

Introduction

Laryngotracheal stenosis (LTS): narrowing of the airway caused by the buildup of fibrotic tissue.

Current treatments:

- management of symptoms, sometimes over a lifetime
- requires surgical correction

Key Question: Is it possible to locally deliver a minimally invasive therapy to **prevent** the development of LTS?

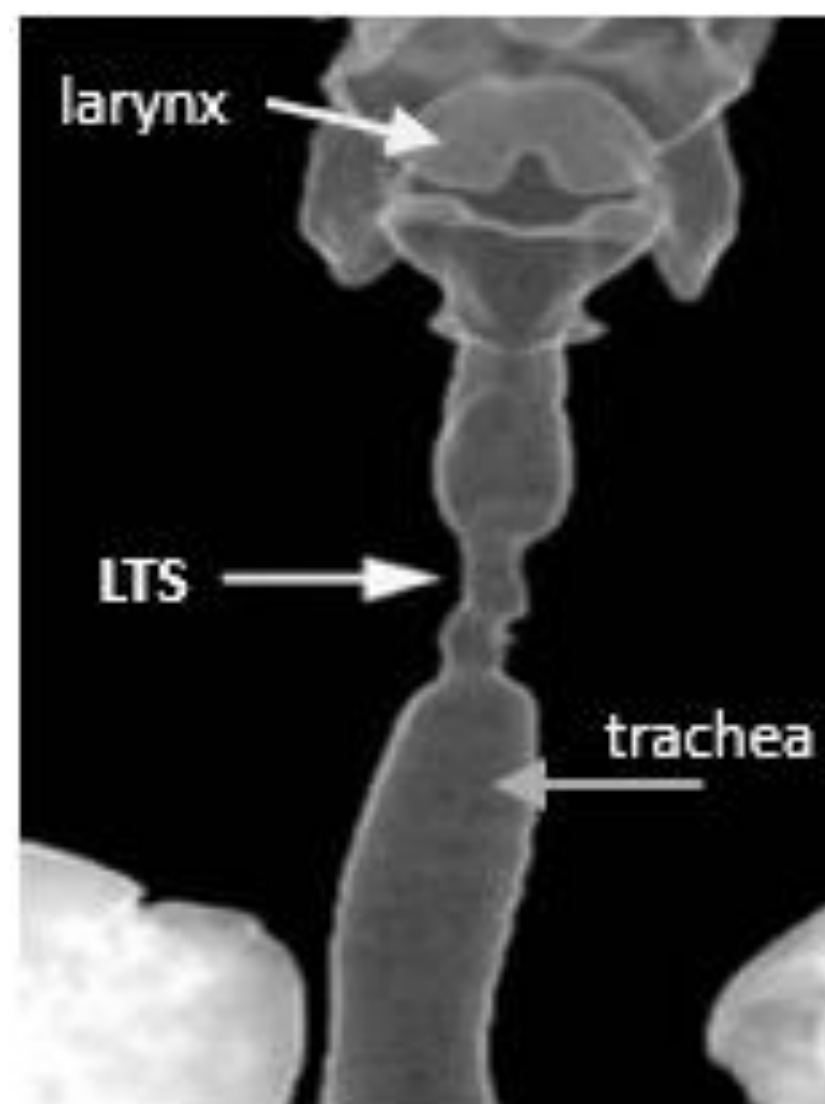


Fig. 1. 3D rendering of human upper airway.

