Less intensive approaches to cure: reduced intensity and nonmyeloablative hematopoietic cell transplantation for sickle cell disease

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Disclosures/Conflicts of Interest

- bluebirdbio provides financial support for Project Sickle Cure
  - I am the PI of this study
  - I receive no personal remuneration from bbb

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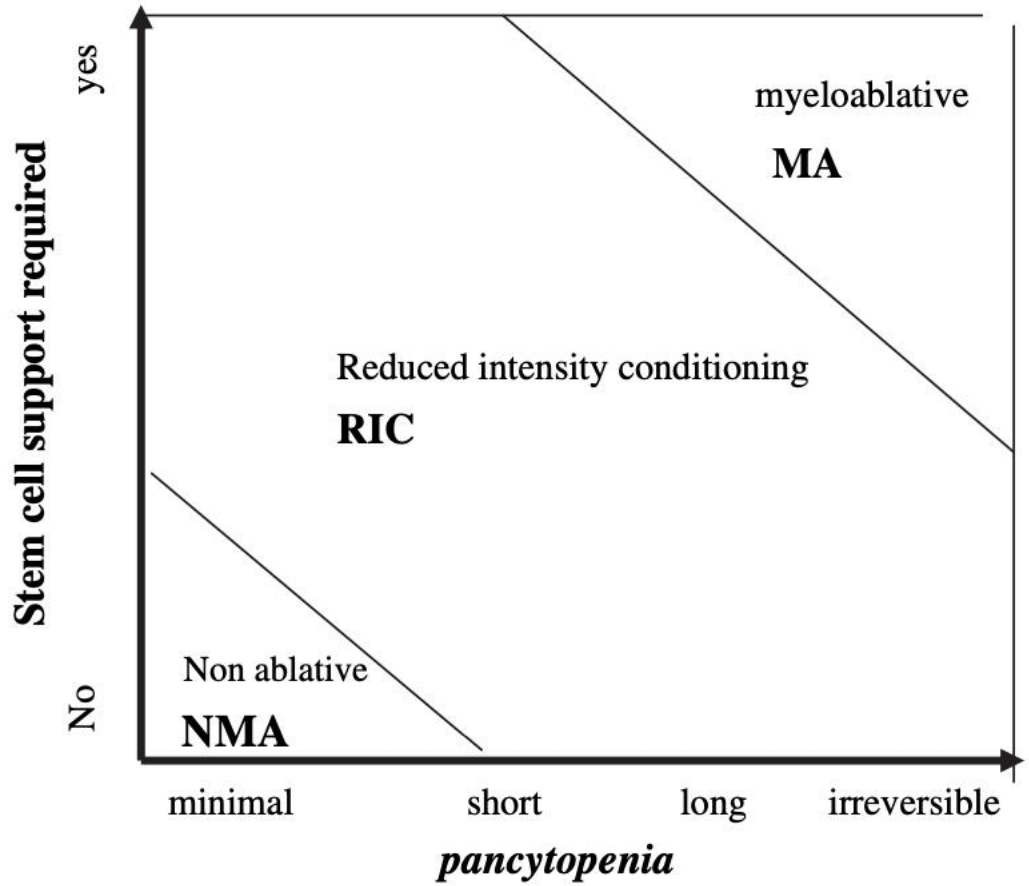
Objectives

To review principles of hematopoietic cell transplantation (HCT)- and why intensity matters

To present key learnings for less intensive HCT for matched sibling and unrelated donors

To discuss future directions to offer safe cure to more people with SCD



(Bacigalupo et al, 2009)

What is our HCT goal?

- What is the definition of cure?
  - **Survival**
  - **Donor hematopoietic cell engraftment to prevent sickling**
  - No hemolysis
  - **No graft-versus-host disease**
  - Minimal impact on quality of life
    - We are trying to make it better!

