Akebia™ THERAPEUTICS

INVESTOR DAY | JUNE 2017

Forward Looking Statements

This presentation includes forward-looking statements. Such forward-looking statements include those about Akebia Therapeutics, Inc.'s strategy, future plans and prospects, including statements regarding the potential indications, dosing and benefits of vadadustat and Akebia's other product candidates, the development plans for vadadustat and Akebia's other product candidates, the potential filing of an IND for AKB-5169, the timing of the vadadustat Phase 3 program and other clinical studies, the potential commercialization of vadadustat if approved by the FDA, anticipated contributions from Otsuka and Mitsubishi Tanabe and the potential benefits of these collaborations, and potential business development opportunities. The words "anticipate," "appear," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement, including the risk that existing preclinical and clinical data may not be predictive of the results of ongoing or later clinical studies; the ability of Akebia to successfully complete the clinical development of vadadustat; the funding required to develop Akebia's product candidates and operate the company, and the actual expenses associated therewith; the actual costs incurred in the Phase 3 studies of vadadustat and the availability of financing to cover such costs; the timing and content of decisions made by the FDA and other regulatory authorities; the actual time it takes to prepare for and initiate clinical studies; the rate of enrollment in clinical studies of vadadustat; Akebia's ability to satisfy its obligations under its collaboration agreements; early termination of Akebia's collaboration agreements with Otsuka or Mitsubishi Tanabe or its Research and License Agreement with Janssen; the success of competitors in developing product candidates for diseases for which Akebia is currently developing its product candidates; Akebia's ability to negotiate commercially reasonable terms with third parties in future transactions; and Akebia's ability to obtain, maintain and enforce patent and other intellectual property protection for its product candidates. Other risks and uncertainties include those identified under the heading "Risk Factors" in Akebia's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, and other filings that Akebia may make with the Securities and Exchange Commission in the future. Akebia does not undertake, and specifically disclaims, any obligation to update any forward-looking statements contained in this presentation.

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Corporate Strategy

John P. Butler

President and Chief Executive Officer

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Vision

Build the Innovation-Driven, Renal Company, while Confirming the Therapeutic Value of the Hypoxia Inducible Factor (HIF) Pathway

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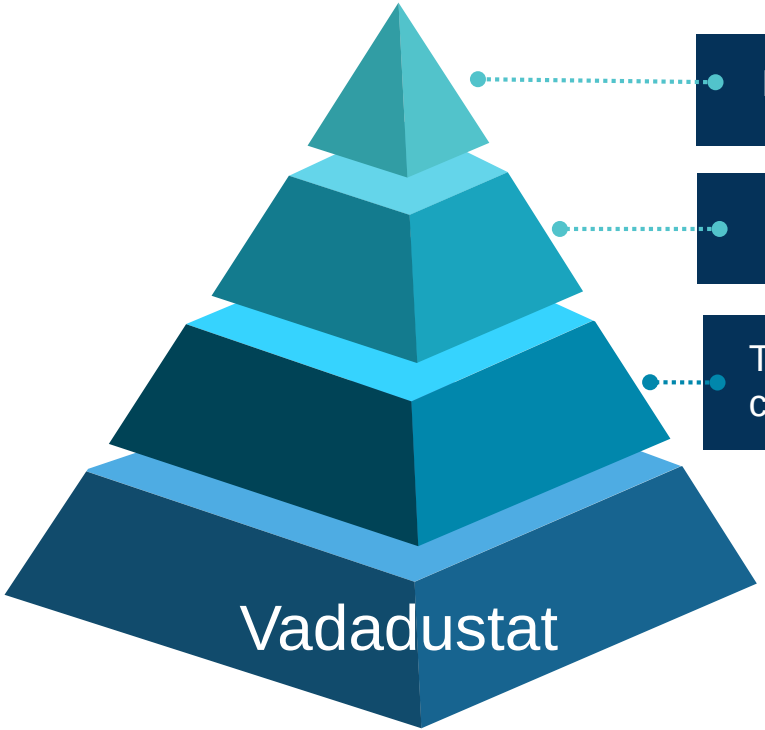
Vadadustat is Foundation of Our Vision

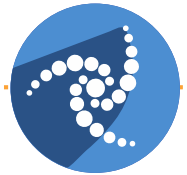


- Building the innovation-driven renal company
- Confirming therapeutic potential of HIF
- Transforming from development to commercial organization

Execution and Transformation

Development Program Financed while Retaining Significant Value

- Otsuka U.S.
- Otsuka E.U.
- Mitsubishi Tanabe
- Vifor Pharma



Commercial Readiness and Launch Acceleration

- Otsuka U.S.
- Vifor Pharma
- Intellectual property validation

HIF Pipeline Development

- Johnson & Johnson

Expanded and Strengthened Management Team

- Rita Jain, CMO
- Karen Tubridy, CDO
- Michael Rabinowitz, VP Research

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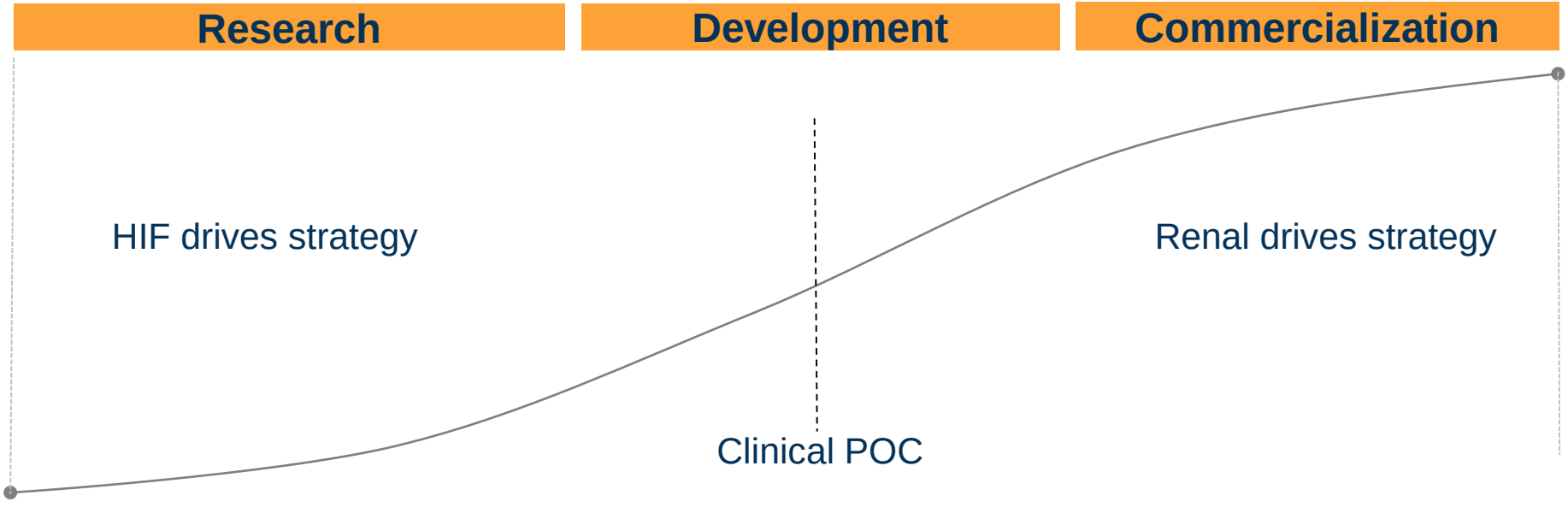
Clear Strategy Driven by Vadadustat Potential and Promise of HIF Pathway



Strategic shift from HIF to renal along the value chain

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Continuing to Transform the Company while Building Value

Execute on vadadustat Development Program

- Comparison with Standard of Care
- Single comparator globally
- Optimal data quality
- Single sponsor globally

HIF Pipeline Development

- AKB-5169
- Large compound library
- Clear target indication priorities

Business Development

- Renal disease
- Leveraging HIF

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Agenda

Maximizing Vadadustat Potential Through Value Enhancing Deals
Michel Dahan, Senior Vice President and Chief Business Officer

A Clinician's Perspective on Unmet Need in Renal Anemia
Geoffrey A. Block, M.D., Director of Research, Denver Nephrology

Vadadustat Clinical Program
Karen Tubridy, PharmD, Senior Vice President and Chief Development Officer

Targeting Hypoxia-dependent Pathways in Disease
Cormac Taylor B.Sc., Ph.D., Professor of Cellular Physiology,
University College Dublin, School of Medicine

Expanded Therapeutic Potential of HIF Stabilizers
Michael Rabinowitz, Ph.D., Vice President of Research

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THANK YOU

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Maximizing Vadadustat Potential Through Value Enhancing Deals

Michel Dahan
SVP, Chief Business Development Officer

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Our Strategic Goals

Maximize vadadustat potential and value

Build capabilities for commercial success and growth

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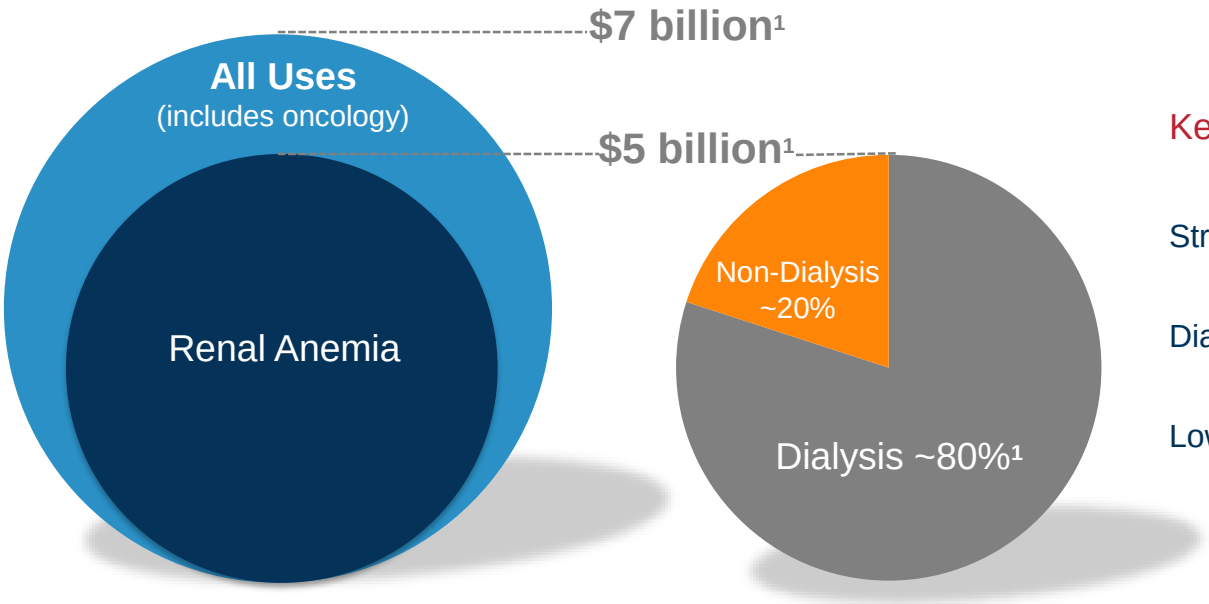
Current Global ESA Market Remains Large, with Most Use in Dialysis and Rising Prevalence of Chronic Kidney Disease Worldwide



Key Observations:

- Strong CKD prevalence increase
- Dialysis ESA use driven by hyporesponse[2]
- Low treatment rate in Non-Dialysis

[1]Sources ESA sales 2015: audited sales data for total ESA sales by regions, DRG report for Renal vs Oncology use, and disclosed LDOs budget with market research for NDD vs DD split
[2][DaVita/Akebia paper reference, AJKD]

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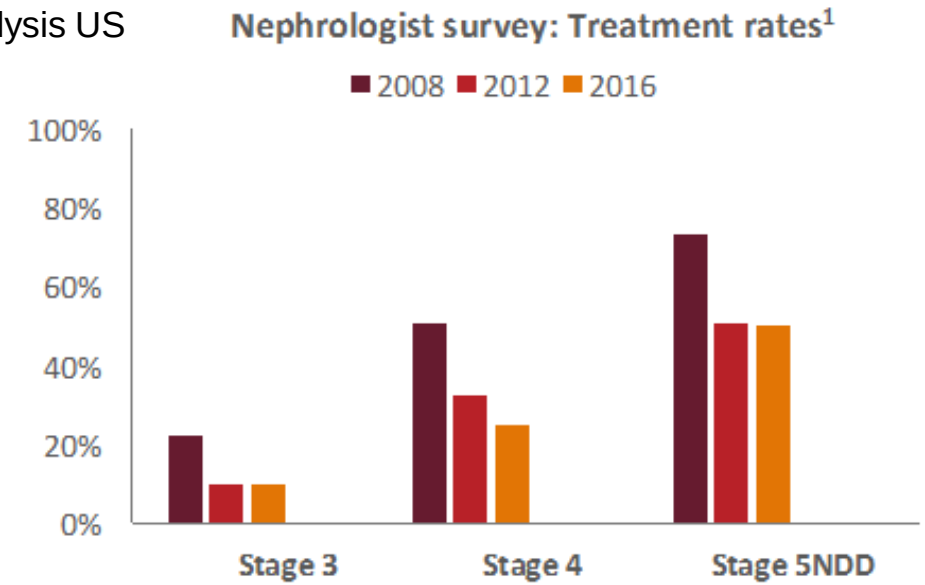
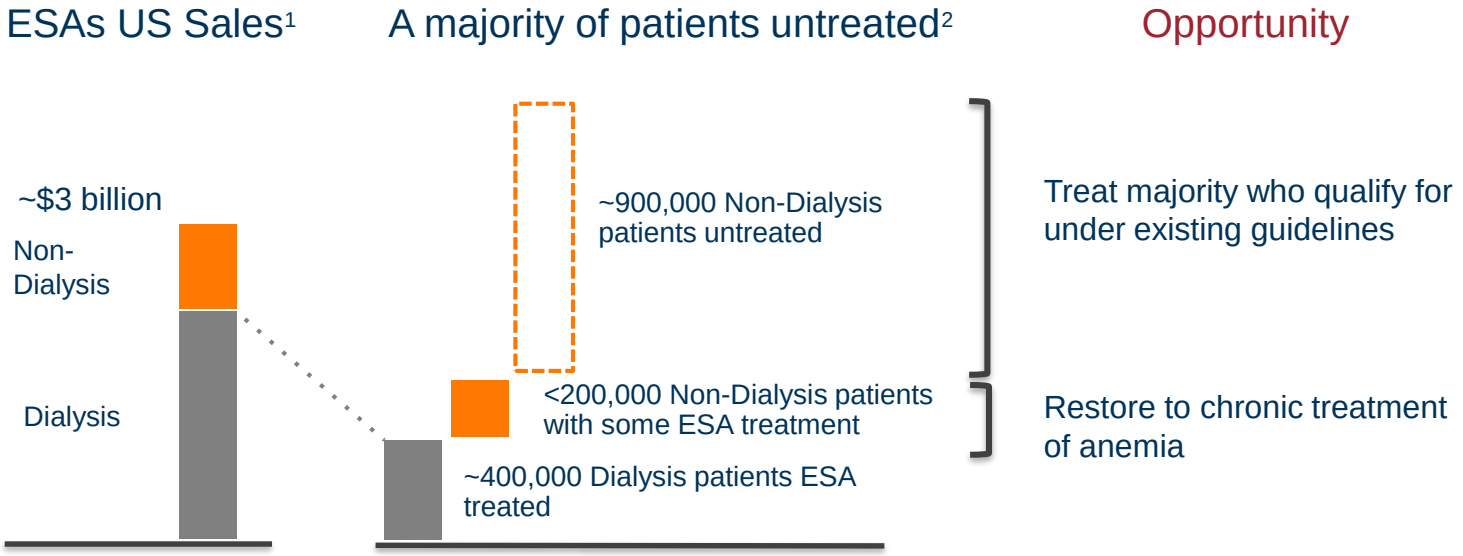
Major Opportunity to Restore and Potentially Exceed Treatment Rates as They Existed Before Impact of CV Safety Concerns with ESAs

Non-Dialysis US



[1]Akebia primary market research, internal analysis of chart-based nephrologists surveys (Decision Resources ChartTrends Renal Anemia in ND-CKD, 2014, Decision Resources ChartTrends Nephrology in Dialysis, 2015), and management assumptions

Major Growth Opportunity for the HIF Class in Non-Dialysis: Increase Number of Patients Treated Chronically



[1]Sources ESA sales 2015: audited sales data for total ESA sales by regions, DRG report for Renal vs Oncology use, and disclosed LDOs budget with market research for NDD vs DD split
[2]US Census Bureau; NHANES 2009-2014; McFarlane, Am J Kidney Disease 2008. Note anemia defined as Hb<13g/dL for men and <12g/dL for women; Market Research and Akebia estimates

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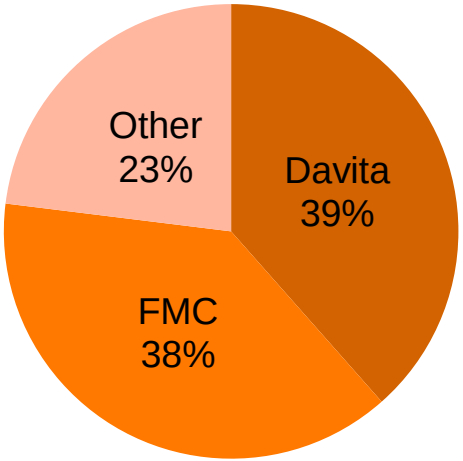
Major Opportunity for Rapid Adoption in Dialysis Globally with Additional Growth Potential in Emerging Markets

Key Dynamics	Implications	Opportunity
Bundle reimbursement creates margin pressure for LDOs[1]	Treatment protocols strongly influenced by LDOs	Rapid adoption opportunity leveraging access to LDOs
Hyporesponse associated with high ESA use and poor outcomes	Improve hyporesponders outcomes and managing costs	
Growing access to dialysis procedure in emerging markets	Importance of oral option without need for cold supply chain	Growth potential in emerging markets

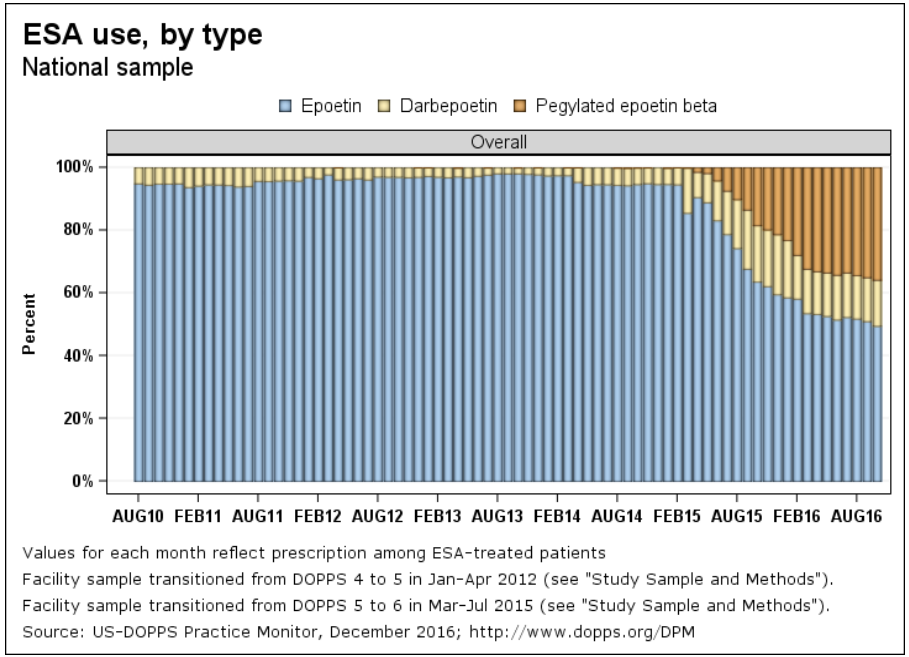
[1] Large Dialysis Organizations

Strong Potential for Rapid Adoption Driven by Access to Large Dialysis Organizations and their Influence on Treatment Protocols

US Dialysis Market (2016)[1,2]



Mircera uptake illustrates opportunity for rapid adoption following protocol update



[1]FMC and Davita reported dialysis patients.
[2]USRDS ESRD Prevalence.

