Proposals for system pharmacology project

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Title:

Understanding polypharmacology of antibodies: what are the benefits of using a bispecific vs combination of monospecifics.

Project outline

Our aim is to understand the scenarios where using a bispecific mAb would be preferential to using a combination of monospecific mAbs.

Background

Antibodies can provide highly specific high affinity binding to almost any molecule. While most therapeutic mAbs are monospecific, protein engineering has allowed to create bispecific varieties (bs-mAb) that can bind two different target molecules simultaneously. Many alternative formats for bs-mAbs exist but in this instance we shall only consider two of them: those with one binding site per mAb molecule for either target (two in total, A on Figure 1) and those where there are two for either target (four in total, B on Figure 1).[1]

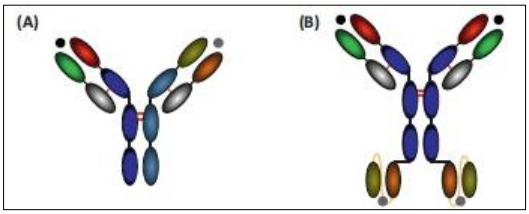

Figure 1: Bispecific antibody formats. Taken from Byrne *et al* 2013.[1]

Traditional antibodies have 2 binding sites, but typically only bind to a single molecule of a soluble target due to high molar excesses when used as a therapeutic. However, when the target is membrane-bound, bivalent interaction may occur that results in improved binding through the avidity effect[2,3]. In the case of bispecific mAbs, it is conceivable that two different targets present on the surface of the same cell may be cross-linked in similar manner.

Aims of project

There are 2 primary aims of this project and 2 secondary aims. For the first two, we are using simulation to understand if there are benefits (reduced dose, reduced dosing frequency, target engagement, etc) in using a bispecific molecule over a combination of monospecific antibodies when the targets are in solution or expressed on the same cell. The last two are concerned with situation when the interacting proteins are on different cells: bs-mAb mediated cell-cell cross-linking and TCR-pMHC interactions.

Primary Aim 1: 2 independent soluble targets (for example TNFα and IL17)

Soluble targets are considered to be well mixed (equilabrated) within a given volume. The output from this aim will be:

1. Understand whether there are concentration dependent scenarios where it is preferential to use a bispecific mAb over a combination of monospecific ones
2. Model the probability of bivalent binding to occur with bispecific molecules
3. Model how the concentration of different targets affects the require affinities of a bispecific molecule

Primary Aim 2: Two independent membrane targets on same cell surface

Membrane targets are considered to be anchored on the surface of a cell. The output from this aim will be to understand whether there are scenarios where it is preferential to use a bispecific molecule over a combination of two monospecific ones. Model the scenarios when the effect of antibody binding is agonistic as well as when the effect is antagonistic.

1. Compare the target engagement of bivalent binding to occur with bispecific molecules.
2. Model how receptor density and mobility of different targets affects the required affinities of a traditional antibody.
3. Model how receptor density and mobility of different targets affects the required affinities of a bispecific mAb.

Consider two cell populations: The first one carries membrane-bound targets A and B both at 100000 per cell while the other one has just target A at the same level. The output would be target A engagement as a concentration-response curve for both cell populations. Is the lateral diffusion of target molecules on the cell surface expected to be of any significance?

Secondary Aim 1: Two independent membrane targets on the surface of two different cells. Cross-linking of these two cells by a bispecific mAb

Cell-cell interactions lie at the heart of immune response. Bispecific antibodies have the potential to bind to 2 targets simulatenously that are expressed on independent cells and hence can facilitate this interaction. The output from this aim will be:

1. Model the dose-response curve for cell-cell crosslinking and target engagement by a bispecific antibody when the respective 2 targets are expressed on 2 independent cells. Analyse the effect of bispecific mAb affinities and differences in target densities.

References

1. Byrne, H., et al (2013) A tale of two specificities: bispecific antibodies for therapeutic and diagnostic applications. *Trends in Biotechnology*. 31:621-632.
2. Gibiansky, L., et al (2008) Approximations of the target-mediated drug disposition model and identifiability of model parameters. *Journal of Pharmacokinetics Pharmacodynamics*. 52:83-124.
3. Nieba, L., et al (1995) Competition BIAcore for easuring true affinities: large differences from values determined from binding kinetics. *Analytical Biochemistry*. 234:155-165.