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Meeting reports

Frontiers and Opportunities: Highlights of the 2nd Annual Conference of the Chinese Antibody Society

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ABSTRACT

The Chinese Antibody Society (CAS) convened the second annual conference in Cambridge, MA, USA on 29 April 2018. More than 600 members from around the world attended the meeting. Invited speakers discussed the latest advancements in therapeutic antibodies with an emphasis on the progress made in China. The meeting covered a vast variety of topics including the current status of therapeutic antibodies, the progress of immuno-oncology, and biosimilars in China. The conference presentations also included the development of several novel antibodies such as antibodies related to weight loss, T-cell receptor-mimicking antibodies that target intracellular antigens, and tumor-targeting antibodies that utilize both innate and adaptive immune pathways. At the meeting, the CAS announced the launch of its official journal—*Antibody Therapeutics*—in collaboration with Oxford University Press. The conference was concluded by a panel discussion on how to bring a therapeutic drug developed in China to the USA for clinical trials.

Statement of Significance: The CAS convened the second annual conference in Cambridge, MA, USA on 29 April 2018. The meeting covered a variety of topics, including therapeutic antibodies being tested in clinical trials, new antibodies (e.g., programmed cell death protein 1/programmed death-ligand 1 inhibitors) being developed in China, and T-cell receptor-mimicking antibodies that target intracellular antigens.

KEYWORDS: antibody therapeutics; biosimilars; bispecific antibodies; CAR T cells; Chinese Antibody Society

OPENING REMARKS

The second annual conference organized by the Chinese Antibody Society (CAS) was held on 29 April 2018 in Cambridge, MA. Dr Fubao Wang, the associate vice president (VP) of Sanofi, the chair of the conference organizing committee, and the board director of CAS, delivered the opening remarks. He welcomed all attendees of the conference and thanked the speakers, panelists, and session chairs, the conference organizing committee, and CAS volunteers (Fig. 1), and partners and sponsors of the conference. Wang mentioned that it is the golden age for antibody therapeutics since the number of monoclonal antibodies (mAbs) approved by the Food and Drug Administration (FDA) has increased in recent years. As of 2017, the total number of FDA-approved mAbs and mAb biosimilars

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Figure 1. A group portrait of the conference speakers, panelists, CAS advisors and volunteers taken during the second annual conference.

is 74 and 7, respectively. In particular, the FDA recently approved Trogarzo, which is the first mAb manufactured in China. Additionally, 13 therapeutic antibodies that were developed in China have received Investigational New Drug (IND) clearance from the US FDA. There are also many significant licensing deals linked to drug companies in the USA and China. Wang highlighted the theme of the conference—Antibody Therapeutics: Frontiers and Opportunities—with an agenda that covered all major aspects related to antibody therapeutics: science, technology, clinical, regulatory, business, and intellectual property. He welcomed the attendees to enjoy the event, to network with fellow attendees, and to fully immerse in the full-day activities.

MORNING SESSION

Yearly review and announcements of the CAS

Dr Shouye Wang, the director of WuXi Biologics and the president of CAS, shared the milestone achievements and the progress of CAS with the audience. Founded on 27 April 2016, CAS is the only global organization for Chinese professionals whose work focuses on therapeutic antibodies. It is a rapidly growing society with 1200+ members worldwide and 10 000+ WeChat followers. It is a non-profit society that is operated fully by volunteers. The mission of CAS is to serve as the gateway to the globalization of therapeutic antibodies developed in China, and the platform is to foster the productive collaboration and networking among its members. The current focus of CAS is the "1111" plan that is to launch one journal—*Antibody Therapeutics*—in collaboration with Oxford University Press (launched June 2018) and to organize a series of one monthly webinar, one biannual PharmaConnect function, and one annual conference. Wang announced that **the third annual conference will be held on 7 April 2019 in Cambridge, MA**. Another key announcement that Wang made is that Dr Zhidan Tu is the president-elect of the CAS; Tu is the director of Legend Biotech; and is currently the general manager and VP of CAS.

Current status of therapeutic antibodies—2018

Following Wang's introduction of the CAS, the next presentation was delivered by Dr William Strohl, founder of BiStro Biotech Consulting LLC and the former VP of BioTherapeutics at Janssen. Strohl discussed the current status of therapeutic antibodies approved by the FDA for marketing and for use at the clinical stages. There has been a large increase in FDA-approved antibodies in the recent 5 years with a trend of around six approvals per year

