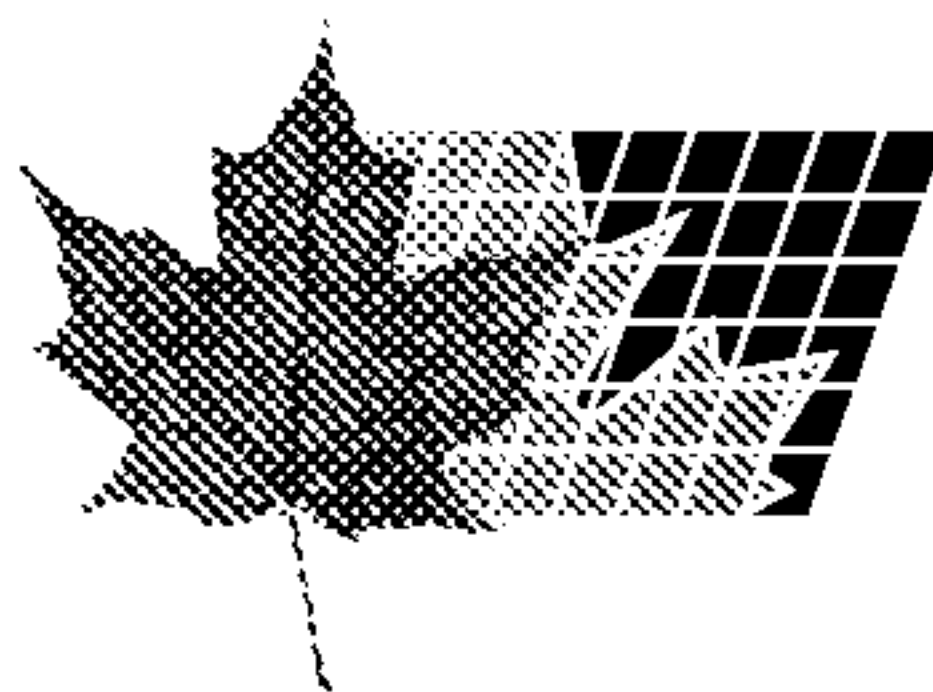




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(22) 1996/01/19  
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(45) 2000/05/23

(72) Matsuda, Michiyuki, JP

(72) Kurata, Takeshi, JP

(73) Research Development Corporation of Japan, JP

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(30) 1995/01/19 (006775/1995) JP

(54) **GENE ADN-C OU DOCK ET PROTEINE DOCK180**

(54) **CDNA OF DOCK180 GENE AND DOCK180 PROTEIN**

(57) The present invention provides a cDNA of DOCK180 gene, which has a nucleotide sequence of SEQ ID NO: 1 and of which translation product binds to the proto-oncogene product CRK, a recombinant vector containing this cDNA, a DOCK180 protein expressed from the cDNA which has a amino acid sequence of SEQ ID NO: 2, and an antibody to the DOCK180 protein. According to the present invention, It is possible to develop new diagnosing and therapeutic techniques using DOCK180 protein and antibody against the protein.

## ABSTRACT

The present invention provides a cDNA of DOCK180 gene, which has a nucleotide sequence of SEQ ID NO: 1 and of which translation product binds to the proto-oncogene product CRK, a recombinant vector containing this cDNA, a DOCK180 protein expressed from the cDNA which has a amino acid sequence of SEQ ID NO: 2, and an antibody to the DOCK180 protein. According to the present invention, It is possible to develop new diagnosing and therapeutic techniques using DOCK180 protein and antibody against the protein.

## cDNA of DOCK180 Gene and DOCK180 Protein

## FIELD OF THE INVENTION

The present invention relates to a cDNA of DOCK180 protein, which binds to the proto-oncogene product CRK, a recombinant vector containing this cDNA, a DOCK180 protein expressed from the cDNA, and an antibody to the DOCK180 protein. The cDNA of the present invention, the DOCK180 protein, and the antibody are very useful for diagnosis of tumor cells and development of a cancerocidal method for suppressing tumor cells.

## PRIOR ART

Recent progress of cellular biology and molecular biology is really remarkable. Active research efforts are being made on carcinogenesis on the genetic level, and such efforts have identified many oncogenes and antioncogenes associated with human. It is also known that various proteins are expressed from these genes.

