New Directions for IPF Treatments: Updates on Clinical Trials

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What are clinical trials?

- Clinical trials are at the heart of medical advances
- Clinical trials look at every aspect of patient care
  - new ways to prevent, detect, monitor or treat diseases
- Clinical trials determine if a new test or treatment
  - is safe
  - Is effective

Clinical trials are conducted in “phases”

- Each phase has a different purpose and helps researchers answer different questions.
- **Pre-clinical studies:** Researchers first test new therapies or procedures in the laboratory and in animal studies – the most promising experimental treatments are moved into clinical trials
- **Phase I trials:** Researchers test an experimental drug or treatment in a small group of people for the first time. The purpose is to evaluate its safety.
- **Phase II trials:** The experimental drug or treatment is administered to a larger group of people to determine its effectiveness.
- **Phase III trials:** The experimental drug or treatment is administered to large groups of people to compare it with standard or equivalent treatments.

Randomization

- Many or most Phase II and III clinical trials are **randomized**
- **Randomization** is the process by which two or more alternative treatments are assigned to volunteers by chance
- **Randomization** is done to avoid any bias with investigators assigning volunteers to one group or another
- The results of each treatment are compared at specific points during a trial, which may last for months or years
- When one treatment is found superior, the trial is stopped so that the fewest volunteers receive the less beneficial treatment

What is a placebo?

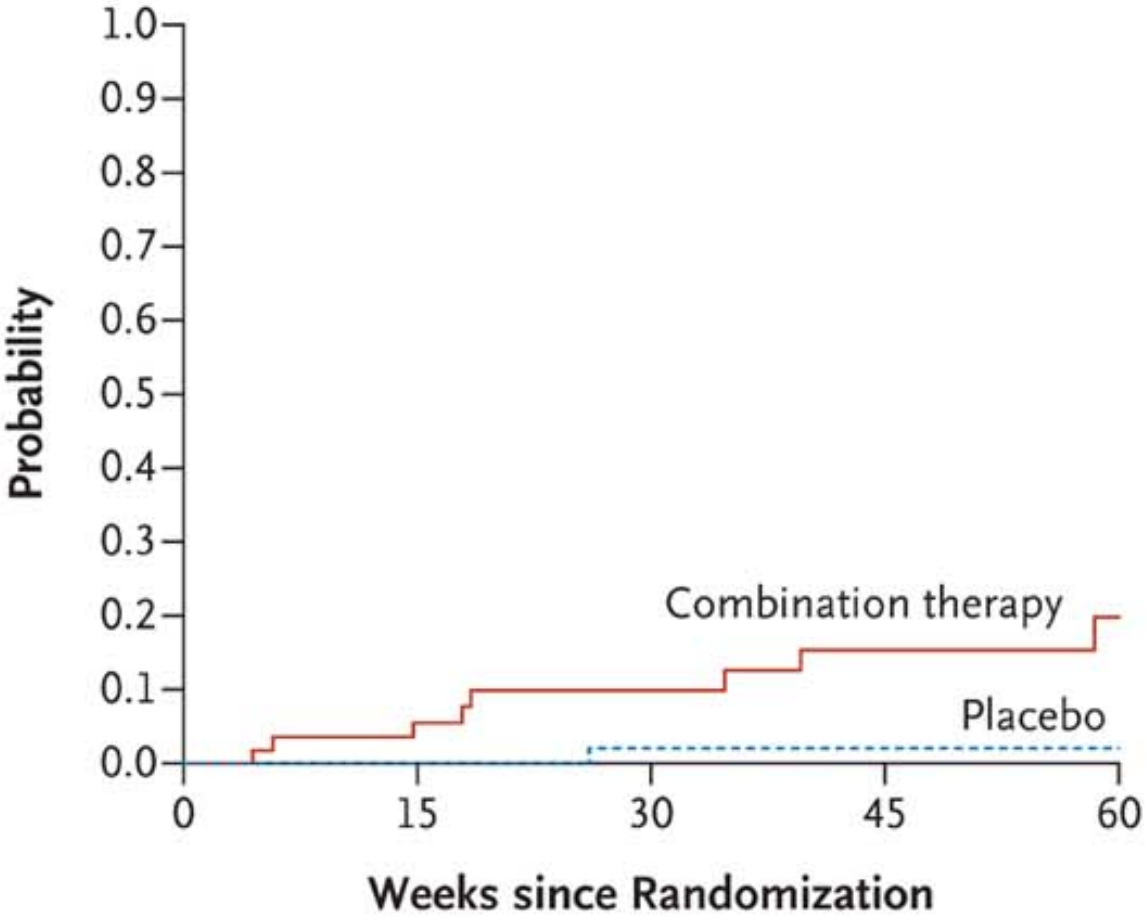
- In some studies, participants may be randomized to receive a **placebo** (an inactive product that resembles the test product, but without its treatment value)
- In diseases which have no effective therapies, new products or therapies are compared with placebos in order to determine whether the new therapies have therapeutic effectiveness
- In diseases which have effective therapies, clinical trials compare a new product or therapy with another that already exists, to determine if the new one is as successful as, or better than, the existing one

