Thank you for participating in the All In Movement (AIM 2021), the CDCN’s initiative to gather and prioritize questions from the CDCN community to drive the next generation of high-impact studies on Castleman disease.

There was strong community participation, with 48 individuals participating in both the idea submission and voting stage. A total of 155 ideas/questions were submitted. Our team grouped the 155 ideas/questions into 10 broad research categories and 69 condensed ideas/questions. In the voting phase, 48 individuals participated, casting a total of 1086 votes. After several SAB meetings, we narrowed it down to the following top 20 research questions to focus on as the CDCN International Research Agenda for the upcoming years:

**TOP 20 RESEARCH QUESTIONS**

**TOP TIER (TOP 3)**

- Is JAK inhibition an effective treatment for iMCD patients refractory to siltuximab and sirolimus?
- What treatment options are available for patients who have a failed or incomplete response to anti-IL6 therapy?
- What biomarkers can be used to improve diagnosis and tracking (preventing relapse) of iMCD (ex: sFLT-1)?

**SECOND TIER (4-9)**

- Why don’t all iMCD patients respond to anti-IL6 therapy?
- How long should a patient remain on CD treatment (such as siltuximab or sirolimus)? What are recommendations for treatment spacing? Can doses be spaced further apart or discontinued? Can the route of administration be changed?
- What biomarkers can be used to predict a high likelihood of treatment response in individual patients?
- Besides IL-6, what circulating or lymph node cytokines, cytokine receptors, and cell-signaling pathways are involved in Castleman disease? Can these cytokines/pathways be targeted with therapies?
- What circulating or lymph node cell types are responsible for Castleman disease and/or contributing to key elements of Castleman disease(e.g., IL-6 production, increased mTORC1 activation)?
- What are the indicators/predictors of iMCD relapse?

**THIRD TIER (10-20)**

- What are effective treatment approaches for unresectable UCD?
- Are somatic (potentially cancer-causing) mutations in circulating immune cells or rare lymph node populations responsible for iMCD?
- What are the risks of long term CD treatment (ex: malignancies, autoimmune diseases, etc.)? Is there any way of reducing side effects?
- How can we identify new therapeutic targets and treatment options for anti-IL-6 non-responders?
- What is the lasting psycho-emotional impact of CD (ex: PTSD-like symptoms)? How can we provide adequate supportive care to CD patients to improve quality of life?
- Are somatic (potentially cancer-causing) mutations in circulating immune cells or rare lymph node populations responsible for iMCD?
- What are the specific risks for lymphoma and other associated diseases? Should Castleman patients be screened?
- Is there an association with having a family history of other autoimmune conditions (diabetes, Hashimoto’s/autoimmune thyroiditis, rheumatoid arthritis, multiple sclerosis (MS), lupus, or myasthenia gravis)?
- Can CD be activated by pregnancy-related autoimmune phenomena? What are the effects of CD on pregnancy and risk of miscarriage?
- Does CD in diagnosed in childhood and adolescence have the same causes and risk factors as CD in adults? How should CD be treated or managed in childhood and adolescence?
- What are the treatment options for non-resectable UCD in children and young adults?

**NEXT STEPS**

We need to use these research questions to A) determine the best studies to answer them and B) the best researchers to perform those studies.

Please reach out to your networks! We need to identify researchers who are best placed based on their prior experience and skillset to lead research studies that will answer the above questions. If you or someone you know would be a good fit please reach out to Dr. David Fajgenbaum at david@castlemannetwork.org.