

An "I" (Immunogenicity Risk Assessment) for an Eye (Ophthalmology Biologics)

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PURPOSE

As new products are brought forward to the clinic for treatment of eye diseases, immunogenicity needs to be carefully considered, despite the reputation of the eye as an immune-privileged site. An Immunogenicity Risk Assessment is now considered to be an integral part of IND (Investigational new drug) applications to the FDA.

Various strategies are employed to assess immunogenicity risk. In this context, three prominent approaches stand out:

1) in silico prediction models

2) in vitro T cell assays

3) MAPPs assays

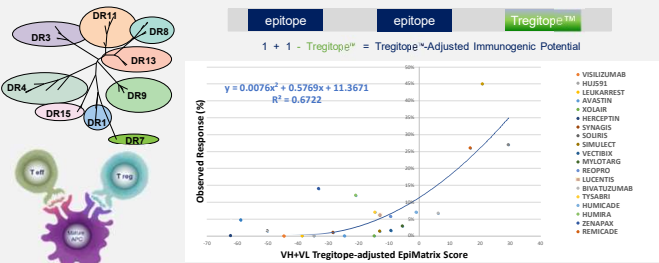


We have developed and applied an in silico risk assessment platform called ISPRI, that can rapidly assess the immunogenic potential of a biologic, identifying key 'clusters' of immunogenic or tolerogenic potential that may be relevant to immune responses and for immunogenic clusters, that may also be modified to reduce immunogenicity. Here we apply ISPRI analysis to an ophthalmologic biologic that has been associated with intra-ocular inflammation (IOI) and anti-drug antibody responses (ADA). Brolicizumab is a humanized monoclonal single chain variable fragment (scFv) for the treatment of neovascular age-related macular degeneration.

METHODS

We retrieved the amino acid sequence of brolicizumab, an scFv consisting of a variable heavy chain domain and a variable light chain domain. We then used ISPRI to assess its potential for immunogenicity. For each input sequence and domain of the scFv, ISPRI provides Tregitope-adjusted Immunogenicity Scores.

The Tregitope-adjusted Immunogenicity Score can be used to predict the ADA response rate for novel antibody products using a regression model based on a set of clinical benchmark monoclonal antibodies whose observed ADA response rates are known.



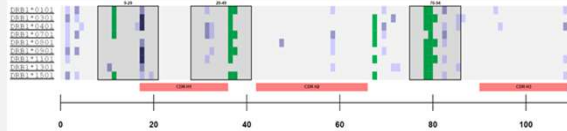
RESULTS

- The variable light chain domain has a very high score as compared to many non-immunogenic antibodies.
- As a result, the ISPRI-generated combined score of the variable heavy and variable light chain domains of brolicizumab is in the upper range of the antibody immunogenicity scale.
- This score indicated that the biologic would likely be associated with ADA, as was observed in several clinical trials.
- According to the FDA label for this product, "After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 76% of patients treated with ..." the biologic, and "Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during ... clinical trials."

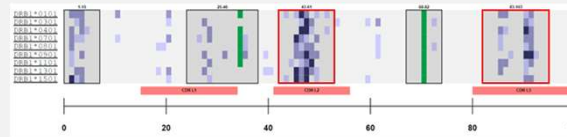
Within the VL domain, the ISPRI algorithm identified several hot spots, two of which scored very high on the scale. Deimmunization of these identified hot spots could have resulted in a less immunogenic therapeutic.

Protein Sequence	Length	EpiMatrix Hits	EpiMatrix Score	tReg Adjusted EpiMatrix Score	Paired tReg Adjusted EpiMatrix Score	Predicted T-Dependent Ab Response ¹
BROLUCIZUMAB_VH	120	56	9.21	-65.03		
BROLUCIZUMAB_VL	110	84	77.1	44.79	-12.68	5.27%

Brolucizumab VH Cluster Epitope Map

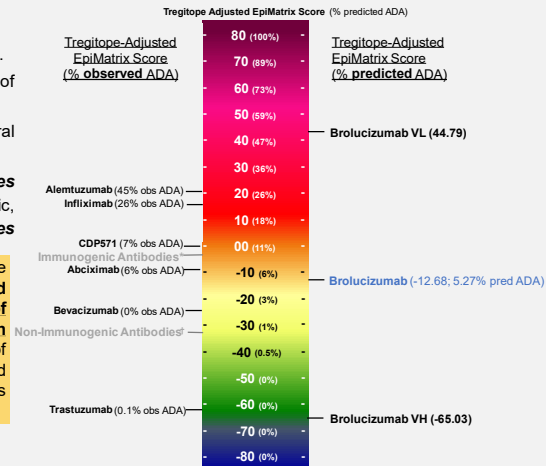


Brolucizumab VL Cluster Epitope Map



Top 1% Epitope
Top 5% Epitope
Top 10% 'Near-Miss'

- The Clusterer algorithm identified several "hot spots" especially in the VL domain.
- Two of those "hot spots" contain several promiscuous non-human epitopes.



