# The phenotypic association theory and its application in nanomedicine design

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The central dogma in biological interactions and its application to drug design states that the higher the drug or ligand affinity (i.e. the most negative binding energy) to its cognate receptor, the higher its ability to target cells or tissues expressing the same receptor. However, such a maximal selectivity at the single molecules imposes that high-affinity ligands target indiscriminately any cells expressing the given receptor. The chemical nature of biological units extends beyond single molecules. As biomolecules combine into single cells, the number of configurations increases so much that we can confidently say that each cell of our body is different from the other. We may not need to dissect the complexity of the single cell down to the quantum level to create more selective drugs. Still, we need to upgrade our molecular design to include more holistic effects to distinguish biological targets more precisely. In the last decade, we have assessed biological targets' internal state energetic configurations matching them with complementary multivalent units to favour selective associations based on multiple bonds. We have borrowed statistical and soft matter physics tools to address this challenge.

We know from the super-selectivity theory (SST) [2] that multivalent units interact via the collective effect of the single affinities (or avidity) and association changes with receptors or ligand numbers, not linearly, giving rise to entropy-driven interactions. This unique nature means that if we combine low-affinity ligands, we can have association only when receptors are high in numbers, effectively targeting cells that overexpress the desired receptor. We have proven SST experimentally [3-5] and demonstrated that the overall interaction combines the specific ligand/receptor bonds with mean-field repulsive potential arising from steric effects. Borrowing similar nomenclature used in quantum physics to handle the multidimensional nature of the problem, I here define the different states that characterise a cell phenotype and the multivalent unit to target using a vector of features, one that defines the cell phenotype as $|\varphi_j\rangle$ representing the specific cell receptors compositions and is the mean-field steric potentials. We can define a multivalent unit vector of features is defined as $\langle\nu_j|$ and state that two are complementary if

$$\langle\nu_i|\Theta|\varphi_j\rangle = \delta_{ij} = \begin{cases} 1, & \text{if } i \equiv j \\ 0, & \text{if } i \not\equiv j \end{cases} \quad (1)$$

The *ith* multivalent unit, the *jth* cell phenotypes are complementary via the hierarchical operator $\Theta$ defined in **fig.1**. Using such a formalism, I will show that we can adapt molecular engineering tools to design highly selective drugs.

## Figures

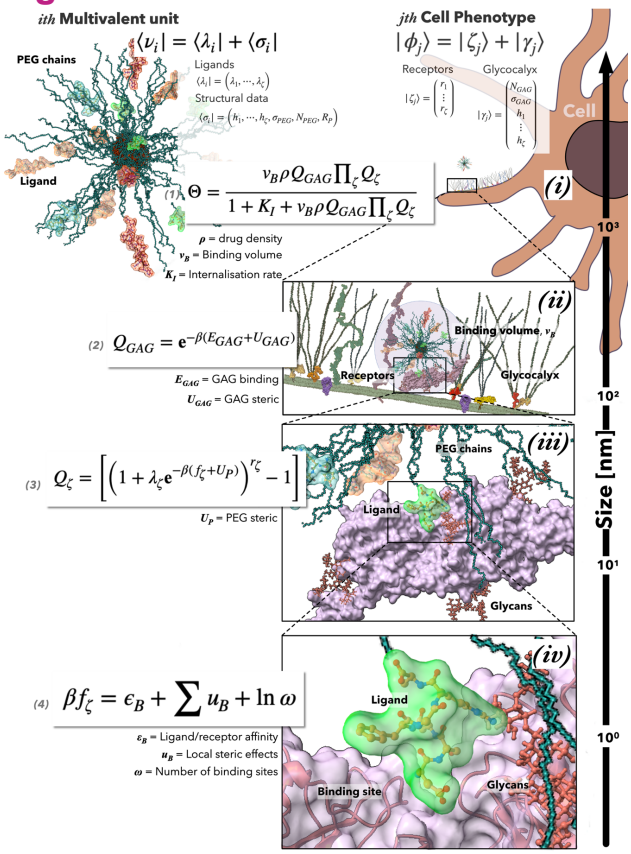


**Figure 1.** Schematics of the interaction between a given jth cell characterised by a unique phenotype and its complementary multivalent unit9)

## References

[1] P. Ehrlich, F. Himmelweit, and M. Marquardt, *The collected papers of Paul Ehrlich*. 1957, London: Pergamon Press.

[2] F.J. Martinez-Veracoechea and D. Frenkel, 'Designing super selectivity in multivalent nano-particle binding'. *PNAS*, **108**, 10963 (2011)

[3] X. Tian, S. Angioletti-Uberti, and G. Battaglia, 'On the design of precision nanomedicines'. *Sci. Adv.*, 2020. **6**, eaat0919.

[4] M. Liu, A. Apriceno, A., M. Sipin, E. Scarpa, L. Rodriguez-Arco, A. Poma, G. Marchello, G. Battaglia and S. Angioletti-Uberti 'Combinatorial entropy behaviour leads to range selective binding in ligand-receptor interactions. *Nat Commun.* **11**, 4836 (2021)

[5] S. Acosta-Gutiérrez, D. Matias, M. Avila-Olias, V. M. Gouveia, E. Scarpa, J. Forth, C. Contini, A. Duro-Castano, L. Rizzello, and G. Battaglia 'A Multiscale Study of Phosphorylcholine Driven Cellular Phenotypic Targeting' *ACS Cent. Sci.* 8, 7, 891–904 (2022)