AB Science Web Conference

Masitinib in Sickle Cell Disease

30 November 2023

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Overview of Sickle Cell Disease and Scientific Rationale

Sickle cell disease (SCD)

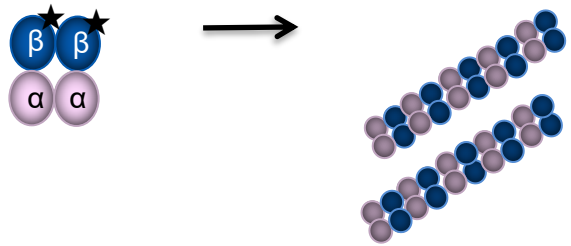
SCD is a disease different from thalassemia

β-thalassemias

Reduced or absent synthesis of β-globin chain (α-globin precipitates) → Intramedullary death of red blood cell precursors → Anemia

Sickle-cell disease (SCD)

Glu → Val substitution (★) → HbS polymerization upon deoxygenation → Sickle-shaped RBCs → Vaso-occlusion Anemia



Sickle cell disease (SCD)

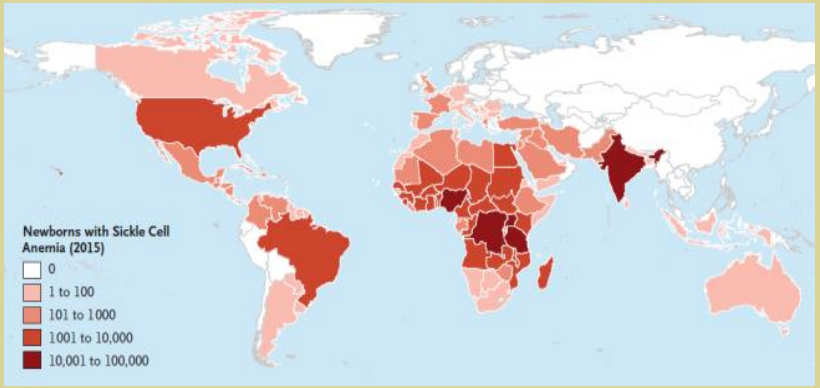
SCD is the largest monogenic disease worldwide, with a disproportionate burden on Black and Hispanic communities and masitinib will address severe form of SCD

SCD is a group of inherited red blood cell disorders

- Red blood cells contain hemoglobin, a protein that carries oxygen. Healthy red blood cells are round, and carry oxygen to all parts of the body.
- In SCD, a genetic mutation causes abnormal hemoglobin to clump together, causing the red blood cells to turn sickle shaped.
- There are several types of sickle cell disease, depending on the genes a person inherits from their parents.
  - **Hemoglobin SS (HbSS)** is a severe form (~65%)
  - Hemoglobin SC (HbSC) is a mild to moderate form (~25%)
  - Hemoglobin beta (HbS) thalassemia (~10%)
- Sickle cells die early, leading to a constant shortage of red blood cells (anemia). They also get stuck in small blood vessels, causing pain and other serious complications.

SCD affects millions of people throughout the world

- The number of people living with SCD globally increased by 41·4%, from 5.5 million in 2000 **to 7.7 million in 2021** [1] .
- SCD affects approximately **100,000 Americans** and 1 in 13 Black or African-American babies [2]
- SCD affects **between 19,800 and 32,400 patients in France** [3]
- In some areas of Saudi Arabia, SCD affects up to 2.6% of the population [4].



Piel, NEJM 2017

[1] Lancet Haematol. 2023 Aug;10(8) ; [2] Center For Disease Control and Prevention (CDC) ; [3] PLoS One. 2021; 16(7) ; [4] Jast *ania 2011, Ann Saudi Med*

Symptoms and mortality

SCD represents a major public health challenge and leads to early death

SCD is a major public health challenge

- Lifelong affliction of **hemolytic anemia** requiring blood transfusions
- **Multiple severe multi-organ complications** [1]
  - **Pain crisis** leading to hospitalization
  - **Vaso-Occlusive Crises** (VOC): occurs when sickled red blood cells block blood flow to the point that tissues become deprived of oxygen.
  - **Infection**, such as flu, meningitis, and hepatitis.
  - **Acute Chest Syndrome** (ACS): due to blockage of the flow of blood to the lungs
  - **Stroke** as sickle cells can clog blood flow to the brain
- **Widespread risk of organ damage or organ failure** [2]
- **75% report difficulty completing daily tasks** [3]

SCD is a life-threatening disease

- **Total SCD deaths put at 376,000 for 2021, 'cause-specific' estimate was 34,400** [4]
- **1 in 4 patients have a stroke by age 45** [2]
- In the USA, **the median age at death is 43 years** [1]
- SCD-related deaths were most often related to
  - chronic heart conditions such as high blood pressure (27%)
  - Acute cardiac events, such as heart attacks (24%)
  - Infections (22%)

[1]CDC ; [2] Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005 3 Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010. [3] Holdford et al 2021 ; [4] GBD 2021 Sickle Cell Disease Collaborators. Lancet Haematol. 2023.

Scientific rationale

Mast cells appear to play a critical role for the severe forms of SCD

Hemolysis SCD is responsible for nitric oxide depletion, which is known to activate mast cells

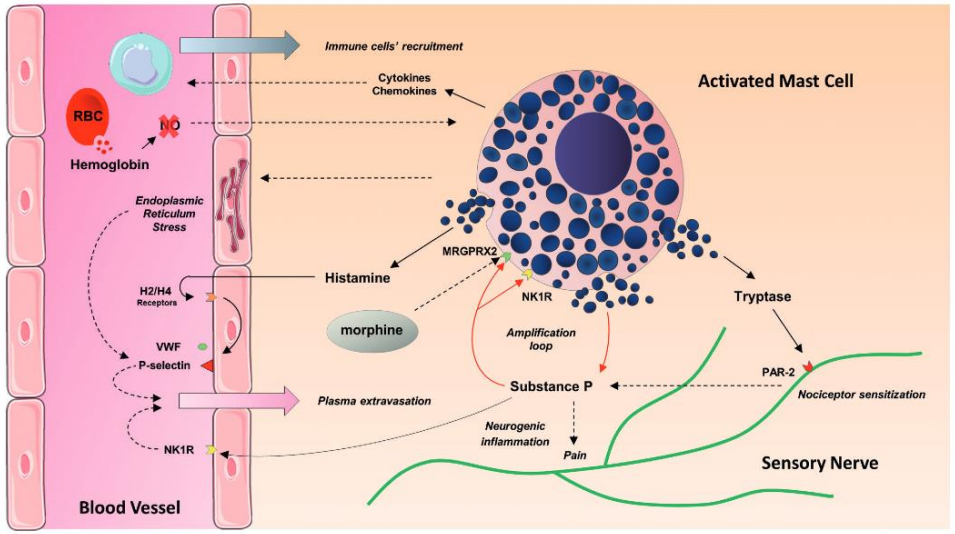
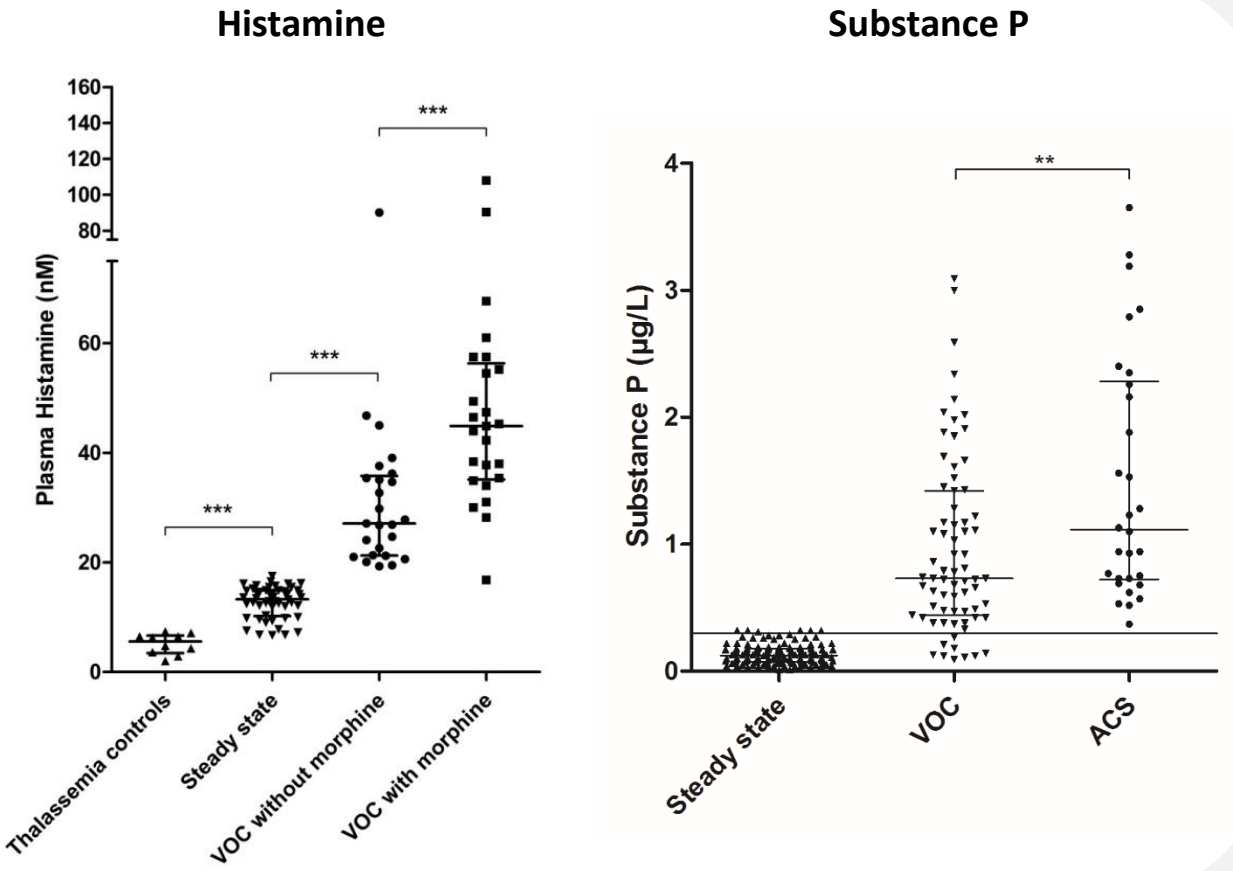