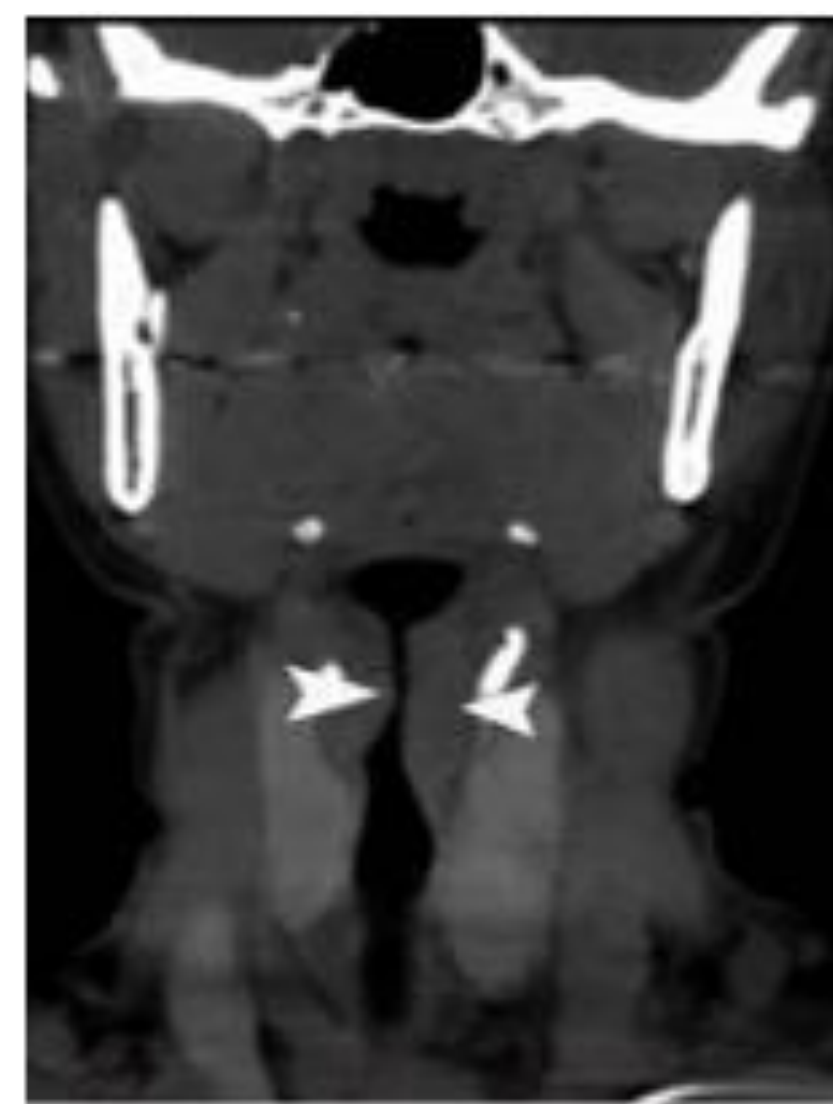


Fig. 2. X-ray of human upper airway.

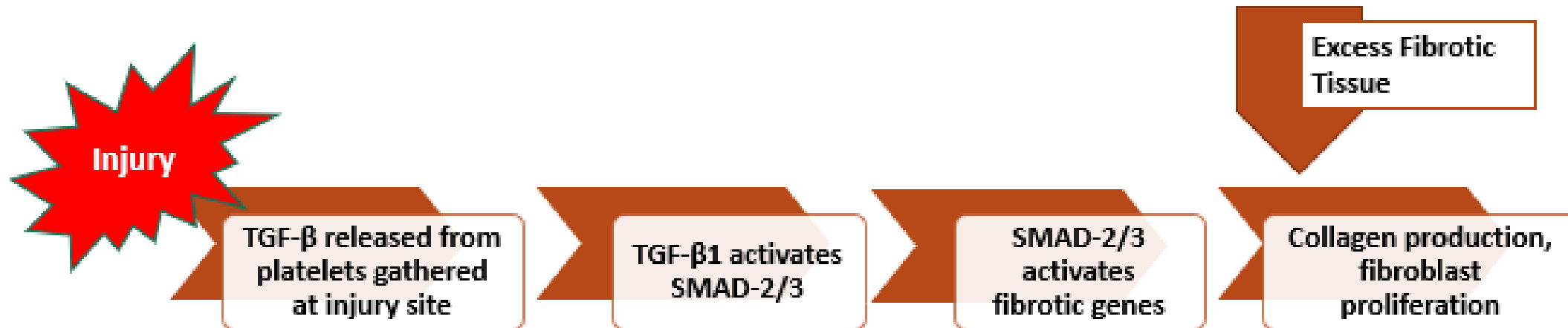
Intubation is required in many of the over 20,000 premature births that take place every year in the United States.

