

Prediction of Aggregation Propensity and Monitoring of Aggregation of Antibody-Drug Conjugates (ADC) using ProteoStat® Reagents

ProteoStat® Protein Aggregation Standards (IgG) (ENZ-51039-KP002)

ProteoStat® Protein Aggregation Assay (ENZ-51023-KP002)

ProteoStat® Thermal Shift Stability Assay (ENZ-51027-K400)

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Abstract

Innate Pharma has developed an antibody-drug conjugate (ADC) coupling technology. The stability of unglycosylated SGN30 Q and S mutants coupled to the MMAE toxin by either one-step (SGN30 Q/S-linker-vcMMAE) or two-step technology (SGN30 Q/S-Linker-Click-Linker-vcMMAE) was compared to the first FDA-approved ADC, ADCETRIS®, and evaluated to validate the technology concept for clinical applications. The temperatures of aggregation, determined via the ProteoStat® Thermal Shift Assay, established the following aggregation propensity prediction ladder: SGN30 Q ADCs coupled with four MMAE toxins are less stable than SGN30 S ADCs coupled with only two MMAE toxins; ADCs coupled with lipophilic linkers are less stable than ADCs coupled with hydrophilic ones; and ADCETRIS® is more stable than a SGN30 Q ADC coupled to a lipophilic linker but less stable than a SGN30 Q ADC coupled with a hydrophilic one. An accelerated degradation study confirmed this hierarchy (with the exception of ADCETRIS® likely due to a higher fragmentation of its antibody element) and provided confirmation that the ProteoStat® Thermal Shift Assay is predictive of aggregation propensity for ADC products.

Introduction

Antibody-drug conjugates (ADCs) are monoclonal antibodies coupled to cytotoxic agents via stable linkers. ADCs travel to nearby target cells where the antibody binds to its antigen, expressed on the cell surface. Upon binding, the full ADC can be internalized by a process called receptor-mediated endocytosis. This process is followed by lysosomal degradation of ADC complexes, which ultimately leads to the release of the cytotoxic agent and apoptosis of the target cell. Drugs used in ADCs can be up to a thousand times more potent than current chemotherapeutics (1).

A well-known example of ADCs is Brentuximab vedotin which is more often found in the

literature by its trade name, ADCETRIS®. It was a recent ADC approved by the FDA for the treatment of relapsed or refractory cases of classical Hodgkin lymphoma. It is directed to CD30, which is expressed on the surface of malignant cells, and is linked to three to five units of the anti-mitotic and anti-tumor agent, monomethyl auristatin E (MMAE). In clinical trials, ADCETRIS® led to 40% partial and 34% complete remission in patients with refractory Hodgkin lymphoma. Tumor shrinkage was also observed in 94% of patients treated with ADCETRIS® (2). More recently, a second ADC called KADCYLA® was authorized for the treatment of HER2-positive metastatic breast cancer. This biotherapeutic consists of the HER2/neu interfering monoclonal

antibody, Trastuzumab (Herceptin[®]), linked to the cytotoxic agent, mertansine (DM1).

Successful development of an ADC requires optimization of several different components including the antibody, the potency of the cytotoxic drug, the stability of the linker, the site of conjugation and the stoichiometry of the resulting adducts. Typically, drugs can be linked to antibodies through cysteine or lysine residues resulting in ADCs with a heterogeneous number of drug molecules ranging from zero to 11 per antibody. Variations in drug distribution can have adverse effects on patient health. Antibodies without drugs are ineffective and compete with ADC for binding to the antigen-expressing cells whilst products with high DAR (Drug-to-Antibody Ratio) have less favorable pharmacokinetics resulting in less favorable *in vivo* efficacy (3, 4).

