CONCLUSION

We have demonstrated that nonspecific mechanisms contribute minimally to the localization of ^{99m}Tc-chemotactic peptide analogs at sites of infection and the majority of accumulation appears to be receptor mediated. Also, we have demonstrated that chemotactic peptide receptor antagonists can be used for infection imaging. These results put the receptor hypothesis for chemotactic peptide localization on firmer theoretical ground and provide important new insights for the future development of improved radiopharmaceuticals.

ACKNOWLEDGMENT

This work was supported in part by National Institutes of Health grants 5P50 GM21700 and RO1 A131094.

REFERENCES

1. Showell HJ, Freer RJ, Zigmond SH, Schiffmann E, Aswanikumar S, Corcoran B, Becker EL. The structural relations of synthetic peptides as chemotactic factors and inducers of lysosomal enzyme secretion for neutrophils. *J Exp Med* 1976;143:1154–1169.
2. Schiffmann E, Corcoran BA, Wahl SM. Formylmethionyl peptides as chemoattractants for leukocytes. *Proc Natl Acad Sci USA* 1975;72:1059–1062.
3. Williams LT, Snyderman R, Pike MC, Lefkowitz RJ. Specific receptor sites for chemotactic peptides on human polymorphonuclear leukocytes. *Proc Natl Acad Sci USA* 1977;74:1204–1208.
4. Snyderman R, Verghese MW. Leukocyte activation by chemoattractant receptors: roles of a guanine nucleotide regulatory protein and polyphosphoinositide metabolism. *Rev Infect Dis* 1987;9:S562–S569.
5. Fletcher MP, Seligman BE, Gallin JI. Correlation of human neutrophil secretion, chemoattractant receptor mobilization and enhanced functional capacity. *J Immunol* 1988;128:941–948.
6. Niedel J, Wilkinson S, Cuatrecasas P. Receptor mediated uptake and degradation of ^{125}I-chemotactic peptide by human neutrophils. *J Biol Chem* 1979;10:700–710.
7. Babich JW, Solomon H, Pike MC, et al. Technetium-99m-labeled hydrazino nicotinamide derivatized chemotactic peptides for imaging focal sites of bacterial infection. *J Nucl Med* 1993;34:1964–1974.
8. Babich JW, Graham W, Barrow SA, Dragotakes SC, Tompkins RG, Rubin RH, Fischman AJ. Technetium-99m-labeled chemotactic peptides: comparison with indium-111-labeled white blood cells for localizing acute bacterial infections in rabbits. *J Nucl Med* 1993;34:2176–2181.
9. Niedel J, Davis J, Cuatrecasas P. Covalent affinity labeling of the formyl peptide chemotactic receptor. *J Biol Chem* 1980;255:7063–7066.
10. Fischman AJ, Pike MC, Kroon D, et al. Imaging of focal sites of bacterial infection in rats with indium-111-labeled chemotactic peptide analogs. *J Nucl Med* 1991;32:483–491.
11. Babich JW, Graham W, Barrow SA, Fischman AJ. Comparison of the infection imaging properties of a ^{99m}Tc-labeled chemotactic peptide with ^{111}In IgG. *Nucl Med Biol* 1995;22:643–648.
12. Fischman AJ, Rauh D, Solomon H, et al. In vivo bioactivity and biodistribution of chemotactic peptide analogs in non-human primates. *J Nucl Med* 1993;34:2130–2134.
13. Fischman AJ, Babich JW, Barrow SA, Graham W, Carter E, Tompkins RG, Rubin RH. Detection of acute bacterial infections within soft tissue injuries using a ^{99m}Tc-labeled chemotactic peptide. *J Trauma* 1995;38:223–227.
14. Merrifield RB. Solid phase peptide synthesis: I. synthesis of a tetrapeptide. *J Am Chem Soc* 1963;15:2149–2154.
15. Stewart JM, Young JD. *Solid phase peptide synthesis*. San Francisco, CA: W.H. Freeman & Company; 1969.
16. Pike MC, Snyderman R. Leukocyte chemoattractant receptors. *Methods Enzymol* 1988;162:236–245.
17. ike MC, Jakoi L, McPhail LC, Snyderman R. Chemoattractant-mediated stimulation of the respiratory burst in human polymorphonuclear leukocytes may require appearance of protein kinase activity in the cells' particulate fraction. *Blood* 1986;67:909–913.
18. Abrams MJ, Juweid M, tenKate CI, et al. Technetium-99m human polyclonal IgG radiolabeled via the hydrazino nicotinamide derivative for imaging focal sites of infection in rats. *J Nucl Med* 1990;31:2022–2028.
19. Krejcarek GE, Tucker KL. Covalent attachment of chelating groups to macromolecules. *Biochem Biophys Res Commun* 1977;77:581–585.
20. Khaw BA, Mattis JA, Melincoff G, Strauss HW, Gold HK, Haber E. Imaging of experimental myocardial infarction. *Hybridoma* 1984;3:11–23.
21. Rubin RH, Fischman AJ, Callahan RJ, et al. The utility of ^{111}In-labeled nonspecific immunoglobulin scanning in the detection of focal inflammation. *N Engl J Med* 1989;321:935–940.
22. Fischman AJ, Rubin RH, Khaw BA, et al. Detection of acute inflammation with ^{111}In-labeled nonspecific polyclonal IgG. *Semin Nucl Med* 1988;18:335–344.
23. McAfee JG, Gagne GM, Subramanian G, et al. Distribution of leukocytes labeled with indium-111-oxine in dogs with acute inflammatory lesions. *J Nucl Med* 1980;21:1059–1068.
24. McAfee JG, Subramanian G, Gagne GM. Technique of leukocyte harvesting and labeling: problems and perspectives. *Semin Nucl Med* 1984;14:83–106.
25. Duncan DB. Multiple range tests and multiple F-tests. *Biometrics* 1955;11:1–42.
26. Babich JW, Barrow SA, Graham W, Fischman AJ. Infection imaging with technetium-99m chemotactic peptides in dogs. *J Nucl Med* 1995;36:230P.
27. Senda M, Fischman AJ, Weise S, Alpert NM, Correia JA, Rubin RH, Strauss HW. Evaluation of regional perfusion, oxygen metabolism, blood volume and permeability to IgG in experimental skeletal muscle infection in the rabbit. *Eur J Nucl Med* 1992;19:166–172.
28. Babich JW, Fischman AJ. Influence of coligand on the distribution of ^{99m}Tc-labeled hydrazino nicotinic acid derivatized chemotactic peptides in normal rats. *Nucl Med Biol* 1995;22:25–30.

