7th World ADC San Diego
Post Event Report

Summary of Key Findings from World ADC San Diego 2016

The 7th World ADC Conference was held recently in San Diego, CA on October 10-13, 2016. If your research team is working on the clinical translation of antibody-drug conjugates (ADC), this is the ideal summit for you. This year's meeting successfully united more than +650 attendees from all over the world who are actively pursuing ADC research in discovery, development, clinical and manufacturing. The audience for this meeting was fairly broad and included major pharmaceutical industry leaders, biotech companies, academics including PhD students and contract and non-profit research organizations. They shared their views on successfully translating a multitude of ADC platforms for the treatment of various type of cancers.

Over two days we had 96 thought provoking sessions across 4 streams from leading ADC organizations such as Seattle Genetics, Genentech, Pfizer, Stemcentrx etc. During this time we extensively discussed: the importance of site-specific conjugation technologies, stability of cleavable/non-cleavable linkers *in vivo*, LC/MS based characterization of ADCs, target tumor receptor density and its direct relation with clinical outcomes, pharmacokinetic issues associated with the successful translation of ADCs, improving the therapeutic index of ADCs candidates, screening for the identification of new cancer targets for ADC design, and challenges associated with the development of new payloads and their possible use in combination with immune checkpoint inhibitors.

This report summarizes some of the key findings. **Manish S. Hudlikar, PhD Candidate in Chemistry, University of Georgia, Athens, GA.**

Conference Day 1, October 11 2016

Chair: Scott Dylla

Plenary Session - What is the Present and Future of ADC Technology?

Speakers: Jagath Reddy Junutula (JRJ), Megan O'Meara (MM) and John Lambert (JL)

The 7th World ADC San Diego began with a general overview of current ADC platforms by classifying them into four major subtopics - site specific conjugation, novel payloads, linker design and new ADC targets. **JRJ** showed that site specific conjugation by engineered cysteine substitutions at positions on light and heavy chains provide reactive thiol groups and do not perturb immunoglobulin folding and assembly or alter antigen binding. This approach can improve the therapeutic index of an ADC by 2-4 folds. These results were obtained when pyrrolobenzodiazepine (PBD) and monomethyl auristatin E (MMAE) were used as payloads. **JRJ** continued his discussion on the future of ADCs by identifying novel AML tumor antigens such as CSC030 and CSC012 and building ADCs that can target both cancer stem cells and bulk tumor using DNA-damaging agents as a payload class. **"CSC030 lacks in most of the normal hematopoietic stem cells while present in more than 90% of the AML patients. In addition to this CSC030 has much broader expression than CD33" JRJ** .

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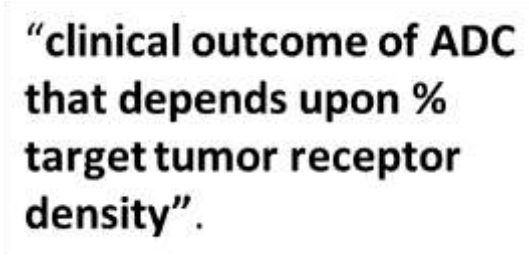
Plenary Session - Clinical update on Vadastuximab Talirine (SGN-CD33A) and Mirvetuximab Soravtansine (Advancing Towards Phase III)

Continuing our discussion on AML, **MM** from Seattle Genetics gave an insightful talk on SGN-CD33A. SGN-CD33A is a novel antibody-drug conjugate (ADC) targeting CD33, which is expressed on most acute myeloid leukemia (AML) cells. One of the major issues associated with AML treatment is multidrug resistance caused by the high expression of P-glycoprotein (MDR protein), **MM** said. SGN-CD33A utilizes a dimer warhead (PBD) conjugated via cysteine engineered site-specific conjugation technology. Vadastuximab Talirine (SGN-CD33A) is a protease cleavable ADC with high stability in blood circulation. **PBD warheads were not found to be substrate for MDR glycoprotein and can work in synergistic manner with various hypo-methylating agents (gemcitabine, azacitidine, and decitabine), MM** added.

