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# Human DNA sequence homologous to the transforming gene (*mos*) of Moloney murine sarcoma virus

(*onc* genes/*mos* nucleotide sequence/recombinant DNA/transfection)

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**ABSTRACT** We describe the molecular cloning of a 9-kilobase-pair *BamHI* fragment from human placental DNA containing a sequence homologous to the transforming gene (v-*mos*) of Moloney murine sarcoma virus. The DNA sequence of the homologous region of human DNA (termed hu*mos*) was resolved and compared to that of the mouse cellular homolog of v-*mos* (termed mu*mos*) [Van Beveren, C., van Straaten, F., Galleshaw, J. A. & Verma, I. M. (1981) *Cell* 27, 97–108]. The hu*mos* gene contained an open reading frame of 346 codons that was aligned with the equivalent mu*mos* DNA sequence by the introduction of two gaps of 15 and 3 bases into the mu*mos* DNA and a single gap of 9 bases into the hu*mos* DNA. The aligned coding sequences were 77% homologous and terminated at equivalent opal codons. The hu*mos* open reading frame initiated at an ATG found internally in the mu*mos* coding sequence. The polypeptides predicted from the DNA sequence to be encoded by hu*mos* and mu*mos* also were found to be extensively homologous, and 253 of 337 amino acids were shared between the two polypeptides. The first five $NH_2$-terminal and last two COOH-terminal amino acids of the hu*mos* gene product were in common with those of mu*mos*. In addition, near the middle of the polypeptide chains, four regions ranging from 19 to 26 consecutive amino acids were conserved. However, we have not been able to transform mouse cells with transfected hu*mos* DNA fragments or with hybrid DNA recombinants containing hu*mos* and retroviral long terminal repeat (LTR) sequences.

Results from studies of the acute transforming retroviruses have provided the first knowledge of the role of specific cellular sequences in malignant transformation. A portion of the genome of these viruses is homologous to host chromosomal sequences. These sequences acting in concert with viral transcription control elements have been implicated in tumor formation in animals and morphological transformation in tissue culture (1–8). In general, these host sequences are called *onc* genes with the prefix v- or c- used to distinguish viral and cellular homologs, respectively (9). Although the normal biological functions of c-*onc* genes are unknown, it is known that they are present in low or single copy number in host chromosomes and are generally conserved between species (1, 9). One such *onc* gene is present in the acute transforming Moloney murine sarcoma virus (Mo-MuSV). This virus arose spontaneously during the passage of Moloney murine leukemia virus (Mo-MuLV) in BALB/c mice (10) and is a recombinant between Mo-MuLV and a mouse chromosomal sequence designated *mos* (2, 9, 11–15).

The acquired Mo-MuSV v-*mos* has been used as a probe to isolate bacteriophage λ recombinants containing fragments of mouse cell DNA bearing the homologous c-*mos* gene (2, 13). A direct comparison of the nucleotide sequences of v-*mos* and mouse-derived c-*mos* [referred to here as mu*mos* from c-*mos* (murine)] has revealed only 21-nucleotide and 11-amino-acid differences within 1,111 nucleotides of an open reading frame coding for the putative *mos*-transforming gene product (16). The transforming potential of the cloned cellular DNA containing mu*mos* has been tested in DNA transfection assays, and, although it does not transform fibroblasts by itself, it can be activated to transform efficiently by inserting the long terminal repeat (LTR) of the provirus at variable distances 5′ to the mu*mos* gene (2, 3, 6).

By molecular hybridization in liquid it was demonstrated that v-*mos* homologous sequences were conserved in the DNA of a variety of animal species, including human (17). We were interested in determining how closely the nucleotide sequence of the gene present in human DNA was related to mu*mos* and whether the human gene homolog had transforming potential. We used a *mos*-specific DNA probe to select a bacteriophage λ recombinant (λHM1) containing a 9-kilobase-pair (kbp) *BamHI* fragment of human placental DNA possessing sequences with homology to the mu*mos* gene. This DNA fragment was compared to the v-*mos* and mu*mos* genes by blot-hybridization analyses and DNA sequence determinations. In this way, we have identified a human DNA sequence that is strongly homologous to mu*mos* and which, in consequence, we have termed hu*mos* [derived from c-*mos* (human)]. The polypeptide predicted from an open reading frame in the DNA sequence of the hu*mos* gene is remarkably similar to the putative product of the mu*mos* gene.

