Review

Update on Selection of Optimal Radiopharmaceuticals for Clinical Trials

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ABSTRACT

Multiple formulations of radiopharmaceuticals (RPs) are possible because of engineering at the nanometer scale. Yet, numbers of patients are limited, and the cost of each clinical trial is high. Thus, there is the need of preclinical evaluation of one agent versus another for the selection of an optimal choice. In the application of RPs to cancer, this selection involves both visualization and treatment aspects. In this paper, we propose the use of imaging and therapeutic figures of merit (IFOM and TFOM, respectively) to select the optimal structure and radiolabel for subsequent clinical trials given animal biodistribution results. Limiting cases and Monte Carlo simulation were used to demonstrate that these modern figures of merit are superior to traditional ratio functions that have been employed in these two contexts. Finally, there is the question of how animal and human results resemble each other kinetically. We considered allometry and compared mouse and human results for several of the cognate cT84.66 antibodies (anti-CEA; carcinoembryonic antigen). While kinetics of intact and 120-kDa engineered proteins are similar across the two species, the 80-kDa cognate shows a manifest difference in the RP first moment in the blood. In particular, human blood clearance is slower than that seen in the nude mouse. We suggest that such allometric comparisons become standard in the reporting of clinical trials.

Key words: figures of merit, IFOM, TFOM, allometry, radiopharmaceutical selection, antibodies

INTRODUCTION

Multiplicity of Possible Agents

One characteristic of contemporary clinical drug development is the search for greater specificity. To achieve this end, multiple, often novel, tech-

nologies are applied to target specific tissues or even particular molecules *in vivo*. Many different types of chemical and biologic entities are aggressively pursued in search of greater and greater specificity. These include peptides,¹ antibodies,² liposomes,³ SHALs,⁴ segments of RNA,⁵ aptamers,^{6*} and nanostructures of various

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types.⁷ An engineer is not limited to a single technology; combinations are being investigated, such as liposomes with antibodies in their outer shell. In the following, we will emphasize radiopharmaceutical (RP) applications that allow tissue measurements, using well counters and external detectors. For other agents, sampling may be limited to the chemical evaluation of blood and excreta, unless a radiolabel is attached prior to injection.

Available Resources and Cost of Clinical Trials

In contrast to the multiplicity of potential agents, there are very limited numbers of individuals locally available for a clinical trial. If we require, for example, 20 previously untreated cancer patients of a specific type, it may be necessary to utilize a single institution's relevant population for an entire year. There is likely to be competition for these patients from a number of groups advocating other agents or strategies for that specific malignancy. Thus, selecting an inappropriate pharmaceutical may lead to a resultant delay in discovering any improved therapy. Regulatory agencies and health care advocates may retrospectively question the use of an incorrect agent or strategy on this manifestly at-risk group. Costs of clinical evaluation are an additional burden and may approach \$100,000 per patient. Thus, initial choice of an inferior agent will prove expensive as well as ineffective.

Preclinical Rating of Pharmaceuticals

From the standpoint of engineering and the pharmaceutical industry, it is important to differentiate one potential clinical pharmaceutical (and potential label) from another as soon as possible during preliminary development. After evaluat-

ing the specificity of the agent with cellular measurements, there will be testing via animal—usually murine—biodistributions. From the latter, a prioritized list should be generated to indicate which agent is the best for a clinical trial. This may be done by using figures of merit⁸ as is common in engineering practice. In this paper, we describe this strategy below for radiopharmaceuticals. In this case, both imaging and therapeutic applications are possible.

Types of Data Used in RP Analysis

There are a number of possible parameters for use in RP comparisons. Generally, the fundamental animal measurement is decay-corrected organ uptake (u) in units of percent-injected dose per gram of organ tissue (%ID/g). Division of organ activity by mass corrects for size of the tissue in this analytic form that is the most common type of animal biodistribution result found in the literature. Such data can be relatively accurate ($\pm 10\%$) due to sacrificing cohorts of 5–10 mice at given time (t) points. All uptakes are functions of time, so that their kinetic variation and areas under the curve (AUC) are likewise of interest. Organ activity (a) in units of %ID/organ is the most common form of clinical result because of constraints described below. In the AUC case, decay is included in the integral if we are concerned with radiation therapy applications. Table 1 contains a summary of these parameters.