(Fig. 2A). Antibodies drive the value of all biologics since their sales accounted for 66% of biologics revenues in 2017 [1]. Until now, there are 84 FDA-approved antibody-based drugs, including two chimeric antigen receptor (CAR)-T therapies approved in 2017 (Fig. 2A). In addition, there are about 800 antibody-based drugs that are undergoing clinical development with close to 600 antibodies in various formats with naked immunoglobulin G being predominant (BiStro Biotech Database[1]). The remaining 200 are CAR antibodies loaded onto T and natural killer (NK) cells. Many CAR-Ts are currently developed in major universities and pharmaceutical companies in China. Approaches to cancer antibody therapy include blocking receptor and ligand interaction, interfering with the tumor support, inducing tumor cell death, delivering toxic payloads, activating the immune system with checkpoint modulators, and targeting tumor cells with the immune system such as complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC). The therapeutic areas targeted by clinical candidate antibodies and CARs are mainly oncology and immunology, followed by infectious diseases, neurobiology, and cardiovascular diseases (Fig. 2B). This correlates well with the fact that a vast majority of targets are identified in oncology, inflammation, and autoimmune diseases (Fig. 2B). Cluster of differentiation (CD) 19, a B-cell specific surface antigen that is often overexpressed in many leukemia and lymphomas, is by now the largest targeting pool, especially in the CAR-T field (Fig. 2B).

In the second part of his talk, Strohl focused on antibodies and T cells. He first discussed the development of checkpoint inhibitor or agonist antibodies to improve T-cell activity. Over 100 checkpoint inhibitor antibodies are currently in clinical trials. Several have reached Phase III, and three are from companies in China. He mentioned that one emerging question in the field is why T-cell immunomodulators are working in some patients but not others. Strohl next discussed the development of bispecific antibodies for T-cell redirection. The orientation of the CD3 arm that targets T cells is critical for potency. There is also an interesting correlation of size and potency. The smaller they are, the more potent they are [2]. One hypothesis is that small molecules may lead to efficient synapse formation between T cells and tumors, and the number of interactions in synapse seems to be critical with an optimal number of around 10 to 15. However, one should bear in mind that smaller molecules have a shorter half-life [3]. The third approach is CAR-T antibody-based cell therapy. Strohl gave a brief overview of four generations of CARs and described the differences between autologous and allogeneic CAR-T designs [4]. The autologous CAR-T is an individualized and patient-specific therapy because it engineers T cells directly isolated from the patient. On the contrary, the allogeneic CAR-T, which is also known as the off-the-shelf therapy, is to engineer primary T/NK cells isolated from healthy donors. This type of CAR-T is to reduce the expensive cost arising from individualized autologous therapy. There are four sources of allogeneic cells [3, 5, 6]. One can directly engineer primary T/NK cells or use T cells differentiated from induced pluripotent stem cells. Alternatively, one could genetically engineer an established cell line or use cord blood cells that naturally lack major histocompatibility complexes (MHCs). However, both autologous and allogeneic CAR-Ts have the potential problems of delivering heterogeneous T cells and uncontrolled T-cell expansion. Strohl concluded by saying that only when we can achieve delivery of homogenous cell types, will we be able to effectively treat tumors with T cells.

Progress and status of Immuno-Oncology in China

In this talk, Dr Michael Yu, the president and CEO of Innovent Biologics, summarized the progress and status of immuno-oncology (IO) in China. As stated in his introduction, many IO investigative drugs were filed in China either for clinical trials or for marketing. The star candidates are programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. Twenty-nine PD-1/PD-L1 inhibitors were filed for INDs in China as of 29 April 2018; 23 from domestic companies and 6 from multi-national companies. In terms of progress, 18 out of 29 are at clinical stage (11 for PD-1 and 7 for PD-L1) including 5 biologics license applications (BLAs) filed with China National Drug Administration (CNDA). IO programs against other popular targets such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), OX-40, lymphocyte-activation gene 3, T-cell immunoglobulin and mucin-domain containing-3, CD47, and PD-1/CTLA-4 bispecific are also being carried out in China.

In addition to the above-mentioned antibody programs, Yu also introduced the flourishing INDs of engineered T-cell therapy in China. The US FDA has approved one dendritic cell therapy (Sipuleucel-T, Provenge) and two CAR-T products [7, 8]. China has 15 CAR-T filed for IND as of 29 April 2018. Most of the 15 CAR-T targeting CD19 and one CAR-T targeting BCMA from Nanjing Legend were approved for Phase I clinical trial. There are 153 CAR-T clinical trials from China registered in ClinicalTrials.gov. As a comparison, 155 US CAR-T clinical trials are registered. Statistically, China and the USA play leading roles in CAR-T clinical trials (accounting for >70% of clinical trials in the world).

In the second part of his talk, Yu reported on the current progress of Innovent, which has a diversified pipeline with four advanced products (in Phase III trials) and other innovative I/O therapies. IBI308 mAb (sintilimab) is a fully human anti-PD-1 antibody currently under Phase II/III trials for Hodgkin lymphoma, esophageal cancer, NK/T lymphoma, squamous non-small cell lung cancer (NSCLC), and NSCLC. As shown in the crystal structures, IBI308 binds to a different epitope from Pembrolizumab and Nivolumab, which are the first two FDA-approved mAbs targeting PD-1 (Fig. 3). IBI308 also shows 10- and 50-fold higher affinity to human PD-1 expressed on the surface of Chinese hamster ovary cells than Pembrolizumab and Nivolumab, respectively. A collaborative study carried out in Lilly Laboratory shows that IBI308 has

[1] From BiStro Biotech Consulting database on clinical stage biologics. Database lock for these data was 25 April 2018.

