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48th annual meeting organizing committee

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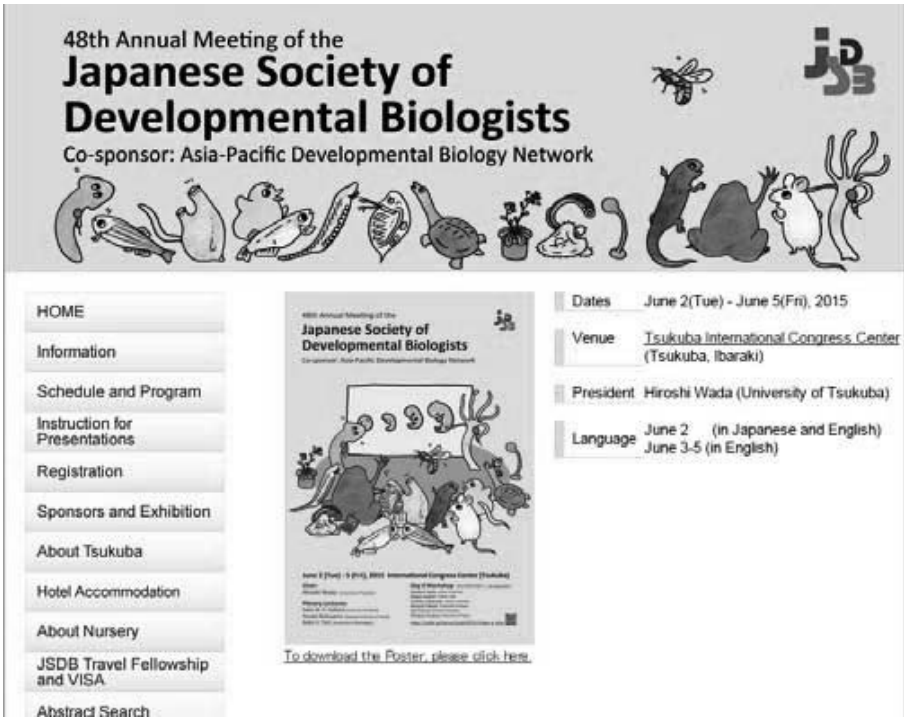

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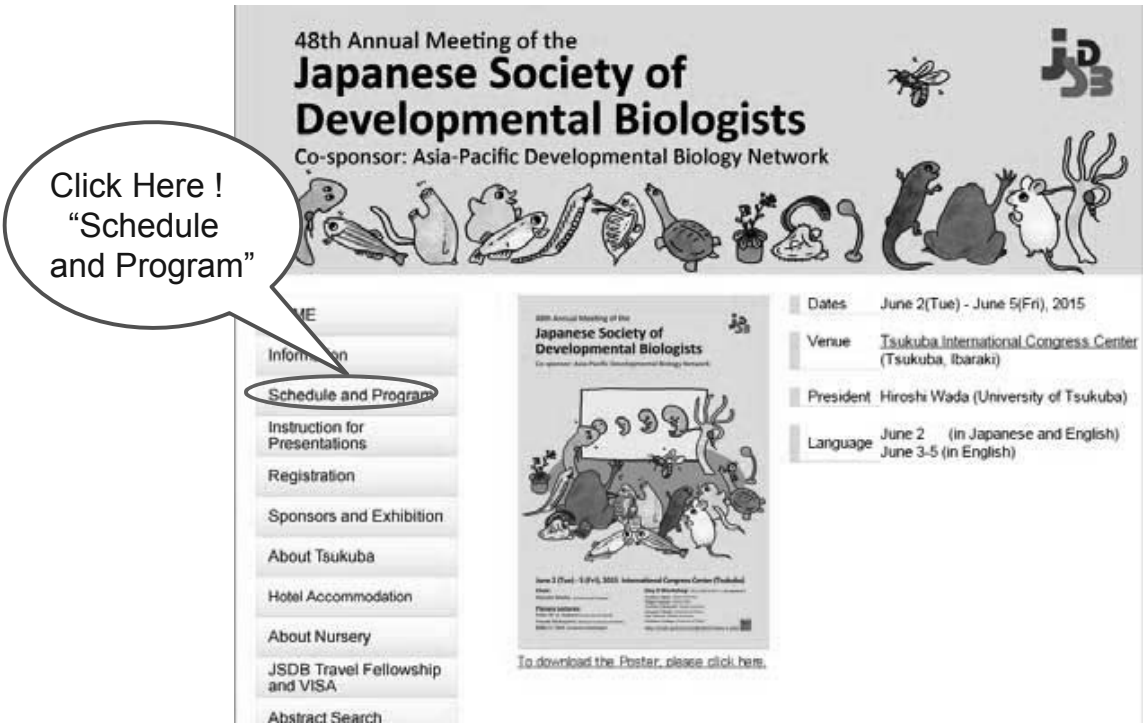

