TRANSCRIPT OF OPEN DISCUSSION

Session chairs were Linda Sherman and Gerald Nepom. The following is an excerpt of the discussion and has been edited for clarity and readability. Italics appear for emphasis, highlighting central points.

Linda Sherman: The issues we thought we might address include:

What are the relevant epitopes in autoimmunity and tumors? Several people had discussed the possibility that there's a difference in terms of how the immune system deals with dominant versus subdominant epitopes, both in tolerance and in responsiveness. Which of these would be important in terms of causing autoimmunity? And, Which of these would be most important in terms of trying to immunize against tumor antigens?

Also relevant to this same issue is the idea that there might be a different type of T cell repertoire available for recognition of these two different types of epitopes. Tolerance to dominant antigens may be more effective than to subdominant antigens. Are subdominant epitopes preferentially recognized in autoimmune disease? Applying this concept to tumor therapy, if you're trying to eliminate a tumor, you might want to target those epitopes to which you may be less tolerant, perhaps the subdominant ones. This raises the issue: *Tumor cell epitopes that are naturally recognized might not be necessarily the ones that are most immunotherapeutic.* And here we can discuss the fact that TILs recognize certain epitopes, MART1, for example; however, these may not be the most curative epitopes that are present.

We also know that in autoimmunity there are certainly very good examples of epitope spreading. Can we learn something from autoimmunity in terms of how to try to direct an anti-tumor response in order to promote epitope spreading?

Can mechanisms of tumor evasion be applied to autoimmunity? Certainly there is a great deal of evidence that both the immune responses to tumors and viruses can lead to loss of antigen, loss of MHC. Can there be ways that we can use this to perhaps cure autoimmune situations by, for example, down-regulating expression of MHC?

What is the optimal cytokine milieu for vaccination and suppression of an immune response? and How do we establish the optimal milieu in vivo? This is very related to what people have tried to do with immune deviation and also in terms of the use of particular cytokines in vivo. Also, there was the issue of what would be required in order to target delivery of particular cytokines to an automimmune site? We can use T-cells to deliver such cytokines if we can raise T cells that would home to the autoimmune site and also have the right cytokine profile, and we've heard several presentations about that kind of strategy at the meeting.

How does the method of preparation and delivery of dendritic cells affect their ability to stimulate T cells in vivo? Do they need helper epitopes to be effective in stimulation of CD8+ T cells? We have heard that perhaps they must pick up fetal bovine serum or some other foreign protein in order to deliver helper epitopes before they can work ... so what would be perhaps the best way of preparing DCs for optimal T cell stimulation?

So, returning to the first question ... There may be some strong opinions here in terms of what would be the best type of antigen that is targeted, both intentionally by us in vaccination, but also in terms of what the immune system is targeting in autoimmune disease. Is it dominant or subdominant and how does that relate to the repertoire? Does anyone care to comment?

1040-8401/98/$5.00

Bhagirath Singh: I think what strikes me with all the presentations is the major difference that exists between autoimmunity and tumor immunity. Tumor immunity seems to be CTL mediated, so that it may be an issue primarily of class I-restricted responsiveness. On the other hand, most of the presentations in autoimmunity dealt with class II-restricted or CD4 T cell responses and immune deviation regarding Th1 or Th2 immunity.

While I'm not saying that autoimmunity will not involve CTL, *a clear distinction is suggested by the way we look at the regulation of tumor immunity and autoimmunity. Discussions both in the human system and in animal systems dealing with tumors have dealt primarily with CTL/class I while those involving autoimmunity have focused exclusively on Th cell/class II.* Maybe you can comment on that.

L. Sherman: Yes. That's definitely the dichotomy that's appeared, and whether rightly or wrongly, I think we've all come to focus, in tumor immunity, on class I epitopes. And I believe that this is the first meeting where I've heard some good reasons that maybe we should re-think that, in terms of trying to propagate tumor immunity. *Certainly, the immune system propagates autoimmunity by enhancing CD4 responses to self antigens, and if that's the case, maybe we need to follow this model in order to have lasting immunity to tumor antigens.*

Gerald Nepom: Vijay, you had a slide you wanted to lead off this discussion with?

