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The Simplest Pharmacokinetic Equation in ADC (Antibody Drug Conjugate) or PDC (Peptide Drug Conjugate) Research

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Abstract: ***It has been known that devising a suitable pharmacokinetic equation in ADC(Antibody Drug Conjugate) or PDC(Peptide Drug Conjugate) is exceptionally difficult as there are many factors which affect to distribution of this drug in vivo. Some address the three portions, antibody, linker, and drug can be differently behave in the bloodstream makes them difficult to monitor it. Also other issues like solubility, liphophilicity(cell penetration ability), molecular weight, ionization, enzyme degradation, renal clearance, aggregation, and poor adsorption are mentioned as a big barrier to devise a delicate pharmacokinetic equation. Herein, the most simple mathematic pharmacokinetic equation could be argued with the following three hypotheses in ADCs or PDCs development; all drugs are attached only the target cells not any other sites till their complete function, the speed of drug working is constant with time, and all cancer cells have equal shape, mass, and size placed in a list of petri dishes with same number in the same environment. Though in reality, these are not being kept, but knowing the parameters of pharmacokinetic equation could bring about a rough estimation of distribution when the synthesized drug is administrated to the selected animal at the stage of animal test. Thus, the additional modifications which reflect the real status could be developed from this backbone equation, Y= -(r/2p) X + r/2 (p = time(minutes), r/2 = demolished amount of cancer cells(gram)) in the near future. I expect many real problems like solubility, liphophilicity (cell penetration ability), molecular weight, ionization, enzyme degradation, renal clearance, aggregation, and poor adsorption, etc. could be discussed from this suggested equation model.***

Keywords: ***Antibody-Drug-Conjugate(ADC), Peptide-Drug-Conjugate(PDC), pharmacodynamic, IC_{50}, pharmacokinetic, distribution, bio-distribution.***

I. INTRODUCTION

Many articles deal with the difficulty to obtain a certain pharmacokinetic equation in ADC(Antibody-Drug Conjugate) development due to many reasons. Especially, the problem described as DAR(Drug Antibody Ratio) caused from the detachment of one portion in ADC which constitutes of three parts, antibody, drug, and linker makes pharmacokinetic expectation remarkably difficult. [1] [2] Also, other problems like solubility, liphophilicity(cell penetration ability), molecular weight, ionization, enzyme degradation, renal clearance, aggregation, and poor adsorption give more challenge to develop a suitable pharmacokinetic model with the effect of DAR.[3] [4] [5] [6] [7]This is also same in PDC(Peptide-Drug Conjugate) development. [8] Although this job seems quite challenging, there is the simplest method to obtain basic pharmacokinetic equation which reflects absorption, distribution, metabolism, and elimination with the following three hypotheses.

Let me start from the pharmacodynamic(how drug affects to our body.) first. This was known as IC_{50} test, the first after-synthesis work in the peptide synthesis laboratories.

Because of PDC's or ADC's targeting property only to the target cells, pharmacodynamics is not like normal drug transferred by the ligand or receptor to the needed organs. Because of homing peptide sequence in PDC or antibody in ADC, the drug is automatically delivered to the target cells, without any help of ligand or receptor. And it attaches on them until all of them are functioned to kill the cancer cells. [9] This also should be assumed in pharmacokinetics(how our body affects drug, ADME(absorption, distribution, metabolism, and elimination)).[10]

1. Actually, the first postulate is just simple, all are directing to the certain target cancer cells and attached onto them with 100 % efficiency till all of them function to kill the targets. There will be no amount circulating in blood vessels without any function or wasting as urine.

This hypothesis is consistent with the concept of DAR. [11] Because there would be no amount to circulate within blood vessels without function, the fraction or amount of un-conjugated drug would be zero. All drugs are connected to their corresponding antibodies. Simply, DAR is just 1.

