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Chemistry in Cancer Research: A Vital Partnership

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The first Chemistry in Cancer Research Conference, jointly presented by the American Chemical Society (ACS) and the American Association for Cancer Research (AACR), was hosted this February in San Diego by the Chemistry in Cancer Research Working Group of the AACR. The purpose of the meeting was to provide an interactive and cross-disciplinary forum for scientists engaged in cancer research with a unifying focus on chemical structure and reactivity. Research areas spanned fields such as biomarker analysis, carcinogenesis, chemical biology, drug discovery and development, molecular modeling, proteomics, and structural biology. The packed and stimulating meeting provided an outstanding group of 26 invited presentations, including two keynote talks; 22 proffered talks from selected abstracts, including early career scientists and students; and 109 poster presentations. More than 240 registrants attended, including 122 ACS members, 31 AACR members, and 42 members of both organizations. Travel awards were provided for 13 Scholars-in-Training and 1 Minority-Serving Institution Faculty. A number of session- and discipline-spanning concepts emerged, such as predictive strategies for responsiveness of individual cancers to specific therapies and chemical pathways in drug toxicity and carcinogenesis. In addition, a lunchtime session was held to discuss chemistry careers in cancer research. Information was presented by John Hunt, Oncology Drug Discovery at Bristol-Meyers Squib, and Lawrence Marnett, Vanderbilt University. Hunt discussed recent trends in industry, including an increasing integration of science throughout the drug pipeline. Marnett overviewed traditional tenure-track positions involving some combination of teaching and research as well as research professorships and opportunities in core academic research facilities. He gave useful hints and advice for developing research ideas and seeking funding. Representatives from academia and industry participated in roundtable discussions with participants.

The meeting was considered highly successful by participants, and a consensus called for developing a regularly scheduled event. Participants indicated that the ACS–AACR union represented by this conference marked a beginning of alliances that will greatly benefit cancer research. This meeting report presents highlights from each oral presentation, organized by session; a complete listing of oral and poster session presentations can be found in Supporting Information. Further details, including reaction schemes with chemical structures available for some presentations, are also available as Supporting Information as indicated.

Opening Keynote Talks. The opening keynote lectures were presented by Stephen Fesik and Paul Wender. Research presented by Fesik opened with a question directed at the underlying basis for how members of the B cell lymphoma (Bcl) 2 family cross-modulate function. Structure–activity relationships (SARs) by NMR were discussed: small-molecule fragments are combined with a protein, and changes in NMR chemi-

cal shift are associated with binding, allowing a greater sampling of chemical space than high-throughput screening. ABT-737, a candidate that potentiates chemo- and radiotherapy and displays single-agent activity in cell lines, thus was designed. Fesik stressed that the most likely stage for mistakes in drug development is in clinical trials and that any preclinical information with the potential to influence clinical trials is extremely important and valuable. Understanding the mechanistic basis of unresponsiveness to ABT-737 in certain cell lines can guide patient population selection and the design of improved therapies. For example, high myeloid cell leukemia (Mcl 1) is associated with resistance to ABT-737, and current work is underway to design a drug to reduce Mcl 1 that may synergize with ABT-737. An orally active ABT-737 analogue is currently in phase 1 trials, and Abbott Laboratories plans to move forward with single-agent trials, expecting that an understanding of mechanism will influence the success of trials. In response to questions, Fesik indicated that extensive and difficult medicinal chemistry was required to develop an orally bioavailable analogue and that known Bcl 2 single-nucleotide polymorphisms occur at sites other than in the binding pocket.

Wender then discussed new directions in cancer-related research with a focus on concepts and approaches transcending individual projects. New therapies from new chemistries, diagnostic methods, and prevention strategies are anticipated to revolutionize cancer research. Chemistry in Cancer Research has evolved from using available material to a rational approach to designed molecules that achieve a desired function and can be obtained in a practical way: function-oriented synthesis. Illustrative examples included the apoptolidins and bryostatins. Simpler natural product analogues reduce drastically the number of synthetic steps needed to make molecules with picomolar-range activity. A final concept centered on breaching biological barriers, with examples of drug–probe-transporter conjugates to enhance bioavailability and change efficacy of existing agents. Wender shared thoughts about the value of individuals involved in research, training programs, methods to bridge academia and industry, and the problems of limited resources available to support the richness of researcher ideas. After the lecture, Wender discussed that "rules" are good guidelines but that it is important for researchers to be open to eclectic agents and ultimately seek the "biggest bang" from the smallest amount of chemical information. He also talked about the benefits of luciferase labeling for analysis.