What is Blinding?

- Many or most randomized trials are ***double-blind studies***
- In a double-blind study, only the study pharmacist knows what is being administered; neither the patients nor the members of the research team are told which patients are getting which medication. (If medically necessary, however, it is always possible to find out what the patient is taking)
- Studies are “blinded" in order to prevent members of the research team or study participants from biasing the results. This allows scientifically accurate conclusions

Why do we do clinical trials?

- Treatments that become standard care without clinical trial evidence may not be effective, or even safe

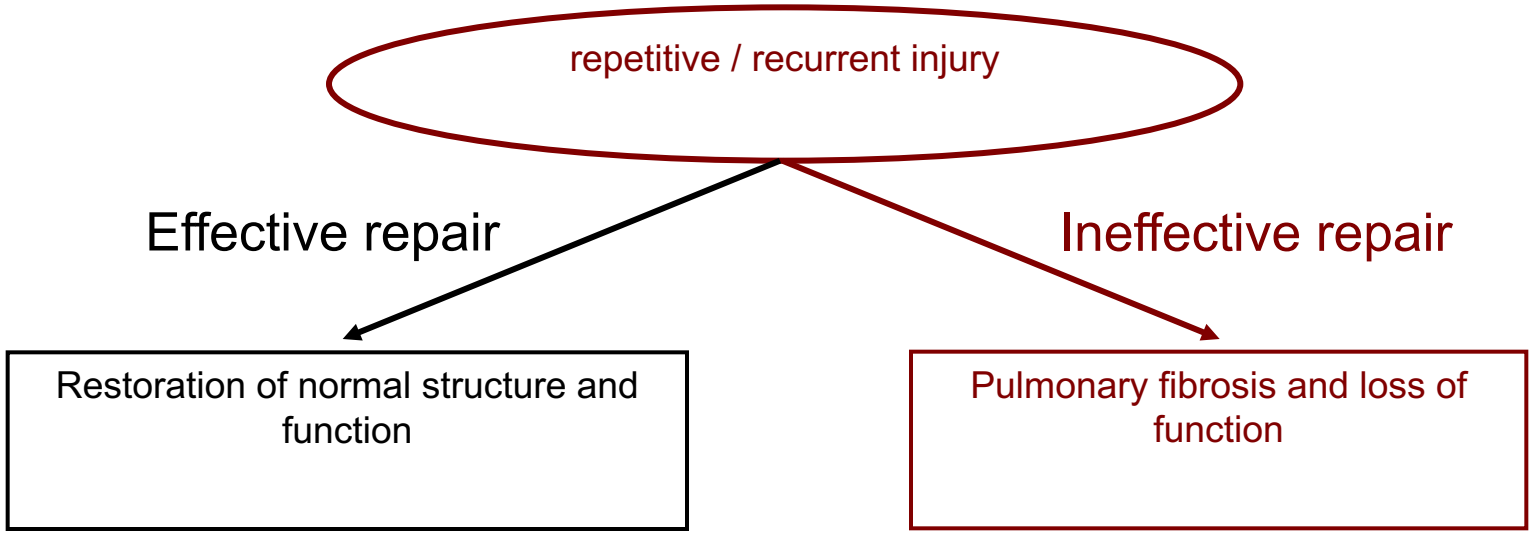


Why do people participate?