For example, CRK protein, which is expressed from a proto-oncogene CRK, is one of the major proteins controlling proliferation of higher eukaryote, and is known to regulate proliferation of tumor cells in many malignant tumors.

It has now been revealed that this CRK protein functions through binding to DOCK180 protein. DOCK180 is therefore attracting general attention as a diagnostic indicator of tumor cells and as a target for missile therapy using various antitumor agents.

However, because no information has been available about a gene encoding the DOCK180 protein, it has conventionally been impossible to effectively utilize this protein widely for diagnosis of cancerous diseases, clarification of carcinogenesis mechanism, or development of a new cancer therapy.

## SUMMARY OF THE INVENTION

The present invention has an object to provide a cDNA of

DOCK180 gene, and a genetic engineering material permitting easy manipulation of this cDNA and expression of the protein in a large scale.

The present invention has another object to provide a DOCK180 protein which is expressed from the above-mentioned cDNA, and an antibodies against this protein.

The present invention provides a cDNA of the DOCK180 gene, which has the nucleotide sequence defined in Sequence Listing by SEQ ID No: 1.

Furthermore, the present invention provides a recombinant vector containing the cDNA of DOCK180 gene. More concretely, the present invention provides the plasmid pDOCK180 held by E. coli DOCK180 (FERM BP-5362).

The present invention further provides a DOCK180 protein having the amino acid sequence defined in Sequence Listing by SEQ ID NO: 2, and antibodies to DOCK180 protein prepared by using the DOCK180 protein as an antigen.

#### BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a constitutional diagram of pDOCK180, which is a cloning vector of the present invention.

#### DETAILED DESCRIPTION OF THE INVENTION

The cDNA of the present invention can be isolated and purified from higher eukaryotes such as cells derived from human, mouse, and chicken by the application of, for example, the method of Sambrook et al. (Molecular Cloning, second edition, Cold Spring Harbor Laboratory, New York, 1989). More specifically, the cDNA can be obtained by purifying mRNA of DOCK180 protein gene from animal cell, and then synthesizing a cDNA chain from the mRNA by the use of reverse transcriptase. From among the thus synthesizable cDNAs of DOCK180 protein, the nucleotide sequence of cDNA derived from human cells and the amino acid sequence of the translation domain thereof are defined in Sequence Listing by SEQ ID NOs: 1 and 2.

Then, the recombinant vector of the present invention can be

prepared by inserting a fragment of the resultant cDNA into known cloning vectors. Ligation of the cDNA fragment and the vectors may be accomplished by, for example, the above-mentioned method of Sambrook et al. Preferable vectors include a plasmid and a  $\lambda$ -phage for *Escherichia coli* as the host, and an applicable plasmid is, for example, one derived from pBR322. A preferable  $\lambda$ -phage is  $\lambda$  gt11.

Transfer of the thus prepared recombinant vectors into the host may be conducted through infection by  $\lambda$ -phage as presented in the above-mentioned paper by Sambrook et al. For example, a transformed cells with the recombinant vector containing the above-mentioned cDNA are available by inoculating the recombinant  $\lambda$  gt11 into *Escherichia coli* Y1090 at 37°C.

Selection of a transformed cell may be accomplished by appropriately using a known method, depending upon the kind of the cloning vector. For example, selection of a transformed cell with  $\lambda$  gt11 can be performed as follows. The above-mentioned recombinant  $\lambda$  gt11 containing the cDNA can be inoculated into *Escherichia coli* Y1090 under a temperature condition of 37°C, and the *E. coli* cells are cultured on an agar plate containing trypton, yeast extract, NaCl and ampicillin (hereinafter abbreviated as an "agar medium"). Then, a nitrocellulose membrane containing isopropyl thio-D-galactoside (hereinafter abbreviated as "IPTG") is placed on the plate for another several hours to induce transcription from the integrated cDNA. After the binding of an enzyme-labelled CRK protein to the membrane (Matsuda et al., *Mol. Cell. Biol.*, 12: 3482-3489, 1992), an lamda phage plaques having the recombinant vector can be selected by putting a substrate for the enzyme in it. A preferable labelling enzyme is alkaline phosphatase or peroxidase. CRK protein may be manufactured as a fusion protein with glutathione-S-transferase (hereinafter abbreviated as "GST"), and selection may be accomplished by using an antibody against this GST.