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Vadadustat Target Product Profile Studied in Phase 3 Seeks to Address Key Unmet Needs and Establish the New Standard of Care

KEY GOALS

Improve Hgb[1] response	• Less Hgb variability with clear titration • Efficacy in hyporesponders • Lower risk of RBC[2] transfusions
Improve safety profile	• Cardio-Vascular events • Hypertension and vascular access complications • No drug-drug interactions with common non-CKD meds (e.g. statins)
Improve convenience and cost-effectiveness	• Oral, QD in Non-Dialysis, QD and TIW in Dialysis (PD and HD)[3] • No impact of timing for dialysis procedure • I.V. iron sparing

[1] Hemoglobin
[2] Red Blood Cells
[3] QD = Once a Day, TIW = Three Times per Week, PD = Peritoneal Dialysis, HD = Hemodialysis

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Vadadustat Strong Potential to Establish New Standard of Care for Renal Anemia

COMMERCIAL POTENTIAL

Major Opportunity for Growth in Non-Dialysis

Major Opportunity for Rapid Adoption in Dialysis

KEY VALUE DRIVERS

- Create strong value proposition in time for launch
- Secure required capital and retain high asset value
- Create optimal commercial setup for launch globally
- Secure access and accelerate commercial uptake in dialysis

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Strong Value Proposition in Time for Launch will be Established Through Optimally Designed Phase 3 Program

Create Strong Value Proposition in time for Launch

Optimal design for CVOT[1] and safety assessment

- Comparison with current Standard of Care
- Optimal data quality
- Single comparator globally
- Single sponsor globally

Optimal design to show stable and sustained efficacy

- Hgb response over time
- Hyporesponse in Phase 3
- Specific study in hyporesponse patients

Optimal package to show convenience for patients and HCP[2]

- Three-times weekly and once daily
- Drug-drug interaction studies
- Conversion studies

[1] Cardio-Vascular Outcome Trial
[2] Healthcare Professionals

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Required Capital for Vadadustat Phase 3 Program and Retention of High Asset Value Achieved

Secure Required Capital and Retain High Asset value

Company funded to Phase 3 data minimizing dilution

- $623M in committed capital[1]
- Additional funding above defined R&D cost threshold

Retaining high share of asset value

- 50% of profits in U.S. market
- High double-digit royalties up to 20% in Japan, 30% in E.U.
- ~$1.7B in development and commercial milestones

Retaining key decision making for vadadustat

- R&D final decision making with limited exceptions
- Pricing final decision making in U.S.
- Global brand plan
- Full rights in Latin America

Mitsubishi Tanabe

Otsuka

VIFOR PHARMA

[1]Includes recent Vifor equity investment of $50 million

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Optimal Commercial Setup for Launch Secured Globally Through Partners with Strong Infrastructure and Portfolio in Renal

Create optimal commercial setup for launch globally

50-50 Profit Split agreement in U.S.

- Enable focus on core capabilities building
- Access to Otsuka strong infrastructure (1,000 reps)
- Costs sharing allows optimal investment at launch

Partners with strong capabilities in E.U. & Japan

- Strong renal portfolio fit for MTPC (Japan) and Otsuka (E.U.)
- Strong market access and KOL relationships
- Established field force in key markets

Additional value from international markets

- Strong R&D and commercial presence in China (Otsuka)
- Commercial presence in all major markets
- Optionality for expansion or further partnering in LatAm

Mitsubishi Tanabe

Otsuka

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Access to Dialysis Market Secured through Vifor Pharma Deal, with Potential for Accelerated Commercial Uptake following Approval

Secure access and accelerate commercial uptake in Dialysis

Applicable upon inclusion in the bundle

- HIF class in bundle as base case. If not, Akebia retains all rights
- Joint Venture between Vifor-FMC
- Vadadustat is exclusive HIF to Vifor for supply to FMC

Enable rapid commercial uptake following approval

- Optimal setting for pilot studies and protocol optimization
- Subject to FMC decision to source HIF supply from their JV
- Facilitate adoption in appropriate Non-Dialysis patients following approval

Strong economics

- $50M equity investment at a premium
- $20M milestone following approval and inclusion in bundle
- Majority of profit on sales retained by Akebia and Otsuka

VIFOR PHARMA

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Strong Foundations are Established…

KEY VALUE DRIVERS

- Create Strong Value Proposition in time for Launch ✓
- Secure Required Capital and Retain High Asset value ✓
- Create optimal commercial setup for launch globally ✓
- Secure access and accelerate commercial uptake in Dialysis ✓

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What's Next? Grow Late Stage Pipeline and Expand Portfolio in HIF Biology

Build unique position in promising HIF areas

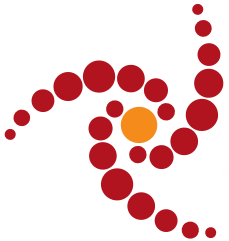
- GI inflammation promising area for new HIF-based Standard of Care
- Portfolio deals similar to license with Johnson & Johnson

Leverage our core capabilities

- Expand renal pipeline as vadadustat Phase 3 progresses
- Priority given to capability-enhancing opportunities

The Innovation Renal Company leveraging HIF pathway

- Accelerate shift to improved all oral treatment paradigm
- Build HIF portfolio of choice as clinical and regulatory validation occurs



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ANEMIA OF CKD

A Clinician’s Perspective on Unmet Need in Renal Anemia

Geoffrey A Block, M.D.,
Director of Clinical Research, Denver Nephrology

Anemia has a Significant Negative Impact on Patients' Quality of Life, in Addition to Clinical and Economic Implications

Clinical Burden

- Congestive heart failure
- Left ventricular hypertrophy
- Progression to renal replacement
- Mortality

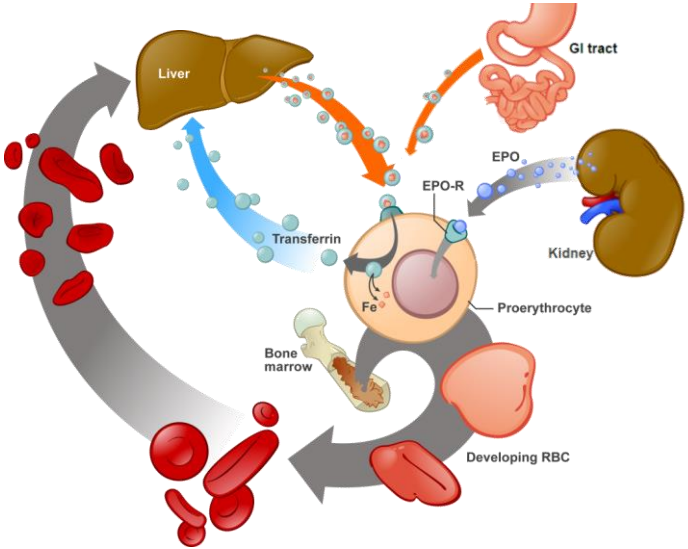
Patient Burden

- Severe fatigue
- Cognitive deficits
- Depression
- Ability to work

Economic burden

- More hospitalization
- Cost of therapy (primarily ESAs)
- Indirect costs (lost workdays, reduced productivity, disability payments) for patient & caregiver

Mechanism

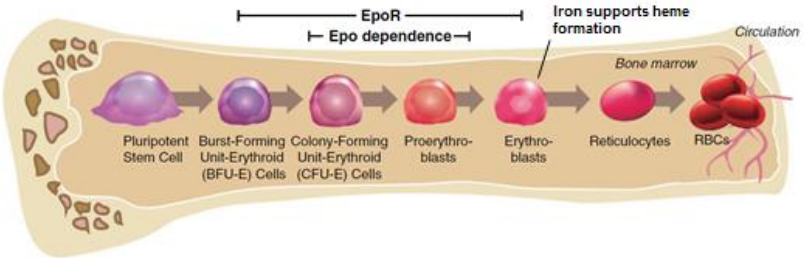


Circulating iron comes from dietary and internal sources[4-7]

- RBCs contain ~80% of the body's iron
- Iron essential for Hb synthesis
- Majority of circulating iron comes from senescent RBCs phagocytized by macrophages in the liver spleen and bone marrow

Erythropoiesis – Coordinated Production

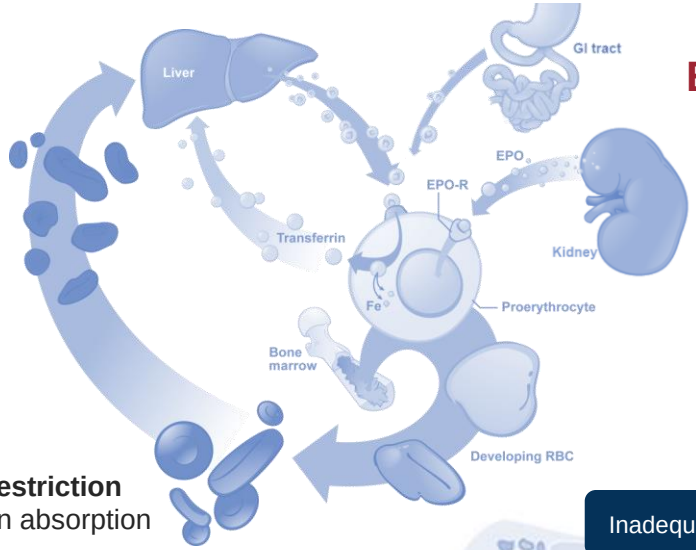
- Kidneys responsible for ~90% of EPO production[1-4]
  - EPO supports maturation and differentiation of RBC precursors – binding of EPO to EPO receptor activates antiapoptosis and proliferative pathways[1-4]
  - Iron is an essential element of heme in hemoglobin[1]



1. Hodges VM, et al. *Crit Rev Oncol Hematol.* 2007;64(2):139-158. 2. Babitt JL, et al. *Am J Kidney Dis.* 2010;55(4):726-741. 3. Elliott S, et al. *Ann Hematol.* 2014;93(2):181-192. 4. Kalantar-Zadeh K, et al. *Adv Chronic Kidney Dis.* 2009;16(2):143-151. 5. Koury MJ, et al. *Annu Rev Nutr.* 2004;24:105-131. 6. Knutson MD, et al. *Proc Natl Acad Sci U S A.* 2005;102(5):1324-1328.

Mechanism Perturbations in Chronic Kidney Disease

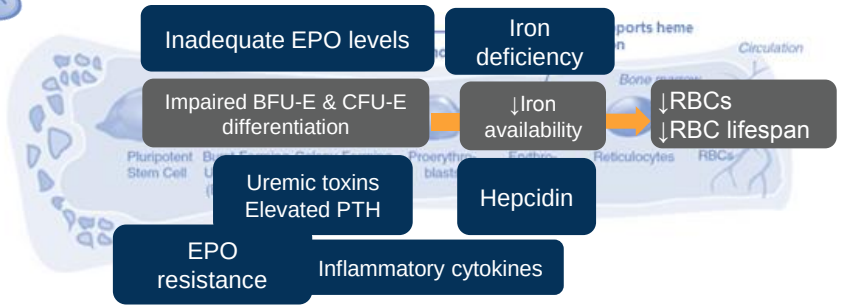
Inadequate EPO production
- Peritubular cells that produce EPO may be partially or completely depleted or injured as renal disease progresses
- EPO production is inappropriately low relative to degree of anemia



Erythropoiesis in CKD

Inflammation
- ESA resistance
- ↑Hepcidin by liver, which impairs iron absorption and promotes iron sequestration away from bone marrow

Iron deficiency and restriction
- Impaired dietary iron absorption
- Blood loss
- Diminished iron transport and inability to release stored iron from macrophages and hepatocytes



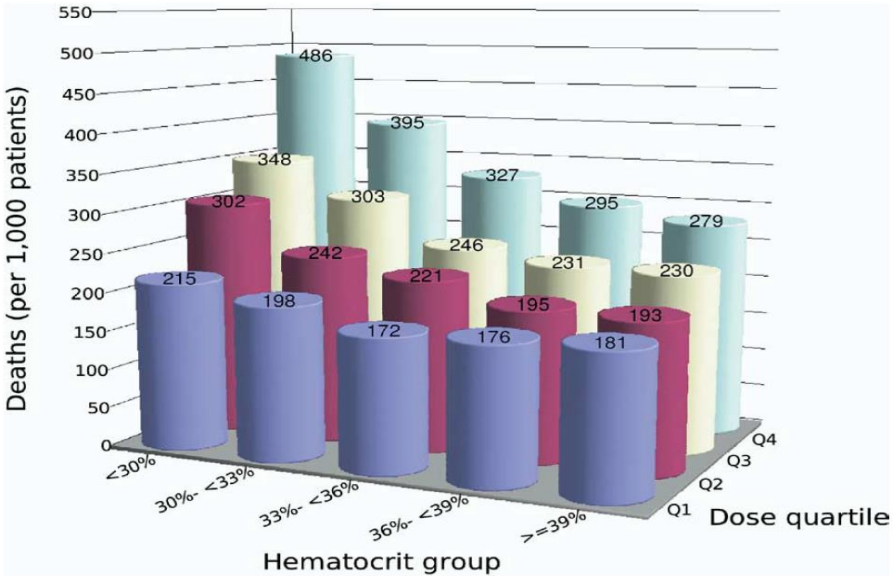
Anemia of Chronic Kidney Disease

Relationship between ESA dose and Risk:
Retrospective Cohort Study of 94,569
Prevalent Hemodialysis Patients

USRDS, 2000-2001*
EPO-Analogue Dose and Risk

EPO-analogue dose

Q1 1388–7905 U/wk	Q2 7906–13,377 U/wk
Q3 13,378–22,068 U/wk	Q4 >22,068 U/wk

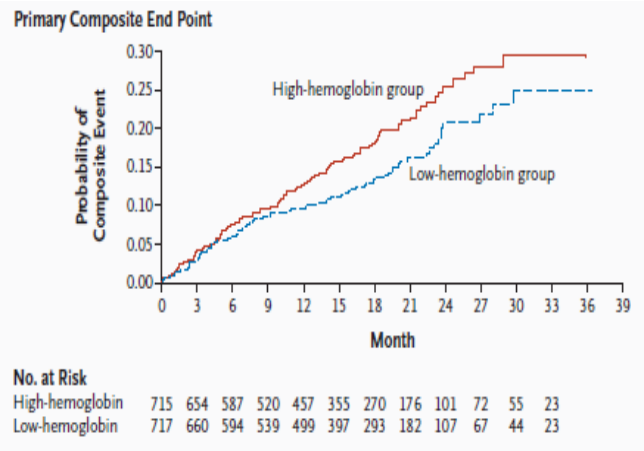


Zhang Y, et al. *Am J Kidney Dis.* 2004;44(5):866-876.

*US Renal Data System Administrative claims data, 2000 and 2001

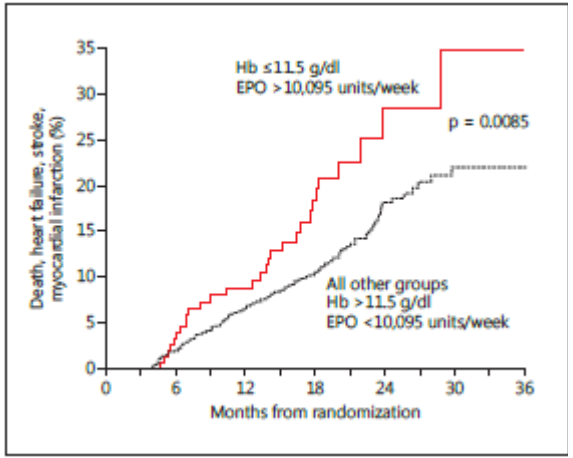
Hb Targets Lowered Based on Increased CV Risk in TREAT & CHOIR, but Newer Data Suggest CV Risk may be Correlated to EPO, not Hb

CHOIR: High vs low Hb target



- CHOIR evaluated epoetin dosed to Hb 13.5g/dL vs 11.3g/dL in NDD-CKD patients, and showed increased risk of CV events in the 13.5g/dL arm[1]
- TREAT evaluated darbepoetin dosed to Hb 13g/dL vs placebo with darbepoetin rescue at Hb<9g/dL, and showed an increased risk of stroke in the darbepoetin 13g/dL arm[2]

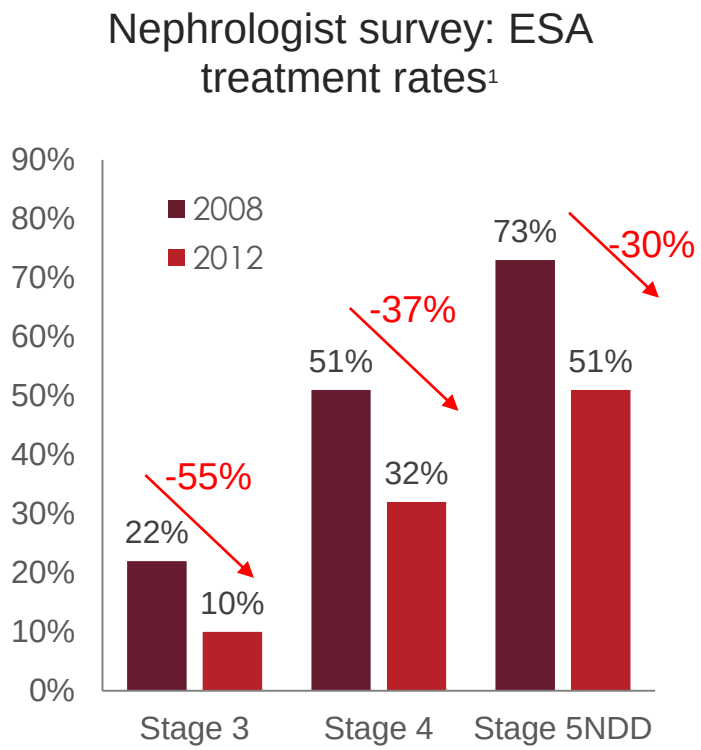
CHOIR: High vs low dose epoetin

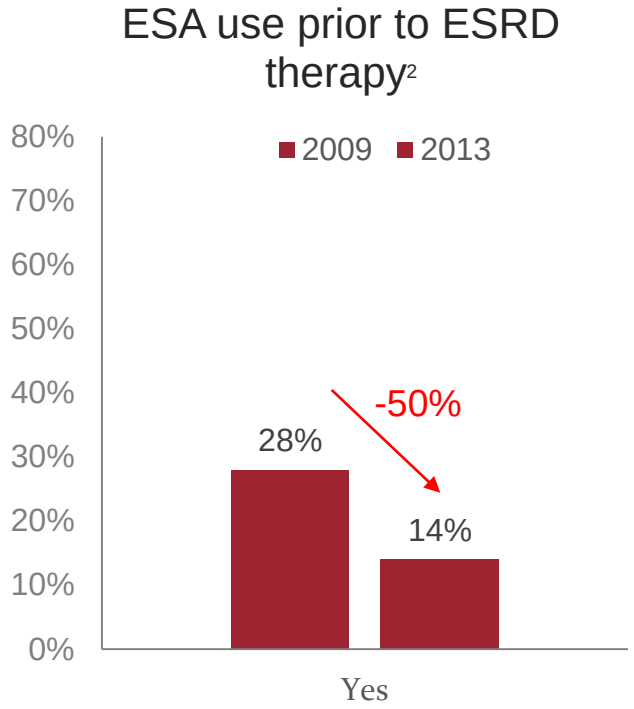


- Post hoc analysis of CHOIR showed that higher doses of epoetin were associated with increased CV risks rather than higher Hb levels[3]
- Patients in the middle Hb tertile (>11.5 to <12.7 g/dl) and the lowest epoetin tertile (<5,164 units/week) had lowest risk of CV events[3]

[1]Singh, NEJM 2006.
[2]Pfeffer, NEJM 2009.
[3]McCullough, Am J Nephrology 2013

ESA Treatment Rate in Non-dialysis Patients has Decreased by Approximately Half following Kidney Disease Guideline Updates*



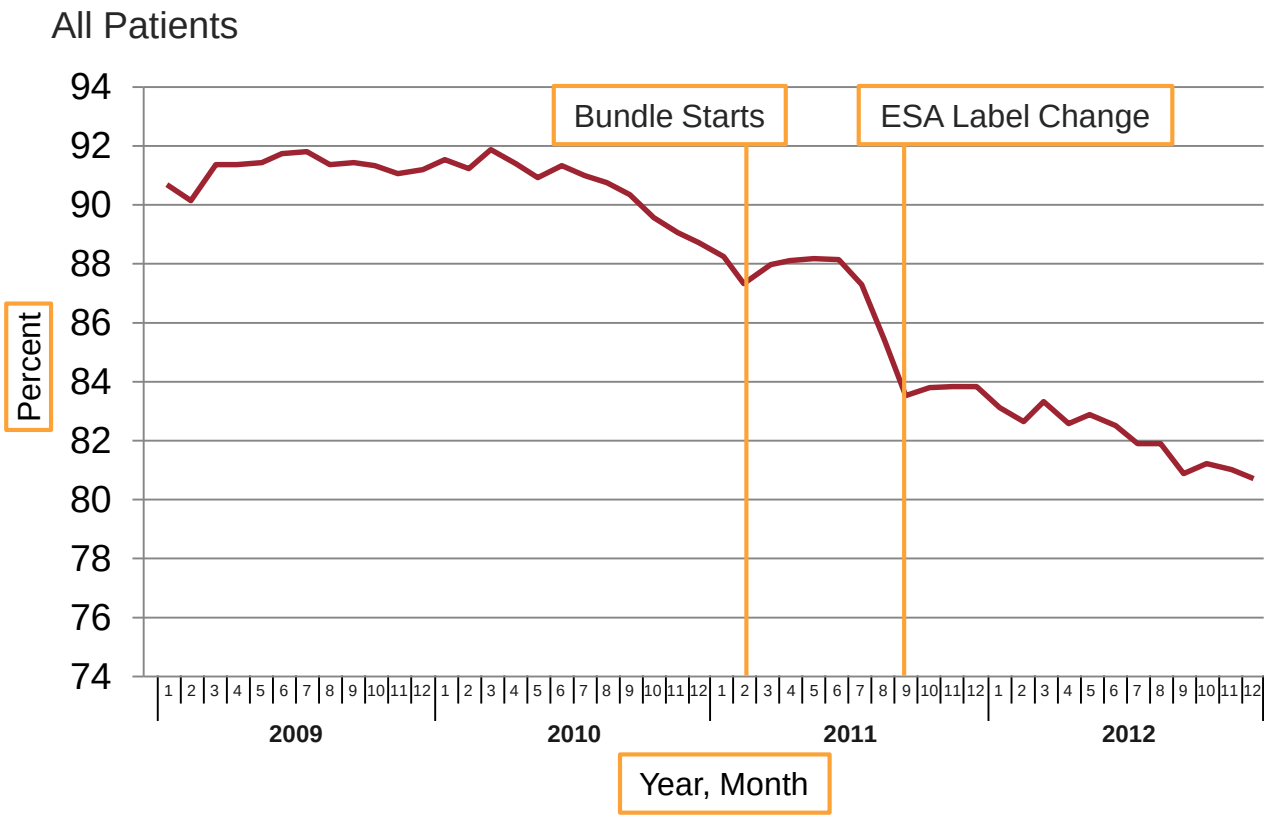


*Kidney Disease - Improving Global Outcomes (KDIGO)

