Targeting the TGF-β superfamily in Myelodysplastic Syndromes (MDS)

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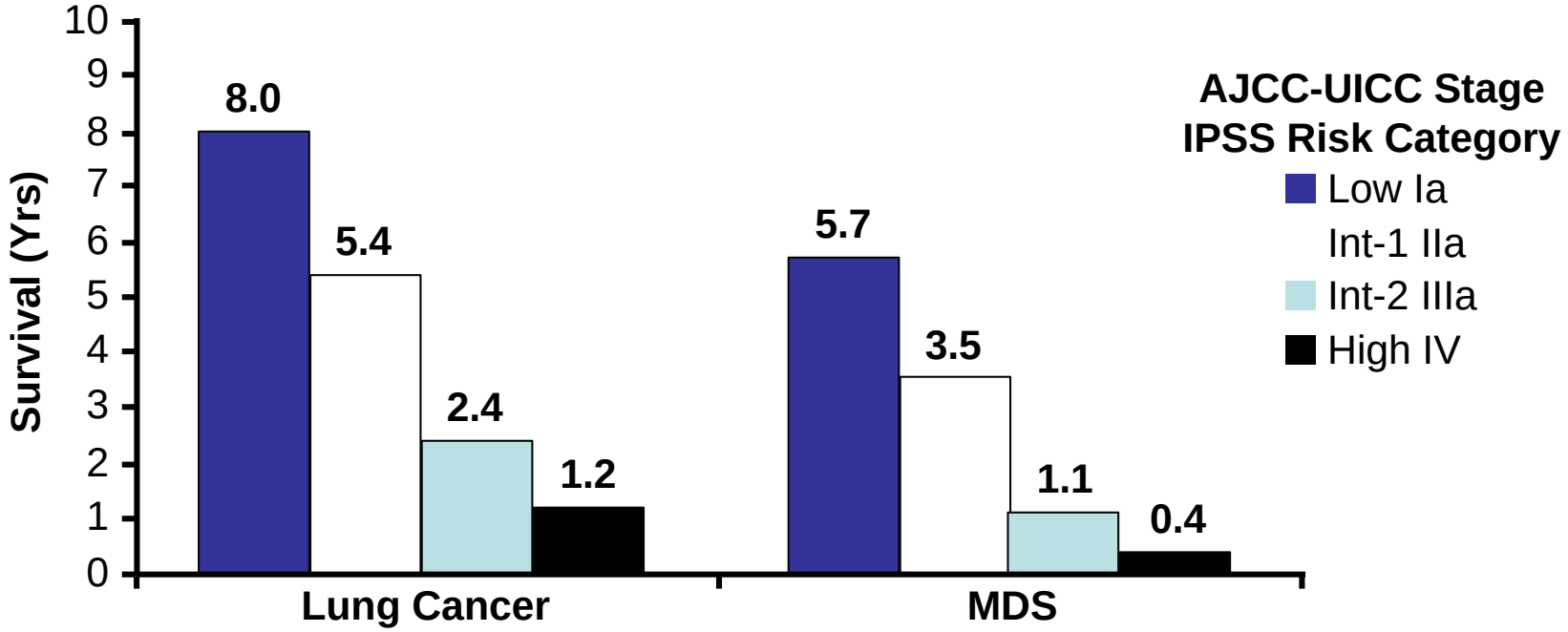
Reduced Survival Is an Inherent Feature of MDS: Even for low risk subgroups

Life expectancy is shorter for US patients with MDS than those with lung cancer*†[1,2]

Need for therapeutic approaches that increase blood counts



*Adjusted for age (lung cancer, median 66 yrs; MDS, median 69 yrs) and risk/stage.[1,2]
†All histological subtypes.[1,2]

1. Greenberg P, et al. Blood. 1997;89:2079-2088. Erratum in Blood. 1998;91:1100.
2. Adebonojo SA, et al. Chest. 1999;115:1507-1513.

Ineffective Hematopoiesis is seen in MDS

Hypercellular marrows with decreased peripheral blood counts

↑ Increased Cell death (Apoptosis/Cell cycle arrest)
Decreased Proliferation / Differentiation

↑ Pro Apoptotic / Myelosuppresive/
Inflammatory cytokine signaling

Tumor necrosis factor α

↑ TNFα mRNA in MDS BMs

↑ TNF production by MDS Macrophages

Pro-apoptotic Type **1** receptors increased in low grade MDS and decreased in high grade cases and AML

Anti-TNF therapies (Remicaid & Enbrel) show efficacy

Thalidomide can degrade TNF mRNA

Transforming growth factor β

↑ membrane bound TGF β on progenitors

↑ conc. in serum

Other TGF-β family members

GDF11, GDF15

Vascular Endothelial growth factor (VEGF)

Secreted by malignant clone and ALIP cells

Expression in BM correlates with disease severity

Higher expression of high affinity VEGFR1

Interferon γ (IFN g)

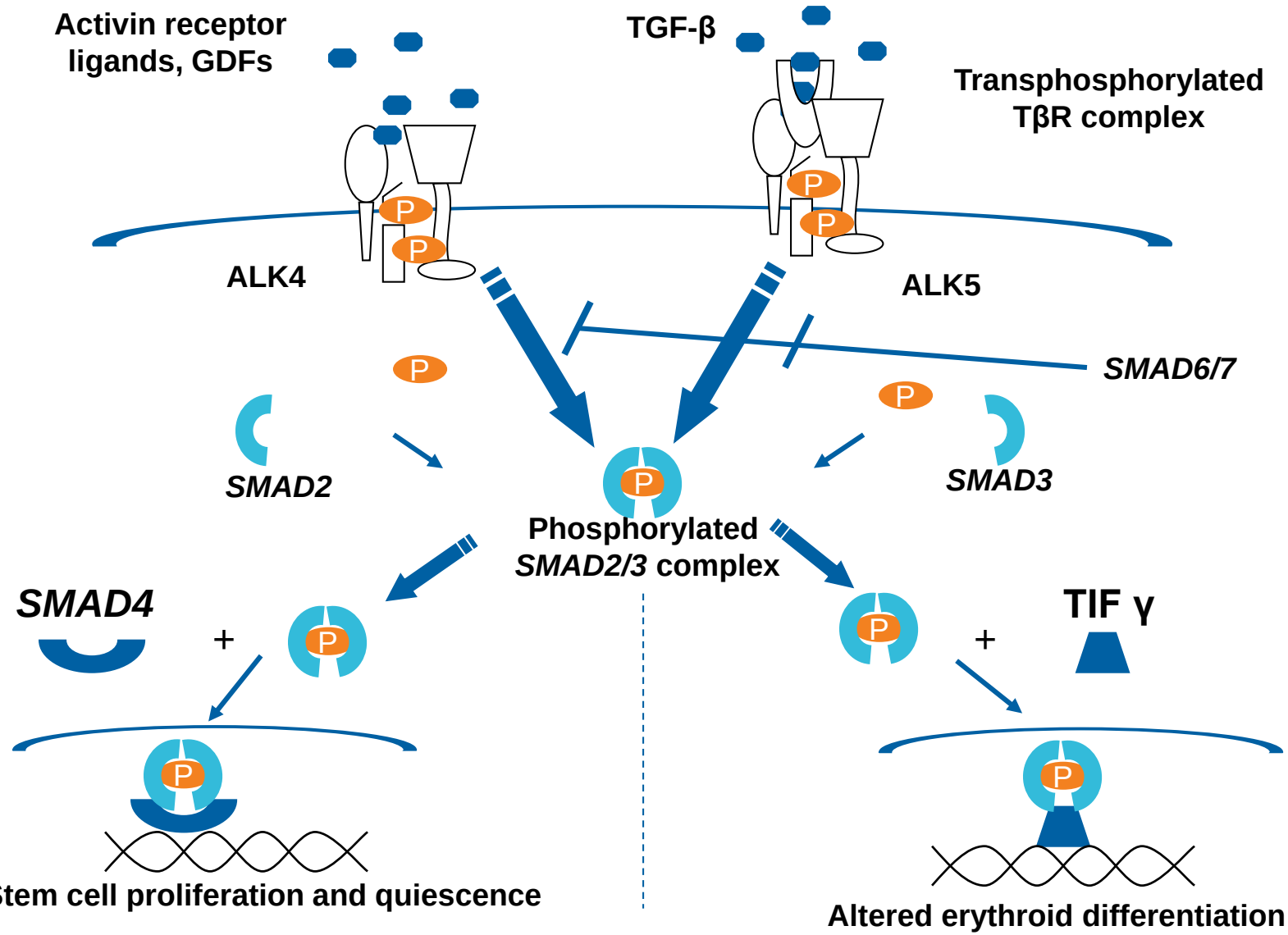
Interleukin 1β

Fibroblast Growth factor (FGF)

Hepatocyte growth factor (HGF)

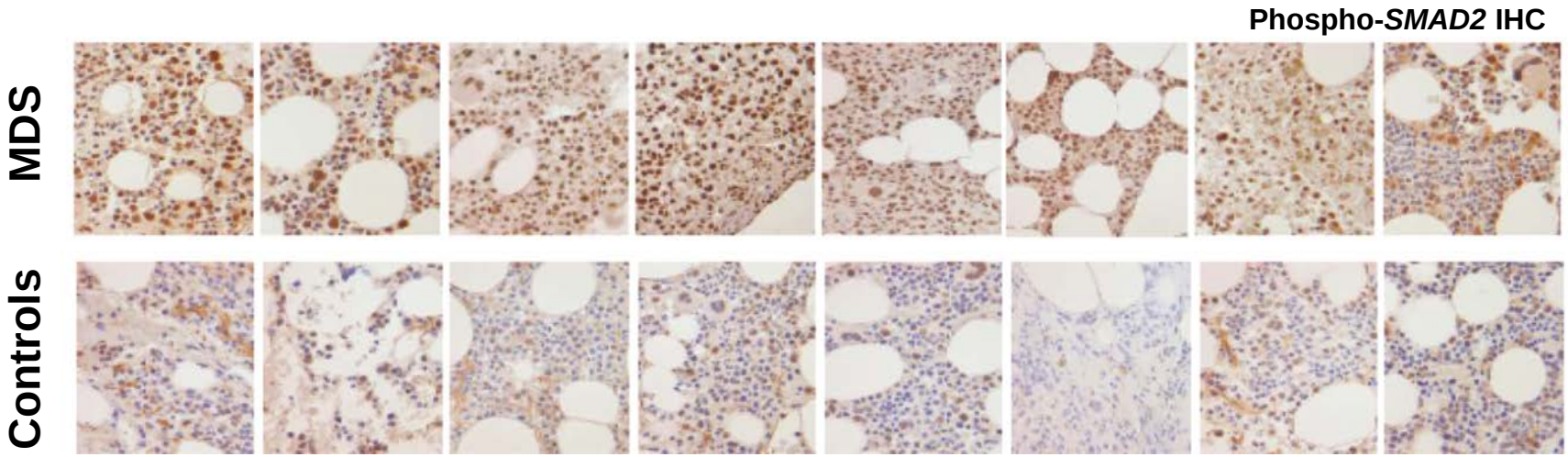
Macrophage Inhibitory Protein (MIPα)

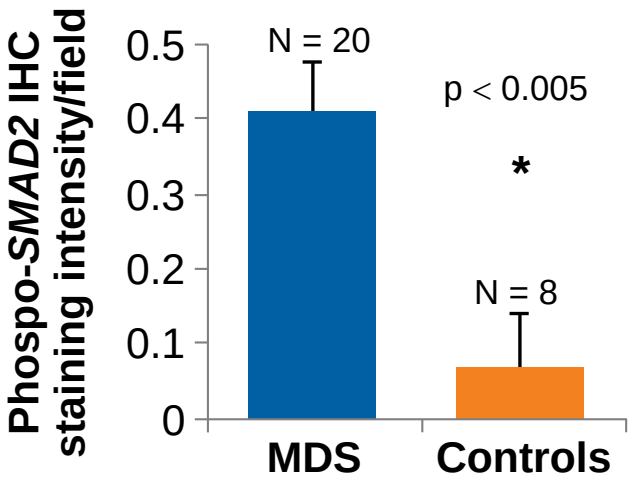
TGF-beta family members regulate hematopoiesis

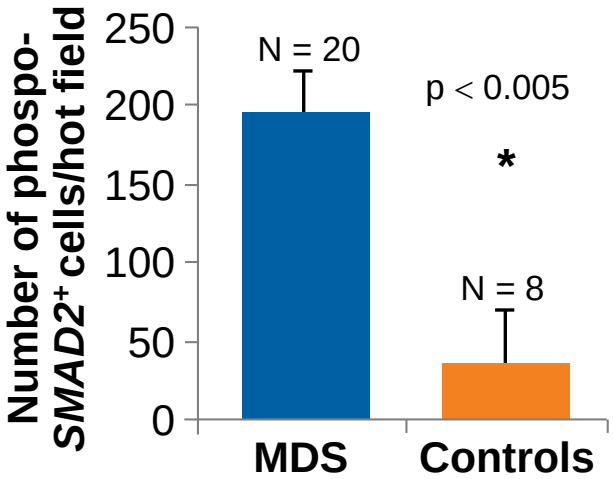


ALK, activin-like kinase receptor; GDF, growth differentiation factor; TGF-β, transforming growth factor β.

