AN EXAMPLE OF CLINICAL TRIAL PROTOCOL

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Université de Paris-Cité

Hôpital Necker Enfants malades AP-HP

AP-HP. Centre Université Paris Cité

Inserm

Université Paris Cité

Clinical Research Unit-Center of Clinical Investigation (URC-CIC)

An identified structure, dedicated to clinical research, at the interface between clinical services and research units



Hôpital Necker

AP-HP. Centre Université Paris Cité

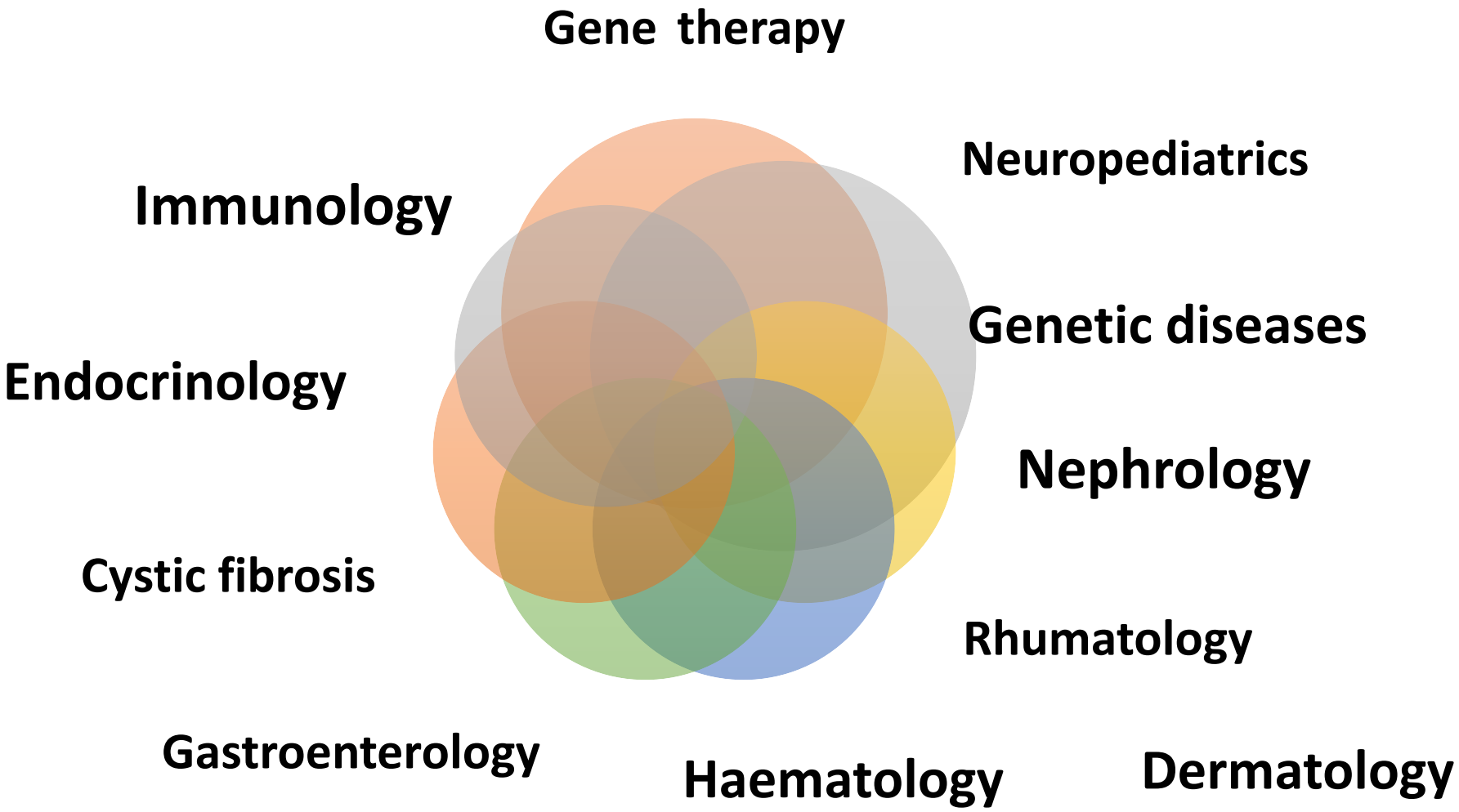
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Hôpital Cochin-Port Royal

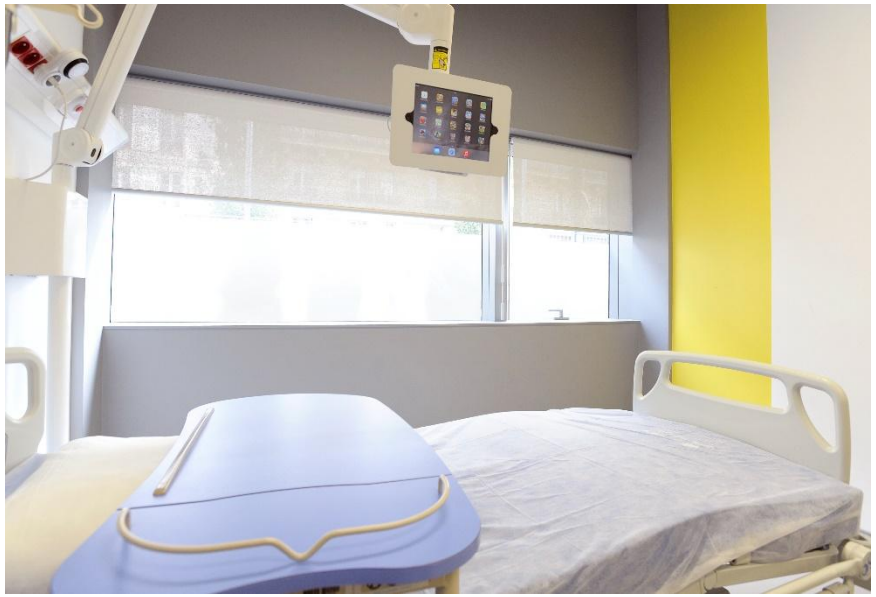
Under the aegis of the Clinical Research and Innovation Department (DRCI-APHP)

