

THE SICKLE CELL CURE FOUNDATION, INC.
(SCCF)

A 501(c) (3) NON-PROFIT CHARITY



Board-Approved
BUSINESS PLAN
ABRIDGED
FOR
THE PUBLIC AND VENDORS

August, 2008
Oklahoma City, OK USA

www.sicklecellcurefoundation.org

Written by Gary W. Bricker^{CFP} with Robert H. Broyles, Ph.D

SCCF'S GLOBAL MISSION: "Pro Humanitate"*

Sickle cell disease (SCD) is a global problem. As the most common genetic disease in the world, SCD touches the lives of millions and affects many more. People of at least five racial groups and numerous ethnic origins have inherited the sickle gene. SCD is correctly classified as a "tropical disease", since it is most common among populations living close to the equator, in tropical and subtropical regions.

The populations in which SCD occurs most frequently live in Africa (which has about 75% of the cases), in Mediterranean countries, in the Middle East, and in India, with significant numbers in the Caribbean, Brazil, and Oceania. Migrations of people from these regions have resulted in significant numbers of SCD sufferers in North America, South America, and Europe. The prevalence and continued high incidence of sickle cell is due in large part to resistance to the chronic effects of malaria that is conferred by the presence of sickle hemoglobin in the red blood cells of carriers, as well as SCD patients fortunate enough to survive childhood. However, this benefit of the sickle trait comes at a very high cost to those who inherit two copies of the sickle gene. SCD is a terrible disease that brings with it pain that is frequent and often severe, life-threatening organ damage, and limitations to the daily lives of the sufferers and their families. In developing countries short on comprehensive medical care, SCD is a death sentence that terminates life early, often within the first two years.

The **SCCF** is committed to alleviating this terrible disease in as many sufferers as can be reached with a cure that prevents manifestations of the bodily damage which results from SCD. To this end, the **SCCF** has a **global plan** for distribution of the cure at a cost that 80% of the SCD sufferers in the world can afford. Our plan combines safety and clinical trials with a cost-effective business plan that includes a "north-south" dialogue and "west-east" cross subsidies from advanced economies to economically less affluent regions in such a way that **all** people may receive the "cure" at a cost much lower than what they now incur for inferior, much less effective treatments. This global plan has **SCCF** partnering with other charities to create **teams** with the management skills, medical knowledge, multi-cultural experience, timely funding, and – above all -- passionate commitment necessary to deliver this long-awaited cure to humanity.

How Oklahoma came to be the discovery location for a tropical disease is a story in its own right composed of new facts, sound growth policies, and the occasional stroke of genius. Without the insights of the Human Genome project, researchers remained stymied. Oklahoma's pro-business policies certainly favor economic development of the bio-medical sector. Insights into evolutionary zoology influenced how to structure the "search". Readers are reminded that discoveries in basic science rarely unravel on schedule, within budget, with no detours. In a field as creative as bio-medical research, there will always be the "unknown" where insight and intuition merge.

"Pro Humanitate" is the motto of Wake Forest University, North Carolina USA
The alma mater of Dr. Robert H. Broyles, discoverer of the cure.

TABLE OF CONTENTS

SCCF’S GLOBAL MISSION: “PRO HUMANITATE”	ii
ACRONYMS AND ABBREVIATIONS.....	v
KEY NUMERICAL VALUES USED IN THIS BUSINESS PLAN	vi
SOURCES and REFERENCES – SELECTED.....	vii
EXECUTIVE SUMMARY (English)	1
PRECIS DESTINE AU CONSEIL D’ADMINISTRATION (français)	4
I. OVERVIEW OF THE SCCF FOUNDATION	9
A. Who We Are	
B. Vision Statement, Mission Statement, and First Business Opportunity	
C. A Critical Need: Proven Business Experience	
II. BACKGROUND	10
III. THE CURE: ITS EXPECTED IMPACT	11
A. Medical	
B. Social	
C. Financial	
IV. TECHNOLOGY & THE DISEASE	12
V. MARKET OPPORTUNITY	14
VI. POTENTIAL COLLABORATORS AND COMPETITORS	16
A. Collaborators	
B. Competitors	
C. Prevailing Atmosphere and Tone	
D. Implications for the Future	
VII. MARKETING STRATEGY AND IMPLEMENTATION	18
A. Corporate Governance and Management Principles	
B. Tax Exempt Charity (501c3) Business Form	
C. Implementation of This Business Plan	
D. Milestones	
E. SMART Evaluation and Audit	

VIII. MANAGEMENT	22
A. The Management “Team”	
B. SCCF	
C. Orderly Business Transfer and/or Exit	

IX. FINANCIALS	24
A. Demand & Market Segmentation	
B. Projected Expense Budget	
C. Prospective Cash Inflows and Outflows	
D. Return-on-Investment Ratios	

Figures

1. Global Incidence of Sickle Cell and Other Blood Disorders.....	13
2. “Explosion” of Prevalents under Care: 2010-2016.....	14
3. “Explosion” of Prevalents under Care: 2010-2028.....	15

Table

1. Program Budget Categories – Tabular	25
--	----

Appendices

ix - xvii

A. The Truth Be Told - Political Economics of Sickle Cell Disease	
C. A Model of Acceptance, Responsibility, and Accommodation	
D. Poverty, Bureaucracy, and Ignorance	
F. SCCF Board Membership and Other Relationships	
G. Broyles, Robert H. <i>et al.</i> <i>Ferritin Heavy Chain Stimulates HbS-to-HbF Switching in Erythroid Precursor Cells from Sickle Cell Patients.</i> 48 th American Society of Hematology Annual Meeting. Orlando, Florida. December 2006.	
H. Broyles, Robert H. <i>et al.</i> <i>Gene Regulation Therapy for Sickle Cell Disease Utilizing Ferritin Heavy Chain</i> . International Biolron Society’s World Congress. Kyoto, Japan. April 2007.	

ACRONYMS AND ABBREVIATIONS

BMS	Bristol-Myers Squibb
CEO	Chief Executive Officer
CFO	Chief Financial Officer
DNDi	Drugs for Neglected Diseases Initiative
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (U.S.)
FtH	ferritin-heavy chain (the cure)
GRT	gene regulation therapy
HGN	Human Genetics Programme/WHO
Hb	hemoglobin
HbF	fetal hemoglobin
ITFDE	International Task Force for Disease Eradication
IRR	internal rate-of-return
NE	Near East
NGO	non-governmental organization
NIH	National Institute of Health (U.S.)
NPV	Net Present Value
OIDL	Organisation Internationale de Lutte contre la Drépanocytose
OMRF	Oklahoma Medical Research Foundation
pp/py	per patient/per year
PRO	ProteomTech, Inc.
R&D	research and development
RBC	red blood cell(s)
RFP	request for proposal
ROI	return-on-investment
SCD	sickle cell disease (anemia)
SMART	specific-measurable-attainable-realistic-timely
TCC	The Carter Center
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases
TVM	Time Value of Money (calculations)
UK	United Kingdom
UN	United Nations
USA	United States of America
USG	United States Government (federal)
USPO	U.S. Patent Office
WHO	World Health Organization
WIPO	World Intellectual Property Organization
XECHEM	XEChem International, Inc.

KEY NUMERICAL VALUES USED IN THIS BUSINESS PLAN

340,300 estimated incidence of SCD-positive newborns - 2008
 Source: March of Dimes. Global Report on Birth Defects. 2006.
 Executive Summary p. 2 extrapolating 2001 figures.

107,000 USA (72,000), UK (8,000), France (27,000) - prevalent
 receiving "standard" care - 2008

PROPOSED CROSS-SUBSIDIZED PRICING – ONE YEAR DOSAGE
 (offered as an example; actual numbers subject to negotiation among partners)

Resident	Price		
Africa	\$120	€ 77	
Europe	\$1,200	€ 770	
Latin Am Caribbean	\$500	€ 320.5	
Northern America	\$1,100	€ 705	
Oceania	\$400	€ 256	
Asia	\$700	€ 449	
World average (weighted)	\$653 start	\$550 midway	\$455 end
	(€418.5)	(€352.56)	(€291.67)

\$14,443 estimated annual out-patient costs - full current treatment
 (€9,258) (HU, transfusions, antibiotics, chelation) – 2008
 Source: Table 34.3 World Bank. "Disease Control Priorities
 Project"

4.9% Increase in cost of SCD medical care
 Source: U.S. Bureau of Labor Statistics. Medical Care Change
 during 2007.

1.56 ----- US Dollar to Euro exchange rate at time of writing

Contact: Dr. Robert H. Broyles 011 (405) 706-5802
robert-broyles@ouhsc.edu www.sicklecellcurefoundation.org

Curricula vitae for Dr. Broyles and Mr. Bricker available on request

SOURCES and REFERENCES SELECTED

Anionwu, Elizabeth. The Politics of Sickle Cell and Thalassaemia. Open University Press: London, June 2001. <http://www.mcgraw-hill.co.uk/html/0335196071.html>

Bachir, Dora et Galacteros, Frédéric. docteurs à l'Hôpital Henri Mondor. "La Drépanocytose: Maladie du Tiers-Monde, Maladie Négligée". Plein Droit No. 12, novembre, 1990.

Bricker, Gary W. "Commercializing the Cure: Preliminary Analyses of the Global Market". Board Meeting: Sickle Cell Cure Foundation. Oklahoma City, August 30, 2007.

Broyles, Robert H. et al. *Gene Regulatory Protein Therapy Using Ferritin Heavy Chain: Towards a Phenotypic Cure for Sickle Cell Disease*. **29th Annual Meeting of the National Sickle Cell Disease Program**. Memphis, Tennessee. April 2006.

Broyles, Robert H. et al. *Specific Repression of Beta-Globin Promoter Activity by Nuclear Ferritin*, **Proceedings of the National Academy of Sciences**. vol.98: no.16, July 31, 2001, pp. 9145-9150

Core document that may guide the future of SCD research and treatment.

Director. World Health Organization , Regional Committee for Africa. "Sickle Cell Disease in the African Region: Current Situation and the Way Forward." Addis Abeba, Ethiopia. AFR/RC56/17. 17 June 2006. *Authoritative annual review*.

ECOSOC/UN. World Population Prospects. The 2006 Revision. *Population growth rates*.

<http://www.ghanaweb.com/GhanaHomePage/NewsArchive/artikel.php?ID=76368>

L'Economie des Brevets et de l'Industrie Pharmaceutique.
zonecours.hec.ca/documents/A2006-1-932701.brevets.ppt

March of Dimes and World Health Organization. Management of Birth Defects and Haemoglobin Disorders. Geneva. 17-19 May 2006.

Modell, Bernadette. "Geographical Distribution of Haemoglobin Disorders". Department of OB-GYN, University College, London Medical School.
http://www.thalassaemia.org.cy/articles/01Geog_Distrib.htm

National Institutes of Health. "Consensus Development Conference Statement – Hydroxyurea Treatment for Sickle Cell Disease." February 25-27, 2008.

Ohene-Frempong, Kwaku. (pediatrics professor, University of Pennsylvania and founder of the Sickle Cell Disease International Foundation for Research and Treatment). "Newborn Screening for Sickle Cell Disease in Ghana," General News (television news spot). Accra. March 2, 2005.
Solid empirical research in the footsteps of Witherall.