Drug Discovery. The drug discovery session began with Dale Boger and the message that problems dictate the choice of chemistry and the approaches used. For example, when structural information is scarce and no leads are known, combinatorial chemistry is a powerful tool. Natural products studies allow the definition of the biological target, the nature of the interaction with the target, and the origin (if any) of tumor selectivity. Finally, structure-based drug design can generate novel design concepts. Boger expanded on studies in each area. In collaboration with the structural biology group of Ian Wilson (Scripps Research Institute), potent glycinamide ribonucleotide transformylase inhibitors such as **1** have been designed (Figure 1). Boger described solution-phase combinatorial chemistry, which can produce a library of 80,000 compounds stored in ~80 96-well plates, about the screening limit expected of an academic laboratory. Finally, Boger briefly highlighted DNA-binding duocarmycins and their parabolic SARs: compounds need to be sufficiently stable to reach the target but reactive enough to alkylate the target when they arrive. The next presentation again demonstrated the importance of how target structure drives chemistry. Gustavé Bergnes presented the development of motor kinesin spindle protein (KSP) inhibitors. The Cytokinetics philosophy is "design, synthesize, assay, and learn." An initial small-molecule library screen, then structural modification, resulted in ispinesib **(2)**, with >70,000-fold selectivity for KSP *versus* other kinesin proteins. The progression of **2** into clinical trial is a significant development for a small- to medium-sized company, and Bergnes described further goals to anticipate potential risks and pitfalls that can block progress to the clinic.

Thomas Penning described an inhibitor of the DNA repair enzyme poly(ADP-ribose) polymerase. Penning detailed structural changes that led to ABT-888, a molecule that crosses the blood–brain barrier, potentiates temozolamide, and is currently in the first-ever phase 0 clinical trial. Mark Mulvihill described the development of imidazopyrazine-derived insulin-like growth factor-I receptor (IGF-1R) inhibitors. IGF-1R, a transmembrane tyrosine kinase, has been implicated as a key oncology target, signaling primarily through the Akt pathway, suppressing apoptosis of cancer cells. Co-crystal structures of 1,3-disubstituted imidazopyrazines with IGF-1R and IR afforded key structural insights that resulted in constraining the C(1) substituent, "northern domain", into a rigid quinolinyl moiety that interacted with a lipophilic pocket within the protein. The C(3) substituent, "southern domain", accessed a solvent-exposed region and was optimized to a substituted cyclobutyl moiety, affording lead compound OSI-PQIP (Figure 1). OSI-PQIP has an excellent pharmacokinetic profile in mouse, rat, dog, and monkey, yields >90% inhibition of IGF-1R phosphorylation in pharmacodynamic studies, and displays significant tumor growth inhibition/delay with no significant effect on blood glucose; a compound from the series, OSI-906, is currently in clinical development. Louis Lombardo described the Bristol-Myers Squibb approach to the development of vascular endothelial cell growth factor receptor inhibitors fol-

