SPEAKER: Focus number one, how does ECP activate dendritic cells? A quick word about them. Normally, of course, these dendritic cells, which are commonly derived from monocytes, the form in which they pass through the blood, are needed in sites of inflammation, in sites of infection, in sites of cancer, not in the blood. The blood is the highway.

And in the blood, only 1/10 of 1% roughly of the white blood cells are actually dendritic cells. You may have 10% of your peripheral blood mononuclear cells being monocytes as precursors of dendritic cells. But the blood contains very few.

How, therefore, did ECP-- this became the mystery that is now answered-- how did ECP get the dendritic cells activated? How did it convince monocytes to become dendritic cells? And how did it load those dendritic cells with the relevant antigens that needed to be attacked or that needed to be tolerized against?

So the answer to that question, which as you might surmise, was not that simple to find, is, in fact, quite simple, elegantly simple. It turns out that in the ECP plate, the anti-coagulated blood contains, of course, a large amount of plasma. And dissolved in that plasma are soluble precursors of fibrinogen. Fibrinogen, which in the tissues, will polymerize into a long chain and is instrumental in both clotting and in wound healing.

Instrumental in the tissues because in wounds, polymerized fibrinogen, the fibrals, stick very avidly to collagen fibers. And secondarily in those wounds, platelets stick to the fibrinogen, specifically to the gamma chain of the fibrinogen, and become quite activated to initiate either wound healing or clotting. What we discovered in an accelerating way over the past decade was that in the ECP plate, the first thing that happens is that the soluble fibrinogen sticks avidly to the plastic, the walls of the one millimeter film that's being processed through ECP.

Remember that we initially devised a very thin film so that the light could get through to activate the drug psoralen and then target the malignant cells. That does happen, but we'll return to it. We hadn't contemplated the roll of fibrinogen and platelets.

But what happens is, as the blood passes through the plate, literally within seconds, that plastic surface becomes a fibrinogen surface. The fibrinogen, a fact known to those individuals who are expert in blood clotting and wound healing but not very well known to immunologists like myself, plastic is a tremendously attractive surface, just like fibrinogen in tissue, just like collagen in tissue, excuse me, for the fibrinogen to stick. And so it sticks.

Indeed, people that work with fibrinogen have known for many years that the best way to isolate soluble fibrinogen from the plasma is to let the plasma sit on a plastic surface, remove the supernatant, and then scrape away the inherent fibrinogen. That's going on in the ECP plate, initially unbeknownst to us.

The next thing that happens, however, is that platelets come through. They're the smallest cellular component and the first thing to come off from ECP centrifuge component. They pass through and they stick immediately to the gamma chain of fibrinogen. And if you look inside the plate, it now looks very much like a Boston cobblestone road with tremendous numbers, literally billions of platelets sticking avidly to the invisible fibrinogen, stuck to the plate themselves.

Now what comes through are the large monocytes, looking like sailboats. Bigger than lymphocytes, including the T cells that we were originally targeting. And they literally can be seen to jump from platelet to platelet. From activated platelet to platelet. What's happened to the platelets, just as is happening in wounds all the time, a molecule called p-selectin, which sits on the inside of the platelet membrane.

As soon as it gets activated by the fibrinogen that it is now stuck to, it quickly, instantaneously, transposes that preformed p-selectin to the outside of the platelet. And it is p-selectin to which the monocyte, for which the monocytes have receptors. They stick to transiently and they get activated to become dendritic cells.

So what was discovered? Let this settle in for a second because it's a big, surprising thought. No one knew previously how monocytes in vivo are signaled to become antigen presenting cells, the dendritic cells, where needed and when needed. There have been tricks that are used because all cancer immunotherapists have been interested in trying to utilize dendritic cells for cancer immunotherapy.

So large tricks, chemical tricks with cytokines, growth factors, way beyond whatever happens physiologically in the body are used to make dendritic cells. It's happened in thousands of laboratories, including our own, throughout the world. But the question of how monocytes normally in a physiologic sense are induced to become dendritic cells in wounds was not known.

And it's through the ECP apparatus that we jump in to normal physiology and make countless numbers of new dendritic cells, all maturationally synchronized because it's all happening at the same time in the plate. They come out the other end of the plate and they internalize, if given a chance, the injured T cells, the pathologic T cells, whether they be the malignant cells or the cells that are auto reactive.

And so that's a lot to swallow. But ECP clearly had an underlying principle. ECP, in those 1,200 papers that have been published, does almost everything that anybody can measure in the immune system. But the big bang, the one that starts it all, is ECP's co-opting normal physiologic mechanism by which platelets signal perhaps if not all, a high percentage of normal T cell function. Through their induction of the trigger, the ignition of the immune system, the dendritic cells.

And everything I will suggest can now happen with that insight. In transforming ECP from a one-size-fits-all treatment where everybody that currently gets treated with ECP gets treated precisely the same way, with the same instrument, it now can be polarized to only the on switch and only the off switch, and can be intelligently augmented.

We're entering an entirely new phase of what could actually be the first genuinely physiologic immunotherapy which might be applicable to any disease in which the antigen or the antigen source can be isolated. Which means, and this is another big thing to swallow, but extremely exciting to us. And that is that ECP can now be personalized, theoretically at least, in ways that can be tested for virtually any immunologically-driven disease or immunogenic cancer.