ANTIBODIES

INTRODUCTION

The present disclosure relates generally to the fields of immunology and molecular biology. More specifically, provided herein are antibodies and other therapeutic proteins directed against the ADP-ribosyl cyclase 2, nucleic acids encoding such antibodies and therapeutic proteins, methods for preparing monoclonal antibodies and other therapeutic proteins, and methods for the treatment of diseases, such as cancers mediated by the ADP-ribosyl cyclase 2 expression/activity and/or associated with abnormal expression/activity of ligands therefore.

BACKGROUND OF THE INVENTION

ADP-ribosyl cyclase 2 (also known as Bone marrow stromal antigen 1 (BST1) or CD157) is a lipid-anchored, bi-functional ectoenzyme that catalyses ribonucleotide cyclisation and hydrolysis. It generates the nucleotide second messengers cyclic ADP-ribose and ADP-ribose that are capable of activating calcium release and protein phosphorylation (FEBS Lett. 1994, 356(2-3):244-8). It is able to support growth of pre-B cells in a paracrine fashion, possibly through generation of NAD+ metabolites (Proc. Natl. Acad. Sci. USA 1994, 91:5325-5329; J Biol Chem. 2005, 280:5343-5349).

ADP-ribosyl cyclase 2 and its homolog, CD38, appear to act as receptors, generating second messenger metabolites that induce intracellular Ca2+ release via the ryanodine receptor (Biochem Biophys Res Commun. 1996, 228(3):838-45). It may also act via CD11b integrin to effect Ca2+ release through the PI-3 Kinase pathway (J Biol Regul Homeost Agents. 2007;21(1-2):5-11). BST1 has not been previously reported to originate from acute myeloid leukemia (AML), breast cancer, colorectal cancer, kidney cancer, lung cancer or pancreatic cancer cell membranes and represents a protein of new therapeutic and diagnostic value. BST1 is also shown to be expressed on monocytes and granulocytes, both of which can be associated with and activated in diseases such as asthma, gout, crohns, lupus and diabetes. Monocytes are also implicated in the development of atherosclerotic plaques.

SUMMARY OF THE INVENTION

The present disclosure provides antibodies directed against the BST1, nucleic acids encoding such antibodies and therapeutic proteins, methods for preparing anti-BST1 antibodies and other therapeutic proteins, and methods for the treatment of diseases, such as the BST1 mediated disorders, e.g. human cancers, including acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia, breast cancer, colorectal cancer, kidney cancer, head and neck cancer, lung cancer, ovarian cancer, pancreatic cancer and human inflammatory diseases, including asthma, gout, crohns, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, diabetes and atherosclerotic, hereinafter referred to as 'the diseases of the invention'.

Using an antibody known to incite cell-kill via ADCC as a positive control and a human IgG1 isotype control as a negative control, the results show BST1_A2 and BST1_A2_NF were capable of eliciting ADCC on BST1-expressing A549 and U937 cells. On BST1-expressing A549 cells, BST1_A2_NF were shown to approximately 45% killing at 10nmol/L (Figure 8a). On BST1-expressing U937 cells, BST1_A2 were shown to approximately 20% killing at 1nmol/L and BST1_A2_NF were shown to approximately 45% killing at 1nmol/L (Figure 8b).

Example 8: Specificity of Monoclonal Antibodies to BST1 Determined by Flow Cytometry Analysis in AML patients

The ability of BST_A2 to bind to lymphoblasts from patients with AML was tested by Flow Cytometry Analysis. Blood was taken from 20 AML patients. Using the procedure as described in the Example3, BST_A2 was shown to bind to AML blasts of approx. 80% of the AML patients.