- Participation in clinical trials is strictly VOLUNTARY!
- People participate in clinical trials for a variety of reasons
- Participants often express the desire to help others with their disease and to contribute to moving medical treatments forward
- Participants may also want the opportunity to possibly receive the newest treatments
- Participants may find the additional care and attention from the clinical trial staff helpful
- Clinical trials offer hope for many people and an opportunity to help researchers find better treatments for others in the future.

Injury / Abnormal Repair Paradigm of IPF

IPF pathology suggests:

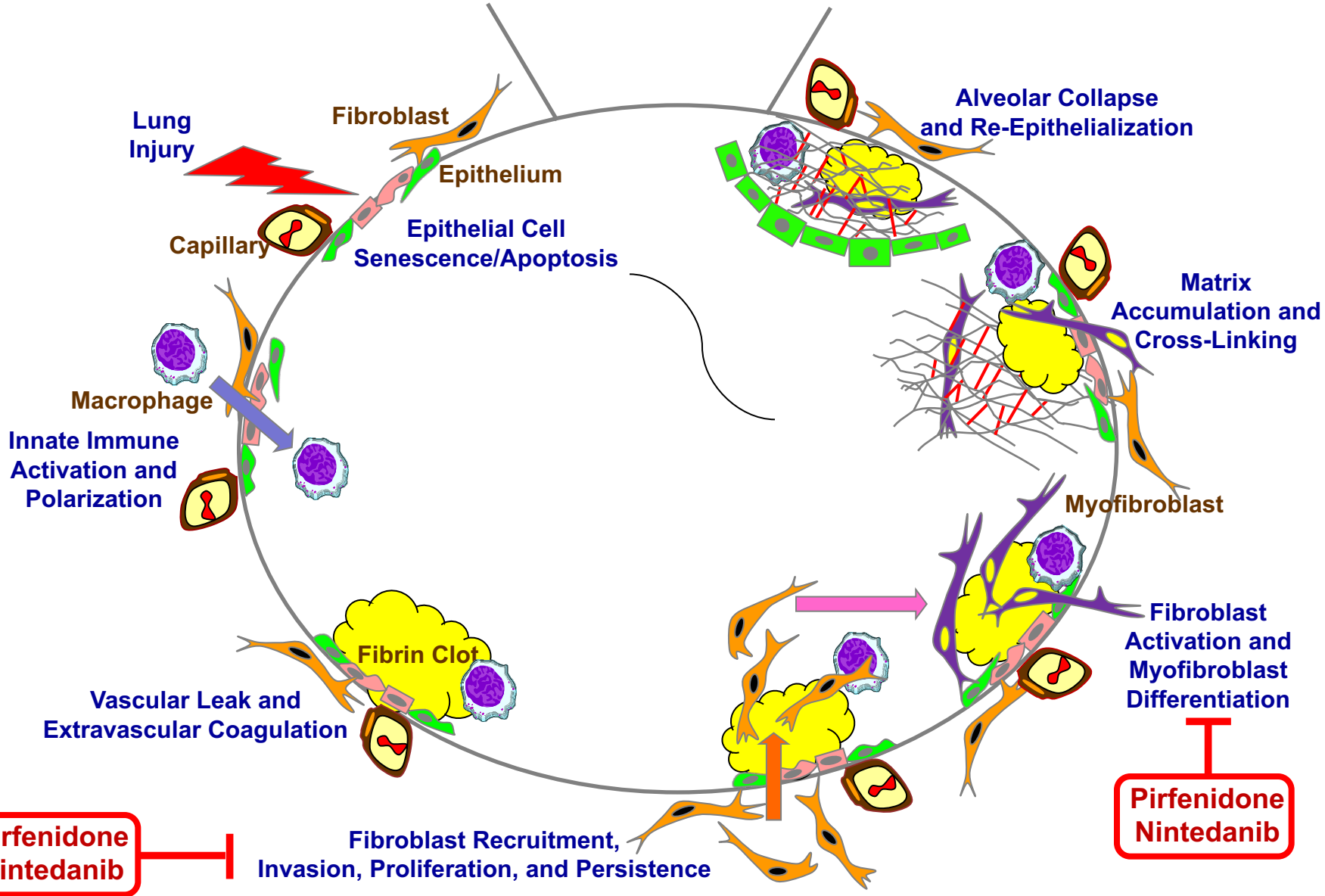


- What injures the lung in IPF?
  - Unknown / may be different in different patients