In recent years, this surge in interest and activity in the field of ADCs has led to the development of various technologies such as the addition of cysteine residues (5, 6), the incorporation of non-natural amino acids (7, 8), or the targeting of the carbohydrate moiety of an antibody (9, 10) to allow the generation of ADCs with a defined number of drugs per antibody without the prerequisite of genetically modifying the antibody sequence. Unfortunately, presence of unpaired reactive sulfhydryl groups, use of a huge excess of toxin or drug loss are some of the severe drawbacks associated with these chemical modification strategies.

Enzymatic modification of antibodies represents an interesting alternative. Transglutaminases are a family of enzymes capable of forming a covalent bond between the γ -carbonyl amid group of glutamines and the primary amine of lysines. They can also accept substrates other than lysine as the amine donor to modify proteins. For instance, microbial transglutaminase (MTGase) can specifically recognize Gln295 within the heavy chain of unglycosylated IgG1 and be employed as a substrate to produce ADCs (11, 12, 13). Using MTGase, Dennler and colleagues recently demonstrated that a one-step enzymatic or a two-step chemo-enzymatic approach was a reliable

strategy to generate homogenous ADCs from native monoclonal antibodies with a defined DAR of 2 (14).

Innate Pharma is a biopharmaceutical company developing first-in-class immunotherapy drugs for cancer and inflammatory diseases. Their focus is on a new class of therapeutic agents, consisting of monoclonal antibodies, aimed at regulatory checkpoints of the innate immune system. Their long history in the generation of these antibodies enabled them to diversify and develop a brand new ADC-coupling technology. The evaluation of the stability of these ADC products in aqueous liquid form was paramount in order to validate the technology concept for clinical applications. This study was designed to monitor the stability of ADC products of SGN30 S/Q aglycosylated mutants coupled to the MMAE toxin by one step (SGN30 S/Q-linker-vcMMAE) or two-step technology (SGN30 S/Q-Linker-Click-Linker-vcMMAE). The following results compare the aggregation propensity as well as the physical and chemical stability of these ADC products with ADCETRIS[®]. Data obtained with the ProteoStat[®] dye were correlated with results obtained with other analytical methods, such as size exclusion-high performance liquid chromatography (SE-HPLC) and liquid chromatography-mass spectrometry (LC-MS).

Materials and Methods

Materials

This study was designed to monitor the stability of ADC products of SGN30 aglycosylated mutants S and Q coupled to the MMAE toxin by two-steps technology (SGN30 S/Q-Linker-Click-Linker-vcMMAE) and one-step technology (SGN30 S/Q-linker-vcMMAE) as liquid aqueous form. The stability of the following ADC products was evaluated to validate the technology platform for clinical applications (Table 1).

Material	Type	Manufacturers
SGN30 S-sp1a-Click-sp2-vcMMAE	ADC Product	Innate Pharma
SGN30 Q-sp1a-Click-sp2-vcMMAE	ADC Product	Innate Pharma
SGN30 S-sp1b-Click-sp2-vcMMAE	ADC Product	Innate Pharma
SGN30 Q-sp1b-Click-sp2-vcMMAE	ADC Product	Innate Pharma
SGN30 S-sp1b-vcMMAE	ADC Product	Innate Pharma
SGN30 Q-sp1b-vcMMAE	ADC Product	Innate Pharma
ADCETRIS [®]	Reference Control	Seattle Genetics
ADCETRIS [®] DIL	Diluent	Innate Pharma

Table 1: ADC products and ADCETRIS[®]

The stability of these ADC products was compared to ADCETRIS[®], which was used as a reference control. In order to give comparable results, all the ADC products were formulated in the aqueous formulation of ADCETRIS[®] with an upgraded Polysorbate 80 concentration from 0.2 mg/ml (original ADCETRIS[®] formulation) to 1 mg/ml (Table 2).

Ingredients	Function	Quantity / Concentration
ADCETRIS [®] / ADC products	Active	5 mg/ml
Sodium citrate (dihydrate)	Buffer	5.60 mg/ml
Citric acid (monohydrate)	Buffer	0.21 mg/ml
Trehalose (dihydrate)	Isotonic agent	70 mg/ml
Polysorbate 80	Surfactant	1 mg/ml
Water for injection	Diluent	Qs.