The opening session was concluded by **JL**, one of the pioneers in the field of ADCs. **JL** presented an important hypothesis - "**clinical outcome of ADCs depend upon % target tumor receptor density"**. **JL** shared a clinical update of Mirvetuximab Soravtansine (IMGN853) that targets folate receptor alpha (FRα). A target highly expressed in the majority of cases of epithelial ovarian cancer. **JL** and co-workers found that patients with 50-75% expression of FRα could be an important marker for early clinical success of Mirvetuximab Soravtansine, an ADC that is active at well-tolerated doses. Mirvetuximab soravtansine is advancing into a Phase III clinical trial in FRα-positive, platinum-resistant epithelial ovarian cancer, **JL** added.



Discovery Stream - Optimize Linker & Payload Chemistry Design

Speakers: Jenny Thirlway (JT), Hervé Bouchard (HB), and **John Babcock (JB)**

Linker payload design is one of the crucial areas of research for tuning various clinical aspects of ADCs. **JT** from Glythera started this session by introducing **PermaLink™** technology, which makes use of vinylpyridine based chemistry to site selectively attach payloads from various classes to cysteine residues of the therapeutic antibody, such as trastuzumab with DAR of 4. PermaLink™ based ADCs demonstrate a significant improvement in tolerability compared with maleimide conjugates **JT** added. **JT** concluded her talk by summarizing 7 ADC programs targeting solid tumors that make use of PermaLink™ platform. **JT** and her colleagues are designing various other classes of payloads that act by **new cell killing mechanisms such as CDK11 inhibitors, vascular disruptive agents, agents that can induce apoptosis through mitochondrial pathways, new generation of DNA-modifying agents** etc.

Next, **HB** from Sanofi gave an elegant talk summarizing challenges associated in the development of a new class of warheads, Cryptophycins. **HB** and co-workers chose this payload due to its high potency. **According to HB Cryptophycins are (5-10x) more potent than DM4 and MMAE**. **HB** and his team could selectively install cleavable peptide (val-cit) linker on the para benzylic position of cryptophycins and showed 40-50 pM IC_{50} values *in vitro*. However, after evaluation of *in vivo* PK studies, they found that C52 ADCs were unstable in mice and were metabolized in circulation. After performing HRMS analysis of plasma samples of SCID mice treated with C52 ADCs, hydrolysis and fragmentation of C52 macrocycle was observed. Hence, **HB** and co-workers designed new derivatives of Cryptophycins, which can't be metabolized *in vivo* and are as potent as the original molecule. They are currently investigating *in vivo*/therapeutic index studies in monkeys to further support the development of this new payload **HB** added.

JB concluded this session by discussing how **AlbuCORE™ and Zymelink™** platforms can improve the therapeutic index of ADCs with **DAR 8**. The AlbuCORE™ platform is a novel and proprietary family of multi-valent scaffolds based on human serum albumin (HSA). AlbuCORE™ is a novel engineered amino, carboxyl termini to which other functional domains can be fused or chemically conjugated, to form a multi-valent and multi-functional molecules. On the other hand, Zymelink™ conjugation platform is a suite of novel protein site-specific conjugation technologies and customizable cleavable and non-cleavable linkers, which are compatible with a variety of small molecule therapeutics, **JB** explained. In this presentation, **JB** and his colleagues explored a **new class of tripeptide like molecule such as Hemiasterlin (isolated originally from marine sponge) with N-acylsulfonamide modification. N-acylsulfonamide can increase the potency of hemiasterlin** and can also provide a handle for linker attachment. Moreover, they also made some novel derivatives of auristatin class that can be tolerated at higher dose than traditional MMAE conjugates and possess higher therapeutic index for both type of payload classes.

Discovery Stream - Optimize Linker & Payload Chemistry Design

Speakers: Paul Davis (PD), Robert Garbaccio (RG), and **Naresh Jain (NJ)**

PD from Qunta Biodesign started the afternoon session by discussing dPEG® as a framework to uniquely load and protect payloads in an ADC. He showed that his team can synthesize **dPEG® oligomers as a single molecule on large scale with high purity and not as polydisperse ethylene glycol.** dPEG® can be fine tuned for its hydrodynamic volume, *in vivo* compatibility (solubility, stability, PK protection) and non-toxic all by design, **PD** added. In addition to this, dPEG® can be functionalized at one end with conjugation arm, while the middle part of the dPEG® can be used to introduce amino acid residues. The other end of the **dPEG® can be linear or a branch that in turn can modulate PK/BD modulating site.** This sidewinder dPEG® platform is highly versatile and can used in ADCs with a DAR of 6 to 24 with favorable PK/ *in vivo* cytotoxicity profiles. Moreover, various payloads, various modalities, such as Near Infrared Region (NIR) dyes, radiolabelled materials such as DOTA, and various clickable groups, can also be introduced using dPEG® at multiple branching points.

