Published in final edited form as:

Eur J Cancer. 2009 November ; 45(17): 3098–3103. doi:10.1016/j.ejca.2009.09.007.

The ratio of maximum percent tumor accumulations of the pretargeting agent and the radiolabeled effector is independent of tumor size

Guozheng Liu, Shuping Dou, Minmin Liang, Xiangji Chen, Mary Rusckowski, and Donald J. Hnatowich

Division of Nuclear medicine, University of Massachusetts Medical School, Worcester, MA 01655

Abstract

Our previous studies have indicated that the optimal dosage ratio of pretargeting antibody to effector is proportional to their maximum percent tumor accumulations (MPTAs). This study quantitatively describes how both MPTAs and their ratio change with tumor size, to simplify pretargeting optimization when tumor size varies. The CC49 antibody dosages below saturation of the tumor antigen level were first examined for the LS174T tumor mouse model. Then the MPTAs of the antibody in mice bearing tumors of different size were determined, always at antibody dosages below antigen saturation. Historical data from this laboratory were used to collect the MPTAs of the ^{99m}Tc -cMORF effector for different tumor sizes, always at effector dosages below that required to saturate the MORF in tumor. The MPTAs vs tumor sizes for both the antibody and the effector were fitted non-linearly. The best fit of the antibody MPTA (Y_{antibody}) with tumor size (x) in grams was $Y_{\text{antibody}} = 19.00 x^{-0.65}$ while that for the effector was $Y_{\text{effector}} = 4.51 x^{-0.66}$. Thus, even though the MPTAs of both vary with tumor size, the ratio ($Y_{\text{antibody}}/Y_{\text{effector}}$) is a constant at 4.21. In conclusion, the MPTA ratio of the antibody to the effector was found to be constant with tumor size, an observation that will simplify pretargeting optimization because remeasurement of the optimum dosage ratio for different tumor sizes can be avoided. Theoretical considerations also suggest that this relationship may be universal for alternative antibody/effector pairs and for different target models, but this must be experimentally confirmed.

Keywords

Tumor accumulation; Tumor size; Pretargeting; Effector; Optimization

Introduction

That tumor size has an influence on tumor accumulation of antibodies has been recognized for more than 20 years (1). Although tumor accumulation in %ID/g usually decreases with increasing size (1,2), this relationship is not without exceptions (3,4). The tumor size influence

2. Reprint request may be sent to: Guozheng Liu, Ph D, Phone: (508) 856-1958; Fax: (508) 856-6363, guozheng.liu@umassmed.edu, Division of Nuclear Medicine, Department of Radiology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655-0243.

Conflict of Interest Statement: None declared

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

on the accumulation of tumor targeting agent is very important both pre-clinically and clinically, because tumor size differences are common in animal tumor model and especially in patients.

Unlike conventional tumor direct-targeting with radiolabeled antibodies, optimization of dosage and timing is more complicated in tumor pretargeting and the influence of tumor size is required to be considered. In conventional direct-targeting, as long as the antibody dosage does not exceed that required to saturate the tumor antigens and is nontoxic, any dosage may be used (5-8). Instead of only one dosage to consider, pretargeting requires selecting two dosages and one interval (even more if imaging process or clearing agents are involved). Optimization requires that the dosages of antibody and effector be selected to provide the maximum percent tumor accumulation (MPTA) of the effector and the highest tumor/non-tumor ratios of the effector (9).

Previously, we established experimentally that optimal pretargeting will be achieved when the dosage of antibody (D_{antibody}) is equal to or below that required to saturate the antigen levels in tumor and the dosage of the effector (D_{effector}) is just equal to that required to saturate the pretargeting antibody in tumor (9). Under these conditions, both the antibody and effector are at their MPTAs and the tumor to normal tissue ratios are at their maximum values. For any given tumor, the optimal dosages and their MPTAs are related by the equation below, which represents the quantitative relationship under the conditions mentioned above (9) and shows that the optimal dosage ratio is proportional to the ratio of the MPTAs of the antibody to the effector.

$$\text{Optimal } \frac{D_{\text{effector}}}{D_{\text{antibody}}} = \frac{MW_{\text{effector}} \times gpm \times \text{accessibility}}{MW_{\text{antibody}}} \times \frac{MPTA_{\text{antibody}}}{MPTA_{\text{effector}}}$$