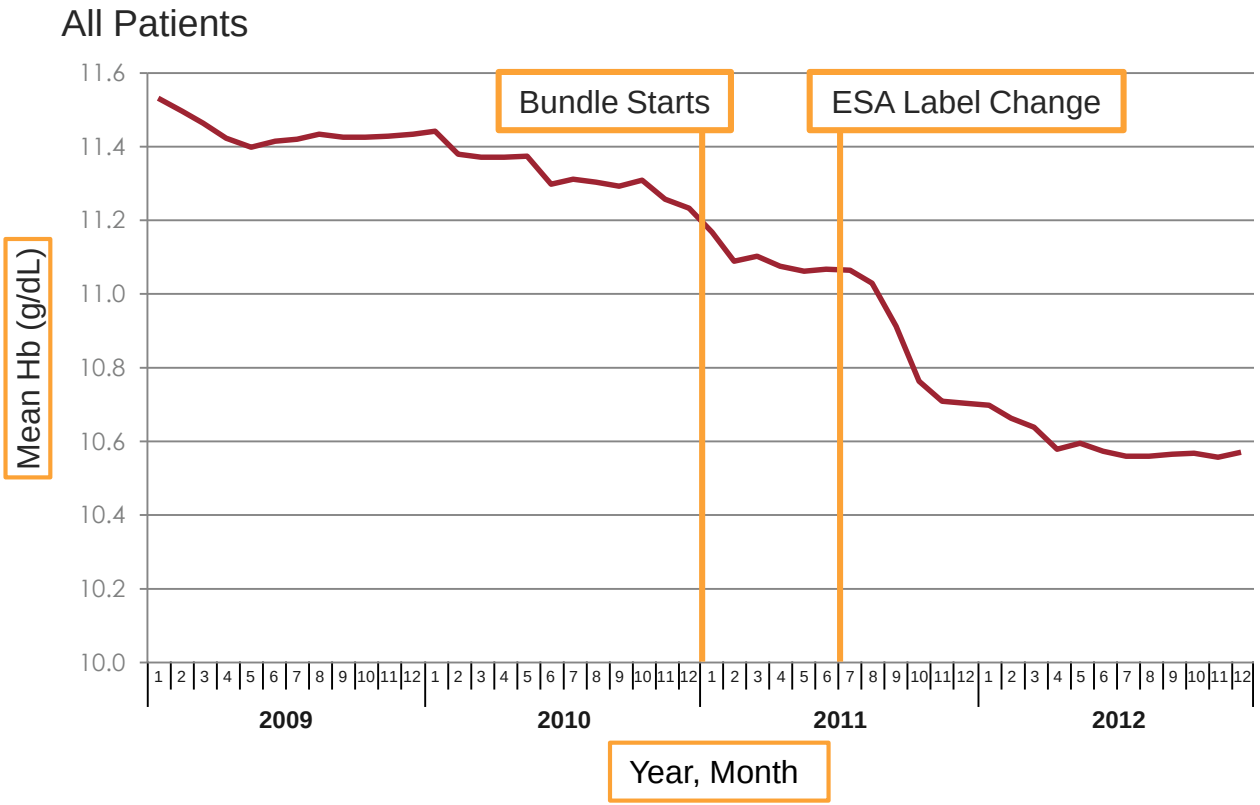
[1] Decision Resources, ChartTrends Renal Anemia in ND-CKD (2014). Note use of ESAs is likely overestimated due to nephrologist survey sample.

[2] USRDS Patient Characteristics (ESA use prior to ESRD therapy/incident patients with completed Medical Evidence forms)

Percentage of Dialysis Patients with ESA Use

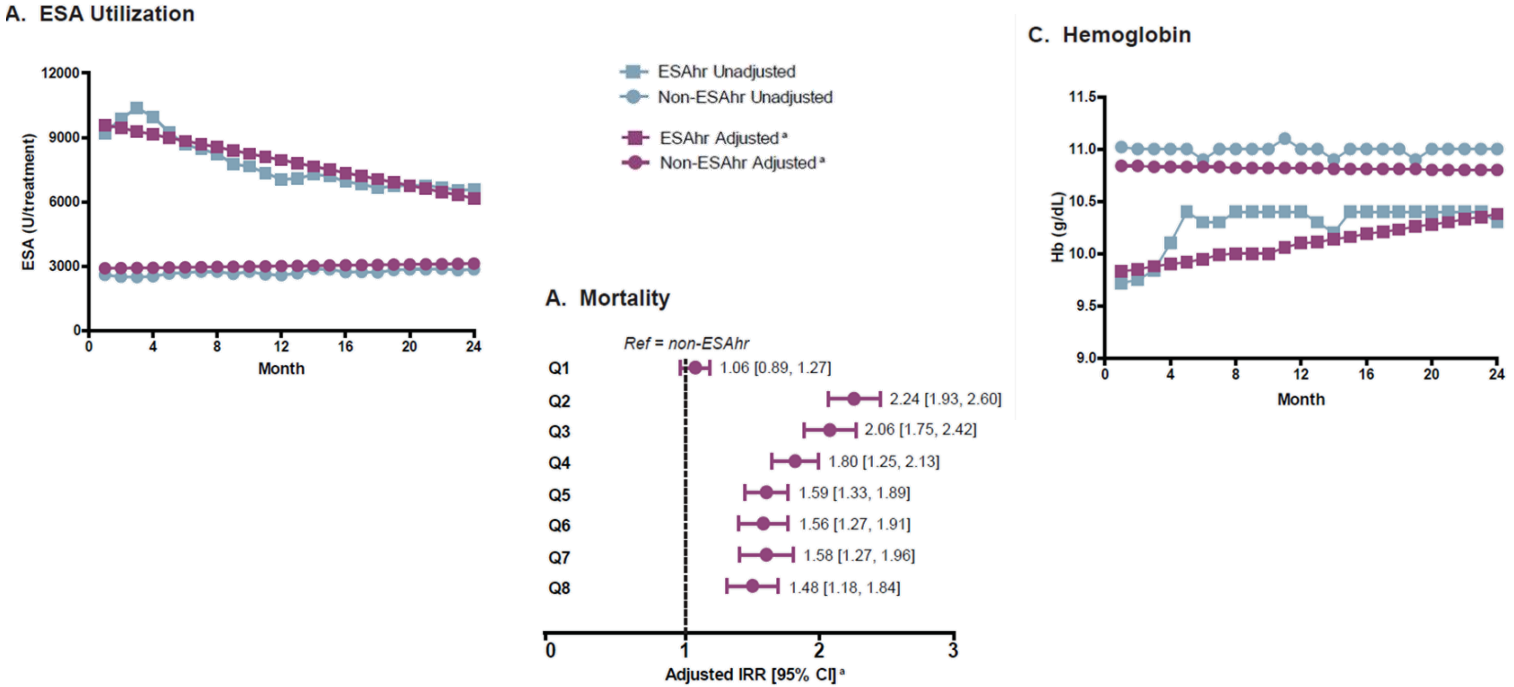


Mean Monthly Hb Among ESA Users



Hyporesponders Comprise 10-15% (Depending on Definition) of a Dialysis Patient Sample Set within the DaVita Network (N=103,357)

Approximately 10-15% of CKD-DD patients do not respond optimally to ESA treatment and are unable to achieve the targeted Hb concentration or require high ESA doses to do so

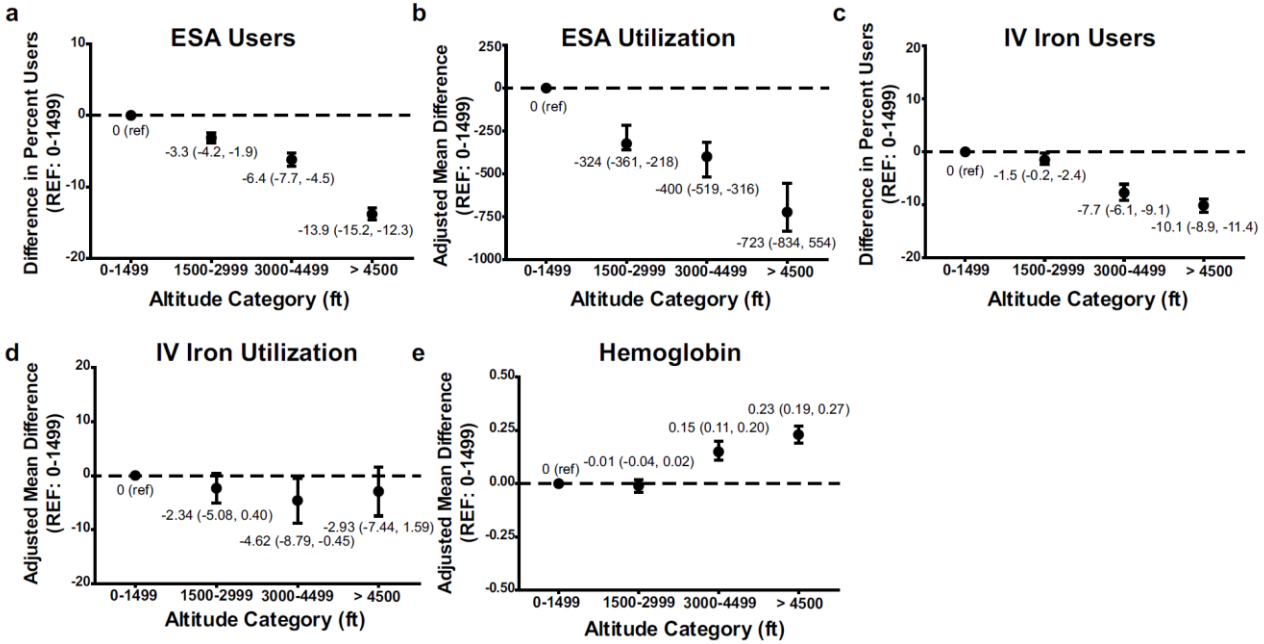


Jiacong, L et al. Spectrum and Burden of Erythropoiesis-Stimulating Agent Hyporesponsiveness Among Contemporary Hemodialysis Patients. AJKD 2016

Anemia of CKD
Unmet Needs: My Perspective

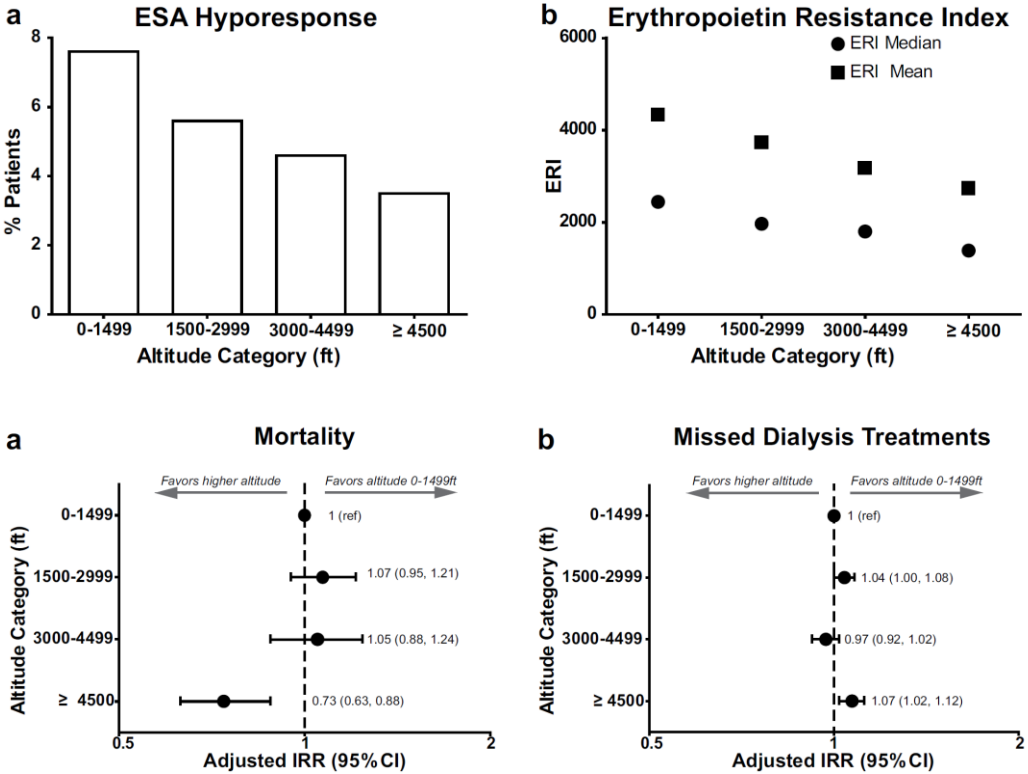
- Anemia is multifaceted – it is not just EPO deficiency
- Goal is to treat anemia without increasing risk of adverse events – especially events that REALLY matter to patients (e.g. Cerebral Vascular Accidents [CVA])
- There are comorbidities associated with inadequately treated anemia – how can we improve patient QOL?
  - Is waiting for a 30% drop in Hb really optimal?
- Can we improve dosing convenience for NDD-CKD patients? Oral and parenteral options?
- How can we address the subpopulation with Functional Iron Deficiency (FID) with or without epo-resistance?
- Can we reduce dependence on intravenous iron (NDD- and DD-CKD)?
- How can we ascertain definitively whether targeting normal Hb is associated with harms related to ESA dose/route or Hb itself?

Effect of Altitude on Anemia, ESA Use, Iron Use and Mortality



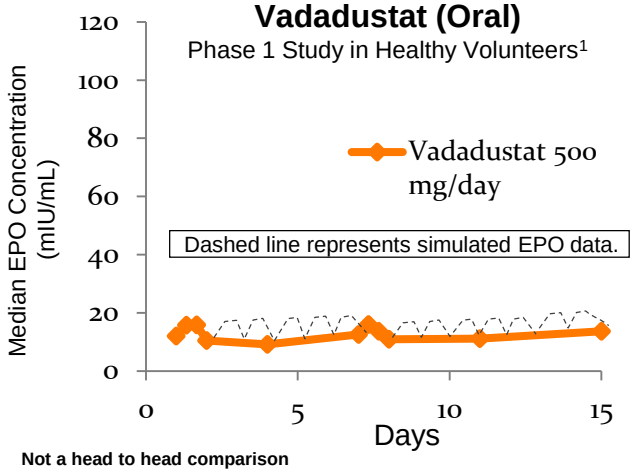
Sibbel, J Neph 2016

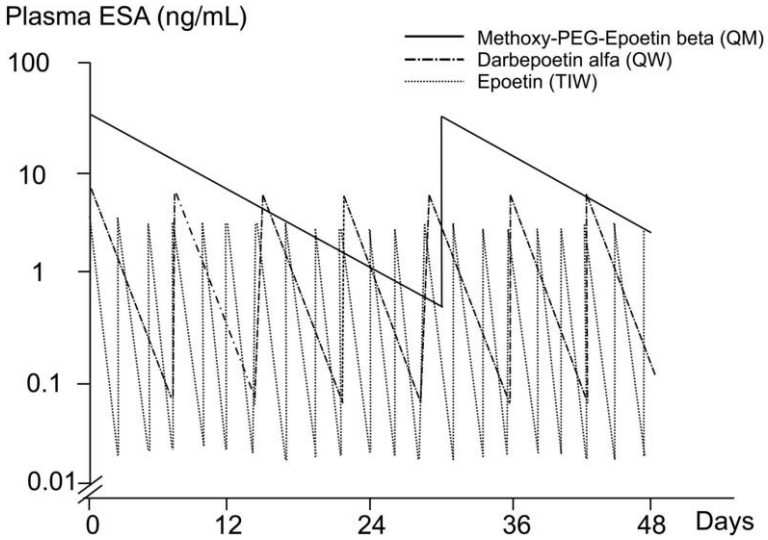
Effect of Altitude on Anemia, ESA Use, Iron Use and Mortality



Sibbel, J Neph 2016

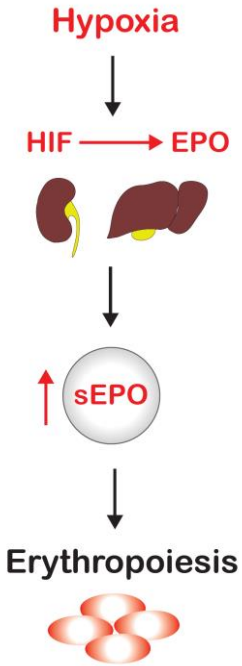
Vadadustat Maintained Physiologic Erythropoietin (EPO) Profile





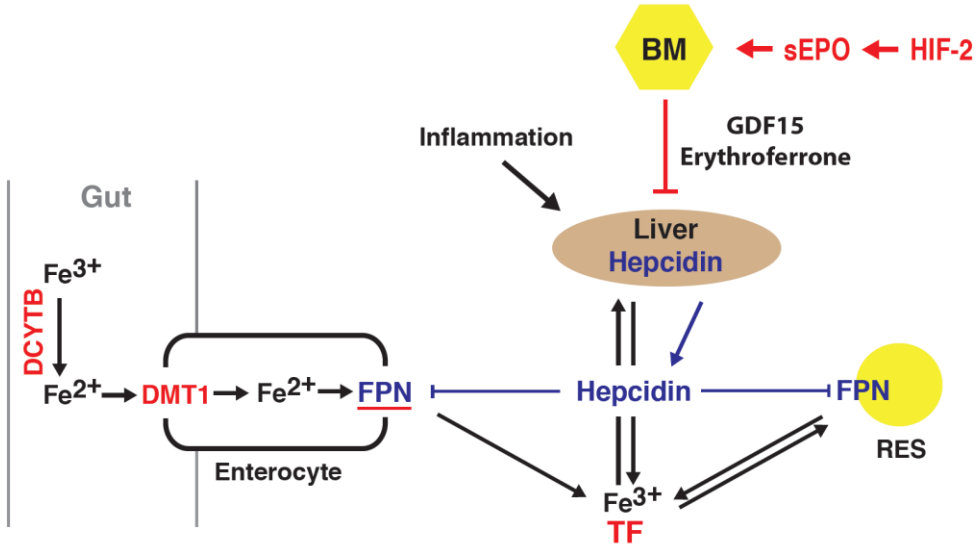
1. Akebia Therapeutics, Inc. Data on File (2010). Data from Phase 1 study in healthy volunteers with vadadustat once daily dosing. Pre-dose EPO concentrations evaluated on Days 1, 4, 7, 11, 15 and 22. Post-dose data to assess acute rise in EPO following vadadustat dosing completed on Day 1 and Day 7 (8 and 16 hours post-dose). Dashed line represents estimated EPO levels based on post-dose data from Day 1 and Day 7.
2. Doshi S et al. Journal of Clinical Pharmacology, 2010;50:75S-90S. Original figure redrawn to depict darbepoetin alfa serum concentration (ng/mL/(mcg/kg)) converted to mIU/mL. Data from 6 clinical studies conducted with extensive PK sampling in NDD-CKD patients following subcutaneous (SC) administration of a single dose or first dose of a monthly dosing regimen ranging from 0.4-0.6mcg/kg, dose normalized to 0.45 mcg/kg.

HIF Controls the Hypoxic Induction of EPO



VH Haase, unpublished

HIF in Iron Metabolism



Haase VH; Hemodialysis International, 2017

HIF-Prolyl Hydroxylase Inhibition: Beyond Erythropoiesis, What To Look For…..