- Why are repair responses ineffective in IPF?
  - Recurrent nature of injury may overwhelm repair mechanisms
  - Repair mechanisms may be abnormal / overly exuberant

Moisés Selman M, King TE, Pardo A, *Ann Intern Med* 2001

Injury / Abnormal Repair Paradigm of IPF



Ahluwhalia N, Shea BS, Tager AM, *AJRCCM* 2014

ASCEND 2014

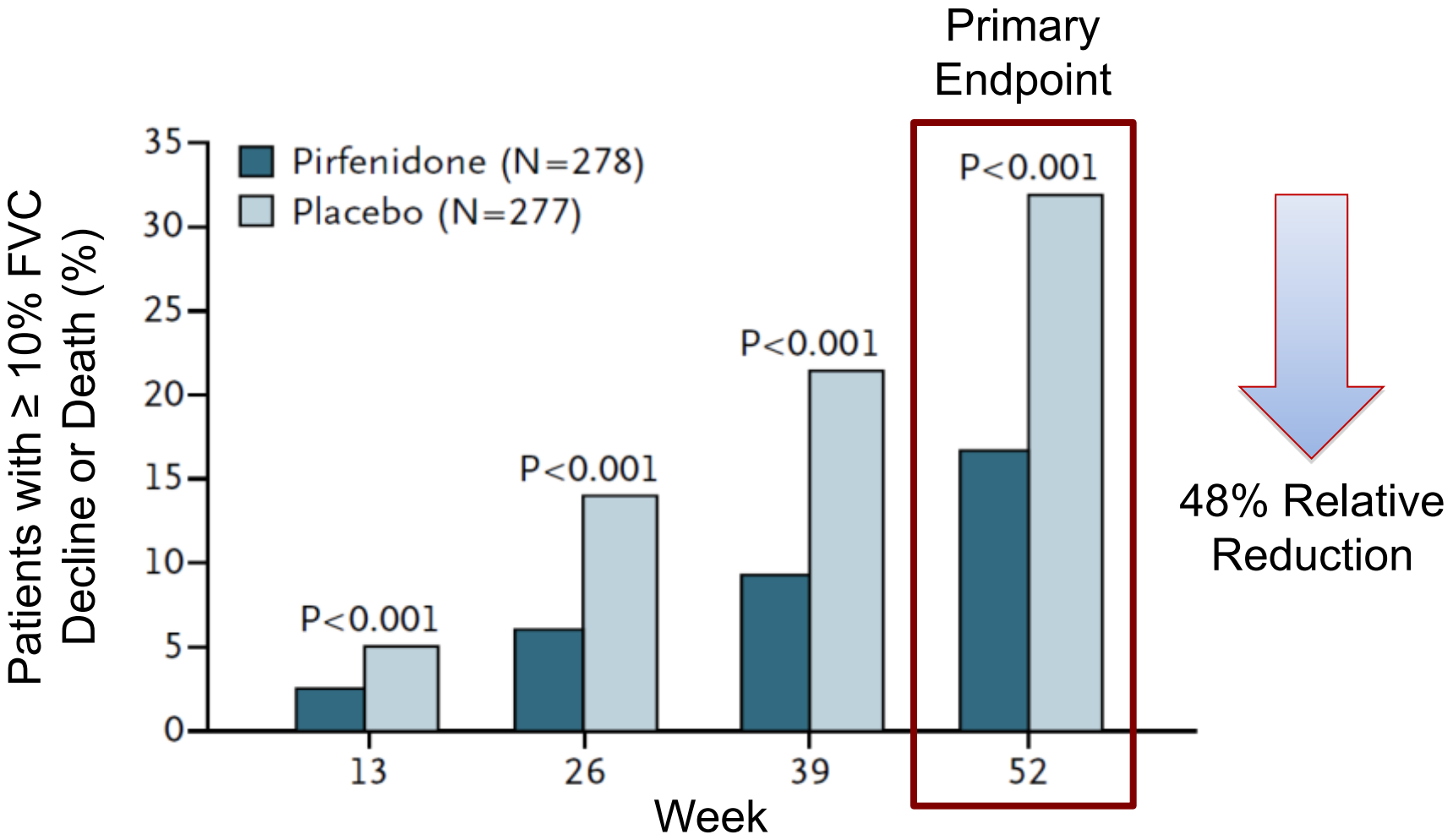
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