Allometry (Closing the Circle)

An obvious issue is the correspondence, if it exists, between animal and patient data sets. While murine-uptake measurements are standard, clinical measurements of $u(t)$ are relatively difficult due to two reasons. First is the present-day lack of a quantitative imaging method, comparable in

Table 1. Types of Data Used in Analyses

<i>Quantity</i>	<i>Pharmacological (decay-corrected) variable</i>	<i>Measured (radiologic) variable</i>
Uptake	$u(t)$ in %ID/g	$u(t) \exp(-\lambda t)$ in %IA/g
Organ activity	$a(t)$ in %ID/organ	$a(t) \exp(-\lambda t)$ in %IA/organ
Tissue concentration	$c(t)$ in %ID/mL	$c(t) \exp(-\lambda t)$ in %IA/mL
AUC	$\int a(t) dt$	$\int a(t) \exp(-\lambda t) dt$

The decay constant of the label is λ . Areas under the curve (AUC) are generally from zero to infinity for total absorbed-dose estimates or other effects.

accuracy to well-counter measurements, for evaluating activity, at-depth, in the patient. Second, uptake necessitates the use of tissue mass as its denominator, so that the investigator requires a simultaneous size measurement on the imaged tissues. This additional requirement may not be possible due to cost concerns, such as with magnetic resonance imaging or computed tomography (MRI or CT), or ethical issues involving radiation dose (CT). With the advent of single-photon emission computed tomography (SPECT)/CT and positron emission tomography (PET)/CT, these restrictions will be relaxed somewhat in the future, and direct comparison of murine and human general organ uptake data will become more common. Presently, only blood and occasional surgical samples provide human uptake values with accuracy comparable to those found in animal studies. However, the surgical sample may be criticized as incomplete.

In attempting to project human results from animal data, there is an extensive tradition of allometric analysis for normal tissue sizes. Here, the researcher compares organ masses (m) across mammalian species of total body mass, W . Generally, log-log correlations⁹ are seen, such that the anticipated mass result is as shown in Equation 1:

$$m = g * W^b \quad (1)$$

where g and b are best-fit parameters that depend on the organ of interest. A typical exponent (b) in these analyses lies between 0.70 and 0.80.⁹ Because metabolic rates vary, with b being approximately 0.75, it is sometimes assumed that a relationship and exponent similar to the above will also hold for kinetic quantities. For example, $T_{1/2}$ values measured in drug targeting could be conjectured to follow such a correlation across species. There has, however, been relatively little reported in allometric kinetic analyses.

STRATEGY FOR AGENT SELECTION

Molecular and Cellular Results

Prior to *in vivo* evaluation, the targeting of possible agents must be first evaluated *in vitro* with the appropriate target tissue cells. For a putative cancer agent, tumor cells of the appropriate type may be tested for accumulation in a context of normal cells in a matrix format. Once association is shown, affinity constants between the agent and target are measured; generally, these should

be in the range of 10^8 – 10^9 M for eventually useful clinical results. Such values, while necessary, are not sufficient to decide on an optimal agent for a patient trial. Preliminary biodistributions are needed in order to test targeting in the context of a living animal.

Comparisons of Animal Data

Comparative analysis of animal biodistribution data is the next step in the drug-selection process. Several similar agents may be injected into a test species and organ uptakes measured. If a radiopharmaceutical, multiple tissues may be simultaneously assayed by either quantitative small-scale imagers (SPECT or PET) or by a well-counter measurement of necropsy specimens. The former method is preferred to the latter, as there is no animal sacrifice, and the same individual may be followed over the course of the experiment.

To the lowest order in animal data, an investigator may begin a comparison by doing an organ-by-organ, time-point-by-time-point, statistical search to see if significant differences ($p < 0.05$) actually occur in $u(t)$ values between one possible engineered agent and another. This has been reported for a number of cognate antibodies by our group¹⁰ and others.¹¹ For tumor targeting, obvious tissues for such comparisons would be derived from murine models involving implanted human cancers in nude mice or spontaneously arising tumors in genetically engineered mice.¹² No mathematical modeling is required in this analysis and the statistical results give a direct answer to the question: Do the agents significantly differ? Such simple analyses, however, will not give a complete picture of what is going on inside the test species.