EpiMatrix Cluster Detail Report

Sequence: BROLUCIZUMAB_VL Cluster: 43

Start	End	AA	Frame	Hydro	DRB1*0101	DRB1*0201	DRB1*0301	DRB1*0401	DRB1*0501	DRB1*0601	DRB1*0701	DRB1*0801	DRB1*0901	DRB1*1001	DRB1*1101	DRB1*1201	DRB1*1301	DRB1*1401	DRB1*1501	DRB1*1601	DRB1*1701	DRB1*1801	DRB1*1901	DRB1*2001	DRB1*2101	DRB1*2201	DRB1*2301	DRB1*2401	DRB1*2501	DRB1*2601	DRB1*2701	DRB1*2801	DRB1*2901	DRB1*3001	DRB1*3101	DRB1*3201	DRB1*3301	DRB1*3401	DRB1*3501	DRB1*3601	DRB1*3701	DRB1*3801	DRB1*3901	DRB1*4001	DRB1*4101	DRB1*4201	DRB1*4301	DRB1*4401	DRB1*4501	DRB1*4601	DRB1*4701	DRB1*4801	DRB1*4901	DRB1*5001	DRB1*5101	DRB1*5201	DRB1*5301	DRB1*5401	DRB1*5501	DRB1*5601	DRB1*5701	DRB1*5801	DRB1*5901	DRB1*6001	DRB1*6101	DRB1*6201	DRB1*6301	DRB1*6401	DRB1*6501	DRB1*6601	DRB1*6701	DRB1*6801	DRB1*6901	DRB1*7001	DRB1*7101	DRB1*7201	DRB1*7301	DRB1*7401	DRB1*7501	DRB1*7601	DRB1*7701	DRB1*7801	DRB1*7901	DRB1*8001	DRB1*8101	DRB1*8201	DRB1*8301	DRB1*8401	DRB1*8501	DRB1*8601	DRB1*8701	DRB1*8801	DRB1*8901	DRB1*9001	DRB1*9101	DRB1*9201	DRB1*9301	DRB1*9401	DRB1*9501	DRB1*9601	DRB1*9701	DRB1*9801	DRB1*9901	DRB1*10001	DRB1*10101	DRB1*10201	DRB1*10301	DRB1*10401	DRB1*10501	DRB1*10601	DRB1*10701	DRB1*10801	DRB1*10901	DRB1*11001	DRB1*11101	DRB1*11201	DRB1*11301	DRB1*11401	DRB1*11501	DRB1*11601	DRB1*11701	DRB1*11801	DRB1*11901	DRB1*12001	DRB1*12101	DRB1*12201	DRB1*12301	DRB1*12401	DRB1*12501	DRB1*12601	DRB1*12701	DRB1*12801	DRB1*12901	DRB1*13001	DRB1*13101	DRB1*13201	DRB1*13301	DRB1*13401	DRB1*13501	DRB1*13601	DRB1*13701	DRB1*13801	DRB1*13901	DRB1*14001	DRB1*14101	DRB1*14201	DRB1*14301	DRB1*14401	DRB1*14501	DRB1*14601	DRB1*14701	DRB1*14801	DRB1*14901	DRB1*15001	DRB1*15101	DRB1*15201	DRB1*15301	DRB1*15401	DRB1*15501	DRB1*15601	DRB1*15701	DRB1*15801	DRB1*15901	DRB1*16001	DRB1*16101	DRB1*16201	DRB1*16301	DRB1*16401	DRB1*16501	DRB1*16601	DRB1*16701	DRB1*16801	DRB1*16901	DRB1*17001	DRB1*17101	DRB1*17201	DRB1*17301	DRB1*17401	DRB1*17501	DRB1*17601	DRB1*17701	DRB1*17801	DRB1*17901	DRB1*18001	DRB1*18101	DRB1*18201	DRB1*18301	DRB1*18401	DRB1*18501	DRB1*18601	DRB1*18701	DRB1*18801	DRB1*18901	DRB1*19001	DRB1*19101	DRB1*19201	DRB1*19301	DRB1*19401	DRB1*19501	DRB1*19601	DRB1*19701	DRB1*19801	DRB1*19901	DRB1*20001	DRB1*20101	DRB1*20201	DRB1*20301	DRB1*20401	DRB1*20501	DRB1*20601	DRB1*20701	DRB1*20801	DRB1*20901	DRB1*21001	DRB1*21101	DRB1*21201	DRB1*21301	DRB1*21401	DRB1*21501	DRB1*21601	DRB1*21701	DRB1*21801	DRB1*21901	DRB1*22001	DRB1*22101	DRB1*22201	DRB1*22301	DRB1*22401	DRB1*22501	DRB1*22601	DRB1*22701	DRB1*22801	DRB1*22901	DRB1*23001	DRB1*23101	DRB1*23201	DRB1*23301	