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Applying a new paradigm of epidermal homeostasis to analyse the clonal evolution of cancer

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It has long been held that cells lost from adult epidermis are replaced by the continuous proliferation of self-renewing stem cells (SC), which generate differentiated cells via an intermediate population of short-lived transit amplifying (TA) cells. This hypothesis implies cancer develops in SC, the only cells in which oncogenic mutations may accumulate.

By tracking the fate of a representative sample of proliferating keratinocytes in inducible *cre/lox* mice over a one year time course *in vivo*, we show that epidermal progenitor cells (EPCs) generate clones that continue to expand by symmetric and asymmetric cell division up to one year post labelling, behaviour irreconcilable with the SC/TA cell hypothesis. Quantitative analysis reveals normal epidermis is maintained by a single population of EPC which undergoes self-renewal (SR) and asymmetric division (AD) at rates that ensure epidermal homeostasis. This remarkably simple model successfully predicts clone size after long term retinoid treatment. All cycling EPC have an equal probability of persisting in a tissue and are potential targets of oncogenic mutation.

We have recently generated conditional Gli1 transgenic mice to analyse the effects of oncogene expression in individual EPC in a wild type background by measuring SR, AD and proliferation in mutant clones. We will then test the ability of drugs predicted to alter SR and AD rates to extinguish mutant clones. By combining *in vivo* clonal fate sampling with biophysical analysis we have developed a powerful approach to study both the earliest steps in carcinogenesis and the chemoprevention of cancer.