Figure 3. Mast cells in sickle cell disease. Histamine released from mast cells (MC) stimulates endothelial H_2 and H_4 receptors, thereby inducing the release of von Willebrand factor and expression of P-selectin. Tryptase released from MC activates protease-activated receptor 2 on peripheral nerve endings, thus contributing to nociceptor sensitization and stimulating the release of substance P (SP). SP released from MC and from sensory nerve endings increases plasma extravasation via neurokinin 1 receptor (NK1R) and promotes neurogenic inflammation. SP also acts on MC via NK1R and MAS-related G-protein-coupled receptor X2 (MRGPRX2), thus inducing more SP release in an amplification loop of MC activation. MRGPRX2 stimulation by SP induces the release of several cytokines and chemokines, which promotes immune cell recruitment. MC degranulation in response to morphine is also mediated by MRGPRX2. Hemolysis in sickle cell disease (SCD) may contribute to MC activation because it is responsible for nitric oxide depletion, which is known to activate MC. MC activation appears to contribute to endothelial dysfunction in SCD, via endoplasmic reticulum stress-mediated P-selectin expression and increased endothelial permeability. NO: nitric oxide; PAR-2: protease-activated receptor 2; RBC: red blood cell; VWF: von Willebrand factor.

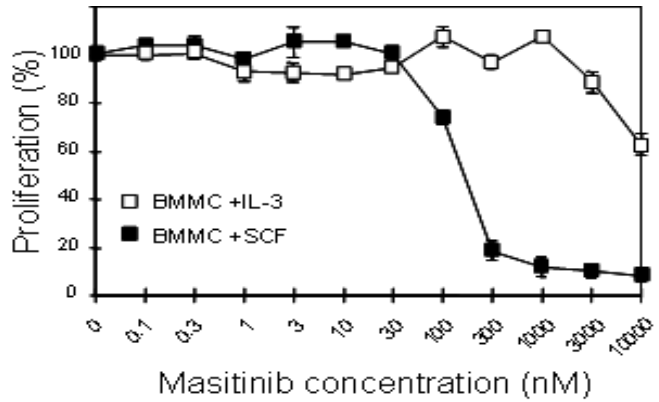
High levels of mast cell mediators in steady state and even more during Vaso Occlusive Crises (VOC)

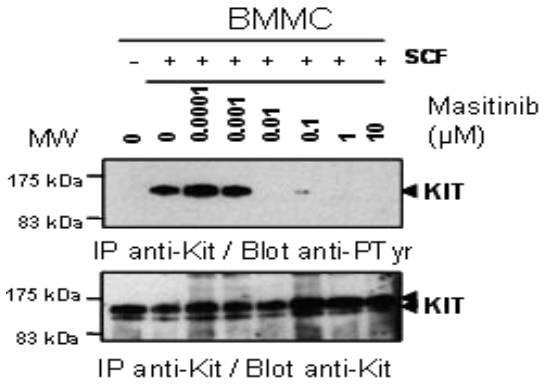


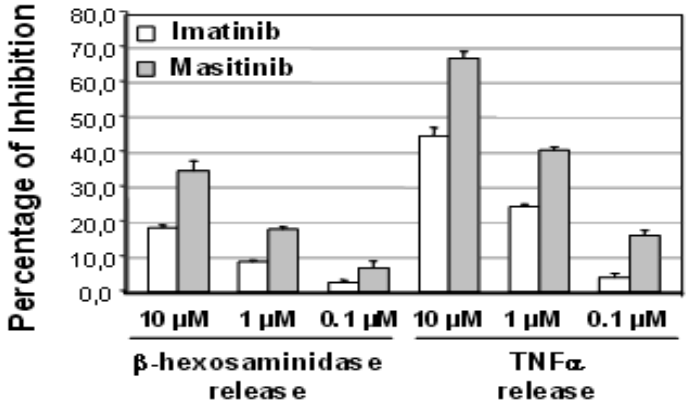
Allalli, Maciel et al Blood advance 2021, British J Hematol 2019

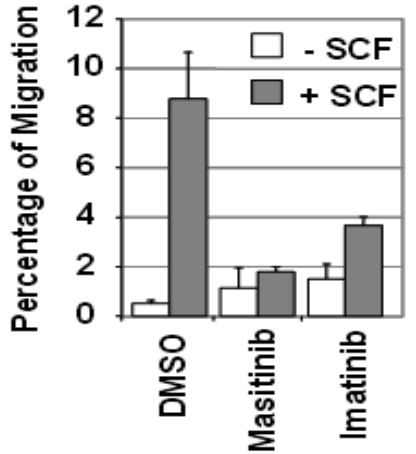
Activity of masitinib on mast cells

Masitinib inhibits mast cell survival, degranulation and migration via c-Kit inhibition



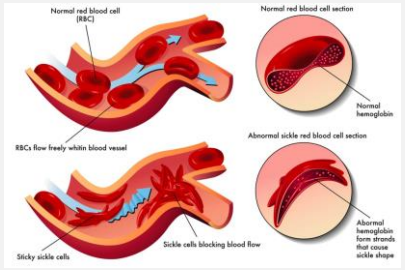


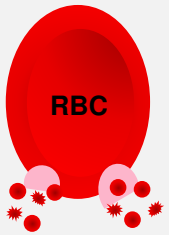




Focus on mast cells and basophils in SCD pathophysiology

Role of mast cells and basophils in the pathophysiology of sickle cell disease



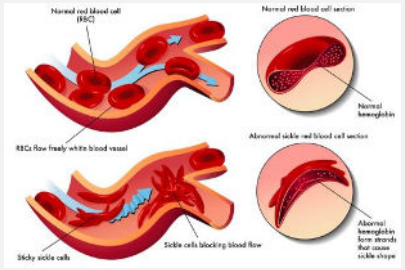


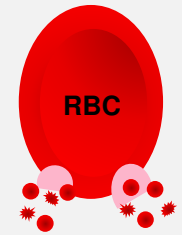
Hemoglobin S

Heme

Allalli, Maciel et al Blood. 2022.

