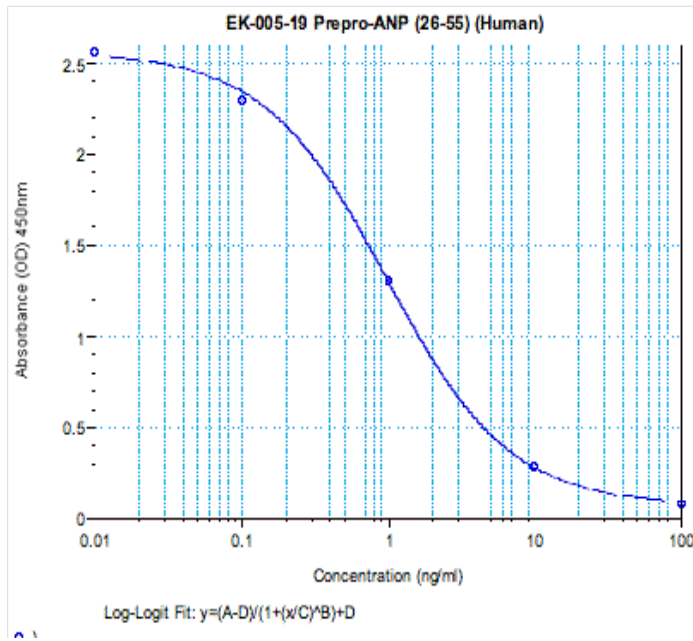


LANP

Long-Acting Natriuretic Peptide

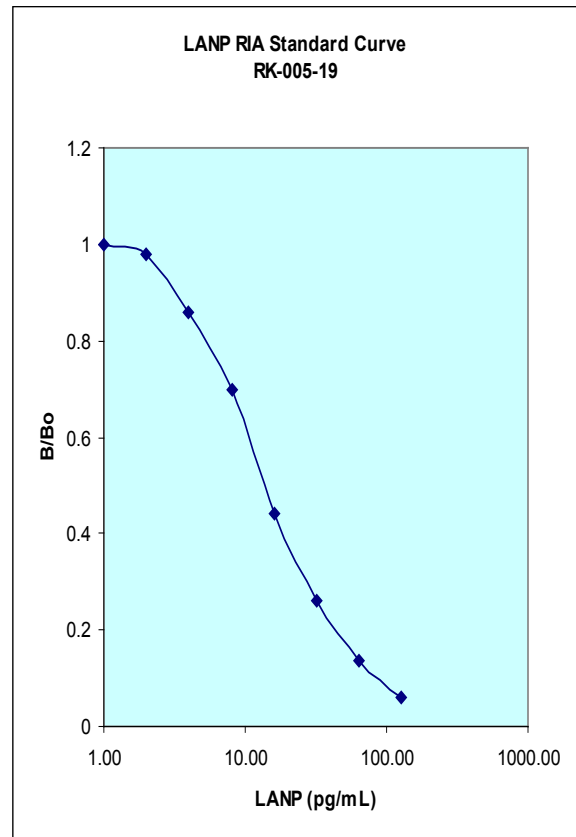
Anti-Cancer Effects, Higher Circulating Level than ANP

LANP, derived from the pro-ANP gene, has been demonstrated to have potent anti-cancer effects. It also has a longer half-life than ANP. LANP is also known as Long-Acting Natriuretic Peptide, LANH, LANF, ANP (1-30) or Prepro ANP (26-55)



Natriuretic peptides we offer that have demonstrated anti-cancer effects include:

alpha-ANP (ANP 1-28)	Cat # 005-06
Kaliuretic Peptide (ANP 104-123)	Cat # 005-22
LANP (ANP 26-55)	Cat # 005-19
Vessel Dilator (ANP 56-92)	Cat # 005-20



