

# IARC Meeting 11: April 13th 2018: minutes

The meeting commenced at 22:00 AEST. AC, MC, MO and CS were in attendance.

1. The minutes of Meeting 9 and 10 were accepted.
2. The committee briefly discussed progress with aligning utilities with the submission fields being developed by William Lees and others.
3. The committee was informed of discussions between MO and others regarding a test TPA submission. The committee supported this endeavour, and will consider these new inferences at the conclusion of their deliberations of B16 data.
4. The committee believes that their work will be facilitated if the GLWG could form a sub-group to explore differences in the performance of the various inference utilities. The committee would like to better understand the kinds of data that lead to differences in their inferences.
4. The committee considered  
>IGHV2-70D\*04\_S2803 (C6T) from B16  
CAGGTTACCTGAAGGAGTCTGGTCCTGCGCTGGTCAAACCCACACAGACCCTCACACTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACTAGTGAATGCGTGTGAGCTGGATCCGTCAGCCCCAGGGAAGGCCCTGGAGTGGCTTGACGCATTGATTGGGATGATGATAAATTCTACAGCACATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGCCACGTATTACTGTGCACGG  
The sequence is present at low frequency (0.09%), above the 0.05% threshold, in the IgDiscover analysis. It was only inferred by IgDiscover, and not by Tlger or Partis. Haplotype analysis was complicated by the apparent duplication of a major section of the locus in B16. Analysis for chimerism did not provide evidence against the existence of the sequence. It was agreed that the sequence should be moved to Level 0.
5. The committee discussed the fact that many inferences from B12 and B16 were being designated as Level 0 sequences, and considered whether or not this will be a long term. It was agreed that until we better understand why the different utilities are making different calls, and where duplications or chimerism raise concerns, we must presently designate sequences as Level 0. This will happen even when there is no obvious evidence pointing against acceptance of an inference. The IARC sees these sequences as being ones about which we have real confidence, but lack absolute certainty. The committee discussed whether or not Level 0 sequences should be made public, and it was unanimously agreed that at present, this should not be done. It was also agreed that sequences that are rejected by the IARC should not be retained in an additional database. The committee acknowledges that in moving sequences to a 'rejected' category like this, some real alleles will be overlooked.
6. The committee considered  
>IGHV4-28\*01\_S5219 (C210T) from B16  
CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCGGACACCCTGTCCCTCACC  
TGCCTGTCTCTGGTTACTCCATCAGCAGTAGTAACTGGTGGGGCTGGATCCGGCAGCCCCA  
GGGAAGGGACTGGAGTGGATTGGGTACATCTATTATAGTGGGAGCACCTACTACAACCCGTCTC

TCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTC  
TGTGACCGCCGTGGACACGGCCGTGTATTACTGTGCGAGA

This sequence is present at very low frequency (0.01%) in the IgDiscover analysis, and was inferred by IgDiscover, but not Tlger and Partis. Haplotype analysis was inconclusive because of the low frequency of the sequence in the dataset. The sequence was moved to Black (rejected).

7. The committee considered

>IGHV4-30-4\*01\_S4754 (T120C) from B16

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACC  
TGCCTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGCCAGCCCC  
CAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTACTACAACCCGTC  
CCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGC  
TCTGTGACTGCCGCAGACACGGCCGTGTATTACTGTGCCAGAGA

The sequence is present at high frequency (1.3%), in the IgDiscover analysis. It was inferred by IgDiscover, Tlger and Partis. Haplotype analysis was supportive of the inference, as the sequence was strongly associated with the IGHJ6\*03 haplotype. The sequence has previously been reported from genomic sequencing, and by inference from VDJ data, and is documented in IgPdb as IGHV4-30-4\*p08. It was agreed that the sequence should be moved to Level 1.

8. The committee considered

>IGHV4-4\*01\_S5769 from B16

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTCCGGGGACCCTGTCCCTCAC  
CTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGTAACTGGTGGAGTTGGGTCCGCCAGCCCC  
AGGGAAGGGCTGGAGTGGATTGGGGAAATCTATCATAGTGGGAGCACCAACTACAACCCGTC  
CCTCAAGAGTCGAGTCACCATATCAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGAGC  
TCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCCGAGAG

The sequence is present at relatively high frequency (0.6%), in the IgDiscover analysis. It was inferred by IgDiscover, Tlger and Partis. Haplotype analysis showed two IGHV4-4-like sequences associated with the IGHJ6\*02 haplotype - this inference and a second inference that is most similar to IGHV4-4\*08. The likely major duplication of B16 is associated with the IGHJ6\*03 haplotype. Given the similarities between IGHV4-4\*08 and IGHV4-61, and given that this haplotype does not include an IGHV4-61 sequence, the committee concluded that this sequence could be accepted as Level 1. Although in this analysis the sequence was shown to be most similar to IGHV4-4\*01, the committee believes that this inference extends the partial sequence IGHV4-4\*03. Whether or not this sequence should remain as a Level 1 sequence, given its identity with IGHV4-4\*03, is a matter that will be clarified in consultation with IMGT.

The next meeting (Meeting 12) will be on Friday April 20th at 21:00 AEST.

The meeting ended at 22:00 AEST.