Primary ASCEND Endpoint Achieved



King TE et al, *N Engl J Med* 2014; 370:2083-2092

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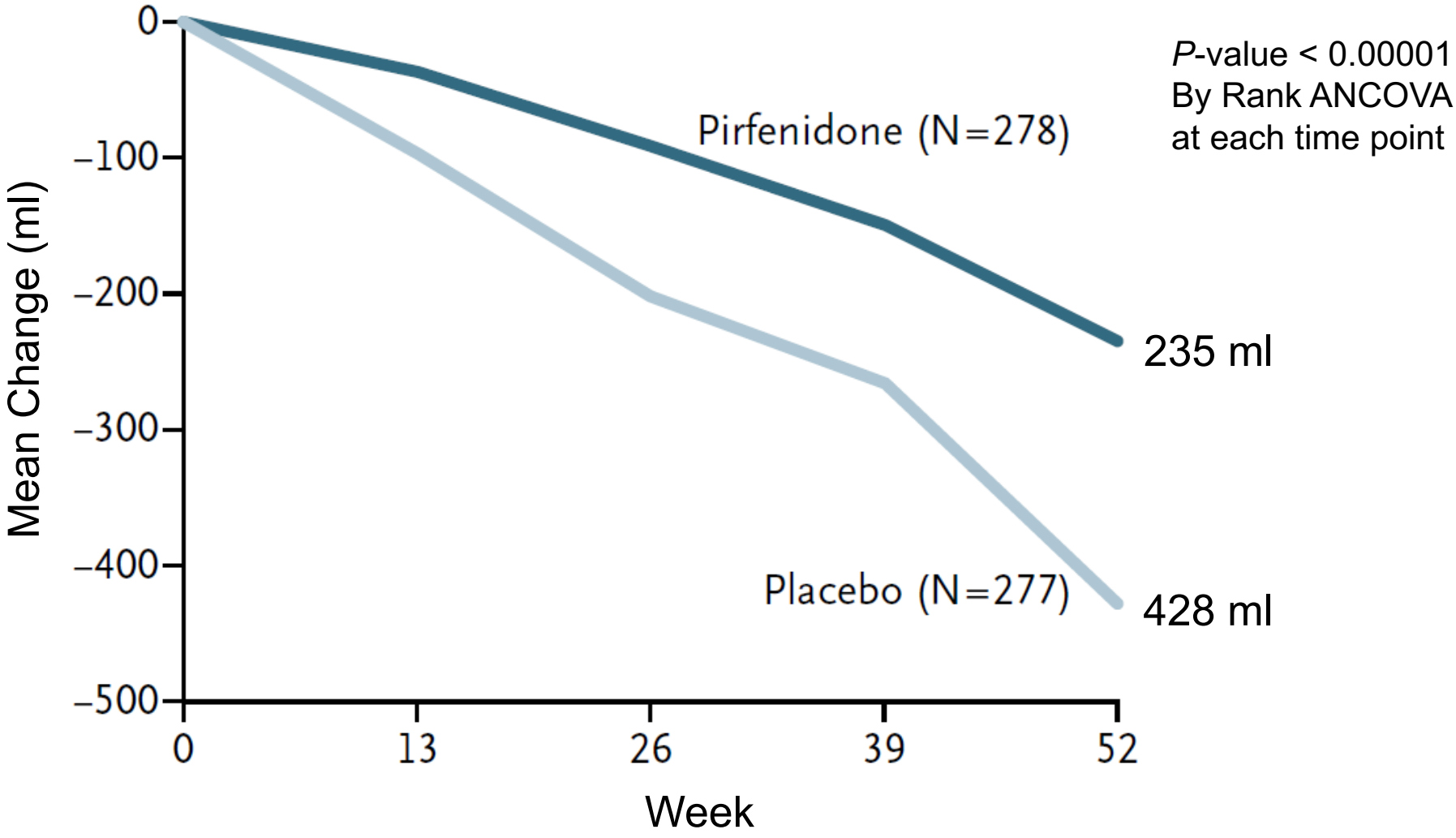
Pirfenidone Reduced Loss of FVC



King TE et al, *N Engl J Med* 2014; 370:2083-2092

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ASCEND Adverse Events

Adverse Event	Pirfenidone (%) (N = 278)	Placebo (%) (N = 277)	Δ (%)
Nausea	36	13.4	22.6
Rash	28.1	8.7	19.4
Dyspepsia	17.6	6.1	11.5
Anorexia	15.8	6.5	9.3
GERD	11.9	6.5	5.4
Weight Loss	12.6	7.9	4.7
Insomnia	11.2	6.5	4.7
Dizziness	17.6	13	4.6
Vomiting	12.9	8.7	4.2
…	…	…	…
Dyspnea	14.7	17.7	-3
Cough	25.2	29.6	-4.4
IPF	9.4	18.1	-8.7

King TE et al, *N Engl J Med* 2014; 370:2083-2092.