The cDNA fragment inserted into  $\lambda$  phage can be cleaved out and re-inserted into a plasmid vector, if necessary. An example of recombinant plasmid vector of the invention is pDOCK180 which

is prepared by inserting the cDNA of SEQ ID NO: 1 into vector plasmid pBlue ScriptIIKS(+), for which details are presented in Example 2 later. The pDOCK180 was transfected into the XL1-Blue strain derived from Escherichia coli K12 strain, and the transformant E. coli DOCK180 having the pDOCK180 was deposited to National Institute of Biocience and human Technology, a international depository, under Budapest Treaty as a deposit No. FERM BP-5362.

Then, the DOCK180 protein of the present invention can be expressed from the cDNA of SEQ ID NO: 1. For production of the protein, an expression vector is prepared by inserting the cDNA fragment into a known expression vector. The cDNA fragment can be isolated from the above-mentioned cloning vector, pDOCK180. While there is no particular limitation as to the expression vector, a preferable one is pGEX1, pGEX2T or pGEX3X using E. coli as the host. The expression vector containing the cDNA fragment can be introduced into an Escherichia coli (for example, DH5 strain derived from Escherichia coli K12 strain) by a known method. The DOCK180 protein of the present invention is easily produced in a large scale by culturing the transformed cells. More specifically, a concrete example comprises the steps of culturing the transformed Escherichia coli at 37°C for 3 to 24 hours on L-broth containing ampicillin, bacteriolyzing through ultrasonic blending, and adsorbing this sample to a carrier such as glutathione sephalose (made by Pharmacia P-L Biochemicals Company), thereby isolating and purifying the target DOCK180 protein.

An antibody against DOCK180 protein is available by inoculating the thus purified DOCK180 protein to an animal by a conventional method. Applicable animals include rabbit, mouse, goat, sheep, horse and hamster, and among others, rabbit or mouse is preferable.

The thus obtained anti-DOCK180 protein antibody can be used, for example, for quantitative determination or separation of DOCK180 protein in a sample, and further, serves as a useful material for missile therapy using an antitumor agent with DOCK180



as a target.

The cDNA, the protein and the antibody of the present invention provide various genetic manipulation materials useful for development of a new cancer therapy. These materials include an antisense RNA of DOCK180 gene, a variant protein of DOCK180, and a virus vector which expresses these RNA, variant protein, and anti-DOCK180 protein antibody in tumor cells.

The present invention will be described below in further detail by means of examples. It is needless to mention that the present invention is not limited in any manner by the following examples.

#### EXAMPLE 1

A cDNA fragment to human DOCK180 protein gene was isolated and cloned as follows.

An mRNA of DOCK180 gene was isolated from human spleen and a cDNA fragment was synthesized from the mRNA. The cDNA fragment was then integrated into  $\lambda$  gt11, and a recombinant vector thereof was infected to Escherichia coli Y1090, which was plated onto LA agar culture medium. After six hours, a nitrocellulose membrane containing 1mM IPTG was placed on this medium, and after three hours of culture, this nitrocellulose membrane was incubated for an hour with a phosphate buffer solution (pH: 7.5) containing 2% skim milk and 0.05% Tween 20. Then, after reaction for an hour with a phosphate buffer solution containing 1  $\mu$ g/ml GST-CRK and 1  $\mu$ g/ml anti-GST monoclonal antibody, and for an hour with 1  $\mu$ g/ml alkaline phosphate-labelled anti-mouse antibody (made by TAGO Company), the phage having an ability to bind to CRK protein was identified by means of AP PURPLE (made by Bio 101 Company), a substrate for alkaline phosphatase. This phage was purified through three runs of plaque formation, and then DNA thereof was isolated by the phenol extraction method, and cleaved with a restriction enzyme EcoRI. Next, part of cDNA of DOCK180 gene was prepared through electrophoresis. This cDNA fragment was isotope-labelled with random oligo primer (made by Behlinger Company) and  $^{32}$ P-deoxycytidine triphosphate. With the use of this labelled cDNA, the above-mentioned recombinant  $\lambda$  gt11 with cDNA

