Leukotrienes are lipid mediators with important roles in immunity. The enzyme 5-lipoxygenase initiates leukotriene synthesis; nuclear import of 5-lipoxygenase modulates leukotriene synthetic capacity. In this study, we used structural and functional criteria to identify potential nuclear import sequences. Specifically, we sought basic residues that 1) were common to different 5-lipoxygenases but not shared with other lipoxygenases, 2) were found on random coil/loop structures, and 3) could be replaced without eliminating catalytic activity. Application of these criteria to the putative bipartite nuclear import sequence of 5-lipoxygenase revealed that this region formed an α-helix rather than a random coil, that the critical residue arginine 651 serves a structural role, and that mutation of this residue eliminated catalytic activity. A previously unrecognized region corresponding to residues 518–530 on human 5-lipoxygenase was found to be unique to 5-lipoxygenase and on a random coil. This region alone was sufficient to drive import of green fluorescent protein to the same degree as complete 5-lipoxygenase. Replacement of basic residues in this region of the complete protein was capable of eliminating nuclear import without abolishing catalytic activity. Surprisingly, two subpopulations of cells expressing 5-lipoxygenase with this mutated region could be discerned: those with strongly impaired import and those with normal import. Taken together, these results show that the previously identified region with a bipartite motif is not a functional import sequence, whereas the newly identified basic region constitutes a true nuclear import sequence. Moreover, we suggest that another sequence that can mediate nuclear import of 5-lipoxygenase remains to be identified.

Leukotrienes are lipid messengers that play central roles in immune response and tissue homeostasis (reviewed in Ref. 1). However, abnormal production of leukotrienes contributes to a variety of diseases. The enzyme 5-lipoxygenase (5-LO) catalyzes the initial steps in the synthesis of leukotrienes from arachidonic acid. For this reason, leukotriene synthesis is critically dependent on processes that modulate 5-LO activity.

One such process is nuclear import of 5-LO. In leukocytes circulating in peripheral blood, 5-LO is found exclusively in the cytoplasm (2–4). However, import of 5-LO into the nucleus can be induced by recruitment of cells into sites of inflammation (2, 5), by adherence to different surfaces (2, 5, 6), or by cytokine treatment (3). Import of 5-LO is linked to activity since nuclear import of 5-LO can strongly enhance (2, 3) or suppress (5) leukotriene synthesis upon subsequent cell stimulation.

The regulation of nuclear import of 5-LO is poorly understood. In particular, our understanding of the regions on 5-LO that act as nuclear import sequences (NISs) is incomplete. Previously, Funk and colleagues (7) identified three candidate regions based on the abundance of the basic amino acids Arg or Lys. Partial mutagenesis of these basic regions (BR) indicated that none of these sites acted as an NIS (7). A more complete study of one of these BRs, which matched the motif for bipartite NISs, led to the conclusion that this region, and in particular Arg<sup>651</sup>, was necessary for nuclear import of 5-LO (8, 9). However, further analysis of Arg<sup>651</sup> mutants of 5-LO indicated that these had limited enzymatic activity (9), suggesting that these mutants were misfolded and that this might be the basis for impaired nuclear import.

Until now, candidate nuclear import regions on 5-LO have been identified solely on the presence of basic residues, which facilitate binding with importin proteins. In this study, additional structural and functional criteria were used. First, 5-LO from mouse, rat, and human leukocytes all show nuclear import (10), but the related 12-LO and 15-LO do not (11). As a result, the primary sequence structure of candidate NISs should be both unique to 5-LO and common across species. Second, to interact with importin proteins, both monopartite and bipartite NISs must conform to an appropriate secondary structure. Resolved crystal structures indicate that both the monopartite SV40 large T antigen NIS and the bipartite nucleoplasmin NIS must reside on random coil/loop structures to interact with importin α (12–14). Thus, candidate regions on 5-LO should have a random coil or loop secondary structure. Finally, Funk and colleagues (7) demonstrated that mutations that eliminated enzymatic function could also abolish nuclear import. This showed that import can be inhibited nonspecifically, by general changes in protein structure, as well as specifically, by eliminating NIS binding to importin. More importantly, it showed that enzymatic function may be used to distinguish specific and nonspecific effects of mutagenesis on import.

