Figure 1: Lists of preferred residues

A: List of the preferred CDR positions, of which all positions or a subset should be diversified to form the two binding regions in the most preferred dual targeting antibodies (all numbering according to Kabat)

Group "Lib1" = VL24, VL25, VL26, VL27, VL28[#], VL29[##], VL93, VL94, VL95[$], VL95a[$], VL95b[$], VH58, VH59, VH60, VH61, VH62, VH63, VH64, VH65
Group "Lib2" = VH26*, VH27*, VH28*, VH29*, VH30*, VH31, VH32, VH94**, VH96-VH99, VH102, VL49**, VL53, VL54, VL55, VL56

This residue having number 28 in the Kabat nomenclature assumes that CDR-L1 length is 11; if the length is 10, then the residue number is 29; if the length is 12 or more, then the residue number is 27a.
This residue having number 29 in the Kabat nomenclature assumes that CDR-L1 length is 11; if the length is 10, then the residue number is 30; if the length is 12, then the residue number is 28; if the length is 13 or more, then the residue number is 27b.
$ Only in case of libraries comprising Vlambda light chains
* These residues are not included in the Kabat definition of CDR residues (Kabat et al., 1991), but they are included in the Chothia definition of CDR residues (Chothia et al., 1992), and they are included in our definition of CDR residues.
** These residues are not included in the Kabat definition of CDR residues (Kabat et al., 1991), but they are included in the Contact definition of CDR residues (MacCallum et al., 1996), and they are included in our definition of CDR residues.

B: List of preferred enhancing positions that can be diversified in some library designs to enhance the properties of the two binding regions in the novel dual targeting antibodies (all numbering according to Kabat)

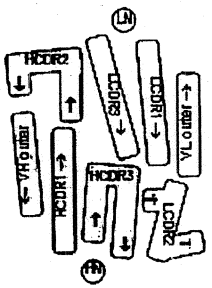
Group "Lib1E" = VL1, VL2, VL3, VL69, VL70, VL100, VH46
Group "Lib2E" = VH1, VH2, VH3, VH25, VH76, VH105, VL45, VL57, VL58

C: List of preferred CDR positions, of which all positions or a subset is preferably left invariant or subjected to restricted diversification in both Lib1 and Lib2 library designs, to create an antibody core region that allows the two binding regions comprising Lib1 and Lib2 residues to behave independently (all numbering according to Kabat)

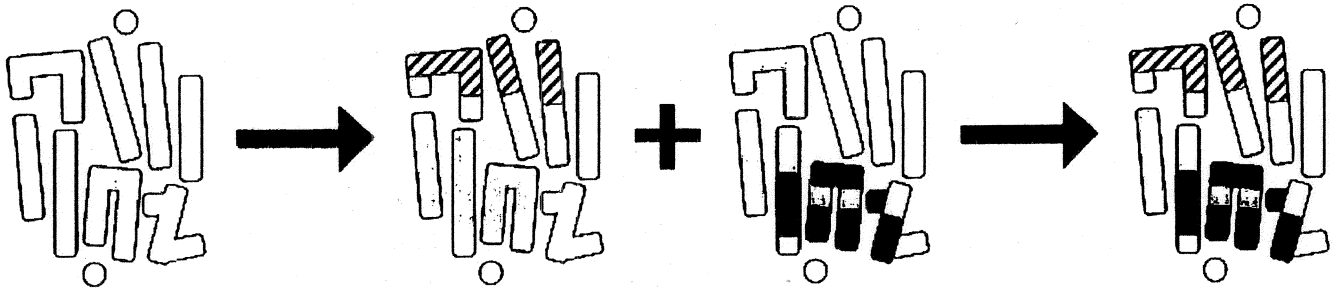
VL residues = VL32, VL33, VL34, VL50, VL51, VL52, VL89, VL90, VL91, VL96
VH residues = VH33, VH34, VH35, VH50, VH51, VH52, VH52a, VH52b if present, VH52c if present, VH53, VH54, VH55, VH57, VH95, and the residue directly before VH101 (which can have variable numbering depending on HCDR3 length)

Figure 2: Novel discovery process

A) Schematic illustration of a heterodimeric VH-VL antibody variable domain (top view):



B) Method of Discovery:



C) Residue Definitions:

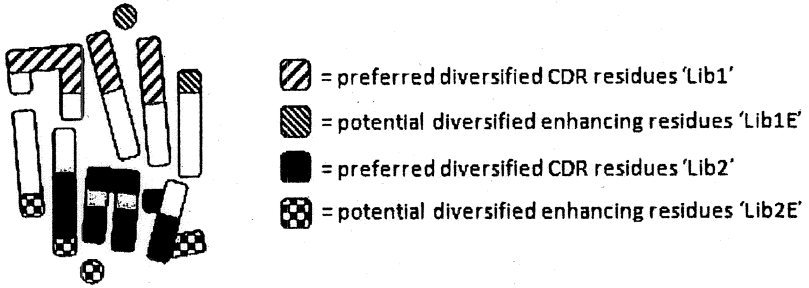


Figure 3: Library Designs

X = diversified position

```
                                10        20        30        40        50        60        70        80        90       100
                     ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|...
Dummy 1 VK           DTQMTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPKLLIYAASSLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSLPYTFGQGTKVEIKR
Lib D1L1 VK          XXQMTQSPSSLSASVGDRVTITCRXXXXXSSYLAWYQQKPGKAPKLLIYAASSLYSGVPSRFSGSGSGXXFTLTISSLQPEDFATYYCQQYSXLPYTFGQGTKVEIKR
Lib D1L2 VK          XXXMTQSPSSLSASVGDRVTITCRXXXXXSSYLAWYQQKPGKAPKLLIYAASSLYSGVPSRFSGSGSGXXFTLTISSLQPEDFATYYCQQYSXXPYTFGQGTKVEIKR

                                10        20        30        40        50        60        70        80        90       100       110
                     ....|....|....|....|....|....|....|....|....|..a..|....|....|....|....|....|..abc..|....|....|....|....|....|...