Activated *SMAD2/3* seen in MDS BM samples



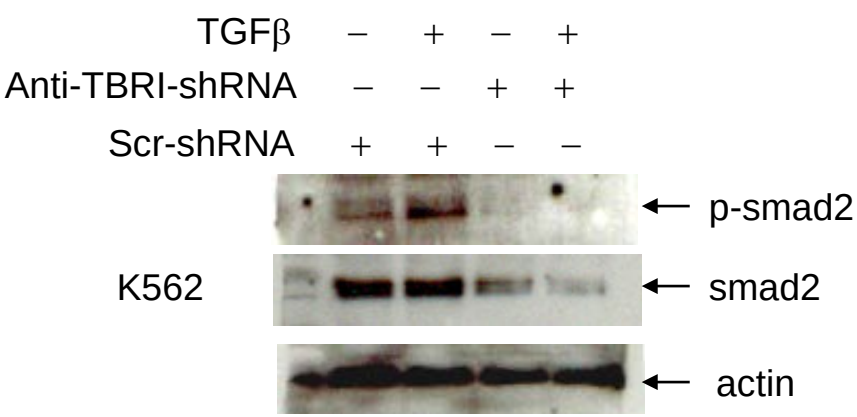


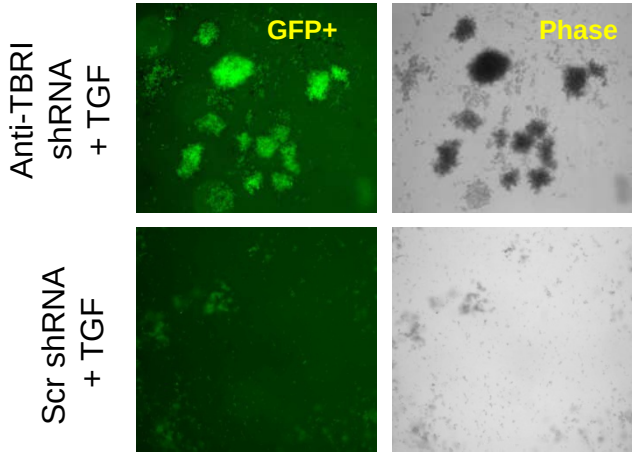


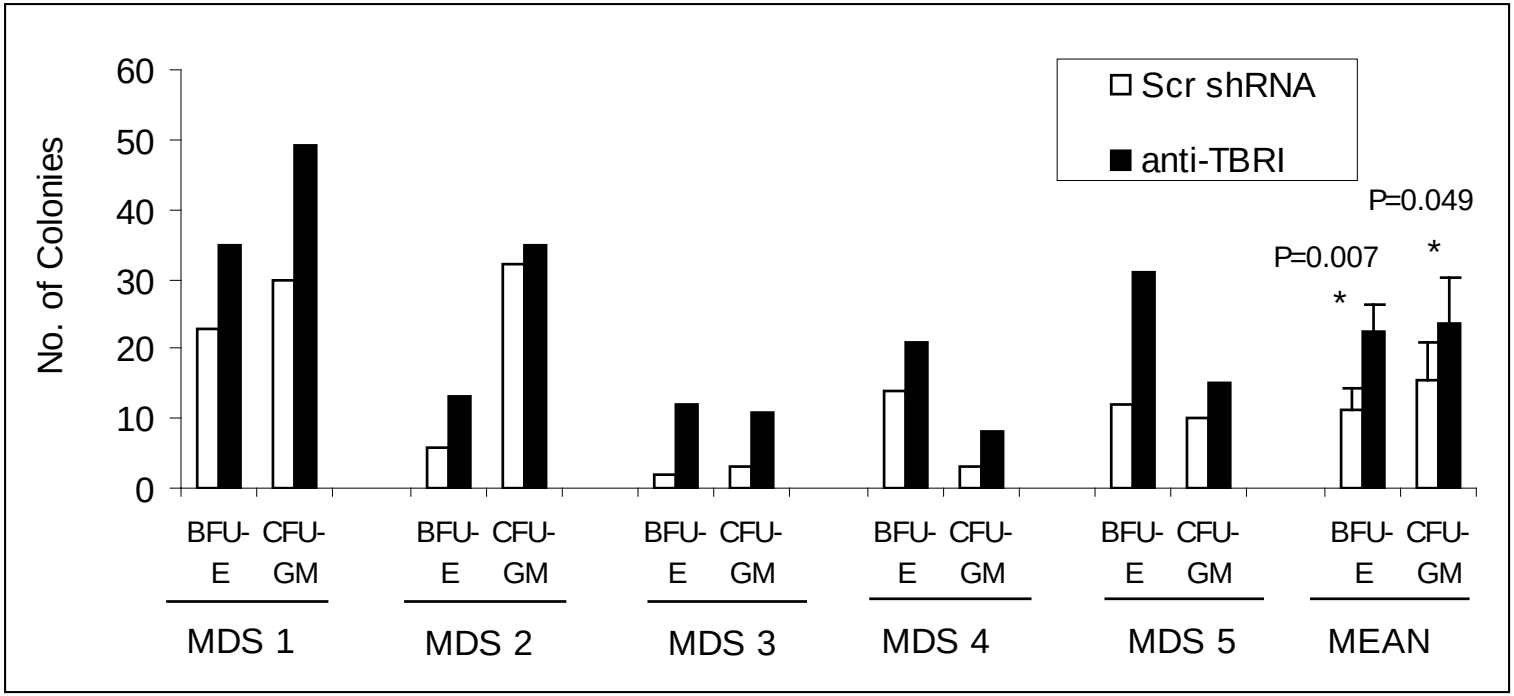
BM, bone marrow; IHC, immunohistochemistry.

Zhou L, et al. Blood. 2008;112:3434-43.

Inhibition of SMAD2 activation can stimulate MDS hematopoiesis in vitro

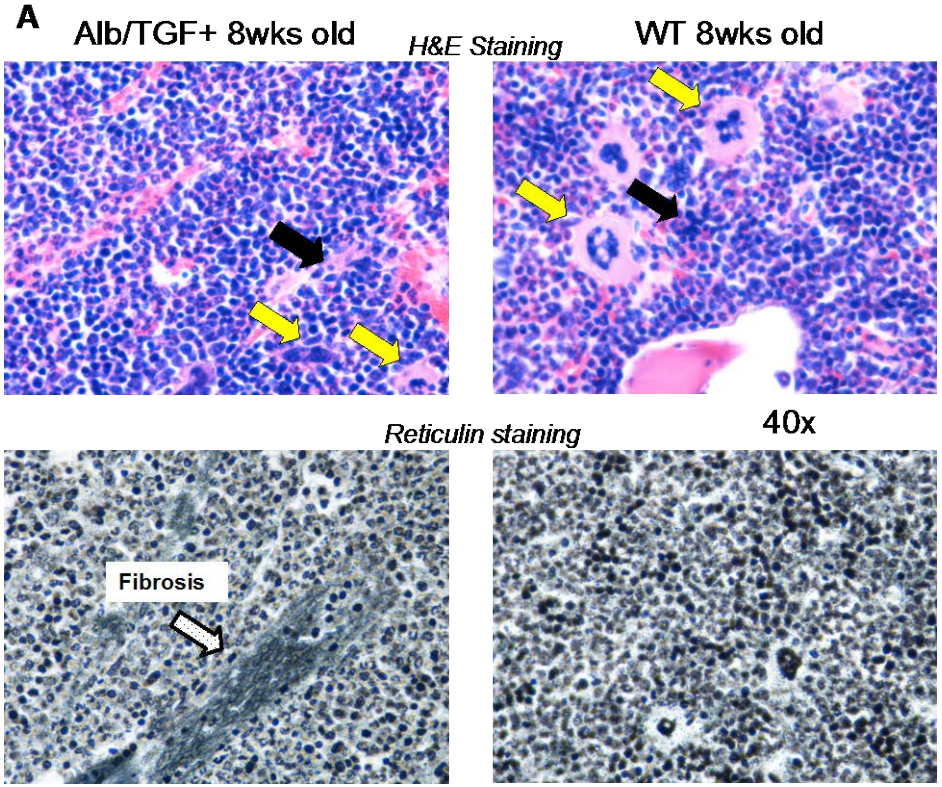


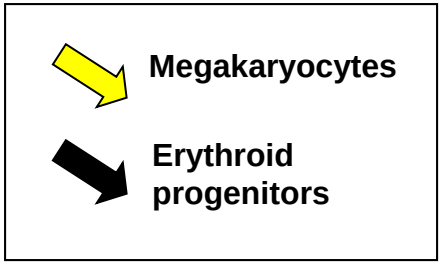


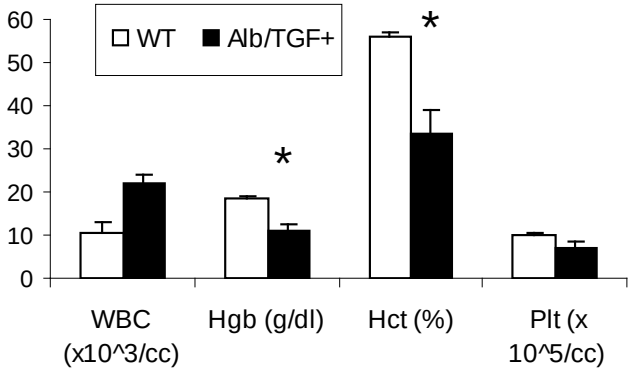


Zhou et al, Blood, 2008

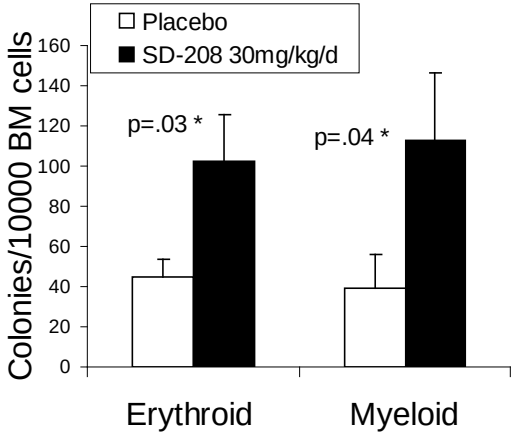
Alb/TGF+ transgenic mice develop anemia and mimic human bone marrow failure