SEQUENCE LIST

SEQ ID No	Description	Sequence
1	aa VH_A1	MKQSTIALALLPLLFTPVAKAQVKLQQSGAELVRPGSSVKISCKASGYAFSNSWINWV KQRPGQGLEWIGQIYPGDYDTNYNGKFKGKATLTADYSSSTAYMQLNSLTSEDSAVY FCARGGSIYYGNLGFFDVWGAGTTVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCL VKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA HPASSTKVDKKIVPRDCHHHHHHH
2	aa VH_A2	MKQSTIALALLPLLFTPVAKAQAYLQQSGPELVKAGASVKMSCKASGYSFIEYTINWVK QSHGKSLEWIGNIDPYYGTTYYNQMFTGKATLTVDQSSNTAYMQLKSLTSEDSAVYF CARGSAWFPYWGQGTLVTVSAAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTK VDKKIVPRDCHHHHHHH
3	aa VK_A1	MKYLLPTAAAGLLLLAAQPAMAEMVLTQSPAIMSTSLGERVTMTCTASSRVSSSYLH WYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQY HRSPYTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK SFNRNES
4	aa VK_A2	MKYLLPTAAAGLLLLAAQPAMADIVMSQSPAIMSASPGEKVTMTCSASSSVTYMYWY QQKPGSSPRLLIYDTSNLASGVPVRFSGSGSGTSYSLTISRMEAEDTATYYCQQWSN YPLTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSF NRNES
5	nt VH_A1	acgctttgtacatggagaaaataaagtgaaacaaagcactattgcactggcactcttaccgctcttgtttaccccctgtggca aaagcccaggtgaagcttcagcagtccggggctgagctggtgaggcctgggtcctcagtgaagatttcctgcaaggctt ctggctacgcattcagtaactcctggataaactgggtgaagcagaggcctggacagggtcttgagtggattggacagatt tatcctggagattatgatactaactacaatggaaaattcaagggtaaagccacactgactgcagactacttcctccagcac agcctacatgcagctcaacagcctaacatctgaggactctgcggtctatttctgtgcaagggggggatcgatctactatggt aacctcgggttcttcgatgtctggggcgcagggaccacggtcaccgtctcctcagccaaaacgacacccccatctgtcta tccactggcccctggatctgctgcccaaactaactccatggtgaccctgggatgcctggtcaagggctatttccctgagcc

6 nt VH_A2

agtgacagtgacctggaactctggatccctgtccagcggtgtgcacaccttcccagctgtcctgcagtctgacctctacact
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ccaacctggcttctggagtcccagctcgcttcagtggcagtgggtctgggacctcttactctctcacaatcagcagcatgga
ggctgaagatgctgccacttattactgccaccagtatcatcgttccccgtacacgttcggaggggggaccaagctggaaa

7 nt VK_A1

25	nt VH_CDR3_A1	gcaaggggggatcgatctactatggtaacctcgggttcttcgatgtc
26	nt VH_CDR3_A2	gcaagaggctccgcctggtttccttac
27	nt VK_CDR1_A1	actgccagctcacgtgtaagttccagttacttgcac
28	nt VK_CDR1_A2	agtgccagctcaagtgtaacttacatgtac
29	nt VK_CDR2_A1	agtacatccaacctggcttct
30	nt VK_CDR2_A2	gacacatccaacctggcttct
31	nt VK_CDR3_A1	caccagtatcatcgttccccgtacacg
32	nt VK_CDR3_A2	cagcagtggagtaattacccactcacg
33	IGHV1-80*01 (Genebank: AC160990 Musmus) nt 138392-138424	ggctacgcattcagtagctactggatgaactgg
34	IGHV1-80*01 (Genebank: AC160990 Musmus) nt 138461-138511	ggacagatttatcctggagatggtgatactaactacaacggaaagttcaag
35	IGHV1-39*01 (Genebank: AC079181 Musmus) nt 153362-153394	ggttactcattcactgactacaacatgaactgg
36	IGHV1-39*01 (Genebank: AC079181 Musmus) nt 153431-153481	ggagtaattaatcctaactatggtactactagctacaatcagaagttcaag
37	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 496-531	actgccagctcaagtgtaagttccagttacttgcac
38	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 577-597	agcacatccaacctggcttct
39	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 691-718	caccagtatcatcgttccccaccca
40	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 523-552	agtgccagctcaagtgtaagttacatgtac
41	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 598-618	gacacatccaacctggcttct
42	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 715-739	cagcagtggagtagttacccaccca
43	ADP-ribosyl cyclase 2 (CD157; BST1)	MAAQGCAASRLLQLLLQLLLLLLLLAAGGARARWRGEGTSAHLRDIFLGRCAEYRALL SPEQRNKNCTAIWEAFKVALDKDPCSVLPSDYDLFINLSRHSIPRDKSLFWENSHLLV NSFADNTRRFMPLSDVLYGRVADFLSWCRQKNDSGLDYQSCPTSEDCENNPVDSF WKRASIQYSKDSSGVIHVMLNGSEPTGAYPIKGFFADYEIPNLQKEKITRIEIWVMHEIG GPNVESCGEGSMKVLEKRLKDMGFQYSCINDYRPVKLLQCVDHSTHPDCALKSAAA ATQRKAPSLYTEQRAGLIIPLFLVLASRTQL
44	aa 29 – 292 of ADP-ribosyl cyclase 2 (CD157; BST1)	GARARWRGEGTSAHLRDIFLGRCAEYRALLSPEQRNKNCTAIWEAFKVALDKDPCSV LPSDYDLFINLSRHSIPRDKSLFWENSHLLVNSFADNTRRFMPLSDVLYGRVADFLSW CRQKNDSGLDYQSCPTSEDCENNPVDSFWKRASIQYSKDSSGVIHVMLNGSEPTGA YPIKGFFADYEIPNLQKEKITRIEIWVMHEIGGPNVESCGEGSMKVLEKRLKDMGFQYS CINDYRPVKLLQCVDHSTHPDCALKSAAAATQRK
45	A2 VH (amino acids 21-137	QAYLQQSGPELVKAGASVKMSCKASGYSFIEYTINWVKQSHGKSLEWIGNIDPYYGT