Dummy 1 VH           EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWIRQAPGKGLEWIGQISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYFDIWGQGTLVTVSS
Lib D1L1 VH          EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWIRQAPGKGLEWIGQISGSGGSTXYXXXXXGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYFDIWGQGTLVTVSS
Lib D1L2 VH          EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWIRQAPGKGLXWIGQISGSGGSTXYXXXXXGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYFDIWGQGTLVTVSS

                                10        20        30        40        50        60        70        80        90       100
                     ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|...
Dummy 1 VK           DTQMTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPKLLIYAASSLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSLPYTFGQGTKVEIKR
Lib D1H1 VK          DTQMTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPXLLIXAASXLXXXXPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSLPYTFGQGTKVEIKR
Lib D1H2 VK          DTQMTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPXLLIXAASXLXXXXPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSLPYTFGQGTKVEIKR
Lib D1H3 VK          DTQMTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPKLLIXAASXLXXXXPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSLPYTFGQGTKVEIKR

                                10        20        30        40        50        60        70        80        90       100       110
                     ....|....|....|....|....|....|....|....|....|..a..|....|....|....|....|....|..abc..|....|....|....|....|....|...
Dummy 1 VH           EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWIRQAPGKGLEWIGQISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYFDIWGQGTLVTVSS
Lib D1H1 VH          XXQLVESGGGLVQPGGSLRLSCAAXGFXFSXYAMSWIRQAPGKGLEWIGQISGSGGSTYYNDNVLGRFTISRDNSKXTLYLQMNSLRAEDTAVYYCAXDSGYFDXWGQGTLVTVSS
Lib D1H2 VH          XXXLVESGGGLVQPGGSLRLSCAAXGXXXSXYAMSWIRQAPGKGLEWIGQISGSGGSTYYNDNVLGRFTISRDNSKXTLYLQMNSLRAEDTAVYYCARDSGYFDXWGQGTLVTVSS
Lib D1H3 VH          XXQLVESGGGLVQPGGSLRLSCAASGXXXSXXAMSWIRQAPGKGLEWIGQISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDXGXFDXWGQGTLVTVSS

                                     20        30        40        50        60        70        80        90       100
                     ....|........|....|....|..ab..|....|....|....|....|....|....|....|....|....|....|....|ab....|....|..
Dummy 2 VL           SSVLTQPPSVSGAPGQRVTISCSGSSSNIGSNTVSWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCAAWDDSLNGYVFGTGTKVTVL
Lib D2L1 VL          XXVLTQPPSVSGAPGQRVTISCSGXXXNIGXNTVSWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGXSASLAITGLQSEDEADYYCAAWDXXXXGYVFGTGTKVTVL

                                10        20        30        40        50        60        70        80        90                 110
                     ....|....|....|....|....|....|....|....|....|..a..|....|....|....|....|....|..abc..|....|....|.........|....|...
Dummy 2 VH           EVQLVESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVGTISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARTSSGYFDYWGQGTLVTVSS
Lib D2L1 VH          EVQLVESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVGTISGSGGSTXYXXXXXGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARTSSGYFDYWGQGTLVTVSS

                                     20        30        40        50        60        70        80        90       100
                     ....|........|....|....|..ab..|....|....|....|....|....|....|....|....|....|....|....|ab....|....|..
Dummy 2 VL           SSVLTQPPSVSGAPGQRVTISCSGSSSNIGSNTVSWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCAAWDDSLNGYVFGTGTKVTVL
Lib D2H1 VL          SSVLTQPPSVSGAPGQRVTISCSGSSSNIGSNTVSWYQQLPGTAPKLLIXGNNXRXXXXPDRFSGSKSGTSASLAITGLQSEDEADYYCAAWDDSLNGYVFGTGTKVTVL

                                10        20        30        40        50        60        70        80        90       100       110
                     ....|....|....|....|....|....|....|....|....|..a..|....|....|....|....|....|..abc..|....|....|....|....|....|...