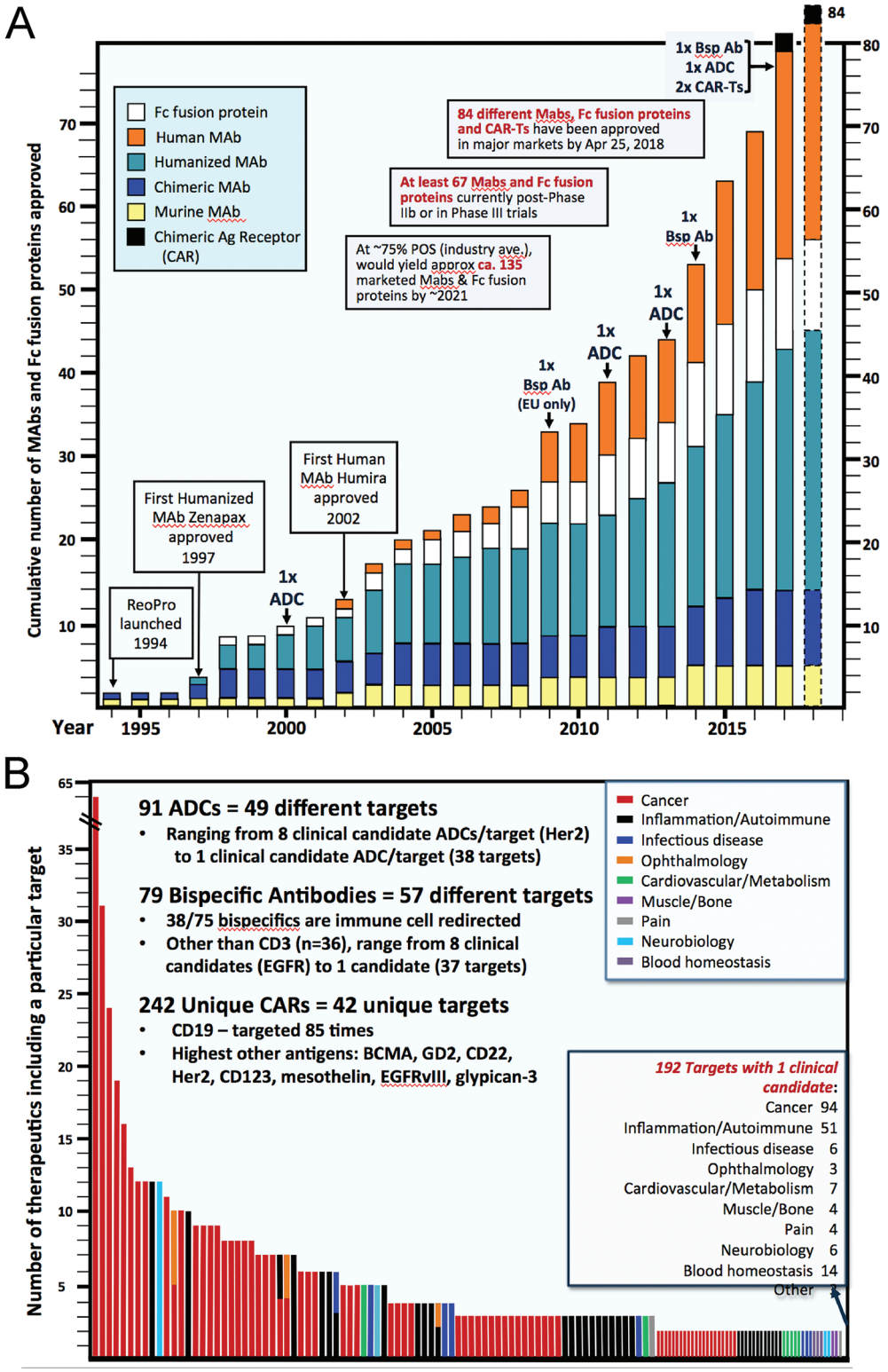

Figure 2. Current status of approved therapeutic antibodies. **(A)** The total number of approved therapeutic antibodies and antibody-like molecules such as Fc fusion proteins and CARs is 84 as of 25 April 2018. This number is increasing at a rate of around six per year. **(B)** There are 325 unique targets recognized by antibodies and antibody-like molecules that are in clinical trials. Most targets are identified from cancer and inflammation/autoimmune diseases.