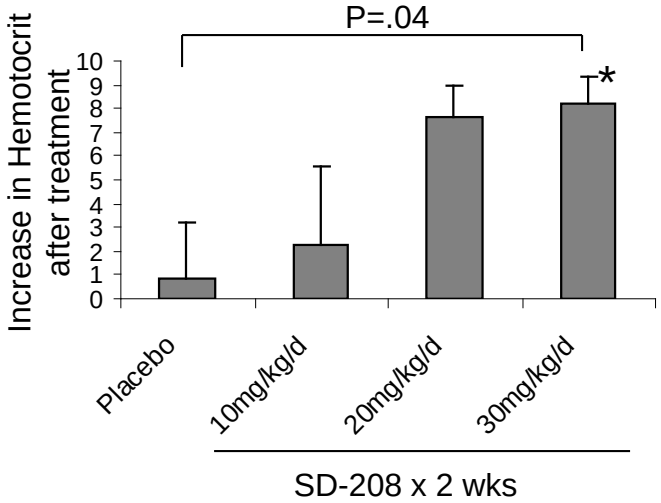






Small molecule inhibitor of ALK5 (TGF-b receptor I), SD-208, can improve hematopoiesis in TGF overexpressing mice and can raise their hematocrit

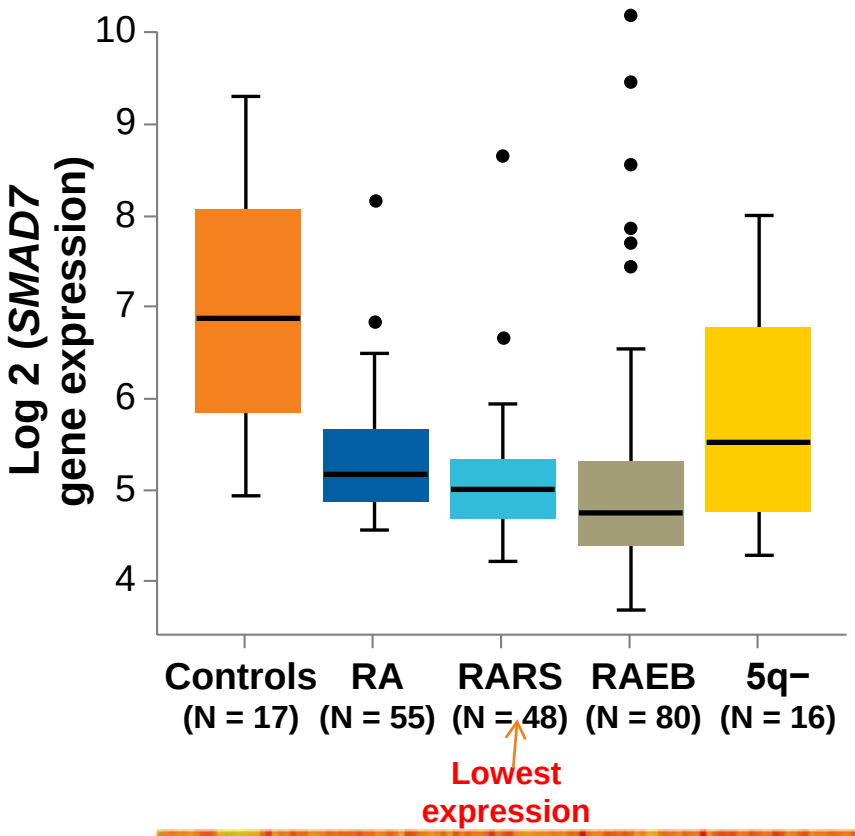


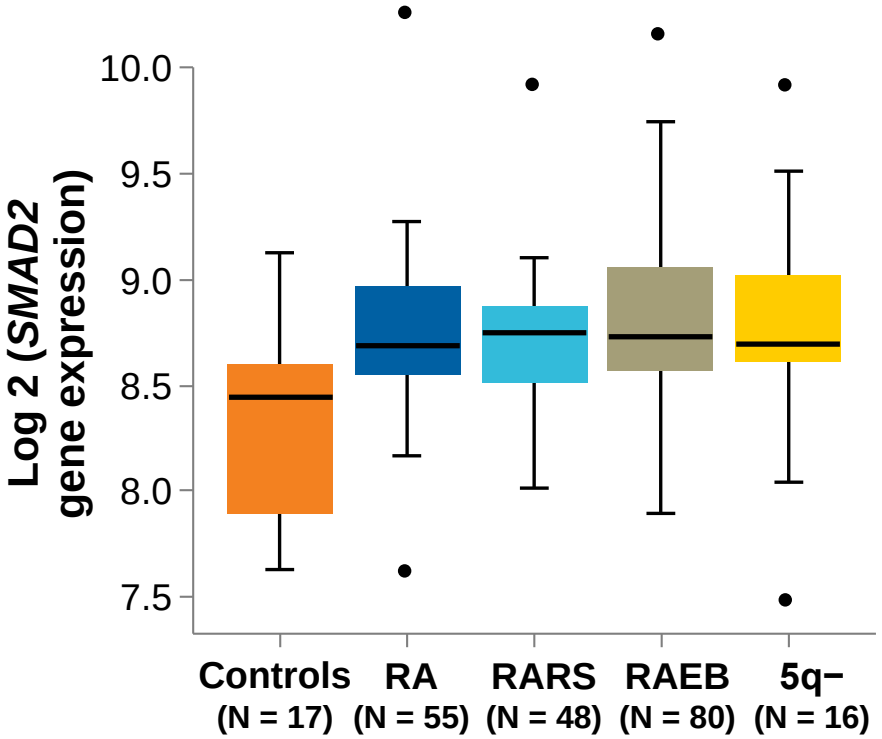


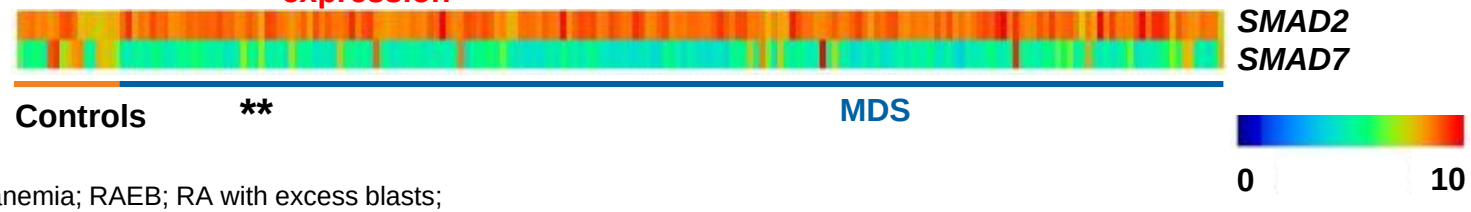
Zhou et al, Blood, 2008

Why is SMAD2/3 signaling activated in MDS?

Negative regulator Smad7 is reduced



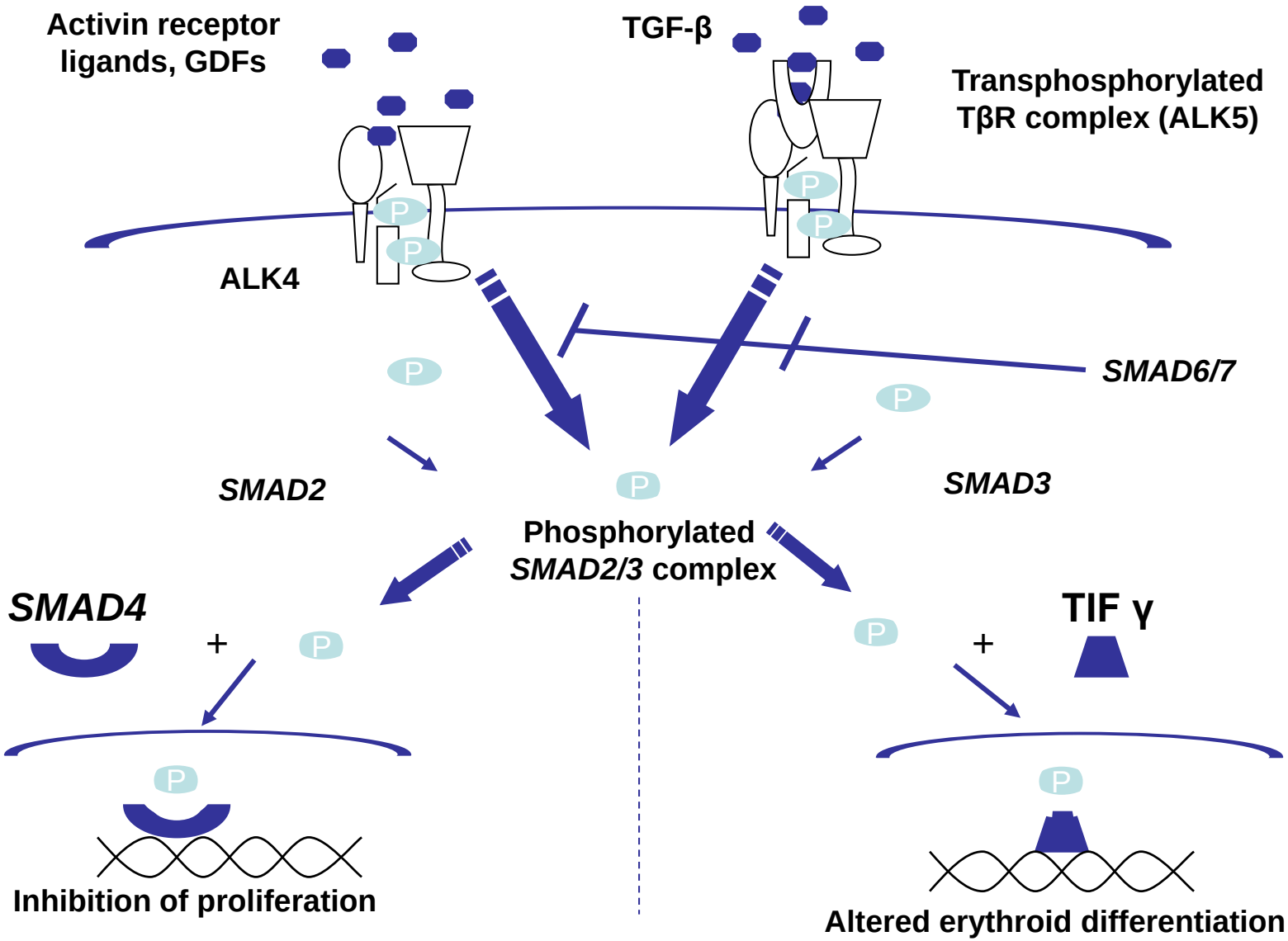




RA, refractory anemia; RAEB; RA with excess blasts;
RARS, RA with ringed sideroblasts.

