



The collaborative network approach: a new framework to accelerate Castleman’s disease and other rare disease research

Despite technological advances and substantial investments of time and funding, many challenges exist for rare disease research and drug development. Basic disease mechanisms are often poorly understood, selection of suitable research participants can be difficult, and endpoints for clinical trial registration might not be established. Progress is further impeded by limited collaboration and data coordination,¹ misaligned incentives, funding decisions made in isolation from community consensus, and inter-institutional barriers to tissue sharing. Although frequently used, off-label treatments are infrequently tracked, and thus valuable opportunities to build on observations are lost.¹ One coauthor (DCF) comments, “Despite being a physician, I didn’t fully understand the barriers that slowed down life-saving progress until I was dying from a rare illness. I received my last rites in 2010 while battling idiopathic multicentric Castleman’s disease and found that [the disease] had no Food and Drug Administration [FDA]-approved therapies, a poorly understood model of pathogenesis, and a 65% 5-year survival rate.”²

After surviving three life-threatening episodes, DCF began to assess how non-profit research funding was allocated for rare diseases, for which 95% of conditions do not have an FDA-approved therapy.³ Disease research organisations (DROs) make important contributions by funding research. However, the framework through which many (but not all) DROs traditionally distribute funding can present challenges (figure). DROs typically fundraise first and then invite researchers to apply through a request for proposals (RFP) to use the funding for their specific purposes. In parallel, these organisations often provide patients with supportive resources and facilitate referrals to experts, who collect and store clinical data and biomaterials at their respective institutions. This model can in some cases result in organisations funding studies targeted at questions proposed by a small selection of researchers with requisite tissue samples rather than the studies that may have the highest impact on the field, which might require collaboration and sample sharing.

A more efficient, collaborative, and consensus-driven framework than exists at present is needed to fully

harness the opportunities afforded by technological advances for the approximately 7000 rare diseases and 350 million individuals afflicted globally. One such neglected rare condition is Castleman’s disease, which describes a heterogeneous group of lymphoproliferative disorders straddling the fields of immunology, oncology, and virology. Castleman’s disease ranges from a single region of enlarged lymph nodes (unicentric Castleman’s disease) to multicentric lymphadenopathy with systemic inflammation and multiple organ system dysfunction (multicentric Castleman’s disease) caused by immune activation and proinflammatory hypercytokinaemia, often including interleukin 6. Multicentric Castleman’s disease is either caused by human herpesvirus 8 (HHV8) infection, which is called HHV8-associated multicentric Castleman’s disease, or is idiopathic in HHV8-negative patients and called idiopathic multicentric Castleman’s disease.⁴ The absence of a unique international classification of disease (ICD) code for Castleman’s disease has made epidemiological studies difficult. The estimated incidence of all forms of Castleman’s disease is 6500–7700 individuals of all ages every year in the USA or about 2.2 per 100 000.⁵

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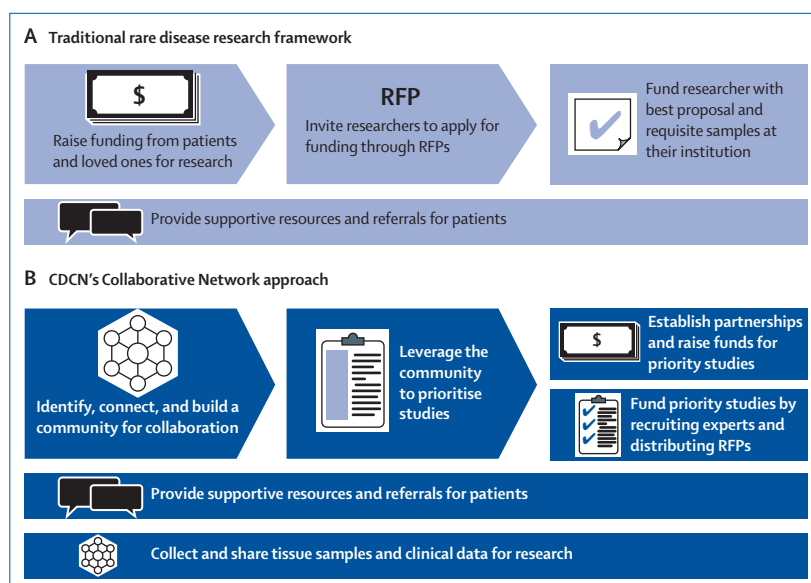


Figure: Traditional rare disease research framework (A) and the Castleman Disease Collaborative Network (CDCN)'s Collaborative Network approach (B)
 RFP=request for proposals.

For more on the Castleman Disease Collaborative Network see <http://www.CDCN.org>

In 2011, after another life-threatening exacerbation, DCF identified several factors hindering research progress for idiopathic multicentric Castleman's disease. Experts rarely collaborated, the community used different classifications, and no diagnostic criteria existed. Although well understood for HHV8-associated multicentric Castleman's disease, the cause and pathogenesis of the idiopathic form were unknown, and the working model of pathogenesis had several inconsistencies.⁴ Furthermore, researchers studying the idiopathic form had never received National Institutes of Health funding, and a single DRO (Castleman's Awareness & Research Effort [CARE]; CA, USA) was the only source of research funding. Small sample sizes at individual institutions prevented research from being adequately powered for significance. Several therapies, including rituximab and other chemotherapeutics, were being used off-label with variable success, but no effectiveness data were available. One drug in development, the anti-interleukin 6 monoclonal antibody siltuximab had positive phase 1 results for idiopathic multicentric Castleman's disease,⁶ but the absence of a well connected DRO made enrolment challenging.