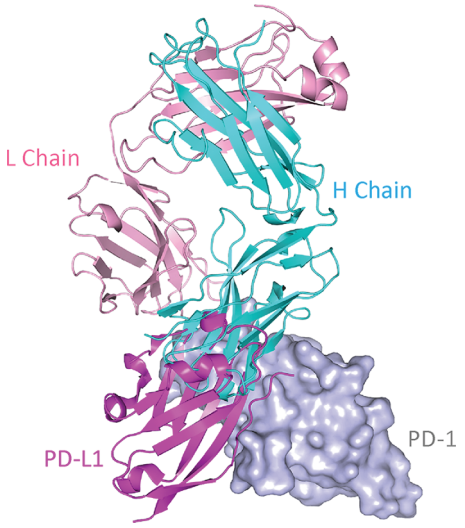

Figure 3. Crystal structure of the IBI308 (Sintilimab) Fab-PD-L1-PD-1 complex. The light (L) and heavy (H) chains of Sintilimab Fab are shown in salmon and cyan, respectively. PD-L1 is in pink and PD-1 is in light blue (surface representation). The structure suggests that IBI308 can efficiently block PD-1/PD-L1 and PD-1/PD-L2 interactions (PD-L1 and PL-L2 binding sites on PD-1 are mostly overlapped). In addition, the binding epitope of IBI308 is distinct from that of Pembrolizumab and Nivolumab.

a much stronger *in vivo* anti-tumor efficacy in humanized NOD scid gamma mouse model where IBI308 at 1% dose achieves better anti-tumor activity than Nivolumab. *In vitro* functional assay shows that IBI308 stimulates higher activation of T cells, which is further supported by *ex vivo* assay in MC38 tumor-bearing mouse model that shows IBI308 promotes higher effector: regulatory T cell ratio than Pembrolizumab and Nivolumab. A very recent report shows that IBI308 has a similar safety profile to Pembrolizumab and Nivolumab in Phase II study for Hodgkin lymphoma. A new drug application was filed with CNDA in April 2018 and granted with priority review status. Further results on the efficacy of IBI308 were reported at the 2018 ASCO Annual Meeting in Chicago. The trial result showed positive response in patients with a 74.0% objective response rate and 24.0% complete response rate, making it a new treatment for relapsed/refractory classical Hodgkin's lymphoma patients [9].

Innovent IBI322, an anti-CD47/PD-L1 bispecific mAb, is currently under pre-clinical study. CD47 is a well-characterized cell surface receptor that conveys a "don't eat me" signal to immune cells [10]. However, the broad expression of CD47 on normal cells limits its therapeutic potential. IBI322 has both anti-CD47 and anti-PD-L1 arms in which the affinity to PD-L1 is stronger than CD47. This suggests that IBI322 has the potential to preferentially bind to PD-L1 positive tumor cells over healthy cells. This could lead to a superior toxicity profile. Preliminary studies show that IBI322 selectively binds to PD-L1 positive tumor cells over red blood cells so that it does not induce hemagglutination. Moreover, there is evidence that IBI322 has more potent phagocytosis activity and anti-tumor efficacy than individual anti-CD47 and anti-PD-L1 controls whereas it retains a normal antibody-like pharmacokinetics (PK) profile. In conclusion, preliminary study results have shown great potential for IBI322 as a novel therapeutic in the IO family.

Anti-GFRAL antibodies

Next, Dr Wenyan (David) Shen, the Senior VP of Biologics Research, Bioanalytical and Chemistry, Manufacturing & Control (CMC) at NGM Biopharmaceuticals, described recent novel therapeutic development in NGM with a primary focus on GDF15, a soluble hormone that is related to obesity. GDF15 is known as growth and differentiation factor 15, and its administration lowers body weight and reduces food intake in mice in a dose-dependent manner. The recent identification of its cognate receptor, GDNF Family Receptor Alpha Like (GFRAL), has shed light on the mechanism of action of GDF15. GFRAL was identified by NGM via unbiased cell-based/biochemical screenings approach [11]. Binding of GFRAL to GDF15 has been demonstrated both *in vitro* using recombinant proteins with a dissociation constant (K_D) of 8 nM and in tissue culture cells with a K_D in low molar concentration (nM) [11]. GFRAL knockout mice are resistant to GDF15-induced weight loss. Both GDF15 and GFRAL are therefore two potential drug targets for diseases related to weight changes. Despite the promising efficacy of GDF15, the recombinant protein presents manufacturing challenges because of its solubility issue at higher concentration. Mutational analysis based on the co-crystal structure of GDF15 and GFRAL [11] led to the generation of two highly potent GDF15 variants that display significant solubility improvement. Currently, these GDF15 agonists are under development by Merck through licensing from NGM. In addition, NGM also develops an anti-GFRAL antagonist antibody that is currently under Phase I clinical trial. This antibody reverses GDF15-induced weight loss and promotes weight gain in mice. It is intended to be used in cancer patients to prevent or to minimize weight loss induced by chemotherapy.

TCR-mimicking antibodies

The next talk from Dr Cheng Liu, founder and CEO of Eureka Therapeutics, featured recent developments toward intracellular cancer targets. The traditional therapy, such as mAbs and CAR-Ts, recognizes extracellular or surface proteins. However, the cancer targeting proteome comprises nearly 90% of the intracellular targets [12]. MHC class I complexes present peptides derived from intracellular targets on the cell surface, and this makes them attractive targets. One example is Wilms Tumor (WT-1) peptide presented by the MHC class I A0201 complex. WT-1 is expressed broadly in many types of cancer but rarely in normal adult tissues. The proprietary in-house phage display platform for fully humanized antibodies allows Eureka to develop a first-in-class monoclonal, fully human antibody against WT-1 [13, 14]. The antibody mediates ADCC *in vitro* and shows strong anti-tumor effects *in vivo*. It is one of the first therapeutic antibodies that directly target an intracellular oncogene, and it is currently in the IND-enabling development process.

