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AMERICAN COLLEGE of CARDIOLOGY

Next-generation Tyrosine Kinase Inhibitors for Pulmonary Arterial Hypertension

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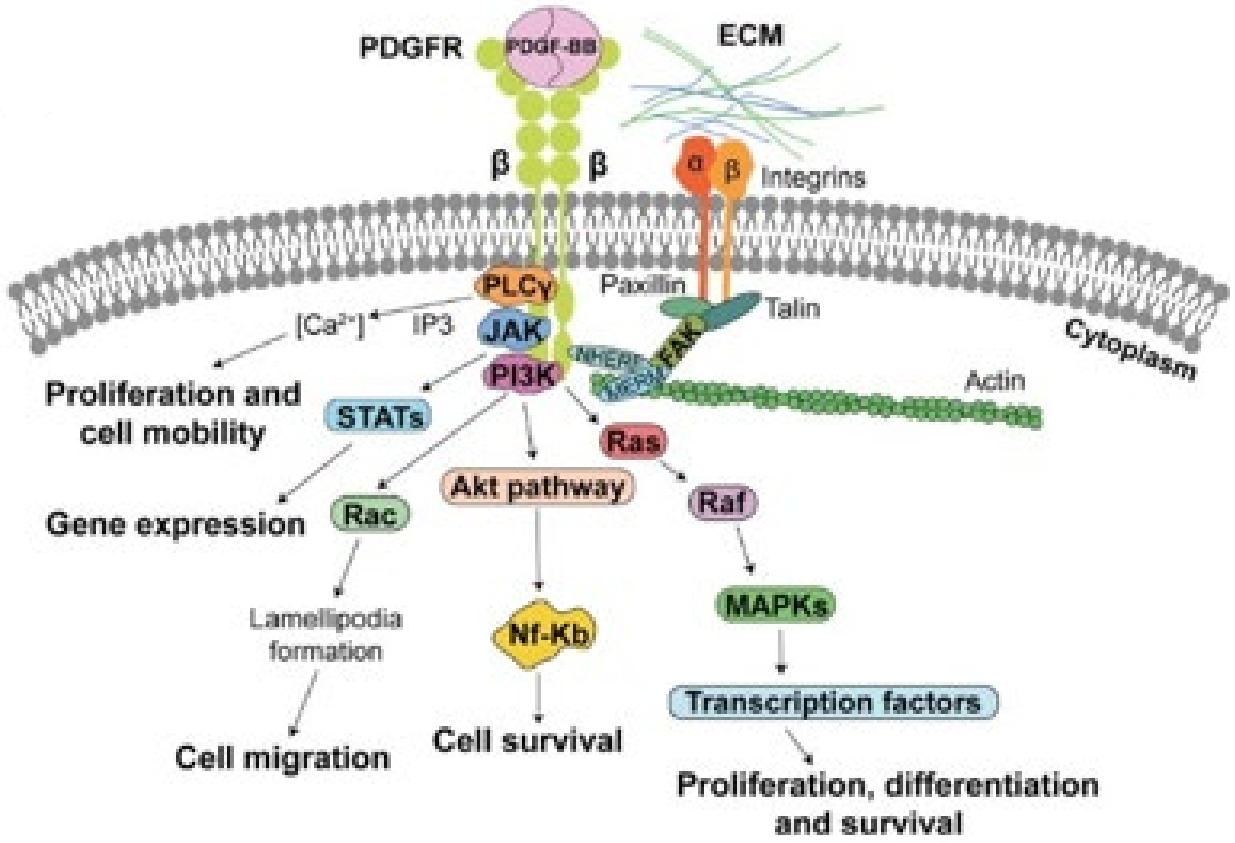
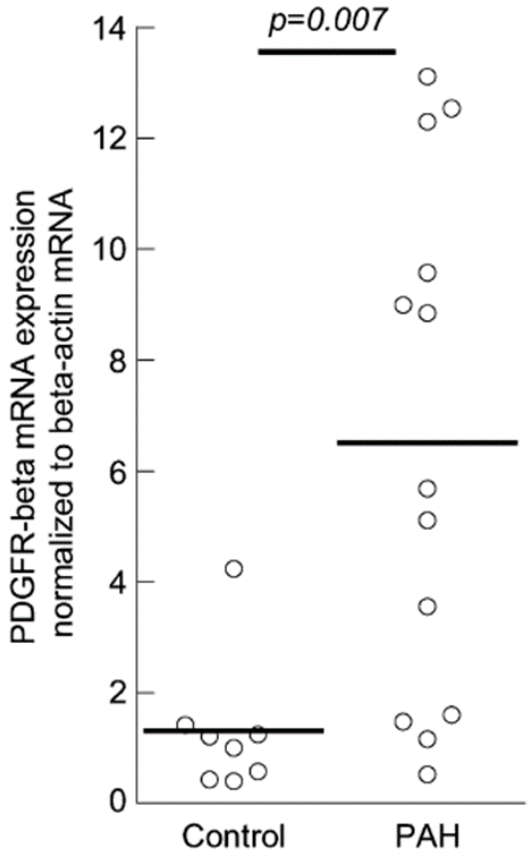
How might PAH be linked to tyrosine kinase activity?



