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Researchers devise powerful new approach to drug design and demonstrate its potential against cancer cells

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Exploring the fundamental mechanism by which a cell-surface receptor transmits its signal, an international team of Ludwig researchers and their colleagues has established proof of concept for an entirely new approach to drug design. They report that a class of synthetic molecules known as diabodies can, from outside the cell, latch onto a target receptor and manipulate it in such a manner as to induce distinct and varying effects within cells and tissues. Led by Christopher Garcia of Ludwig Stanford, the researchers show in lab experiments how this might work, using a diabody to stall the growth of cancer cells isolated from patients with myeloproliferative neoplasms.

Published in the current issue of *Cell*, the study describes how diabodies that bind the erythropoietin receptor (EPO-R), which is involved in the generation of red blood cells, might be fashioned to essentially "tune" the signal it transmits into the cell. This is surprising, since the family of receptors to which EPO-R belongs—the cytokine family—are thought to be the biochemical equivalent of standard light switches: they're either on, or they're off.

"What we've shown is you can use diabodies to dial a cytokine receptor to induce a particular type and intensity of signal and so induce different effects in target cells and tissues," says Garcia.

Though cytokines are involved in many processes relevant to

disease—especially those related to the immune system—their activation can have severe side effects. As a consequence, drug manufacturers have largely (though not exclusively) focused on blocking their signaling rather than activating it. A different class of receptors known as G protein-coupled receptors are, by contrast, far more amenable to "tuned" activation. This is partly why about half of all drugs in use today target such receptors, working in many cases like dimmers rather than switches.

"We wanted to test whether diabodies could be used to similarly tune the signaling of cytokine receptors," says Garcia. "This would open a new approach to therapeutics through the uniquely tailored manipulation of this medically important family of receptors."

Cytokine receptors are activated when their ligands—erythropoietin, in the case of EPO-R—bring two receptors together. This coupling has the effect of juxtaposing molecules already attached to each receptor known as Janus kinases (JAKs). JAK activation initiates a signaling cascade that, depending on the receptor and JAK type involved, turns on the expression of unique suites of genes. Mutations that affect either the JAKs or proteins further down in the cascade play a big role in autoimmune diseases and cancer, among other illnesses.

Garcia and his colleagues show that diabodies—and by extension, EPO—activate EPO-R by variably altering the structure of the part of the receptor outside the cell. Those changes, it appears, alter the geometry of the EPO-R segment inside the cell in a manner that activates JAK2, the JAK family member associated with EPO-R. Crucially, different diabodies induce different structural changes, affecting how vigorously the JAK2s are activated.

Myeloproliferative neoplasms, however, are fueled by a mutant JAK2 known as JAK2V617F that is constantly activated even in the absence of

EPO. "To our surprise, one of the diabodies that only weakly activates EPO-R on normal cells was actually blocking signaling by the mutant JAK," says Stefan Constantinescu, a Ludwig Brussels researcher who participated in the study and is an authority on EPO-R signaling. "Our findings suggest this was due to the mutant JAKs being pulled further apart by the change induced in the receptor's structure."

Drugs devised from diabodies—if they prove effective against other cytokine receptors and are stable in the body—could be used to very specifically block pathologic signals while leaving the healthy variety alone, ameliorating symptoms of disease with minimal side effects.

Other Ludwig researchers involved in the study include Ignacio Moraga—a post-doctoral researcher in Garcia's lab who is first author on the study—Gerlinde Wernig, Irving Weissman and Ravindra Majeti of Ludwig Stanford. The work was supported by Ludwig Cancer Research, the Howard Hughes Medical Institute, the Belgian Federal Science Policy Office, the de Duve Institute at the Université catholique de Louvain and the Fondation contre le Cancer in Belgium. Chris Garcia is also an investigator with the Howard Hughes Medical Institute.

More information: *Cell*, www.cell.com/cell/abstract/S0092-8674(15)00176-2

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