Dummy 2 VH           EVQLVESGGGLVQPGGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVGTISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARTSSGYFDYWGQGTLVTVSS
Lib D2H1 VH          XXQLVESGGGLVQPGGSLRLSCAASGXXXSXXYMSWVRQAPGKGLEWVGTISGSGGSTYYNDNVLGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAXTXXGXFDXWGQGTLVTVSS
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Figure 4: Examples of bi-specific antibodies

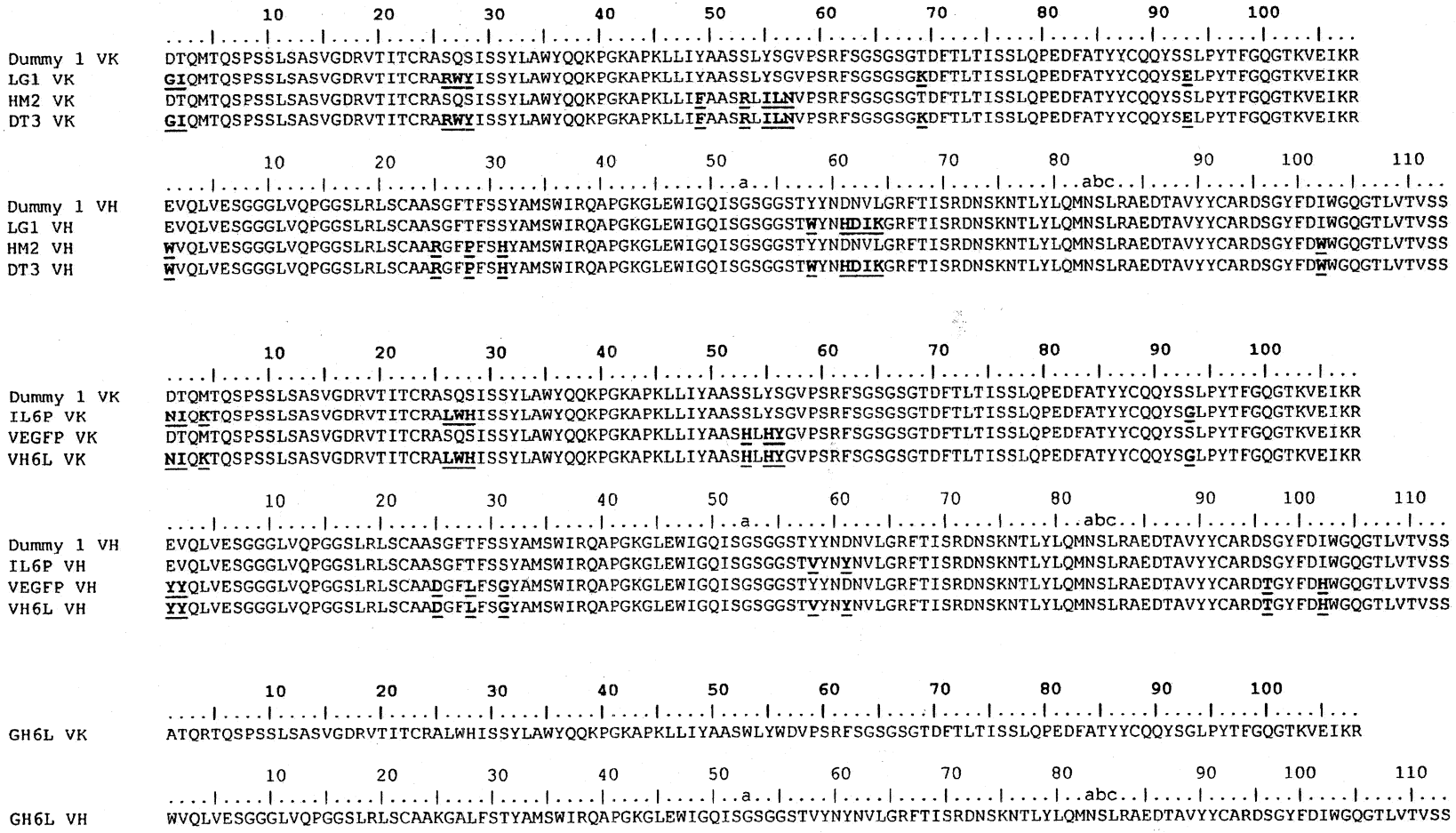
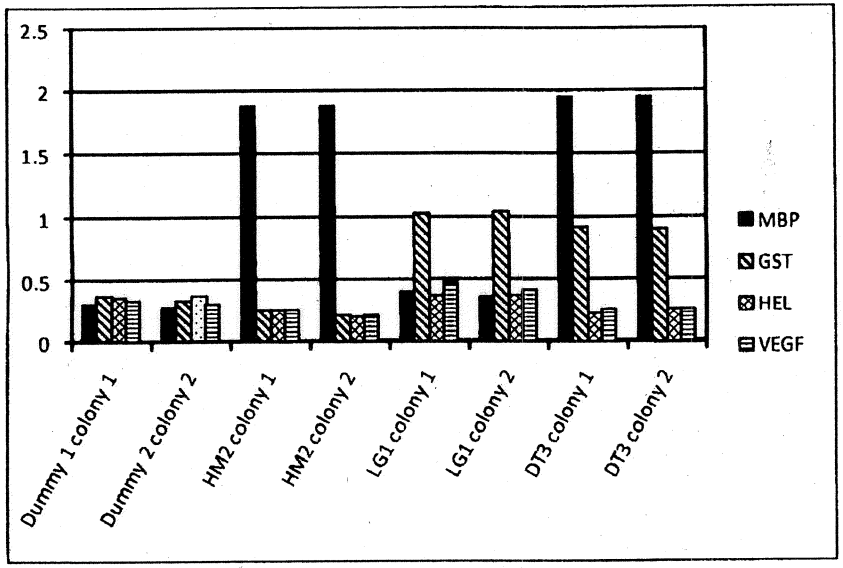


Figure 5: ELISA data of anti-MBP anti-GST dual targeting Fab clone DT3, using Dummy 1 Fab and irrelevant targets HEL and VEGF as controls

A: Heavy chain of Fab detected with anti-Strep tag antibody



B: Light chain of Fab detected with anti-human kappa antibody

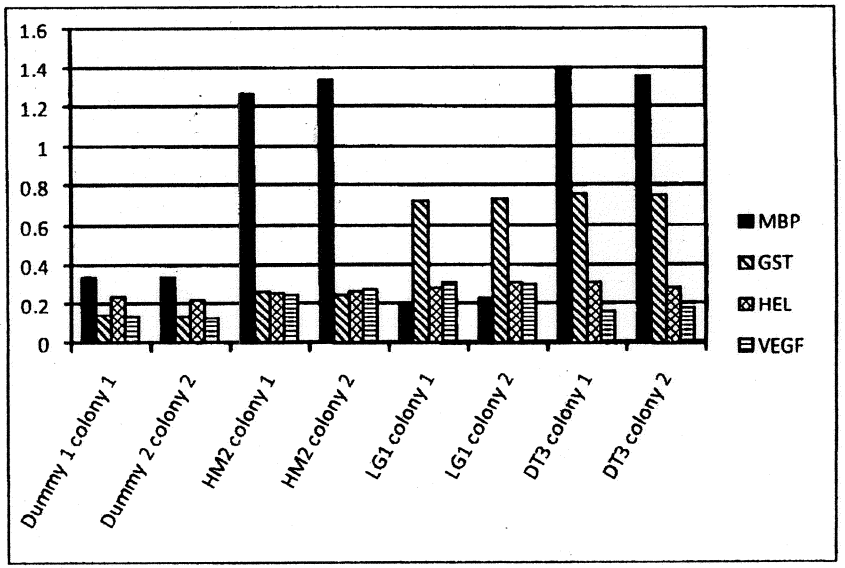


Figure 6: Biacore™ data of anti-MBP / anti-GST dual targeting Fab clone DT3