CLINICAL TRIALS IN RARE DISEASES



Center of Clinical Investigation









UHTI: Hospitalization Unit for Advanced Therapies

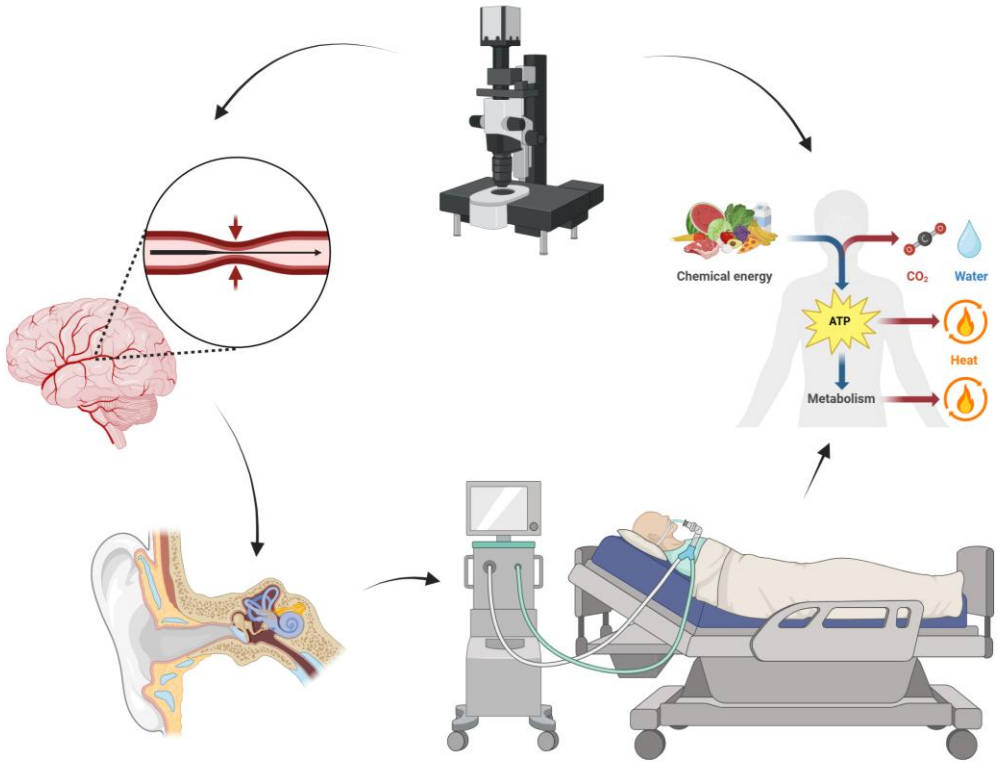
Dedicated to innovative therapies for young and adult patients





CLINICAL TRIALS IN RARE DISEASES

A care pathway bringing together multiple healthcare units for comprehensive management and a multidisciplinary approach

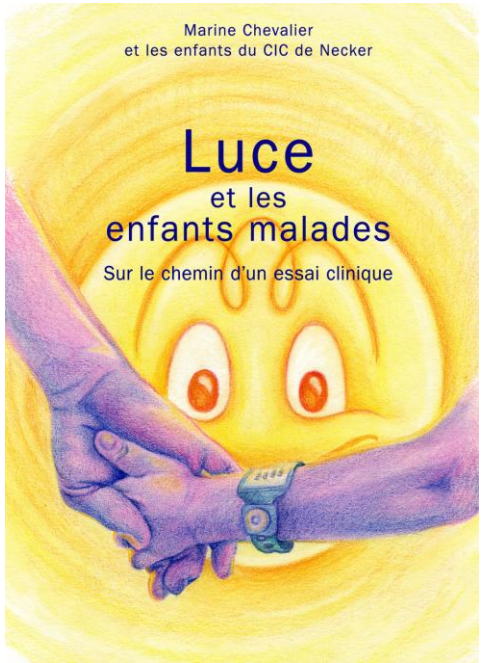




Mobile Unit



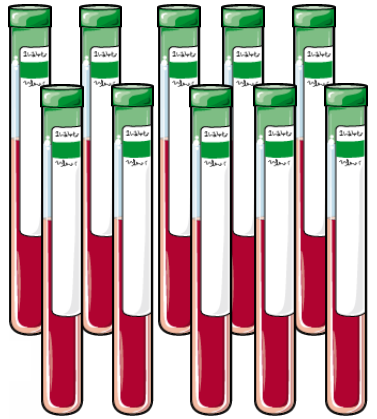
And…. a Clinical research partner

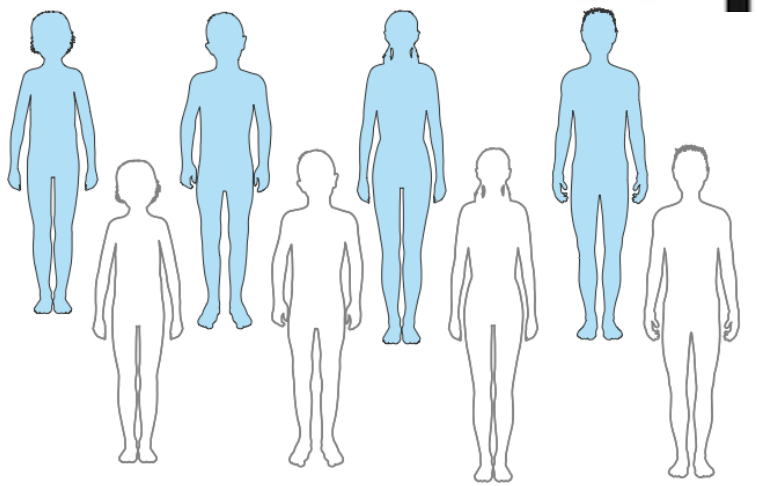


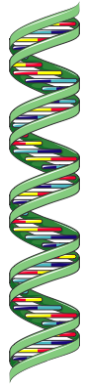
The Origins of a Clinical Research Protocol











From Concept to Application









Research idea → Drafting the Protocol and Consent → Submission to Regulatory Authorities → Study initiation

From the research to the clinical trial

Fundamental Research

Pre clinical studies

Clinical trials

Phase I/II

Fundamental Pharmacology (2 to 3 y)

In vitro and in vivo studies (2 to 3 y)









Created with the help of AI

From the research to the clinical trial

Fundamental Research

Pre clinical studies

Clinical trials

Market access

Fundamental Pharmacology (2 to 3 y)

In vitro and in vivo studies (2 to 3 y)

Phase I/II

Phase III

Phase IV

5 to 7 y

Risk-benefit ratio







Some examples

Importance of Informed Consent in Trials



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Importance of Informed Consent in Trials

Informed consent is more than a form — it's a process of trust, clarity, and respect

Understanding

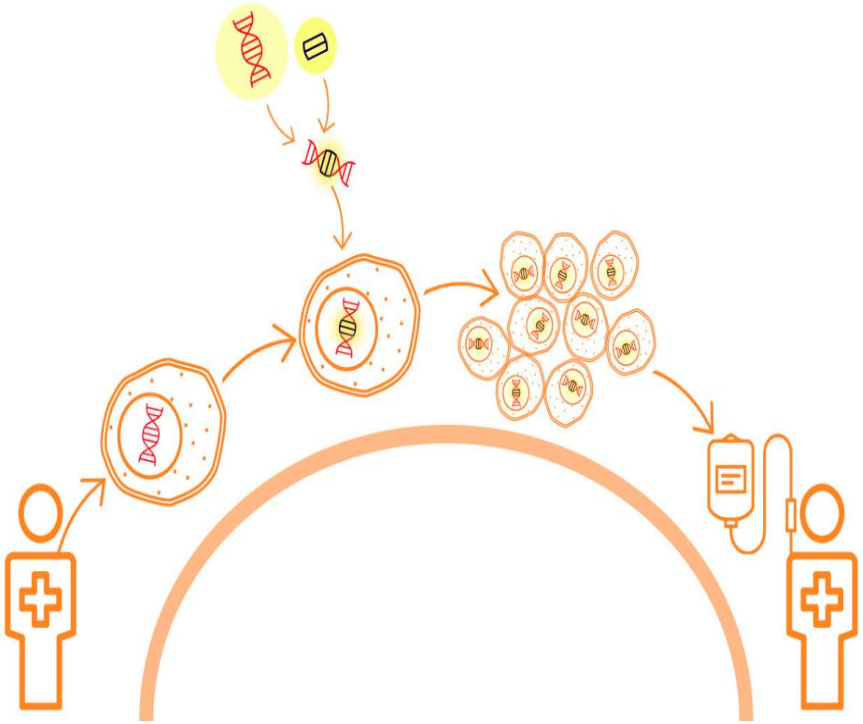


- Clear explanation of therapy, risks, and alternatives
- Acknowledge uncertainty and possible side effects
- Long-Term Impact

