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Talk title: The Simple QTY Code for Protein Design

The simple QTY code is based on two key molecular structural facts: **1**) all 20 amino acids are found in naturally occurring alpha-helices regardless of their distinct chemical properties: (a) hydrophilic, (b) hydrophobic and (c) amphiphilic; **2**) several amino acids share striking structural similarities despite their different chemical properties; for example, glutamine (Q) *vs* Leucine (L); Threonine (T) *vs* Valine (V) and Isoleucine (I); and Tyrosine (Y) *vs* Phenylalanine (F). Using the simple QTY code, we replace 40%-60% amino acids L, I, V, F in transmembrane α-helices with amino acids Q, T, Y, the water-soluble QTY variants still maintain the stable structures and ligand-binding activities in the chemokine receptors. The AphlaFold2 predictions proved the QTY code validity. The simple QTY code is a likely useful tool and has big impact for designs of water-soluble variants of previously water-insoluble GPCRs, glucose transporters, solute carrier transporters, ABC transporters, potassium ion channels, and perhaps aggregated proteins.

The QTY code publications:

Zhang, S., et al (2018) QTY code enables design of detergent-free chemokine receptors that retain ligand-binding activities. *Proc. Natl. Acad. Sci. USA* **115** (37) E8652-E8659.

Qing, R., et al. (2019) QTY code designed thermostable and water-soluble chimeric chemokine receptors with tunable ligand-binding activities. *Proc. Natl. Acad. Sci. USA* **116 (51)** 25668-25676.

Qing, R., et al (2020) Non-full-length water-soluble $CXCR4^{QTY}$, $CCR5^{QTY}$ chemokine receptors and implication for overlooked truncated membrane receptors *iScience*, Cell Press, **23** (12): 101670.

Hao, SL., et al. (2020) QTY code-designed water-soluble Fc-fusion cytokine receptors bind to their respective ligands. *QRB Discovery* **1 (e4)** 1-9, Cambridge University Press

Tegler, L.T., et al (2020) G protein-coupled receptor CXCR4 designed by the QTY code becomes more hydrophilic and retains cell-signaling activity. *Scientific Reports* UK **10**, 21371.

Skuhersky, M., et al (2021) Comparing native crystal structures and AlphaFold2 predicted water-soluble G protein-coupled receptor QTY variants. *Life* 11(12) 10.3390/life11121285

Smorodina, E., et al (2022) Comparing 2 crystal structures and 12 AlphaFold2 predicted human membrane glucose transporters and their water-soluble QTY variants. QRB Discovery 3, e5, 1-11.

Smorodina E, et al (2022) Structural informatic study of determined and AlphaFold2 predicted molecular structures of 13 human solute carrier transporters and their water-soluble QTY variants. *Scientific Reports* 12, 20103. doi: 10.1038/s41598-022-23764-y.

Zhang, S. & Egli, M. (2022) Hiding in plain sight: three chemically distinct α-helix types. Quarterly Review of Biophysics (QRB) 55, e7. 55EB6C1845791F987565FC5BE93715C4

Qing, R., et al. (2022) Protein design: from the aspect of water solubility. *Chemical Reviews*, **122**. https://doi.org/10.1021/acs.chemrev.1c00757

Zhang, S. (2022) Life has its ups and downs, but always ask questions. *Molecular Frontiers Journal*, https://doi.org/10.1142/S252973252240003X

Meng, R., et al & Zhang, S. (2023) Reverse-QTY code design of active human serum albumin self-assembled amphiphilic nanoparticles for effective anti-tumor drug doxorubicin release in mice. *Proc. Natl. Acad. Sci USA* **120 (21)** E222017120. doi: 10.1073/pnas.2220173120

Qing R, et al Zhang S. (2023) Scalable biomimetic sensing system with membrane receptor dual-monolayer probe and graphene transistor arrays. Sci Adv. 2023 Jul 21;9(29):eadf1402. doi: 10.1126/sciadv.adf1402. PMID: 37478177.

Sajeev-Sheeja A, Smorodina E, Zhang S. (2023) Structural bioinformatics studies of bacterial outer membrane beta-barrel transporters and their AlphaFold2 predicted water-soluble QTY variants. PLoS One. 18(8):e0290360. doi: 10.1371/journal.pone.0290360. PMID: 37607179.

Karagöl, H. A., Karagöl, M.T., Smorodina, E., & Zhang, S. (2023) Structural bioinformatics studies of glutamate transporters and their AlphaFold2 predicted water-soluble QTY variants and uncovering the natural mutations of L->Q, V->T, F->Y and Q->L, T->V, Y->F. *PLoS ONE,* (**In press**).