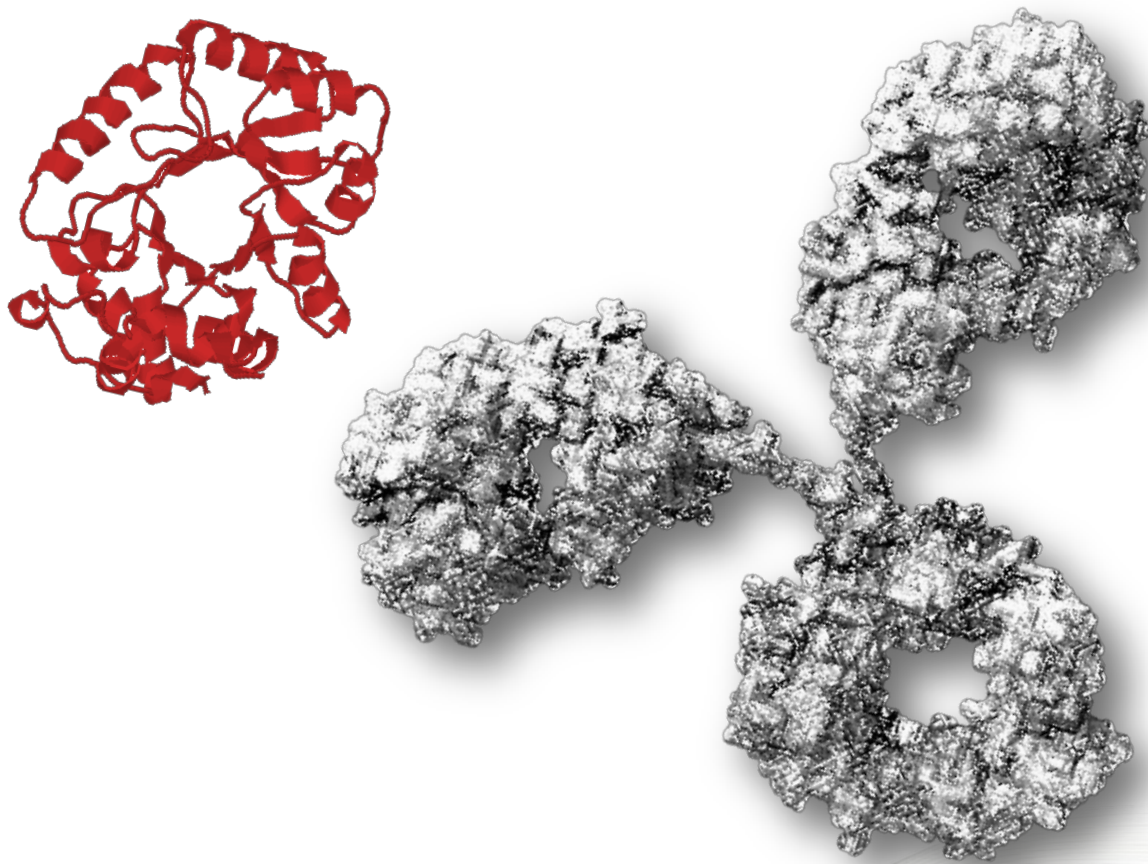


Biosimilar Drug Targets

All proteins validated in binding assay against reference drugs



Introduction

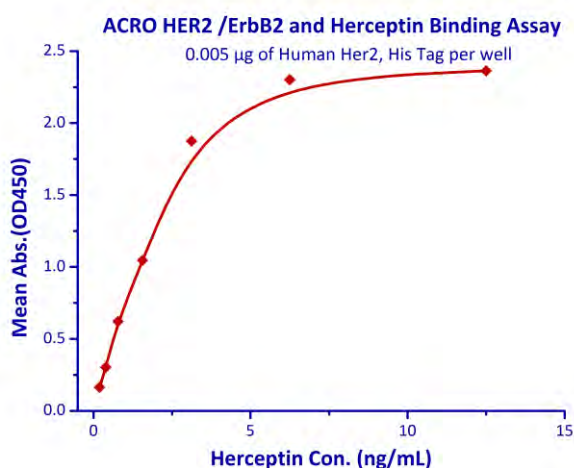
Biosimilars are biologic drugs that are “highly similar” to a previously approved biologic (also known as reference innovator product). A biosimilar must undergo stringent similarity testing at every step of its development to demonstrate that potential differences from the reference product are not clinically meaningful, with regard to quality, safety, and efficacy [EMA], or safety, purity, and potency [FDA].

