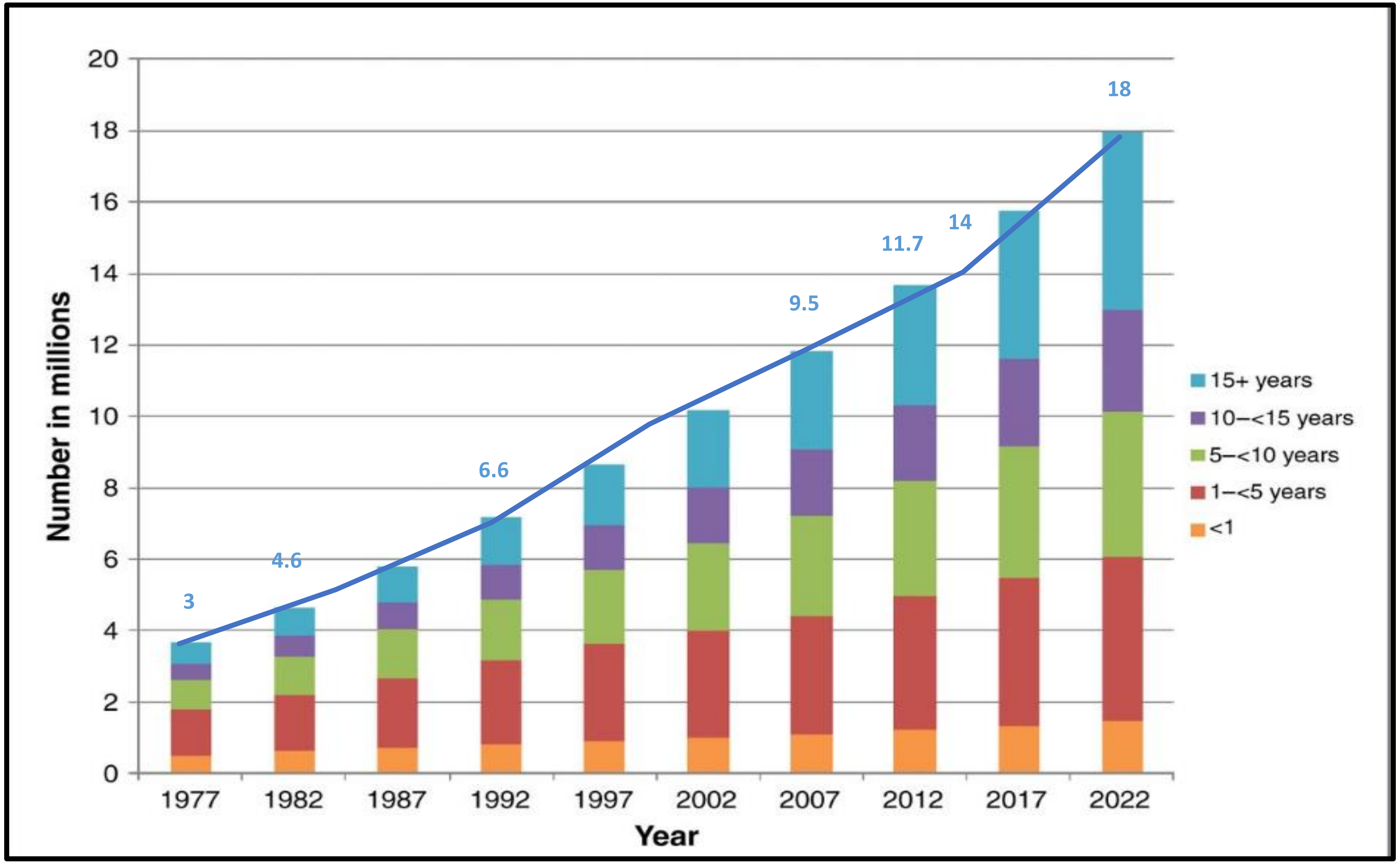
# Diseases and Treatments as Aging Accelerators

Anju Nohria, MD, MSc
Director, Cardio-Oncology Program
Dana Farber Cancer Institute/Brigham and Women's Hospital
Boston, MA

# Disclosures

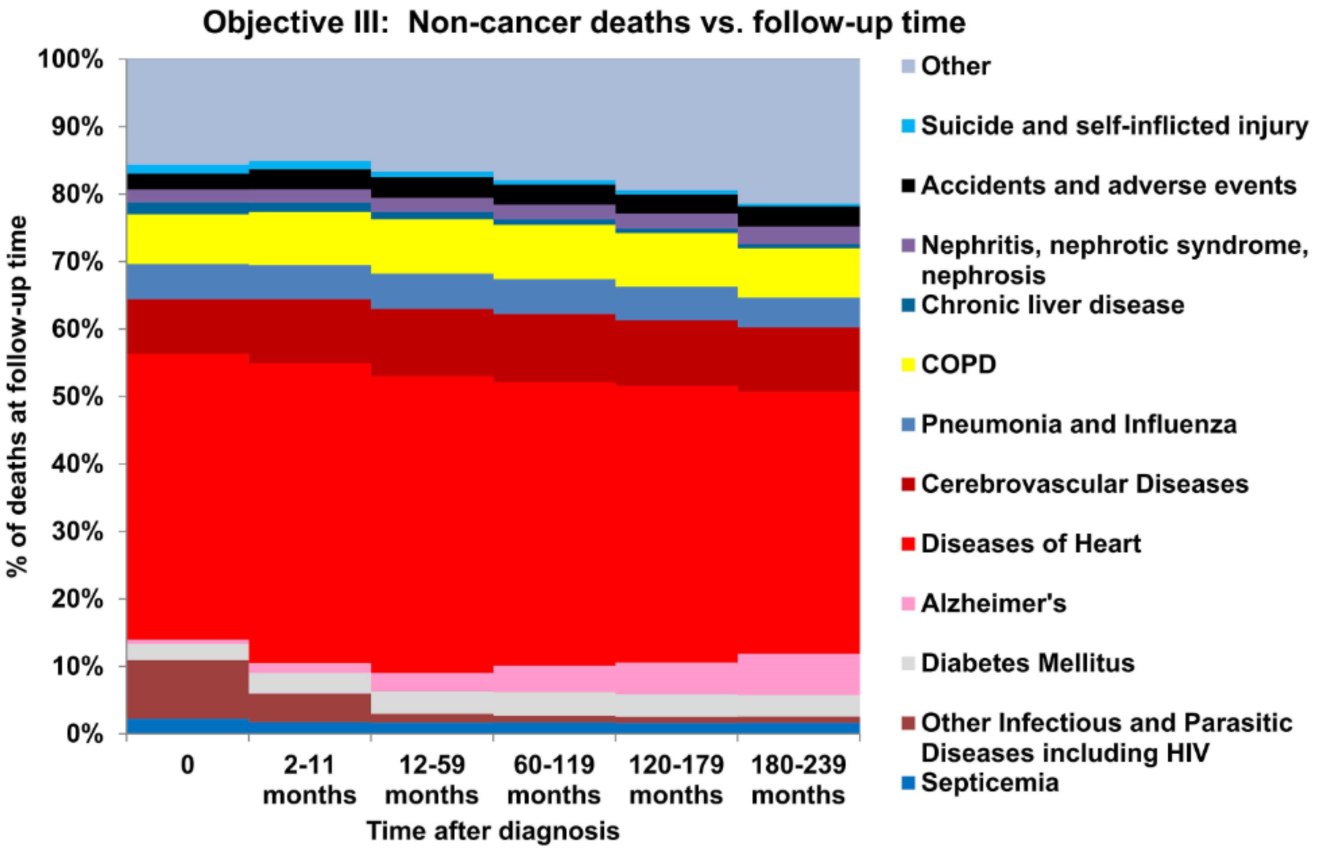
- Research Support – Amgen, Inc.
- Consultant – AstraZeneca, Boehringer Ingelheim, Takeda Oncology