Oklahoma Technology Commercialization Center. "Business Plan Guidelines" 2007.
Resource Management Systems, Inc. "FAQs: IT Budgeting"
http://www.rms.net/lc_faq_other_roi.htm

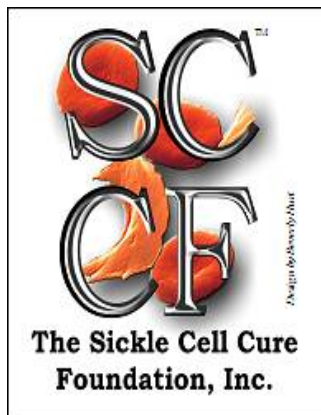
The Associated Press. "Former Duke Player's Son Battles Sickle Cell", March 30, 2008. abc11.com:22-month-old son of Jazz's Boozer battles sickle cell 3/30/08

The Sickle Cell Information Center, Atlanta. "Newborn Screening Saves Lives Act" passed into law 24 April 2008. Senate Bill No.1858.

Weatherall, David. The World Bank. "Inherited Disorders of Hemoglobin". Disease Control Priorities Project. <http://www.dcp2.org/pubs/DCP/34/Section/10761>. *The expert*.

WHO Executive Board. Recommendation 117/3. Jan-07.

World Intellectual Property Organization, "What Is WIPO?" Geneva, Switzerland.
http://www.wipo.int/about-wipo/en/what_is_wipo.html



EXECUTIVE SUMMARY:

----- SICKLE CELL CURE -----

Foundation Overview, Disease Burden, and Management Style

The Sickle Cell Cure Foundation, Inc. (SCCF) is a new 501c3 bio-medical research firm located in Oklahoma City, USA. Under the leadership of **Dr. Robert H. Broyles**, SCCF has discovered and patented a cure for sickle cell disease (SCD), humanity's oldest and most frequent genetic disorder. The cure tentatively branded DREPAC® (FTH-GRT, scientific designation) treats the cause instead of the symptoms. The name DREPAC is derived from *drépanocesse*, a combination of the ancient Greek *drépano* meaning pruning hook or scythe and the French *cesser* meaning *to stop*.

This year some 340,300 children will be born with SCD. Most will die before their first birthday. Today over 107,000 patients are receiving conventional SCD treatment primarily in Europe and North America averaging \$14,443/year only to die an early death at age 42-45. Peer reviews of Dr. Broyles' cure have brought acclaim to SCCF for its non-invasive, non-surgical breakthrough. It has no observed side effects, is 100% effective, and costs 4% the price of today's comprehensive care. Presentations to the world's scientific community are noted below.

SCCF's co-op management style dubbed "more-than-non-profit" has five goals: (1) market drugs worldwide at affordable prices reducing prices as soon as feasible; (2) maximize distribution first and profits second; (3) share independent research as a north-south norm; (4) educate the public; and (5) grow the SCCF asset base. These "more-than-non-profit" goals reflect our belief that basic health care is an obligation and a right – not an option or a privilege. Numerous patents have already been issued.

Solicitation for Funds and Search for Management Partners

SCCF seeks grant funding to finance safety and Trial II activities leading up to field activities under Trial III. Recognizing SCCF's newness to the world of drug development, we are searching for seasoned fellow charities at home and abroad to raise \$5.30 million to bring the cure up to Phase III within four years. SCCF would offer a portion of royalties to compensate cooperating partners for their upfront financial and managerial assistance in this venture. Competitively procured and negotiated pharmaceutical license holder(s) would conduct Phase III trials. As patent holder and

SCCF founder, Dr. Broyles intends to extend licensing and distribution rights consistent with guidance from the World Intellectual Property Organization. SCCF would consider awarding partner charities with reciprocal board memberships and/or a stream of royalty payments as negotiated among licensee(s), patent holders, non-governmental organizations, and participating charities both local and expatriate.

We expect to eliminate 58% of the expression of SCD by 2016 and 87% by 2028.

FTH-GRT (DREPAC©) and Technology

The product is ferritin-heavy chain (FtH), a protein that occurs naturally in the body. It has been shown to deactivate the sickle cell gene and to reactivate a dormant, healthy replacement gene. Yet, FtH does not permanently alter the genes. The cure addresses the embedded genetic cause of SCD – not its external symptoms. The cure is specific to the ailment and easy to administer. Quite stable, FtH requires no refrigeration making it easier to market and distribute in tropical, developing countries where over 90% of SCD sufferers reside. The drug's detailed identification, its modes of application, and salutary effects are unique, proprietary, and patent-protected.

Of course, the biggest barriers to marketing are time-consuming regulatory hurdles: continued patent applications, safety trials, clinical trials here and abroad, and approval from regulatory bodies such as the U.S. Food & Drug Administration (FDA) or the European Medicines Agency (EMA).

Anticipated Benefits of the "Cure" for SCD Sufferers

- + 100% medical efficacy + No side effects + No high risk surgery or chemo
+ up to 340,300 infants saved each year (2008 estimate)
- + 4% cost of current care + 107,000 current SCD patients each save \$13,865/year
- + Sufferers can look forward to a full lifespan (age 82) instead of dying about age 45

SCCF Management Team

Robert H. Broyles, PhD – President and Founder of SCCF, Professor of Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, College of Medicine. Specializes in molecular biology and developmental biology; discoverer of the SCD cure. Strengths: comprehensive scientific analysis, able to identify multi-talented teams, biomedical grant management. B.S. chemistry and PhD biochemistry, Wake Forest University; National Institute of Health fellowship/grants. Community service: American Red Cross, Boy Scouts (Eagle Scout), First Unitarian Church.

Gary W. Bricker^{CFP} - Program Director (designate) of SCCF. B.A. economics University of Connecticut, M.S. urban planning (Third World) Columbia University. 25 years in developing country economic planning, specialized in sub-Saharan Africa grants/loans in public health sector. Strengths: overseas financial planning, technical contract and charity management. Community service: United Nations intern (New York), Habitat for Humanity, School without Boundaries, primary school creation, Black Sea University lecturer, First Unitarian Church. Work/study: Zambia, Somalia, Ghana, Burkina Faso.

To Be Identified – Director for Public Relations and Fund Raising, SCCF. 5+ years experience in finance, fund-raising, investment syndication, project incubator skills, 501c3 advice, corporation tax, legal requirements and filings. Strengths: objective personnel assessments, leadership skills, team builder advice, mentoring others in bookkeeping. CPA and/or MBA. Resident in Oklahoma City. Community service: TBD.

Market Opportunity

Market size historically small due to estimated 75% infantile and child mortality. With the cure tentatively branded as DREPAC © (FTH-GRT), the SCD survivor community could grow by as much as 340,300 per year. Few viable competitors. Product free to assume major market niche limited only by logistics and distribution barriers in remote rural areas, presuming cross-subsidization pricing is effective.

Funds Sought, Financial Projections, and Exit Strategy

Seeking \$5.259 million in grants/concessional rate loans over five years (\$1.188 million in 2008; \$1.152 million in 2009; \$1.496 million in 2010; \$1.330 million in 2011; \$0.093 million in 2012). **Option “A”** -- NGOs, parastatals, and/or governments would contract with one another for these final field testing services as appropriate. **Option “B”** – One or more licensed pharmaceutical companies will fund and conduct Phase III trials costing approximately \$12.0 million and begin marketing 12 months later.

Participating NGOs and/or parastatals may continue as a consortium after patents have expired. Since coops do not issue voting stock, there is no risk of an unfriendly stockholder take-over. Many coops thrive beyond the death of their founding members. There is no mandatory “exit”.

Hypothetical financial example for the Year 2019:

pharmaceutical licensee(s) projected to gross \$214 million, while a 7.5% royalty stream of \$16.0 million will compensate partnering charities, pay management employees, fund more research, and expand charity’s asset base until license expires in 2028. The annual “surplus” of \$26 million would be shared among partnering groups and employees.

Example continued with SCCF as patent holder under USG charity rules:

144.5% ----- Internal Rate of Return (2008-2028)
\$396 million ----- Net Present Value at an 18% discount (2008-2028)
1X Break-even of \$17.259 million ----- 1year 4 months
2X Break-even of \$34.518 million ----- 2 years 1 month
5X Break-even of \$86.259 million ----- 4 years 9 months

Contact: Dr. Robert H. Broyles 011 (405) 706-5802
robert-broyles@ouhsc.edu www.sicklecellcurefoundation.org

Curricula vitae for Dr. Broyles and Mr. Bricker available on request

PRECIS DESTINE AU CONSEIL D'ADMINISTRATION

La Fondation de Guérison Drépanocytaire (FGD)
La Découverte, l'Etendue de la Maladie, la Confirmation
Continue, et Notre Mode de Gestion



La Fondation de Guérison Drépanocytaire (la FGD) est une société à but non-lucratif récemment établie et dédiée à la recherche biomédicale. Sous la direction du docteur Robert Broyles, la FGD a découvert la voie d'une guérison drépanocytaire pour laquelle l'Union Européenne lui a accordé un brevet afin de combattre cette maladie génétique – la maladie la plus fréquemment documentée et la plus vieille de toute l'histoire humaine. La guérison porte DREPAC © (FTH-GRT, désignation scientifique) comme nom de marque provisoire et traite les causes profondes de la maladie au lieu de ses symptômes externes. La genèse du nom DREPAC provient du grec ancien **drépano** qui veut dire faucille et du mot **cesser** en français.

Cette année environs 340.300 enfants seront nés avec la drépanocytose. Malheureusement la plupart sera morte avant leur premier anniversaire. Aujourd'hui 107.000 patients reçoivent le traitement anti-drépanocytaire standard à un coût moyen de €9.029 (\$US 14,447) par an. En dépit de ces dépenses extraordinaires, ces victimes parmi les mieux soignés du monde ne cessent pas de mourir assez jeunes entre l'âge de 42 et 45 ans à la moyenne.

Les études analytiques et les recherches indépendantes suite aux présentations rendues par le docteur Broyles au cours des colloques de savants n'ont fait que confirmer la découverte. Ces examens aux laboratoires par collègues et par inconnus ont fait accroître la renommée de la FGD puisque le nouveau protocole n'a pas besoin d'intervention chirurgicale ni de visites fréquentes à l'hôpital. Il n'y a pas d'effets secondaires reconnus. Le remède est efficace à 100%, et ne coûte que 4% du prix typique des soins compréhensifs. Prière de consulter la liste des présentations offertes par le docteur lors des colloques annuels de savants et de chercheurs.

La FGD se sert d'un style de gestion dit "non-lucratif et encore". Il comporte cinq éléments dont quelques uns cherchent un bénéfice tandis que les autres poursuivent un but social:

1. Vendre la guérison aux prix à la portée du monde entier en essayant de la vendre aux prix mêmes plus réduits aussitôt que possible.
2. Au début de la campagne de vente, agrandir le réseau de distribution même s'il faut réduire la marge de bénéfice.
3. Partager les fruits de recherche indépendante autant qu'un dialogue normatif qui renforce les rapports Nord-Sud.
4. Renseigner le public (du village jusqu'à l'université) au sujet de la guérison drépanocytaire, y compris son dépistage.

5. Faire accroître les fonds de recherche disponibles à la FGD, y compris le nombre des échanges entre instituts et leur personnel.

Ces « buts non-lucratif et encore » rappellent notre croyance que l'accès aux soins médicaux doit être un devoir et un droit. En plus, cet accès ne doit pas être facultatif mais obligatoire pour tous – non seulement les privilégiés. Plusieurs brevets ont été déjà accordés.

