A Concise History of the Cancer and Leukemia Group B

Richard L. Schilsky,1 O. Ross McIntyre,2 James F. Holland,3 and Emil Frei III4

Abstract A formal National Cancer Institute Clinical Trials Cooperative Group Program was conceived in 1955 when Dr. Sidney Farber, Mary Lasker, and others approached Congress with a proposal to increase support for studies of chemotherapy of cancer. In response, Congress awarded US $5 million to the National Cancer Institute to establish the Chemotherapy National Service Center. The founders of the Cancer and Leukemia Group B, James Holland and Emil (Tom) Frei, III, envisioned that successful chemotherapy for leukemia and other hematologic malignancies could be expeditiously realized through carefully designed clinical trials executed uniformly as a cooperative effort among several institutions. In 1956, the group was designated the Acute Leukemia Group B by the Chemotherapy National Service Center Clinical Studies Panel, and Frei was elected chairman. In the ensuing 50 years, the Cancer and Leukemia Group B has expanded to national and even international membership, and its research programs have expanded to include all of the common adult solid tumors and hematologic malignancies in a multidisciplinary effort to improve the outcomes for patients with cancer and to better understand the biology of malignant disease.

The Cancer and Leukemia Group B (CALGB) began to take shape in 1953 when James F. Holland arrived at the National Cancer Institute (NCI) upon the opening of the Clinical Center and initiated a clinical trial that combined two “targeted” therapies for treatment of acute leukemia (methotrexate and 6-mercaptopurine). The trial was based on studies by Lloyd Law of analogues of these agents in mice bearing L1210 leukemia that showed the combination to be curative. Holland moved to Roswell Park Memorial Institute (RPMI) in 1954, before the trial was completed, but Gordon Zubrod, the newly arrived chief of oncology at NCI, agreed to continue the study in Bethesda, thus initiating the first multicenter study of acute leukemia. The founders of the CALGB, James F. Holland and Emil (Tom) Frei, III, who had been recruited by Zubrod, envisioned that successful chemotherapy for leukemia and other hematologic malignancies could be expeditiously realized through carefully designed clinical trials executed uniformly as a cooperative effort among several institutions.

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Complete remission was prospectively defined as <10% leukemic blasts in the bone marrow, hemoglobin >11 g/dL with normal WBC and platelet counts, no evidence of organ infiltration by leukemia on physical examination, and no symptoms that could be ascribed to leukemia. Notably, the protocol contained no background section to justify the

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In 1956, the group was designated the Acute Leukemia Group B by the Chemotherapy National Service Center Clinical Studies Panel, and Frei was elected chairman. The Group expanded to national and even international membership during the ensuing years, and its research programs embraced the entire spectrum of hematologic neoplasia in children and adults.

Tom Frei resigned as Group Chair in 1962, and Holland was elected chairman. Under his leadership over the ensuing 18 years, pediatric neoplasms other than leukemia came under study; for example, multimodality treatment involving surgery, radiotherapy, and chemotherapy for Wilm's tumor began in 1965. Studies of metastatic carcinoma in adults were initiated in 1968, and trials assessing adjuvant chemotherapy for breast cancer began in 1974. Because of the increasing scope of the research program, the focus on solid tumors and hematologic malignancies, and the recruitment of other oncologic specialists, the Group voted in 1976 to change its name to the CALGB.

A formal disease committee structure, including committees on Breast Cancer, Respiratory Cancer, GI Cancer, and Other Tumors, was put in place at that time.

In 1979, the pediatric division of CALGB was disapproved in peer review. The bulk of that membership joined with the former pediatric members of the Southwest Oncology Group to form the Pediatric Oncology Group. Many of the fundamental principles of chemotherapy and the groundbreaking studies that showed the curability of childhood acute leukemia were accomplished by ALGB. In a coherent and interrelated series of studies spanning 25 years, the Group first showed the importance of combination chemotherapy for ALL, the value of maintenance chemotherapy after remission induction, the role of vincristine and prednisone for remission induction, the importance of methotrexate dose scheduling, the use of intrathecal methotrexate, and the importance of timing in the scheduling of asparaginase. These observations and principles provided the foundation for combination chemotherapy studies of solid tumors and the framework for conducting multicenter clinical trials. Indeed, the founders of CALGB and the other cooperative groups invented many of the standard clinical trial procedures used today. Eligibility criteria, toxicity grading, response criteria, uniform data collection tools, quality assurance measures, and the fundamental principles of statistical analysis of clinical trials can all trace their origins to early cooperative group studies.

Immunotherapy studies, focused on the use of the methanol extractable residue of Bacillus Calmette-Guerin, were initiated by CALGB in 1975. This agent was studied in detail across multiple disease areas, and the correlative studies that accompanied the clinical trials led to the formation of an Immunology Committee with expertise in immunodiagnosis and monitoring of immune function. Under the leadership of Clara Bloomfield, this committee evolved over time to become the Immunology and Cytogenetics Committee, the forerunner of the Correlative Science for Leukemia and Lymphoma Committee and the current Leukemia Correlative Science Committee.

A Psychiatry Committee was formed under the leadership of Jimmie C. Holland in 1976 to bring quantitative assessment to important aspects of cancer therapy, such as quality of life, symptom management, and patient compliance. Pathology was also established as a modality committee in 1976, and the Group adopted a new Constitution and By Laws in 1978 that affirmed the primacy of multidisciplinary research in CALGB and the key role of modality committees in the scientific leadership of the Group.

In 1980, Tom Frei was again elected Group Chair and put in place the scientific and administrative structure that supports CALGB to this day. Oliver Glidewell was succeeded by Jim Anderson as Group Statistician; Brad Patterson was appointed Chief of Staff in the Central Office; and Karen Antman, now Dean of the Boston University School of Medicine, served as Assistant to the Chairman, a role analogous to that of Executive Officer today.

Since then, the CALGB research program has become even more diverse and multidisciplinary. In 1990, Ross McIntyre was elected Chairman, and in the next 5 years, he organized the Solid Tumor Correlative Science, Surgery, and Prostate Cancer Committees. He also conducted a national search for a new Group Statistician and Statistical Center that led to the
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acknowledgments

we have been privileged to lead an extraordinary group of creative and dedicated physicians, laboratory scientists, statisticians, nurses, clinical research associates, administrative staff, and other oncology specialists over the past 50 years. the accomplishments of CALGB belong to them and to our colleagues in the other cooperative groups and at the NCI. none of the accomplishments of the cooperative group program would have been achieved without the courageous participation of tens of thousands of patients with cancer and their family members. We are inspired by them and devoted to using all the tools at our disposal to extend their survival and improve the quality of their lives.

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Reference