Where MW_{antibody} and MW_{effector} are the molecular weights of the antibody and effector; gpm is the average number of the effector-binding groups on each antibody; and the accessibility is the fraction of the antibody in tumor still accessible to the effector at the time of effector administration. As the equation makes clear, the optimum dosage ratio depends upon the ratio of the MPTAs of antibody and effector. Since the two MPTAs vary differently with tumor size, selecting the optimum dosage ratio will be difficult unless it can be shown that the ratio of the MPTAs is a constant. If so, optimization of the dosage ratio will be simplified since the optimal dosage ratio obtained from one tumor size will then be applicable to all others.

We have now examined how both the MPTAs of the MORF-CC49 antibody and labeled cMORF effector as well as their ratio vary with the size of LS174T tumors in nude mice. The pharmacokinetics of the CC49 antibody was reexamined (by assuming that the biodistribution of ^{111}In -DTPA-CC49 is sufficiently similar to that of native CC49 and MORF-CC49) to select a time post administration when tumor accumulation was essentially completed. The antibody dosage was then varied within a large range and the tumor accumulation measured at the selected time (48 h) post administration. By demonstrating a linear increase in absolute tumor accumulation with increasing antibody dosage, it was possible to select with confidence a dosage that was greatly below that required to saturate the antigen level in the tumor. Thereafter, the antibody MPTAs were all measured for dosage below saturation in mice with different size tumors. In the case of the cMORF effector, the results of multiple historical pretargeting studies from this laboratory were used to provide a series of effector MPTAs and tumor sizes at sacrifice. These data, both published and unpublished (listed in the appendix) were obtained in the same LS174T tumor mouse model administered either the MORF-CC49 or MORF-

MN14 antibody. In all cases, the effector dosages were below the MORF saturating dosage established earlier. Thereafter, both the MPTAs of the antibody and effector vs. tumor size were fitted and their MPTA ratio calculated.

Material and Methods

The CC49 antibody was custom produced by Strategic Biosolutions (Ramona, CA) from the CC49 hybridoma. Labeling of the antibody with ^{111}In was as previously described (4,10). The base sequences of MORF and its complement (cMORF) were as previously described (11). The p-SCN-Benzyl-DTPA was from Macrocyclics (Dallas, TX). The P-4 resin (Bio-Gel P-4 Gel, medium) was purchased from Bio-Rad Laboratories (Hercules, CA) and the Sephadex G-100 resin was from Pharmacia Biotech (Uppsala, Sweden). The $^{111}\text{InCl}_3$ was from Perkin Elmer Life Science Inc (Boston, MA). All other chemicals were reagent grade and used without purification.

Biodistribution and tumor accumulation of ^{111}In labeled CC49

All animal studies were performed with the approval of the Institutional Animal Care and Use Committee of UMass Medical School. For tumor induction, 10^6 LS174T colon cancer cells were injected into the left thigh of each Swiss NIH nude mouse (Taconic Farms, Germantown, NY). After injection of radiolabeled antibody, the mice were sacrificed by exsanguination via heart puncture under halothane anesthesia. For biodistribution, samples of blood and other organs were removed, weighed, and counted in a NaI(Tl) well counter (Cobra II automatic gamma counter, Packard Instrument Company, CT) along with a standard of the injectate as previously described (11). Blood was assumed to constitute 7% of body weight.

Three animal studies were performed. First, the pharmacokinetics of ^{111}In labeled CC49 was examined in five groups (N=4) of LS174T tumored mice with tumors implanted 9 days earlier. Each animal received 30 μg (17 μCi) of ^{111}In labeled CC49 and were sacrificed at 11, 24, 48, 72 or 96 h. Secondly, the influence of antibody dosage on tumor accumulation was examined in six groups (N=4) with tumors implanted 13 days earlier. Each animal received 20, 40, 80, 120, 160, or 200 μg of ^{111}In labeled CC49 (12 μCi) and were sacrificed at 48 h. Finally, the influence of tumor size on the antibody MPTA was examined in 20 mice. From day 9 to day 13 post tumor implantation, four mice per day were each administered 30 μg of ^{111}In labeled CC49 (24 μCi at day 9) and each mouse was sacrificed 48 h after injection. The antibody MPTAs were plotted individually against the tumor weight and the curve fitted into a power function using Excel. As will be shown, the 200 μg dosage of CC49 did not saturate the tumors. Therefore, the convenient 30 μg dosage was selected with assurance that the tumor would not be saturated at all tumor size.