What are the data that the increased expression of tyrosine kinases underlie human PAH?

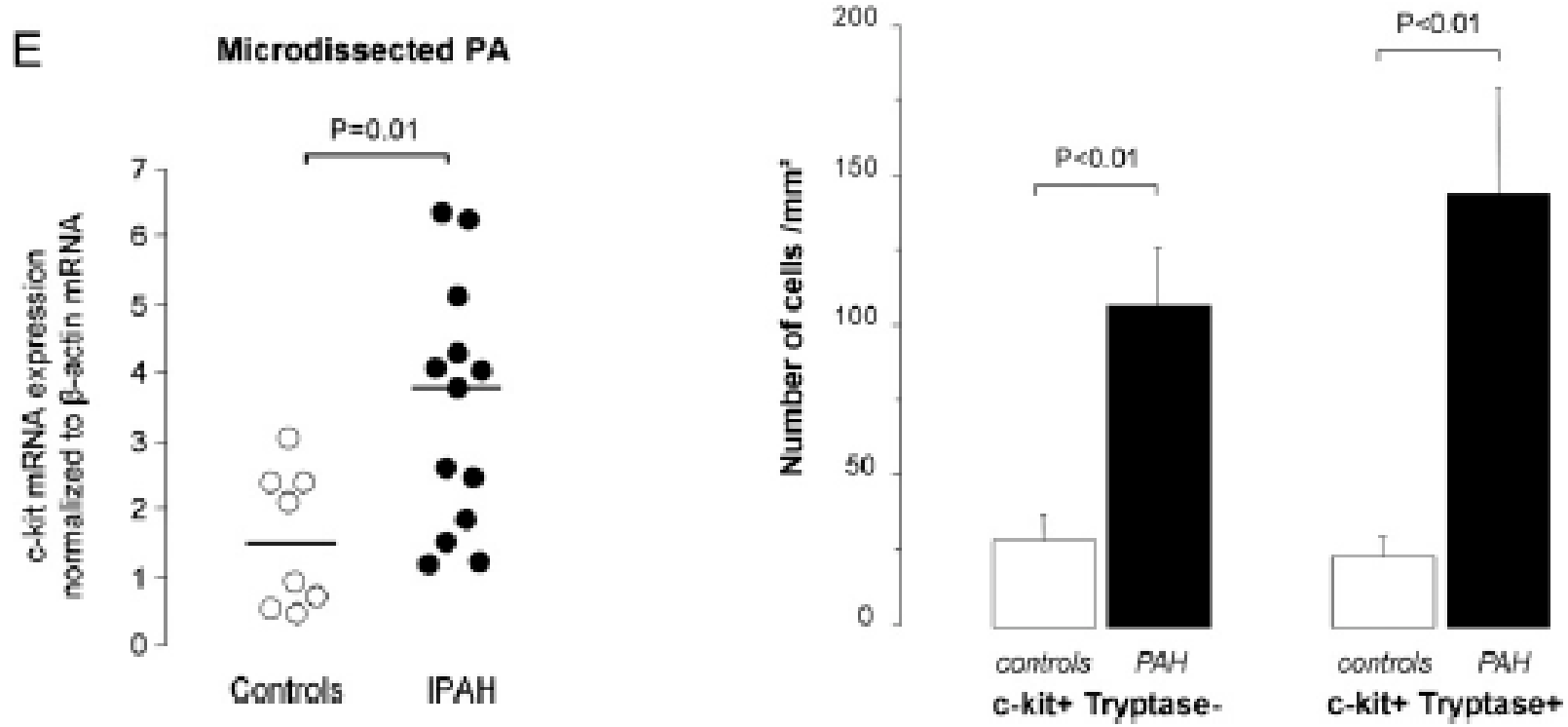


"Because PASMC proliferation and migration are believed to be a major contributor to pulmonary vascular remodeling, these findings plead in favor of the potential relevance of **PDGF** inhibition in the treatment of human PAH."

Am J Respir Crit Care Med Vol 178. pp 81–88, 2008