## MATERIALS AND METHODS

**Cloning of hu*mos*-Containing DNA Fragments.** Human placental DNA, extracted as described for tissue culture cells (18), was digested with *BamHI* and subjected to RPC-5 chromatographic and gel electrophoretic enrichment procedures (18). A nick-translated (19) $^{32}$P-labeled *mos*-specific probe was prepared by using a 966-base-pair (bp) *Ava* I/*Hin*dIII DNA fragment isolated from a previously described plasmid, pMS1 (6). A single 9.0-kbp *BamHI* human DNA fragment hybridizing with the *mos* probe was identified by Southern analyses (20) and cloned into the Charon 30 λ phage vector.

**DNA Sequence Determination.** The nucleotide sequences of both strands of plasmid pBR322 subclones of hu*mos* (described below) were determined by the procedure of Maxam and Gilbert (21). DNA fragments to be sequenced were $^{32}$P-labeled at the 5′ or 3′ termini by procedures as described (22).

## RESULTS

**Isolation of λHM1 and Localization of hu*mos* Sequences.** A *mos*-specific $^{32}$P-labeled *Ava* I/*Hin*dIII DNA fragment was

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Abbreviations: Mo-MuSV, Moloney murine sarcoma virus; Mo-MuLV, Moloney murine leukemia virus; LTR, long terminal repeat; kbp, kilobase pair(s).

used as probe to detect homologous *mos* sequences in *Bam*HI-digested human placental DNA. The DNA was first fractionated by RPC-5 chromatography, and column fractions were further subjected to Southern blot analyses (20) after gel electrophoresis (Fig. 1). Only one band in the human DNA was found to hybridize with the *mos* probe. By using the Charon 30 λ phage vector, recombinants were made with DNA from this region, and the *mos* probe was used to select a recombinant possessing homologous *mos* sequences (referred to as λHM1). A restriction map of the cloned fragment in λHM1 is shown in Fig. 1. The same *mos* probe also was used to localize homologous sequences in the λHM1 DNA insert. In a number of blot-hybridization experiments, it was found that homology between the *mos* probe and λHM1 DNA was contained entirely within a 960-base-pair *Eco*RI/*Bgl* II fragment of human DNA. This region is indicated in Fig. 1.

**Comparison of Human and Mouse c-*mos* Nucleotide Sequences.** The nucleotide sequence of the *mos* region of λHM1 was determined by the procedure of Maxam and Gilbert (21) and compared to the mu*mos* nucleotide sequence of Van Beveren *et al.* (16). The nucleotide sequence homology between mu*mos* and hu*mos* begins to the right of the *Eco*RI site at 5.4 kbp in the λHM1 insert and extends to the right of the *Bgl* II site at 6.3 kbp.

The nucleotide sequences of hu*mos* and mu*mos* were found to be extensively homologous, and a comparison is shown in Fig. 2. To maximize sequence homology, one gap of nine bases was introduced into the hu*mos* DNA sequence between positions 333 and 334. Additional gaps of 5, 15, and 3 bases were introduced into the mu*mos* DNA sequence (at positions 103, 717, and 745). Introduction of these gaps did not alter the putative protein coding reading frames of either sequence. Moreover, this aligned the two coding sequences so that they terminate at equivalent opal codons (position 1,279 in the hu*mos* sequence), and the open reading frame of the hu*mos* initiates at position 241, where an ATG is found in both sequences. As represented in Fig. 2, the hu*mos* open reading frame extends from the ATG at nucleotide position 241 for a further 346 codons. Short regions of homology with mu*mos* have been conserved in the 5′ region preceding the putative coding region of hu*mos* (Fig. 2). The preceding ATG codons at positions 11, 95, and 165 are followed almost immediately by in-frame termination codons. However, an ATG codon at position 137 in hu*mos* begins an additional open reading frame of 120 codons (see *Discussion*). The mu*mos* does not possess a similar open reading frame, but there are similarities in this region in tracts rich in purine (line 81–160) and pyrimidines (line 161–230). Both tracts are in the beginning of the open reading frame of mu*mos* (16) (ATG equivalent to position 95 in hu*mos*). Indeed 18 or 20 nucleotides surrounding this ATG (underscored) are conserved in both sequences (positions 81–102). However, as noted above, this ATG could not be used in initiation of translation of hu*mos*, as it is followed immediately by a termination codon.

