GTC
Global Technology Community

2nd NOVEL CANCER THERAPEUTICS SUMMIT

FEBRUARY 25-26, 2013 • LAS VEGAS, NV

4th CANCER TARGETS AND THERAPEUTICS

- NOVEL KINASE INHIBITORS & BEYOND THE KINOME
- FUNCTIONAL GENOMICS & FUTURE CANCER TARGETS
- NOVEL ANTIBODY-BASED MODALITIES
- PROGRESS IN CANCER IMMUNOTHERAPY
- CANCER STEM CELLS, METABOLISM, CANCER EPI-GENETICS
- PATIENT SELECTION RATIONALE & STRATEGY

2nd ONCOLOGY PARTNERING AND DEAL-MAKING

- HOW BIG PHARMA VALUES YOUR INNOVATION
- INVESTMENTS, PARTNERSHIPS & ACQUISITIONS: TRENDS & RECENT DEALS
- INNOVATIVE PARTNERING & DEAL-MAKING
- REGULATORY GUIDANCE & UPDATES
- ALLIANCE MANAGEMENT
- NOVEL ADVANCES & TECHNOLOGIES IN ONCOLOGY

3rd UBIQUITIN RESEARCH AND DRUG DISCOVERY

- PROTEASOME STRUCTURE AND FUNCTION
- STRUCTURE/FUNCTION STUDIES OF E3 LIGASE CATALYSIS
- UBIQUITIN IN AUTOPHAGY
- DEUBIQUITINATING ENZYMES AS DRUG TARGETS
- NOVEL DRUG TARGETS IN THE UBIQUITIN SYSTEM
- UBIQUITIN-LIKE MODIFICATIONS – NEW OPPORTUNITIES

Agendas last updated on 2/8/2013. Please visit **www.gtcbio.com** for the most updated program.

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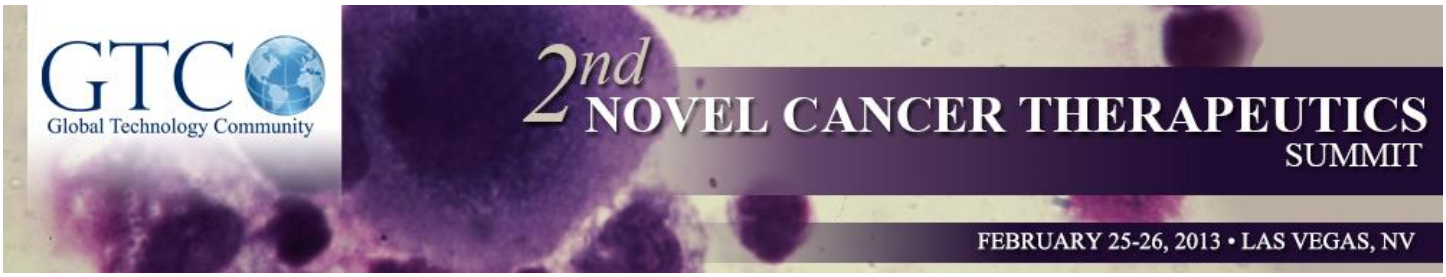

About the 2nd Novel Cancer Therapeutics Summit

This summit brings together experts from academia and industry to discuss the emerging targets, therapeutics and strategies against cancer, as well as showcase ubiquitins' huge potential in the development of therapeutics. Attendees will also receive updates on government policy, recent regulations, important investments and partnering strategies.

GTC's **2nd Novel Cancer Therapeutics Summit** will be held on February 25 - February 26, 2013 in Las Vegas, NV. The three concurrent conferences are:

- *4th Cancer Targets & Therapeutics*
- *3rd Ubiquitin Research and Drug Discovery*
- *2nd Oncology Partnering & Deal-making*

With about 150-200 anticipated attendees, the Novel Cancer Therapeutics Summit is the perfect venue to network with leaders in cancer targets and therapeutics field.

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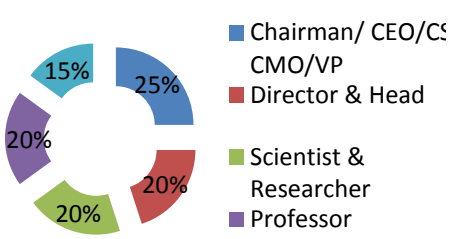

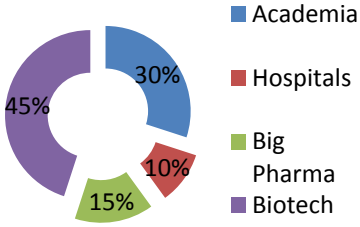

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Day 1 - Monday February 25, 2013

7:00 **Continental Breakfast & Registration**

7:55 **Welcome & Opening Remarks**

KEYNOTE PRESENTATION

8:00 **Intracellular Proteolysis and the Ubiquitin System: From the Backyard to the Center Stage of Biomedicine**

Aaron Ciechanover
Distinguished Technion Professor
Technion-Israel Institute of Technology

Structure/function studies of E3 Ligase Catalysis

Moderator: Christian Loch, Assistant Director, Research & Development, LifeSensors, Inc.

8:45 **Decoding the Ubiquitin Code for Lysine-48 Ubiquitin Chain Synthesis**

Zhen-qiang Pan, Professor, Oncological Sciences, **Mount Sinai School of Medicine**

The covalent attachment of ubiquitin to a substrate protein can direct a multitude of cellular fates in eukaryotes, including signaling, endocytosis, autophagy, and protein degradation. Ubiquitination involves the formation of an isopeptide bond between the C terminus of one ubiquitin (donor Ub) and either a lysine on a substrate protein, or one of seven lysine residues on another ubiquitin in a growing chain (receptor Ub). With regards to protein degradation, the attachment of four or more lysine 48 (K48) linked ubiquitins to a substrate results in its recruitment to the 26S proteasome and subsequent proteolysis. This ubiquitin proteasome system is deregulated in many diseases, particularly cancer, and its components have become an attractive point of therapeutic inhibition in recent years. While it is well established that K48-ubiquitin chains form a signal that ultimately results in protein degradation, much less is known about the mechanism of how these chains are formed and what are the determinants that govern K48 selectivity as opposed to other linkages. We will discuss our recent work on the identification of the ubiquitin code critical for K48-ubiquitin chain synthesis by SCF E3 ubiquitin ligase and Cdc34 E2 conjugating enzyme.

9:10 **New Insights into the Mode of Action of an Inhibitor of the Ubiquitin Conjugating Enzyme Cdc34**

Gary Kleiger, Assistant Professor, Biochemistry, Chemistry, **University of Nevada, Las Vegas**

Ubiquitin conjugating enzymes (E2s) recognize and bind to specific ubiquitin ligases (E3s) during the assembly of poly-ubiquitin chains onto protein substrates. Cdc34 is an E2 that functions with approximately one-third of the E3s in mammalian cells. Together, Cdc34 and its cognate ubiquitin ligases control the ubiquitylation of some 20 percent of all proteins that are to be degraded by the proteasome, making Cdc34 a potentially attractive drug target for human therapy. Recently, a small molecule inhibitor of human Cdc34 function was described. The inhibitor (named CC0651) binds in a pocket on Cdc34 that is located on the opposite side of the molecular surface as the active site. Initial biochemical characterization showed that the inhibitor interferes with the discharge of ubiquitin to substrate, however it remains unclear how inhibition is achieved at the molecular level. We present recent biochemical and structural results that shed light on how CC0651 exerts its influence on Cdc34 activity from such a great distance from the active site.

9:35 **Crystal Structure and Biochemical Function of Parkin RBR Ligase Reveals Aspects of HECT and RING Ligases**

Jennifer Johnston, Vice President of Research, **Elan Pharmaceuticals**

10:00 **Networking and Refreshment Break**

10:30 **Regulation of Cullin-RING E3 Ligases by CAND1 and the COP9 Signalosome**

Thimo Kurz, Programme Leader in Protein Ubiquitylation, Scottish Institute for Cell Signalling, **College of Life Sciences, University of Dundee**

Cullin-RING ligases (CRLs) are modular multi-subunit ubiquitin E3 enzymes. CRL complexes consist of a cullin scaffold protein, which at its C-terminus interacts with a small RING-finger protein (Rbx1/2), and at the N-terminus recruits substrate adaptor and receptor subunits. Nedd8 modification of a conserved lysine residue in the cullin C-terminus promotes the activity of CRLs by inducing structural flexibility. De-neddylation by the COP9 Signalosome (CSN) is also important for CRL function and non-neddylated Cullin-Rbx core complexes can interact with the protein CAND1. In vitro, the CSN and CAND1 behave like inhibitors of Cullin-RING ligases, while in cells they both appear to be activators. We have studied the budding yeast orthologs of these proteins to better understand the molecular mechanism behind this paradoxical behavior. Using an extracellular signal that allowed us to rapidly activate and inactivate a specific CRL complex, we were able to delineate the requirements for the CSN and CAND1 in CRL regulation and assembly. Our data demonstrates that the exchange of substrate adapters from Cullin-RING ligases requires the sequential activity of CSN and CAND1 and that this activity is especially important for CRLs to rapidly respond to external signals. In particular, we show that during CRL inactivation, de-neddylation by the CSN precedes CAND1 activity, which is subsequently required to release substrate adaptors from the CRL. This release is essential to allow the formation of new substrate-specific complexes during reactivation, which explains why substrate degradation is defective in CSN and CAND1 mutant cells.

Novel Drug Targets in Ubiquitin Pathways Part 1

10:55 **Small-molecule Regulation of Protein Quality Control: Lessons from Sterol Regulation**

Randolph Hampton, Professor, Cell and Developmental Biology, **UCSD**

The majority of drugs operate by alteration of evolved binding sites that accommodate natural ligands. Examples include opiates, histamine, cannabinoids, adrenergic agonists, prostaglandins, and a wide variety of natural regulatory molecules. However, there are many clinically relevant proteins that do not have "active site" based actions for which inhibitory targeting would be advantageous. One strategy for lowering the activity of such targets would be to take advantage of the many high specificity quality control pathways that selectively target misfolded or damaged proteins. Our work with protein quality control has revealed that this high degree of specificity often is due to subtle and manipulable structural features. Of particular interest to this idea of "degradation-based antagonism" is our work on the regulated degradation of the rate-limiting enzyme of sterol biosynthesis HMG-CoA reductase (HMGR). As is often the case, nature has manifested this useful idea long before ideas existed in the world. We will show how the molecular details of HMGR regulated degradation indicate the feasibility of harnessing quality control pathways pathways as a novel avenue for regulation of normally unassailable drug targets.

