Antibody Design LABORATORIES

TGEX-HC-mG1 Expression Vector

INSTRUCTION MANUAL

TGEX-HC Transient Mammalian Expression Vector

Catalog #: MX007

Version: A1.2 – September 2020

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Description

Introduction

The **TGEX™** vector series is designed for the rapid expression of antibody molecules by transient gene expression in mammalian cell suspension culture. The vector series features a CMV promoter, the adenovirus tripartite leader sequence (TPL) (Logan 1984, Mariati 2010), a variable antibody domain leader sequence with its intron and convenient cloning sites to insert antibody variable regions. The constant regions are derived from the human IgG1 and kappa sequences. There is no selection marker and the overall small size of the vectors is optimized for transient transfection; expensive antibiotics to prepare large quantities of plasmid for transient transfections are not required. Using widely available cell lines and large scale transfection technologies (see experimental procedure) yields of antibody between 10 mg/L and 100 mg/L in serum-free conditions are routinely achieved in the laboratory in just a few days.

The **TGEX™-HC-mG1** vector is designed for the expression of a heavy chain variable region with the constant region of the murine IgG1 heavy chain. Expression of full length antibody molecules is achieved by co-transfection with a light chain variable region cloned into one the vector **TGEX™-LC** series.

Content, Shipping & Storage

Content

VECTOR	COMPOSITION	AMOUNT
TGEX-HC-mG1	20 µl at 0.5 µg/µl of DNA vector in DNA Conservation Buffer (Tris-HCL 5 mM, EDTA 0.1 mM, pH 8.5)	10 µg

Shipping & Storage

TGEX-HC-mG1 vector is shipped on wet ice. Upon receipt, store the vector at -20ºC.

Limited Product Warranty

This warranty limits our liability to the replacement of this product. No other warranties of any kind express or implied, including, without limitation, implied warranties of merchantability or fitness for a particular purpose, are provided by Antibody Design Labs. Antibody Design Labs shall have no liability for any direct, indirect, consequential, or incidental damages arising out of the use, the results of use, or the inability to use this product.

For research use only; not intended for any animal or human therapeutic or diagnostic use.

TGEX Vector Series

Characteristics of the TGEX vector series

VECTOR	CATALOG	USE	DESCRIPTION
TGEX™-HC	MX001	Cloning of VH domain	For the expression of human IgG1 heavy chain
TGEX™-LC	MX002	Cloning of VL domain	For the expression of human Kappa light chain
TGEX™-FC	MX003	Cloning of VH domain	For the expression of human IgG1 Fc fusion.
TGEX™-FH	MX004	Cloning of VH domain	For the expression of human IgG1 Fab fragment
TGEX™-HChis	MX005	Cloning of VH domain	For the expression of human IgG1 heavy chain with a HIS tag
TGEX™-SCblue	MX006	scFv cloning vector	For the transfer of scFv from any PADL phagemid vector and expression as an scFv-Fc fusion

Combination of vectors to desired antibody format

COMBINATION	FORMAT	PURIFICATION[1]
TGEX™-HC + TGEX™-LC	Full length human or chimeric human IgG1/K	Protein A or G
TGEX™-HChis + TGEX™-LC	Full length human or chimeric human IgG1/K	Protein A , G or IMAC
TGEX™-FH + TGEX™-LC	Human or chimeric IgG1/K Fab fragment	Protein L, G or IMAC
TGEX™-FC	Fc fusion	Protein A or G
TGEX™-SCblue	scFv-Fc fusion	Protein A or G