PHOENIX PHARMACEUTICALS, INC.
330 BEACH ROAD, BURLINGAME CA, 94010, USA
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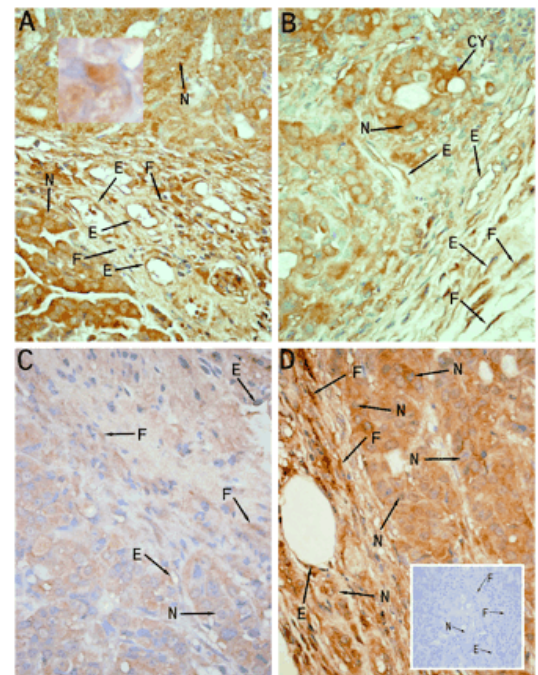
PHOENIX EUROPE GMBH
VIKTORIASTRASSE 3-5, D-76133 KARLSRUHE, GERMANY
PHONE: +49-721-1611950 EMAIL: germany@phoenixpeptide.com
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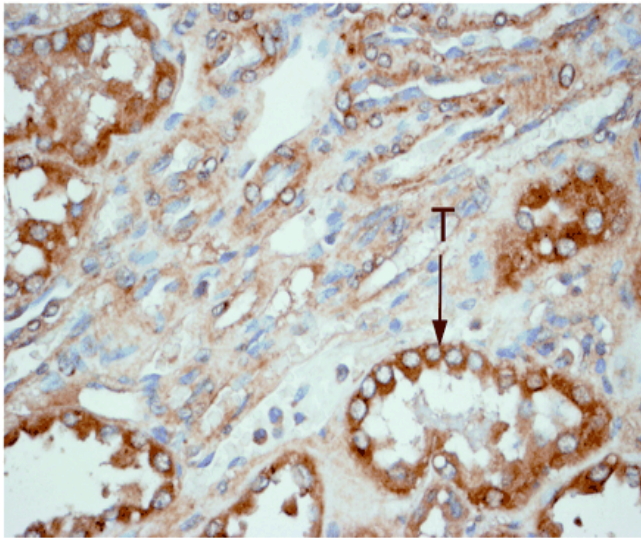
Elimination of up to 80% of human pancreatic adenocarcinomas in athymic mice by cardiac hormones.

BACKGROUND: Four cardiac hormones have anticancer effects in vitro: i) atrial natriuretic peptide (ANP), ii) vessel dilator, iii) long acting natriuretic peptide (LANP), and iv) kaliuretic peptide. **MATERIALS AND METHODS:** These cardiac hormones were infused subcutaneously for 28 days with weekly fresh hormones at 3 nM min⁻¹ kg⁻¹ body weight in athymic mice bearing human pancreatic adenocarcinomas. **RESULTS:** ANP, vessel dilator, LANP and kaliuretic peptide eliminated 80%, 33%, 20% and 14% of the pancreatic adenocarcinomas. Even in the treated animals which did not have a total cure, their tumor volume decreased to less than 10% (and with vessel dilator to 2%) of that of the untreated animals. The natriuretic peptide receptor (NPR)-A receptor was decreased 33% to 55% in the metastatic lesions compared to the primary pancreatic adenocarcinoma. **CONCLUSION:** Four cardiac hormones eliminated up to 80% of human pancreatic adenocarcinomas in athymic mice.

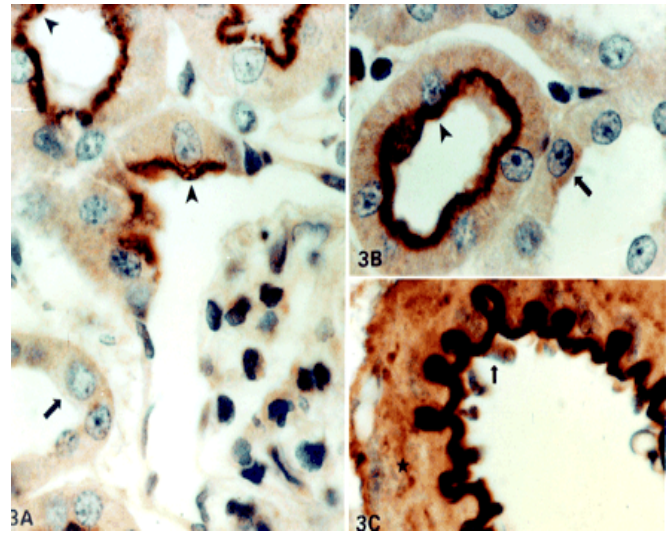
David L Vesely, Ehrentraud J Eichelbaum, et al. *In Vivo.* ;21 (3):445-51 17591353 (P,S,E,B)

Immunoperoxidase localization of vessel dilator, long-acting natriuretic peptide (LANP) [Rabbit Anti-LANP/ANP, Prepro (26-55) (Human) Cat. No.: H-005-19], kaliuretic peptide [Rabbit Anti-Atrial Natriuretic Peptide (ANP) (104-123)-Prepro (Human), Cat. No.: H-005-22], and atrial natriuretic peptide (ANP) [Rabbit Anti-Alpha-ANP (1-28) (Human) Antibody, Cat. No.: H-005-06] within human pancreatic adenocarcinomas with each of these peptide hormones strongly localizing to cytoplasm (Cy), nucleus (N), endothelium (E), and fibroblasts (F). The light blue stain in the fibroblasts is the nuclei of the fibroblasts. (A) Vessel dilator treated, (B) LANP treated, (C) kaliuretic peptide treated, and (D) ANP treated. Primary antibody of each peptide was diluted 1:800. Original magnification x60. The inset in (A) is an isolated nuclei illustrating that vessel dilator has immunoperoxidase staining within the nucleus. The inset in (D) is a negative control using the human pancreatic adenocarcinoma with substitution of the primary antibodies with normal rabbit serum.