derived from a human spleen was screened through plaque hybridization by the method of Sambrook et al. (Molecular Cloning, second edition, Cold Spring Harbor Laboratory, New York, 1989), and further six clones of recombinant  $\lambda$  gt11 having DOCK180 protein cDNA were obtained. DNAs of these phages were cleaved with restriction enzyme EcoRI to isolate cDNA of DOCK180 gene and subcloned into phagemid vector pUC119. A single stranded DNA was purified from the thus obtained recombinant vector, and the nucleotide sequence thereof was determined by the use of an automatic nucleotide sequence reader (made by ABI Company). The identified nucleotide sequence thereof is shown in Sequence Listing by SEQ ID NO: 1, and the amino acid sequence of the anticipated translation product, by SEQ ID NO: 2. As a result of retrieval of this amino acid sequence in the database in the GenBank of the European Molecular Biology Laboratories (EMBL), the amino terminal end of DOCK180 protein shares homology with Fyn and Yes of tyrosine kinase by more than 20%. This domain has a structure known as SH3, and is present in various protein groups involved in signal transduction of cell proliferation in addition to that of tyrosine kinase. However, DOCK180 protein was found to be different from any known proteins and to be a new signal transduction factor.

#### EXAMPLE 2

From the group of recombinant pUC119 obtained in Example 1, the DNA fragments excluding overlapping portions were isolated and ligated each other to prepare a fragment containing all the translation domain of the cDNA. The resultant cDNA fragment was then inserted into the plasmid vector pBlue Script II KS(+) to obtain the recombinant vector pDOCK180. This pDOCK180 has a constitution as shown in Fig. 1.

Further, this cloning vector pDOCK180 was introduced into an XL1-Blue strain derived from Escherichia coli K12 to obtain a transformant E. coli DOCK180 (FERM BP-5362).

#### EXAMPLE 3

The cloning vector pDOCK180 obtained in Example 2 was cleaved with a restriction enzyme to prepare a cDNA domain of DOCK180 protein. The resultant cDNA fragment was then inserted into plasmid pGEX1, thereby preparing expression vectors. Transformant cells were prepared by introducing the expression vectors into *Escherichia coli* DH5. After culturing this transformant cells in 1ℓ L-broth containing ampicillin up to an absorbance of 0.6, IPTG was added to 0.5mM, and culturing was continued for another three hours. After collection, the bacteria were ultrasonic-treated to remove crushed pieces of bacteria, and the supernatant was mixed with glutathione sephalose (made by Pharmacia P-L Biochemicals Company). After rinsing glutathione sephalose with a phosphate buffer solution, DOCK180 protein was eluted with the use of a phosphate buffer solution containing 5mM glutathione. This protein was dialyzed with a phosphate buffer solution, and then a portion thereof was analyzed with SDS-polyacrylamide gel: a GST fused-DOCK180 protein having a purity of over 90% was synthesized.

#### EXAMPLE 4

The DOCK180 protein purified in Example 3 was subcutaneously inoculated three times to a rabbit, together with complete Freund's adjuvant, and then, serum was sampled.

Reactivity of this serum with the purified DOCK180 protein was investigated by the Western blotting technique: a clear reactivity was demonstrated with the DOCK180 protein even when diluted to about 1,000. This permitted confirmation of applicability thereof as an antibody against DOCK180 protein.



## SEQUENCE LISTING

## (2) INFORMATION FOR SEQ ID NO: 1:

## (i) SEQUENCE CHARACTERISTIC:

(A) LENGTH: 6519 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) ORIGINAL SOURCE: spleen cell of homo sapiens

## (ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 24..5619

## (x) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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## (2) INFORMATION FOR SEQ ID NO: 2:

## (i) SEQUENCE CHARACTERISTIC:

(A) LENGTH: 1865 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) ORIGINAL SOURCE: spleen cell of homo sapiens

## (ix) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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Gly Asp Thr Val His Ile Leu Glu Thr Tyr Glu Gly Trp Tyr Arg Gly
      35              40              45
Tyr Thr Leu Arg Lys Lys Ser Lys Lys Gly Ile Phe Pro Ala Ser Tyr
      50              55              60

