Reconstituting the blood system is important in a clinical setting but this maybe not be stem cell function in normal setting. How to test this in vivo with no transplantation?

Lineage tracking can be done in vivo... can trace where cells come from and where they go. Called Cre-Lox recombination:
- Site specific recombinase technology, allowing the targeting of a specific sequence of DNA
- Cre recombinase protein catalyses the recombination of DNA between specific sites called loxP sequences. GFP expressed when this occurs.

This won't work for SC lineage tracking, as SC have no specific Cre and no one SC marker.

For SCs need to use transposons which are genetic elements that are movable when transposase is expressed.
- e.g. transposon inserted into embryo into chr 9, so whole mouse has it in chr 9 in every cell.
- When transposase is expressed, the transposon 'hops' out of Chr 9 and into another chr.
- In every individual cell it is in a different location.

Insert individual transposons into all SCs and progenitors of the bone marrow. The transposons will go on to be in almost every cell in the blood system. Wait a few months and then look at all the adult cell types. If the SC model is true, then all cells will be marker with transposon from the SCs. BUT actually shows that all the re-generating blood cells are not from SCs! The progenitors are doing the regeneration, (the progenitors are not self renewing, but come in waves). In normal physiological settings, the SCs are thought to be short lived and lay down big pools of progenitors.

Test this again, but in a transplant setting. Label all cells, but just transplant SCs. The SCs now recapitulate the whole blood system, which it didn't do in normal situations! Transplant just progenitors and the transplant fails!

So the SC definition of regenerating whole blood system is the Transplant definition of a HSC. In normal physiology haematopoiesis SC are doing nothing... the progenitors are the sustaining cells for the rest of your life (although they can't do this in transplants as no self renewal).

This makes sense if you think of cancer... have a much higher risk of cancer the SCs are continuously living in the bone marrow for 90 years compared to inducing progenitors and dying.

Cancer SCs (CSC) - cancer results from the accumulation and concerted action of a number of genetic events in SC or their daughters.

Tumours are heterogeneous... not all cells re-initiate/maintain tumour.

Need to target the original stem cell as can keep self renewing, compared to the daughter cells.