The binding between a biosimilar and its target antigen (and Fc receptors) is considered an important indicator to its efficacy. ACROBiosystems has developed high quality target antigen proteins and Fc receptors to facilitate biosimilar research.

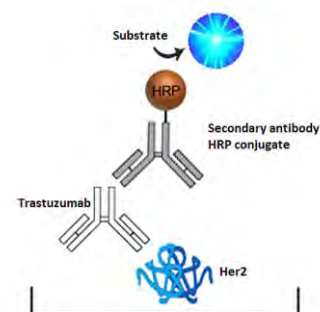
Validated with Reference Innovator Drugs

Most target antigens and Fc receptors offered by ACROBiosystems have been validated with the reference innovator drugs in functional ELISA, BLI, or SPR. The reference innovator drugs include Herceptin[®], Avastin[®], MabThera[®], Erbitux[®] and Humira[®], which are purchased from Roche, Merck KGaA, and AbbVie, respectively.

Her2 Antigen Binding Affinity was Determined by ELISA Using Trastuzumab (Herceptin[®])

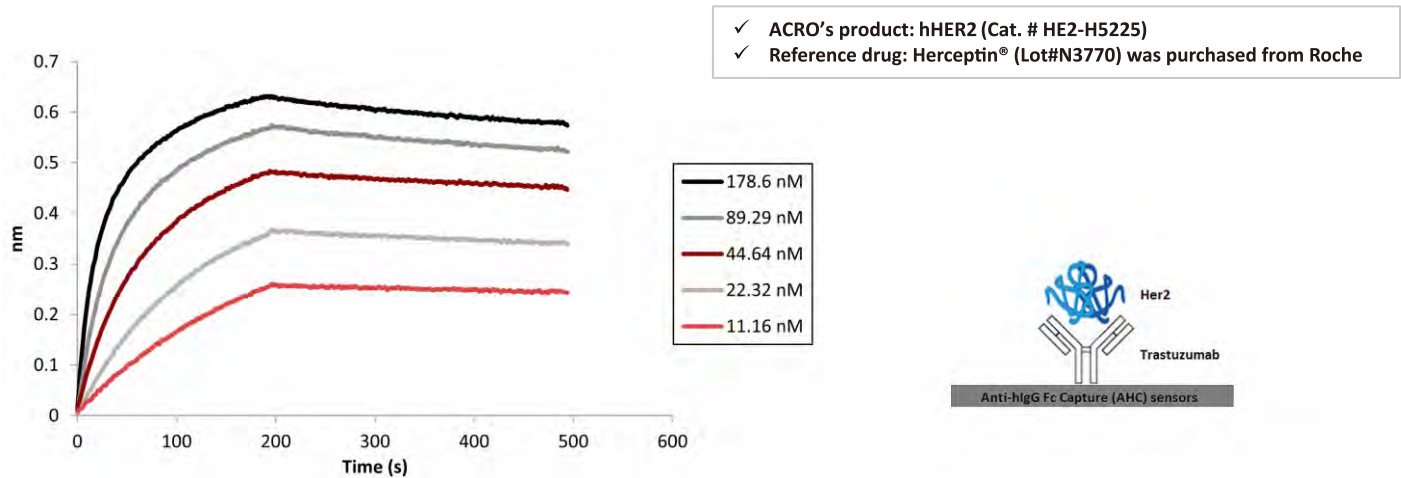


- ✓ ACRO's product: hHER2 (Cat. # HE2-H5225)
- ✓ Reference drug: Herceptin[®] (Lot#N3770) was purchased from Roche



