

DOI: 10.4172/1989-8436.100064

Sickle Cell Sperm Selection with Hb-S Mab: A Future Application for Intracytoplasmic Genotypically Selected Sperm Injection (IGSI)

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Received Date: December 12, 2016; **Accepted Date:** February 22, 2017; **Published Date:** February 28, 2017

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Citation: Adenmosun OO, Asghar W, Kumi-Diaka J. Sickle Cell Sperm Selection with Hb-S Mab: A Future Application for Intracytoplasmic Genotypically Selected Sperm Injection (IGSI). Arch Clin Microbiol. 2017, 8:1.

Abstract

There is no clear scientific consensus on the possibility of characterizing sperm cells based on the expression profile of the Hbb gene which codes for hemoglobin. Sickle cell births on the other hand is being facilitated by the union of heterozygous carriers whose genetics predispose them to a twenty-five per cent chance of birthing a sickle cell child. Current conventional assisted conception procedures such as IVF/PGD are expensive and ethically controversial. This short research review therefore suggests the possibility of being able to further characterize sickle cell sperms with specific sickle cell hemoglobin monoclonal antibodies (Hb-S Mab). This may also have a future application in being able to select sperm cells for micro-injection IVF procedures.

– mostly African-Americans; and a current prevalence of 1 in 12 persons in that ethnic subgroup have the sickle cell trait in a heterozygous state [2]. In the African continent, the prevalence of heterozygous subjects is 1 in 4 persons [3]. Being a genetic predisposition, there is no known cure for sickle cell disorder except for the immunologically-invasive treatment by stem cell transplant from bone marrow or cord blood [4]. Sickle cell trait among African descents is associated with natural selective pressures for survival where protective adaptive mechanisms against malaria have been recorded for individuals with the sickle cell trait. However, the consequences of continued inbreeding among surviving heterozygotes further increases the global pool of sickle cell births [5]. A genetic outcross of couples with the sickle cell trait usually predisposes them to a twenty-five per cent chance of having a sickle cell progeny [3].

Keywords: Sickle cell sperm; IVF/PGD; Hb-S; Monoclonal antibodies; Hbb; Hemoglobin; IGSI

Introduction

Sickle cell disorder is a genetic disease that denotes all genotypes that includes the presence of at least one Hb-S gene in a homozygous state. Its distribution cuts across Africa, some parts of Asia, and as a result of the vagaries of war and slave trade in the mid twentieth century – the disease was further disseminated in diaspora including Europe and the Americas. Five genotypes have been indicated in its pathophysiology and they include – HbSS, HbSC, HbSβ⁰, HbSβ⁺, and HbS/HbE syndrome [1].

Sickle Cell Epidemiology

The epidemiology of sickle cell disorder as reported by the Centers for Disease Control (CDC) from a 2008 census indicates about 100,000 known cases of homozygous subjects in the USA

Preventing Sickle Cell Births

There are no medical alternatives known to prevent sickle cell births from heterozygous couples (each with the sickle cell trait), other than the bio-ethically controversial processes of IVF/PGD (Preimplantation Genetic Diagnosis following In-Vitro Fertilization) or prenatal testing-including amniocentesis, chorionic villus testing or percutaneous umbilical cord testing-all of which require that a difficult ethical decision be made on whether or not to terminate growing embryos or fetuses bearing sickle cell genes. To enable the preservation of growing embryos and eliminate genetic combinations that give rise to sickle cell embryos; a scientific method to select sickle cell sperm prior to the events of fertilization and eventual conception is proposed.

Myths Surrounding Hbb Gene Expression in Sperm Cells

Consistent with previous studies, sperm antigen characterization [4,5] may be achievable with known antigenic features that are attributable to specific genotypic

characteristics [6]. There is however no study that has yet shown the characterization of hemoglobin or its associated proteins expressed on the sperm cell membrane. Though it is usually hypothetically asserted that specialized gametocytes like the sperm cell do not express the hemoglobin protein; no study has equally shown its total absence as well. The Hbb protein truly has no physiological use in gamete cells, hence it is down-regulated by the GATA-1 transcription factor during pre-meiotic stages [6]. The concept of down-regulation does not however mean that protein expression is out-rightly excluded, but rather reduced. In a study by Ike et al. (2007) [7] on the DNA microarray analyses of gene expression in testes producing haploid germ cells, Hbb proteins were found to be well expressed in juvenile mice testes contrary to the expected pattern of deregulated expression in gamete tissues [7]. Bioinformatics data from studies pooled on GeneCards also show significant expression profiles for Hbb in human reproductive tissues such as the prostate and testes. For a well-known gene such as Hbb (Alias – CD113t-C), its characterization – as a translated protein on/in a haploid germ cell may be achievable by immuno-assay studies with specific monoclonal antibodies.