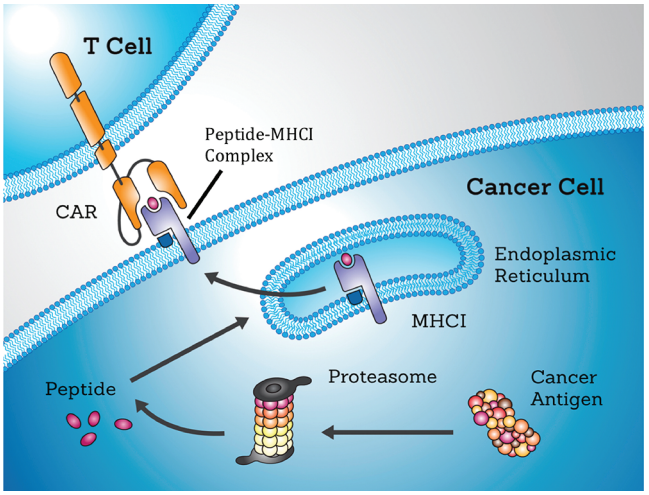

Figure 4. A schematic diagram showing a TCR-mimicking monoclonal antibody binding to a peptide/MHC complex on a cancer cell. Intracellular tumor-associated antigens (TAAs) are processed and presented on the surface of malignant cells in the context of MHC class I molecules. Highly specific TCR-mimicking mAbs can now be isolated and used to specifically target malignant cells exhibiting specific TAA/MHC complexes on their surface. TCR-mimicking antibodies can be used for CAR-T immunotherapy as well as therapeutic mAbs.

Liu also shared another significant progress that the company has made on the development of T-Cell Receptor (TCR)-mimicking antibodies. *Alpha-fetoprotein* (AFP) is a fetal protein highly and specifically expressed in liver tissues, and its peptide is presented by the MHC class I A0201 complex on the cell surface. To develop a TCR-like antibody, they took a different approach, which was to develop CAR-T that recognizes the MHC class I complex presenting the AFP peptide (Fig. 4). A highly specific single-chain variable fragment against the MHC complex with the AFP peptide was isolated from a phage library and was cloned into a CAR structure [15]. The resulting AFP-CAR T cells selectively kill cancer cells that express both MHC class I A0201 and AFP and triggers antigen-dependent activation of antigen-positive tumor cells [16]. The intratumoral or intraperitoneal delivery of AFP-CAR T cells causes robust tumor regression [16]. This is the first-in-human TCR-mimicking antibody developed for liver cancer and is currently undergoing Phase I clinical trial.

Development of biosimilars in China

Dr Scott Liu gave a comprehensive talk on the development of biosimilars in China. He started with a discussion on the medicine affordability issue in China where there is a large population of cancer patients, most of whom cannot afford the expensive mAb treatment. Although there is a steady improvement on China's healthcare, the ratio of Trastuzumab's price to the annual healthcare expense ratio in China, for example, is still over 9-fold greater than in the USA, resulting in a low human epidermal growth factor receptor 2 $(HER2)^{+}$-breast cancer treatment rate in China (<10%) [17]. Treatment rates for other popular mAbs are far from ideal in China as well: 18.9% for Rituxan, 0.02% for Humira, 1.9% for Avastin, and 1.1% for Erbitux (IMS data, 2017). This is primarily due to the affordability issue of mAb treatment.

Liu also criticized the lack of availability of biologics in China. During 2010–14, China's patients only had access to 6 newly approved cancer drugs from a total of 49 in the world, whereas patients in the USA had access to 41 of them [18]. In contrast to the poor accessibility to mAb treatment, China has a big cancer patient population. Lung cancer patients, for example, accounted for 37% of the world's incidence and liver cancer accounted for 52% of the world's incidence in 2015 [19]. This indicates that there are enormous unmet medical needs and a huge potential biosimilar market in China as evidenced in the flourishing trends in venture capital/private equity investment for biotech companies in China. From the prospect of government policy, reforms of China healthcare regulations have sped up since 2015. The new policies have encouraged innovation and competition resulting in increased accessibility and affordability of quality medicines to patients in China. Moreover, CNDA issued a series of guidelines and policies to speed up the development of innovates, generic drugs, and biosimilars. These efforts have paved the way for a booming age of biosimilars in China where the number of mAb biosimilar IND submissions surged to a historical peak in 2015. At present, clinical trials are highly centralized on the biosimilars of the top five hot targets on the market (bevacizumab, adalimumab, rituximab, cetuximab, and trastuzumab). Among them, there are 24 biosimilars under Phase I clinical trials, 23 in Phase II/III, and 43 just received IND approvals. Nearly each of the top five mAbs (except for trastuzumab) has 10–30 players in China. However, this market was once in chaos as most of the early filings before 2012 were not genuine biosimilars, which should have the same amino acid sequences as the originals, according to the biosimilar guidelines. Even today, the number of "genuine biosimilars" in China remains low. Only less than five true biosimilars for each popular mAb originators are in clinical development. Liu concluded that the limitation of R&D capability is the major hurdle for more players to jump into this game.