(Bernaudin et al, 2020)

Other important goals

- Minimal acute and long-term complications
  - From the HCT and from SCD
  - Can organ function not only stabilize but improve with HCT?
  - Treatment-related neoplasms
    - Genotoxicity and risk of myeloid malignancy
  - **Fertility preservation**
- **Less intensive conditioning seems like a way to achieve these goals**

How much is enough?

Minimum chimerism

20-25% to prevent sickling crises

25-50% donor chimerism can result in hemolytic markers without sickling crises and Hb S <50%

Vol. 105 No. 1 (2020): January, 2020 > Long-term event-free survival, chimerism and fertility...

ARTICLES

Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France

Françoise Bernaudin, Jean-Hugues Dalle, Dominique Bories, Regis Peffault de Latour, Marie Robin, Yves Bertrand, Corinne Pondarre, Jean-Pierre Vannier, Benedicte Neven, Mathieu Kuentz, Sébastien Maury, Patrick Lutz, Catherine Paillard, Karima Yakouben, Isabelle Thuret, Claire Galambrun, Nathalie Dhedin, Charlotte Jubert, Pierre Rohrlich, Jacques-Olivier Bay, Felipe Suarez, Nicole Raus, Jean-Paul Vernant, Eliane Gluckman, Catherine Poirot, Gérard Socié, for the Société Française de Greffe de Moelle et de Thérapie Cellulaire

Vol. 105 No. 1 (2020): January, 2020 https://doi.org/10.3324/haematol.2018.213207

(Bernaudin et al, 2020; Fitzhugh et al, 2017; Abraham et al, 2017))

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CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation

Julie Kanter,[1] Robert I. Liem,[2] Françoise Bernaudin,[3,4] Javier Bolaños-Meade,[5] Courtney D. Fitzhugh,[6] Jane S. Hankins,[7] M. Hassan Murad,[8] Julie A. Panepinto,[9] Damiano Rondelli,[10] Shalini Shenoy,[11] John Wagner,[12] Mark C. Walters,[13] Teonna Woolford,[14] Joerg J. Meerpohl,[15,16] and John Tisdale[6]

Recommendation 6a. For children with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* using myeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

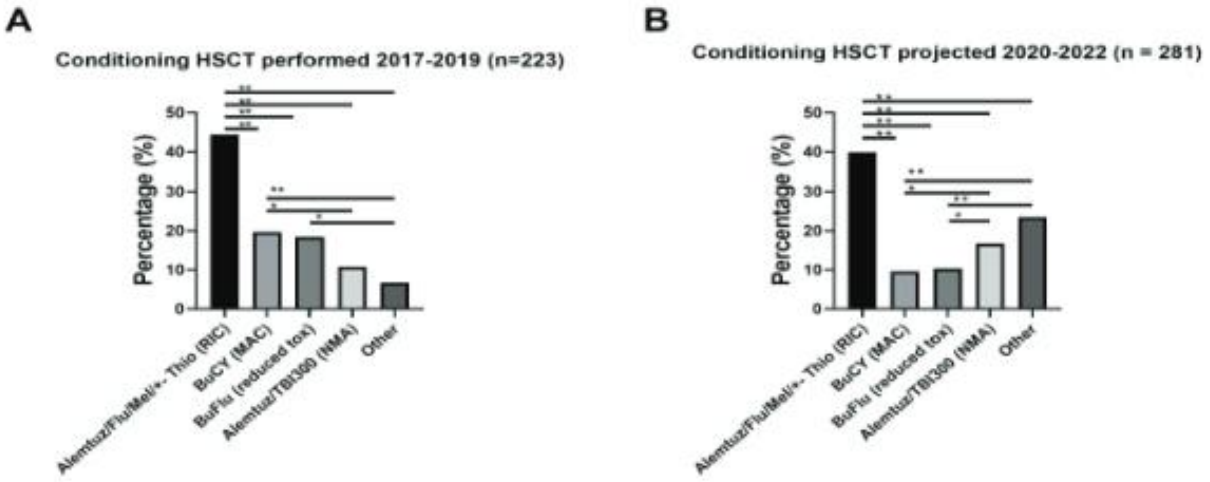
Recommendation 6b. For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

