MAJOR RESEARCH ACHIEVEMENTS

of

The Chemotherapy Foundation Grant Programs 1968 through 2016

The Chemotherapy Foundation®

THE CHEMOTHERAPY FOUNDATION

Years ago "cancer" was a word people whispered – the name of a dread, mysterious and fatal disease. Today, medicine has taken us from those dark ages to a time when many disseminated cancers can be controlled and even cured.

We have developed this brochure to tell you about some of the major research achievements, specifically those inspired and supported initially by funding from The Chemotherapy Foundation, that have contributed to this progress in cancer control.

The Chemotherapy Foundation was founded in 1968 by Ezra M. Greenspan, M.D. with the philanthropic efforts of Jack Alpern, Mannie Halbert and Abe Margolies. The pioneer efforts of Dr. Greenspan (deceased 2004) over a 50-year period are acknowledged as having introduced modern curative combination chemotherapy for solid tumors, particularly in breast cancer and ovarian cancer. His concepts and clinical studies, together with the fundamental work of Dr. Richard Cooper, established the curative potential of adjuvant chemotherapy.

As Chairman and Medical Director from 1968-2004, Dr. Greenspan, Clinical Professor of Medicine (Oncology) Emeritus, Mount Sinai School of Medicine, guided The Chemotherapy Foundation's support of innovative research studies and professional and public education programs.

Now under the guidance of Franco M. Muggia, M.D., Chairman and Medical Director, Professor of Medicine (Oncology), Laura and Isaac Perlmutter Cancer Center, NYU Langone School of Medicine, The Chemotherapy Foundation continues its mission to realize a cancer-free future for every family.

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• **Developed** a program for submyeloablative chemotherapy with allogeneic mini-transplants for patients with hematologic malignancies, kidney cancer and melanomas. This represents an important advance in the treatment of these resistant cancers. The autologous bone marrow transplant program is using new and innovative methods for transplantations for multiple myeloma. The Leukemia Service has developed innovative chemotherapy protocols for people with acute and chronic leukemia. The Histogenetics Laboratory working with the Division has identified new HLA Class II antigens. The gene therapy program, established in collaboration with the Department of Pharmacology, was a retroviral construct with the interferon gene and has been shown to reliably transect human stem cells. *Dr. Tauseef Ahmed, Chief—Division of Oncology, Westchester Medical Center & New York Medical College; Professor of Medicine, New York Medical College; Director—Blood Cell Transplant and Collection Center, Westchester Medical Center.*

▲ **Initiating** in the coming year (2017), the Aifantis Laboratory will pilot a clinical trial that will test the efficiency of CDK4/6 inhibition (in combination with chemotherapy) in pediatric acute lymphoblastic leukemia, justified by pre-clinical findings supported by the Chemotherapy Foundation and published in the journal *Cancer Cell* (*Sawai et al. 2012; Carroll et al. Clinical Cancer Research, 2017*). Moreover, and in collaboration with Dr. Ari Melnick's lab at Weill Cornell, Dr. Aifantis and his team identified an antagonistic relationship between BCL6 and NOTCH2 in follicular lymphoma, suggesting that NOTCH2 activators could lead to suppression of disease progression (*Valls et al. Cancer Discovery, 2017*). In addition, the Aifantis group identified the member of the Mediator complex MED12 as a molecular regulator of promoter-enhancer activity and initiation of gene transcription in hematopoiesis and leukemia (*Aranda-Orgilles et al. Cell Stem Cell, 2017*). MED12 is frequently mutated in both solid tumors and blood malignancies. These studies suggested that these mutant forms affect enhancer activity altering the gene expression landscape in these diseases. *Dr. Iannis Aifantis, Professor and Chair—Department of Pathology, New York University School of Medicine.*

• **Demonstrated** the selective exposure of a unique cryptic collagen epitope (CLK) within malignant brain tumors (glioblastomas). Importantly, exposure of this cryptic epitope was shown to be associated with angiogenic tumor blood vessels, as well as surrounding malignant tumor cells. Little, if any, expression of this cryptic ECM epitope was detected in association with normal blood vessels or normal brain tissue. A small synthetic peptide, as well as a monoclonal antibody directed to this cryptic collagen epitope, were shown to inhibit endothelial and glioblastoma tumor cell adhesion and migration in vitro. Taken together, these novel findings are consistent with the possibility that this non-cellular CLK cryptic collagen epitope may represent a highly selective new therapeutic target for the treatment of human brain tumors. *Dr. Peter C. Brooks, formerly Associate Professor and Director—Angiogenesis and Radiation Research, New York University School of Medicine; now Senior Scientist, Center for Molecular Medicine, Maine Medical Center Research Institute.*