Exploratory Data Analysis (EDA) and Modeling

One can imagine a higher level of organ data comparisons. Given a unique radiopharmaceutical, exploratory data analysis (EDA)¹³ attempts to establish which tissues have significant uptake of the RP. Here, one can look for those organs having uptake beyond that expected by uniform dilution of the activity into the whole body of the test animal. For the mouse, that would be a u -value exceeding approximately 5% ID/g; (i.e., 100% ID divided by a 20-g animal). Such organs would then be incorporated into a modeling context.

Tissues having such manifest correlations may be represented via a single or multicompartmental model.¹⁴ One immediate advantage of modeling is that interpolation and extrapolation of organ data may be obtained directly for time-dependent as well as integral analyses. A single compartmental form would represent each organ via a separate equation, using multiexponentials or other functions. Either $u(t)$ or $a(t)$ data may be analyzed. An example of this is given below for blood curves of various antibodies. On the other hand, the organs may be represented as communicating to each other through the blood as the central (mammillary) space. Because of the conservation of total activity, $a(t)$ is the appropriate variable to model in this context. Compartment-to-compartment rate constants (k_{ij}) may then be determined in a differential equations approach. A number of least-squares methods and software packages are available to find the optimal parameters for either model type.

Since every model is generated by using a predetermined mathematical picture, it can be criticized as being overly specific. Some investigators have, therefore, used spline-fitting methods as an alternative.¹⁵ Spline fits are essentially cubic or higher order polynomials of time, which represent $u(t)$ or other measured functions over the relevant time interval. Splines can, likewise, be used to interpolate or integrate these organ functions.

Figures of Merit

Given the results of modeling or spline analysis, an evaluator is ultimately left with the question of which curve-associated parameter(s) to use in multiagent comparisons. By limiting our viewpoint to single curves, values such as tissue uptake or rate constants may be selected. For kinetic values, one can select one or more of possibly several half-times ($T_{1/2\alpha}$ and/or $T_{1/2\beta}$) as a single parameter. It is unlikely that any of these will be satisfactory for a complete analysis, however, since we need to find relationships between organs, rather than any such single organ's uptake or kinetic values. For imaging, we would need at least a statistical comparison of the desired gamma-camera signal (tumor) versus the general background signal (blood). Analogously, radiation therapy would require a comparison of tumor-absorbed dose to blood-absorbed dose. While we emphasize blood as the background tissue, other organs such as liver, kidney, or mus-

cle may also prove important and our argument changed accordingly. Blood has been a traditional surrogate for the red marrow, using the AAPM Task Group algorithm developed by Siegel et al.¹⁶ and further advanced by Sgouros et al.¹⁷

Such composite parameters are called figures of merit (FOMs).⁸ By definition, they do not depend on single organ results, but instead require a combination of uptake values and/or their integrals over time for a set of relevant tissues. Invoking this strategy is consistent with the concept of engineering; an inventor may investigate multiple experimental designs, yet must generally limit real-world trials to a single optimal prototype chosen by a figure of merit. The bioengineer has the clinical trial as the ultimate test of the (presumed) optimal radiopharmaceutical.

It is important to notice that any given FOM must be acknowledged as subjective. Just as in the case of agent design, there is an anticipated evolution of FOM parameters to allow improved predictions of clinical results given various animal biodistributions. In the following, we compare the two traditional radiopharmaceutical figures of merit with two more recent candidates.

RESULTS

For the intact anti-CEA (carcinoembryonic antigen) antibody, cT84.66, exploratory analyses in mice demonstrated blood, liver, and tumor to be tissues of elevated uptake.¹⁸ When patient data were added to the analysis, it was found that colon tumors could not be observed in every patient, so that malignant tissue was omitted from the eventual multicompartment model. As a result, the model contained blood, liver, and its included blood, residual body, and the two routes of excretion: urine and feces. This model is shown in Figure 1.

Traditional and Revised FOMs

Among most investigators, the historic figure of merit for RP imaging has been the ratio R of tumor uptake to blood uptake (u_T/u_B).¹⁹ This parameter, however, can be shown to be inadequate in at least three distinct aspects:

1. It has already been shown that R is unbounded as time increases for each in a sequence of five cognate anti-CEA monoclonal antibodies (mAbs)²⁰ labeled with radioiodine. This is

clearly an unrealistic prediction for the traditional R FOM.

2. Since R is a ratio of activities, it is independent of radiolabel as the decay factor, $\exp(-\lambda t)$, simply cancels out. Yet, the label is vitally important, since a very short physical half-life,

for example, would render imaging impossible for a slowly targeting agent.