Role of mast cells and basophils in the pathophysiology of sickle cell disease





Hemoglobin S

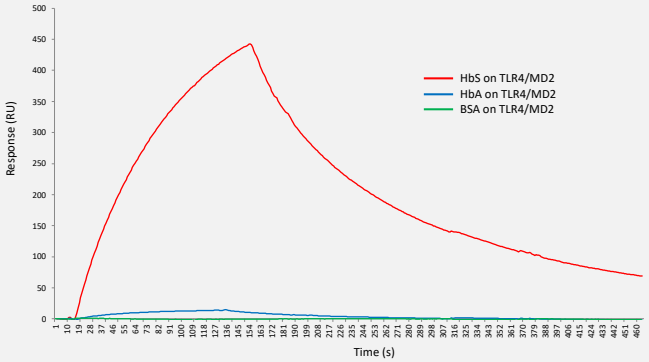
Heme

Mast cells

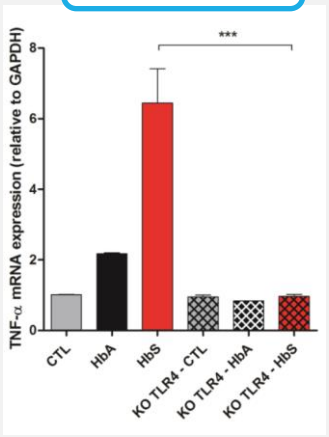
Kinase, IRAP

TLR4

Kinase, IRAP



Basophils



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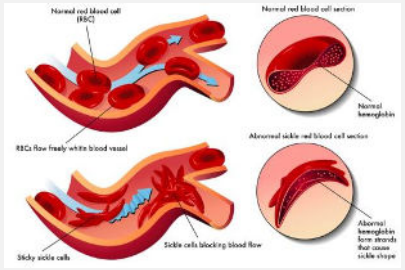
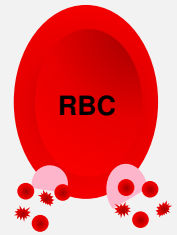
Role of mast cells and basophils in the pathophysiology of sickle cell disease





Hemoglobin S

Heme

Mast cells

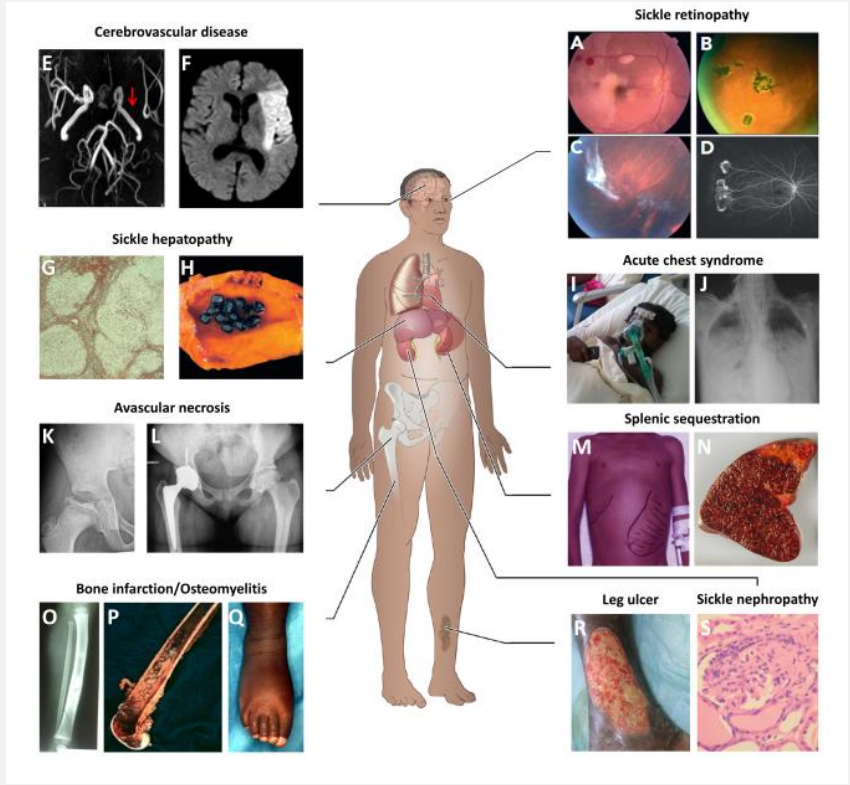
Kinase, IRAP

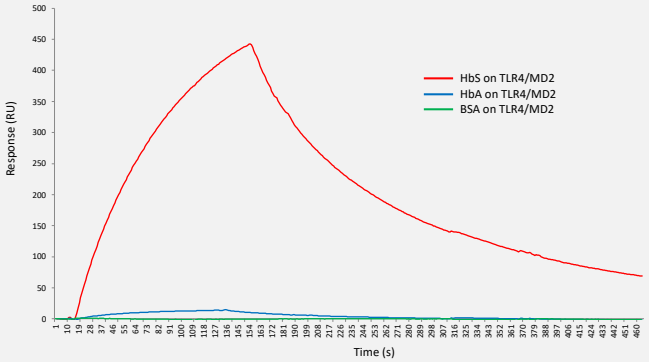
TLR4

Kinase, IRAP

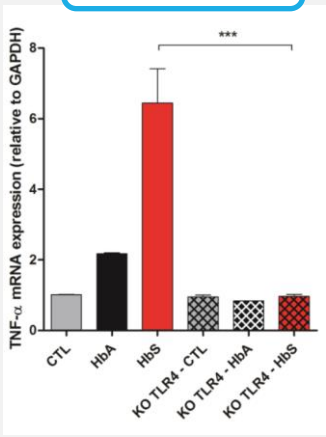
SP, Histamine

new biomarkers



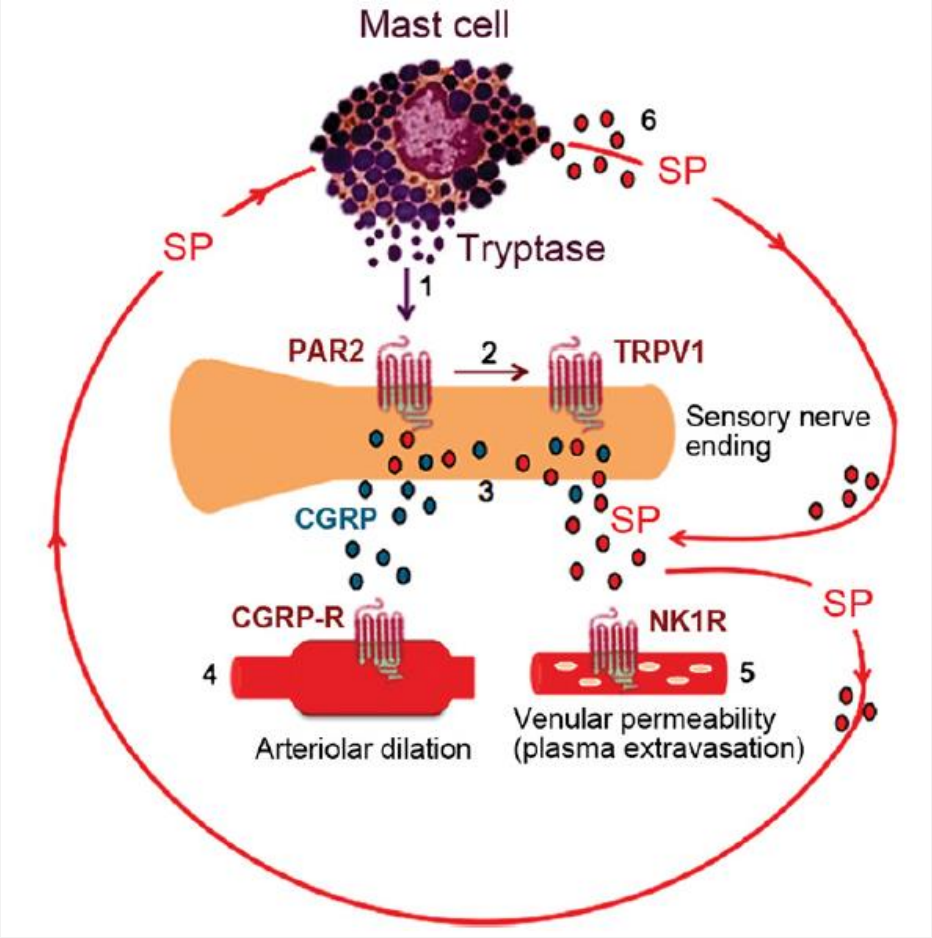


Basophils

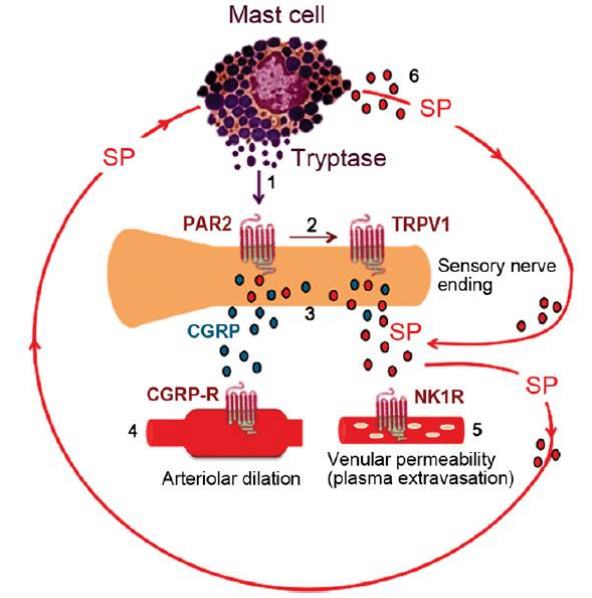


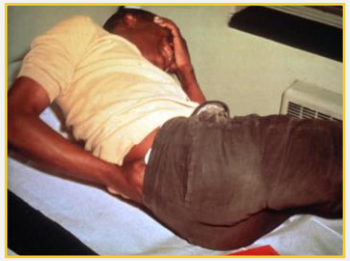
Allalli, Maciel et al Blood. 2022.