- VEGF
- Metabolic effects (glucose, cholesterol, fat metabolism, uric acid, FGF-23)
- Pulmonary artery pressures
- Systemic blood pressure
- Effects on kidney disease progression
- Liver toxicity
- Pro-oncogenic potential

HIF-Prolyl Hydroxylase Inhibition Overview of Compounds

Table 1: HIF-PHIs in clinical development for the treatment of anemia

Compound	Ref	Development status	HIF-α stabilization	HIF-PHD targets
AKB-6548 (Vadadustat) Akebia Therapeutics	86, 99, 100	Phase 3	HIF-2α > HIF-1α	PHD3 > PHD2
GSK-1278863 (Daprodustat) GlaxoSmithKline	81, 95, 115, 128	Phase 3	HIF-1α and HIF-2α	PHD2 and PHD3
FG-4592 (Roxadustat) Fibrogen/Astellas Pharma/ AstraZeneca	82-85	Phase 3	HIF-1α and HIF-2α	PHD1, 2 and 3
BAY 85-3934 (Molidustat) Bayer Pharma	88, 101, 102	Phase 2	HIF-1α and HIF-2α	PHD2 > PHD1/PHD3
JTZ-951 Japan Tabacco, Inc. / Akros Pharma, Inc.	89	Phase 2	not published	not published
Zyan1 Cadila Healthcare	91, 92	Phase 1	not published	not published
JNJ-42905343 Janssen Pharmaceutica	90	pre-clinical	HIF-1α and HIF-2α	PHD1, 2 and 3
DS-1093 Daiichi Sankyo, Inc.	-	discontinued for anemia under evaluation for other indications	not published	not published

The above table is based on a review of the literature and other publicly available resources such as patent applications. A direct comparison of half maximal inhibitory concentrations (IC50) of various compounds for HIF-PHDs, FIH and other dioxygenases has not yet been published.

Haase V.H.; Hemodialysis International, 2017

HIF-Prolyl Hydroxylase Inhibition: Summary

- Clinical studies to date suggest that HIF-PH inhibitors may be effective in stimulating erythropoiesis and in treating anemia
- Possible effects beyond erythropoiesis are being investigated (e.g., lipid metabolism)
- The effects on CKD progression are not known
- Ongoing trials will further evaluate efficacy and safety of these molecules as a potential treatment option for anemia associated with CKD

Personal Thoughts on Potential Utility of HIF-PHI in CKD

- There is a significant unmet need related to anemia in CKD
  - Current Rx patterns are driven by risks and not by ‘need’ or the perceived benefit
  - Historical data on ESA use and achieved Hb are better indicators of need

- An alternative to ESA designed to mimic normal physiology might ultimately allow for treating anemia earlier and with less need for exogenous iron (coordinated response)

Personal Thoughts on Potential Utility of HIF-PHI in CKD (Cont'd)

- Mechanism and the data supporting the potential clinical benefit of altitude/ HIF-biology is important:
  - PK differences in EPO will matter to clinicians
  - Route of administration matters to patients

- Modest rise in EPO is BETTER!
  - Clinicians will be more comfortable with a molecule that does not exaggerate non-anemia effects as it suggest less PAN-HIF stabilization

- Ability to effectively treat inflamed patients, including those with high Erythropoietin Resistance Index (ERI) could be a substantial benefit

Thank you

Vadadustat Clinical Program

Karen Tubridy, PharmD
Senior Vice President and Chief Development Officer

Akebia™ THERAPEUTICS

Vadadustat Global Program Strategy: Setting a New Standard of Care in Treatment of Renal Anemia

- Optimal trial designs maximize probability of success and allow for analysis of data across studies
- Align with the regulatory pathway for approval in major geographies
- Address anemia of CKD in dialysis and non-dialysis patients including high risk hyporesponder patients
- Utilize a long-acting ESA comparator
- Address several dosing regimens (QD and TIW)
- Key drug-drug interaction (DDI) studies

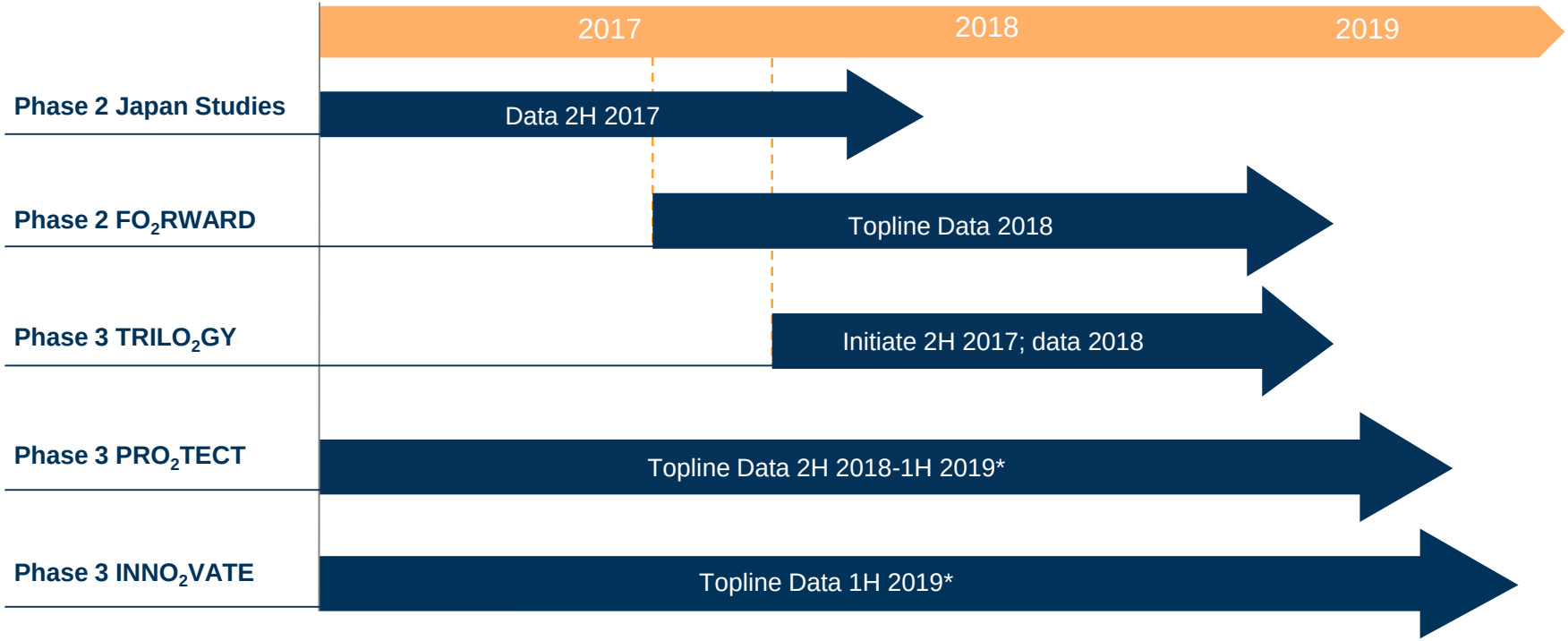
15 Phase 1 and Phase 2 Trials Provided a Strong Foundation for Vadadustat Phase 3 Program

Study	Design
Phase 1	Single and multiple dose, dose escalation studies, PK, mass balance, thorough QT, and DDI studies
Phase 2a	Double-blind Randomized Placebo-controlled, 4 dose groups, 6 weeks dosing
Phase 2b Non-Dialysis	Double-blind Randomized (2:1) Placebo-controlled, Dosing algorithm 20 weeks dosing
Phase 2 Dialysis	Open-Label, multicenter, 3 dosing cohorts (Daily 300mg & 450mg; and 450mg three times per week)

Evaluated safety, PK, dose levels, frequency, and effect on hemoglobin

Akebia™ THERAPEUTICS

Vadadustat Global Clinical Program



*Timeline dependent on major adverse cardiovascular events (MACE) endpoint.

Akebia THERAPEUTICS

Global Clinical Program Assessments

Demonstrate effect on Hgb & Iron	• Assessing Hgb in the target range over time • RBC transfusions and I.V. iron requirements • ESA rescue
Dosing and PK Profile	• Dosing regimens (QD, TIW) • Evaluating range of vadadustat doses
Characterize Safety Profile	• MACE rate • Thromboembolic events • Heart failure • Drug-drug interactions
Other Assessments	• Number of hospitalizations • Rate of CKD progression • Biomarkers

Akebia™ THERAPEUTICS

Randomized, Open-Label, Active-Controlled, Non-Inferiority Phase 3 Cardiovascular Outcomes Studies

Non-dialysis dependent (NDD)
N = 3700

PROTECT CORRECTION
Rx Naïve

Vadadustat vs Darbepoetin Alfa

PROTECT CONVERSION
Rx with ESAs

Vadadustat vs Darbepoetin Alfa

Dialysis dependent (DD)
N = 2600

INNOVATE CORRECTION
Rx Naïve

Vadadustat vs Darbepoetin Alfa

INNOVATE CONVERSION
Rx with ESAs

Vadadustat vs Darbepoetin Alfa

Primary Efficacy Endpoint: Change in hemoglobin (Hgb) from baseline
Primary Safety Endpoint: Major Adverse Cardiovascular Events (MACE)

Allows for Superiority Assessments of Key Endpoints

Akebia THERAPEUTICS

Additional Vadadustat Global Program Studies in Dialysis

FO_2RWARD Trial – Hyporesponders

Based on retrospective analysis[1] conducted with DaVita Clinical Research, hyporesponders have:

- Higher mortality rate
- Greater need for iron and ESA use
- Lower hemoglobin levels compared to non-ESA hyporesponsive patients

$TRILO_2GY$ Trial - Three-Times Weekly

Based on positive Phase 2 study results showing vadadustat can be dosed TIW in CKD patients on dialysis

- Design similar to $INNO_2VATE$ program in dialysis patients

[1] Jiacong, L et al. Spectrum and Burden of Erythropoiesis-Stimulating Agent Hyporesponsiveness Among Contemporary Hemodialysis Patients. AJKD 2016

Akebia THERAPEUTICS

Vadadustat Global Program Strategy: Setting a New Standard of Care in Treatment of Renal Anemia

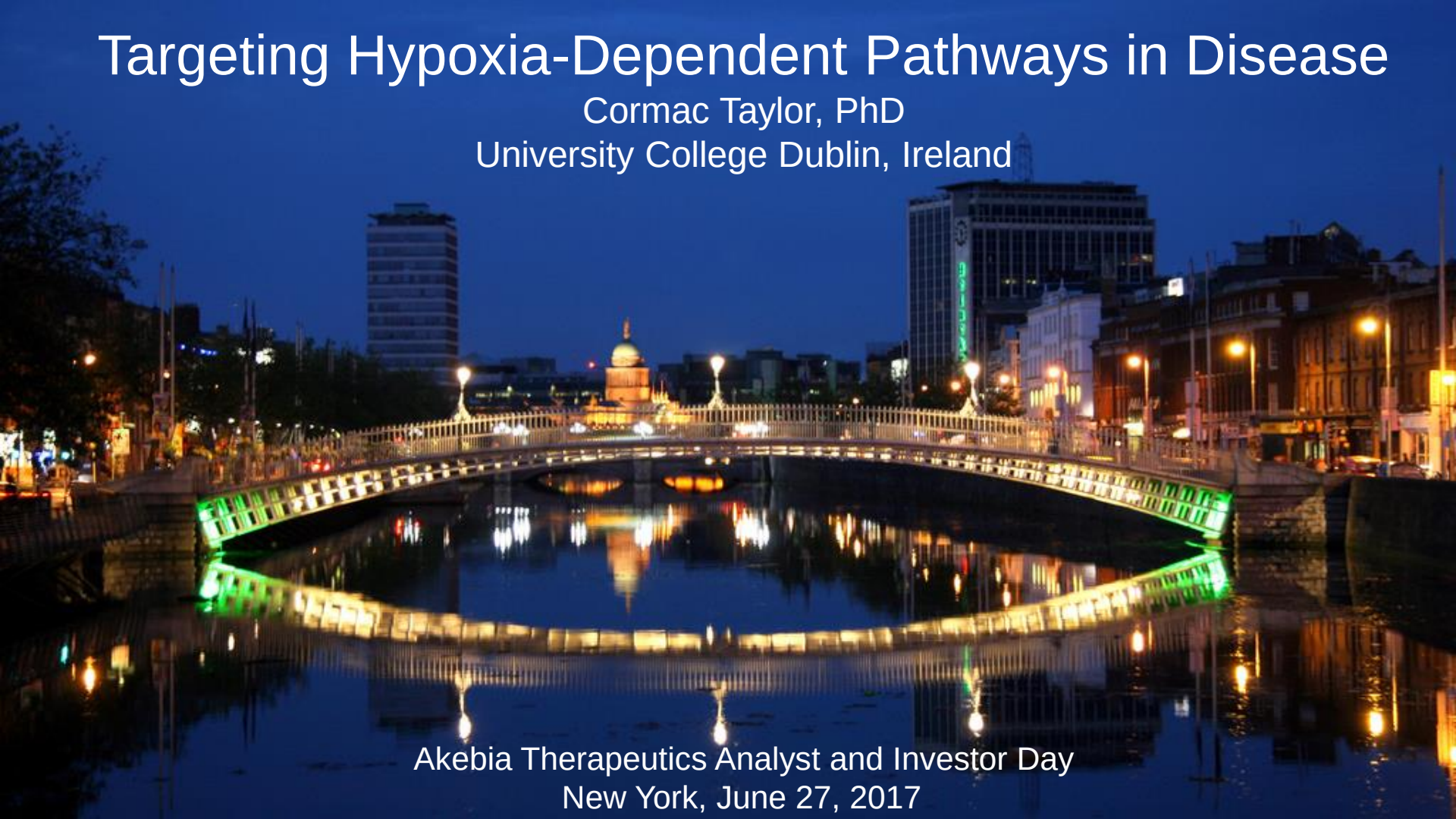
- Program will provide a robust dataset for licensure in key geographies
- Addressing important patient segments
- Data will inform initiating therapy in treatment naïve patients, switching from standard of care and long-term treatment with vadadustat

THANK YOU

Akebia™ THERAPEUTICS

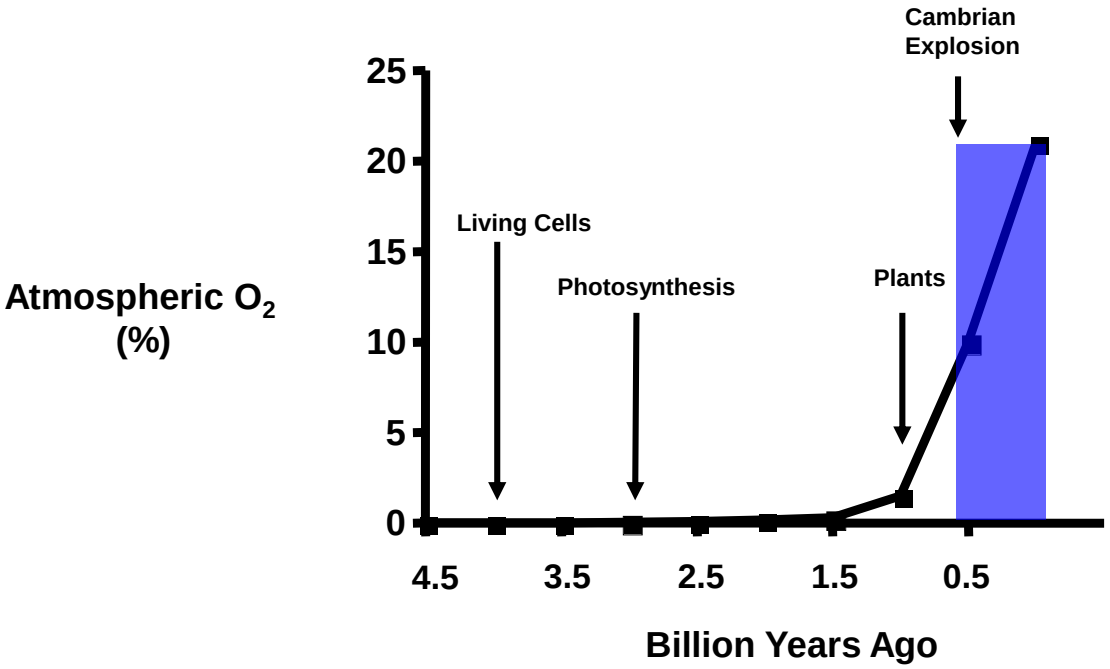
Targeting Hypoxia-Dependent Pathways in Disease