• **Introduced** cisplatin moderate high-dose therapy and superiority of drug therapy (in combinations) for ovarian cancer, subsequently confirmed in Mayo Clinic studies. Also accomplished fundamental research in increasing the anticancer effects of 5-FU by altering the biochemistry of the cancer cell with a vitamin related to folic acid. This regimen, tested and modified by the investigator, has now been demonstrated to reduce the rate of recurrence after surgery for colon cancer. Altered the biochemistry of stomach cancer cells with three drugs, which has been confirmed to double the survival of patients with advanced disease. Developed a new algorithm for sensitivity testing of human tumors, leading to new clinical treatments for patients with natural highly resistant or drug-induced resistant tumors. Treatments have achieved more than 50% rates of benefit in resistant pancreatic, stomach and ovarian cancers, some even using unique combinations of failed or normally ineffective drugs, thereby offering drugs a second chance through new partners. *Dr. Howard W. Bruckner, formerly Professor, Division of Medical Oncology, Mount Sinai School of Medicine; subsequently Chief of Medical Oncology, Cabrini Medical Center; now at Bruckner Oncology, Manhattan, NY.*

• **Demonstrated** that somatostatin inhibits breast cancer cells and that it improves the safety of some major breast and gastrointestinal cancer drugs: fluorouracil, irinotecan and adriamycin. *Drs. Howard W. Bruckner, Takao Ohnuma and Rodrigo Erlich.*

• **Following** Dr. Greenspan's demonstration of the

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superiority of two-, three-, and four-drug combinations for advanced breast cancer, Dr. Cooper pioneered curative postoperative adjuvant chemotherapy for breast cancer. This five-drug (polychemotherapy) combination became widely known as the Cooper regimen. *Dr. Richard G. Cooper (retired), formerly Chief—Division of Medical Oncology, Buffalo General Hospital, Clinical Professor of Medicine, SUNY.*

▲ **Demonstrated** that chemotherapy and radiation, which are considered immunosuppressive, can be employed to promote antitumor immunity. First, the dogma that apoptosis, a form of tumor cell death induced by chemotherapy and ionizing radiation, is always immunologically silent, and leads to tolerance rather than immune activation against the tumor, was successfully challenged *(J. Leukoc. Biol. 2005)*. Second, it was shown in pre-clinical breast cancer models that local radiation therapy enhances responses to immunotherapy *(Int. J. of Radiat. Oncol. Biol. Phys. 2004* and *2005,* and *Clin. Cancer Res. 2005, 2006, 2009; Cancer Res. 2015)*. Third, the role of immunoregulatory circuits in determining the response to treatment was demonstrated *(J. Immunol. 2008, Clin. Cancer Res. 2009, Cancer Invest. 2011, J. Clin. Invest. 2012)*. Recently, the immune stimulant imiquimod applied topically was seen to control tumors in patients with skin metastases of breast cancer (*Clin. Cancer Res. 2012*). The combination of imiquimod with local tumor radiotherapy and low-dose cyclophosphamide was shown to cause complete and long-lasting tumor regression in a mouse model of breast cancer metastatic to skin (*Clin. Cancer Res. 2012*), providing the rationale for a clinical trial. Overall, this work shows the potential of employing local radiation as a means of vaccinating patients against their own tumor *(Lancet Oncology 2009, J. Natl. Cancer Inst. 2013, Semin. Radiat. Oncol. 2015, JAMA Oncl. 2015)*. Current efforts are focused on studying the molecular mechanisms of these effects and translating findings to the clinic. *(Clin. Cancer Res. 2016, Trends in Cancer 2016). Dr. Sandra Demaria, Professor of Radiation/Oncology and Pathology, Weill Cornell Medical College.*

▲ **Developed** the reversion of malignant phenotype in human and mouse mammary tumor cells by retinoic acid receptor (RAR) isotype-specific therapy and by targeted epigenetic reprogramming, A hallmark of tumor progression is the loss of cell differentiation coupled with increased cell proliferation and later on acquisition of invasive phenotype that leads to metastatic dissemination and residual disease. It is well known that Vitamin A (retinol) signaling is abnormal in breast cancer, in part due to the loss of some of their receptors and in part because of the reduction in the retinoic acid itself. We found that RARα and RARγ display opposite effects under oncogenic stress in which RARγ promotes tumor development and progression. This finding has important clinical implications because by using RARα isotype-specific agonist it will be possible to re-introduce retinoids for the treatment of solid tumors. The targeted epigenetic reprogramming developed by interfering with the chromatin modulator Sin3 function induce the re-expression of estrogen receptor and RARα/β, making triple negative breast cancer cells responsive to estrogen receptor antagonists, such as tamoxifen, and to retinoids, opening a new window of opportunity for the treatment of these patients. *Dr. Eduardo F. Farias, Assistant Professor, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai.*