21%

Up to 21% of intubated patients are at risk of developing LTS.

What causes Laryngotracheal Stenosis?

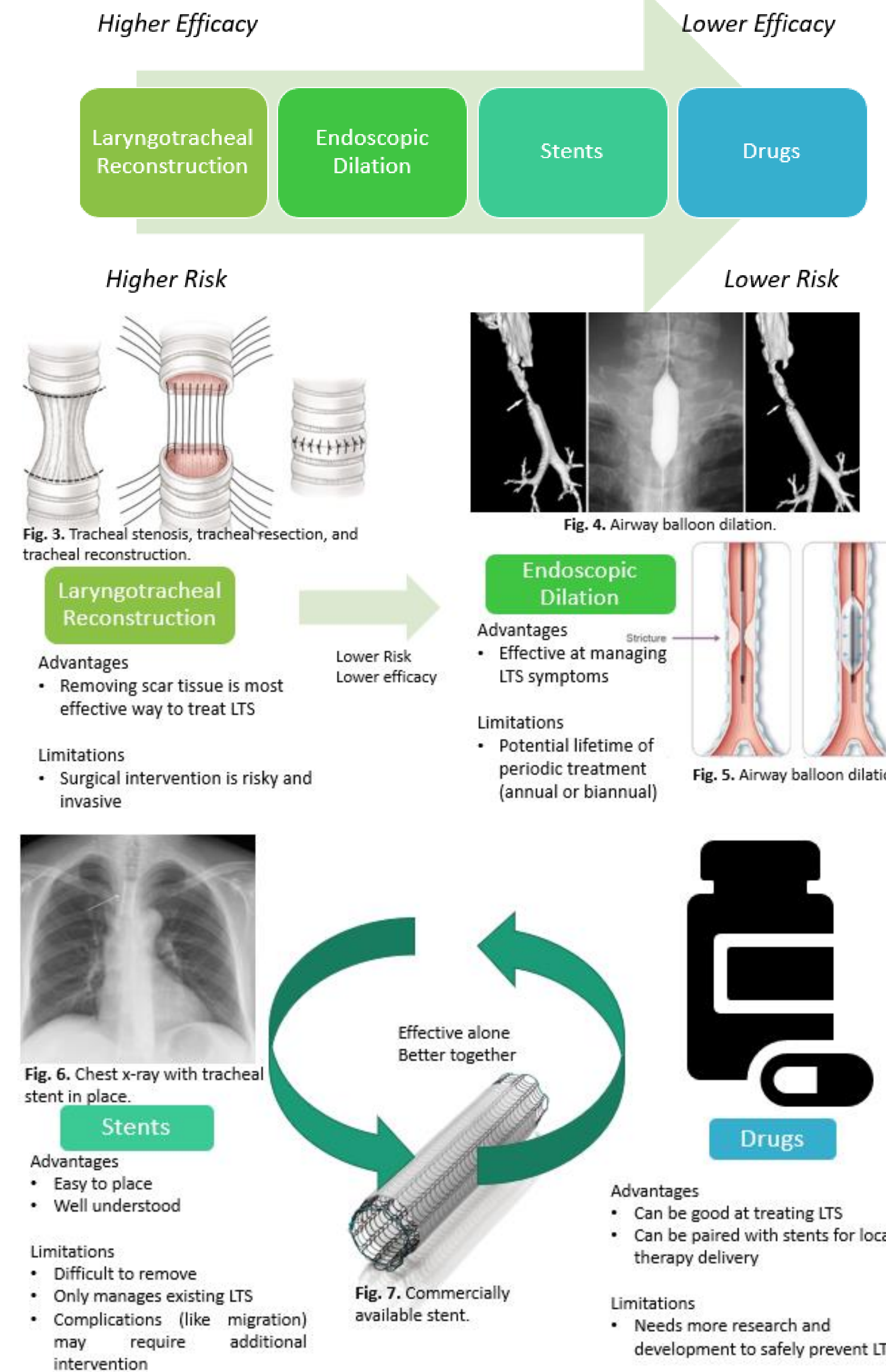
Over 90% of LTS cases in children are acquired, following an abnormal healing response after airway injury during intubation.