Comparison of the nucleotide sequences (Fig. 2) indicated that, excluding the short insertions and deletions introduced for alignment, there are 231 differences in the 1,021-base hu*mos* coding region as compared to mu*mos*. Thus, the sequences are 77% homologous. Of the codons containing a single base change, 30 substitutions occur in the first position of the codon, 19 in the second, and 94 in the third position. The 94 third-position changes result in only 2 amino acid changes (positions 432 and 1,263), whereas 4 of the 30 first-position changes (positions 424, 679, 757, and 1,016) do not result in amino acid changes. There are 31 two-base codon changes, and of these 26 have changes in the third base, which is shared with almost equal frequency between changes in either the first (12 changes) or the second (14 changes) base of the codon. Sequence homology is greater in the 5′ region than in the 3′ region of these

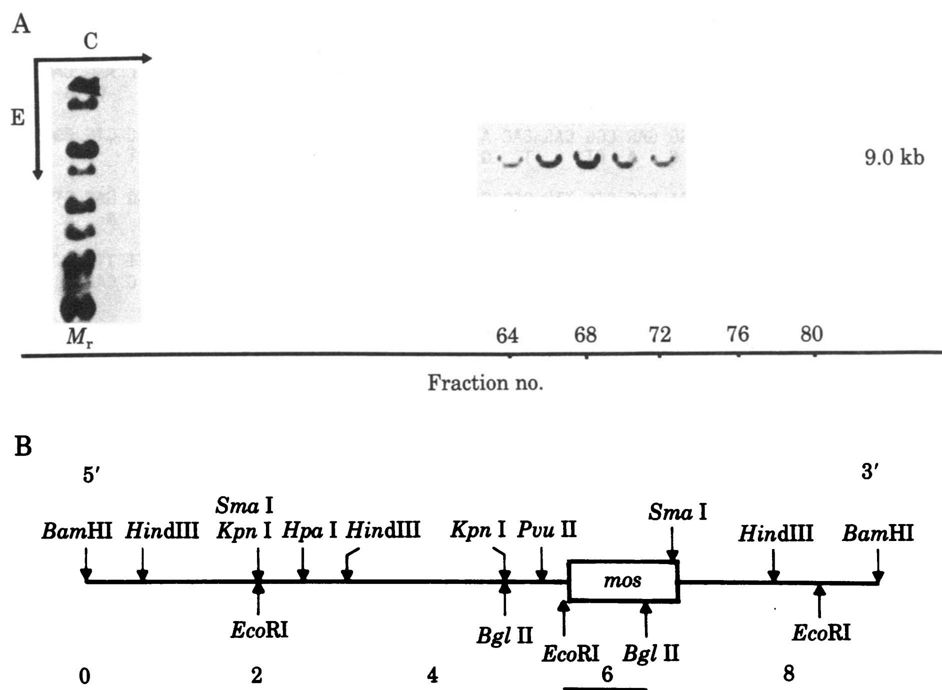


FIG. 1. (*A*) Identification of *mos* sequences in human DNA by Southern analysis (20) of *Bam*HI-digested human placental DNA fractionated by RPC-5 chromatography and gel electrophoresis with a nick-translated $^{32}$P-labeled *mos*-specific DNA fragment as probe. The directions of RPC-5 chromatography (C) and electrophoresis (E) and the $M_r$ markers are indicated on the autoradiograph of the Southern transfer. (*B*) Restriction endonuclease map of the 9-kbp *mos*-containing human DNA fragment. The orientation is 5′ → 3′ with respect to the mu*mos* sequence. Restriction endonuclease sites are approximate, and not all sites are indicated. The underlined region between the 5.4-kbp *Eco*RI and 6.3-kbp *Bgl* II site represents the extent of the region homologous with the *mos* probe described in *A* under the hybridization conditions of Wahl *et al.* (23).