Demande des Fonds et la Recherche d'un Directeur de Gestion

La FGD sollicite des dons pour financer les essais de sureté jusqu'aux essais de l'Etape No. II qui amènent au chantier d'essais de l'Etape No. III. En se rendant compte que la FGD vient d'arriver au monde du développement de produits pharmaceutiques neufs, nous cherchons d'autres sociétés pareilles à but non-lucratif qui sont déjà rodées pour travailler avec nous en partenariat dont le siège social pourrait être domestique ou étranger. Le budget estimatif à travers ces années d'essais (2008-2012) est de l'ordre de €3.313 millions (\$US 5.293 million) -- fonds suffisants pour nous amener au seuil de l'Etape No. III.

A ce point, la FGD – toujours en partenariat -- se propose solliciter parmi les sociétés pharmaceutiques celles qui voudraient financer et diriger toute l'Etape No. III en échange du droit exclusif de recevoir le transfert de brevet, en particulier les droits de commercialisation et du marketing. La sollicitation suivra les protocoles compétitifs d'acquisition internationale conformes aux principes internationaux prônés par l'Organisation Mondiale de la Propriété Intellectuelle. La société la plus compétitive payera des rentes à la FGD, qui à son tour payera un pourcentage de ses rentes à tous les collègues qui auront participé dans cette aventure selon la durée et le niveau de chaque effort individuel.

Nous nous attendons éliminer 58% de l'expression drépanocytaire avant l'an 2016 et 87% avant 2028.

DREPAC © et la Technologie

Le remède (dont le nom commercial sera DREPAC ©) est lié à la féretine à la lourde chaîne (FtH), une protéine que le corps produit naturellement. On a déjà montré que la FtH peut dé-activer le gène drépanocytaire muté et simultanément réveiller le gène sain qui le remplace. Néanmoins, FtH ne change pas les gènes pour toujours. La guérison s'adresse aux causes profondes de la drépanocytose au lieu des symptômes externes. La guérison est spécifique à la maladie. Son administration est facile. Le produit est si stable du point de vue chimique qu'il n'est pas nécessaire le mettre au frais, une situation favorable pour marchander et distribuer ce remède salubre dans les pays tropiques en voie de développement où habitent plus de 90% des victimes drépanocytaires. La composition moléculaire du produit pharmaceutique, ses effets salutaires, et ses modes de traitement sont reconnus autant que de la propriété intellectuelle déjà protégée par des brevets.

Certes, la barrière la plus prolongée est l'approbation du permis de vente de la part des autorités régulatrices telles que le European Medications Agency (EMA) ou le U.S. Food and Drug Administration (USFDA).

Les Bienfaits Attendus pour Ceux qui Souffrent de la Drépanocytose et Qui Suivent un Traitement DREPAC©

- Efficacité médicale à 100%
- Aucun effet secondaire
- On peut éviter les risques importants liés aux interventions chirurgicales et aux thérapies chimiques
- 340.300 enfants sauvés chaque année (l'an 2008 estimatif)
- Le coût projeté du traitement DREPAC © ne sera que 4% des tarifs actuels
- Environ 107.000 patients pourront épargner €8.888 (\$US 13,865) par an
- Les victimes drépanocytaires pourront s'attendre à une durée de vie normale de 82 ans au lieu de mourir à l'âge de 45 ans

L'Equipe de Gestion FGD

Robert Broyles, docteur – Président-Directeur Général (PDG) et Fondateur de la FGD, professeur en biochimie et biologie moléculaire. Spécialiste en biologie moléculaire et la biologie du radical libre, il a découvert la guérison pour la drépanocytose. Points forts: analyse compréhensif et scientifique, peut identifier des membres des équipes doués de talents multiples, gestion des dons de recherche. License ès science en chimie et doctorat en biochimie – Wake Forest University. Chercheur et savant au National Institute of Health. Activités communautaires : la Croix Rouge Américaine, Boy Scouts, First Unitarian Church.

Gary Bricker, Certified Financial Planner - Directeur du Développement (nommé) pour la FGD. License ès lettres en science économique University of Connecticut, Maîtrise ès sciences en urbanisme (option Tiers Monde) Columbia University. 25 ans en planification économique dans les pays en voie de développement. Spécialiste dans la gestion des dons et des prêts du secteur santé publique des pays au sud de Sahara. Points forts: planification financière d'outre-mer, la gestion technique des contrats et des dons. Activités communautaires : l'internat auprès de l'Habitat pour l'Humanité (Nations Unies) New York, conseiller – Schools without Boundaries, démarrages d'écoles primaires, professeur adjoint – Black Sea University (Tbilisi), First Unitarian Church – conseil d'administration. Lieux de travail/d'études : la Zambie, la Somalie, le Ghana, le Burkina Faso.

Directeur des Finances, à recruter. Au moins cinq ans d'expérience dans les finances, la collecte des fonds caritatifs, l'organisation du placement des investissements, du talent dans le démarrage de projets, dans le conseil fiscal pour les sociétés à but non-lucratif, dans les impôts pour sociétés anonymes, preuves égales et leur documentation. Points forts : évaluation du personnel, conseils sur le renforcement d'équipe, programme de formation en comptabilité. Maîtrise de gestion ou expert-comptable. Habitant d'Oklahoma City, USA. Activités communautaires- à voir.

L'Opportunité du Marché

A travers les années la taille de ce marché restait petite à cause du taux de mortalité à l'ordre de 75% pour les nouveaux nés et les enfants moins de cinq ans.

DREPAC ©, le nom de marque provisoire, sera réservé pour toute publicité au sujet du remède.

La population des survivants drépanocytaires pourrait atteindre un débit de croissance de 340.300 par an. Quant aux concurrents, il n'y a que très peu qui soient prêts. Le nouveau remède est bien placé pour contrôler une grande partie du marché. Si on réussit à établir une péréquation de prix parmi les marchés variés, la taille de ce marché sera limitée par deux facteurs seulement : 1) une infrastructure logistique et des barrières de transport qui empêchent une bonne distribution dans les endroits ruraux lointains et 2) le manque d'un programme national de dépistage.

Les Fonds Sollicités, les Chiffres Budgétaires, et Comment Sortir du Marché:

Nous cherchons €3.371 millions (\$5.259 million) sous forme de dons ou de prêts aux taux d'intérêt subventionnés sur cinq ans : 2008 – €0,762 millions (\$1.188 million) ; 2009 - €0,738 millions (\$1.152 million) ; 2010 - €0,959 millions (\$1.496 million) ; 2011 - €0,853 millions (\$1.330 million) ; et l'an 2012 - €0,060 millions (\$0.093 million).

Option A - travaillant comme membre d'un consortium la FGD signera avec les organisations non-gouvernementales, les sociétés para-étatiques, et/ou les gouvernements concernés autant que sociétés à but non-lucratif un contrat pour les services d'essais définitifs rendus au chantier comme Etape No. III. Le consortium lancera une Demande de Propositions de Projet à cet effet.

Option B – A la suite d'une compétition technique et financière, la FGD attribuera un transfert de son brevet pourvu que la société pharmaceutique la mieux placée, à ses propres frais internes, finance et conduise les essais de l'Etape No. III, et commence la vente du produit au plus tard 12 mois après les approbations des autorités régulatrices. Les participants dans le consortium (Option A) ou la société pharmaceutique (Option B) pourront continuer leur entreprise après la date terminale du brevet. En plus, il vaut bien remarquer qu'un consortium n'émet pas d'actions, et ainsi ne court pas de risque d'une reprise inamicale de la part des actionnaires. Beaucoup de consortium ou de sociétés à but non lucratif fleurissent longtemps après la mort de leurs fondateurs. Il n'y a pas de sortie obligatoire.

Exemple d'un scénario financier : Pour l'an 2019 l'entreprise pharmaceutique projette des revenus de \$214 million ; la même année l'entreprise payera des rentes de 7,5% pour couvrir les dons secondaires et les dépenses suivantes : du soutien aux partenaires bénévoles, les frais de l'équipe de gestion ; une hausse dans les frais de recherches ; l'élargissement de la base financière de la FGD jusqu'à ce que le brevet se termine en 2028. A la moyenne, un surplus annuel valorisé à \$US 16 millions sera partagé parmi les membres du partenariat.

Exemple continu en chiffre avec la FGD comme détenteur du brevet (l'an 2018):

144,5% ----- taux de rentabilité interne (2008-2028)
€253,8 millions (\$US396 millions) ----- valeur actuelle nette liée à un taux
d'escompte de 18% 2008-2028)
1X – seuil de rentabilité (\$US 17.259 million) ----- 1an 4 mois
2X - seuil de rentabilité (\$US 34.518 million) ----- 2 ans 1 mois
5X - seuil de rentabilité (\$US 86.259 million) ----- 4 ans 9 mois

Contacteur : Robert Broyles 011 (405) 706-5802
robert-broyles@ouhsc.edu www.sicklecellcurefoundation.org

Les curricula vitae de Messieurs Broyles et Bricker disponibles sur demande.

I. OVERVIEW OF THE SCCF FOUNDATION

A. Who We Are

As research scientists and medical professors, generally, we author grant requests and journal articles as opposed to business plans and annual reports. Career advancement is based more on breakthroughs rather than profits. However, with a recent emphasis on translational research, more discoveries may be applied to clinical problems. **SCCF** is a non-profit formed for the express purpose of taking basic discoveries from “bench to bedside”.

SCCF staff members focus on investigations and discoveries and pursue basic research. We recognize the need for new partners specialized in finance, law, fund-raising, accounting, and tax procedures with an emphasis on the “bottom line”.

As purveyors of the cure, SCCF management must remind itself that we are not debating the efficacy of aspirin and degrees of comfort. Rather, we are dealing with thousands of lives – often of children - suffering bouts of excruciating pain. Their medical treatment can quickly consume most of their household savings with the victim left to live only half a normal life span.

Passionately shared complementary visions are critical to the success of complex missions. Dedication to a vision can often overcome all odds, can muster hidden resources, and can achieve insurmountable goals. Our “more-than-non-profit”, cooperative vision colors our mission, our business plan, and our corporate relationships.

B. Vision Statement, Mission Statement and First Business Opportunity

- Vision Statement - conduct and sponsor basic medical research, pursue breakthroughs in medical knowledge and technology, and apply for patents on health-related intellectual property that can be licensed for commercialization and distribution in exchange for royalties and/or non-taxable considerations among other non-profits on an affordable and accessible basis consistent with World Intellectual Property Organization guidance.
- Mission Statement – expand the patented Gene Regulation Therapy (GRT) process in hopes of spear-heading a series of gene-based discoveries and treatments; to make the findings of this research available to other non-profits consistent with World Intellectual Property Organization guidance.
- First Business Opportunity – to negotiate with partners and pharmaceuticals the commercialization of FtH as part of a genomic treatment to stop the expression of SCD. This would be the world’s first clinical application of GRT, a patented procedure developed by Dr. Robert Broyles of the University of Oklahoma’s Health Sciences Center.

C. A Critical Need: Proven Business Experience

SCCF was established July 28, 2006 and was accorded 501c3 status on February 12, 2007 as a tax-exempt, independent medical research center.

We had thought that investors would be “knocking down the doors” to help us. Instead, we quickly concluded that a host of specialists both part-time and full-time would probably be required to move this discovery “from lab bench to boardroom to bedside”. To sustain the momentum of product development, SCCF has concluded that partnering with substantially larger U.S.-based and Africa-experienced charities or government-sponsored research centers (parastatals) is likely to garner more funds and attract talent with more relevant experience.