References

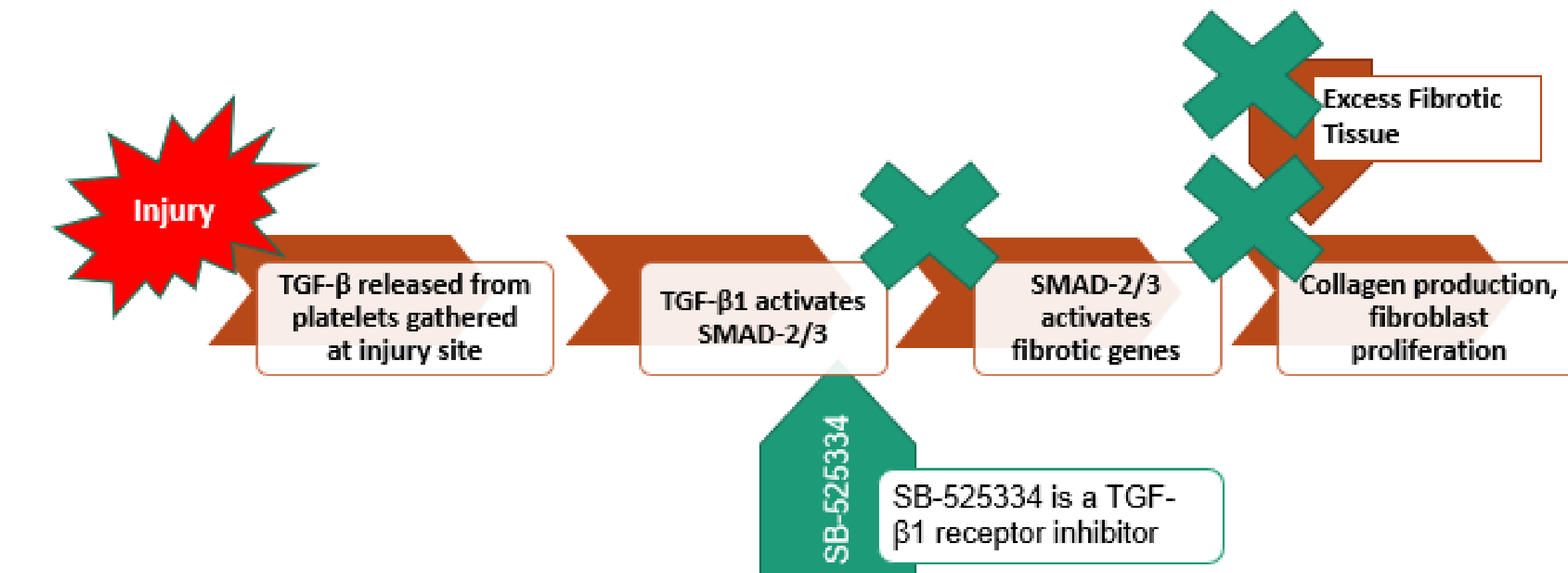
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Review of LTS Treatments



TGF-β1 pathway and tissue healing

- Growth factors are crucial for normal and abnormal healing processes.
- TGF-β1 stimulates ECM production, and increased TGF-β1 production is associated with normal and pathological repair processes, including fibrosis. TGF-β1 has a natural affinity for the ECM and can exacerbate a fibrotic response.
- Regulating TGF-β may prevent the buildup of pathological fibrotic tissue.



Delivery

Because the target TGF-β receptors are located on cell membranes, the SB-525334 inhibitor should be delivered locally rather than systemically.