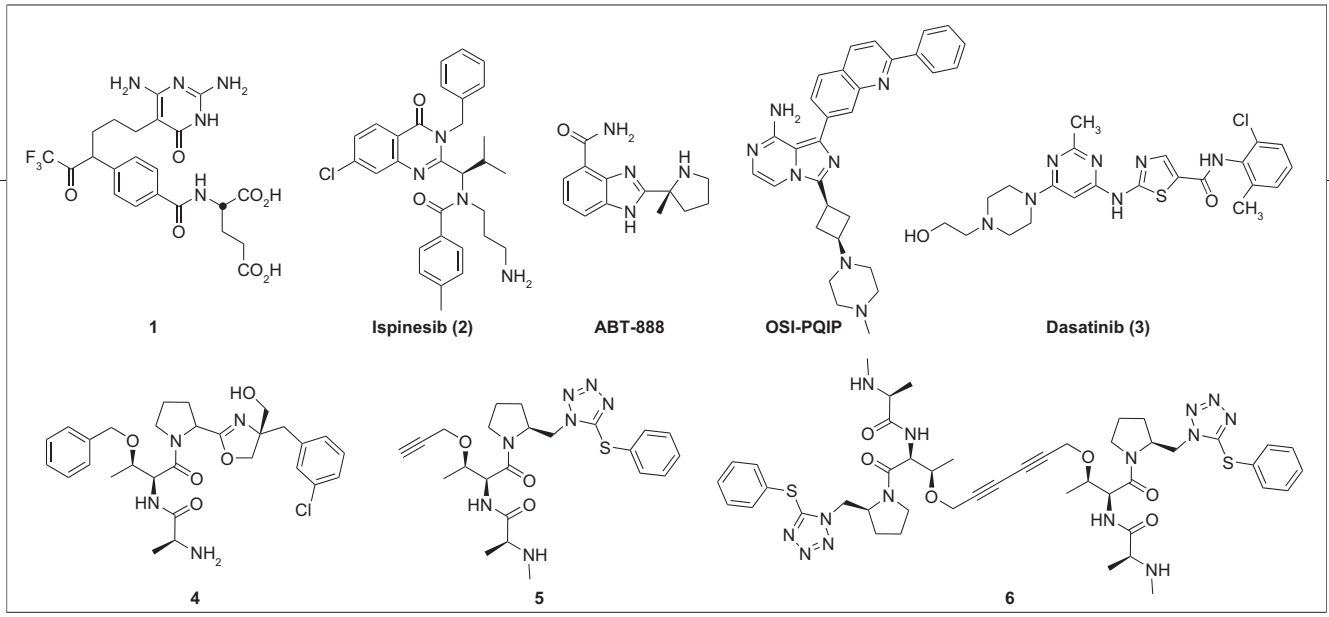
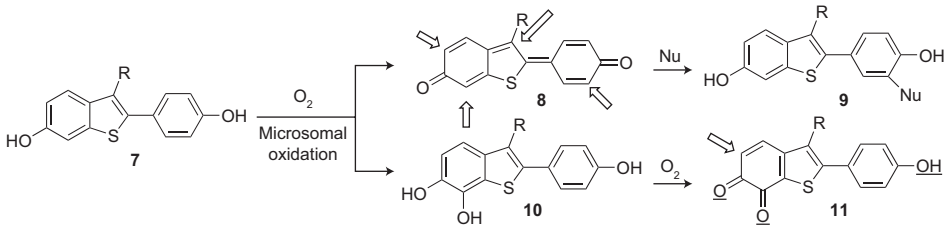


Figure 1. New chemical entities discussed in the Drug Discovery session. Compound 1 is a glycinamide ribonucleotide transformylase inhibitor; ABT-888 is a poly(ADP-ribose) polymerase inhibitor; OSI-PQIP is a lead IGF-1R inhibitor; ispinesib 2 is a KSP inhibitor in clinical trial; dasatinib 3 is a marketed kinase inhibitor for CML; compounds 4–6 were described by Harran as Smac-binding compounds.

lowed by dasatinib **3**, a marketed kinase inhibitor (Sprycel) for the treatment of chronic myeloid leukemia (CML). Since the advent of imatinib mesylate (Gleevec or Glivec), research on kinase inhibitors has exploded and is a major part of the new drug pipeline. Compounds that bind the ATP pocket, however, have potential selectivity problems. A key to the success of **3** lies in the lack of cross-resistance with imatinib; the molecule received accelerated approval from the U.S. Food and Drug Administration in 2006. Patrick Harran described how serendipity and a prepared mind can lead to unexpected discoveries of new antitumor agents. Smac (second mitochondria-derived inhibitor of caspases) is a protein that binds to inhibitor of apoptosis proteins and sensitizes cells to apoptosis. Analogue **4**, with nonpeptidic replacements for proline and phenylalanine, did not outperform the peptide AVPF in a competition assay but did lead to **5** and the serendipitous dimer **6**, which bind comparably; however, **6** has greater activity in a cell-based functional assay. Work of this nature is re-establishing the balance between replication and death, the ultimate aim of all anticancer programs. Eileen Kennedy discussed the use of stapled peptides to target inhibition of the androgen-receptor ligand binding domain. This involves inserting amino acids that contain alkene side chains into the peptide and carrying out a metathesis reaction to generate the intrapeptide cross-link or staple. Frank Gu described nanoparticles for targeting prostate cancer. The nanoparticles consist of an RNA aptamer, poly(ethylene) glycol to increase circulation half-life, and a segment of poly(D,L-lactic-*co*-glycolide) to encapsulate the drugs and allow sustained release. The series of presentations demonstrated the many different approaches that chemists in industry and academia are applying to the discovery and potentiation of new molecules with therapeutic potential. The presentations were powerful demonstrations of the contributions of chemistry to cancer research.