RG continued the discussion on linker design and payload chemistry by introducing the audience to the **discovery of pyrophosphate diesters, as tunable, soluble and bioorthogonal linkers for site-specific ADCs. RG** discussed the challenges associated with the delivery of glucocorticoids as a payload to CD70, a receptor specifically expressed in immune cells but also found aberrantly expressed in multiple human carcinomas. The pyrophosphate linker is designed to covalently attach glucocorticoids that can be cleaved by cathepsin B and improves solubility of glucocorticoids, **RG** added. Moreover the other end of the peptide fragment can be functionalized with a biorthogonal functional group, such as strained alkyne, and can be ligated to antibodies containing azides through click chemistry. This novel linker expands the scope of potential ADC payloads by allowing an aliphatic alcohol to be a stable, yet cleavable attachment

site. This phosphate linker may have broad utility for internalizing ADCs as well as other targeted delivery platforms, **RG** concluded.

NJ concluded the afternoon session of linker design and payload chemistry by discussing **Thiobridge™ technology** developed by his company. Thiobridge™ can remodel various therapeutic antibodies with a **DAR ranging from 0-8**. This approach uses **bis-sulfone reagents that are selective for the cysteine sulfur atoms from a native disulfide.** These reagents undergo bisalkylation to conjugate both thiols derived from the two-cysteine residues of a reduced native disulfide bond such as the interchain disulfide bonds of a mAb. The reaction results in covalent rebridging of the disulfide bond via a three-carbon bridge, leaving the protein structurally intact, **NJ** explained. ThioBridge™ targets natural disulfides with highly reproducible conjugation profiles at milligram to gram scales, **NJ** added.

Plenary Session - 5 Minute Short-Fire Poster Presentation Talks

Speakers: Grazia Piizzi (GP), and Megan Minnix (MM)

The 5 minute rapid-fire poster presentation was an amazing experience. **GP** began this session by explaining utilization of novel payloads such as kinesin-5 (Eg5, KIF11) inhibitors. **Small molecule Eg5 inhibitors can potentially inhibit Eg-5, a motor protein/mitotic ATPase involved in spindle pole assembly. This class of molecules are highly potent (IC_{50}=0.1-0.5 nM)** however they tend to aggregate when conjugated to antibodies depending upon which part of the molecules are modified. Aggregation is less than 10% when MC-ValCit linker is installed through *(R)* 3-fluoropyrrolidine-ring system.

Continuing this interesting session, **MM** talked about the development of **CC49 ADC that targets a novel tumor antigen - Tumor associated glycoprotein-72 (TAG-72)**. TAG-72 is a mucin

like molecule and a pancarcinoma antigen overexpressed on many cancer cell surfaces. In this work **MM** and her co-worker developed CC49 ADC against ovarian cancers using TAG-72 as the target. **CC49 possess MMAE as a payload with a DAR of 10** and exhibits a blood clearance comparable to the antibody alone, whilst maintaining its efficacy.

Plenary Session - Optimization of ADCs: Maximize Efficacy & Minimize Toxicity

Speakers: Gang Chen (GC), Scott Dylla (SD), and **John Gebler (JG)**

In this session, GC showed preclinical development of some of the superior ADCs incorporating novel linkers and warhead design. **GC** said that their company has developed **K-lock** and **C-lock** approach to systematically incorporating DAR-2 to DAR-4 respectively. The data in his presentation signifies remarkable clinical outcomes for **ZV0203 (anti-HER2) and CBT-161 (anti-c-met) ADCs incorporating both duostatins and duomycins as a new waheads**. **ZV0203 outperformed T-DM1 in various animal models showing superior PK, PD & toxicity profiles, GC** concluded. According to him, his company has developed a robust screening panel from antibody to ADC leads in 2 months, from target to IND within 2 years.

