form a new C–C bond. The second radical adds to a nickel complex to form the carbon–nickel bond of an organonickel compound. And the third radical reacts with the carbon–nickel bond of the organonickel compound to form another C–C bond, thereby generating the final product.

So how do the reactivities of the radicals govern their roles in the reaction? The first radical is different from the others in that it is electrophilic – which means that it selectively adds to the electron-rich alkene to form a new bond.

The second and third radicals are not electrophilic, but they are different sizes: the second radical is not bulky, which enables it to react readily with the nickel complex.

The third radical is produced from the reaction of the first radical with the alkene. However, the alkene is chosen to ensure that the third radical is bulky. Because of its bulk, this radical does not attack the original nickel complex, but is well suited to attacking the carbon–nickel bond formed when the second radical reacts with that complex.

Overall, the triple radical sorting reported by Wang *et al.* enables reactions in which a variety of alkyl halides and primary alcohols – the precursors of the first and second radical types, respectively – can be reacted with a range of alkenes. This breakthrough makes it easy to design huge numbers of products, each of which can now be synthesized in a single operation. About 270,000 primary alcohols, 29,000 suitable alkyl chlorides and 269,000 alkenes are commercially available, which means that about 2×10^{15} compounds could be made in this way. The chemistry might be useful for selective synthesis of individual target molecules or for creating libraries of compounds for screening in drug-discovery programmes.

Radical sorting is still in its infancy, and there are great opportunities to enhance this approach to incorporate a wider range of radicals. In the future, the sorting systems might also extend beyond reactions of alkenes. The solution Wang and colleagues describe for enabling ordered reactions of three radicals that would previously have been considered incompatible blazes the trail.

Kenneth F. Clark is in the Department of Early Chemical Development, Pharmaceutical Sciences, R&D, AstraZeneca, Macclesfield, SK10 2NA, UK. **John A. Murphy** is in the Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, UK.
e-mails: kenny.clark@astrazeneca.com; john.murphy@strath.ac.uk

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Ageing

Anti-ageing antibodies revive the immune system

Yasar Arfat T. Kasu & Robert A. J. Signer

Depleting an expanding pool of aberrant stem cells in aged mice using antibody therapy has been shown to rebalance blood cell production, diminish age-associated inflammation and strengthen acquired immune responses. **See p.162**

Ageing is a major risk factor for most chronic diseases. As the global population continues to age, interventions that mitigate effects of ageing could profoundly affect wellness, the economy and society at large by extending human healthspan. Many age-associated diseases and declines in tissue function are associated with alterations in the fitness and function of stem cells, including those in the blood[1]. On page 162, Ross *et al.*[2] report that an antibody-based therapy that depletes aberrant stem cells can rejuvenate the immune system in aged mice by rebalancing the production of blood cells.

Haematopoietic stem cells (HSCs) regenerate blood cells throughout life. Most HSCs in young individuals have the potential to differentiate into blood cells of any lineage (balanced HSCs), but some subsets of HSCs exhibit lineage-biased differentiation[3,4]. With age, there is a substantial increase in the proportion of HSCs that are biased towards generating myeloid lineage cells[5–7] – which include red blood cells, platelets and cells of the innate immune system, such as monocytes, macrophages and neutrophils. In older people, increased production of myeloid cells is linked to compromised adaptive (acquired) immunity, chronic inflammation and a higher incidence of a group of blood cancers called myeloproliferative neoplasms. Interventions that restore 'youthful' HSC function could thus have an outsized impact on enhancing immunity, reducing the incidence and severity of chronic inflammatory diseases and preventing blood disorders.

Several changes – both cell-intrinsic and cell-extrinsic – have been reported to contribute to the preferential expansion in the number of myeloid-biased HSCs during ageing[8]. Yet the underlying mechanisms remain incompletely understood, which has hampered efforts to effectively rejuvenate and rebalance the aged HSC pool. To overcome this roadblock, Ross *et al.* sought to use an antibody-mediated therapy to target and deplete myeloid-biased HSCs in old mice, thereby enabling residual youthful HSCs to boost adaptive immune responses and attenuate systemic inflammation by rebalancing blood cell production (Fig. 1).

The authors took advantage of a key feature of myeloid-biased HSCs: a set of proteins expressed on their cell surface that makes them distinct from balanced HSCs[9]. By mining transcriptional data sets, the authors identified three cell-surface proteins that could perhaps be used to identify, isolate and target myeloid-biased HSCs in aged mice, and potentially in humans, with minimal off-target effects.