II. BACKGROUND

A. Nomads Inspire Search for of a Genetic “Trigger”

As recently as 1975 the Western medical research community was rocked to discover that members of a nomadic group in Saudi Arabia carried homozygous (SS) sickle cells but manifested absolutely no clinical symptoms! Adult blood samples from this small group revealed the presence of fetal type hemoglobin (HbF) at a 25% to 40% frequency. Since the bone marrow of normal people typically stops producing HbF a few months after birth, this group was the subject of intense international medical scrutiny. Apparently, high HbF levels were imparting resistance to sickling.

With this observation, the race was on! The search for the genetic “trigger” drove the agenda of the more sophisticated SCD research centers for 25 years, as scientists located and attempted to resuscitate the naturally occurring but now dormant HbF (fetal hemoglobin) gene. Scientists sought to understand how newborns accomplish the switch from HbF to adult Hb, in hopes of partially reversing this transition. This approach is a quintessential example of GRT in which no genes are deleted or permanently altered. GRT is the essence of a phenotypic cure: locate then resuscitate the dormant expression of a gene without destroying or altering it.

Finally, in 2006 Dr. Broyles demonstrated how to activate the HbF “trigger”.

B. Hb-F Is Also a Possible Deterent To Malaria

Not only does it appear that HbF suppresses the expression of sickle cell disease. But a recent literature review by the eminent Sir Dr. David J. Weatherall also suggests that HbF protects infants from the on-set of malaria during the first year of life until HbF levels decline to a certain frequency as stated below:

In vitro studies have shown that β -thalassaemic red cells are invaded at the same rate as normal red cells and that the rate of parasite growth is also indistinguishable from normal. However, both in human red cells and in transgenic mice carrying human γ -genes, it has been found that those which contain human fetal Hb are associated with ineffective development of *P. falciparum* or *P. yoelli* (Pasvol *et al*, 1977; Shear *et al*, 1998). As there is strong evidence that the rate of decline of fetal Hb after birth is delayed in β -thalassaemia heterozygotes (Weatherall & Clegg, 2001a), this could provide a mechanism of protection during the first year of life, but no longer; the studies of Passvol *et al* (1977) suggested that retardation of parasite growth required 5-7 pg/Hb F per cell.

Source: Weatherall, David J. (Professor Sir). “Genetic Variation and Susceptibility to Infection: the Red Cell and Malaria” British Journal of Haematology. Vol. 141, 2008. p. 280.

Indeed! If one were to revive and sustain the body's production of HbF --- the infantile "mechanism of protection" (HbF) of which Dr. Weatherall speaks so eloquently --, then one would have discovered by association not only a cure for SCD but also a novel, genetically based approach to the control and management of malaria.

Such a discovery would be on a totally different order of magnitude. To wit, some 370 million new cases of malaria occur each year – over a thousand times the incidence of new SCD cases. WHO and CDC estimate global malaria mortality to be 800,000 with 90% of the victims children below the age of 5.

In 2006 Dr. Broyles demonstrated how to activate and sustain the HbF "trigger" – a discovery which forms the operational basis for the SCCF project. SCCF is in possession of a discovery that provides a phenotypic "cure" for SCD **and may also confer a resistance to malaria!**

III. THE CURE: ITS EXPECTED IMPACT

A. Medical

The product is ferritin-heavy chain (**FtH**), a protein that occurs naturally in the body. FtH deactivates the sickle cell gene and reactivates a dormant, healthy replacement gene. For the first time in medical history, we will use our patented technology known as "**Gene Regulation Therapy**" to control gene expression without permanently altering any genes. Quite stable, it requires no refrigeration. The drug's identification, application, and salutary effects are unique, proprietary, and patent-protected. Today, a typical Third World couple with a confirmed SCD pregnancy has only two options: death in infancy or a risky abortion. Advanced economies present the couple with several costly sometimes risky options: bone marrow transplantation, umbilical cord stem cells, a safe abortion, or a lifetime of hospital bills. Thanks to the cure, no longer will a positive SCD test be a "death warrant".

Dr. Broyles has successfully submitted his discovery to peer review in numerous countries and has been awarded patents to protect this hard-earned intellectual property. SCCF is now engaged in the early stages of the development of this new drug that provides a phenotypic cure.

The cure is expected to deliver prompt relief like the "Lazarus effect" experienced by AIDS sufferers upon first using anti-retrovirals. The cure will establish a new "standard of care" to treat SCD and will bring an end to this age-old scourge by providing FtH treatment for all who inherit symptomatic SCD.

Public policy arguments are also substantial. If only one year's cohort of SCD victims (340,300) were to live and contribute to the gross domestic product at \$US1,600 (€1,000) per capita, a total of \$716 million (€447.5M) in goods and services could be added to the economy in one year.

B. Social

This drug will change lives and social relationships. No longer will couples who have conceived an SCD child have to suffer the trauma of terminating an unwanted and unaffordable SCD pregnancy.

C. Financial

Indications are that FtH will be far more affordable than current therapy. The potential cost savings of this new drug are remarkable. The current “standard of care” averages \$14,443 (€9,027) a year in the USA for the administration of a series of palliative measures that gradually poison the sufferer for 40+ years until death. This cost compares with a proposed \$1,200 (€750) per year to purchase the new drug in Europe or \$120 (€75) in Africa. A doubling of the expected average age of death means that many patients can remain active during their prime income-earning years. The impact on a family’s budget will be substantial and long lasting.

IV. TECHNOLOGY & THE DISEASE

If both mother and father carry the recessive “trait” but are otherwise symptom free, they stand a 25% chance of conceiving an SCD child according to Mendel’s square. Deformation of affected cells impedes normal blood flow thereby slowly asphyxiating the victim at the cellular level and jeopardizing vital organs. Victims - both treated and untreated - eventually die from heart failure, kidney failure, or stroke.

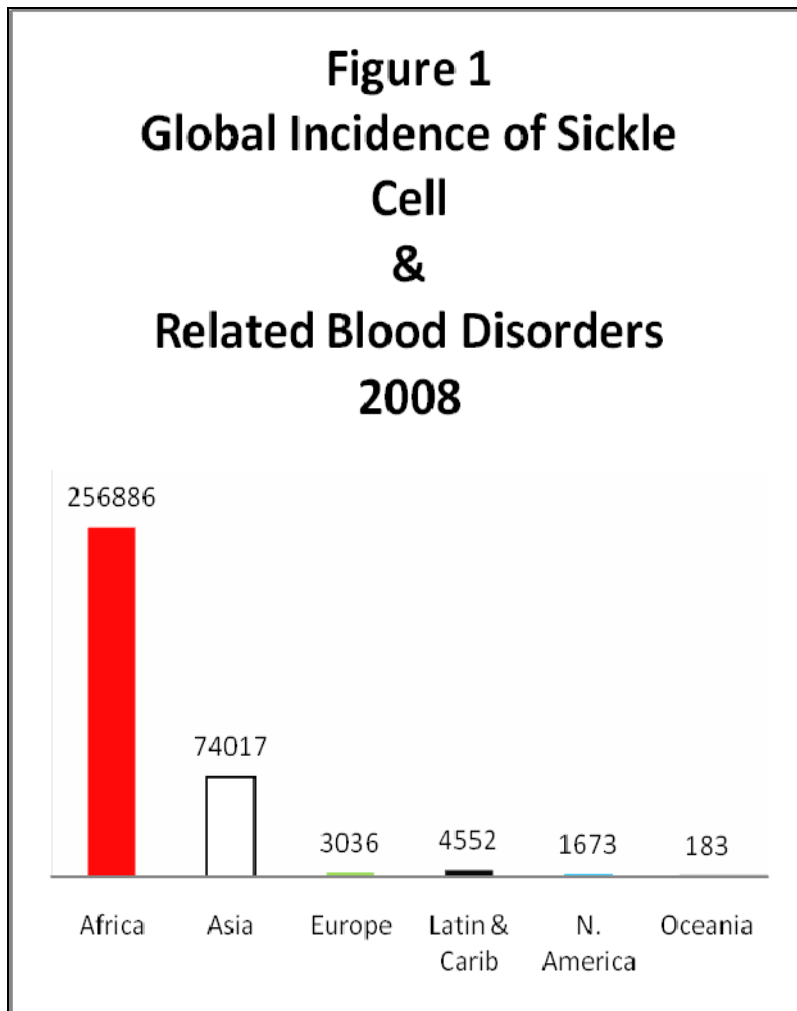
Manipulation of Modell’s 2001 data on births incident with SCD reveals the relative intensity and geographic localization of the SCD phenomenon. For example, sub-Saharan Africa shows an incidence of 2.5 newborns with SCD per 10,000 births. Compared to Northern America’s rate of 0.050 per 10,000 births and Europe’s 0.0370 rate, Africa’s incidence is 50 times and 68 times more frequent, respectively. FtH provides a “phenotypic” cure meaning the appearance of the cell and its various functions are normalized. “Phenotypic” cure is opposed to a “genotypic” (genetic) cure where the actual DNA code is irreversibly altered.

In most tropical, developing countries where SCD is a major public health concern, its management has remained inadequate according to United Nations advisors. National control programs do not exist. Basic facilities are absent. Systematic screening is not a common practice, and diagnosis is usually made when a patient presents with a severe complication.

Simple, cheap, and very cost-effective procedures such as the use of penicillin to prevent infections and to retard the onset of clinical SCD are not widely available. Few survive to make the transition from incidence to prevalence. The exact manner in which FtH triggers and un-triggers gene activity is proprietary and “reserved” until broader patent protection is granted. Burkina Faso reports the highest SCD newborn incidence with 10.5 per 10,000. In fact, the 16 countries with the highest incidence of SCD newborns are all in tropical Africa and all are low-income countries with the one exception of Gabon.

Each year there are an estimated 340,300 incidents of newborn victims worldwide. Yet, there is no systematic, mandatory screening for SCD in many countries. Why? Health policymakers perceive no public benefit to be gleaned by frustrating new parents with mandatory screening for an “incurable” disease. **Figure 1 “Global Incidence of Sickle Cell and Related Blood Disorders”** shows that 75% of new SCD cases are in Africa,

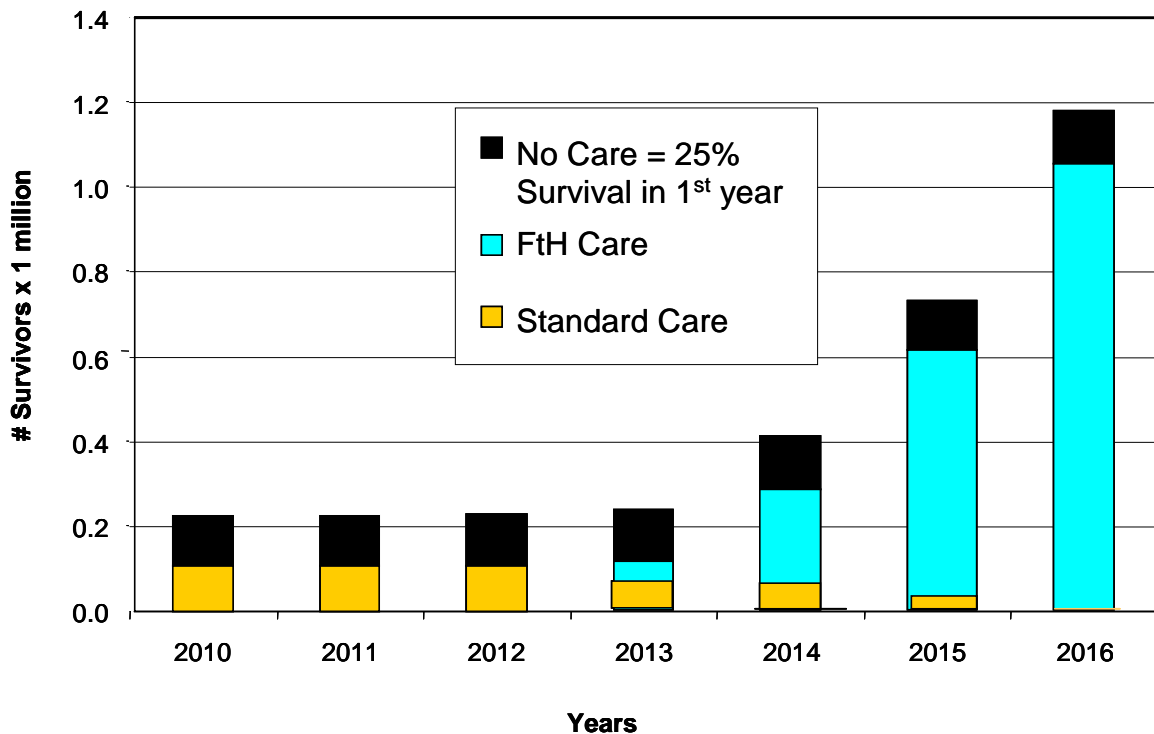
22% from Asia, with the remaining 3% appearing in Europe, Oceania, and Northern America (i.e., the U.S.A. and Canada).