EDITORIAL

Technetium-99m-Labeled Chemotactic Peptides: Specific for Imaging Infection?

In 1991, Fischman et al. *(1)* were the first to report the potential diagnostic use of ^{111}In-labeled chemotactic peptide analogs of N-formyl-methionyl-leucyl-phenylalanine (ForMLF), a bacterial product for imaging infection. Subsequently, Babich et al. *(2,3)* reported that in the same rat model, ^{99m}Tc-labeled hydrazinonicotinamide (HYNIC) derivatized chemotactic peptides also localize at the site of infection. They identified that N-formyl-methionyl-leucyl-phenylalanine-lysine (fMLFK) conjugated to HYNIC and labeled with ^{99m}Tc had the most favorable distribution characteristics for infection imaging. While these reports clearly documented the uptake of radiolabeled peptides at the infection site, the specificity of these tracers for infection and the exact mechanism(s) of localization are not well understood. It was assumed that the mechanism of uptake of chemotactic peptides in the infection/inflammation foci is mediated by high-affinity binding to For-MLF receptors on leukocytes.

In this issue, Babich et al. *(4)* and van der Laken et al. *(5)*, report that ^{99m}Tc-labeled chemotactic peptides specifically localize at the site of infectious foci in a rabbit model of acute infection. Despite the differences in experimental design, the two investigators studied the infection uptake and specificity of the same radiotracer, the high-affinity chemotactic peptide agonist ^{99m}Tc-fMLFK-HYNIC. While the results reported in these two articles are encouraging for further work, it is important to analyze the different lines of evidence presented here to demonstrate the in vivo specificity of ^{99m}Tc peptides for infection.

