



Trip Report for
**“Cambridge Healthtech Institute’s 15th International
Molecular Medicine Tri-Conference”**

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Abstract: *The 15th International Molecular Medicine Tri-Conference took place in San Francisco, CA from March 25-28, 2008. The four-day event, which aims to bridge biology, chemistry, and business, provided scientific presentations from 11 concurrent tracks and 10 pre-conference short courses on a broad range of topics. The track on Mastering Medicinal Chemistry included reports on current discovery and development in various therapeutic areas such as pain, oncology, hepatitis C, metabolic disease, and CNS disease. It also covered topics related to the key industry strategies for productive medicinal chemistry and the recent approvals of new chemical entities. This report highlights selected materials from this track.*

“Risk Diagnosis for Disease Prevention”

C. Thomas Caskey, M.D., F.A.C.P., Director and DEO, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center

Dr. Caskey gave a plenary keynote presentation on recent progress in utilizing the presymptomatic diagnostic options to link a specific diagnostic to a therapeutic decision and FDA approval. Presymptomatic diagnosis has been routine practice for years in the newborn diagnostics/therapy and prenatal carrier screening, as well as some adult disease screening such as HIV, human papilloma virus, hemochromatosis, breast cancer and cardiovascular disease. The developments in genetic technology have strengthened our abilities to diagnose disease before onset. For example, PCSK9 (proprotein convertase subtilisin/kexin type 9) is a human gene that provides instructions for making a protein that regulate the amount of cholesterol in blood stream. There are a number of known SNPs (single nucleotide polymorphisms) at the PCSK9 locus that are associated with cholesterol metabolism. A group of scientists in Boston, along with scientists from Sweden, have created a genotype score on the basis of the number of these unfavorable alleles and use the score to determine independent risk factor for incident cardiovascular disease. Moreover, candidate gene association studies recently have identified as many as nine genetic loci reproducibly implicated in the development of type-2 diabetes. Application of these discoveries to understanding genetic mechanisms may allow healthcare providers the ability to tailor behavioral and pharmacologic therapies and to alleviate the tremendous disease burden suffered by type-2 diabetes patients.

Studying approved drugs for maximal efficacy is another realistic and reasonable strategy toward developing personalized therapies for the management of diseases, since it is estimated that many approved drugs are effective in less than 50% of patients. It is well recognized that most medications exhibit wide inter-patient variability in their efficacy and toxicity. For many medications, these inter-individual differences are due in part to single nucleotide polymorphisms. Polymorphisms in genes encoding drug metabolizing enzymes, drug transporters and/or drug targets is the genetic basis for differences in drug efficacy and toxicity among groups of patient populations. For example, warfarin is a blood-thinning drug and is typically prescribed for patients who are experiencing irregular heartbeat or those who have had a heart attack or heart valve replacement surgery. Warfarin can be a difficult drug to use because rapidly achieving the optimal dose is important. Patients who receive doses that are higher than needed are at risk of life-threatening bleeding. Those who receive doses that are too low may remain at risk of life-threatening blood clots. It was found that the people with variations of two genes CYP2C9 and VKORC1 may respond differently to the drug. A FDA-cleared genetic test for the variants of these two genes, along with other clinical information, allows physicians to assess whether a patient may be an appropriate candidate for the use of warfarin. This is apparently one step in the commitment to personalized medicine.

In summary, the risk diagnosis for disease prevention has received a lot of attention in healthcare circles. Successful applications have been found in newborn screening, carrier testing and prenatal diagnoses. The developments in genome technology have brought a few FDA approvals for disease risk identification and/or for diagnosis and treatment match. Moreover the new biomarker process shows the potential to predict the drug safety. The FDA now is prepared to support biomarker tests as another safety standard for preclinical drug packages in addition to the traditional animal safety studies. For more information, see: S. Kathiresan, *et al.*, *NEJM* **2008**,

358, 1240; A. Moore and J. C. Florez, *Ann Rev. Med.* **2008**, 59, 95; U. I. Schwarz, *et al.*, *NEJM* **2008**, 358, 999; S. B. Shurin and E. G. Nabel, *NEJM* **2008**, 358, 1061.

