Current Developments in Fluorescent PET (Photoinduced Electron Transfer) Sensors and Switches


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Following a brief introduction to the principle of fluorescent PET (photoinduced electron transfer) sensors and switches, the outputs of laboratories in various countries from the past year or two are categorized and critically discussed. Emphasis is placed on the molecular design and the experimental outcomes in terms of target-induced fluorescence enhancements and input/output wavelengths. The handling of single targets takes up a major fraction of the review, but the extension to multiple targets is also illustrated. Conceptually new channels of investigation are opened up by the latter approach, e.g. ‘lab-on-a-molecule’ systems and molecular keypad locks. The growing trends of theoretically-fortified design and intracellular application are pointed out.

Key learning points:

1. Being miniature, molecular sensors can open a window into the small worlds which are common in living things.
2. Photoinduced electron transfer (PET) is an engineering-style design principle with quantitative features and a proven predictive ability, once basic photo- and electro-chemical parameters are provided.
3. Fluorescent sensors are a particularly useful category of switchable molecular devices.
4. Molecular logic-based computation arose from fluorescent sensors research and is now seen to be an organizing principle for various chemical and biochemical phenomena.
5. Molecular logic is also beginning to find use in small spaces where semiconductor-based information processors have difficulties.

1. Introduction

When we established the generality of the fluorescent PET (Photoinduced Electron Transfer) sensor/switch principle three decades ago, we were convinced of its semi-quantitative engineering design and of its visual appeal.1-3 After all, Weller had given us a strong thermodynamics basis for the 35 difficulties.

2. Figure 1a and 1b. Approximate world maps of sources of fluorescent PET sensors and switches aimed at single targets. Only the names of corresponding authors from the literature are given.

This week goes by without a fluorescent PET sensor being reported’ was our observation in 2009,11 and the situation is no different in 2014. Indeed, 59 references from 2014 are specifically cited in this review, with a substantial fraction coming in for detailed
discussion, subject to space limitations. Of course, older references are cited in strength, so that the historical threads are fully exposed, theoretical foundations are suitably developed, and adequate contexts are set out from the viewpoint of our experience in establishing the generality of the field.

Binary possibilities arose from instances where the fluorescence signal change was large enough to be considered as ‘off-on’ or ‘on-off’. These took on added significance in a world which was increasingly conscious of information technology. Thus, molecular information processors became possible in 1993.24 Although a myriad ways became available for molecules to be interrogated like semiconductor devices, the fluorescent PET sensor/switch principle provided the first approach and still remains a very profitable avenue.13-18

In this review, we concentrate on fluorescent PET sensors and switches which have appeared during the last year or so, while offering some context from the past. The emphasis of this review is on small-molecule sensors.

2. The fluorescent PET sensor/switch principle

It might be prudent to give a brief summary of the principle at the outset. In its commonest manifestation, a fluorophore is weakly coupled electronically with a receptor so that the two modules quantitatively maintain their individual properties in the photochemistry and supramolecular chemistry spheres. The two modules are chosen so that the excited fluorophore has sufficient energy to transfer an electron, say, from the receptor to the fluorophore. This means that the excited state energy is larger than the sum of the moduli of the oxidation and reduction potentials of the receptor and fluorophore respectively. If the experimental redox potentials are unavailable, modern quantum chemistry software can supply adequate estimates of the energies of the frontier orbitals of the two modules, and these can do the job almost as well. When the analyte/target species was bound to the receptor module, the oxidation potential would be significantly increased,19 so that the PET process fails and fluorescence re-asserts itself.

While electrochemical experiments and frontier orbital energy calculations are very useful as design tools, experimental proof of fluorescent PET sensor/switch behaviour requires the observation of radical ion species following fast laser photolysis. While Weller provided such evidence in intermolecular PET,4 intramolecular PET sensor/switch systems have been studied rarely.20,21 The laboratories of McClenaghan and Jonusauskas join forces to provide a timely example 1.22 A broad absorption between 520 and 570 nm, which corresponds to the previously known radical anion band of the borodipyromethene (BODIPY) fluorophore, appears and decays within 1 ns in THF solution. The radical cation of the receptor also appears, though less unequivocally, at 330 nm. The radical ions recombine at longer times to produce the fluorophore’s triplet excited state. A very fast PET rate of 3.3x10$^{13}$ s$^{-1}$ could be calculated under these conditions.

3. Proton targets

It is apt that protons represent the first target to consider. Their binding to appropriate receptors (Bronsted bases) is less complex than those of larger ions. Also, their role near membranes in bioenergetics is disproportionately important25 given their small size.

A first-generation dendron containing a tertiary amine is employed as a receptor by Bojinov’s team within 2.26 When excited at 302 nm, the emission at 397 nm shows a H$^+$-induced fluorescence enhancement (FE$_{H^+}$) of 7.6 with an associated pK$_a$ of 9.5. Research on related naphthalimide fluorophores is available.27 Interestingly, transition metal ions do not interfere significantly with 2’s performance perhaps because they would be held rather distant from the fluorophore.