Table 1: ADCETRIS[®] / ADC Products Formulation

The diluent ADCETRIS[®] DIL was an aqueous solution formulated like ADCETRIS[®], with a 1mg/ml concentration of Polysorbate 80 and without active product (Table 3).

Ingredients	Function	Quantity / Concentration
Sodium citrate (dihydrate)	Buffer	5.60 mg/ml
Citric acid (monohydrate)	Buffer	0.21 mg/ml
Trehalose (dihydrate)	Isotonic agent	70 mg/ml
Polysorbate 80	Surfactant	1 mg/ml
Water for injection	Diluent	Qs.

Table 2: ADCETRIS[®] DIL Formulation

ProteoStat[®] Protein Aggregation Standards (IgG) (ENZ-51039-KP002), ProteoStat[®] Protein Aggregation Assay (ENZ-51023-KP002) and ProteoStat[®] Thermal Shift Stability Assay (ENZ-51027-K400) were sourced from Enzo Life Sciences (Farmingdale, NY).

Methods

Preparation of ProteoStat[®] Protein Aggregation Standards

Sheep IgG (4 mg/ml) were incubated in low pH buffer (0.2M Glycine-HCl, pH 2.5) at 50°C overnight with shaking at 400 rpm in shaking heat block for 20 hours. 100% IgG aggregates were diluted with native sheep IgG monomers to a final concentration of 1mg/ml comprised of 12.5%, 6.25%, 3.13%, 1.56%, 0.78%, 0.39%, 0.20% and 0% aggregated IgG.

ProteoStat[®] Protein Aggregation Assay

ProteoStat[®] Protein Aggregation Assay (Enzo Life Sciences) was used to quantify and compare the soluble/non-soluble and non-covalent aggregates levels between the studied ADC products. ADC and ProteoStat Protein Aggregation Standards were mixed with ProteoStat[®] Detection Reagent (final dye dilution of 1:2000). After 15-minute incubation in the dark at room temperature, fluorescence levels were recorded using excitation/emission setting of 550/600 nm.

ProteoStat® Thermal Shift Stability Assay

The temperature of aggregation (T_{Agg}) was measured using ProteoStat® Thermal Shift Stability Assay (Enzo Life Sciences). ADC products with a 5 mg/ml initial concentration were diluted five times in ADCETRIS® DIL to obtain sample volumes of 180 μl at a concentration of 1.0 mg/ml. 50 μl of each sample was run in triplicate. 1000X ProteoStat® Thermal Shift Detection Reagent was diluted with 1X ProteoStat® Thermal Shift diluent (final dye dilution of 2X). LS55 spectrofluorometer (Perkin Elmer), fluorescence was read and recorded continuously while the temperature was ramping from 40°C to 100°C by 0.5°C step (5-second equilibrium step duration). The T_{Agg} was determined as the maximum point in the first derivative (slope) of the fluorescence curve (dF/dT°).

SE-HPLC

The analysis of ADC products and ADCETRIS® was performed with the Acquity UPLC from WATERS® with a BEH200 SEC 1.7 μm column. Single runs were performed for each sample and for each condition.

LC-MS

ADC products were eluted on a C18 RP-HPLC column and were identified using double detection by UV (DAD from Agilent Technologies) and ESI-Q-TOF (microTOF QII, Bruker). The analysis of ADC products was performed with the “intact antibody” method (C18 PLRP-S polymeric column). As the ADCETRIS® product is not compatible with the “intact antibody” method (the antibody is partially reduced), ADCETRIS® samples were analyzed with the “reduced antibody” method (C18 Aeris column) after N-deglycosylation with PNGase F. A standard deviation of ± 0.1 was established with this technique.