Characterization of Sickle Cell Sperm with an Hb-S Mab

A blind immuno-assay study using a monoclonal antibody (Mab) for sickle cell hemoglobin (HuS 1&2 – described elsewhere) [8] was therefore conducted on a semen sample belonging to one of the authors who is a heterozygous sickle cell carrier (Hemoglobin Genotype - AS).

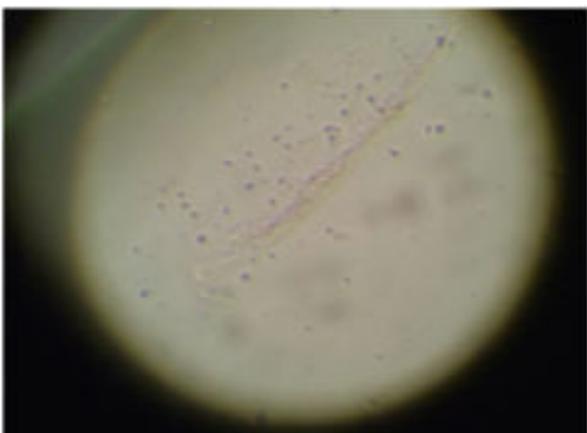


Figure 1 Hb-S Mab negative well.

The methodology adopted included pre-treating a 96-well plate with Hb-S Mab for 48 hours, which were then washed with PBS to remove excess unattached Mabs in the wells. Incapacitated sperm cells disrupted by pre-treating with 30% alcohol were introduced into antibody-activated wells and incubated at room temperature on a plate-rocker at a gentle oscillating speed for an hour. Wells were gently washed with PBS after one hour incubation before observing under a dissecting microscope for any binding or agglutination activity. We

observed more sperm cells immobilized in wells functionalized with Hb-S Mabs (**Figure 2**) compared to the negative control (well without Hb-S Mabs – **Figure 1**).

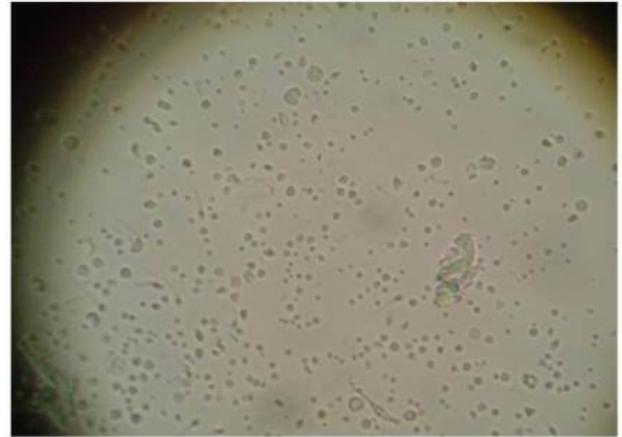


Figure 2 Hb-S Mab positive well.

Future Prospects

This preliminary experimental observations suggest a possible presence and antigenic activity of hemoglobin or its associated proteins on/in the sperm cells of a heterozygous sickle cell carrier. However, before a final scientific assertion can be made regarding the efficacy of this sperm selection method, extensive protein characterization studies are recommended to well delineate the Hb-S molecule on/in haploid germ cells of at-risk couples – who may consider seeking assisted conception alternatives such as ICSI (Intracytoplasmic Genotypically Selected Sperm Injection) to select genetically healthy sperm cells, in a bid to further reduce the chances of having a sickle cell birth. It may also be possible to selectively remove Hb-S positive sperm cells leaving behind normal non-sickle cell sperms that can be used for in vitro fertilization. And in such cases, selection of fertilized embryo may be further confirmed by genetic testing.

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