

# Treating the Cure:

## Grappling with cGvHD after Hematopoietic Stem Cell Transplants

*The second phase of a consensus project on chronic Graft versus Host Disease showcases a decade of progress.*

Hematology/oncology specialists have been doing allogeneic transplants of hematopoietic stem cells to cure cancers of the blood like leukemia and lymphoma for 45 years; and, it works. The number of transplants is increasing worldwide, availability of donors is increasing through the unrelated donor registry, patients can be treated at an older age and with comorbid conditions, and the safety with respect to early complications and mortality is greatly improved.

But, because there are more long-term survivors, later complications from the therapy have risen to prominence. One in particular, chronic Graft versus Host Disease (cGvHD), develops on average about one year after the transplant and can take five years to resolve. cGvHD is a multisystem disorder, resembling systemic autoimmune disorders like lupus and scleroderma, involving many organs including the skin, joints, eyes, mouth, and lungs.

cGvHD has a tremendous impact on quality of life, and can even be life-threatening. Like autoimmune diseases, the causes are poorly understood.

“It has been very difficult for the oncology field to address the complicated needs of these patients,” explained Steven Pavletic, M.D., M.S., Head of the GVHD and Autoimmunity Unit in CCR’s Experimental Transplantation and Immunology Branch. “Oncologists are equipped to treat cancer, but these patients no longer have cancer. Primary internists don’t know what to do.”

To further complicate the issue of cGvHD, it appears that this disease is finely balanced with curing the original cancer. Bone marrow transplants are given to cure very aggressive cancers; most are done for patients that will likely otherwise die within a year. This form of immunotherapy relies in part on graft-derived cells eradicating the remaining cancer of the host. “Mild GVHD is actually desirable in some patients; with a little bit, they have better cure rates. Our goal is to find ways to effectively treat or prevent GVHD without harming the beneficial immunological effect. It’s a challenge,” said Pavletic.

Research into the disease has been severely hampered by the difficulties of organizing studies around outpatients and the need for multidisciplinary teams to analyze the multisystem causes and effects. To address this issue, in 2004, NCI decided to create a program within CCR to study cGvHD. Pavletic came

to CCR to establish the program, which brings together clinical investigators from eight institutes and five departments of the NIH Clinical Center.

“We started reaching out to people for referrals to the clinic, and soon we found that 85 percent of our patients were coming from the extramural community,” said Pavletic. “Because we have access to the NIH Clinical Center, we had a unique opportunity to mobilize researchers to create a model that could hopefully be exported.”

Having established the NIH program, the next step was to engage a broader community to advance research and improve treatments. There were no standard criteria for diagnosis, disease staging, or therapeutic response. There were no developed pathways to do clinical trials, nor recommendations for biomarker development. “We needed to create a whole medical discipline to study a disease that had been unstudyable,” said Pavletic.