V. MARKET OPPORTUNITY

The cure's potential market niche is currently "wide open" but volatile and burdened with secrecy. With vigilant patent defense, the cure presents the "ultimate" business opportunity – a global monopoly experiencing accelerating demand. As the SCD-positive members of each cohort of newborns "come on line", they will become lifetime patients requiring periodic doses of the drug to sustain their atypical phenotypic production of HbF proven to stop SCD symptoms. Figure 2 "**Explosion of Prevalents: 2010-2016**" and Figure 3 "**Explosion of Prevalents: 2010-2028**" (next page) depict the anticipated, rapid market growth. In addition, Figure 2 depicts the gradual market penetration of FtH treatment beginning in 2013, plus gradual replacement of standard treatment as FtH becomes more widely used.

Figure 2
Explosion of Prevalents: 2010-2016

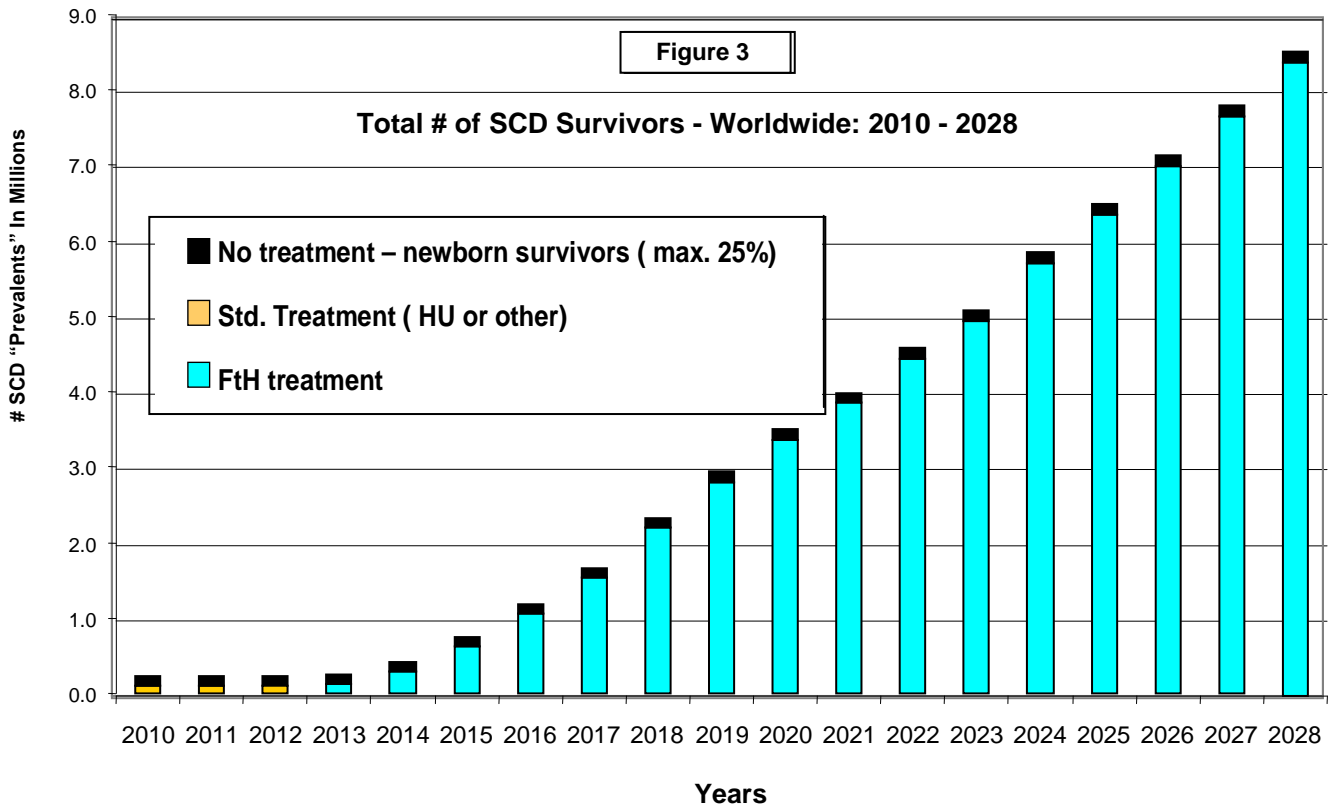


An estimated 365,845 newborn "incidents" will occur in 2013 with only a small minority surviving beyond five years thereby creating a demographic "wash" or status quo. In the past, the survivors were almost exclusively the 107,000 individuals in the USA, UK, and France fortunate enough to have easy access to modern comprehensive medical care. Once the FtH cure becomes available, the surviving newborns can join the ranks of the 107,000 "prevalents", thereby adding to a rapidly growing permanent client base.

Thus, the number of SCD-positive individuals demanding the cure will increase every year in a cumulative fashion. Given the alarming global rise in malaria, another important result of this SCD cure is expansion of a population that is resistant to malaria, since all who carry one or more copies of the “sickle gene” have been shown to be resistant to the chronic, deadly phase of the malaria infection.

The new GRT therapy may also prove applicable to Parkinson’s, Huntington’s, and certain liver disorders. The patents have been written broadly in hopes of including GRT in the treatment of these other diseases. If so, SCCF partners will be well-positioned to contribute to future cures and to benefit from future investments.

Figure 3
Explosion of Prevalents: 2010-2016



VI. POTENTIAL COLLABORATORS AND COMPETITORS

A. Collaborators

Obviously, NGOs expressly established to respond to SCD will take center-stage in our efforts to amass resources be they financial, artistic, athletic, spiritual, or intellectual. We believe that four groups will play key roles in supporting Trials II and III as well as in the selection of one or more winning pharmaceutical companies:

- U.S. hospitals and physicians maintaining close collegial relationships with foreign counterparts in Europe and/or Africa on the subject of SCD,
- U.S.-based charities demonstrating active links with SCD counterpart organizations,
- Western government agencies recruiting long-term volunteers in public health, medicine, and education and associated grantees and contractors,
- celebrities (e.g., sports and music) affected by symptomatic SCD in their families who wish to advocate, endorse, and raise funds.

B. Competitors

Potential competitors come from academic medical research centers, government-sponsored research and development centers, pharmaceutical companies and for-profit drug manufacturers.

C. Prevailing Atmosphere and Tone

The American Sickle Cell Anemia Association (ASCAA) website reports how research centers are closing in on HbF creation as the path to the cure and that some form of genetic correction or manipulation will be necessary.

Some scientists are looking into whether correcting this gene and inserting it into the bone marrow of people with sickle cell anemia will result in the production of normal adult hemoglobin. Others are looking at the possibility of turning off the defective gene and simultaneously reactivating another gene that turns on production of fetal hemoglobin.

D. Implications for The Future

It is a strongly considered opinion that none of the hospital-based, physician-dependent, toxic treatments that constitute the gold standard will have broad appeal for three reasons: cost, efficacy, and side-effects.

- a) They simply cost too much. To wit, \$4.9 billion would be required to fund only one year of “standard” care for just one cohort of SCD-positive newborns (340,300 in one patient cohort x \$14,443/year). This is more than twice the entire 2004 foreign assistance health budget of

the U.S. Agency for International Development. The implicit upheaval in budget priorities is highly unlikely.

b) These treatments do not really “work”. They address the symptoms – not the cause. In short, they are a “standard” adopted by default.

c) They do not hold out the promise of long-term efficacy with few side effects.

- The business plan must move forward with all deliberate speed.
- The board needs to promulgate criteria to reduce chances for litigation.
- Given the secretive SCD research environment, the market could change over night.
- Dr. Broyles wisely saw fit to seek patent protection as early as possible.

VII. MARKETING STRATEGY AND IMPLEMENTATION

Working as a consortium of local and expat health NGOs -- with the backing of local clergy, Mission hospitals, and government clinics -- has proven to be a practical and productive management approach in combating the HIV/AIDS epidemic in Africa. A parallel marketing effort for the SCD cure could easily follow in the administrative footsteps of the much larger, well seasoned HIV/AIDS programs. Furthermore, SCCF's education, community development, and basic health outreach would make our SCD efforts stand out as distinctly "user-friendly". With a collegial, developmental approach, our marketing strategy will pre-empt any discouraging, adverse, or behind-the-scene host country behaviors such as compulsory licensing, parallel importing, or Bolar provisions. SCCF's winning licensees would be asked potentially to set-up shop in neighboring advanced or emerging economies serving known centers of SCD prevalence (e.g., Thailand, South Africa, India, Malaysia, Paris, and London). To this end, SCCF may need to seek additional patent approvals from graduating economies with strong, independent judiciaries.

A. Corporate Governance and Management Principles

Our "more-than-non-profit" approach to corporate governance is a blend of classic "profit maximization" incentives tempered with charitable, philanthropic intent. As such, the SCCF Board – possibly in consortium with other charities either here or abroad --- will allocate surplus balances from royalty payments to fund (1) "user maximization" programs that promote a broader beneficiary base for public health, (2) medical research for common ailments, (3) breakthrough treatments affordable and accessible to the global majority, and (4) including education as noted in our By-Laws and Articles of Incorporation. The seven management principles espoused by the Rochdale cooperative movement over the last century will guide SCCF's governance policies:

1. Voluntary and open membership
2. Democratic member control
3. Member economic participation
4. Autonomy and independence
5. Education, training, and information
6. Cooperation among cooperatives
7. Concern for community.

This cooperative form of governance reflects SCCF's basic premise that health care is a public responsibility and a fundamental right. Just as compulsory primary and secondary education is provided at no charge to the student, so "basic" health care services should also be accessible to all residents. SCCF will emphasize maternal and child care services not only because SCD is a childhood affliction but also because women and newborns have historically been the most vulnerable health care recipients.

In addition to maintaining a reasonable profit margin or surplus, we will consider several tactics to increase affordability and expand accessibility:

1. Competitive selection of short-listed providers
2. Cross-subsidization from high- to low-income beneficiaries
3. Mobile “outreach” clinics
4. Proven judicial record of patent protection
5. Compliance with guidelines recommended by WIPO
6. Production of high quality pharmaceuticals nearer their retail markets

SCCF believes that the cooperative management approach will be especially well-received in a developing county setting given its holistic, integrated style of grass-roots decision-making that focuses on development of a consensus.