This study applies these structural and functional criteria for NISs to 5-LO. Re-examination of the putative bipartite NIS shows that it fails to meet both structural and functional criteria and cannot be a true NIS. This contrasts with a novel region, spanning residues 518–530 on human 5-LO, that meets these new criteria and is both sufficient and necessary for
nuclear import. Interestingly, we find that although this region functions as an NIS, at least one other NIS must also exist on 5-LO.

**EXPERIMENTAL PROCEDURES**

Sequence and Structural Analysis—Amino acid sequences were obtained from SwissProt (Expert Protein Analysis System) proteomics server of the Swiss Institute of Bioinformatics. Primary accession numbers for proteins are: for 5-LOs, human P08917, mouse P48999, rat P12527, hamster P51399; for 15-LOs, rabbit P12630, human P16050; for human platelet-type 12-LO P18054. Alignment of protein sequences was performed using CLUSTALW (15). Structural analysis utilized the resolved structures of rabbit 15-LO (Protein Data Bank identifier 1lox) and the theoretical model of the 5-LO catalytic region (16).

Flasminids and Mutagenesis—To construct a fusion peptide joining BR518 to a green fluorescent protein (GFP), complementary oligonucleotides encoding Val133–Leu356 (YVIMGKRGSSGFPSVSQSKSREQL) were annealed and ligated to the BamHI and HindIII sites of pEGFP-C1. To construct GFP/BR/BR, two copies of the above mentioned oligonucleotides were ligated in tandem to the BamHI and HindIII sites of pEGFP-C1.

Specific amino acids within the putative 5-LO NISs were substituted in the pEGFP-C1/5-LO template (8) using the QuikChange site-directed mutagenesis kit (Stratagene). Briefly, two complementary primers (125 ng each) containing the desired mutation and 20 ng of template in 1× reaction buffer were denatured at 95 °C for 3 s and annealed at 55 °C for 30 s, and DNA synthesis was carried out by Pfu polymerase at 68 °C for 14 min. This cycle was repeated 12–18 times, depending on the number of bases substituted, according to the manufacturer’s directions. The methylated template was removed by incubation with 10 units of DpnI at 37 °C for 1 h. The mutation BR518a was R518Q/G519G/–, and BR518b was K527Q/S528V/S529V/K530Q.

All substitutions and constructs were verified by DNA sequence analysis (DNA Sequencing Core, University of Michigan). Oligonucleotides (the sequences of which are available upon request) were synthesized by Integrated DNA Technologies Inc. (Coralville, IA) or Invitrogen.

Cell Culture, Transfection, and Imaging—NIH 3T3 cells were obtained from American Type Culture Collection (Manassas, VA) and grown under 5% CO2 in Dulbecco’s modified Eagle’s medium (Invitrogen) supplemented with 10% calf serum, 100 units/ml penicillin, and 100 units/ml streptomycin. Cells were transfected using FuGENE 6 (Roche Molecular Biochemicals) or Polyfect (Qiagen, Inc.) transfection reagents according to the manufacturer’s specifications. Transfected cells were examined as early as 9 h after transfection.

Immunoblotting—As described previously (8), cells were disrupted by sonication on ice, and protein concentrations were determined by a modified Coomassie dye binding assay (Pierce). Samples containing 10 μg of protein were separated by SDS-polyacrylamide gel electrophoresis under reducing conditions and transferred to nitrocellulose. Membranes were probed with a rabbit polyclonal antibody raised against purified human leukocyte 5-LO (a generous gift from Dr. J. Evans, Merck Frost Centre for Therapeutic Research) (17) or rabbit polyclonal anti-GFP (Santa Cruz Biotechnology, Inc.; titer 1:500) followed by peroxidase-conjugated secondary antibody and enhanced chemiluminescence detection (Amersham Biosciences).

Cell Stimulation and Analysis of Leukotriene Synthesis—To stimulate 5-LO activity, cells transfected with various 5-LO constructs were incubated for 30 min at 37 °C in serum-free medium containing 10 μM calcium ionophore A23187 and 10 μM arachidonic acid. Immunoreactive leukotriene B4 in conditioned media was quantitated by enzyme immunoassay (Cayman Chemical, Ann Arbor, MI) according to the supplier’s instructions.