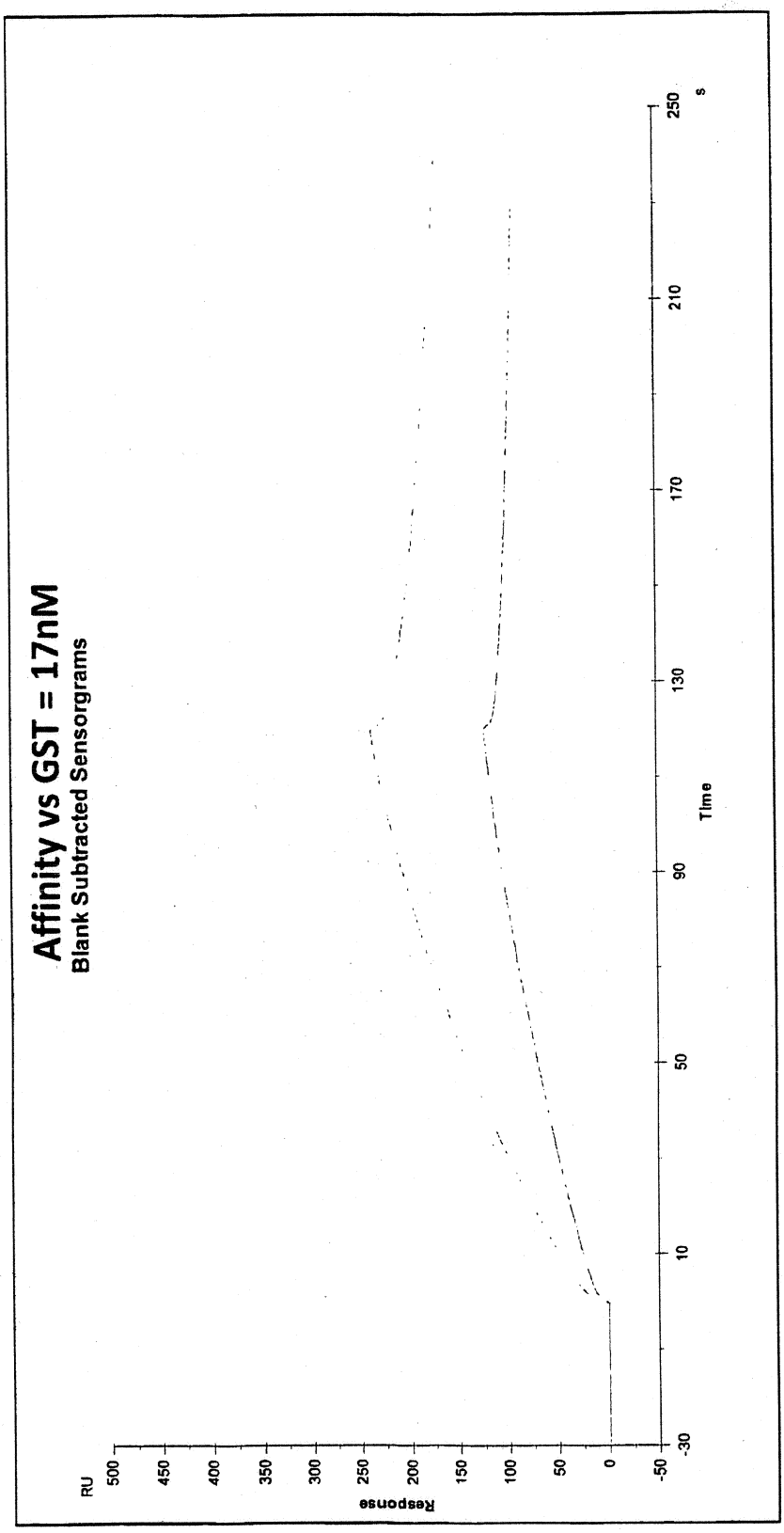
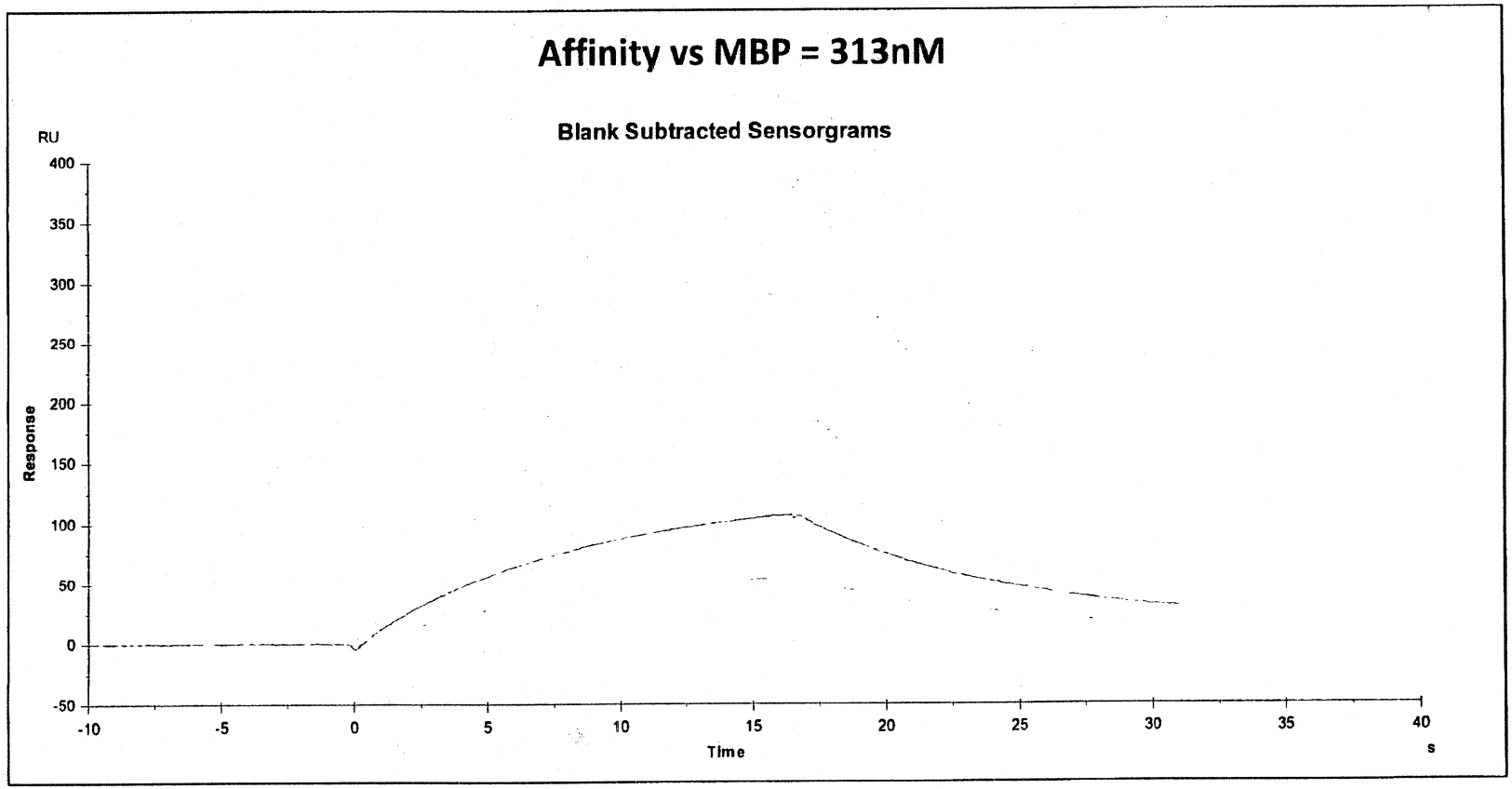


Figure 6: Biacore™ data of anti-MBP / anti-GST dual targeting Fab clone DT3 (contd.)



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Figure 7: Biacore™ analysis of parental and bi-specific antibodies against VEGF and IL6

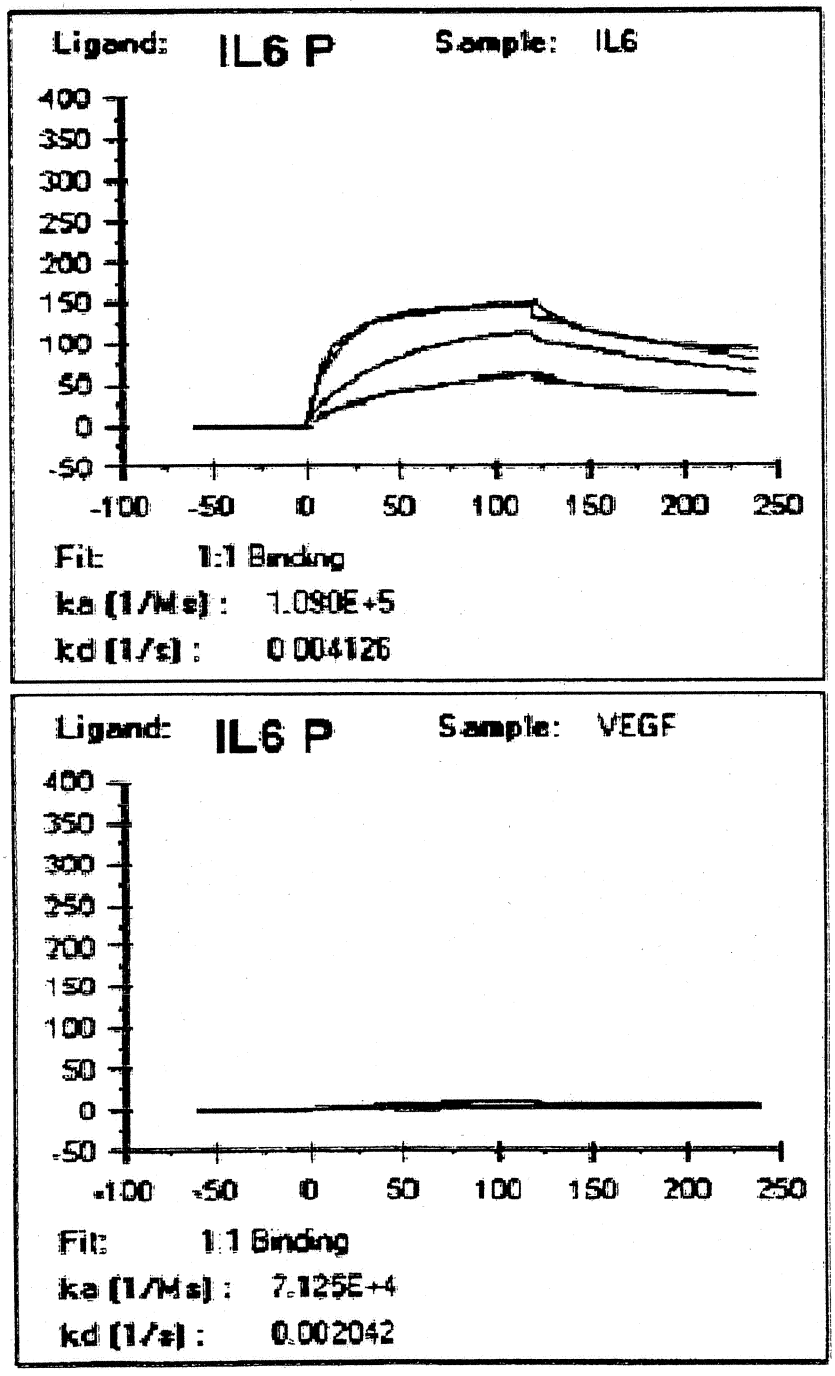


Figure 7: Biacore™ analysis of parental and bi-specific antibodies against VEGF and IL6 (contd.)