Building on their extensive expertise with antibody-based therapeutics, Ross and colleagues established an antibody conditioning protocol in which aged mice were treated with antibodies that targeted the cell-surface proteins that the authors had identified. Using a technique called flow cytometry, they confirmed that antibody conditioning preferentially depleted myeloid-biased HSCs, and that balanced HSCs were mostly spared. They further validated these findings by analysing the gene-expression profiles of HSCs after treatment, and found that 'old' myeloid-biased HSC gene signatures had declined and that

'young' balanced HSC gene signatures had been retained.

The depletion of myeloid-biased HSCs *in vivo* raised a key question: could residual HSCs in old adult mice restore youthful, balanced blood production in a lasting way, or would lingering cell-intrinsic defects, along with extrinsic alterations in the ageing tissue microenvironment, prevent rejuvenation? Strikingly, the authors found that a single course of antibody conditioning was durable: the relative number of myeloid-biased HSCs remained depressed for at least two months after treatment.

Furthermore, aged mice that underwent antibody conditioning accumulated lymphoid progenitor cells, which can give rise to cells of the adaptive immune system (T cells and B cells), for at least four months after treatment. These animals also had an elevated number of naive T cells and mature B cells, both of which are capable of mounting immune responses to new antigens. This drove a subsequent reduction in the relative abundance of cells linked to age-related immune decline, known as exhausted T cells and age-associated B cells. This result was surprising in view of a previous study in which myeloid-biased HSCs were depleted by eradicating inflammatory plasma cells (antibody-producing B cells); this was found to reduce myeloid-cell production, but it did not promote the recovery of lymphoid-cell production[10].

The increased production of B and T cells that followed antibody conditioning in the current study raised an exciting possibility: could depletion of myeloid-biased HSCs boost adaptive immune function in older adults? Older individuals are typically more susceptible to severe infection and less responsive to vaccines than are younger people. Ross *et al.* demonstrated that, compared with untreated aged mice, those that underwent antibody conditioning generated more virus-specific T cells following vaccination, and were more capable of robustly fighting off a subsequent viral infection.

Although depletion of myeloid-biased HSCs was not sufficient to fully rejuvenate adaptive immune responses, the results clearly demonstrate that disruptions in the determination of stem cell fate and normal haematopoietic differentiation can contribute to immune dysfunction in older adults. Declines in adaptive immunity are also driven by intrinsic age-related defects in lymphoid progenitors and by the declining function of mature B cells and T cells in peripheral immune organs. Even so, Ross and colleagues' study raises the possibility that targeting myeloid-biased HSCs could improve immunity in older people, which could reduce infection-related morbidity and mortality. In addition to partially rebalancing blood cell production and restoring adaptive immunity, depleting myeloid-biased HSCs in aged mice reduced the abundance of several inflammation-mediating molecules that circulate in the blood. Therefore, this approach has the potential to attenuate 'inflammageing' and reduce the incidence and severity of diverse age-related inflammatory diseases.

