low because most people have the same low level of educational attainment. As access to schooling expands, inequality as measured by the AID rises because the population now contains many people who have no education and many who have several years of schooling. As school enrolment becomes universal and members of the population begin to achieve similarly high levels of education, the AID declines again. From this metric, Friedman and colleagues conclude that global educational inequality peaked in 2017 and is projected to decline until 2030.

Even though this project involves an impressive volume of data, it is still limited by problems of data scarcity. Whereas some high-income countries, such as France and Germany, contribute more than 55 data points to the model, the time series for many resource-constrained and small-population countries or territories are extrapolated from fewer than 5 data points, or rely on data last collected in or before 2008. Although the validity of the model was evaluated by checking how well its predictions matched real data across many simulations in which one subset of data had been removed, there is no way of assessing how well it estimates attainment trajectories for places such as Malaysia, for which no data were available after 2003. The authors leverage regional trends to inform analyses of countries or territories for which data are scarce, but the results should be interpreted with caution.

The smoothed trajectories of predicted change in the study also hide the profound and often sudden impact of education policies on schooling. The authors note nonlinearities in the rates of change consistent with a sudden increase in schooling, which might result from the elimination of school fees or an increase in the years of compulsory schooling. The recent expansion of free secondary education in many lower-income countries has the potential to further advance progress towards the SDG education goals, beyond what is currently predicted by Friedman and colleagues' model.

Ultimately, we can monitor only what we can measure: we track trends in educational attainment and in gaps between the sexes because those are the data that exist. Socio-economic gaps in schooling are now substantially larger than are gender gaps in most world regions[7], but sufficient data on the socio-economic status of students are scarce. Likewise, almost three-quarters of countries have inadequate data with which to monitor progress in learning outcomes (such as mathematics or reading skills), rather than merely in years of schooling (see go.nature.com/39kd4o1). Global commitments to inclusive and equitable quality education run the risk of failing to achieve their true goals when we lack the data to properly track progress.

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Organic chemistry

Methyl groups make a late entrance

Emily B. Corcoran & Danielle M. Schultz

The addition of a methyl group to a drug molecule can greatly alter the drug's pharmacological properties. A catalyst has been developed that enables this 'magic methyl effect' to be rapidly explored for drug discovery. **See p.621**

Developing a small-molecule drug requires iterations of building and testing new compounds to find one that strikes the right balance of pharmacological properties. The process typically takes more than 10 years and costs billions of dollars, because, for every 5,000 compounds made and tested, only one will become an approved drug[1,2]. Indeed, a high-school basketball player is twice as likely to end up playing in the US professional league as any single compound tested in a drug-discovery programme is to become a marketed drug (see go.nature.com/2v8pnfm). One approach to accelerating drug discovery is late-stage functionalization, in which previously prepared test compounds are decorated with new atoms in the hope of favourably adjusting their pharmacological properties. On page 621, Feng *et al.*[3] report an outstanding advance towards this long-standing and historically challenging strategy.

> **"This work is a superb example of a symbiotic collaboration between academia and the pharmaceutical industry."**

Introducing just one cluster of atoms (a functional group) into a drug molecule can drastically alter the molecule's properties. For instance, adding a methyl group (CH_3, one of the smallest functional groups) can enhance a compound's binding affinity for its biological target more than 1,000-fold, a phenomenon termed[4] the 'magic methyl effect'. This is because the installation of a methyl group alters the shape of the molecule such that it can readily nestle inside a targeted protein's active site, akin to how an ergonomic computer mouse fits snugly in the palm of your hand.

However, making even small adjustments to molecules is frequently a major undertaking, one that effectively requires chemists to break apart the entire structure and reassemble a dozen or more smaller pieces for each change. Imagine how much time and money it would cost if adding a new window to your home required the entire house to be taken apart and rebuilt from scratch. Chemists working in drug discovery regularly have to do this with their molecules.

Late-stage functionalization has therefore emerged as a desirable approach to accelerate drug discovery[5,6]: much as a construction crew saws through existing walls to insert new windows, chemists aspire to cut through existing chemical bonds to insert new functional groups into molecules. C–H functionalization, a type of reaction that converts ubiquitous carbon–hydrogen (C–H) bonds in complex molecules into alternative functional groups, has garnered much attention for this purpose. Feng *et al.* report a substantial advance in this area with the design of a metal catalyst that cuts through specific C–H bonds to insert methyl groups, thus allowing the magic methyl effect to be explored in myriad complex and drug-like compounds.

Selective late-stage C–H functionalization is constantly used in nature. For example, iron-based metalloenzymes known as cytochrome P450s (CYP450s) are omnipresent throughout the animal kingdom because of their crucial role in regulating metabolism[7,8].