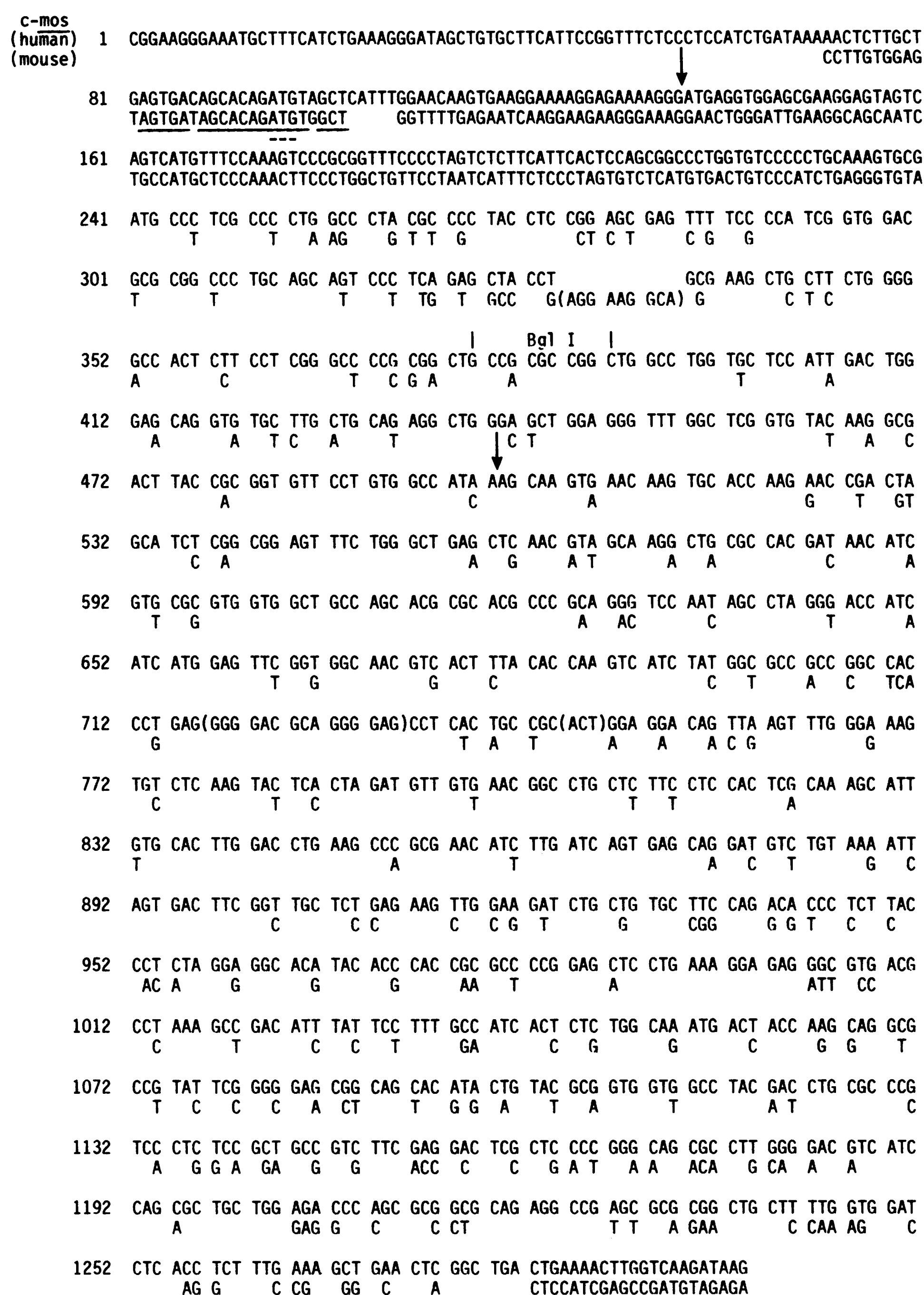

FIG. 2. Comparison of hu*mos* DNA sequences to the mu*mos* sequence of Van Beveren *et al.* (16). DNA sequence analysis of hu*mos* was by the procedure of Maxam and Gilbert (21) using pBR322 subclones pHB1 (the *Bgl* II fragment at 4.8–6.3 kbp; Fig. 1) and pPS1 (a *Pst* I fragment from position 427 to ≈250 base pairs 3′ to the *Sma* I site at position 1,165). The complete nucleotide sequence of the hu*mos* gene is given (residues 1–1,303). In the putative coding sequence of the hu*mos* gene (residues 241–1,281), the DNA sequence is represented as triplets corresponding to the codons. The mu*mos* sequence (16) is represented as an uninterrupted sequence in the hu*mos* noncoding regions and is given in the hu*mos* coding sequence only where the corresponding bases differ. Where spaces were inserted to align the two sequences in the hu*mos* coding region, the bases, which have no homologs in the other sequence, are enclosed by parentheses. In the 5′ noncoding regions, the first ATG in the mu*mos* open reading frame (16) and the surrounding region of homology with hu*mos* are underscored. ↓, Limits of the second human open reading frame, which begins at position 137 and has an amber termination codon at position 497.

open reading frames, consistent with the observation that homology to the right of the hu*mos* *Bgl* II site (Fig. 2, position 1,021) was not observed by blot hybridization. Likewise, little sequence homology is observed in the 3′ noncoding regions.

**Comparison of humos and mumos Open Reading Frames.** The protein predicted from the nucleotide sequence to be encoded by hu*mos* was compared to the mu*mos* amino acid sequence (16) (Fig. 3). The codons were aligned on the basis of maximum DNA sequence homology as discussed above. Thus, the first ATG of hu*mos* was aligned with the 48th internal codon of the mu*mos* (16). Excluding gaps and insertions, this resulted in a direct comparison of a sequence of 337 amino acids. As expected from the conservation of nucleotide sequence, the amino acid sequences of the two polypeptides are remarkably similar. Indeed, 253 of 337 amino acids (or 75%) are shared between the two polypeptides. The regions of least homology

