

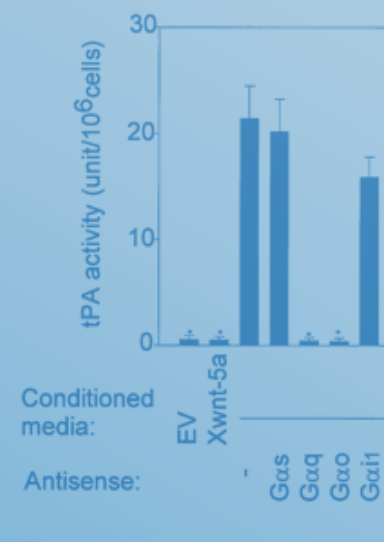
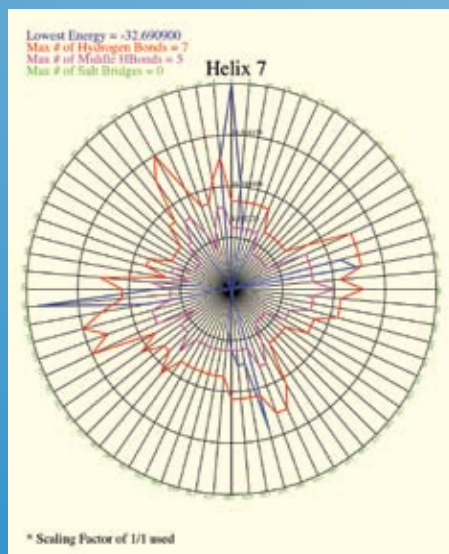
DESIGNING SMARTER DRUGS

MODELING G-PROTEIN COUPLED RECEPTORS

Many drugs in use today were created by “trial and error” methods that result in a compromise: The drugs work, but carry risks of unwanted side effects. Yet clues to designing smarter pharmaceuticals with fewer side effects are hidden within the three-dimensional structures of biomolecules that these drugs turn on or off.

Among the most important therapeutic drug targets in the human body are G-protein coupled receptors (GPCRs) a large, diverse group of proteins that play crucial roles in health and disease. Woven through cell membranes, GPCRs act as signal posts, sensing changes in the environment and directing the cell to respond. By binding with neurotransmitters, hormones, immune substances, odorants and other molecules, GPCRs influence growth, metabolism, brain response and other central life processes. GPCRs called chemokine receptors are also implicated in the spread and growth of many cancers, including those of the lung, breast, prostate and colon. With rising rates of age-related and environmental cancers, better-targeted “magic bullet” GPCR drugs would have widespread benefits.

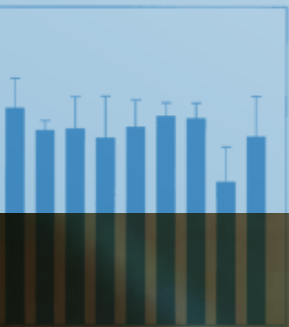
In fact, half the drugs in use today target GPCRs, activating or inhibiting them. They are used to lower blood pressure, combat allergies, treat depression, calm arthritis, heal stomach ulcers and block pain. Yet their actions are often too broad, leading to side effects that can be serious, even dangerous.



Upper right:
Nagarajan Vaidehi, Ph.D.,
City of Hope

Center:
3-D computer models of
proteins help researchers
more quickly investigate
Wnt signal transduction
pathways involved in
development and disease.