And this postulate1 let the last categories of ADME be simple. Because it is attached onto targeted cells with 100 %, there will be no amount excreted as a form of urine, etc. So elimination is ignored. Also, there would be no amount to go inside liver and proceed 'metabolism' because 100% of ADC will go into target cells. So, metabolism is also not considered in this hypothesis. The absorption could be blood injection to block digestion of peptide sequences in PDC or ADC. [12]

The remaining problem is distribution. We want to obtain a simple distribution equation which is just became pharmacokinetic equation. [13]

2. Let me just allow to hypothesize working speed of drug(consumption of drug + growth of cancer cell in all three dimentional directions) as a zero order equation according to the time passage.

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So this graph could be drawn in a two dimensional plane with the time(horizontal) axis and reacted mass of cancers(vertical) axis which means the cancer cells are demolished in a regular speed (Fig. 1).

To obtain the graph in hypothesis 2, the reaction time(p minutes) and the mass of cancers(r g when initially, and r/2 g when finally, so the reacted amount is r/2 g in IC_{50}(half maximal Inhibition Concentration) experiment) should be measured. Because this is possible, this most simple linear equation could be suggested as a distribution model(or even pharmacokinetic equation) in ADC(or PDC) research. (See 'Result and Discussion' Section.)

3. The third postulate is all used petri dishes during these experiments which contain cancer cells are same. The number of cells in each petri dish is same and the mass is also same. The environment in each petri dish should be kept in the same condition with each other. Also, in each petri dish, the cancer cells have the same weight, same size and shape each other. So, by conducting 'cell counting' method [14] the whole mass of cancer cells in one petri dish can be known.

In reality these cannot be kept as there would be some ADCs(PDCs) which circulate within blood vessels without correct function and after this useless circulation the drug conjugates could be excreted as a form of urine. Also, the speed of function could be varied according to the location of cancer and the irregular shape of cancer in each person. Actually, in more specific, the second hypothesis means the speed of drug consumption+ the growing speed of cancer in all three dimensional direction should be equal one value during certain time interval. And, as you imagine this is not easy. Furthermore, in the third hypothesis, in every petri dish, the density of cell cultured would be different each other and in one specific petri dish, of course, the size, shape, and mass are not consistent so the variation cannot be ignorable. However, even though this crucial disadvantages when we postulate like above the most simple and beautiful equation is obtained like the following.

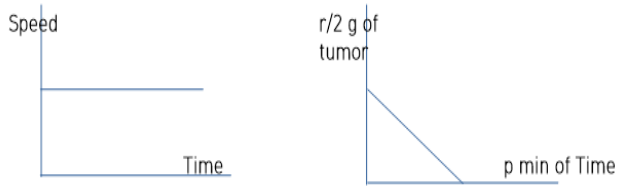

Fig. 1. Hypothesis 2.

II. METHOD

A. Experimental plan

In most peptide synthesis laboratories just right after purification of synthesized ADCs(PDCs) the afterwork of synthesis is proceeded altogether. This is generally IC_{50} check. They cultured a certain type of cancers in the petri dish and these cancer cells are exposed to synthesized ADCs or PDCs. After some times, or just several days(as the speed of working is not the same in each petri dish, some react very slowly so much more time is necessary to know the correct IC_{50} value) the cancer cell is reduced with the help of ADCs or PDCs and the scientist checks the amount of reduction being caused by their synthesized drug conjugates(ADCs or PDCs) to find the IC_{50} value. Actually, the problem is in this procedure. Here, I will suggest the second experiment which must be conducted together with this IC_{50} check experiment. Ideally, the definition of IC_{50} is the amount of ADCs (or PDCs) which affects only half amount of survival when this is administered in the cancer cells. To know the exact amount of IC_{50} values, the different amount of ADCs (or PDCs) should be administered in several petri dishes which contain the same mass of cancer cells (Fig. 2).