▲ **Used** genomic approaches to uncover the molecular circuitry driving aberrant cell growth, proliferation and survival downstream of NOTCH1, a critical oncogene activated in over 50% of human T-cell lymphoblastic leukemias (T-ALL). These studies have identified a central role of NOTCH1 in the control of cell growth and proliferation in leukemia cells and established a prominent role of MYC and the PI3K-AKT pathway in NOTCH induced transformation. In addition, by testing the effects of blocking NOTCH1 signaling in combination with chemotherapy, has demonstrated that inhibition of NOTCH1 signaling can effectively reverse glucocorticoid resistance in T-cell leukemias. Glucocorticoids are central drugs in the treatment of leukemias and lymphomas and glucocorticoid resistance is an important clinical problem. Moreover, has also shown that glucocorticoids have a protective effect against gamma-secretase inhibitor-induced gut toxicity. These studies have set the basis for clinical trials testing the safety and efficacy of glucocorticoids and NOTCH1 inhibitors in the treatment of relapsed and refractory T-ALL. Most recently used genomic approaches to elucidate the mechanisms of the NT5C2 mutations as drivers of resistance to chemotherapy in relapse ALL. *Dr. Adolfo Ferrando, Professor of Pediatrics and Pathology at the Institute for Cancer Genetics, Columbia University Medical Center.*

● **Demonstrated** in a pilot study of genome-wide RNA

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expression analysis of tumor foci from 10 radical prostatectomy specimens after 3 months of androgen deprivation therapy that the surviving prostate cancer (PC) cells (eADT) acquired a unique transcriptome profile compared to untreated localized PC in the TCGA database and metastasis of castration resistant PC (mCRPC). In collaboration with S. Yegnasubramanian, Ph.D., (Johns Hopkins) and Ying Chen, Ph.D., (Bioinformatics Analysts at Rutgers CINJ), they determined that the highest differentially expressed genes in eADT vs. TCGA vs. mCRPC tumors were non-coding RNA's involved in epigenetic regulation of gene expression. Whereas cell cycle and DNA replication pathways were highly down-regulated (log $q<10^{-17}$) in eADT vs. untreated PC and mCRPC, six pathways were significantly upregulated in eADT vs. untreated PC. These included Wnt, adherence junction, steroid biosynthesis, unsaturated fatty acids, citrate cycle, ErbB. The Calcium, MAPK, insulin, GnRH and Hedgehog were also upregulated pathways in eADT vs. mCRPC. AR full-length was marginally higher in eADT than untreated PC and lower than mCRPC, with no differences in gene targets expression. They concluded that PC cells adapt to the stress of androgen deprivation by activating epigenetic mechanisms of gene regulation and by acquiring a quiescent state in which stem cell pathways and growth factor signaling support cell survival and AR activity without proliferation. Validation of these findings in a larger set of androgen deprived PC cases is necessary
to identify the best therapeutic targets to enhance the efficacy of androgen deprivation and eliminate PC cell survivors fostering recurrence. This work will be presented at ESMO and AACR 2017. *Dr. Anna C. Ferrari, Professor of Medicine, formerly Director—Medical Oncology Genitourinary Program, New York University Cancer Institute and NYU Langone Medical Center; now Director—Genitourinary Cancer Program, Rutgers Cancer Institute of New Jersey.*

• **Developed** laboratory-based therapeutic-translational regimens and approaches for pancreatic cancer and neuroendocrine cancer. For pancreatic cancer, the lab team created the GTX and T-GX regimens, which are in prospective phase II studies and have produced unprecedented increases in response rates and median survival in metastatic patients, and a high conversion rate (67%) from inoperable to operable status with negative margin Whipple procedures. Developed and patented two new therapies for pancreatic cancer including: (1) A novel gene therapy which only kills cells with mutant ras/mutant p53, and effective in animal models. (2) A customized, cell permeable p53 peptide which restores wild-type p53 function to mutant p53 cancer cells and is completely non-toxic to normal cells. For pancreatic cancers with BRCA1 or 2 mutations, the team has begun clinical testing of a new lab-based regimen which exploits this mutation. Dr. Fine's lab found that BRCA mutant pancreatic cancer cells are hypersensitive to cross-linking alkylators. To date, 14 of 20 BRCA mutant pancreatic cancer patients have
had responses to their chemotherapy regimen. For metastatic neuroendocrine cancers, the lab team has developed a novel regimen of Capecitabine/Temozolomide, which has a 61% response rate to date in their prospective phase II study. *Dr. Robert L. Fine, Associate Professor of Medicine, Director—Experimental Therapeutics, Division of Medical Oncology, Columbia University Medical Center.*

• **Demonstrated** that marrow fibrosis that is seen in myeloproliferative disorders (MPDs) and results in marrow failure can be eradicated by either syngeneic or allogeneic HLA identical stem cells with restoration of normal hematopoiesis, transfusion independence, obliteration of fibrosis and massive organomegaly that is seen in these patients. To date, there are no curative medical therapies for this disorder. This approach was presented at the American Society of Hematology meeting, and the initial report accepted for publicaton in the journal *Blood*. *Dr. Steven M. Fruchtman, formerly Associate Professor* of *Medicine, Director—MPD Program, Divison of Hematology/Oncology, Mount Sinai School of Medicine; now Chief Medical Officer and Senior Vice President, Onconova Therapeutics, Newton, Pennsylvania.*