# Increasing Cancer Survivorship



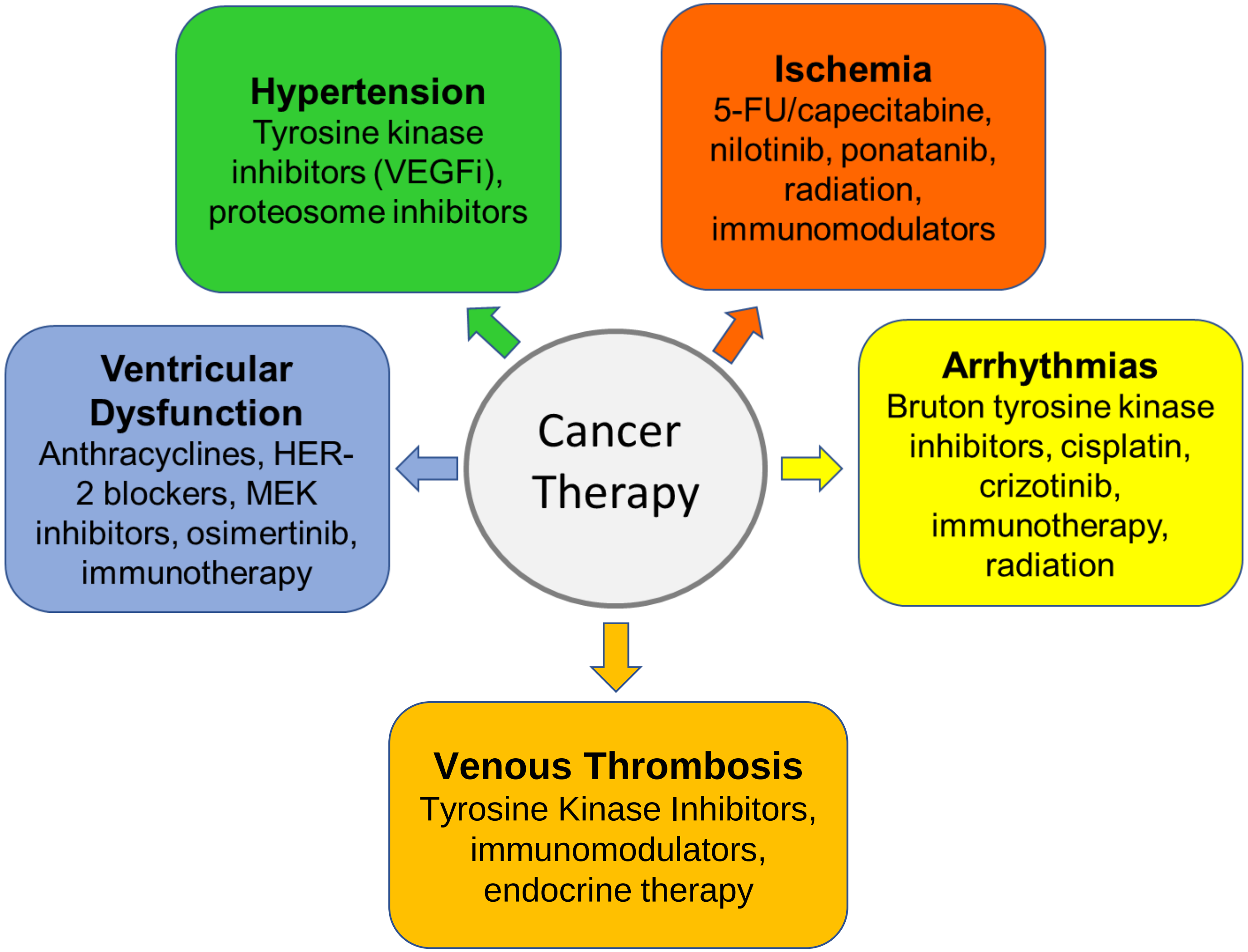

De Moor et al. Cancer Epidemiol Biomarkers Prev. 2013;22(4):561-70.

# CV Disease is the Leading Cause of Non-Cancer Related Death in Cancer Survivors




Ann Oncol 2017;28(2):400-7.