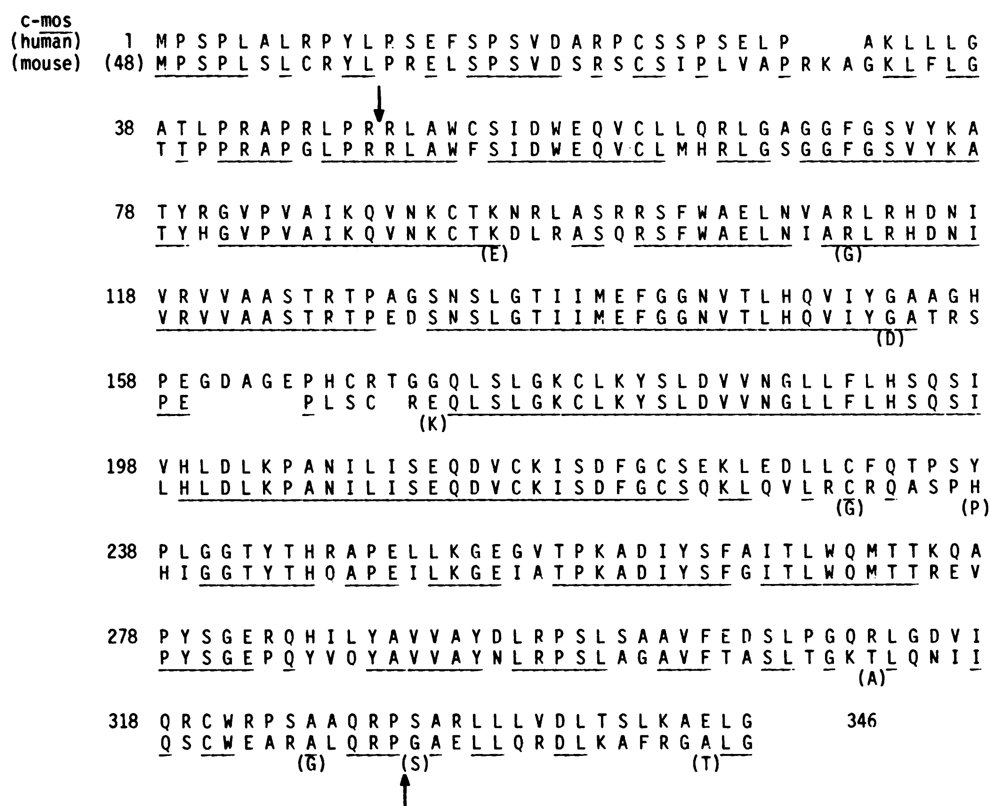


FIG. 3. Comparison of the amino acid sequences of the proteins predicted to be encoded by hu*mos* and mu*mos*. The mu*mos* and v-*mos* sequences are from Van Beveren *et al.* (16). Amino acid residue 48 of mu*mos* is numbered according to Van Beveren *et al.* (16). Amino acids common to both polypeptides are underlined. Amino acids different in the v-*mos* sequence of MuSV127 are in parentheses. The letter code for the amino acids is: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. ↓, Position 48, where the sequences 5′ to this codon were replaced with m1MuSV sequences in the construction of an MuSV–hu*mos* hybrid used in transfection/transformation experiments with hu*mos*; ↑, position 329, where the 3′ COOH-terminal open reading frame sequence of Reddy *et al.* (24, 25) differs from Van Beveren *et al.* (16, 26).

are near the $NH_2$ and COOH termini of the polypeptides and between positions 160 and 171, where it was necessary to introduce gaps into mu*mos* to maximize homology. However, it is remarkable that the coding specificity of the first 5 hu*mos* codons and the last two codons (three if the opal termination codon is included) of both open reading frames are conserved. There are four regions of 19 or more consecutive amino acids conserved between the two polypeptides; two of these regions or a total of 52 amino acids are separated by only one amino acid difference (position 198). These highly conserved regions fall within the middle of the polypeptide chains. Specifically from position 38 to 226, >85% of the amino acid sequence is conserved. The comparison of the mu*mos* open reading frame with v-*mos* revealed 11 amino acid changes (16). Five of the changes in v-*mos* remain unchanged between hu*mos* and mu*mos* (Fig. 3, positions 94, 111, 153, 231, and 325) and 249 of 337 amino acids (or 74%) are shared between v-*mos* and hu*mos*.