Babich et al. *(4)* performed three studies in rabbits with E. Coli infection. The first compares the infection/background or target-to-background ratios (T/B) of ^{99m}Tc-fMLFK-HYNIC with that of ^{111}In-labeled DTPA, RBC and IgG. Since the RBCs and IgG remain in circulation longer than the peptide, T/B ratios are expected to be lower than the labeled peptides. Imaging studies at 2–3 hr, however, show that T/B ratios of all three tracers are between 2.0–3.0. The most striking difference is seen only at 16–18

Received May 2, 1997; accepted May 12, 1997.

For correspondence or reprints contact: Shankar Vallabhajosula, PhD, Professor of Radiopharmacy in Radiology, Division of Nuclear Medicine, New York Hospital-Cornell University Medical College, 525 East 68th St., New York, NY 10021.

hr when the T/B ratio of the ^{99m}Tc peptide is significantly higher than RBC and IgG. These imaging studies imply that, with this peptide, early imaging (2–3 hr) of infection is not optimal. The tissue uptake data is only reported at 16–18 hr and at which time the activity of ^{99m}Tc-fMLFK-HYNIC in normal muscle (% ID/g) is similar to that of RBC and IgG but was almost 10 times that of ^{111}In-DTPA. In the infected muscle, the activity, however, is five times that of RBC and IgG suggesting that the infection uptake is significantly higher than the blood-pool activity. Dual isotope studies with ^{99m}Tc peptides and ^{111}In-labeled RBC or IgG might be ideal for gamma camera studies. The more appropriate comparisons, however, would have been with ^{99m}Tc-labeled RBC and IgG since ^{99m}Tc chemistry and in vivo behavior of ^{99m}Tc complexes is quite different compared to that of ^{111}In chemistry and its complexes.

The second study compares the T/B ratios of ^{99m}Tc-fMLFK-HYNIC with a low-affinity agonist (^{99m}Tc-Ac-MLFK-HYNIC) and a moderate affinity antagonist (^{99m}Tc-iBoc-MLFK-HYNIC). Once again, the imaging studies clearly showed that T/B ratios of all three peptide preparations was between 2.0–3.0. Only at 16–18 hr, was there a significant improvement in T/B ratios with a high-affinity peptide. The tissue uptake data clearly documents that the absolute uptake of a high-affinity peptide is 3–4 times that of a low-affinity agonist and a moderate affinity antagonist. These results provide some evidence that the uptake of a high-affinity peptide at the site of infection is specific. Since the early images with all three radiolabeled peptides provide similar T/B ratios, it is difficult, however, to identify the potential clinical advantage of ^{99m}Tc-fMLFK-HYNIC over the other tracers.

The third study evaluates the effect of co-injection of a cold peptide (moderate antagonist, 1.0 mg) on the T/B ratios of a high-affinity peptide, ^{99m}Tc-fMLFK-HYNIC. At the early imaging time, the antagonist clearly did not have a significant effect on the T/B ratios of a high-affinity agonist. Only the delayed images showed a 50% reduction. This is an interesting observation and provides some evidence for receptor specificity. But the study is incomplete since no data was presented on the absolute tissue uptake (% ID/g) of high-affinity peptide with the co-injection of antagonist. The specificity of a high-affinity agonist can be demonstrated clearly only if the antagonist decreases the absolute uptake of high-affinity agonist in the infection muscle and pus. It is also important to demonstrate if this effect of the antagonist is dose dependent, or if the effect is nonspecific. The T/B ratio does not define the real effect. Since the affinity of the antagonist is higher than the low-affinity agonist, the effect of co-injection of the antagonist on the infection site uptake of the low-affinity agonist should also have been investigated to demonstrate if the antagonist can completely inhibit the uptake of ^{99m}Tc-labeled low-affinity agonist.

