# Regulation of cyclin D1 expression in mouse embryonic stem (ES) cells : the role of the Ras/MAPK and PI3K/Akt pathways

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# Molecular and Genetic Basis of Cell Proliferation

*Gordon Research Conference*

**July 1 - 6, 2001**

**Chair**
Benjamin G. Neel

**Vice Chair**
Jacqueline Lees

**Colby-Sawyer College**
541 Main Street
New London, NH, US
Venue and Travel Information

**Venue**
Office Manager: Ashleigh Wilson
Office Manager Email: ColbySawyer_SM@grc.org
Office Phone: 603-526-3477

## Conference Program

### Sunday July 1, 2001

Evening — **I. Keynote Addresses**

**Elaine Fuchs** (University of Chicago, IL)
*Balancing Proliferation, Differentiation and Development in Skin*

### Monday July 2, 2001

Morning — **II. Signal Transduction I**

*__Tony Pawson__ (Samuel Lunenfeld Institute, Mt Sinai Hospital, Canada)
*Receptors and adaptors in cytoskeletal control*

**Lew Cantley** (Beth Israel-Deaconess Medical Center, MA)
*Signaling via PI 3-kinase*

**Dafna Bar-Sagi** (State University of New York, NY)
*Positive and negative regulation of RTK-Ras signaling*

**Natalie Ahn** (University of Colorado)
*Proteomic analysis of signaling pathways*

Evening — **III. Signal Transduction II**

*__Nick Tonks__ (Cold Spring Harbor Laboratory, NY)

**Jack Dixon** (Univ. Michigan, MI)
*Phosphoryl transfer: a key element of signal transduction*

**Doug Hilton** (Walter and Eliza Hall Institute for Medical Research, Australia)
*SOCS proteins - negative regulators of cytokine signaling*

**Mike Dustin** (New York University School of Medicine, New York, NY)
*The immunological synapse and sustained T cell signaling*

### Tuesday July 3, 2001

Morning — **IV. Transcription**

***Carol Prives** (Columbia University, New York)

**Doug Dean** (Washington University School of Medicine, MO)
*Rb and cell cycle control*

**Michael Karin** (Univ. of California, San Diego and HHMI, CA)
*NF-kB, AP-1 and the Control of Cell Proliferation*

**Erin O'Shea** (Univ. of California, San Francisco Medical School and HHMI, CA)
*Quantitative studies of signal transduction*

Evening — **V. Development**

***Cynthia Kenyon** (Univ. of California, San Francisco Medical School, CA)
*Endocrine regulation of lifespan in the nematode C. elegans*

**Nancy Hopkins** (MIT, Cambridge, MA)
*Insertional mutagenesis identifies genes required for growth and development in zebrafish*

**Morris Birnbaum** (University of Pennsylvania)
*Akt/PKB as regulator of growth and metabolism*

## Conference Links


» Conference History
» Similar Conferences

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| Wednesday July 4, 2001 | |
|---|---|
| Morning | **VI. Cell Cycle/Checkpoints** |
| | *__Angelica Amon__ (Massachusetts Institute of Technology, MA)<br>*Exit from mitosis in budding yeast* |
| | **Greg Hannon** (Cold Spring Harbor Laboratory, NY)<br>*Transformation of normal human cells by E1a* |
| | **Lea Harrington** (Samuel Lunenfeld Institute, Mt Sinai Hospital, Canada)<br>*Telomeres, telomerase, and cell proliferation* |
| | **Mike Tyers** (Amgen Institue, Canada)<br>*Multi-site phosphorylation of a CDK inhibitor sets a threshold for S-phase onset* |
| Evening | **VII. Checkpoints/Cancer** |
| | ***Jackie Lees** (MIT, Cambridge, MA)<br>*The role of the E2F transcription factors in proliferation contro* |
| | **Ron DePinho** (Dana Farber Cancer Institute, MA)<br>*Mechanisms of cellular senescence and crisis in mice and humans* |
| | **Alan D'Andrea** (Dana Farber Cancer Institute, MA)<br>*Convergence of the ATM and Fanconi anemia signaling pathways* |
| | **Thomas Jenuwein** (IMP, Vienna, Austria)<br>*Histone Methylation and chromosome stability during mouse development* |

| Thursday July 5, 2001 | |
|---|---|
| Morning | **VIII. Extracellular Matrix** |
| | *__Benny Geiger__ (Weizmann Institute, Israel)<br>*Mechanochemical regulation of focal adhesion assembly and signaling* |
| | **Rick Assoian** (Univ. of Pennsylvania,PA)<br>*Growth factors, the ECM, ERK and cyclin D1: trying to fit the pieces together* |
| | **David Schlaepfler** (Scripps Institute, CA)<br>*Role of FAK in promoting integrin and growth factor-stimulated cell motility* |
| | **Frank Gertler** (Massachusetts Institute of Technology, MA)<br>*Regulation of cell motility by Ena/VSP proteins* |
| Evening | **IX. Programmed Cell Death** |
| | *__Craig Thompson__ (University of Pennsylvania, PA)<br>*Why do mitochondria play a central role in cell survival and proliferation* |
| | **Sally Kornbluth** (Duke Univerity School of Medicine, NC)<br>*Reconstitution of apoptosis in a cell free system* |
| | **Josef Penninger** (Amgen Institute, Canada)<br>*AIF-identification of a potential second, mitochondrially regulated cell death pathway* |
| | **Gerard Evan** (University of California-San Francisco, CA)<br>*Myc Induced Oncogenesis; The Roles of Proliferation and Angiogenesis* |
| | **Linda Penn** (Ontario Cancer Institute, Canada)<br>*Mechanism of Myc-induced apoptosis* |

*indicates Session Chair

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## Abstract

# Regulation of cylin D1 expression in mouse Embryonic Stem (ES) cells : the role of the Ras/MAPK and PI3K/Akt pathways.

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**Mouse embryonic stem (ES) cells are known to express D-type cyclins at very low levels and these levels increase dramatically during *in vitro* and *in vivo* differentiation. Here, we investigate some of the signalling pathways regulating expression of cyclin D1 and progression to S phase, the Ras/Extracellular signal-regulated protein kinase (ERK) pathway and the phosphatidylinositol 3-kinase (PI3-kinase) pathway. We demonstrate that ERK phosphorylation is fully dispensable for the regulation of cyclin D1 level and for the progression from G1 to S phase in ES cells. By contrast, PI3-kinase activity is required for both. Differentiation induced by retinoic acid results in the gain of ERK-dependent control of cyclin D1 expression and of S phase progression. Differentiation is also paralleled by an increase in PI3-kinase activity. This leads (a) to an increase in the p70 S6 kinase-dependent regulation of the steady-state level of cyclin D1, and (b) to a concomitant decrease in the GSK3$\beta$-dependent rate of cyclin D1 degradation. Altogether, these multiple pathways account for the dramatic increase in the level of cyclin D1 protein which parallels ES cell differentiation. Our studies suggest that PI3-kinase is an important regulator of the ES cell cycle and that its activity is not regulated by mitogen stimulation.**