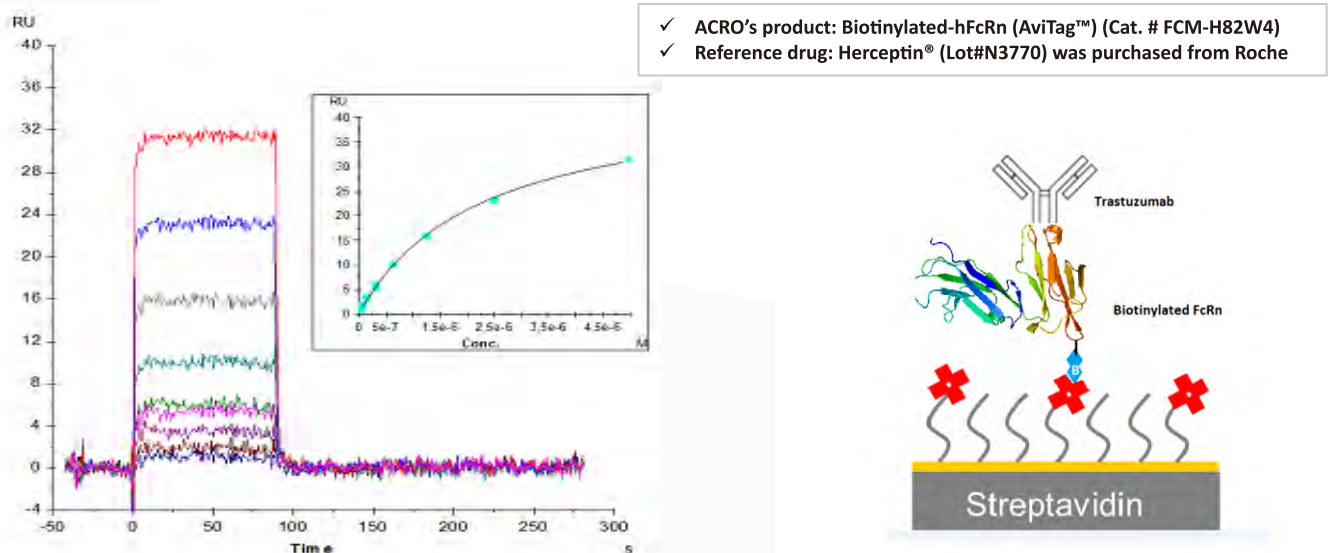
ACROBiosystems Human HER2, His Tag (Cat. # HE2-H5225) at 0.05 µg/mL (100 µL/well) can bind Trastuzumab (Herceptin[®]) with a linear range of 0.2-3 ng/mL.

Her2 Antigen Binding Affinity was Determined by BLI Using Trastuzumab (Herceptin®)



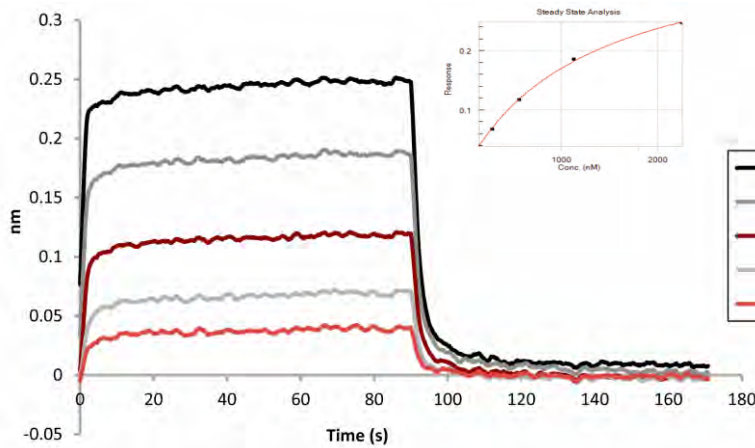
Immobilized Trastuzumab (Herceptin®) coupled to AHC Biosensors can bind human HER2, His Tag protein (Cat. # HE2-H5225) with an affinity constant of 0.93 nM as determined in a BLI assay (Fortebio Octet 96).

FcRn Binding Affinity was Determined by SPR (against Trastuzumab (Herceptin®))

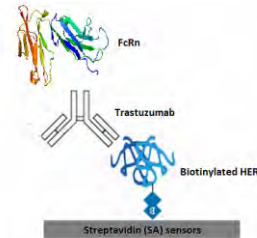


Biotinylated Human FcRn / FCGRT & B2M, Avi Tag (AviTag™) (Cat. # FCM-H82W4) coupled to SA coated sensor chip can bind Trastuzumab (Herceptin®) with an affinity constant of 2.24 μ M as determined in a SPR assay (Biacore 2000). The data is generally provided by Biaffin GmbH & Co KG, Germany