Dual-tracer studies with ^{111}In-WBCs are interesting, but lack of effect of the antagonist on ^{111}In-WBC localization does not suggest specific infection focus targeting of ^{99m}Tc-fMLFK-HYNIC. Is it possible that the antagonist did not influence the migration of WBCs to the site of infection because the chemotactic peptides generated in vivo were able to bind to WBCs without displacement effect by the antagonist? This third issue is most important concerning the specificity of ^{99m}Tc-labeled chemotactic peptides and more work needs to be done to clearly document receptor specificity.

In order to document the specificity of ^{99m}Tc-labeled chemotactic peptides for infection localization, van der Laken et al. (*5*) performed two different types of experiments. They first compared the kinetics of uptake and retention of ^{99m}Tc-fMLFK-HYNIC with that of a low-affinity control peptide, ^{99m}Tc-HYNIC-ML-FOMe, in a rabbit with acute E. Coli infection. The blood clearance of both high-affinity and low-affinity radiotracers was similar, suggesting that in blood the radioactivity associated with WBCs was similar for both high-affinity and the control peptide. In addition, they observed a minimal transient reduction in peripheral leukocyte levels of high-affinity peptide within the first 3 min after injection into normal rabbits. No blood clearance data on the control peptide were reported.

The imaging studies showed that the T/B ratios gradually increased significantly with the high-affinity peptide only. In addition, the abscess-to-whole-body ratios gradually increased with the high-affinity peptide, while the control peptide showed a decrease with time. The tissue distribution studies at 20 hr showed that the absolute infection uptake of high-affinity peptide is 10 times that of the control peptide (0.05 versus 0.005 %ID/g). These results do suggest that the infection uptake of high-affinity peptide is significatly higher compared to that of the control peptide. While these results provide indirect evidence for the specificity of a high-affinity peptide for infection, no data were reported demonstrating specific binding of a ^{99m}Tc-labeled high-affinity peptide to WBCs, either in circulation or at the infection site.

Subsequently, van der Laken et al. (*5*) report high-affinity peptide localization in both infection (E. coli, S. aureus) and sterile inflammation (zymosan induced). These findings contradict results previously reported by Fischman et al. (*6*) who observed that ^{99m}Tc-labeled chemotactic peptides were accumulated only in the infectious foci and not in sterile inflammation induced by intramuscular injection of anesthetic agents. This apparent discrepancy is attributed to the fact that only the sterile inflammation induced by zymosan was associated with increased infiltrations of PMNs and monocytes while inflammation induced by local injection of chemical agents is not associated with greater accumulations of WBCs. These results, however, demonstrate that the ^{99m}Tc-labeled high-affinity chemotactic peptides cannot distinguish inflammation from infection. In other words, these tracers are not specific for detecting infection as opposed to sterile inflammation.

While the data reported in these two papers are complementary and provide some evidence for the specificity of ^{99m}Tc-fMLFK-HYNIC for infection localization, it is important to identify some major points of confusion between these two papers and in other literature concerning the preclinical evaluation of chemotactic peptides.

RADIOLABELING OF PEPTIDES WITH TECHNETIUM-99M

The peptides are generally conjugated with a chelating agent, such as HYNIC, and subsequently labeled with ^{99m}Tc by an exchange reaction using prelabeled ^{99m}Tc complex containing a wide variety of co-ligands, such as glucoheptonate, mannitol and tricine. In this issue, Babich et al. (*4*) used glucoheptonate as a co-ligand while van der Laken et al. (*5*) used tricine. At 20 hr postinjection, the absolute uptake (%ID/g) in the infection (0.1 versus 0.05) and the control muscle (0.003 versus 0.001) are different. The infection-to-muscle ratios are 33 with glucoheptonate and 50 with tricine. What exactly do these results suggest? In a previous study, Babich et al. (*7*) reported that, for infection imaging, the co-ligand mannitol provided the highest absolute uptake in the infection muscle followed by glucoheptonate and tricine. The data reported by van der Laken et al. (*5*) do show that the absolute infection uptake was reduced by 50% with tricine, but the