"Lack of efficacy at tolerated doses in humans reflects the fact that many efficacy models do not accurately predict clinical success."

SD continued and shared some of the hard lessons his team have experienced while advancing 3 ADCs - DLL3-PBD, PTK7-Auristatin, and EFNA4-Calicheamicin into the clinic. **SD** and his team found that 50,000 copies of tumor antigen/cell were generally needed for efficacy. CCI payloads like calicheamicin were found to be more potent over CCD (auristatins) and can kill even quiescent cells. However, for targets like DLL3 and EFNA4 3,000 – 14,000 copies of tumor antigen per target cell is enough and efficacy in this case are dependent upon internalization

rate and payload type. One of the key factors for the improvement of ADC clinical translation is to make them more safe and efficacious in their population, **SD** added. According to him, many ADCs failed previously due to "**Lack of efficacy at tolerated doses in humans reflects the fact that many efficacy models do not accurately predict clinical success.**" Based on his experimental data, *in vitro* results **do not always correlate with *in vivo* efficacy,** and vice versa. Furthermore linker/drug selection can impact internalization rate *in vitro*, which may or may not impact *in vivo* efficacy. **SD** concluded his impressive talk by stating some of the advantages of patient derived xenografts (PDX) models. They found that PDX models better retain primary tumor characteristics; PDXs can better model clinical responses of approved drugs, protein expression is conserved in propagated PDXs. Moreover, genome integrity is also conserved in PDXs models. They also observed that orthotopic implantation better retains tumor architecture in some cases. Another major advantage of PDXs models, according to **SD,** was circulating tumor cells can be characterized in PDX models, and can greatly aid in the selection of linker/drugs. **SD** stated that ultimate off-target effects of ADC in humans can differ and each payload type can have the following off target effects such as DM4 (ocular toxicity), DM1 (thrombocytopenia), MMAE (neutropenia and peripheral neuropathy), MMAF (Ocular toxicity and thrombocytopenia), Calicheamicin (thrombocytopenia, VOC and mucositis) and PBD (thrombocytopenia, pleural effusions, edema and rash).

JG concluded the first day of the meeting by discussing bio-analysis of ADCs using LC/MS techniques. **JG** presented various case studies such as LC/MS analysis of T-DM1 that contain heterogeneous mixture of DARs from +2 to +6. According to him, ionization efficiency of various ADC conjugates depends upon the location of the residue where linker-drug is conjugated. **JG** and his team published several papers illustrating new LC/MS based method for the quantification of payload residues in ADCs, total antibody *in vivo* and intact antibodies in the plasma samples.

Conference Day 2, October 12 2016

Plenary Session – Explore Payloads with Differentiated Mechanisms of Action from Discovery to Clinical Development

Speakers: Chris O' Donnell (CD), Takeshi Honda (TH), Andreas Pahl (AP) and **Norbert Koper (NK)**

Discovery of novel linker payloads is highly essential for the development of next generation ADCs. **CD** started his talk by disclosing some of the novel DNA damaging agents and structure-activity relationship studies. He started his presentation by giving brief background about **Pfizer's efforts about developing novel payloads (PF-06380101, an analog of dolastatin 10) for new ADC targets (PTK7, Notch3, NG-Her2 so on and so forth).** In addition, performing SAR based modification in -C and N- terminal site of tubulysin can modulate its potency while acetylation at a specific position can modulate stability of this class of payload, **CD** added. **CD** and co-workers have also explored thailanstatins as new class of linkeless ADCs to target HER (+) ve gastric cancers. **Thailanstatins are splicesosome (RNA-polymerase-II) inhibitors and are extremely potent class of payloads**, **CD** demonstrated. Then, **CD** showed some of the most