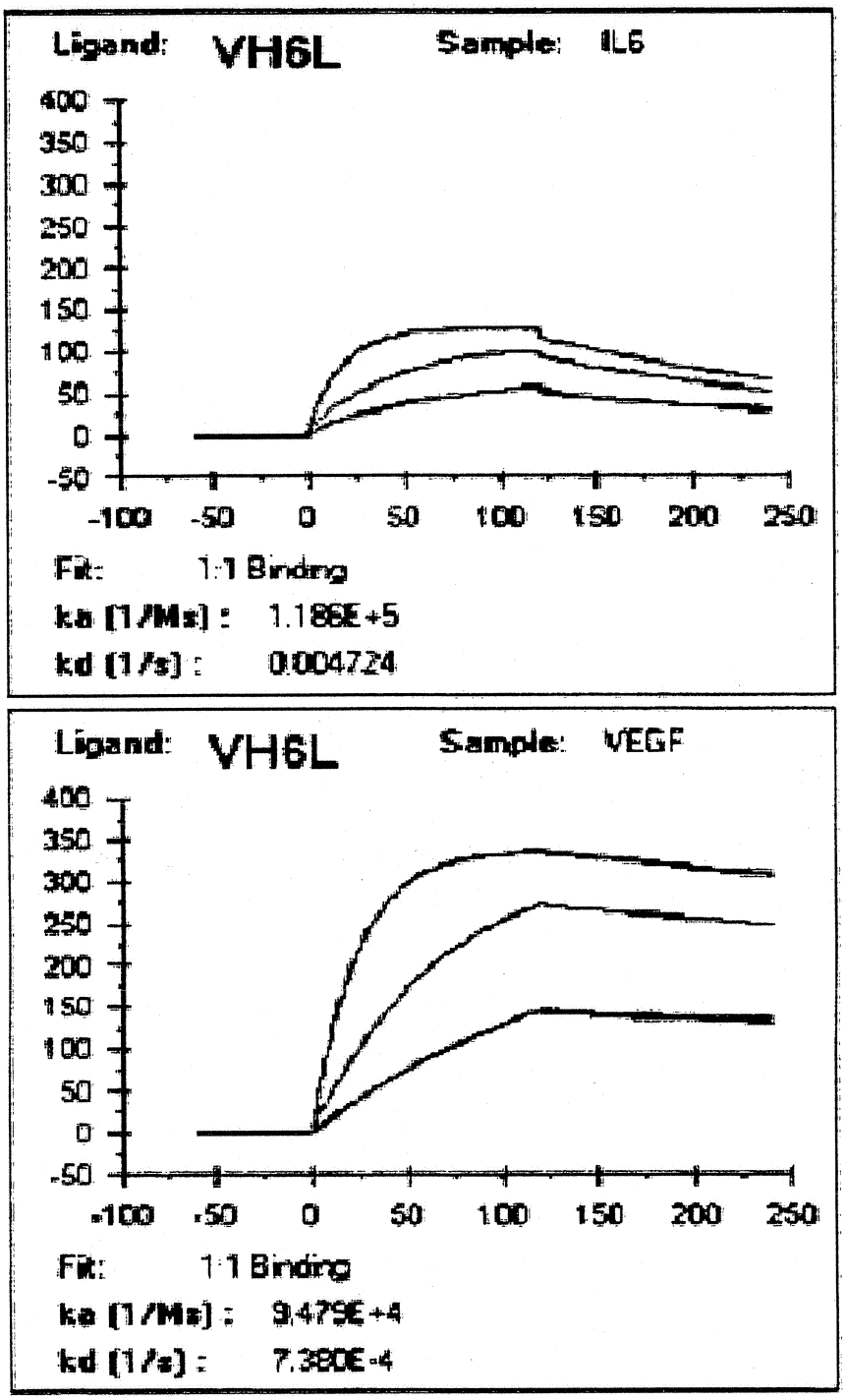


Figure 7: Biacore™ analysis of parental and bi-specific antibodies against VEGF and IL6 (contd.)