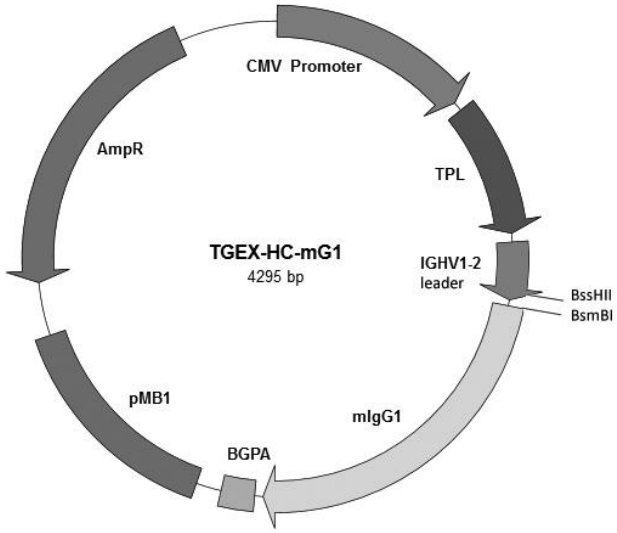
1. Purification by protein A, G and L may require testing.

TGEX vector series for desired isotype

VECTOR	CATALOG	ISOTYPE	DESCRIPTION
TGEX™-HC-hG1	MX001	Human IgG1	Heavy chain expression plasmid for human IgG1, same as TGEX-HC
TGEX™-HC-hG2	MX014	Human IgG2	Heavy chain expression plasmid for human IgG2
TGEX™-LC-hK	MX002	Human Kappa	Light chain expression plasmid for human Kappa, same as TGEX-LC
TGEX™-LC-hL	MX013	Human Lambda	Light chain expression plasmid for human Lambda
TGEX™-HC-mG1	MX007	Murine IgG1	Heavy chain expression plasmid for murine IgG1
TGEX™-HC-mG3	MX009	Murine IgG3	Heavy chain expression plasmid for murine IgG3
TGEX™-LC-mK	MX008	Murine Kappa	Light chain expression plasmid for murine Kappa

Vector Map

The figure below illustrates the main features of **TGEX-HC-mG1** expression vector. The full vector sequence is available online for download in varied formats on the product web page; the total length of the vector is 4295 bp.



Cloning Site

Following is an illustration of **TGEX-HC-mG1** cloning site from the EcoRI site and onward. The VH domain is inserted between the BssHII site and the BsmBI site; after excision of the intron sequence, the IGHV1-2 sequence encodes the leader peptide MDWTWRILFLVAAATGAHS. SA/SD donor and acceptor sites.

```
        tgex-S3                                                    EcoRI
        ──────────────────────▶                                      |
971     GAAAGGCGTC TAACCAGTCA CAGTCGCAAG TTTAAACGGA TCTCTAGCGA

        Start of IGHV1-2 leader sequence
        |                                  1131
                                           MetAspTrpT hrTrpArgIl
1021    ATTCATCCCC TGAGAGCTCC GTTCCTCACC ATGGACTGGA CCTGGAGAAT

        eLeuPheLeu ValAlaAlaA laThr SD
1071    CCTCTTCTTG GTGGCAGCAG CCACAGGTAA GAGGCTCCCT AGTCCCAGTG

1121    ATGAGAAAGA GATTGAGTCC AGTCCAGGGA GATCTCATCC ACTTCTGTGT

                  BSSHII          VH start      BsmBI     mIgG1 constant region
                  |               |             |         ┌──────────────────
              S A  AlaHisS er                             Al aLysThrThr
1171    TCTCTCCACA GGCGCGCACT CCCAGGTGCA CCGTCTCTGC CAAAACGACA

        ──────────────────────────────────────────────────────────────────…
        ProProSerV alTyrProLe uAlaProGly SerAlaAlaG lnThrAs...
1221    CCCCCATCTG TCTATCCACT GGCCCCTGGA TCTGCTGCCC AAACTAA...
```

Feature Table

The features of **TGEX-HC-mG1** transient expression vector are highlighted in the following table.