11:20 **Ubiquitin Editing by A20: Molecular Mechanisms and Physiological Significance**

Ingrid Wertz, Scientist, Early Discovery Biochemistry, **Genentech**

Inactivating mutations in the ubiquitin editing protein A20 regulate cell death by promoting persistent nuclear factor (NF)-kB signaling and are genetically linked to inflammatory diseases and hematologic cancers. A20 tightly regulates NF-kB signaling by acting as a dual ubiquitin editing enzyme, removing K63-linked ubiquitin chains via the ovarian tumor (OTU) de-ubiquitinase domain and mediating addition of ubiquitin chains that target substrates for degradation via the A20 zinc finger 4 (ZnF4) motif. Structural analysis reveals additional mechanistic details of A20-mediated ubiquitin editing. A20 ZnF4 does not directly interact with E2 enzymes but instead can bind mono-Ub and K63-linked poly-Ub. Mutations of the A20 ZnF4 Ub-binding surface result in decreased A20-mediated ubiquitination and impaired regulation of NF-kB signaling. Ubiquitin linkage-specific antibodies and the generation mice harboring specific mutations in residues that functionally inactivate A20 confirm A20-mediated ubiquitin editing of NF-kB signaling components and the resultant effects on NF-kB activity. Collectively, our studies illuminate the mechanistically distinct but biologically interdependent activities of the A20 ZnF and OTU DUB domains that are inherent to the Ub editing process and to regulation of NF-kB signaling.

11:45 **Targeting the Immunoproteasome**

Dustin McMinn, Associate Director, Medicinal Chemistry, **Onyx Pharmaceuticals**

12:15 **Lunch on Your Own**

FEATURED PRESENTATION

1:30 **How RING E3s Work: Allostery Revealed**

Rachel Klevit
Professor
Biomolecular Structure Center
University of Washington

E3 Ubiquitin (Ub) ligases constitute the largest family of proteins in the human genome with over 600 members, including many known tumor suppressors such as BRCA1 and MDM2. Despite their importance in a broad range of cellular processes and in numerous diseases, fundamental understanding of how the RING-type E3s activate ubiquitin-conjugating (E2) enzymes for ubiquitin transfer has been lacking. Our recent identification of the conserved allosteric linchpin of RING/U-Box E3s provides a key insight to understand how E3s work. I will discuss the source of allosteric activation of E2~Ub conjugates by RING/U-Box E3s and will present examples of variants based on our new understanding that have altered activities. The ability to engineer mutant E3s with lower or higher activity than wild-type enzymes provides new opportunities to investigate the cellular functions of members of the largest class of E3 ligases. Lessons learned from our studies are generalizable to other E3 ligases and E2 Ub-conjugating enzymes and therefore have broad applicability.

Key points:

• Residues highly conserved among RING/U-box E3 ligases provide the allosteric link responsible for conformational activation of E2~Ub.
• The binding and activation functions of E3s can be uncoupled, providing an opportunity to design E3 ligase species that can still bind to their cognate E2s but cannot activate them for Ub transfer.
• It is possible to engineer RING/U-Box mutants that are more active than their wild-type counterparts.

Deubiquitinating Enzymes as Drug Targets

Jason Brown, Managing Director, Ubiquigent Ltd

2:05 **DUBs: Therapeutic Challenges and Opportunities**

Xavier Jacq, Head, Biology and Screening, **MISSION Therapeutics**

Ubiquitin is covalently linked to many cellular proteins to regulate their activities, stability, localisation or interactions. Ubiquitylation is a reversible process carried out by Ubiquitin ligases and by deubiquitylating enzymes (DUBs). The human genome encodes approximately 100 DUBs, while additional DUBs are found in many organisms, including viruses and bacteria. Out of the 5 families of DUB enzymes, four (USP, UCH, MJD and OTU) belong to the cysteine peptidases, while one (the JAMM family) belongs to the metallo-peptidases. DUBs have been shown to play critical roles in many pathological processes, particularly cancer, infective diseases and neuro-degeneration, and have thus begun to attract much attention from the pharmaceutical industry. This presentation will describe past challenges faced by the industry in targeting DUBs as well as exiting emerging opportunities in developing drug discovery cascades to overcome inherent thiol protease liabilities and, more specifically, to yield small-molecule drugs targeting DUBs. MISSION Therapeutics' efforts at targeting DUBs involved in the DNA-damage response will be used to illustrate the challenges and opportunities.

2:30 **Deciphering the "ubiquitin code": Structure and Recognition of the Polyubiquitin Signal**

David Fushman, Professor, Chemistry and Biochemistry, **University of Maryland, College Park**

Polyubiquitin chains function as molecular signals in the regulation of a host of cellular processes involved in practically all aspects of eukaryotic cell biology. Uncovering the mechanisms that allow differently linked polyubiquitin chains to serve as distinct molecular signals requires understanding of the conformational and recognition properties of these chains and how they depend on the linkage type and chain length. While a substantial amount of biological and structural data has already been accumulated on polyubiquitin chains homogeneously linked through lysine-48 or

lysine-63, we know very little about the so-called non-canonical chains, formed through the other five lysines or the N-terminus of ubiquitin or containing more than one type of linkages, either alternating or branched. Understanding of the roles the non-canonical chains play in cellular processes is lacking, and studies of these chains have been impeded by the inability to make these chains in vitro. We developed several methods, both enzymatic and non-enzymatic, that allow controlled assembly of fully natural polyubiquitin chains (free of any mutations and linked through native isopeptide bonds) of any desired length and linkage composition and in sufficient quantities for structural and other studies. Using these chain-assembly methods, we produced various types of non-canonical chains and characterized their structure and recognition by known ubiquitin-receptors. Our results provide insights into the broad signaling repertoire available through various combinations of chain linkages.

Benefits:
How to make any polyubiquitin chain without E2 and E3
Understanding the structure, recognition, and processing of non-canonical chains
Structure, recognition, and processing of Rub1/Nedd8—ubiquitin conjugates

2:55 **Afternoon Break**

3:40 **Conformational Stabilization of Ubiquitin Yields Potent and Selective Inhibitors of USP7**

Jacob Corn, Scientist, Early Discovery Biochemistry, **Genentech**

Ubiquitin is a highly conserved eukaryotic protein that interacts with a diverse set of partners to act as a cellular signaling hub. Intriguingly, ubiquitin has recently been shown to be conformationally flexible, which may underlie its multifaceted recognition. Using computational and library-based means, we interrogated core mutations of human ubiquitin to stabilize deubiquitinase (DUB) binding conformations. These conformationally-engineered DUB probes specifically bind and inhibit the catalytic domain of USP7/HAUSP with nanomolar potency. Crystal structures and reversion mutagenesis indicate that altered packing within the ubiquitin variants disposes surface residues to make new interactions with USP7, such that the mutagenized cores are essential for affinity. One such ubiquitin variant expressed in human tumor cell lines specifically binds and inhibits endogenous USP7, thereby enhancing proteasomal turnover of Mdm2 and stabilizing p53. Our results suggest an effective method to probe the complexities of ubiquitin signaling and provide first steps towards semi-rational conformational engineering of protein domains.

4:15 **Investigating the Ubiquitome through Biochemical Proteomics**

Christian Loch, Assistant Director, Research & Development, **LifeSensors, Inc.**

4:40 **[Oral Presentation from Exemplary Submitted Abstracts]**

5:10 **Networking Reception & Poster Session**

Day 2 - Tuesday, February 26, 2013

8:00 **Breakfast**

Ubiquitin-like Modifications – New Opportunities

Jacob Corn, Scientist, Early Discovery Biochemistry, Genentech

8:30 **Cellular Pathways of Protein Quality Control**

Judith Frydman, Professor, Biology, **Stanford University**

8:55 Jason Brown, Managing Director, **Ubiquigent Ltd**

9:20 **Novel Mechanism for Inhibiting HIV-1 Maturation Revealed by a Family of Desumoylation Inhibitors**

Yuan Chen, Professor, Molecular Medicine, **Beckman Research Institute of City of Hope**

HIV integrase is regulated by post-translational modifications, including those by the small ubiquitin-like modifiers (SUMO); however, these mechanisms have not been exploited for developing an anti-viral strategy. Enzymes known as SENPs catalyze the maturation of SUMO precursors and removal of SUMO from modified proteins. Here we report the identification and characterization of a class of small molecule inhibitors of SENPs using in silico screening, enzyme kinetic and NMR analysis. These studies revealed a substrate-dependent mechanism to inhibit the SENPs. These compounds were known to confer anti-HIV activities, but their cellular targets and mechanism of inhibition were unknown. We found that the inhibitors significantly reduce the production of infectious virions, which can carry out reverse transcription but cannot integrate into the host genome. Thus, this study has identified a novel class of SENP inhibitors that inhibit HIV maturation by a distinct mechanism from that of previously known HIV inhibitors.

Identification of novel SENP inhibitors that work in cells
Structural analysis of the inhibition mechanism
Novel inhibitors of HIV maturation
A mechanism to inhibit HIV integrase

9:45 **Morning Networking Breaking**

Proteasome Structure and Function

Moderator: Gary Kleiger, Assistant Professor, Biochemistry, Chemistry, University of Nevada, Las Vegas

10:30 **New Insights into Proteasome Function**

Alfred Goldberg, Professor, Cell Biology, **Harvard Medical School**

Inhibitors of the proteasome's chymotrypsin-like activity have greatly improved the treatment of multiple myeloma (e.g. bortezomib) and have also been enormously valuable as research tools (e.g. MG132) to clarify the functions of the UPS. However, protein breakdown by the 26S proteasome involves many other steps that may also be targets for drug development. The capacity of the proteasome for proteolysis is tightly regulated and is enhanced upon binding of a ubiquitinated protein, which stimulates 20S gate opening. This stimulation occurs when the ubiquitin chain binds to the 19S-associated deubiquitinating enzymes, Usp14/Ubp6 or Uch37. This mechanism enhances the selectivity of the proteasome for ubiquitinated proteins and links ubiquitin chain disassembly to proteolysis. This gating step is also affected in pathological states e.g. by Bovine Spongiform Encephalitis, (Mad Cow Disease). Initially, the ubiquitinated chain on the substrate binds reversibly to the 19S receptors. The conjugates then become more tightly bound and committed to degradation by a step that requires ATP hydrolysis and an unfolded or loosely-folded domain in the proteins, which appears to interact with the ATPase ring. Ubiquitin conjugates also activate ATP hydrolysis 2-4 fold. This stimulation of the ATPase requires both an unfolded domain on the protein and also an interaction of the Ub chain with Usp14 or Uch37. Tight binding precedes activation of the ATPase allowing the substrate to be deubiquitinated, unfolded and translocated into the 20S. During proteolysis, ATP hydrolysis proceeds around the hexameric ring in an ordered manner. Although PAN has six identical subunits, it binds ATPs in pairs, and two subunits exhibit high, two low, and two have no affinity for ATP. When PAN or the 26S binds two ATP?S molecules (and 2 ADPs), it is maximally active in promoting 20S gate opening and other reactions. Thus, the two para-positioned ATPase subunits bind ATP simultaneously and their C-termini dock into the 20S. These findings imply a cyclical mechanism in which ATP binding alters the nucleotide affinity of its neighbors. This cyclic mechanism can explain many features of 26S function and has been supported by studies of yeast mutants in individual ATPase subunits. We demonstrated a definite stoichiometry between ATP and protein hydrolysis, in which the amount of ATP consumed in degrading a ubiquitinated substrate depends on the tightness of its folding.