# Cancer Treatment Associated Cardiotoxicity

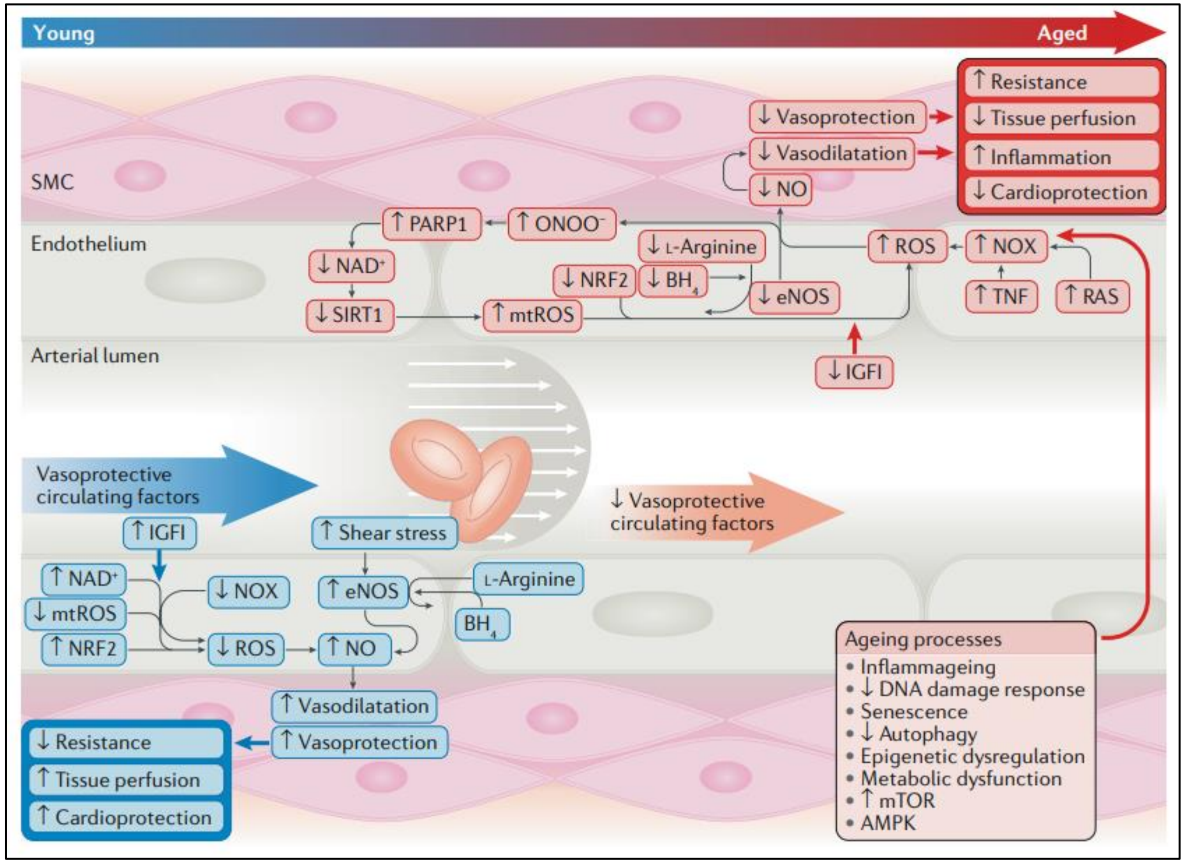


# Outline

- Pathophysiology of vascular aging
- Potential mechanisms by which cancer therapies may accelerate vascular aging
- Potential therapeutic targets to mitigate cancer-therapy associated vascular aging

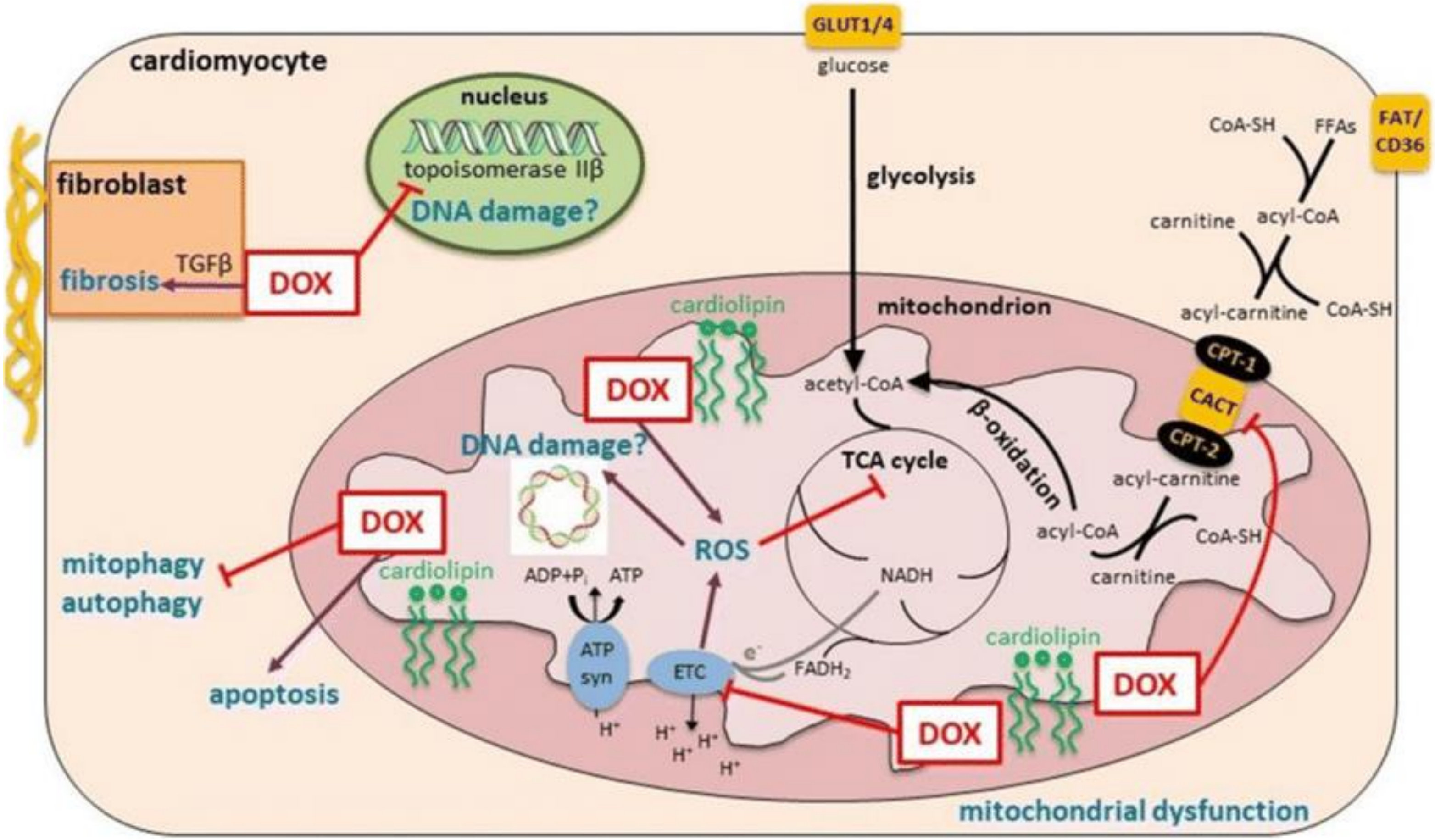
# Characteristics of Vascular Aging

- Increased arterial stiffness
  - ↑SBP and pulse pressure
  - LV hypertrophy
  - End-organ damage via ↑ pulsatile flow
- Endothelial dysfunction
  - Impaired vasodilation
  - Thrombosis
  - Inflammation
  - Abnormal mitochondrial function and cellular energy metabolism



