

# Uncovering the Biology of Cancers in Adolescents and Young Adults

The first scientific journal dedicated to cancers in adolescents and young adults (AYAs) published its first issue in March, marking a milestone for the emerging field of AYA oncology. But as experts noted in a [roundtable discussion](#) in the issue, the field faces many challenges, particularly when it comes to understanding the biology of these diseases.

At one point in the conversation, Dr. Archie Bleyer of the St. Charles Regional Cancer Center in Bend, OR, shared a concern about the state of the science. "My concern, most of all, is that we have not understood the biology of these diseases because we have not researched them thoroughly enough," said Dr. Bleyer. "And therefore we may not know how to treat them as well as we could."

The participants agreed that a lack of tumor samples for study has slowed progress. Most specimens are collected during clinical trials, and AYAs have long been underrepresented in the limited number of trials open to them, though this may be changing.

Although the biology of AYA cancers is poorly understood, recent evidence suggests that some of these diseases may have unique [genetic](#) and [biological](#) features. Much of the research to date has involved [acute lymphoblastic leukemia](#) (ALL), which is the most common pediatric cancer but also occurs in teens and young adults.

"We now have more evidence that there are distinct AYA subtypes of ALL, though the [genomics](#) of these subtypes needs to be clarified," said Dr. Bleyer, who is also a clinical research professor at Oregon Health and Science University.

He cited work done by Dr. Christine Harrison of Newcastle University in the United Kingdom. Her team of researchers found that some AYAs with ALL have genetic changes that are typical of younger patients, whereas others have previously unknown alterations.

## Profiling Tumors

A clearer picture could emerge from a genomic analysis of more than 500 tumors from AYAs with ALL. The [study](#), now under way, extends a [recent analysis of tumors](#) from children with ALL to teens and young adults.

This study is a major first step toward understanding how the biology of ALL differs between early childhood and early adulthood, noted Dr. Stephen Hunger of Children's Hospital Colorado and the University of Colorado School of Medicine. He also chairs the ALL committee of the Children's Oncology Group.

Some clues have already emerged from this work, according to Dr. Cheryl Willman, director of the University of New Mexico Cancer Center and a leader of the study. For instance, some AYA tumors have genetic alterations that are often seen in older children with ALL who are at high risk of [relapse](#). (AYAs and high-risk older pediatric patients tend to have worse outcomes than the vast majority of younger children with ALL.)

"We're very interested in the final results," said Dr. Nita Seibel of the [Clinical Investigations Branch](#) in NCI's Cancer Therapy Evaluation Program. "The analysis could support the premise that ALL in AYAs is a different disease than what we see in pediatrics, where the cancer tends to respond to treatments."

The first phase of the AYA genomic profiling study is nearly complete. "We should have results to share in approximately 3 months," co-leader Dr. Charles Mullighan of St. Jude Children's Research Hospital wrote in an e-mail.

## Discovering Potential Targets

By focusing on patients with poor outcomes, Drs. Mullighan and Willman and their colleagues have tried to elucidate the biology of these diseases and identify potential therapeutic targets.

The strategy appears to be paying off. In the pediatric study (part of the [Childhood Cancer TARGET Initiative](#)), the researchers [identified cancer-related mutations](#) in members of the *JAK* kinase gene family, along with other alterations. Mutations that increase the activity of JAK proteins have been seen in several cancers, and drugs that inhibit JAK are in early-phase clinical trials.

"The discovery of these mutations has allowed us to develop clinical trials of [targeted therapies](#) that we hope will improve the care of these patients," said Dr. Willman. Eventually, the researchers would like to analyze the genomes of adult tumors and compare the age groups.

"We think the spectrum of genetic lesions in the disease changes with age," said Dr. Willman, noting that ALL could be a model for investigating other AYA cancers.

## A Workshop on AYA Biology

Two years ago, NCI and the Lance Armstrong Foundation convened a workshop on the biology of cancers in AYAs. The meeting focused on ALL, as well as **breast** and **colorectal** cancers, and there was no clear consensus about whether these diseases have distinct biological features.

"At the time, the best evidence for a biological difference was in colorectal cancer, but some of that evidence was from small studies that were limited in scope," said Dr. James V. Tricoli of NCI's **Cancer Diagnosis Program** and a co-author of a recent **commentary** about the meeting. "None of the evidence was clear-cut," he added.

The authors of the commentary agree with many in the field that more research is needed on the underlying biology of AYA cancers. It will also be important to learn whether these differences influence the clinical behavior of these cancers, they added.

"We need to understand the biology of the disease to ensure that we're giving patients the most appropriate treatment without over-treating them," said Dr. Anna Franklin, medical director of the Adolescent and Young Adult Program at the University of Texas M. D. Anderson Cancer Center. Other nonbiological factors may also influence outcomes, such as compliance with treatment and the unique **psychological and social issues** facing AYA patients.