10:55 **Proteasome Inhibitors for Cancer Therapy**

Larry R. Dick, Director of Biochemistry, **Millennium: The Takeda Oncology Company**

The proteasome inhibitor bortezomib (VELCADE®) has approval from the U.S. Food and Drug Administration for the treatment of patients with multiple myeloma. The bortezomib drug substance is an N-capped dipeptidyl boronic acid and it interacts with its target enzyme by "slow-tight binding" to the ?5, ?5i, and ?1i active sites. Because of the great abundance of proteasomes in cells throughout the body relative to the number of drug molecules in a standard dose, the slow rate of dissociation of bortezomib (110 minute half-life) from its binding sites on the proteasome becomes a major factor limiting the drug's tissue distribution. Based on the hypothesis that more rapid dissociation from the proteasome could improve tissue distribution, we have developed an investigational, dipeptidyl boronic acid proteasome

inhibitor, MLN9708. MLN9708 (ixazomib citrate) displays comparable potency to bortezomib for the proteasome active sites, but has a faster rate of dissociation (18 minute half-life). This property is manifested in vitro by rapid recovery of proteasome activity upon washout of the drug from cells in culture, and in vivo by reduced blood/plasma partitioning in mice. In turn, MLN9708 produces greater tumor pharmacodynamic responses in mouse models of cancer correlating with improved antitumor activity.

11:20 **Dissecting the Ubiquitin Code**

Michael Rape, Associate Professor, Cell and Developmental Biology, **University of California at Berkeley**

Ubiquitin chain formation can occur through seven Lys residues or the amino-terminus of ubiquitin, leading to the assembly of eight homogenous and multiple branched chain types. All linkages have been detected in cells, and as seen for canonical chains, the connection between ubiquitin molecules can determine the outcome of this modification: K48-linked chains drive proteasomal degradation, yet K63-linked chains regulate assembly of oligomeric protein complexes. However, the roles of most non-canonical and all branched chain types are poorly understood. Here, we have developed a novel approach, reprogramming of a ubiquitin ligase, to determine the cellular functions of non-canonical ubiquitin chains. Our work identifies a novel type of ubiquitin modification, whose assembly and function will be discussed.

11:45 **Lunch Provided by GTC**

FEATURED PRESENTATION

1:00 **Towards Development of a Third-generation Proteasome Inhibitor**

Ray Deshaies
Professor
Caltech Investigator
Howard Hughes Medical Institute

Novel Drug Targets in Ubiquitin Pathways Part 2

1:35 **Targeting both the UPS and Autophagy with p97 ATPase Inhibitors to Impair Cancer Growth**

Tsui-Fen Chou, Assistant Professor, Pediatrics, Medical Genetics, **Harbor Medical Center UCLA**

To discover more potent p97 inhibitors, we have carried out a structure-activity relationship study of the quinazoline scaffold previously identified from our HTS campaigns. Two improved inhibitors, ML240 and ML241, inhibited p97 ATPase with IC50s of 100 nM. Both compounds inhibited degradation of a p97-dependent but not a p97-independent proteasome substrate in a dual-reporter cell line. They also impaired the endoplasmic reticulum associated degradation (ERAD) pathway. Unexpectedly, ML240 potently stimulated accumulation of LC3-II within minutes, inhibited cancer cell growth, and rapidly mobilized the executioner caspases 3 and 7 whereas ML241 did not. This striking difference suggests that simultaneous blockade of both proteasome and autophagy degradation pathways leads to more rapid activation of apoptosis than is observed with a proteasome inhibitor. Further characterization revealed that ML240 has broad anti-proliferative activity towards the NCI-60 panel of cancer cell lines but slightly lower activity towards normal cells. ML240 also synergizes with the proteasome inhibitor MG132 to kill multiple colon cancer cell lines. Meanwhile, both probes have low off-target activity towards a panel of protein kinases and central nervous system targets. Our results nominate ML240 as a promising starting point for the development of a novel agent for chemotherapy of cancer, and provide a rationale for developing pathway-specific p97 inhibitors.

2:00 **Discovery of Improved Agents Affecting Novel Targets in Ubiquitin Pathways**

Dave Wustrow, Vice President, Chemistry, **Cleave Biosciences**

In spite of progress of the past 10 years in the discovery and development of targeted anti-cancer therapies there remains a large unmet need in the treatment of solid tumors. Many patients do not respond to standard treatments or their response is not durable. Therefore, there is a need for targeted treatments with broad cellular effects which can address the cellular heterogeneity found in many solid tumors. The success of the proteasome inhibitors bortezomib

and carfilzomib as treatments for multiple myeloma demonstrate the potential of targeting enzymes in the 26S proteasome as a successful way to target difficult to treat cancers. While proteasome inhibitors successfully treat hematological cancers their impact on solid tumors has so far been limited. Current proteasome inhibitors act by blocking the b subunits in the core of the proteasome. At Cleave Biosciences we are targeting other enzymes which have the potential to more precisely regulate ubiquitin pathways involved in protein homeostasis. One such enzyme is Rpn11, a deubiquitinase found in the regulatory particle of the 26S proteasome. Rpn11 removes the poly ubiquitin chains from proteins which is necessary prior to their entry into the channel of the proteasome. This talk will summarize the validation, development of biochemical and cellular assays, lead discovery and development strategies related to Rpn11 inhibitors.

Benefits:
A discussion of the architecture of the 26S proteasome and the position of Rpn11 in the 19S regulatory particle
Validation of Rpn11 as a potential cancer treatment
A description of biochemical and cellular assays
Discovery and validation of small molecule Rpn11 inhibitors

2:25 **Ubiquitin-like Proteins Regulate the Cancer Stem Cell Growth and Death**

Charlie Hao, Associate Professor, Pathology & Laboratory Medicine, **Emory University School of Medicine**

Post-translational modification by ubiquitin-like proteins (UBLs) modulates the protein properties including protein-protein interaction and protein half life. UBL conjugation pathways are elevated in human cancers, inhibiting the cancer stem cell (CSC) death pathway, promoting the CSC self-renewal and driving the cancer progression. In examining CSC-enriched neurospheres derived from human glioblastomas, we have shown that A20 UB E3 ligase adds Lys 63 (K63)-linked polyubiquitin (poly-UB) chains to receptor-interacting protein 1 (RIP1). Through the conjugated K63-linked poly-UB chain, RIP1 interacts with the apoptosis-initiating protease, caspase-8 and thus inhibits the caspse-8-initiated, TRAIL-induced apoptosis pathway in the CSC. The successful development of A20 UB E3 ligase inhibitors will lead to the combination of the inhibitor and TRAIL in treating human cancers. In contrast to UB, small ubiquitin-like modifier (SUMO) drives the CSC self-renewal and thus cancer progression through conjugation of cell cycle proteins. SUMO exists in three functional isoforms: SUMO1-3, but SUMO2 and SUMO3 are referred to as SUMO2/3 because they share 97% amino acid sequence. Targeting of either SUMO1 or SUMO2/3 leads to the cell cycle arrest, thus blocking CSC self-renewal and cancer progression. SUMO conjugation of cell cycle blocks the ubiquitination and degradation of the proteins, thus driving the CSC self-renewal and cancer progression. Targeting of the SUMO pathways will provide novel therapeutic strategies in treating human cancers.

2:50 **Development and Utilization of Novel Tools in Targeting of E3 Ligases**

Zohar Biron-Sorek, Head, Protein Production and Molecular Biology, **Proteologics**

Proteologics is a biopharmaceutical company exploiting the ubiquitin system for the discovery and development of novel therapeutics. The company focuses primarily on the discovery of small molecule inhibitors for specific E3 ubiquitin ligases (E3). The E3 enzymes control the conjugation of ubiquitin to target proteins, regulating protein degradation and a variety of other cellular mechanisms. Two of the major families of the E3 ligases are the RINGs and the HECT family. The RING proteins mediate the direct transfer of ubiquitin from E2 to specific substrates, while in the HECT protein activity involves an obligate thioester intermediate with the active-site of cysteine.

One of the major challenges in the ubiquitin drug discovery efforts is to identify novel and robust chemical starting points that bind to the active domains (RING or HECT) in the E3 ligases and modulate the ubiquitination reaction. To address this challenge we have developed two proprietary tools that may be useful in the discovery of selective hit compounds: a focus library of small molecules that specifically target the RING domain and a selectivity panel, comprising of a large number of RING and HECT E3 ligases.

A focused compound library targeting the RING domain was designed based on our proprietary data on the chemical and biological properties of a novel chemical scaffold. A library of thousands compounds was generated around this scaffold and was then screened against the RING selectivity panel. The selectivity panel currently includes 8 RING ligases for which we have developed a standardized HTRF-based ubiquitination assay. Molecules derived from this scaffold are active against RING-type proteins. Moreover, our screen results identified molecules that are active against a broad-range of RING E3 ligases, as well as selective molecules which are active against a sub-group or a single ligase.
These tools could add significant contribution in future ubiquitin-based drug discovery efforts.

3:15 **Conference Concludes**

Day 1 - Monday, February 25, 2013

7:00 **Registration & Continental Breakfast**

7:55 **Welcome & Opening Remarks**

JOINT KEYNOTE PRESENTATION

8:00 **Intracellular Proteolysis and the Ubiquitin System: From the Backyard to the Center Stage of Biomedicne**

Aaron Ciechanover
Distinguished Technion Professor
Technion-Israel Institute of Technology

Novel Antibody Based Therapies

Moderator: Juswinder Singh, Founder & Chief Scientific Officer, Celgene Avilomics Research

KEYNOTE PRESENTATION

8:55 **The Potential of Antibody Drug Conjugates: Hype or Reason to Hope?**

Jeremy Barton
Vice President, Head of Oncology Clinical Research
Pfizer

One of the first publications describing the use of antibodies serving as “guided missiles” to deliver therapeutic agents to cells containing specific antigens appeared in Nature in 1964.

Nearly 50 years later there is one such antibody drug conjugate (ADC) on the market (a second one was launched and then withdrawn) and at least 25 in clinical development. Most major pharma companies have invested in the field.

Enthusiasm for the potential of ADCs has been driven by the remarkable efficacy of Adcetris® which is approved for relapsed refractory Hodgkins Disease and trastuzumab DM1for metastatic breast cancer which is expected to be approved in 2013.

The importance of selecting a target which is preferentially expressed on tumor cells has long been self evident but what has become apparent in the last 5 years is the increasing complexity of the underlying technology used to make these conjugates. The type of therapeutic agent, the way in which it is linked to the antibody and the site of linkage to the antibody can all have dramatic impact on the pharmacokinetics, safety and efficacy of the total construct.

