KEY QUESTIONS POSED BY PARTICIPANTS

MECHANISMS OF DISEASE

1. How does germline brachyury amplification contribute to chordoma pathogenesis?
2. How does the chordoma-associated SNP in brachyury contribute to chordoma pathogenesis?
3. Is brachyury crtical for chordoma survival/maintenance in-vivo?
4. What cofactors and downstream targets are important for mediating brachyury's role in chordoma?
5. How does brachyury become activated in chordoma? Conversely, what keeps brachyury from being expressed in other tissues?
6. Aside from alterations in brachyury, what somatic or germline genetic events contribute to chordoma pathogenesis?
7. What are the key initiating events that cause chordomas to develop? What causes benign notochordal cell tumors to progress into chordomas?
8. What epigenetic alterations are found in chordoma? What is the impact of epigenetic dysregulation on chordoma cells and how can this be exploited for patient benefit?
9. What biological characteristics distinguish primary versus recurrent chordomas?
10. What role does the immune system play in controlling disease progression, particularly metastases?
11. Why do chordomas tend to only metastasize late in the disease process?
12. What causes chordomas to metastasize? What does the low metastasis rate tell us about the disease and/or immune interaction?
13. Why are some chordomas so aggressive, while others grow so slowly?
14. Why are chordoma cells physaliferous and what does their morphology tell us about their biology? Can this be exploited in some way?

THERAPEUTIC DEVELOPMENT

15. Can we effectively deliver small molecules, antibodies, or imaging agents to chordoma?

16. What accounts for the chemoresistance and radioresistance of chordoma?

17. Are there any tumor specific antigens that could be targets for immunotherapy?

18. What vulnerabilities can be exploited with existing agents?

CLINICAL MANAGMENT

19. How should systemic therapy be selected for chordoma patients? What role should tumor profiling play in the personalization of treatment for chordoma?

20. What studies need to be performed to confirm the apparent benefit of preoperative RT? How do we generate evidence needed to incorporate preoperative RT into practice?

21. Among many prognostic markers reported, which are significant? Which should be used to guide clinical practice?

22. What can be done now to improve the quality of life for chordoma patients? What clinical problems need to be solved to improve quality of life in the future?