Immunoperoxidase localization of vessel dilator [Rabbit Anti-Atrial Natriuretic Peptide (ANP) (56-92)-Prepro (Human) Antibody, Cat.No. H-005-20] within the kidney demonstrating staining throughout the kidney but of increased intensity of staining in the proximal tubules (T) of this normal rat kidney. Original magnification x60. Primary antibody diluted 1:800



Vessel dilator immunoperoxidase staining in the rat kidney reveals strong staining of the sub-brush border of proximal convoluted tubules (arrowheads in A and B), including a proximal tubule (A) originating directly from the top left portion of the glomerulus. The interstitial artery (C) had strong proANP-(31—67) staining of the elastica with moderate staining of endothelial cells (arrow) and media (). The distal tubules and collecting ducts (arrows in A and B) had weak staining with no demonstrable staining in some of the collecting duct cells.*

Cardiac natriuretic peptides: hormones with anticancer effects that localize to nucleus, cytoplasm, endothelium, and fibroblasts of human cancers.

Four cardiac peptide hormones, i.e., vessel dilator, long acting natriuretic peptide (LANP), kaliuretic peptide, and atrial natriuretic peptide (ANP) synthesized by the same gene decrease within 24 hours up to 97% the number of human breast, colon, pancreatic, and prostate adenocarcinoma cells as well as human small-cell and squamous carcinomas of the lung cells. These peptide hormones completely inhibit the growth of human pancreatic adenocarcinomas growing in athymic mice. Immunocytochemical investigations have revealed that LANP, vessel dilator, kaliuretic peptide and ANP localize to the nucleus and cytoplasm of human pancreatic adenocarcinomas, which is consistent with their ability to decrease DNA synthesis in the nucleus of this cancer mediated by the intracellular messenger cyclic GMP. These peptide hormones also localize to the endothelium of capillaries and fibroblasts within these cancers. These are the first growth-inhibiting peptide hormones ever demonstrated to localize to the nucleus. Their ability to decrease the activation of growth promoting substances such as Extracellular Receptor Kinase (ERK)-1/2 and Nuclear Factor Kappa Beta (NFkappaB) suggests that in addition to inhibiting DNA synthesis their ability to decrease the activation of growth promoting substances helps to mediate their ability to inhibit the growth of human cancers.

Saba SR, Vesely DL. Eur J Clin Invest. 2005 Jun;35(6):388-98

Amino acid sequences of the natriuretic peptides.

Each of the sequences are the human sequences except for *Dendroaspis* natriuretic peptide (DNP), whose sequence is only known in the snake. The brackets illustrate the location of cystine bridges that help to form a ring structure in a number of these peptides. BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide.

David L. Vesely *Am J Physiol Renal Physiol* 285: F167-F177, 2003

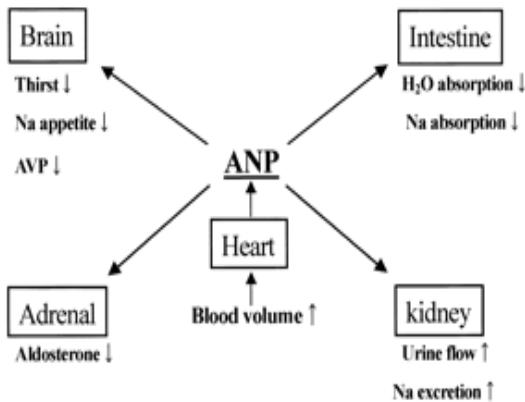
Natriuretic Peptides	
LANP	Asn-Pro-Met-Tyr-Asn-Ala-Val-Ser-Asn-Ala-Asp-Leu-Met-Asp-Phe-Lys-Asn-Leu-Leu-Asp-His-Leu-Glu-Glu-Lys-Met-Pro-Leu-Glu-Asp
Vessel dilator	Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Pro-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Glu-Val-Ser-Pro-Ala-Gln-Arg
Kaliuretic peptide	Ser-Ser-Asp-Arg-Ser-Ala-Leu-Leu-Lys-Ser-Lys-Leu-Arg-Ala-Leu-Leu-Thr-Ala-Pro-Arg
ANP	Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr
Urodilatin	Thr-Ala-Pro-Arg-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr
BNP	Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-Cys-Phe-Gly-Arg-Lys-Met-Asp-Arg-Ile-Ser-Ser-Ser-Ser-Gly-Leu-Gly-Cys-Lys-Val-Leu-Arg-Arg-His
CNP	Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys
DNP	Glu-Val-Lys-Tyr-Asp-Pro-Cys-Phe-Gly-His-Lys-Ile-Asp-Arg-Ile-Asn-His-Val-Ser-Asn-Leu-Gly-Cys-Pro-Ser-Leu-Arg-Asp-Pro-Arg-Pro-Asn-Ala-Pro-Ser-Thr-Ser-Ala
Adrenomedullin	Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg-Ser-Phe-Gly-Cys-Arg-Phe-Gly-Thr-Cys-Thr-Val-Gln-Lys-Leu-Ala-His-Gln-Ile-Tyr-Gln-Phe-Thr-Asp-Lys-Asp-Lys-Asp-Asn-Val-Ala-Pro-Arg-Ser-Lys-Ile-Ser-Pro-Gln-Gly-Tyr