3. As our group has demonstrated earlier,²¹ $u_T(t)$ generally exhibits a mass dependence, which goes as an inverse power of m_T . Yet, R is directly proportional to u_T , so that using R as a figure of merit would imply that smaller tumors would be more readily imaged—a decidedly unphysical assertion. Even if no mass dependence were seen in u_T ,²¹ R would imply that imaging would be independent of tumor size. Again, this is not a realistic prediction, since larger tumors should be more visible.

As given in Table 2, a better imaging parameter is the more recently developed imaging figure of merit (IFOM).²² Table 2 demonstrates that IFOM gives realistic predictions in these three imaging aspects. Here, IFOM predicts a finite time for optimal imaging, an explicit dependence upon radiolabel and has realistic variation with tumor mass.

Similar mathematical inadequacies are seen for the traditional therapy figure of merit (R'). It is defined as the ratio of tumor area under the curve (AUC) divided by the blood AUC. Note that radiodecay is implicitly contained in the AUC

Table 2. Comparison of Figures of Merit

<i>Imaging</i>	<i>Traditional figure of merit result</i>	<i>IFOM result</i>
Formula	$R = u_T/u_B$	IFOM = $k \exp(-\lambda t) m_T [1 - 1/R]^2 u_T / [1 + 1/R]$ where m_T is lesion mass and k is a constant
Optimal time for imaging	Infinity for 5 iodinated cognates	Finite time for each cognate
Radiolabel Dependence	None	Varies as $\exp(-\lambda t)$
Tumor mass dependence (if u_T varies with tumor mass as $m^{-1/3}$)	$m_T^{-1/3}$	$m_T^{2/3}$
Tumor mass dependence (if u_T is independent of tumor mass)	None	m_T
<i>Therapy</i>	<i>Traditional figure of merit result</i>	<i>TFOM result</i>
Formula	$R' = \text{AUC}(T)/\text{AUC}(B)$	TFOM = $k' [1 - 1/R']^2 \text{AUC}(T) / [1 + 1/R']$ where k' is a constant.
Limit as R' becomes large	Infinity	Integral of activity in tumor
Two R' values are equal	No choice is possible	TFOM favors agent with higher tumor AUC

value. Because of its ratio format, R' is not generally useful and two conceptual experiments illustrate its limitations:

1. Consider an example where tumor area becomes very large, compared to that of the blood. In this case, R' could become arbitrarily large and interagent comparisons problematic.
2. In a second illustrative case, one can consider two agents: x and y , where $R'(x)$ is equal to $R'(y)$. Yet, what if the tumor $AUC(x)$ is much less than the tumor $AUC(y)$? Obviously, y is the superior agent, since it requires less activity to treat the lesion to a given absorbed dose. Yet, both agents have the same historic FOM.

A better therapy indicator is the therapeutic figure of merit or TFOM,²² as given in Table 2. In

the first example, TFOM²² remains finite and simply becomes equal to the tumor AUC. This is a more realistic result than that predicted by R' . In the ambiguous case of the second example, TFOM is also proportional to tumor AUC, such that the correct optimal agent (y) is selected for clinical trials.

While mathematical manipulation can be used to argue for IFOM and against R , the Monte Carlo simulation provides an additional piece of visual evidence. Figures 2 and 3, respectively, illustrate a hypothetical gamma camera and imaging results of two iodinated α -CEA cognates²⁰ being imaged with that device. Activity curves for tumor and blood were taken directly from earlier biodistribution data. It was shown that the IFOM is a better predictor of optimal imaging time than is the traditional R parameter, which is symbolized here as the tumor-to-blood (T/B) ratio. Notice that T/B

Figure 3. Demonstration of the camera results using Monte Carlo 20-m simulations at the time points indicated. For mini and diabody cT84.66 cognates labeled with ^{123}I , traditional and imaging figures of merit (IFOM) indicators are shown along with corresponding tumor images. Note the monotone increase of R, the traditional ratio of tumor-to-blood uptakes (here shown as T/B). Maxima in IFOM correspond relatively well with the image clarity. Figure taken from the Proceedings of the World Congress on Medical Physics and Biomedical Engineering, Sydney, Australia, August 24–29, 2003 (ISBN 1877040142, paper 737, by permission).

increases monotonically with time for both antibodies, implying optimal imaging at infinite time—a decidedly unphysical result.