This presentation will review some of the exciting data which have already been generated and will objectively review some of the challenges which must be overcome in the future in order to maximize the promise of ADCs as a new class of therapeutic agent.

BENEFITS

- Review of past history of ADC development
- Understanding of technological challenges in constructing an ADC
- Review of available technologies
- Importance of patient selection strategies

9:40 **Antibody Fusion Proteins for the Immunotherapy of Cancer**

Alan Epstein, Professor of Pathology, **USC, Keck School of Medicine**

10:05 **Morning Networking Break**

Functional Genomics & Future Cancer Targets

Moderator: Domagoj Vucic, Senior Scientist, Genentech, Discovery Biochemistry

10:30 **Targeting Inhibitor of Apoptosis (IAP) Proteins for Anti-cancer Therapies**

Domagoj Vucic, Senior Scientist, **Genentech, Discovery Biochemistry**

Evasion of cell death is a characteristic feature of human cancers and represents a key cause of resistance to current treatment approaches. Therefore, reactivation of cell death programs in cancer cells is a promising strategy to overcome treatment resistance, one of the major unsolved problems in clinical oncology. Inhibitor of apoptosis (IAP) protein family members block cell death in response to diverse stimuli and are expressed at elevated levels in the majority of human malignancies, which makes them attractive targets for developing a novel class of cancer therapeutics. We have designed small-molecule IAP antagonists (smac mimetics) that bind with high affinities to select baculovirus IAP repeat (BIR) domains of IAPs resulting in a dramatic induction of c IAP auto-ubiquitination activity and rapid proteasomal degradation. Our IAP antagonists inhibit tumor growth in vivo as single agents and in combination with a number of anti-tumor agents. Using several different proteomic approaches we have discovered novel binding partners for IAP proteins and determined the spatial and temporal pattern of endogenous ubiquitination during proliferative, apoptotic and necrotic signaling. The differential expression levels and posttranslational modifications of identified proteins will be used to build diagnostic tools for the treatment with IAP antagonists. These compounds can be used in the treatment of malignancies in which IAP expression contributes to tumor progression and resistance to conventional chemotherapeutic agents.

Benefits:
- understand the mechanistic reason for the resistance of cancer to standard of care therapies
- identification of relevant resistance factors
- update on current clinical trials
- understand the mechanism(s) of relevant cellular signaling pathways

10:55 **Efforts to Identify Druggable Targets in Medulloblastoma and Glioblastoma**

Nagi Ayad, Associate Professor, Psychiatry & Behavioral Sciences, **University of Miami, Epigenetix**

Our studies are aimed at identifying druggable targets in medulloblastoma and glioblastoma. Medulloblastoma is the most common malignant pediatric brain tumor while glioblastoma is the most prevalent malignant adult brain tumor. Aggressive forms of medulloblastoma and glioblastoma are largely untreatable and therefore represent unmet medical needs. We are employing a systems approach to identifying kinases, ubiquitin ligases, and epigenetics enzymes, which may be misregulated in medulloblastoma and glioblastoma. For medulloblastoma, we find that stabilization of Wee1 kinase inhibits medulloblastoma cell proliferation in vitro and in vivo. This stabilization is due to inhibition of an upstream kinase required for Wee1 degradation. This mode of inhibiting cancer cell proliferation is also applicable to glioblastoma cells and stem cells, and thus may be a general means of inhibiting cancer cell growth. We are currently combining our Wee1 stabilization method in combination with inhibition of epigenetics enzymes to identify synergy in eliminating medulloblastoma and glioblastoma growth in vivo.

11:20 **Opposing Effects of Androgen Deprivation and Targeted Therapy on Prostate Cancer Prevention**

Shidong Jia, Scientist, **Genentech**

Prostate cancer is an ideal target for chemoprevention. To date, chemoprevention clinical trials with 5?-reductase inhibitors (5-ARI) have yielded encouraging yet ultimately confounding results. Using a pre-clinical mouse model of high-grade prostatic intraepithelial neoplasia (HG-PIN) induced by PTEN loss, we observed unprecedented deteriorating effects of androgen deprivation, where surgical castration or MDV3100 treatment accelerated disease progression of the otherwise stable HG-PIN to invasive castration-resistant prostate cancer (CRPC). As an alternative, targeting the PI3K signaling pathway via either genetic ablation of PI3K components or pharmacological inhibition of PI3K pathway reversed the PTEN loss-induced HG-PIN phenotype. Finally, concurrent inhibition of PI3K and MAPK pathways was effective in blocking the growth of PTEN-null CRPC.

Together, these data have revealed the potential adverse effects of anti-androgen chemoprevention in certain genetic contexts (such as PTEN loss) while demonstrating the promise of targeted therapy in the clinical management of this complex and prevalent disease.

11:45 **The JAX Patient Derived Xenograft Resource for Clinical Advancement**

Neal Goodwin, Director, Research & Development**, The Jackson Laboratory**

A unique collaborative effort between The Jackson Laboratory (JAX), the UC-Davis Comprehensive Cancer Center, UCSD Moores Comprehensive Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center and other research centers has been established for advancing cancer therapeutic development. Solid and liquid tumor specimens from consenting patients are being transplanted into the JAX-NSG mouse which has been engineered to ideally propagate human tissue due to its being completely immune deficient.

• These patient derived xenograft (PDX) tumors can be screened with standard-of-care and experimental therapeutics and tumor response can be compared to clinical patient response.
• New therapeutic strategies to overcome resistance to cancer therapeutics and molecular genomics signatures predictive of patient benefit from targeted therapies can both be determined using the NSG-PDX models.
• To date, over 400 patient specimens including hematological malignancies have been xenografted into NSG mice and over 100 PDX tumor models have been advanced for use in research including co-clinical predictive tumor response studies.
• The NSG mouse has proved to be uniquely efficient for engrafting hematological malignancies such as acute myeloid leukemia (AML) due to its being completely replete of NK cells.

12:10 **Lunch on Your Own**

Novel Kinase Inhibitors & Beyond the Kinome

Moderator: Pei-Pei Kung, Senior Principal Scientist, Pfizer

1:30 **Preclinical Evaluation of the Mitotic Kinesin CENP-E Protein as a Therapeutic Target for Triple Negative Breast Cancers**

Pei-Pei Kung, Senior Principal Scientist, **Pfizer**

The centromere protein E (CENP-E) plays an essential role in regulating mitosis during cell division and its expression, as indicated by the Ki67 marker, is associated with the high proliferation rate of cancer cells. Poor prognosis and long-term survival rates for triple-negative breast cancers clearly support a need for new therapeutic agents other than anthracyclin and platinum based therapies. A small molecule CENP-E inhibitor was evaluated against a panel of triple-negative breast cancer cell lines to investigate the outcome of inhibiting CENP-E function. In vitro evaluation using western blot analysis and immunofluorescence assays confirmed the anti-mitotic effects caused by this small molecule inhibitor in the cell-based setting. The relationship between the compound's plasma exposure (pharmacokinetic, PK) and pharmacodynamic modulation of downstream mitotic arrest effects (PD) as measured by the elevation of phosphohistone-H3, and anti-tumor activity was also investigated in pre-clinical animal models to further evaluate the therapeutic potential of this target. In vivo therapeutic effects of this compound were also demonstrated in several triple-negative breast cancer models as well as in patient-derived triple-negative breast cancer xenografts. These results provide good evidence that CENP-E could serve as a therapeutic target for triple negative breast cancers.

1:55 **The Resurgence of Covalent Drugs**

Juswinder Singh, Founder & Chief Scientific Officer, **Celgene Avilomics Research**

Historically, drug discovery has been driven by pharmacology rather than molecular biology. Breakthrough pharmacologic profiles have frequently and serendipitously been provided by drugs later demonstrated to act through a molecular mechanism of action relying on covalent modification of the target protein. Prominent examples include aspirin, beta-lactam antibiotics, and the proton pump inhibitors. Yet, despite the prevalence, efficacy, and safety of this therapeutic modality, there has been a widespread reluctance to design and develop drugs that employ covalent mechanisms against their targets. This lecture will focus on the design principles and benefits of targeted covalent inhibitors that are designed to silence their targets completely and selectively.

1) Historical overview of covalent drugs
2) Overview of Avilomics platform to design targeted covalent drugs
3) Examples of recent progress in the design of covalent drugs for cancer and viral targets
4) Clinical progress for targeted covalent drugs

Cancer Epigenetics, Cancer Stem Cells, Metabolism

Moderator: Nagi Ayad, Associate Professor, University of Miami, Epigenetix

FEATURED PRESENTATION

2:20 **Targeting the "New" Hallmarks of Cancer: Promises and Challenges in the Era of Tailored Therapeutics**

Robert Wild
Chief Scientific Officer, Oncology Research
Eli Lilly

More than ten years ago Drs. Weinberg and Hanahan published their seminal manuscript on the “hallmarks of cancer” comprising key six biological capabilities acquired during the multistep development of human tumors. Since then, a number of revolutionary therapies aimed at some of these key hallmarks have entered the oncology market place, proving the concept and value of molecular targeted therapies; i.e. matching the right patient to the right drug. While the original six hallmarks remain central to the development of tumors, it is now generally well accepted that cancers acquire or hijack additional capabilities which may function as promising targeting opportunities for drug discovery and development. Specifically, the reprogramming of metabolic pathways (cancer metabolism) and epigenetic mechanisms in regulating the expression of genes critical to cellular transformation pathways have been proposed as novel targeting opportunities. In addition, the concept of cancer stem cells (CSCs) or tumor initiating cells (TICs) playing a critical role in the development and progression of cancer has gained significant interest in recent years. This presentation will introduce the current state of these emerging oncology drug discovery areas and review key pathways and targets of interest. In addition, the potential promises and challenges of targeting these “new” hallmarks of cancer in the era of molecular targeted therapies will be discussed.

2:45 **Epigenetics: The Breaking Frontier of Drug Discovery**

Keith Dionne, President & Chief Executive Officer, **Constellation Pharmaceuticals**

We now understand that the DNA packaging around nucleosomes or “Chromatin biology” is often as, if not more, important than the underlying genetic code in guiding cell programing. Together, three of the prominent classes of Epigenetic targets: the Bromodomains, methyl transferases, and demethylases account for close to 200 novel targets. Many of these targets have already been shown to direct major pathways in cellular differentiation and disease development in Oncology, Inflammation and several other major diseases. Examples of this control include the role of BET in regulating Myc – a key oncogenic transcription factor in oncology and NF-KB - a key pathway in oncology and inflammation amongst others. Whereas some downstream signals of epigenetic modification are immediate, other chromatin modifications are subtle and require days to observe their effects. Differing signatures between protein ablation through RNAi and specific domain inhibition through chemical probes are enabling a surprising degree of selectivity across targets. We are now seeing an emerging generation of selective chromatin modulators progressing to the clinic that offer the ability to selectively redirect cellular programing in disease states.