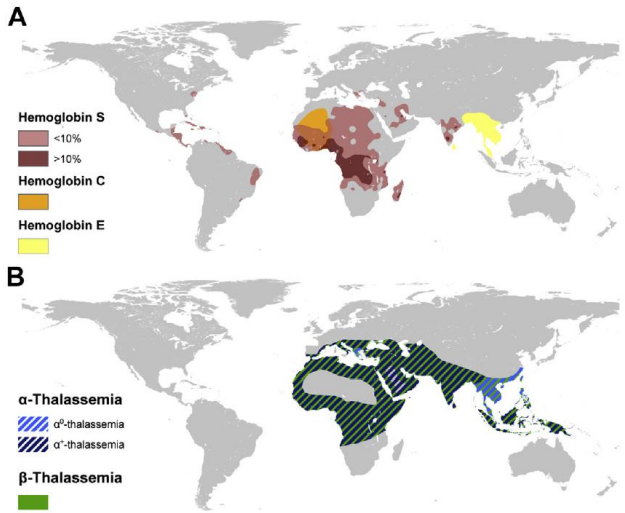
Autonomy & ethics



- Empower patients to make voluntary, informed decisions
- Build confidence and supports strong patient-clinician communication
- Meet ethical and legal standards for clinical trials



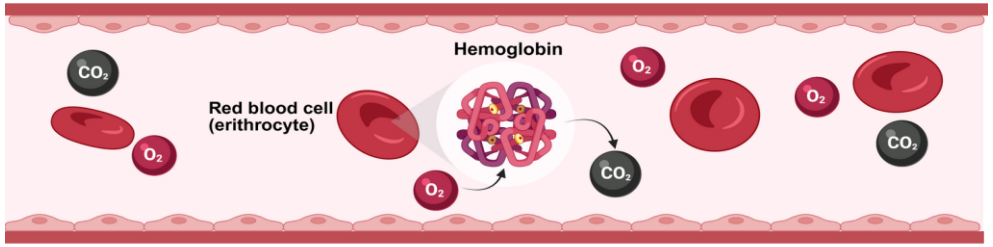
THE EXEMPLE OF GENE THERAPY TRIALS FOR SICKLE CELL DISEASE AND BETA THALASSEMIA

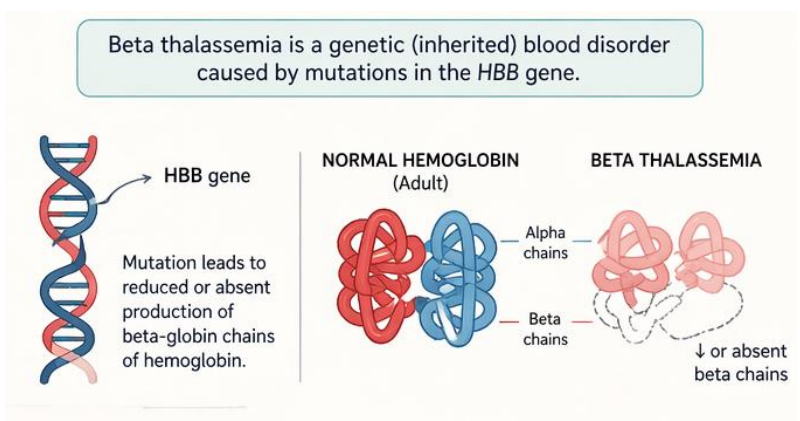


WHO, June 2008; Piel FB, Hematol Oncol Clin N Am, 2016

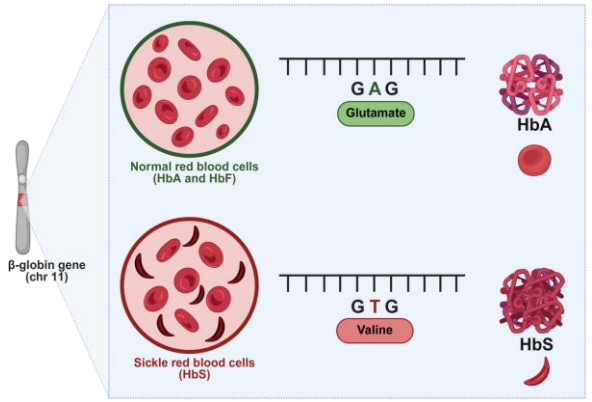
- **>350,000 children are born each year with a severe inherited Hb disorder**
- **~ 80% of affected children are born in low or middle income countries**
- **3.4% of deaths in children aged under 5 years**
- **>9 million carriers become pregnant annually**
- **5.2% of the world population carries a significant variant**

NORMAL HEMOGLOBIN





BETA THALASSEMIA



SICKLE CELL DISEASE

Different steps in a clinical research study

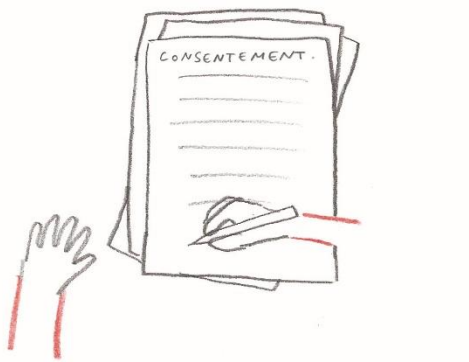
Information on the hopes, risks, and uncertainties of the research therapy. Provision of information and informed consent documents

Inclusion in the study

Study treatment administration

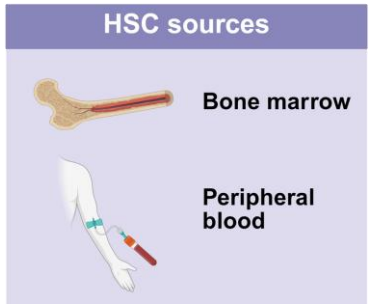
Hospital discharge and medical follow-up: assessment of treatment tolerance and blood measurements of biological parameters. Regular follow-up and hospital/CIC consultations.