Quantitation of Subcellular Distribution—As an initial approach to quantitation, slides were fixed 1 h after transfection, and 100 positive cells were scored as to whether nuclear fluorescence was greater than, equal to, or less than cytosolic fluorescence. Care was taken to avoid damaged, dead, or autofluorescent cells. Results from at least three independent transfections per construct were used for statistical analysis. As a second approach, 100 individual cells per construct were scored for cytosolic and nuclear fluorescence intensity: using Adobe Photoshop 5.5, grayscale digital images were adjusted to include the full black-to-white range, and representative gray values, from 0 (white) to 100 (black), were obtained for the cytoplasm and nucleoplasm. Cytosolic and nuclear values for each cell were summed to give total cellular fluorescence, and the percentage of fluorescence values for the nuclear compartment were calculated.

**RESULTS**

**Reassessment of BR638 as a Functional NIS—**As noted above, nuclear import of 5-LO is common across species but does not occur in other LOs. This suggested that the primary sequence should be strongly conserved in 5-LO from different species and should not be found in other LOs. The putative bipartite NIS, characterized as RKX11RNKKK in human 5-LO (residues 638–655), is largely conserved across different species of 5-LO, although the terminal grouping, RNKKK, changes to RNLKK in rodent 5-LOs (Fig. 1A). In other LOs, only the initial arginine, as well as the critical arginine (Arg651 in human 5-LO) are conserved. By primary structure alone, this region would remain a reasonable candidate functional NIS.

Interaction with importin requires that both simple and bipartite NISs have a coil or loop secondary structure. On 5-LOs and other LOs, almost the entire region corresponding to BR638 forms an α-helix (Fig. 1B). This suggested that this region does not have an appropriate structure to mediate interaction with importin. One consequence of having the amino acids arranged in a helix is that the positively charged side groups of basic residues may not be oriented for accessibility to interact with importin. Most notably, the critical residue Arg651 projects inward with its side chain apparently interacting with the negatively charge side group of Asp473 (Fig. 1C). Further examination of the 628–654 helix (Fig. 1B) revealed that the majority of the residues that are conserved across different LOs (Fig. 1A) are hydrophobic and oriented toward hydrophilic residues on the sister 470–489 helix (data not shown). This indicated that the interaction between Arg651 and Asp473 serves a critical role in maintaining the correct positioning of the two helices.
These structural features indicated that mutation of Arg_651 stopped nuclear import not because it prevented interaction of 5-LO with importin but rather because it eliminated the key Arg_651–Asp_473 association. If so, then mutation of Asp_473 should similarly stop nuclear import. Consistent with this, replacement of Asp473 with Gln, like the R651Q mutation, eliminated nuclear import of GFP/5-LO (Fig. 2). Importantly, both the R651Q mutant and the D473Q mutant of GFP/5-LO were catalytically inactive, both when tested in intact 3T3 cells and when tested in cell-free assays (data not shown). This result was consistent with these residues serving critical structural functions.

Evaluation of BR_518 as a Functional NIS—A novel basic region, beginning at Arg_518 on human 5-LO, was identified after aligning numerous mammalian 5-, 12-, and 15-LOs simultaneously using CLUSTALW. Correct alignment was suggested by high levels of amino acid similarity on both sides of the region as well as alignment of the GFPXS core (Fig. 3A). This region, BR_518, contained three clustered basic residues at one end (RGR/KK) and three at the other (KSI/VKSR), which were conserved across 5-LOs and not found in 12- or 15-LOs (Fig. 3A). This region was found on a random coil of the catalytic domain of 5-LO (Fig. 3B). The presence of conserved glycine and proline residues, which can serve as “helix breakers,” also indicates that this region would retain a random coil structure. Since the region was conserved across different 5-LOs, not found on other LOs, and was on a coiled structural element, it met our primary and secondary structural criteria for a good candidate NIS.

To determine whether this region was sufficient to mediate nuclear import, a sequence encoding the entire BR_518 region was appended to GFP. As published previously (8), GFP alone was found to be equally distributed between the nucleus and cytoplasm of transfected 3T3 cells, presumably because its small size allowed free diffusion into and out of the nucleus of 3T3 cells. As shown in Fig. 4, the GFP/5-LO fusion protein, as demonstrated previously (8), showed strong nuclear accumulation. Fusion of the BR_518 peptide to GFP (GFP/BRpeptide) produced nuclear import that mimicked that of GFP/5-LO, although the small size should still allow free diffusion of the protein back out of the nucleus. Fusion of two sequential BR_518 peptides to GFP (GFP/BR/BR) produced stronger nuclear import.