Her2 Antigen and FcRn Binding Affinity was Determined by BLI Using Trastuzumab (Herceptin®)



- ✓ ACRO's product: Biotinylated-hHER2 (Cat. # HE2-H822R) and hFcRn (Cat. # FCM-H5286)
- ✓ Reference drug: Herceptin® (Lot#N3770) was purchased from Roche

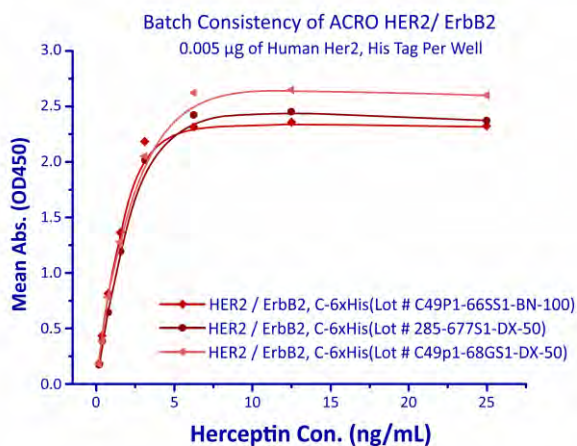


Immobilize Biotinylated HER2, His tag Protein (Cat. # HE2-H822R) to SA Biosensors to capture Trastuzumab (Herceptin®) and Trastuzumab (Herceptin®) can bind human FcRn, His Tag protein (Cat. # FCM-H5286) with an affinity constant of $1.32 \mu\text{M}$ as determined in a BLI assay (Fortebio Octet 96).

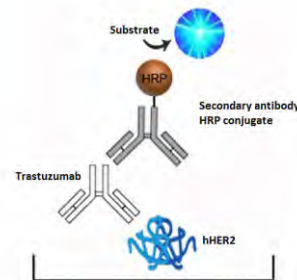
High Batch-to-batch Consistency

We routinely apply rigorous quality control measures to ensure consistent performance of our products. Newly produced products are subjected to side-by-side comparison with our internal standard in a variety of assays. Only those within an acceptable margin of difference are allowed to be released.

Batch Consistency of Her2 Antigen was Determined by ELISA Using Trastuzumab (Herceptin®)

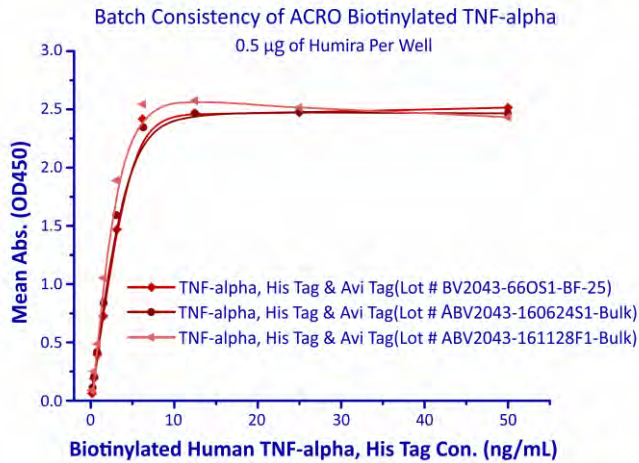


- ✓ ACRO's product: hHER2 (Cat. # HE2-H5225)
- ✓ Reference drug: Herceptin® (Lot#N3770) was purchased from Roche

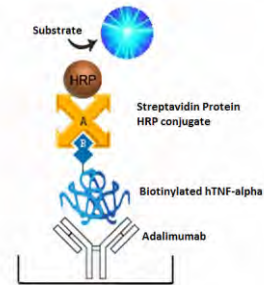


Binding activity of three different lots of hHER2 (Cat. # HE2-H5225) were evaluated in the above ELISA analysis against Trastuzumab (Herceptin®). The result showed that the batch variation among the tested samples is negligible.