Cormac Taylor, PhD
University College Dublin, Ireland

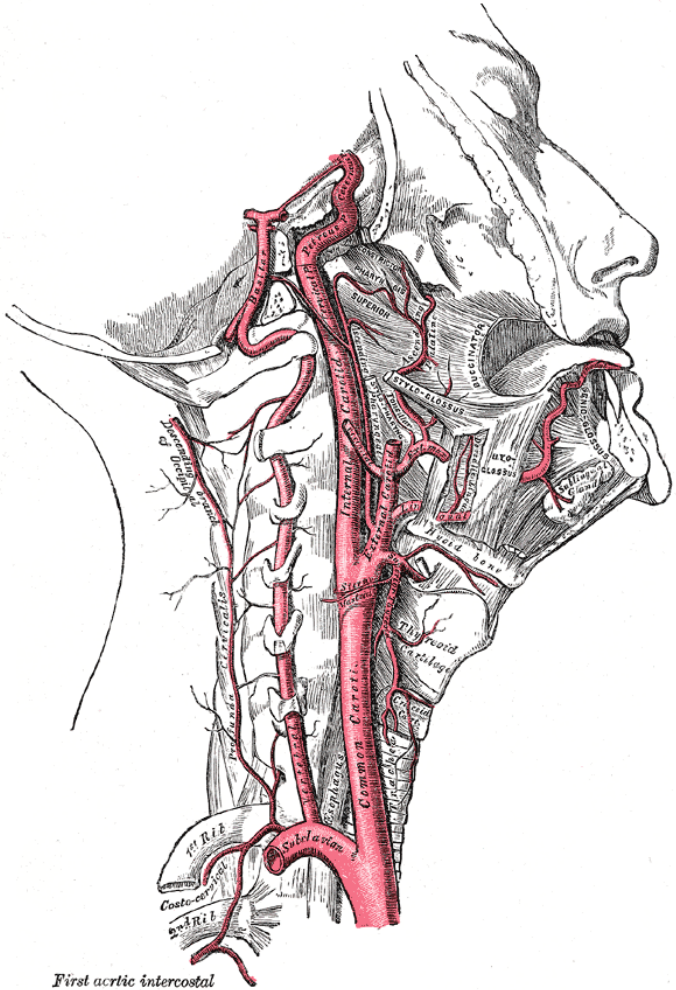


Akebia Therapeutics Analyst and Investor Day
New York, June 27, 2017

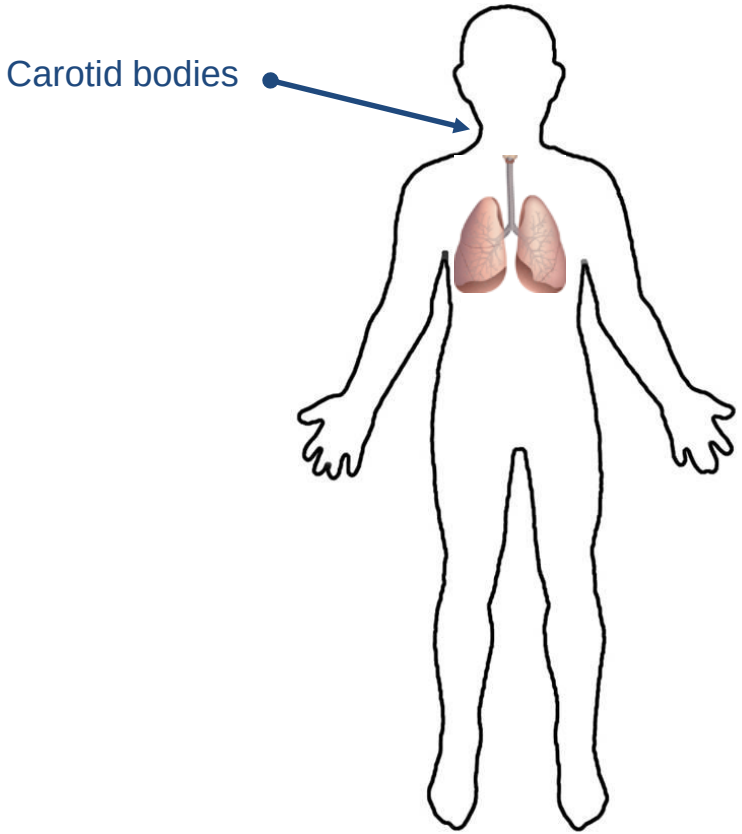
O_2 Levels in Ancient Atmospheres

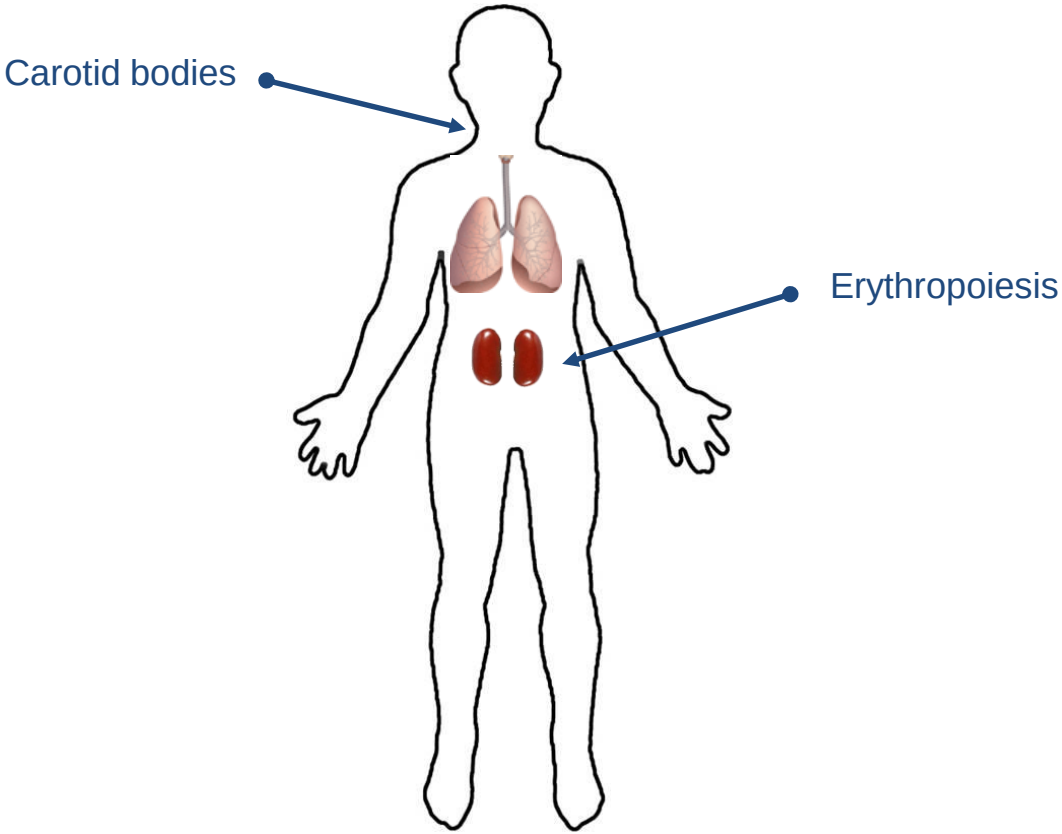


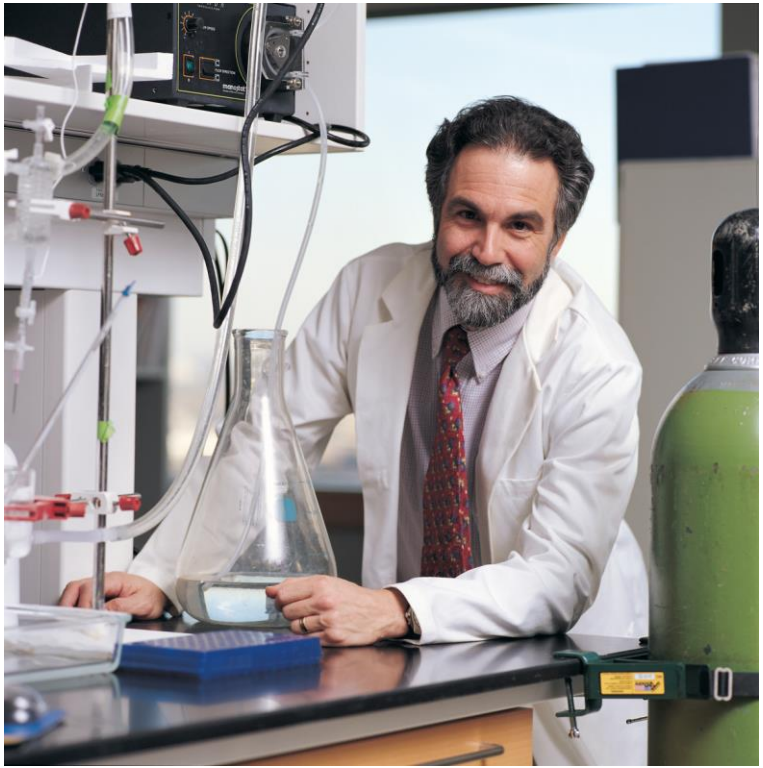
Taylor, CT & McElwain J (2010) *Physiology 25; 272-279.*



First aortic intercostal


Carotid bodies


Carotid bodies
Erythropoiesis

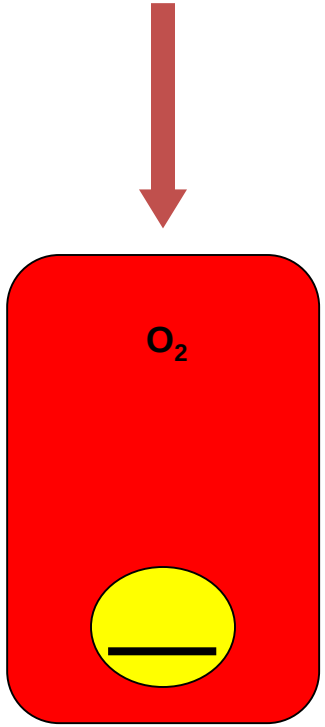


Semenza GL & Wang GL (1992) A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 12(12):5447-54.

Wang GL & Semenza GL (1993) Characterization of hypoxia-inducible factor 1 and regulation of DNA binding activity by hypoxia. J Biol Chem.;268(29):21513-8.

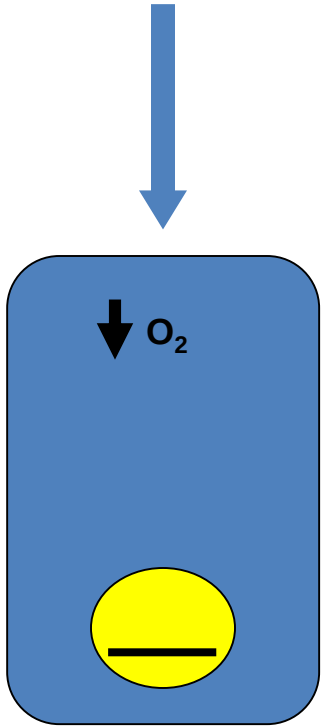
Adaptive Response to Hypoxia

O_2 Supply exceeds Demand



Adaptive Response to Hypoxia

O_2 Demand exceeds Supply



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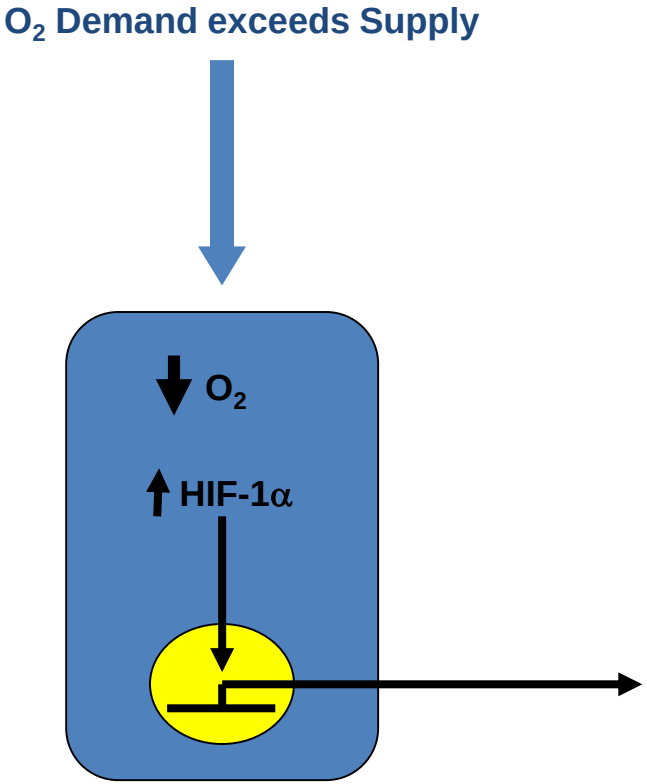
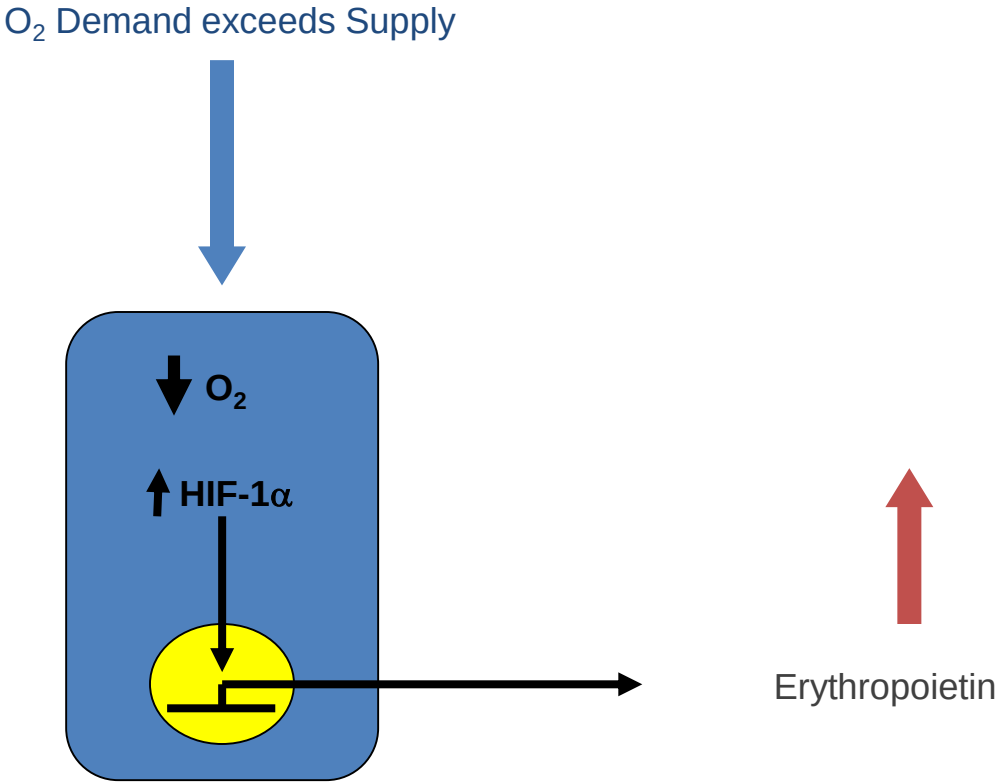
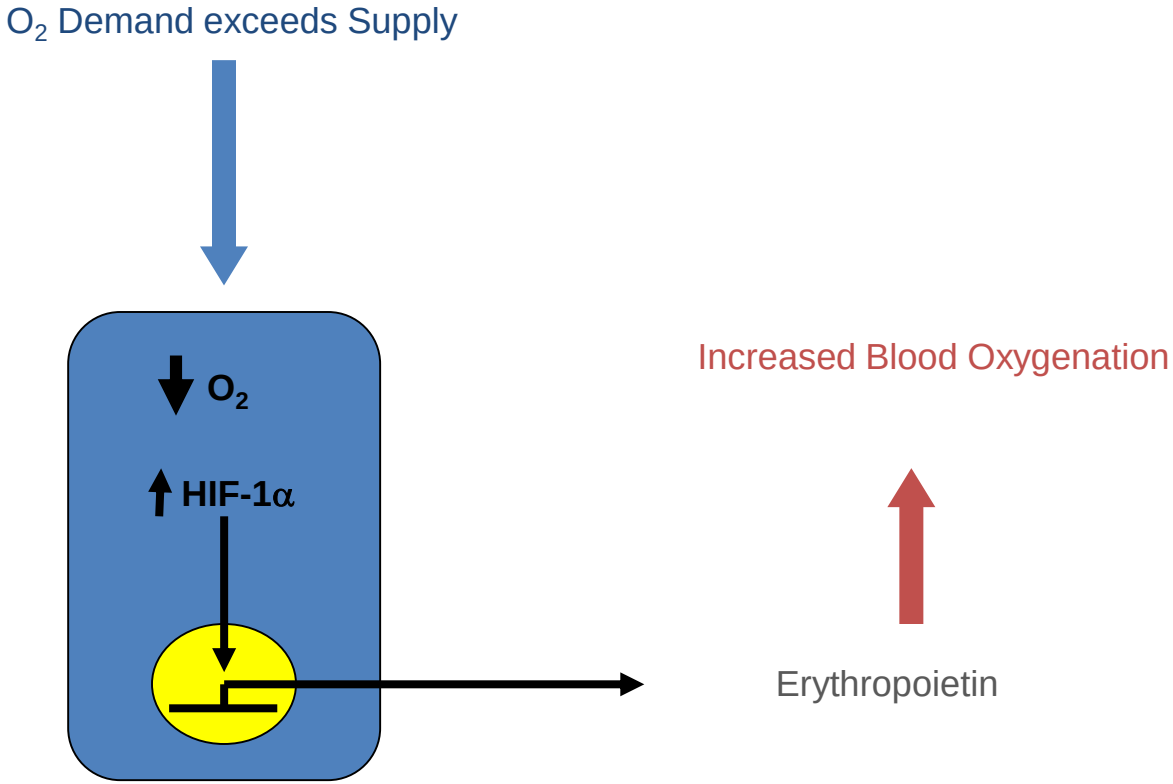


Adaptive Response to Hypoxia



Adaptive Response to Hypoxia



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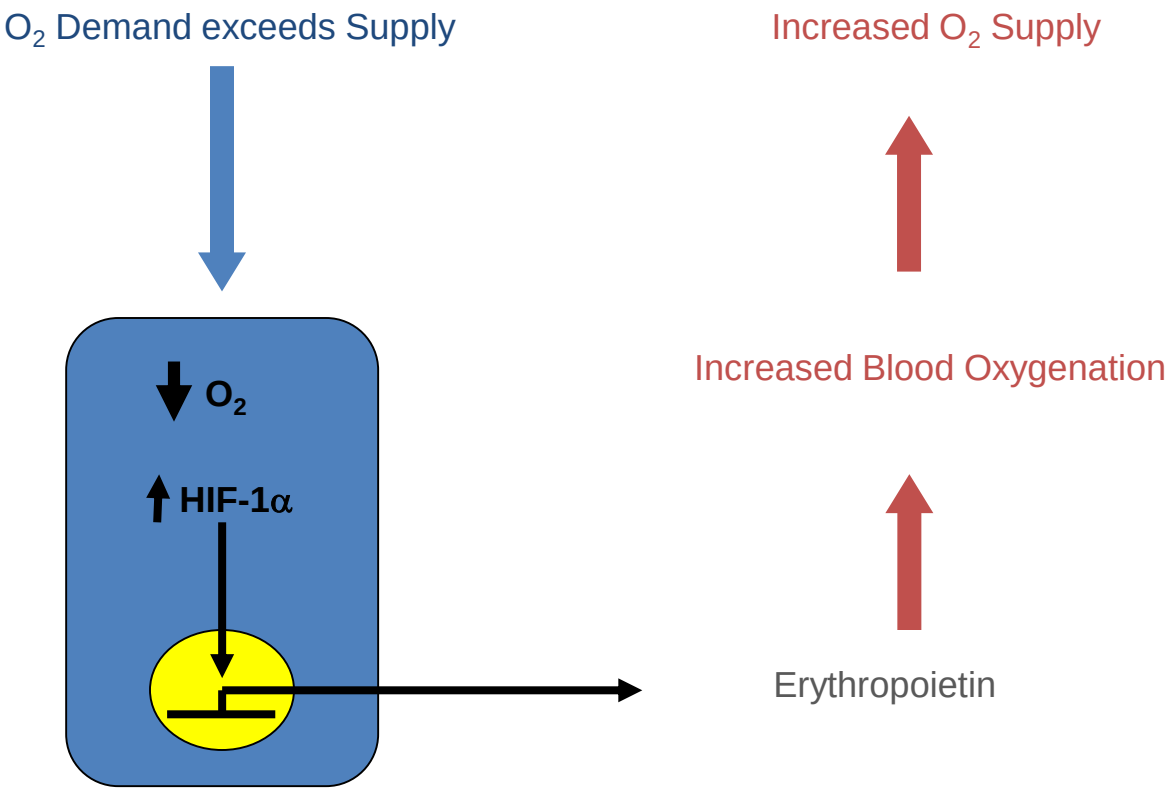

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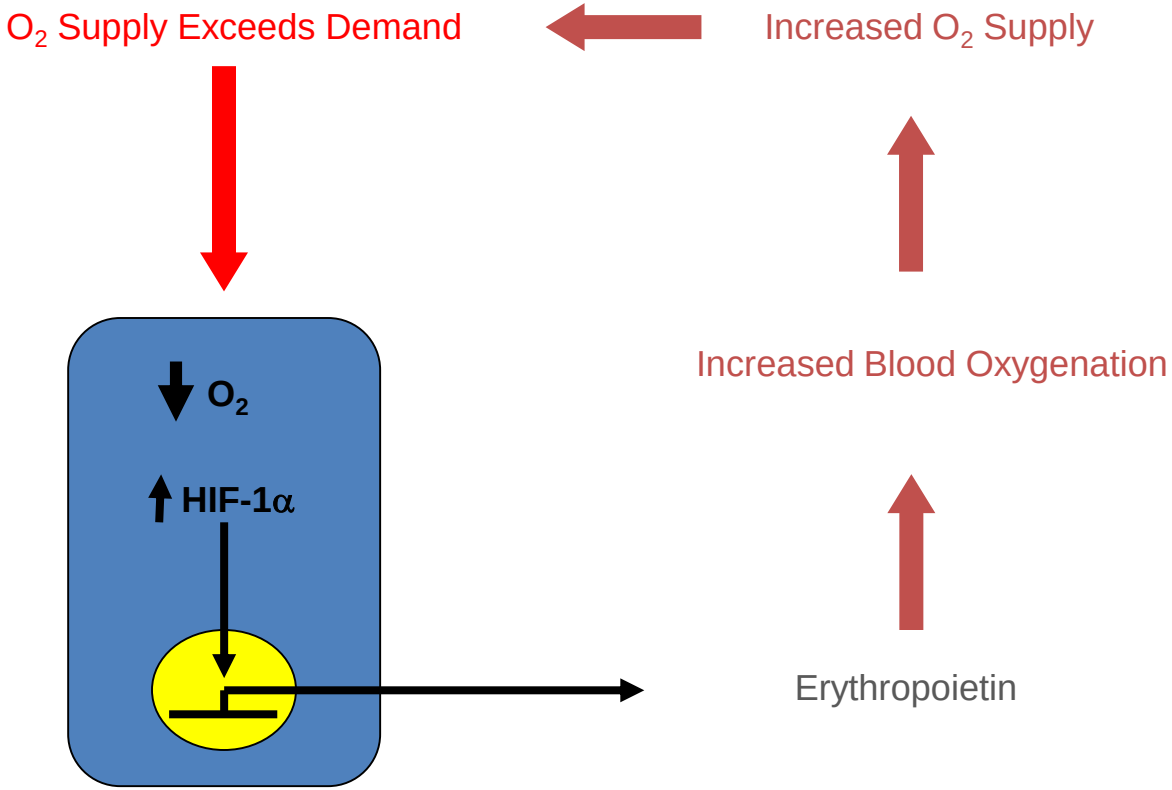
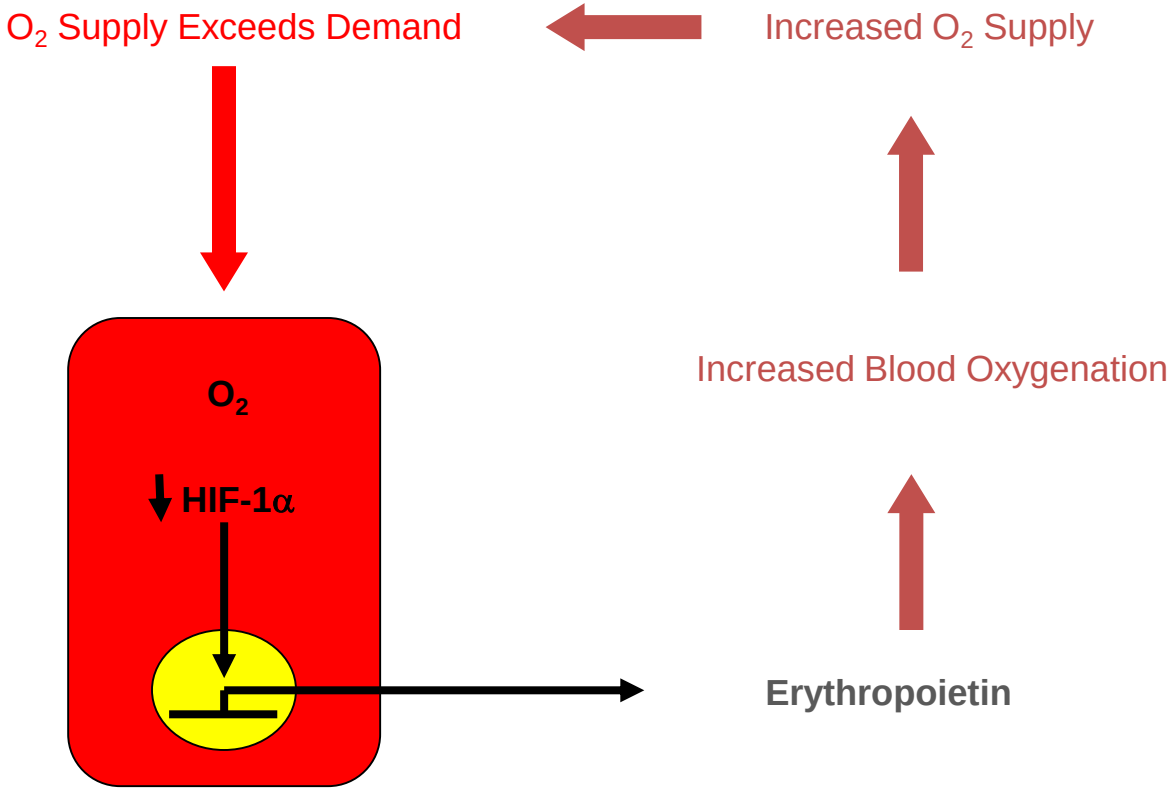
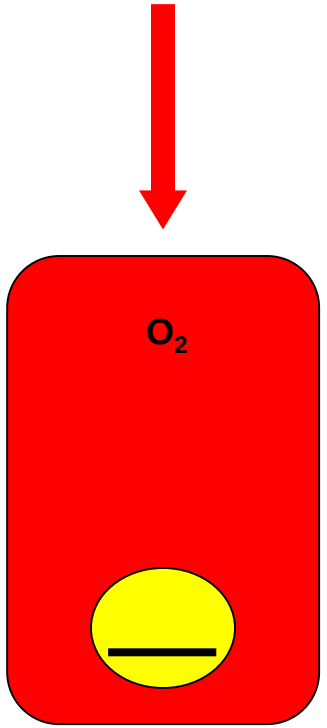


Adaptive Response to Hypoxia



Adaptive Response to Hypoxia

O_2 Supply Exceeds Demand



Features of the HIF Pathway

- It is present in all cells.
- It is highly conserved across all metazoans.
- It regulates many genes.

