

Yale CANCER CENTER
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**SMILOW CANCER HOSPITAL
AT YALE-NEW HAVEN**

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YALE CANCER CENTER
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breakthroughs

THE YEAR IN REVIEW

Ranjit S. Bindra, MD, PhD

Fighting Gliomas by Disabling DNA Repair

Most radiosensitizers – drugs that are supposed to make tumor cells more sensitive to radiation – work poorly on the malignant brain tumors called gliomas. For that reason, the treatment of gliomas has not advanced much in recent decades. Patients typically have surgery, followed by radiotherapy and chemotherapy. But gliomas are notorious for being resistant to radiation and for recurring in the same location. This usually leads to another invasive round of treatment.

The tumors' resistance and recurrence both seem to stem from their ability to repair double-strand breaks of DNA quickly and then start growing again. Ranjit S. Bindra MD, PhD, Assistant Professor of Therapeutic Radiology and Pathology, wanted to find a radiosensitizer that could disable a glioma's DNA repair system. A glioma that can't repair itself likely can't recur. The challenge was to find such a compound among the hundreds of thousands of possibilities.

Before joining Yale, Dr. Bindra had developed a new way to measure double-strand break repair by using fluorescent proteins that glow red or green when a cell repaired a double-strand break. This technique allowed him to devise a powerful screen to test compounds that might inhibit DNA repair.

"Surprisingly, we ended up with 80 to 90 of them, mostly unknown structures," he said. "But one of them was previously an FDA-approved drug. That interested us very much." Its name was mibefradil, popular for

hypertension in the 1990s but long off the market.

As Dr. Bindra tested the drug further, it kept surprising him. There are two main DNA repair pathways: homologous recombination (HR) and non-homologous end joining (NHEJ). HR repairs DNA breaks by using a copy from within the cell. NHEJ simply sticks together the two ends of a double-strand break. About 90 percent of our cells, both normal and tumorigenic, repair DNA through NHEJ, because this pathway is easier and a second copy for HR is not always available in the cell.

"We found that mibefradil was specifically blocking non-homologous end joining," Dr. Bindra explained. He tested it with radiation on glioblastoma cell lines and learned that it not only blocked double-strand repair but was relatively nontoxic to normal tissues.

The drug works on gliomas like this: one of the proteins within the NHEJ pathway is called DNA-PK (protein kinase). "It basically orchestrates the process of trimming and preparing the ends of double-strand breaks for religation," Dr. Bindra said. "Our preliminary data suggested that mibefradil blocks the ability of DNA-PK to function."

During his investigation of the drug, he also learned that a start-up biotechnology company in Virginia, Tau Therapeutics (now called Cavion), was also researching the potential of repurposing mibefradil against gliomas. Dr. Bindra connected with the company and the two groups are now closely collaborating. Researchers at Cavion discovered that

the drug not only blocks the function of DNA-PK, but it also cleaves the protein in two.

With Cavion's support, Dr. Bindra has been designing a Phase I trial to open at Smilow Cancer Hospital for patients with recurrent glioblastomas. He hopes to enroll 20 to 30 patients for this study, and to begin treatments by late spring, finishing in about a year and a half.

"Since mibefradil is already available as an Investigational New Drug (IND) for cancer applications," he said, "we can give it to patients a week before surgery and get a tissue specimen during surgery. We then will be able to study in vivo tissue and see whether the drug is getting into the tumor and is cleaving DNA-PK. It's a highly translational study. We're quite excited, and because of the collaborative nature of Yale, the neurosurgeons, neuro-oncologists, pathologists, and radiation oncologists are all excited to get involved."

The hope is that using mibefradil with radiation will greatly prolong survival in patients with recurrent gliomas. If the trial is a success, Dr. Bindra hopes that the drug will become a standard treatment for glioblastomas. He also hopes that this trial will add to the growing momentum of bench-to-bedside research at Yale Cancer Center. "We want to test as many new therapies in glioma patients as possible," Dr. Bindra concluded. "If you build it they will come...and we want drug companies and patients to know that this is the place to come for novel, cutting-edge therapies."