3:10 **Afternoon Networking Break**

3:40 **New Protein Arginine Methyltransferase Inhibitors as Cancer Therapeutics**

Yujun George Zheng, Associate Professor, Chemistry, Georgia Cancer Coalition Distinguished Scholar, **Georgia State University**

Epigenetic decoration of the chromatin, which includes DNA methylation and histone modifications, has been established as a fundamental molecular mechanism for control of cell proliferation, differentiation, and development. Notably, many histone modifying enzymes are implicated in various types of human diseases. Protein arginine methyltransferases (PRMTs) catalyze the transfer of a methyl group from S-adenosyl-L-methionine (AdoMet) to the guanidino group of arginine residues in protein substrates, resulting in mono and di-methylarginine residues in substrate proteins. This type of chromatin modifying enzymes is

closely related with co- and post-transcriptional regulation of gene expression in eukaryotic cells. Several PRMT genes and proteins are promising new disease biomarkers and therapeutic targets. Our recent work has revealed interesting biochemical mechanisms of arginine methylation as regard to enzyme-substrate interaction and PRMT intercommunications. We discovered and developed several groups of small molecule PRMT inhibitors with different structural scaffolds and inhibitory activities. Recently, we synthesized and evaluated a class of carbocyanine compounds containing indolium, benz[e]indolium or benz[c,d]indolium heterocyclic moieties that bind to the predominant arginine methyltransferase PRMT1 and inhibit its methyltransferase activity at low micromolar potencies. In particular, the developed molecules have long wavelength colorimetric and fluorometric photoactivities, which can be used for optical and near-infrared fluorescence imaging in cells or biological tissues. I will report our recent research progress in PRMT inhibition and anticancer applications.

4:05 **Regulation of Cancer Growth by Metabolites in Pentose Phosphate Pathway**

Barden Chan, Instructor, Medicine, **Beth Israel Deaconess Medical Center, Harvard Medical School**

Altered cellular metabolism is a hallmark of cancer. Tumors have a tendency to use glycolysis to generate ATPs even under high oxygen tension, a phenomenon known as aerobic glycolysis or the Warburg effect. The pentose phosphate pathway (PPP) is another branch of the metabolism known to be hyperactive in cancer. The PPP consists of an oxidative branch and a non-oxidative branch. While the importance of the non-oxidative branch in tumor progression has been characterized at the step of transketolation, the potential role of the oxidative branch in cancer has received less attention in comparison. Using lung cancer cells as a model system, we recently found that 6 phosphogluconate dehydrogenase (6PGD), the third enzyme in PPP, is indispensable in lung cancer growth and can be a novel target in treatment of lung cancer. Additionally, while knockdown of glucose-6-phosphate dehydrogenase (G6PD), the first enzyme in PPP, has a minimal effect in proliferation, knockdown of G6PD in cells lacking 6PGD surprisingly restored cell growth. Currently, we are specifically addressing the following questions:

1. How does 6PGD regulate cancer growth and metastasis?
2. Does 6PGD affect cell functions by modulating key signaling pathways?
3. Does accumulation of metabolites in the oxidative PPP modulate tumor phenotype?
4. What is the optimal strategy to target 6PGD for maximal anti cancer effect?

4:30 **4SC-202: A Novel Epigenetic Modulator to Target Cancer Stem Cells**

Hella Kohlhof, Manager, Translational Pharmacology, **4SC AG**

4SC-202 is an oral HDAC inhibitor with a unique combination of anti-cancer mode of actions, namely epigenetic regulation, proliferation inhibition and targeting of stemness. 4SC-202 treatment leads to very distinct histone modifications and inhibition of protein deacetylation. Analysis of gene expression suggests unique features of 4SC-202 compared to other class I specific HDAC inhibitors. Via epigenetic modifications, 4SC-202 mediates modulation of the Wnt signaling pathway that provokes the inhibition of stemness-related properties like anchorage independent growth, spheroid formation, invasion and metastasis. Proliferation inhibition with subsequent induction of apoptosis in cancer cell lines is the consequence of a strong G2/M arrest. These properties translate into excellent effectiveness in in vivo cancer models. Currently, 4SC-202 is tested in a phase I clinical trial (TOPAS) in hematological indications to investigate safety, tolerability and pharmacokinetics as primary objective. As secondary objective several PD/biomarker readouts are evaluated including ex vivo assays to determine the extent of HDAC inhibition in PBMCs and protein acetylation and regulation of gene expression.

- Insight into epigenetic modulation by 4SC-202 mediated HDAC inhibition.
- Combination of mode of actions within a single compound.
- Candidate is already investigated in a clinical trial.

4:55 **Strong and Specific LSD1 Inhibitors for the Treatment of Cancer**

Tamara Maes, Chief Scientific Officer, **Oryzon**

Lysine specific demethylase 1 (LSD1, KDM1A), a protein able to demethylate histones, is a regulator of gene expression. LSD1 over-expression has been described in different cancer cell types and has been associated with bad prognosis. The weak LSD1 inhibitor tranylcypromine and ATRA synergically induce differentiation of non PML-RARA (APL) AML to a combo treatment with ATRA (Schenk et al. 2012). Oryzon LSD1 inhibitors were shown to selectively abrogate the clonogenic potential of acute myeloid leukemia cells with MLL translocations, sparing the repopulating potential of normal hematopoetic stem cells (Harris et al., 2012).

We have selected an enantiomerically pure LSD1 inhibitor that is >1000x stronger than tranylcypromine, highly selective over related enzymes such as MAO-A/B, IL4I1, SMOX and LSD2 and has excellent pharmacological characteristics, and designated

it as a candidate for development. Our LSD1 inhibitor affects reduces leukemic stem cell potential, potently inhibits colony formation and can be used to effectively overcome the differentiation block in AML cell lines. The compound also induces apoptosis and inhibits proliferation at sub-nanomolar concentrations in selected AML cell lines.

Our candidate can be orally administered and is pharmacologically active at doses below 0.05mg/kg daily in mice. We will report on the development status of the candidate in preclinical proof of concept and regulatory pre-clinical toxicology studies.

5:20 **Rewiring of Glucose Metabolism in Human Cancer**

Jason Locasale, Assistant Professor, **Cornell University**

This seminar topic will discuss advances in our understanding of the rewiring of metabolism in cancer pathogenesis. At the core of this effort lies the utilization of computational modeling and mass spectrometry. Using these tools, we have studied the effects of an alternative glycolytic pathway observed in proliferating cells that we recently identified. These efforts have enumerated several principles of glycolytic regulation in cancer cells. I will further discuss the characterization of a metabolic pathway that was identified using this approach, which is genetically selected for and possibly drives the development of human cancer. This pathway involves the diversion of glycolytic flux into de novo serine metabolism through phosphoglycerate dehydrogenase (PHGDH).

5:45 **Targeting Epigenetic Readers for Cancer Therapy**

Jun Qi, Senior Research Scientist, **Dana-Farber Cancer Institute, Harvard Medical School**

In cancer, epigenetic proteins are promising and intensely studied targets for therapeutic drug discovery. Already, inhibitors of DNA methyltransferases and histone deacetylases have demonstrated substantial clinical efficacy leading to regulatory approval for use in hematologic malignancies. These successes have stimulated broad-based efforts to develop inhibitors of chromatin modifying enzymes, so-called epigenetic “writers” and “erasers”. Perhaps owing to perceptions regarding the difficulty of targeting protein-protein interactions, chromatin binding modules or epigenetic “readers” have received comparatively little attention. Motivated by this challenge, we have developed first-in-class, drug-like inhibitors of “bromodomain and extraterminal domain” epigenetic readers (BETs) for mechanistic study and therapeutic application in cancer. Our recent studies are showing that these inhibitors (BETi) have compelling activity in preclinical models of multiple myeloma and acute myeloid leukemia, and BETi downregulate the MYC and E2F transcriptional programs. We are continuously integrating the transcriptional consequences of BETi with changes in the epigenomic landscapes of cancer cells to elucidate the mechanisms underlying response to BETi using chemical and genetic perturbations.

6:05 **Networking Reception and Poster Session**

Day 2 - Tuesday, February 26, 2013

Novel Advances & Technologies in Oncology (Joint Session)

Moderator: *Charles Theuer, President & Chief Executive Officer, Tracon Pharma*

8:00 **Development of Next Generation Angiogenesis Inhibitors Targeting Pathways Other than VEGF**

Charles Theuer, President and Chief Executive Officer, **Tracon Pharma**

Monoclonal antibodies have revolutionized cancer care and four antibodies now have annual commercial revenues of greater than $1B annually. One of these antibodies, bevacizumab, targets the VEGF pathway, which is essential for angiogenesis. Bevacizumab has been approved in two of the most prevalent tumor types and its success has prompted the development of a host of biologics therapies targeting this pathway. Most recently aflibercept, another protein that binds VEGF was approved in colorectal cancer.

While of proven clinical benefit, VEGF inhibitors do not “cure” cancer and efforts have now focused on targets that complement the VEGF pathway to further inhibit angiogenesis and positively impact cancer care. Examples of a second generation angiogenesis targets are endoglin (CD105) and angiopoietin.

The antibody TRC105 binds to endoglin, a target that (like VEGF) is required for angiogenesis, prognostically relevant and expressed within the vasculature of multiple solid tumors. CD105 is up-regulated following the treatment of human cancer xenografts with VEGF inhibitors, indicating that targeting the endoglin pathway may be a useful strategy to combine with VEGF inhibition. TRC105 has been studied with bevacizumab and radiographic regressions have been noted in bevacizumab

refractory patients.

The antibody AMG386 binds to angiopoietins and is being studied in several studies of ovarian cancer patients in combination with chemotherapy. Additional studies in combination with VEGF inhibitors are underway.

The goal of the talk will be to review the current state of angiogenesis inhibition in oncology and emphasize antibody therapies directed to targets that complement the VEGF pathway.

8:25 **Using FDHT-PET and Preclinical Projections to Optimize Dose Selection of ARN=509 in mCRPC**

Isan Chen, Chief Medical Officer, **Aragon Pharmaceuticals**

Phase I dose selection is a crucial step in the early clinical development. The traditional paradigm of dose escalation until 'maximum tolerated dose' (MTD) with cytotoxic chemotherapeutic agents is suboptimal since in most instances, the dose and schedule selection are based on relatively small number of patients and it may or may not be applicable in the clinical development of hormonal or biological agents and TKIs.

The concern about 'leaving efficacy on the table' by proceeding to late stage clinical trial with doses below that of MTD may be real; however, there are also examples of agents that required further dose de-escalation studies due to excessive toxicity of the recommended phase 2 dose.

An integrated and careful assessment of preclinical models of maximal antitumor activity with clinical safety, PK and PD can be helpful in optimizing the recommended phase 2 dose with hormonal agents.