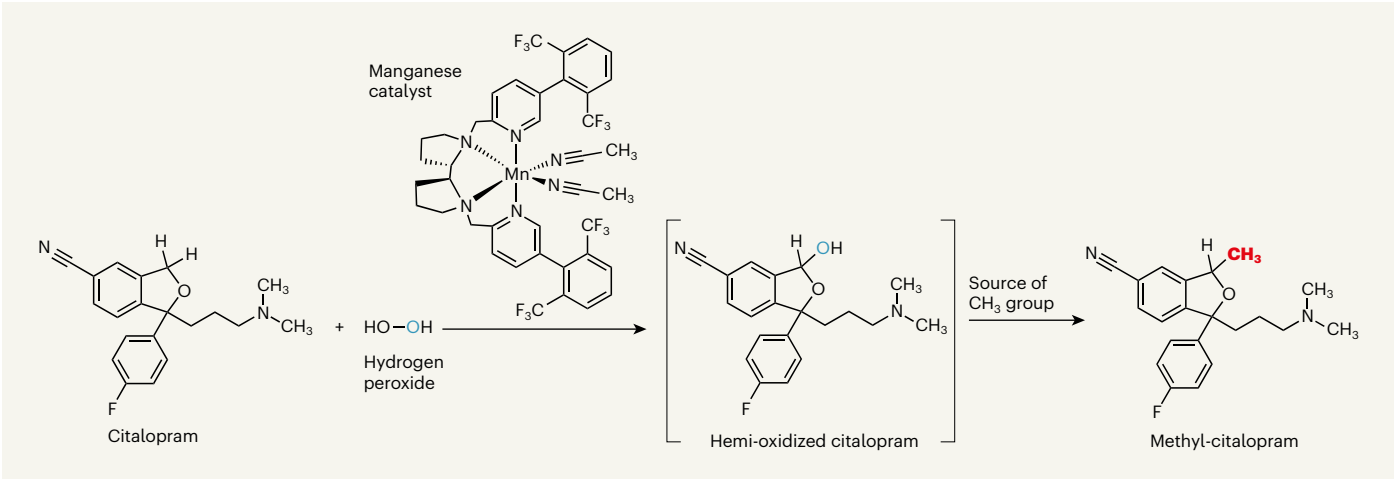

Figure 1 | Late-stage methylation of biologically relevant targets. Feng *et al.*[3] report that a highly tuned manganese (Mn) catalyst enables methyl (CH_3) groups to be incorporated at specific sites into complex molecules, particularly those that have structures typical of drugs. The manganese catalyst inserts an oxygen atom from hydrogen peroxide into the carbon–hydrogen bond that the human body can most easily metabolize, yielding a reactive hemi-oxidized intermediate (square brackets indicate that the intermediate is formed *in situ* and is not isolated) that is poised for reaction with a methyl-group source. The reaction was used successfully on 38 biologically active molecules, including the antidepressant citalopram. It could therefore be used to rapidly explore the magic methyl effect — a phenomenon in which the addition of a methyl group to a drug molecule greatly enhances the molecule's pharmacological properties.

The iron atom of a CYP450 binds to biologically active molecules and triggers their metabolism by inserting oxygen into C–H bonds to form double carbon–oxygen (C=O) bonds, a type of C–H functionalization. The elaborate enzyme architecture around the iron centre tames the metal's otherwise rampant catalytic activity, thus allowing these reactions to proceed precisely and specifically, such that only those substrates that fit in the enzyme's pocket are oxidized.

Feng and colleagues are part of a research group that has long been interested in making ligand molecules that mimic the CYP450-enzyme architecture, in the hope of broadening the ability of iron complexes to transform C–H bonds into C=O bonds in diverse substrates, using hydrogen peroxide as the source of oxygen[9]. Scientists from that group had previously made great strides in taming the reactivity of iron complexes for C–H functionalization, but even the best catalysts proved promiscuous (they reacted at many different C–H bonds, rather than at just one) and could not be used in the presence of many functional groups commonly found in drug-like molecules. The same research group had therefore also investigated manganese — iron's less-oxidizing neighbour in the periodic table — as an alternative metal centre for catalysts that oxidize specific C–H bonds in complex molecules[10].

Feng *et al.* hypothesized that a less-oxidizing manganese catalyst would target the C–H bonds that are most easily metabolized on drug-like molecules. Moreover, they thought that the oxidation reaction could be halted midway to produce a hemi-oxidized intermediate, into which a methyl group could be inserted (Fig. 1). This group would essentially block the molecule's metabolic degradation, invoking the magic methyl effect.

The challenge with this approach is that the hemi-oxidized intermediate is more readily oxidized than is the starting material — so, if the oxidation reaction were a train, it would be a non-stop service to a C=O bond. To circumvent this complication, Feng *et al.* tuned the reaction conditions to contain the precise amount of catalyst and hydrogen peroxide needed to deliver the hemi-oxidized intermediate, effectively pulling the train into a station en route to the C=O terminus. The resulting hemi-oxidized species can then be seamlessly transformed into a methyl group under a variety of conditions, depending on the functional groups present in the rest of the molecule.

Feng and colleagues' work is a superb example of a symbiotic collaboration between academia and the pharmaceutical industry, with cutting-edge chemistry being used to solve real-world problems. The industrial influence is evident throughout the work: the molecules selected to demonstrate this methodology accurately reflect the types frequently encountered in drug development. More specifically, the authors report that 38 biologically relevant targets (drugs, natural products, peptides and steroids) and their building blocks undergo the new reactions with excellent selectivity and functional-group tolerance.

For more than a century, drug discovery focused mainly on small molecules. However, the field is now turning to more-elaborate molecules, such as peptides, which can potentially target complex biological targets with high specificity. Peptides are usually stitched together from amino acids in a linear sequence of reactions. The functional groups that provide the structural diversity of peptides are built into the amino acids, and are therefore introduced at each step of the sequence. Some of the groups in a target peptide are inevitably installed in the first step, and can be changed only by running the whole sequence again, but using a different amino acid at the start.

Feng *et al.* upend this norm by demonstrating that methyl groups can be installed on a tetrapeptide (a peptide built from four amino acids) at the end of the synthetic sequence. Further extension of this chemistry to more-complex linear and macrocyclic (ring-forming) peptides would be game-changing for drug discovery. Continued breakthroughs on complex catalytic processes in the spirit of Feng and colleagues' work might finally enable medicinal chemistry to cruise at the same speed as biological research.

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