## DISCUSSION

The nucleotide sequence and predicted protein product of hu*mos* are strikingly homologous to mu*mos*, indicating that this gene has been strongly conserved in the estimated 70 million yr since evolutionary divergence of man and mouse. Nucleotide sequence homology is greater in the open reading frame sequence of hu*mos* than in the region 5′ to its first possible initiation codon. The greatest homology between these sequences occurs in the middle portion of the hu*mos* sequence. Other features of similarity are that both *mos* genes appear to lack intervening sequences, their open reading frames terminate in the same two amino acids and opal codons, and the hu*mos* initiation codon begins in a conserved block of five amino acids found internally in the mu*mos* sequence (position 48; ref. 16). It has been shown that the first ATG in v-*mos* is not essential for transformation (D. Dina, personal communication). The next ATG in v-*mos* is the first of the five conserved amino acids of the beginning of the hu*mos* open reading frame. Mu*mos* RNA has not been detected in any mouse cells tested (17, 27), which raised the question of whether this gene is normally expressed. The strong selection for maintaining conserved sequences in the cellular open reading frames suggests that both proteins are essential.

An additional open reading frame begins in hu*mos* at position 137 (Fig. 2) and proceeds for 120 codons. It has the predicted amino acid sequence:

M-R-W-S-E-G-V-V-S-H-V-S-K-V-P-R-F-P-L-V-S-S-F-
T-P-A-A-L-V-S-P-C-K-V-R-C-P-R-P-W-P-Y-A-P-T-S-
G-A-S-F-P-H-R-W-T-R-G-P-A-A-V-P-Q-S-Y-L-R-S-C-
F-W-G-P-L-F-L-G-P-R-G-C-R-A-G-W-P-G-A-P-L-T-G-
S-R-C-A-C-C-R-G-W-E-L-E-G-L-A-R-C-T-R-R-L-T-A-
Y-F-L-W-P.