▲ **Discovered** a novel gene implicated in pregnancy-associated breast cancer. The risk of breast cancer increases after pregnancy, but the mechanism of this effect is unknown. Dr. Germain's group discovered that mice that express Pappalysin-1 in their mammary gland develop mammary tumors, but only following pregnancy. Further, they also discovered that long but not short lactation inhibits this effect of Pappalysin-1. Long breast-feeding has been shown to be associated with decreased risk of breast cancer in humans, but the mechanism of this effect was also unknown. The Germain group reported that molecules able to block the action of Pappalysin-1 are produced during lactation. When

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lactation is prolonged, these molecules prevent the action of Pappalysin-1; however, when lactation is short, sufficient amount of Pappalysin-1 remains active to promote tumor formation. This is the very first mechanism that explains the protective effect of breast-feeding. *Dr. Doris Germain, Professor, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai.*

▲ **Established** experimental systems for investigating the question of how tumor cells elaborate transcriptional outputs embedded in embryonic development. Traced the molecular repertoire of pathways targeted by the MYC and Id transcription factors and implicated modifications of these factors as casual oncogenic events. Applied global and unbiased computational approaches to dissect the transcription factor networks that implement the most aggressive phenotype of human gliomas. The established integrated platforms provide novel and intriguing tools to dissect and pharmacologically target the master transcriptional programs that control neural development and cancer. *Dr. Antonio Iavarone, Professor, Departments of Neurology and Pathology and the Institute of Cancer Genetics, Columbia University Medical Center.*

▲ **Established** that patients with inflammatory bowel disease who have a history of cancer and receive immunosuppressant medicines for their IBD are at no greater risk of new or recurrent cancer than those who did not receive these medicines. This should reassure patients and oncologists that their IBD can still be treated appropriately even in those with a history of cancer. *Dr. Steven Itzkowitz, Professor of Medicine, Director—Gastroenterology Fellowship Program, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai.*

● **Determined** that two novel agents used to treat preleukemia, MS-275 and azacytidine, when given together can turn on genes involved in cell signaling, this correlating with clinical response. Determined that MMSET, a protein turned on abnormally in 15% of cases of multiple myeloma, alters how genes are turned off in the cell, potentially contributing to the genesis of the disease. *Dr. Jonathan D. Licht, formerly Chief—Division of Hematology/Oncology at Northwestern University Feinberg School of Medicine; Associate Director—Clinical Sciences, Robert H. Lurie Comprehensive Cancer Center, Chicago, Illinois; now Director—University of Florida Health Cancer Center, Gainsville, FL.*

● **Developed** the foundations for intraperitoneal (IP)-based chemotherapy and study of new drugs that may be given by the IP route. Studies by Muggia, Liebes and Newman have extended to gastric cancer (with IP FUDR or floxuridine) and to new drugs for ovarian cancer given by the IP route. The effect of bevacizumab (Avastin) on altering the handling of Doxil by tumors was studied by Liebes and Muggia in a trial combining the two agents for recurrent ovarian cancer. Other studies in ovarian cancer have examined the role of erlotimib in combination with topotecan, and the role of hydroxyurea in modulating the effects of gemcitabine. Liebes and Brooks have also examined the value of serial measurements of collagen fragments in plasma as an index of invasion. These measurements utilized an antibody directed against altered sites of collagen, which has antitumor properties, and may be developed not only as a diagnostic but also as a unique therapeutic reagent. New studies with a novel peptide discovered by Brooks and Liebes that is also directed against denatured collagen sites are aimed at developing a PET imaging peptide. These studies involve the multidisciplinary collaboration of Drs. Silvia Formenti*, Kent Friedman, Yu-Shin Ding and James Canary of respectively the Radiation Oncology, Radiology, and Chemistry Departments at NYU. (*Dr. Formenti relocated in 2015 to Weill Cornell Medical College). *Dr. Leonard Liebes, formerly Research Director, Division of Hematologic Malignancies and Medical Oncology, NYU Cancer Institute, New York University School of Medicine; currently Adjunct Research Professor, Department of Pharmaceutical Sciences, College of Pharmacy, University of New England, Portland, Maine, Campus.*

● **Demonstrated** a novel region of loss of heterozygosity (LOH) in human lung cancer, caused by two different mechanisms. Adenocarcinomas have gene amplification, while squamous cancers have deletion of 14q13.3. Studies of a mutant mouse led to these human studies, because they showed that loss of Nkx2.8 caused bronchial dysplasia and lung cancer. Deletion is the hallmark of tumor suppressors, and Nkx2.8 and nearby genes are candidates to be the suppressor within 14q13.3. In 2012, NextGen sequencing analyzed a 4 Mb interval around Nkx2.8 and demonstrated inactivating mutations in the same nearby gene in two cases of squamous cancer with deletion. Further studies may determine the