When the time is passed enough, (let me allow the time should be infinite as the speed of function of drug is not known actually, but we made an assumption in hypothesis 2 this is just one specific value.) only one petri dish shows 50 % of survivals. There will be other survival rates like the Fig. 3. The administered amount of ADCs (or PDCs) to the 50 % survival petri dish is the IC_{50} value. Let me define this amount is q g.

Next, the same experiment only with q g of ADCs (or PDCs) and one petri dish which has the same condition with the above experiment should be repeated one more time. And in this moment, the time (let me define this is p minutes.) must be checked (Fig.4).

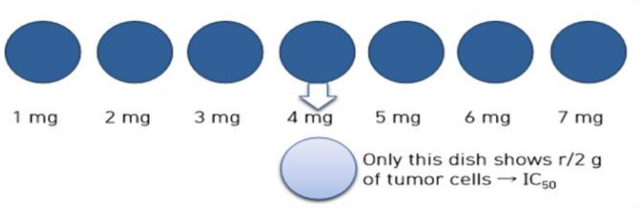

Fig. 2. The IC_{50} Value.

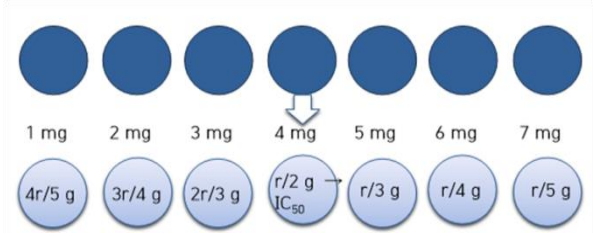

Fig. 3. Possible result of IC50 experiment.

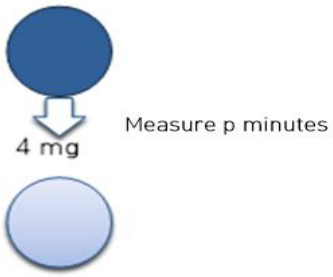

Fig. 4. Measuring p minutes.

Now, the IC_{50} value (q g of ADCs(PDCs)) and the time of this IC_{50} value (p minutes) are obtained. What we need to obtain a linear pharmacokinetic equation according to hypothesis 2 is just the r/2 g of cancer cells. (Let me define the mass of cancer cells in one whole petri dish is r g.

The demolished amount is then r/2 g. Hypothesis 3 says that all the petri dishes used in the above experiments are same.)
Luckily, this could be measured by hand. The popular cell counting technique [14] is the answer.
Before doing this experiment the whole cell numbers can be counted or after the experiment the remaining half amount can be also counted. If the third hypothesis is applied in this moment, every cell has the same mass, shape, and size. So the counting number can be just multiplied with the one cell's mass which must be measured in manual.
Or, simply, the total amount of one petri dish which contains the cultured cancer cells can be directly measured via delicate balance and after that the empty petri dish with other lysogeny broth can be measured separately. The deduction of these two is the total mass of cancer cells, r g.
(Though in this paper, the solid cancer cells are cultured in a liquid medium inside petri dishes, and analyzed by measuring the weight of one of the cells and multiplying the counted number of cells, the other solution medium is also possible with the similar logic with modified version of hypothesis 3 (the solution is homogeneous and each cell has the same shape, size, and weight. Therefore, the absorbance or OD(Optical Density) value is proportional with the number of cancer cells in that medium.) by measuring OD value or absorbance.)
So Fig. 1 is obtained. r/2 g of cancer cells are demolished by q g of ADCs or PDCs (IC_{50} values) during p minutes of time. This is the so-called pharmacokinetic equation in drug development which explains how our bodies functions to the administered drug. The measured IC_{50} value, pharmacodynamic value represents how the drug functions to our bodies.