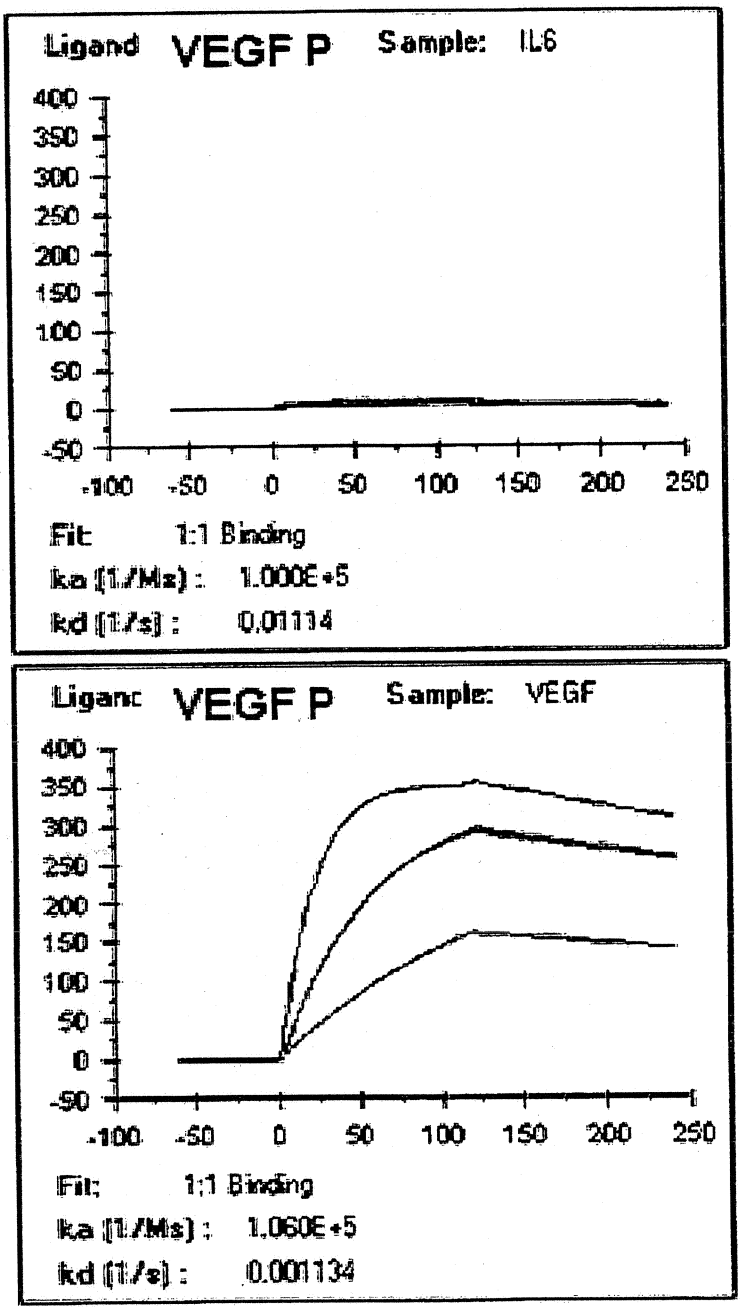


Figure 8:

A: Co-binding of GMCSF + Antibody + IL6

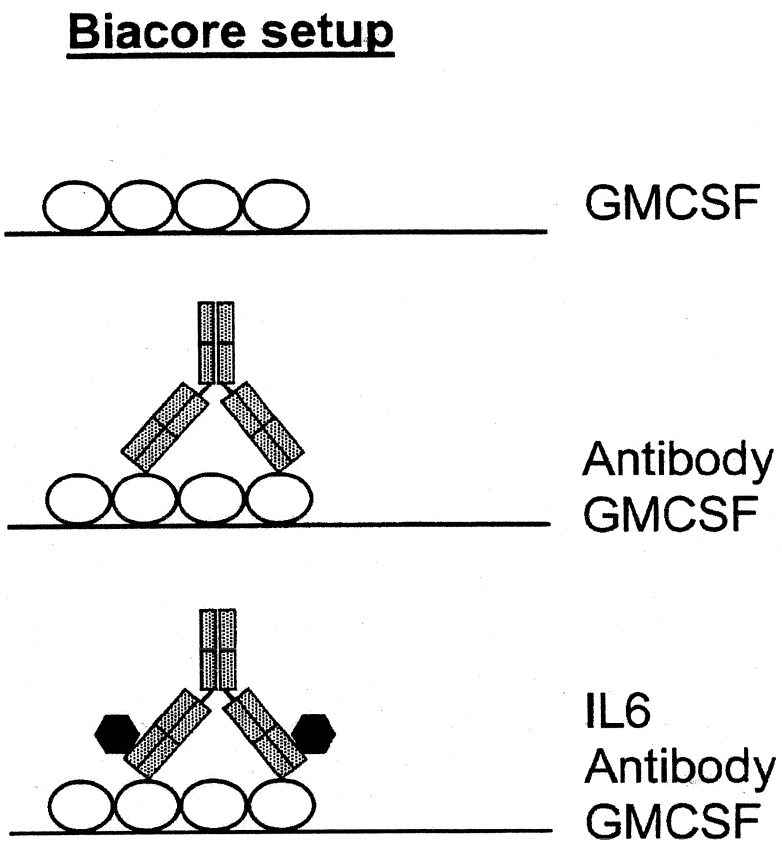
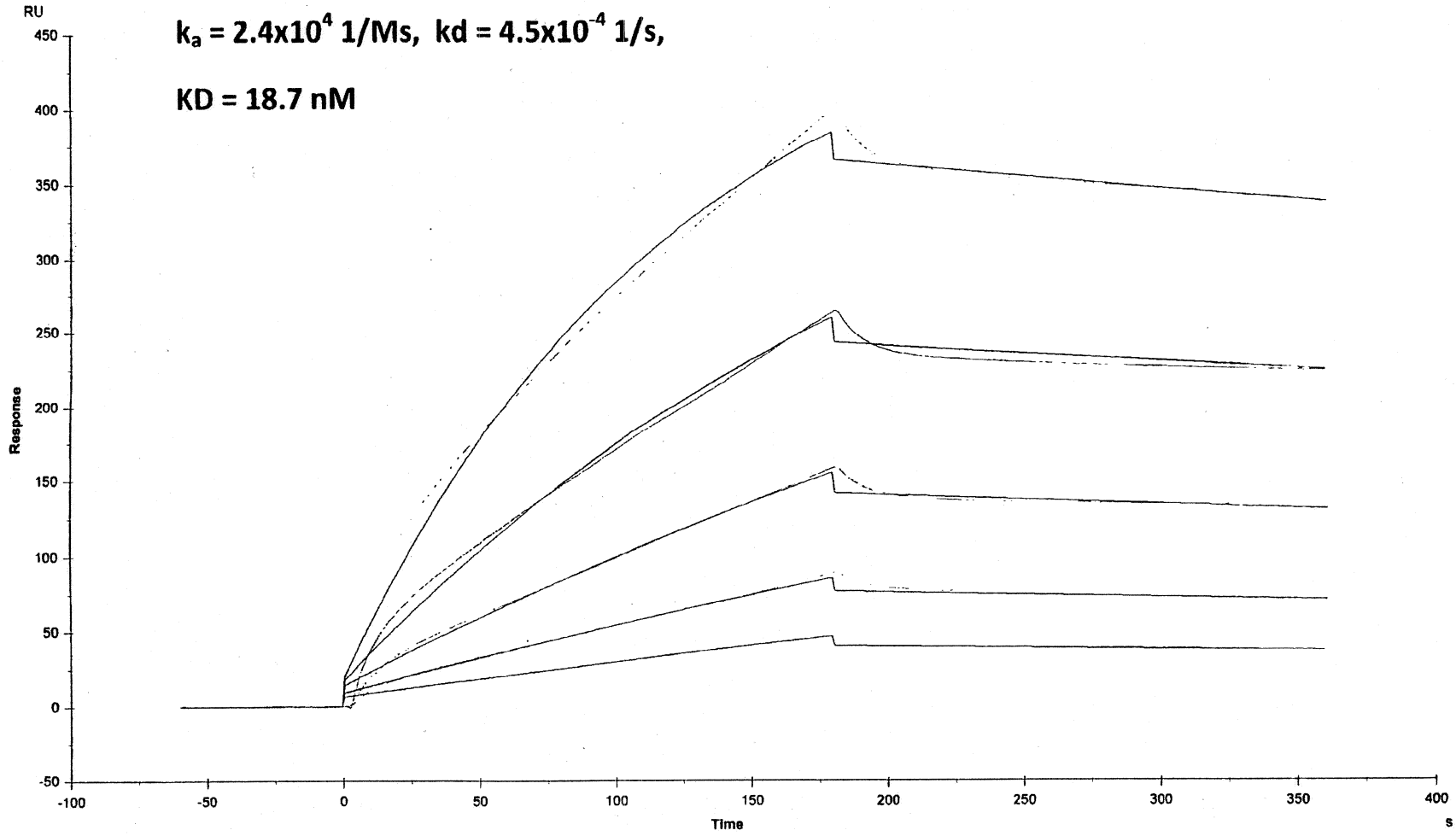


Fig. 8 A: Co-binding of GMCSF + Antibody + IL6 (contd.)