Pain and Mast cells

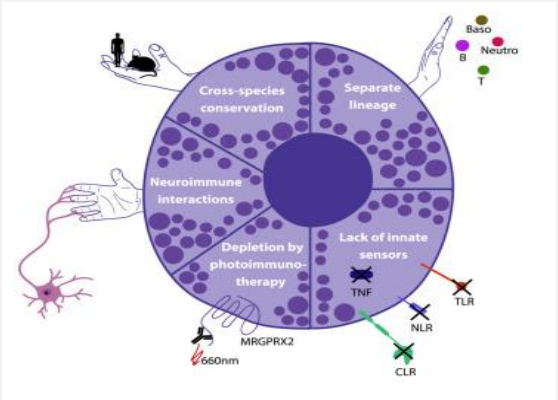


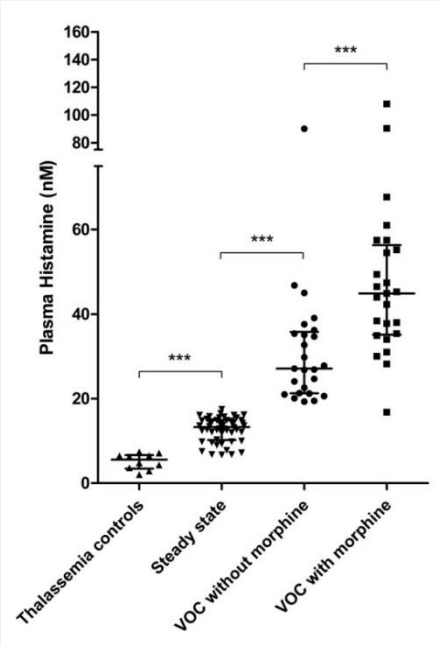
Mast cells and SCD complications





Vaso occlusive crisis VOC
Neurological dysfunction





Allalli, Maciel et al Blood advance 2021, British J Hematol 2019

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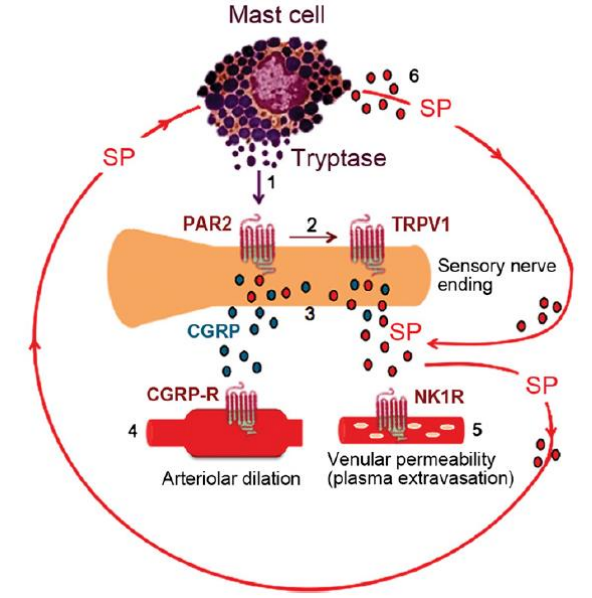

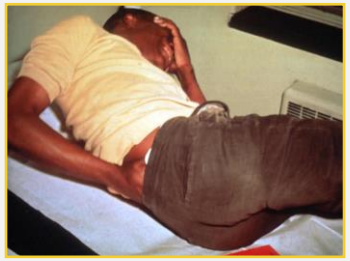

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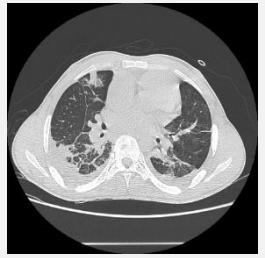
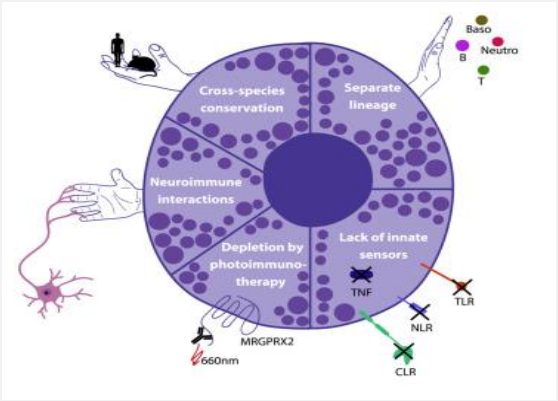
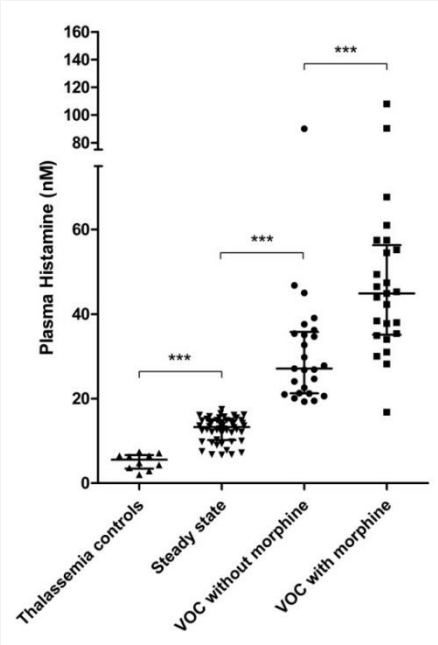
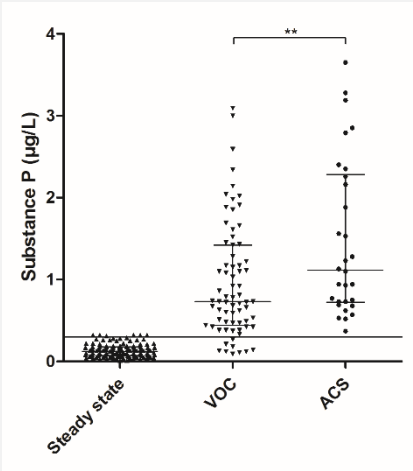


Acute chest Syndrome (ACS)







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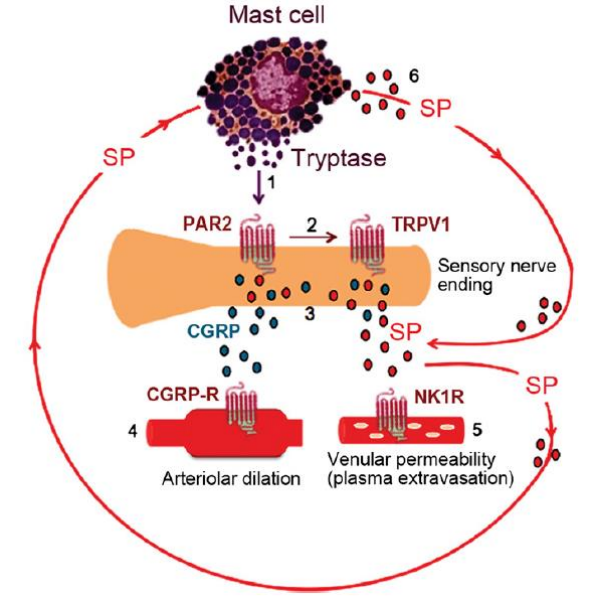
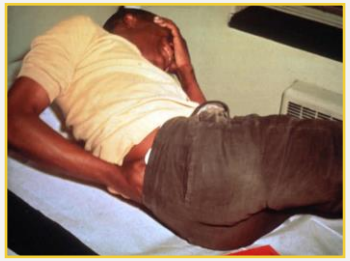
Mast cells and SCD complications





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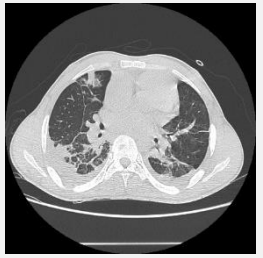

