The good? The bad? The mutant! Characterization of cancer-related somatic mutations and identification of a selectivity hotspot in adenosine receptor

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PROPOSITIONS

The Good? The Bad? The Mutant!

Characterization of cancer-related somatic mutations and identification of a selectivity hotspot in adenosine receptors

1. Studying mutant organisms that have acquired changes or deletions in their nucleotide sequences is a time-honored practice in biology.
   Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; ***2002.***

2. Some passenger mutations might occur in genes involved in metabolism and could be mildly deleterious for cancer cells.
   Monticelli M, Viscove M, Riccio G, Andreotti G, Hay-Mele B, Cubellis MV. PeerJ Preprint; ***2018.***

3. Know your GPCR mutations (and target them right).
   Villanueva, M. Nat Rev Drug Discov ; ***2018,*** *17, 94*

4. Higher mutation rates are often observed for certain conserved residues, and given the (evolutionary) importance of these residues the exact impact of these mutations in receptor pharmacology warrants considerable investigation.
   O'Hayre, M et al. Nat. Rev. Cancer; ***2013****, 13; This thesis, chapter 3-6*

5. Complete identification and understanding of GPCR functionality will provide opportunities for novel drug discovery.
   This thesis

6. In general, at the amino acid side chains within the helical bundle a mutation with increased hydrophilicity can destabilize the receptor.
   Rasmussen, SGF et al. Nature; ***2011****, 469; This thesis*

7. GPCRs and their cancer-specific mutations, together with linked signaling circuitry, present novel biomarkers as well as therapeutic targets for cancer prevention and treatment.
   This thesis, chapter 3

8. It is possible that a mutation located in or near key positions, including micro-switches, GPCR-G protein interaction interface and ligand-dependent trigger residues, can partially mimic the conformational changes of the receptor, resulting in altered receptor functionality.
   This thesis

9. A few small changes in your DNA can turn your eyes blue, make you lactose intolerant, put some curl in your hair or switch your GPCRs off.

   Adapted from Anne Wojcicki

10. You will never know how a cat behaves until it wakes up. Similarly, you will never know how a mutant GPCR behaves until you try to activate it.

11. There's hardly anywhere in literature where you don't find a triangle.

    -Leonard Michaels

12. In science, you're exploring and trying to understand something out in the external world. In art, the exploration is internal—it's a personal journey.

    -Dr. Radhika Patnala