Chasing Sickle Cell Disease Globally: Capacity building

Jacques Elion, MD, PhD

French National Reference Centers for Sickle Cell Disease
Inserm UMR 1134
Paris and Guadeloupe (French West Indies)
National Institute of Blood Transfusion
Laboratory of Excellence on the Red Cell
University of São Paulo, FMRP-USP, Brazil

jacques.elion@inserm.fr
Independent origins of SCD in Africa and India

Probably at the beginning of the Neolithic period
≈ 6,000 years BC
Begining of agriculture

Labie et al
Proc Natl Acad Sci U S A. 1984
Spread by the slave trade to the new world
...and to Europe by contemporary migrations
Healthy carriers ≈ 5% of the world population
300,000 newborns/year (80% in low income countries)
Present SCD geographic distribution

clearly SCD is a global issue
SCD is recognized as a global public health issue

- African Union: Assembly decision/AU/ Dec. 81 July 2005
- UNESCO General Assembly September 2005
- WHO resolutions: WHA59.20 and EB 118 May 2006
- UN General Assembly resolution: A/63/237 December 2008
- WHO-AFRO resolution: AFR/RC60/8 August 2010

*Sickle-cell disease: a strategy for the WHO African Region*
The burden of the hemoglobinopathies

- The years lived with disability (YLDs) for hemoglobinopathies and SCD is **10,197**, a dramatic observation since the YLDs for cardiovascular disorders is **21,985**

- The disability-adjusted life years (DALYs) to measure the disease burden for hemoglobinopathies and SCD is **15,640**, an impressive figure compared to the DALYs for diabetes that is **75,000**

Murray et al. The Lancet 2012; Vos T eet al The Lancet 2012

*Courtesy of Lucia De Franceschi*
In the North, median life expectancy of SCD patients is steadily increasing:

- Daily penicillin: 1986
- Neonatal screening: 1988
- Immunization
- Hydroxycarbamide (HU): 1995
- Trans-Cranial Doppler: 1998
- Rational transfusion therapy
This progress is impressive but interestingly results mostly from rather simple interventions.

Inserm U1134

![Graph showing SCD Mortality rate/100,000 Black children, with markers for Newborn screening, Manage Infection, USA, and Comprehensive Care, Hydroxyurea.]
Geographic disparity of the distribution of newborns affected with SCD
estimated evolution 2010-2050

Figure 2. Cartograms of the estimated number of newborns with SCA per country. Cartograms of the estimated number of newborns with SCA per country in 2010 (A), 2050 (B), and overall from 2010 to 2050 (C), based on data presented in Table S2. The estimates are based on the median of the posterior predictive distribution for SCA frequencies generated by our Bayesian geostatistical model described in Piel et al. [21] and the medium fertility variant of the birth projections from the 2010 revision of the UN World Population Prospects [22].

Courtesy of Fred Piel
Worldwide disparity of resources

- 100,000 SCD patients in the US
- 50,000 SCD patients in Europe
The Two Worlds of SCD

SCD Babies life expectancy

Poor Countries
- 10%
- Birth → 6 ms
- 6 ms → 60 ms
- 5 yrs → 15 yrs

Wealthy Countries
- 99%
- Birth → 6 ms
- 6 ms → 60 ms
- 5 yrs → 15 yrs

95% SSA and India
5% Rest of the World
Priority n° 1: extend newborn screening and comprehensive care programs
In the North, median life expectancy of SCD patients is steadily increasing.

US National Sickle Cell Act Research
2017: tremendous progresses have been achieved

**Epidemiology**

**Pathophysiology**
- Molecular mechanism
- Genetics and cell biology
- Animal models

**Clinics**
- Natural history of SCD (*in the US and Europe*)
- Impact of antibiotics, immunization & transfusions
- Hydroxycarbamide
- Curative potential of hematopoietic stem cell transplant
2017: tremendous progresses have been achieved

Epidemiology

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• Molecular mechanisms
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.....SCD still raises major unresolved issues and challenges
Epidemiology

the present data must be taken with extreme caution

- based mainly on studies that were carried out before 1980
- obtained from a very limited number of centers in each country
- even in many richer countries, data of this kind are scarce

Recent micromapping studies, which are analyses of samples taken from many different centers in a particular country or region, have disclosed a remarkable heterogeneity in the distribution of the haemoglobin disorders, often within short geographical distances.