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Ile His Leu Lys Glu Ala Ile Val Glu Gly Lys Gly Gln His Glu Thr  
 65 70 75 80  
 Val Ile Pro Gly Asp Leu Pro Leu Ile Gln Glu Val Thr Thr Thr Leu  
 85 90 95  
 Arg Glu Trp Ser Thr Ile Trp Arg Gln Leu Tyr Val Gln Asp Asn Arg  
 100 105 110  
 Glu Met Phe Arg Ser Val Arg His Met Ile Tyr Asp Leu Ile Glu Trp  
 115 120 125  
 Arg Ser Gln Ile Leu Ser Gly Thr Leu Pro Gln Asp Glu Leu Lys Glu  
 130 135 140  
 Leu Lys Lys Lys Val Thr Ala Lys Ile Asp Tyr Gly Asn Arg Ile Leu  
 145 150 155 160  
 Asp Leu Asp Leu Val Val Arg Asp Glu Asp Gly Asn Ile Leu Asp Pro  
 165 170 175  
 Glu Leu Thr Ser Thr Ile Ser Leu Phe Arg Ala His Glu Ile Ala Ser  
 180 185 190  
 Lys Gln Val Glu Glu Arg Leu Gln Glu Glu Lys Ser Gln Lys Gln Asn  
 195 200 205  
 Ile Asp Ile Asn Arg Gln Ala Lys Phe Ala Ala Thr Pro Ser Leu Ala  
 210 215 220  
 Leu Phe Val Asn Leu Lys Asn Val Val Cys Lys Ile Gly Glu Asp Ala  
 225 230 235 240  
 Glu Val Leu Met Ser Leu Tyr Asp Pro Val Glu Ser Lys Phe Ile Ser  
 245 250 255  
 Glu Asn Tyr Leu Val Arg Trp Ser Ser Ser Gly Leu Pro Lys Asp Ile  
 260 265 270  
 Asp Arg Leu His Asn Leu Arg Ala Val Phe Thr Asp Leu Gly Ser Lys  
 275 280 285  
 Asp Leu Lys Arg Glu Lys Ile Ser Phe Val Cys Gln Ile Val Arg Val  
 290 295 300  
 Gly Arg Met Glu Leu Arg Asp Asn Asn Thr Arg Lys Leu Thr Ser Gly  
 305 310 315 320  
 Leu Arg Arg Pro Phe Gly Val Ala Val Met Asp Val Thr Asp Ile Ile  
 325 330 335  
 Asn Gly Lys Val Asp Asp Glu Asp Lys Gln His Phe Ile Pro Phe Gln  
 340 345 350



Pro Val Ala Gly Glu Asn Asp Phe Leu Gln Thr Val Ile Asn Lys Val  
 355 360 365  
 Ile Ala Ala Lys Glu Val Asn His Lys Gly Gln Gly Leu Trp Val Thr  
 370 375 380  
 Leu Lys Leu Leu Pro Gly Asp Ile His Gln Ile Arg Lys Glu Phe Pro  
 385 390 395 400  
 His Leu Val Asp Arg Thr Thr Ala Val Ala Arg Lys Thr Gly Phe Pro  
 405 410 415  
 Glu Ile Ile Met Pro Gly Asp Val Arg Asn Asp Ile Tyr Val Thr Leu  
 420 425 430  
 Val Gln Gly Asp Phe Asp Lys Gly Ser Lys Thr Thr Ala Lys Asn Val  
 435 440 445  
 Glu Val Thr Val Ser Val Tyr Asp Glu Asp Gly Lys Arg Leu Glu His  
 450 455 460  
 Val Ile Phe Pro Gly Ala Gly Asp Glu Ala Ile Ser Glu Tyr Lys Ser  
 465 470 475 480  
 Val Ile Tyr Tyr Gln Val Lys Gln Pro Arg Trp Phe Glu Thr Val Lys  
 485 490 495  
 Val Ala Ile Pro Ile Glu Asp Val Asn Arg Ser His Leu Arg Phe Thr  
 500 505 510  
 Phe Arg His Arg Ser Ser Gln Asp Ser Lys Asp Lys Ser Glu Lys Ile  
 515 520 525  
 Phe Ala Leu Ala Phe Val Lys Leu Met Arg Tyr Asp Gly Thr Thr Leu  
 530 535 540  
 Arg Asp Gly Glu His Asp Leu Ile Val Tyr Lys Ala Glu Ala Lys Lys  
 545 550 555 560  
 Leu Glu Asp Ala Ala Thr Tyr Leu Ser Leu Pro Ser Thr Lys Ala Glu  
 565 570 575  
 Leu Glu Glu Lys Gly His Ser Ala Thr Gly Lys Ser Met Gln Ser Leu  
 580 585 590  
 Gly Ser Cys Thr Ile Ser Lys Asp Ser Phe Gln Ile Ser Thr Leu Val  
 595 600 605  
 Cys Ser Thr Lys Leu Thr Gln Asn Val Asp Leu Leu Gly Leu Leu Lys  
 610 615 620  
 Trp Arg Ser Asn Thr Ser Leu Leu Gln Gln Asn Leu Arg Gln Leu Met  
 625 630 635 640