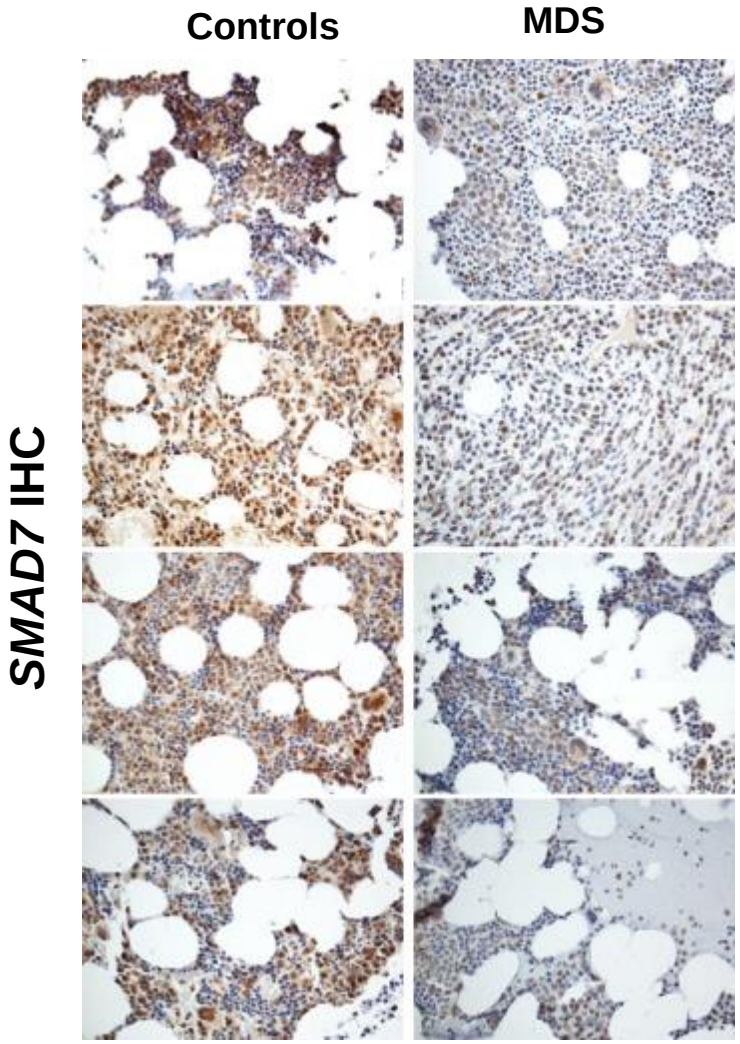
Zhou L, et al. Cancer Res. 2011;71:955-63.

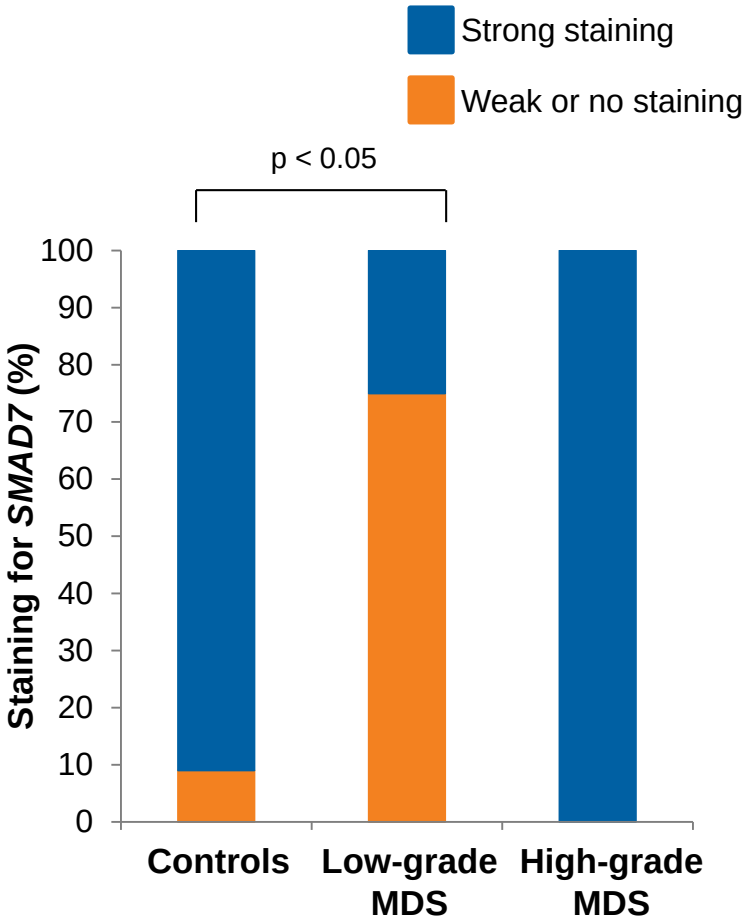
SMAD7 is a negative regulator of ALK4 and ALK5



ALK, activin-like kinase receptor; GDF, growth differentiation factor; TGF-β, transforming growth factor β.

SMAD7 is reduced in MDS

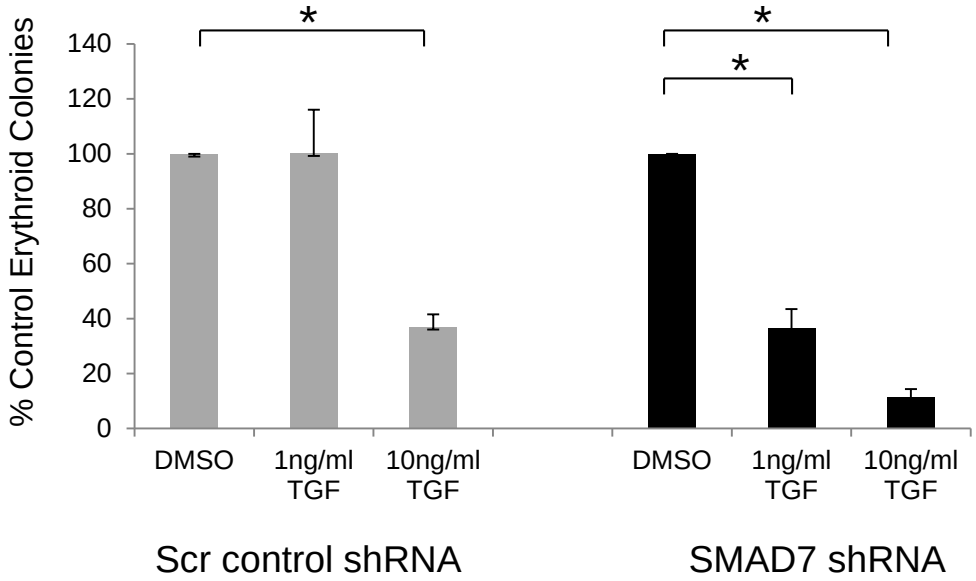


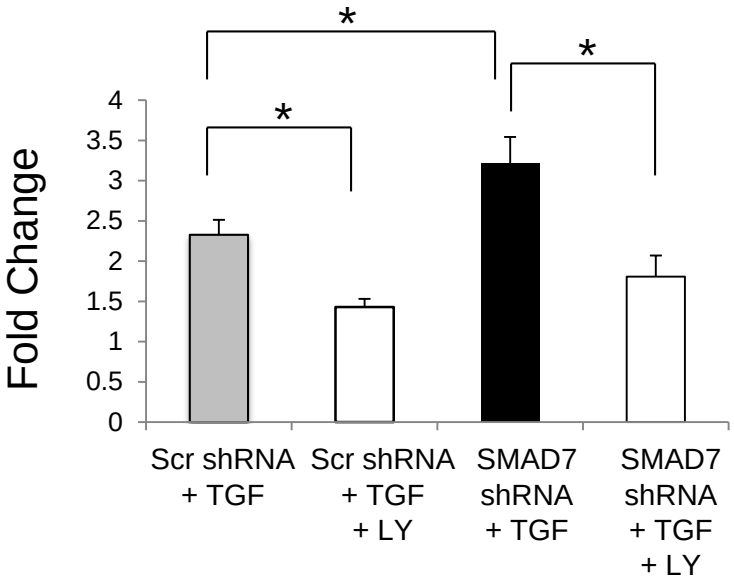


Zhou L, et al. Cancer Res. 2011;71:955-63.

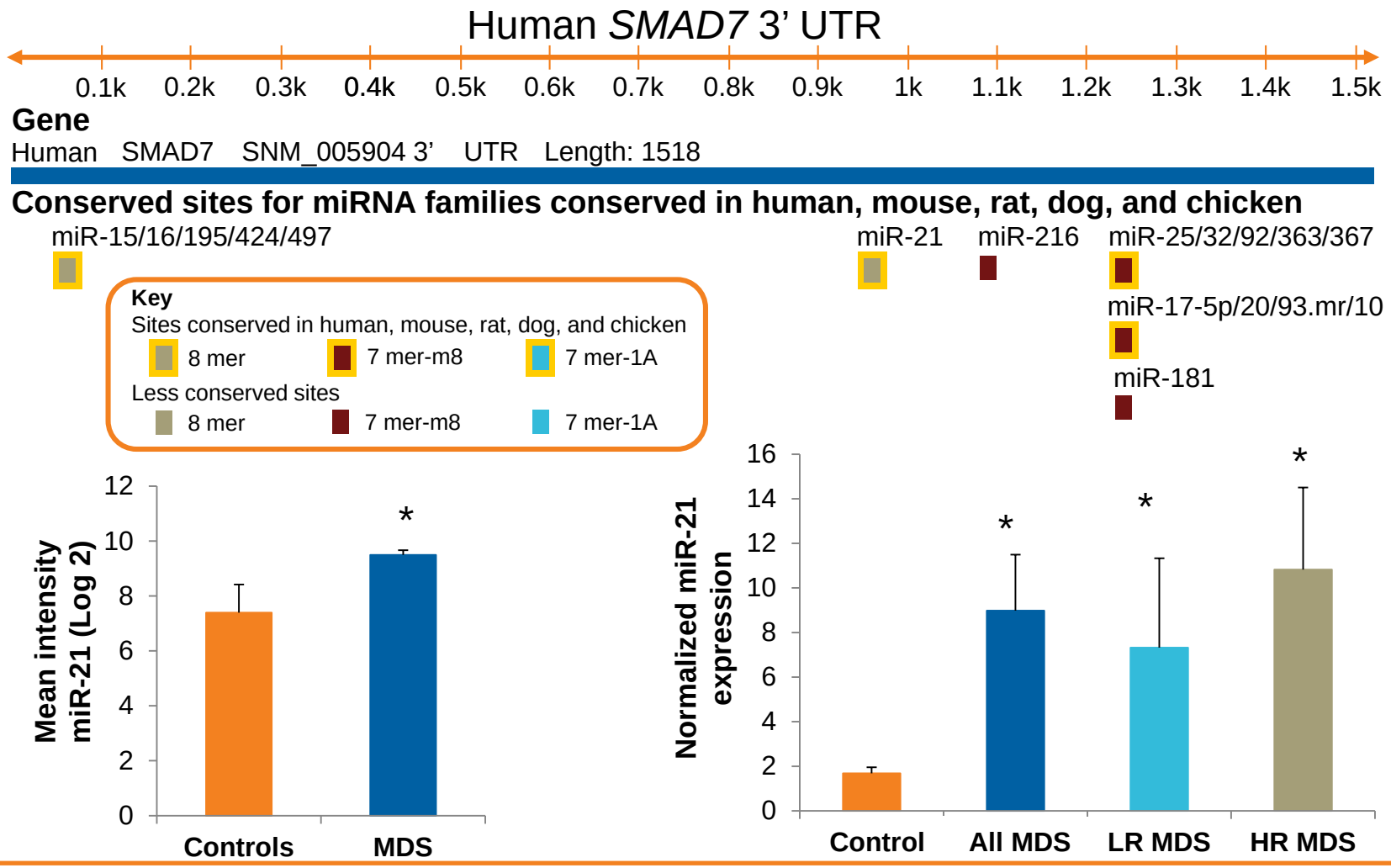
Reduced SMAD7 leads to increased sensitivity to TGF-β

…….That can be reversed by inhibition of TGF-b receptor kinase





Why is *SMAD7* decreased in MDS?