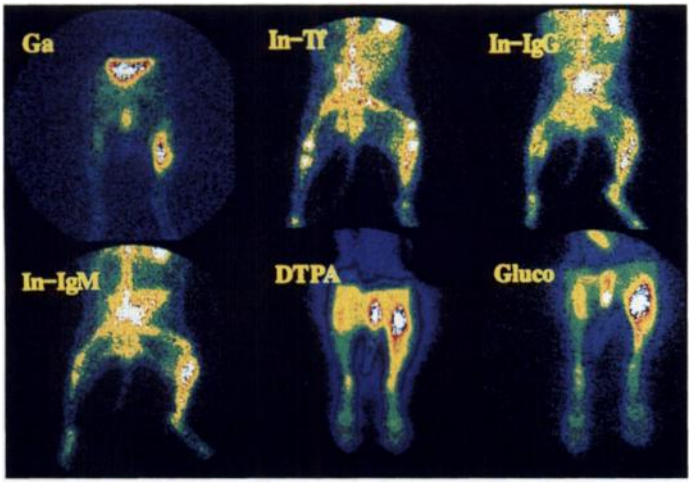

FIGURE 1. Noninvasive imaging studies of different radiopharmaceuticals in rabbits with focal infection (left leg) induced by *E. coli* bacteria. Anterior images were obtained at 4 hr postinjection of the radiotracer.

infection-to-muscle ratio is higher than with glucoheptonate. It is important to perform control experiments with various ^{99m}Tc-co-ligand complexes to determine which agent has the minimal infection uptake. Van der Laken et al. (*5*) point out that they selected tricine as a co-ligand because ^{99m}Tc-tricine has minimal uptake in the infection uptake. These are interesting observations and provide enough material for several publications. The ultimate success of a radiolabeled peptide for infection imaging in patients, however, depends on the biodistribution of the tracer and exact location of the infectious focus. Preclinical studies in rat and rabbit models with acute focal infection are not necessarily useful for optimizing in vivo characteristics of an ideal infection imaging agent.

IMAGING STUDIES VERSUS TISSUE DISTRIBUTION DATA

In the last five years, several investigators evaluated the potential diagnostic value of infection imaging tracers based on imaging studies with minimal tissue distribution data. Infection-to-background ratios ranged from 2–10. Not all these tracers are specific for infection and the mechanism of uptake was not based on binding to specific receptors on WBCs. For example, radiolabeled IgG, IgM (*8*) and liposomes (*9*) provided excellent images of focal infection in rabbits. Recently, Oyen et al. (*9*) reported that ^{99m}Tc-labeled stealth liposomes provided high-quality infection images with infection-to-background ratios of 5–15 in several infectious models. The mechansim of localization of liposomes was not presumed to be due to any specific-receptor binding and might even be nonspecific like the radiolabeled proteins. Figure 1 shows imaging studies performed in rabbits with *E. Coli* infection with six different radiotracers (unpublished data). Nonspecific tracers like ^{99m}Tc-glucoheptonate and DTPA provide excellent images of the infected tissue that are as good as ^{67}Ga-citrate and ^{111}In-IgG. To identify the mechanisms of localization of radiotracers for infection, extreme caution is required in the interpretation of quantitative data based on gamma camera imaging data because both specific and nonspecific tracers might provide similar infection-to-background ratios.

To compare different radiotracers and identify the specific mechanism(s) of localization at the site of infection, it is crucial that one obtains the kinetics of uptake (% ID/g) and clearance of the radiotracer from the infectious muscle, control muscle and blood based on tissue distribution studies. Subsequently, one also can present the data as infection-to-muscle (I/M) and infection-to-blood (I/B) ratios. Tissue distribution data at one time point postinjection (especially 18–24 hr) are not necessarily optimal for understanding the infection localization characteristics of ^{99m}Tc-labeled chemotactic peptides. We have previously reported (*10*) the kinetics of several radiotracers in rats with focal infection and demonstrated that the time-activity curves of % ID/g, I/M and I/B would provide necessary quantitative information to distinguish specific tracers from nonspecific tracers for infection imaging.