To determine whether either part of the BR_518 region was necessary for nuclear import, site-directed replacement of basic residues on GFP/5-LO was performed. The clusters, designated BR_518a and BR_518b, on either side of the Gly-Phe-Pro spacer were analyzed separately or together. Since the terminal argi-
Novel NIS on 5-LO

Effect of mutations within the BR518 domain of 5-LO. A, immunoblot showing protein expression in 3T3 cells transfected with GFP/5-LO with mutations in regions a, b, or a+b of BR518, as indicated in the legend for Fig. 3. Membranes were probed with anti-GFP. WT = wild type GFP/5-LO. B, representative population showing the major phenotypes of subcellular distribution in 3T3 cells transfected with the BR518(a+b) mutant of GFP/5-LO. Cells show clear nuclear accumulation (Nuc), relatively balanced distribution (Bal), or cytosolic (Cyto).

either GFP (Fig. 5A) or 5-LO (data not shown). Surprisingly, several distinct patterns of subcellular distribution of the mutants were observed in a given transfection: some cells showed clear nuclear accumulation of the expressed protein, other cells showed a balanced distribution, and others showed cytosolic accumulation (Fig. 5B). This result was quantitated by scoring cells individually as having nuclear fluorescence greater than, equal to, or less than the cytosolic fluorescence. Representative images and numbers are given in Fig. 6. Although the majority (78%) of wild type GFP/5-LO cells had nuclear accumulation, a significant number (22%) had a balanced distribution. A balanced distribution of 5-LO, associated with nuclear envelope breakdown during mitosis, has been described (18) and quantitated (9). Mutation at either the BR518a or the BR518b site reduced the number of cells with nuclear import and increased those with cytosolic fluorescence. Mutation at both sites appeared to be additive.

Statistical analysis of results from multiple transfections showed that both the reduction of cells with nuclear import and the increase in cells with cytosolic fluorescence were statistically significant (Table I). This analysis also showed that mutation of both basic regions produced statistically greater changes in both distribution groups. No statistically significant change in the group showing balanced distribution was found for any mutation. Significantly, all mutants were functionally impaired, producing leukotriene B4 when stimulated with the calcium ionophore A23187 in the presence of 10 μM arachidonic acid. Closer examination of Arg532 indicated that its side chain is oriented toward the center of 5-LO and is conserved across different LOs, supporting a structural role. However, Arg132 and Lys133 are oriented outward and are unique to the 5-LOs, suggesting that these residues were structurally important. Indeed, Arg132 is oriented toward the center of 5-LO and is conserved across different LOs, supporting a structural role. However, Arg132 and Lys133 are oriented outward and are unique to the 5-LOs, suggesting that they might be relevant to nuclear import. Mutation of these two residues had no effect on import when compared with WT 5-LO (Table III). Also, mutation of these

![Image](http://www.jbc.org/)

**TABLE I**

| Plasmid         | Nuclear > Cytosolic | Nuclear = Cytosolic | Nuclear < Cytosolic | Activity |
|-----------------|---------------------|--------------------|--------------------|----------|
| Wild type       | 80.8 (1.7)          | 17.9 (2.3)         | 1.3 (0.6)          | ++ +     |
| mBR518a         | 64.4 (4.1)*         | 21.7 (3.3)         | 13.9 (1.3)*        | ++ +     |
| mBR518b         | 69.3 (0.6)*         | 18.8 (0.7)         | 11.9 (1.0)*        | ++ +     |
| mBR518 (a + b)  | 54.1 (3.1)*,**     | 22.5 (1.5)         | 23.4 (2.5)*,**     | ++ +     |

activity was assessed as amount of leukotriene B4 produced by transduced cells, adjusted for protein expression, as measured by enzyme immunoassay.

**Fig. 6.** Quantitation of the distribution phenotypes observed with the different GFP/5-LO constructs. 3T3 cells were transfected with GFP/5-LO that was unmodified (wild type) or mutated in the BR518 (mBR518a), BR518b (mBR518b), or both regions (mBR518a+b). After 16 h, 100 positive cells were scored for nuclear accumulation (Nuc>Cyto), balanced (Nuc=Cyto), or cytosolic (Nuc>Cyto) distribution, and representative cells were imaged. Numbers indicate results from one experiment.