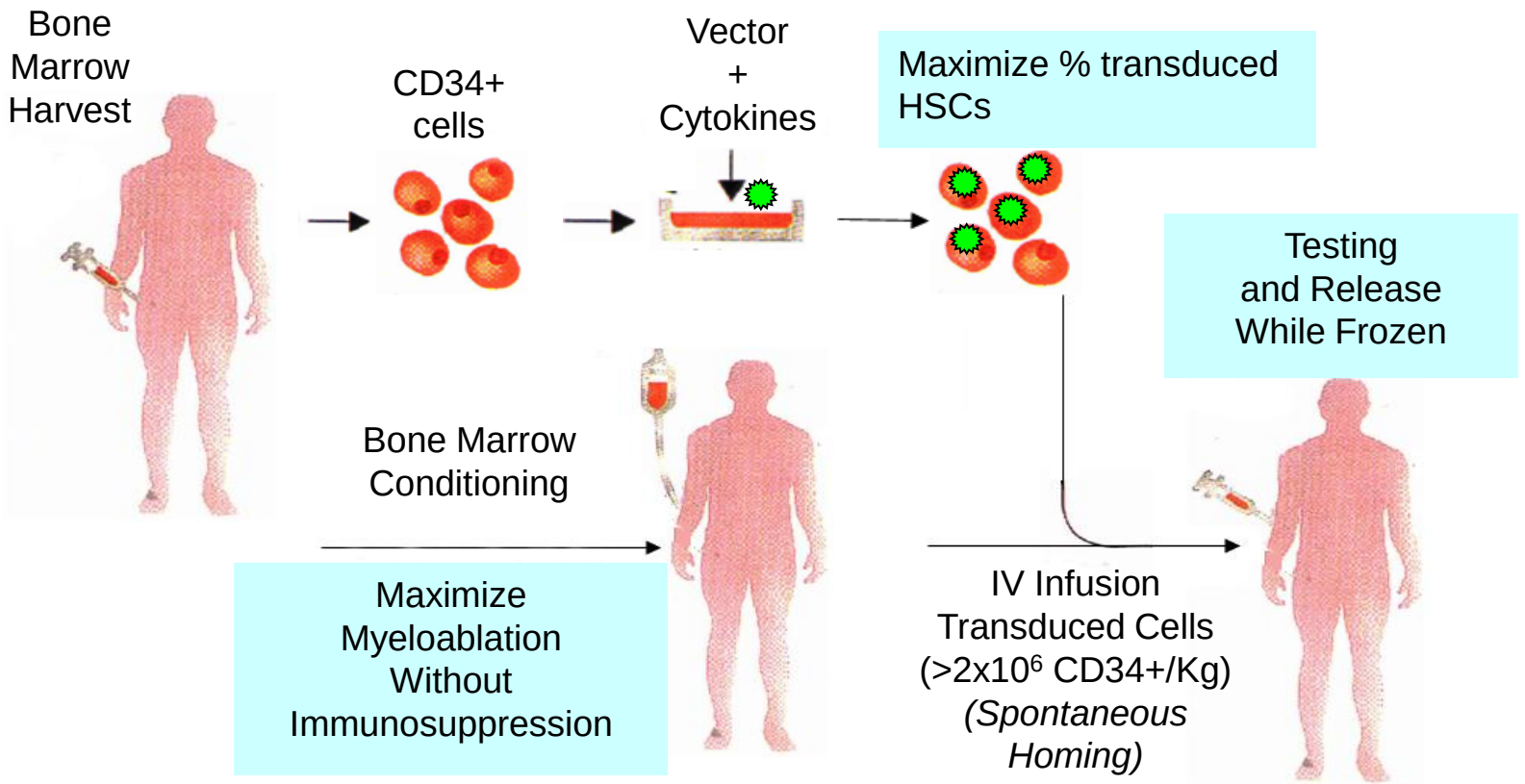
If applicable: new visits for re-administration + regular follow-up and hospital/CIC consultations





TRIAL DESIGN FOR EX VIVO GT



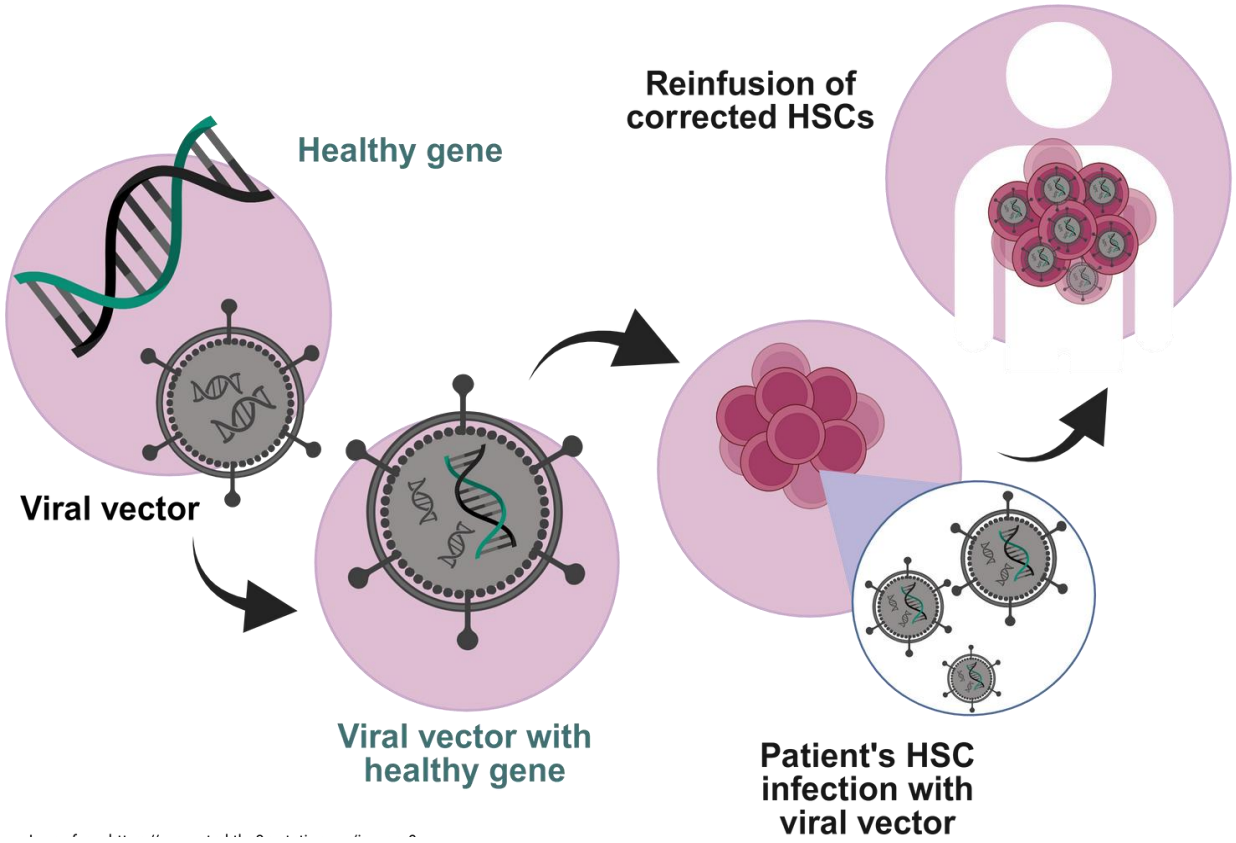


Exemple for HSC transduction

Modifying HSCs using viral vectors

Gene therapy allows us to modify the patient's HSCs

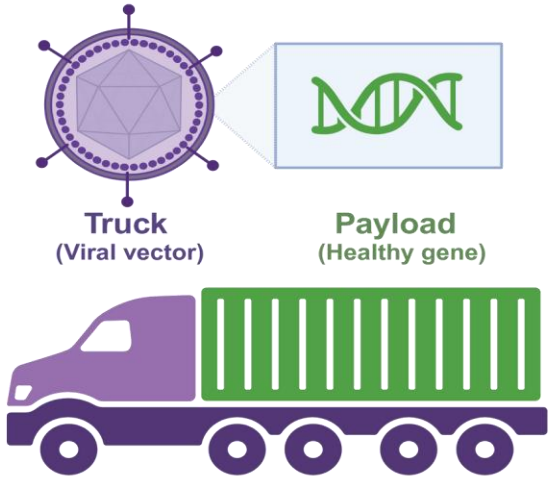
By providing a correct copy of the mutated gene, we can fix the patient's HSCs and re-implant them, avoiding compatibility issues.