potent payloads having picomolar to femtomolar IC_{50}'s including PBD dimers and CBI dimers, which was the main focus of his talk. CBI dimers, a group of natural products (antibiotics class) are highly toxic but have a limited efficacy due to these toxicity issues. Hence, **modifying these CBI dimers at specific positions where the linker can be installed without loosing cytotoxicity/stability is an extremely daunting task.** To achieve this, **CD** and team did some SAR studies and found that a self-immolative linker could be installed by replacing one of the acetates. The original CBI dimer can then be released by the chemical/enzymatic action of cathepsins B and cytosolic esterase. They have achieved total synthesis of CBI dimer linker in 32 steps with a 0.002% overall yield. However, one of the problems associated with CBI dimers is high lipophilicity, and hence they precipitated out even in w/20% organic solvent. But replacing one of the acetates with phosphate could solve this issue and phosphate derived CBI thiophene derivatives are found to be extremely potent in MDR (+) ve cancer cells. When **CD** and his team studied the stability of CBI-thiophene conjugated ADC in mouse serum, they found complete decomposition of active metabolite due to plasma hydrolases. To solve this difficult issue, his team **replaced aromatic amides with various carbocyclic spacers (Bicyclo [1.1.1] pentane as a phenyl ring isostere).** These modifications lead to better plasma stability but less potency *in vivo* (0.22 nM). Finally, **CD** and his team replaced CBI core with CPI (Interstrand DNA cross-linking agent) and obtained IC_{50} of 0.0047 nM but ADCs with CPI core possessed poor pharmacokinetic profile**. To improve PK profiles, CPI dimer containing (Bicyclo [1.1.1] pentane as a phenyl ring isostere) derivative was conjugated to anti-CD33 antibody (DAR 2) via transglutaminase type modification to obtained more efficacious ADC against MDR (+) ve *in vivo* models.**

Continuing this session, **TH** from Daiichi Sankyo discussed the preclinical evaluation of various Exatecan derivatives (DXd1 and 2). ADCs covalently connected with various exatecan derivatives through a **cleavable (–gly-gly-phe-gly-) linker** were found to be more stable in the blood circulation, **TH** said. Using interchain cysteine modification their team prepared anti-

HER2 ADCs with DAR of 2 to 8 without facing any aggregation/instability problems (for derivatives DXd2 and 1). **One of the plausible reasons why DAR 8 containing DXd1 showed good stability and efficacy is due to equilibrium ratio between the lactone ring and hydroxyl-carboxylic acid (in case of DXd1) was pH dependent.** Moreover, hydrophilic properties of the payload (DXd1) and the amino methylene group keep the ADC with DAR 8 highly stable and without insignificant aggregation, **TH** added. According to **TH's** data, DS-8201a containing DXd1 as a payload was not only effective in a T-DM1-insensitive PDX model with high HER2 expression, but also effective against several breast cancer PDX models with low HER2 expression.

Second session of the day started by **AP** of Heidelberg Pharma. **AP** talked about development of **Amanitin (RNA polymerase-II inhibitor, isolated from mushrooms)** as a new payload for ADC. Amanitins are **bicyclic octapeptides with a pM range IC_{50} and kills quiescent/dividing cancer cells**. In addition, they are hydrophilic (no aggregation problems), 1:1 binding, no drug resistance has been shown by cancer cells and they can be used to target antigens with low copy number (1,000 to 10,000 per cell*). However, their use in clinic has been hampered by very high liver toxicities, low membrane permeability and supply of stable amanitin analogs, **AP** said. **AP and his team developed a solid phase peptide (SPPS) synthesis method to synthesize new synthetic analogs of the natural amanitin without compromising its potency with superior stability.** One of their amanitin conjugated anti-HER2 ADC showed complete tumor remission in T-DM1 resistant JIMT-1 xenograft model with superior efficacy. **AP** pointed out some of the key positions in amanitin that could be utilized to synthesize more stable and potent analogs of amanitin. **AP** concluded his talk by showing some of the promising data from the development of **humanized anti-BCMA (BCMA is a promising target found in multiple myeloma and mature B-cell neoplasm) ADC containing amanitin as a payload attached via site-specific cysteine engineering.**

NK continued this session by giving a talk on the challenges of developing SYD985, a Duocarmycin containing anti-HER2 ADC for the treatment of locally advanced or metastatic solid tumors. **NK** presented some of the clinical trial results. He pointed out some of the severe ocular toxicities that more than 50% of the patients treated with SYD985 were facing. However, **NK** and his team saw recovery from ocular toxicity but results show this to be very slow, **NK** concluded.