What are the data that the increased expression of tyrosine kinases underlie human PAH?

c-KIT: a receptor tyrosine kinase for stem cell factor, considered as a marker for bone marrow–derived hematopoietic stem cells

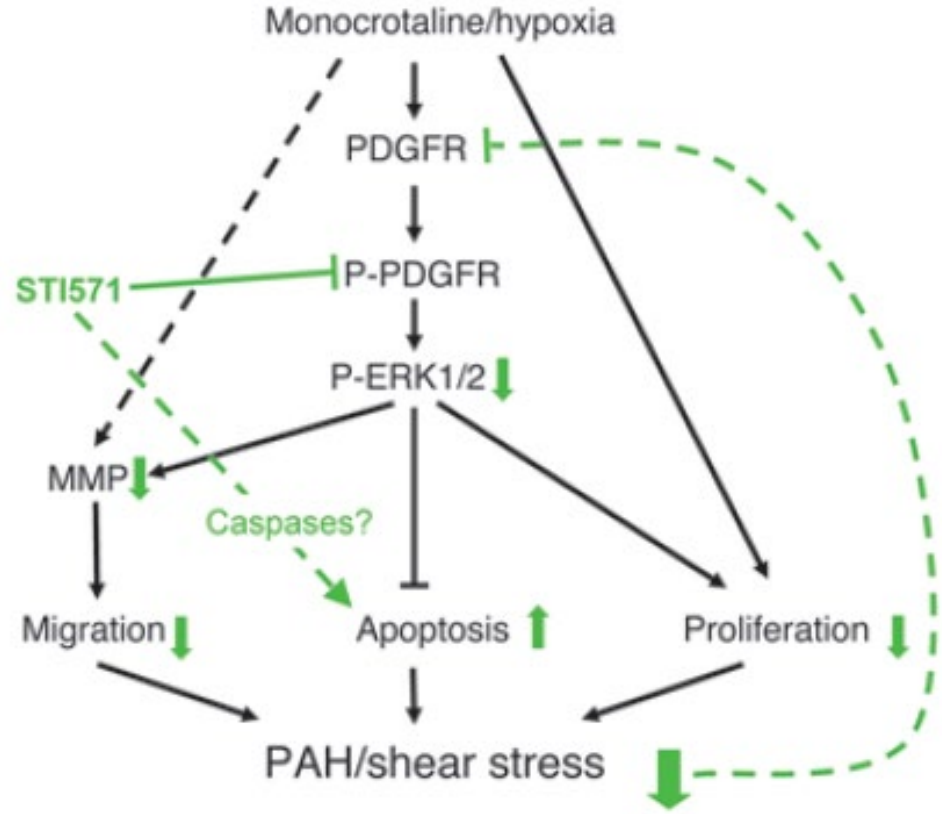


C-Kit–Positive Cells Accumulate in Remodeled Vessels of Idiopathic Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med Vol 184. pp 116–123, 2011*

By what mechanism might TKIs work to improve the pulmonary vascular disease in PAH?

