On Saturday, October 19, 2013 5:00 PM, [redacted] wrote:

Oh I see. Im sorry as I didnt even think about you not having it and I know you are probably correct about it being cross protective too.

ok. Ill see you in two weeks. :)

On Saturday, October 19, 2013 4:42 PM, "whalford@siumed.edu" <whalford@siumed.edu> wrote:
Hi [redacted]

Regarding the ICP4 in the Genocea vaccine, I do not personally think that ICP4 is a great antigen. If I had to pick one HSV protein to use in my vaccine, this one would be low on my priority list; I can think of at least 20 HSV-2 proteins that are better candidate immunogens / antigens.

Regarding your next immunization, let's stick with HSV-2 for two reasons. First, the HSV-2 vaccine should be very highly cross-protective against HSV-1, so there is really no reason at this juncture to assume that it would not elicit protection against HSV-1. Second, I spent 2008 to now developing a data set that says the particular HSV-2 mutant virus I am using would be safe and highly protective, I simply don't have a HSV-1 ICP0 mutant virus that has been similarly vetted in the same way. It would take me at least a year or two (assuming I had funding) to catch up on the HSV-1 side, so I will be sticking with what I have for now.

See you in a couple of weeks.

- Bill

Quoting [redacted]:

> Thanks for the info. Some how I didn't think it would increase 10
> fold every time. I couldnt help notice that the Genocea vaccine had a
> 10 fold increase in ICP4 antigen without the adjuvent and that got me
> thinking about things.
>
> Anyway, I was also wondering if you'd be interested it testing the
> hsv-1 version on me. Maybe get my hsv-2 booster in 1 leg and the

> hsv-1 version in the other. Or I could return later just for the
> hsv-1 if thats better.
> Looks like I will be driving again and thats fine. I wont have to
> worry about getting off work in time to make it to the airport.
>
>
>
>
> On Saturday, October 19, 2013 10:42 AM, "whalford@siumed.edu"
> <whalford@siumed.edu> wrote:
>
> October 19, 2013
> Hi [redacted]
>
> I am finally out from under my latest grant-writing binge, and
> have a moment
> to breathe before I start into the next writing project.
>
> I answer your questions below.
>
> - Bill
>
> ---
>
> 1. Regarding your first question, a 10-fold increase in T-cells specific for
> HSV-1 would almost certainly be a significant (i.e., real) increase.
>
> ---
>
> 2. Your second question was....."Would a vaccine capable of doing that
> (eliciting a 10-fold increase in HSV-1-specific T-cells) do that every time?
>
> No. The most profound change in HSV-specific T-cell number would like happen
> after the first vaccination, where the number of HSV-specific T cells
> that were
> functionally useful (i.e., active, awake, differentiated) would increase from
> somewhere close to 0 (1 per 1 million T cells) to a low, but
> significant number
> like 1 per 100,000 T cells.....that's a 10-fold increase in absolute T-cell
> frequency but is still too few to provide very good protection against HSV-1.
>
> Perhaps on a secondary booster vaccination (3-6 weeks later) you might get
> another 10-fold increase in HSV-specific T-cell frequency, bring you up to a
> useful number of virus-specific T cells in the bloodstream (about 1
> per 10,000
> T-cells).

>
> Subsequent shots, 3rd, 4th, 5th, etc. would serve to keep these
> HSV-specific T
> cells active (awake, not in a coma, differentiated, available to
> engage in the
> fight, etc), but the ceiling on the absolute number of HSV-specific T cells
> someone could have in their bloodstream would be about 1 per
> 1,000.....we need
> T-cells to do other things than just beat back HSV (e.g., Staph, Strep, CMV,
> EBV, gut bacteria, lung bacteria, etc, etc). So, painting broad
> brushstrokes,
> the goal of a good HSV-vaccine is to get your bloodstream levels of
> HSV-specific T-cells into the realm of 1 per 1,000 to 1 per 10,000 (0.1% -
> 0.01%).
>
> Two vaccinations with a good HSV vaccine is adequate to get you most of
> the way
> there, and subsequent booster vaccinations would serve only to keep your
> HSV-specific T-cells awake / on active duty.
>
> ---
>
> 3. The third important point that you did not ask, but I will bring up
> because
> it is important relates to the concept of "antigenic breadth." What
> this means
> is that a given T-cell clone recognizes about 8- to 25-amino acids of
> HSV-1 or
> HSV-2, but in total these viruses encode 40,000 amino acids worth of viral
> proteins. For a vaccine to be effective, I believe that history / the
> available evidence says that (1) a good viral vaccine will present close to
> 100% of the possible viral proteins to the T-cells / immune cells and
> then (2)
> the T-cells / immune cells can pick and choose their "Top 10 list" of viral
> protein pieces-parts they like the best and will make the focal point
> of their
> subsequent immune attacks on virus-infected cells. This is precisely what a
> live HSV vaccine does. In contrast, for the past 30 years scientists in my
> field have been trying to use man-made snippets of virus (one protein like
> glycoprotein D or a few T-cell targets of HSV like the Agenus vaccine) and
> drive T-cell expansion in precisely the way you described in your e-mail. I
> generically refer to this as the "subunit vaccine" approach because
> people are
> cherry-picking their favorite snippet of a virus (i.e., a subunit of
> the virus)
> and making a "vaccine" out of it. The problem is that we now have 30

> years of
> data from human clinical trials that tells us that the overall rate
> of success
> of viral "subunit vaccines" is less than 1%.....Gardasil and the Hep B
> vaccine are the exceptions, and there are good reasons why these particular
> vaccines worked. The other >200 subunit vaccines that have been proposed and
> tested in people have fallen flat on their face.
>
> So, bottom line, it is good to have a ">10-fold T-cell expansion to HSV
> proteins" as you suggest, but it is important that those T-cells that are
> responding to HSV antigens also be allowed to respond to the full breadth of
> HSV's 40,000 amino acids worth of antigens and choose their own "Top 10
> list." In contrast, when we vaccinate with a single HSV protein like
> glycoprotein D
> (300 of HSV's 40,000 amino acids of foreign proteins), it does not matter how
> many vaccinations we deliver to the body. Our immune system needs to be able
> to recognize a wide variety of HSV proteins if it is going to win
> this battle,
> and the data clearly says that a single HSV protein or T-cell peptide
> approach
> is not sufficient to get our immune systems to that level of
> "battle-readiness."
>
> Probably more info than you wanted or needed.
>
> See you in a couple of weeks!
>
> - Bill
>
>
>
>
> Quoting [redacted]:
>
>> Hi, I had a question for you.
>>
>>
>> Would a 10 fold increase in t-cells for a specific hsv-1
>> antigen/proteinbe fairly significant?
>>
>> They would have 10 x more t-cells, correct?
>>
>> Would a vaccine capable of doing that produce a 10 fold increase every time?
>>
>> In other words, if the same individual received the vaccine every 3
>> weeks for several months his t-cells would increase 10 fold every

>> time minus whatever he naturally lost between shots? cumulative?
>>
>>
>> Sorry that was a lot of questions but I have my reasons for
>> wanting/needing to know.
>>
>> Thanks,
>> [redacted]
>>