

INTERVIEWS WITH THE EXPERTS

## MDS and Inflammation

**Q What is inflammation and its relationship to MDS?**

**A** Inflammation is a complex biological response to an injury or an irritant. Inflammatory responses protect the body and cells from specific insults, with the purpose to rapidly neutralize the injury or the insult the body has experienced. This could be a pathogen like bacteria, or even the result of cell death, where intracellular components are released into the environment. The immediate cellular effectors of inflammatory responses involve white blood cells, immune cells, blood vessels and additional molecular factors. This process reflects what we refer to as the 'innate immune system' at work, and which specifically appears to be activated in MDS.

**Q What are MDSCs?**

**A** The main cells that seem to be involved in operationalizing the inflammatory response are called myeloid-derived suppressor cells (MDSCs). We found that these cells are markedly expanded in the bone marrow of MDS patients and their role appears to be to suppress blood formation. They will suppress and kill neighboring cells in the bone marrow and are genetically distinct or separate from the MDS clone. This finding suggests that MDSCs may have come first, and driven the emergence of the MDS clone.

We have also learned that MDSC's are expanded and activated by a specific inflammatory protein, called S100A9, which together with its binding partner, S100A8, can drive the expansion of these cells. MDSCs and S100A9 also trigger a specific type of cell death. Targeted cells die by a unique process called pyroptosis, an inflammatory form of cell death. In cell death, the cells swell and get larger. These are known as macrocytic cells that are often seen in MDS, and the also drive the proliferation. They appear to have a very important role in the disease biology, signaling through a protein complex called the inflammasome.

**Q What are some inflammatory symptoms?**

**A** We have known for years that there are increased inflammatory complications in MDS. There was a large Swedish registry study showing that people who sustained chronic inflammation – such as asthma, rheumatoid arthritis, or some sort of autoimmune disorder had a much higher risk of developing MDS. MDS patients can develop rashes, profound fatigue, vasculitis (inflamed

**Dr. Alan List**



Dr. Alan List is the president and CEO of Moffitt Cancer Center in Tampa, Florida. He is a senior member

in the Department of Malignant Hematology and the Experimental Therapeutics Program. Prior to joining Moffitt in 2003, Dr. List was a professor of medicine and director of the Leukemia and Bone Marrow Transplant Program at the University of Arizona Tucson, as well as director of the Division of Translational/Clinical Research.

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blood vessels), and Sweet's Syndrome (painful flares in the skin associated with fever and inflamed, swollen joints). There are a number of inflammatory symptoms that are all related to activation of innate immunity.

For people who have MDS and experience inflammatory disorders, I think we are on the cusp of having some new therapies that will help suppress this process. I have many patients where their hemoglobin is not low enough to have symptoms, but they have profound fatigue and aches with inflammatory symptoms. These novel kinds of treatment that are coming may have a role in treating all of the symptoms and the initiating biological events. They represent an unprecedented opportunity for the future, not just for treatment, but also for prevention.

We have heard about gene mutations that can be detected at a very low level in the peripheral blood of people who are otherwise hematologically normal. These individuals have about an eleven-fold increase in risk for developing MDS later on. If the inflammatory process drives it, it could eventually be as simple as taking a pill to prevent MDS from occurring.

## Our **MarrowStrong** Community

One of the most remarkable things we've learned over the past three decades is that working hand-in-hand with our many constituents has created an INFORMED and EMPOWERED community centered around bone marrow failure disease. This is good news for all of the patients, friends, family members, doctors, nurses and other health care professionals who we serve and educate, as well as the corporate partners who help support our work.

AAMDSIF remains the sole global nonprofit organization that provides the resources patients and their family members need to understand what happens in the wake of a bone marrow failure diagnosis. As you know, we receive some funding from pharmaceutical companies but rely heavily on generous contributions from the community that we serve. Thank you for your support in 2016. In 2017, I ask that you give often and as generously as you can so that we can continue to serve all of you.

[www.aamds.org/donatenow](http://www.aamds.org/donatenow)

Thank you,



**Kevin Lyons-Tarr**, Chairman of the Board

### **Q** What are some possible directions for future research?

**A** I think the most important take home message is that understanding this biology which is very new allows us to target the MDS clone therapeutically in a very specific way that we never could before. The convergence points in this process are the inflammasome, as well as S100A9, the key soluble mediator of expansion of MDSCs or activation of the cell death pathway we call pyroptosis.