Discovery Stream – Validation of Site Specific Conjugation Technologies

Speakers: Chetana Rao (CR), Changshou Gao (CG), Feng Tian (FT), and Toshiyuki Mori (TM)

CR began this session by stating some of the key facets of site-specific conjugations. She gave a concise overview of current methods available for the preparation of ADC with well-defined DAR's. This included Kadcyla and Adcetris (random conjugation-heterogeneous mixture) that have several disadvantages such as poor bio-distribution in liver and spleen, Di-sulfide bridging which involves thiol reduction, Glycan remodeling strategy (Chemo-enzymatic modeling), and use of BTGase (bacterial transglutaminase). **CR** and her team used transglutaminase method to prepare ADC's with DAR of 2 or 4 (using tubulysins as a payload with cleavable or non-cleavable linkers) by removing glycan's of the antibody in first step, followed by the modification of aspartic acid (Asp 295) and glutamic acid using BTGase. Moreover the removal of glycan's from the antibody didn't affect the overall stability in this case. **One of the advantages of this method is transglutaminase are very cheap and yet highly specific, and can work on high scale for antibody modification**, **CR** added.

After this interesting talk, **CG** continued to talk on development of tubulysins as a potent warhead. His team have designed several novel analogs by modifying **Tuv** and **Mep** positions,

which are often required to produce linkable ADCs without compromising the potency (IC_{50} of 0.3 nM). Along with this, **CG** showed novel designed N-phenyl-maleimide based linkers, which produce more stable ADCs over a conventional thiol-maleimide type linker. **CG** concluded his talk by discussing the development of Trastuzumab-scfv and biparatopic/bispecific ADCs using MMAE as a payload attached through lysine modification.

One of the representatives of Ambrx gave the next talk on behalf of **FT**. She discussed **EuCODE** as a site-specific non-natural amino acid incorporation in mammalian cells. This technology uses **oxime ligation-chemistry** and allows **FT** and co-workers to **site-specifically install a payload of choice**. Payloads such as amberstatins (anti-PSMA/anti-HER2), hemiasterins, MMAE etc. were successfully installed using EuCODE technology. ADCs developed using EuCODE technology have shown superior properties, the speaker concluded.

TM started this session by introducing Nanocarrier technology. This involves covalently attaching an antibody of interest on the surface of the polymeric nanocarrier (composed of hydrophilic polyethylene glycol and hydrophobic core made up of PCL/PLGA polymers) and the encapsulation of payload of interest in the hydrophobic core. This method can incorporate 100-drug molecules/nanocarrier with good *in vivo* efficacy, **TM** added. They have applied this technology for the delivery of many anticancer drugs such as cisplatin, paclitaxel, doxorubicin etc. His team are conducting phase-1/2 clinical trials in Japan and United States, **TM** concluded.

Discovery Stream – Accelerate Discovery & Development of Next Generation ADC Technologies

Speakers: Magdalena Dorywalska (MD), Philip Howard (PH), and **Ken Geles (KG).**

The afternoon Discovery Stream lecture series began with a discussion on the issues regarding molecular basis of Valine-Citruline (VC)-PABC linker instabilities, which is one of the universal linkers present in many ADCs. **MD** discussed two main problems:

A) **Occurrence of retro Michael reaction when ADCs are constructed using SMCC-DM1 linker.** It has been shown recently that, some loss of maytansinoid from Ab-SMCC-DM1 conjugates can occur via thiol elimination but at a slower rate than the corresponding rate of loss reported for thiol-maleimide links formed at thiols derived by reduction of endogenous cysteine residues in antibodies.

B) **The importance of conjugation site in determining the VC-PABC linker stability in mouse plasma, and that the stability of the linker positively correlates with the ADCs cytotoxic potency both *in vitro* and *in vivo*. MD** showed that VC-PABC linker is susceptible to cleavage in mouse plasma and is not mediated by cathepsin B, the protease thought to be primarily

responsible for linker processing in the lysosomal degradation pathway. VC-PABC cleavage can however occur in mouse but is not significant in human primates, **MD** concluded.