- **Antiproliferation (maybe)**
  - Based on animal models of disease reversal
    - Monocrotaline/hypoxia **is not PAH**

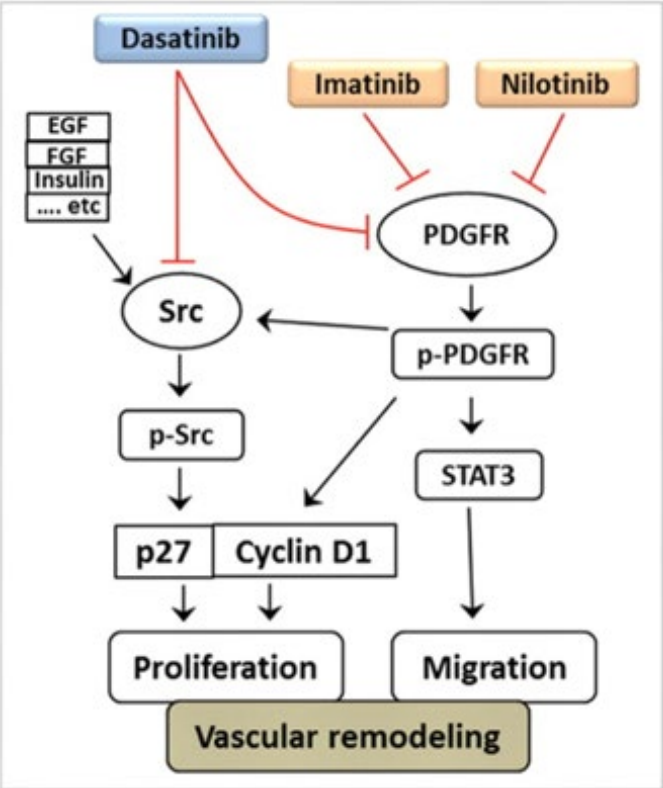
There has never been documentation of disease modification of PAH from imatinib in humans



Reversal of experimental pulmonary hypertension by PDGF inhibition
J Clin. Invest. **115**:2811–2821 (2005).

Role of Src Tyrosine Kinases in Experimental Pulmonary Hypertension

Src plays an important role in tumor cell growth, proliferation and invasion.



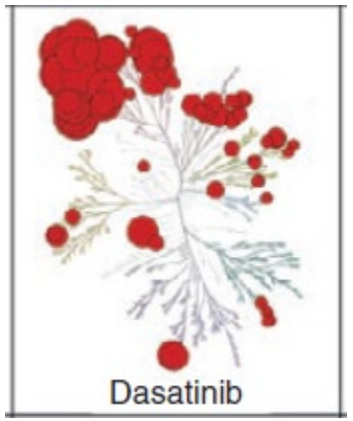
Dual inhibition of PDGF receptor and Src kinases potently inhibits mitogenic responses to growth factors in PASMCs and pulmonary vascular remodeling *in vivo* and may represent a better alternative therapeutic approach for pulmonary arterial hypertension.

Kinase Inhibitors for Pulmonary Arterial Hypertension
What are the possibilities?

- **Imatinib** (2010)
  - Successful efficacy (6MW) in Phase 3 trial (IMPRES).
  - Excessive dropouts prevented regulatory approval.
- **Dasatinib** (2011)
  - Most effective TKI in animal models of PH.
  - FDA reports onset of severe PAH in several patients with leukemia.
- **Nilotinib** (2014)
  - Phase 2 trial terminated due to SAEs (worsened PH in 25%).
- **Selonsertib** (2017)
  - Phase 2 trial completed (ARROW). No efficacy detected.
- **Seralutinib** (2021)
  - Currently in Phase 1b/2 trial (TORREY)