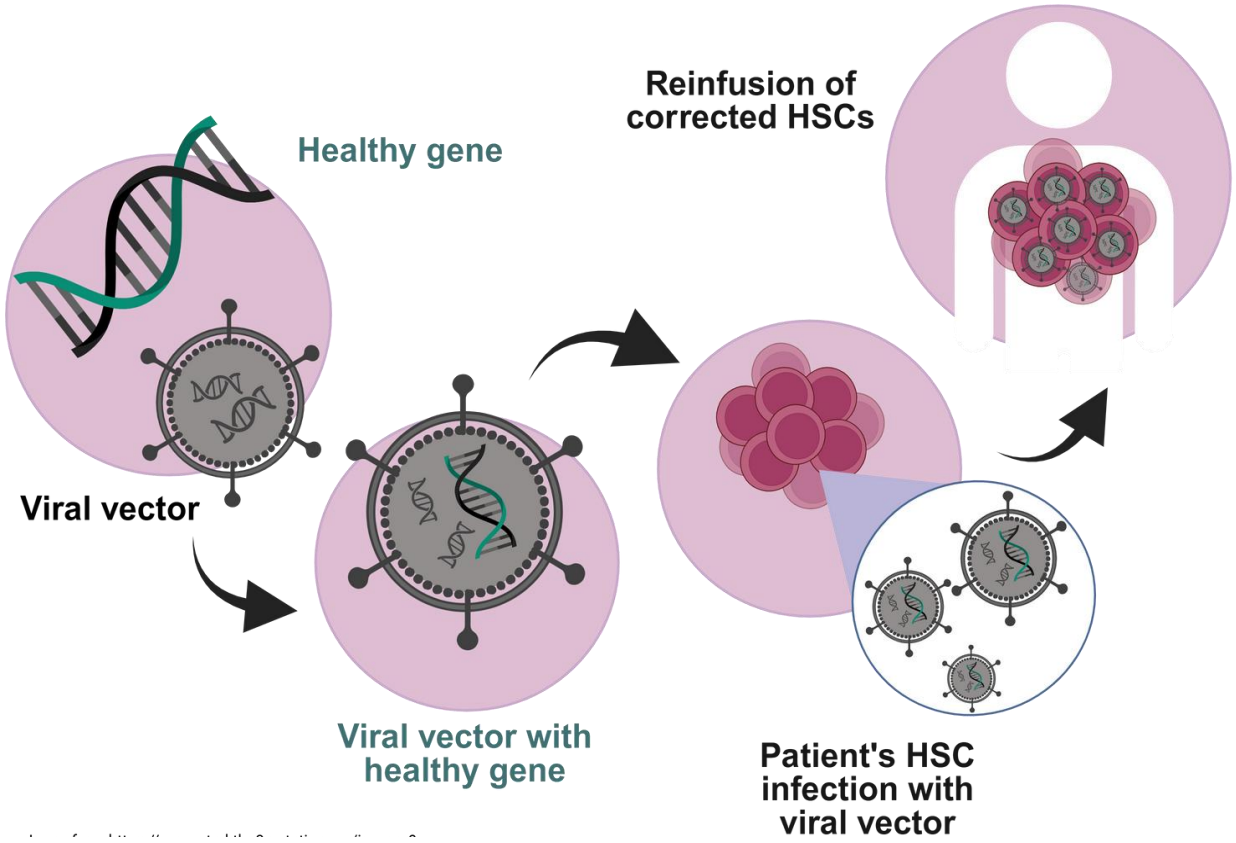


Modifying HSCs using viral vectors

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The development of innovative therapy therapeutic trials: GENE THERAPY

Clinical biological complete remission for 4 patients with homozygous β thalassemia TDT

nature medicine

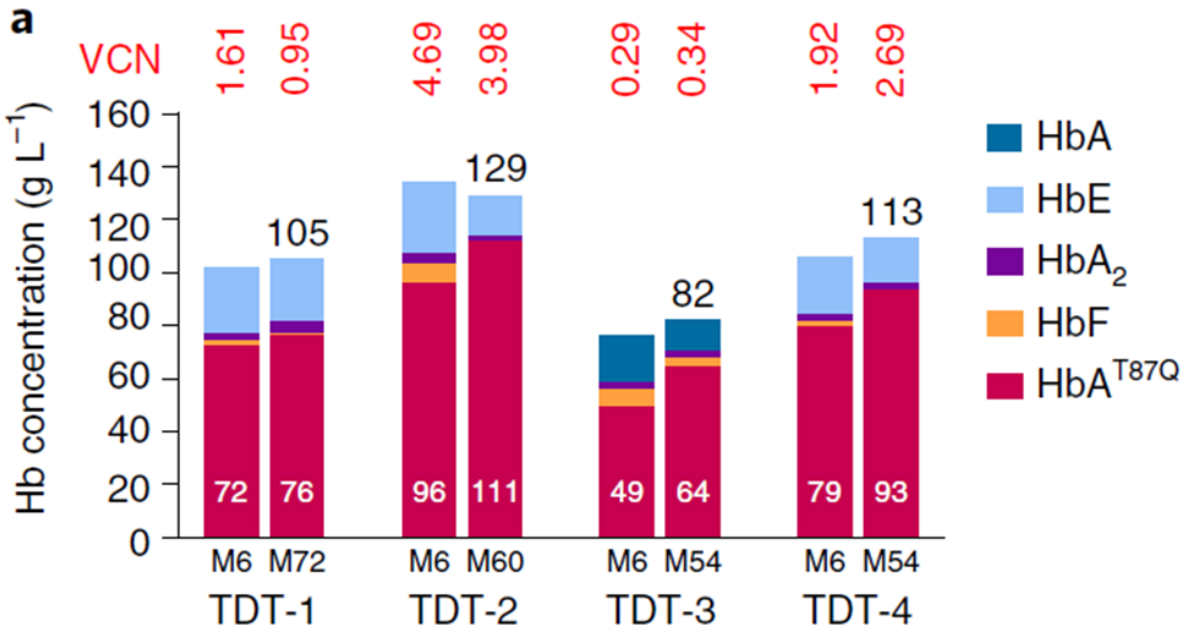
ARTICLES

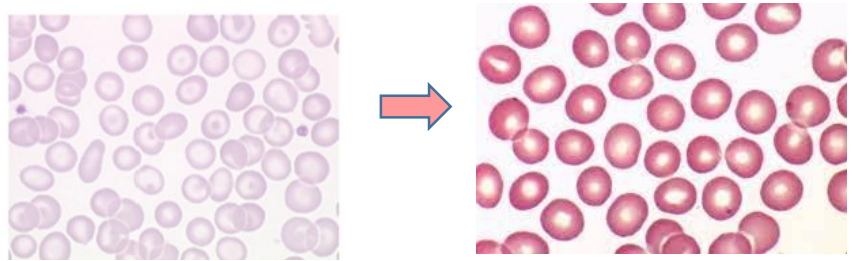
https://doi.org/10.1038/s41591-021-01650-w