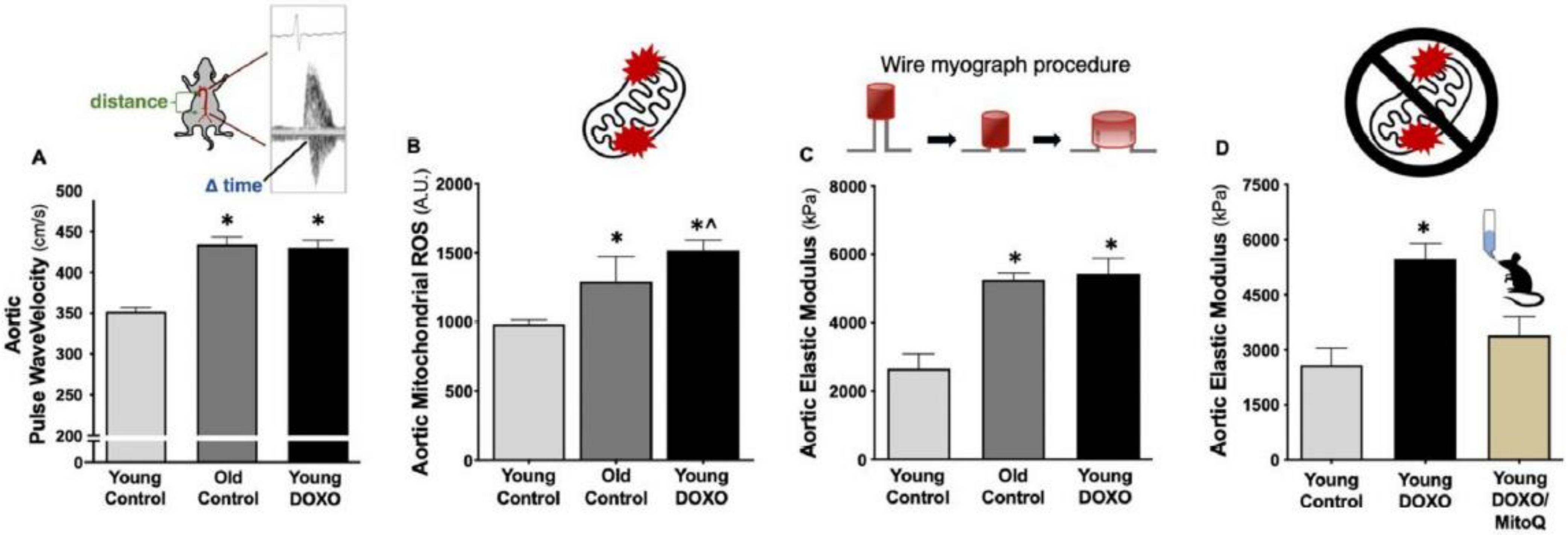

Nature Reviews Cardiology, 2018;15:555-65.

# Mechanisms of Anthracycline Cardiotoxicity



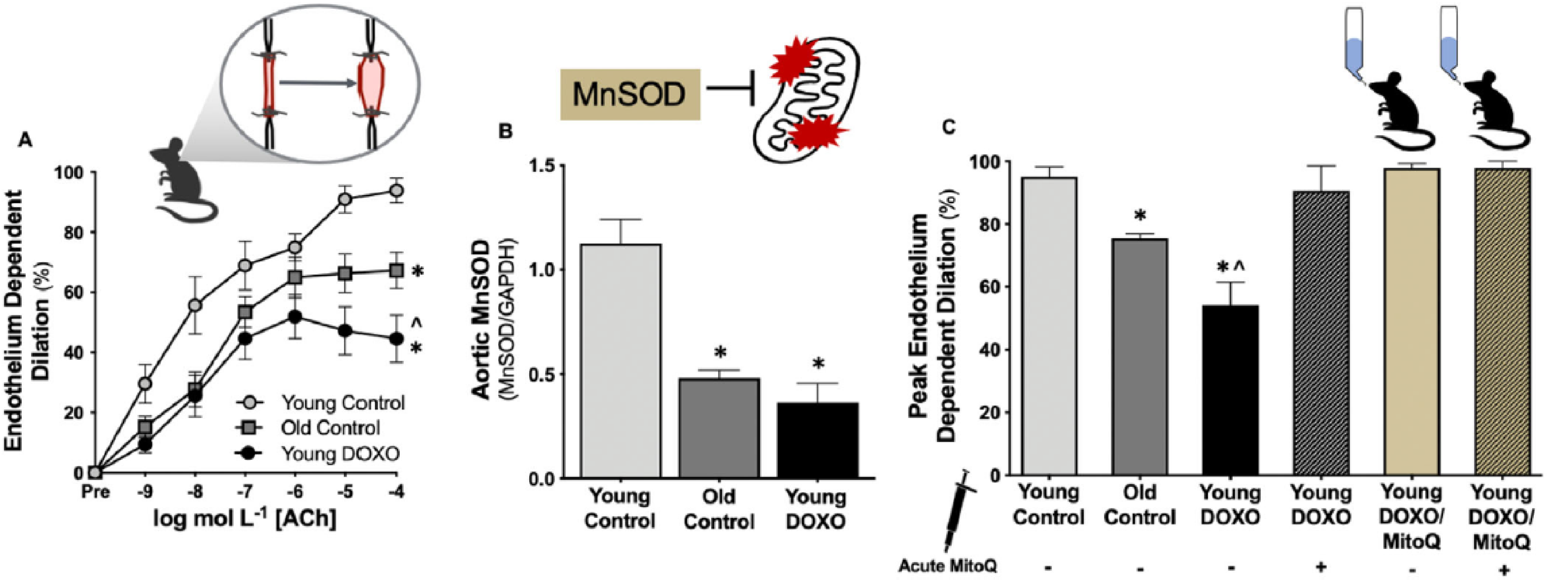

Cardiovascular Drugs and Therapy (2020) 34:255–269

# Doxorubicin Increases Vascular Stiffness




Aging and Cancer 2021;2:45-69.

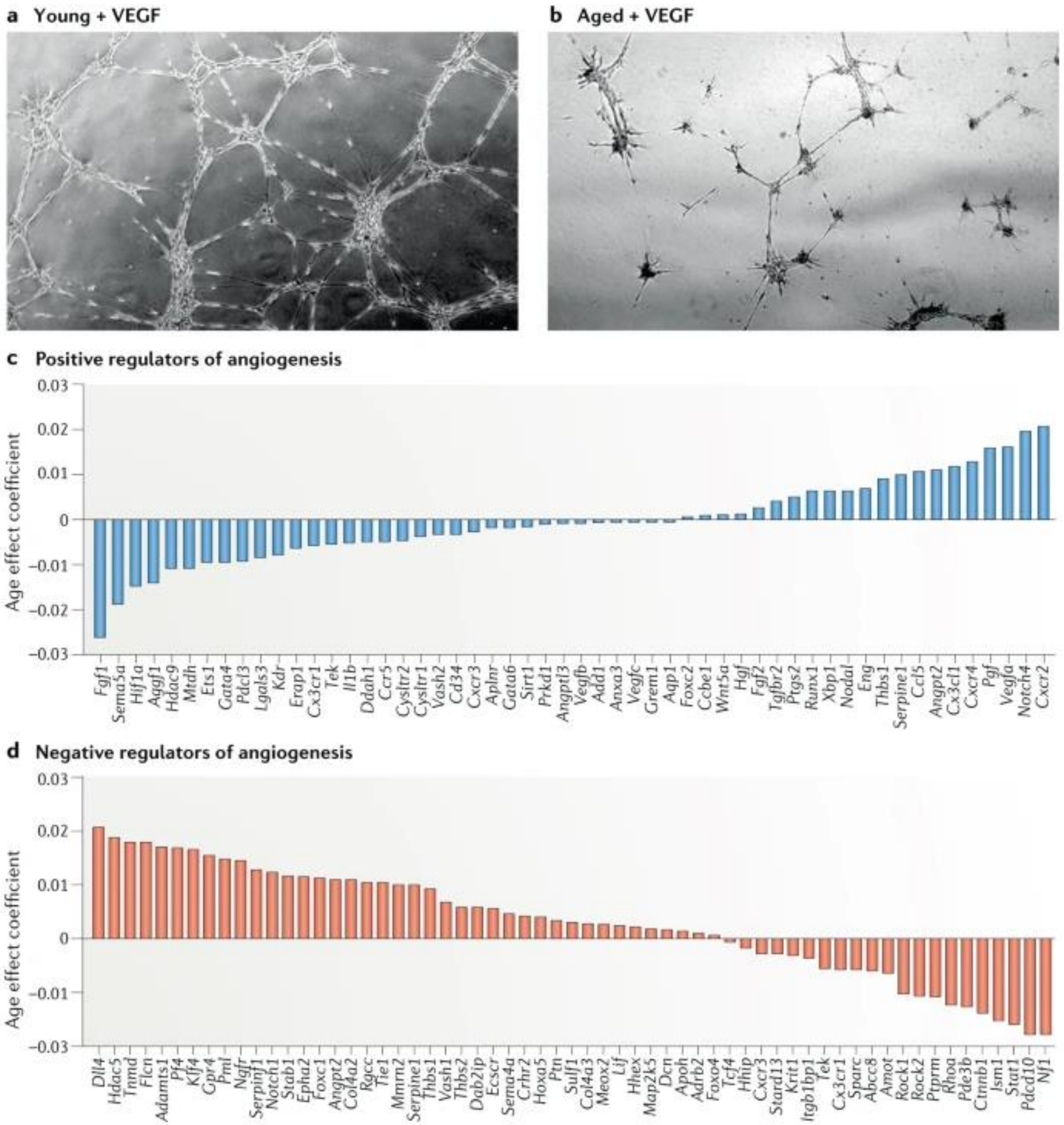
# Doxorubicin Promotes Endothelial Dysfunction