Table 1. Site(s) of synthesis, molecular weight, and hemodynamic and natriuretic properties of natriuretic peptides

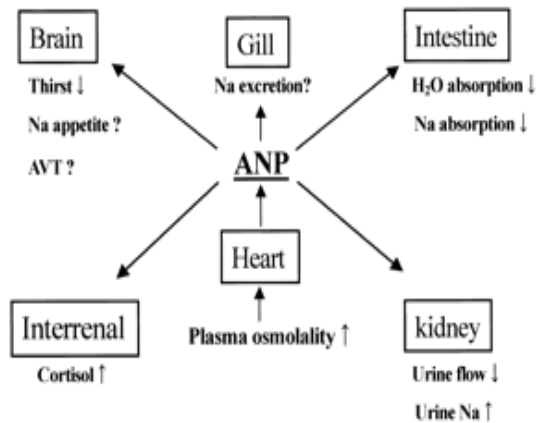
	Molecular Wt	Site of Synthesis	MAP	Diuresis	Natriuresis
LANP	3,508	Atria, ventricle, GI, lung, kidney, brain, adrenal	↓	↑	↑
Vessel dilator	3,878	Atria, ventricle, GI, lung, kidney, brain, adrenal	↓	↑	↑
Kaliuretic peptide	2,184	Atria, ventricle, GI, lung, brain, adrenal	↓	↑	-
ANP	3,078	Atria, ventricle, GI, lung, kidney, brain, adrenal	↓	↑	↑
Urodilatin	3,503	Kidney	↓	↑	↑
BNP	3,462	Atria, ventricle, brain, adrenal	↓	↑	↑
CNP	2,198	Endothelium, CNS	↓	↑	-
DNP	4,191	Atria, ventricle	↓	↑	↑
Adrenomedullin	6,029	Adrenal, kidney	↓	↑	↑

LANP, long-acting atrial natriuretic peptide; ANP, atrial natriuretic peptide; MAP, mean arterial pressure; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; CNS, central nervous system; DNP, *Dendroaspis* natriuretic peptide; GI, gastrointestinal tract; ↓, decrease; ↑, increase; -, no significant effect. The sites of synthesis are listed in approximate order in which they contribute to synthesis.

A. Rat



B. Eel



Mammals

Human ANP	SLRRSSCFGGRMDRIGAQSSGLGNSFRY	(42)
Human BNP	SPKMQVQSGGCFGRKMDRISSSSGLGCKVLRH	(80)
Human CNP	GLSKGCFGLKLDRI GSMSGLGC	(100)

Birds

Chicken BNP	MMRDSGCFGRRIDRIGLSGSGCNGSRKN	(60)
Chicken CNP	GLSRSCFGLKLDRI GSMSGLGC	(5)

Amphibians

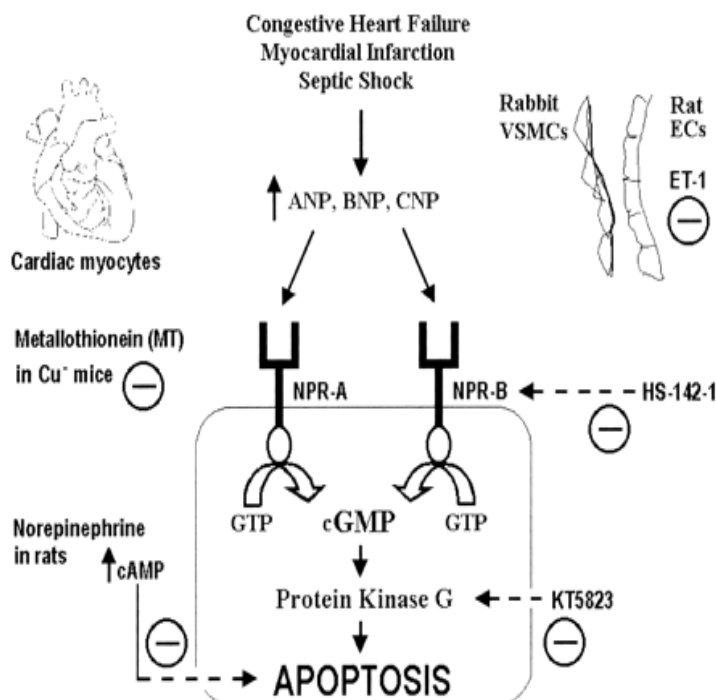
Bullfrog ANP	SSDCFGSRIDRIGAQSSGMC-GRRF	(74)
Bullfrog BNP	SNCFGRRIDRIDSVSGMGCNGSRNRY	(30)
Bullfrog CNP1	GYSRGCFGVKLDRI GAFSGLGC	(104)
Bullfrog CNP2	GTSKGC FGLKLDRI GAMSG LG	(48)