Vijay Kuchroo: A point was made a number of times during the talks—I think it was very eloquently described by Noel Rose that we all have autoreactive T cells, but we all do not get autoimmune diseases. I think if you checked the blood of normal humans, mice, or rats you will find autoreactive T cells. The question then is: At what stage do these, presumably benign autoreactive T cells, get activated to induce autoimmunity? I think that's a very important question.

In this figure I have shown the thymic development of T cells, and obviously we all know that for these cells there's a negative selection window and a positive selection window. In the case of auto-antigens, for example, those tumor antigens that also are auto-antigens, there may be a very

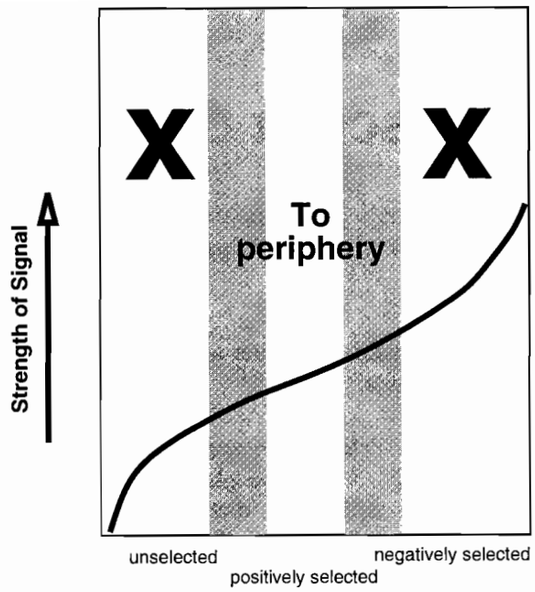

FIGURE 1. Simplified scheme showing the relationship between the interaction strength of TCR with thymic MHC/peptide complexes and the resulting effect on T cell maturation. Below a given threshold, T cells fail to be selected and are destined for "death by neglect", whereas cells with moderate affinity develop and are exported to the periphery. Above a given threshold of interaction strength, T cells undergo induced cell death and the associated TCR specificities are said to be deleted from the repertoire.

strong negative selection. **Joan Goverman** has shown that peptide $_{121\text{-}140}$ of myelin basic protein MBP is a strong binder to MHC, but in a normal mouse, you don't see many of the $MBP_{121\text{-}140}$ reactive cells in the periphery. Many of the high-affinity cells, particularly the autoreactive cells, get deleted, and we are left with this low-affinity T cell repertoire to auto-antigens, which get seeded to the periphery.

So in central deletion, we have not only cut down the size of the repertoire, but we have also cut down the affinity of the repertoire. We have presumably very low-affinity T cells, specifically for auto-antigens that get seeded to the periphery. The window of autoreactive T cells that gets selected is very small compared with that of T cells reactive to foreign antigens, by virtue of auto-antigens being in the thymus—being present during ontogeny. And here is where most of our efforts have been, and there is data from a number

of groups showing that if you somehow differentiate a T cell in the periphery, autoreactive cells in the periphery are either TGFβ-producing T cells or Th2 cells, and you don't get autoimmunity.

But if you differentiate them into a Th1 phenotype, you all of a sudden get autoimmune disease. Some of this data is based on the results that we have in our lab, and I think Kim Bottomly and Anne O'Garra have similar data. What I am suggesting is that these autoreactive T cells have low-affinity T cell receptors for auto-antigens, and whenever they come in contact with an autoantigen in the periphery, this low-affinity interaction leads to differentiation of T cells to produce TGFβ, IL-4, or IL-10. Because of this low-affinity interaction, the cells don't expand—they don't increase the size of peripheral repertoire, but they produce immunosuppressive or anti-inflammatory cytokines and mediate peripheral tolerance, or may be essential for maintaining peripheral tolerance.