Aging and Cancer 2021;2:45-69.

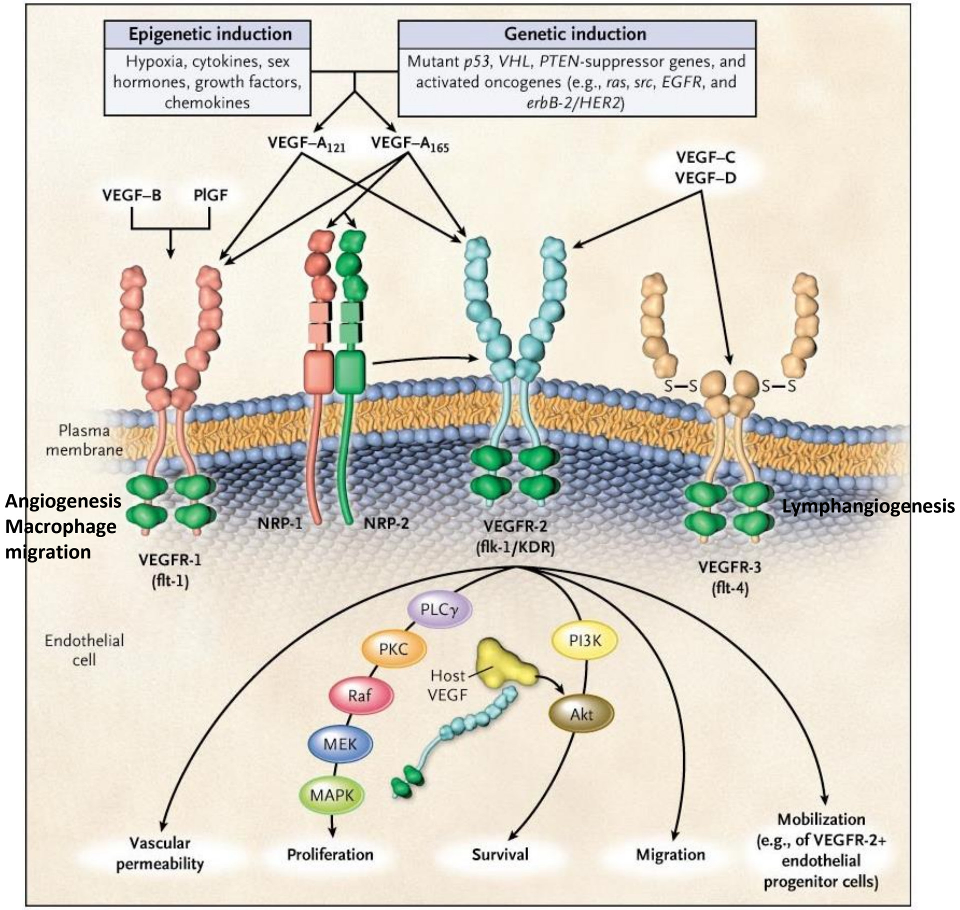
# Characteristics of Vascular Aging

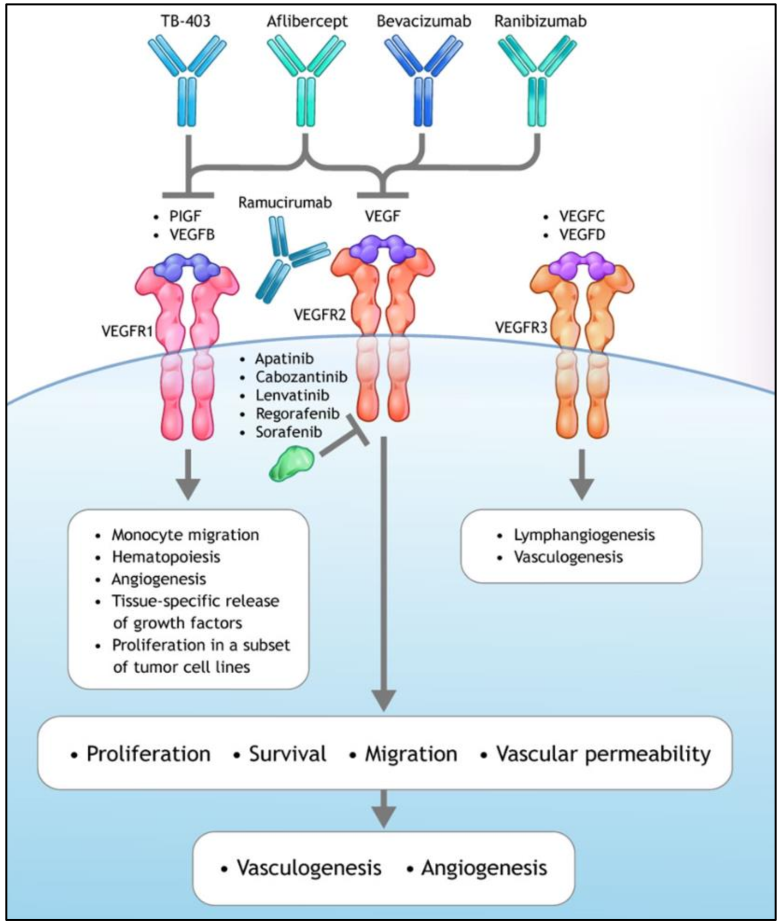
- Decreased responsiveness to angiogenic stimuli
- Altered expression of genes regulating angiogenesis
- Microvascular rarefaction → ↓tissue oxygenation → ↓mitochondrial activity→ metabolic perturbations → multi-organ dysfunction




Nature Reviews Cardiology, 2018;15:555-65.