Liu further expounded on Henlius' leading position in biosimilar development in China. In this highly competitive market of biosimilars, where speed is the key, Henlius' first four biosimilar products (HLX01–HLX04) pioneer the competitive landscape in China. In 2018, HLX01 (Rituximab biosimilar) is expected to be approved for marketing and, therefore, is likely to be the first genuine biosimilar to be launched in China.

Liu then took HLX02 as a case study to elaborate the successful development of biosimilars in China. HLX02 is an anti-HER2 trastuzumab biosimilar. Its proposed action mode includes Trastuzumab-mediated ADCC and inhibition of the mitogen-activated protein kinase and Phosphatidylinositol-4,5-bisphosphate 3-kinase/alpha serine/threonine-protein kinase pathways, which leads to cell cycle arrest [20]. In the CMC perspective, the physical and chemical properties, biological activity, purity, and stability were assessed for HLX02. HLX02 has exactly the same amino acid sequences as Genentech's Herceptin as assessed with peptide mapping, mass spectrometry, and N- and C-terminal sequencing. Similar structures between the

biosimilar and originator were shown in circular dichroism spectra, and similar charge heterogeneity was shown in cation exchange chromatography. Highly similar glycan profile, though slightly increased in salicylic acid content for HLX02, was shown in comparison to trastuzumab. Moreover, HLX02 has highly similar anti-proliferation, ADCC activities, antigen binding, C1q binding, apoptosis activities, and Fc receptor binding to trastuzumab.

In the non-clinical study of HLX02, it showed similar potency and inhibitory effect with Herceptin in tested cyno monkey and mouse models. Toxicology with single- and multiple-dosed study in cyno monkey shows no significant change in physiological presentations. Thus, toxic characteristics of HLX02 were highly similar to those of Herceptin. In terms of clinical study, Phase I of HLX02 established the similarity in PK and safety profile compared to Herceptin. Phase III study is currently ongoing globally, which endorsed HLX02 as the first Trastuzumab biosimilar produced by a Chinese biotech company advancing into Phase III study in European Union (EU) regions.

Finally, Liu described that HLX04 (a bevacizumab biosimilar) has completed a randomized, double blind, parallel group and four-arm comparison Phase I trial in 208 healthy male participants over a period of 120 days. $AUC_{(0-\infty)}$ and C_{max} data between HLX04 group and three control groups (CN-source Avastin, US-source Avastin, and EU-source Avastin) are all highly similar. This demonstrates PK bioequivalence between HLX04 and Bevacizumab. HLX04 is currently under Phase III for metastatic colorectal cancer (the first of its kind in China).

AFTERNOON SESSION

Tumor-targeting antibodies

Dr Yang-Xin Fu from the Department of Pathology and Immunology at UT Southwestern discussed how tumor-targeting antibodies kill tumors. Using anti-HER2/neu antibody and anti-CD20 as examples, he showed that these antibodies control tumor regression in a T-cell and interferon (IFN)-dependent manner [21, 22]. It is likely that antibodies that block oncogenic receptors can trigger innate sensing. This leads to an increased cross-priming of T cells that is essential for tumor killing. He also discussed the mechanisms of anti-CD47 antibodies. Tumor cells that highly express CD47, which presents a "do not eat me" signal, are often more resistant to conventional treatment [23]. It is thought that anti-CD47 antibody that blocks signal-regulatory protein signaling by CD47 regresses tumors via macrophage-mediated phagocytosis. Interestingly, studies from Fu's group show that the therapeutic effect of anti-CD47 depends on type I IFN and that the STING pathway is essential for type I IFN production [24]. Dendritic cells, but not macrophages, respond to IFN for cross-priming mediated by anti-CD47 antibody [25]. Fu's studies suggest that tumor-targeting antibodies involve both innate and adaptive immune responses to control tumor killing [26]. Fu ended his presentation by raising an interesting point on the potential use of type I IFN. His group fused IFN with antibody in various ways. Current studies show that IFN antibody fusion proteins are able to induce CD8-dependent T-cell responses through an increased cross-priming [27]. Fu termed them next-generation antibodies and proposed that they are able to bring more IFN to tumor tissues to enhance immune responses and to help kill tumors that become antibody resistant.