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INPULSIS 2014

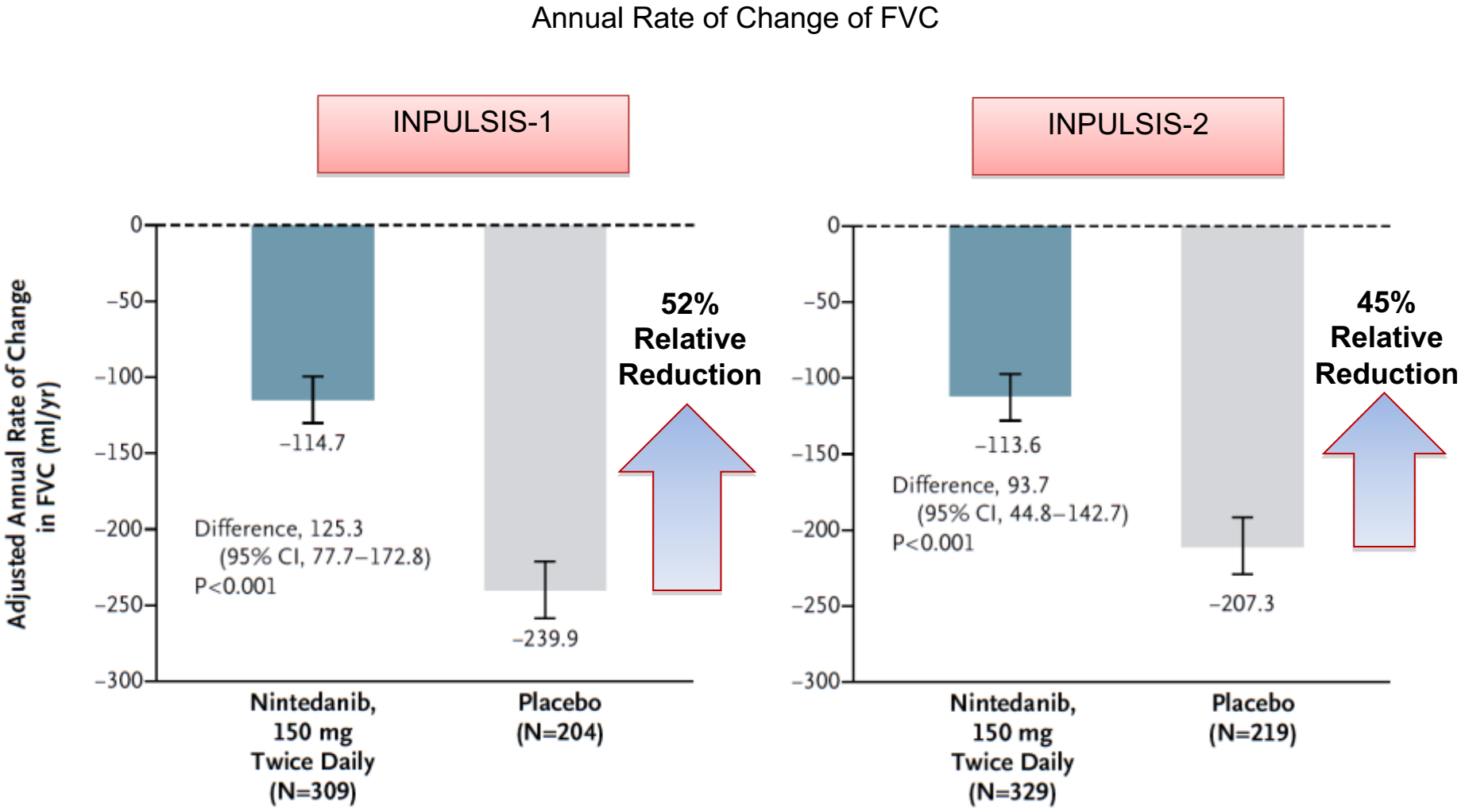
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