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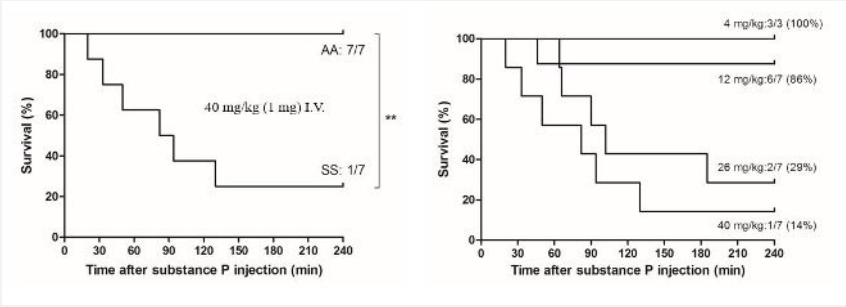
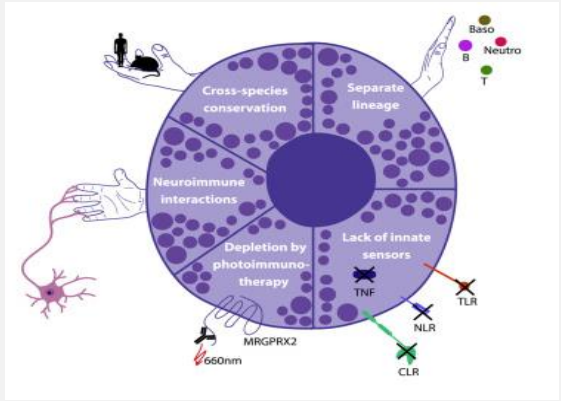
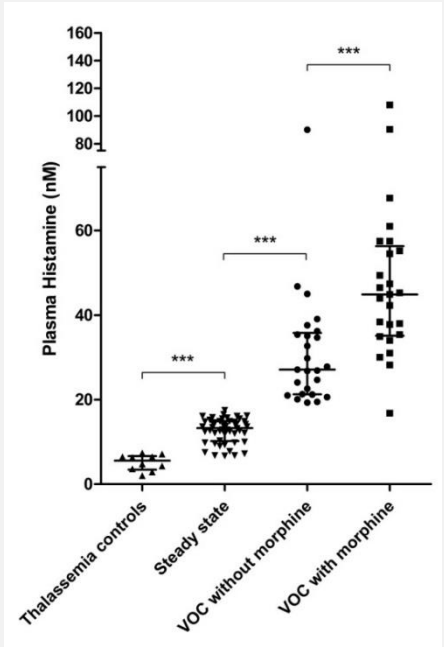
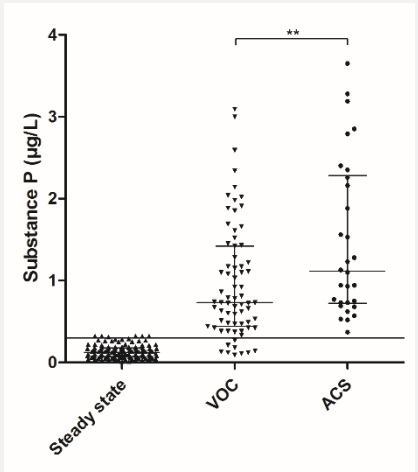
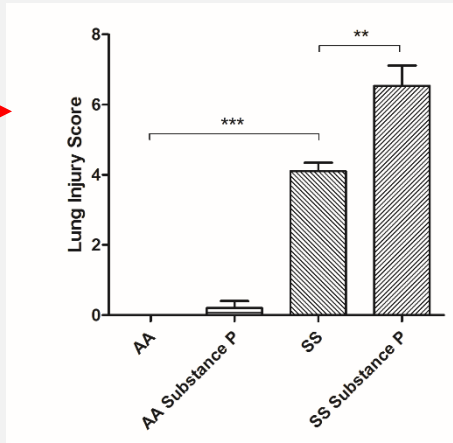
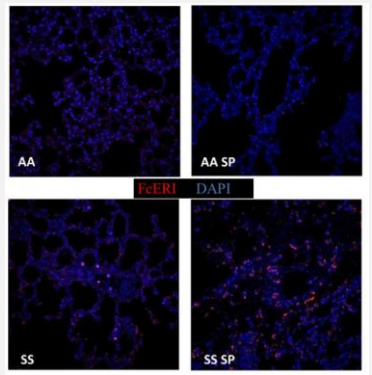


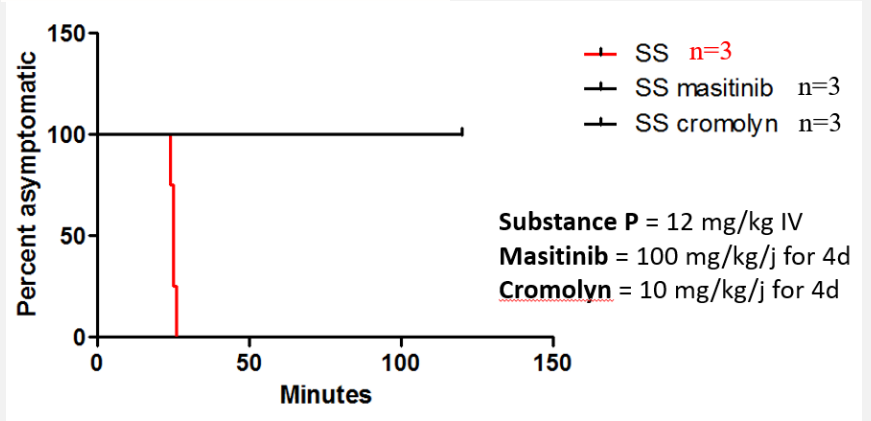












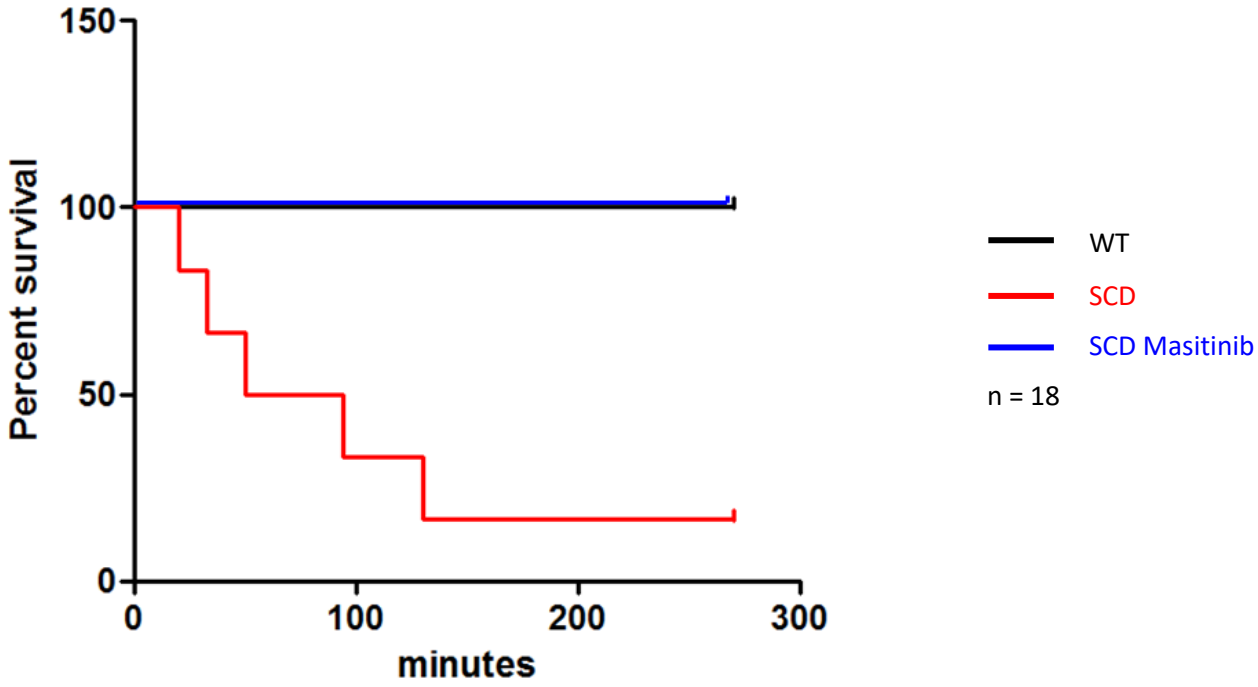
Allalli, Maciel et al Blood advance 2021, British J Hematol 2019