B. Tax Exempt Charity (501c3) Business Form

A research grant is the “business form” with which the SCCF members are most familiar. A consortium of overlapping charities making sub-grants or sub-contracts as necessary would appear adequate under current circumstances to meet our needs.

Before transferring exclusive licensing rights to a pharmaceutical company to commercialize the cure, the professional experience of board members recommends the following remedial “homework” to make this product attractive to investors and less prone to patent infringement:

- Conduct animal and safety trials under direct supervision
- Conduct Phase II trials in SCD-prone cultural environments
- Hire local development anthropologists to serve “on location”
- Include imminent scientific and managerial talent from SCD-prevalent countries to serve on the RFP review

C. Implementation of This Business Plan

Stage 1: Basic research has been completed.

Stage 2; Pre-clinical research to repress the “S” gene and to reactivate the dormant fetal blood gene has been achieved in laboratory settings as documented in Appendices G and H.

Stages 3 through 6: The **business plan** seeks grant, loan, and /or venture capital funding for Stage 3 through Stage 6 to develop an SCD drug: Stage (3) - completion of patent issuances in the USA and Canada; Stage (4) - safety and efficacy trials in animals; Stage (5) - Phases I through Phase II-A limited clinical trials in developing country settings and the preparation of a Request for Proposals to conduct Phase III licensing and expanded global trials; and Stage (6) - evaluation of the management challenges such as injectables vs. tablets, logistics and distribution, and various delivery approaches from walk-in clinics in upper Manhattan to floating clinics serving fishermen on the lower Zambezi.

These remaining implementation steps (3) - (6) are detailed below:

Stage 3 - Continued Patent Issuance

“Gene Regulation Therapy Involving Ferritin”. Patents issued in Australia, Albania, France, Germany, Greece, Italy, Luxembourg, Portugal, Spain, Turkey, and the UK. (issuance pending in the USA and Canada).

Filing Date: 01-Nov-00.

“[Phytochemical X (PhyX)] and Derivatives Thereof for the Treatment of Disease” (issuance pending in USPO). Filing Date: 04-Mar-05.

Request: \$105,000

Stage 4 - Pre-Clinical Safety & Efficacy Animal Trials

Determine:

- Whether the FtH treatment is safe in mice, using a 4-log range of doses.
- The efficacy of FtH for hemoglobin (Hb) switching in mice with FtH delivered as a protein.
- Whether the PhyX treatment is safe in mice, using a 4-log range of doses.
- The efficacy of PhyX as an inducer of FtH expression, especially in bone marrow, spleen, and brain, and of the FtH protein as an inducer of Hb switching in baboons.

Main Methods: Gene arrays/Quantitative Reverse Transcription-Polymerase Chain Reaction to measure marker genes for expression in 10 tissues of mice for different doses & times and to quantify human & mouse ferritins, mouse Hb genes. Motor activity by rotorod & exercise wheel for mice. Veterinary exam for baboons.

Toxicity measure: gene arrays, motor activity, death.

Time-frame: 9 months

Request: \$602,000

Stage 5 – Phase I, II, and II-A Clinical Trials in SCD Patients & Healthy Humans (for Efficacy & Safety) including Orphan Drug Pharmaceutical Collaboration

Phase I – 12 months:

Clinical trials will conduct safety experiments on healthy human volunteers.

Methodology: Comply with ethical criteria in “International Conference of Harmonisation Guidelines for Good Clinical Practice”.

- Source of pharmaceutically pure FtH and PhyX in large quantities. Adequate clinical facilities and personnel for in-patient and out-patient trials.

Oklahoma City & Paris - 240 subjects

Request: \$399,000

Phase II – 18 months:

Approach: Random, double blind, “active comparator” studies; pairing of “national hospitals/mission hospitals” with on-going SCD screening and prior US donor experience.

Atlanta, Kampala, Ouagadougou, and Kumasi 1,200 subjects Request: \$1,101,000

Pre-approved plans to renovate sickle cell clinical facilities & expand services.

Kampala, Ouagadougou, & Kumasi 3 sites/programs Request: \$150,000

Phase II-A – 6 months:

Design, compete, negotiate, award proposal to expand trials to 15,000 subjects & submit the cure for exclusive global licensing, production, & distribution under patents. OKC & nearby “off-site” location (e.g., state lodge) Request: \$96,000

Stage 6 & total managerial costs of Phases I-IIA, to identify cultural, managerial, financial, legal, logistical, and medical practices that may impede the broad distribution of the cure in suburban/slum municipal environments and in commercial/subsistence rural settings. Assess adequacy of adherence, compliance, storage, distribution, and security measures to ensure proper and timely usage of drug.

request: \$2,578,000

Total costs of medicines for trials, and for contingencies (5%):

costs: \$228,000

TOTAL Funding requested for Stages 3-6

\$5,259,000

D. Milestones

Appendix I **Time Line: Program and Support** depicts the following milestones for programmatic and managerial achievements and associated budget increments, years 2008 through 2012 (up to 2013):

- | | |
|--|--------------------------------------|
| 1. create NGO agreements,mgt. structure, define roles, expectations, authorities | 7. stage 6 - evaluation (2012) |
| 2. secure first year’s seed capital | 8. issue RFP (2012) |
| 3. secure experienced management counsel | 9. sign licensing agreement (2012) |
| 4. stage 3: renew patents (2008, 2010) | 10. complete Phase III trials (2013) |
| 5. stage 4 - animal safety trials (2009) | 11. EMEA & FDA approval (2011/2012) |
| 6. stage 5 - Phases I-IIA clinical trials (2010 - 2012) | 12. begin sales (2013) |
| | 13. begin royalty flow (2013) |
| | 14. exercise exit strategy options |

E. SMART Evaluation and Audit

During Phases I-IIA and during first year of marketing, identify cultural, managerial, financial, legal, logistical, and medical practices that may impede the broad distribution of the cure in suburban/slum municipal environments and in commercial/subsistence rural settings. Assess adequacy of advertising, adherence, compliance, storage, distribution, and security measures to ensure informed and timely usage of drug.

The business plan and negotiated licensing agreement will track progress towards completion of nine activities:

1. locate more-than-non-profit partners to SCCF which shares its purposes,
2. secure patents and regulatory approvals,
3. initiate or complete efficacy and safety studies on various other cures believed susceptible to similar therapies,

1. license pharmaceutical manufacturers to produce, distribute, and sell similar cures,
2. contract with third parties such as health-related, non-governmental organizations to monitor, audit, and evaluate progress and to report findings to scientific forums and the public at large,
3. conduct affordability analyses and cost-benefit analyses of beneficiary populations,
4. promote and monitor the adoption of infant screening,
5. monitor how pregnant women respond to the new GRT option of SCD treatments when faced with the prospect of delivering an SCD child, and
6. monitor the mortality-morbidity of SCD sufferers.

Activities 3-9 will be validated using SMART criteria (Specific-Measurable-Attainable-Realistic-Timely) to select baseline, interim, and target measures as vetted a priori by peers who will also define “success” for activities 3-9. A university-based bio-statistical and public health institute with a Third World track record and local academicians would be an appropriate source for longer term monitoring service.

VIII. MANAGEMENT

Laboring under a tight grant budget, the Oklahoma Medical Research Foundation (OMRF) was forced to drop any further development of Dr. Browles’ discovery explaining that the 72,000 documented SCD sufferers in America were too few. A minimum 200,000 patient case load is the fiat cut-off level to avoid falling into the U.S. National Institutes of Health’s rare or “orphan” disease category. Once an orphan, further federal funding is usually cut-off. As a gesture of goodwill, OMRF transferred its patent rights to SCCF at no charge.

A. The Management “Team”

Robert H. Broyles, Founder and Chairman of the Board (team member, employee, SCCF rep, and investor). President, The Sickle Cell Cure Foundation. BS (chemistry) and PhD (biochemistry) from Wake Forest University and its Medical Center; post-doctoral training with a National Institute of Health fellowship at Florida State University. Dr. Broyles served five years as an Assistant Professor of Zoology at the University of Wisconsin-Milwaukee, 31 years of professorships in the College of Medicine at the University of Oklahoma, and eight years as an adjunct Research Member of the Free Radical Biology & Aging Research Program at the Oklahoma Medical Research Foundation. His current appointments are Professor of Biochemistry & Molecular Biology, Adjunct Professor of Pediatrics, and Associate Professor of Dental Biochemistry at the University of Oklahoma Health Sciences Center. Community service: American Red Cross, Boy Scouts of America (National Eagle Scout Association), and the First Unitarian Church of Oklahoma City.

To Be Determined, Board Member (team member, employee, possible investor). Director of Fund-Raising and Public Relations. CPA and/or MBA. At least five years of progressively responsible experience in fund raising (grants, loans, venture capital, and “S” corp shares). Project incubator skills, advice on corporation tax and legal requirements and filings. Desired strengths: objective personnel assessments, leadership skills, and team building advice.

Gary Bricker^{CFP}, Director of Development (designate) currently advisor to the SCCF Board holds a BA in economics and African studies from the University of Connecticut and an MS in urban planning (Third World option) from Columbia University (New York). A Third World development and health finance specialist, Mr. Bricker designed one of the earliest HIV/AIDS programs (1991 Indonesia), was appointed by eight ambassadors as multi-national finance diplomat in support of Georgia’s “Rose Revolution”, and served as CFO for the \$152 million “President’s Emergency Program for AIDS Relief” in Zambia. Community activities: United Nations intern, Black Sea University (lecturer), Martin Luther King, Jr. Memorial - speaker, School Without Boundaries – board, First Unitarian Church

B. SCCF

The Sickle Cell Cure Foundation, Inc. (SCCF) was conceived out of a research discovery. The motivation for its formation was to continue research.

From 2013 (Year 5) through 2028 (Year 16), our calculations show that the market (number of patients) and the revenue produced from sales of the cure will increase every year, generating a surplus to support further genomic research. See IX. “Financials” below. The income will be in the form of royalties that flow to Board patent partners. Part of the structure of the multi-NGO relationship will be a formula, mutually agreed upon, for a judicious allocation of royalty proceeds.

In the early marketing years (2013 -2015), SCCF will use a portion of royalty flows to identify better ways to deliver the SCD cure, as well as for proof-of-principle experiments for extending GRT to other diseases, e.g., Parkinson’s disease, skin cancer, liver cancer, and hemochromatosis.

C. Orderly Business Transfer and/or Exit

Ownership transfer presents no particular complexity, since shares or initial stock options will not have been sold or granted. Participating NGOs and/or parastatals may continue as a consortium after patents have expired. Speaking of SCCF, since coops do not issue stock, there is no risk of an unfriendly stockholder take-over. Many coops thrive beyond the death of their founding members. There is no mandatory “exit”.

IX. FINANCIALS

A. Demand and Market Segmentation

UN officials have repeatedly noted that there are few statistically reliable figures profiling sickle cell disease.

The best documented prevalence data for sickle cell is Appendix B in the seminal work entitled Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children” sponsored by the Global Programs division of the March of Dimes Birth Defect Foundation in 2006.

To manipulate this data we used ECOSOC/UN data on regional economic growth rates.

Calculations supporting Figure 1 “**Global Incidence of Sickle Cell & Other Blood Disorders**” indicate an absolute need to cover an estimated 340,300 newborns every year (2008). Other sources confirm there are currently worldwide another 107,000 sufferers who are receiving advanced medical treatment for their SCD condition. These “prevalents under care” are located in the USA, the UK, and France. Actual effective demand will, of course, be decremented in response to weak financial affordability (low income) and challenging logistical accessibility (remote locations and stock-outs).