“Role of Technology in a Winning R&D Strategy”

James B. Summers, Ph.D., Divisional Vice President, Advanced Technology, Global Pharmaceutical Discovery, Abbott Laboratory

Dr. Summers gave a presentation in the session of key industry strategies for productive medicinal chemistry. According to his experiences with the Bcl-2 family inhibitors for an anti-cancer therapy, he brought out four feasible maneuvers incorporated into a winning R&D strategy, namely generation of high quality leads, understanding and solving toxicity problems early, leapfrog programs over challenging problems and an informed development strategy.

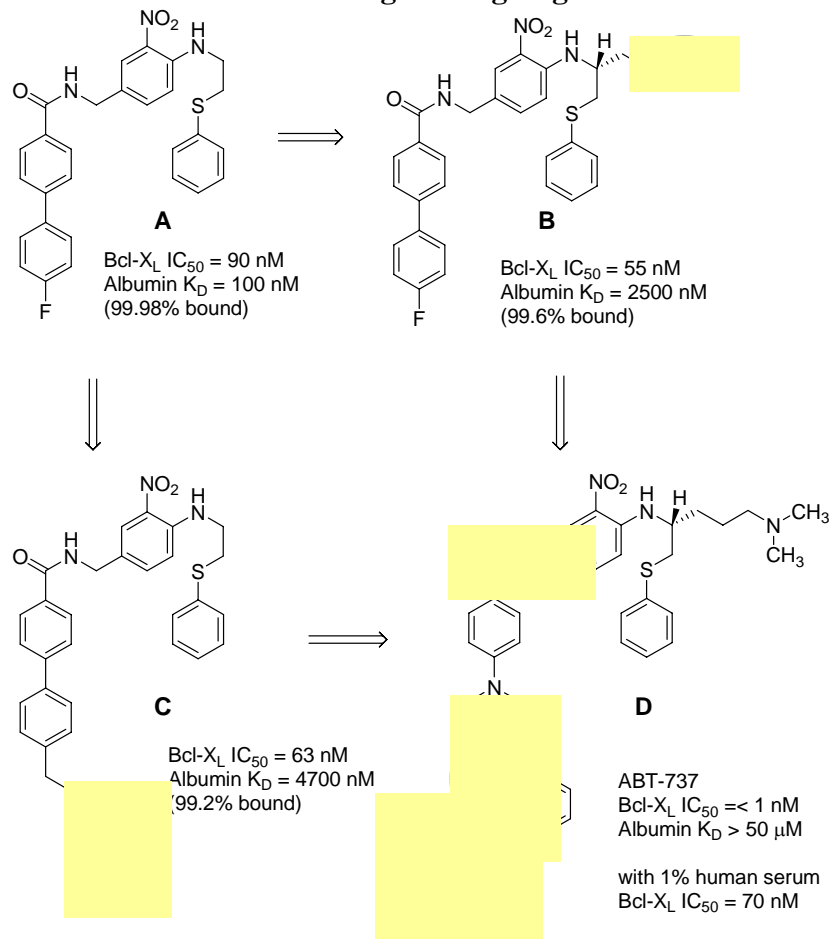
Along with high throughput screening and virtual screening, fragment-based screening has been an important tool for discovery and optimization of new drug leads. Abbott Laboratories have been pioneers in this area and much has been learned in the last decade about working with and manipulating fragment leads. A retrospective analysis has been performed recently on 18 highly optimized inhibitors from Abbott’s internal drug discovery programs. It was found that to achieve potency gains of 3 or 6 log units, the mass of the compound would need to be increased by approximately a factor of 1.9 or 2.9, respectively. A prediction map was generated, with which the molecular weight of a drug candidate with defined potency can be estimated based on the potency and molecular mass values of the initial optimized lead. These results provide a strong empirical support for the success of fragment-based screening approaches in general.

Identifying safety concerns earlier has become a well-recognized strategy for increasing productivity and reducing R&D cost. Traditional safety assessment was executed during the animal studies and further in clinical trials. The newly emerging technologies, such as toxicogenomics, inhibitor affinity capture, protein complementation and molecular imaging, allow the understanding of the molecular basis of toxicity in early stages and to select compounds with optimal safety profiles other than just sufficient profiles. Dr. Summer gave an example to illustrate the advantage of toxicogenomics. With 2-3 g of a drug molecule and within 1-5 days of dosing in mice, the RNA information from the organ of interest can be analyzed and a gene expression pattern can be generated to predict toxicity mechanisms and severity.