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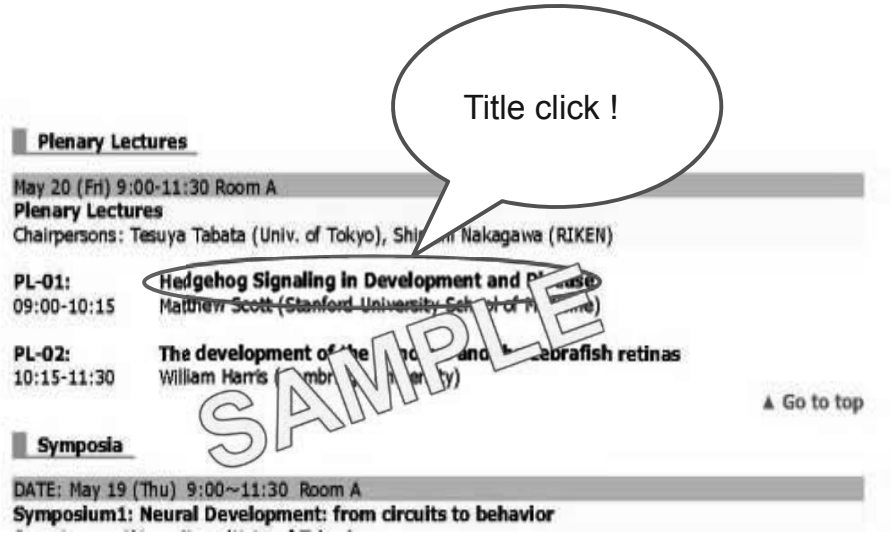

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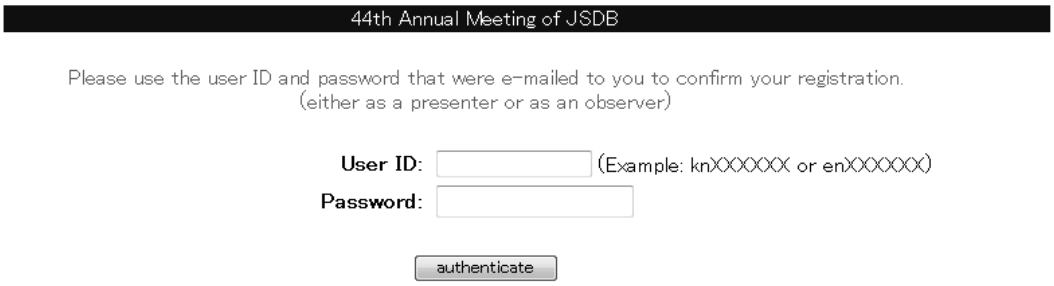

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[PL-01]

Hedgehog Signaling in Development and Disease

*Matthew Scott

(Stanford University School of Medicine)

The development of numerous tissues and organs depends on Hedgehog (Hh) protein signals that influence gene expression in target cells. Defective Hh signaling leads to birth defects and cancer. We are investigating Hh signal transduction and gene regulation mechanisms in the context of cultured fibroblasts and cerebellum development. Reception of the Hh protein signal has many unique features. Primary cilia as a Hh signal transduction organelle. Primary cilia, microtubule-based organelles found on most cells, have been implicated in several signaling pathways. We have observed direct binding of Hh protein to them. We find that the receptor Patched localizes to cilia, where it prevents accumulation of the transmembrane protein Smo. Binding of Hh to Ptc causes departure of both from the cilium, allowing Smo to accumulate there. Smo in the cilium is able to activate Gli transcription factors that control target gene expression. Using tagged proteins, and mutants that affect primary cilia, we are exploring the mechanisms of protein trafficking and target gene activation. We are characterizing direct Hh target genes in responsive cerebellum granule neuron precursors and in the medulloblastoma tumors that arise from the precursors when Ptc function is reduced.

Signaling in development

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