In the case of tumor immunology, where enhanced immune responses to self-epitopes are desired, for example to tyrosinase, thymic selection has already cut down the high-affinity repertoire to tyrosinase-derived peptides so you have these "crummy" cells sitting in the periphery. Despite attempts to boost their activity with peptide, you are not getting enough T-cell response to have an expanded repertoire and have a good Th1 response for anti-tumor immunity. So you are expanding these low-affinity cells that may produce TGFβ or IL-4, IL-10 cytokines without massive expansion of the repertoire and just maintaining peripheral tolerance.

Similarly, an auto-antigen-like myelin basic protein (MBP) or proteolipid protein (PLP), when it comes in contact with these low-avidity cells in the periphery, will elicit anti-inflammatory cytokines and may be responsible for maintaining peripheral tolerance. *So what I'm suggesting is that we all think that autoreactive cells are bad. But I think, under normal circumstances, low avidity interaction may lead to cells that may be regulatory T cells and maintain peripheral tolerance.* Autoimmune disease only occurs under circumstances when we get infections (for example, Coxsackie B Virus, sometimes implicated in autoimmune diabetes) or we have molecular mimicry, where the foreign antigen may act as "super-agonist" and drive this strength of signal from being a low-avidity interaction into a high-avidity interaction. These circumstances lead precursors for Th2 cells to differentiate into Th1 type cells.

So now you have T cells that can produce TNF and IFNγ and become Th1 cells, and these are the cells that become auto-pathogenic. So, depending on the strength of signal they get in the periphery, the same precursor cells could be regulatory T cells if they come in contact with auto antigen. But if they come in contact with a super-agonist peptide that is produced by a virus, a bacterium or by molecular mimicry, you may differentiate precursors and produce this Th1 auto-pathogenic cell. And if the strength of the signal is even stronger—and we know that at a higher strength of signal the same precursor Th1 cell can be deleted—you can have now a reappearance of Th2 cells.

So, based on the strength of the signal, engagement of autoreactive T cells in the periphery can have multiple outcomes. The idea is to understand how such cells, that normally maintain peripheral tolerance, deviate into a Th1 pathway and induce a disease.

G. Nepom: Thank you, Vijay. There are a couple of obvious implications of this model that Vijay didn't mention that I would like to point out.

In terms of developing a tumor vaccine from peptides: To switch from a low-avidity, naturally occurring peptide from, for example, p53 or tyrosinase, to a more efficient immunogen to elicit a Th1 response, it might be a situation of creating a "super-agonist" peptide. This is achieved by modifying the anchor residues of the peptide binding sites, as was discussed in a few examples early in the meeting.

So that's one way of manipulating a natural epitope. The questions that Linda raised earlier had to do with maybe selecting a different epitope altogether in order to change the type of T-cell or find a T-cell that hadn't been so negatively selected.

I'd also just like to comment on one aspect of our perspective on the genetics of the disease. In some of the autoimmune diseases, where there's a strong class II or perhaps even a class I association, such as the class II-associated autoimmune diseases, the window of positively selected, potentially autoreactive T cells widens, perhaps because of specific polymorphisms in the disease-susceptible HLA molecule. So the periphery is seeded

with far more potentially autoreactive cells, and, of course, more T-cells can then become activated.

B. Singh: The problem with the model is that it does not take into account co-stimulation, which may change this whole paradigm, if you look at the co-stimulation pathway. And superimposed on the top of that is antigen processing. If there's a mutation in the antigen, as we have seen, many of these parameters may, in fact, change in the periphery—not just in thymic selection.

V. Kuchroo: By "strength of signal", I am not just including the antigen. A signal is a summation of everything you can think of. You have co-stimulation by B7.1 and B7.2, gp39 and CD40, and you have other active molecules that contribute to the overall avidity of interaction. So instead of saying avidity, I call it strength of signal, which obviously is generated by a summation of all these effects.

In fact, I think one of the reasons why we have to use complete Freund's adjuvant (CFA) to induce autoimmune disease is that when you use CFA with the auto antigen peptide, not only are you up-regulating B7.1 and B7.2 and other co-stimulatory molecules, but you're also getting IL-12 at the same time. So here is a situation where it may be presumed that the low-avidity autoreactive T cells are being differentiated not because you have boosted the strength of the antigen-TCR interaction, but because you have up-regulated other parts of the system. So the strength of signal that's generated is very high. You can differentiate a low-avidity T-cell receptor into a Th1 cell, an auto-pathogenic cell, because you have increased the strength of signal. So that's part of the whole equation of "strength of signal".