Teleosts

Trout ANP	SKAVSGCFGARMDRIGTSSGLGCSPKRRS	(90)
Trout VNP	KSFNSCFGNRIERIGSWSGLGNNVKTGNKKRIFGN	(94)
Trout CNP	GWNRGCFGLKLDRI GSMSGLGC	(Inoue & Takei, unpublished)

Elasmobranchs

Dogfish CNP	GPSRGCFGVKLDRI GAMSG LG	(81)
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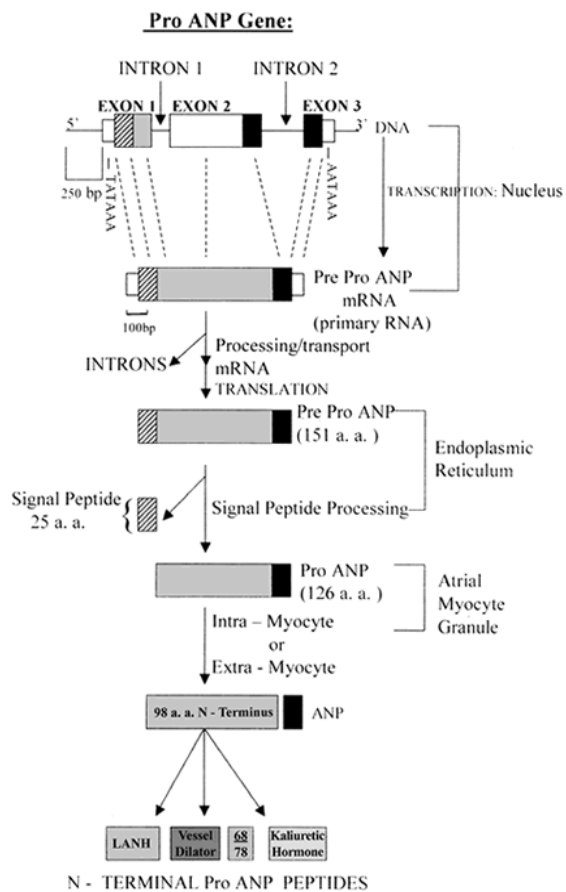


Four cardiac hormones eliminate up to 82% of human medullary thyroid carcinoma cells within 24 hours.

Four cardiac hormones, i.e., atrial natriuretic peptide, vessel dilator, long-acting natriuretic peptide, and kaliuretic peptide, which have anticancer effects, were evaluated for the first time on any endocrine cancer to determine if they have anticancer effects in an endocrine cancer. These four cardiac hormones were evaluated for their anticancer, DNA synthesis, and receptor status in human medullary thyroid cancer cells. There was a significant ($p < 0.001$) decrease in human medullary thyroid cancer cells with each 10-fold increase from 1 to 100 μM of the four cardiac hormones. There was an 81%, 68%, 71%, and 66% elimination within 24 h of medullary thyroid cancer cells secondary to vessel dilator, kaliuretic peptide, atrial natriuretic peptide, and long-acting natriuretic peptide, respectively ($p < 0.0001$). Three days after treatment with these peptide hormones, there was no proliferation of the medullary thyroid cancer cells. These cardiac hormones decreased DNA synthesis in the medullary thyroid cells from 65% to 84% ($p < 0.0001$). Western blots revealed natriuretic peptide receptors-A and -C were present in human medullary thyroid cancer cells. These results indicate the four cardiac hormones have potent anticancer effects by eliminating up to 82% of human medullary thyroid carcinoma cells within 24 h of treatment.