Allometric Comparisons

Most allometric kinetic reports have focused on chemistry measurements of the agent's blood curve near the beginning of the injection phase. For example, antibody initial clearance rate (CL), initial volume of distribution (V_0), and steady-state volume (V_{ss}) were shown by Khor et al.²³ to be correlated with animal W (total body mass) with all exponents [cf. eq.(1)] near unity. These results imply that uptake will be proportional to $1/W$ (i.e., be inversely proportional to the total body mass). In particular, $u(t)$ values will be ap-

proximately three orders of magnitude smaller in man, as compared with the mouse, because of this dilution effect. While useful in predicting uptakes, such results are expected in allometric comparisons and, therefore, are not of primary importance in the analysis.

Kinetic parameters become those of principle interest in RP allometry. A generic representation of most uptake curves is the two-exponential function, as shown in Equation 2:

$$u(t) = A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t) \quad (2)$$

where, as indicated above, correction has been made for radiodecay. Such functions allow representations of curves that pass through maxima as well as those that monotonically decrease with

Table 3. First Moments of Blood Curves for Two Species

<i>cT84.66</i> <i>protein/label</i>	<i>Molecular</i> <i>weight (MW)</i>	<i><t> Nude</i> <i>mouse</i>	<i><t> Man</i>	<i>Ratio</i>
Intact mAb/ ¹¹¹ In	160 kDa	97 h	129 h	1.3
F(ab') ₂ / ¹²³ I	120	8.8	12.7	1.4
Minibody/ ¹²³ I	80	7.2	30.2	4.2

time. The A values are referred to as weights and the k parameters as rate constants in this equality. More exponential terms may be required as the biodistributions are carried out to longer times.

One cannot simply juxtapose one or even two rate constants (or their corresponding $T_{1/2}$ values), since these will have respective weights that will differ between species. It would be useful if a single kinetic parameter were available to compare allometrically various results. We propose to use the first temporal moment of the $u(t)$ distribution to characterize a given agent to the first order. Explicitly, we have the result shown in Equation 3:

$$\langle t \rangle = \int t u(t) dt / \int u(t) dt \quad (3)$$

where each integral goes from zero to infinity. Higher moments are also possible, whereby t in the numerator is replaced by t^n , where n is an integer >1 . A complete description of the associated $u(t)$ curve would, then, be a summary of all such integrations.

In Table 3, results for the first moments of the blood for several of our engineered cT84.66 antibodies for both murine and human data sets are given. The smallest molecular weight (MW) example (minibody) shows greater disparity be-

tween the two species, whereas the intact mAb and F(ab')₂ correspondences are relatively close. In such cases, the equivalent W exponent in Equation 1 is seen to be essentially nil. A similarly small value of the exponent was reported by Khor et al.²³ in their terminal half-life analysis of the rPSGL-Ig antibody across various species. It is important to note that our differences are no more than 4-fold, even for MW values as low as 80 kDa. Thus, the mouse $\langle t \rangle$ data are relatively close to human values—even though the species differ by more than three orders of magnitude in total body mass. This result may not be anticipated from Equation 1 with the expected exponent of 0.75. Such close correspondence makes the comparisons of mouse and clinical data much simpler—at least for blood curves.

Multicompartment models may also be used to compare biodistributions in mouse and man. The model of Figure 1 was used by our group to represent intact cT84.66 antibody activity per organ $[a(t)]$ data for patients¹⁸ and nude mice. Results are given in Table 4.

As expected, the volume of distribution increases by essentially three orders of magnitude in going from mouse to man. We notice that the rate constants for the intact antibody, cT84.66 (MW = 160 kDa), are in rough agreement for most compartments. One striking exception is the

Table 4. Comparison of Intact cT84.66 mAb in Nude Mice and Colorectal Cancer Patients. Label was ¹³¹I for Murine and ¹¹¹In in Clinical Studies