An example of the recommended phase 2 dose selection of ARN-509, a second-generation anti-androgen, combining preclinical projections, clinical safety, PK, and maximal PD effect based on FDHT-PET will be presented.

Benefits of the talk:
1. Importance of dose selection in Phase I,
2. Examples of study failures potentially due to wrong selection of dose/schedule,
3. Integration of preclinical and clinical information in the decision process
4. Use of PET scan to support recommended phase 2 dose with ARN-509

8:50 **CCR5 Antagonists Block Basal Breast Cancer and Prostate Cancer Metastasis in Vivo**

Richard Pestell, Director, Kimmel Cancer Center & Associate Dean, Cancer Programs, Jefferson Medical College Vice President, Oncology Services, Thomas Jefferson University Hospital, Kimmel Cancer Center, **Thomas Jefferson University**

The roles of the chemokine CCL5 and its receptor CCR5 in breast and prostate cancer progression are controversial. Herein, interrogation of microarray analysis of 2,254 human breast cancers demonstrated increased expression of CCL5 and its receptor CCR5, but not CCR3, in the basal and HER-2 genetic subtypes of breast cancer. Human breast cancer cell lines expressed CCR5 by flow cytometry and displayed a functional response to CCL5 by calcium mobilization assays and invasion assays. Using isogenic oncogene transformed breast and prostate cancer cell lines we show oncogene transformation induces CCR5 expression and that the subpopulation of cells that express functional CCR5 display increased invasiveness. The CCR5 antagonists Maraviroc or Vicriviroc, developed to block CCR5 HIV co-receptor function, reduced in vitro invasion of basal breast cancer and prostate cancer cell lines without affecting cell proliferation or viability. In a series of preclinical mouse models, Maraviroc decreased breast pulmonary metastasis. The isogenic prostate cancer cell lines metastasized to bones in immune-competent mice representing an ideal model for testing anti-metastasis therapies. Maraviroc or Vicriviroc, reduced prostate cancer metastasis to brain bones and lungs. Our findings provide evidence for the key role of CCL5/CCR5 in the metastasis of basal breast cancer and prostate cancer cell lines and suggest that CCR5 antagonists may be used as an adjuvant therapy to reduce the risk of metastasis in patients with the basal breast cancer subtype and prostate cancer.

9:15 **Development of the First Selective Oral HDAC6 Inhibitor to Treat Multiple Myeloma**

Simon S. Jones, Vice President, Biology & Preclinical Development, **Acetylon Pharmaceuticals**

Histone deacetylase (HDAC) inhibitors are efficacious in hematologic malignancies either as single agents or in combination with other antineoplastic agents, for example bortezomib a proteasome inhibitor (PI), in patients with relapsed and refractory multiple myeloma (MM); a plasma B-cell malignancy. Significant progress has been achieved in the last ten years in treating MM with novel therapies such as the PIs bortezomib (Velcade®) and carfilzomib (Kyprolis®) and the IMiD class of drugs lenalidomide (Revlimid®). However the rate of relapse in MM and the need for novel drug combinations remains high.

• HDACs are a family of enzymes which regulate critical cellular functions of a broad spectrum of proteins

• HDAC inhibitors Zolinza® and Istodax® have been approved targeting T-cell lymphoma
• Use of first generation, non-selective HDAC inhibitors has been limited due to the substantial side effect profile of severe fatigue, nausea, vomiting, diarrhea and myelosuppression associated with Class I HDAC inhibition
• Development of potent, isoform-selective, second generation HDAC inhibitors is expected to lead to a breakthrough both in basic biology and broadened utility for oncology

ACY-1215 is the first selective HDAC6 inhibitor in Phase 1 clinical trials for the treatment of MM in combination with either bortezomib or lenalidomide. HDAC6 regulates an alternative pathway to the proteasome to remove unfolded, misfolded and excessive amounts of proteins characteristic of MM. The preclinical and clinical development as well as the superior safety profile of ACY-1215 in MM in combination with either bortezomib or lenalidomide will be discussed.

9:40 Sunil Patel, Senior Vice President, Corporate Development, **Oncomed Pharmaceuticals**

10:05 **Morning Networking Break**

Progress in Cancer Immunotherapy

Moderator: James Hodge, Investigator & Head, National Cancer Institute, NIH

10:30 **Development of Highly Active Chimeric Antigen Receptors (CARs) for B-Cell Malignancies: CD19 and CD22**

Rimas Orentas, Associate Scientist, **NCI, CCR/POB**

Immune targeting of B cell antigens using chimeric antigen receptors (CARs) is a promising new approach for B cell leukemias. We tested primary lymphoblasts from patients with BCP (B cell precursor)-ALL for CD22 expression. All were CD22 positive, with an average expression of 3,500 sites per cell, credentialing CD22 as a target. Given the success against leukemia of anti-CD19 CARs, we sought to optimize CD22-based CARs. We explored binding affinity by comparing binding domains (scFv) derived from the CD22-specific immunotoxin HA22 (Moxetumomab pasudotox) and the lower affinity BL22. We explored spatial configuration by extending the scFv away from the membrane using two IgG constant domains, and explored combinations of CD3-zeta chain-, CD28-, and CD137-derived signaling motifs. We also generated a CAR (m971) that bound CD22 at a domain more proximal to the cell membrane than HA22/BL22. We found that binding affinity and an extended conformation had little impact on CAR activity, although the shorter construct (no constant domains) and the higher affinity scFv, were slightly better. The signaling domains had a greater impact. Second generation vectors (two activation motifs) had higher surface expression and higher activity than third generation. Importantly, both antigen density on target cells and the specific CD22 epitope targeted by the scFv significantly impacted CAR activity in vitro and in vivo. Thus, T cells expressing CD22-CARs are a highly promising immunotherapeutic approach for leukemia. Furthermore, unlike soluble therapeutic agents where affinity is key, effective CAR design may benefit more from optimizing the target antigen binding site.

• This talk will highlight CARs (chimeric antigen receptors), an exciting new form of immunotherapy for cancer
• This talk will present important parameters of evaluating CAR design and function on transduced T cells
• This talk will focus our attention on the need to continue evaluating suitable targets in leukemia, lymphoma, and in solid tumors
• Adoptive immunotherapy is a powerful approach that has features of personalized therapy- presenting unique challenges for broad application

10:55 **Adoptive T-cell Therapy for Melanoma: The Road to Commercialization**

Laszlo Radvanyi, Professor, Melanoma Medical Oncology, University of Texas, **M.D. Anderson Cancer Center**

Adoptive cell transfer (ACT) therapy using ex vivo expanded autologous tumor-infiltrating lymphocytes (TIL) for metastatic melanoma has been in development for over 2 decades. It is one of the most powerful immunotherapies against cancer capitalizing on the fact that all tumors are infiltrated with T cells having tumor antigen specificity to differing extents that can be logarithmically expanded in culture systems and infused back into patients. Clinical trials at different sites using TIL infusion together IL-2 therapy, including our site at MD Anderson, have consistently demonstrated durable response rates of 45-50% for unresectable metastatic melanoma with >3-year survival rates that outreach all currently approved modalities. However, despite this powerful clinical data, TIL ACT has remained somewhat of a “fringe” therapy due to the labor-intensive and time-consuming processes needed to expand T cells from tumor fragments as well as the need for open culture steps to initially select tumor-specific TIL for large-scale expansion. I will provide an overview of TIL ACT and its clinical activity, and discuss these and other key issues forming barriers to out-scaling TIL manufacturing and commercialization. To address these issues, recent work from our group on manipulating key T-cell costimulatory molecules to more rapidly and reproducibly expand TIL enriched in T cells with enhanced anti-tumor activity will be presented. In addition, our group is identifying biomarkers within tumors from patients that predict not only who will successfully expand enough of the right types of T cells in TIL for therapy, but who will ultimately respond. These improvements should facilitate the development of closed bioreactor designs for TIL

expansion as well as the ability to better select patients for therapy as critical steps towards commercialization.

BENEFITS:
• Overview of the growing field of TIL therapy in melanoma and the process of TIL expansion
• Knowledge of the current clinical status, clinical response rates, and survival rates of patients receiving TIL therapy
• Overview of the current issues that serve as bottlenecks to commercializing TIL therapy
• Outline of the steps being taken to solve these issues as well as steps towards the development of predictive biomarkers for improved patient selection

11:20 **Therapy-induced Immunogenic Modulation of Tumor Cells Enhances Killing by Cytotoxic T Lymphocytes and is Distinct From Immunogenic Cell Death**

James Hodge, Investigator & Head, Recombinant Vaccine Group, Tumor Immunology & Biology, **National Cancer Institute, NIH**

Certain therapeutic regimens trigger cancer cell death while inducing subsequent immune responses. However, immunogenic cell death (ICD) has thus far been restricted to select agents. In contrast, several therapies modulate antitumor immune responses, despite not inducing classic ICD. Here, using docetaxel as a model therapy, we examined phenotypic and functional consequences of tumor cells that do not die from immunogenic cell death. Docetaxel induced surface calreticulin exposure in all cell lines. Killing by TAA specific CTL was significantly enhanced after docetaxel treatment, and was associated with increases in components of antigen-processing machinery, and mediated largely by calreticulin membrane translocation. This immunogenic modulation was also observed in a chemotherapy-resistant cell line, suggesting that chemotherapy and immunotherapy could improve outcomes in patients who have previously failed chemotherapy alone. Finally, we will discuss clinical responses from breast cancer patients treated with immunotherapy (vaccine) and docetaxel.

• Can one predict optimum immunotherapy combinations based on immunogenic cell death/immunogenic modulation?
• Can one exploit a therapy's differential effects on immune cell populations for optimal use with vaccines (immune conditioning)?
• If a drug has failed in the monotherapy setting, is it possible/feasible/recruitable to utilize it in combination settings targeting an immunomodulatory aspect?

11:45 **Mechanisms of Immune Enhancement by Sub-Lethal Tumor Cell Irradiation**

Charlie Benson, Assistant Professor, Biology, **Georgia State University**

Sub-lethal doses of radiation can alter the phenotype of target tissue by modulating gene products that make tumor cells more susceptible to T-cell–mediated immune attack. Previously, we demonstrated that colorectal cancer lines responded to radiation by up-regulating surface expression of CTL relevant proteins including numerous death receptors, cell adhesion molecules and tumor-associated antigens. The present study was designed to determine the extent of CTL relevant changes induced by radiation in human carcinoma cells. Here, several tumor cell lines were exposed to various sub-lethal doses of radiation (0-10Gy). Experiments quantified changes in the expression of genes that could result in enhanced effector CTL activity against irradiated tumor cells. One to seven days post-irradiation (IR), changes in expression of effector costimulatory molecules (OX40L and 41BBL), as well as expression of other molecules involved in effector T-cell activity against target cells (ICOSL, CD70 and PD-L1) was examined. All cell lines altered expression of one or more of these molecules post-irradiation and, in some tumor cell lines, altered expression could be observed as long as 7-days post-irradiation. Importantly, expression of these gene products correlated with enhanced killing of irradiated tumor cells by TAA-specific CTLs in cytotoxicity assays. Furthermore we saw enhanced survival and activation of CTLs exposed to irradiated tumor cells. Overall, the results of this study suggest that non-lethal doses of radiation can be used to make human tumors more amenable to immune system attack even in the absence of innate immune responses to 'danger' from dying cells. Benefits:1. Exploration of alternate use of common modality of radiation for carcinomas 2. Provides data for rationale application of radiation around immunotherapy strategies 3. Molecular changes by radiation may help better define patient tumor "immunoscore" 4. Provides specific mechanism of enhanced immune activity directly against irradiated tumor cells.

