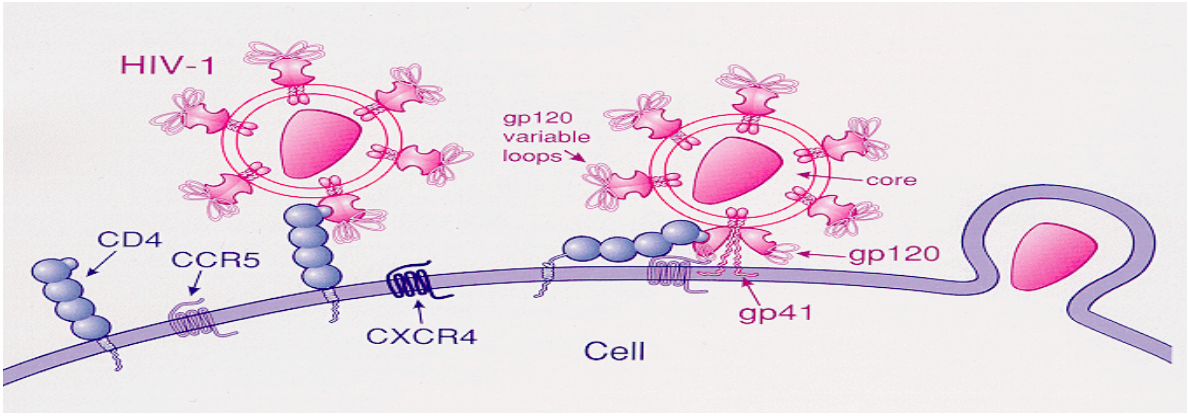
Greetings,

You probably read the news reports last week regarding the birth of twin girls whose genome had been modified with CRISPR-CAS 9 technology. The molecular genetics is fascinating and you should check it out if you can. But being able to do something and doing the right thing are sometimes different, and this is one of those instances. Here is my take on the event from a biosafety officer's perspective.

First, what did they do? The intent of this GMO experiment was to give HIV immunity to the offspring of a couple where the father is HIV positive and the mother HIV negative. The researcher, He Jiankui, modified viable embryos by deleting a gene that codes for a protein expressed on T4 cells, CCR5. This protein is a chemokine receptor found on cells that seem to promote immune response (T cells, macrophages, Eos, and dendritic cells); its exact role is not clearly understood. It facilitates antigen binding of Major Histocompatibility Complex (MHC) signals that allow the immune system to respond to foreign antagonists. With HIV, the CCR5 complexes with CD4 and the HIV viral capsid. This allows the virus to fuse with the cell (definitely nutshell explanation). Here is a simple graphic:



Attachment of HIV to a CD4+ T-helper cell: 1) the gp120 viral protein attaches to CD4. 2) gp120 variable loop attaches to a coreceptor, either CCR5 or CXCR4. 3) HIV enters the cell.

Without CCR5, HIV (HIV-1) is unable to fuse to the T4-cell. Individuals without the gene are much less susceptible to HIV-1. This is known because a mutant gene, (CCR5 delta 32; CCR5,32) is seen in persons with exposure to HIV-1 but without disease. And carriers of the CCR5,32 who also have CCR5 (heterozygous) are infected at much lower rates.

But the CCR5,32 mutation is not a solution to HIV. Homozygous carriers are known to be at risk for auto-immune disorders like Multiple Sclerosis and asthma. On the other hand, genetic studies indicate that selection for this mutant has been involved in a survival strategy for smallpox, cholera and plague. Again, interesting stuff to look up.

So, He modified the embryos for this gene. One twin is homozygous for the deletion and the other is heterozygous. Supposedly, one child will have "immunity" to HIV and the other will be resistant.

Now, there are myriad reasons for faulting this work. From both practical and ethical positions, this study is being ripped apart. Why does it bother a biosafety guy?

I understand the problem as He saw it was to mitigate the risk of HIV infection. Well, mitigating risk is something I think about! And HIV, in particular, is a laboratory risk we've been mitigating for decades now.

Ever since its emergence in the 1980's as a blood borne pathogen, HIV has been at the forefront of risk awareness for laboratorians. It is the major driver of many safety elements we take for granted in the lab today. And donated blood products are universally screened for the virus as another mitigation of transmission. Our understanding of the risk is not new.

The best strategy is elimination. (We only dispense blood products that are free of virus.) The twins still face the prospect of encountering HIV. Nothing about that risk is taken away.

Perhaps the laboratory thought that their effort resulted in a substitution (our next best strategy). By substituting the mutation (CCR,32) for the functional protein, they do mitigate some of the risk of infection. But the risk organism, the virus, is not altered! That risk is not changed at all. The substitution of the gene may help with HIV, but it also increases risk of autoimmune disorders. And HIV-1 is the strain that is deterred but there are other HIV that do not require the CCR5-CD4 complex to infect T cells.

This gene edit would seem to be a PPE mitigation (remember, it's the **last** best way to go). A way to reduce risk that is only helpful to the user (the child) is not a good solution to the risk of HIV infection, in general. The cost alone; both socially and financially are prohibitive. A small band aid for a larger problem.

There are other ways to deal with HIV risk. Established approaches (like sperm washing) and known therapies are already used in confronting the virus and its transmission.

Gene therapy and CRISPR are going to find a place in our toolbox of disease and pathogen battles. Their use in cancer, blood disorders, and other applications is only just now being understood. But laboratories should address problems of risk in ways that mitigate effectively.

He's lab did something significant, right or wrong. Understand that this lab was actually working on a cholesterol gene, initially. They just couldn't get viable embryos for those lineages and the CCR5 work was the one to produce a result. Demonstrating the capabilities of CRISPR is one thing. A poorly regarded use of that science is a shame.

In 2017, over 38,000 U.S. citizens received an HIV diagnosis, 16.000 deaths among HIV positive persons (2016). Worldwide, there were about 1.8 million new cases of HIV in 2017. Nearly 40 million live with the infection and sub-Saharan Africa bears the largest burden. 22 million receive treatment for HIV infection (antiretroviral therapy). This is the risk we should be focused on.

Have a great week and be safe,

Bryan