

**IMCB SCIENTIFIC ADVISORY BOARD SYMPOSIUM  
WEDNESDAY, 22 SEPTEMBER 2010  
VENUE: ASPIRATION THEATRETTE, LEVEL 2M, MATRIX**

<b>SAB Member</b>	<b>Time</b>	<b>Title of Talk</b>
<b>Alexander Schier</b> Harvard University, USA	10:00 am - 10:45 am	From pluripotency to specification: the role of chromatin and morphogens
<b>Cheryll Tickle</b> University of Bath, UK	10:45 am - 11:30 am	The vertebrate limb: a model for pattern formation in embryonic development
<b>Xin Lu</b> Ludwig Institute of Cancer Research, UK	11:30 am - 12:15 pm	ASPP2: a new player of cell polarity
<b>Peter Howley</b> Harvard Medical School, USA	1:30 pm - 2:15 pm	HPV and Cancer: Regulation of Viral Oncogene Expression
<b>Yigong Shi</b> Tsinghua University, China	2:15 pm - 3:00 pm	Mechanisms of Programmed Cell Death through Structural Biology
<b>Arnold Levine</b> Institute for Advanced Study, USA	3:30 pm - 4:15 pm	The Evolution of the p53 Family of Genes: A Structural and Functional Analysis

## Speaker list



SPEAKER: Alexander Schier  
TIME: 10:00 am - 10:45 am  
TITLE: **From pluripotency to specification: the role of chromatin and morphogens**

### **Abstract**

**Alexander Schier**, *Harvard University, Cambridge, Massachusetts, USA*

During early development, embryonic cells transition from genome silencing to genome activation, and from pluripotency to cell fate specification. We wish to understand how chromatin modifications, microRNAs and morphogens regulate these transitions. I will discuss our recent efforts to understand how Nodal signals elicit concentration-dependent effects during embryogenesis and how chromatin modifications change during early development.



SPEAKER: Cheryll Tickle  
TIME: 10:45 am - 11:30 am  
TITLE: **The vertebrate limb: a model for pattern formation in embryonic development**

### **Abstract**

**Cheryll Tickle**, *University of Bath, UK*

The generation of a series of three morphologically distinct digits across the antero-posterior axis of the chick wing is a striking example of pattern formation. Recently, we have refined the model for how signalling by Sonic hedgehog produced by the polarizing region specifies positional values in responding cells in the posterior region of the wing bud by also incorporating the role of Shh in controlling antero-posterior growth. Positional values are subsequently translated into digit identity and the size of the field of responding cells determines digit number. We are currently exploring how this model of paracrine Shh signalling applies to other vertebrate limbs, such as the chick leg which has four digits. In another route to understanding digit pattern formation, we have been studying a chicken mutant, *talpid3*, which has many un-patterned digits. We identified the *talpid3* gene and found that it is a novel gene required for formation of primary cilia which are sites where Shh signalling takes place. We recently made a *talpid3* mutant mouse and, using a conditional approach, we are studying late stages in digit pattern formation and skeletogenesis. One major issue which is still unclear is how positional values are encoded and then translated into digit morphology. We have identified potential candidate genes in the chick wing by various routes and are constructing an atlas of 3D gene expression onto which we can overlay onto 3D fate maps. We are then using computational approaches to identify genes that may be functionally related including genes involved in patterning or growth. One of our aims is to use this computer model of the developing limb to deduce the transcription factor code for positional values that leads to digit pattern formation.

( C.Tickle, M. Towers, F. Bangs, M. Welten, N. Antonio, G. Pavlovska )



**SPEAKER:** Xin Lu  
**TIME:** 11:30 am - 12:15 pm  
**TITLE:** **ASPP2: a new player of cell polarity**

### **Abstract**

**Xin Lu**, *Ludwig Institute for Cancer Research, Oxford, UK*

Cell polarity plays a key role in the development of the central nervous system (CNS). Interestingly, disruption of cell polarity is seen in many cancers. ASPP2 is a haplo-insufficient tumour suppressor and an activator of the p53 family. Here we show that ASPP2 controls the polarity and proliferation of neural progenitors *in vivo*, leading to the formation of neuroblastic rosettes that resemble primitive neuroepithelial tumours. Consistent with its role in cell polarity, ASPP2 influences interkinetic nuclear migration and lamination during CNS development. Mechanistically, ASPP2 maintains the integrity of tight/adherens junctions. It is recruited with Par-3 to cell/cell junctions, and affects their early formation. ASPP2 binds Par-3 and controls its apical/junctional localisation, without affecting its expression or Par-3/aPKC $\lambda$  binding. These results identify ASPP2 as a new regulator of Par-3, which plays a key role in controlling cell proliferation, polarity and tissue organisation during CNS development.



**SPEAKER:** Peter Howley  
**TIME:** 1:30 pm - 2:15 pm  
**TITLE:** **HPV and Cancer: Regulation of Viral Oncogene Expression**

### **Abstract**

**Peter Howley**, *Harvard Medical School, Boston, Massachusetts, USA*

The group of human papillomaviruses that are associated with anogenital and certain upper airway cancers encode two oncoproteins E6 and E7, which are invariably expressed in the HPV positive cancers. The E7 protein functions in cellular transformation, at least in part, through interactions with pRB and its related family of proteins, p107 and p130. E7 also contributes to genomic instability by affecting centrosome duplication. The major target of the E6 is p53; E6 targets the ubiquitylation and degradation of p53 by directing the E6AP ubiquitin ligase to p53. E6 has also been shown to activate the expression of the catalytic subunit of cellular telomerase. Several lines of evidence suggest that E6 and E7 have yet additional targets important to their oncogenic potential and their ability to cause genomic instability.

