DavidsonX – D001x – Medicinal Chemistry
Chapter 5 – Receptors
Part 3 – Occupancy Theory
Video Clip – The Pros and Cons of the Clark Model

The dominant model for discussing receptor-ligand interactions was developed by Clark in the 1920s and 30s and arose directly from the enzyme work of Michaelis and Menten. Clark's **occupancy theory** is based on the idea that the fraction of total receptors bound by a ligand is directly proportional to the response. If 0, 50, or 100% of the receptors in a cell are bound by a ligand, then the level of response will be 0, 50, or 100% of the maximum, respectively.

$$\frac{[\text{R-L}]}{[\text{R}_\text{T}]} = \frac{E}{E_{\max}}$$

Clark's equation relating ligand concentration and response is shown below. It bears more than a passing resemblance to the Michaelis-Menten equation. Clark's equation includes a term, K_D, which is the dissociation equilibrium constant for the receptor-ligand complex.

$$\frac{E}{E_{\max}} = \frac{[\text{L}]}{K_\text{D} + [\text{L}]}$$

$$\text{R-L} \overset{K_\text{D}}{\rightleftharpoons} \text{R} + \text{L}$$

$$K_\text{D} = \frac{[\text{R}][\text{L}]}{[\text{R-L}]}$$

Clark's equation is the relationship that generated the sigmoidal response vs. log [L] plots in the previous section. The point of inflection of the curve corresponds to the log [L] at which the response is 50% of the ligand's maximum. Based on Clark's theory, 50% maximum occurs when 50% of the receptors are bound. When 50% of the receptors are bound as R-L, the 50% of the receptors are also unbound as R. At this point, [R] = [R-L], and [L] = EC_{50}. For the equation immediately above, if the system is at equilibrium and [R] = [R-L], then [L] = K_D. Therefore, $EC_{50} = K_D$.

So, in working with receptors, medicinal chemists will normally compare ligands based on their EC_{50} values. These are actually K_D values. Relating activity to K_D, a measure of binding, reinforces the idea that drugs target proteins.

Clark's occupancy theory is far from perfect, and its key assumption – *binding is directly proportional to response* – does not always hold true. Exceptions abound. One is the idea of constituent activity. Some receptors, without being bound to a ligand, generate a response, albeit small. According to Clark's theory, a receptor without a ligand should not afford a response.

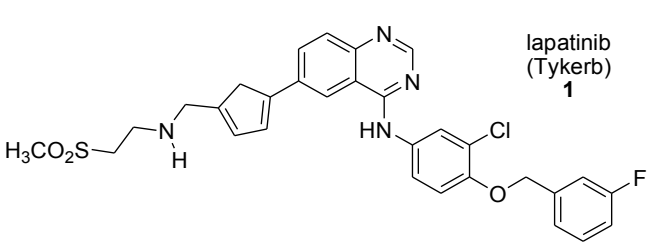
Another exception is that, in some instances, the full response is reached without having all receptors bound. The receptors that are not needed in order to give a full response are called **spare receptors**.

The weakness of occupancy theory is that it is based on the Michaelis-Menten model, a model developed for enzymes. Enzymes are much simpler than receptors. Many receptors involve long and complicated pathways between the ligand binding event and the eventual

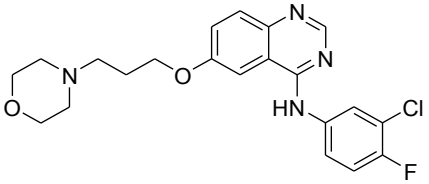
response. With the extra layers of complexities, the occupancy model frequently breaks down.

Elaborations on occupancy theory have been developed, as have competing models predicting ligand-response relationships. One of the newer theories involves an idea called **drug-target residence time**. In the drug-target residence time model, the response is linked to the length of time a ligand binds a receptor. A longer binding time gives a stronger response.

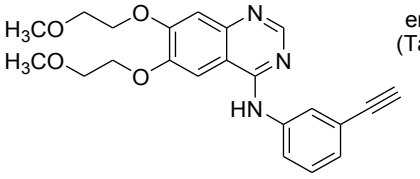
An example of the relevance of drug-target residence time can be found in anti-cancer epidermal growth factor receptor (EGFR) ligands. Three ligands, all of which are FDA-approved drugs, are shown below with their IC_{50} values. Their IC_{50} values are very similar, but lapatinib (**1**) is considerably more active than the other two. When the compounds were instead compared based upon their residence times, lapatinib shows a far longer residence time than the other two compounds. Therefore, when occupancy theory and EC_{50} values fail to explain trends in observed biological activity, other receptor theories must be investigated.



lapatinib (Tykerb) **1** — K_i (nM): 3.0 — residence time (min): 300



gefitinib (Iressa) **2** — K_i (nM): 0.4 — residence time (min): <10



erlotinib (Tarceva) **3** — K_i (nM): 0.7 — residence time (min): <10

One final note is necessary. In the example of lapatinib, ligand for a receptor, was measured in terms of its IC_{50} value. IC_{50} values are normally only used to describe enzyme inhibitors. The receptor bound by lapatinib is EFGR, a tyrosine kinase-linked receptor. Tyrosine kinase-linked receptors have enzymatic activity once they dimerize to their active form. Therefore, it is completely appropriate to refer to lapatinib as both a ligand, specifically as an antagonist, as well as an inhibitor.