FEATURE	LOCATION	DESCRIPTION
Promoter	5-585	CMV promoter.
TPL	612-1000	Adenovirus tripartite leader sequence (Logan 1984, Mariati 2010)
IGHV1-2 leader	1025-1192	Human IGHV1-2 leader sequence with intron. The mature RNA encodes the 18 a.a.–long signal sequence MDWTWRILFLVAAATGAHS; cleavage occurs on the C-terminal side of the terminal serine.
Murine IgG1 CDS	1209-2183	Sequence encoding the murine IgG1 heavy chain sequence comprising the CH1, CH2 and CH3 domains with the hinge region. The sequence is intronless; the C-terminal lysine residue is encoded.
BGpA	2207 -2305	Rabbit beta-globin polyadenylation signal sequence.
pMB1 origin	2379 - 2998	pBR322 origin for replication in *E. coli* with a temperature-sensitive high copy-number phenotype (Lin-Chao 1992).
TEM1 beta-lactamase	3153 - 4013	Ampicillin resistance for selection in *E. coli*.

Restriction Site Summary

Enzyme	Site	Nb	Position	Strand	Isoschizomers
BamHI	G^GATCC	1	1338		
BcgI	(10/12)CGANNNNNNTGC(12/10)	1	3742		
BsePI	G^CGCGC	1	1182		BssHII PauI PteI
BstEII	G^GTNACC	1	1274		BstPI Eco91I EcoO65I PspEI
BstXI	CCANNNNN^NTGG	1	2165		
Bsu36I	CC^TNAGG	1	1608		Eco81I AxyI Bse21I
CspCI	(11/13)CAANNNNNGTGG(12/10)	1	407		
DrdI	GACNNNN^NNGTC	1	2435		AasI DseDI
EagI	C^GGCCG	1	2185		BseX3I BstZI Ecl1XI Eco52I
Eam1105I	GACNNN^NNGTC	1	3221		AhdI BmeRI DriI
EcoNI	CCTNN^NNNAGG	1	1289		BstENI XagI
EcoRI	G^AATTC	1	1019		
Esp3I	CGTCTC(1/5)	1	1202		BsmBI
FalI	(8/13)AAGNNNNNCTT(13/8)	1	784		
FspI	TGC^GCA	1	3446		Acc16I NsbI
HindIII	A^AGCTT	1	2328		
NmeAIII	GCCGAG(21/19)	1	3349		
NotI	GC^GGCCGC	1	2184		CciNI
PmaCI	CAC^GTG	1	1616		AcvI BbrPI Eco72I PmlI PspCI
PmeI	GTTT^AAAC	1	1000		MssI
PstI	CTGCA^G	1	1377		BspMAI
PvuI	CGAT^CG	1	3593		Ple19I
SacII	CCGC^GG	1	740		Sfr303I KspI SgrBI Cfr42I
SmaI	CCC^GGG	1	1711		Cfr9I TspMI XmaI
SnaBI	TAC^GTA	1	357		BstSNI Eco105I
SpeI	A^CTAGT	1	18		AhlI BcuI
XhoI	C^TCGAG	1	966		Sfr274I PaeR7I SlaI
XmnI	GAANN^NNTTC	1	3821		Asp700I MroXI PdmI
AarI	CACCTGC(4/8)	2	1448		
		2	2108		
AloI	(7/12)GAACNNNNNNTCC(12/7)	2	1331		
		2	1715		

ArsI	(8/13)GACNNNNNNTTYG(11/6)	2	851		
		2	1796		
BalI	TGG^CCA	2	1912		MlsI MluNI Mox20I MscI Msp20I
		2	4223		
BbsI	GAAGAC(2/6)	2	1557	-	BpiI BstV2I
		2	1962		
BciVI	GTATCC(6/5)	2	2542	-	BfuI BsuI
		2	4069		
Bpu10I	CCTNAGC(-5/-2)	2	930		
		2	1308		
BseRI	GAGGAG(10/8)	2	715		
		2	1716		
BssSI	CACGAG(-5/-1)	2	2506	-	BauI Bst2BI
		2	3890		
BtgZI	GCGATG(10/14)	2	368	-	
		2	623		
Eco31I	GGTCTC(1/5)	2	1440	-	Bso31I BsaI BspTNI
		2	3293		
OliI	CACNN^NNGTG	2	1160		AleI
		2	1478		
PasI	CC^CWGGG	2	1279		
		2	1503		
SacI	GAGCT^C	2	583		Ecl136II EcoICRI Eco53kI Psp124BI SstI
		2	1034		
SapI	GCTCTTC(1/4)	2	2078	-	BspQI LguI PciSI
		2	2153		
VspI	AT^TAAT	2	25		AseI PshBI
		2	3397		
XcmI	CCANNNNN^NNNNTGG	2	1270		
		2	1900		