**FIG. 5.** Effect of mutations within the BR518 region on subcellular distribution of GFP/5-LO in 3T3 cells. Cells were transfected, incubated for 16 h, and fixed. 100 cells/transfection were scored; results are reported as percent of cells with the given distribution of green fluorescence. Data are means (S.E.) of n = 5 experiments. *, p < 0.05 versus wild type; **, p < 0.05 versus mBR518b. After 16 h, 100 positive cells were scored for nuclear accumulation (Nuc > Cyto), balanced (Nuc = Cyto), or cytosolic (Nuc < Cyto) distribution, and representative cells were imaged. Numbers indicate results from one experiment.
Effect of mutation of Arg651 on the subcellular distribution of GFP/5-LO and GFP/5-LO mBR518 in 3T3 cells

Cell preparation is as described in Table I; results are reported as percentage of cells with the given distribution of fluorescence. Data are means (S.E.) of n = 3 experiments; *, p < 0.05 versus wild type; **, p < 0.05 versus mBR518 (a + b). Activity was assessed as amount of leukotriene B4 produced by transfected cells, adjusted for protein expression, as measured by enzyme immunoassay.

| Plasmid                  | Nuclear > Cytosolic | Nuclear = Cytosolic | Nuclear < Cytosolic | Activity |
|--------------------------|---------------------|---------------------|---------------------|----------|
| Wild type                | 86.9 (0.9)          | 11.7 (1.0)          | 1.4 (0.5)           | ++ +     |
| R531Q                    | 10.0 (2.2)*         | 32.2 (2.4)*         | 57.7 (0.2)*         | -- --    |
| mBR518 (a + b)           | 59.3 (3.0)*         | 22.0 (1.3)*         | 18.8 (1.3)*         | ++       |
| mBR518 (a + b) + R531Q   | 0.0 (0.0)*,**       | 8.6 (1.1)           | 91.4 (1.1)*,**     | -- --    |

Fig. 7. Effect of substitution of Arg652 on the subcellular distribution of GFP/5-LO. A, R532Q combined with the BR518 (a + b) mutation. DAPI, 4,6-diamidino-2-phenylindole. B, R532Q alone.

Discussion

The nuclear import of 5-LO has repeatedly been shown to be a mechanism for regulating the leukotriene synthetic capacity of leukocytes (2, 3, 5). Previous studies have provided evidence that BR653–655 is a bipartite NIS. More specifically, analysis by our group and others has found that Arg651 is absolutely critical for nuclear import (8, 9). In this study, we present evidence that, unlike other bipartite NISs, residues 638–654 reside on a structural α-helix and that Arg651 acts to link that structure to a neighboring helix, indicating that this region does not serve as an NIS function. We have now for the first time identified a new region on 5-LO, involving residues 518–530 on human 5-LO, that meets a more rigorous set of criteria as a functional NIS. Specifically, this region 1) is conserved on other mammalian 5-LOs and is not found on 12- or 15-LOs, 2) forms a random coil secondary structure, 3) can, as a peptide, direct the import of GFP, and 4) retains enzymatic activity when site-directed mutation impairs nuclear import of the full-length protein. These results indicate that this region is a functional NIS on 5-LO. However, mutation of this region produces (at least) two distinct populations. The persistence of nuclear import in some cells, even when BR518 is intensively mutated, suggests that another NIS must exist on 5-LO.

Our current understanding regarding 5-LO action includes acceptance of BR653–655 as a functional bipartite NIS (for example, see Ref. 19). The primary reason for this must be its strong similarity to the signature pattern of bipartite NISs, as indicated by its identification by such tools as PROSITE or MotifScan. However, this pattern has a high probability of occurrence in proteins, leading to false positives: about 4.2% of non-nuclear proteins have such patterns (20). The central function of basic residues in an NIS is to interact with importins, which mediate the import process (21). Structurally, the side chains of these critical residues must extend outward to facilitate this protein-protein interaction. However, structural analysis indicated that the critical residue Arg651 (on 5-LO) is conserved across different LOs and that its side chain is oriented inward. Also, this basic residue was found to interact with a conserved acidic residue, Asp733, on 5-LO. In this study, we found that replacement of either residue with an uncharged amino acid eliminated both nuclear import and enzymatic activity. These findings strongly indicate that this region is not an NIS.