(Kanter et al, 2021)

In North America, RIC/NMA commonly used in children

Conditioning Regimen Trends in Hematopoietic Stem Cell Transplant for Sickle Cell Disease: A Survey from the Sickle Cell Transplant Advocacy and Research Alliance (STAR) Consortium

***Alister Abraham, MD**, Center for Cancer and Immunology Research, Division of Blood and Marrow Transplantation, Children's National Hospital, Washington, DC; Elizabeth Stenger, MD, Children's Hospital of Pittsburgh, Pittsburgh; Scott Gillespie, MS, Emory University, Atlanta, GA; Emily Riehm Meier, MD, Indiana Hemophilia and Thrombosis Center, Inc., Indianapolis, IN; Gregory MT Guilcher, MD, Division of Hematology/Oncology/ Transplant, Alberta Children's Hospital, Calgary, AB, Canada and John Horan, MD, MPH, Dana-Farber Cancer Institute, Boston Children's Hospital, Boston, MA*



(Abraham et al, 2021)

Why the difference between the ASH guidelines and North American practice?

ASH guidelines

- The highest published EFS is with myeloablative conditioning
  - With large numbers
  - Lower rates of graft failure

Reasons to consider RIC or nonmyeloablative conditioning

- Rates of preserved fertility *might* be higher
- Rates of GVHD are equivalent with melphalan/fludarabine and almost non-existent with the NIH regimen
- Less decline in HRQoL early post HCT

(Bernaudin et al, 2007; Kanter et al, 2021; Nickel et al, 2021; Kelly et al, 2012)

RESEARCH ARTICLE

Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies

Allison A. King,[1] Naynesh Kamani,[2] Nancy Bunin,[3] Indira Sahdev,[4] Joel Brochstein,[4] Robert J. Hayashi,[1] Michael Grimley,[5] Allistair Abraham,[2] Jacqueline Dioguardi,[2] Ka Wah Chan,[6] Dorothea Douglas,[7] Roberta Adams,[7] Martin Andreansky,[8] Eric Anderson,[9] Andrew Gilman,[10] Sonali Chaudhury,[11] Lolie Yu,[12] Jignesh Dalal,[13] Gregory Hale,[14] Geoff Cuvelier,[15] Akshat Jain,[4] Jennifer Krajewski,[16] Alfred Gillio,[16] Kimberly A. Kasow,[17] David Delgado,[18] Eric Hanson,[1] Lisa Murray,[1] and Shalini Shenoy[1]*

- Phase II multi-centre trial with less intensive chemotherapy and immunotherapy
  - Alemtuzumab/Melphalan/Fludarabine
- 43 children with SCD
- 94% OS, 92% EFS
  - 3 deaths, all in adolescents with SCD ages 17-18 years
  - 1 graft rejection (cord blood)
- GVHD- 23% acute GVHD
- 13% extensive chronic GVHD- all over 14 years of age

(King et al., 2015)

Nonmyeloablative transplant for Sickle Cell Disease in Adults (MSD)