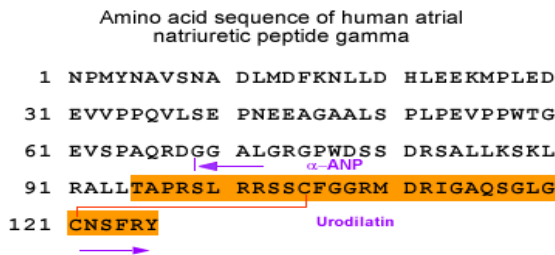
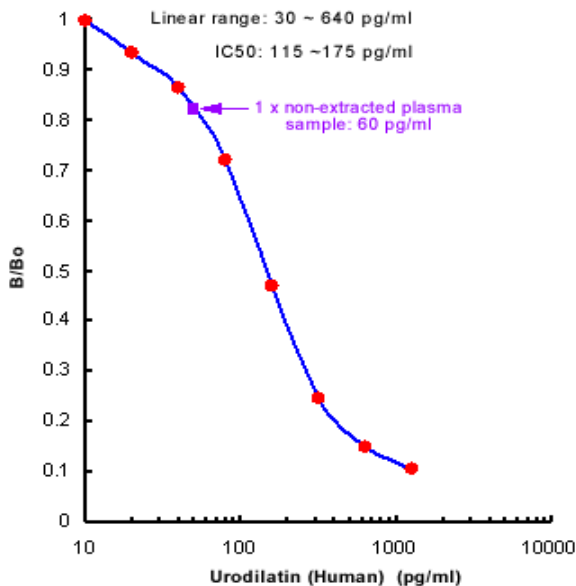
Endocrine. 2006 Dec ;30 (3):325-32 17526945 (P,S,E,B)

Ehrentraud J Eichelbaum, Brian A Vesely, et al



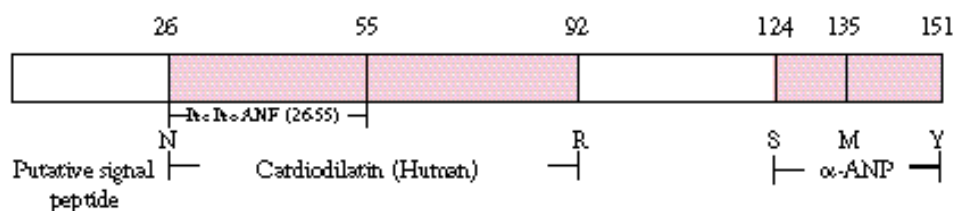
Urodilatin (Human) RIA Kit

Catalog No.: RK-005-18



July 24, 2006, Phoenix Pharmaceuticals, Inc.

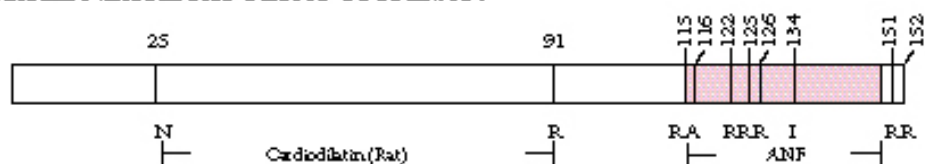
Schematic representation of the structure of the Human Cardiodilatin-Atrial Natriuretic Peptide Precursor:



S. Oikawa et al., *Nature* Vol. 309, 724 (1984)

K. Nakayama et al., *Nature* Vol. 310, 699 (1984)

Schematic representation of the structure of the Rat Cardiodilatin-Atrial Natriuretic Factor Precursor:

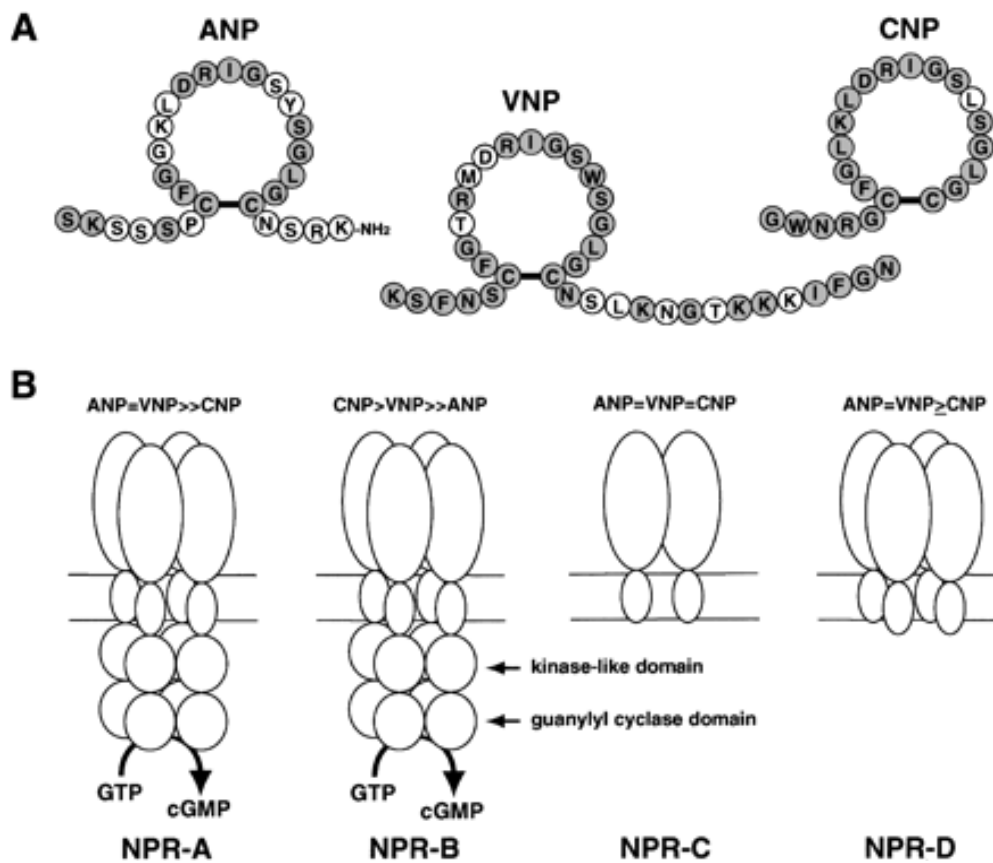


M. Yamanaka et al., *Nature* Vol. 309, 719 (1984)

M. Miki et al., *Nature* Vol. 309, 722 (1984)

C. E. Seidman et al., *Science* Vol. 225, 324 (1984)

K. Kangawa et al., *BBRC* Vol. 121, 385 (1984)



Catalog#	Product Name	Std Size
005-18	Urodilatin / ANP (95-126) / CDD	200 µg
RK-005-18	Urodilatin / ANP (95-126) - RIA Kit	1 kit
G-005-18	Urodilatin / ANP (95-126) - Purified IgG Antibody	400 µg
T-G-005-18	Urodilatin / ANP (95-126) - I-125 Labeled Purified IgG	10 µCi
T-005-18	Urodilatin / ANP (95-126) - I-125 Labeled	10 µCi
H-005-18	Urodilatin / ANP (95-126) - Antibody for Immunohistochemistry	50 µl
MRK-005-18	Urodilatin (ANP (95-126)) - Magnetic Bead RIA kit	1 kit
RK-005-19	LANP / ANP (26-55), prepro (Human) - RIA Kit	1 kit
G-005-19	LANP / ANP (26-55), prepro (Human) - Purified IgG Antibody	400 µg
T-G-005-19	LANP / ANP (26-55), prepro (Human) - I-125 Labeled Purified IgG	10 µCi
T-005-19	LANP / ANP (26-55), prepro (Human) - I-125 Labeled	10 µCi
EK-005-19	LANP / ANP (26-55), prepro (Human) - EIA Kit	1 kit
B-005-19	LANP / ANP (26-55), prepro (Human) - Biotin Labeled	100 µg
H-005-19	LANP / ANP (26-55), prepro (Human) - Antibody for Immunohistochemistry	50 µl
005-19	LANP / ANP (26-55), prepro (Human)	200 µg
005-39	Auriculin B / ANP (126-150) (Rat)	1 mg
005-38	Auriculin A / ANP (126-149) (Rat)	200 µg
005-37	Atriopeptin III Analog / PL-058	200 µg
005-36	Atriopeptin III (Rat, Mouse, Rabbit)	200 µg
005-34	Atriopeptin II (Rat, Mouse, Rabbit)	200 µg
005-32	Atriopeptin I (Rat, Mouse, Rabbit)	200 µg
PG-H-005-06	Atrial Natriuretic Peptide-Alpha (α-ANP) (1-28) (Human, Ovine, Canine) from Guinea Pig - Antibody for Immunohistochemistry	50 µl
005-14	Atrial Natriuretic Peptide, Beta (Beta-ANP) (Dimer, Antiparallel) (Human)	100 µg
005-05	ANP-30 (Frog)	200 µg
005-04	ANP-24 (Frog)	200 µg
005-03	ANP-21 (Frog)	200 µg
RK-005-14	ANP, beta (Human) - RIA Kit	1 kit
005-01	ANP, alpha (Chicken)	200 µg
B-005-07	ANP, alpha (1-28) [Di-Biotinyl-Lys] (Human, Ovine, Canine) - Biotin Labeled	100 µg
RK-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - RIA Kit	1 kit
FR-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Rhodamine Labeled	1 nmol
G-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Purified IgG Antibody	400 µg
T-G-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - I-125 Labeled Purified IgG	10 µCi
T-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - I-125 Labeled	10 µCi
FEK-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Fluorescent EIA Kit	1 kit
FG-005-06A	ANP, alpha (1-28) (Human, Ovine, Canine) - FAM Labeled	1 nmol
EK-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - EIA Kit	1 kit
FC5-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Cy5 Labeled	1 nmol
FC3-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Cy3 Labeled	1 nmol
B-G-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Biotin Labeled Purified IgG	100µl
H-005-06	ANP, alpha (1-28) (Human, Ovine, Canine) - Antibody for Immunohistochemistry	50 µl
005-06	ANP, alpha (1-28) (Human, Ovine, Canine)	200 µg
G-005-14	ANP, β (Human) - Purified IgG Antibody	400 µg
T-G-005-14	ANP, β (Human) - I-125 Labeled Purified IgG	10 µCi
T-005-14	ANP, β (Human) - I-125 Labeled	10 µCi
H-005-14	ANP, β (Human) - Antibody for Immunohistochemistry	50 µl
RK-005-24	ANP (Rat, Mouse) - RIA Kit	1 kit