Daniel Gold: Vijay, I've heard this argument made a lot, and I've always wondered if you or anyone else have tried varying the experiment. What you and others have done is try to find these partial agonists that can, by delivering a weaker signal, switch or "shut down" a Th1 cell to a Th2-like phenotype. But, if you try and induce a response with a super agonist, as you're suggesting, so now you've probably evoked a slightly different repertoire—and now it sees the normal antigen, the self-antigen—shouldn't that act to turn that anti-self response down?

V. Kuchroo: We have made peptides that act as super agonists by making single substitutions at TCR contact points. If you take a T cell that makes a Th2 cytokine profile *in vitro* and add now the super agonist peptide, all of a sudden you can see that the cytokine profile changes: it becomes a more Th1-like cell, producing IFNγ, IL-2, and TNF.

In one of our experiments we made a T-cell clone against an LR (murine leukaemia retrovirus) peptide, and it produces Th2 cytokines. When it goes to the CNS, it recognizes the native (self) peptide and produces TGFβ. So, in that situation the native peptide is pushing down the affinity of interaction from one that elicits IL-4/IL-10 production to TGFβ. We do not have an example where we have made a T-cell clone against an antagonist peptide or an altered peptide, and it comes in contact with native peptide and the native peptide is a super agonist peptide ... but, it's possible that can happen too.

D. Gold: Well, an alternative hypothesis is that in autoimmunity, a naturally occurring autoimmunity, the triggering requirements are different—the cells are actually genetically different. And, because of that, their triggering threshold is lower so that if you want to use your "strength of signal" scale, they're moving up the scale. This is not because of the ligands that they interact with, but because of their innate triggering capacity, and I think there's evidence in BB rats that possibly this is the case and possibly in NODs as well.

It makes me wonder if anyone has ever looked in the literature to see if people who are prone to autoimmunity have a deficiency in tumor because you would expect that their autoreactive cells would be readily triggered, preventing tumors.

L. Sherman: I think that's an interesting issue. I've been asking people: Is there any correlation at all—inverse correlation—between diabetes and cancer?

Ake Lernmark: Of course, in adult onset diabetes, there is a reduced frequency of cancer and tumors among the type II patients, but that may be related to an insufficient or a badly controlled metabolism that may not allow certain tumors to be formed. So that could be the reason why a diabetic has less frequency of tumors. In type I

diabetes: In history there is not a single patient with type I diabetes who has regressed or reverted into a non-diabetic, non-insulin-dependent state, and there is not a single case described, as far as I know, with an insulinoma.

L. Sherman: Well, what about another type of tumor? It doesn't have to be related to the pancreas.

A. Lernmark: But other types of tumor, in diabetes in general, are thought to be reduced.

L. Sherman: In type I diabetes?

A. Lernmark: That is sort of unclear.

L. Sherman: Well, that would be a very interesting study to do because there's still the possibility that in autoimmunity you may have more cells appearing in the periphery that normally are negatively selected, so that they would have a higher affinity for self antigens.

V. Kuchroo: Can I just respond to what **Dan (Gold)** was saying? I totally agree with him—obviously genetics play a very important role in the generation of auto-reactive cells. So there are autoimmune prone mice, rats, and humans. And it doesn't have to be incompatible with what I'm suggesting. For example, you could have a lower-avidity T-cell, but if you have inherited a high-affinity IL-12, it can drive the cells faster in a Th1 direction and make them auto pathogenic ... you can envision multiple different scenarios like that.

L. Sherman: Before we leave this issue, I just want to find out if there is anyone who has an opinion as to whether this type of activation that **Vijay** is referring to for class II-specific T cells is something that might be envisioned for class I-specific T cells?