With X-ray crystallography, protein NMR and molecular modeling widely applied to structure-based drug design, these technologies are also the powerful tools for solving the challenging problems appearing in drug development. For example, protein binding is very critical for drug efficacy. The scientists at Abbott had been successful with a structure-based anti-design strategy to eliminate protein binding while remaining potency. Compound **A** in Figure 1 is a very potent Bcl-X_L inhibitor (IC₅₀ = 90 nM) but in 1% human serum the IC₅₀ value decreases more than 100-fold. It was found that the high affinity of this compound for human serum albumin (HAS) (K_D = 100 nm) is the major reason for the high protein binding. The NMR structural data for the complex of compound **A** with Bcl-X_L and the one with HAS provide useful information for designing compounds with reduced albumin binding. There were two analogues (compounds **B** and **C**) that stand out with promising profiles, in which an amine or a morpholine have respectively been appended on either the right-hand or the left-hand of the parent molecule via a short alkyl chain. These modifications increase the affinity of these analogues to Bcl-X_L and

significantly reduce the binding to albumin. ABT-737 combines these two modifications, which effectuate not only more than a 500-fold decrease in binding to HAS, but also about 100-fold increase in binding to its therapeutic target, Bcl-X_L.

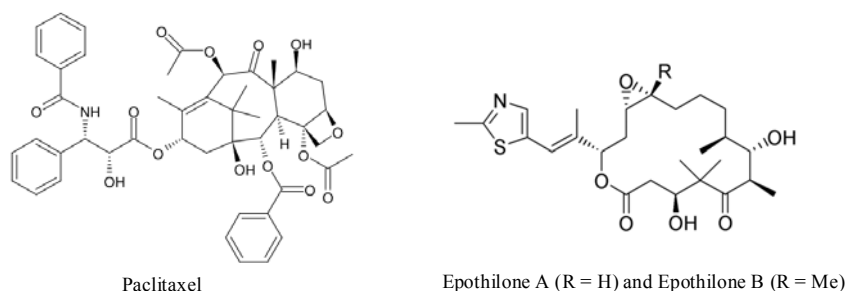
Figure 1. Structure-Based Anti-Design: Designing out Albumin Binding



Another winning R&D strategy that Dr. Summers pointed out is to enable an informed development. As pointed out earlier, many approved medicines are effective in less than 50% of patients. Therefore it is very important to identify patients most likely to respond to a given drug. In the example that Dr. Summers gave, the Bcl-2 family inhibitor ABT-737 had been screened in 67 human small-cell lung carcinoma cell lines. The cells lines were classified into three groups based on the EC₅₀ values (sensitive, intermediate and resistant). The gene profile analyses of these cell lines indicated that the hallmark of sensitivity is the high expression of Bcl-2 and Noxa. The resistance was observed in the cell lines with high expression of Mcl-1. So with this type of Bcl-2 inhibitors, the most effective strategy is to focus on tumors expressing Bcl-2. Additionally, combining with chemotherapies that suppress Mcl-1 may enhance the therapeutic effect. For leading references, see: P. J. Hajduk, *J. Med. Chem.* **2006**, *49*, 6972; S. W. Fesik, *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 10429.

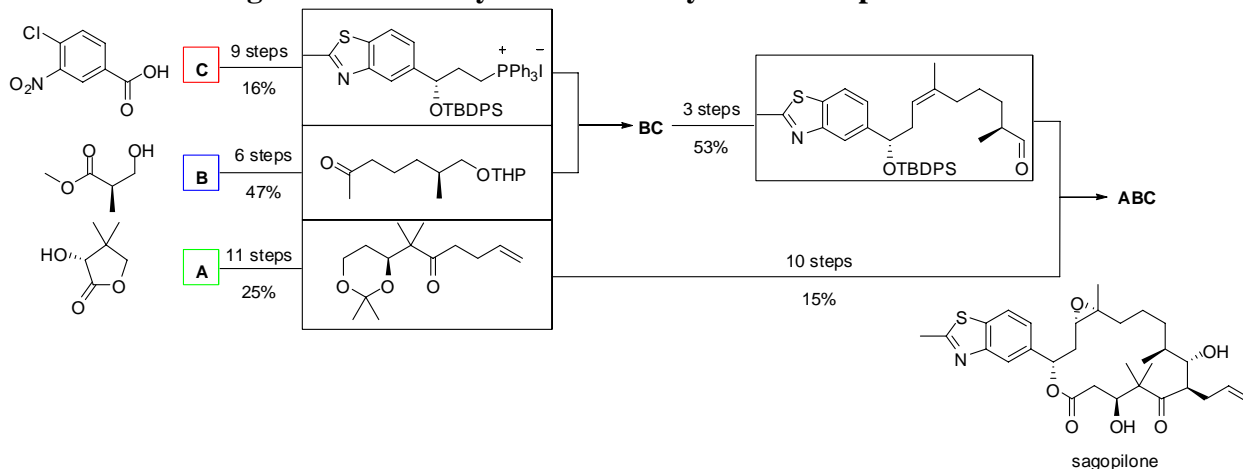
“Sagopilone (ZK-EPO): From a Natural Product to a Fully Synthetic Clinical Development Candidate”