[Oral Presentation from Exemplary Submitted Abstracts]

12:10 **Kinase Inhibitors of Neurotrophin Receptors TrkA, TrkB and TrkC are Effective Against Tumors that Harbor the Oncogenic TPM-TrkA Translocation**

Julia Haas, Research Investigator, **Array Biopharma**

The neurotrophins are a family of nerve growth factors that bind to the Trk tyrosine kinase receptors (TrkA, TrkB and TrkC) and activate survival signaling pathways. Genetic alterations, including point mutations and fusion proteins involving Trk receptors are common in many tumor types, but the role that these altered Trk receptors play in driving the oncogenicity of the tumors in which they are harbored is poorly understood. Efforts in this area have been hampered by a dearth of relevant nonclinical

models and a lack of highly selective Trk kinase inhibitors with suitable in vivo exposure. AR523 is an orally bioavailable, potent Trk kinase inhibitor that blocks TrkA, TrkB and TrkC kinase activity at low nM concentrations and is highly selective against other kinases. In cell culture AR523 exhibited selective anti-proliferative activity toward the cell line KM12, which harbors the oncogenic TPM-TrkA translocation, while exhibiting no activity toward HT29, a cell line with no trk gene rearrangements. Studies in mice engrafted with KM12 tumors revealed significant anti-tumor and pharmacodynamic activity of AR523. Administration of a single oral dose of AR523 reduced tyrosine phosphorylation of downstream kinases ERK and Akt by >90% at one and four hours after dosing. Administration of 100 mg/kg AR523 daily for two weeks to mice with KM12 xenografts produced mean tumor growth inhibition of 86% and a mean 42% tumor regression. AR523 was well-tolerated at this dose and schedule and caused no body weight loss or death. These investigations demonstrate the utility of selective pan-Trk kinase inhibitors, for both in vitro and in vivo studies, and for confirming which Trk rearrangements, mutations or fusions drive tumor growth. In addition, our data supports the clinical investigation of AR523 and other Trk inhibitors for tumor types with Trk alterations that are strong oncogenic drivers.

12:40 **Lunch Provided by GTC**

Day 1 - Monday, February 25, 2013

7:00 **Registration & Continental Breakfast**

7:55 **Welcome & Opening Remarks**

KEYNOTE PRESENTATION
Moderator: Elizabeth Bachert, Senior Director, Pfizer

8:00 **Partnering with AstraZeneca and MedImmune in Oncology**

Timothy Herpin
Vice President
Strategic Partnering & Business Development Oncology
Science & Technology Licensing
AstraZeneca

Oncology is a key disease area for AstraZeneca and MedImmune and we are working with many partners to discover and develop novel therapeutics. The presentation will explore how partnerships have been used to access innovation and will address the following questions:

- What is the approach to oncology that AstraZeneca and MedImmune are pursuing?
- How have recent partnerships been structured?
- How does AstraZeneca work with academic institutions to create innovation?

Panel Discussion: Innovative Partnering & Licensing

Moderator: *Timothy Herpin, Vice President, AstraZeneca*

8:45 Panelist: Anne Altmeyer, Vice President, Business Development & Licensing, Oncology, **Novartis**

Panelist: Ji Li, Executive Director Licensing, **Amgen**

Panelist: Elizabeth Bachert, Senior Director, Worldwide Business Development, **Pfizer**

Panelist: David Snitman, Chief Operating Officer & Vice President, Business Development, **Array BioPharma**

Panelist: Matthew Call, Vice President, Business Development, **Endocyte**

Panelist: Philippe Lopes-Fernandes, Corporate VP, Head of Licensing, Business Development & Alliance Management, **Merck KGaA**

Topics to be Discussed:

- Oncology drug partnering 101
- Rationale driving key deals of 2012 and continued trends into 2013
- Aligning deal structures with corporate strategic goals
- How the heightened risk environment is affecting deals
- Pros and cons of regional deal-making
- At what stage or what type of data makes the asset most attractive to a buyer?
- How do you find and decide who a good partner is?
- What determines the value of the deal?
- What preparation should you do before the deal?
- What kind of terms besides financials should you think about?
- What are the criteria to attract investors?
- Creative partnering appears to be stemming from shrinking R&D budgets at large Pharma and large Pharma interest in sharing risk, how do biotechs feel about sharing funding for projects and sharing risk? How is this balance best achieved?

10:00 **Morning Networking & Refreshment Break**

Investment, Partnerships and Acquisitions: Trends & Recent Deals

Moderator: *Anne Altmeyer, Vice President, Novartis*

10:30 **Partnering - the View from Biotech**

Martin Buckland, Chief Business Officer, **Astex Pharmaceuticals**

Partnerships are in the lifeblood of the biotech industry. Biotech companies depend on partnerships both to validate their technologies and products, and to help provide financing and a route to market. This presentation will outline some of the trials and tribulations of partnering, as well as some of the advantages and benefits of partnering, using examples from Astex's experience.

- How to survive as a private biotech company
- The importance of partnering to help drive financing strategy
- Accessing not-for-profit funding
- Lessons for biotech, and for pharma partners

10:55 **Novel Partnering Structures to Advance Pipeline Development**

Tracey Vetterick, Director, Business Development, **MedImmune**

In a budget constrained environment, it is becoming more challenging to develop the breadth and depth of clinical assets needed to better treat patients. This presentation will discuss novel partnering structures to increase development capacity while also bringing beneficial therapeutic combinations to light earlier in the development process.

Benefits of this talk:
1. Importance of partnering to increase therapeutic options available to patients
2. Considerations for how to progress a broad pipeline and gather important data to enable future development decisions
3. Discussion around novel deal structures which have been implemented

11:20 **Case Studies in Structuring Partnerships to Build Long Term Value**

David Snitman, Chief Operating Officer & Vice President, Business Development, **Array BioPharma**

Array BioPharma is a 14 year old biotech company focused on the development and commercialization of oncology therapeutics. Array has built a portfolio of 15 clinical programs, 11 in Phase 2, through selective deal making and partnerships. This talk will review key partnership deals that have been strategic in allowing Array to advance its own internal programs while bring in ~$600M in non-dilutive financing. The structure of several of these deals and their strategic role in Array's development will be discussed.

11:45 **Is It Time to Get Hitched?**

Elan Ezickson, EVP and Chief Operating Officer, **Aveo Pharmaceuticals**

Biotech companies who are developing late-stage oncology drugs are often faced with the dilemma of becoming a commercial organization or seeking a large partner to launch and market the compound. As this is a critical strategic decision for any biotech company in this situation, it is imperative that all options and potential ramifications are carefully weighed.

This presentation will explore the issues, and potential pros and cons, of striking a commercial partnership vs. "going alone". How do you balance asset dilution vs. equity dilution? Long-term upside vs. near-term capital risk? Lead asset vs. pipeline? Building an infrastructure for the future vs. leveraging an established infrastructure for the present? Just as the decision to partner is typically neither black nor white, nor is the structure of an alliance. In order to make the "right" decision, both companies must understand the pros and cons of a prospective relationship as well as the individual needs of each company.

Benefits of Talk
• Understand the pros and cons of commercializing vs. partnering with larger companies
• Gain an appreciation for the wide variety of potential deal structures (co-promotes, geographic splits, profit splits, etc.)
• Gain insight into some of the operational challenges of alliances (budgets, pricing, etc.)
• Learn from real world examples of the decision making process

12:10 **Lunch on Your Own**

1:30 **Biotech Partnering: Trends & Recent Deals for Sustaining Biotech Innovation**

Eric Risser, Vice President, Business Development, **MacroGenics**

This presentation will highlight recent trends in biotech partnering models. It will cite some specific examples of recent industry deals, and reference the impact on the various stakeholders in the biotech innovation ecosystem, including venture capitalists, biotech entrepreneurs, and major pharmaceutical companies.

1:55 Natasha Hernday, Vice President, Corporate Development, **Seattle Genetics**

1:20 Rita (Glykeria) Theodotou, Director, Global Marketing, Oncology, **Bayer**

2:45 **Addressing the Dilemma of Small Biotech: How To Build A Substantial Pipeline with Limited Resources**

Chris Varma, President and Chief Executive Officer, **Blueprint Medicines**

Small biotech companies with productive product engines, often venture-backed, are challenged to develop robust pipelines because of limited capital. Blueprint Medicines is addressing this issue through the use of creative deal structures called risk-sharing models that leverage non-capital resources of at least two parties. In this context, risk-sharing models enable one party to advance an early program to a later phase with the engagement of a second party. Both parties contribute to the program with their own resources and therefore both parties obtain an ownership interest in the program. If the program successfully reaches a point of higher value creation, then the outcome is a win-win for both parties.

3:10 **Afternoon Networking & Refreshment Break**

3:40 **Teaching an Old Dog New Tricks: Twist on an Anti-viral for Thyroid and Other Solid Tumors**

John Tagliamonte, Chief Business Advisor, **Translational Therapeutics, Inc. (TransRx)**

The need for targeted treatments of high-grade metastatic cancers has never been greater. TransRx is developing small molecules that will be the first-in-class to target the master switch: ieF4E (4E) While many solid tumors express this control switch at high levels, the company plans to enter the clinic to address Thyroid Cancer. Related clinical evidence supporting safety of the company's lead molecule and the ability to test, treat and monitor target activity provide hope for a monotherapy. A capital-efficient structure stretches R&D funds to drive a fast and flexible development plan.