I don't know that we usually think of CD8 cells as being that adaptable, although they can have different cytokine profiles. I'm not sure that it affects their function in ways that we know of. Certainly it would be nice if we thought we could take what was left in the repertoire and then push that for destroying tumors. But it's not clear that a CD8 cell is as flexible in terms of its getting as "angry" as a CD4 cell.

V. Kuchroo: There's already evidence that you have CD8 cells that can produce both Th1 and Th2 cytokines, and we haven't done enough work to say that the avidity of interaction between a given class I/peptide complex and a T-cell receptor would not drive a CD8 cell from being an IL-4 producing CD8 cell to an IFNγ, IL-2-producing CD8 cell.

L. Sherman: And you think that would correlate with the efficiency with which that CD8 cell can clear a tumor?

V. Kuchroo: I personally think that if you had a helper response of Th2 type, where you produce IL-10 and IL-4, that it's not going to be as good in clearing the tumor as if you have IL-2 and IFNγ-producing helper responses, along with the CD8 response.

G. Nepom: I think this is clearly an area where there is just not very much information.

Paul Robbins: There is some information, because if you look at T cells in melanoma patients, those cells are Th1 type, the CD8 cells. You don't see cells generally that make Th2-type cytokines, at least in our experience in the Surgery Branch (NCI, Bethesda) ... they're typical Th1 cells.

Now, whether generating a higher affinity T cell in some way could help you out, I don't know. But switching back to class II, could you generate a better T cell, for example, by altering the ligand and making a better binding peptide and perhaps inducing a T cell of higher affinity? You know you have to come back to what's recognized in the tumor.

It's not going to help you very much I don't think. The peptide epitopes that we have identified from tyrosinase are very, very poor binders to (HLA) DR4 ... you can make a peptide that's 100 or 1000-fold better binder to DR4 by modifying the apparent anchor residues. But I don't think that gets you anywhere because the original tumor is not expressing that epitope. Actually, when we've tried to induce T cells with those peptides now that bind much better, we can get T cells that react with those peptides; however, they don't react with the tumor.

I would think that there would be a strong selection against any T cells that recognize tyro-

sinase with high affinity. Those T cells would have been deleted, and you're just never going to find them. There's just no way you're going to be able to generate them.

G. Nepom: This is a good point to discuss the question that Linda raised earlier, which is: Are the epitopes to which responses are normally observed, such as the weak tyrosinase epitope on the tumor, the only or the best targets for induced immunity?

In autoimmunity we're all comfortable talking about determinant spreading and multiple epitopes coming up over time with the auto-antigens, so in terms of defining the tumor peptide targets—Should we be looking only at the natural immunodominant epitope, even if it's a relatively poor binder? Or should we be trying to induce a situation where there are better epitope targets, either through inducing epitope spreading or through vaccination strategies that will bring those subdominant epitopes to the front?

Michael Nishimura: I have a point I want to make about the model (presented by **V. Kuchroo**), and, actually, it will also kind of address to what you just said. While the model makes sense, we tend to not keep in mind the fact that these are polyclonal responses, involving a variety TCR-epitope affinities. We tend to look at individual T-cell clones ... And probably within a patient or a mouse, you have clones that fit every one of those phenotypes going on at the same time. So you should, according to the model, have a certain amount of autoimmunity going on all the time because this is a population, and it is a dynamic situation.

Regarding modified peptides, we've actually looked at T-cell clones from patients that have been vaccinated with modified peptides, and I think Esteban (Celis) has as well. It appears to us that when we immunize a person with these things, we're just driving the repertoire in a different direction.

And it's not clear whether or not that's going to be beneficial, but clearly these cells are not seeing tumor, the natural peptide, in exactly the same way as they're seeing it before. Now, that may not be a bad thing, but at this point, it's not clear whether or not we're doing this right.

V. Kuchroo: You know, on the population basis, I totally agree ... To a given antigen you have a broad repertoire of T cells available with varying degrees of affinities and avidities. But you have to take into account that you're dealing with an autoreactive repertoire, which has been already deleted a lot. If you compare population to population, you will find a lower affinity repertoire to dominant antigens.