The MPTAs of the $^{99\text{m}}\text{Tc}$ -cMORF effector

In the course of multiple pretargeting studies, we have accumulated numerous pretargeting data, both published and unpublished. Listed in Table 1 of the appendix are only those MPTAs of the $^{99\text{m}}\text{Tc}$ -cMORF effector that were measured at an effector dosage below saturation. The effector MPTAs were also plotted individually against tumor weight and the curve fitted into a power function using Excel.

Results

Pharmacokinetics of ^{111}In labeled CC49

Fig 1 presents blood and tumor accumulations of the radiolabeled antibody over 96 h. The trends shown are consistent with reports from other laboratories using ^{125}I or ^{111}In labeled CC49 (12-14). Tumor levels increased consistently when plotted as %ID/organ, but decreased

after about 48 h when plotted as %ID/g due to tumor growth. In both %ID/organ and %ID/g, blood levels decreased consistently with time such that after about 48 h, levels are too low for further tumor accumulation.

Tumor growth

By measuring the size (product of width and thickness) of tumors in the pharmacokinetic study, the curve of tumor growth vs. time since tumor implantation shown in Fig 2A was obtained. Although tumor growth in this LS174T tumor animal model may vary between studies and will provide either a larger or smaller range of tumor sizes, once tumor growth become visible, the tumor grows roughly at 0.11 g per day. We found that the tumor weight estimated by the product of width and thickness of the tumor thigh (cm²) is in close agreement with the actual tumor weight at sacrifice because of the largely linear relationship as shown in Fig 2B.

Influence of antibody dosage on its tumor accumulation

The influence of antibody dosage on tumor accumulation was examined at 48 h since the antibody blood level thereafter is sufficiently low such that essentially no further tumor accumulation occurs (Fig 1). Saturation of the tumor antigens will appear as a leveling of the absolute tumor accumulation (μg/g) vs. dosage curve. As shown in Fig 3, no such leveling occurs up to at least a dosage of 200 μg, suggesting that antibody accessibility to its antigen in tumor has not been compromised by any mechanism. Therefore, by definition, the percent accumulation of the antibody under these conditions is at its MPTA.

Tumor size influence on the MPTAs of the CC49 antibody and the ^{99m}Tc-cMORF effector

Fig 4 shows that the antibody MPTA at 48 h decreases with tumor weight but not linearly. The best fit of these data is $Y_{\text{antibody}} = 19.00 x^{-0.65}$.

The MPTA of the labeled cMORF effector in a tumor model varies with tumor size and depends on the labeled effector itself but not on the antibody (9). While a qualitative relationship between the effector MPTA and tumor size were recognized earlier (15), a quantitative relationship as shown in Fig 5 has now been established using our historical data (Table 1 in Appendix). When the effector MPTA vs tumor weight data are fitted to a mathematical expression, the resulting function $Y_{\text{effector}} = 4.51 x^{-0.66}$ has almost the identical power to that of antibody ($Y_{\text{antibody}} = 19.00 x^{-0.65}$). Thus, the MPTA of the effector is proportional to the MPTA of the pretargeting antibody, resulting in an essentially constant MPTA ratio of pretargeting antibody to labeled cMORF of 4.21.

Discussion

We had previously shown that the MPTAs of both the antibody and the effector can be expressed as the product of the fraction of cardiac output reaching the tumor, the tumor weight, the tumor trapping fraction (E) and the area under the blood curve (AUC_{blood}) (9). Since the cardiac fraction and tumor weight are common to both MPTAs, the MPTA ratio of antibody to effector will be equal only to the product of the ratios of the tumor trapping fraction and the AUC_{blood}.

$$\frac{\text{MPTA}_{\text{antibody}}}{\text{MPTA}_{\text{effector}}} = \frac{E_{\text{antibody}}}{E_{\text{effector}}} \times \frac{\text{AUC}_{\text{Blood, antibody}}}{\text{AUC}_{\text{blood, effector}}}, \text{ where } \text{AUC}_{\text{blood}} \equiv \int_{t=0}^{t=\infty} C(\% \text{ID/g})_{\text{blood}} \times dt$$

Since the AUC_{blood} ratios are independent of tumor size and we have now shown that the ratio of MPTAs are independent of tumor size, then the ratio of the tumor trapping fractions must

also be independent of tumor size. It is possible that the ratio of trapping fractions may be also independent of other target changes in addition to tumor size variation such as changes in tumor type, shape, and location. Logically, any target change that affects the trafficking of antibody to tumor should also affect the trafficking of effector in the same direction.