Lower left:
Randall T. Moon, Ph.D.,
University of Washington



Xwnt-8
Gα2 Gα5 Gα11 Gα12 Gα13 Gβ1 Gβ2 Gβ3 Gβ4



COLLABORATIONS

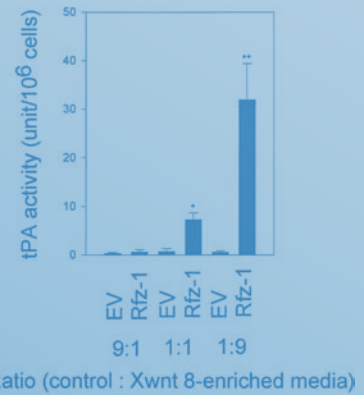
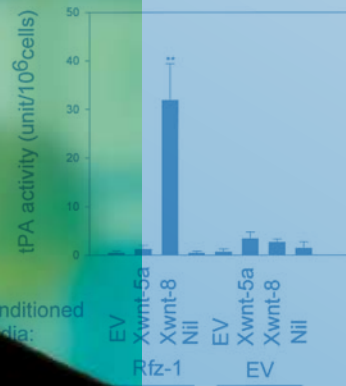
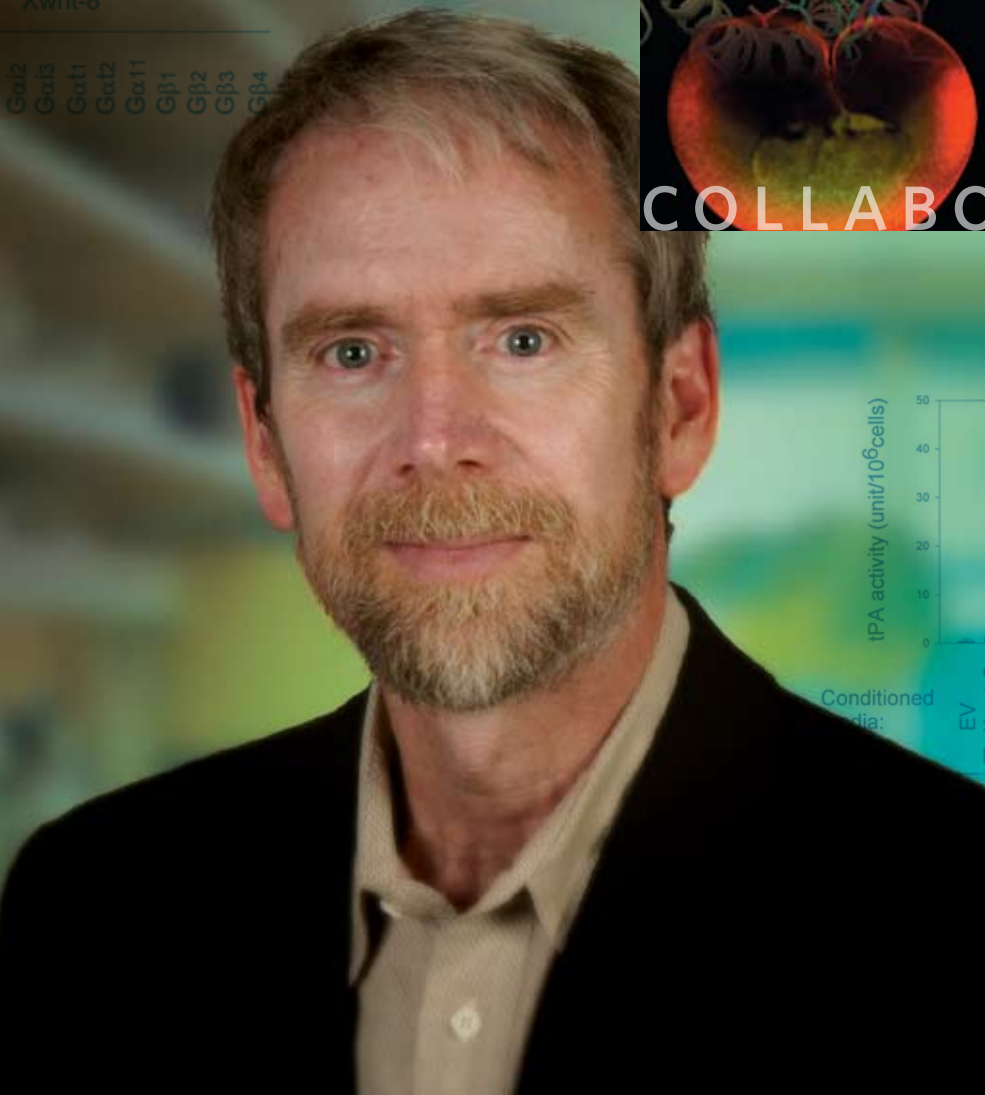


Photo by Elizabeth Lowry, 2006
University of Washington Medicine



Teams of chemists, physicists and computer scientists work to produce virtual GPCR models, then validate and refine them to ultimately bring much-needed GPCR drugs to patients.

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Interest in protein structures is attracting pharmaceutical companies and universities across the globe to work with City of Hope.

Designing the next generation of GPCR drugs requires data on the three-dimensional structure of each receptor protein. But because membrane-bound proteins are hard to crystallize, their structures cannot be visualized directly. One solution is to construct virtual models of these receptor proteins using computational methods based on the fundamental laws of physics. It is a challenge that takes teams of chemists, physicists and computer scientists to solve.

At City of Hope's Division of Immunology, Nagarajan Vaidehi, Ph.D., is leading the charge. Starting with basic atomic forces, she and her colleagues predict the theoretical 3-D structures and binding sites of small molecules within GPCRs. Each structure requires months to generate, using dozens

of computers. Then, further experiments are needed to validate and refine the model.

But while the structures may be theoretical, the need for progress in GPCR drugs is real. Interest in GPCR structures is attracting pharmaceutical companies to work with City of Hope, and promotes collaborations with the universities of California, Texas, Pittsburgh and North Carolina, California Institute of Technology, Jet Propulsion Laboratory, New York University and Imperial College London, among others.

At the University of Washington, scientist Randall T. Moon, Ph.D., had evidence that a certain GPCR was involved in cancer, but needed to understand its structure, as well as identify small molecules that could turn the receptor on or off. Working together with Moon, Vaidehi's team predicted the receptor's structure and rapidly identified 20 possible modulators from a database of hundreds of thousands of molecules — one of which may be a perfect fit.