FR-G-005-24	ANP (Rat, Mouse) - Rhodamine Labeled Purified IgG	100 µl
FR-005-24	ANP (Rat, Mouse) - Rhodamine Labeled	1 nmol
G-005-24	ANP (Rat, Mouse) - Purified IgG Antibody	400 µg
MRK-005-24	ANP (Rat, Mouse) - Magnetic Bead RIA kit	1 kit
T-G-005-24	ANP (Rat, Mouse) - I-125 Labeled Purified IgG	10 µCi
T-005-24	ANP (Rat, Mouse) - I-125 Labeled	10 µCi
FG-G-005-24A	ANP (Rat, Mouse) - FAM Labeled Purified IgG	100 µl
FG-005-24A	ANP (Rat, Mouse) - FAM Labeled	1 nmol
EK-005-24	ANP (Rat, Mouse) - EIA Kit	1 kit
B-G-005-24	ANP (Rat, Mouse) - Biotin Labeled Purified IgG	100 µl
B-005-24	ANP (Rat, Mouse) - Biotin Labeled	100 µg
H-005-24	ANP (Rat, Mouse) - Antibody for Immunohistochemistry	50 µl
005-24	ANP (Rat, Mouse)	200 µg
005-02	ANP (Eel)	200 µg
005-28	ANP (8-33) (Rat)	200 µg
005-13	ANP (7-28) (Human, Ovine, Canine)	200 µg
005-45	ANP (7-23) (Human)	200 µg
T-005-20	ANP (56-92), Prepro [Tyr0] (Human) - I-125 Labeled	10 µCi
RK-005-20	ANP (56-92), Prepro (Human) - RIA Kit	1 kit
G-005-20	ANP (56-92), Prepro (Human) - Purified IgG Antibody	400 µg
T-G-005-20	ANP (56-92), Prepro (Human) - I-125 Labeled Purified IgG	10 µCi
H-005-20	ANP (56-92), Prepro (Human) - Antibody for Immunohistochemistry	50 µl
005-20	ANP (56-92), Prepro (Human)	200 µg
FG-005-12A	ANP (5-28) (Human, Ovine, Canine) - FAM Labeled	0
005-12	ANP (5-28) (Human, Ovine, Canine)	200 µg
005-11	ANP (5-27) (Human, Ovine, Canine)	200 µg
005-10	ANP (4-28) (Human, Ovine, Canine)	200 µg
005-26	ANP (4-23)-Amide Des-[Gln18, Ser19, Gly20, Leu21, Gly22] (Rat)	200 µg
005-46	ANP (104-126) Des-[Cys105, Cys121] (Rat)	200 µg
T-005-25	ANP (104-123), Prepro [Tyr0] (Human) - I-125 Labeled	10 µCi
005-25	ANP (104-123), Prepro [Tyr0] (Human)	100 µg
RK-005-22	ANP (104-123), Prepro (Human) - RIA Kit	1 kit
G-005-22	ANP (104-123), Prepro (Human) - Purified IgG Antibody	400 µg
T-G-005-22	ANP (104-123), Prepro (Human) - I-125 Labeled Purified IgG	10 µCi
H-005-22	ANP (104-123), Prepro (Human) - Antibody for Immunohistochemistry	50 µl
005-22	ANP (104-123), Prepro (Human)	200 µg
T-005-23	ANP (104-116), Prepro [Tyr0] (Human) - I-125 Labeled	10 µCi
005-23	ANP (104-116), Prepro [Tyr0] (Human)	100 µg
RK-005-21	ANP (104-116), Prepro (Human) - RIA Kit	1 kit
G-005-21	ANP (104-116), Prepro (Human) - Purified IgG Antibody	400 µg
T-G-005-21	ANP (104-116), Prepro (Human) - I-125 Labeled Purified IgG	10 µCi
H-005-21	ANP (104-116), Prepro (Human) - Antibody for Immunohistochemistry	50 µl
005-21	ANP (104-116), Prepro (Human)	200 µg
MRK-005-06	ANP (1-28) Alpha (Human, Ovine, Canine) - Magnetic Bead RIA kit	1 kit