and inflammation from that which is essential for memory? And how are these mechanisms disrupted in the context of ageing and neurodegenerative disorders? Do these mechanisms contribute to the cognitive deficits that accompany many neurodevelopmental disorders?

Much effort will be required to answer these questions. It could be that, just as Dalí used his signature surrealist style to depict both memory and its instability, the molecular mechanisms uncovered by Jovasevic *et al.* might underpin both the persistence and disintegration of memories.

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Organic chemistry

Wild beasts of the chemical landscape tamed

Kenneth F. Clark & John A. Murphy

The idea that three different free radicals could be used together to carry out specific steps in a chemical reaction has long been implausible. A 'radical sorting' strategy now achieves this feat to make organic molecules. **See p.104**

The formation of carbon–carbon bonds is at the heart of the chemistry used to synthesize pharmaceuticals, agrochemicals and advanced materials. Chemists' skills in harnessing highly reactive free radicals for this purpose have grown steadily. On page 104, Wang *et al.*[1] describe the ordered construction of molecules using reactions in which three types of radical are present simultaneously, but have distinct roles – a remarkable level of control for such highly reactive chemical species. The secret to success lies in an emerging strategy for organic chemistry, known as radical sorting.

Chemical bonds result from the pairing of two electrons. One way to form new bonds is to start with molecules, called radicals, that have an unpaired electron. Radicals form a new bond by pairing their single electron with an electron that is already paired up in another bond, thereby breaking up the other bond's pairing.

The high reactivity of radicals means that they are usually extremely short-lived and not easy to control – indeed, for many decades, controlling the chemistry of these 'wild beasts' of the chemistry landscape was viewed as a daunting task. However, over the past 50 years, the reactivities of radicals have been studied intensively, so that researchers now understand more than ever about the chemistry of these compounds[2]. The most important radicals for synthesis are those in which the unpaired electron is associated with a carbon atom. These radicals can form bonds to other carbon atoms, or to other elements, to build the organic structures of high-value materials such as pharmaceuticals.

Knowledge of the reactivities of radicals has enabled radical sorting: different radicals can be carefully chosen so that, when generated in the same reaction vessel, each one preferentially and selectively undergoes only one type of chemistry[3–8]. This has opened up opportunities for chemists to use combinations of radicals, so that each type of radical has a specific step in a reaction pathway. For example, some nickel(II) complexes undergo selective reactions with certain types of carbon radical to form carbon–nickel bonds; and the resulting nickel(III) complexes can then undergo selective reactions[9] with a different type of carbon radical to form carbon–carbon (C–C) bonds (similar reactions of radicals with bonds to metal atoms have also been reported[10–15]). Overall, this allows the selective synthesis of products.

So far, radical sorting has focused on selective reactions involving just two types of radical. Wang *et al.* now report a reaction sequence in which three types of carbon radical are generated (Fig. 1). All three are active simultaneously in the reaction mixture, and yet each one attends only to its own task. The first radical adds to an alkene (a molecule that contains a carbon–carbon double bond) to

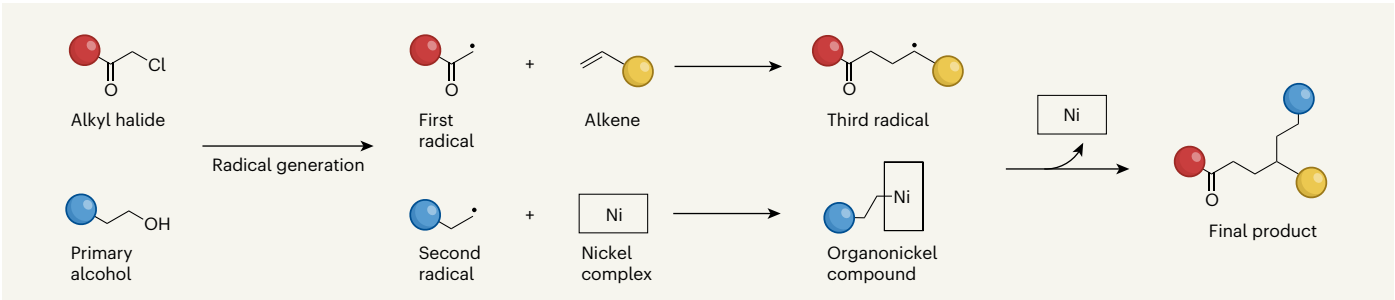

Figure 1 | Molecular construction using three radicals. Wang *et al.*[1] report a reaction in which three radicals selectively perform different tasks. The first and second radicals are generated from precursor compounds (alkyl halides and primary alcohols, respectively; dots on the radical structures indicate the characteristic unpaired electron of a radical). The third radical is formed from the reaction of the first radical with an alkene. The second radical reacts with a nickel complex, forming an organonickel compound. This reacts with the third radical, yielding the final product. The reaction pathway depends on the distinct reactivities of the radicals: the first is electrophilic and therefore reacts with the electron-rich alkene. The second and third radicals are not electrophilic. Because the second radical is not bulky, it reacts preferentially with the nickel complex. By contrast, the third radical is bulky and therefore reacts with the organonickel compound. Spheres represent any chemical group; ligand molecules in the nickel complex are represented by a rectangle.

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.

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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