Such an analysis showed that, in addition to the presence of basic residues, structural criteria could be useful in identifying potential NISs. Also, the observation by Chen and Funk (11) that 12-LOs and 15-LOs do not show nuclear import suggested...
that the 5-LO NIS should not be found on these closely related proteins. Using both primary and secondary structural information, we identified the BR518–530 segment as a potential NIS. Addition of a single copy of this peptide to GFF strongly directed nuclear import; two copies produced greater nuclear accumulation. Replacement of basic residues in this region of the GFF/5-LO fusion protein strongly impaired nuclear import. These results indicate that this region is a functional NIS.

Surprisingly, elimination of basic residues in BR 518–530 of 5-LO resulted in a protein that could be imported in some cells but not others within a given population of transfectants. This result was very different from the essentially total elimination of nuclear import observed when either Arg651 or Asp473 was replaced (Fig. 2) or when protein structure was intentionally disrupted (7). As shown in Figs. 5 and 6, the subpopulations of distributions observed in mBR518(a+b) 5-LO transfectants are visually striking. As shown in Fig. 8B, they are quantifiably distinguishable. The subpopulation demonstrating unquestionable nuclear import (designated as Nuc>Cyt in Fig. 6 and as N1 in Fig. 8B) can only mean that a functional NIS remains on this mutated 5-LO protein. A weak NIS was identified in the opposite end of the protein, in the N-terminal domain (7). On the other hand, the absence of strong nuclear import in other cells in the same population (designated as Nuc<Cyt in Fig. 6 and C1 in Fig. 8B) may indicate that the alternative NIS is inactivated. Alternatively, the export process may be important in determining the subcellular distribution of this protein. It is possible that the export process may also be regulated, that peak N1 corresponds to inactivated export, and that peak C1 and/or the balanced distribution peak (at 50% nuclear fluorescence) corresponds to activated export.

The conclusion that a second NIS, in addition to BR518, may exist and may be inactivated allows additional interpretation of the quantitative data for WT 5-LO, as shown in Fig. 8A. Considering the import process alone, the greater nuclear fluorescence at peak N2 may reflect the action of two active NISs, whereas the lesser peak N1 may result from a single active NIS. This interpretation is consistent with the observation that neutralization of one NIS (BR518) reduces peak N2 more than N1 (Fig. 8B). Alternatively, it is possible that, for WT 5-LO, the export process, when activated, may only be able to diminish nuclear import from N2 to N1.

The nuclear import process is commonly regulated by phosphorylation (for review, see Ref. 22). There is evidence that the metabolic activity of 5-LO can be stimulated by phosphorylation, by protein kinase C (23, 24), a protein tyrosine kinase (25), and by MAP kinase kinase (26), but these studies did not show direct phosphorylation of 5-LO. More recently, two groups have been able to show direct phosphorylation of 5-LO by a tyrosine kinase (27) and by MAPKAP kinase 2 (28). Both groups also found that phosphorylation was necessary for translocation to the nucleus (27, 29). However, it is not known whether any of these phosphorylation events might also modulate nuclear import of 5-LO.

It has been shown previously that when the nuclear envelope breaks down during mitosis, the nuclear accumulation of 5-LO observed in cells in culture is lost (18). Izumi and colleagues (9) found that following the completion of mitosis and re-formation of the nuclear envelope, nuclear import was activated to regenerate the nuclear accumulation of 5-LO. This suggests that at least one of the NISs of 5-LO may be activated during the G1 phase of the cell cycle.

In summary, we have used a combination of structural and functional criteria to re-examine the bipartite NIS-like domain of 5-LO and found that it is not a functional nuclear import sequence. However, we have identified a novel site on 5-LO that is conserved across species but is not found on other lipoxygenases, is distributed over a random coil of the catalytic domain, is sufficient to direct nuclear import of GFP, is necessary for normal import of 5-LO, and whose mutation does not abolish enzymatic activity. These results indicate that the 518–530 basic region of human 5-LO is a functional NIS. Sur-
prisingly, our results indicate that at least one other NIS exists on 5-LO. We expect that a similar search strategy, based on the use of structural and functional criteria, will reveal the other NIS(s).

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Structural and Functional Criteria Reveal a New Nuclear Import Sequence on the 5-Lipoxygenase Protein

Sandra M. Jones, Ming Luo, Annette M. Healy, Marc Peters-Golden and Thomas G. Brock

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