Questions Posed by Participants

Genetics and Molecular Biology

1. What are the key genetic events in the pathogenesis of chordomas?
2. What epigenetic phenomena contribute to chordoma pathogenesis?
3. What are the signaling pathways that regulate the growth and survival of chordoma?
4. What role does the tumor microenvironement play in chordoma initiation and progression?
5. Why do chordomas arise from within the bone and not the intervertebral disc? Is there some factor in the bone that causes notochordal cells to proliferate?
6. What triggers metastasis? Why do some chordomas metastasize while others do not?
7. What explains the difference in age of onset for sacral vs. clival chordomas? Are the mechanisms of pathogenesis different for chordomas of various anatomical sites?
8. Are pediatric chordomas biologically distinct from adult chordomas?
9. What explains the difference in survival based on gender? What explains the difference in anatomical distribution based on gender? Do sex hormones play a role in the initiation or progression of chordoma?
10. Why are chordomas resistant to chemotherapy and radiation?
11. To what extent are chordomas hypoxic?

Brachyury

12. How does germ-line copy duplication of brachyury cause familial chordoma?
13. Are chordomas dependent on brachyury for survival?
14. How does the chordoma-associated SNP in brachyury contribute to chordoma development? What other factors cooperate with the SNP in brachyury to initiate chordoma?
15. What are the relevant downstream targets of brachyury?
16. How does brachyury become activated in chordoma? Conversely, what keeps brachyury from being expressed in other tissues?

Models

17. Are current models biologically relevant?
18. What are the most appropriate and important model for studying chordoma? (e.g. cell lines, patient derived mouse xenografts, genetically engineered mouse models, genetically engineered zebrafish models, zebrafish xenografts)

Questions Posed by Participants

19. How can we establish a genetically engineered model of chordoma?

Therapeutic Development

20. Can we effectively deliver small molecules, antibodies, or imaging agents to chordoma?
21. What role, if any, can immune therapy play in the treatment of chordoma?
22. Of the currently tractable drug targets, which play a role in chordoma?
23. Is there currently sufficient rationale to justify any clinical trials? What additional rationale would be needed?
24. By what measures should agents or trials be prioritized?
25. What are the agents that make the most sense to test next?
26. What is an appropriate end point for a trial in chordoma?
27. If a randomized controlled trial were necessary to achieve drug approval, what would be the appropriate control arm?
28. Would a better understanding of the natural history of chordoma aid in designing trials and/or achieving drug approval?

Clinical Management

29. Does neoadjuvant radiation and/or chemotherapy improve clinical outcome?
30. What radiation total dose and dose fractionation are needed in order to treat chordomas? Is hypofractionation biologically advantageous?
31. Can high-dose radiation alone durably control chordoma?
32. What form of radiation is optimal – protons, carbon ions, radiosurgery?
33. Are there valid clinical predictors of which patients can be successfully treated with surgery alone and which require adjuvant radiation?
34. What are the best treatment approaches for locally recurrent disease?
35. What targeted therapies have demonstrated any evidence of efficacy in treating chordoma patients with advanced disease? What targeted therapies are most likely to be effective?