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prevalence of these mutations and characterize the function of this putative tumor suppressor. *Dr. Joseph Locker, formerly Professor of Pathology, Department of Pathology, Albert Einstein College of Medicine; now Professor of Pathology, Department of Pathology, Division of Molecular Genetic Pathology, University of Pittsburgh School of Medicine.*

• **Developed** a method to deplete energy in cancer cells, thereby increasing their sensitivity to chemotherapy and, most importantly, the killing of drug-resistant cancer cells by chemotherapy. The result is greater anticancer benefit plus less toxicity to the patient. This work complements a history of developing ways of changing the biochemistry of cancer cells to make chemotherapy more effective — treatments that are now in widespread research throughout the world. This research has been extended to highly effective anticancer agents against breast and ovarian cancers, which, when given following administration of the ATP-depleting regimen developed by this research group, have their anticancer activity markedly enhanced. These exciting therapeutic findings are being brought to clinical trial at Memorial Sloan-Kettering Cancer Center with funding by the National Cancer Institute. *Dr. Daniel S. Martin (deceased 2005), Investigator, Department of Medical Physics, Memorial Sloan-Kettering Cancer Center; formerly at the Catholic Medical Center of Brooklyn and Queens.*

• **Discovered** that a chemical produced by human white blood cells triggers, by unique mechanisms, the differentiation of cancer cells toward normality. This will be useful for designing specific anticancer therapy, as well as uncovering processes by which cells control their differentiation. *Dr. Lloyd Mayer (deceased 2013), Professor of Immunobiology and Microbiology; Dorothy and David Merksamer Professor of Medicine; Co-Director—Immunology Institute; Chief—Division of Clinical Immunology, Icahn School of Medicine at Mount Sinai.*

▲ **Discovered** a new cancer mechanism through which lymphoma cells reprogram their genomes to suppress production of proteins, rendering them "invisible" to the immune system. Importantly, Dr. Melnick and colleagues identified a novel drug that can reverse this effect and restore the ability of the immune system to track down and destroy the tumor. These findings are importantly relevant not only to Hodgkin and non-Hodgkin lymphomas but also to solid tumors. Dr. Melnick and collaborators are working to rapidly translate this novel therapeutic agent to the clinic, potentially providing a more cost-effective approach for harnessing the immune system to kill cancer cells. *Dr. Ari Melnick, Gebroe Professor of Hematology/Oncology, Chair of the Hematologic Malignancies Program at the Meyer Cancer Center; Director—Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College.*

• **Devised** a genetic animal model which demonstrated the importance of Vitamin A in the development of breast cancer. *Dr. Rafael Mira-y-Lopez (deceased 2006), Associate Professor of Medicine, Rochelle Belfer Chemotherapy Foundation Laboratory, Division of Hematology/Oncology, Mount Sinai School of Medicine.*

• **Building** on initial encouragement in the 1970s with seed money provided by The Chemotherapy Foundation and supported in the intervening years by major independent sources, Dr. Larry Norton's research using chemotherapy in the improved treatment of breast cancer has resulted in significant accomplishments recognized world-wide for their impact on new opportunities for patients. The following outlines the direction of Dr. Norton's recent studies: Used mathematical models to design more effective ways of using chemotherapy and biological therapies in the treatment of breast cancer, Hodgkin's disease, malignant lymphoma and other diseases. These concepts have proved to be widely applicable to the treatment of many types of cancer. At present, treatments using this work are the most effective and less toxic therapies for patients with breast cancer and non-Hodgkin's lymphoma. Is exploring the biological basis for the mathematical patterns of normal and malignant growth. *Dr. Larry Norton, Professor, Weill Medical College; Deputy Physician-in-Chief (for Breast Cancer Programs), Memorial Hospital; Medical Director—Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center; Past Presidential Appointee to the National Cancer Advisory Board of the NCI; President of ASCO, year 2001-2002.*

• **Identified** a mechanism of action of rigosertib (RGS) against ribosomal protein RPL18A (L18A). RGS is a multi-targeted anticancer agent known to have activity against myelodysplastic syndrome. Previously we reported identification of L18A as a putative binding target of RGS. RPL18A is predicted to form bilobal

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tertiary structure with a cleft in the central hinge area. Each lobe consists of one α-helix and an opposing β-sheet. Based on results of pull-down experiments with biotin-conjugated version of RGS, we found RPL18A mutants with missing structural elements within the lobes lost ability to bind RGS. Loss of the binding was likely due to loss of the lobe's tertiary structure. Taken in its entirety, C-lobe, but not N-lobe, could bind biotin-conjugated RGS, although at half the WT activity. RPL18A mutants with just single aa residue substitution, namely Leu7Ala, Arg8Ala or Glu9Ala, manifested profound loss of specific binding activity while their tertiary structures are not expected to change. In in-silico molecular docking experiments RGS docked well into the cleft between the two lobes. In this orientation, the trimethoxy groups containing styryl ring of RGS was buried inside this cleft, whereas the rest of RGS structure was sandwiched between the two beta strands β2 and β7 (corresponding to N, and C-lobes respectively). Aa residues Arg8 and Glu9 from β1 strand and the flanking residue Leu7 were located in close proximity to buried styryl ring of RGS, which was consistent with our mutagenesis data on the important role of these residues in the drug binding (Oussenko et al. Structure-function analysis of RPL18A, a putative binding target of rigosertib AACR abs#694, 2015). We plan to purify key mutant constructs to homogeneity to confirm our findings in assays with non-modified RGS; expression of the binding-deficient mutant(s) in cancer cells should reveal immediate interacting partners of L18A, whose function is interrupted by RGS. *Dr. Takao Ohnuma (retired), formerly Professor of Hematology/Oncology, Director—Molecular Pharmacology Laboratory, Icahn School of Medicine at Mount Sinai.*