	SEQ ID No:2)	TYYNQMFTGKATLTVDQSSNTAYMQLKSLTSEDSAVYFCARGSAWFPYWGQGTLVT VSA
46	VH1 - Humanised VH_A2	QVQLVQSGA EVKKPGASVK VSCKASGYSF IEYTINWVRQ APGQGLEWIGNIDPYYGTTYY NQMFTGRATL TVDTSISTAY MELSRLRSDDTAVYYCARGSAWF PYWGQGTLV TVSS
47	BF238102 VH	QVQLVQSGA EVKKPGASVK VSCKASGYSF TXXXXXWVRQ APGQGLEWMG XXXXXXXXXXX XXXXXXRVTL TRDTSISTAY MELSRLRSDDTAVYYCARXXXXX XXXWGQGTLV PVSS
48	A2 VL (amino acids 22-128 SEQ ID No:4)	DIVMSQSPA IMSASPGEKV TMTCSAS-SS VTYMYWYQQKPGSSPRLLIY DTSNLASGVP VRFSGSGSGT SYSLTISRMEAEDTATYYCQ QWSNYPLTFG AGTKLELK
49	VL1 - Humanised VK_A2	DIQMTQSPS SLSASVGDRV TITCSAS-SS VTYMYWYQQKPGKAPKLLIY DTSNLASGVP SRFSGSGSGT DYTLTISSLQPEDFATYYCQ QWSNYPLTFG QGTKVEIK
50	X72441 VL	DIQMTQSPS SLSASVGDRV TITCXXXXXX XXXXXWYQQKPGKAPKLLIY XXXXXXXGVP SRFSGSGSGT DFTLTISSLQPEDFATYYCX XXXXXXXXFG QGTKVEIK
51	VH1_CDR2	NIDPYYGTTYYNQMFQ
		MKQSTIALALLPLLFTPVAKAQVQLQQSRAELVMPGASVKMSCKTSGYTFSDYWVHW

59	aa VK_CDR1_A3	RASENIYSYLA
60	aa VK_CDR2_A3	NTKTLGE
61	aa VK_CDR3_A3	QHHYGTPFT
62	nt VH_CDR1_A3	ggctacacattctctgactactgggtacactgg
63	nt VH_CDR2_A3	ggagcgattgatggttctgatacttttaatgactacagtcagaagtttaag
64	nt VH_CDR3_A3	gcaagggggggccttcttcagtac
65	nt VK_CDR1_A3	cgagcaagtgaaaacatttacagttatttagca
66	nt VK_CDR2_A3	aatacaaaaaccttaggagaa
67	nt VK_CDR3_A3	caacatcattatggtactccattcacg
68	IGHV1-69*01 (AC073939)	ggctacaccttcaccagctactggatgcactgg
69	IGHV1-69*01 (AC073939)	ggagagattgatccttctgatagttatactaactacaatcaaaagttcaag
70	IGKV12-44*01 (AJ235955)	cgagcaagtgagaatatttacagttatttagca
71	IGKV12-44*01 (AJ235955)	aatgcaaaaaccttagcagaa
72	IGKV12-44*01 (AJ235955)	caacatcattatggtactcctcc