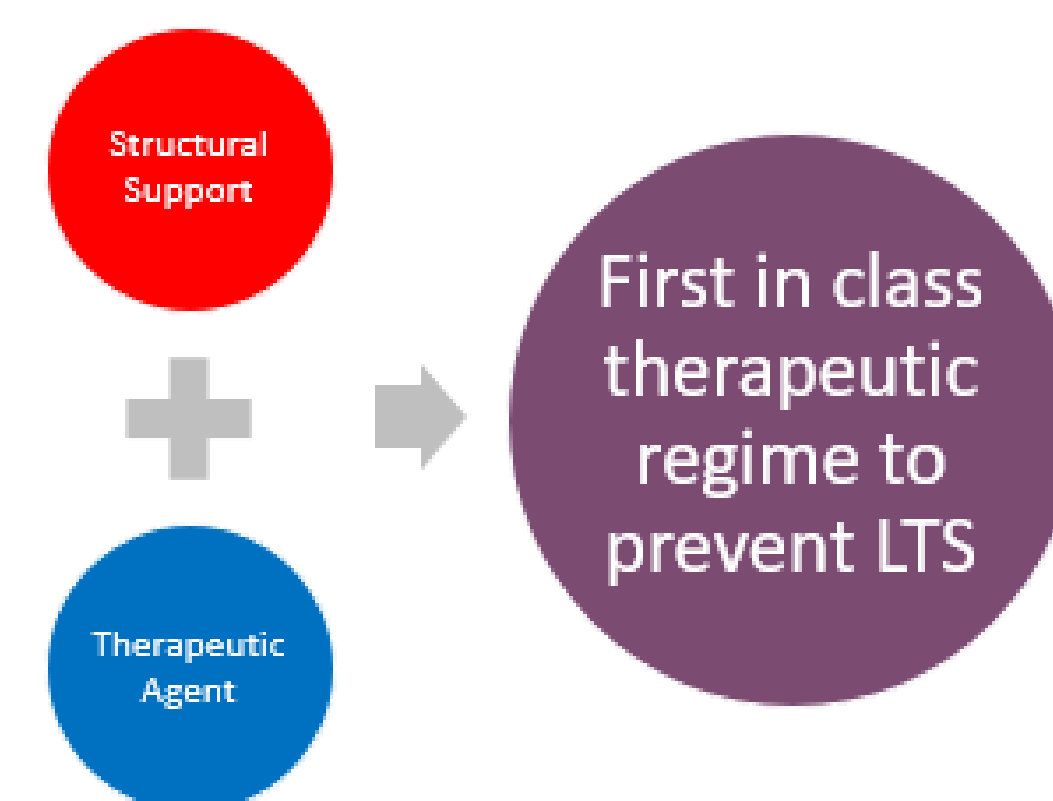
A biodegradable drug-eluting stents can (i) locally deliver the inhibitor and (ii) provide structural small molecules agents cannot provide.

- Easy to place
- Structural support
- Targeted release
- Breaks down over time

Conclusion

Deliver the SB-525334 inhibitor locally with a biodegradable drug-eluting stent.

- Structural Support
- Local Delivery
- Stent degrades when treatment is finished



This proposed solution is an ideal LTS therapy because it provides a targeted **and** effective therapy to inhibit the development of LTS.

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Table 1. Therapeutic agents used to treat LTS.

Agent	Advantages	Disadvantages
Steroids	• May slow abnormal healing process	• Limited ability to minimize or prevent LTS
Antibiotics	• Can reduce stenosis in animal models	• No good human data
Mitomycin	• Can inhibit fibroblast proliferation in vitro	• Carcinogenic
Tacrolimus	• May inhibit the TGF-β/Smad signaling pathway downregulating the TGF-β receptors	• Dose-dependent toxicity
5-FU	• Can reduce stenosis in animal models	• No good human data
Halofuginone	• Reduces the development of fibrosis in animals	• Experimental • Utility in the human airway is unknown
Lathyrogenic Agents	• BAPN may reduce scar tissue	• Data on overall efficacy is inconclusive
Growth factor modulators	• Growth factors, as well as other soluble mediators, are crucial in orchestrating all stages of wound healing	• Modulators need to be targeted to avoid adverse effects.