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Figure 8:

B: Co-binding of anti-LC + Antibody + IL6

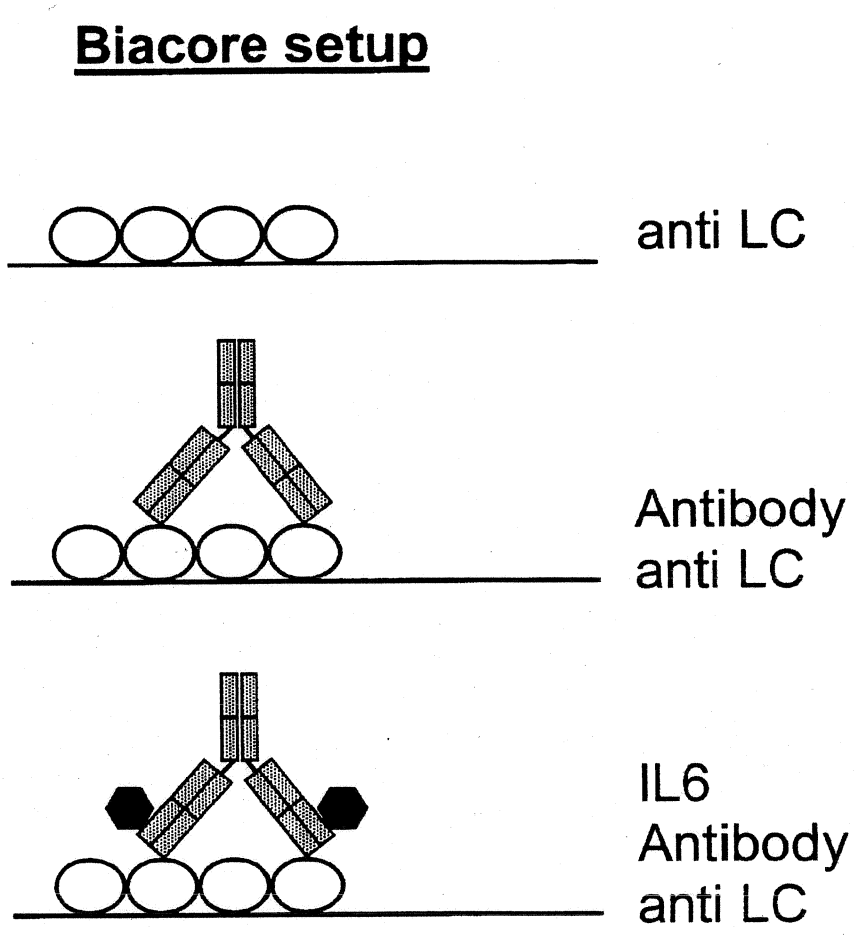


Fig. 8 B: Co-binding of anti-LC + Antibody + IL6 (contd.)