Primary INPULSIS Endpoint Achieved



Richeldi L et al, *N Engl J Med* 2014; 370:2071-2082

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Common Nintedanib Adverse Events

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (n = 309)	Placebo (n = 204)	Nintedanib (n = 329)	Placebo (n = 219)
Any (%)	96	89	94	90
Diarrhea (%)	62	19	63	18
Nausea(%)	23	6	26	7

Richeldi L et al, *N Engl J Med* 2014; 370:2071-2082

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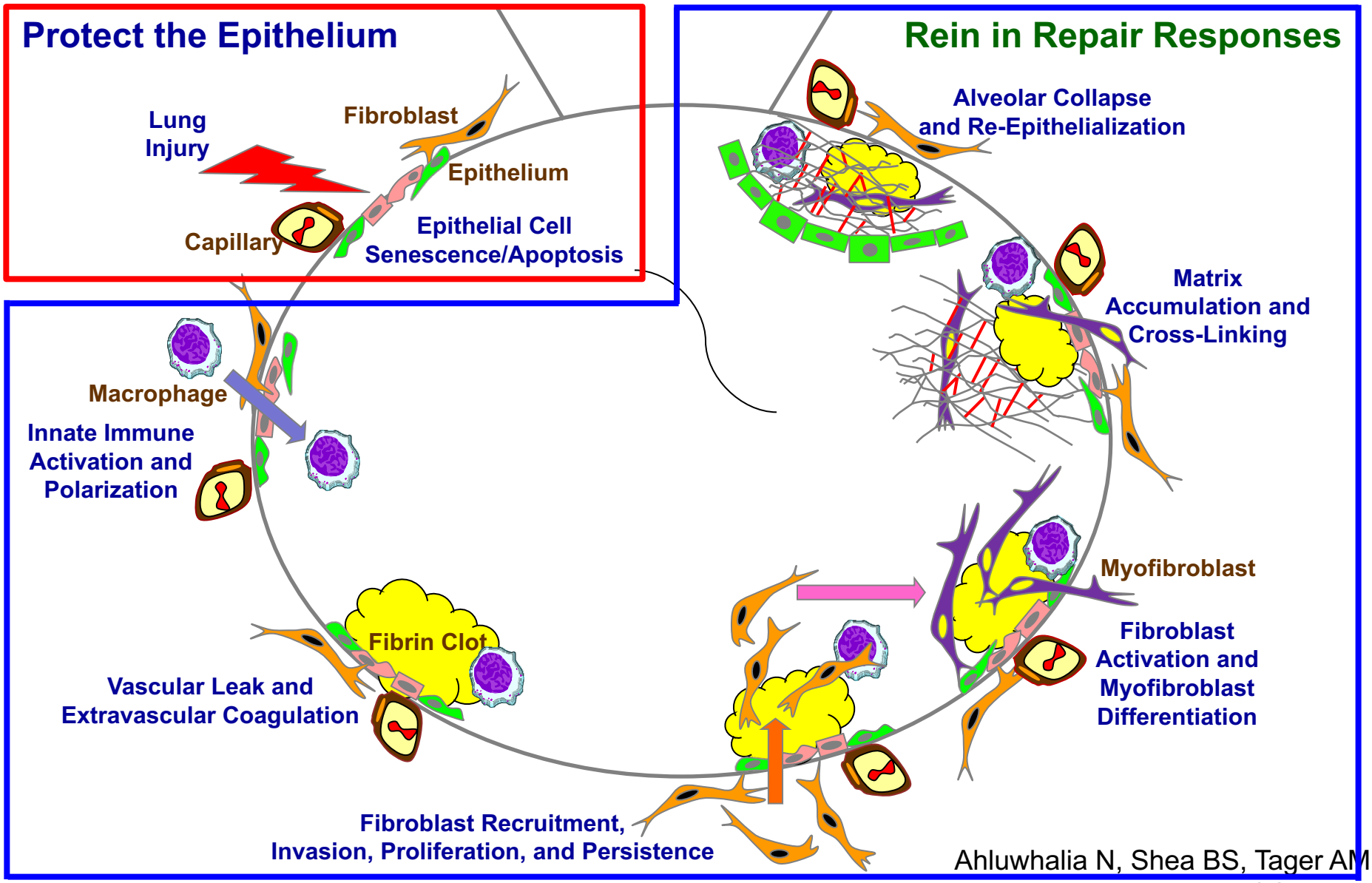
Approaches to Develop New Therapies for IPF