The NEW ENGLAND JOURNAL of MEDICINE

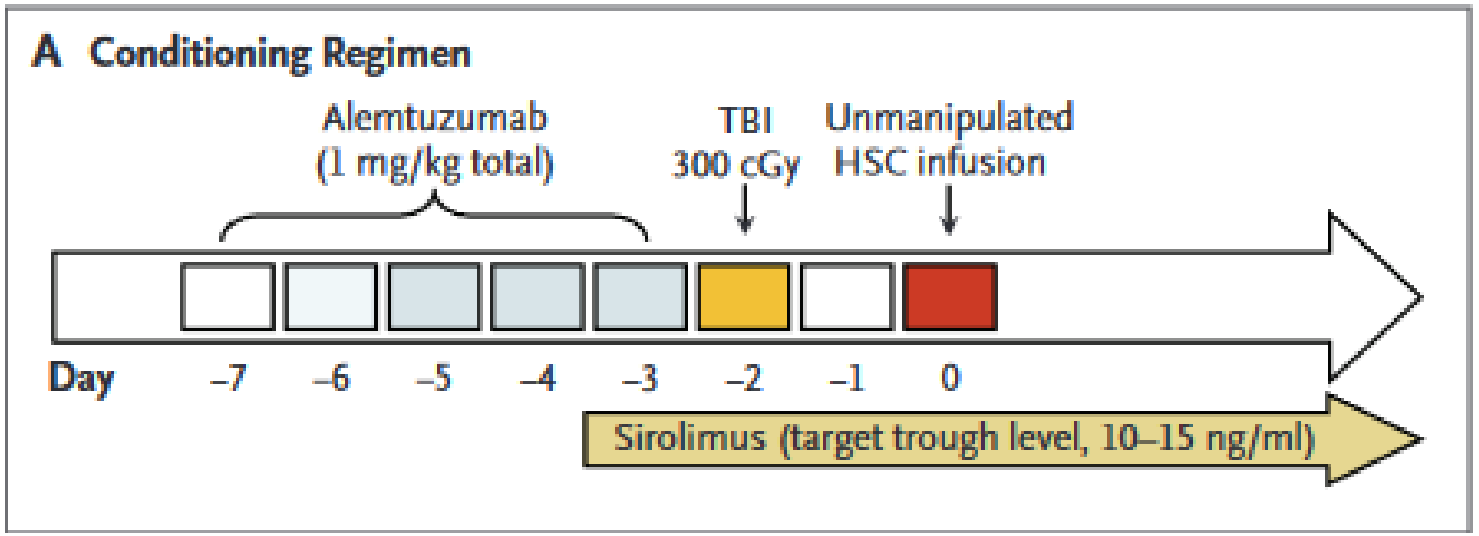
ESTABLISHED IN 1812 DECEMBER 10, 2009 VOL. 361 NO. 24

Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease

Matthew M. Hsieh, M.D., Elizabeth M. Kang, M.D., Courtney D. Fitzhugh, M.D., M. Beth Link, R.N., Charles D. Bolan, M.D., Roger Kurlander, M.D., Richard W. Childs, M.D., Griffin P. Rodgers, M.D., Jonathan D. Powell, M.D., Ph.D., and John F. Tisdale, M.D.

(Hsieh et al, 2009)

Nonmyeloablative



(Hsieh et al, 2009)

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bjh research paper

Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres

Mohsen Alzahrani,[1,†] Moussab Damlaj,[1,†] Neal Jeffries,[2] Bader Alahmari,[1] Avani Singh,[3] Damiano Rondelli,[3] John F. Tisdale,[4] Santosh L. Saraf[3,‡] and Matthew M. Hsieh[4,‡]

[1]*Division of Hematology & Hematopoietic Stem Cell Transplantation, Department of Oncology, King Abdulaziz Medical City, Riyadh, Saudi Arabia,* [2]*Office of Biostatistics Research, National Heart,*

Summary

Non-myeloablative haematopoietic progenitor cell transplantation (HPCT) from matched related donors (MRD) has been increasingly utilized in sickle cell disease (SCD). A total of 122 patients received 300 cGy of total body irradiation (TBI), alemtuzumab, unmanipulated filgrastim-mobilized peripheral blood HPC and sirolimus. The median follow-up was four years; median age at HPCT was 29 years. Median neutrophil and platelet engraftment occurred on day 22 and 19 respectively; 41 patients required no platelet transfusions. Overall and sickle-free survival at one and five years were 93% and 85% respectively. Age, sex, pre-HPCT sickle complications,

(Alzahrani et al, 2021)

What about the NIH protocol in children?