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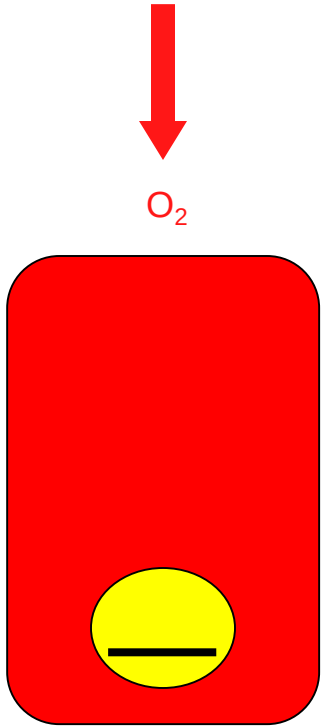
What is the nature of the oxygen sensing mechanism(s) regulating HIF?

Jaakola et al. (2001) Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001 292(5516):468-72.

Ivan et al. (2001) HIFαlpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science. 292(5516):464-8.

Adaptive Response to Hypoxia

O_2 Supply exceeds Demand



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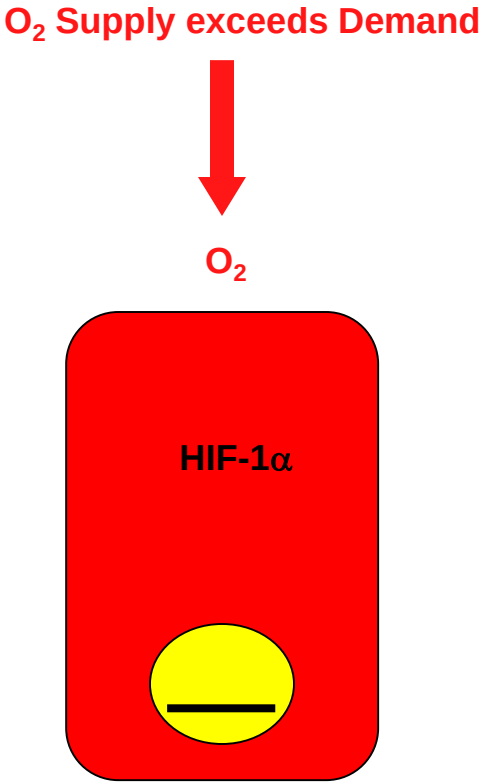

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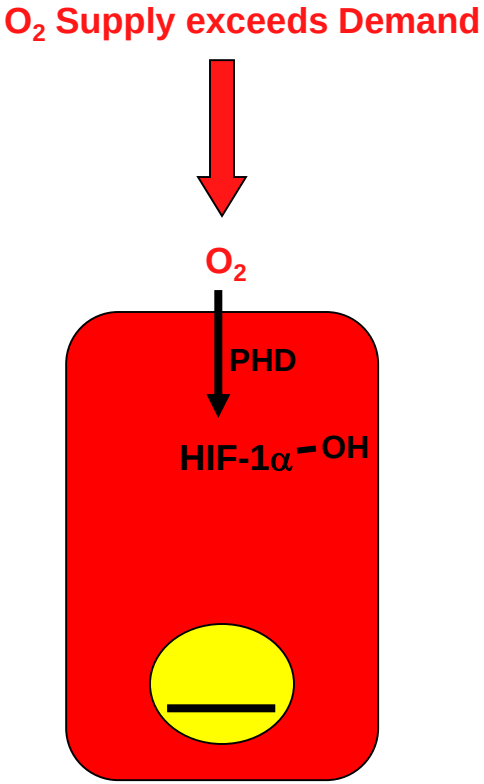

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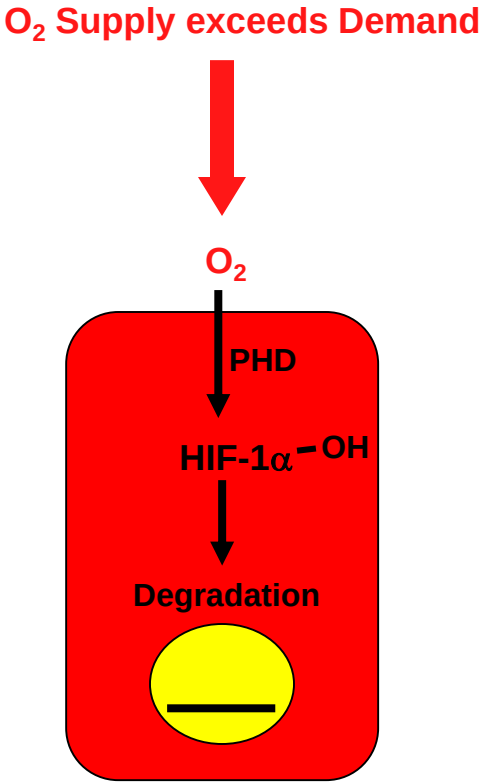

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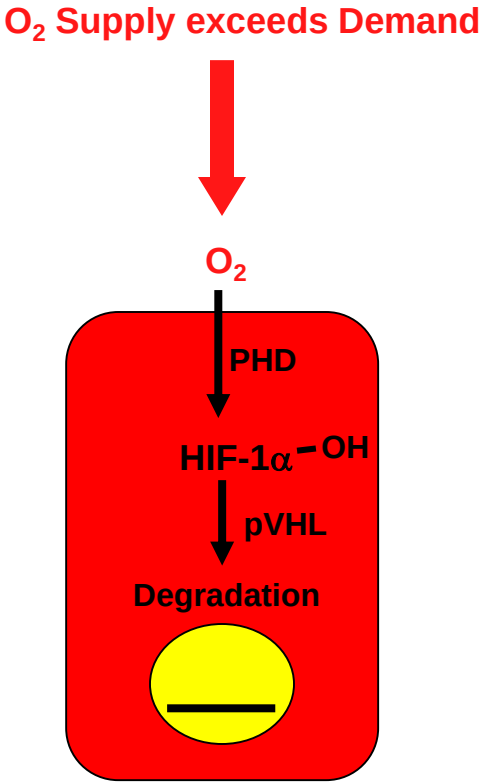

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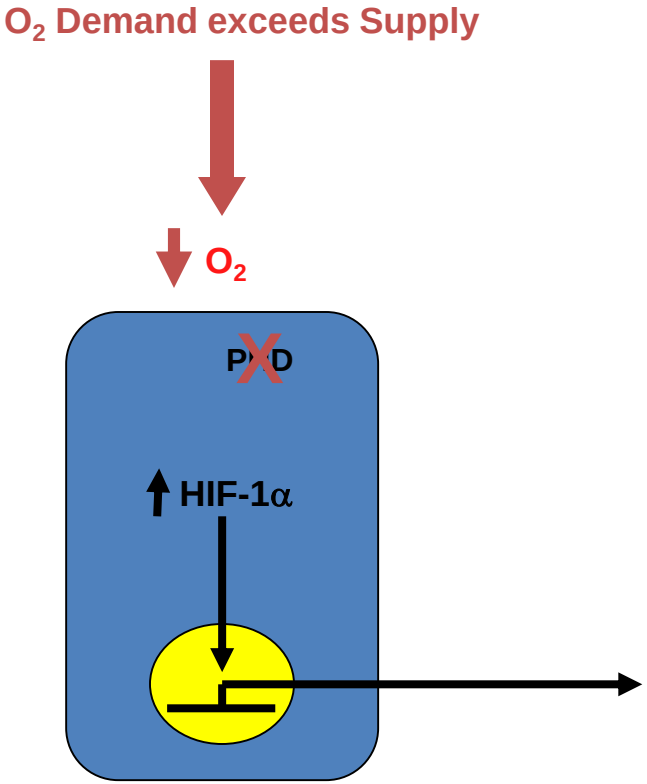

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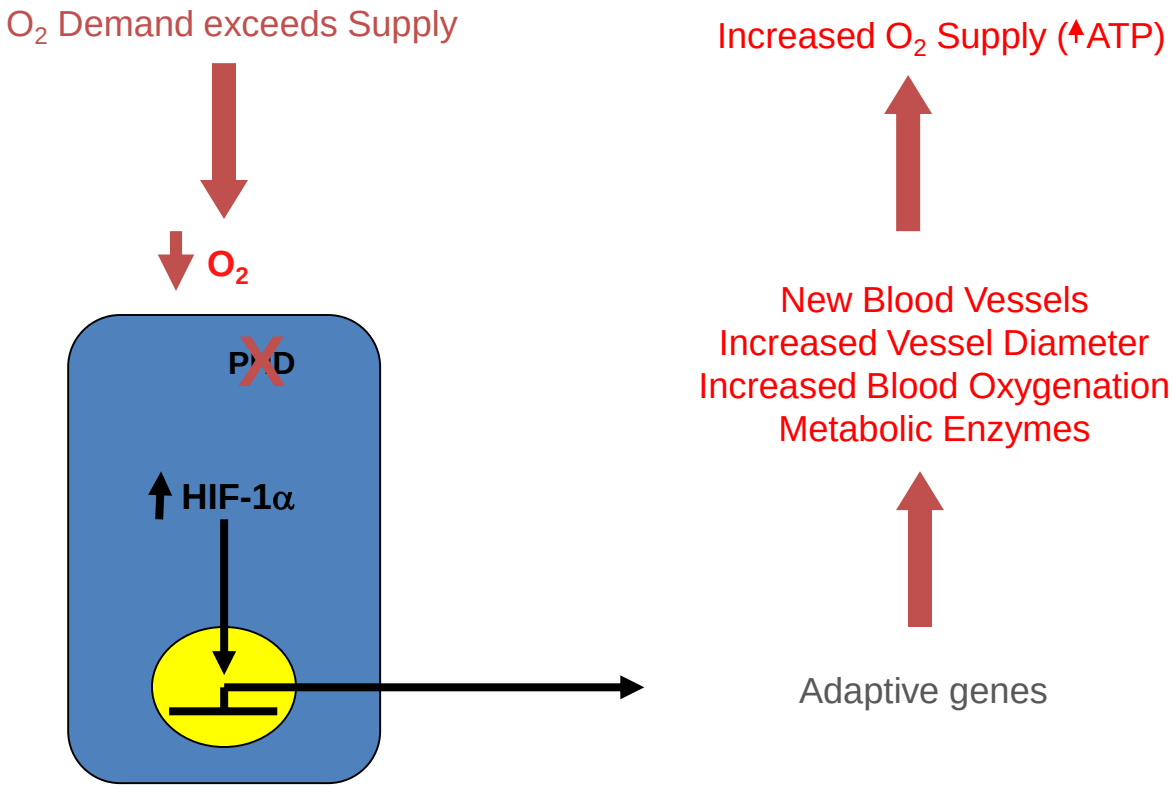

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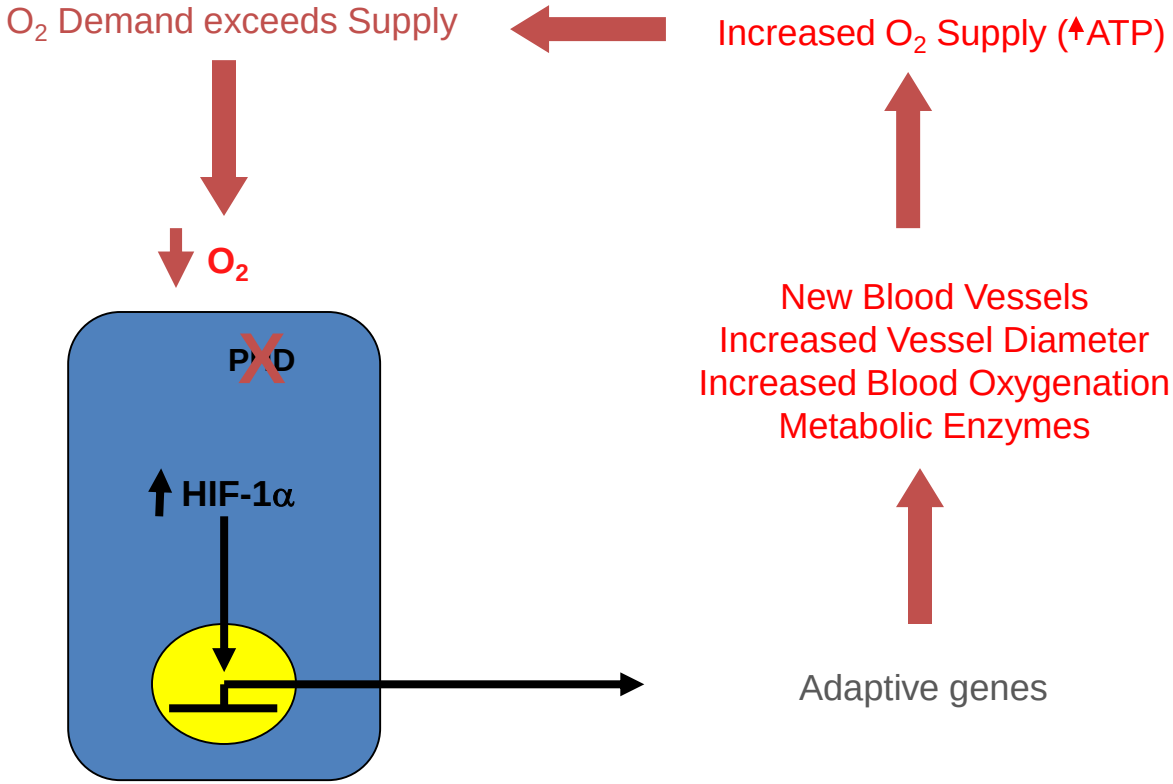

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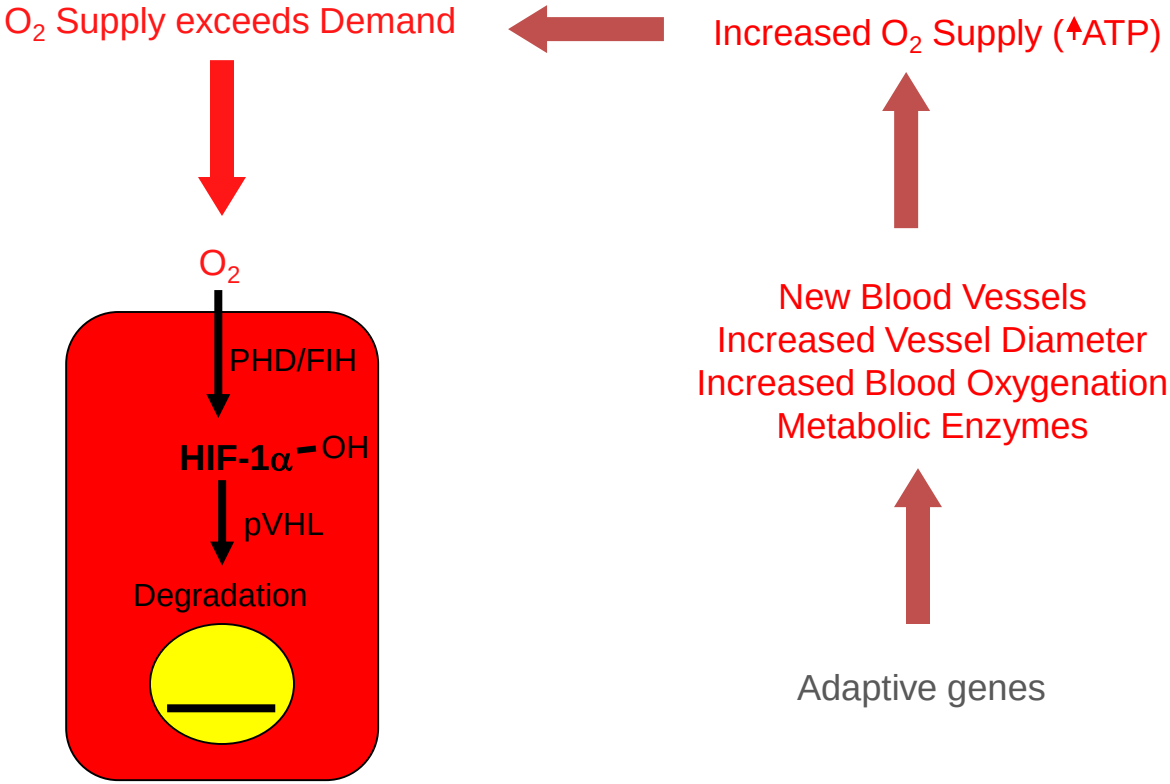

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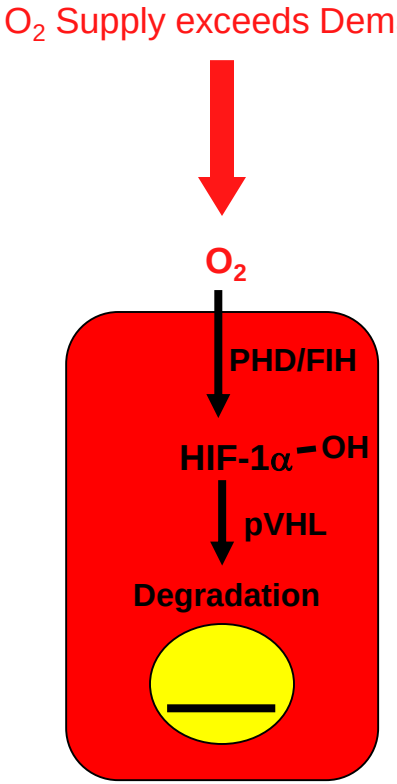
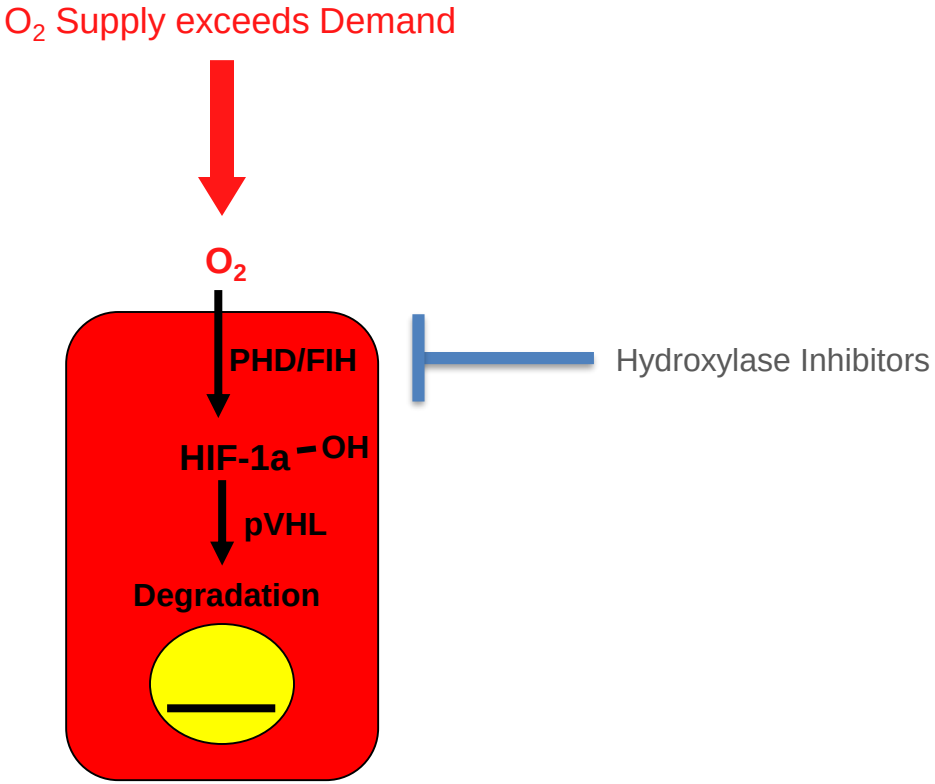