RECEPTOR BINDING AND SPECIFICITY

The two articles in this issue (*4,5*) emphasize that the chemotactic peptide, ^{99m}Tc-fMLFK-HYNIC, localizes at focal sites of infection by a receptor-specific mechanism. Most of the evidence reported, however, is indirect. Based on in vitro receptor binding assays (displacement studies) with human neutrophils and [^{3}H]fMLF, the relative affinitties of cold peptides were measured and expressed as EC_{50} values. Babich et al. (*4*) showed that the peptide, N-for-MLFK clearly has higher affinity (EC_{50} = 2 n*M*) compared to the weak agonist, N-Ac-MLFK (EC_{50} = 830 n*M*) and the weak antagonist (EC_{50} =150 n*M*) suggesting that chemotactic peptides bind to specific f-MLF receptors on WBCs. These studies, however, did not document if ^{99m}Tc-labeled chemotactic peptides are really bound to WBCs. If the mechanism of infection localization is based on specific binding to WBCs in blood or at the site of infection, evidence must be presented that the ^{99m}Tc-labeled peptide is indeed associated with WBCs. This can be accomplished in several different ways. The easiest option is to determine the amount of radiolabeled peptide bound to WBCs in vitro under physiological conditions. For example, we have recently reported preclinical studies of a ^{99m}Tc-labeled WBC-specific imaging agent developed from platelet factor-4 (*11*). Based on in vitro studies and gradient centrifugation techniques, it was observed that 74% of the ^{99m}Tc activity was bound to WBCs (28% with PMNs and 46% with monocytes and lymphocytes). We also demonstrated that depletion of circulating WBCs by prior administration of mechlorethamine significantly reduced infection uptake (% ID/g) and infection-to-muscle ratio. Similar data is needed to validate the concept that ^{99m}Tc-fMLFK-HYNIC localization at the site of infection is mediated by specific binding to receptors on WBCs.

It is important to understand the nature of chemotactic peptide binding to the specific receptors on WBCs. It was assumed that the cells respond to a chemoattractant signal and there is a continuous change in the number of receptors and the affinity of the peptide for the receptor until the cell reaches the site of infection (*1*). Does it mean that, at the site of infection, the cells have low affinity for chemotactic peptides? In addition, after binding of the radiolabeled peptide to the cells:

1. Is the radioactivity on the cell membrane or internalized?
2. How tight is the association of the radioactive label with the cells?
3. Is it possible to prevent ^{99m}Tc-peptide binding to cells by increased concentrations of unlabeled chemotactic peptides?

All these questions have not yet been answered. Interestingly, Corstens and Van der Meer (*12*) have speculated that the specificity of the labeled chemotactic peptides is likely to be greater for sterile inflammation since bacterial infections

TABLE 1
Mechanisms of Radiotracers for Infection

Increased vascular permeability and capillary leakage
^{67}Ga-citrate, ^{111}In-chloride
^{111}In and ^{99m}Tc-human polyclonal IgG
^{111}In-human monoclonal antibody IgM 16.88
^{111}In- and ^{99m}Tc-liposomes
^{111}In-biotin and streptavidin
^{99m}Tc-nanocolloids
Cellular migration of WBCs (diapedesis and chemotaxis)
In vitro: intracellularly labeled, ^{111}In and ^{99m}Tc-leukocytes
In vivo: cell surface antigen bound, ^{99m}Tc anti-WBC antibodies
Binding to WBC in circulation or at the infection site
Chemotactic peptides; interleukins (IL-1, IL-2, IL-8); platelet factor-4
Binding to bacterial cells
^{99m}Tc infection (^{99m}Tc-labeled ciprofloxacin antibiotic)
Metabolically trapped
^{18}F-fluorodeoxyglucose

are rich in N-for-MLF residues and sterile inflammations are devoid of these residues. As a result, infection and sterile inflammation should differ in the uptake of radiolabeled chemotactic peptides. Van der Laken et al. (*5*) showed that there is no significant difference in the amount of ^{99m}Tc-fMLFK-HYNIC uptake between bacterial and sterile inflammations. By contrast, Fischman et al. (*6*) reported that sterile inflammations accumulate less radiolabeled peptide than infection tissue. This discrepancy requires further in vitro receptor binding assays with WBCs using ^{99m}Tc-fMLFK-HYNIC as the radioligand to evaluate the effect of several different agonists and antagonists on the amount of cell-associated ^{99m}Tc radioactivity.