PH started his talk by giving brief introduction about the origin of Pyrrolobenzodiazepine (PBD) in 1960. His team has partnered with multiple companies for the potential application of PBD as a payload in many clinical ADC candidates. **PH** showed data from collaborative research with **Seattle Genetics which showed superior efficacy of Vadastuximab Talirine (SGN-CD33A) even at significantly lower doses say 30 mcg/kg in HL60 AML tumor model. PH** concluded his talk by showing novel PBD analogs having **IC_{50} in the range of 1.59 to 4.84 pM.**

Continuing the Discovery Stream lectures, **KG** gave a brief introduction on biology of NOTCH3 oncogene and how knockdown of NOTCH3 can lead to tumor reduction. NOTCH3 is a validated target for the design of ADCs possessing very high expression on ovarian (58%), breast (40-45%), and lung small cell carcinoma (69%), **KG** said. **KG** and his team developed **anti-NOTCH3 ADCs containing auristatin based microtubule inhibitors and found different *in vivo* IC_{50} values of 218 ng/mL and 118 ng/mL for clone B and A** respectively. Nevertheless, **KG** demonstrated that anti-tumor activity could be achieved by identifying tumors with receptor overexpression instead of addiction to notch signaling in adult patients with advanced solid tumors.

Plenary Session – Pioneering Developments to Fuel ADCs of the Future

Speakers: Brian Mendelsohn (BM), Nandini Rudra-Ganguly (NRG), David Tice (DT), and **Hans Peter Gerber (HPG)**

BM one of the first people to synthesize auristatin started this session. **BM's talk** showed design of new auristatin analogs based on structure-activity relationship studies. His team have

generated many auristatin compounds to improve the pharmacokinetics and potency of existing auristatin containing ADCs. They have found by **replacing side chain methyl group in first amino acid structure with azide and introducing phenylalanine methyl ester in fourth amino acid can generate more potent auristatin analogs, BM** added. However, his team found that ADCs generated using these new derivatives when conjugated to antibody through unnatural amino acid (EuCODE technology) are not well tolerated based on pharmacokinetic/toxicity profiles.

With this **NRG** continued this interesting session. She began talking about the identification and validation of a new clinical target - **FLT3**. **FLT3 has 85% expression in AML (Acute Myeloid Leukemia), NRG** said. With the emergence of various FLT3 inhibitors in clinical trials developing anti-FLT3 against AML is highly attractive. **NRG** showed some promising preclinical data with no off-target toxicities, enhanced CMC properties and a widened therapeutic index. **NRG** concluded her talk by acknowledging **BM** and his team for designing/constructing these ADCs containing auristatins as a payload.

DT and **HPG** concluded 7th World ADC San Diego meeting with a talk on **combining ADCs with immune-oncological agents/immune-check point inhibitors. DT** said that ADCs harnessing the power of immune system was not observed in previous studies since most of the animal work has been done on immuno-competent/deficient mice. He stressed on the **use of PBD's and its DNA damaging/repair pathways could be crucial for the search of synergy. DT** showed complete tumor regression data on combining either **PBD+Tubulysins+Checkpoint inhibitors or PBD+Tubulysins+ TNF-α**. However, according to **DT the dosing schedule for PBD, Tubulysins and immuno-oncological agents is most important elementfor harnessing synergistic effects.**

the use of PBD's and its DNA damaging/repair pathways could be crucial for the search of synergy.

HPG acknowledged efforts of Philip Mueller and co-workers for showing for the first time a successful combination of **T-DM1 ADCs with CTLA-4/PD-1 blockade against HER2+ cancers**. Then, he showed acceptable (Phase-1) efficacy profiles of a clinical candidate **PTK-7, a humanized antibody-containing auristatin as a payload against patients with advanced malignancies, including triple negative breast cancers and non-small cell lung cancer.** PTK-7 can also kill tumor-initiating cells, **HPG** said. **HPG** concluded by sharing some interesting data on the ability of various microtubule inhibitors (auristatins, DM1, PBD) and other chemotherapeutic agents such as doxorubicin, cisplatin, topotecan, and gemcitabine for their ability to induce immunogenic cell (production of Calreticulin surface translocation as a marker) death and dendritic cell activation (CD80 expression) in CT26 murine colon cancer cells.

Special thanks to Manish Hudlikar for taking the time to prepare this report.

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20 - 22 February 2017

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