targeted therapy enzalutamide.

Targeted therapies hold promise for the treatment of many types of cancer. But a common predicament is that in many patients, the drugs eventually stop working because tumors become resistant to the therapy. This resistance often occurs when cancer cells develop additional mutations that allow them to evade the drug.

Now a team led by Charles L. Sawyers , Chair of Memorial Sloan Kettering's Human Oncology and Pathogenesis Program , has used a new approach to find a potential drug to attack cancer cells that have become resistant to enzalutamide (Xtandi®), a targeted therapy for the treatment of advanced prostate cancer .

Charles Sawyers, Chair of Memorial Sloan Kettering's Human Oncology and Pathogenesis Program

"For this drug, we started thinking about resistance before we even saw it happen in patients," Dr. Sawyers says. "We knew resistance to enzalutamide would eventually become a problem based on what we have seen with other targeted therapies."

Dr. Sawyers was part of the team that developed imatinib (Gleevec ®), a targeted therapy for the treatment of chronic myeloid leukemia, and he later helped develop dasatinib (Sprycel®) for patients who become resistant to imatinib.

Blocking an Important Receptor

Laboratory work conducted by Dr. Sawyers and his colleagues was instrumental in the development of enzalutamide. Howard I. Scher , Chief of Memorial Sloan Kettering's Genitourinary Oncology Service, led the clinical trial that resulted in the drug's approval by the US Food and Drug Administration in August 2012 for men with metastatic prostate cancer that has spread to other parts of the body.

The hormone testosterone and other male sex hormones, collectively known as androgens, fuel the growth of prostate tumors. Enzalutamide works by blocking the androgen receptors in tumor cells.

“We postulated that mutations in the androgen receptor might be the cause of resistance, if those mutations prevented the drug from blocking the receptor,” explains Dr. Sawyers, who is also a Howard Hughes Medical Institute investigator.

In the current study, the investigators designed a screening method to look for mutations in the androgen receptor that could prevent enzalutamide from blocking its activity. They discovered that androgen receptors with a certain mutation, called F876L, were not inhibited by the drug. Then they confirmed that this mutation was present in prostate cancer cell lines and mouse models that had developed drug resistance.

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Finding a Different Key

The team used computer modeling of the receptor’s molecular structure to predict how that particular mutation might change its shape and prevent the drug from blocking it. Being able to envision the structure also suggested how enzalutamide might be chemically modified so that it could also block the mutant receptor. The computational models were created by Yang Shen at the Toyota Technological Institute at Chicago.

“It’s like a key fitting in a lock,” Dr. Sawyers says. “Once the mutation happens in the lock, the key doesn’t fit properly anymore. We had to find a way to add another notch to the key, to make it fill in the pocket.”

After designing several drugs, which were synthesized at the Organic Synthesis Core facility at Memorial Sloan Kettering, Dr. Sawyers’s team then tested them in cell cultures. They identified one compound, called DR103, that blocks the mutated receptor. They now plan to begin testing it in mice.

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Rational Drug Design

“The idea of ‘rational drug design’ has been around for some time, but there are not many examples of success. This is a great example of how it can work,” Dr. Sawyers concludes. “Within eight months of a new drug being approved, our team already has insight into one mechanism of resistance and a way to overcome it. It’s exciting that we can stay on top of drug resistance in this way.”

The first author of the study was Minna Balbas, a graduate student in Dr. Sawyers’s laboratory who is enrolled in the Gerstner Sloan Kettering Graduate School of Biomedical Sciences. Michael Evans, a chemist in Dr. Sawyers’s laboratory, designed the new compounds, including DR103.

The study was published April 9 in *eLife*, a new online research journal jointly created by HHMI, the Wellcome Trust in the United Kingdom, and the Max Planck Society in Germany.

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