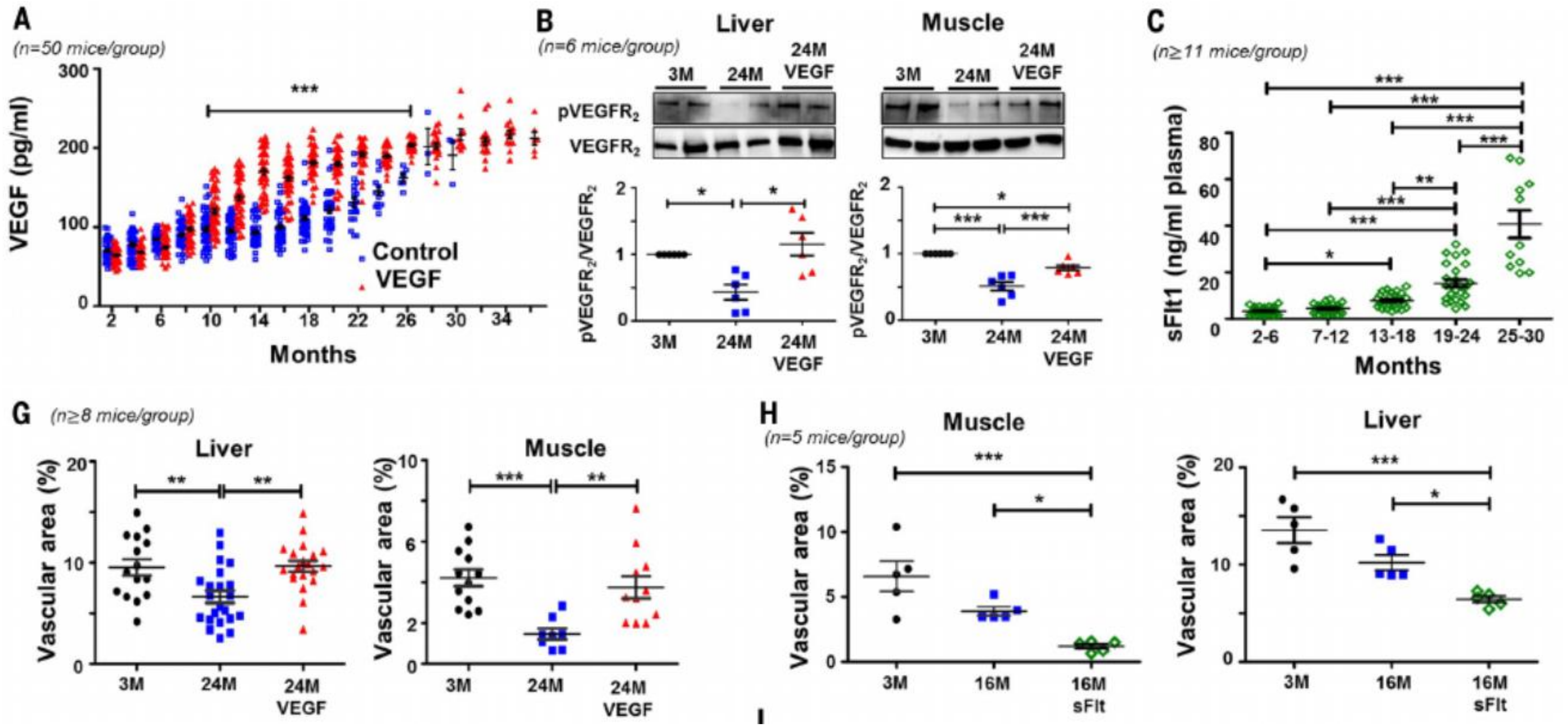
# VEGF and VEGF Inhibitors in Cancer



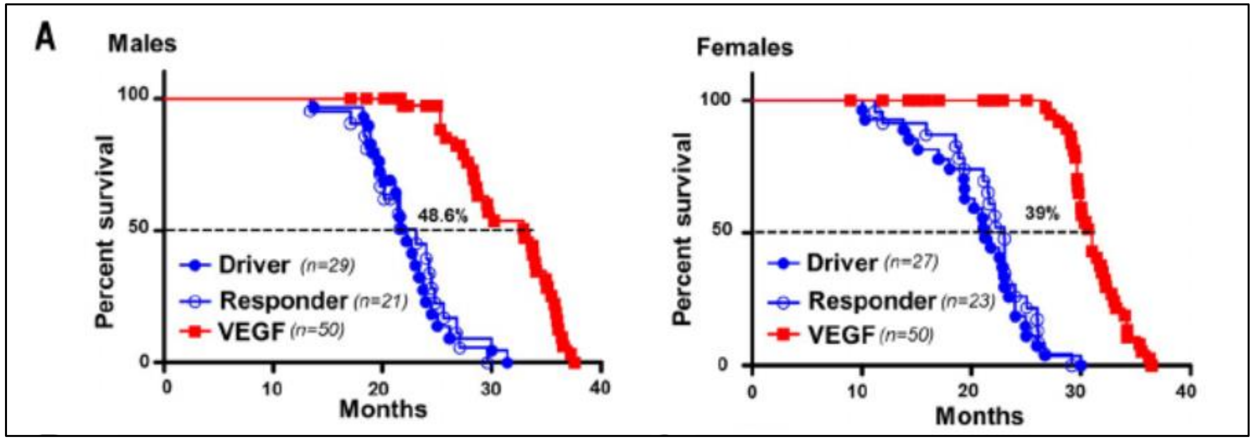

N Engl J Med 2008; 358:2039-2049; Front Immunol 2020;11:598877

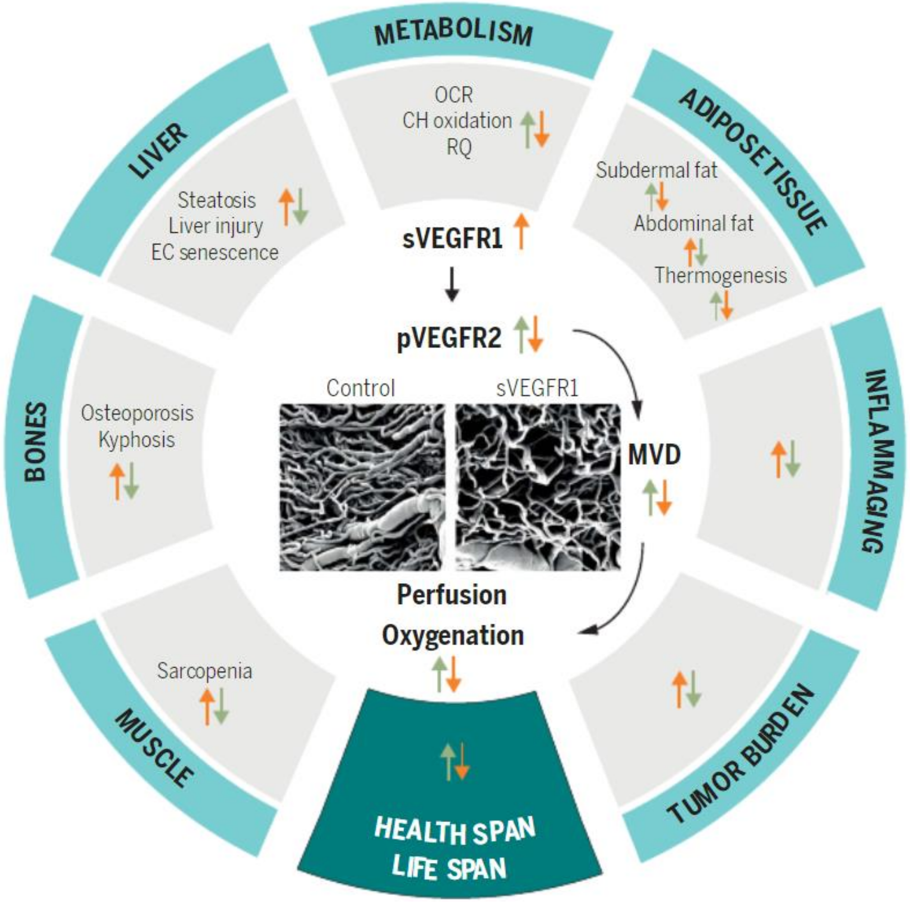
# Decreased VEGF Signaling Contributes to Vascular Aging