In 2012, DCF assembled a group of physicians, researchers, and patients to create the Castleman Disease Collaborative Network (CDCN) to accelerate research through a targeted, collaborative, and patient-centric approach. Soon after its creation, the CDCN merged with CARE and spearheaded the following approach (figure): first, to build a global community; second, to leverage the community to prioritise studies and share research samples; and third, to execute the community-prioritised research through RFPs and strategically directed research grants to experts.

To build a global community for collaboration the CDCN first identified Castleman's disease physicians and researchers worldwide and connected them through an online discussion board and symposium at the 2012 American Society of Hematology meeting. The CDCN then created a scientific advisory board, which now includes 28 members from eight countries. Physicians, researchers, patients, and loved ones joined the volunteer leadership team to advance research and support patients. In 2014, the CDCN submitted an application for a unique ICD-10 code for Castleman's disease to facilitate epidemiological studies. The CDCN has hosted the four largest Castleman's

disease meetings and forged collaborations among a network of 317 physicians and researchers. In the past year, the CDCN has supported more than 6000 patients and loved ones through an online patient forum, patient summit, and website. Engagement of patients in the research process has aligned stakeholder incentives behind conducting research that will have the greatest impact on patients' lives.

To leverage the community to prioritise projects, the CDCN used online surveys, discussion boards, and patient feedback to crowdsource, or gather perspectives from the community to establish the state of knowledge, a common classification system, and a list of prioritised studies called the International Research Agenda. The large patient and physician network now has the scale to successfully conduct large studies.

To execute prioritised projects through reactive and proactive funding mechanisms, the CDCN sought and received funding from both philanthropic and industry stakeholders specifically for the studies in the International Research Agenda. Finally, the CDCN distributes funding through RFPs and strategically directed research grants whereby leading experts or contract research organisations are engaged to perform the highest priority projects. Since the International Research Agenda was established in 2015, the CDCN has funded and provided logistical support to launch five priority projects (appendix). With the solid foundation of an international community, an engaged patient population, a centralised registry to track treatments, and a biobank to overcome inter-institutional barriers, the CDCN expects to generate and invest even more substantial funding from its stakeholders for priority projects.

In the past 3 years, the CDCN's Collaborative Network approach has contributed to important progress for the field by increasing collaboration, focus, and community consensus. Combining findings from the published literature with communications among the CDCN community about hundreds of their unpublished cases of idiopathic multicentric Castleman's disease suggested a novel model of disease pathogenesis.⁴ Previously, benign interleukin 6-secreting lymph node tumours were believed to cause the activated immune system and organ dysfunction in idiopathic multicentric Castleman's disease.⁷ The new model proposes that the enlarged lymph nodes are not interleukin 6-secreting

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tumours, but are caused by excess interleukin 6 and other proinflammatory cytokines produced by immune cells, which are activated for an unknown reason.⁴ The CDCN is now working to identify the cause of the cytokine release, the network of cytokines, and the pathological immune cell type.

In 2014, siltuximab, which neutralises interleukin 6, became the first FDA-approved treatment for idiopathic multicentric Castleman's disease on the basis of durable symptomatic response and lymph node regression in 34% of patients on treatment compared with 0% on placebo.⁸ The new model of idiopathic disease pathogenesis highlights the potential for repurposing existing immune-modulating agents to target other potential drivers in patients with failure or suboptimal response on siltuximab.

Our systematic literature review⁹ published in *The Lancet Haematology* is the largest-ever series of idiopathic multicentric Castleman's disease cases, and it will inform future research and patient care. The CDCN will also use these data to inform the establishment of international, consensus diagnostic criteria for idiopathic multicentric Castleman's disease.

Ultimately, the collaborative network approach has facilitated a previously unrealised level of coordination, leading to a new model of pathogenesis, a systematic literature review, and several studies with requisite scale to investigate new hypotheses for causal pathways and pathogenesis.

We hope that the insights related to our approach will help to speed up progress for other diseases. In the words of DCF, "As a physician-scientist and

patient with a deadly disease, I urge you to consider a more collaborative, strategic, and focused approach to accelerating research to save lives. We must work together to make every dollar and second count, because patients—like me—are waiting."

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- 1 Maher J. Lack of data. *JAMA* 2012; **308**: 1331–32.
- 2 Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. *Am J Hematol* 2012; **87**: 997–1002.
- 3 Miyamoto B, Kakkis E. The potential investment impact of improved access to accelerated approval on the development of treatments for low prevalence rare diseases. *Orphanet J Rare Dis* 2011; **6**: 49.
- 4 Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. *Blood* 2014; **123**: 2924–33.
- 5 Munshi N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. *Leuk Lymphoma* 2015; **56**: 1252–60.
- 6 van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol* 2010; **28**: 3701–08.
- 7 Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 1989; **74**: 1360–67.
- 8 van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2014; **15**: 966–74.
- 9 Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. *Lancet Haematol* 2016; published online March 17. [http://dx.doi.org/10.1016/S2352-3026\(16\)00006-5](http://dx.doi.org/10.1016/S2352-3026(16)00006-5).