required as part of a data gathering tool for further understanding retrospectively.

DR. SALOMON: So, I think what I've heard, so far, again, trying to seek some sort of consensus is, if you have -- if you can prove definitively that your target cell population will not support productive virus in any setting, and that could be, you know, that would be something that you'd have to be convinced that had been proved appropriately by the sponsor, but then it probably would be okay to exclude it.

If you have a procedure that you can't do that, therefore, there is a possibility of amplification, then I think to pick up what Gary said is that if you can do it, then you should do it. And then that really just kind of feeds into what everybody else said, including Bruce's and my points, and that is, if you can do it. And if you can do it prospectively, fine, that's you know an added safety. Why

shouldn't we support that? If you can't do it prospectively, then it should be done retrospectively and, again, that should be a decision based on the protocol being presented. Does every -- Gary.

DR. KETNER: Let me just emphasize again, that we don't have a clue what the risk of injecting any number of adenoviruses are, so, I mean, I guess this is data we sort of collect and then wonder about later until we learn what the infectious dose is. So --

DR. SALOMON: Right, the question on hand now isn't would we not allow delivery of the product if we found replication competent, that's your point and it's well taken.

DR. FREY: I think you also have to keep in mind, when it comes to cell therapies, I think particularly, like T-cells, CD34 cells per, you know, cell populations isolated from the peripheral

blood, rarely do we see purified cell populations. They are mixtures and so, to say that you look at it and say that it's nonpermissive, I think you have to be very careful in saying that, because, like I say, rarely do we have purified cell populations when we deal with this.

DR. SALOMON: Yes, so, but let me point out the way I would think about it. So, and I proposed a gene therapy with T-cells. Well, we'll do leukoferresis and we purify away the DC34 and we take what's left as T-cell enriched, and that's our target. That's the kind of thing that one could specify for any given study, you know, whatever the product was that we were going to use to study on. Even if it's a mixture of cells. You know, you're point is right. You could still reasonably give you ten, I mean, I could, theoretically, get ten patients samples together and do the study, and demonstrate one way or the other whether

they were permissive.

DR. HOROWITZ: Well, I would I assume from what I know about peripheral blood cells that -- stem cells, that they will not be very permissive, but it seems to be before these products should go into patients, that someone should get some preliminary data on cells that will not be transfused but just be obtained to see whether you produce 10 to the 13th, which I doubt, or nothing or, you know, a hundred RCA. I --

DR. SALOMON: You're saying just, that's something the field should do --

DR. HOROWITZ: The field should do it before --

DR. SALOMON: -- to increase the overall safety profile --

DR. HOROWITZ: Exactly -- exactly.

DR. SALOMON: Well that's an interesting --

DR. HOROWITZ: And then, once we

have the data, we could decide how to proceed, I mean there doesn't seen to be the data in the room. I would guess that it's not going to be a problem, but I don't want my guess to set a standard for the field, but the experiment should be done.

DR. SALOMON: Well, Marshall has an interesting point, i mean he is pointing out an interesting irony in that we've been infusing these things directly into the blood and there isn't data that we've heard, specifically, saying that if you took a leukoferresis pack, for example, that he wouldn't get this tremendous amplification of RCA. So, I think that's a very interesting point that hasn't come up yet.

MR. SIEGEL: Well, of particular interest to me is I'm told that probably the single most common application we're seeing of ex vivo cell transduction is tumor cells in the manufacture of potential tumor vaccines, and it would seem to me given what

we heard this morning about, the fact they say teratoma lines might support even replication of noncompetent adenovirus and given that any given tumor line you don't really know what genes are on and off and we don't know which ones are the critical ones, that it would see that, like, both in general in terms of reproduction in tumor lines but also more feasible in the specific cases that it would make sense to get some information so we know what.

DR. SALOMON: So, I think that as far as I'm concerned now, we've answered the three questions that the staff has asked us. And now there are a couple other things I'd like to throw out that in the next ten or fifteen minutes is that I mean what's the Committee's with right now. Is everyone going to run off right now to a plane or can we have another 15 or 20 minutes of your time to raise one or two other issues? Can I get a little bit of feedback here? Okay.

One question, just to put this into context, is that there's another class of adenoviral vector that is intended to be replication competent. And so, I think that you know, I'd like to just throw that out, because I don't think our conversation's quite complete unless we just think for a second that there are people proposing adenoviral trials with vectors that are designed to be replication competent or certainly to be driven by promoters so that you get a relative increase in production, let's say in a tumor cell line, but we all know how leaky promoter systems are in that activated cells and other cells in growing areas, are going to be turning this on to lesser extents but still real, so I mean, does the -- do you want maybe the FDA staff give us some sense of where that fits into the conversations we've had all day?