Science 2020; 373:533

# Restoration of VEGF Signaling Promotes Healthy Aging and Longevity



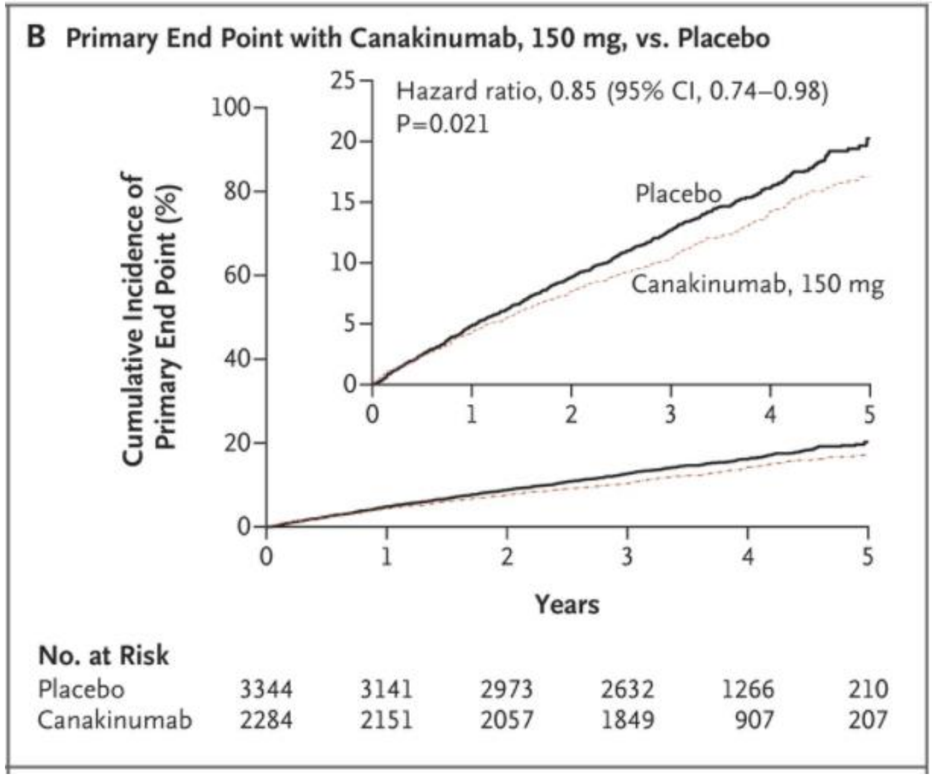




Science 2020; 373:533

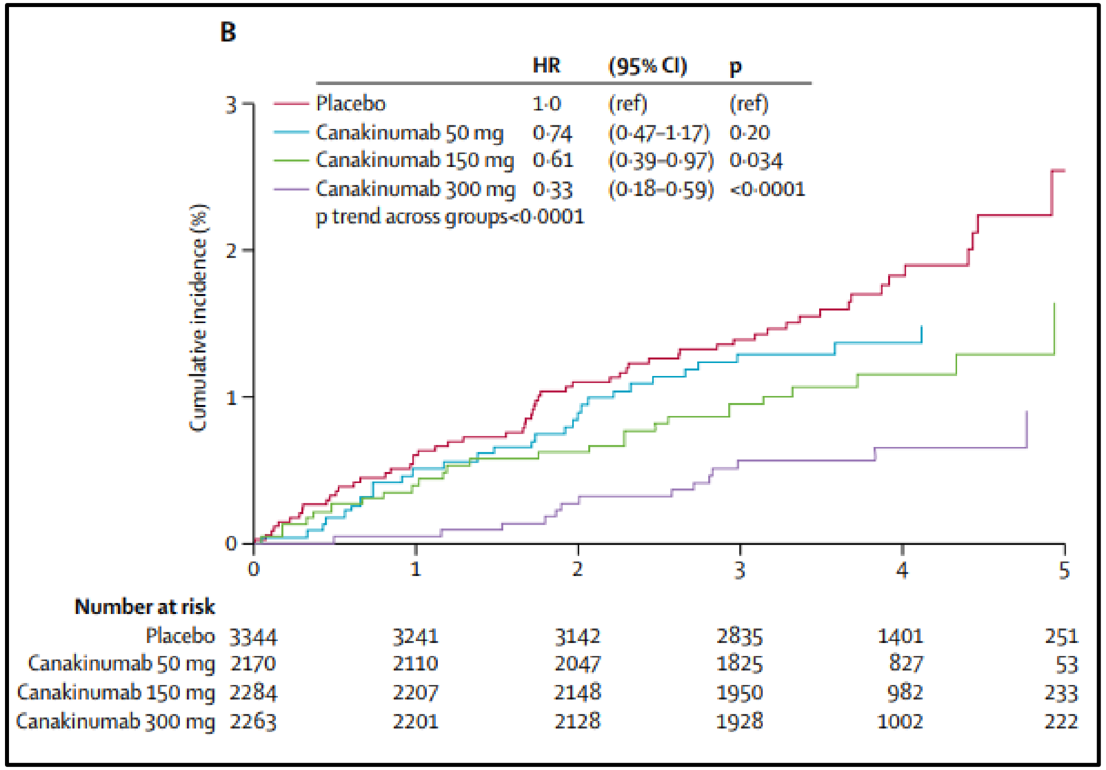
# Inflammation as Mediator of Cancer and CVD

## CANTOS Trial: MI + CRP ≥ 2 mg/L; IL-1ß antagonist; Recurrent CV Events

**Non-fatal MI, non-fatal stroke or CV death**

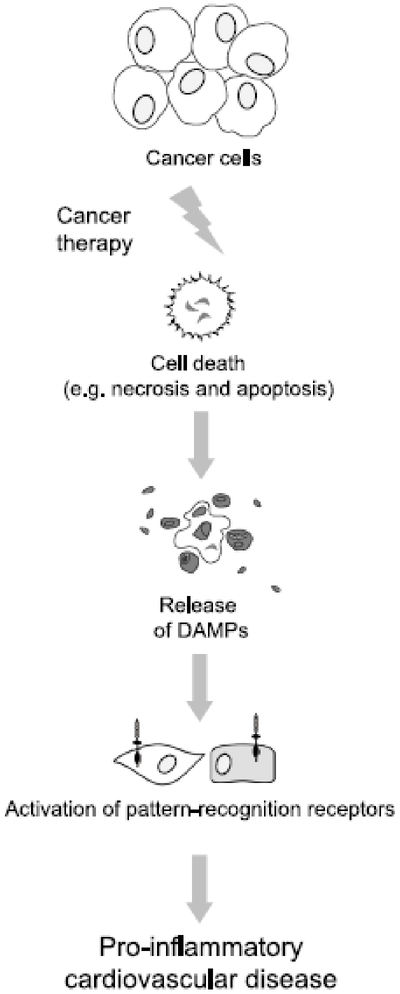



**Incident Lung Cancer**




N Engl J Med 2017; 377:1119-1131; Lancet 2017;390:1833-42.