In vivo data with masitinib in SCD

SCD mice survival with masitinib

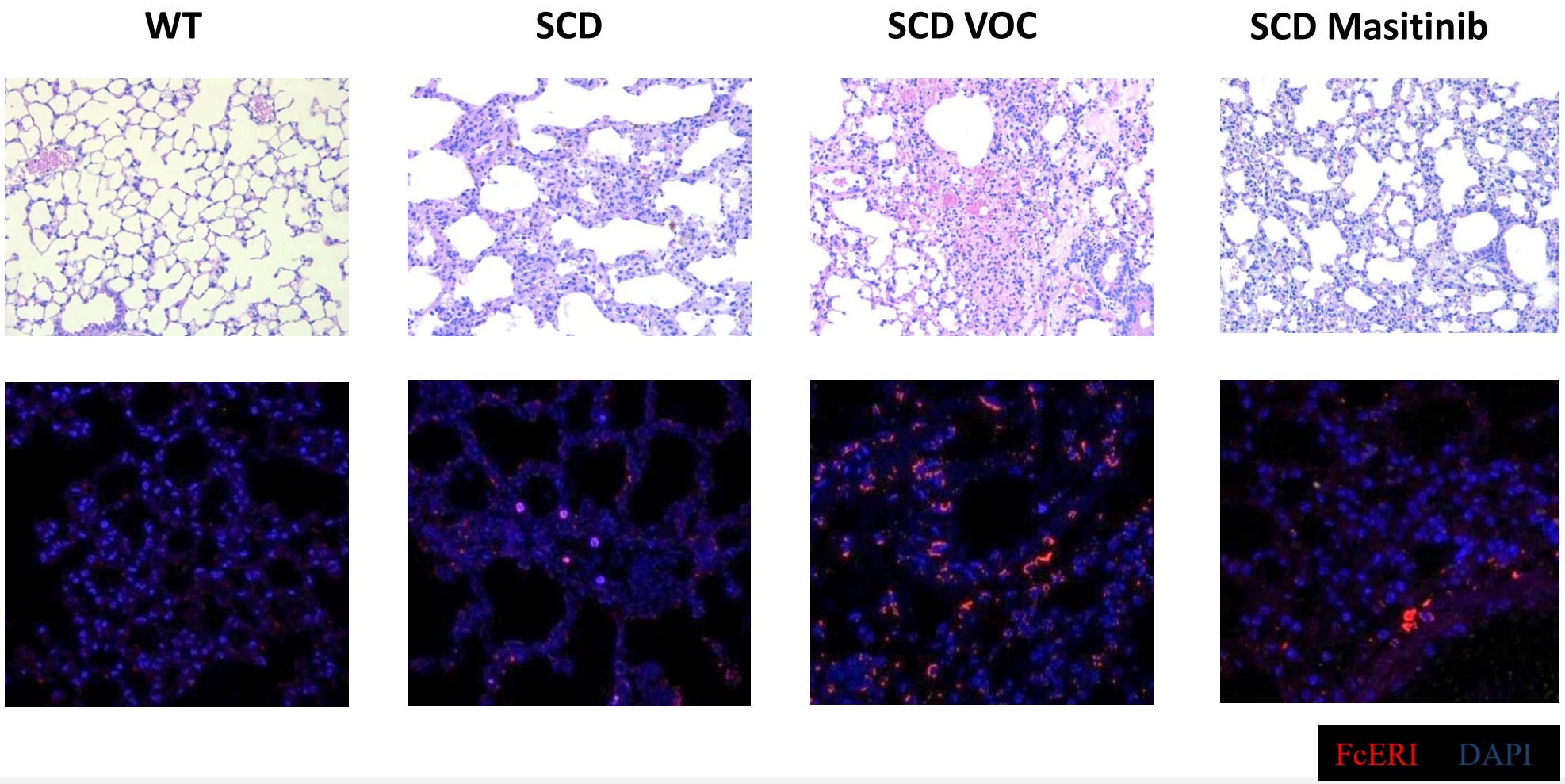
Masitinib has demonstrated survival benefit in an SCD mouse model

- After substance P injection:
  - All control SCD mice experienced VOC and 83% died in the first 3 hours
  - In SCD mice pretreated with masitinib (100 mg/kg/d) during 4 days, there where no VOCs and no deaths



Lung histology and immunohistochemistry

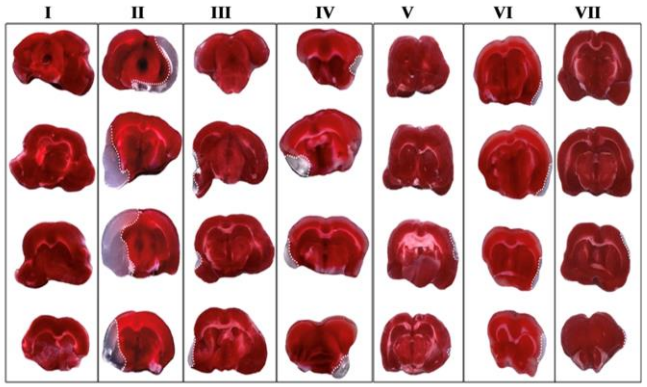
Masitinib protects from acute lung injuries and mast cell infiltration in an SCD mouse model



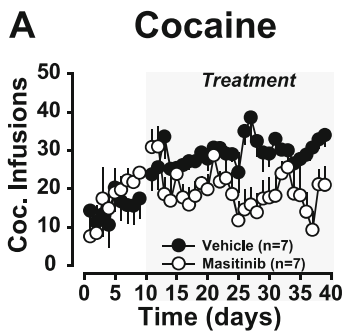
Masitinib and chronic complications

Masitinib has been shown in other conditions to have clinical benefit in complications associated with SCD

Masitinib reduces Infarct size in stroke



Masitinib reduces Cocaïne addiction

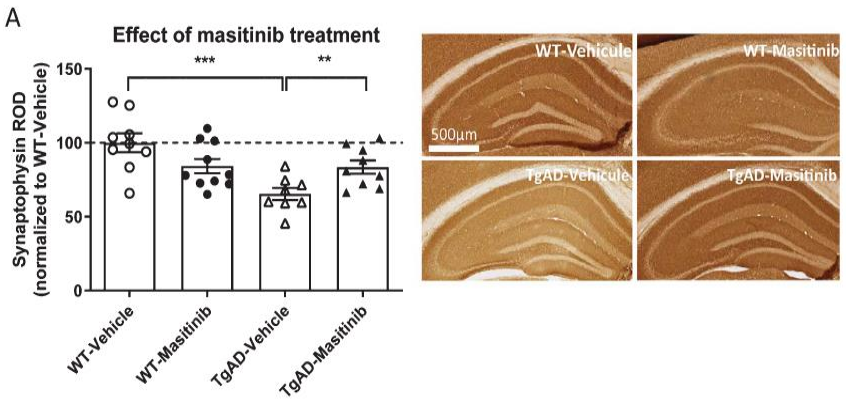


Masitinib reduces PAH in dogs

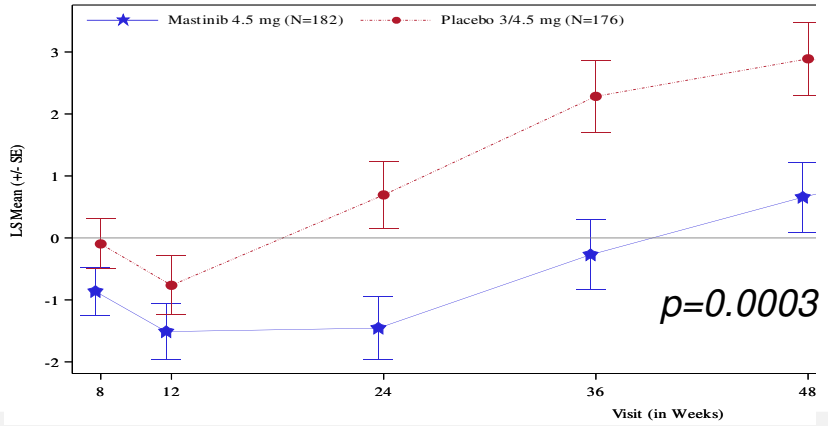
Table 2. Clinical score before and after masitinib administration in seven dogs.