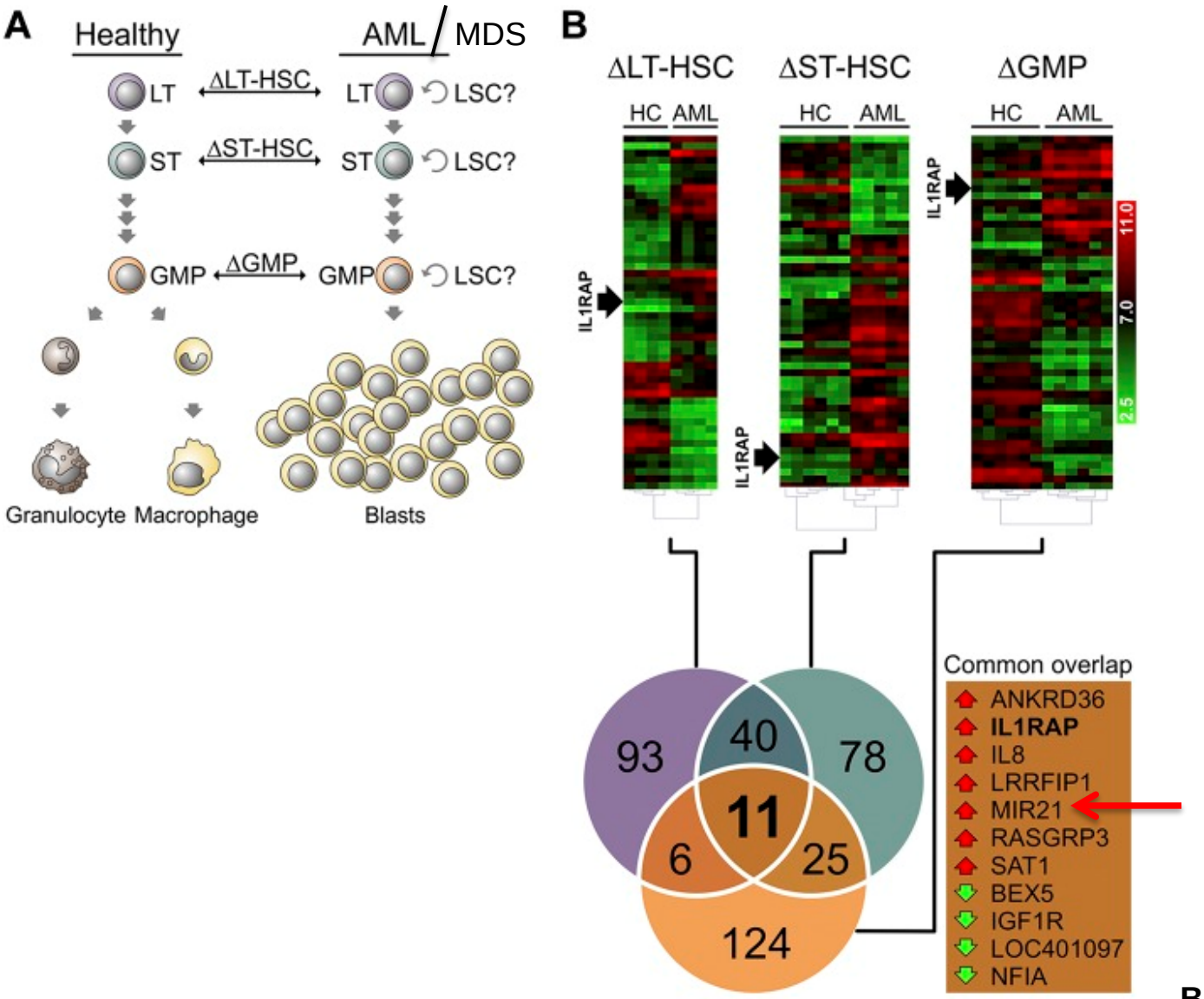


miR-21 is increased in MDS and has a putative binding site on the *SMAD7* 3' UTR

HR MDS, high-risk MDS; LR MDS, low-risk MDS;
miR-21, microribonucleic acid 21; UTR, untranslated region.

Bhagat TD, et al. Blood. 2013;121:2875-81.

Parallel Transcriptional Analysis reveals miR-21 overexpression in MDS/AML Stem and Progenitor cells



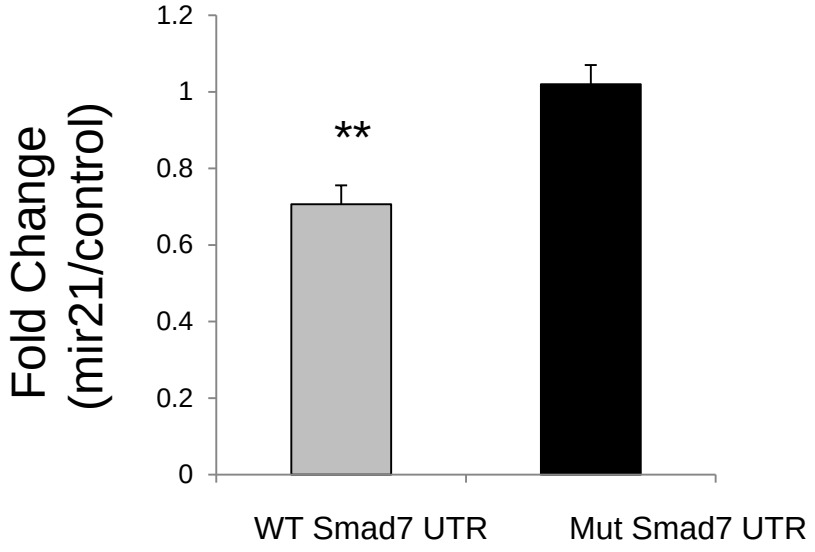
Barreyro et al. Blood 2012

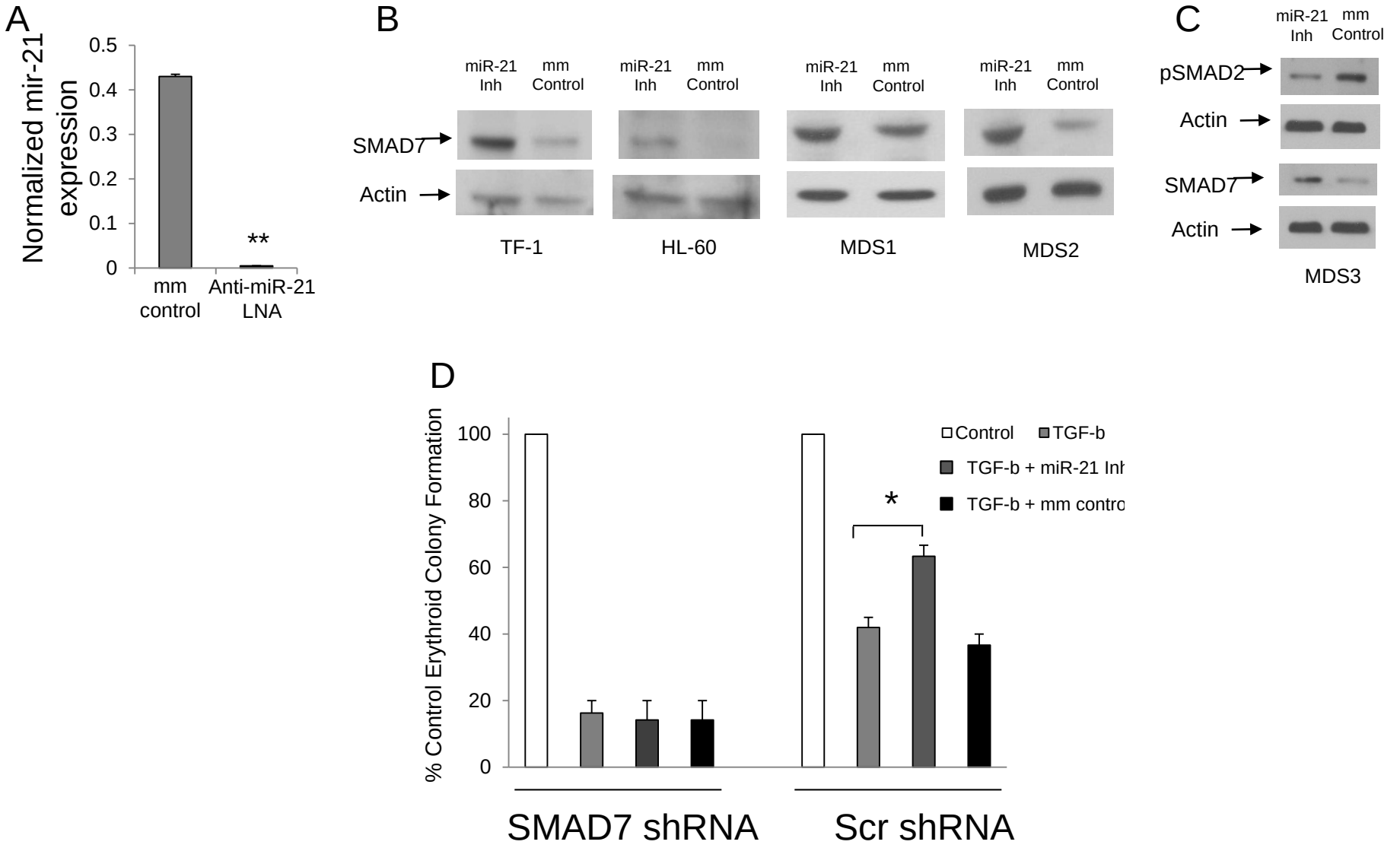
miR-21 binds to SMAD7 3'UTR and leads to reduced levels of SMAD7

A

```
5'  ...UGUUUAGAAUUUAACAUAAGCUA...   Wild-type mouse Smad7 3'UTR
                                 | | || | ||
3'     AGUUGUAGUCAGACUAUUCGAU      miR-21
                                 | | |
5'   UGUUUAGAAUUUAACAUAUCGAA       mutant mouse Smad7 3'UTR
```