Thus, there is an urgent need of sound epidemiological data to estimate the health burden that will be encountered, particularly by the poorer countries as the haemoglobin disorders become even more frequent in the future.

*Weatherall DJ. Blood. 2010*
2017: Despite all the progresses

high contrast between:

- a single mutation
  ...the extreme variability of the clinical presentation

- exquisitely detailed pathophysiology
  ...only one efficient drug: hydroxycarbamide

- SCD in the Northern hemisphere
  ...SCD in the developing countries
2017: Despite all the progresses

high contrast between:

- a single mutation

- genotype – phenotype correlation

- exquisitely detailed pathophysiology

- interaction gene – environment

- only one efficient drug: hydroxycarbamide

- SCD in the Northern hemisphere

- SCD in the developing countries
What is the problem?

- basic research has been done in the North, mostly in the USA
- all the tools are there (pharmalogical labs, facilities for GWAS studies…)

but
- we lack epidemiological data
- we know almost nothing about the natural history of SCD in its natural environment
- affected populations in the USA are genetically mixed
Beginning of the 21st Century: 
the genome era and a ‘new’ medicine

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<td>Intervene before symptoms appear and preserve normal function as long as possible</td>
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<td>Understand preclinical events and detect patients at risk</td>
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Courtesy of Susan B. Shurin, NIH, NHLBI
### Priority:

**Establish the conditions for fine phenotype determination**

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Courtesy of Susan B. Shurin, NIH, NHLBI
Comparative cohort studies are badly needed

Results of projects such as the Jamaican Cohort Study or the USA Cooperative Study of Sickle Cell Disease are clear indications that such initiatives should be pursued in a comparative manner.

Definition of the phenotype is crucial. Given level of complexity of the disease it is not surprising that it has been difficult to achieve an agreed classification of the different degrees of severity.

Regardless of the inevitable deficiencies of any classification of this kind, it is vital to attempt to produce a workable description of severity as a prelude to the potential international collaborations and to normalise clinical and biological data collection.

*Weatherall et al. Blood. 2005*
Why conducting research in the developing world?

Clinical diversity and genomic research

SCD populations in the North are mixed

Africa and India provide
- phenotypic diversity
- genetic diversity
- environmental diversity

a unique opportunity to dissect the respective part of genetic versus environmental factors
Why conducting research in the developing world?

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this can be achieved only via equitable and sustainable North-South, South-South, and global networks promoting international collaboration
Examples of successful regional networks

Africa (1)

REDA
The Central African SCD network

- Cameroon
- DRC
- Congo
- CAR
- Gabon
- Tanzania
- South Sudan

Angola
Ouganda
Zambia
Kenya
Burundi
Rwanda

FONDATION PIERRE FABRE
Examples of successful regional networks

South-South Collaborations

- Cameroon
- DRC
- Congo
- CAR
- Gabon
- Tanzania
- South Sudan
- Angola
- Ouganda
- Zambia
- Kenya
- Burundi
- Rwanda
Examples of successful regional networks

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REDAC
The Central African SCD network
- Cameroon
- DRC
- Congo
- CAR
- Gabon
- Tanzania
- South Sudan

Collaborations:
France
Belgium
Examples of successful regional networks

**Africa (2)**

Research Networks

Cohort of 5,000 patients

**CADRE study**
SCD cardiovascular aspects
Brigitte Ranque, Xavier Jouven et al

Laboratoire d'Excellence GR-Ex
Coordonation: Olivier Hermine

*Lancet Haematol. 2014; 1:e64-73*
*Circulation. 2016;134:923-33*
*Blood, 2017, Sept 20 preprint*
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Africa (2)

- Research Networks
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Examples of successful regional networks