	After masitinib administration (month)					
Variables	Pre (n = 7)	1 (n = 7)	2 (n = 7)	3 (n = 7)	6 (n = 4)	12 (n = 4)
Cough score	1 (1–4)	1 (0–2)	1 (0–2)	1 (1–2)	1.5 (1–2)	1.5 (1–2)
Exercise intolerance score	1 (1–2)	1 (0–1)[a]	1 (0–1)[a]	1 (0–1)[a]	0 (0–1)	1 (0–1)
Syncope score	1 (0–1)	0 (0–1)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)	0 (0–0)
Ascites and edema score	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Total score	4 (3–8)	2 (1–4)[b]	2 (1–3)[b]	2 (1–3)[b]	1.5 (1–3)	2 (2–3)

Masitinib induces a recovery of synaptic markers in transgenic mice model of AD



Significant effect on Cognitive impairment based on ADAS-COG after 48 weeks of treatment



Unmet Medical Need and Market Potential

Limited treatment options

Standard treatment for SCD includes red blood cell transfusions and treatment with hydroxyurea to manage complications, such as vaso-occlusive crises, acute chest syndrome, and pain

Treatment	Mechanism of Action	Comments	Reg Status

Regular Transfusion	Red cell transfusions aim to increase the oxygen carrying capacity of blood and to also reduce the complications of vaso-occlusion.	• Effective in reducing acute and chronic complications
		• Limitation include
		  ○ Limited donors
		  ○ Alloimmunization
		  ○ Iron overload
			Standard of care, but pose significant clinical challenges

Hydroxyurea (Hydroxycarbamide)	Antimetabolite - induction of fetal hemoglobin	• Reduced rate of painful crises • Box Warnings: Myelosuppression, carcinogenic • Estimated use = 27.4% *	Standard of care since 1998

** Unadjusted rate of medication use for the entire SCD population (US) [Cronin RM, et al. Blood Adv. 2023 Jul 11;7(13)].*

Limited treatment options

Treatment for SCD can be curative based on gene therapy (targets the HbS mutation), but such an option remains extremely limited due to scarcity of donors, unresolved safety challenges, and high costs

Drug / Pharma		Mechanism of Action	Comments	Reg Status
Allogeneic HSCT		Curative gene therapy	• Less than 15% of patients have suitable donor • Only 10% eligible patients receive HSCT • Overall, <2% of SCD population treated	Standard of care for severe SCD
Exa-cel (CTX001) CASGEVY	Vertex & CRISPR Therapeutics	Curative gene therapy – Genetically modified autologous CD34+ cell based on editing of the BCL11A gene	• Confirmed (12 mo) freedom from VOCs • Sustained increase in hemoglobin concentration • Estimated cost of ~ $2.8M per patient	MHRA (UK) 2023-11 Under review at EMA & FDA
Lovo-cel (bb1111) LentiGlobin	Bluebird Bio	Curative gene therapy – Autologous hematopoietic stem cell gene therapy based on a modified β-globin gene (βA-T87Q)	• Not approved for SCD in any country • FDA approved for β-Thalassemia (2022) • Estimated cost of ~ $2.8M per patient	Under review at EMA & FDA for SCD

Limited treatment options

Recently, new drugs have been registered by the FDA, but significant unmet need still remains

Drug / Pharma		Mechanism of Action	Comments	Reg Status
Deferiprone (Ferriprox®)	Chiesi Global Rare Diseases	Iron chelator Medicine to treat iron overload from blood transfusions	• Reduction in liver iron • Box Warnings: Agranulocytosis, neutropenia	FDA 2011 EMA 1999
L-glutamine (Endari®)	Emmaus Life Sciences	L-glutamine is an antioxidant that reduces oxidant damage to red blood Medicine to treat pain	• Reduces number of crises requiring hospitalization • No impact on anemia • Estimated use = 3.3% *	FDA 2017 EMA rejected (Xyndari)
Crizanlizumab (Adakveo®)	Novartis	Selectin inhibitor (monoclonal antibody) Medicine to reduce VOCs and pain crises	• Reduces annual rate of VOCs • Estimated use = 2.1% *	FDA 2019 EMA revoked
Voxelotor (Oxbryta®)	Pfizer & Global Blood Therapeutics	HbS polymerization inhibitor Medicine to prevent the sickling of RBC	• Increases hemoglobin • Estimated use = 2.9% *	FDA 2019 EMA 2022

** Unadjusted rate of medication use for the entire SCD population (US) [Cronin RM, et al. Blood Adv. 2023 Jul 11;7(13)].*

Competitive landscape

There is an increasing interest in SCD with several new drugs being in clinical development; however, unlike masitinib, none target mast cells

Drug / Pharma		MoA	Comments	Reg Status
Etavopirat	Novo Nordisk & Forma Therapeutics	Erythrocyte pyruvate kinase (PKR) activator Medicine to reduce VOCs and pain crises	NCT04624659	Phase 2/3
Mitapivat	Agios Pharmaceuticals	Erythrocyte pyruvate kinase (PKR) activator Medicine to reduce VOCs and pain crises	NCT05031780	Phase 2/3
VIT-2763 (Vamifeport)	Vifor Pharma	Oral ferroportin inhibitor Medicine to treat iron overload	NCT04817670	Phase 2
Crovalimab	Genentech Hoffmann-La Roche	Anti-C5 monoclonal antibody Medicine to reduce VOCs and pain crises	NCT05075824	Phase 2
Tak 755	Takeda	Recombinant ADAMTS13 protein	NCT03997760	Phase 1

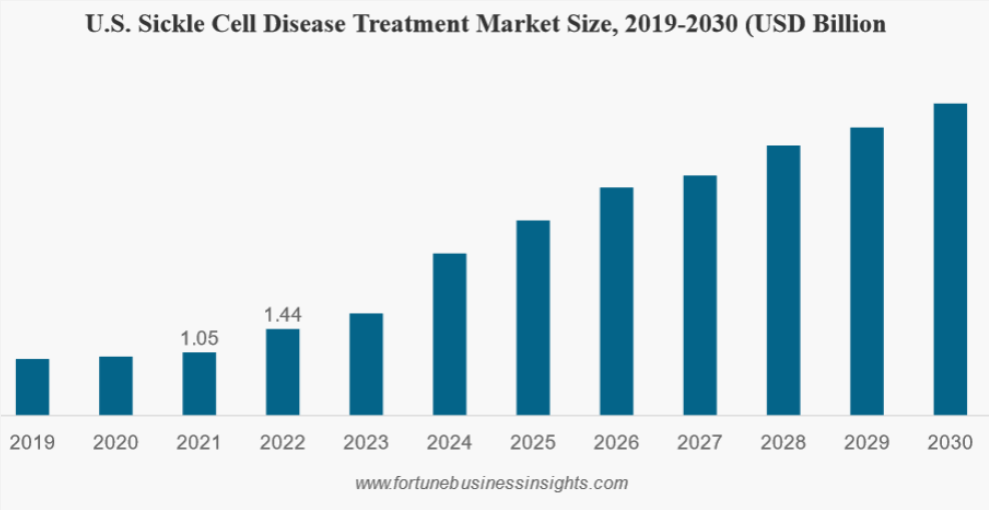
Market potential

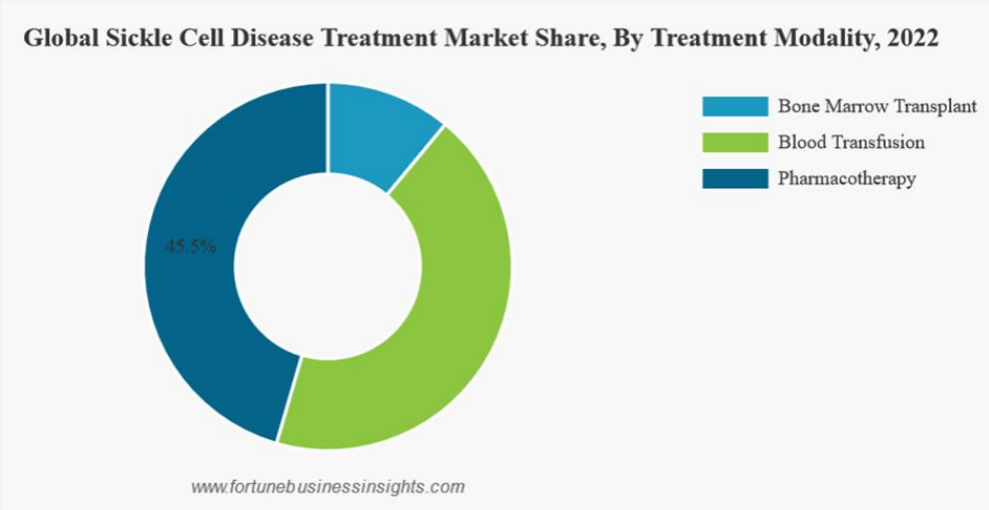
SCD is a growing market, driven by the high cost of novel drugs and rising awareness

- SCD treatment global market size is projected to grow from $2.7 billion in 2023 to **$9.8 billion by 2030** (20.1% CAGR)
- Market is **dominated by the USA** (37.0% market share in 2017)
- Treatment price is high in SCD