This reading frame is terminated by an amber codon (position 497), and an additional in-frame termination codon is present at position 506 (Fig. 2). This polypeptide would contain 16 pro-

line, 14 arginine, 8 cysteine, and 7 tryptophan residues and has no counterpart in the mu*mos* sequence.

The presence of four ATGs before the beginning of the hu*mos* open reading frame (Fig. 2, position 241) is curious. The DNA sequences of the hu*mos* and mu*mos* genes indicated the absence of intervening sequences in the open reading frames. It is possible, however, that intervening sequences are present in these genes, and it requires an analysis of the RNAs present in cells expressing these genes to answer this question. For example, it is possible that the region 5′ to the ATG at position 241 in the hu*mos* DNA sequence is removed by RNA splicing. This could be accomplished by using a possible acceptor site at position 212. It is noted that a possible acceptor site is present in mu*mos* DNA (at the equivalent hu*mos* position 209; Fig. 2). For hu*mos*, at least, excision of these 5′ sequences from the transcript would remove the upstream out-of-frame ATG initiation codons. For mu*mos*, RNA splicing at position 209 would leave present an out-of-frame ATG at position 215. Of course, it remains possible that the hu*mos* and mu*mos* gene products are initiated at an upstream initiation codon and that RNA splicing removes intervening termination codons.

Homology between the predicted amino acid sequences of the v-*mos* gene product and that of the avian sarcoma virus *src* gene product has been described (26). These amino acid sequences were estimated to be 23% homologous in the COOH-terminal region of the ASV *src* gene product—i.e., the strongest homology occurred in v-*mos* sequences corresponding to residues 199–281 of hu*mos* (Fig. 3). The blocks of amino acids conserved between ASV *src* and v-*mos* gene products are also common to the hu*mos* gene product. The conservation of polypeptide sequences between these three proteins suggests that they have biochemical properties in common.

DNA sequence data reveals that the *mos* gene is highly conserved between human and mouse. Thus, it would seem plausible that the hu*mos* gene could be activated to transform mouse NIH 3T3 cells in DNA transfection analyses in a manner analogous to the activation of the transforming potential of mu*mos* (2, 3, 6). The hu*mos* gene was found to be inactive in DNA transfection/transformation assay and, unlike mu*mos* (3, 6), could not be activated by insertion of Mo-MuSV LTR elements 5′ to the coding sequence (M. Oskarsson, personal communication). Moreover, a hybrid gene, consisting of the entire 5′ region of m1MoMuSV fused at a common *Bgl* I site in *mos* (Fig. 2, position 382; Fig. 3, position 48) to 3′ sequences from hu*mos*, was also inactive in the transformation assay. Thus, differences in the *mos* genes after position 54 (Fig. 3) could be responsible for the lack of detectable biological transforming activity of hu*mos*. Two different clones of MuSV124 have been shown to differ in their COOH-terminal sequence (16, 24–26), beginning at a position equivalent to amino acid 329 in hu*mos*. This may indicate that the changes in hu*mos* between position 54 and 329 prevent it from transforming mouse cells. However, additional hybrid genes need to be constructed in order to map the region(s) of the hu*mos* gene responsible for lack of transforming activity. It is not possible to conclude on the basis of these results whether the hu*mos* gene has or has not oncogenic potential. The hu*mos* gene product may fail to interact with the mouse cell components in the same way as the murine v-*mos* or c-*mos* gene products. It may well be appropriate to assay for hu*mos* transforming potential in a human cell line rather than in the heterogenous NIH 3T3 cells. Alternatively, evolutionary pressures may have contrived to select for c-*mos*-related human genes with a lower oncogenic potential while retaining the normal, presumably regulatory, role of the polypeptide product.

**Note Added in Proof.** At position 4,641 in ref. 16, there should be an A, not a T (C. Van Beveren, personal communication). Thus, hu*mos* and mu*mos* have the same sequence and codon at this position (922 in Fig. 2 and 228 in Fig. 3). Papkoff *et al.* (28) have recently identified the Mo-MuSV gene product in transformed cells.

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