**CTO Lecture block 2** **Growth** **Jamie Davies**

**Lecture 1: Introduction to the problems of growth.**
Mature organisms tend to be very much larger than their least mature forms: humans, for example, increase by about 80,000,000x in their 20-year journey from egg to undergraduate. This growth is anisotropic, proportionate and regulated (genetically, environmentally and behaviourally). Organismal growth of the organism emerges not from growth of its smallest constituent parts (molecules etc) but from an increase in their number. Cells can contribute to organism growth by growing larger, by multiplying, or by a combination of the two. Anisotropic growth of tissues is not necessarily reflected in anisotropic growth of their cells. Growth is therefore not as trivial a problem as it looks.

There are limits to cell size: some special tricks can be used to raise these limits to some extent (vacuoles, syncytia) but these bring additional problems for organization. Growth is therefore usually accompanied by cell proliferation. Proliferation does not always imply growth: cleavage divisions occur in the absence of growth and allowed study of the controls of cell division in isolation from growth control. This allowed researchers to identify a progression of cyclins and cdks, each of which 'gates' progression from one phase of the cycle to another.

Coupling division to growth involves alternation of growing ('G') and dividing phases of the cell cycle. The rate of growth is subject to a combination of controls: in order of hierarchy, most-in-charge first; environmental (nutrient), humoral, cell-state and genetic. Most cells are not just responders to humoral controls: they are at the same time sources of them. Generally, growth signals secreted by one cell type are relevant only to others (paracrine signalling): this will be revisited in lecture 3. Sometimes (especially in tumours), autocrine stimulation occurs. Growth of a population of cells does not mean that all cells are involved in proliferation (see later lectures on stem cells).

**Lecture 2: Sources of anisotropy**
Sometimes, anisotropic growth of a tissue emerges directly from anisotropic growth of its constituent cells. This is very common in plants and fungi but uncommon in animals (probably because animals do not have cell walls). Inhomogenous anisotropic expansion alone can account for very complex shapes of leaves and petals, for example (this theme is explored in the practical).

In animals, anisotropic tissue expansion can arise from orientated cell division. Beware: there is a lot of bad science published around this topic, because researchers sometimes mistake correlation for causation and assume that cell-level events must cause tissue-level events rather than the other way round. Hertwig's Rule (cells divide in a direction than minimizes mechanical stress) allows tissue-level events to drive cell-level ones (this is explored in the practicals).

Commonly, anisotropic expansion of animal tissues is driven by planar cell polarity, a sense of direction within the plane of a cell sheet. This is communicated cell-cell by complexes of molecules associated with cell junctions, a 'North' complex on one cell encouraging the formation of a 'South' one to connect to it, so cells pass on their polarity.

Growth that continues in defiance of mechanical constraint is a powerful mechanism of 3-dimensional morphogenesis: it is the mechanism for gut looping, for example.

**Lecture 3: Body size, body shape.**
Body size and shape result from an interplay of genetics and environment. Think of Bonsai trees and full-sized ones (environment), of thin, obese, body-building or pregnant women (environment/ behaviour), of men and women (sexual dimorphism: genetics), of a well-fed Dachshund and a well-fed Great Dane (genetics) etc.

This lecture will concentrate on mammalian body size as seen in a skeleton (soft tissues will be the topic of lecture 4). Mutants fall into two broad classes – Vitruvian and non-Vitruvian. The existence of Vitruvian mutants clearly suggests a global growth controlling system – now known to be Growth Hormone, IGFI, IGFII and their receptors.

Non-Vitruvian mutations demonstrate that different parts of the body use different mechanisms to interpret the global signals. The short limbs of people witth Pycnodysostosis (Toulouse-Lautrec syndrome), for example, have a defect in an enzyme that is more much important in development of long bones of limbs than in the bones of the head and trunk.

Long-bone growth is controlled by a signalling loop that includes a space-dependent component: this provides feedback that makes limbs less sensitive to global growth control the larger they are, making a self-correction negative feedback system that ensures symmetry between left and right sides of the body.

Changes in the sensitivity of different bones to growth signals can (in principle) transform one body plan to another over evolutionary time. This topic will be the focus of some of the exercises in the practical.

**Lecture 4: keeping things in proportion.**
Lecture 3 covered control of size and proportion in the skeleton. It is noticeable that, when a mutation makes a limb bone abnormally short, the limb's soft tissues are proportionate to the bone even though they are not directly affected by the mutation. They must therefore be 'slaves' to the size of the bone. For skin, at least, this seems to be achieved by mechanosensation, a mechanism that has the advantage of being scale-free.

Within tissues, proportion of component parts can be controlled by paracrine mutual dependence. Capillary proliferation, for example, is controlled by [VEGF], and VEGF production by mesenchymal cells is controlled, via the oxygen-sensitive transcription factor Hif-1a, by hypoxia: so is mesenchymal proliferation. A mesenchyme that is growing too fast for its capillary support therefore stops proliferating and signals for more capillary production, proliferation only commencing again when enough capillary growth has happened for normoxia to be restored.

Tissue sizes are also controlled by survival: early development often allows over-production of cells, and survival factors then become limiting so that cell death eliminates excess (the trophic hypothesis). In this way, for example, the motor neuron pool matches the size of limb muscles (the critical experiment was done by subtraction and addition of limbs in chick embryos).

There is an overall theme to much of the above. The size of particular components of the body is determined not by those tissues directly reading some kind of 'instruction' in its genes, but rather by cells exchanging signals (chemical, mechanical) to organize themselves according to the body in which they find themselves. Only a few tissues (eg bone) are affected directly by the alleles of the genome.