Sampling for physical stability study

The freeze/thaw (F/T) and shaking stresses were performed on ADC products and ADCETRIS® at their original concentration (5 mg/ml). Three

conditions were chosen to test physical stability: “No Stress”, “3F/T” (3 Freeze/Thaw cycles) and “Shaken”. 315 μl (equivalent to 1.575 mg) per product and per condition were required to perform the aggregation assay (300 μl), SE-HPLC (10 μl) and LC-MS (5 μl).

Sampling for chemical stability study

The 5°C and 40°C storage conditions were studied on ADC products and ADCETRIS® at their original concentration (5 mg/ml). Five time-points were used to test chemical stability: T0, one week, four weeks, 10 weeks and 24 weeks. At T0, the 5°C storage condition was tested and products quantities required for SE-HPLC (10 μl) and LC-MS (5 μl) testing were already included in the “No Stress” condition of the physical stability study. 15 μl (equivalent to 0.125 mg) per product, per condition and per time-point was required to perform SE-HPLC (10 μl) and LC-MS (5 μl).

Results

Aggregation propensity

Measurement of the temperature of aggregation (T_{Agg}) allows the classification of the ADC products according to their propensity for aggregation. In other words, low T_{Agg} values correlate with a higher aggregation propensity. Using the ProteoStat® dye for T_{Agg} determination, SGN30 Q products were shown to have a higher aggregation propensity than SGN30 S products (Fig. 1). SGN30 Q-Sp1a-Click-sp2-vcMMAE demonstrated a significantly higher aggregation propensity ($T_{\text{Agg}} = 64.82^\circ\text{C}$) than SGN30 Q-sp1b-vcMMAE ($T_{\text{Agg}} = 65.68^\circ\text{C}$) and SGN30 Q-Sp1b-Click-sp2-vc MMAE ($T_{\text{Agg}} = 65.85^\circ\text{C}$) (Fig. 1). The standard deviation between these last two ADC products was $\pm 0.3^\circ\text{C}$ and the difference in T_{Agg} was not significant. For the same reason, the difference in T_{Agg} was also not significant when comparing SGN30 S-Sp1a-Click-sp2-vcMMAE ($T_{\text{Agg}} = 67.97^\circ\text{C}$) and SGN30 S-Sp1b-Click-sp2-vc MMAE ($T_{\text{Agg}} = 67.93^\circ\text{C}$) (Fig. 1). On the other hand, SGN30 S-sp1b-vcMMAE had a significantly higher T_{Agg} than any other ADC product ($T_{\text{Agg}} = 69.38^\circ\text{C}$) (Fig.

1). Taking into account the standard deviation of T_{Agg} measurement ($\pm 0.3^\circ\text{C}$), ADCETRIS® has a similar propensity for aggregation ($T_{Agg} = 66.10^\circ\text{C}$) than the SGN30 Q candidate with the highest T_{Agg} , SGN30 Q-Sp1b-Click-sp2-vc MMAE ($T_{Agg} = 65.85^\circ\text{C}$).

Products	T_{Agg} ($^\circ\text{C}$)
SGN30 Q-sp1a-Click-sp2-vcMMAE	64.82
SGN30 Q-sp1b-vcMMAE	65.68
SGN30 Q-sp1b-Click-Sp2-vcMMAE	65.85
ADCETRIS	66.10
SGN30 S-sp1b-Click-sp2-vcMMAE	67.93
SGN30 S-sp1a-Click-sp2-vcMMAE	67.97
SGN30 S-sp1b-vcMMAE	69.38

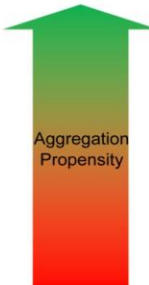


Figure 1: Aggregation propensity of ADC products developed by Innate Pharma and ADCETRIS®.