▲ **Demonstrated** for the first time that hedgehog pathway inhibition is a potential targeted therapy in appropriately selected metastatic melanoma patients. This work supported by The Chemotherapy Foundation revealed that over 40% of the melanoma cell lines examined harbored significantly elevated levels of the hedgehog pathway mediators compared to control melanocytes. Inhibition of hedgehog pathway activator Smoothened (SMO) suppressed melanoma cell growth in vitro, particularly in those cell lines with moderate SMO and GL12 expression levels. SMO small molecule inhibitor also induced apoptosis in vitro and inhibited melanoma cell growth in a xenograft model. Data also revealed evidence of compensatory up-regulation of developmental pathways, Notch and Wnt, in response to hedgehog pathway inhibition. Finally, decreased expression of the hedgehog pathway repressor GL13 correlated with shorter post recurrence survival in metastatic melanoma patients. *Dr. Iman Osman, Professor of Oncology, Director—Interdisciplinary Melanoma Cooperative Group, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center.*

● **Developed** an active and well-tolerated regimen of autologous stem cell transplantation for patients with chemotherapy-sensitive tumors. Confirmed the feasibility of combining immunotherapeutic and chemotherapeutic strategies for the treatment of chemotherapy-insensitive malignancies. Reported the induction by IL2 of Transforming Growth Factor beta (TGFB), a powerful peptide with multiple activities on the immune system and on tumor regression (or progression). *Dr. Paolo Alberto Paciucci, formerly Associate Professor of Medicine, Division of Hematology/Oncology, Mount Sinai School of Medicine; now Associate Clinical Professor of Medicine and Oncological Sciences, Icahn School of Medicine at Mount Sinai, with clinical practice in Manhattan.*

▲ **Demonstrated** that the mantle cell lymphoma genome is aberrantly hypermethylated using a novel high-density custom-designed microarray. Identified five novel tumor suppressor genes that are hypermethylated and silenced in mantle cell lymphoma. Proved that a combination of DNA hypomethylating agents and histone deacetylase inhibitors can overcome resistance to Bortezomib, a promising new therapy in this difficult-to-treat lymphoma. *Dr. Samir Parekh, formerly Assistant Professor of Medicine, Albert Einstein College of Medicine, and Attending Physician, Stem Cell Transplant Unit, Division of Medical Oncology, Montefiore Medical Center; now Associate Professor, Hematology/Oncology and Oncological Sciences, Icahn School of Medicine at Mount Sinai.*

● **Detected** retroviral sequences, similar to those that cause mammary tumors in mice, in 38% of the human breast cancer. The complete proviral structure in two human breast tumors was demonstrated. The origin of these sequences could be from an exogenous virus or from modifications of endogenous retroviral sequences. Also demonstrated specific inhibition of breast cancer cell growth by antisense oligonucleotides to the erbB-2 oncogene, which is expressed in 30% of the human breast cancers. This offers implications for gene therapy

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for a specific type of estrogen treatment. Demonstrated estrogenic potential of certain pyrethroid compounds in human cancer cells. *Dr. Beatriz G.-T. Pogo, Professor of Medicine and Microbiology, Division of Hematology/ Oncology, Icahn School of Medicine at Mount Sinai.*

- **Demonstrated** through his work on CALGB's randomized study on induction therapy of acute myelocytic leukemia (AML) the most effective way to combine cytosine arabinoside and daunorubicin, and subsequently the randomized comparison of fludarabine vs. chlorambucil in chronic lymphocytic leukemia (CLL), which established the role of fludarabine in CLL. The Chemotherapy Foundation support led to Dr. Rai's studies on the monoclonal antibodies alemtuzumab (Campath) and rituximab in CLL. Dr. Rai has remained actively engaged in integrating the recently developed molecular markers with the conventional clinical staging criteria to improve the prognostic assessment in CLL. *Dr. Kanti R. Rai, Professor of Medicine and Professor of Molecular Medicine, Hofstra Northwell School of Medicine; Director—CLL Research and Treatment Program, Northwell Health.*