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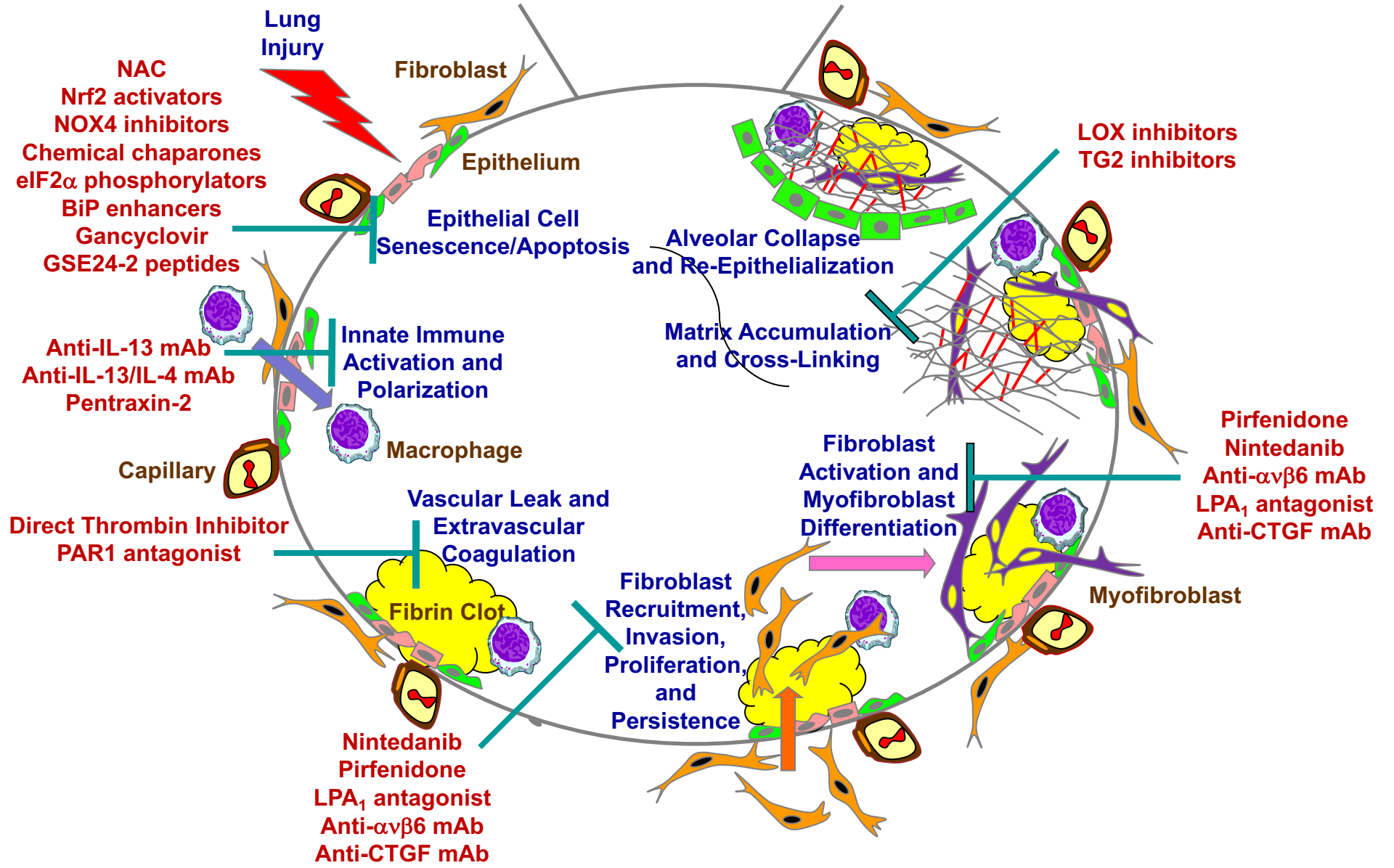
Novel Targets For The Future



Questions