DRB1*23401	DRB1*23501	DRB1*23601	DRB1*23701	DRB1*23801	DRB1*23901	DRB1*24001	DRB1*24101	DRB1*24201	DRB1*24301	DRB1*24401	DRB1*24501	DRB1*24601	DRB1*24701	DRB1*24801	DRB1*24901	DRB1*25001	DRB1*25101	DRB1*25201	DRB1*25301	DRB1*25401	DRB1*25501	DRB1*25601	DRB1*25701	DRB1*25801	DRB1*25901	DRB1*26001	DRB1*26101	DRB1*26201	DRB1*26301	DRB1*26401	DRB1*26501	DRB1*26601	DRB1*26701	DRB1*26801	DRB1*26901	DRB1*27001	DRB1*27101	DRB1*27201	DRB1*27301	DRB1*27401	DRB1*27501	DRB1*27601	DRB1*27701	DRB1*27801	DRB1*27901	DRB1*28001	DRB1*28101	DRB1*28201	DRB1*28301	DRB1*28401	DRB1*28501	DRB1*28601	DRB1*28701	DRB1*28801	DRB1*28901	DRB1*29001	DRB1*29101	DRB1*29201	DRB1*29301	DRB1*29401	DRB1*29501	DRB1*29601	DRB1*29701	DRB1*29801	DRB1*29901	DRB1*30001	DRB1*30101	DRB1*30201	DRB1*30301	DRB1*30401	DRB1*30501	DRB1*30601	DRB1*30701	DRB1*30801	DRB1*30901	DRB1*31001	DRB1*31101	DRB1*31201	DRB1*31301	DRB1*31401	DRB1*31501	DRB1*31601	DRB1*31701	DRB1*31801	DRB1*31901	DRB1*32001	DRB1*32101	DRB1*32201	DRB1*32301	DRB1*32401	DRB1*32501	DRB1*32601	DRB1*32701	DRB1*32801	DRB1*32901	DRB1*33001	DRB1*33101	DRB1*33201	DRB1*33301	DRB1*33401	DRB1*33501	DRB1*33601	DRB1*33701	DRB1*33801	DRB1*33901	DRB1*34001	DRB1*34101	DRB1*34201	DRB1*34301	DRB1*34401	DRB1*34501	DRB1*34601	DRB1*34701	DRB1*34801	DRB1*34901	DRB1*35001	DRB1*35101	DRB1*35201	DRB1*35301	DRB1*35401	DRB1*35501	DRB1*35601	DRB1*35701	DRB1*35801	DRB1*35901	DRB1*36001	DRB1*36101	DRB1*36201	DRB1*36301	DRB1*36401	DRB1*36501	DRB1*36601	DRB1*36701	DRB1*36801	DRB1*36901	DRB1*37001	DRB1*37101	DRB1*37201	DRB1*37301	DRB1*37401	DRB1*37501	DRB1*37601	DRB1*37701	DRB1*37801	DRB1*37901	DRB1*38001	DRB1*38101	DRB1*38201	DRB1*38301	DRB1*38401	DRB1*38501	DRB1*38601	DRB1*38701	DRB1*38801	DRB1*38901	DRB1*39001	DRB1*39101	DRB1*39201	DRB1*39301	DRB1*39401	DRB1*39501	DRB1*39601	DRB1*39701	DRB1*39801	DRB1*39901	DRB1*40001	DRB1*40101	DRB1*40201	DRB1*40301	DRB1*40401	DRB1*40501	DRB1*40601	DRB1*40701	DRB1*40801	DRB1*40901	DRB1*41001	DRB1*41101	DRB1*41201	DRB1*41301	DRB1*41401	DRB1*41501	DRB1*41601	DRB1*41701	DRB1*41801	DRB1*41901	DRB1*42001	DRB1*42101	DRB1*42201	DRB1*42301	DRB1*42401	DRB1*42501	DRB1*42601	DRB1*42701	DRB1*42801	DRB1*42901	DRB1*43001	DRB1*43101	DRB1*43201	DRB1*43301	DRB1*43401	DRB1*43501	DRB1*43601	DRB1*43701	DRB1*43801	DRB1*43901	DRB1*44001	DRB1*44101	DRB1*44201	DRB1*44301	DRB1*44401	DRB1*44501	DRB1*44601	DRB1*44701	DRB1*44801	DRB1*44901	DRB1*45001	DRB1*45101	DRB1*45201	DRB1*45301	DRB1*45401	DRB1*45501	DRB1*45601	DRB1*45701	DRB1*45801	DRB1*45901	DRB1*46001	DRB1*46101	DRB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