One may segment the market along UN-designated income lines that define “poverty” as GDP/capita less than \$US1.00 per day. However, a more practical segmentation of our global plan reflects six groups with cultural, linguistic, and historical ties: Europe (with Mediterranean Near East), Africa (sub-Saharan), Northern America (excluding Mexico), Asia (with Middle East), Latin America and Caribbean (with Mexico), and Oceania.

B. Projected Expense Budget

SCCF needs **\$5.259 million in seed capital over the next four years** to sustain momentum to the day when it announces the winner of a worldwide competition for the exclusive right to fund and conduct Phase III trials and sales in exchange for royalty payments through the year 2028 when associated patents begin to expire. Phase III trials are estimated at \$US 12.0 million. Table 1 **Program Budget Categories - Tabular**” shows the year-by-year expenditure budget.

Table 1							
PROGRAM BUDGET CATEGORIES - TABULAR							
		\$000s					
		2008	2009	2010	2011	2012	Totals
5% Contingency		6	56	73	63	3	201
Eval & Audit		55	25	75	50	46	251
Patents		70	14	7	7	7	105
P.0 - Animal		602	0	0	0	0	602
P.I - Safety		0	399	0	0	0	399
P.II - Efficacy		0	0	680	421	0	1,101
P.II - Medicine		0	5	11	11	0	27
P.II - Med Equip		0	50	50	50	0	150
P.II - RFP Design		0	0	0	96	0	96
P.II - Lic. Nego.Eval		0	23	20	27	0	70
Mgt. Transfer		20	0	0	25	0	45
Mgt. Office		75	100	100	100	25	400
Mgt. Staff		360	480	480	480	12	1,812
TOTAL		1,188	1,152	1,496	1,330	93	5,293

C. Prospective Cash Inflows and Outflows

SCCF holds a **Master Spreadsheet** detailing the projected gross revenues based on different regional growth rates, varying market penetration assumptions, and a wide range of hypothetical prices to consider in the spirit of cross subsidies to improve the affordability of the cure. This interactive spreadsheet allows one to build a variety of scenarios based on the relative size and predictability of the royalty flow. It can help estimate the size of the royalty to reach desired IRRs, NPVs, and Break-even time durations either for the SCCF or its designated pharmaceutical company.

The implicit outlays and number of beneficiaries affected is accumulated for each successive year, under the assumption that “once an FtH user, always an FtH user”. The spreadsheet permits scenario analyses of varying penetration rates and sales prices for each of the 15 years preceding patent expiration.

Excluding the Phase III costs of \$US 12.0 million, annual outflows would include eight line items; (1) 2.0% cost for manufacturing pharmaceutically pure FtH dosages, (2) 32.0% to cover marketing, advertizing, packaging, and administrative costs, (3) 10.0% for storage and distribution, (4) 5.0% for research & development, (5) 7.5% in royalty payments, (6) a presumptive profit margin of

20.0%, (7) corporate federal taxes of 20%, and (8) 3.5% for “others”. Each of these critical cost factors is open to refinement and subject to negotiation.

D. Return-on-Investment (ROI) Ratios

It bears repeating that the largest single factor on ROI ratios is the duration to receive Patent Office, FDA, or EMEA approvals. As such, SCCF’s administrative priority will be to expedite regulatory approvals.

Appendices

A. The Truth Be Told - Political Economics of Sickle Cell Disease

C. A Model of Acceptance, Responsibility, and Accommodation

E. The Seven Cooperative Principles

F. Board Membership

G. Broyles, Robert H. et al. ***Ferritin Heavy Chain Stimulates HbS-to-HbF Switching in Erythroid Precursor Cells from Sickle Cell Patients.*** 48th American Society of Hematology Annual Meeting. Orlando, Florida. December 2006.

H. Broyles, Robert H. et al. ***Gene Regulation Therapy for Sickle Cell Disease Utilizing Ferritin Heavy Chain***". International Biolron Society's World Congress. Kyoto, Japan. April 2007.

Note:

Appendices B, D, I, J, and K appear in the unabridged Business Plan.

The Truth Be Told – The Political Economics of Sickle Cell Disease

Though SCD is the most commonly occurring genetic disease in the world, it has always been difficult to find research money. Investigation into the genomic complexities of SCD have proven so daunting that many medical research centers simply abandoned their efforts at finding a SCD cure.

Absent any viable alternative, even The World Bank-sponsored “Disease Control Priorities Project” focuses exclusively on medical science and mentions only in passing that “economic accessibility” must be “figured into discussions”. See <http://www.dep2.org/pubs/DCP/34>. Expensive, lifelong, hospital-based treatments are recommended despite the fact that such an approach remains unaffordable and inaccessible to 90% of SCD sufferers.

Until recently no government’s official development assistance was funding sickle cell research with the exception of France. The U.S. Agency for international Development terminated SCD programs almost 20 years ago. On the average 12% of Africans carry the SCD trait, yet few know their status. Almost all SCD research is conducted in isolated, competing laboratories driven by rapid commercialization and maximum profitability targets. In fact, the WHO did not even include SCD in its roster of neglected diseases, until country representatives attending the 59th World Health Assembly in May 2006 insisted on the inclusion of SCD, the only non-contagious disease, to the roster. The Assembly reported that the WHO should be more energetic in ascertaining the global burden of SCD and in rectifying the extraordinary inequalities in SCD care. Ironically, Third World victims constitute over 95% of all SCD cases but can rarely afford any care. Today only 1% of USG medical research funds are spent on tropical diseases.

How did the world’s most commonly inherited disease become “hidden”? The probable answer reflects four known parameters:

- Most SCD newborns die by age 5. Infants have no political clout.
- SCD is viewed as a personal disease with no threat of public epidemic. Therefore, authorities are not compelled to mount a public health defense.
- The low income (\$1-\$3 per day per person) of most tropical residents deters pharmaceutical companies from spending R&D funds to develop a cure that few can afford. (Our low price and cross-subsidy approach address this argument.)
- Only a handful of Western scientists are sensitized to Third World barriers - both logistical and cultural - that impede compliance with complex treatment protocols.
- Given the high cost of palliative care for SCD, one erroneously presumes that a cure would also be exorbitant.

We recommend additional policies to reinforce medicine as a patient-centered profession:

- introduce free government-mandated SCD screening for infants;
- accelerate funding, regulatory approvals, and distribution of creative research.

In view of its high death toll, loss of productivity, and projected drain on Western treasuries, authorities can no longer afford to categorize SCD as “orphaned, forgotten, or neglected”.

A Model of Acceptance, Responsibility, and Accommodation

From the late 1950s through the end of the 20th century the government of France adhered to a pro-birth policy to make up for higher than acceptable rates of mortality wrought by war. The Napoleonic wars and World War I shortened the height of the average Frenchman by two inches according to popular belief. With the close of the colonial era, liberal immigration statutes and socialized medicine combined to classify SCD as an illness with public welfare ramifications.

Today almost one out of five youths resident in Paris comes from Africa.* As the colonized Africans exercised their rights to reside in the French “métropole” not only did they bring cheap labor and fresh talent. They also brought their culture and their illnesses. In 2008 at the opening of the first walk-in sickle cell treatment center, the mayor of Paris noted that there were over 4,000 cases of prevalent sickle cell with 640 SCD-positive newborns joining the ranks each year. The mayor was even candid enough to share the official estimate that by 2014 France would have 27,000 cases of sickle cell.

To attain such growth, France would be granting six permanent residency permits for each SCD-positive birth. Message: all citizens play a role in managing the devastating effects of disease – be it infectious or inherited.

*

“Almost one out of five youths living in l’Ile-de-France has African roots (Afrique noire, the Maghreb, or Turkey).”

Tribalat, Michelle.- Research Director, National Institute of Demography. La Concentration Ethnique en France defines “youth” as less than 18 living in a household of which sh/he is not the head.

The Seven Cooperative Principles

Voluntary and Open Membership — Cooperatives are voluntary organizations, open to all persons able to use their services and willing to accept the responsibilities of membership, without gender, social, racial, political or religious discrimination.

Democratic Member Control — Cooperatives are democratic organizations controlled by their members, who actively participate in setting their policies and making decisions. Men and women serving as elected representatives are accountable to the membership. In primary cooperatives, members have equal voting rights (one member, one vote) and cooperatives at other levels are organized in a democratic manner.

Member Economic Participation — Members contribute equitably to, and democratically control, the capital of their cooperative. At least part of that capital is usually the common property of the cooperative. They usually receive limited compensation, if any, on capital subscribed as a condition of membership. Members allocate surpluses for any or all of the following purposes: developing the cooperative, possibly by setting up reserves, part of which at least would be indivisible; benefiting members in proportion to their transactions with the cooperative; and supporting other activities approved by the membership.

Autonomy and Independence — Cooperatives are autonomous, self-help organizations controlled by their members. If they enter into agreements with other organizations, including governments, or raise capital from external sources, they do so on terms that ensure democratic control by their members and maintain their cooperative autonomy.

Education, Training and Information — Cooperatives provide education and training for their members, elected representatives, managers and employees so they can contribute effectively to the development of their cooperatives. They inform the general public — particularly young people and opinion leaders — about the nature and benefits of cooperation.

Cooperation among Cooperatives — Cooperatives serve their members most effectively and strengthen the cooperative movement by working together through local, national, regional and international structures.

Concern for Community — While focusing on member needs, cooperatives work for the sustainable development of their communities through policies accepted by their members.

MANAGEMENT

The “Team”:

Robert H. Broyles, Founder and Chairman of the Board. President of the Sickle Cell Cure Foundation. BS (chemistry) and PhD (biochemistry) from Wake Forest University and its Medical Center; post-doctoral training with a National Institute of Health fellowship to Florida State University. Dr. Broyles served five years as an Assistant Professor of Zoology at the University of Wisconsin-Milwaukee, 31 years as Associate Professor and Full Professor (since 1985) in the College of Medicine at the University of Oklahoma Health Sciences center, and eight years as an adjunct Research Member in the Free radical Biology & Aging Research Program at the Oklahoma Medical Research Foundation. His current appointments are Professor of Biochemistry & Molecular Biology, Adjunct Professor of Pediatrics, and Associate Professor of Dental Biochemistry at the University of Oklahoma Health Sciences Center. Community service: American Red Cross, Boy Scouts of America (Eagle Scout), and the First Unitarian Church of Oklahoma City.

To Be Determined, Board Member (team member, employee, possible investor) - Director of Fund-Raising and Public Relations. CPA and/or MBA. At least five years of progressively responsible experience in fund raising (grants, loans, venture capital, and “S” corp shares). Project incubator skills, advice on corporation tax and legal requirements and filings. Desired strengths: objective personnel assessments, leadership skills, and team building advice.

Gary Bricker, Board Member, Director of Development (designate), studied at the Institut d’Etudes Politiques (la Sorbonne), holds a BA in economics and African studies University of Connecticut, an MS in urban planning from Columbia University’s School of Architecture, Planning, and Preservation, and earned the Certified Financial Planner designation. United Nations intern. Policy fellowship at the School of International Affairs (New York). Grant – la SAED (Burkina Faso). Casady School Alumni Achievement Award. A Third World development and health finance specialist, Mr. Bricker designed and executed the world’s first urban slum improvement in situ (Tunisia), established the Centre de Développement des Energies Renouvelables (Morocco), pioneered El Salvador’s private home improvement lending, designed one of the earliest HIV/AIDS programs (1991 Indonesia), served as Refugee and Disaster Relief Officer (Somali civil war), appointed by eight ambassadors as multi-national finance diplomat to ensure funding for Georgia’s “Rose Revolution”, and CFO/Contract Manager for the \$152 million “President’s Emergency Program for AIDS Relief” in Zambia. Community activities: lecturer – Black Sea University, Habitat for Humanity, Martin Luther King, Jr. memorial speaker, School Without Boundaries, board member - First Unitarian Church of Oklahoma City.