Proteomics. Proteomics, the study of the whole of the protein content of the cell, has the potential to revolutionize the way cancer diagnosis and treatment are approached. This session demonstrated the potential of proteomics to make a significant contribution to the identification of new targets and the effects of new drugs in both tumor cells and tissues. However, it also clearly highlighted the ingenuity of the various groups working in the area in solving problems associated with the analysis of information derived from studies of the global expression of proteins. Catherine Fenselau began the afternoon session with the clear statement that "chemistry enables proteomics" and described protein changes in MCF-7 tumor cells that are resistant to various antitumor agents. The strategy focuses on specific subcellular organelles prior to protein analysis, and incorporation of ^{18}O using labeled water during trypsin digestion allows for quantitation. Thus, protein labeling in normal cells (forward labeling) is followed by protein labeling in resistant tumor cell lines (reverse labeling). Fourteen proteins were changed by a factor of 2 and included novel potential targets. Ben Cravatt described activity-based protein profiling, which, when combined with mass spectrometry (MS), can aid in the identification of proteins with varying activities between cell types, such as metastatic *versus* nonmetastatic. Probes that carry a reporter group bind and label enzymes in the proteome with a dependence on activity. The laboratory aims to develop an integrated enzyme and metabolite profile for tumor cells. James Veal gave insight into an approach that uses chemoproteomics and proteome mining and described an application to drug discovery involving a heat shock protein 90 inhibitor that was refined and optimized to ultimately generate a clinical candidate. Colin Barry discussed the use of a modified stable isotope labeling of amino acids by cell culture approach for proteomic analysis of the folate-homocysteine pathway. Changes in the expression levels of ~770 proteins were found between cells grown in a low-folate medium against nor-



Scheme 1. Benzothiophene SERMs discussed by Bolton. Reactive intermediates scavenge cellular nucleophiles (Nu) by addition at the positions shown with the large block arrows.

mal folate. Bill Griffith described cytochrome P450 (CYP450) expression in tumor cells and potential implications for individualized drug and prodrug administration as the basis of personalized medicine in cancer. This pervasive concept was addressed throughout the conference. A comparison of the CYP450 expression profile of the microsomal fraction of primary colorectal cancer tissue, liver metastases, and surrounding liver tissue demonstrates differences in individual CYP450s. The second part of the presentation focused on cholangiocarcinoma and the potential of CYP450 as biomarkers for this disease, which would allow earlier detection and possible intervention. Forest White addressed the general question of how phosphorylation regulates biological response. He discussed phosphoproteomics, or global analysis of protein phosphorylation, by looking at the epidermal growth factor receptor signaling pathway. The methodology developed in his group probes phosphotyrosine peptides in a time-dependent manner and was used to identify the kinase that phosphorylates a key residue in the activation of migration in HER2. Virginia Espina discussed the importance of preserving tissue samples in the real world of clinical practice. This is obviously extremely important if proteomic techniques are going to be used in clinical settings, such as in the development of personalized cancer therapy. Finally, Yuebiao Yao discussed the use of 2D gels in colorectal cancer to analyze primary *versus* metastatic tumors and the identification of 63 landmark proteins.

Chemical Biology of Carcinogenesis. Chemists have played and continue to play an important role in cancer prevention through research on carcinogenesis. Traditionally, this has involved various fields of chemistry: development of sensitive instrumentation and methods to gauge exposure, organic and inorganic chemical model studies on mechanisms of carcinogen formation and bioactivation studies, the determination of putative carcinogen metabolic paths, the elucidation of endogenous pathways that may have carcinogenic potential, and the generation and utilization of relevant synthetic procedures. Although accidental exposures and subsequent clear-cut epidemiology resulted in the positive identification of a small number of human carcinogens, many more substances are known to be animal carcinogens. How can the true human carcinogenic potential of a substance or an endogenous chemical/biochemical process be assessed? The presentations given at the Chemical Biology of Carcinogenesis session and the Biomarkers session demonstrate the current research in this field. All of the talks emphasized the elucidation of DNA/protein-carcinogen modification and the consequences and significance of this chemistry.