Batch Consistency of TNF-alpha Antigen was Determined by ELISA Using Adalimumab (Humira®)



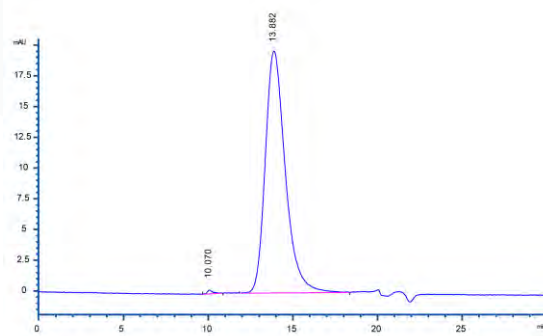
- ✓ ACRO's product: Biotinylated-hTNF-alpha (Cat. # TNA-H82E3)
- ✓ Reference drug: Humira® (Lot# 63169XH02) was purchased from AbbVie



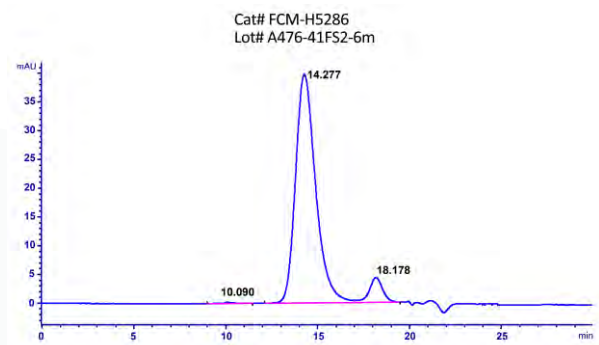
In the above ELISA analysis, three different lots of biotinylated hTNF-alpha (Cat. # TNA-H82E3) were used to detect immobilized Adalimumab (Humira®) (5µg/ml). The result showed that the batch variation among the tested samples is negligible.

High Purity & High Quality

ACRO's target antigens and Fc receptor proteins demonstrate high purity and quality as shown in HP-SEC analyses.



Over 95% of Biotinylated Human TNF-alpha (Cat. # TNA-H82E3) presents as active trimers with a molecular mass of 57 kDa, as determined by SEC-HPLC analysis.



The purity of human FcRn (Cat. # FCM-H5286) was greater than 95% as determined in a HPLC analysis.

Biosimilar Target Antigens

Molecule	Cat. No.	Species	Product Description	Tag
Her2 / ErbB2 (Biotin-labeled)	HE2-H822R	Human	Biotinylated Human Her2 / ErbB2, primary amine labeling, long spacer	His
Her2 / ErbB2	HE2-H5225	Human	Human Her2 / ErbB2 Protein	His
Her2 / ErbB2	HE2-H5253	Human	Human Her2 / ErbB2 Protein	Fc
Her2 / ErbB2	HE2-H5287	Human	Human Her2 / ErbB2 Protein	Twin Strep
Her2 / ErbB2	HE2-H521y	Human	Human Her2 / ErbB2 Protein	Tag Free
TNF-alpha (Biotin-labeled)	TNA-H82E3	Human	Biotinylated Human TNF-alpha (HPLC-verified)	His & AviTag™
TNF-alpha	TNA-H5228	Human	Human TNF-alpha Protein	His
TNF-alpha (Biotin-labeled)	TNA-H8211	Human	Biotinylated Human TNF-alpha, primary amine labeling	Tag Free
TNF-alpha (Biotin-labeled)	TNA-H821R	Human	Biotinylated Human TNF-alpha, primary amine labeling, long spacer	Tag Free
TNF-alpha (HPLC-verified)	TNA-H4211	Human	ActiveMax® Recombinant Human TNF-alpha (HPLC-verified)	Tag Free
EGF R	EGR-H5222	Human	Human EGF R Protein	His
EGF R	EGR-H5252	Human	Human EGF R Protein	Fc
EGF R	EGR-H5285	Human	Human EGF R Protein	Twin Strep
VEGF165 (Biotin-labeled)	VE5-H82Q0	Human	Biotinylated Human VEGF165 Protein	His & AviTag™
VEGF165	VE5-H5248	Human	Human VEGF165 Protein	His
VEGF165 (Biotin-labeled)	VE5-H8210	Human	Biotinylated Human VEGF165, epitope tag free, primary amine labeling	Tag Free
VEGF165 (HPLC-verified)	VE5-H4210	Human	ActiveMax® Recombinant Human VEGF165 (HPLCverified)	Tag Free
VEGF121 (Biotin-labeled)	VE1-H82E7	Human	Biotinylated Human VEGF121	AviTag™ & His
VEGF121	VE1-H5246	Human	Human VEGF121 Protein	His
CD20	CD0-H5143	Human	Human MS4A1 / CD20 Protein	TrxA