Robert A. Floyd, Board Member, Vice-President of the Sickle Cell Cure Foundation, received the BS and MS degrees from the University of Kentucky and a PhD in chemistry from Purdue University. Dr. Floyd received postdoctoral training at the University of California (Davis) and the University of Pennsylvania. Dr. Floyd's current appointments are as Merrick Foundation Chair and Head, Experimental Therapeutics Research Program (formerly Head, Free Radical Biology & Aging Research Program) at the Oklahoma Medical Research Foundation; and Adjunct Professor of Biochemistry & Molecular Biology at the University of Oklahoma Health Sciences Center. Dr. Floyd has had the valuable experience of seeing laboratory discoveries progress to the point of clinical trials.

Annette Johnson, is a Founding Board Member of the SCCF, and is also a Board Member of the Sickle Cell Disease Association of America (SCDAA), Oklahoma Chapter. She holds a BS in nursing and works as the head R.N. at Children's Hospital of Oklahoma's Sickle Cell Clinic and as Sickle Cell Nurse Coordinator in the Department of Pediatrics, the University of Oklahoma Health Sciences Center. Mrs. Johnson is active in community affairs, especially in promoting education and awareness concerning sickle cell disease.

Jean McLaughlin, Board Member, is a board member of World Neighbors, an international development organization that works in marginalized rural communities to find innovative, practical, and lasting solutions to pressing needs including public health. Mrs. McLaughlin is a board member for the Child Abuse Response Center. She is past president and a founding member of the Citizens League of Central Oklahoma and served as state president of the Oklahoma League of Women Voters. Mrs. McLaughlin graduated from the University of Minnesota and has taught English and social studies in Iowa and Texas. The McLaughlins are active in and benefactors of the First Unitarian Church of Oklahoma City.

Senator Angela Monson, Board Member, has been a national leader in health care policy for over 25 years. She is Associate Provost and Director of Health Policy Development and Analysis at the Oklahoma University Health Sciences Center. She also serves as an adjunct associate professor, Department of Family and Preventive Medicine. Mrs. Monson has served as an Oklahoma State Senator (1993-2005) and State Congresswoman (1990-1992). She has sponsored legislation pertaining to health care coverage, financing and delivery systems in Oklahoma and was one of the chief architects of the Oklahoma Health Care Authority, the state's Medicaid agency. Senator Monson is a past president of the National Conference of State Legislatures (NCSL). During her chairmanship of the NCSL Health Committee she was developed the Conference's position and actions on the Tobacco Settlement between the states' attorneys general and the tobacco companies. In 1998, U.S. Secretary of Health and Human Services Donna Shalala appointed Ms. Monson to the National Advisory Council for the National Health Service Corps. Senator Monson is a board member of the Families USA foundation. Mrs. Monson holds a BS in corrections from Oklahoma City University and a Masters of Public Administration from the University of Oklahoma.

Paula Davidson Wood, Board Member, is an attorney with the Legal Aid Services of Oklahoma, Inc., and works primarily with victims of domestic violence in the area of

family law. Ms. Wood has been engaged in the practice of civil law in the Oklahoma City metropolitan area for over 25 years. Ms. Wood is very influential in the community and active in the First Unitarian Church of Oklahoma City, the oldest Unitarian-Universalist congregation in the Southwest being founded in 1893. She has lectured at state and national conferences on various topics relating to management, leadership, and legal issues. Wood received her BS in microbiology from Oklahoma State University and her law degree from Oklahoma City University. She is a Certified Public Manager and has been active in various professional organizations throughout her career, often serving in a leadership capacity.

Advisors:

Carter A. McBride, advisor to the Board, holds a BS in zoology from the University of Central Oklahoma and an MBA from the Executive Development Program of the Wharton School of Business, University of Pennsylvania. Mr. Carter brings over 20 years of insight from the pharmaceutical industries. He currently serves as Senior District Manager for EISAI, Inc., a pharmaceutical company headquartered in Japan.

Laboratory Technician/Innovator - TBD

Jan Greene, CPA, has over 28 years experience as financial advisor to corporations as well as non-profit organizations in the region. She is well acquainted with the structures and IRS rules for both C and S corporations and for their interactions with nonprofits.

CV's and resumés of all personnel are available upon request.



48th ASH Annual Meeting

Orange County Convention Center, Orlando, Florida

December 9-12, 2006

Ferritin Heavy Chain Stimulates HbS-to-HbF Switching in Erythroid Precursor Cells from Sick Cell Patients

Robert H. Broyles, Ph.D.^{1,2}, Visar Belegu, Ph.D.^{1,2,3*}, Austin C. Roth, B.S.^{1*}, Emily J. Clarkson, B.S.^{1*}, Kelly S. Williamson, M.S.^{1*}, Charles A. Stewart, Ph.D.^{1*}, Quentin N. Pye, M.S.^{1*}, Robert A. Floyd, Ph.D.^{1,2*}, Klodiana Jani, Ph.D.^{4*}, Marie Trudel, D.Sc.^{4*}, Paolo Santambrogio, Ph.D.^{5*}, Sonia Levi, Ph.D.^{5*}, Paolo Arosio, Ph.D.^{6*} and Joan Parkhurst Cain, M.D.^{7*}

¹Free Radical Biology & Aging Research, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States, 73104; ²Department of Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, 73104; ³Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, 21205; ⁴Molecular Genetics & Development, Institut de recherches cliniques de Montréal, Montréal, Québec, Canada, H2W 1R7; ⁵DIBIT-IRCCS, H.San Raffaele, Milano, Italy, 20132; ⁶Materno Infantile e Tecnologia Biomedicine, University of Brescia, Brescia, Italy, 25123 and ⁷Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, 73104.

We have found that ferritin heavy chain (FtH), an antioxidant/stress response/iron-storage protein, localizes to the nucleus in K562 cells and represses the human adult beta-globin promoter in transient assays in primate cells (Broyles et al., *PNAS* 98: 9145, 2001). Since other work indicates FtH is also a gene activator of fetal-globin genes, we hypothesize that FtH is a long-sought developmental hemoglobin (Hb) switching factor and that delivery of FtH to human adult erythroid cell precursors will reverse the phenotype to HbF, offering a phenotypic cure for sickle cell disease (SCD). Chromatin immunoprecipitation (ChIP) assays, antisense treatments, and an FtH transgenic mouse have confirmed that FtH is a globin gene regulatory protein *in vivo*. With erythroid precursor cells from pediatric SCD patients, under an IRB-approved protocol, we have used a two-phase culture system for *in vitro* maturation of erythroid cells in the presence of FtH, delivered to the cells as pure protein, as an expression plasmid, or as a priority inducer compound that activates the endogenous FtH gene. HPLC with a PolyCAT A column was used to separate and quantify human Hbs. With each mode of delivery, FtH stimulated a complete switch from HbS to HbF. This result was repeatable in multiple experiments using erythroid precursor cells from three different SCD donors. Fluorescently-labeled recombinant human FtH protein was taken into red cell precursors in culture, suggesting that the purified protein can be directly delivered without gene therapy. This method of producing a phenotypic cure in SCD patients should be easy and inexpensive to deliver *in vivo*.

Certification for Human Subjects: I certify that this study abides by the rules of the appropriate internal review board and the tenets of the Helsinki protocol.



Appendix H

April 1-6, 2007
Kyoto International Conference Hall
Kyoto, Japan

GENE REGULATION THERAPY FOR SICKLE CELL DISEASE UTILIZING FERRITIN HEAVY CHAIN

Robert H. Broyles, Ph.D.1,2, Visar Belegu, Ph.D.1,2,3, Austin C. Roth, B.S.1, Emily J. Clarkson, B.S.1, Kelly S. Williamson, M.S.1, Charles A. Stewart, Ph.D.1, Quentin N. Pye, M.S.1, Robert A. Floyd, Ph.D.1,2, Klodiana Jani, Ph.D.4, Marie Trudel, D.Sc.4, Paolo Santambrogio, Ph.D.5, Sonia Levi, Ph.D.5, Paolo Arosio, Ph.D.6 and Joan Parkhurst Cain, M.D.7

1Free Radical Biology & Aging Research, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States, 73104; 2Department of Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, 73104; 3Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, 21205; 4Molecular Genetics & Development, Institut de recherches cliniques de Montréal, Montréal, Québec, Canada, H2W 1R7; 5DIBIT-IRCCS, H.San Raffaele, Milano, Italy, 20132; 6Materno Infantile e Tecnologia Biomedicine, University of Brescia, Brescia, Italy, 25123 and 7Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, 73104.

We have found that ferritin heavy chain (FtH), an antioxidant/stress response/iron-storage protein, localizes to the nucleus in K562 cells and represses the human adult beta-globin promoter in transient assays in primate cells (Broyles et al., *PNAS* **98**: 9145, 2001). The nuclear localization of FtH (but not ferritin light chain, FtL) has been confirmed in several laboratories for several cell types, and at least two groups are investigating the nuclear transport mechanisms. During development of all vertebrates including humans, FtH is expressed in high amounts in embryonic erythroid cells but at only transient, very low levels in adult erythroid cells where FtH disappears at the beginning of erythroid differentiation. Since other work indicates FtH is a gene activator of fetal-globin genes and we have found that FtH repressed adult beta-globin, we hypothesize that FtH is a long-sought developmental hemoglobin (Hb) switching factor and that delivery of FtH to human adult erythroid cell precursors will reverse the phenotype to HbF, preventing sickling and offering a phenotypic cure for sickle cell disease (SCD). Chromatin immunoprecipitation (ChIP) assays show that FtH is bound *in vivo* to the previously mapped CAGTGC promoter site of the adult beta-globin gene, in K562 cells in which the beta-globin gene is repressed. Conversely, treatment of K562 cells with an antisense oligonucleotide to FtH relieves the beta-globin repression. Interestingly, the FtH antisense, which knocks down FtH expression by 90%, also knocks down fetal gamma-globin expression by 90%, confirming the previous suggestion that FtH is an inducer of fetal globin expression. Construction of FtH transgenic mice, in which the regulated FtH transgene is expressed in adult Hb-producing definitive erythroid cells, yield founder mice born with reduced beta-globin expression and a mild beta-thalassemia, confirming that FtH acts as a beta-globin gene repressor protein *in vivo*. With erythroid precursor cells from pediatric SCD patients, under an IRB-approved protocol, we have used a two-phase culture system for *in vitro* maturation of erythroid cells in the presence of FtH, delivered to the cells as pure protein, as an expression plasmid, or as a priority inducer compound that activates the endogenous FtH gene. HPLC with a PolyCAT A column was used to separate and quantify human Hbs. With each mode of delivery, FtH stimulated a complete switch from HbS to HbF. This result was repeatable in five experiments using erythroid precursor cells from three different SCD donors. FITC-labeled recombinant human FtH protein was taken into red cell precursors in culture, suggesting that the purified protein can be directly delivered without gene therapy. This method of producing a phenotypic cure in SCD patients should be easy and inexpensive to deliver *in vivo*.