Development of specific radiotracers to image infectious foci remains a major challenge for investigators in nuclear medicine. Twenty-five years ago, ^{67}Ga-citrate was first introduced as a radiotracer to image tumor and inflammatory/infectious lesions. The exact mechanism of localization, however, is still not well understood. Despite the lack of specificity, ^{67}Ga is still widely used clinically for the detection of infectious foci. The specificity of radiolabeled WBCs to detect infectious foci was easily recognized since WBCs, particularly polymorphonuclear leukocytes (PMNLs) and monocytes, accumulate at the site of acute infection as a response to inflammation induced by bacterial cells.

McAfee (*13*) has suggested that the most suitable radiotracer to image inflammatory foci may vary under different clinical conditions and in different institutions. Even though ^{111}In-WBCs are highly specific for acute infection, no agent is worse than dead labeled leukocytes to image infectious foci. Since 1990, several radiotracers (Table 1) were introduced as potential candidates to image infection based on a wide variety of mechanisms (*14,16*). Some of these agents include: nonspecific tracers, such as IgG (*15*), IgM (*14*) and liposomes (*9*), and specific tracers, such as antiganulocyte monoclonal antibodies (*16,17*), chemotactic peptides (*4,7,18*), interleukins (*19,20*) and antibiotics (*21*). All these tracers showed potential diagnostic value in preclinical studies. Besides specificity, the criteria for an ideal radiotracer for infection imaging (Table 2) includes many different characteristics. It is difficult for any one agent to qualify as an ideal radiotracer. Finally a radiotracer might have diagnostic value or use even though it is not absolutely specific. Although it is meritorious to try to develop an understanding of the specificity of an infection/inflammation imaging agent, it would seem worthwhile to evaluate the effectiveness of Tc-labelel chemotactic peptides in clinical situations before spending up to a decade on preclinical studies in animal models with focal infection.

TABLE 2
Criteria for an Ideal Radiotracer for Infection Imaging

1.	Specific localization at the site of infection/inflammation (high specificity; no false-positives).
2.	Ability to identify focal infections (even small) in all patients with infection (high sensitivity; no false-negatives).
3.	Ability to differentiate infection from sterile inflammation.
4.	Ability to differentiate infection from tumor.
5.	Ability to differentiate acute from chronic infection.
6.	Rapid detection of infection; early localization (within 3 hr).
7.	Ability to monitor therapeutic response.
8.	Rapid clearance from blood with minimal uptake in liver, spleen, kidneys, GI tract and bone/bone marrow.
9.	Easy to prepare, nontoxic, low cost and widely available.

Shankar Vallabhajosula
Division of Nuclear Medicine
Department of Radiology
New York Hospital-Cornell Medical Center
New York, New York