Physical stability

Three conditions were chosen to test the physical stability of these ADC products: “No Stress”, “3F/T” (three freeze/thaw cycles) and “Shaken”. The ProteoStat® dye demonstrated that freeze/thaw cycles and shaking had no significant impact on the amount of protein aggregates in solution when compared to control (Fig. 2A). SE-HPLC was used to measure the levels of soluble and covalent/non-covalent aggregates that could be generated following these stresses. Shaking had no impact on the percentages of soluble aggregates (Fig. 2B). Finally, LC-MS showed that freeze/thaw cycles and shaking did not significantly alter the integrity of the molecular structures of these ADC products and that the drug-antibody ratio remained the same regardless of the induced stress (Fig. 2C).

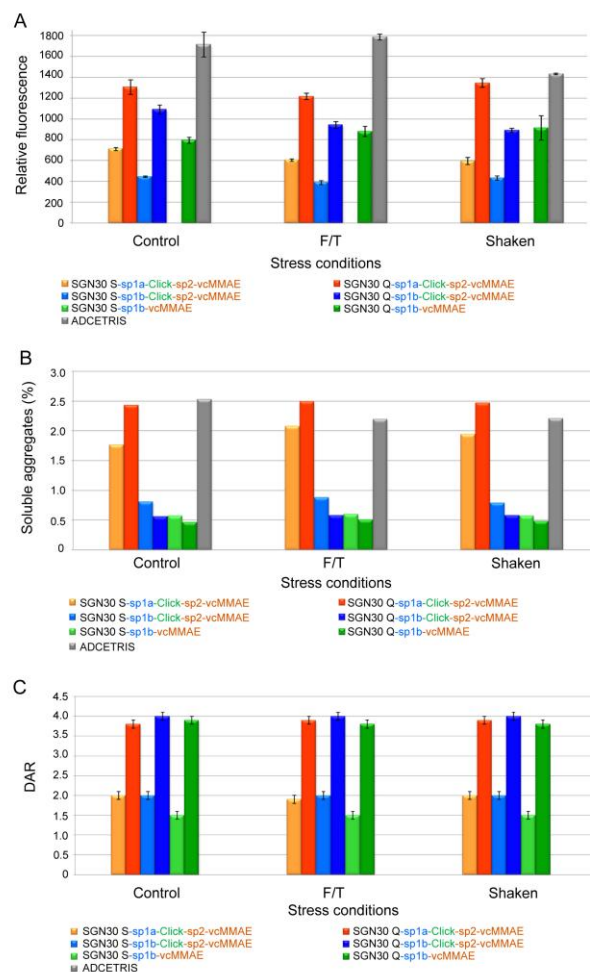


Figure 2: Measurement of aggregation, protein fragments and drug-antibody ratio (DAR) in ADC products upon the induction of a physical stress. Resistance to three freeze-thaw cycles (F/T) and shaking was determined using ProteoStat dye (A), SE-HPLC (B and C), and LC-MS (D) and compared to control.

Chemical stability

ADC products and ADCETRIS® were stored for six months in conditions of normal storage (5°C) or accelerated degradation (40°C). SE-HPLC, LC-MS and capillary SDS-PAGE were used to monitor their chemical stability after one week, four weeks, 10 weeks and 24 weeks.

