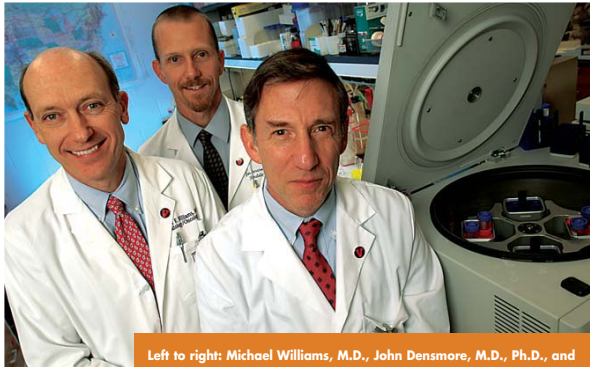




DYNAMIC RESEARCH DRIVES CANCER CENTER TO CUTTING EDGE

The fight against cancer is increasingly moving to the cellular and even molecular level. Building on strengths in molecular biology, cell signaling, cytogenetics and pathology, the **UVA Cancer Center** is emerging as a leader in cancer research. At the forefront of UVA's work are novel approaches that explore genetically targeted therapies and human immune therapies for patients with some of the most problematic cancers.



Left to right: Michael Williams, M.D., John Densmore, M.D., Ph.D., and Ronald Taylor, Ph.D., collaborate in a translational investigation of the mechanism of action of rituximab in patients with CLL.

BASIC SCIENCE/CLINICAL PRACTICE TEAM LAUNCHES PROMISING LEUKEMIA STUDY

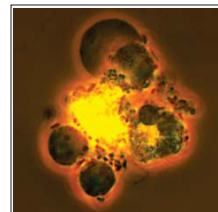
Despite the success of immune therapies on some types of hematologic cancers, effective treatment options are still limited. A team of basic scientists and clinicians at UVA is exploring the use of monoclonal antibodies and vaccine therapies to improve outcomes for patients with the most common forms of leukemia and lymphoma.

Because the field of hematologic oncology focuses on biological and molecular mechanisms that control the development and spread of cancer, it has traditionally been integral to identifying new cancer treatments – particularly in the area of immunotherapy. But the effectiveness of immune therapies can vary depending on cancer type. Rituximab, a genetically engineered monoclonal antibody, can destroy many types of lymphoma cells, but is only modestly effective against chronic lymphocytic leukemia (CLL).

Intrigued by this contradiction, UVA biochemistry professor Ronald Taylor, Ph.D., and hematology/oncology professors Michael Williams, M.D., and John Densmore, M.D., Ph.D., initiated a study to determine why rituximab was less effective in CLL. They discovered that a standard weekly dose led to “shaving,” wherein leukemia cells lose the protein target and become resistant to rituximab. The team launched a pilot study using frequent, low doses of rituximab in 12 patients and saw a significant reduction in leukemia cells in 11 cases.

“We are excited by the possibility of offering less toxic, more effective therapies that can provide better and longer responses and provide patients with an improved quality of life,” says Williams, leader of UVA's hematologic malignancies team. “This study shows a very promising new approach to making the treatment more effective and safer for treating patients with CLL.”

The team is planning to open a Phase II clinical trial in early 2006 that combines a dose-modified schedule of rituximab with an immune-system stimulator. “We're hopeful that our findings could have important implications for the future use of immune therapies in the treatment of many other cancers,” Williams says.



This blood sample from a CLL patient was processed and stained to demonstrate bound rituximab and complement on targeted cancer cells. This image was on the cover of the March 2004 issue of the *Journal of Immunology*.

A FRESH LOOK AT BRAIN TUMOR TREATMENT

Another groundbreaking area of cancer research at UVA is the targeted treatment of adult brain tumors. Patients diagnosed with brain tumors have few effective treatments available to them. A leading neuro-oncologist at UVA seeks to improve the odds – and options – by leading a multi-center clinical trial focused on low-grade gliomas: slow-growing but nonetheless fatal tumors with a historically poor prognosis.

“Current forms of treatment leave a lot to be desired,” says David Schiff, M.D., co-director of UVA's Neuro-Oncology Center. “In the world of brain tumors, low-grade gliomas are considered almost benign. At the same time, when you're 30 or 40 years old and told you have six years to live, it doesn't sound very benign – it sounds pretty terrible.”

The Phase III trial will explore the relationship between radiation and chemotherapy. In addition to improving survival rates, Schiff hopes to refine treatment criteria so more patients receive effective treatment while minimizing side effects. “If you knew that your tumor was not going to be sensitive to a certain type of chemotherapy – even if that therapy helped other patients – you wouldn't take it,” he says. “It would be ideal to pre-select which patients are going to benefit from the drug.”

Low-grade gliomas have historically been treated with radiation, which slows growth and occasionally shrinks them, but is not a cure. Even then, the average survival rate is about seven years. A new chemotherapy called temozolomide offers some benefit for patients with gliomas.

A recent national trial for glioblastomas – the most common and deadliest form of adult brain tumor – showed a combination of radiation and temozolomide was more effective than radiation alone. Schiff's trial examines the potential of using the same approach in patients with low-grade gliomas.

Schiff is using chromosomal changes and the presence of a certain protein to target chemotherapy treatment more precisely. Some evidence suggests chemotherapy is most effective in those with a loss of certain chromosomes, he says. “The trial will examine whether these chromosomes help determine if a patient will benefit from the addition of chemotherapy to radiation.”

Studies also show that patients who produce large quantities of a protein that “rescues” tumor cells from temozolomide receive only marginal benefits from the drug. Those who produce minimal amounts derive substantial benefits. Schiff's team will use this information to determine which low-grade glioma patients will benefit from chemotherapy. Says Schiff, “We have not had good tests historically for determining which patients will benefit from chemotherapy, so it will be a real step forward if we find these tests are predictive.”

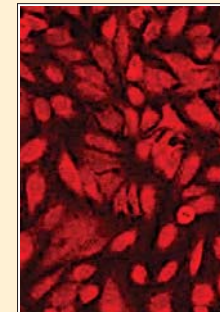
To refer a patient to the UVA Cancer Center, call 800-552-3723.

Saliva Screen Holds Promise for Ovarian Cancer Detection

Gynecological tumors are among the most difficult to detect early and accurately, but two UVA physicians are exploring painless and non-invasive methods so patients can begin suitable treatment as early as possible.

Amir Jazaeri, M.D., and Kristen Atkins, M.D., have established a protocol to investigate new genetic markers – including proteins found in saliva – to screen and diagnose gynecologic malignancies.

Because it is rarer and more difficult to detect than some other gynecological problems, ovarian cancer is the primary focus. “The problem of screening for ovarian cancer is that it's not a very common disease,” Jazaeri says. “Many women will be told it is possible they have ovarian cancer and need to undergo a surgical procedure to remove an ovary or cyst. But only a fraction will turn out to have ovarian cancer.”



Molecular beacons (fluorescently labeled DNA probes) can be used to visualize the expression levels of target genes in cancer cells. This figure demonstrates the expression of GAPDH, a “house-keeping gene” in SKOV3 ovarian cancer cells. Multiple probes tagged with different fluorochromes can be used to investigate the expression of several targets simultaneously.

Besides being non-invasive, saliva testing precludes problems associated with blood sampling: The presence of fewer red and white blood cells makes it easier to detect significant proteins, and samples are easier to obtain.

Jazaeri and Atkins will continue preliminary experiments over the next year and move on to clinical testing and trials based on the results. “This is really a novel approach for early detection and diagnosis of ovarian cancer,” Jazaeri says. “But its ultimate utility remains to be seen.”