Dr. Klar gave this presentation in the session of case studies in oncology chemistry. The presentation detailed the tremendous efforts ongoing around the natural product epothilone B to support the fully-synthetic clinical development candidate sagopilone (ZK-EPO). Epothilones represent a new class of natural compounds isolated from myxo-bacteria. They bind to β -tubulin and stabilize microtubules, induce cell cycle arrest in G2/M stage and induce apoptosis. Epothilones show high cytotoxic activity in a variety of relevant tumors and have the potential to be active against multidrug-resistant tumors. The action mechanism of epothilones is similar to that of paclitaxel, but their structures are much simpler and they have better solubility in water. Therefore, the solubilizing agents used in paclitaxel, which can induce allergies, are no longer needed in the formulation of epothilone derivatives. Although epothilone B proved to be highly active in proliferation assays, it also is highly toxic in animal models.



Dr. Klar and his team at Schering AG have performed intensive structural modifications to overcome the limitations associated with natural epothilone B. During this optimization process, more than 350 biologically active epothilone derivatives were synthesized, from which sagopilone was selected for clinical development due to its outstanding preclinical properties. The total synthesis of sagopilone was very challenging, involving 24 steps in the longest linear route and with an overall yield of 1.3% (Figure 2). Tedious chromatographies were required for some steps to separate the stereo- and regioisomers. With this synthetic route, 32 g of sagopilone had been produced, which is sufficient to perform nearly all the preclinical investigation. The chemical development for the synthesis of Sagopilone on kilogram scale is in progress.

Figure 2. Summary of Research Synthesis: Steps and Yields



A study with a panel of 100 different human tumor cell lines indicated that sagopilone was more active than paclitaxel and other anticancer chemotherapies such as adriamycin, cisplatin and camptothecin. The mean IC₅₀ of sagopilone on most of tumor cell lines is less than 1 nM. Sagopilone maintains its activity even in multi-drug-resistant (MDR) tumor cells. It has no toxicity against quiescent cells such as human umbilical vein endothelial cell (Huvec) and displays high accumulation in the cytoskeletal compartments.

In the human cervix cancer mice model, sagopilone displays better activity than paclitaxel, with a superior dose-response and no apparent toxicity. Further studies indicated that sagopilone strongly inhibited tumor growth in a wide spectrum of human tumor xenografts, including MDR tumor models that are resistant to the treatment with widely used cytotoxic drugs such as doxorubicin, vincristine, paclitaxel and cisplatin. In a tumor response analysis with 22 nude mice xenografted with patient-derived non-small cell lung carcinoma (NSCLC) tumors, sagopilone showed the highest response rate (64%) compared to carboplatin, paclitaxel and gemcitabine. Moreover sagopilone also has activity in cancer models representing tumor types that are normally not suitable for chemotherapy (*e.g.* melanoma, glioblastoma, pancreatic and cholangio cancers).

Sagopilone has shown signs of activity in Phase I clinical trials including objective responses and is currently being evaluated in a broad Phase II program. Of more than 300 patients treated in Phase II, the main clinically relevant adverse event is target-related peripheral neuropathy (rare significant myelosuppression, no significant diarrhea and low alopecia). Sagopilone has achieved “proof of concept” in a Phase II study of platinum-resistant ovarian cancer. The further clinical studies will be conducted to confirm if the advantages of sagopilone seen in preclinical studies and early clinical studies will translate into a clear benefit for patients. For a leading reference, see U. Klar, *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 7942.