all F(ab)s are italicized). In F(ab)-2 VL, 9 human consensus residues were changed to murine, including only one murine framework residue, *Leu* L4. F(ab)-2 is the variant with the minimal number of changes to the human framework which, in our judgment, should be required for maintenance of binding.

An additional 10 variants were constructed to 1) test the effects of buried residues on CDR conformation, 2) determine whether the models had been successful in directing which framework residues should be included in the humanized MaE11, and 3) evaluate the importance of an unusual sequence present in the murine MaE11 (Table I). To test the effects of buried residues on CDR conformation, F(ab)-3 to F(ab)-7 were constructed in which murine residues were changed back to human ones. In F(ab)-3 the buried murine VL residues *Leu* L4 (framework residue) and *Met* L33 (CDR-L1) were exchanged for human sequence Met L4 and Leu L33 to determine their effect on CDR-L1. Chothia et al. (19) have proposed that the residue at position L33 may be important in maintaining proper conformation of CDR-L1. The models suggested that the side chain at L4 might also affect CDR-L1 conformation by its interaction with the side chain at L33. However, binding of F(ab)-3 was only slightly impaired over F(ab)-2. In F(ab)-4 only position L4 was altered and no significant difference in binding compared with F(ab)-2 was found. Together, F(ab)-3 and F(ab)-4 show that, at least for this humanized antibody, the side chains at L4 and L33 have minimal affect on binding and presumably on the conformation of CDR-L1.

The models also suggested that framework residue H24 could affect the conformation of CDR-H1 and framework residue H37 could affect the VL-VH interface (Fig. 2). Substitution of the murine with the human residue at H24 (F(ab)-5) or H37 (F(ab)-7) showed minimal reduction in binding. In contrast, replacing the murine *Phe* at framework position H78 with the human Leu (F(ab)-6) affected a larger reduction in binding. Our models suggest that this side chain is influencing the conformation of CDR-H1 and/or CDR-H2 (Fig. 2). H78 has not previously been considered important in maintaining the conformation of either CDR-H1 or CDR-H2 (19).

In F(ab)-8 to F(ab)-12 human residues were replaced

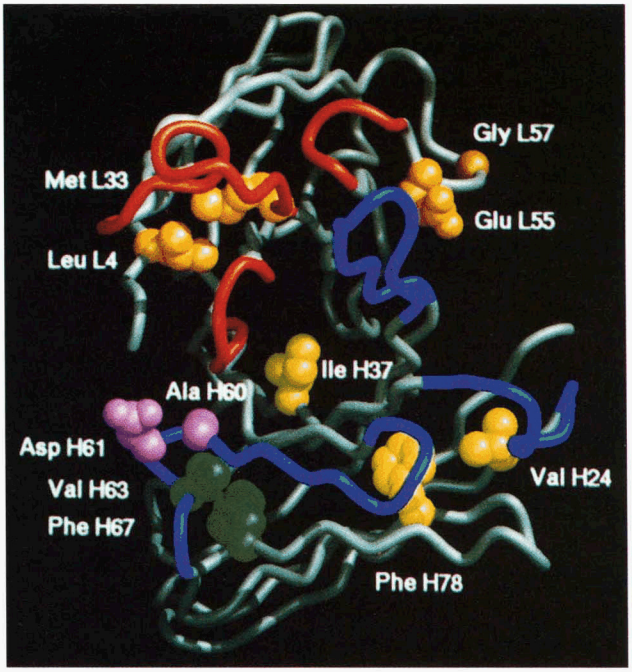

FIGURE 2. Framework residues altered in various humanized MaE11 variants. VL and VH backbone traces are *grey*, VL CDRs are *red*, and VH CDRs are *blue*. Selected framework residue side chain atoms are represented as *spheres*. Leu L4, Met L33, Glu L55, Gly L57, Val H24, Ile H37, and Phe H78 are *yellow*. Ala H60 and Asp H61 are *purple*. Val H63 and Phe H67 are *green*.

provement in binding compared with F(ab)-2 (Tables I and II; Fig. 3). In F(ab)-9, which exhibited a fivefold better binding than F(ab)-2, two residues in CDR-H2 (as defined by Kabat et al. (42)) were changed to murine residues: Ala H60 *Asn* and Asp H61 *Pro*. The *Pro* substitution could have altered the CDR-H2 conformation and/or rigidity and *Asn* H60 is anticipated to be buried at the VL-VH interface, possibly interacting with Asp L1 (Fig. 2).

F(ab)-10, which also exhibited improved binding relative to F(ab)-2, was a variant in which all buried residues (defined as residues with accessible surface area less than 5% that of the free amino acid) in both VL and VH domains were those of the murine MaE11. In essence F(ab)-10 can be considered as murine MaE11 in which only exposed, non-CDR residues in VL and VH were changed to human sequence. This type of humanized variant was suggested by the recent proposal of Padlan (43). However, the possibility remained that the improved binding exhibited by F(ab)-10 was due to only one or a few residues. For example, F(ab)--10 contains Ala H60 *Asn* that, based on F(ab)-9 (Table I), could alone account for much of the improved binding of F(ab)-10.

Two additional variants were evaluated to test this possibility. For these two variants, instead of using F(ab)-2 as the basis, we used F(ab)-9 because this variant showed a fivefold improved binding (Table I). According to the mod-

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