NEWS

Consideration with "Intratumoral gene therapy versus intravenous gene therapy for distant metastasis control with DDMC non-viral vector–p53"

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A Baliaka et al. has reported below: "Lung cancer has not yet been resolved by new treatments. New topical targeting is a way to enhance treatment and reduce side effects. Intratumoral gene therapy is a method of topical treatment that can be used either in early-stage lung cancer before surgery or in advanced stages as palliative care. There is also an increasing demand for efficient gene transfection to target local cancer tissues using novel non-viral vectors while at the same time protecting normal tissues. In this study, C57BL/6 mice inoculated with the LL/2 cell line were divided into three groups: (a) control, (b) intravenous, and (c) intratumoral gene therapy. The novel 2-diethylaminoethyl-dextran methyl methacrylate copolymer non-viral vector (DDMC) (Ryujyu Science Corporation) was the first to conjugated to Addgene's plasmid pSicop53. The purpose of this study was to evaluate the safety and efficacy of targeted gene therapy in the Lewis lung cancer model. Indeed, different dosing regimens have different pharmacokinetics, but intratumoral administration has shown increased survival and decreased distant metastases. Intratumoral gene therapy can be considered as an efficient topical treatment for lung cancer. The average survival rate was expressed as follows from the viewpoint of efficiency: intratumor (17.4 days)> intravenous (12.6 days)> control (12.6 days)."

However, in the table of mice survival by A Baliaka et al. [1], Smirnov-Grubbs test [2] are done for Outlier detected a normal distribution as shown in Table 1. In this paper, it may be better to delete 4 samples of 3 and 7 survival days of both control and intravenous, statistically.

The ANOVA-Test for three groups are also done as Table 2, and good results are obtained ($P < 0.05$). The mean survival should be displayed as intratumoral (17.3 days)> intravenous(15.6 days) >control(13.2 days) after correction.

It may be depended on rapid intravenous injection that four mice died earlier after administration containing control. It is difficult for the viral vectors to select multiple-dose because of neutralized antibody with its immunogenicity such as AAV vector. The lipofection reagents are also not suitable to transfect in-vivo for its unstable properties.

Results show that the complexes by DDMC/p53 have an excellent anticancer activity for systemic administration by depending on EPR effect [3] and avoidance of RES [4, 5].

Polymer-based drug delivery systems (DDS) are widely used as carriers for targeted drug delivery due to promoting EPR effect and avoidance of RES.

DDS technology by transfection reagents (DDMC) [6] in vivo compose of

1. A long retention time in body by control of renal excretion.
2. An antigenicity reducing by reticuloendothelial system (RES).
3. A high protect facility for DNase or RNase degradation.
4. A drug to a target effectively by the enhanced permeation and retention (EPR) effect.

DDMC will become the most important DDS technology after the COVID-19 pandemic.

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Table 1. Statistical evaluation of outliers in data analysis (Smirnov-Grubbs test).

(a) Control									
7	**10**	**10**	**10**	**14**	**14**	**14**	**14**	**16**	**17**
# of values	**Max**	**Min**	**Mean**	**STD**					
10	17	7	12.6	3.169297					
	For Max	For Min							
T	1.38832	1.766953							
t	1.580527	2.24							
p	9.236792	9.722873							
	0.950006								
For Min, as <9.722872762, 7 is outlier value.									
Modified control									
	10	10	10	14	14	14	14	16	17
# of values	Max	Min	Mean	STD					
9	17	10	13.22222	2.635231					
	For Max	For Min							
T	1.433566	1.222747							
t	1.686798	1.365124							
p	8.390236	8.034907							
	1.044223								
Not a significant outlier ($P < 0.05$).									
(b) Intravenous									
3	**7**	**7**	**15**	**15**	**15**	**16**	**16**	**16**	**16**
# of values	**Max**	**Min**	**Mean**	**STD**					
10	16	3	12.6	4.926121					
	For Max	For Min							
T	0.690198	1.948795							
t	0.70703	2.657455							
p	7.501895	9.855403							
	0.761196								
For Min, as <9.855403041, 3,7, and 7 are outlier value.									
Modified intravenous									
			15	15	15	16	16	16	16
# of values	Max	Min	Mean	STD					
7	16	15	15.57143	0.534522					
	For Max	For Min							
T	0.801784	1.069045							
t	0.845154	1.195229							
p	5.471942	6.000432							
	0.911925								
Not a significant outlier ($P < 0.05$).									
(c) Intatumoral									
13	**13**	**15**	**15**	**17**	**17**	**20**	**21**	**21**	**21**
# of values	**Max**	**Min**	**Mean**	**STD**					
10	21	13	17.3	3.267687					
	For Max	For Min							
T	1.132299	1.315916							
t	1.226538	1.474888							
p	8.725656	9.107618							
	0.958061								
Not a significant outlier ($P < 0.05$).									

1 (b) group is done three times trial till not a significant outlier ($P < 0.05$).
2 They are deleted four samples of three and seven survival days, statistically.
The Smirnov-Grubbs method, which is one of the statistical methods of the rejection of outliers, tried to find outliers. The analysis indicated that an additional one data for (a) and three data for (b) were significant outliers.
3 (c) group does not contain a significant outlier ($P < 0.05$).

Table 2. ANOVA.

Summary						
	Sample	**Total**	**Mean**	**Variance**		
(a)	9	119	13.22222	6.944444		
(b)	7	109	15.57143	0.285714		
(c)	10	173	17.3	10.67778		
ANOVA						
Variable factors	**Variation**	**df (degrees of freedom)**	**Variance**	**Observed variance ratio**	***P* value**	**F boundary value**
Inter group	78.97631258	2	39.48815629	5.921813488	0.008422704	3.422130135
Intra group	153.3698413	23	6.668253968			
Total	232.3461538	25				

1. Data were analyzed using an one-way ANOVA.
2. Group (a), (b) and (c) are differ significantly ($P < 0.05$).
3. The mean survival was displayed as (c) intratumoral (17.3 days)> (b) intravenous(15.6 days)> (a) control (13.2 days) after correction.

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AUTHOR CONTRIBUTIONS

YO, PZ, RJ, MO, NK, and YE designed research. YO, PZ, RJ, MO, NK, and YE performed research. YO, PZ, RJ, MO, and YE analyzed the data. YO, PZ, RJ, MO, and YE wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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