C6 Questions: Bench to clinic

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1. Which areas of skin receive the most UVR?
2. How — and why— is ageing related to skin cancer risk?
3. Why might global warming increase skin cancer rates in some populations ?
4. What is meant by sun-sensitive?
5. What are the clinical features of sun-sensitivity?
6. What does the melanocortin-1 receptor (MC1R) control?
7. Why are mutations of some genes recessive at the cellular level, but show a dominant pattern of inheritance in families?
8. Why do patients with the Basal Cell Nevus syndrome present at a young age?
9. Name two reasons that *some* patients with organ transplants have an elevated risk of some skin cancers.
10. Why is the mechanistic relation between some viruses and some skin cancers problematic?

Answers: Sunburn, DNA and cancer

1. Tops of the (bald) head, tops of ears (hair length?), backs of hands, face.
2. As far as we know it is not the changes in any repair capacity with age that are the issue, rather that age is a proxy for cumulative UVR exposure.
3. Temperature is a big determinant of people's behaviour. If the weather is pleasantly warm, people wear fewer clothes and spend more time outside.
4. Sun-sensitive: there is no precise definition, but the term is useful. It refers to people who react to UVR at lower doses than others. It is relative, in the sense that we are comparing one group with another.
5. Sun sensitive: Often these people may have red hair, freckles, and pale skin — and solar damage including dysplastic and malignant lesions.
6. The MC1R controls or influences the ratio of eumelanin to pheomelanin. Homozygous loss of function variants ('mutations') at this locus result in red hair.
7. This is what you might expect, under certain assumptions. If a mutation is recessive, both alleles must be mutated to give a phenotype (show an effect). If you inherit a mutation of one allele in all your cells, a further mutation causes a homozygous loss, and then there is a phenotype at the cellular level. The pattern of people affected in a family is a Mendelian dominant, because inheriting only one mutated allele means only one more change is required to show a phenotype (given that the defect is recessive at the cellular level). This is called the Knudson two-hit hypothesis. (Better explained in the video).
8. This is a consequence of the Knudson two-hit hypothesis. Basal Cell Nevus is a genodermatosis caused by a mutation in a tumour suppressor gene ('*patched*'). One further 'hit' (from UVR damage) leads to a phenotype. In people who do not inherit one mutation, two hits will be required — this will take much longer. Therefore, as with many inherited cancer syndromes, patients present at a young age and possibly with multiple tumours.
9. The fact is that the risk of some skin cancers is greatly increased in this patient group. This — in theory — may be because of a lack of immunosurveillance; virus in-

fection, due to the impaired immune system; or because some drugs such as azathioprine cause DNA damage in the presence of UVR.

10. Because proving causality is hard. Just finding (say) HPV in a skin cancer does not prove the virus caused the cancer. It may be an unrelated symptom of immunosuppression (just as common HPV warts are more common in this patient group). The known oncogenic HPV do not seem to be involved in skin cancer. We *do not* think the common HPV cause skin cancer in this group of patients.