# Damage Associated Molecular Patterns and Inflammation




| DAMP | Cancer type | Treatment | Author(s) | Corresponding PRR(s) |
|---|---|---|---|---|
| Actin | Lung squamous cell carcinoma/ adenocarcinoma | Photodynamic therapy | Tracy *et al.*[129] | DNGR-1 (CLEC9A) |
| Adenosine | Hairy cell leukemia | Pentostatin (2′-deoxycoformycin) | Johnston[130] | A1, A2A, A2B, A3 |
| ATP | Bladder carcinoma | Photodynamic therapy | Garg *et al.*[131] | $P_2X_7$, $P_2Y_2$ |
| | Colorectal carcinoma and osteosarcoma | Mitoxantrone and oxaliplatin | Michaud *et al.*[132] | |
| | Colorectal carcinoma and sarcoma | Various chemotherapeutic agents | Ghiringhelli *et al.*[133] | |
| | Fibrosarcoma | Doxorubicin | Ma *et al.*[134] | |
| | Cutaneous melanoma | Amino acid derivative LTX-401 | Eike *et al.*[135] | |
| | T-cell leukemia | Ultraviolet light | Elliott *et al.*[136] | |
| Calreticulin | Bladder carcinoma | Photodynamic therapy | Garg *et al.*[131] | CD91, scavenger receptors (LOX-1, SREC-1, and FEEL-1/CLEVER-1) |
| | Bladder carcinoma | Photodynamic therapy | Garg *et al.*[137] | |
| | Colorectal carcinoma | Doxorubicin | Obeid *et al.*[138] | |
| | Colorectal carcinoma | Electrohyperthermia | Andocs *et al.*[139] | |
| | Colorectal carcinoma and osteosarcoma | Mitoxantrone and oxaliplatin | Michaud *et al.*[132] | |
| | Colorectal carcinoma, cutaneous melanoma, lung carcinoma, esophageal squamous cell carcinoma, and pancreatic carcinoma | Various chemotherapeutic agents | Yamamura *et al.*[140] | |
| Cytochrome *c* | Cutaneous melanoma | Amino acid derivative LTX-401 | Eike *et al.*[135] | Unknown |
| | Lung squamous cell carcinoma/ adenocarcinoma | Photodynamic therapy | Tracy *et al.*[129] | |
| HSP60 | Squamous cell carcinoma | Photodynamic therapy | Korbelik *et al.*[141] | CD91, scavenger receptors (LOX-1, SREC-1, & FEEL-1/ CLEVER-1), TLR2, TLR4 |
| HSP70 | Bladder carcinoma | Photodynamic therapy | Garg *et al.*[137] | |
| | Colorectal carcinoma | Oxaliplatin and 5-fluorouracil | Fang *et al.*[142] | |
| | Colorectal carcinoma | Electrohyperthermia | Ma *et al.*[134] | |
| | Lung squamous cell carcinoma/ adenocarcinoma | Photodynamic therapy | Tracy *et al.*[129] | |
| | Prostate adenocarcinoma | Heating and UVC irradiation | Brusa *et al.*[143] | |
| | Squamous cell carcinoma | Photodynamic therapy | Korbelik *et al.*[141] | |
| HSP90 | Colorectal carcinoma | Electrohyperthermia | Ma *et al.*[134] | |
| | Lung squamous cell carcinoma/ adenocarcinoma | Photodynamic therapy | Tracy *et al.*[129] | |
| | Myeloma cells | Bortezomib | Spisek *et al.*[144] | |
| GRP78 (BiP) | Squamous cell carcinoma | Photodynamic therapy | Korbelik *et al.*[141] | |
| GP96 (GRP94) | Squamous cell carcinoma | Photodynamic therapy | Korbelik *et al.*[141] | |
| HMGB1 | Colorectal carcinoma | Doxorubicin and linoleic acid | Luo *et al.*[145] | RAGE. TIM3, TLR2, TLR4, TLR9 |
| | Colorectal carcinoma | Electrohyperthermia | Ma *et al.*[134] | |
| | Colorectal carcinoma | Oxaliplatin and 5-fluorouracil | Fang *et al.*[142] | |

Ther Adv Cardiovasc Dis 2017;11:297-317

# Potential Therapeutic Targets To Reduce Negative Impact of Oxidative Stress

| Therapeutics | Description |
|---|---|
| *Mitochondria-targeted compounds* | |
| MitoQ | Mitochondria-targeted antioxidant |
| SS-31 | Mitochondria-targeted peptide |
| Urolithin-A | Gut microbiome-derived mitophagy activator |
| Dexrazoxane | Mitochondria DNA damage inhibitor |
| *$NAD^+$ boosting compounds* | |
| Nicotinamide mononucleotide | $NAD^+$ salvage pathway activator |
| Nicotinamide riboside | $NAD^+$ salvage pathway activator |
| *CD-38 inhibitors* | |
| Apigenin | Food-derived (flavonoid) CD-38 inhibitor |
| Daratumumab | Synthetic CD-38 inhibitor |
| Thiazologuin(az)olin(on)e | Synthetic CD-38 inhibitor |

| Therapeutics | Description |
|---|---|
| *Sirtuin activators* | |
| Resveratrol | Food-derived (plant polyphenol) sirtuin activator |
| SRT1720 | Synthetic sirtuin activator |
| *PARP inhibitors* | |
| Nicotinamide | Inhibits PARP and increases $NAD^+$ bioavailability |
| Rucaparib | Inhibits PARP and increases $NAD^+$ bioavailability |
| *AMPK activator* | |
| AICAR | AMP analog (increases circulating AMP) |
| *mTOR inhibitor* | |
| Rapamycin | Immunosuppressive compounds that inhibit mTOR |

PRRI agonists
Calorie restriction, aerobic exercise

Aging and Cancer 2021;2:45-69.

# Summary

- Cardiovascular disease is a significant cause of morbidity and mortality in cancer survivors
- Many cancer therapies are associated with cardiotoxicity
- Cancer therapies can lead to increased oxidative stress and inflammation that may promote vascular aging
- A better understanding of these mechanisms is needed to identify therapeutic targets to reduce cancer therapy associated cardiotoxicity and potentially reduce adverse impact on vascular aging