



US005352664A

United States Patent [19]

[11] Patent Number: 5,352,664

Carney et al.

[45] Date of Patent: Oct. 4, 1994

[54] **THROMBIN DERIVED POLYPEPTIDES; COMPOSITIONS AND METHODS FOR USE**

[75] Inventors: **Darrell H. Carney**, Galveston, Tex.; **Kevin C. Glenn**, St. Louis, Mo.

[73] Assignees: **Board of Regents, The University of Texas System**, Austin, Tex.; **Monsanto Company**, St. Louis, Mo.

[21] Appl. No.: 925,201

[22] Filed: Oct. 31, 1986

[51] Int. Cl.⁵ **A61K 37/02**; A61K 37/547; C07K 7/10; C12N 9/74

[52] U.S. Cl. **514/13**; 530/326; 435/214; 424/94.64

[58] Field of Search 530/330, 327, 326; 514/2, 13, 14, 18; 435/214; 424/94.64

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,427,651 1/1984 Stroetmann 424/45
4,606,337 8/1986 Zimmermann et al. 604/358

OTHER PUBLICATIONS

Butkowski et al. (1977) *JBC*, 252:4942-4957, "Primary Structure of Human Prethrombin 2 and α -Thrombin".
Ruoslahti and Pierschbacher (1986), *Cell*, 44:517-518.
Carney et al. (1985), *Cell*, 42:470-488.
Carney et al. (1984), *J. Cell. Biochem.*, 26:181-195.
Pierschbacher and Ruoslahti (1984), *Proc. Natl. Acad. Sci. USA*, 81:5985-5988.
Pierschbacher and Ruoslahti (1984), *Nature*, 309:30-33.
Degen et al. (1983), *Biochem.*, 22:2087-2097.
Perdue et al. (1981), *J. Biolog. Chem.*, 256:2767-2776.
Glenn et al. (1980), *J. Biolog. Chem.*, 255:6609-6616.

Carney and Cunningham (1978), *Cell*, 15:1341-1349.
Carney and Cunningham (1978), *Cell*, 14:811-823.
Chen and Buchanan (1975), *Proc. Natl. Acad. Sci. USA*, 72:131-135.
CA vol. 102, 1985 Ginsberg et al.
CA vol. 90, 1979 Asstov et al.

Primary Examiner—George C. Elliott
Attorney, Agent, or Firm—Arnold, White & Durkee

[57] **ABSTRACT**

Thrombin is now known to mediate a number of potent biological effects on cells bearing high-affinity thrombin receptors. These effects depend, at least in part, upon receptor occupancy signals generated by thrombin's interaction with the high affinity thrombin receptor. The present inventors have formulated synthetic thrombin derivatives capable of selectively stimulating or inhibiting thrombin receptor occupancy signals. The stimulatory thrombin derivatives to bind to cell surface thrombin receptors and stimulate DNA synthesis in cells treated with non-mitogenic concentrations of alpha-thrombin or phorbol myristate acetate. Thus, these peptides, which have both a thrombin receptor binding domain and a segment of amino acids with a sequence common to a number of serine proteases, appear to generate receptor-occupancy dependent mitogenic signals. The inhibitory derivatives, which have no serine esterase conserved amino acid sequences bind to thrombin receptors without generating receptor-occupancy dependent mitogenic signals. This invention describes the peptides and methods for using them to promote cell growth and wound healing or to inhibit scar formation, tissue adhesions, and tumor metastasis and angiogenesis.

6 Claims, 6 Drawing Sheets