Launch of *Antibody Therapeutics*, a new open access journal

Dr Mitchell Ho, from the US National Cancer Institute (NCI), is the founding Editor-in-Chief of *Antibody Therapeutics*, the official journal of CAS. Ho started by reviewing the progression of the launch of the new peer-reviewed journal. After more than 1 year of preparation, Oxford University Press was selected as its publisher, and the first issue was scheduled to be released from June to August. Unlike traditional journals that publish all of the papers of an issue at one time, *Antibody Therapeutics*, as an open access journal, will publish papers as they are accepted. Ho stated that the scope of this new journal is to serve as a forum to report the latest advances and challenges in the discovery, research, development, manufacturing, and methodology of therapeutic antibodies for the global scientific community as well as members of CAS. Its contents will include original research, reviews, methods, regulations and policies, news, interviews, and meeting highlights. Ho also introduced the editors and editorial board members of the journal and called for manuscript submissions. Ho's inaugural editorial appeared on 20 June 2018 [28].

In his talk, Ho overviewed the history of therapeutic antibody discovery and engineering. He believes that a major challenge in the field of antibody therapeutics is to develop effective therapies for solid tumors that are killing most cancer patients worldwide. For solid tumors we know little about what tumor antigens can be safely and effectively targeted to discriminate cancers from normal tissues. He then discussed what are potentially good tumor antigens in four categories: first, antigens are expressed on cancers and on non-essential normal tissues including mesothelin [29, 30] and glypican-3 [31, 32], two examples that his laboratory research has focused on for many years; second, shared antigens/mutations are unique to cancer (e.g., epidermal growth factor receptor variant III, KRAS mutations) [33, 34]; third, mutations/variants unique to each individual (e.g., patient-specific neoantigens) [35]; and fourth, protein conformations, splice variants, or glycosylations and other post-translational modifications unique to cancer. Near the end of his talk, Ho described the single-domain antibodies developed by his laboratory that are capable of reaching buried functional sites in tumor antigens and inhibiting cancer signaling [36–38]. Ho believes that single-domain antibodies that are easy to express and bind buried functional sites of the protein complexes that are involved in tumor progression are worth pursuing as a new class of cancer therapeutics.

Challenges in the clinical development of antibody-drug conjugates

In the next talk, Dr Yong-jiang Hei gave an introduction on the ADCs that are either approved or under trial.

Even though there have been a few ADCs approved and marketed in the USA, notable examples of which are Brentuximab vedotin (Adcetris), Trastuzumab-emtansine (T-DM1) (Kadcyla), Inotuzumab ozogamicin (Besponsa), and Gemtuzumab ozogamicin (Mylotarg), the failure rate of clinical trials remains high for ADCs (most stopped in Phase I or II). First, Hei introduced Trastuzumab-MCC-DM1 (T-DM1), which is composed of an anti-HER2 Trastuzumab, anti-mitotic toxin payload (DM1), and a stable and non-reducible thioether-linkage [39]. T-DM1 was approved based on the EMELIA trial, which showed improved progression-free survival (PFS) as well as overall survival (OS) versus lapatinib plus capecitabine in the second-line treatment of Her2-positive metastatic breast cancer (MBC). However, T-DM1 later suffered failures in the first-line MBC (MARIANNE trial). T-DM1 or T-DM1 plus pertuzumab failed to show an improvement in PFS when compared to trastuzumab plus taxane chemotherapy, which was the standard of care in the first-line treatment of MBC at the time the trial was conducted. In another Phase III trial known as GATSBY, T-DM1 was compared to chemotherapy in the second-line treatment of advanced gastric cancer and showed no difference in OS. In addition, the KRISTINE trial tested T-DM1 in early breast cancer in the neoadjuvant setting whereas the data show the pathological complete response rate was not improved when compared to the control group. There are two ongoing clinical trials on T-DM1: Kaitlin and Kathrine, the results of which are much anticipated.

Another ADC that Hei introduced is Brentuximab Vedotin (Adcetris). This ADC shows a high objective response rate in Phase II pivotal trial for Hodgkin's lymphoma patient population and PFS benefit in a Phase III study (ECHELON-1 study). In another study (AETHERA), brentuximab vedotin was used as consolidation therapy after autologous stem-cell therapy for Hodgkin's lymphoma patients and showed improved PFS, but the result showed no difference in OS. This is likely due to the crossover that means patients in both arms receive the investigational agent but patients in the control arm receive it at a later time point.

Hei also commented on newly approved ADCs: (1) Inotuzumab Ozogamicin showed improved rate of complete remission compared to the standard therapy for acute lymphoblastic leukemia. Improvement of PFS and OS were also observed. (2) Gemtuzumab ozogamicin (Mylotary), which was re-approved based on cumulative evidence and an investigator-initiated trial, after it was withdrawn from the US market in 2010. Hei remarked that a few lessons we could learn from ADC clinical trials are that people could make smart clinical design to improve probability of trial success, for example, a good management of toxicity in early phase trials, and careful patient selection.

Hei then shared his insights into the molecular design of ADCs that could improve their performance. He stressed the expertise on linker chemistry that could minimize payload release prior to reaching tumor cells. This in turn increases stability and half-life of ADCs and its chances of internalization. Payload is another key element. It should maximize tumor-killing efficacy while avoiding cross resistance and toxicity toward normal cells. Current clinical evidence indicates how integration of these attributes is critical to the success of the molecule.