B

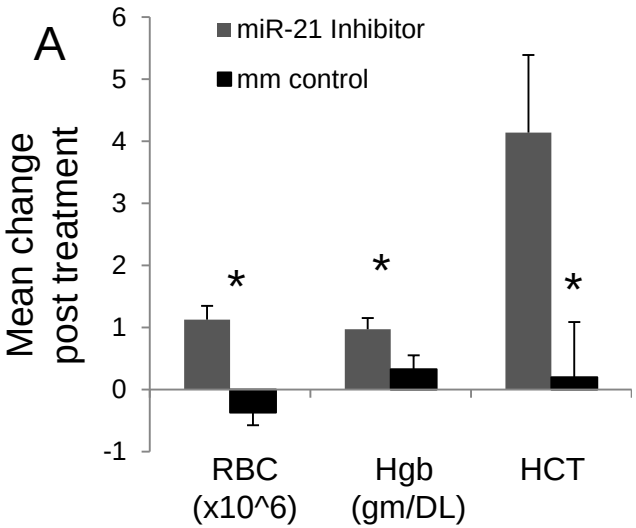


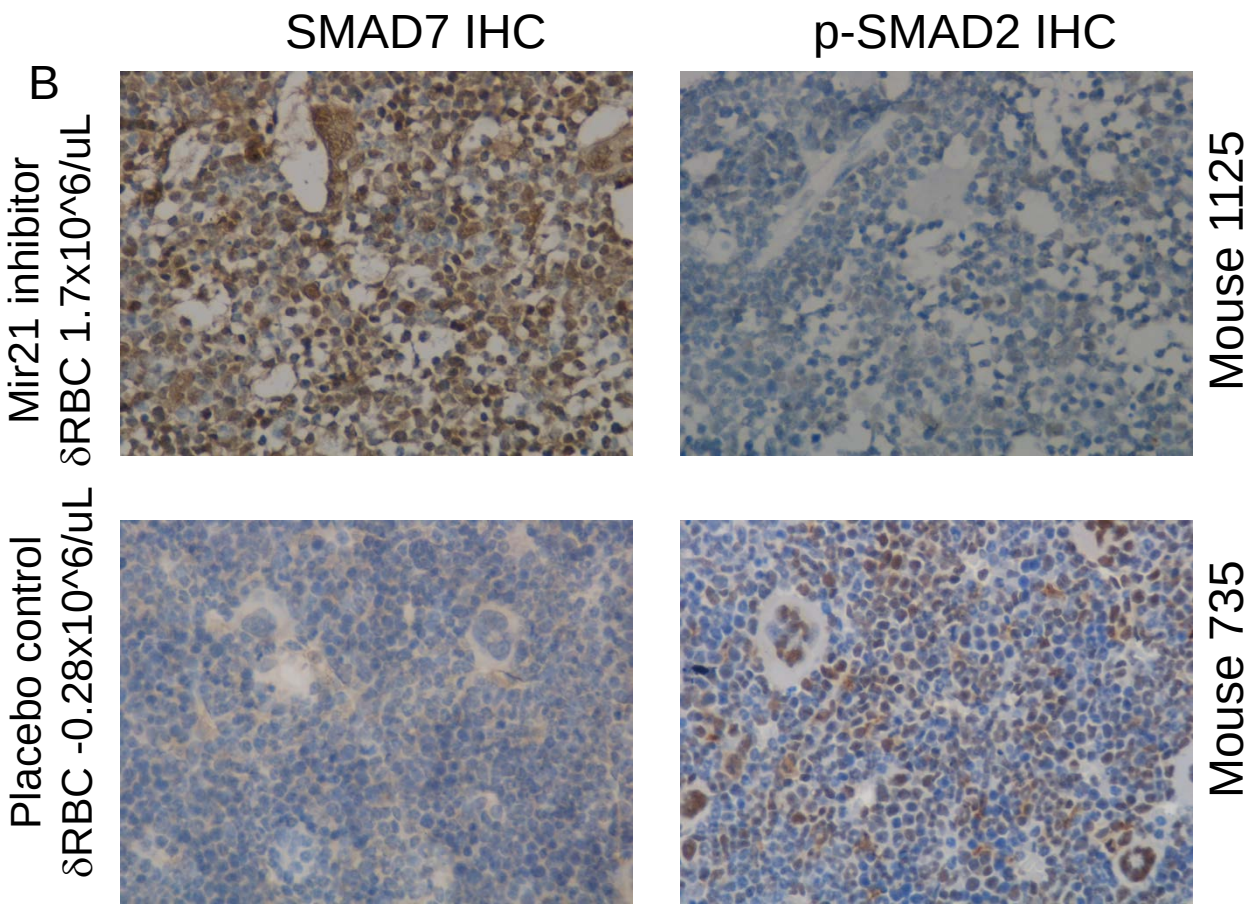


Inhibition of miR-21 can abrogate the effects of TGF–β on hematopoietic cells

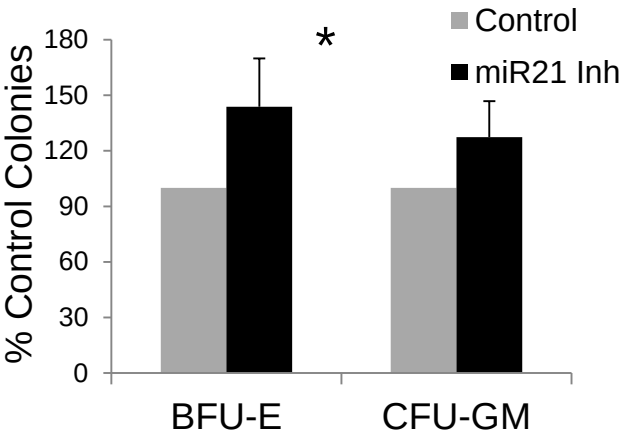
Bhagat et al, Blood, 2013

Treatment with mir21 inhibitor leads to increase in red blood cells in TGF transgenic mice:

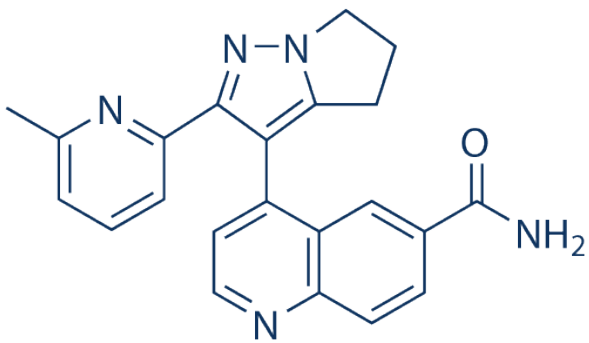




Inhibition of miR-21 stimulates erythropoiesis in MDS.

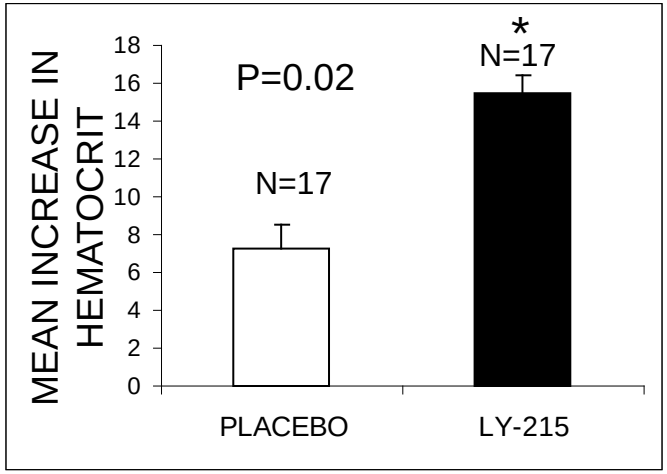


LY-2157299 (Galunisertib) is an oral ALK5 inhibitor

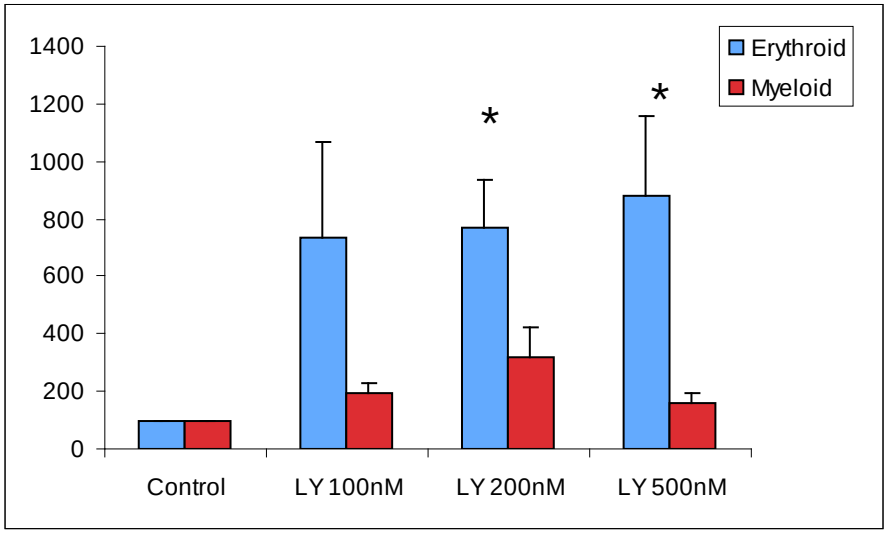


A Study of LY2157299 in Participants With Low/Int-1 Myelodysplastic Syndromes; ClinicalTrials.gov Identifier: NCT02008318

LY-215 is effective in vitro and in vivo in MDS



TGF transgenic mice treated for 2 weeks



MDS BM samples

Zhou L, et al. Cancer Res. 2011;71:955-63.

Phase 2 Study of Monotherapy Galunisertib (LY2157299 Monohydrate) in Very Low-, Low-, and Intermediate-risk Patients with Myelodysplastic Syndromes

David Valcarcel[1], Amit Verma[2], Uwe Platzbecker[3], Valeria Santini[4], Aristoteles Giagounidis[5], Maria Diez-Campelo[6], Jan Janssen[7], Richard F Schlenk[8], Gianluca Gaidano[9], Jaime Perez de Oteyza[10], Ann L Cleverly[11], Alan Y Chiang[12], Michael M Lahn[12], Durisala Desaiah[12], Susan C Guba[12], Alan List[13], Rami Komrokji[13]

[1]Hematology, Vall d'Hebrón University Hospital, Vall d'Hebrón, Barcelona, Spain; [2]Department of Medicine, Albert Einstein Cancer Center, Bronx, NY, USA; [3]Universitätsklinikum Carl Gustav Carus an der Technischen Universität, Dresden, Germany; [4]AOU Careggi, University of Florence, Florence, Italy; [5]Hematology, Oncology and Palliative Care, Marien Hospital, Düsseldorf, Germany; [6]Hospital Clinico De Salamanca, Salamanca, Spain; [7]Onkologische Gemeinschaftspraxis Dres Westerstede, Germany; [8]Internal Medicine, University of Ulm, Ulm, Germany; [9]Hematology, Department of Translational Medicine, Amedeo Avogadro Novara, Italy; [10]Hematology, Hospital HM Sanchinarro, Madrid, Spain; [11]Eli Lilly and Company, Erl Wood, ELCL, UK; [12]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA; [13] H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

57th American Society of Hematology Annual Meeting; December 5-8, 2015; Orlando, Fl., USA