The viral E6 and E7 oncoproteins are under the control of the viral E2 gene, which is a critical regulatory gene encoded by the papillomaviruses that has roles in viral transcription, DNA replication and genome maintenance in dividing cells. One important function of the E2 protein is its ability to repress the viral LCR promoter that directs expression of the E6 and E7 oncogenes. We have recently conducted a whole genome siRNA screen to identify the cellular genes and pathways involved in E2 mediated transcriptional repression. We have confirmed that Brd4, a major E2 interacting protein, has a role in this repression function and show that there are also Brd4 independent pathways that function in an additive manner with Brd4.

There is a second spliced E2 isoform in which a short amino acid segment of E8 is spliced to the C-terminal DNA binding/dimerization domain of E2. This E8<sup>Δ</sup>E2 protein can also function as a transcriptional repressor but does so in a manner distinct from that of the full length protein. We have conducted proteomic and genetic studies to determine the mechanism by which this second form of E2 functions as a transcriptional repressor.

The identification of specific HPV types in cancer together with the uncovering of the mechanisms by which these cancer-associated types contribute to cancer progression has led to the development of a preventive vaccine for some of the specific HPV types associated with cancer. To date however, there are no specific HPV therapies or therapeutic strategies for HPV infections. Possibilities could include therapeutic vaccines or small molecule drug strategies. Two potential drug targets for the papillomaviruses would be E6 and E2. Interfering with E6 function in cells expressing the viral E6 and E7 oncoproteins could lead to cellular apoptosis. E2 is a critical viral regulatory protein involved in viral transcription, viral DNA replication and viral genome persistence. By exploring the cellular mechanisms by which E2 functions and the cellular molecule through which it mediates its various functions we hope to identify potential targets for small molecule inhibitor/drug development.



**SPEAKER:** Yigong Shi  
**TIME:** 2:15 pm - 3:00 pm  
**TITLE:** **Mechanisms of Programmed Cell Death through Structural Biology**

### **Abstract**

**Yigong Shi**, *Tsinghua University School of Medicine, Beijing, China*

Programmed cell death, also known as apoptosis, is central to the development and homeostasis of metazoans. Dysregulation of apoptosis leads to a variety of human pathologies, including cancer, autoimmune diseases, and neurodegenerative disorders. Since the concept of apoptosis was established in 1972, research efforts have led to the identification of hundreds of genes that govern the initiation, execution, and regulation of apoptosis primarily in three model organisms: *Caenorhabditis elegans*, *Drosophila melanogaster*, and mammals. The central pathway of apoptosis is conserved among the three organisms and involves the activation of cell-killing proteases known as caspases. In this lecture, I describe systematic characterization of the molecular mechanisms of programmed cell death by an integrated approach of structural biochemistry and biophysics.



**SPEAKER:** Arnold Levine  
**TIME:** 3:30 pm - 4:15 pm  
**TITLE:** **The Evolution of the p53 Family of Genes: A Structural and Functional Analysis**

### **Abstract**

**Arnold Levine**, *Institute for Advanced Study, Princeton, New Jersey, USA*

The human genome contains three transcription factors termed p53, p63 and p73 which are related orthologues. The function of the p53 protein is to respond to a wide variety of stresses which can disrupt the fidelity of DNA replication and cell division in somatic cells of the body. These stress signals, such as DNA damage, increase the mutation rate during DNA duplication and so an active p53 protein responds by eliminating clones of cells with mutations by employing apoptosis, senescence or cell cycle arrest. In this way the p53 protein acts as a tumor suppressor preventing the mutations that can lead to cancers. The p63 and p73 proteins act in a similar fashion to protect the germ line cells in females (eggs). In addition the p63 protein plays a central role in the formation of bone and epithelial cell layers and p73 plays a critical role in the formation of several structures in the central nervous system and the immune system.

Based upon amino acid identities and structural considerations some invertebrates have a p53-like gene while others appear to contain a p63/p73 ancestral hybrid gene. The present day representatives of these animals that contain a p63/p73 like ancestor gene (flies and worms) have a protein that functions in the germ cells of animals to enforce the sequence fidelity of DNA after exposure to stresses. The withdrawal of a food source from a worm (glucose starvation) results in the p63/p73 mediated apoptosis of the eggs so that new organisms will not be hatched into a poor environment. Thus this ancestor gene ensures the fidelity of the next generation of organisms.

In vertebrates a clearly distinct new p53 gene arises is in the cartilaginous fish and in the bony fish a separation of the p63 and p73 gene occurs. After that there are very limited evolutionary changes that are found in the p63 gene and only a few changes in the p73 gene DNA binding core. By contrast the p53 gene evolves rapidly and extensively obtaining the new functions of surveillance of DNA replication and cell division after stress in the somatic tissues of the body. This appears to coincide with the enhanced use of the strategy of stem cells to regenerate tissues throughout the life of the organism.

As Caucasians and Asians evolve from their African ancestors polymorphic changes in the p53 gene occur and are rapidly selected for in these populations. This results in the further selection of alleles in genes whose products interact with and regulate the p53 protein. These polymorphisms impact the reproductive fecundity of a population. The p53 protein is required for efficient implantation of a fertilized egg into the uterus of a female and this helps to explain the strong selection pressures upon this gene in Caucasians and Asians. The transcriptional regulation of genes by p63 and p73 play a role in DNA repair and meiosis in the female germ line. Polymorphisms in these genes impact the quality of eggs in older women, and the frequency of recombination in their offspring. This may lead to a higher rate of copy number variations in their offspring as has been observed in children with autism. Thus these genes are not only selected by evolutionary forces but help to set the rate at which evolutionary changes can occur. For those reasons these genes have been preserved over a one billion year history.