<i>Pharmacokinetic variable</i>	<i>Murine result</i>	<i>Mean patient result</i>
k_{bl}	$1.4 \pm 3 \times 10^{-3} \text{ h}^{-1}$	$17 \pm 4 \times 10^{-3} \text{ h}^{-1}$
k_{lb}	$37 \pm 61 \times 10^{-3} \text{ h}^{-1}$	$13 \pm 9 \times 10^{-3} \text{ h}^{-1}$
k_{br}	$87 \pm 21 \times 10^{-3} \text{ h}^{-1}$	$27 \pm 10 \times 10^{-3} \text{ h}^{-1}$
k_{rb}	$0.60 \pm 0.15 \times 10^{-3} \text{ h}^{-1}$	$28 \pm 24 \times 10^{-3} \text{ h}^{-1}$
k_{rf}	$12 \pm 14 \times 10^{-3} \text{ h}^{-1}$	$7 \pm 2 \times 10^{-3} \text{ h}^{-1}$
k_{lu}	$0.15 \pm 0.75 \text{ h}^{-1}$	$7 \pm 1 \times 10^{-3} \text{ h}^{-1}$
V	$2.3 \pm 0.20 \text{ mL}$	$5.36 \pm 0.52 \times 10^3 \text{ mL}$
f_{bl}	0.12 ± 0.01	0.17 ± 0.01

clearance from the liver (via the kidneys) to the outside environment. The corresponding k_{out} parameter is several orders of magnitude greater for the iodinated mAb in the mouse—presumably due to dehalogenation. This analysis also points out that similar labels should be employed in going from one species to another.

CONCLUSIONS

Preclinical differentiation of possible imaging and therapeutic agents is important in view of the multiplicity of possible moieties and lack of sufficient patients with a given diagnosis. Cost of clinical trials is an additional motivation for such analyses. After doing binding and other cellular assays, we propose using animal-derived FOMs to permit agent prioritization for clinical trials. For the imaging of radiolabeled pharmaceuticals, IFOM appears to a better predictor of optimal agents as well as their optimal time of imaging. It is superior to the traditional imaging figure, the ratio of tumor to blood uptake. While the latter being greater than one is a necessary condition, the amount in the tumor (or target tissue) may not be large enough to obtain statistically useful imaging results in any finite counting time. In addition, IFOM allows the estimation of the effects of possible label changes and of tumor-size variation on the agent's targeting efficacy.

Similar radiotherapy considerations lead to a TFOM that allows an analogous ordering of radiopharmaceuticals. While the traditional therapeutic index (ratio of tumor AUC to blood AUC) being >1 is, again, a necessary condition, it is not sufficient for use as a therapy figure of merit. The postulated TFOM is superior, in that it predicts that, even in the case of very large such ratios, the FOM would be proportional to the tumor AUC.

Given a preferential ordering of agents by preclinical testing in appropriate animals, one must ask if nonhuman data do indeed predict clinical results. If we consider engineered radiolabeled antibodies, intact mAbs (~ 160 kDa) have similar first-moment blood kinetics in both mouse and man. Lower molecular weight engineered cT84.66 Mabs tend to leave the blood sooner in the mouse, with a ratio of first temporal moments on the order of between 1.5/1 and 4/1, with humans having the larger values. Thus, while total-body and organ masses vary by three orders of

magnitude between the two species, mAb kinetics are much more similar.

The Food and Drug Administration (FDA) has generally accepted a form of equivalence of RP kinetics between mouse and man in IND applications for phase 1 clinical trials of radiopharmaceuticals. Here, the AUCs for various organs (i) scale simply as the ratio of the i -th organ mass to whole-body mass, as shown in Equation 4:

$$\text{AUC}_i (\text{man}) = \frac{\text{AUC} (\text{mouse}) * m_i (\text{man})/W(\text{man})}{m_i (\text{mouse})/W(\text{mouse})} \quad (4)$$

This equivalence is seen to be essentially correct for the intact cT84.66 antibody and its F(ab')_2 fragment in the blood. But it would not hold for the minibody cT84.66-engineered protein. In that case, because of the extended residence times in patients, blood AUC and associated bone marrow radiation dose would be correspondingly enhanced in the clinical situation, as compared to murine values. Further investigation for other MW proteins, as well as other engineered agents, would be useful.

We would, therefore, suggest that the FDA require eventual allometric reports from investigators as a precondition of clinical trial approval. Applicants would be required to measure clinical uptakes and kinetic values and compare these results to the corresponding original animal data. In this way, kinetic correspondences for various classes of agents could be established. This closing of the allometry circle is one of the important, and unanswered, questions of radiopharmaceutical evaluation. Such knowledge may help lead to the prevention of unwise, expensive clinical trials.

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