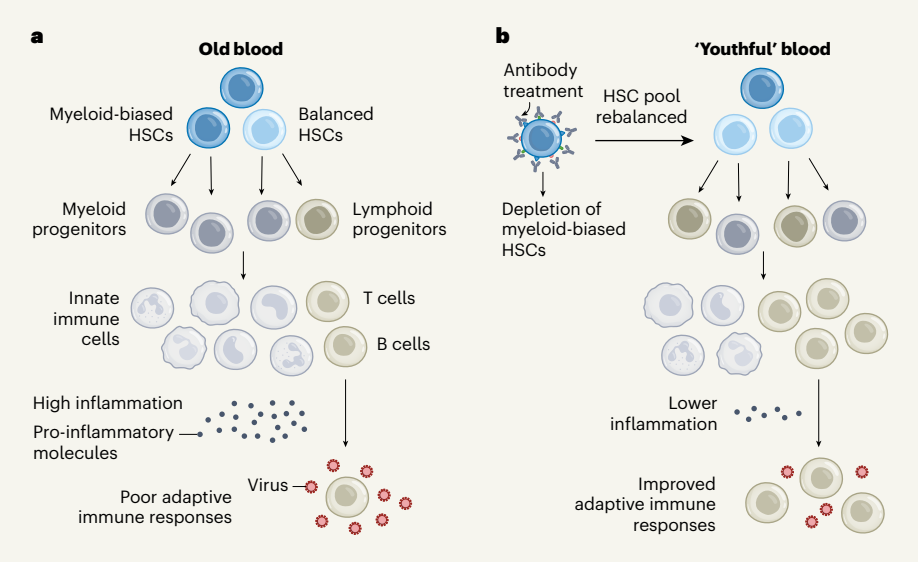

Figure 1 | Depleting biased stem cells rejuvenates blood in aged mice. **a**, Ageing in blood is characterized by an expansion in the number of myeloid-biased haematopoietic stem cells (HSCs), which preferentially produce myeloid progenitor cells that give rise to cells of the innate immune system. This happens at the expense of the production of lymphoid progenitor cells, which give rise to cells of the adaptive immune system (T cells and B cells) and originate from balanced HSCs, which do not preferentially produce a particular lineage. The imbalanced blood cell production results in poor adaptive immune responses to infection and high levels of inflammation caused by an increase in the production of pro-inflammatory molecules. **b**, Ross *et al.*[2] designed a therapeutic strategy to revitalize the aged immune system. Aged mice were treated with antibodies that target proteins preferentially expressed on the surface of myeloid-biased HSCs, thereby depleting these cells and sparing balanced HSCs. Residual HSCs rebalance the production of myeloid- and lymphoid-lineage cells, which attenuates inflammation and increases the abundance of naive T and mature B cells. This improves responsiveness to vaccination and control of viral infection — returning the blood to a 'youthful' state.

Ageing is associated with an increased prevalence of a condition called clonal haematopoiesis, in which a subpopulation of HSCs with the same genetic mutation expands and, in some cases, dominates the pool of HSCs; this, in turn, can increase the risk of developing blood cancer and cardiovascular disease. Ross *et al.* contend that targeted depletion of myeloid-biased HSCs could preferentially eradicate these dominant or pre-cancerous HSC clones. However, antibody conditioning could, in fact, exacerbate the emergence of clonal haematopoiesis by narrowing the total repertoire of HSCs. Depletion of myeloid-biased HSCs could force a compensatory expansion of the remaining HSC pool and confer a selective pressure on residual HSCs harbouring advantageous mutations; ultimately, this could accelerate clonal dominance and progression to cancer.

Although a reduction in the production of lymphoid cells (lymphopoiesis) probably contributes to impaired adaptive immunity in older individuals, previous studies have shown that this reduction could come with the benefit of tumour suppression[11]. Lymphoid leukaemias are the most common form of cancer in children, and age-related activation of tumour-suppressor genes in lymphoid progenitors helps to prevent these cells from becoming cancerous in adulthood, but this occurs at the expense of maintaining robust lymphopoiesis[11]. Boosting lymphopoiesis in older adults could therefore raise the risk of their developing lymphoid cancers. However, the burden of an increased risk of lymphoid leukaemia could be offset by the greater protection from infection, and the reduced risk of other cancers, that would be afforded by enhanced immune surveillance.

Eliminating the underlying drivers of ageing is central to preventing several age-related diseases. Advances with a class of drugs called senolytics, which broadly target senescent cells in tissues, have so far been at the forefront of this effort. Ross and colleagues now demonstrate that specifically targeting aberrant, lineage-biased HSCs is an exciting approach that could revitalize the immune system and alleviate some of the detrimental effects of ageing.

Yasar Arfat T. Kasu and **Robert A. J. Signer** are in the Division of Regenerative Medicine,

Department of Medicine, Stem Cell Discovery Center, Sanford Stem Cell Institute, Moores Cancer Center, University of California, San Diego, La Jolla, California 92093, USA.
e-mail: rsigner@health.ucsd.edu

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Machine learning

Can lessons from infants solve the problems of AI?

Linda B. Smith

Words and images experienced by an infant wearing sensors during their daily life have led to efficient machine learning, pointing to the power of multimodal training signals and to the potentially exploitable statistics of real-life experience.

Current advances in artificial intelligence (AI) seem to be transforming science into science fiction, as large-data machine-learning models approach and, in some ways, surpass human abilities. But such models are trained on vast amounts of data. Writing in *Science*, Vong *et al.*[1] have thrown down a challenge on behalf of humans by using 61 hours of one infant's real-life experiences to demonstrate the efficiency of a multimodal learning model.