Absent Sites:

AanI, AbsI, Acc65I, AccIII, AdeI, AfeI, AflII, AgeI, AjiI, AjuI, AlfI, Aor13HI, Aor51HI, ApaI, AscI, AsiGI, AsiSI, Asp718I, AspA2I, AsuII, AsuNHI, AvrII, BaeI, BarI, BbvCI, BclI, BfrI, BlnI, BlpI, BmgBI, BmtI, BoxI, BplI, Bpu1102I, Bpu14I, Bsa29I, BsaBI, Bse8I, BseAI, BseCI, BseJI, BshTI, BshVI, BsiWI, BsmI, Bsp119I, Bsp120I, Bsp13I, Bsp1720I, Bsp68I, BspDI, BspEI, BspOI, BspT104I, BspTI, BssNAI, Bst1107I, BstAFI, BstAPI, BstBI, BstPAI, BstZ17I, Bsu15I, BsuTUI, BtrI, BtuMI, ClaI, CpoI, CsiI, CspAI, CspI, DinI, DraIII, Eco147I, Eco32I, Eco47III, EcoRV, EcoT22I, EgeI, EheI, FbaI, FseI, FspAI, HpaI, I-CeuI, I-PpoI, I-SceI, KasI, KflI, Kpn2I, KpnI, KroI, Ksp22I, KspAI, MabI, MauBI, MfeI, MluI, Mly113I, Mph1103I, MreI, MroI, MroNI, MspCI, MunI, Mva1269I, NaeI, NarI, NgoMIV, NheI, NruI, NsiI, NspV, PI-PspI, PI-SceI, PacI, PaeI, PalAI, PceI, PciI, PctI, PdiI, Pfl23II, PflFI, PfoI, PinAI, PluTI, PscI, PshAI, PsiI, PspLI, PspOMI, PspXI, PsrI, PsyI, RgaI, RigI, RruI, Rsr2I, RsrII, SalI, SbfI, SdaI, SexAI, SfaAI, SfiI, SfoI, SfuI, SgfI, SgrAI, SgrDI, SgsI, SmiI, SphI, SrfI, Sse8387I, SseBI, SspDI, StuI, SwaI, Tth111I, Vha464I, XbaI, XmaJI, Zsp2I.

Experimental Procedures

General Molecular Biology Techniques

Molecular biology should be conducted under the supervision of a qualified instructor trained to standard safety practice in a molecular biology laboratory environment. Standard molecular biology procedures can be found in a general molecular biology handbook such as Sambrook (1989).

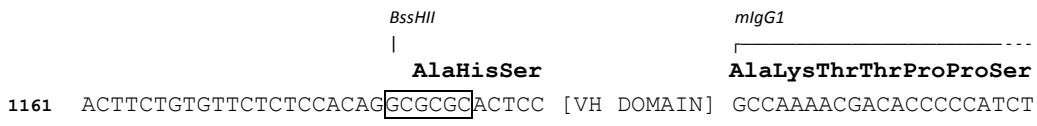
Plasmid Maintenance

Propagation and maintenance of **TGEX-HC-mG1** is obtained on any *recA1, endA1 E. coli* strain using LB or 2xYT medium supplemented with ampicillin (100 µg/ml) as a selection marker and incubated at 37ºC with agitation. **TGEX-HC-mG1** is a derivative of pBR322 with a high copy number origin of replication and usually gives high yields of plasmid DNA with most standard laboratory strains such as XL1-blue or DH5α. The high copy number phenotype is temperature sensitive and requires incubation at 37ºC (Lin-Chao 1992). Some DNA stabilizing strains are known to produce smaller amounts of plasmid DNA. In case of issues, we recommend using XL10-Gold® from Agilent Technologies, Inc., on which **TGEX-HC-mG1** plasmid DNA can be isolated in large quantities.