Hematological Improvement in Patients Treated with Galunisertib, 150 mg BID

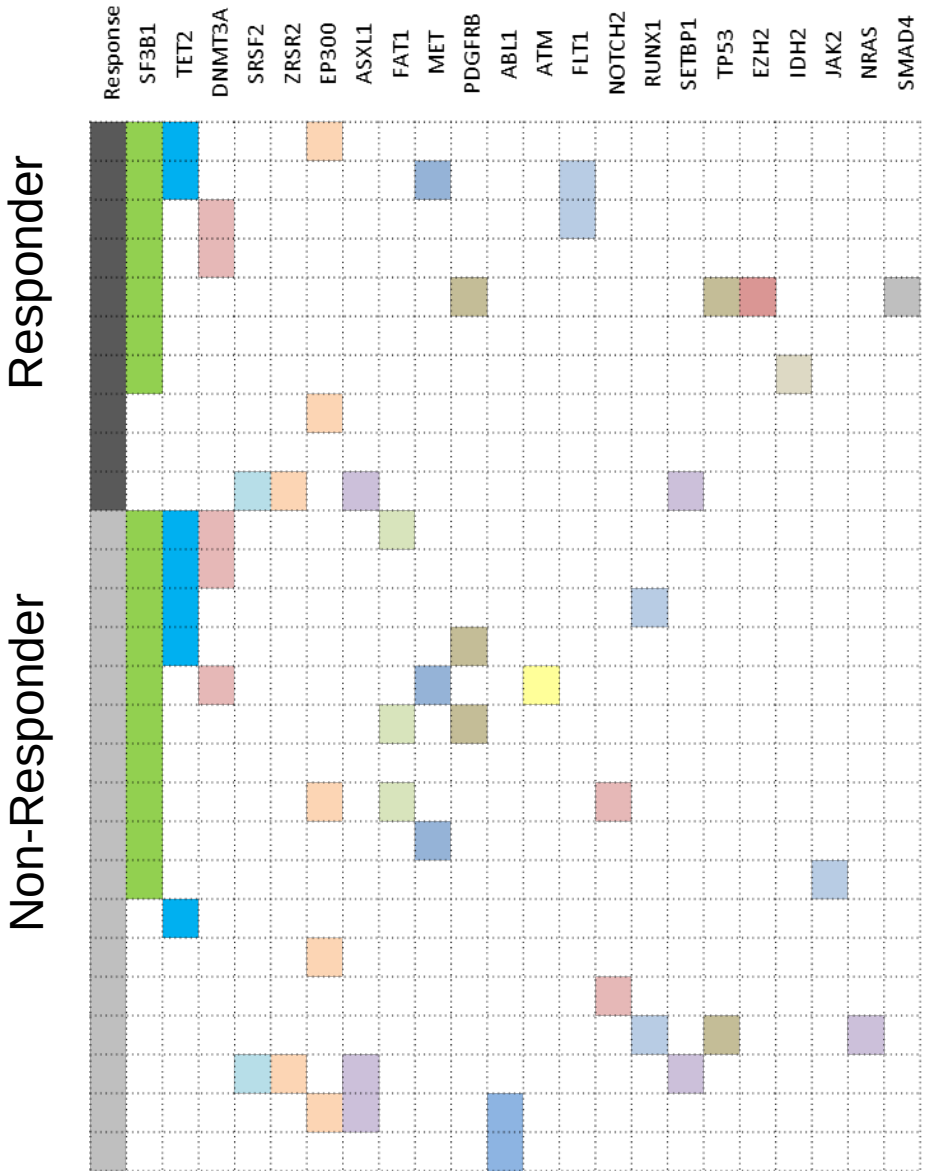
Baseline Trans-Fusion Need	Number of Patients (N)	Median number of transfused units at baseline	Post Treatment (N)	
			TI During any 8 Weeks	HI (TR/TI or HGB Increase) During any 8 weeks
≥ 4 Units	24	7.5	4	9/24 (37.5%)
1-3 Units	4	2.5	2	0
0 Units	10	0	9	1
Total	38			10/38 (26.3%)

]14*

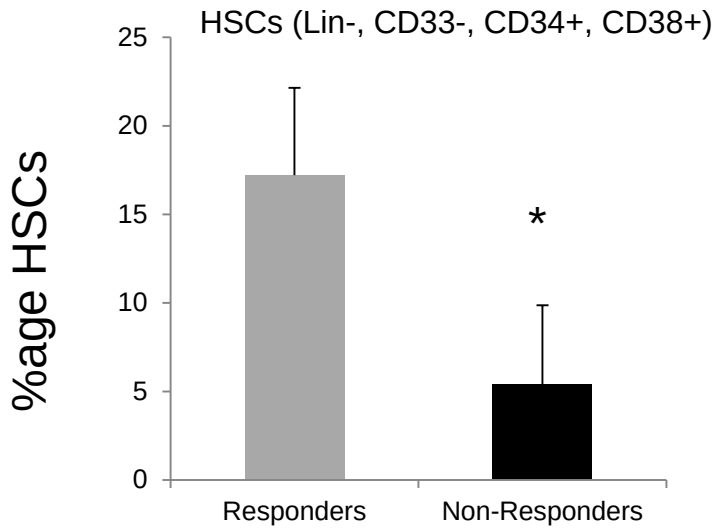
*14 patients could not decrease their transfusion requirement by 4 units/8 weeks per IWG 2006 criteria.
If only the ≥4 units at baseline patients are included, then the response rate is 9/24 or 37.5%

TI, transfusion independence; HI, hematological improvement; TR, transfusion reduction; HGB, hemoglobin

Heatmap of Biomarkers vs. Response Demonstrated no Correlation with mutations

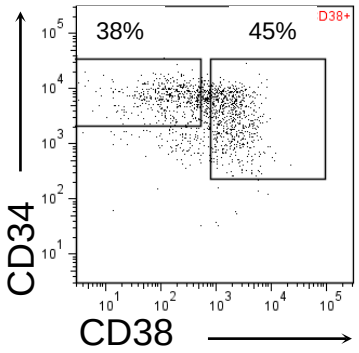


Stem Cell Differentiation Block (CD34+CD38-Lin-CD33-) is associated with response to TGF-β inhibitor



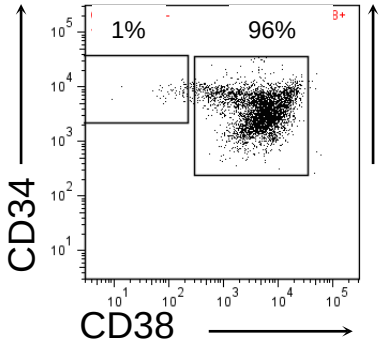
Responder

Lin-CD33- cells



Non-Responder

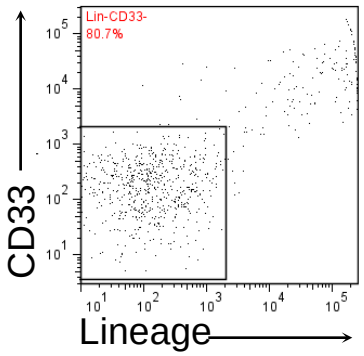
Lin-CD33- cells



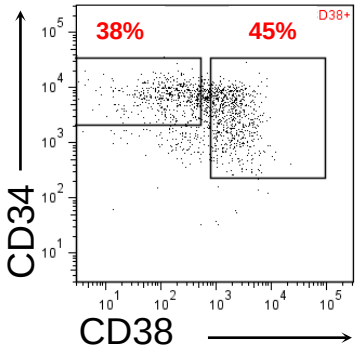
Response to TGF-β inhibition associated with increased progenitor differentiation

Pre-treatment

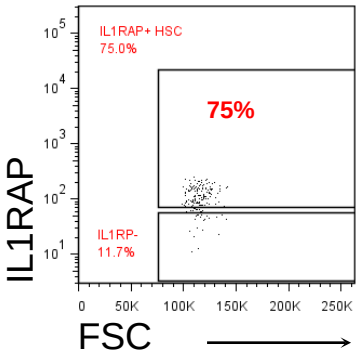
Viable, single cells



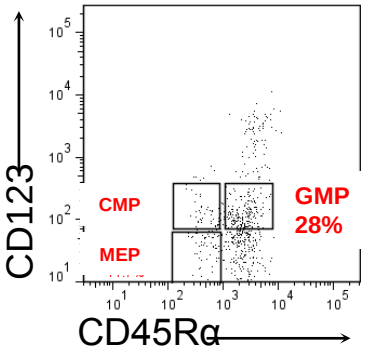
Lin-CD33- cells



CD123-CD45Rα- cells



CD34+CD38+ cells

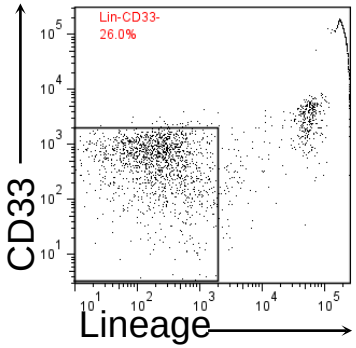


Increased %age of CD34+/CD38+ progenitors

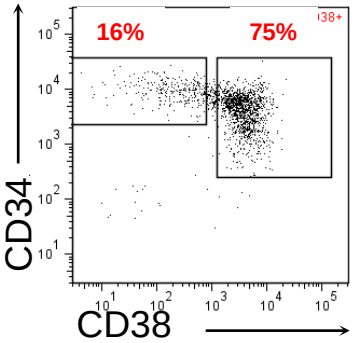
Decreased %age of Aberrant (IL1RAP) HSCs

Cycle 6

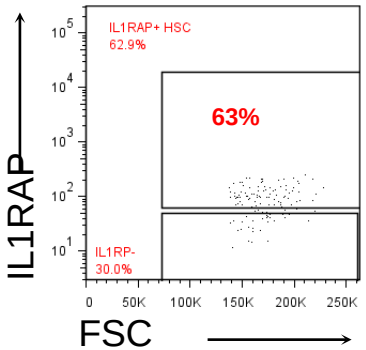
Viable, single cells



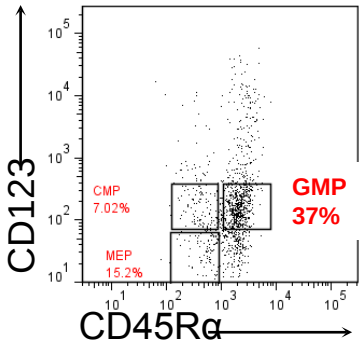
Lin-CD33- cells



CD123-CD45Rα- cells



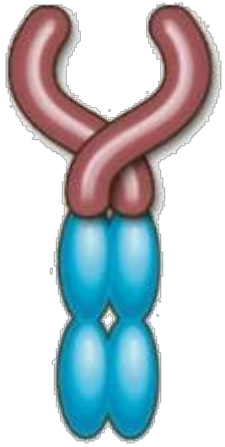
CD34+CD38+ cells



Sotatercept and Luspatercept (ACE-536) act as novel ligand traps for TGF-β superfamily ligands

Sotatercept

(ACE-011)

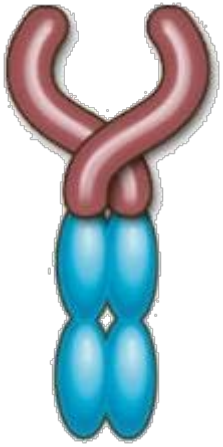


Extracellular domain of **ActRIIA**

Fc domain of human IgG_1 antibody

Luspatercept

ACE-536



Modified extracellular domain of **ActRIIB**

Fc domain of human IgG_1 antibody

Amino acid homology between ECD of sotatercept and ACE-536 is ~ 60%

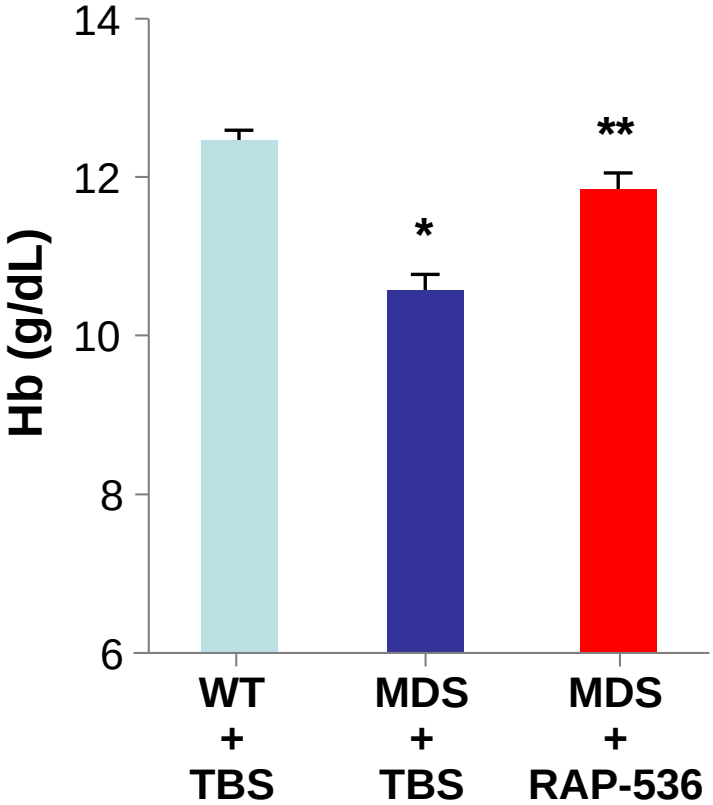
The murine orthologues of these molecules are RAP-011 and RAP-536; extracellular domains are identical, but linked to murine IgG2a Fc domain

IgG, immunoglobulin G.