Claims

1. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), said antibody or antigen binding fragment thereof comprising:

a) a heavy chain variable region comprising:
   i) a first vhCDR comprising SEQ ID NO: 10;
   ii) a second vhCDR comprising SEQ ID NO: 12 or SEQ ID NO: 51; and
   iii) a third vhCDR comprising SEQ ID NO: 14; and

b) a light chain variable region comprising:
   i) a first vlCDR comprising SEQ ID NO: 16;
   ii) a second vlCDR comprising SEQ ID NO: 18; and
   iii) a third vlCDR comprising a SEQ ID NO: 20

2. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), said antibody or antigen binding fragment thereof comprising:

a heavy chain variable region comprising SEQ ID NO: 2, and
a light chain variable region comprising SEQ ID NO: 4.

3. An antibody according to claim 1 comprising:
a heavy chain variable region comprising SEQ ID NO: 46, and
a light chain variable region comprising SEQ ID NO: 49.

4. An isolated monoclonal antibody, or an antigen binding portion thereof, which competes for binding to BST1 with an antibody set forth in claim 1 or 2.

5. The antibody of claims 1 or 2, wherein the antibody is of an IgG1 isotype.

6. The antibody or an antigen-binding portion thereof, of claim 1 further comprising a covalently attached moiety.

7. The antibody or an antigen-binding portion thereof, according to claim 6 wherein said moiety is a drug selected from the group consisting of a maytansinoid, a dolastatin, an auristatin, a trichothecene, a calicheamicin, CC1065 and derivatives thereof.

8. The antibody or an antigen-binding portion thereof, of claim 2 further comprising a covalently attached moiety.

9. The antibody or an antigen-binding portion thereof, according to claim 8 wherein said moiety is a drug selected from the group consisting of a maytansinoid, a dolastatin, an auristatin, a trichothecene, a calicheamicin, CC1065 and derivatives thereof.

10. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the heavy chain variable region comprises SEQ ID NO: 2.

11. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the light chain variable region comprises SEQ ID NO: 4.

12. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the heavy chain variable region comprises SEQ ID NO:46

13. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the light chain variable region comprises SEQ ID NO: 49.

14. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO: 46 and a light chain variable region comprising SEQ ID NO: 49.

ANTIBODIES TO ADP-RIBOSYL CYCLASE 2

INTRODUCTION

The present disclosure relates generally to the fields of immunology and molecular biology. More specifically, provided herein are antibodies and other therapeutic proteins directed against the ADP-ribosyl cyclase 2, nucleic acids encoding such antibodies and therapeutic proteins, methods for preparing monoclonal antibodies and other therapeutic proteins, and methods for the treatment of diseases, such as cancers mediated by the ADP-ribosyl cyclase 2 expression/activity and/or associated with abnormal expression/activity of ligands therefore.

BACKGROUND OF THE INVENTION

ADP-ribosyl cyclase 2 (also known as Bone marrow stromal antigen 1 (BST1) or CD157) is a lipid-anchored, bi-functional ectoenzyme that catalyses ribonucleotide cyclisation and hydrolysis. It generates the nucleotide second messengers cyclic ADP-ribose and ADP-ribose that are capable of activating calcium release and protein phosphorylation (FEBS Lett. 1994, 356(2-3):244-8). It is able to support growth of pre-B cells in a paracrine fashion, possibly through generation of NAD+ metabolites (Proc. Natl. Acad. Sci. USA 1994, 91:5325-5329; J Biol Chem. 2005, 280:5343-5349).