M. Nishimura: Well, I'm not sure they're deleted, per se. Just because you don't see them doesn't mean they're deleted.

V. Kuchroo: If you look at **Joan Goverman's** data, which has been repeated by others, it's clear that peptide $MBP_{121-140}$ is a high binder to MHC, a high-avidity epitope. But in a normal mouse, you don't see very many $MBP_{121-140}$-reactive cells.

But if you look at shiverer* mice, you all of a sudden see a very high preponderance of $MBP_{121-140}$-reactive high-affinity T cells. So there is a selection going on in the thymus that deletes—

M. Nishimura: It doesn't mean you get deletion. Just because you have a shiverer mouse that has reactive cells, it does not mean they're being deleted in the normal mouse. You could have peripheral anergy going on and it's the same phenotype.

V. Kuchroo: It's semantics. Okay, you don't see the responses to that epitope as readily. Will that fit your criteria?

M. Nishimura: That I agree with.

V. Kuchroo: Okay. So you don't see responses to that epitope very readily because there has been some sort of censorship, whether it's in thymus or in periphery. It doesn't matter.

M. Nishimura: Well, in the case of cancer, we see the same thing. For many of these peptides and epitopes, you just don't see responses very readily. If you try hard enough, you can find them. You can find T cells that react to them.

L. Sherman: But you don't know whether it's a tolerant repertoire, and whether you've already

[* *Shiverer mutant mice carry a large deletion in the MBP gene.*]

lost, for example, most of the best tyrosinase-specific T cells, which might be present if you had a major tyrosinase knock out.

M. Nishimura: Right.

L. Sherman: You might have gotten a totally different repertoire of cells that could have eliminated those tumors very easily.

Esteban Celis: I wanted to make a comment regarding "fixing" peptides because I don't agree 100 percent with Mike. It's obvious that if one is looking for epitopes that are, in theory, subdominant, one should be looking for peptides that are going to be suboptimal binders. So I think the powerful approach of making those epitopes bind to a greater extent to MHC is valid. But you have to expect that the suboptimal binder is still present in the tumor cell.

So, if the suboptimal peptide doesn't bind at all, no matter how much you fix it, you're not going to get recognition of the tumor. So the only thing that we're doing, by fixing the peptides, is allowing us to pulse more peptide onto the dendritic cell.

If one can do the same thing without modifying the peptide, like overexpressing that particular peptide as a mini gene in a dendritic cell, that might be a better effect.

So the ultimate goal is just to create enough MHC peptide complexes on the surface of a professional APC to activate those cells that are "ignorant" because they've seen sub-optimal numbers of peptide on the tumor cell.

G. Nepom: That's a very good point. When we talk about avidity, we really should be talking about thresholds of activation that are dependent on antigen density as well as avidity.

M. Nishimura: I'm not talking about antigen density. I'm talking about repertoire changes due to conformations that occurred upon binding a modified peptide to the MHC. You're just modifying the repertoire, is what I'm talking about. And (to **E. Celis**) by your argument, if you want to get more antigen on the surface, then a T2 cell should be the best antigen-presenting cell that you can find.

E. Celis: The problem with T2 cells is that they create so much garbage response that you cannot see the specific response. You get a fantastic anti-EBV response because there are endogenous peptides from EBV that are presented. And I'm not sure that an EBV-transformed cell is a good professional antigen-presenting cell, at least I don't think so. That's the other point. You're trying to tickle a naive cell that's never seen antigen before.

G. Nepom: Since we've solved the question of what peptides we really want to get (*Laughter*)—how do we best get them? What is the environment for priming in tumor immunity to augment the kind of response we want, either with dendritic cells or the cytokine milieu.

And in autoimmunity the issue is: What cytokine and APC environments are necessary to alter the response in a therapeutic manner?

Who would like to lead off the discussion there with your favor priming protocol?

E. Celis: We've tried several priming protocols *in vitro* using different types of APCs—everything from insect cells that have empty MHC, to T2 cells, to *Staphylococcus aureus*-treated cells. And we've had a lot of good luck with those cells from which we acid-stripped the endogenous peptide in order to overload them with exogenously added peptide.