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Nonmyeloablative Matched Sibling Donor Hematopoietic Cell Transplantation in Children and Adolescents with Sickle Cell Disease

Gregory M.T. Guilcher[1,*], Dania A. Monagel[2], Alberto Nettel-Aguirre[2], Tony H. Truong[1], Sunil J. Desai[3], Aisha Bruce[3], Ravi M. Shah[1], Michael T. Leaker[2], Victor A. Lewis[1]

[1] *Section of Oncology/BMT, Departments of Oncology and Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, Canada*
[2] *Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, Canada*
[3] *Section of Pediatric Immunology/Hematology/Oncology/Palliative Care, Stollery Children's Hospital, University of Alberta, Edmonton, Canada*

(Guilcher et al., 2019)

Calgary Results with the NIH Protocol

- 25 patients have undergone sibling donor HCT for SCD with this protocol
  - All alive
  - No GVHD
  - No sickling crises and 24/25 have donor HbS levels
  - All have weaned sirolimus
    - Not true for all adults
  - Fertility preservation possible

(Guilcher et al., 2019 with updates)

The SUN Clinical Trial in Children and Adolescents

721.ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TOXICITIES | NOVEMBER 5, 2021

Nonmyeloablative HLA-Identical Sibling Donor Transplantation for Children and Young Adults with Sickle Cell Disease: Interim Results of the SUN Multicenter Phase II Trial

Robert Sheppard Nickel, KY Chiang, Steven J. Hardy, Hemalatha G Rangarajan, Sonali Chaudhury, Michael Kent, Monica Bhatia, Jeremy Zack, Vivitha Mani, Gregory M.T. Guilcher, Allistair Abraham

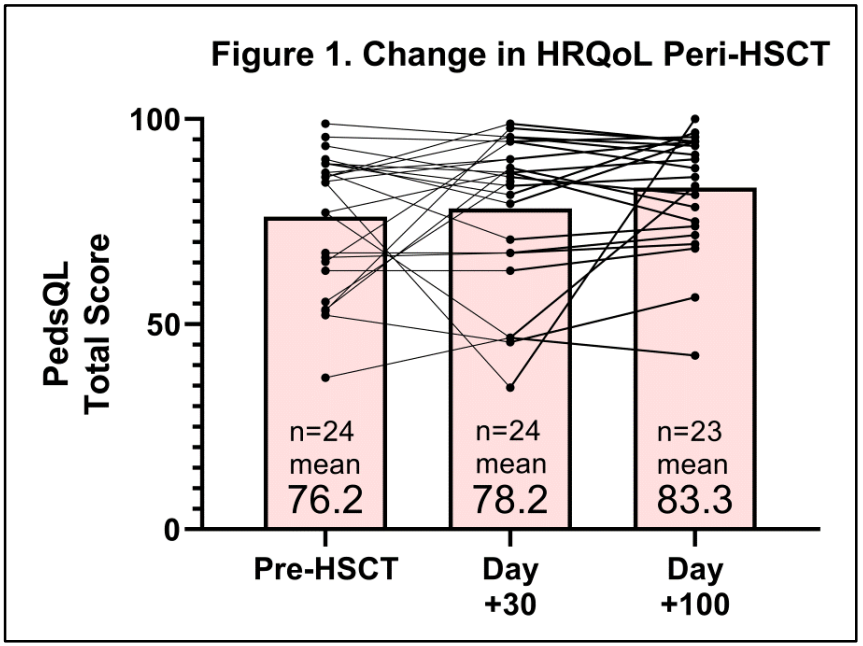
Blood (2021) 138 (Supplement 1): 1799.

SUN Outcomes

Outcomes

- 100% survival
- 17% graft rejection
- 25% poor engraftment
  - Graft rejection
  - Stem cell boost
  - Myeloid chimerism <50%
- ? IV vs SC alemtuzumab

HRQoL



(Nickel et al, 2021)

Unrelated donor HCT

Recommendation 4. For patients with SCD with an indication for HSCT who lack an MSD, the ASH guideline panel *suggests* using transplants from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Alternative donor transplantation has the potential to improve or resolve disease manifestations in patients with severe SCD. The risks related to transplantation complications should be balanced with benefits derived from successful transplantation.