Tamoxifen, a selective estrogen receptor modulator (SERM), is used to treat and prevent breast cancer and osteoporosis, but it has been associated with an increased risk of uterine cancer. Judy Bolton discussed microsomal bioactivation of benzothiophene SERMs (**7**) (Scheme 1) being examined as safe replacements for tamoxifen. Common intermediates include reactive diquinomethide **8** and quinone **11**, which arise from the catechol **10** (Scheme 1). Cellular protein targets were found by the invention and utilization of COATag methodology: the SERM is covalently linked to a biotin tag, and this permits immunoisolation and identification. Bolton emphasized that covalent SERM–protein binding may not be strictly deleterious but could contribute to chemoprevention through Keap1 alkylation and induction of detoxification enzymes. Guanine bases in DNA are readily oxidized to their 8-oxo derivatives (**12**, see Supporting Information) by biologically relevant reactive oxygen species (ROS), but the carcinogenic consequences of this chemistry are not clear. Cynthia Burrows reported on her group's work that is directed at understanding how the products and mechanisms of guanine oxidation (see Supporting Information) may provide a basis for mutagenesis and the possible role of DNA–protein cross-linking therein. Yelena Margolin presented another aspect of guanine and base oxidation in DNA: the chemical basis of site selectivity for oxidation by ROS and other oxidants. Striking differences in sequence selectivity for most one-electron oxidants, nitrosoperoxycarbonate ($ONOOCO_2^-$, a potent endogenous 1-e oxidant arising from inflammation) and hydroxyl radical are being probed by Margolin and collaborators. She showed that Fenton chemistry produced a DNA oxidation pattern similar to γ-radiation-generated OH but that unligated Fe^{2+}/H_2O_2 is sequence-selective; coordination of Fe^{2+} to **N-7** of guanine in dsDNA appears to be responsible. Sensitive assays developed by the Marnett group have shown surprisingly low levels of an endogenous oxidative-damage-associated nucleoside adduct (**18**, Supporting Information) in human urine. Charles Knutson presented data from ^{14}C-labeling studies showing the metabolism and excretion of **18**,

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which is expected to impact biomarker studies of oxidative DNA damage by this pathway. John Essigmann began the second session with a discussion of the value of chemically based mutagenesis studies. By site-specifically modifying DNA oligomers with modified bases and incorporating them into viral genomes, Essigmann and his group have developed a method that produces a "fingerprint" for each type of adduct that scores its replication efficiency: whether it induces the error-prone SOS response, types of mutations, and relative frequencies. Essigmann discussed chemical mechanisms of repair by the AlkB protein (see Supporting Information), which may protect bacteria against macrophage action (humans also have homologues of AlkB). Fred Guengerich used his group's research to illustrate complex connections between the chemistry and biochemistry of reactive intermediates and mutagenesis. For example, Aflatoxin, a potent human carcinogen, is activated by P450-mediated conversion to two stereoisomeric epoxides. Although the more reactive isomer has a $t_{1/2}$ of only ~1 s, it is vastly more genotoxic and binds DNA efficiently. Guengerich presented his group's extensive research on interactions of DNA polymerases with adducted bases and the effects on insertion and extension of the strand being copied by a translesional DNA polymerase. Methodology involved traditional gel sequencing, polymerization kinetics, MS/MS determination of product oligomer identity and yield, and X-ray diffraction studies of polymerase-adducted DNA structures. Guengerich emphasized the value of the latter two techniques because they allowed discrete mechanisms to be determined.

The process of establishing a suspected carcinogen to be a human carcinogen is an arduous task involving varied approaches. In significant measure because of the extensive research of Stephen Hecht and his collaborators, the International Agency for Research on Cancer (France) has declared the tobacco-specific carcinogens [2′-^{14}C]*N*′-nitrosonornicotine (NNN) (**28**, see Supporting Information) and [carbonyl-^{14}C]4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to be human carcinogens. However, given the complex and numerous protective mammalian defenses against carcinogenesis, biomarkers and the nature of DNA adducts need to be established. Pramod Upadhyaya provided an illustration on the use of model α-acetates in P450-mediated metabolism. Upadhyaya identified products of DNA binding (illustrated in Supporting Information) that have a potential future use as biomarkers. Recent concerns have been raised about the possible genotoxicity of acrylamide (**36**, see Supporting Information), which is found in some fried foods, because it is activated through the epoxide (**37**, glycidamide, Supporting Information). Further, it is structurally akin to carcinogens, which were described by Guengerich. Matthias Baum discussed comparisons of the genotoxicity of glycidamide in several different assays with *N*-nitroso compounds known to be potent alkylating agents.