Fc Receptor Family Proteins

Molecule	Cat. No.	Species	Product Description	Tag
FcRn	FCM-H5286	Human	FcRn / FCGRT & B2M Heterodimer Protein	His & Strep II
FcRn (Biotin-labeled)	FCM-H8286	Human	Biotinylated FcRn / FCGRT & B2M, primary amine labeling	His & Strep II
FcRn (Biotin-labeled)	FCM-H82W4	Human	Biotinylated FcRn / FCGRT & B2M	AviTag™ & His & Strep II
Fc gamma RIIIA / CD16a	CD8-H52H4	Human	FCGR3A / CD16a (V176) Protein	His
Fc gamma RIIIA / CD16a	CDA-H5220	Human	FCGR3A / CD16a (F176) Protein	His
Fc gamma RIIIA / CD16a (Biotin-labeled)	CDA-H82E8	Human	Biotinylated Fc gamma RIIIA / CD16a (F176)	AviTag™ & His
Fc gamma RIIIA / CD16a (Biotin-labeled)	CDA-H82E9	Human	Biotinylated Fc gamma RIIIA / CD16a (V176)	AviTag™ & His
Fc gamma RIIIB / CD16b	CDB-H5222	Human	Fc gamma RIIIB / CD16b Protein	His
Fc gamma RIIIB / CD16b (Biotin-labeled)	CDB-H82E1	Human	Biotinylated Fc gamma RIIIB / CD16b	AviTag™ & His
Fc gamma RIIA / CD32a	CD1-H5223	Human	FcGR2A / CD32a (H167) Protein	His
Fc gamma RIIA / CD32a	CDA-H5221	Human	Fc gamma RIIA / CD32a (R167) Protein	His
Fc gamma RIIA / CD32a (Biotin-labeled)	CDA-H82E6	Human	Biotinylated Fc gamma RIIA / CD32a (H167)	AviTag™ & His
Fc gamma RIIA / CD32a (Biotin-labeled)	CDA-H82E7	Human	Biotinylated Fc gamma RIIA / CD32a (R167)	AviTag™ & His
Fc gamma RIIIB / CD32b	CDB-H5228	Human	Fc gamma RIIIB / CD32b Protein	His
Fc gamma RIIIB / CD32b (Biotin-labeled)	CDB-H82E0	Human	Biotinylated Fc gamma RIIIB / CD32b	AviTag™ & His
Fc gamma RI / CD64	FCA-H52H2	Human	Fc gamma RI / CD64 Protein	His

References

- [1] European Medicines Agency. Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf); 2014 [accessed 15.05.15]
- [2] U.S. Department of Health and Human Services. Food and Drug Administration. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf> (last accessed 10 November 2015)
- [3] Bui, L.A. et al. Key considerations in the preclinical development of biosimilars, *Drug Discov Today* (2015), <http://dx.doi.org/10.1016/j.drudis.2015.03.011>
- [4] Al-Sabbagh A. et al. Development of biosimilars, *Seminars in Arthritis and Rheumatism* (2016), <http://dx.doi.org/10.1016/j.semarthrit.2016.01.002>

TIM-3 **CTLA-4** **4-1BB**
Immune Checkpoint
Biotinylated **HER2**
B7-H4 TIGIT 4-1BB Ligand
FCRn **CD40** **GITR**
PD-L2 **HER2**
DNAM-1 **B7-1**
TIM-3 **FCRn**
TNF- alpha **LAG-3**
CD19 **OX40** Ligand **B7-H2**
PD-1 **CD47** **PCSK9**
Immune Checkpoint
Biotin-labeled
VEGF165 **CD48** **PD-L1**
FCRn **HER2** **ICOS** **CD27** **CD48** **Checkpoint**
B7-H4 **BTLA** **CTLA-4**
TIM-3 **CTLA-4**
Biotin-labeled
HER2 **PD-L2** **B7-H4** **DNAM-1**
VEGF165 **FCRn** **PD-L1**
BTLA **CTLA-4**
PCSK9 **FCRn**
DNAM-1 **PD-L2** **PD-L1**
VEGF165 **4-1BB** **Immune Checkpoint**
GITR Ligand **Biotinylated** **PD-1**
TNF-alpha **PD-L2**