Lys Val Asp Gly Gly Glu Val Val Lys Phe Leu Gln Asp Thr Leu Asp  
 645 650 655  
 Ala Leu Phe Asn Ile Met Met Glu Asn Ser Glu Ser Glu Thr Phe Asp  
 660 665 670  
 Thr Leu Val Phe Asp Ala Leu Val Phe Ile Ile Gly Leu Ile Ala Asp  
 675 680 685  
 Arg Lys Phe Gln His Phe Asn Pro Val Leu Glu Thr Tyr Ile Lys Lys  
 690 695 700  
 His Phe Ser Ala Thr Leu Ala Tyr Thr Lys Leu Thr Lys Val Leu Lys  
 705 710 715 720  
 Asn Tyr Val Asp Gly Ala Glu Lys Pro Gly Val Asn Glu Gln Leu Tyr  
 725 730 735  
 Lys Ala Met Lys Ala Leu Glu Ser Ile Phe Lys Phe Ile Val Arg Ser  
 740 745 750  
 Arg Ile Leu Phe Asn Gln Leu Tyr Glu Asn Lys Gly Glu Ala Asp Phe  
 755 760 765  
 Val Glu Ser Leu Leu Gln Leu Phe Arg Ser Ile Asn Asp Met Met Ser  
 770 775 780  
 Ser Met Ser Asp Gln Thr Val Arg Val Lys Gly Ala Ala Leu Lys Tyr  
 785 790 795 800  
 Leu Pro Thr Ile Val Asn Asp Val Lys Leu Val Phe Asp Pro Lys Glu  
 805 810 815  
 Leu Ser Lys Met Phe Thr Glu Phe Ile Leu Asn Val Pro Met Gly Leu  
 820 825 830  
 Leu Thr Ile Gln Lys Leu Tyr Cys Leu Ile Glu Ile Val His Ser Asp  
 835 840 845  
 Leu Phe Thr Gln His Asp Cys Arg Glu Ile Leu Leu Pro Met Met Thr  
 850 855 860  
 Asp Gln Leu Lys Tyr His Leu Glu Arg Gln Glu Asp Leu Glu Ala Cys  
 865 870 875 880  
 Cys Gln Leu Leu Ser His Ile Leu Glu Val Leu Tyr Arg Lys Asp Val  
 885 890 895  
 Gly Pro Thr Gln Arg His Val Gln Ile Ile Met Glu Lys Leu Leu Arg  
 900 905 910  
 Thr Val Asn Arg Thr Val Ile Ser Met Gly Arg Asp Ser Glu Leu Ile  
 915 920 925

Gly Asn Phe Val Ala Cys Met Thr Ala Ile Leu Arg Gln Met Glu Asp  
 930 935 940  
 Tyr His Tyr Ala His Leu Ile Lys Thr Phe Gly Lys Met Arg Thr Asp  
 945 950 955 960  
 Val Val Asp Phe Leu Met Glu Thr Phe Ile Met Phe Lys Asn Leu Ile  
 965 970 975  
 Gly Lys Asn Val Tyr Pro Phe Asp Trp Val Ile Met Asn Met Val Gln  
 980 985 990  
 Asn Lys Val Phe Leu Arg Ala Ile Asn Gln Tyr Ala Asp Met Leu Asn  
 995 1000 1005  
 Lys Lys Phe Leu Asp Gln Ala Asn Phe Glu Leu Gln Leu Trp Asn Asn  
 1010 1015 1020  
 Tyr Phe His Leu Ala Val Ala Phe Leu Thr Gln Glu Ser Leu Gln Leu  
 1025 1030 1035 1040  
 Glu Asn Phe Ser Ser Ala Lys Arg Ala Lys Ile Leu Asn Lys Tyr Gly  
 1045 1050 1055  
 Asp Met Arg Arg Gln Ile Gly Phe Glu Ile Arg Asp Met Trp Tyr Asn  
 1060 1065 1070  
 Leu Gly Gln His Lys Ile Lys Phe Ile Pro Glu Met Val Gly Pro Ile  
 1075 1080 1085  
 Leu Glu Met Thr Leu Ile Pro Glu Thr Glu Leu Arg Lys Ala Thr Ile  
 1090 1095 1100  
 Pro Ile Phe Phe Asp Met Met Gln Cys Glu Phe His Ser Thr Arg Ser  
 1105 1110 1115 1120  
 Phe Gln Met Phe Glu Asn Glu Ile Ile Thr Lys Leu Asp His Glu Val  
 1125 1130 1135  
 Glu Gly Gly Arg Gly Asp Glu Gln Tyr Lys Val Leu Phe Asp Lys Ile  
 1140 1145 1150  
 Leu Leu Glu His Cys Arg Lys His Lys Tyr Leu Ala Lys Thr Gly Glu  
 1155 1160 1165  
 Thr Phe Val Lys Leu Val Val Arg Leu Met Glu Arg Leu Leu Asp Tyr  
 1170 1175 1180  
 Arg Thr Ile Met His Asp Glu Asn Lys Glu Asn Arg Met Ser Cys Thr  
 1185 1190 1195 1200  
 Val Asn Val Leu Asn Phe Tyr Lys Glu Ile Glu Arg Glu Glu Met Tyr  
 1205 1210 1215