The training data were captured by a head-mounted camera as multiple brief samples between the ages of 6 months and 25 months. This is the period of rapid vocabulary expansion at the start of language learning. Video clips from the head camera and transcripts of adults speaking to the infant were fed to the authors' model, which used a 'contrastive' approach for both visual and language learning.

Contrastive learning is a widely used method in machine learning[2]. It involves feeding pairs of training examples into an algorithm with a label indicating the similarity of the two examples. Evidence that two items are in the same category changes the model parameters to make those items more similar in the learnt representational space of all pairings. Evidence to the contrary changes the model parameters that define the space to push items apart.

Vong and colleagues' model integrated contrastive representational learning with associative learning — that is, the learnt links between the utterances and the images. It did so by using the learnt representations in one modality as the teaching signal (for increasing or decreasing the similarity of the pairs) for the other modality. In this way, learning was self-supervised because of the co-occurrence of text and images. This is a form of the bi-directional exchange of learning signals across different neural systems (such as the visual and language-processing parts of the brain) that was first introduced by Nobel laureate Gerald Edelman[3] and called re-entrance.

Re-entrant signals are a potentially powerful form of self-supervised learning because the teaching signals from one neural system change as a function of learning driven by the other system (Fig. 1). Multimodal models with re-entrance learn rapidly as a consequence of the simultaneous coordination of different representational components, as is demonstrated by Vong and co-workers' model.

The everyday experiences of infants are challenging for any learning algorithm to use successfully. Objects and co-occurring words are well known to produce noisy data, leading to many spurious pairings[4]. Moreover, the presence of object names in language heard by children is remarkably sparse. For example, the word 'basket' (which is comprehended by a child before the age of 25 months) occurs just 8 times in a 6-million-word corpus[5] of language that parents use when talking to children. Nonetheless, young children learn object names and immediately generalize those names to never-seen-before instances. The authors' model, which was trained with child-egocentric data, did the same. The re-entrance in the model provides a potential theoretical path for explaining infants' rapid learning and generalization.

Vong *et al.* characterize their contribution as a demonstration that object names and visual categories can be learnt from a small amount

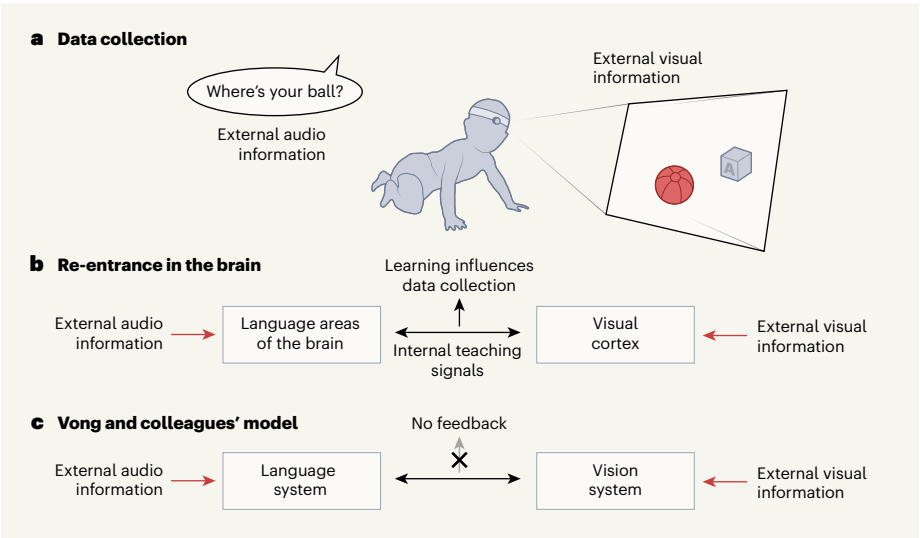

Figure 1 | Self-supervised learning. a, Vong *et al.*[1] used audio and video recordings from the daily life of an infant wearing a sensor to train an artificial-intelligence model to learn language. The co-occurrence of images and words made the training process 'self-supervised', meaning that it required only internal teaching signals. **b**, This is reminiscent of re-entrance[3], which is the continuous exchange of teaching signals between different neural systems, such as the visual system and the areas of the brain in which language develops. Re-entrance allows the brain to collect data that are relevant to its current learning state by actively selecting and creating sensory events. **c**, The authors' model does not include this feedback, but the data used by their model might still reflect some properties of infant-generated-data structures that benefited the model's ability to learn.