Check for updates

Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial

Elisa Magrin[1,2,26], Michaela Semeraro[3,4,26], Nicolas Hebert[5,6,26], Laure Joseph[1], Alessandra Magnani[1,2], Anne Chalumeau[7], Aurélie Gabrion[1,2], Cécile Roudaut[1,2], Jouda Marouene[3], Francois Lefrere[1], Jean-Sebastien Diana[1], Adeline Denis[7], Bénédicte Neven[8], Isabelle Funck-Brentano[8], Olivier Negre[9,10,27], Sylvain Renolleau[11], Valentine Brousse[12], Laurent Kiger[5], Fabien Touzot[1,2], Catherine Poirot[13,14], Philippe Bourget[15], Wassim El Nemer[16], Stéphane Blanche[8], Jean-Marc Tréluyer[3,4], Mohammed Asmal[10,27], Courtney Walls[10], Yves Beuzard[5,9], Manfred Schmidt[17], Salima Hacein-Bey-Abina[1,2], Vahid Asnafi[18], Isabelle Guichard[19], Maryline Poirée[20], Fabrice Monpoux[21], Philippe Touraine[22], Chantal Brouzes[23], Mariane de Montalembert[12], Emmanuel Payen[9], Emmanuelle Six[7], Jean-Antoine Ribeil[1,2,10,27], Annarita Miccio[7,28], Pablo Bartolucci[5,6,28], Philippe Leboulch[9,24,28] ✉ and Marina Cavazzana[4,7,25,28] ✉





The development of innovative therapy therapeutic trials: GENE THERAPY

Long-term complete remission for 2/3 patients with homozygous sickle cell disease

nature medicine

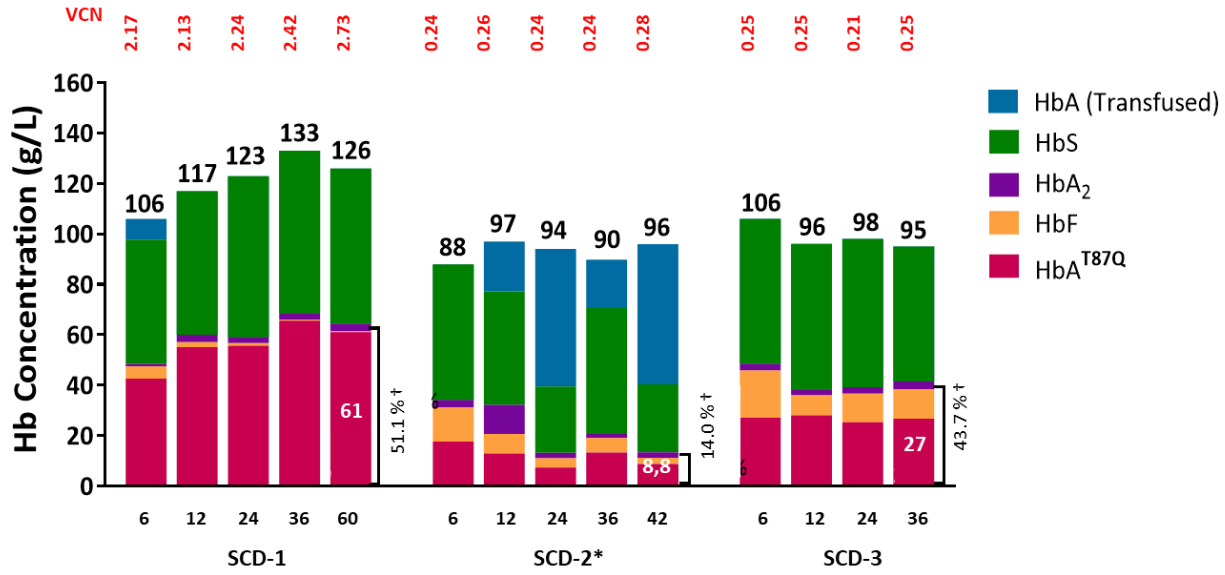
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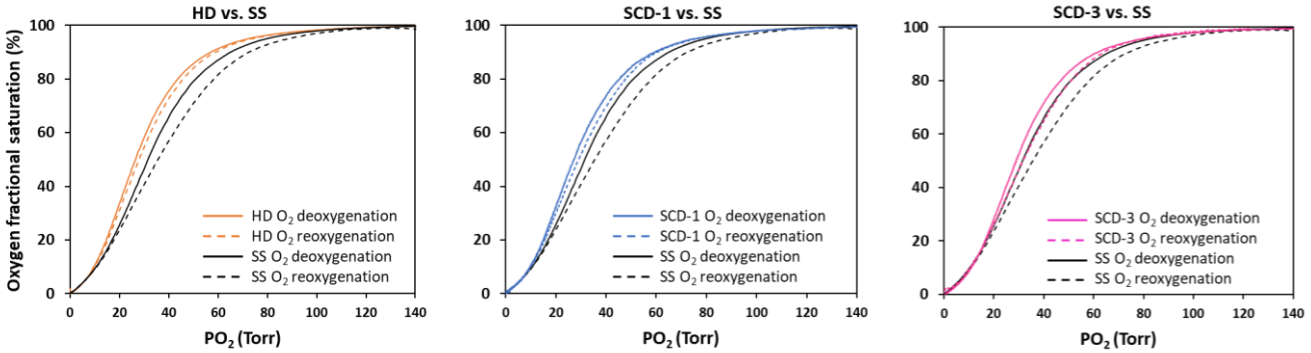
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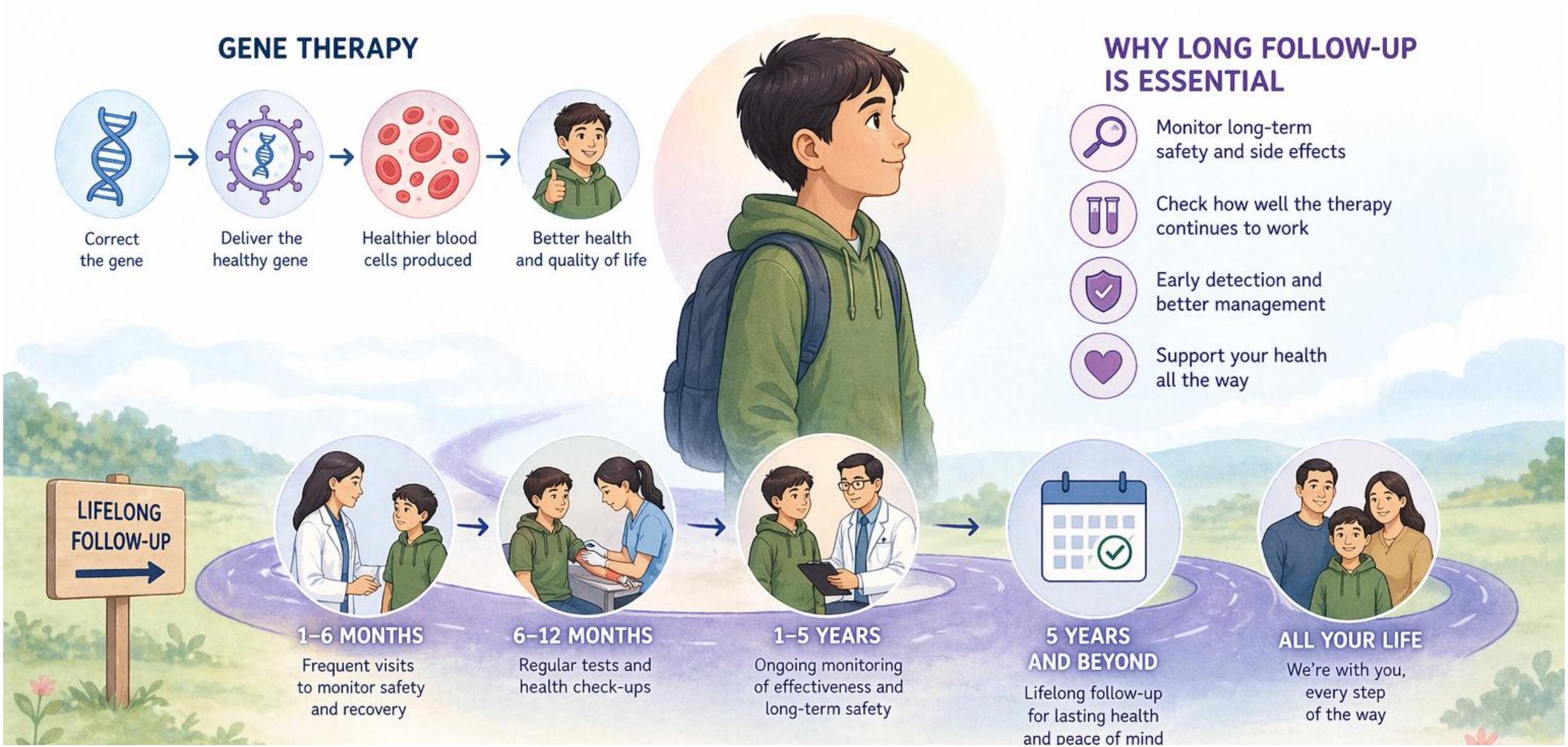
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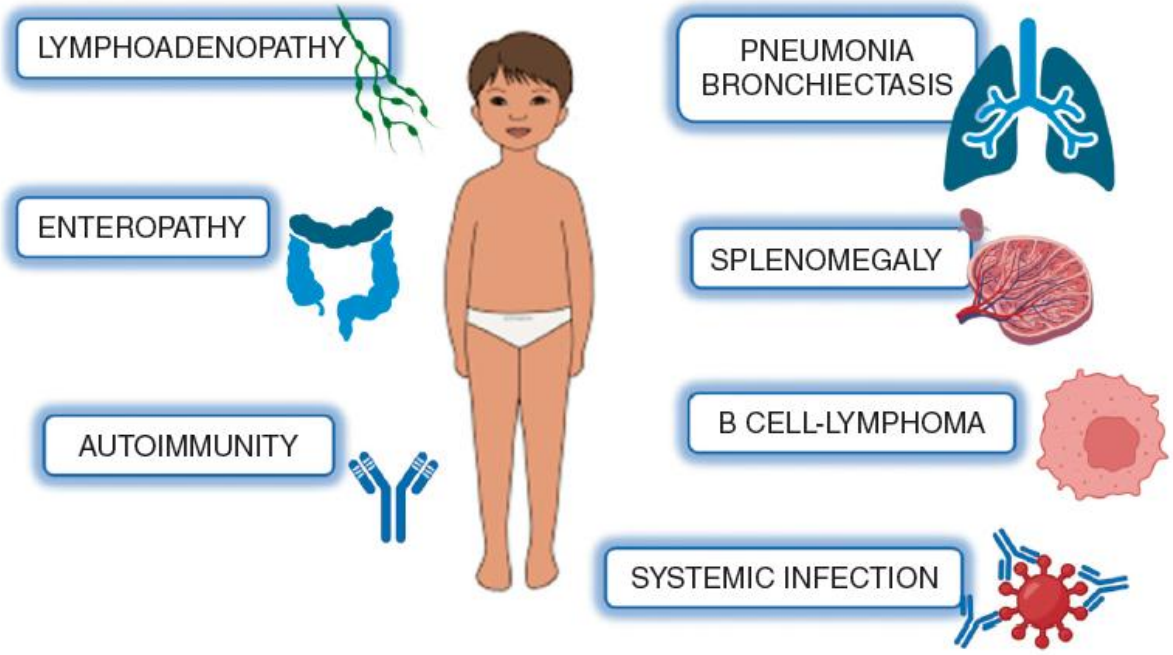
LONG-TERM FOLLOW UP