Ravi Kumar, Acceleron

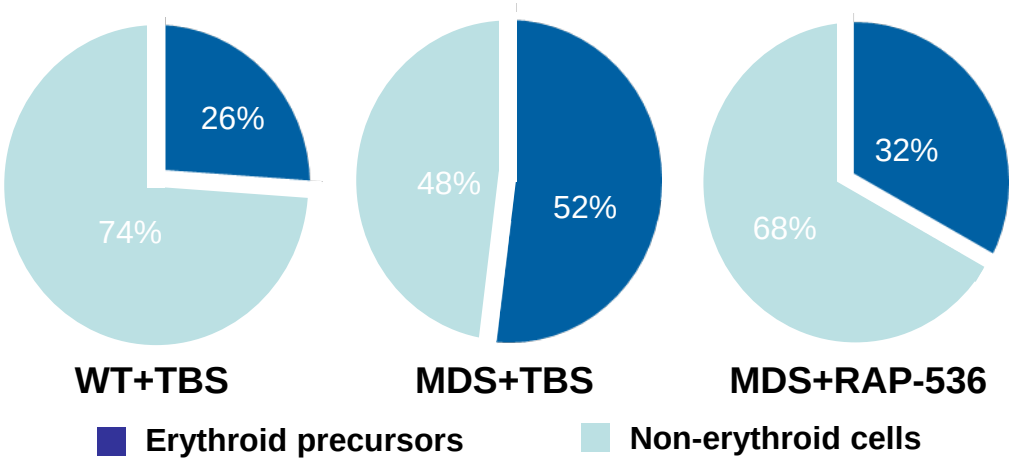
ACE-536 correct anemia by promoting late stage erythropoeisis

Increases Hb

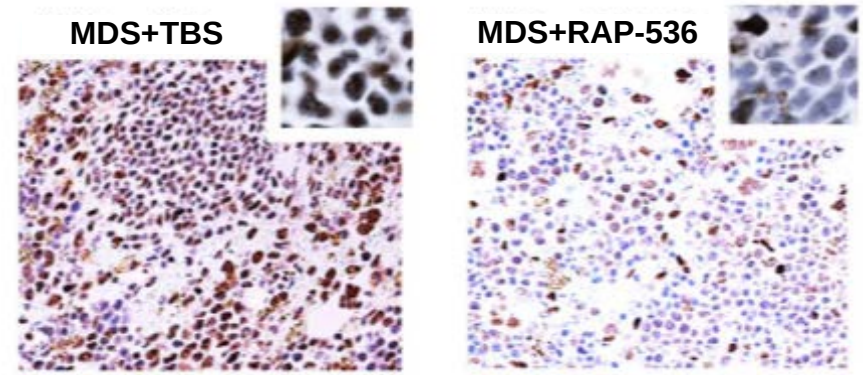


* p < 0.001 vs WT+TBS
** p < 0.05 vs MDS+TBS

Normalizes M:E ratio in BM



Inhibits *SMAD2/3* signaling



Studies using RAP-536, murine analogue of luspatercept

TBS, tris-buffered saline; M:E, myeloid:erythroid.

Suragani RN, et al. Nat Med. 2014;20:408-14.

ACE-536 increases hemoglobin and reduces transfusion burden in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS): Final results from a phase 2 study

Uwe Platzbecker, MD[1], Ulrich Germing, MD*[,2], Aristoteles Giagounidis, MD PhD[3], Katharina Götze, MD*[,4], Philipp Kiewe, MD*[,5], Karin Tina Mayer, MD*[,6], Oliver Ottmann, MD[7], Markus Radsak, MD*[,8], Thomas Wolff, MD[9], Detlef Haase, MD*[,10], Monty Hankin*[,11], Dawn Wilson*[,11], Xiaosha Zhang*[,11], Abderrahmane Laadem, MD[12], Matthew L. Sherman, MD[11], and Kenneth M. Attie, MD

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D·MDS
Deutsche MDS-Studiengruppe

Study supported by Acceleron and Celgene

Platzbecker U, et al. Presentation presented at ASH 2014.
Blood. 2014;124:abstract 411.

HI-E response rate by ring-sideroblast morphology, SF3B1 mutation

Response rate at higher dose levels (0.75–1.75 mg/kg)

Patient Subgroup	IWG HI-E Response Rate (0.75-1.75 mg/kg)
RS positive[1]	19/35 (54%)
EPO < 200 U/L	14/23 (61%)
EPO ≥ 200 U/L	5/12 (42%)
RS negative[1]	0/4 (0%)
SF mutation[2] present	18/30 (60%)
SF mutation[2] absent	1/9 (11%)

Data as of 03 October 2014.

An open-label, phase 2, dose-finding study of sotatercept (ACE-011) in patients with low or intermediate-1 (Int-1)-risk myelodysplastic syndromes (MDS) or non-proliferative chronic myelomonocytic leukemia (CMML) and anemia requiring transfusion

Rami Komrokji,[1] Guillermo Garcia-Manero,[2] Lionel Ades,[3] Abderrahmane Laadem,[4] Bond Vo,[4] Thomas Prebet,[5] Aspasia Stamatoullas,[6] Thomas Boyd, MD,[7] Jacques Delaunay,[8] David P. Steensma,[9] Mikkael A. Sekeres,[10] Odile Beyne-Rauzy[11],
Jun Zou[4], Kenneth Attie[12], Matthew L. Sherman[12], Pierre Fenaux[13], and Alan F. List[14]

[1]Moffitt Cancer Center, Tampa, FL; [2]University of Texas M.D. Anderson Cancer Center, Houston, TX; [3]Hôpital St Louis, Paris, France; [4]Celgene Corporation, Summit, NJ; [5]Institut Paoli Calmettes, Marseille, France; [6]Centre Henri Becquerel, Rouen, France; [7]North Star Lodge Cancer Center, Yakima, WA; [8]CHU de Nantes – Hôtel Dieu, Nantes, France; [9]Dana Farber Cancer Institute, Boston, MA; [10]Leukemia Program, Cleveland Clinic, Cleveland, OH; [11]Centre Hospitalier Universitaire Purpan Pavillion de Médecines, Toulouse, France; [12]Acceleron Pharma, Cambridge, MA; [13]Service d'Hématologie Séniors, Hôpital St Louis, Université Paris 7, Paris, France; [14]Malignant Hematology, Moffitt Cancer Center, Tampa, FL

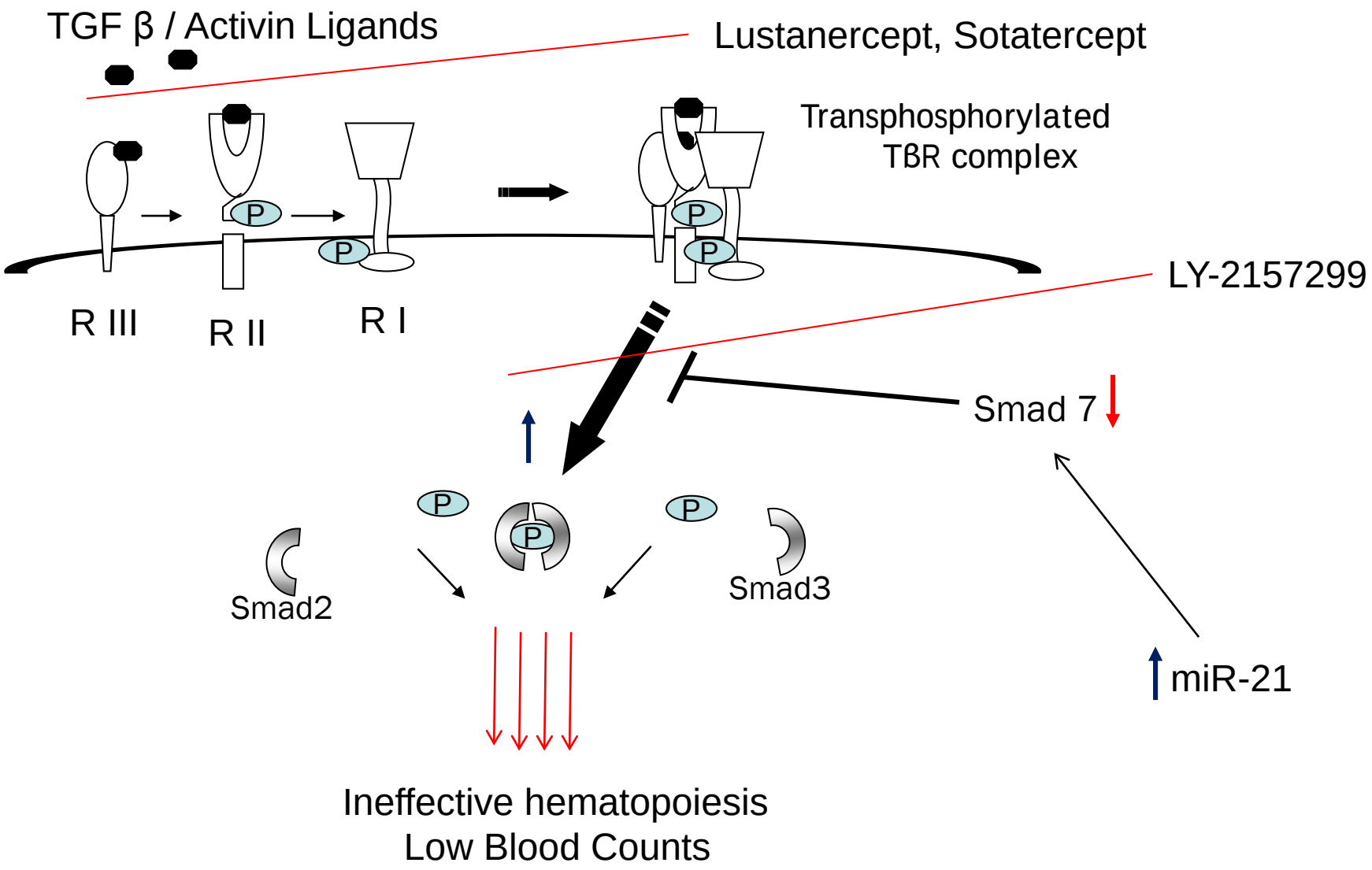
Komrokji R, et al. Blood. 2014;124:abstract 3251.

Results: efficacy in HTB patients

	Sotatercept dose cohort				Overall (N = 45)
	0.1 mg/kg (n = 7)	**0.3 mg/kg (n = 6)**	**0.5 mg/kg (n = 17)**	**1.0 mg/kg (n = 14)**	
Transfusion burden reduction ≥ 4 RBC units/8 weeks, n (%)	0	4 (66.7)	7 (41.2)	8 (57.1)	19 (42)
Duration of longest response, median (range), days	NA	67.5 (62–144)	150 (83–345)	87.5 (62–154)	106.0 (62–345+)
RBC-TI ≥ 56 days, n (%)	0	1 (16.7)	2 (11.8)	2 (14.3)	5 (11)

Komrokji R, et al. Blood. 2014;124:abstract 3251.

Conclusions: Pathogenesis of ineffective hematopoiesis



Conclusions

- SMAD2/3 pathway is overactivated in MDS HSPCs
- SMAD7 is a negative regulator of ALK4/5 and is decreased in MDS
- Luspatercept and Sotatercept show promising evidence of clinical activity in a cohort of lower-risk MDS patients who were anaemic and refractory to ESAs
- Lustanercept is being evaluated in a multicenter Phase III trial in RARS

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Epigenetics
John Greally

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EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

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Acceleron
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Eli Lilly
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