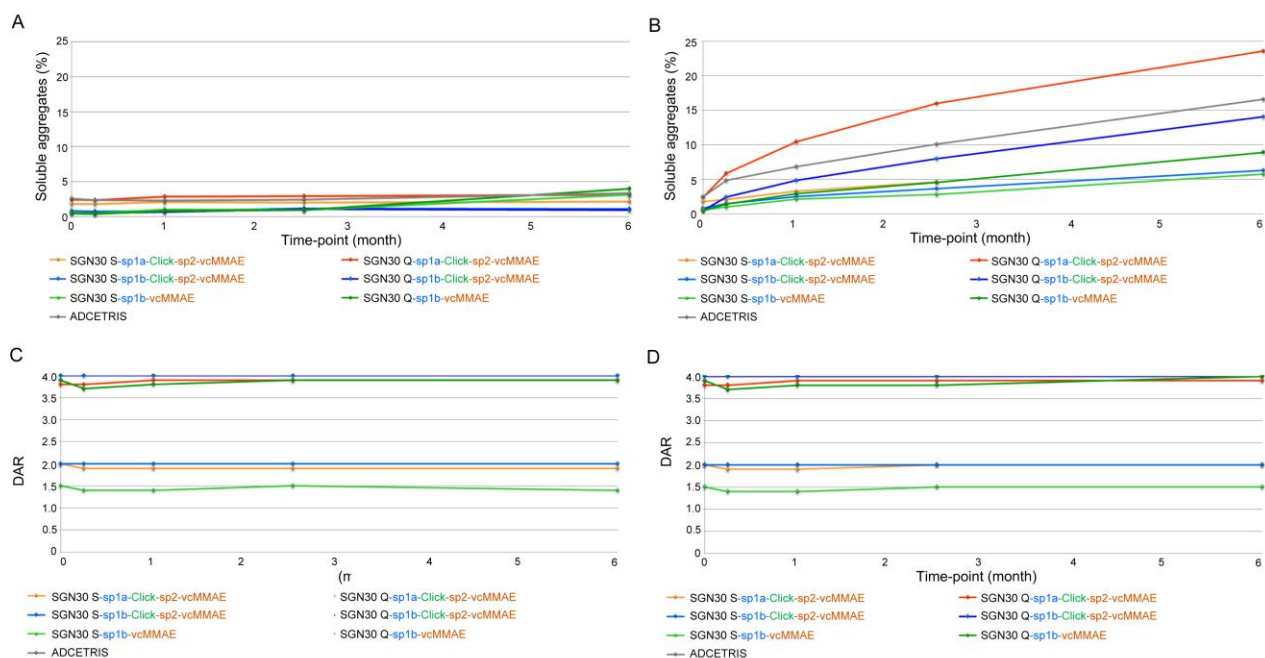


Figure 3: Measurement of aggregation, protein fragments and drug antibody ratio (DAR) in ADC products stored at 5°C or 40°C over a period of six months. Stability at 5°C (A and C) and 40°C (B and D) was determined using SE-HPLC (A and B) and LC-MS (C and D).

By SE-HPLC, a slight increase in the percentage of soluble aggregates was seen after 24 weeks at 5°C with SGN30 Q-sp1b-vcMMAE (from 0.46% to 3.96%) and SGN30 S-sp1b-vcMMAE (from 0.57% to 3.14%). The other ADC products were not affected by this treatment (Fig. 3A). On the other hand, storage at 40°C led to a more notable increase in the percentage of soluble aggregates, especially for SGN30 Q products that are coupled with four MMAE lipophilic toxins (e.g. up to 23.58% after six months) as compared to SGN30 S products with only two (Fig. 3B). For both SGN30 Q and S products, those with a Sp1a lipophilic linker showed the highest increase in the percentage of soluble aggregates over time (from 2.43% to 15.99% for SGN30 Q-Sp1a-Click-sp2-vcMMAE and from 1.77% to 4.60% for SGN30 S-Sp1a-Click-sp2-vcMMAE over 10 weeks) (Fig. 3B). Interestingly, ADCETRIS® had one of the highest increases in soluble aggregates over time (from 2.53% to 16.59% over 24 weeks). Finally, the DAR value remained the same over six months

regardless of the storage temperature, as demonstrated by LC-MS (Fig. 3C and 3D).