How do the TKIs for PAH compare in selectivity?
Apples vs. Oranges vs. Lemons

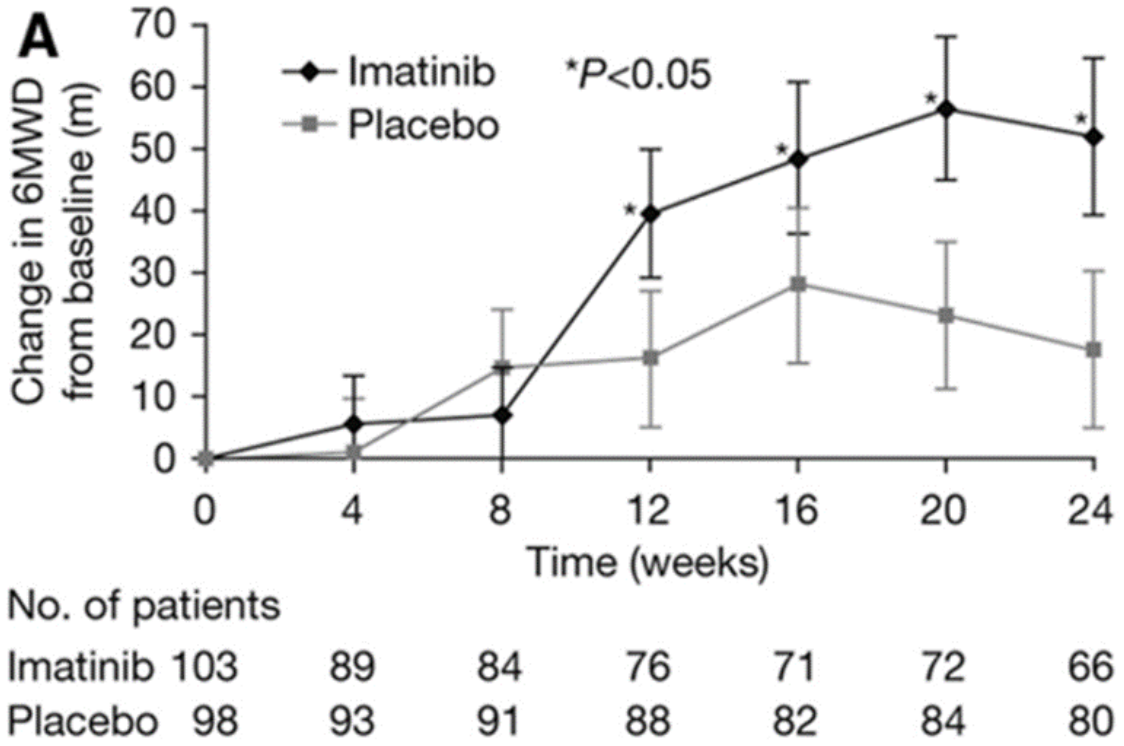
- **Imatinib**
  - PDGFR; c-KIT, BCR-Abl, DDR1
    - Considered narrow spectrum, moderate affinity
- **Seralutinib**
  - PDGFR; c-KIT, CSF1R
    - Considered narrow spectrum, high affinity
    - Very little human data published
- **Dasatinib**
  - BCR-Abl, Src family, PDGFR, c-KIT, many others
    - Considered broad spectrum, high affinity

