Emerging Technologies – same questions, new toys

simplyblood.org/2016/12/emerging-technologies-same-questions.html

ISEH Headquarters December 15, 2016

One of the most formative moments of my PhD training was an afternoon in my supervisor Professor Connie Eaves' office discussing potential ways to study the direct progeny of single blood stem cells. At this point (~2005), a handful of groups had shown that a single cell could be transplanted into a recipient mouse and durably give rise to all of the mature blood cell types. We were interested in trying to formally demonstrate whether one blood stem cell could create two in vitro, and if so, at what frequency. The question had actually stemmed from a thesis committee meeting that the student above me (Brad Dykstra) had just had where his committee discussed possible ways to get at the question (the value of strong thesis committees cannot be underestimated, and I should note that longstanding ISEH member Kelly McNagny was on both mine and Brad's and was an idea machine!). Anyhow, Connie sat and politely listened to our "really novel" idea and the sort of MacGyver approach that we were planning to use to split the first two progeny of an HSC and assay them separately. At the end of the meeting, she calmly said, "David, you should go and dig up Makio's papers from 1982 and 1983 and have a look through those first". I left Connie's office wondering, "Who is Makio and what could papers written in the first two years of my life possibly have to do with the cutting edge of science?" Well, it turns out that Makio was Professor Makio Ogawa and the work that he published in the early 1980s in hematopoietic colonies were conceptually almost exactly the same as the ones we were pitching in our primitive stem cell populations. For me, this was a real lesson in the value of reading older studies – in particular the discussion sections where scientists aim to communicate why they were trying to answer a question in the first place and what it might mean for future studies. Perhaps the most humbling aspect of the whole experience was that this team of researchers in 1982 would have gladly done the exact same experiment that we were proposing if they'd only had the same tools at their disposal – so much for our "really novel" idea.

In recent years, several new technologies have come online for use in the blood system (e.g., cellular barcoding, lineage tracing, single cell RNA-sequencing, mass cytometry) and these are opening up new opportunities to ask questions that have typically been relegated to more speculative sections of research papers and reviews. As an example, monitoring steady-state hematopoiesis by lineage tracing (e.g., Busch et alhas shown us that traditional transplantation-based assays have vastly underestimated the length of blood cell production of multi-lineage progenitor cell populations. The next technological breakthrough in this area is just around the corner – using endogenous genetic barcode-like sequences to track clones – and has already been predicted in the final sentence from an excellent 2012 review by past-ISEH president Gerald de Haan: "Future experiments are likely to exploit induced or

naturally occurring barcode-like sequence variations to improve our understanding of clonal dynamics of multicellular systems” In our lab’s recent work, we took an old technology (flow-cytometric index-sorting) and coupled it with new developments in single cell RNA-sequencing and computational biology to link cell function with molecular profiles. A not-so-bold prediction would be that future studies will be undertaken in other tissues where single cell functional assays are being developed or that more single cell measurements (e.g., protein expression, cell cycle status) will be recorded in index-sorted hematopoietic stem cells – we simply need to develop the tools and the questions are already there to be answered. Overall, I guess I’m making a case for thinking more deeply about the types of questions that have not yet been answered simply because of technological barriers and taking on the challenge. Find old papers and read them – where would the experiments go next? what did the authors wish they could do but was not possible at this time? Just because it isn’t online doesn’t mean that it isn’t valuable. We should regularly scour the literature from our field to dig up the “oldies” to understand and build on the thinking that has already been done. In my lab’s journal club, we pick a recent paper to discuss and then I tack on an old paper that is a precursor to the study because the reality is that all studies build on the solid foundations of other people’s work. The other, sadder reality is that many researchers do not spend nearly enough time reading or considering the history of their own field before undertaking their studies or writing their papers. However, I hope this will change with efforts such as ISEH’s where the goal is to build easy-to-access resources (like the webinarsand Hematology 101) for educating its membership.

"That men do not learn very much from the lessons of history is the most important of all the lessons of history."
~Aldous Huxley

David Kent, PhD
Former ISEH Publications Committee Member
Group Leader
Cambridge Stem Cell Institute
Cambridge, UK