Discussion

Using the ProteoStat® Thermal Shift Stability Assay to measure T_{Agg} of ADC products, the results confirm the initial hypothesis that the greater the number of MMAE toxins coupled to the monoclonal antibody, the higher the aggregation propensity. SGN30 Q products were shown to have a higher aggregation propensity than SGN30 S products due to differences in the lipophilic nature of the MMAE toxin and the drug-antibody ratio (DAR) value of SGN30 Q and S products. SGN30 Q and S have a respective DAR value of 4 and 2 making SGN30 Q products more lipophilic and therefore more prone to aggregation. Moreover, SGN30 S-sp1b-vcMMAE showed a significantly higher T_{Agg} than any other ADC product tested. A one-step coupling reaction was used to generate this ADC and because of this, the target DAR value of 2 could not be reached. The

actual DAR value for this ADC is 1.5, indicating that it is less lipophilic since it contains less MMAE toxin molecules. Consequently, it is less prone to aggregation than other SGN30 S products with a DAR value of 2. This assay also validated the hypothesis that a more lipophilic linker between the monoclonal antibody and the toxin, leads to a higher aggregation propensity. Indeed, SGN30 Q-Sp1a-Click-sp2-vcMMAE, containing the most lipophilic linker, Sp1a, demonstrated a significantly higher aggregation propensity than other ADC products. However, this is only true for SGN30 Q products that are coupled with four linkers to four MMAE molecules. This variation is not significant for SGN30 S products as they are coupled with only two linkers to two MMAE molecules. Based solely on this technique, SGN30 Q-Sp1b-Click-sp2-vcMMAE and SGN30 S-Sp1b-Click-sp2-vcMMAE were deemed to be the most stable Q and S products. ADCETRIS® contains three to five molecules of MMAE toxins per antibody while SGN30 S products contain only two, hence a higher position of ADCETRIS® in the aggregation propensity ladder than SGN30 S products. In addition, SGN30 Q and S products are unglycosylated mutants while ADCETRIS® is glycosylated. Glycosylation is known to stabilize proteins and protect against aggregation, which can explain why ADCETRIS® is situated lower on the aggregation propensity ladder than SGN30 Q products despite having in average a similar number of MMAE toxins per antibody. However, ADCETRIS® had one of the highest increases in percentage of soluble aggregates observed in SE-HPLC over time and could be considered as the second worst candidate with SGN30 Q-Sp1a-Click-sp2-vcMMAE.

Physical stresses tested here had little to no impact on Innate Pharma's ADC products. Levels of aggregation and DAR values remained the same regardless of the induced stress. Both the protein element, created by Innate Pharma, and the link with the MMAE toxin were found to be stable when such physical pressures were applied. Results obtained using the ProteoStat® Protein

Aggregation Assay correlated with the data obtained by SE-HPLC and LC-MS.

Using normal storage conditions, the integrity of the protein element and the linkers used in the Innate Pharma's antibodies remained uncompromised over a period of six months. Both Innate Pharma's ADC products and ADCETRIS are stable over six months when stored at 5°C. Conversely, ADC products showed a significant increase in levels of aggregation using storage conditions of accelerated degradation, especially for SGN30 Q products and ADCETRIS®. These observations matched with the aggregation propensity predictions obtained with the ProteoStat® Thermal Shift Stability Assay. To summarize, the aggregation propensity increased with the number of MMAE toxins coupled to the antibody and the lipophilic character of the linker. Furthermore, the DAR value remained the same throughout the experiment, implying that the linkers developed by Innate Pharma are stable and robust even when stored at 40°C.

Conclusion

The aim of this work was to determine the stability of novel ADC products, created by Innate Pharma, as well as the suitability of the ProteoStat® dye for the analysis of the antibody-drug conjugates. The combination of aggregation propensity, along with physical and chemical stability studies highlighted several important facts about Innate Pharma's ADC coupling technology. Notably, the stability of an ADC is largely dependent on the number of toxins conjugated to the antibody and the lipophilic nature of the linkers used to conjugate these toxins. Application of the ProteoStat® dye resulted in the successful prediction of the propensity for aggregation of ADC products; thereby, validating Innate Pharma's coupling technology as an ideal platform for the development of stable, robust ADC products.

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