- **Demonstrated** that a novel clotting protein, referred to as alternatively-spliced human Tissue Factor (asHTF), is expressed in a wide range of human pancreatic cancers. While the previously recognized form of Tissue Factor promotes clotting, and contributes to the thrombotic tendency in cancer patients, expression of asHTF by cancer does not promote coagulation, yet does promote aggressive cancer growth. Further, asHTF expression enhances tumor growth by promoting angiogenesis, a new blood supply to sustain and promote tumor growth. These studies show that asHTF may be a novel target to treat cancer. Studies are ongoing to characterize the expression patterns of Tissue Factor isoforms in human cancers, and ultimately to develop novel therapeutic tools. *Dr. Gerald Soff, formerly Chief—Division of Hematology/Oncology, SUNY Downstate Medical Center; now Chief—Hematology Service, Memorial Sloan-Kettering Cancer Center.*

- **Identified** novel proteins, termed coactivators, that regulate the function of the androgen receptor, a critical stimulant for prostate cancer growth. Determined that one of these proteins, ART-27, slows the growth of prostate cancer cells and is produced during development when prostate cells mature and stop growing. Determined that mutations of the ART-27 gene occur in prostate cancer and prevent ART-27 from binding to the androgen receptor. Determined that ART-27 regulates proteins which control the cell cycle in prostate cancer cells. Future studies will determine if prostate cancer therapies can be directed to the ART-27/androgen receptor interaction. *Dr. Samir S. Taneja, James M. Neissa and Janet Riha Neissa Professor of Urologic Oncology, Professor of Urology and Radiology; Director—Division of Urologic Oncology; Co-Director—Smilow Comprehensive Prostate Cancer Center, Department of Urology, New York University Langone Medical Center.*

- **Opened** the first national trial of Folfox—Avastin—Erbitux for metastatic colon cancer. Demonstrated that gene therapy is effective treatment for refractory tumors of the liver and bile ducts, and that this can be given safely as an intratumoral injection. Furthermore, the viral vectors employed in this gene therapy were shown not to be disseminated to family members or staff. Demonstrated that the family of biological agents called interferons can increase the clinical activity of the antimetabolite fluorouracil, the standard chemotherapy for colon cancer; that high doses of the human enzyme somatostatin can ameliorate the toxic effects of fluorouracil, preventing hospitalization and severe complications of the therapy; and that combining fluorouracil with another antimetabolite, hydroxyurea, can result in enhanced anticancer effects in patients with stomach cancer. Organized the New York Gynecologic Oncology Group, a city-wide consortium of medical and gynecologic oncologists, to study novel treatments of gynecologic malignancies, and received first funding award from the National Cancer Institute for this effort. *Dr. Scott Wadler (deceased 2007), Richard T. Silver Distinguished Professor of Medicine, Division of Hematology/ Oncology, Weill Medical College of Cornell University.*

- **Pioneered** use of Leucovorin to enhance 5 fluorouracil; discovered proteins that control folic acid metabolism, pioneered non-toxic differentiation therapy for leukemia demonstrating the abilities of Vitamin A derivatives and arsenic trioxide to make leukemia cells mature into normal cells. This work has led directly to the best modern therapy curing 90% of certain advanced leukemias. Helped show sorafenib useful for treatment of hepatocellular carcinoma. Described fusion gene in cholangiocarcinoma. Developing a targeted differentiation therapy for triple negative breast cancer. Reported Avermectin as a

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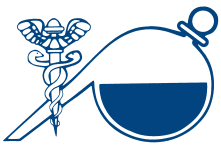
targeted therapy to prevent and treat metastasis in triple negative breast cancer. *Dr. Samuel Waxman, Distinguished Service Professor of Medicine; Chief—Rochelle Belfer Chemotherapy Foundation Laboratory, Division of Hematology/ Oncology, Icahn School of Medicine at Mount Sinai; Founder and CEO—Samuel Waxman Cancer Research Foundation; Honorary Professor—Shanghai Jiao Tong University.*



OTHER PROGRAM ACCOMPLISHMENTS

Progress in the fight against cancer has also been accomplished by the Foundation's innovative support and leadership:

Medical Research

In 1970, two years after our founding, we built, equipped and staffed the Chemotherapy Foundation Laboratory in the Division of Medical Oncology at the Mount Sinai School of Medicine. In 1974 we added a tumor cell lab. With support from the Foundation and other major sources, the Rochelle Belfer Chemotherapy Foundation Laboratory was rebuilt in 1989 and relocated to larger premises in Mount Sinai in 2004. It has the latest facilities for utilizing molecular biology in cancer treatment.

We have also provided funds to start and support an ever-growing number of innovative cancer research projects in other Divisions at the now Icahn School of Medicine at Mount Sinai and at three other major New York City medical centers: New York University School of Medicine, NYU Langone Medical Center; Weill Cornell Medical College; and Columbia University Medical Center. These include grants to leading investigators who have conducted research studies in breast cancer, brain tumors, gastrointestinal cancer, hematology malignancies and malignant melanoma, among others.