DR. BAUER: I think that one of the perspectives we have is that with those

kinds of indications or those kinds of vectors we're looking very closely at what the indications are. Most of them have been in cancer patients so far, and then the other thing is that we have an increased level of concern reflected in preclinical studies and clinical monitoring for those vectors right now. But I think it is a very difficult and challenging task to try to separate out replication competent recombinants from a replication selective preparation. I think that's a difficult task.

One possibility that is being explored is PCR, but I think we've heard some discussion that the limitations of that and the caveats that come along with that, you don't know if you're looking at just a piece of DNA or something that's really a biological event.

DR. SALOMON: Yes, though this PCR thing still is -- there may be some

sensitivity issues, but in some of the newer tack ---- allow you to do rather long pieces and so it wouldn't be impossible to generate a quantitative PCR assay where you had a up -- your downstream primer was in your transgene and your up-stream primer -- your sense primer was up in the above the or in the first part of the E1 region and argue that if you got, you know, you got the right-size construct -- a reasonable construct there and sequenced a little bit of it then that's a replication competent retrovirus -- I mean, adenovirus sorry. I did pretty good today, that's the first time I did that.

DR. BAUER: I think we would agree that that's, you know, there's just some assay development that's needed there, but that's, perhaps, the most promising avenue is PCR, at this point.

DR. SALOMON: Do we agree, though, that for the group for the sponsors that are

thinking about going forward, I guess you called them replication- selective adenoviruses, that you wouldn't hold these -- you couldn't hold the same criteria, obviously, for RCA levels, right.

DR. BAUER: Yes, that's correct, we acknowledge it is not a reasonable way to measure them in a biological assay.

DR. HOROWITZ: Well, I was just going to say, I mean, the experiments are already going on, of course, with the onyx 015 which one of us believe is replication competent in so many situations that, in a sense, the data that's being obtained should be very helpful in this regard.

DR. BAUER: But also I didn't say, again, that we are looking at PCR data, such as it is, to make sure that the replication competent recombinents are looked for.

DR. SALOMON: Another question I had was, you know, we've talked about replication competent adenovirus and all

this in terms of a context of safety and we go back to a reference standard that's based on a wild-type adeno, so our risks are in the context of what the risks of replication of a wild- type adeno. Do we need to be concerned about the additional risks of replicating a construct that has a transgene it in? I mean, it's one thing to have a wild-type adeno replicating in the patient, but it's another, you know, delivering, let's say an anti-A poptosis or a pro-A poptosis gene into multiple cells and to what extent is that a risk factor that we haven't discussed at all today, relevant?

DR. BAUER: I could make one --

DR. SALOMON: Beginning to look, like, don't go there.

DR. BAUER: I can make one comment that most of the events with the vectors that are currently used that result in a replication competent virus, eliminate the transgene.

DR. HOROWITZ: ----

DR. BAUER: It's the part of the genome that needs to be replaced in the recombination event.

DR. HOROWITZ: That would be my answer, always and --

DR. SALOMON: That's a good answer, I mean that --

DR. HOROWITZ: Yes --

DR. SALOMON: That would raise the safety quality, a bit.

DR. HOROWITZ: For most of those considerations that's exactly correct and the answer I give when people worry about working with recombination will eliminate the transgene. There are some ways that you could think of getting around it, but in general that would be the most common thing.

DR. RAO: It's just a question for the FDA though, is, do you have, right now, in a standard, what is the absolute limit of wild particles that you can infuse in a

patient in any of these trials? So there is no standard? So it's impossible --

MR. SIEGEL: The standard we have, as I understand it is based solely on the proportion, if you will, of the total, that is RCA, not on the total that would be infused. Now, of course this is what happens in clinical research is that one does dose escalation from levels that one has a lot of information about gradually into levels that one has less information about. So, on wouldn't suddenly push the boundaries tremendously, but on the other hand there is no specific top limit of what could be given set at this point.

DR. SALOMON: I think what we talked about before, and it's just beyond the agenda we set for this meeting, but it is a good message, I think, Mahendra, that the probably the bigger risk of -- in terms of to the patient, not a public risk, but a personal patient risk is the effect of these

different viral proteins and the immune reactions and the cytokine release. And that is probably going to be a function of the total dose given at any one time and the total dose given over by the protocol, though I'd be more concerned about the total dose given in one shot than I would be over, you know, ten shots of a relatively small amount over a period of time because of the antibody data that we've seen from the sponsors, but. Okay, any comments, last questions from the FDA staff?

DR. BAUER: I'd just like to say thank you very much for these deliberations. They're going to be very helpful and I don't have anymore questions for you folks.

DR. SALOMON: Okay, well, if, anyone else on the Committee have anything or public? No? Well then thank you all very much for a good job done and see you guys in a few months.

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