That system worked very well, but we got a lot of these responding cells that only recognized peptide-pulsed targets and not the endogenously processed peptide, and we feel that a lot of those are low-affinity CTLs.

We haven't seen that problem happen with dendritic cells. So we made this hypothesis, which we haven't tested yet, that maybe the dendritic cells have the capacity to kill, or to eliminate, or to turn off low-affinity CTL and that they are more capable of selecting for the high-affinity CTL.

I don't know if anybody has any comment in regard to whether this makes sense or has made similar observations.

B. Singh: Let's get back to the issue of cytokines and the epitope. If you look at the issue of autoimmunity versus tumor immunity it seems that in

one case you want to induce a CTL response, which will kill off something. On the other hand, in autoimmunity, you want to do down-regulate that response. I think the first thing we have to resolve is how you want to present the antigen; in a synthetic form, naturally processed or added from outside of the vaccine, which would then modulate the response.

And if we know that, then we can ask what will trigger a CD8 cell or a CD4 cell and that may resolve what cytokine one would want to use in this sort of modulation protocol and whether you need adjuvant to achieve that effect.

V. Kuchroo: One of the issues raised is the cytokine milieu at the site of immunization. If you have a peptide that seems to induce Th2 cells, you're going to produce IL-4, which is going to, within the vicinity, act as an autocrine growth factor and almost every cell around there will turn out to be a Th2 cell.

We always say the cytokine is the most important driving factor in the differentiation of Th1 and Th2 responses. But experimentally, if you take an altered peptide, put it in CFA with added mycobacteria in it, immunize a mouse, and look at the T-cell responses, they turn out to be all Th2 cells—when we know that the mycobacteria, when picked up by APCs, will turn up IL-12. So, besides cytokine milieu, I think we have not appreciated that the antigen itself has a very important effect on which way the T cell is going to differentiate.

L. Sherman: So what you're saying is that the most important thing in determining whether it's a Th1 or Th2 response is actually the affinity of the T-cell receptor for the MHC/peptide complex?

V. Kuchroo: I would say that it should be considered because we have been so brainwashed saying that the cytokine milieu is important, which is true. But you can also consider that at one point, the precursor cell comes in contact with antigen, and if that precursor cell is stimulated to produce, for instance, IL-4, it will make every cell around there respond to antigen as a Th2 cell.

So that is an added effect that drives differentiation. Cytokine milieu is important, but I think antigen/MHC-TCR affinity is also very important.

L. Sherman: But that's if it's a naive environment?

V. Kuchroo: Yes.

Noel Rose: First of all, I think this has been a very good discussion, and I do think it reflects the thought that the central issue is going from benign autoimmunity to pathogenic autoimmunity, and it's a matter of which way you want to go.

The auto-immunologists want to go from pathogenic to benign, and the tumor immunologists want to go from benign to pathogenic. I do think the scheme that Vijay put up is a very good way of explaining that, and I think it shows one additional point that I just wanted to add.

It relates to the cytokine milieu. *I would like to make an appeal that we disenthrall ourselves from the paradigm of Th1 and Th2 because I think it creates a lot of mischief in our thinking, from two points of view.*

First of all, in terms of autoimmunity, there are many autoimmune disorders that happen to be antibody mediated, and so *I think to just make a blanket statement that in autoimmunity it's Th1 products that do the damage and Th2 that are the more desirable is absolutely wrong. It depends on the disease.*

And I would opine that the same is probably true in tumor immunity. More than that, I think we probably very much overplay the concept of Th1/Th2 cytokines as a blanket generic classification. *I think we would do ourselves a favor by looking at the evolution of both CD4 and CD8 T cells as a spectrum and looking at individual cytokines, rather than looking at two polar groups.*

And I think that particularly it's going to be useful to see which cytokine can push a response in the direction we want. As I said, it will be in one direction for one kind of disease or one kind of tumor and the other direction in another.

So I think we need to begin to think about the effects of individual cytokines on the maturation and function of T cells, rather than thinking of polar groups as Th1 and Th2.