(Kanter et al, 2021)

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A trial of unrelated donor marrow transplantation for children with severe sickle cell disease

Shalini Shenoy,[1] Mary Eapen,[2] Julie A. Panepinto,[2,3] Brent R. Logan,[2] Juan Wu,[4] Allistair Abraham,[5] Joel Brochstein,[6] Sonali Chaudhury,[7] Kamar Godder,[8] Ann E. Haight,[9] Kimberly A. Kasow,[10] Kathryn Leung,[11] Martin Andreansky,[12] Monica Bhatia,[13] Jignesh Dalal,[14] Hilary Haines,[15] Jennifer Jaroscak,[16] Hillard M. Lazarus,[17] John E. Levine,[18] Lakshmanan Krishnamurti,[19] David Margolis,[3] Gail C. Megason,[20] Lolie C. Yu,[21] Michael A. Pulsipher,[22] Iris Gersten,[4] Nancy DiFronzo,[23] Mary M. Horowitz,[2] Mark C. Walters,[24] and Naynesh Kamani[25]

- Phase II multi-centre trial
  - Less intensive conditioning
  - 30 subjects
- 10% graft rejection
- Overall survival 86%
- Acute GVHD (grades II-IV) 17%
- Chronic GVHD 62%, 38% extensive

Key Points

- Children with sickle cell disease engrafted unrelated donor marrow after reduced intensity conditioning.
- A high incidence of GVHD and associated mortality compromised safety of the trial.

(Shenoy et al, 2016)

The major challenge is GVHD

21

Abatacept for Gvhd Prophylaxis after Hematopoietic Cell Transplantation (HCT) for Pediatric Sickle Cell Disease (SCD): A Sickle Cell Transplant Advocacy and Research Alliance (STAR) Trial

Sonali Chaudhury MD*[1], *Brian Volonte*[2], *Hemalatha G. Rangarajan MD*[3], *John Horan MD, MPH*[4], *Ann E. Haight MD*[5], *Allistair Abraham MD*[6], *Alexander Ngwube MD*[7], *Jennifer Krajewski MD*[8], *Gregory M.T. Guilcher MD*[9], *Monica Bhatia MD*[10]. [1] *Ann & Robert H. Lurie Children's Hospital

(Chaudhury et al., 2020; arthritis.co.za)

STAR AYA Trial for MSD/MUD

- Reduced intensity conditioning
- Calcineurin inhibitor-free approach
- Goal:
  - High levels of donor myeloid engraftment
  - Minimal GVHD
  - Low toxicity

Sickle Cell Transplant Advocacy & Research Alliance

Cure beyond survival and engraftment

- Myeloablative conditioning is a risk factor for organ dysfunction post-HCT
- Restrictive lung disease usually stabilizes
- Urine concentrating ability may improve

Table 1: Post-HCT neurologic dysfunction

Variable	N (%)
Stroke (n=242)	8 (3.3%)
Brain MRI (pre- vs post-HCT; n=159)	
Normal	45 (28.3%)
Stable findings	80 (50.3%)
Progressive vasculopathy	6 (3.8%)
New vasculopathy	6 (3.8%)
Progressive infarct	6 (3.8%)
New infarct	7 (4.4%)

(Monagel et al, submitted; Pedersen et al, 2020; Stenger et al, 2022)

Future Directions

- Eliminating GVHD
- High rates of donor engraftment and full donor chimerism
  - Myeloid malignancy in adults
    - Gene therapy and adults post HCT with graft failure
    - Non-genotoxic conditioning
- Better understanding of long-term outcomes
- We need several options for patients
  - Most patients will still not have a suitable related or unrelated donor

(Bernaudin et al, 2020; Liggett et al, 2022; Ghannam et al, 2020; Fitzhugh, personal communication)

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Thank you for listening!

Photo courtesy of Dr. Nicolas Prud'homme