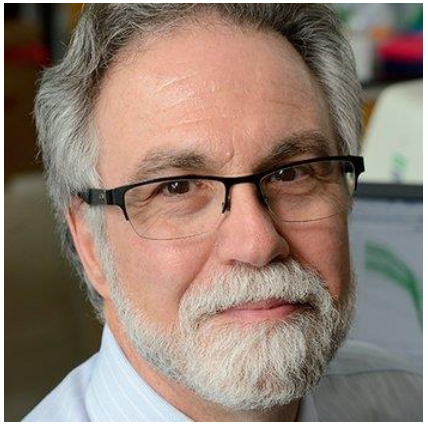
Adaptive Response to Hypoxia



2016 Albert Lasker Basic Medical Research Award

Peter Ratcliffe

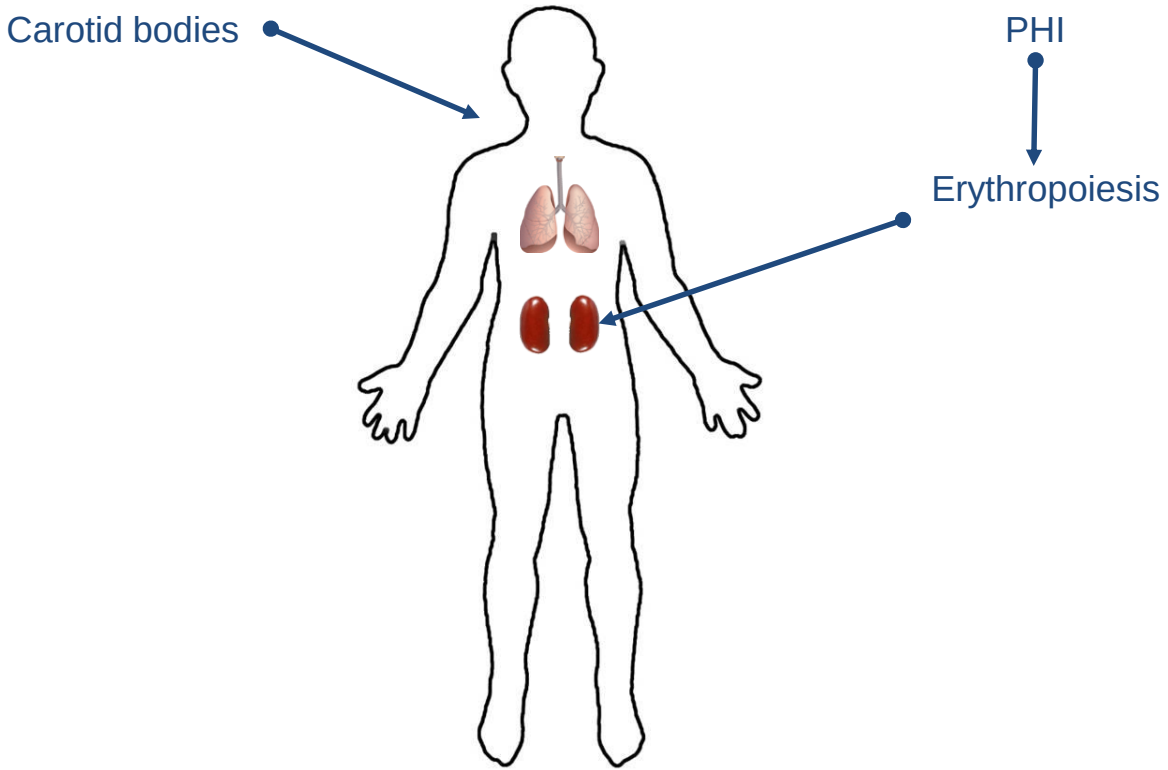
Bill Kaelin



Gregg Semenza

Anemia

PHD Inhibitors and Anemia

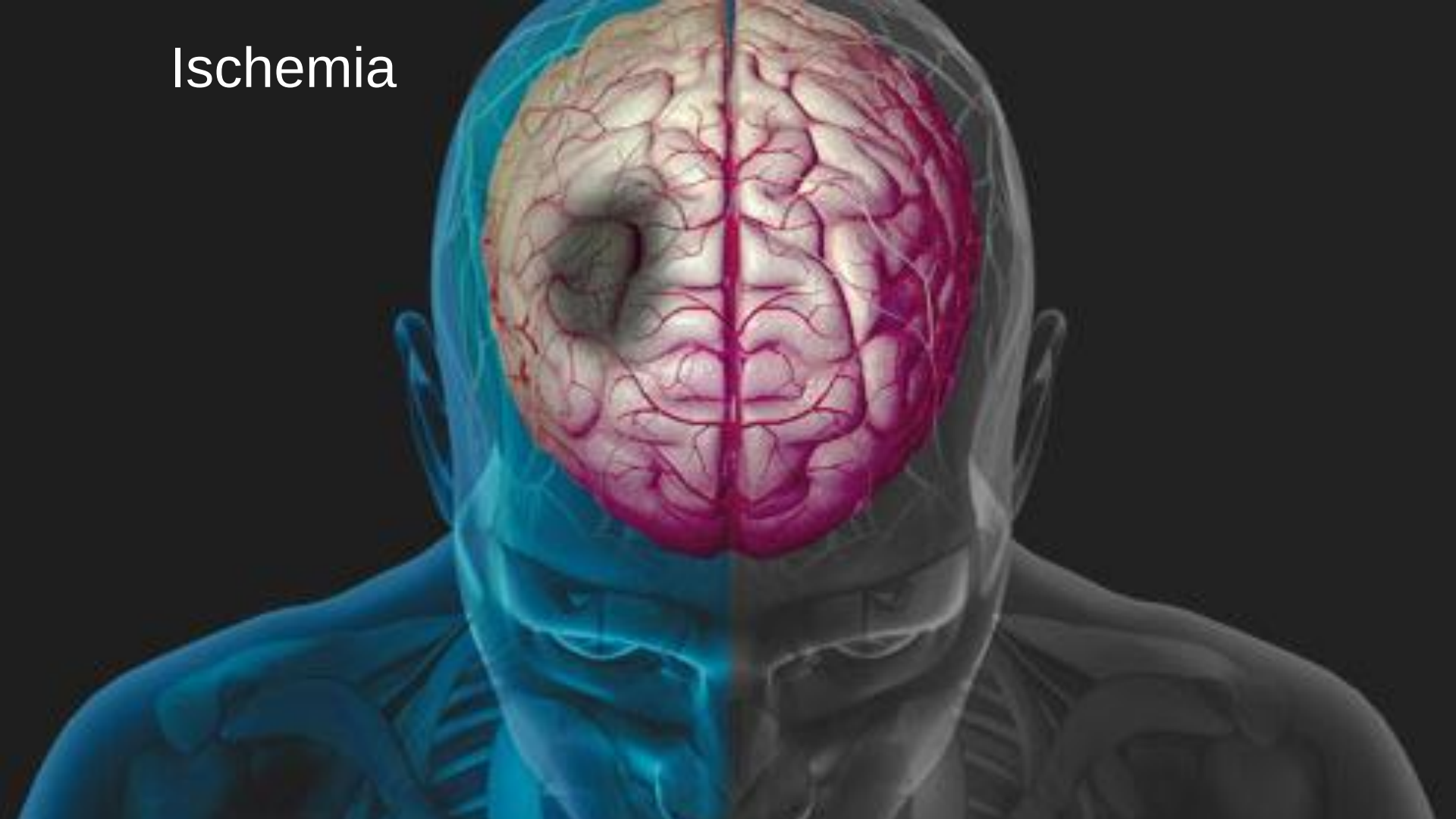


Maxwell and Eckardt, *Nature Reviews in Nephrology* (2016)

Take-home Message

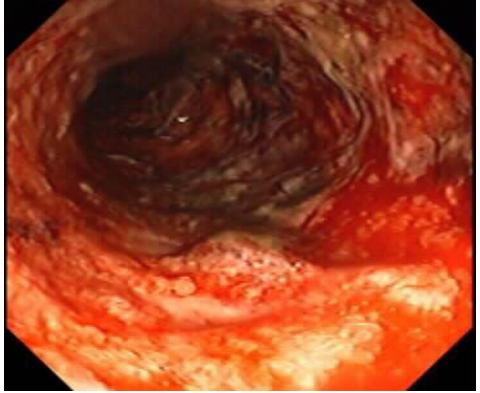
Ten published clinical studies suggest that hydroxylase inhibitors may be effective in the treatment of anemia.

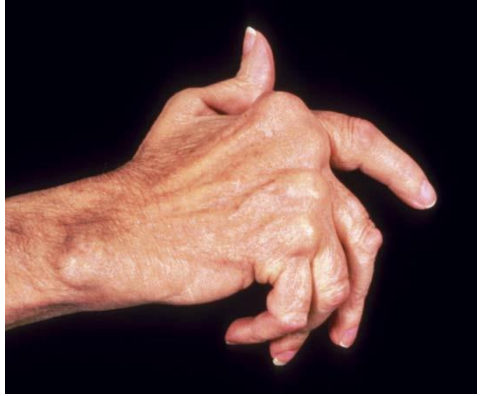
Ischemia



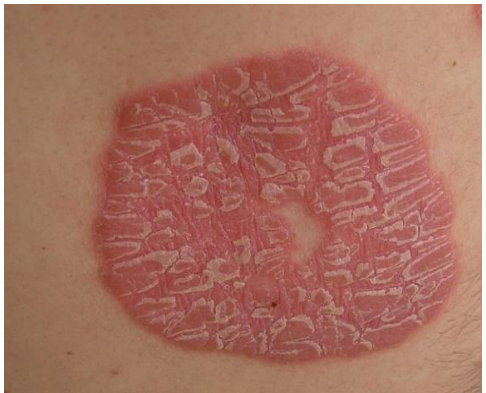
Take-home Message

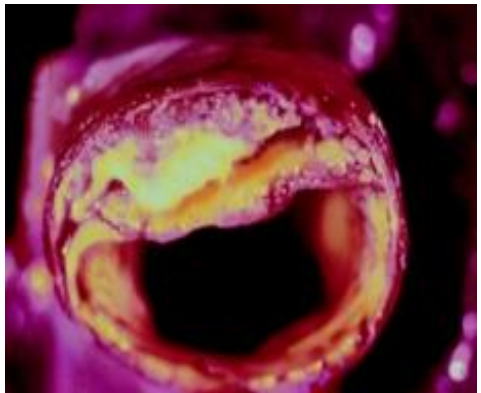
Fifteen published preclinical studies suggest that hydroxylase inhibitors may be effective in the treatment of ischemia.



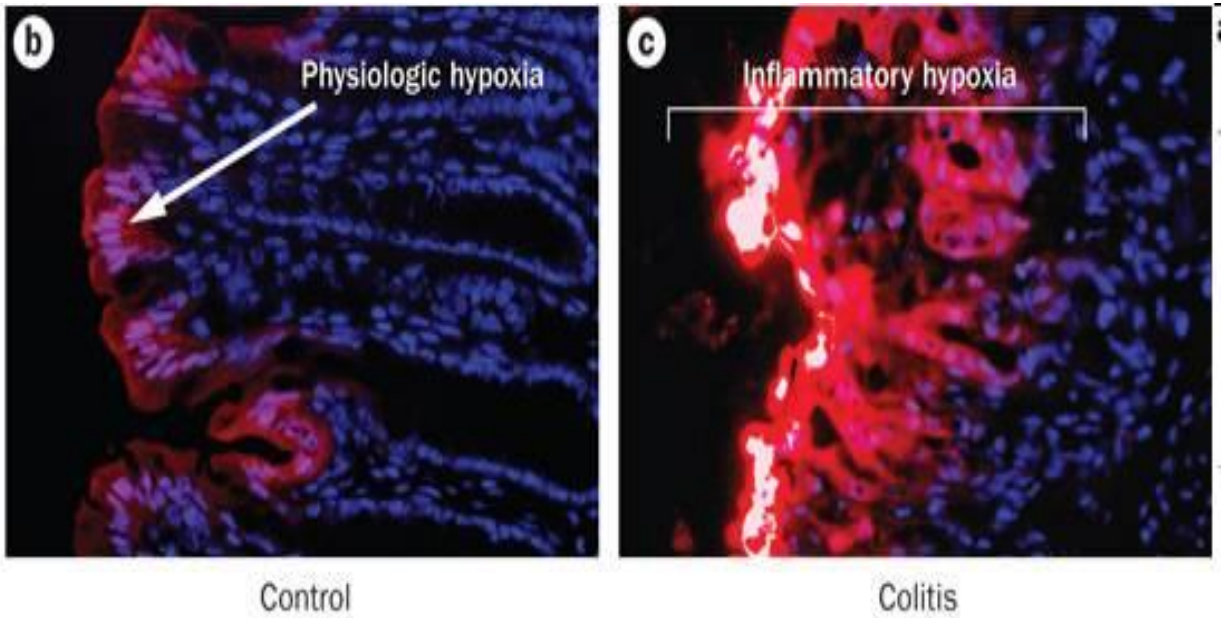



Inflammation



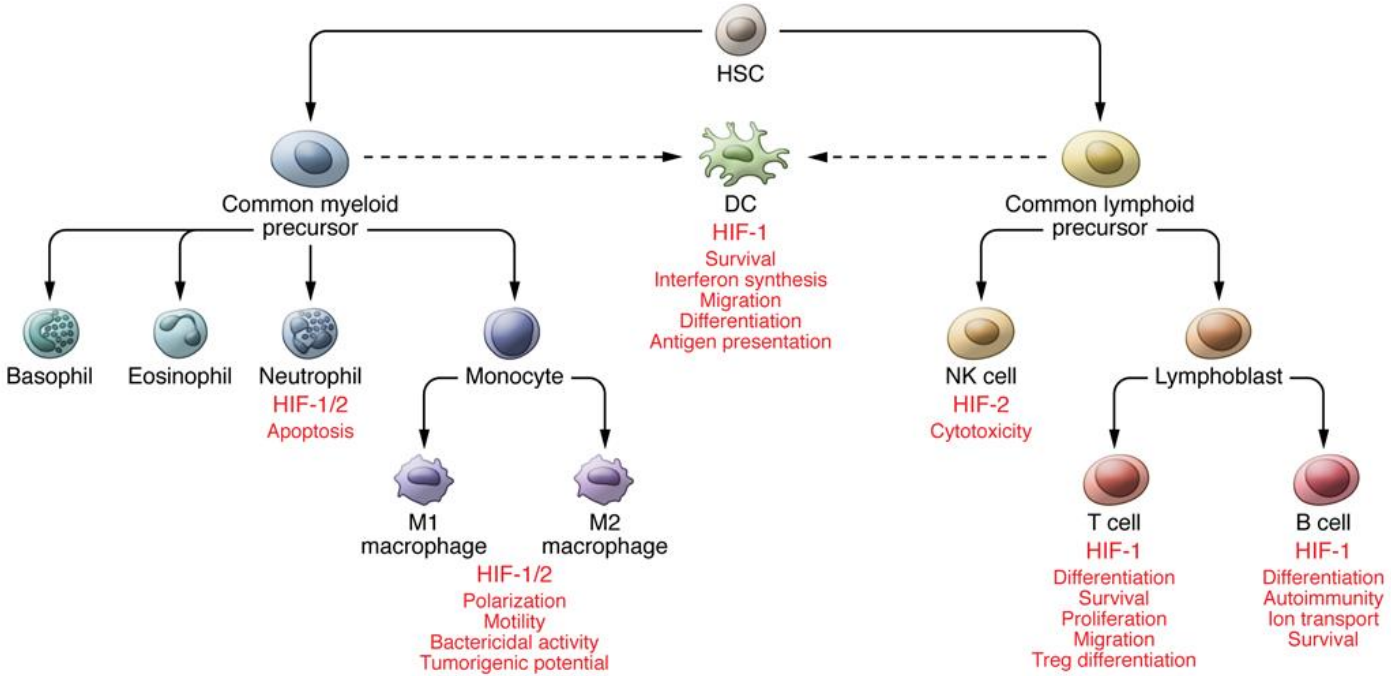


Hypoxia is a Feature of Inflammation



Colgan & Taylor, *Nat Rev Gastro. Hepatol.* (2010)

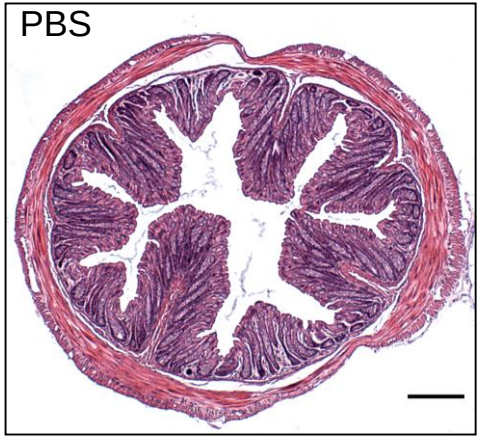
PHD Inhibitors and Inflammation



Taylor et al. *J. Clin. Invest.* 2016

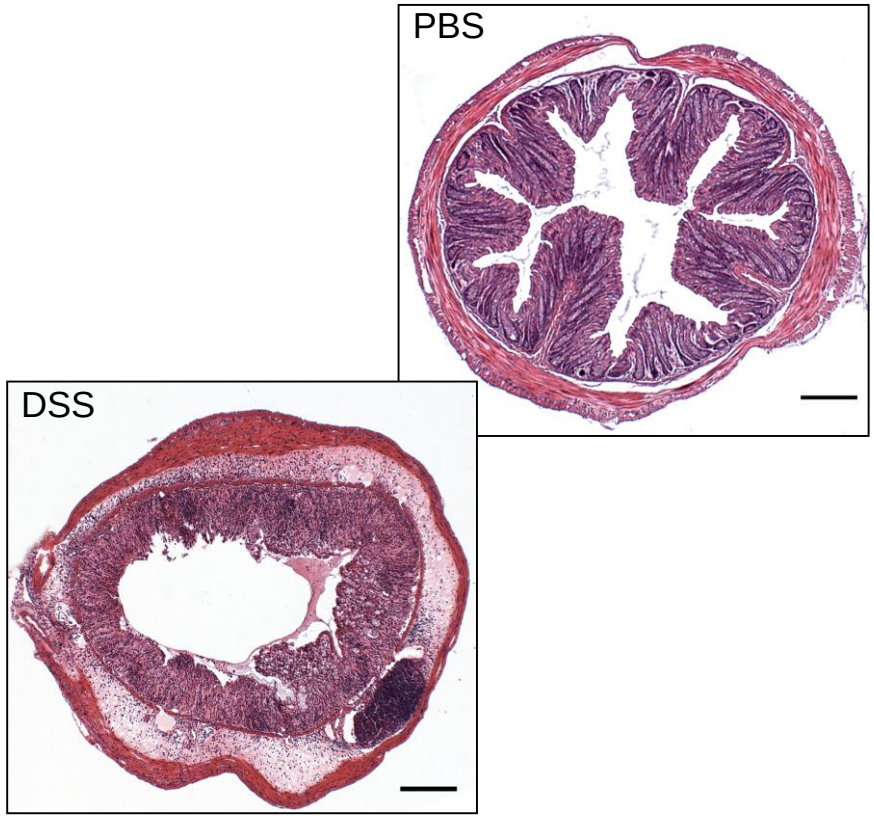
What is the potential impact of hydroxylase inhibition on inflammation?