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ANOTHER EXEMPLE: Activated PI3K Delta syndrome (APDS)

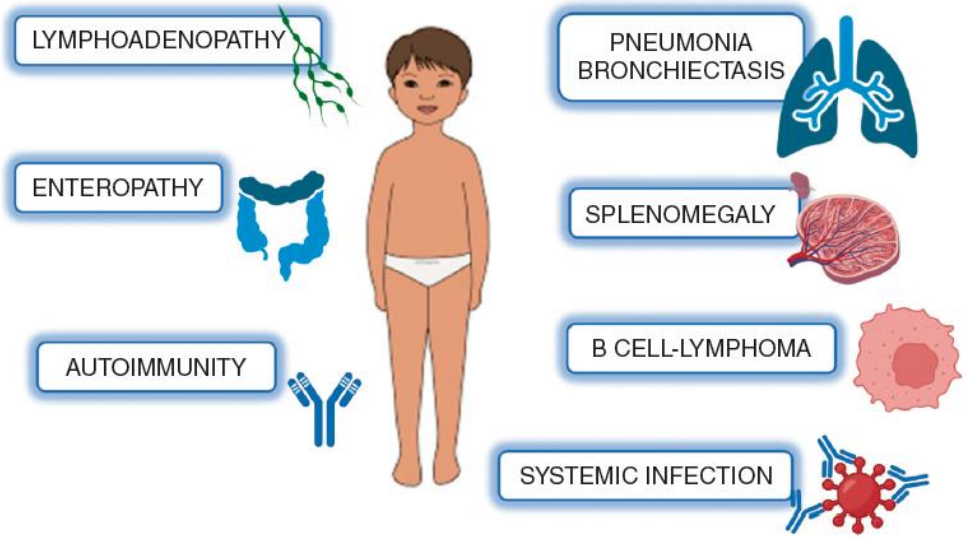
- APDS is an **ultra-rare IEI** that affects 1–2 people per 1,000,000[1]
- APDS is caused by pathogenic variants in genes encoding subunits of the PI3Kδ enzyme complex, leading to **hyperactive signalling**[2–5]
- Hyperactive PI3Kδ signalling results in **abnormal development** and maturation of B and T lymphocytes[6–8]
- These changes lead to immunodeficiency and immune dysregulation, resulting in **people with APDS experiencing severe and chronic symptoms within multiple organ systems**[8,9]



References: **1.** Vanselow S et al., Front Immunol. 2023;14:1208567; **2.** Tangye SG et al., J Clin Immunol. 2020;40(1):24–64; **3.** Lucas CL et al., Nat Immunol. 2014;15(1):88–97; **4.** Coulter TI et al., J Allergy Clin Immunol. 2017;139(2):597–606; **5.** Fruman DA et al., Cell. 2017;170(4):605–635; **6.** Johansen KH et al., Front Immunol. 2021;12:708908; **7.** Avery DT et al., J Exp Med. 2018;215(8):2073-2095; **8.** Preite S et al., Immunol Rev. 2019;91(1):154–173; **9.** Coulter TI and Cant AJ, Front Immunol. 2018;9:2043; **10.** Jamee M et al., Clin Rev Allergy Immunol. 2019;59(3):323-333; **11.** Maccari ME et al., J Allergy Clin Immunol. 2023;152(4):984−996. **Abbreviations**: APDS: activated PI3Kδ syndrome; CD: cluster of differentiation; IEI: inborn error of immunity; PI3Kδ: phosphoinositide 3-kinase delta.