In colorectal cancer, she noted, the standard treatments are designed for older patients, and these regimens may not be the most effective in young adults where the disease may have a distinct biology. Dr. Franklin is starting a study of colorectal cancer biology in young adults. The study, done with colleagues at M. D. Anderson and the University of Colorado, will compare different biologic features of tumors from younger and older patients, using freshly collected tissue and samples from tumor banks.

In breast cancer, few, if any, molecular differences have been identified in AYA patients that could distinguish these tumors from those that arise later in life.

"Most of the evidence [at the workshop] suggested that there were relatively few unique molecular differences in breast cancers that occur in the younger age group compared to when the disease occurs in older women," noted Dr. Donald Blair of NCI's **Division of Cancer Biology**.

This conclusion was supported by a **recent study** that also found few age-specific differences in the biology of breast tumors. Age alone, the study authors concluded, "does not appear to provide an additional layer of biologic complexity" above that of the particular subtype and grade of breast cancer.

But younger women are more commonly diagnosed with more aggressive breast cancer subtypes than their older counterparts, noted the study's lead author, Dr. Carey Anders of the UNC Lineberger Comprehensive Cancer Center. "At present, the reason for this difference is not completely understood and is certainly worthy of further study," she wrote in an e-mail.

## Comparing Tumors in a Single Patient

Genomic approaches have also been used to investigate the biology of **neuroblastoma**, a cancer that arises in immature **nerve cells**. The disease primarily affects infants and children, but it can also occur in young adults. As with other AYA cancers, young adults tend to do worse than children.

"This disease in young adults is also very different biologically than the disease that occurs in childhood," said Dr. Javed Khan of the **Pediatric Oncology Branch** in NCI's Center for Cancer Research.

His group recently sequenced all of the protein-coding regions of the genome (known as the exome) in four samples from a 19-year-old woman with neuroblastoma whose cancer had spread to several organs. By comparing the exomes of normal cells, the primary tumor, and metastatic lesions, the researchers identified six potentially cancer-related mutations shared by the primary tumor and two metastases.

"The finding supports the hypothesis that all of the tumors originated from a common progenitor cell, and that few significant changes occurred during more than 3 years of treatment," said Dr. Khan. His group plans to publish the results this year.

Because of the poor outcomes associated with cancers in AYAs, more research is needed in this field, Dr. Khan added. He is planning a scientific meeting next year that will address the genomics of AYA cancers, particularly **sarcomas**.

## Insights from Clinical Trials

Along with genomic studies, **clinical trials will be critical** for advances in treating AYA cancers, several researchers said. In ALL, for instance, prospective trials could help resolve a debate about whether AYAs with the disease should receive pediatric rather than adult regimens.

For a decade, researchers have known that some AYAs with ALL fare better when treated with pediatric regimens. These observations have come from retrospective analyses of clinical trials, however, and the reasons for the findings are unknown.

A prospective trial, [CALGB-10403](#), could provide answers. This NCI-sponsored study is evaluating the effectiveness and side effects of a pediatric regimen in adolescents and young adults. "This is an important study because there has been debate over whether AYAs can tolerate the toxicities associated with pediatric-based approaches," said Dr. Seibel.

Prospective trials are also under way in Europe and at the Dana-Farber Cancer Institute, where pediatric ALL regimens have been the standard of care for patients between the ages of 1 and 50 since 2001.

Many doctors are hoping that the results of these studies will lead to a consensus about how to treat ALL in AYAs, noted Dr. Daniel J. DeAngelo, director of the adult leukemia clinic at Dana-Farber. He frequently receives phone calls from community doctors seeking advice about how to treat young adults.

"This question creates a lot of angst in the community," said Dr. DeAngelo. The National Comprehensive Cancer Network is reviewing the issue and will likely make a recommendation, he noted.

### **Provocative Questions**

Meanwhile, the Dana-Farber group is trying to learn about the biology of ALL in AYAs. This work, they hope, will lead to a genetic or biological test that can identify, at the time of diagnosis, which young adults are most likely to respond to pediatric ALL regimens.

The researchers are also considering some provocative questions. "When does a younger adult become an older adult?" said Dr. DeAngelo. "We don't really have a handle on that yet."

As answers to this and other questions about AYA cancers emerge in the coming years, researchers can share their results in the *Journal of Adolescent and Young Adult Oncology*.

"I really believe we're going to prove in the years ahead that the biologic features of these cancers are different from the same cancers that arise in other age groups," said the journal's editor, Dr. Leonard Sender of the University of California, Irvine, and the Hyundai Cancer Institute at Children's Hospital of Orange County. "But we have to do the science."

—*Edward R. Winstead*