Cellular Programs

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Winter Semester 2020/21 — Chair of Computational Biology

Assignment 5 (about paper #9)

Handed out: 12.1.20

Due: 19.1.2021 10:15

Submit your solutions by e-mail with a single PDF attachment to

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Every student should submit his/her own solution. Plagiarism of solutions will be penalized. Don't forget to label your assignment sheet with your name and Matrikelnummer.

Don't exceed specified page lengths by more than 0.25 pages.

Problem 1:

Why didn't the authors determine the X-ray structure of the entire CTLA-4 receptor bound to the entire ipilimumab antibody? Is the contact between the 1-118 fragment of CTLA-4 and the Fab fragment of the antibody "enough" for characterizing the molecular contact? (0.25 page)

Problem 2:

What is the point of a testing a library of 118 dimeric CTLA-4 mutants? Doesn't the experimental X-ray structure answer all questions about this protein-protein interaction? (0.25 page)

Problem 3:

Summarize briefly the relationship between CD28, CTLA-4, B7 ligand and ipilimumab in cancer progression and inhibition. (0.25 page)

Problem 4:

Determine whether these statements are True or False. If False, please correct the statement and cite the supporting information you found from the paper (by providing page + column + line number)

(a) The FG loop serves major importance in both recognition of ipilimumab and ipilimumab specificity for CLTA-4.

(b) Light chain complementarity determining regions (CDR), but not heavy chain CDR, help ipilimumab to distinguish between CD28 and CLTA-4.

(c) The sequence differences in G strand residues after FG loop (Figure 7) perturb the linkage between F and G strands in CD28, thereby disable the interaction between CD28 and light chain CDR of ipilimumab.

Problem 5:

The paper states "KDs exhibited by ipilimumab and B7 ligands for CTLA-4 are ∼10 nM and ∼0.1–1 μM range, respectively" and "It is this direct competition between ipilimumab and the B7 ligands that, in part, underlies the therapeutic efficacy of ipilimumab".
Does this mean that the effectiveness of a monoclonal antibody in cancer treatment is proportional to its binding efficiency to CTLA-4? In other words, the stronger it binds, the higher will be its effectiveness? Justify your answer with evidence.

Paper #9 Ramagopal et al. (2020) PNAS 114, E4223, Structural basis for cancer immunotherapy by the first-in-class checkpoint inhibitor ipilimumab**.**