Dosage optimization in pretargeting is an involved procedure if accuracy is required. Optimization always requires that the pharmacokinetics and tumor saturation dosages of the antibody and effector be determined by dosage escalation. If tumor size is now added as a variable, the process of dosage optimization may be expected to become increasingly complex given that the MPTAs of both antibody and effector will vary with tumor size differently. Fortunately, the ratio of MPTAs is a constant of tumor size such that these measurements for other tumor sizes are no longer necessary. In addition, although experimental verification will be required, the ratio of the two MPTAs is reasonably likely to be also a constant with tumor size for other antibody/effector pairs and to be independent of tumor type, location, shape, etc. It is also reasonably likely that this ratio will be a constant for pretargeting of normal tissues such as pancreatic islet cells.

The importance of this observation may become apparent in future clinical studies. Whereas tumor size in animal models can often be controlled, that is certainly not the case in the clinic. If, as we believe likely, the MPTA ratio is a constant of tumor size in patients as in our mouse tumor model, then regardless of size, all tumors in any individual patient will be targeted with the same optimal dosage ratio.

Conclusion

The ratio of the MPTA for the pretargeting antibody CC49 to the MPTA for the radiolabeled cMORF do not change with the size of LS174T tumor growing in nude mice. The MPTA ratio is likely to be a constant for other pretargeting methods and other antibody/effector pairs, although this remains to be verified experimentally. This observation should simplify dosage optimization in pretargeting studies.

Acknowledgments

The authors are grateful to Dr Jeffery Schlom (Laboratory of Tumor Immunology and Biology, Center for Cancer Research, NCI, NIH, Bethesda, MD) for providing the CC49 hybridoma. Financial support was from the National Institute of Health (CA94994 to DJH and CA107360 to GL) and the Juvenile Diabetes Research Foundation International (JDRF 37-2009-7 to GL).

1. Financial support was from the National Institutes of Health (CA94994 to DJH and CA107360 to GL) and the Juvenile Diabetes Research Foundation International (JDRF 37-2009-7 to GL).

Appendix

The MPTAs of the ^{99m}Tc -cMORF effector used in Fig 5 that were measured in LS174T tumored mice pretargeted with MORF-CC49 or MORF-MN14 antibody are listed in Table 1 individually along with tumor size at sacrifice. The data are from our historical pretargeting studies (published and unpublished). In all cases, sacrifice was at 3 h post effector administration and both the dosages of antibody and effector were at their MPTA.

References

1. Moshakis V, McIlhinney RAJ, Raghaven D, Neville AM. Localization of human tumour xenografts after i.v. administration of radiolabelled monoclonal antibodies. *Br J Cancer* 1981;44:91–9. [PubMed: 6789857]

