CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Group Chair
Peter C. Adamson, M.D.
adamson@email.chop.edu

Group Vice Chair
Susan Blaney, M.D.
smblaney@txch.org

Chief Operating Officer
Elizabeth O'Connor, M.P.H.
econnor@childrensoncology group.org

Chief Administrative Officer
Maria Hendricks, M.S.N, R.N. C.C.R.P.
hendricksm@email.chop.edu

Group Statistician
Meenakshi Devidas, Ph.D.
mdevidas@cog.ufl.edu

Associate Group Statistician
Todd Alonzo, Ph.D.
talonzo@childrensoncology group.org

Group Chair's Office
The Children's Hospital of Philadelphia
3501 Civic Center Blvd
CTRB 10060
Philadelphia, PA 19104

P 215 590 6359
F 215 590 7544

Group Operations Center
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

Statistics & Data Center Headquarters
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
P 626 445 4334

Gainesville Office
6011 NW 1st Place
Gainesville, FL 32607

P 352 273 0556
F 352 392 8162

Dear cancer research advocate & supporter,

We are truly grateful for the programs, advocacy work, research funding and other investments that you have made in the fight against cancer. We understand that you have some specific involvement and interest in funding promising cancer research. Recently, **Julie Guillot, a pediatric cancer parent and advocate, approached our team for input in identifying the single, highest priority, strategic research project** that could make the most significant impact on improving outcomes for young people fighting Acute Myeloid Leukemia (AML). This letter outlines the most current and informed recommendation of the Children's Oncology Group (COG), the world's largest organization dedicated to childhood and adolescent cancer research. **We support Julie's efforts, as well as Michael Copley's and other committed AML parents and advocates, in championing the TARGET Pediatric AML Initiative, outlined in this letter, and encourage you to meet with them (and the COG team) to learn more and get involved.**

As you many know, AML is the deadliest leukemia in both children and adults. Today's treatments have changed little in decades, and are highly toxic (resulting in significant short and long-term side effects). They can be as life-threatening as the cancer itself. Both young patients and their families suffer terribly, as some struggle for years through multiple rounds of intense inpatient therapy, dangerous complications, and relapses.

AML is a highly complex, diverse group of diseases driven by multiple genetic mutations, some occurring in combinations that can be patient-specific. As such, "one size fits all" or single-agent therapeutic strategies may be less effective against this disease. Also, because COG has recently demonstrated that the biology of AML in young people (up to about age 35) differs significantly from seniors, **studies that focus on older patients with AML may not yield breakthroughs that can be applied to younger populations.** Since the mutations driving the disease vary by age, therapeutic targets for each patient group will likely differ as well. **The focused discovery of new targets will be key to maximizing both existing and emerging therapies**, including new precision drugs and immunotherapies like re-engineered T-cells.

The *TARGET Pediatric AML Initiative* was identified by COG AML leadership as the "highest potential and greatest need" effort in our research portfolio to benefit children, adolescents and young adults fighting AML. The goal of this multi-year, strategic initiative is to establish intellectual and physical resources, creating a robust infrastructure or "rapid discovery platform" using the most advanced tools available (genomic and RNA sequencing, proteomic and epigenomic profiling). New therapeutic targets will be identified and validated. These findings will be quickly translated into novel therapeutics and clinical trials/protocols for AML in young people.

We propose to:

1) **Discover and validate biomarkers to maximize the use of existing drugs** and
2) **Guide development of new targeted therapies**
3) **Design smarter, patient-specific clinical trials** geared to patients most likely to respond
4) **Improve early disease detection & monitoring** (especially early relapse detection)
5) **Develop personalized therapy** recommendations (to improve outcomes and reduce toxicity)
6) **Benefit current patients now** by leveraging genomic sequencing and the analysis of a newly diagnosed patient's specific cancer profile to discover and maximize best available treatment options

Enormous investments and progress have been made in developing new weapons to fight cancer. However, **new treatments will be effective only to the extent they are matched to the correct patients.** Combined (and personalized) targeting may also be necessary to improve outcomes in very heterogeneous cancers like AML.

COG believes it is critical to fully analyze the molecular landscape of pediatric AML, including the genome, epigenome, transcriptome and proteome (via sequencing of a large cohort of approximately 1000 patients) to exploit leukemia-associated variants for therapeutic targeting. Early analysis of 250 patient samples has identified variants that are unique to childhood AML and appear likely to be targets for small molecule inhibitors or targeted immunotherapies. For example, an existing lung cancer drug, a modified T-cell (TCR) in development for pancreatic cancer, and a new CAR T-cell design were recently identified as having potential benefit in the pediatric AML population as a direct result of this early-stage research. We believe there is more to discover. We would gladly present these promising findings to you and your organization, as well as more detailed information about this initiative.

Because this new research initiative is a large-scope, highly strategic, and costly effort, funding via traditional grant mechanisms has been challenging. *However, for perspective, the total cost of this effort is less than treating a handful of complex AML patients.* As such, Julie Guillot and Michael Copley have, with other pediatric AML families and advocates, volunteered to lead the charge in raising awareness and funds (and encouraging collaboration) to accelerate this effort.

While COG is very thankful for grants it has received to date to move this, and other, work along, **the current practice of funding individual and independent projects has led to incremental and slow progress.** ***We believe we can move faster and more efficiently.*** **We propose restructuring our approach to pediatric AML research and therapy by creating a central leadership and funding mechanism, through which discoveries can be more rapidly validated, prioritized, and tested in the clinic.** The current, rapid pace of discovery in cancer research coupled with breakthroughs in immune-based and targeted therapies have fueled our increased sense of urgency, especially our drive to gain a comprehensive understanding of pediatric AML biology and targetable mutations.

We envision a day, in the next 12-24 months, when a child with newly diagnosed AML will undergo comprehensive testing to identify patient-specific leukemic lesions for targeting. These findings will translate into a tailored treatment protocol that will not only spare the patient unnecessary side-effects and risks, but also increase chances for cure. At the current pace of discovery, this vision will not be realized for years and maybe even decades. **Donors and foundations teaming together and pooling resources can dramatically accelerate the pace of discovery.**

The Children's Oncology Group is fortunate to have many of the world's leading experts in childhood cancer, and in AML, as actively collaborating members, as well as an unparalleled collection of well annotated biospecimens to make this vision reality. **COG leadership, as well as pediatric oncologists who care for children with AML, have uniformly expressed unsurpassed support to further define, validate and exploit possible targets in childhood AML and make progress in tailored/targeted therapy capabilities.** We would welcome the opportunity to explore and partner on such an effort with you and your organization.

Thank you in advance for considering this initiative. Feel free to contact Julie (julie@bestrongfighton.com, 512-497-6495), Michael Copley (baydays@mac.com, 619-980-8118) or Dr. Soheil Meshinchi (smeshinc@fredhutch.org, 206-667-4077) with questions.

Sincerely,

E. Anders Kolb, MD
Chair, COG Myeloid Disease Committee
Alfred DuPont Hospital for Children, Wilmington, Delaware

Soheil Meshinchi, MD, Ph.D.
Chair, COG Myeloid Disease Biology Committee
Seattle Children's Hospital & Fred Hutchinson Cancer Research Center, Seattle, Washington

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