ADP-ribosyl cyclase 2 and its homolog, CD38, appear to act as receptors, generating second messenger metabolites that induce intracellular Ca2+ release via the ryanodine receptor (Biochem Biophys Res Commun. 1996, 228(3):838-45). It may also act via CD11b integrin to effect Ca2+ release through the PI-3 Kinase pathway (J Biol Regul Homeost Agents. 2007;21(1-2):5-11). BST1 has not been previously reported to originate from acute myeloid leukemia (AML), breast cancer, colorectal cancer, kidney cancer, lung cancer or pancreatic cancer cell membranes and represents a protein of new therapeutic and diagnostic value. BST1 is also shown to be expressed on monocytes and granulocytes, both of which can be associated with and activated in diseases such as asthma, gout, crohns, lupus and diabetes. Monocytes are also implicated in the development of atherosclerotic plaques.

SUMMARY OF THE INVENTION

The present disclosure provides antibodies directed against the BST1, nucleic acids encoding such antibodies and therapeutic proteins, methods for preparing anti-BST1 antibodies and other therapeutic proteins, and methods for the treatment of diseases, such as the BST1 mediated disorders, e.g. human cancers, including acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia, breast cancer, colorectal cancer, kidney cancer, head and neck cancer, lung cancer, ovarian cancer, pancreatic cancer and human inflammatory diseases, including asthma, gout, crohns, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, diabetes and atherosclerotic, hereinafter referred to as 'the diseases of the invention'.

Using an antibody known to incite cell-kill via ADCC as a positive control and a human IgG1 isotype control as a negative control, the results show BST1_A2 and BST1_A2_NF were capable of eliciting ADCC on BST1-expressing A549 and U937 cells. On BST1-expressing A549 cells, BST1_A2_NF were shown to approximately 45% killing at 10nmol/L (Figure 8a). On BST1-expressing U937 cells, BST1_A2 were shown to approximately 20% killing at 1nmol/L and BST1_A2_NF were shown to approximately 45% killing at 1nmol/L (Figure 8b).

Example 8: Specificity of Monoclonal Antibodies to BST1 Determined by Flow Cytometry Analysis in AML patients

The ability of BST_A2 to bind to lymphoblasts from patients with AML was tested by Flow Cytometry Analysis. Blood was taken from 20 AML patients. Using the procedure as described in the Example3, BST_A2 was shown to bind to AML blasts of approx. 80% of the AML patients.

Claims

1. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), said antibody or antigen binding fragment thereof comprising:

a) a heavy chain variable region comprising:
   i) a first vhCDR comprising SEQ ID NO: 10;
   ii) a second vhCDR comprising SEQ ID NO: 12 or SEQ ID NO: 51; and
   iii) a third vhCDR comprising SEQ ID NO: 14; and

b) a light chain variable region comprising:
   i) a first vlCDR comprising SEQ ID NO: 16;
   ii) a second vlCDR comprising SEQ ID NO: 18; and
   iii) a third vlCDR comprising a SEQ ID NO: 20

2. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), said antibody or antigen binding fragment thereof comprising:

a heavy chain variable region comprising SEQ ID NO: 2, and
a light chain variable region comprising SEQ ID NO: 4.

3. An antibody according to claim 1 comprising:
a heavy chain variable region comprising SEQ ID NO: 46, and
a light chain variable region comprising SEQ ID NO: 49.

4. An isolated monoclonal antibody, or an antigen binding portion thereof, which competes for binding to BST1 with an antibody set forth in claim 1 or 2.

5. The antibody of claims 1 or 2, wherein the antibody is of an IgG1 isotype.

6. The antibody or an antigen-binding portion thereof, of claim 1 further comprising a covalently attached moiety.

7. The antibody or an antigen-binding portion thereof, according to claim 6 wherein said moiety is a drug selected from the group consisting of a maytansinoid, a dolastatin, an auristatin, a trichothecene, a calicheamicin, CC1065 and derivatives thereof.

8. The antibody or an antigen-binding portion thereof, of claim 2 further comprising a covalently attached moiety.

9. The antibody or an antigen-binding portion thereof, according to claim 8 wherein said moiety is a drug selected from the group consisting of a maytansinoid, a dolastatin, an auristatin, a trichothecene, a calicheamicin, CC1065 and derivatives thereof.

10. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the heavy chain variable region comprises SEQ ID NO: 2.

11. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the light chain variable region comprises SEQ ID NO: 4.

12. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the heavy chain variable region comprises SEQ ID NO:46

13. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises heavy and light chain variable regions, and wherein the light chain variable region comprises SEQ ID NO: 49.

14. An isolated antibody or antigen binding fragment thereof that specifically binds to bone marrow stromal antigen 1 (BST1), wherein said antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO: 46 and a light chain variable region comprising SEQ ID NO: 49.

SEQUENCE LIST

SEQ ID No	Description	Sequence
1	aa VH_A1	MKQSTIALALLPLLFTPVAKAQVKLQQSGAELVRPGSSVKISCKASGYAFSNSWINWV KQRPGQGLEWIGQIYPGDYDTNYNGKFKGKATLTADYSSSTAYMQLNSLTSEDSAVY FCARGGSIYYGNLGFFDVWGAGTTVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCL VKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA HPASSTKVDKKIVPRDCHHHHHHH
2	aa VH_A2	MKQSTIALALLPLLFTPVAKAQAYLQQSGPELVKAGASVKMSCKASGYSFIEYTINWVK QSHGKSLEWIGNIDPYYGTTYYNQMFTGKATLTVDQSSNTAYMQLKSLTSEDSAVYF CARGSAWFPYWGQGTLVTVSAAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTK VDKKIVPRDCHHHHHHH
3	aa VK_A1	MKYLLPTAAAGLLLLAAQPAMAEMVLTQSPAIMSTSLGERVTMTCTASSRVSSSYLH WYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQY HRSPYTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK SFNRNES
4	aa VK_A2	MKYLLPTAAAGLLLLAAQPAMADIVMSQSPAIMSASPGEKVTMTCSASSSVTYMYWY QQKPGSSPRLLIYDTSNLASGVPVRFSGSGSGTSYSLTISRMEAEDTATYYCQQWSN YPLTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSF NRNES
5	nt VH_A1	acgcttgtacatggagaaaataaagtgaaacaaagcactattgcactggcactcttaccgcctctatttacccctgtggca aaagcccaggtgaagcttcagcagtccggggctgagctggtgaggcctgggtcctcagtgaagatttcctgcaaggctt ctggctacgcattcagtaactccttggataaactgggtgaagcagaggcctggacagggtcttgagtggattggacagatt tatcctggagattatgatactaactacaatggaaaattcaagggtaaagccacactgactgcagactcatcctccagcac agcctacatgcagctcaacagcctaacatctgaggactctgcggtctatttctgtgcaagggggggatcgatctactatggt aacctcgggttcttcgatgtctgggcgcagggaccacggtcaccgtctcctcagccaaaacgacaccccccatctgtcta tccactggccctggatctgctgcccaaactaactccatggtgaccctgggatgcctggtcaagggctatttcccgagcc
6	nt VH_A2	atgaaacagagcactattgcactggcactcttaccgcctctatttacccctgtggcaaaagcccaggtgaagcttcagcag tccggggctgagctggtgaggcctgggtcctcagtgaagatttcctgcaaggcttctggctacgcattcagtaactcctt ggataaactgggtgaagcagaggcctggacagggtcttgagtggattggacagattttatcctggagattatgatactaa ctacaatggaaaattcaagggtaaagccacactgactgcagactcatcctccagcacagcctacatgcagctcaacagc ctaacatctgaggactctgcggtctatttctgtgcaagggggggatcgatctactatggtaacctcgggttcttcgatgt ctgggcgcagggaccacggtcaccgtctcctcagccaaaacgacaccccccatctgtctatccactggccctggatctg ctgcccaaactaactccatggtgaccctgggatgcctggtcaagggctatttcccgagcc

ที่ นม ๑๖๐๐๑/ว ๑๔๔๑

ศูนย์ดำรงธรรม ๑๗ จังหวัด

ตามที่ สำนักงานปลัดกระทรวงมหาดไทย ได้ขอความร่วมมือจังหวัดนครราชสีมา ในการเป็นเจ้าภาพจัดงานวันดำรงธรรม ประจำปี ๒๕๖๗ ในวันที่ ๑๖ พฤศจิกายน ๒๕๖๗ ณ ศูนย์ราชการจังหวัดนครราชสีมา นั้น