ANOTHER EXEMPLE: APDS

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Target Treatment: LENIOLISIB

Pharming

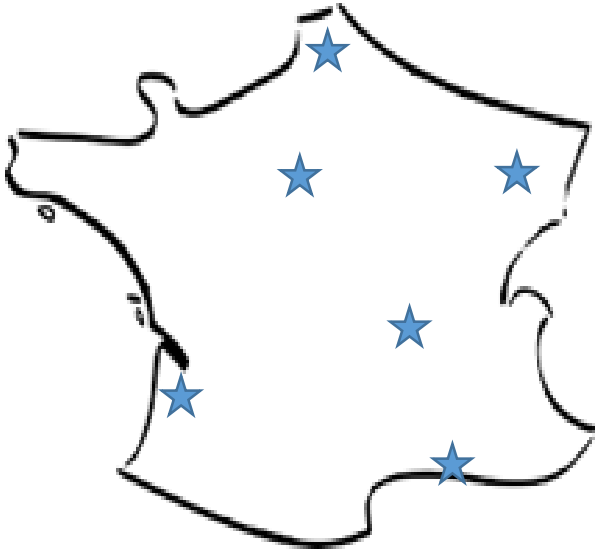


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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

"Nouvelle stratégie basée sur les biomarqueurs pour dépister et surveiller le syndrome de la phosphoinositide 3-kinase δ activée"

Etude BIO-APDS



Primary objectif: we aim to identify new biological characteristics (markers) to measure. These markers will help improve the screening and monitoring of the progression of APDS syndrome under Leniolisib treatment.



RESEARCH TRIAL DESIGN

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

"Nouvelle stratégie basée sur les biomarqueurs pour dépister et surveiller le syndrome de la phosphoinositide 3-kinase δ activée"

Etude BIO-APDS

Cette recherche est promue par l'Assistance Publique - Hôpitaux de Paris
Représentée par la Directrice de la
Délégation à la Recherche Clinique et à l'Innovation (DRCI)
1 avenue Claude Vellefaux
75010 Paris

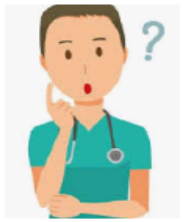
NOTE D'INFORMATION pour les 6 -11 ans

Pour les enfants du Groupe 1 – Patient débutant le traitement

Le Docteur (nom, prénom) ..... travaillant à l'hôpital ....., te propose de participer à une recherche concernant votre maladie.

Lis bien les explications de cette page. Tu pourras aussi poser toutes les questions que tu veux au médecin.

Pourquoi on te parle de cette recherche ?



Tu as une maladie rare qui s'appelle le syndrome APDS. Tu vas prendre un médicament qui s'appelle Leniolisib®. Nous espérons que ce médicament aidera ton corps à mieux se défendre contre cette maladie. Tu dois souvent venir à l'hôpital, et on voudrait profiter de ces visites pour faire une recherche pour mieux comprendre ta maladie et comment ton corps réagit à ce médicament.

Pour cela, on aimerait regarder ce qu'il y a dans ton sang, ton urine et tes selles. Ces éléments peuvent nous donner des indices (qu'on appelle « marqueurs ») pour mieux soigner d'autres enfants comme toi.

Comment ça va se passer ?



Si toi et tes parents êtes d'accord, tu pourras participer à cette recherche pendant 2 ans. Tu ne viendras pas plus souvent à l'hôpital, tout se passera pendant tes rendez-vous habituels.

Pendant ces visites, au maximum 6, on te demandera :

- 3 petits tubes de sang en plus que d'habitude. Si tu veux, on pourra mettre une crème spéciale pour ne pas avoir mal.
- un peu de ton urine et de tes selles, dans des petits pots spéciaux. Une infirmière ou un infirmier t'expliquera comment faire.

Ensuite, tout sera envoyé au laboratoire, pour qu'on puisse chercher ces indices.

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	V0 = début du traitement	Visite 1 3 mois après le début du traitement	Visite 2 6 mois après le début du traitement	Visite 3 12 mois après le début du traitement	Visite 4 18 mois après le début du traitement	Visite 5 24 mois après le début du traitement
	2 ans de suivi					
Présentation et explication de la recherche	X					
Initiation du traitement	X					
Recueil de quelques données cliniques pertinentes pour la recherche (essentiellement les bilans biologiques et l'évolution de sa maladie)	X	X	X	X	X	X
Prélèvement de sang (pour son suivi clinique et pour la recherche)	X	X	X	X	X	X
Prélèvement urinaire	X	X	X	X	X	X
Prélèvement fécal	X	X	X	X	X	X

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

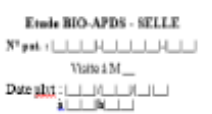
"Nouvelle stratégie basée sur les biomarqueurs pour dépister et surveiller le syndrome de la phosphoinositide 3-kinase δ activée"

Etude BIO-APDS

The objective of this study is
Collect data from approximately ***30 patients*** *in order to better characterize:*

(1) their long-term outcomes, and
(2) potential biomarkers that may allow improved monitoring of disease progression over time.

=> **This study does not provide a direct benefit to patients but aims to enhance scientific understanding of the disease**

Analyse	Tube	Quantité	Traçabilité	Devenir des tubes
ETAPE 1 :	Tube hépariné (10 mL) 	20 mL (15 mL pour les patients de – de 30 kg)	- Compléter et coller une étiquette « héparine » sur le tube 	Envoi immédiat au laboratoire à température ambiante
ETAPE 2 :	Tube sec 4 mL 	2 mL	Compléter et coller une étiquette « sec » sur le tube 	Envoi immédiat au laboratoire à température ambiante
ETAPE 3:	Tube EDTA 5 mL 	5 mL	Compléter et coller une étiquette « EDTA » sur le tube 	Envoi immédiat au laboratoire à température ambiante
ETAPE 4 :	Tube sec stérile 		Compléter et coller une étiquette « urine » sur le tube 	Envoi immédiat au laboratoire à température ambiante
ETAPE 5 :	Pot plastique TP50 		Compléter et coller une étiquette « selle » sur le tube 	Envoi immédiat au laboratoire à température ambiante

THANK YOU



michaela.semeraro@aphp.fr