Biomarkers/Analytical Chemistry. The session on Biomarkers and Analytical Chemistry involved a range of methodological approaches for the identification and analysis of chemical biomarkers important in cancer (Figure 2). Ian Blair described reaction pathways related to the overproduction of ROS, with a focus on understanding the impacts of this process when various enzymes involved are up-regulated, such as in cells under oxidative stress mediated by the overproduction of the cyclooxygenase 2 (COX2) enzyme. Reactions of specific lipid peroxidation products with DNA and glutathione (GSH) produce adducts such as **41**. Moving from DNA and GSH to proteins, Daniel Liebler continued the discussion of lipid peroxidation and addressed problems and solutions in identifying targets. Conjugated lipid-biotin probes such as **42** were used to survey adducts, and MS was used to identify streptavidin binding and proteins; this approach is analogous to the COATag method discussed earlier in Bolton's talk. Helpful analytical strategies were suggested, such as the construction of model peptides to determine MS behavior, mild ammonia hydrolysis methods, and wideband activation. The team is well positioned to address the predominant adducts from endogenous lipids *in vivo* and whether these are markers for various disease states. Elizabeth Grimm introduced inducible nitric oxide synthase (iNOS), an enzyme that catalyzes intracellular NO production from L-arginine, and has carried out studies to establish iNOS expression as a predictive marker that correlates inversely with survival in stage 3 melanoma patients. In the discussion that followed, Grimm indicated that other proteins are involved in the pathway but that minimal evidence exists for their potential as strongly correlated markers and that the potential role of smoking status in patients is unknown and may be an interesting issue to address. The presentation by Chenguo Xing directly related to Fesik's talk on apoptotic regulation by the Bcl2 family of proteins. Cells that overexpress Bcl-2 or Bcl-X_L are resistant to standard chemotherapies, and HA 14-1 (**43**) can selectively eliminate tumors with increased levels of Bcl-2. Xing has established that HA 14-1 can synergize various standard chemotherapies, and data indicate that HA 14-1 induces cell death by two distinct pathways, possibly converting antiapoptotic Bcl2 to a proapoptotic form. Natalia Tretyakova transitioned the focus of the session to exogenous carcinogens. Tretyakova explained that the three potential isomers (*S,S*; *R,R*; and meso) of diepoxybutane (DEB, **44**) influence resulting patterns of DNA alkylation. DEB reacts to form a monoadduct with a pendant epoxide, and this initially formed adduct is subject to hydrolysis, cross-linking, or intramolecular cyclization. The biological role of novel intramolecular cyclization products is under investigation. In the question-and-answer period, links between findings for DEB and the nitro-

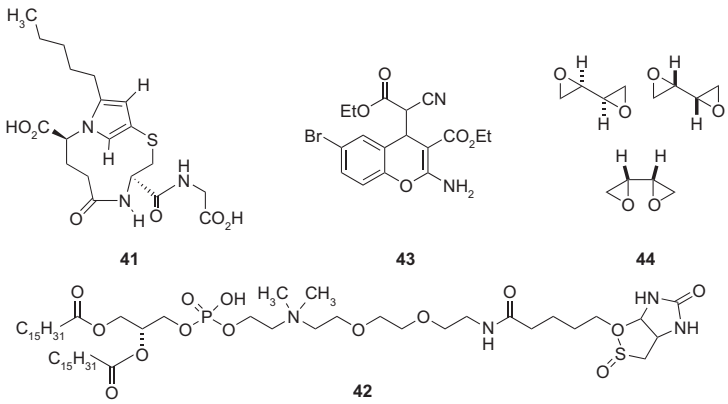

Figure 2. Structures addressed in the chemical biomarker session. A glutathione adduct of a lipid peroxidation product (41); conjugated lipid-biotin probe for surveying protein adducts (42); HA 14-1 (43), an agent that selectively eliminates cells that overexpress Bcl-2; and isomers of the exogenous carcinogen diepoxybutane (44).