PHD Inhibition is Protective in Experimental Colitis



Cummins et al., *Gastroenterology* (2008)

PHD Inhibition is Protective in Experimental Colitis



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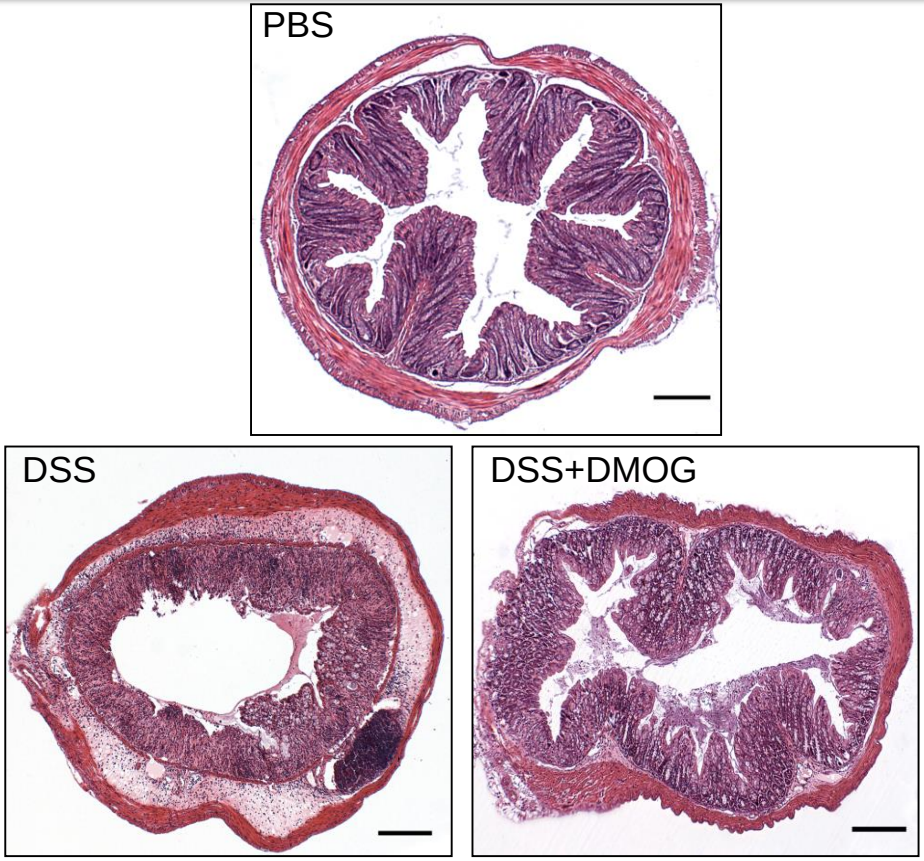
PHD Inhibition is Protective in Experimental Colitis

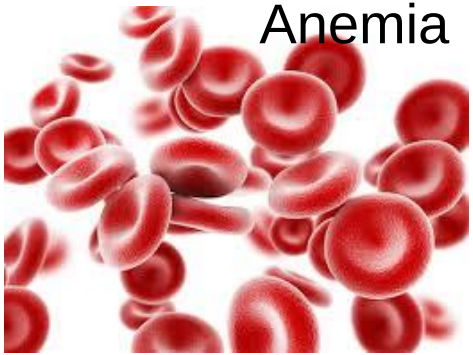


Cummins et al., *Gastroenterology* (2008)

Take-home Message

Twenty published preclinical studies suggest that hydroxylase inhibitors may be effective in the prevention and reversal of inflammation.

Potential Therapeutic Applications of Activating the HIF Pathway

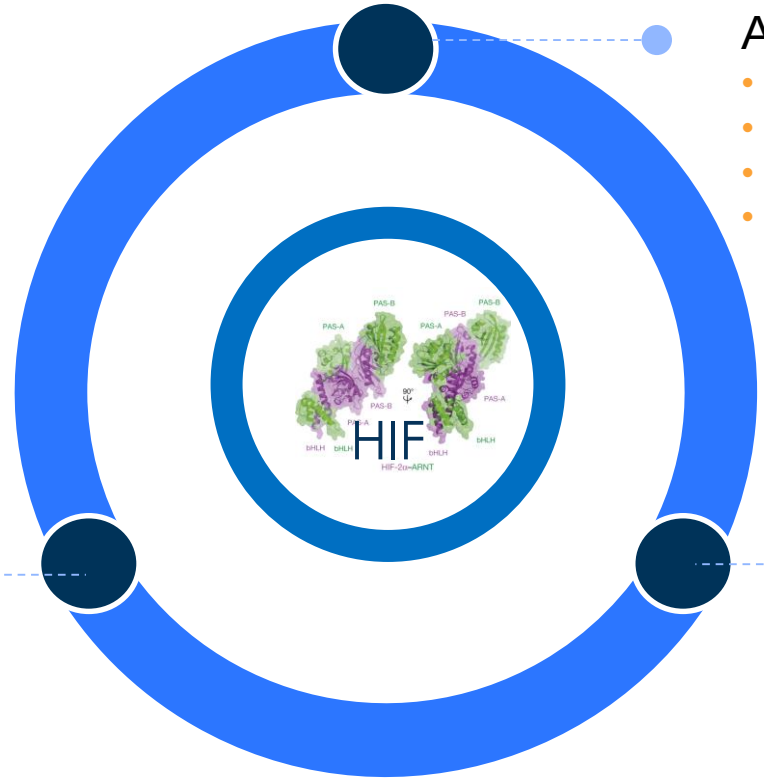


Expanded Therapeutic Potential of HIF Stabilizers

Michael H. Rabinowitz, Ph.D., VP of Research

Akebia™ THERAPEUTICS

Disease Areas Where HIF Stabilization May Play a Therapeutic Role



Anemias

- Anemia of CKD
- Anemia of chronic disease
- MDS
- Sickle cell

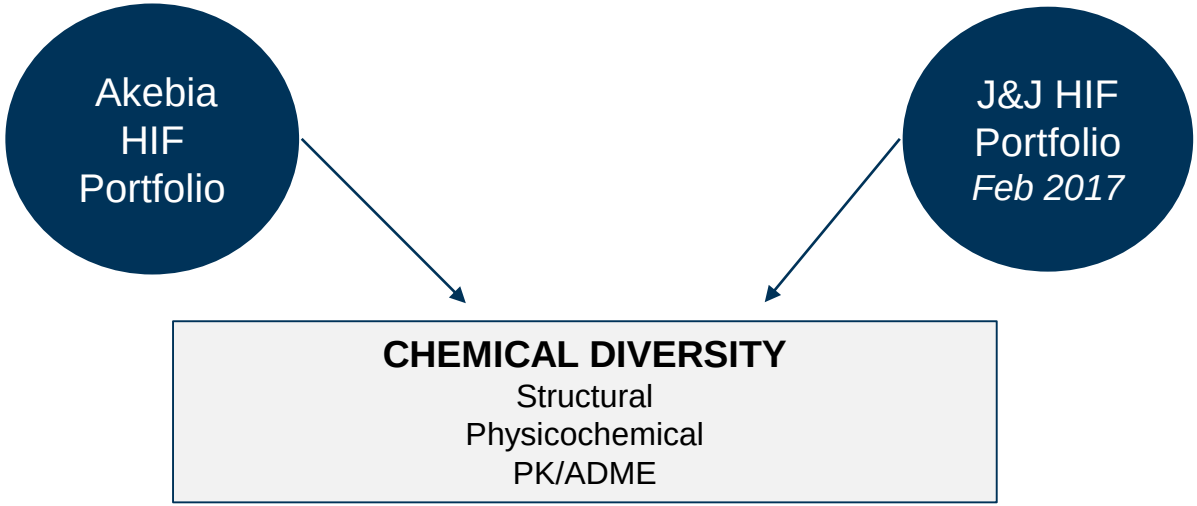
Inflammation

- Ulcerative colitis
- Radio protection
- Wound healing

Ischemia

- Reperfusion injury
- Organ preservation

J&J Deal Broadens and Accelerates Development of HIF Portfolio

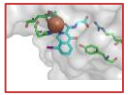


Structural	Physicochemical	Biochemical	PK/Toxicity
• Hydrogen bonding • Mol. Wt. • pKa • Polar surface area • Shape • Reactivity	• Solubility • Lipophilicity • Permeability • Chemical stability	• Metabolism (Phase I & II) • Protein & tissue binding • Transport (uptake, efflux)	• Clearance • Half-life • Bioavailability • Drug-drug interaction • LD_{50}

Akebia THERAPEUTICS

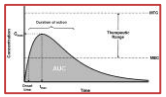
Selection of Compound to Explore HIF Biology

Akebia Compound Portfolio

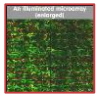


1500 analogs synthesized and assayed

PK data for 100 compounds



Dozens of compounds with *high systemic exposure*



Potency in *in vivo* EPO response and anemia model

AKB-5343

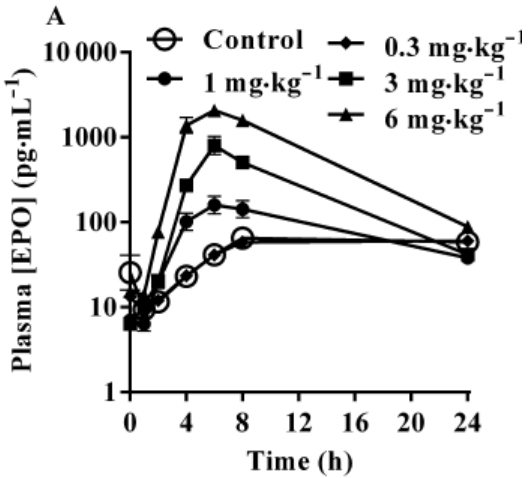
Potent, High Systemic Exposure

ADME properties tailored for each potential disease indication

Akebia THERAPEUTICS

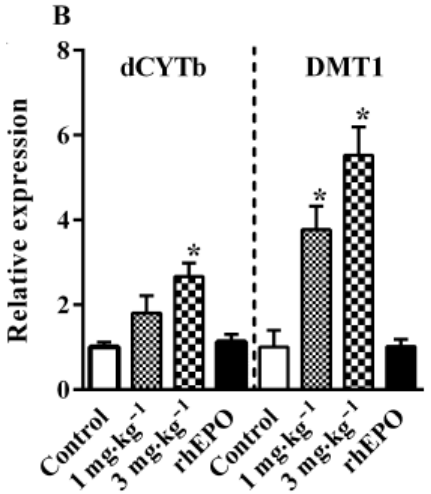
HIF Compound Affects Genes Important for Iron Mobilization, While ESA (rhEPO*) Does Not

EPO Secretion



Effect of a Single Dose of AKB-5343 in Normal Female Lewis Rats

Iron Mobilization Genes



- Highly potent, dose-responsive EPO production
- Increases gene expression for proteins *critical* in dietary iron uptake and mobilization

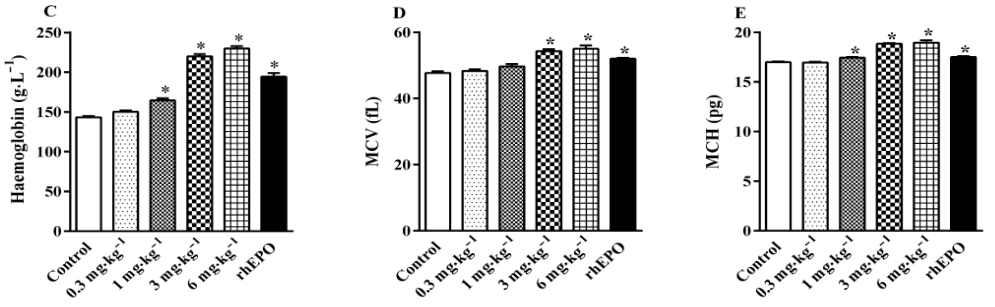
*rhEPO = Recombinant Human Erythropoietin

British Journal of Pharmacology (2015) **172** 4078–4088

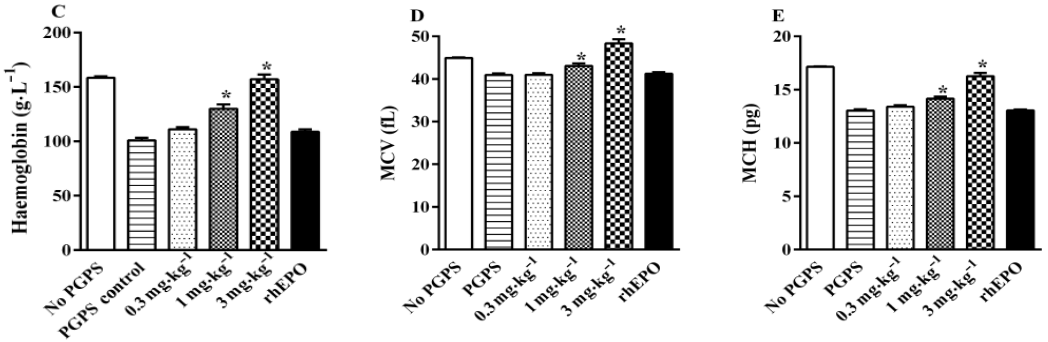
Akebia THERAPEUTICS

HIF Compound Reverses Anemia Associated with Inflammation, While ESA (rhEPO) Does Not

Healthy rats:



Chronically-Inflamed Rats (PGPS):



28-Day Repeat Dose of AKB-5343 in Female Lewis Rats

- Significant improvement in hemoglobin and quality measures of red blood cell health
- Demonstrates hematologic improvements in chronically inflamed rats while ESA does not

British Journal of Pharmacology (2015) **172** 4078–4088

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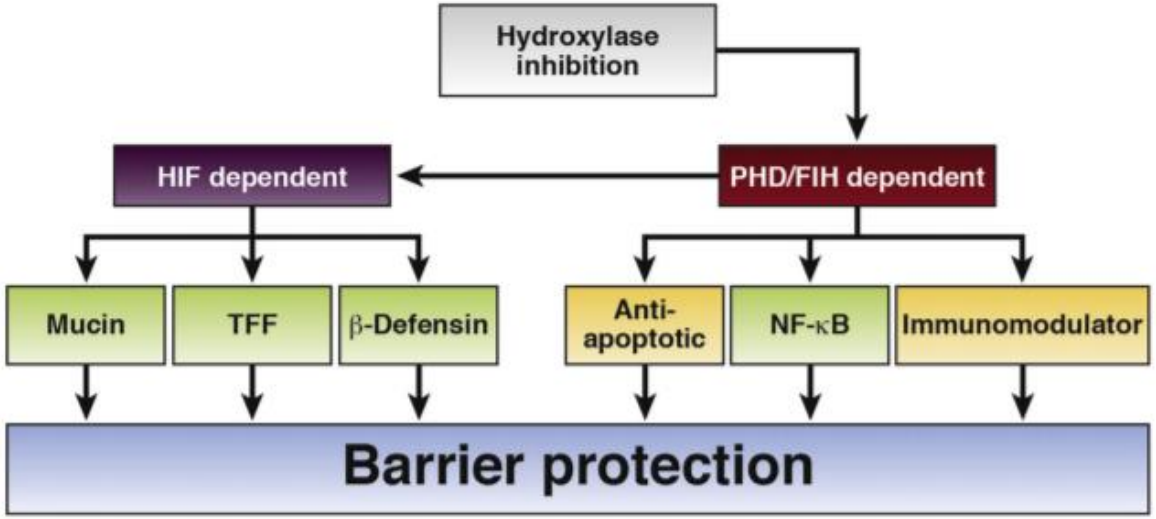
Inflammatory Bowel Diseases

Akebia™ THERAPEUTICS

HIF Plays a Key Role in Barrier Protection in Inflammatory Bowel Diseases (IBD)



Manresa and Taylor Cellular and Molecular Gastroenterology and Hepatology Vol. 3, No. 3

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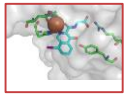
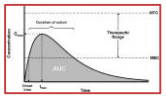
Selection of HIF Compound for IBD

Structure Based Drug Design Program

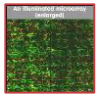


1000s analogs synthesized and assayed

PK data for 100 compounds



15 compounds with *low systemic exposure*



3 compounds with validated *in vivo* mechanism

AKB-5169

Chronic and Acute Models:

T-cell transfer and DSS

ADME properties tailored for each potential disease indication

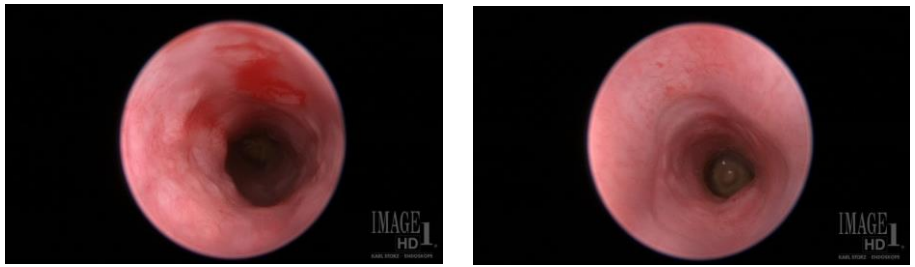
Akebia THERAPEUTICS

AKB-5169: Targeting the Unmet Need in IBD

- Unmet need remains in IBD for both improved efficacy and safety profile
- Small molecule in preclinical development as oral treatment for mild to moderate disease
- Limited systemic exposure
- Preclinical DSS model illustrates positive endoscopy impact
- Planned mid-2018 IND submission

Endoscopic Evaluation of Efficacy

Vehicle Control *AKB-5169*



Library of Compounds and Potential Indications

Compounds

- AKB-6899
- AKB-5169
- AKB-5343
- AKB-7414
- AKB-7895
- AKB-…
- AKB-…

Indications

- Anemia
  - Sickle Cell Disease
  - Myelodysplastic Syndrome
  - Anemia of Chronic Disease
- Inflammation
  - Ulcerative colitis
  - Radio protection
  - Wound healing
- Ischemia
  - Reperfusion injury
  - Organ preservation
- Bacterial infection
- NAFLD/NASH

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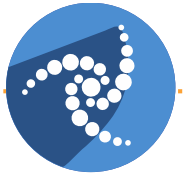
THANK YOU

Akebia™ THERAPEUTICS

Building the Innovation-Driven Renal Company

Execute on vadadustat Development Program

- Comparison with Standard of Care
- Single comparator globally
- Optimal data quality
- Single sponsor globally



Commercial Readiness and Launch Acceleration

- Otsuka U.S.
- Vifor Pharma
- Intellectual property validation

Pipeline Development

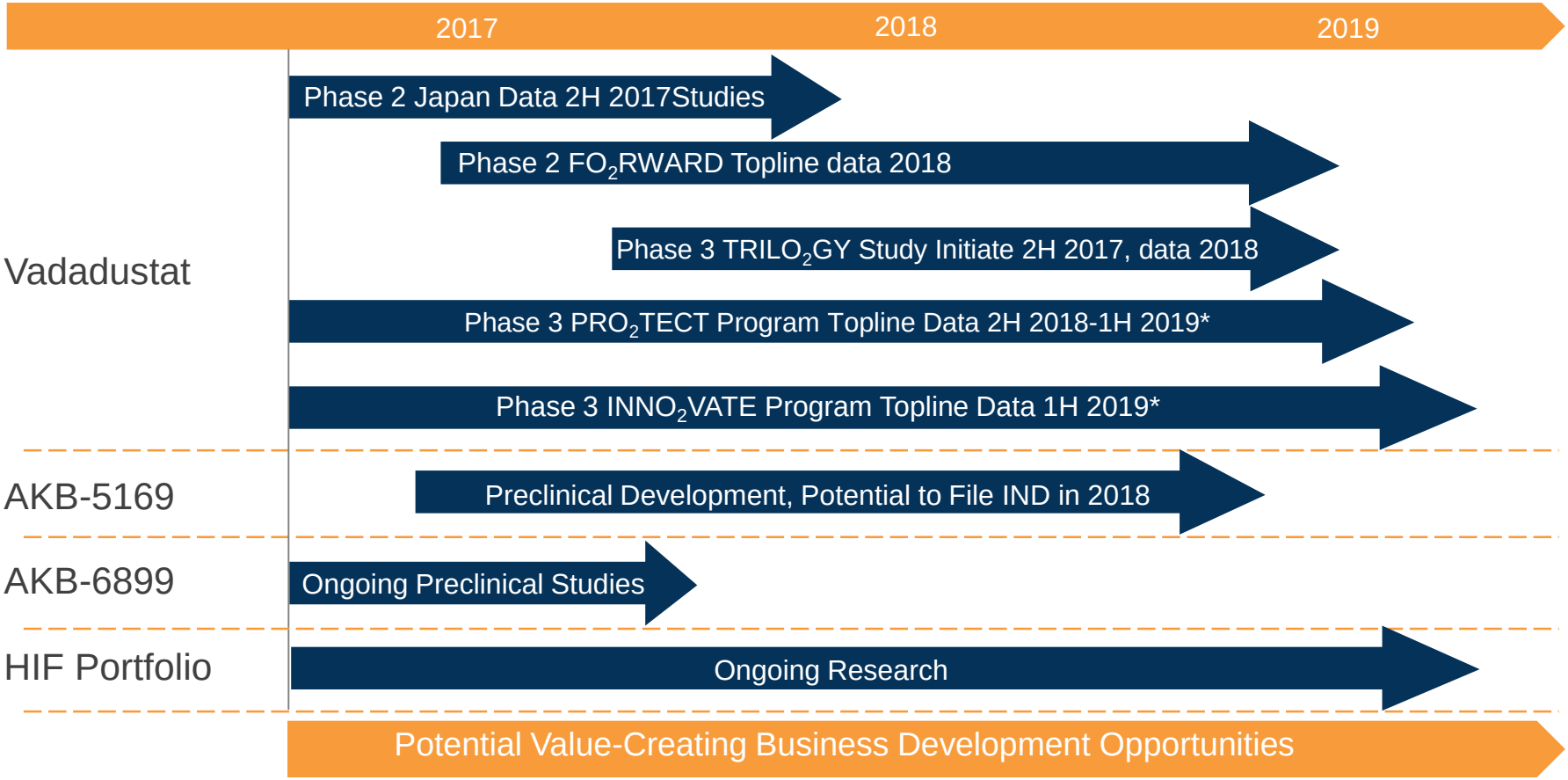
- AKB-5169
- Large compound library
- Clear target indication priorities

Business Development

- Renal disease
- Leveraging HIF

Akebia THERAPEUTICS

Upcoming Milestones



*Timeline dependent on major adverse cardiovascular events (MACE) endpoint.

Q&A