Cloning into TGEX-HC-mG1

In Silico Clone Design

A complete IGHV1-2 leader sequence MDWTWRILFLVAAATGAHS is necessary for secretion of the antibody in the culture supernatant and proper removal of the leader peptide by host proteases. In the following schema, after cutting by BssHII and BsmBI, the end of the leader encoding sequence 5'-CGCGCACTCC will be removed. This short sequence must be included back in the final clone for proper protein maturation and secretion. The BsmBI site will be eliminated during the cloning.



Vector Digestion

BssHII and BsmBI restriction enzymes are fully active at 50ºC and 55ºC, respectively. The double digestion of the vector can be either conducted at 50ºC with both enzymes together or at 55ºC with BsmBI initially alone and together with BssHII after cooling the reaction to 50ºC. Esp3I is an isoshiszomer of BsmBI with an optimal working temperature of 37ºC. Please, consult the documentation of your restriction enzyme provider for optimal double digestion conditions.

Cloning with FAST-Licase

Homologous recombination is the easiest and most efficient method to clone seamlessly antibodies into TGEX vectors. We recommend the **FAST-Licase™** (Antibody Design Labs cat# MB101S & MB101L) with the following overhangs. For synthetic constructs, the overhangs are added on each side. For amplified constructs, primers contain the overhang (BssHII overhang or BsmBI reverse-complement overhang) followed by the antibody priming area. The **FAST-Licase™** reaction contains the insert plus the purified vector digested with BssHII and BsmBI (see kit instructions).

BssHII overhangs 5’-GTGTTCTCTCCACAGGCGCGCACTCC

BsmBI overhangs 5’-GCCAAAACGACACCCCCATC (reverse complement for PCR primers)

Primer Design for Restriction Cloning with the BssHII Site

Oligo1 is an example of primer designed to amplify a VH domain sequence and clone it into the BssHII site. A minimum of 2 nucleotides is recommended to cut BssHII site close to the end (source New Englands BioLabs); these 2 N are followed by the BssHII site GCGCGC and the end of the leader sequence ACTCC encoding the end of the leader peptide; the resulting NNGCGCGCACTCC extension is added 5’ to the VH domain primer.

Oligo1 5’-NNGCGCGCACTCC-VH-start

Primer Design for Restriction Cloning with the BsmBI Site

Oligo2 is an example of primer designed to amplify the VH domain from the end of the J region and includes a BsmBI site compatible with **TGEX-HC-mG1** cloning site. BsmBI is a type IIS restriction enzyme that cuts outside of its recognition site. BsmBI will cut immediately before the start of the human IgG1 constant region sequence, exactly 1 base after the end of the site and 5 bases further on the opposite strand, thus freeing a 5’ 4-bases overhang GCAT on the sense strand. In Oligo2, a BsmBI site situated symmetrically to the vector will generate a complementary overhang. After digestion and ligation, the two BsmBI sites, the one in the vector and the one in Oligo2, will be removed. We added two nucleotides on the 5’ end of the primer although a minimum of one nucleotide is recommended to cut BsmBI site close to the end (source New Englands BioLabs).

Oligo2 5’-NNcgtctcNATGC-JH-end

Removing BsmBI Sites in J Regions

As shown in Table 1, many heavy chain J regions contain a BsmBI site near their 3’ end. These sites can be eliminated by modifying the codon usage in the sequence encoding the TVS amino acid sequence. We suggest using GTT instead of GTC for the codon encoding the valine residue; the resulting mismatch will create minimal perturbation and simply adding one extra nucleotide to the J primer is sufficient to ensure strong amplification of the VH domain.