gen mustards and the CML drug sulfam were discussed. Following on the theme of DNA–small-molecule adduct formation, Peter Farmer presented an overview of current analytical methodologies. The focus was on MS as an approach for obtaining an accurate indication of dose that takes into account individual biological differences. Farmer established a detection limit benchmark of 1 damaged base in 10^8 nucleotides, or fewer. Specific recent examples included alkylation of the 7- and N^2-positions of guanine by ethylene oxide and benzo(*a*)pyrene, respectively. A comparison of adduct levels between MS methods and ^{32}P postlabeling indicated that the methods correlate, but in some cases ^{32}P assay may underestimate adduct levels. Finally, Farmer presented a new site-selective mutation assay as a variant on the SupF assay for human cells. He concluded that future studies should address the biological influences of low levels, one or two adducts per cell, of DNA damage. Robert Diaz addressed the identification of peptides recovered from *in vivo* biopanning of T7 libraries from animal tumors. Finally, Surojit Sur presented an overview of steps that were taken that led to the discovery of a selective, water-soluble, nanomolar inhibitor of the protein tyrosine phosphatase PRL-3, which resulted from a 60,000-compound-library screen, chemical synthesis, and SAR studies.

Modeling and Bioinformatics. In the first talk, Dave Covell presented bioinformatic and chemical informatics strategies for mining the screening data from the NCI60 panel of 60 immortalized human-derived cell lines that have been accumulated at the National Cancer Institute (NCI) over the past 19 years. Recently, cell screening has been augmented with high-content DNA, protein-microarray, and xenograft data to create a database with >2 million datapoints. Interpretation of data that link small molecules, molecular targets, and mechanisms of action remains an area of active research. John Irwin talked about the ZINC database, a collection of commercially available compounds in biologically relevant representations for virtual screening and chemical informatics applications. Irwin discussed the importance of the representation of molecules in their bioactive forms, particularly of protonation and tautomeric variants, as well as in forms appropriate for metalloenzymes. He presented the DUD database for benchmarking docking programs; he challenged the programs in order to expose their weaknesses and to improve docking methods. James Wright talked about the problem of quinone formation *via* P450 metabolism of estradiol used in hormone replacement therapy. A goal is to develop new estrogen mimics that possess good relative bioavailability and that cannot form dangerous quinones. Lei Jiam discussed molecular modeling and dynamics studies of oxidative lesions in the DNA glycosylase hNeil1 part of the base excision repair pathway. Lei described how structural features of lesions permit versatility of recognition of purine and pyrimidine oxidation products. Bill Jorgensen discussed computer-aided lead generation and optimization, focusing on non-nucleoside inhibitors of HIV reverse transcriptase as a therapeutic context. Jorgensen described the Biochemical and Organic Model Building program, which generates conformers of a dynamically created combinatorial *in silico* library. His approach trains a scoring function against experimental data, and ligands are filtered for properties (*e.g.*, solubility and cell permeability) *via* Qikprop and Monte Carlo/free energy perturbation to refine predictions, including water molecules and flexible ligand and receptor. Brian Shoichet presented virtual screening for structure-based inhibitor discovery, describing simple, artificial protein binding sites for studying the performance of docking programs. Docking works well for simple binding sites but poorly against real drug targets. Experiments to address this involved docking against AmpC β-lactamase in a head-to-head comparison of docking and high-throughput screening in collaboration with the National Chemical Genomics Center. Of 70,500 compounds screened, 1274 were primary hits, but after follow-up, none were single, noncovalent, reversible competitive inhibitors. Docking the same library left 16 compounds for testing; two were found to be active, the best with a K_i of 37 μM. Lihua Wang presented a water-mediated and substrate-assisted catalytic mechanism for *Sulfolobus solfataricus* P2 DNA polymerase IV, using quantum mechanical/molecular mechanical calculations to investigate reaction mechanisms. Mark Klein discussed small-

The presentations spanned a range of areas that were unified in illustrating that continued advances can result from continued research efforts involving chemistry.

molecule mimetics of $p16^{INK4}$ identified from peptide SAR-derived pharmacophore and database screening. An NMR and alanine scanning-derived 3D pharmacophore was used to search the NCI database for compatible small molecules, which were filtered for "drug likeness". Glide was used to dock the resultant collection to the NMR model, and the top scoring ligands were selected as putative CDK4/6 inhibitors. Experimental testing of the docking predictions is underway.