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Ile Arg Tyr Leu Tyr Lys Leu Cys Asp Leu His Lys Glu Cys Asp Asn |      |      |      |
| 1220                                                            | 1225 | 1230 |      |
| Tyr Thr Glu Ala Ala Tyr Thr Leu Leu Leu His Ala Lys Leu Leu Lys |      |      |      |
| 1235                                                            | 1240 | 1245 |      |
| Trp Ser Glu Asp Val Cys Val Ala His Leu Thr Gln Arg Asp Gly Tyr |      |      |      |
| 1250                                                            | 1255 | 1260 |      |
| Gln Ala Thr Thr Gln Gly Gln Leu Lys Glu Gln Leu Tyr Gln Glu Ile |      |      |      |
| 1265                                                            | 1270 | 1275 | 1280 |
| Ile His Tyr Phe Asp Lys Gly Lys Met Trp Glu Glu Ala Ile Ala Leu |      |      |      |
| 1285                                                            | 1290 | 1295 |      |
| Gly Lys Glu Leu Ala Glu Gln Tyr Glu Asn Glu Met Phe Asp Tyr Glu |      |      |      |
| 1300                                                            | 1305 | 1310 |      |
| Gln Leu Ser Glu Leu Leu Lys Lys Gln Ala Gln Phe Tyr Glu Asn Ile |      |      |      |
| 1315                                                            | 1320 | 1325 |      |
| Val Lys Val Ile Arg Pro Lys Pro Asp Tyr Phe Ala Val Gly Tyr Tyr |      |      |      |
| 1330                                                            | 1335 | 1340 |      |
| Gly Gln Gly Phe Pro Thr Phe Leu Arg Gly Lys Val Phe Ile Tyr Arg |      |      |      |
| 1345                                                            | 1350 | 1355 | 1360 |
| Gly Lys Glu Tyr Glu Pro Arg Glu Asp Phe Glu Ala Arg Leu Leu Thr |      |      |      |
| 1365                                                            | 1370 | 1375 |      |
| Gln Phe Pro Asn Ala Glu Lys Met Lys Thr Thr Ser Pro Pro Gly Asp |      |      |      |
| 1380                                                            | 1385 | 1390 |      |
| Asp Ile Lys Asn Ser Pro Gly Gln Tyr Ile Gln Cys Phe Thr Val Lys |      |      |      |
| 1395                                                            | 1400 | 1405 |      |
| Pro Lys Leu Asp Leu Pro Pro Lys Phe His Arg Pro Val Ser Glu Gln |      |      |      |
| 1410                                                            | 1415 | 1420 |      |
| Ile Val Ser Phe Tyr Arg Val Asn Glu Val Gln Arg Phe Glu Tyr Ser |      |      |      |
| 1425                                                            | 1430 | 1435 | 1440 |
| Arg Pro Ile Arg Lys Gly Glu Lys Asn Pro Asp Asn Glu Phe Ala Asn |      |      |      |
| 1445                                                            | 1450 | 1455 |      |
| Met Trp Ile Glu Arg Thr Ile Tyr Thr Thr Ala Tyr Lys Leu Pro Gly |      |      |      |
| 1460                                                            | 1465 | 1470 |      |
| Ile Leu Arg Trp Phe Glu Val Lys Ser Val Phe Met Val Glu Ile Ser |      |      |      |
| 1475                                                            | 1480 | 1485 |      |
| Pro Leu Glu Asn Ala Ile Glu Thr Met Gln Leu Thr Asn Asp Lys Ile |      |      |      |
| 1490                                                            | 1495 | 1500 |      |