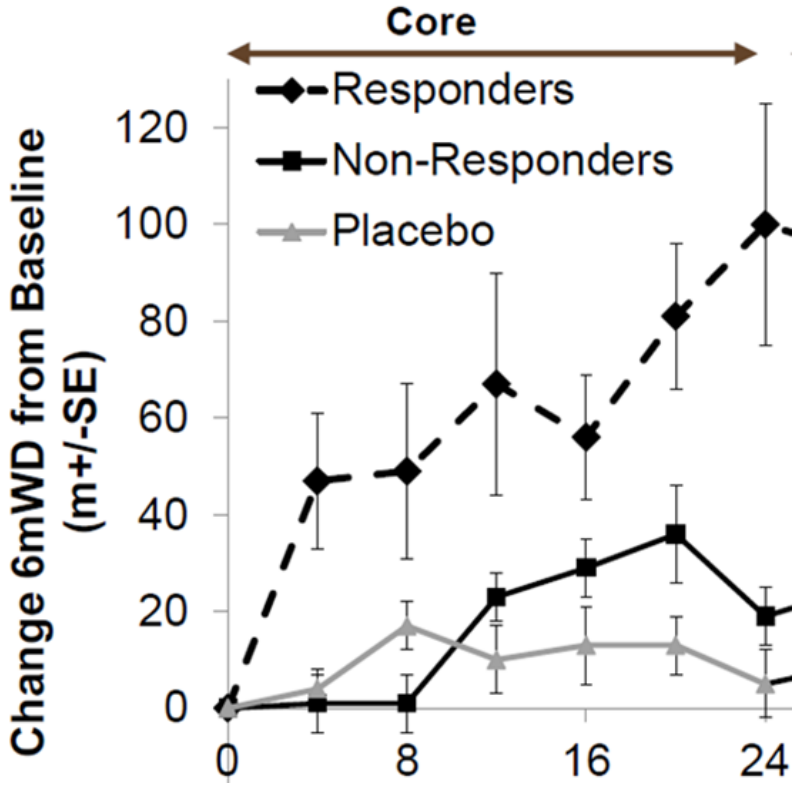


A quantitative analysis of kinase inhibitor selectivity.
Nature Biotechnology Volume 26 Number 1 January 2008

TKIs for PAH: Here's what we know

Imatinib works…if you can manage the side effects.



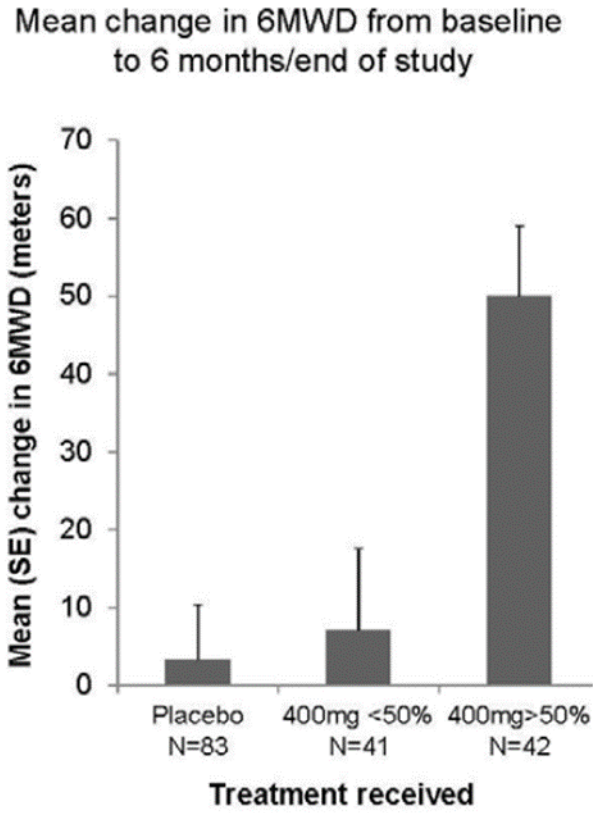


Circulation. 2013;127:1128-1138

TKIs for PAH: Here's what we know

Seralutinib might work…if enough drug is absorbed

- The IMPRES trial demonstrated that in patients who took imatinib 400mg daily the majority of the time, the treatment effect on 6MWD was 59 meters.
- Those patients who took imatinib 400mg daily less than half of the time had a treatment effect on 6MWD of only 12 meters.
- Seralutinib is being administered **via inhalation.**



EMA Assessment report:
Ruvise (International non-proprietary name: imatinib mesilate) 2013

TKIs for PAH: Current status of clinical trials

IMATINIB

- TNX 201 (Tenax Therapeutics) Modified release oral formulation
  - Phase 3 trial to begin 2H of 2022
- AV-101 (Aerovate Therapeutics) Dry powder inhaled formulation
  - Phase 2b/3 ongoing
- AER 901 (Aerami Therapeutics) Aerosolized formulation via nebulizer
  - Phase 1 ongoing

SERALUTINIB

- GB 002 (Gossamer Bio) Dry powder inhaled formulation
  - Phase 1b/2 trial ongoing

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