Benefits of the talk are:
1. Learn about a new target and new molecule to treat a highly unmet medical need.
2. Hear about developing drugs without traditional venture investment
3. Discuss the companion diagnostic model
4. Find non-dilutive sources of funding

Oral Presentations from Exemplary Submitted Abstracts

4:05 **Safely Enhancing Brain Drug Delivery in the Treatment of Brain Cancer**

Frederik Lonnqvist, Chief Medical Officer, **to-BBB**

to-BBB is focused on the treatment of CNS diseases. Since 98% of all drugs have a poor blood-brain barrier penetration and many medical needs in CNS diseases are still unmet we have developed a technology that safely and selectively enhances the delivery of various types of small molecule drugs across the blood-brain barrier. Our

lead product (2B3-101) builds on the success of Doxil. Thus, 2B3-101 is a targeted liposomal formulation of doxorubicin that utilizes our G-Technology® platform to enhance the delivery of doxorubicin to the brain. The G-Technology® concept is built upon the conjugation of glutathione onto the tips of the pegylated liposomes, which then actively transports the encapsulated compound across the blood-brain barrier by use of endothelial glutathione transporters. 2B3-101 can be used to treat the same indications as Doxil. The important difference vs. Doxil is that treatment with 2B3-101 results in 5 times higher concentrations of doxorubicin in the brain as compared to Doxil (based on preclinical data). Thereby, 2B3-101 also provides an opportunity to treat primary and secondary brain tumors, in contrast to Doxil. As of mid-January 2013, our phase I/IIa trial with 2B3-101 is at the end of the MTD phase (60 mg/m2 every 3 weeks) and the data look very promising, without any DLTs so far. The side effect profile is in line with Doxil and we are starting to see early signs of preliminary efficacy on brain tumors in the 40, 50 and 60 mg/m2 cohorts in patients with solid tumor brain metastases as well as in patients with recurrent gliomas. We also see signs of preliminary efficacy on the systemic, extra-cranial disease. We will shortly initiate the expansion phase and should be able to provide a more consolidated picture of the safety and efficacy when expansion phase has been completed around August 2013. We have started to actively look for licensing partners for 2B3-101.

4:15 **Oral Presentations from Exemplary Submitted Abstracts**

4:25 **Oral Presentations from Exemplary Submitted Abstracts**

4:35 **Networking Reception and Poster Session**

Day 2 - Tuesday, February 26, 2013

7:30 **Continental Breakfast**

Novel Advances & Technologies in Oncology (Joint Session)

Moderator: *Charles Theuer, President & Chief Executive Officer, Tracon Pharma*

8:00 **Development of Next Generation Angiogenesis Inhibitors Targeting Pathways Other than VEGF**

Charles Theuer, President and Chief Executive Officer, **Tracon Pharma**

Monoclonal antibodies have revolutionized cancer care and four antibodies now have annual commercial revenues of greater than $1B annually. One of these antibodies, bevacizumab, targets the VEGF pathway, which is essential for angiogenesis. Bevacizumab has been approved in two of the most prevalent tumor types and its success has prompted the development of a host of biologics therapies targeting this pathway. Most recently aflibercept, another protein that binds VEGF was approved in colorectal cancer.

While of proven clinical benefit, VEGF inhibitors do not “cure” cancer and efforts have now focused on targets that complement the VEGF pathway to further inhibit angiogenesis and positively impact cancer care. Examples of a second generation angiogenesis targets are endoglin (CD105) and angiopoietin.

The antibody TRC105 binds to endoglin, a target that (like VEGF) is required for angiogenesis, prognostically relevant and expressed within the vasculature of multiple solid tumors. CD105 is up-regulated following the treatment of human cancer xenografts with VEGF inhibitors, indicating that targeting the endoglin pathway may be a useful strategy to combine with VEGF inhibition. TRC105 has been studied with bevacizumab and radiographic regressions have been noted in bevacizumab refractory patients.

The antibody AMG386 binds to angiopoietins and is being studied in several studies of ovarian cancer patients in combination with chemotherapy. Additional studies in combination with VEGF inhibitors are underway.

The goal of the talk will be to review the current state of angiogenesis inhibition in oncology and emphasize antibody therapies directed to targets that complement the VEGF pathway.

8:25 **Using FDHT-PET and Preclinical Projections to Optimize Dose Selection of ARN=509 in mCRPC**

Isan Chen, Chief Medical Officer, **Aragon Pharmaceuticals**

Phase I dose selection is a crucial step in the early clinical development. The traditional paradigm of dose escalation until 'maximum tolerated dose' (MTD) with cytotoxic chemotherapeutic agents is suboptimal since in most instances, the dose and schedule selection are based on relatively small number of patients and it may or may not be applicable in the clinical development of hormonal or biological agents and TKIs.

The concern about 'leaving efficacy on the table' by proceeding to late stage clinical trial with doses below that of MTD may be real; however, there are also examples of agents that required further dose de-escalation studies due to excessive toxicity of the recommended phase 2 dose.

An integrated and careful assessment of preclinical models of maximal antitumor activity with clinical safety, PK and PD can be helpful in optimizing the recommended phase 2 dose with hormonal agents.

An example of the recommended phase 2 dose selection of ARN-509, a second-generation anti-androgen, combining preclinical projections, clinical safety, PK, and maximal PD effect based on FDHT-PET will be presented.

"Benefits' of the talk:
1. Importance of dose selection in Phase I,
2. Examples of study failures potentially due to wrong selection of dose/schedule,
3. Integration of preclinical and clinical information in the decision process
4. Use of PET scan to support recommended phase 2 dose with ARN-509

8:50 **CCR5 Antagonists Block Basal Breast Cancer and Prostate Cancer Metastasis in Vivo**

Richard Pestell, Director, Kimmel Cancer Center & Associate Dean, Cancer Programs, Jefferson Medical College Vice President, Oncology Services, Thomas Jefferson University Hospital, Kimmel Cancer Center, **Thomas Jefferson University**

The roles of the chemokine CCL5 and its receptor CCR5 in breast and prostate cancer progression are controversial. Herein, interrogation of microarray analysis of 2,254 human breast cancers demonstrated increased expression of CCL5 and its receptor CCR5, but not CCR3, in the basal and HER-2 genetic subtypes of breast cancer. Human breast cancer cell lines expressed CCR5 by flow cytometry and displayed a functional response to CCL5 by calcium mobilization assays and invasion assays. Using isogenic oncogene transformed breast and prostate cancer cell lines we show oncogene transformation induces CCR5 expression and that the subpopulation of cells that express functional CCR5 display increased invasiveness. The CCR5 antagonists Maraviroc or Vicriviroc, developed to block CCR5 HIV co-receptor function, reduced in vitro invasion of basal breast cancer and prostate cancer cell lines without affecting cell proliferation or viability. In a series of preclinical mouse models, Maraviroc decreased breast pulmonary metastasis. The isogenic prostate cancer cell lines metastasized to bones in immune-competent mice representing an ideal model for testing anti-metastasis therapies. Maraviroc or Vicriviroc, reduced prostate cancer metastasis to brain bones and lungs. Our findings provide evidence for the key role of CCL5/CCR5 in the metastasis of basal breast cancer and prostate cancer cell lines and suggest that CCR5 antagonists may be used as an adjuvant therapy to reduce the risk of metastasis in patients with the basal breast cancer subtype and prostate cancer.

9:15 **Development of the First Selective Oral HDAC6 Inhibitor to Treat Multiple Myeloma**

Simon S. Jones, Vice President, Biology & Preclinical Development, **Acetylon Pharmaceuticals**

Histone deacetylase (HDAC) inhibitors are efficacious in hematologic malignancies either as single agents or in combination with other antineoplastic agents, for example bortezomib a proteasome inhibitor (PI), in patients with relapsed and refractory multiple myeloma (MM); a plasma B-cell malignancy. Significant progress has been achieved in the last ten years in treating MM with novel therapies such as the PIs bortezomib (Velcade®) and carfilzomib (Kyprolis®) and the IMiD class of drugs lenalidomide (Revlimid®). However the rate of relapse in MM and the need for novel drug combinations remains high.

• HDACs are a family of enzymes which regulate critical cellular functions of a broad spectrum of proteins
• HDAC inhibitors Zolinza® and Istodax® have been approved targeting T-cell lymphoma
• Use of first generation, non-selective HDAC inhibitors has been limited due to the substantial side effect profile of severe fatigue, nausea, vomiting, diarrhea and myelosuppression associated with Class I HDAC inhibition
• Development of potent, isoform-selective, second generation HDAC inhibitors is expected to lead to a breakthrough both in basic biology and broadened utility for oncology

ACY-1215 is the first selective HDAC6 inhibitor in Phase 1 clinical trials for the treatment of MM in combination with either bortezomib or lenalidomide. HDAC6 regulates an alternative pathway to the proteasome to remove unfolded, misfolded and excessive amounts of proteins characteristic of MM. The preclinical and clinical development as well as the superior safety profile of ACY-1215 in MM in combination with either bortezomib or lenalidomide will be discussed.

9:40 Sunil Patel, Senior Vice President, Corporate Development, **Oncomed Pharmaceuticals**

10:05 **Morning Networking & Refreshment Break**

How Big Pharma Values Your Innovation

Moderator: *Charles Theuer, President & Chief Executive Officer, Tracon Pharma*

10:30 **How AstraZeneca Values Innovation**

John Gustofson, Director, Business Development, Strategic Partnering & Business Development, Oncology, **AstraZeneca**

AstraZeneca is a global pharmaceutical company working in the areas of Oncology, Infection, Cardiovascular, Gastrointestinal, Respiratory, Inflammation and CNS. AstraZeneca is continuously looking for and evaluating both clinical and preclinical oncology opportunities for in-license. Sources of opportunities include academics, biotechnology companies and peer pharma from all over the world. AstraZeneca uses traditional financial evaluations of discounted cash flows and internal rates of return but also utilizes a strategic evaluation called the 5R's. This 5R assessment includes preclinical data, clinical data and commercial assessment such as payor analysis. This presentation will review AstraZeneca's methodology of evaluation and details of the 5R analysis. This talk will also compare and contrast how AstraZeneca evaluates early stage opportunities that are in emerging areas of science along with established areas. Finally, this talk will outline how a company with an asset to license should approach AstraZeneca including 1) with what type of data and 2) how to present the data to facilitate rapid evaluation.

Benefits of this talk
• Understanding how AstraZeneca evaluates both preclinical and clinical opportunities
• Knowledge how to pitch an opportunity to AstraZeneca
• Overview of what key oncology opportunities AstraZeneca is looking for

10:55 **How to Think About Valuation When You are Seeking a Pharma Partner - A Business Development Consultant's Advice**

Linda Pullan, Business Development Consultant, **Pullan Consulting**

When contemplating partnerships (collaborations, JVs, Licensing deals, etc) to advance an early drug candidate, a company naturally asks "how much is this drug candidate worth to a partner?". Linda Pullan will talk about different techniques, key variables and how to use approximations and short cuts for the hugely uncertain variables. And the partner's perspective of what adds value will be discussed.

Panel Discussion: Regulatory Guidance & Updates

Moderator: *Linda Pullan, Pullan Consulting*

11:20 Panelist: Laurie Strawn, Senior Director, Worldwide Regulatory Strategy, **Pfizer**

Panelist: Isan Chen, Chief Medical Officer, **Aragon Pharmaceuticals**

Panelist: Graham Robinson, Partner, **Skadden Arps**

Topics to be Discussed:

- Accelerated approval opportunities and break through therapies
- Endpoints for registrational oncology studies
- Single-arm vs. randomized studies
- Orphan drug designation
- Pediatric studies

12:00 **Lunch Provided by GTC**

1:30 **Conference Concludes**

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