We can target this in the laboratory now, by creating a soluble receptor that will neutralize S100A9, and using an inflammasome inhibitor which could be taken as a pill. These agents have been licensed to Celgene for clinical development in the years ahead. In the laboratory they work beautifully to enhance the survival of the cells and the effective production of blood cells.

For future research, the real question is what is the mechanism of activation of this pathway within the cells. If we can find the specific internal activators, we can make more specific inhibitors to help arrest the process. This needs to be a key priority of research in the next few years. ■

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## PATIENT STORY

### Doing His Part to Assist MDS Research



#### Tom Coccagna

The first indication that something was wrong came with a routine blood test. Lots of H's (high) and L's (low) dotted my CBC (complete blood count). My primary care provider said it probably was 'nothing', but I might want to follow up with a hematologist just to be sure.

I was thirty-nine, a husband and father of three girls. I was an avid runner who ran 10k races, half marathons and full marathons. I had a healthy diet, didn't drink or smoke. I wasn't supposed to be sick. I thought it was all a terrible mistake.

I was convinced the hematologist would have a simple answer for what was clearly a medical mix-up. I couldn't possibly be sick; I felt great.

Unfortunately, the hematologist didn't have good news. That was when I was introduced to those three letters that have forever changed my life ... MDS. He told me what it meant, that we caught it early and that I was much younger than most people who have it. He told me I had a serious illness, that it was progressive and the only cure was a bone marrow transplant.

Over the next few years, my new reality became hematology appointments, bone marrow biopsies, CBCs, transfusions, chemotherapy and a clinical trial became my new reality.

For now, I'm responding to an experimental drug. I try not to think about what comes next. What happens when this miracle drug stops being miraculous? When my body stops responding to it, what then? More transfusions? More chemotherapy? A bone marrow transplant?

When you have a life-threatening disease, you consume everything you can about that disease. When I heard about PACCT+ via the AAMDSIF newsletter, I was in the middle of a clinical trial and I thought I might be able to shed some light on the clinical trial process from a patient's perspective. I feel those developing clinical trials would benefit greatly from patient input. I can't imagine developing a clinical trial without it.

The PACCT+ orientation was something special. I had the pleasure of meeting others who have been touched by MDS. Some were at the same place on their journey, while others have had transplants and have come out the other side – not

unscathed, but alive. I saw hope in their eyes. I heard them speaking about their diseases in the past tense. For the first time I had hope that I would one day say, 'I had MDS'.

As an MDS patient and PACCT+ participant, I hope to use my clinical trial experience to help others develop more effective clinical trials. I feel patient input is going to change the face of clinical trials as well as for other diseases. This is just the beginning and I'm thrilled to be a part of it. ■

## SHARE YOUR STORY!



**We are looking for MDS patients, family members and caregivers who are interested in sharing their personal stories with our community.**

They can be funny or poignant, a chronology of key events or a single anecdote that sums up the ways in which your world has changed because you live with a chronic disease.

There's no right or wrong way to talk about how MDS has affected your life. You might reflect on the impact on your family or the ways you are coping with treatments, transfusions and fatigue. Are you participating in a clinical trial? Have you developed new skills to help you stay positive? Whatever story you choose to tell, we'd love to read it.

Please consider sharing your health journey with us in a 500-700 word article. If you're not sure where to start, you can find lots of patient stories at:

**[www.aamds.org/support/stories-of-hope](http://www.aamds.org/support/stories-of-hope).**

**Email [editor@aamds.org](mailto:editor@aamds.org) to submit your story, and remember to include your photo in .jpg format. Be sure to include the date of diagnosis, age at diagnosis, age today, name, address, daytime phone and email address.**



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#### Peer Support Network

Our Peer Support Network is a national group of trained volunteers, offering information, guidance and coping strategies from a personal perspective. To connect with a Peer Support Network volunteer, call (800) 747-2820, option 2, and speak with our information specialist who will match you with one of our volunteers. You can also email [help@aamds.org](mailto:help@aamds.org).