III. RESULT AND DISCUSSION

PDCs which are synthesized in many laboratories are used to the measurement of IC_{50} value which represents cell cytotoxicity. This pharmacodynamic value is well reported with the synthesis yield. [15] However, none of the recently performed PDC synthesis as well as IC_{50} check is not being conducted together this suggested pharmacokinetic experiment. So here is the purpose of this article to be published. Furthermore, the obtained Fig.1 could be converted to the different form. The meaning of Fig.1 is r/2 g of cancer cells are killed with the effect of q g of ADCs or PDCs during p minutes of time. If the y axis is changed to the q gram of made drug, as the drug working speed(consumption of drug + growth of cancer cells in three dimentional directions) is constant (Fig.1), in case of the latter, growth of cancer cell in all directions is certain value, then automatically the consumption speed of drug will be also certain one specific value. That leads the concentration of remaining drug or amount of drug in human body would be linearly decreasing according to the time flow(Fig.5). More specific, the administered drug is only in the cancer cell surface with the help of hypothesis 1 and as it is regularly consumed with a certain speed (hypothesis 2 and the case of constant rate of growth cancer) the amount or concentration of remaining drug would be linearly decreased with time flow. To sum up, the regular speed of working drug makes both results; 1.the regularly working drug diminishes cancer cells regularly (Fig.1) and 2. the regular speed of drug consumption(not drug working speed) causes the distribution is linearly decreasing (Fig.5).

IV. CONCLUSION

This Like the above explanations this method has several crucial drawbacks which cannot be met in real situations. Though this could be regarded as a funny trial to some pharmacists who always dream to devise a delicate pharmacokinetic equation, the logics that are mentioned in this paper is not nonsense. So I hope this simplest and most beautiful equation could help the struggling scientists in worldwide scale is the reason why I publish this article.
Finally, many problems like solubility, liphophilicity(cell penetration ability), molecular weight, ionization, enzyme degradation, renal clearance, aggregation, and poor adsorption should be discussed modifying this suggested equation. [3] (In fact, all those effects are cleared in this paper because of hypothesis 1. Solubility: Drug conjugates are dissolved very well in blood stream so all are directing to the target cells. There is no amount not to be delivered; Liphophilicity: All drug conjugates pass cell membrane. There is no amount to be stuck in the cell membrane; Molecular weight: All drug conjugates are not so heavy to be transferred via blood stream. There is no amount to be remained without transfer; Ionization: All drug conjugates are not ionized so there is no interaction with other unexpected molecules in the body. There is no amount to be wasted via ion interaction; Enzyme degradation: All drug conjugates are not be consumed by unknown enzyme. There is no amount to be lost via enzyme degradation; Renal clearance: With hypothesis 1, excretion as urine is 0; Aggregation: All drug conjugates are not aggregated each other so there is no amount not working at the target cells; Poor adsorption: Hypothesis 1 says all are attached onto targeted cell surface.) Also the problem caused from the individual difference of solid tumors or targeted cells should be discussed for modification of this equation because the speed of drug working would be different in another patient. [16]