จังหวัดนครราชสีมา ได้ดำเนินการจัดงานวันดำรงธรรม ประจำปี ๒๕๖๗ เรียบร้อยแล้ว ในการนี้ จึงขอขอบคุณจังหวัดที่ได้ส่งคณะเข้าร่วมงานวันดำรงธรรม ประจำปี ๒๕๖๗ ในครั้งนี้ ทั้งนี้ ขอให้ศูนย์ดำรงธรรมทุกจังหวัดได้ร่วมกันประชาสัมพันธ์ผลการดำเนินงานของศูนย์ดำรงธรรมให้ประชาชนได้รับทราบอย่างต่อเนื่อง เพื่อสร้างความเชื่อมั่นและความไว้วางใจให้แก่ประชาชนในการมาใช้บริการศูนย์ดำรงธรรม

จึงเรียนมาเพื่อทราบ

ขอแสดงความนับถือ

(นายวิทยา ศรีสุข)

ผู้ว่าราชการจังหวัดนครราชสีมา

ศูนย์ดำรงธรรม

โทร. ๐ ๔๔๒๑ ๗๗๐๐

โทรสาร ๐ ๔๔๒๑ ๗๗๐๑

25	nt VH_CDR3_A1	gcaagggggggatgcgactacgtaggtaaccccgggttctacgatgtc
26	nt VH_CDR3_A2	gcaagaggatcgcgctggttcctac
27	nt VK_CDR1_A1	actgccagtcaaagtgtaagttccagttacttgcac
28	nt VK_CDR1_A2	agtgccagctcaagtgtaacttacatgtac
29	nt VK_CDR2_A1	aggacatccaacctggctct
30	nt VK_CDR2_A2	gacacatccaaactggctct
31	nt VK_CDR3_A1	cagcaggattatagttccccgctcacg
32	nt VK_CDR3_A2	cagcaggggaggtaataccccactcacg
33	IGHV1-80*01 (Genebank AC160990 Musmus) nt 138322-138424	ggctacgcattcagtagctacggtatgagctgg
34	IGHV1-80*01 (Genebank AC160990 Musmus) nt 136451-136511	ggctcagattatactggagagggtatcctaactacaacgggaagttcaag
35	IGHV1-39*01 (Genebank AC079181 Musmus) nt 153352-153394	ggtctccattcactgactacgcagtgagctgg
36	IGHV1-39*01 (Genebank AC079181 Musmus) nt 153431-153481	ggagtaatcaatcctaactatggtagcactagctccaatcgcgagttcaag
37	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 480-531	actgcaagtcaaagtgtaagtcccagttatttgtac
38	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 577-597	agcacatccaacctggctct
39	IGKV4-74*01 (Genebank: AJ231217 Musmus) nt 681-710	cagcagtatcatagttccccgtacacg
40	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 523-552	agtgccagctcaagtgtaagttacatgtac
41	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 589-618	gacacatccaacctggctct
42	IGKV4-55*01 (Genebank: AJ231225 Musmus) nt 715-739	cagcaggggaggtaccccacca
43	ADP-ribosyl cyclase 2 (CD157; BST1)	MAAQGCAASRLLQLLLCLLLLLLLLAAGGARARVHGEGTSAHLRDIFLGRCAEYRALL SPEQRNKNCTAIVEAFKVALDKDPCSVLPSDYDLFINLSRHSIPRDKSLFWENSHLLV NSFADNTRRFMPLSDVLYGRVADFLSWCRQKNDSGLDYQSCPTSEDCENNPVDSF WKRASIQYSKDSSGVIHVMLNGSEPTGAYPIKGFFADYEIPNLQKEKITRIEWVMHEIG GPNVESCGEGSIMKVLEKRLKDMGFQYSCINDYRPVKLLQCVDHSTHPDCALKSAAA ATQRKAPSLYTECRAGLIIPLFLVLASRTQL
44	aa 29 - 292 of ADP-ribosyl cyclase 2 (CD157; BST1)	GARARVVRGEGTSAHLRDIFLGRCAEYRALLSPEQRNKNCTAIVEAFKVALDKDPCSV LPSDYDLFINLSRHSIPRDKSLFWENSHLLVNSFADNTRRFMPLSDVLYGRVADFLSW CRQKNDSGLDYQSCPTSEDCENNPVDSFWKRASIQYSKDSSGVIHVMLNGSEPTGA YPIKGFFADYEIPNLQKEKITRIEWVMHEIGGPNVESCGEGSIMKVLEKRLKDMGFQYS CINDYRPVKLLQCVDHSTHPDCALKSAAAATQRK
45	A2 VH (amino acids 21-137	QAYLQQSGPELVKAGASVKMSCKASGYSFIEYTINWVKQSHGKSLEWIGNIDPYYGT