SickleCHARTA

PI: Julie Makani
Tanzania

Establish a network of Excellence SCD Centres in Africa

- Epidemiological genetics
  GWAS studies
- Healthcare
- Training

Cohort:
goal 10,000 SCD patients
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Cohort: goal 10,000 SCD patients

Collaborations: UK
Examples of successful networks

Collaborations:

Africa

USA
Examples of successful regional networks

ICMR Indian Network

CMC, Ludhiana

RMRC, Dibrugarh

Valsad Raktadan Kendra

Govt. Medical College, Vadodara

Rural Hospital, Karjat

NIIH, Mumbai

Co-ord. Centre

St. Johns Medical College, Bangalore

NRS Medical College, Kolkota

R. M. R. C. Bhubaneshwar

Govt. Medical College, Nagpur

Nilgiri Adivasi Welfare Ass. Kotagiri

Courtesy of Roshan Colah
Examples of successful regional networks

Caribbean Network

President : MD Hardy-Dessources

11 Caribbean countries

- Newborn screening
- Follow-up
- Education
- Research

Haematologica. 2011; 96:1589-94
C R Biol. 2013;336:173-6
Examples of successful networks

Caribbeans ↔ USA

Hydroxyurea

SCATE

Jamaica

EXTEND

Dominican Rep
Examples of successful regional networks

REDS-III Brazil Program
Belo Horizonte, Recife, Rio de Janeiro, São Paulo

Cohort of 3000 SCD pa. ens

USA
Blood Systems Research Institute
San Francisco CA

Cohort of 3000 SCD pa. ens
Global Globin 2020 Challenge (GG2020)
Thalassaemia / SCD / G6PD deficiency
(www.humanvariomeproject.org/gg2020)
Steering Committee

Helen M Robinson,
HVP International
Co-ordinating Office
Australia

Thalassaemias
Zilfalil bin Alwi, Malaysia
Carsten W. Lederer, Cyprus

SCD
Raj Ramesar, Cape Town South Africa
Jacques Elion, Paris

G6PD deficiency
Zilfalil bin Alwi, Malaysia
NA
Goals

1. To see growth in the quality and quantity of curated inputs from low and middle-income countries into internationally recognized genetic databases.

2. To harmonize the sharing of all relevant genetic data between countries in accordance with international best practice that includes all the relevant ethical and regulatory frameworks and policies required to serve and protect patients at the same time the biotechnical systems and procedures are developed.

3. To ensure that the storage, curation and sharing of the relevant DNA variation information is sustainable in the medium and longer term by expanding and strengthening the international network of professionals, including curators, researchers, clinicians, bioinformaticians, counsellors, patients groups and health bureaucrats.
Goals cont.

At the same time this will

- raise the profile of genomic medicine in low and middle income countries among health bureaucrats in national, regional and international health organizations.

- develop the capability of health professionals required for diagnosing, treating and counseling carriers in low and middle income countries thus giving them a greater voice and profile among genomic researchers and clinicians globally so they can actively participate in regional and international partnerships related to
  
  - genomic medicine research and
  
  - innovative health service delivery in low resource settings.
How will it be done?

This project will not duplicate the work of other bodies and organizations already tackling haemoglobinopathies - the relevant individuals, bodies and agencies already working in the field will be included in the project and that international cooperation and collaboration will result in optimal translation of locally-relevant genomic information according to best clinical utility and practice.

Work bottom-up through local groups at national level- identifying relevant data, partners

Provide training for health professionals, patients and families and broader public
Existing HVP nodes
Existing HVP nodes
The TOPMed initiative

**TOPMed** *Trans-Omics for Precision Medicine*

Whole genome sequencing of 20,000 individuals with different pathologies NHLBI including SCD (3 cohorts)

- Largest cohort = REDsIII Brazilian cohort

  (3,000 patients)

  Brazilian geneticists steering group: Wilson Silva coordinator
  Jacques Elion Intl Adv
The role of GSCDN is pivotal in informing, coordinating, and reinforcing the whole.