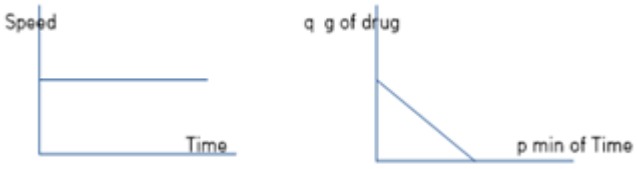

Fig. 5 Pharmacokinetic equation about amount (concentration) of drug

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REFERENCES

1. Heather E Vezina, M.onette Cotreau, Tae H. Han, Manish Gupta, Antibody Drug Conjugate as Cancer Therapeutics: Past, Present and Future, J Clin Pharmacol, 2017, 57(S10), p.11-25 [CrossRef]
2. Leonid Gibiansky, Ekaterina Gibiansky, Simulation Investigation of the Integrated Pharmacokinetic Model for Antibody-Drug-Conjugates, QuantPharm LLC, North Potomac, MD, https://www.quantpharm.com/pdf_files/ACoP_2019_ADC_Poster.pdf
3. Antoine Henninot, James C. Collins, and John M. Nuss, The Current State of Peptide Drug Discovery: Back to the Future?, Med. Chem. 2018;61: 1382−1414, p.1393,1399-1401 [CrossRef]
4. Isabel Figueroa, et al., Prediction of non-linear pharmacokinetics in humans of an antibody-drug conjugate(ADC) when evaluation of higher doses in animals is limited by tolerability : Case study with an anti-CD33 ADC, mAbs, 2018, 10:5, p.738-750 [CrossRef]
5. Yue Huang, et al., Characterization of Antibody-Drug Conjugate Pharmacokinetics and in Vivo Biotransformation Using Quantitative Intact LC-HRMS and Surrogate Analyte LC-MRM, Anal. Chem., 2021, 93, p.6135-6144 [CrossRef]
6. Esteban Cruz, Veysel Kayser, Monoclonal Antibody Therapy of Solid Tumors: clinical limitations and novel strategies to enhance treatment efficacy, Biologics, 2019, 1;13:33-51 [CrossRef]
7. Amrita V.Kamath, Suhasini Iyer, Challenges and advances in the assessment of the disposition of antibody-drug conjugates, Biopharmaceutics & Drug Disposition,2016;37:66-74, p.69 [CrossRef]
8. Bethany M Cooper, Jessica Iegre, Daniel H. O' Donovan, Maria Olwegard Halvarsson, David R. Spring, Peptides as a Platform for Targeted Therapeutics for Cancer : Peptide – Drug Conjugates (PDCs), Royal Society of Chemistry, 2021, p.1480 – 1482, 1486 [CrossRef]
9. Michael J. Neal, Medical Pharmacology at a Glance, Seventh Edition, Oxford, John Wiley & Sons, Ltd. 2012, p.10-11
10. Michael J. Neal, Medical Pharmacology at a Glance, Seventh Edition, Oxford, John Wiley & Sons, Ltd. 2012, p.12-15
11. Louisette Basa, Drug-to-Antibody Ratio (DAR) and Drug Load Distribution by LC-ESI-MS, Antibody Drug Conjugates. Methods in Molecular Biology; L. Dury(Ed.); Humana Press, 2013, 1045, p.285-293 [CrossRef]
12. Bethany M Cooper, Jessica Iegre, Daniel H. O' Donovan, Maria Olwegard Halvarsson, David R. Spring, Peptides as a Platform for Targeted Therapeutics for Cancer : Peptide – Drug Conjugates (PDCs), Royal Society of Chemistry, 2021, 50, p.1481,1491 [CrossRef]
13. Chang D-K, Lin C-T, Wu C-H, Wu H-C, A novel peptide enhances therapeutic efficacy of liposomal anti-cancer drugs in mice models of human lung cancer, PLos One, 2009, 4(1): e4147, p.5 [CrossRef]
14. Cell counting using a hemocytometer, www.sigmaaldrich.com/technical-documents/protocols/biology/cell-quantification.html
15. Mona Alas, Azam Saghaeidehkordi, K.Kaur, Peptide-Drug Conjugates with Different Linkers for Cancer Therapy, J Med Chem., 2021, 14; 64(1), p.216-232 [CrossRef]
16. Antoine Deslandes, Comparative clinical pharmacokinetics of antibody-drug conjugates in first-in-human Phase 1 studies, mAbs, 2014 6:4, p.859-870 [CrossRef]

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Heejin Park was edudcated both in chemistry and biology(bio-engineering) at the bachelor level in South Korea made her to write this broaden realm of master degree thesis in Hungary. Her master degree thesis includes from the very basic concept of cancer to the application of synthesized homing peptides-anticancer drug conjugates which is the combination of medicinal, biological and chemical realm of studies. This article is the aftermath of synthesis in her degree thesis as written in acknowledgment. She has a plan to do PhD level of study in the near future. E-mails: fourleavee555@yahoo.com

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