Foundation support with initial funds also helped to establish two Bone Marrow Transplantation Units (Hackensack University Medical Center and Mount Sinai Medical Center) and three Oncology Units (NYU Medical Center, New York Medical College, and Long Island Jewish Medical Center).

Professional Education

Since the early 1970s we have sponsored professional symposia to inform physicians of practical advances to improve patient-care management and survival, and to foster the exchange of concepts that will lead to tomorrow's new treatments.

We were at the forefront in promoting another new approach in 1983, when we organized and solely supported the first breast cancer chemoprevention conference to discuss the feasibility of a controlled chemotherapy study for women at high risk of developing breast cancer. In 1987 we continued that innovative tradition by sponsoring the first international

workshop on breast cancer chemoprevention. Researchers concluded that a major study of breast cancer prevention with Tamoxifen was justified by available reported data. Five years later (summer 1992) the NCI launched a five-year clinical trial using Tamoxifen for the chemoprevention of breast cancer that involved 13,000 patients. Spearheaded by Dr. Bernard Fisher, scientific director of the National Surgical Adjuvant Breast and Bowel Project (NSABP), he and his NSABP colleagues, working with the National Cancer Institute, designed and implemented this first breast cancer prevention trial in the United States. The results were published by Dr. Fisher in 1997 and showed the ability of Tamoxifen to reduce recurrence of either invasive or pre-invasive events by 40%.

Our annual three-day Chemotherapy Foundation Symposium, now managed by Physicians' Education Resource, LLC (PER), is an outstanding event on the professional calendar. We are confident that our ongoing efforts to stimulate the scientific imagination will continue to reap rewards in our progress against cancer.

THE CHALLENGE CONTINUES — WHY NOW IS THE TIME TO HELP

We are in the midst of a period of unprecedented rapid expansion of biomedical knowledge. The BRCA breast and ovarian cancer susceptibility genes were discovered in the 1990s and greatly enhanced our understanding of these cancers. In June 2000 the sequence of genes on human chromosomes was completely deciphered. These discoveries are spearheading the development of new molecules for diagnosis and treatment.

Going forward we need to continue to learn the answer to our deepest questions, and participate in the translation of dramatic new scientific information into breakthrough improvements in cancer management. The challenge is to meet this potential with adequate research support, so as not to let this opportunity slip away, for the failure to follow-up these discoveries will delay key cancer breakthroughs. Clinical trials based on these new discoveries are an essential component of such advances.

While chemotherapy made significant inroads into improving outcomes, science has moved beyond targeting cell division and its DNA. Modern drug regimens are now partnering with drugs arising from new concepts seeking targets beyond the tumor cells into the tumor microenvironment, including blood vessels and other cells present in tissues. The early intense focus on the tumor cell diverted us from key aspects of this environment that is being increasingly studied in the era of molecular targeted therapy. The best example of a successful story in this regard is the greatly improved eradication of breast tumor cells that have high expression of the growth factor receptor HER2 or erbB2 when combined with chemotherapy. In addition to these conceptual advances, there are technical advances in drug delivery. These weapons include monoclonal antibodies, and anti-body drug complexes that are used as "smart bombs" zeroing in on the cancer cell and delivering cancer-killing drugs. Because we have identified key molecules on the surface of cancer cells, which mark them as distinct from normal cells, we have been able to make anticancer vaccines that instruct the body to kill the cancer by natural methods. This, in turn, has led to better understanding of the immune system and new molecules that release the natural brakes that our body activates to limit normal tissue damage as bystanders in the body's reaction to infection (and to tumors). This new ability to unleash the

immune system against cancer cells has revolutionized the treatment of melanoma, and is revitalizing immunotherapy for lung cancer and is gradually extending to treat a great variety of advanced cancers heretofore resistant malignancies. These developments are being worked through trials in a vast array of human malignancies and represent the most exciting possibilities for prolonged control of advanced malignancies that have become realities only in the last few years.

It is clear that your support at this critical moment can do more than it ever could, because the scientific tools are more refined and the goals more sharply defined. The Chemotherapy Foundation has long led the fight against cancer by supporting the best scientists, physicians, and educators, those best positioned to use modern science to defeat an ancient enemy. Now is the time for all of us to work together even harder to grasp the victory against many additional cancers within our reach. The strength of our Foundation is our capacity to seek out talent among institutions to improve emerging multidisciplinary treatments across the cancer spectrum.

The Chemotherapy Foundation is a public foundation dedicated to the control, cure, and prevention of cancer through innovative medical therapies. The Foundation funds selected laboratory and clinical research at four major New York City medical centers. Our annual three-day Chemotherapy Foundation Symposium each November, now managed by Physicians' Education Resource, LLC (PER), is an outstanding event on the professional calendar. The Foundation also publishes free public education literature. Continuing contributions from the public, the business community and the profession are needed to increase the range and reach of these essential programs. Donations to The Chemotherapy Foundation, 183 Madison Avenue—Suite 403, New York, NY 10016, are tax deductible.