Nobel Prize in Medicine/Physiology 1998

"...for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system."
Background

- Mechanism of action of nitroglycerin unknown until 1970s
- Acetylcholine as vasodilator in vivo, but vasoconstrictor in vitro
Born: 4 June 1916, Charleston, SC, USA

Died: 19 May 2009, Seattle, WA, USA

Affiliation at the time of the award: SUNY Health Science Center, Brooklyn, NY, USA

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Born: 31 May 1941, Brooklyn, NY, USA

Affiliation at the time of the award: University of California School of Medicine, Los Angeles, CA, USA

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Born: 14 September 1936, Whiting, IN, USA

Affiliation at the time of the award: University of Texas Medical School at Houston, Houston, TX, USA
Acetylcholine

ENDOTHELIAL CELL

Ca$^{2+}$ Calmodulin

NO Synthase
arginine + O$_2$ → citrulline + NO

NO

SMOOTH MUSCLE CELL

Fe

Guanylate Cyclase
GTP → cGMP → RELAXATION
Key findings

Robert F. Furchgott
CCh = Carbachol (similar to Ach)
-> „endothelium-derived relaxing factor“ (EDRF)
CONTROL

- 2 μl NO₂
- 5 μl
- 10 μl

SOD 30 U/ML

- 2 μl NO₂
- 5 μl
- 10 μl

R Furchgott, Nobel lecture 1998
Key findings

Louis J. Ignarro
Guanylate Cyclase

SMOOTH MUSCLE CELL

GTP → cGMP → RELAXATION

Guanylate Cyclase
basal vs activated

Fe

Heme

Protoporphyrin-IX

NO-Heme

Activated

Activated

Basal and Unactivated

Basal and Unactivated

L Ignarro, Nobel lecture 1998
Deoxy-Hb + NO
Deoxy-Hb + EDRF

Absorbance

Wavelength (nm)
Key findings

Ferid Murad
NOS-1 (155kD) - neuronal, brain, Type I-NOS; central and peripheral neurons, NANC neurons, islets, endometrium, skeletal muscle, etc.

NOS-2 (125kD) - inducible, Type II-NOS; macrophage, liver, smooth muscle, endothelium, heart, etc.; effects of LPS, cytokines and glucocorticoids

NOS-3 (135kD) - endothelial, Type III-NOS; endothelium, brain, heart, etc.; acylation, phosphorylation
L-arginine $\rightarrow$ N-hydroxy-L-arginine $\rightarrow$ L-citrulline
Oncology
Platelet function
Erectile dysfunction/Pulmonary hypertension

**NITRIC OXIDE AS A MEDIATOR OF RELAXATION OF THE CORPUS CAVERNOsum IN RESPONSE TO NONADRENERGIC, NONCHOLINERGIC NEUROTRANSMISSION**

Jacob Rajfer, M.D., William J. Aronson, M.D., Peggy A. Bush, B.S., Frederick J. Dorey, Ph.D., and Louis J. Ignarro, Ph.D.

T.Lue, NEJM 342:1802, 2000
Acetylcholine

ENDOTHELIAL CELL

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Fe

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GTP → cGMP → RELAXATION