Finally, Hei listed a few ADCs to watch in 2018: (1) IMMU-132, the BLA of which was submitted in May 2018, with potential approval for marketing in Q4 2018; (2) Rova T (originally developed by Stemcentrx and purchased by AbbVie); poor Phase II data blocked its accelerated approval; (3) DS-8201a, which has an outstanding linker stability and high cytotoxic agent potency; (4) nectin-4 ADC (enfortumab vedotin), which is under Phase I/II clinical trial and was granted breakthrough therapy designation; and (5) epithelial cell adhesion molecule-ADC, ongoing Phase III trial in bladder cancer.

Bio-innovation & global IP strategy—practical insights

Dr Teresa Lavoie from Fish & Richardson gave a talk on intellectual property (IP) strategy for bio-innovations and strategies for global patent filing. First, she shared a few examples of patent portfolios related to therapeutic antibodies of big biopharmaceutical companies. She then pointed out that this is a very competitive market. There have been reports on the $625 million settlement between Merck and Bristol-Mayer Squibb to resolve the PD-1 antibody patent litigation. For the IP strategy, she also used Humira, the best-selling mAb in the world, as an example. Though the patent for the composition expired in 2016, Humira is still well protected by a huge patent portfolio. For example, the indications, methods of treatment, formulations, and manufacturing methods, among others, are still under patent protection. Clearly, it is very expensive to build a huge portfolio around a biopharmaceutical, but it can be worth it if it can effectively protect the product by keeping competitors and biosimilar products off the market.

Lavoie further commented on recent changes of the US patent law that are significant for patenting in the biopharmaceutical field. Based on this, she gave a few suggestions on portfolio strategy from the perspective of a patent lawyer: (1) for products that bind to first-in-class targets, avoid premature filing of applications that do not include significant description of the product, as such an approach might reduce the ability to obtain a broad claim—aim to include significant description of exemplary antibodies, preferably described both by sequence and by functional parameters; and (2) for best-in-class products, focus on sequence and functional features, demonstrate an unexpected advantage over existing products (including, for example, new or improved biological activity, significant improvement in affinity, lower immunogenicity, better PK properties, better expression level, and better stability in solution). These unexpected advantages are necessary for overcoming the obviousness rejection in certain jurisdictions (e.g., in Europe).

PANEL DISCUSSION

During the past few years, more and more Chinese pharmaceutical companies have submitted or are in the process of preparing the submission of IND applications in the

USA. Filing an IND application is the first step in obtaining permission from the FDA to conduct clinical trials in the USA. As of 11 May 2018 at least 14 US INDs have been filed for therapeutic antibodies (including ADCs and single-domain antibodies) that were developed in China. In the panel discussion, the four panelists—Dr Daotian Fu, General Manager from Livzon MabPharm; Dr Scott Liu, CEO from Henlius Biopharmaceuticals; Dr Weikang Tao, CEO from Hengrui R&D Center; and Dr Wendy Yan, SVP from BeiGene—shared their experiences and insights regarding successful filing of INDs with the US FDA.

According to the panelists, many major Chinese biopharmaceutical companies choose to file IND applications in the USA as part of their global strategy. These Chinese biopharmaceutical companies have demonstrated strong interest in making inroads into the US market as a testament of their ability to win the endorsements and approvals by the US FDA and indeed have the ambition to use the USA as the first stepping stone to become a major player in this global drug market.

The US FDA applies the same regulatory and scientific standards to all regulatory applications submitted by sponsors, including Chinese companies. Many Chinese companies typically work through their US subsidiaries or contract agents based in the USA to directly interact with the FDA for their IND filings.

China recently joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use in pursuant of global harmonization of drug development standards and adopted a new guideline for clinical trials. The new guideline has made filing of IND applications in both the USA and in China at the same time much easier. However, difference in filing of INDs with CNDA and FDA still exists. Thus, if a company plans to submit an IND in the USA and in China at the same time, the company should plan in advance and be more strategic about the filing process.

In order to obtain the FDA's approval, many Chinese biopharmaceutical companies take advantage of a pre-IND meeting with the FDA. A pre-IND meeting gives the sponsor company the opportunity to introduce their product to the FDA and gain the FDA's concurrence with their clinical development plan. In order to ensure the success of the pre-IND meeting, the pharmaceutical company is expected to provide a solid package with all data collected to date (including data from pre-clinical animal studies).

Entering the US market is a long and complicated process. Aside from regulatory requirements, IP protection is also very important. There is a fair degree of uncertainty regarding how Chinese biopharmaceutical companies could address potential patent infringement issues (e.g., various PD-1 patents). While many Chinese pharmaceutical companies currently focus on advancing their molecules in clinical development in order to win the FDA's approval for marketing, a clear path forward is still needed to address these potential IP issues. Chinese biopharmaceutical companies should work more closely with reputable IP law firms in the USA that have experience in patent filing and can provide advice on US IP issues.

In summary, successful filing of an IND with the FDA is a critical step to move a product to the next stage of clinical development, and is one of the most important milestones on the protracted drug development process that leads to final approval, which on average can take around 12 years.

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