Approved Treatment	Year of approval	Annual List price in the USA
Endari	2017	$40,540
Adakveo	2019	$132,000
Oxbryta	2021	$127,000
*Zynteglo**	*2023*	*$2,800,000**

** gene therapy for beta thalassemia, on-time cost*





Market potential

As a result, SCD is triggering large acquisitions

Company	Transaction	Development stage of main asset	Deal size (USD)	Year
Novartis	▪ Acquisition of Selexys Pharmaceuticals based on results from phase 2 study	End of phase 2	665 million upfront + milestones	2016
CSL Behring	▪ Acquisition of Calimmune ▪ Calimmune develops *ex vivo* hematopoietic stem cell (HSC) gene therapy	HSC gene therapy candidate	416 million upfront + milestones	2017
Novo Nordisk	▪ Acquisition of Forma Therapeutics and expand presence in sickle cell disease and rare blood disorders ▪ Forma Therapeutics is a clinical-stage company focused on SCD and rare blood disorders	Phase 2/3 on-going	1.1bn	2022
Pfizer	▪ Acquisition of Global Blood Therapeutics ▪ GBT discovered and developed Oxbryta®	Approved	5.4bn	2022

Description of the SICKMAST Program and Next Step

RHU program

The "Hospital-University Research in Health" (RHU) program, provides a strong endorsement of the masitinib development program in SCD, following diligence from international experts

Strategic government initiative

- RHU program is part of the *Programme d'investissements d'avenir (PIA)*, set-up by the French government to finance innovative and promising investments
- Supports research projects with strong potential for application to industry or society
- Funding of 160 million Euros in 2023 for selected projects in healthcare

Search for excellence

- International jury
- Concept due diligence done
- Selection based on criteria of scientific quality, innovation, and potential for medical and socio-economic impact
- 19 projects selected from a list of 62 pre-selected projects

SICKMAST program

SICKMAST is a collaborative program aimed to develop in phase 2 masitinib as a new treatment of SCD for patients harboring a specific biomarker

Collaborative program

- 6 partners (4 academic, 2 industrial partners)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS — Université Paris Cité — institut imagine GUÉRIR LES MALADIES GÉNÉTIQUES — Inserm La science pour la santé From science to health — AB SCIENCE — codoc

- Funding of 9.2 million Euros distributed among the partners

Objectives

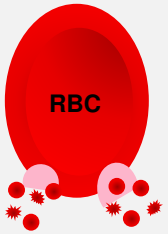
▪ Part 1 : characterization and biomarker	Identify and validate biomarkers highlighting the role of mast cells and basophils in orchestrating acute and chronic complications of sickle cell disease
▪ Part 2 : Phase 2	Demonstrate in a phase 2 clinical trial the efficacy of masitinib in the treatment of acute and chronic complications of sickle cell disease in patients identified based on biomarkers

SICKMAST program

SICKMAST program will validate the role of mast cells and basophils in the pathophysiology of SCD and the therapeutic benefits of masitinib on SCD complications

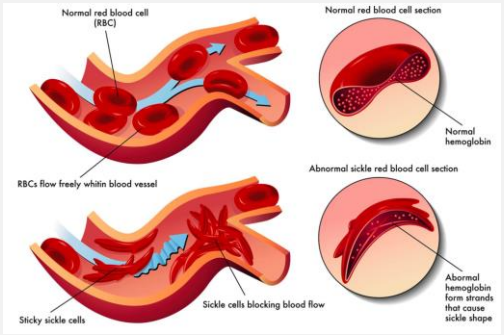
SICKMAST

Coordinator: Olivier Hermine
Scientific director : Thiago Maciel
Medical director S Alali and JB Arlet



Hemoglobin S
Heme

Unmet medical need (HU, Transfusions Transplantation Gene therapy)



D4: New therapy for SCD based on inhibition of mast cell/basophil activation by Masitinib

Mast cells

Kinase, IRAP

TLR4

Kinase, IRAP

Basophils

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Masitinib

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New biomarkers

Substance P, Histamine

D1: Predictive markers of Acute and chronic Complications

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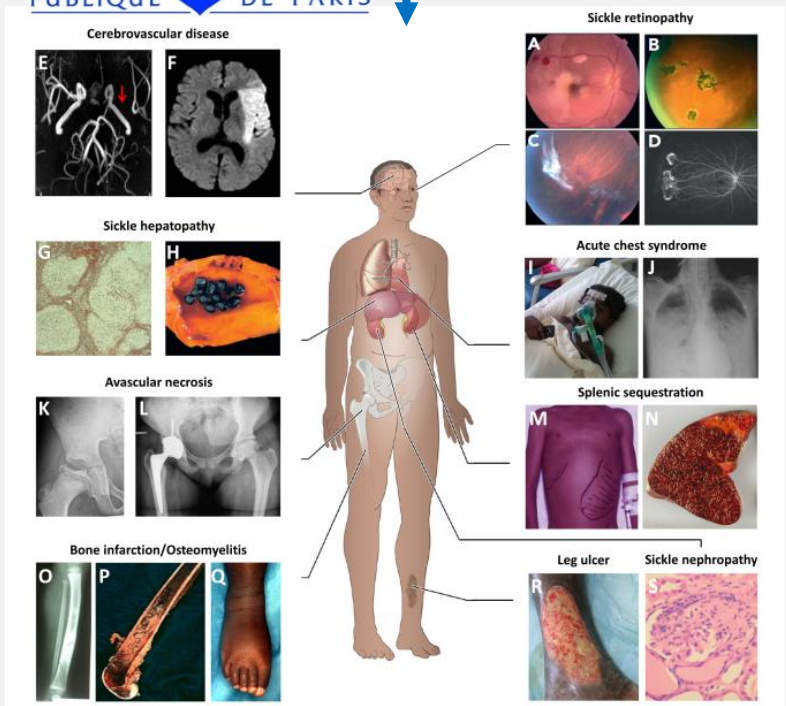

CEREMASTOCYTOSES

D2: Mast cell/basophil phenotypic signature

D3: Selection and Companion tests

codoc

Université Paris Cité

institut imagine
GUÉRIR LES MALADIES GÉNÉTIQUES

Inserm

Allali S et al, Blood 2022, BJH 2019

SICKMAST program

Sickmast program will characterize patients who are likely to benefit from masitinib and will identfy biomarker

- Implementation of a large SCD database of 3,000 SCD patients across four AP-HP hospitals (700 patients already included)

AP-HP Hospital	Active cohort of patients	Patients enrolled
Hôpital Necker Enfants malades AP-HP Hôpital européen Georges-Pompidou AP-HP Hôpital Tenon AP-HP Hôpital Robert-Debré AP-HP	Above 3,000 SCD patients	Above 700 patients (target of 1,500)

- Characterization of novel biomarkers of mast cell/basophil activation (including cellular, metabolomic, proteomic, and genomic markers) in 1,500 SCD patients (750 children and 750 adults)
- Correlations with acute (VOC, ACS, splenic sequestration) and chronic (chronic pain, addiction to opioids, chronic organ dysfunction) SCD complications and identification of predictive and theranostic markers
- Validation of therapeutic approach examined in the appropriate mouse model of SCD

SICKMAST program

Sickmast program will bring clinical evidence of targeting mast cells for the treatment of SCD based on a phase 2 study sponsored by AP-HP

- Step 1 : Dose safety analysis of masitinib treatment, with or without hydroxyurea
- Step 2 : Randomized phase 2 study assessing safety and efficacy of masitinib in patient harboring biomarker
  - Inclusion : patient with identified biomarkers and experiencing VOC (at least 3 times per year) and ACS (two episodes in the past medical history) and with chronic complications
  - Monitoring of all relevant diagnostic and theranostic mast cell/basophil biomarkers in order to analyze their kinetics in response to the administration of masitinib
  - Correlation analyses to confirm the association between these new theranostic biomarkers and the clinical outcomes

Development of masitinib in SCD

AB Science will be free to continue the development of masitinib in SCD based on phase 2 data and biomarker

- AB Science remains free to carry out, as it sees fit, any potential phase 3 development following the success of phase 2
- As part of the consortium agreement established for its patents, AB Science will pay royalties to APHP in the event of commercialization of masitinib in sickle cell disease.
- Partnering of masitinib for SCD is an option

Patent protection

A new patent has been filed, which, if granted, will extend the international protection of masitinib in sickle cell disease until 2040

Protection	Item	Duration of protection	Status
Second medical use patent	Provisional patent application filed for use of masitinib in the treatment of Sickle Cell Disease	Until 2040 if granted	Filed

- SCD is eligible for orphan drug status. Orphan drug status will be discussed in the USA and Europe