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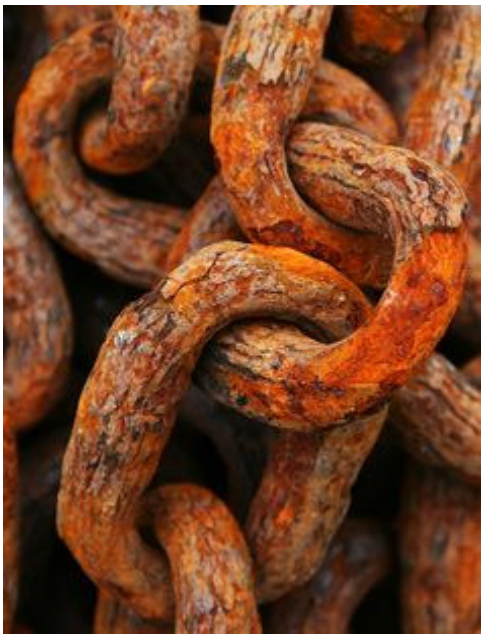
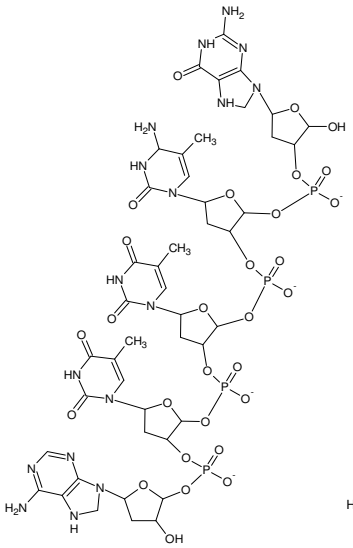
Newsletter # 6: RNA aptamers vs. DNA aptamers



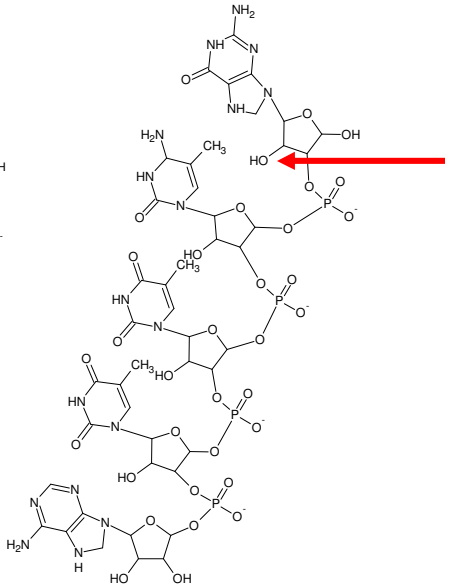
This is a subject on for which there are very clear and strong opinions, I am not however convinced that a lot the dogma accumulating in the aptamer community concerning RNA or DNA aptamers is based on either empirical observations or logic. By this I mean the ***concept that RNA aptamers are better than DNA aptamers because RNA is a more flexible molecule.***

Let's think about it. RNA only differs from DNA by having an additional hydroxyl group on the ribose. This makes RNA less flexible than ssDNA. I think that there has been some confusion because clearly RNA is more flexible than dsDNA. However, if we think of either ssDNA or RNA as a chain, then the presence of the hydroxyl group makes RNA more like a rusty, stiff chain than ssDNA. It is possible to form more shapes with a very flexible chain, but they all collapse if left on their own. A rusty chain will hold secondary and tertiary structures better than a more flexible chain. Thus, RNA has the inherent capacity to form more stable structures than ssDNA.

ssDNA



RNA



Is this necessarily a good thing though? The binding of an aptamer to a target is based on the structure that is created when the two are together. This structure must have a lower free energy than the structures that are formed when the molecules are free. The concept that a molecule that has greater capacity to form structures on its own is a good thing, if we assume that aptamer/target binding is analogous to key/lock interactions. If however, we assume that aptamer/target binding is due to mutual chaperoning of a combined lower free energy complex, and that this mutual chaperoning process is aided by flexibility, then ssDNA may provide a better template for aptamer development. In practice I suspect that binding structures vary along a continuum between the two analogies.

Why did nature appear to pick RNA instead of ssDNA to form the first enzymatic structures if RNA is not implicitly better? The answer is that RNA would be better in an evolutionary system where sequence sampling is limiting. In the early origins of life the capacity to sample 10^{15} different sequences to come up with a solution to a problem did not exist. The first structure that worked at all would be better than any other structure. If you are testing one sequence at a time then RNA would be a much better bet than ssDNA for the identification of a structure that works. Then, this structure can be improved upon by adding sequences, or domains, or making substitutions over time. With aptamer development, we can select for 10^{15} completely different sequences simultaneously. This is an entirely different kind of power. Given this capacity it is possible to select more flexible chains that will form stable complexes with target molecules. I would argue that given the increased flexible of ssDNA it may actually be possible to select better aptamers.