

# THREE DRUGS ARE BETTER THAN ONE

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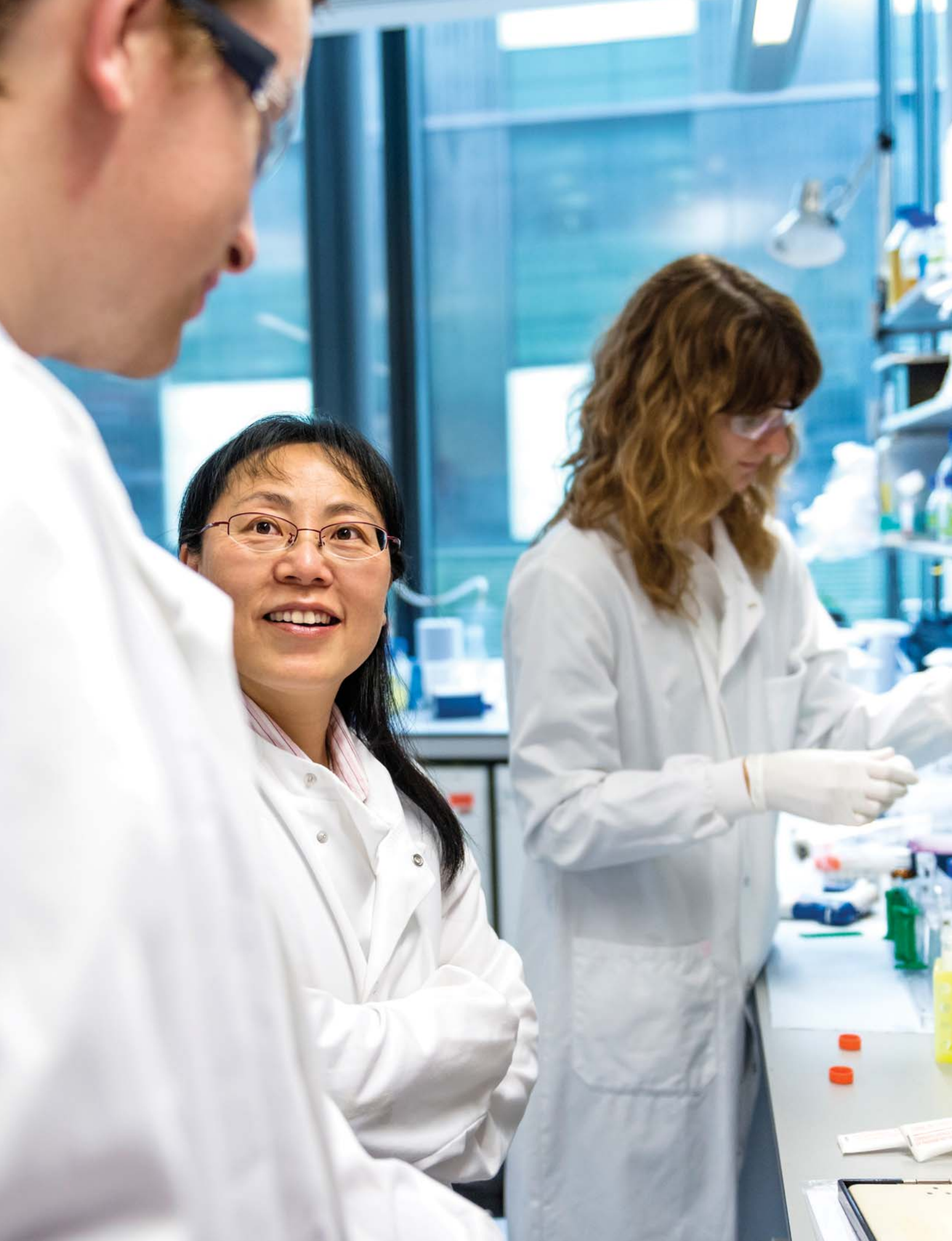
Cancer treatment is rapidly undergoing a shift toward “targeted” drugs, which are designed to act on specific molecules that drive cancer or modulate its growth and metastasis. But these drugs have not all lived up to their original promise; they often only temporarily fend off disease.

One such drug is vemurafenib. It targets a molecule found in more than half of melanoma cancers, a mutant form of the protein B-RAF, which fuels cancer by instructing cells to divide. Vemurafenib inhibits mutant B-RAF, and it can have dramatic effects in melanoma patients, shrinking tumors throughout the body. But the effects of vemurafenib are transient. Tumors invariably roar back, often within several months. [Xin Lu](#), director of Ludwig Oxford, is working on a solution to this issue: combination therapy.

“If we could target a parallel pathway we could potentially create a better therapy,” says Lu. She is conducting experiments combining vemurafenib with drugs targeted to a parallel pathway involving p53, a molecule that puts the brakes on tumors. p53 is nonfunctional in many tumors, including about 90 percent of melanomas. Lu’s approach is to “wake up” p53 with experimental drugs, enabling it to arrest cancer.

Although experimental drugs to reactivate p53 have been developed previously, they are not as effective as researchers had hoped. Lu went back to the laboratory bench to identify molecular regulators of p53 and find new ways to target this molecule. After years of research, she landed on a protein







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called iASPP that binds to p53 and modulates its actions. She and her colleagues then developed a drug-like agent that targets iASPP and wakes up p53. The new agent comes with an added bonus: it synergizes with a previously developed drug that targets p53. Together, the two agents activate p53 more powerfully than either one alone.

The researchers tested these two p53-activating agents in combination with vemurafinib. They observed that the triple combination had a strong effect, killing melanoma cells in culture and resulting in sustained tumor shrinkage in mice. The findings, published in *Cancer Cell*, have implications beyond melanoma. The two p53-activating agents, for instance, could be used in combination with other targeted drugs.

For this project, Lu worked together with her Oxford colleagues, as well as Ludwig melanoma researchers in Melbourne and Baltimore. Lu also credits Ludwig with providing the stable funding needed for the years of basic research that led to this study. “That stability allowed me to tease out the whole difficult molecular pathway involving iASPP,” she says.

Meanwhile, Lu continues to untangle the complicated molecular networks that propel tumors. In 2012 she published a study on the mechanics of another protein that binds p53, a molecular relative of iASPP that helps drive tumors into a dormant state. With time, this work could also lead to new approaches to treat cancer.

## REFERENCES

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## BACK TO THE BASICS



Ludwig's long-term commitment to basic research propels the science necessary to replenish the drug pipeline at its earliest stages. Its strong support of the work of Xin Lu in Oxford is mirrored in Uppsala, Sweden, in the laboratory of Ingvar Ferby, who was recently recruited to Ludwig. Ferby is dissecting the molecular pathways that impinge on epidermal growth factor receptors (EGFRs). EGFRs are a target of cancer drugs such as gefitinib, which shuts down the receptor. The effectiveness of such drugs could be bolstered by the development of combination therapy.

Last year Ferby identified a molecular pathway that prompts cell death—a blow to cancer—when EGFR is shut down. The pathway involves a protein, Mig-6, that binds to the receptor. When the receptor is inactive, Mig-6 initiates cell suicide. The findings could lead to new targeted anticancer agents to tweak cellular processes such as cell death. Some of these agents might be useful in combination with drugs such as gefitinib.