Structural Biology. The structural biology session covered NMR and X-ray crystallography studies of diverse proteins, with a focus on novel techniques, gaining an understanding of mechanism, and the design of small-molecule inhibitors. These topics are highlighted here, and details from the studies presented are described in Supporting Information. Andrew Byrd presented high-field (900-MHz) NMR work centered on the signal transducer and activator of transcription (STAT) proteins, a family of cytoplasmic proteins that mediate cellular responses to cytokines *via* membrane receptors coupled to Janus kinases. Their large size (~100 kDa) has limited solution NMR studies, and structures have been solved primarily by X-ray crystallography. The STAT-N-terminal domain is highly conserved and has been implicated in several activities crucial to cytokine signaling. Byrd's recent solution structure of STAT4-NT indicates that interactions other than those seen in the crystal structures may be important. Byrd's group concluded that both X-ray and NMR dimer arrangements can exist in solution and that both are relevant. Stephen Burley gave an overview of SGX and its capabilities, highlighting its fragment-based drug discovery (FBDD) approach and noting that many of the fragment hits are more selective than one would predict on the basis of their low molecular weight and lack of complexity. This concept was discussed in the context of kinases, including Met, a kinase implicated in several cancers through overexpression or mutation. He and his group converted an FBDD hit into a lead compound, SGX-523, which is progressing into the preclinical investigational new drug (IND)-track stage, with an IND filing predicted for the end of 2007 or early 2008. He noted the high potency and selectivity of this compound: when tested at 1 μM against 214 kinases, the only kinase that was inhibited at >40% was Met. The debate will continue about the clinical outcome observed for a selective *versus* multikinase inhibitor (Sprycel, Bristol-Myers Squibb and Sutent, Pfizer) in reference to efficacy and tolerability as a single agent and in combination therapies. Wei Yang discussed her group's interest in applying X-ray crystallography, molecular biology, and various biochemical and biophysical approaches to elucidate the molecular mechanisms behind the Y-family of DNA polymerases. These catalyze template-dependent DNA synthesis with low fidelity and low processivity for normal DNA but synthesize through damaged template bases. The structures reveal a conventional right-hand-like catalytic core, with unusually small finger and thumb domains, resulting in an open and capacious active site. Ann McDermott presented solid-state NMR studies of binding and function of membrane-associated proteins. NMR spectra of uniformly labeled (^{15}N, ^{13}C) solid-state proteins can be well resolved and may provide a basis for structural and functional studies. Her group uses a magic angle spinning technique (40 μL of solvent with a few milligrams of protein) and has studied many small proteins, including bovine pancreatic trypsin inhibitor and ubiquitin, and several intrinsic membrane proteins. She also highlighted work in determining CYP450-ligand binding. Ian Hardcastle discussed his work on small-molecule inhibitors of murine double minute 2(MDM2)–p53 protein interactions. Inhibition of the MDM2–p53 protein–protein complex is expected to reactivate normal p53 pathways in cells that overexpress MDM2, and this would consequently cause proapoptotic effects. Heteronuclear single quantum coherence NMR structural studies indicated a plausible binding mode for a compound in complex with MDM2; NMR studies further indicated a key H-bonding interaction. A dihydroisoindolinone analogue with an IC_{50} value of ~650 nM was identified. Ann Alcaraz closed the session, further elaborating on the ligand binding site of colchicine and the development of a model that incorporates available experimental data, which indicate a new binding site.

The presentations spanned a broad range of research areas that were clearly unified in illustrating that continued advances—understanding biological systems and processes, and developing effective therapeutic and prevention strategies for cancer and related diseases—can result from continued research efforts involving chemistry. During the subsequent AACR National Meeting, Chemistry in Cancer Research organizers discussed the overwhelmingly positive feedback resulting from the gathering and announced that plans are underway to hold the meeting on a biannual basis, with the next session in spring 2009.

Acknowledgment: We acknowledge the conference chair, Stephen S. Hecht, members of the program committee (see Supporting Information), and Chemistry in Cancer Research organizers. We thank AACR staff for preparation of the appendices (see Supporting Information) for this report.

Supporting Information Available: This material is available free of charge *via* the Internet.

Editorial Note: A similar commentary will be published in a forthcoming issue of *Cancer Research*.