	SEQ ID No:2)	TYYNQMFTGRATLTVDQSSNTAYMQLKSLTSEDSAVYFCARGSAWFPYWGQGTLVT VSA
46	VH1 - Humanised VH_A2	QVQLVQSGA EVKKPGASVK VSCKASGYSF IEYTINWVRQ APGQGLEWIGNIDPYYGTTYY NQMFTGRATL TVDTSISTAY MELSRLRSDDTAVYYCARGSAWF PYWGQGTLV TVSS
47	BF230102 VH	QVQLVQSGA EVKKPGASVK VSCKASGYSF TXXXXXWVRQ APGQGLEWMG XXXXXXXXXXX XXXXXXRVTL TRDTSISTAY MELSRLRSDDTAVYYCARXXXXX XXXWGQGTLV PVSS
48	A2 VL (amino acids 22-128 SEQ ID No:4)	DIVMSQSPA IMSASPGEKV TMTCSAS-SS VTYMYWYQQKPGSSPRLLIY DTSNLASGVP VRFSGSGSGT SYSLTISRMEAEDTATYYCQ QWSNYPLTFG AGTKLELK
49	VL1 - Humanised VK_A2	DIQMTQSPS SLSASVGDRV TITCSAS-SS VTYMYWYQQKPGKAPKLLIY DTSNLASGVP SRFSGSGSGT DYTLTISSLQPEDFATYYCQ QWSNYPLTFG QGTKVEIK
50	X72441 VL	DIQMTQSPS SLSASVGDRV TITCXXXXXX XXXXXWYQQKPGKAPKLLIY XXXXXXXGVP SRFSGSGSGT DFTLTISSLQPEDFATYYCX XXXXXXXXFG QGTKVEIK
51	VH1_CDR2	NIDPYYGTTYYNQMFQ
52	aa VH_A3	MKQSTIALALLPLLFTPVAKAQVQLQQSRAELVMPGASVKMSCKTSGYTFSDYWVHW VRQRPGQGLEWIGAIDGSDTFNDYSQKFKGRATLTVDESSSTVYMQLSSLTSEDSAV YYCARGGLLGYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFP

59	aa VK_CDR1_A3	RASENIYSYLA
60	aa VK_CDR2_A3	NTKTLGE
61	aa VK_CDR3_A3	QHHYGTPFT
62	nt VH_CDR1_A3	ggxxacacattctctgactactggctacactgg
63	nt VH_CDR2_A3	ggatcgatttgatggtaatgttaatattaatgatcctacattcaagggcgaagttaag
64	nt VH_CDR3_A3	gcaagggggggcctttactatggtatc
65	nt VK_CDR1_A3	cgagcaagtgaaaacattttacagttatttagca
66	nt VK_CDR2_A3	aatactaaaacctctggagaa
67	nt VK_CDR3_A3	caacatcattatgggactccattcacg
68	IGHV1-69*01 (AC073389)	ggxxacacattctctgactactggatgcactgg
69	IGHV1-69*01 (AC073389)	ggatcgatttgatggtaatgttaatattaatgatcctacattcaagggcgaagttaag
70	IGKV12-44*01 (AJ235955)	cgagcaagtgagaacattttacagttatttagca
71	IGKV12-44*01 (AJ235955)	aatgctaaaacctctggagaa
72	IGKV12-44*01 (AJ235955)	caacatcattatgggactccctc