REFERENCES

1. Fischman AJ, Pike MC, Kroon D, Fucello AJ, Rexinger D, ten Kate C, Wilkinson R, Rubin RH, Strauss HW. Imaging focal sites of bacterial infection in rats with indium-111-labeled chemotactic peptide analogs. *J Nucl Med* 1991;32:483–491.
2. Babich JW, Graham W, Barrow SA, Pike MC, Kroon D, et al. Technetium-99m-labeled hydrazino derivatized chemotactic peptide analogs for imaging focal sites of bacterial infection *J Nucl Med* 1993;34:1964–1974.
3. Babich JW, Graham W, Barrow SA, Dragotakes SC, Tompkins RG, Rubin RH, Fischman AJ. Technetium-99m-labeled chemotactic peptides: comparison with indium-111-labeled white blood cells for localizing acute bacterial infection in the rabbit *J Nucl Med* 1993;34:2176–2181.
4. Babich JW, Tompkins RG, Graham W, et al. Localization of radiolabeled chemotactic peptide at focal sites of E. Coli infection in rabbits: evidence for a receptor specific mechanism *J Nucl Med* 1997;1316–1322.
5. Van der Laken, Boerman OC, Oyen WJG, et al. Technetium-99m-labeled chemotactic peptides specifically localize in acute infection and sterile inflammation. *J Nucl Med* 1997;1310–1315.
6. Fischman AJ, Babich JW, Barrow SA, et al. Detection of acute bacterial infection within soft tissue injuries using a ^{99m}Tc-labeled chemotactic peptide. *J of Trauma Injury, Infection, and Critical Care* 1995;38: 2:223–227.
7. Babich JW, Fischman AJ. Effect of "co-ligand" on the biodistribution of ^{99m}Tc-labelled hydrazino nicotinic acid derivatized chemotactic peptides. *Nucl Med Biol* 1195;22:25–30.
8. Subramanian R, Vallabhajoshula S, Lipszyc H, et al. Indium-111-labeled IgM, a human monoclonal antibody for infection imaging: preclinical studies in rats and rabbits. *J Nucl Med* 1997: in press.
9. Oyen WJG, Boerman OC, Storm G, et al. Detecting infection and inflammation with technetium-99m-labeled stealth® liposomes. *J Nucl Med* 1196;37:1392–1397.
10. Vallabhajosula, Moyer BR, Lee H, et al. Acute focal inflammation (inf) model in rats: comparison of seven different radiotracers. *Eur J Nucl Med* 1994; 21:775P.
11. Moyer BR, Vallabhajosula S, Lister-James J, et al. Developemnt of a ehite blood cell specific technetium-99m imaging agent from platelet factor 4 for detecting infection. *J Nucl Med* 1996;37:673–679.
12. Corstens FHM, Van der Meer JWM. Chemotactic peptides: new locomotion for imaging of infection? [Editorial] *J Nucl Med* 1991;32:491–494.
13. McAfee JG. What is the best method for imaging focal infections? [Editorial] *J Nucl Med* 1990;31: 413–416.
14. Oyen WJG, Boerman OC, van der Laken CJ, Claessens RAMJ, van der Meer JWM, Corstens FHM. The uptake mechanisms of inflammation and infection-localizing agents. *Eur J Nucl Med* 1996;23: 459–465.
15. Corstens FHM, Claessens AMJ. Imaging inflammation

with human polyclonal immunoglobulin: not looked for but discovered. *Eur J Nucl Med* 1992;19:155–158.
16. Becker W. The contribution of nuclear medicine to the patient with infection. *Eur J Nucl Med* 1995;22:1195–1211.
17. Thakur ML, Henneman MP, Butler J, et al. Imaging inflammatory diseases with neutrophil-specific technetium-99m-labeled monoclonal antibody anti-SSEA-1. *J Nucl Med* 1996;37:1789–1795.
18. Pollak A, Goodbody AE, Ballinger JR, et al. Imaging inflammation with technetium-99m-labeled chemotactic peptides: analogues with reduced neutropenia. *Nucl Med Commun* 1996;17:132–139.
19. Van der Laken CJ, Boerman OC, Oyen WJG, et al. Specific targeting of infectious foci with radioiodinated human recombinant interlleukin-1 in an experimental model. *Eur J Nucl Med* 1995;22:1249–1255.
20. Signore A, Chianelli M, Toscano A, et al. A radiopharmaceutical for imaging areas of lymphocytic infiltration: ^{123}I interleukin-2 labeling procedure and animal studies. *Nucl Med Comm* 1992;13:713–722.
21. Vinayamuri S, Hall AV, Solanki KK, et al. Comparison of ^{99m}Tc infecton imaging with radiolabeled white-cell imaging in the evaluation of bacterial infection. *Lancet* 1996;347:233–235.