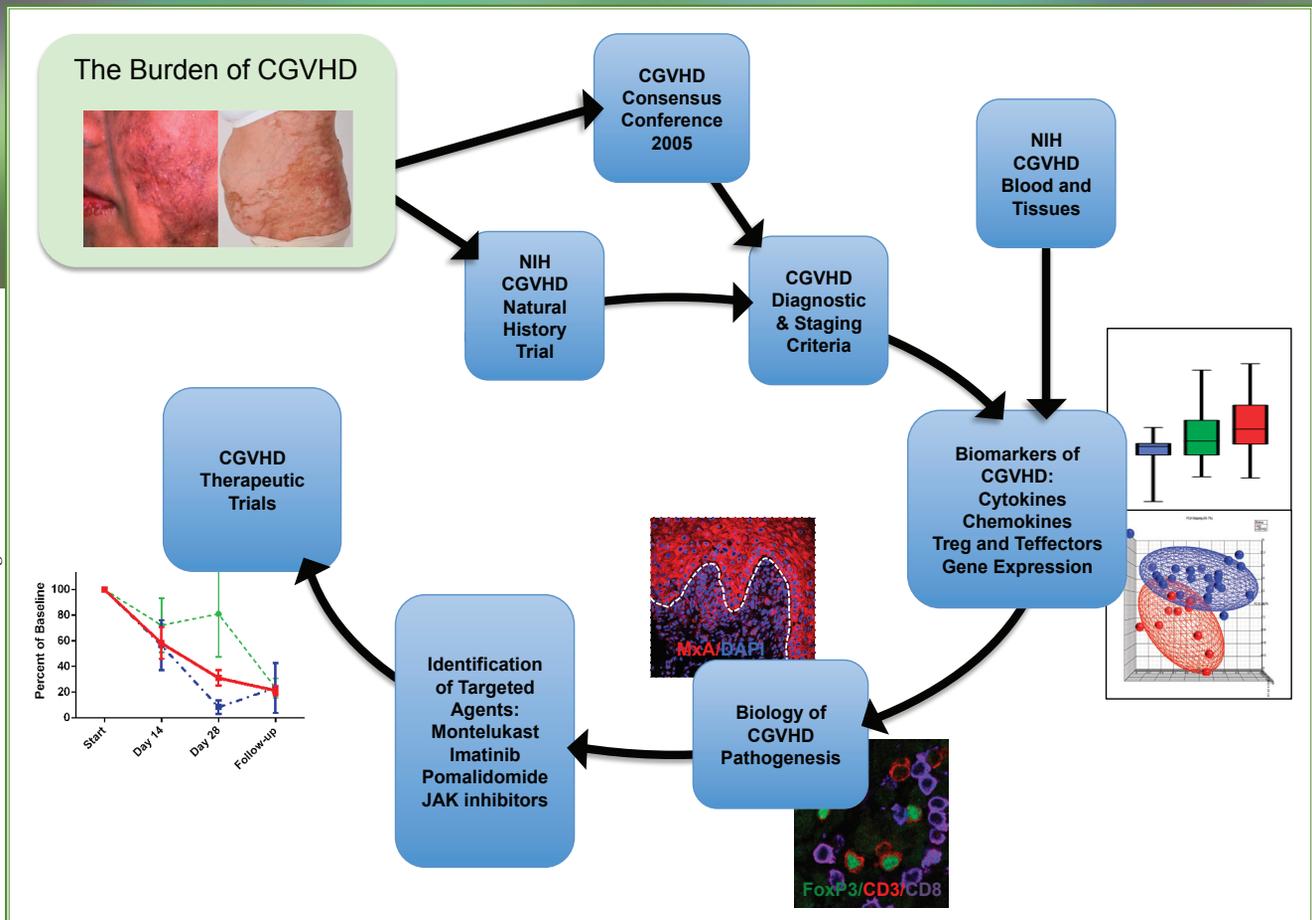
Thus, the first cGvHD consensus project was formed to provide expert-driven recommendations for the conduct of cGvHD clinical trials. From 2004–2006, it led to the publication of six papers that covered key areas to define the field. “Today, there have been 1,600 citations in peer-reviewed literature to those papers—a high number, especially for a relatively small field—showing the impact of this effort,” said Pavletic. “More importantly, the field became better organized. Collaborations improved nationally and internationally. Extramural



(Photo: B. Brantson)

Steven Pavletic, M.D., M.S.

(Image: S. Proletic and F. Hakim, CCR)



Generating new understanding of GVHD and developing new treatments per the NIH consensus project algorithm

investigators began submitting grant proposals to NCI. We were able to pursue multicenter prospective studies to look at the course of disease and initiate phase 1/2 trials here at the NIH.”

The first consensus project had very little hard data to work with. Ten years later, with the accumulation of research spurred by the project, the leadership felt the time was right to re-examine the guidelines and recommendations for cGvHD. On June 17, 2014, NCI hosted the second meeting of the cGvHD consensus project on criteria for clinical trials.

“Thanks to the support of CCR, we were able to invite panelists to come here for a conference. We reconvened 200 stakeholders from across the world: clinicians, scientists, as well as representatives from the pharmaceutical industry, patient advocacy, and key associations,

to refine and clarify the original recommendations,” said Pavletic.

Once again, the project examined six key areas: diagnosis and staging, measuring therapeutic response, histopathology, biomarkers, ancillary therapy and supportive care, and design of clinical trials. “This time we added a special focus on the biology of cGvHD. What are we missing that we still can’t decipher this whole complex pathophysiology?” said Pavletic. The findings of the second project will be published in the *Biology of Blood and Marrow Transplantation* in 2015.

“We have a much better understanding of the disease manifestations. We have new tools to measure the disease and conduct clinical trials. We have common language. None of this existed when we met for the first time,” said Pavletic.

“In parallel, certainly, everybody is asking can we cure or prevent this? The short answer is no; we don’t have any magic drugs yet. But the amount of information about potential points of intervention has dramatically increased, the number of molecules available to be tested has increased. So now it’s our job and task to overcome the main bottleneck in drug development: pursuing clinical trials effectively to apply emerging knowledge to benefit these patients,” concluded Pavletic.

*To learn more about the NIH 2014 Chronic GVHD Consensus Project on Criteria for Clinical Trials, please visit <http://ncifrederick.cancer.gov/events/GoHD/resources.asp>.*