J Region	3’ Sequence
Human IGHJ1	ctggtcac**cgtctc**ctca g
Human IGHJ2	ctggtcactgtctcctca g
Human IGHJ3	atggtcac**cgtctc**ttca g
Human IGHJ4	ctggtcac**cgtctc**ctca g
Human IGHJ5	ctggtcac**cgtctc**ctca g
Human IGHJ6	acggtcac**cgtctc**ctca g
Mouse mus. IGHJ1*01	acggtcac**cgtctc**ctca g
Mouse mus. IGHJ1*02	acggtcaccgtttcctca g
Mouse mus. IGHJ1*03	acggtcac**cgtctc**ctca g
Mouse mus. IGHJ2*01	actctcacagtctcctca g
Mouse mus. IGHJ2*02	tctctcacagtctcctca g
Mouse mus. IGHJ2*03	agtctcacagtctcctca g
Mouse mus. IGHJ3*01	ctggtcactgtctctgca g
Mouse mus. IGHJ4*01	tcagtcac**cgtctc**ctca g

Rabbit IGHJ1	ctggtcaccatctcttca g
Rabbit IGHJ2	ctggtcaccgtctcctca g
Rabbit IGHJ3	ctggtcaccgtctcctca g
Rabbit IGHJ4	ctggtcaccgtctcctca g
Rabbit IGHJ5*01	ctggtcaccgtctcttca n
Rabbit IGHJ5*02	ctggtcactgtctcttca g
Rabbit IGHJ6	ctcgtcaccgtctcttca g
Translation	T V S S/A

Table I. Occurrence of BsmBI sites on the 3' end of human, mouse musculus and rabbit functional J regions (source IMGT [5]).

Alternative to BsmBI Sites

All restriction enzymes that generate 4-bases long 5' overhangs can be used in place of BsmBI; this is the case for example of BsaI (GGTCTC(1/5)) , another type IIS restriction enzyme. This option could come in handy when the VH domain contains another BsmBI preventing cloning.

Sequencing of Inserts

The following primers give a strong PCR amplification of the TGEX vector series inserts between the EcoRI site and the NotI site. The primer tgex-S3 can be used to sequence the VH domain in full.

tgex-S3 5'- AGGCGTCTAACCAGTCACAGTC

tgex-R2 5'- CAAAAAATTCCAACACACTATTGC

Antibody Expression

Cell lines

Cell lines adapted for culture in suspension and serum-free conditions are recommended. HEK293 and CHO cells are often used for antibody expression by transient transfection; you can either adapt your own cell line or get it from a supplier (e.g. Life Technology). HEK293 cells are particularly well suited for expression using **TGEX™** vector series.

Transient Transfection

Many transfection reagents especially designed for transient transfection are commercially available from multiple providers (e.g. Life Technologies, Mirus Bio LLC). We recommend testing the transfection conditions with a reporter plasmid first to determine the percentage of cells effectively transfected and optimal transfection conditions; fluorescent reporters are often used with that purpose. Similarly, any condition known to boost expression should be carefully tested in your system before being scaled up. We did observe a strong increase in expression in 293 cells upon exposure to sodium valproate (Backliwal 2008).

LIGHT CHAIN TO HEAVY CHAIN RATIO

We recommend starting with a 1:1 light chain to heavy chain ratio during transfection. We observed many antibodies with a better expression at a 2:1 light chain to heavy chain ratio although each antibody requires fine tuning for optimal expression.

Appendix

MSDS Information

MSDSs (Material Safety Data Sheets) are available on **Antibody Design Labs** website at the corresponding product page.

Quality Control

Specifications and quality control are detailed on the online product page. **Antibody Design Labs** certifies that the product will perform according to these specifications.

Technical Support

Visit **Antibody Design Labs** website at **www.abdesignlabs.com** for technical resources, including manuals, vector maps and sequences, application notes, FAQs, etc.

For more information or technical assistance, call, write, fax, or email us at:

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San Diego, CA 92117

Email: support@abdesignlabs.com
Phone: 1-877-223-3104 (Toll Free)
(Monday – Friday 9:00 AM – 5:00 PM PST)

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