Asn Ser Met Val Gln Gln His Leu Asp Asp Pro Ser Leu Pro Ile Asn  
 1505 1510 1515 1520  
 Pro Leu Ser Met Leu Leu Asn Gly Ile Val Asp Pro Ala Val Met Gly  
 1525 1530 1535  
 Gly Phe Ala Asn Tyr Glu Lys Ala Phe Phe Thr Asp Arg Tyr Leu Gln  
 1540 1545 1550  
 Glu His Pro Glu Ala His Glu Lys Ile Glu Lys Leu Lys Asp Leu Ile  
 1555 1560 1565  
 Ala Trp Gln Ile Pro Phe Leu Ala Glu Gly Ile Arg Ile His Gly Asp  
 1570 1575 1580  
 Lys Val Thr Glu Ala Leu Arg Pro Phe His Glu Arg Met Glu Ala Cys  
 1585 1590 1595 1600  
 Phe Lys Gln Leu Lys Glu Lys Val Glu Lys Glu Tyr Gly Val Arg Ile  
 1605 1610 1615  
 Met Pro Ser Ser Leu Asp Asp Arg Arg Gly Ser Arg Pro Arg Ser Met  
 1620 1625 1630  
 Val Arg Ser Phe Thr Met Pro Ser Ser Ser Arg Pro Leu Ser Val Ala  
 1635 1640 1645  
 Ser Val Ser Ser Leu Ser Ser Asp Ser Thr Pro Ser Arg Pro Gly Ser  
 1650 1655 1660  
 Asp Gly Phe Ala Leu Glu Pro Leu Leu Pro Lys Lys Met His Ser Arg  
 1665 1670 1675 1680  
 Ser Gln Asp Lys Leu Asp Lys Asp Asp Leu Glu Lys Glu Lys Lys Asp  
 1685 1690 1695  
 Lys Lys Lys Glu Lys Arg Asn Ser Lys His Gln Glu Ile Phe Glu Lys  
 1700 1705 1710  
 Glu Phe Lys Pro Thr Asp Ile Ser Leu Gln Gln Ser Glu Ala Val Ile  
 1715 1720 1725  
 Leu Ser Glu Thr Ile Ser Pro Leu Arg Pro Gln Arg Pro Lys Ser Gln  
 1730 1735 1740  
 Val Met Asn Val Ile Gly Ser Glu Arg Arg Phe Ser Val Ser Pro Ser  
 1745 1750 1755 1760  
 Ser Pro Ser Ser Gln Gln Thr Pro Pro Pro Val Thr Pro Arg Ala Lys  
 1765 1770 1775  
 Leu Ser Phe Ser Met Gln Ser Ser Leu Glu Leu Asn Gly Met Thr Gly  
 1780 1785 1790



Ala Asp Val Ala Asp Val Pro Pro Pro Leu Pro Leu Lys Gly Ser Val  
1795 1800 1805  
Ala Asp Tyr Gly Asn Leu Met Glu Asn Gln Asp Leu Leu Gly Ser Pro  
1810 1815 1820  
Thr Pro Pro Pro Pro Pro Pro His Gln Arg His Leu Pro Pro Pro Leu  
1825 1830 1835 1840  
Pro Ser Lys Thr Pro Pro Pro Pro Pro Pro Lys Thr Thr Arg Lys Gln  
1845 1850 1855  
Thr Ser Val Asp Ser Gly Ile Val Gln  
1860 1865

WHAT IS CLAIMED IS:

1. A cDNA of a DOCK180 gene, which has a nucleotide sequence defined in Sequence Listing by SEQ ID No: 1, and of which translation product binds to proto-oncogene product CRK.
2. A recombinant vector containing the cDNA as claimed in claim 1.
3. Plasmid pDOCK180 held by E. coli DOCK180 (FERM BP-5362).
4. A DOCK180 protein having an amino acid sequence defined in Sequence Listing by SEQ ID NO: 2.
5. An antibody to a DOCK180 protein, which is prepared by using the DOCK180 protein as claimed in claim 4 as an antigen.

*Fig. 1*