2. Siegel JA, Pawlyk DA, Lee RE, Sharkey RM, Horowitz J, Goldenberg DM. Tumor, red marrow, and organ dosimetry for ¹³¹I-labeled anti-carcinoembryonic antigen monoclonal antibody. *Cancer Res* 1990;50:1039s–42s. [PubMed: 2297717]
3. Sharkey RM, Karacay H, Richel H, et al. Optimizing bispecific antibody pretargeting for use in radioimmunotherapy. *Clin Cancer Res* 2003 Sep 1;9(10 Pt 2):3897S–913S. [PubMed: 14506188]
4. Liu G, Dou S, Pretorius PH, Liu X, Rusckowski M, Hnatowich DJ. Pretargeting CWR22 prostate tumor in mice with MORF-B72.3 antibody and radiolabeled cMORF. *Eur J Nucl Med Mol Imaging* 2008;35:272–80. [PubMed: 17909792]
5. Krug LM, Milton DT, Jungbluth AA, et al. Targeting Lewis Y (Le(y)) in small cell lung cancer with a humanized monoclonal antibody, hu3S193: a pilot trial testing two dose levels. *J Thorac Oncol* 2007;2:947–52. [PubMed: 17909358]
6. Czito BG, Bendell JC, Willett CG, et al. Bevacizumab, oxaliplatin, and capecitabine with radiation therapy in rectal cancer: Phase I trial results. *Int J Radiat Oncol Biol Phys* 2007;68:472–8. [PubMed: 17498568]
7. Wong JY, Chu DZ, Williams LE, et al. A phase I trial of ⁹⁰Y-DOTA-anti-CEA chimeric T84.66 (cT84.66) radioimmunotherapy in patients with metastatic CEA-producing malignancies. *Cancer Biother Radiopharm* 2006;21:88–100. [PubMed: 16706629]
8. Crane CH, Ellis LM, Abbruzzese JL, et al. Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. *J Clin Oncol* 2006;24:1145–51. [PubMed: 16505434]
9. Liu G, Hnatowich DJ. A semiempirical model of tumor pretargeting. *Bioconjug Chem* 2008;19:2095–104. [PubMed: 18839978]
10. Liu G, Dou S, Pretorius PH, et al. Tumor pretargeting in mice using phosphorodiamidate morpholino oligomer (MORF) conjugated CC49 antibody and radiolabeled complimentary MORF effector. *Q J Nucl Med*. 2008 in press.
11. Liu G, He J, Dou S, et al. Pretargeting in tumored mice with radiolabeled morpholino oligomer showing low kidney uptake. *Eur J Nucl Med Mol Imaging* 2004;31:417–24. [PubMed: 14691611]
12. Colcher D, Minelli MF, Roselli M, Muraro R, Simpson-Milenic D, Schlom J. Radioimmunolocalization of human carcinoma xenografts with B72.3 second generation monoclonal antibodies. *Cancer Res* 1988;48:4597–603. [PubMed: 3396011]
13. Davda JP, Jain M, Batra SK, Gwilt PR, Robinson DH. A physiologically based pharmacokinetic (PBPK) model to characterize and predict the disposition of monoclonal antibody CC49 and its single chain Fv constructs. *Int Immunopharmacol* 2008;8:401–13. [PubMed: 18279794]
14. Chinn PC, Morena RA, Santoro DA, et al. Pharmacokinetics and tumor localization of ¹¹¹In-labeled HuCC49DeltaC(H)2 in BALB/c mice and athymic murine colon carcinoma xenograft. *Cancer Biother Radiopharm* 2006;21:106–16. [PubMed: 16706631]
15. Liu G, Dou S, He J, Liu X, Rusckowski M, Hnatowich DJ. Predicting the biodistribution of radiolabeled cMORF effector in MORF-pretargeted mice. *Eur J Nucl Med Mol Imaging* 2007;34:237–46. [PubMed: 17021815]
16. Liu G, Dou S, Rusckowski M, Hnatowich DJ. An experimental and theoretical evaluation of the influence of pretargeting antibody on the tumor accumulation of effector. *Mol Cancer Ther* 2008;7:1025–32. [PubMed: 18483292]
17. Liu G, He J, Dou S, Gupta S, Rusckowski M, Hnatowich DJ. Further investigations of morpholino pretargeting in mice-establishing quantitative relations in tumor. *Eur J Nucl Med Mol Imaging* 2005;32:1115–23. [PubMed: 16133391]

Fig 1.

Tumour (open circle) and blood level (solid circle) vs. time post antibody administration plotted as %ID/organ (panel A) and %ID/g (panel B) for ^{111}In labeled CC49 administered at 30 μg to LS174T tumored mice. Error bars signify one standard deviation of the mean (N = 4).

Fig 2.

Tumor weight at sacrifice vs. time since tumor implantation showing a steady increase (panel A) and a good correlation between tumor weight and the product of the width and thickness of the tumored thigh (panel B). Error bars in panel A signify one standard deviation of the mean (N=4).

Fig 3. Absolute accumulations ($\mu\text{g/g}$) in tumor 48 h after intravenous administration of ^{111}In labeled CC49 at increasing dosages. Error bars signify one standard deviation of the mean ($N=4$).

Fig 4.
The relationship of the MPTA of CC49 antibody with tumor weight at sacrifice

Fig 5.
The relationship of the MPTA of the labeled cMORF effector with tumor weight at sacrifice

Individual MPTAs (%ID/g) of ^{99m}Tc-cMORF at 3 h in mice pretargeted 48-96 h earlier with MORF-CC49 or MORF-MN14 listed along with tumor weight at necropsy. The table also lists the gpm of MORF-antibody, its dosage and the dosage of the ^{99m}Tc labeled cMORF.

Table 1

(a) 48 h															
MPTA (%ID/g)	5.17	6.23	6.36	5.56	6.04	5.47	6.83	5.71	6.34	6.13	8.99	8.98	8.17	9.30	10.8
Tumor weight (g)	0.86	0.58	0.59	0.70	0.76	0.60	0.82	0.52	0.74	0.57	0.49	0.62	0.56	0.81	0.51
Pretargeting conditions	20 µg MORF-MN14, (gpm=0.83), 1.05 µg ^{99m} Tc-cMORF.			20 µg MORF-MN14, (gpm=0.83), 0.87 µg ^{99m} Tc-cMORF.			30 µg MORF-MN14 (gpm=0.37), 0.40 µg ^{99m} Tc-cMORF			30 µg MORF-CC49 (gpm=1.12), 0.87 µg ^{99m} Tc-cMORF					
Reference	unpublished			unpublished			unpublished			unpublished					
MPTA (%ID/g)	7.89	7.74	8.66	7.08	7.89	7.74	8.66	7.08	6.59	5.83	6.54	5.69	7.49	9.47	8.27
Tumor Weight (g)	0.47	0.42	0.29	0.49	0.47	0.42	0.29	0.49	0.64	0.61	0.47	0.42	0.72	0.33	0.17
Pretargeting conditions	30 µg MORF-CC49 (gpm=0.68), 1.0-2.5 µg ^{99m} Tc-cMORF.			23 µg MORF-MN14 (gpm=0.83), 1.0 µg ^{99m} Tc-cMORF.			11 µg MORF-CC49 (gpm=1.22), 1.0 µg ^{99m} Tc-cMORF.			48 µg MORF-B72.3 (gpm=0.53), 1.0 µg ^{99m} Tc-cMORF.					
Reference	10			16			16			16					
MPTA (%ID/g)	5.80	7.38	4.82	6.51	6.77	8.57	5.51	5.98	5.70	3.92	6.93	3.88	3.79	3.01	4.29
Tumor Weight (g)	1.07	0.63	1.19	0.74	0.79	0.33	0.78	1.07	0.84	1.19	0.74	0.92	1.51	1.62	0.98
Pretargeting conditions	30 µg MORF-MN14 (gpm =0.99), 0.89-2.28 µg ^{99m} Tc-cMORF														
Reference	15														
MPTA (%ID/g)	0.74	0.51	0.40	0.95	0.95	5.65	6.43	5.95	6.29	6.60	5.41	3.04	3.04	3.46	2.81

Tumor Weight (g)	4.66	5.70	7.00	4.08	0.52	0.46	0.71	0.56	0.55	0.78	1.55	1.63	1.66	1.64
Pretargeting conditions	30 µg MOREF-MN14 (gpm =0.99), 0.89-2.28 µg ^{99m} Tc-cMORF				>25 µg MOREF-MN14 (gpm=1.05), 48 h, 1.61 µg ^{99m} Tc-cMORF				30 µg MORE-MN14 (gpm=0.125), 0.30 µg ^{99m} Tc-cMORF					
Reference	15				15				17					
(b) 72 h or 96 h														
MPTA (%ID/g)	3.14	3.31	3.88	2.74	2.41	2.37	4.96	1.59						
Tumor Weight (g)	1.21	1.15	1.10	1.64	1.82	1.35	0.61	2.11						
Pretargeting conditions	30 µg MOREF-MN14 (gpm=0.125), 72 h, 0.30 µg ^{99m} Tc-cMORF								30 µg MOREF-MN14 (gpm=0.125), 96 h, 0.30 µg ^{99m} Tc-cMORF					
Reference	17				17									