Emission in the redder regions of the spectrum is preferred for intracellular studies, owing to less scattering and better penetration. Sun, Ge and co-workers provide an easily synthesized example 3,28 where x-ray crystallographic proof is available for the substantial rotation of the plane of the aniline ring with respect to the xanthene tricycle. Thus, PET across a virtual spacer from the aniline to the xanthene fluorophore becomes feasible, especially because the calculated HOMO of the aniline lies higher in energy than the HOMO of the xanthene. Thus, excitation of an electron from the xanthene HOMO would leave a vacancy into which another electron can be transferred from the aniline HOMO. Protonation of the aniline removes this PET process and indeed, the fluorescence at 592 nm gives FE$_{H^+}$ = 400 (pK$_a$ = 4.7) when excited at 535 nm. Many other cell constituents do not interfere and acidic lysosomal regions of HeLa cells show up nicely in fluorescence microscopic experiments.

We return to the blue region where sensor 429 responds in an ’on-off’ (or NOT logical) manner to H$, following protonation of one pyrimidine and the diethylamino group. The second pyrimidine, which is nearby, does not protonate owing to electrostatic considerations.1H nmr evidence is offered for this double protonation. An H$^+$-induced blue shift of 70 nm in the ultraviolet spectrum is also suggestive. Frontier orbital energy calculations show that, upon protonation of the diethylamino group, the fluorophore HOMO falls in energy below the HOMO of the unprotonated pyrimidine ring. Thus PET can occur from the unprotonated pyrimidine to the protonated aminocoumarin. The fluorescence at 460 nm indicates FE$_{H^+}$ = 0.025 (pK$_a$ = 2.1) when excited at 385 nm. E. Coli grown in media as acidic as pH 0.6 shows appropriately weak fluorescence from 4 within.

4. Alkali and alkaline earth ion targets

The next logical step would be to consider light metal ions. Since the McClenaghan-Jonusauskas case 12 carries the famous Tsien receptor for Ca$^{2+}$, it is no wonder that a FE$_{Ca^{2+}}$ value of 122 (log$\log_{Ca^{2+}}$ = 6.3) is found by monitoring the fluorescence at 514 nm while exciting at 475 nm. As is the trend these days, frontier orbital energy calculations produce the appropriate HOMO energy ordering, i.e. the HOMO energy of the receptor lies higher in energy than the HOMO of the fluorophore.

K$^+$ is the target for a strong team assembled by Holdt.30 They construct 5, which interestingly shares the diethylaminocoumarin motif with 4.29 However, this unit is clicked onto a
phenylazacrown receptor and results in an excellent selectivity for the target over several potential interferents like Na\(^+\) and H\(^+\) at their normal intracellular levels. This is a very positive result for such a simple receptor and therefore it is not surprising that sensor 5 succeeds inside NRK cells. The fluorescence at 493 nm gives FE\(_{Hg^{2+}}\) = 3.0 (Log\(_{FE_{Hg^{2+}}} = 1.5\)) when excited at 420 nm, due to K\(^+\)-induced arrest of PET across the virtual spacer.

K\(^+\) was also the target, though not so selectively, for our very old work with 6.\(^{31}\) This work, along with that of Desvergne, Bouas-Laurent and Lehn\(^{32}\) launched fluorescent PET sensors and switches as an important branch of supramolecular chemistry. Now, Wang and co-workers\(^{33}\) support the outcome of their old work with 6 by performing a detailed theoretical study of the PET process from the azacrown ether receptor to the anthracene fluorophore.

5. Transition metal and post-transition metal ion targets

Now, we move to heavier metal ions. For instance Pd\(^{2+}\) has been fluorometrically sensed only rarely,\(^{34}\) but Kaur, Singh and colleagues build a phenylazacrown receptor carrying two sulfurs which communicates via a virtual spacer with the BODIPY fluorophore\(^{35}\) (as seen in 12\(^\text{5}\)). The soft base atoms in the receptor prepare 7 for selective binding to soft metals like Pd\(^{2+}\), though the impressive selectivity achieved cannot be explained away so simply. Indeed, Hg\(^{2+}\) is the only significant interferent which could be masked with cysteine. The fluorescence at 520 nm gives FE\(_{Hg^{2+}}\) = 57 (Log\(_{FE_{Hg^{2+}}} = 7.2\), in MeCN) when excited at 488 nm.\(^{35}\) Frontier orbital energy calculations for the separate receptor and fluorophore support the Pd\(^{2+}\)-induced arrest of the PET process.

In spite of 7’s relative insolubility in water, the authors bravely conduct microscopy studies in a breast cancer cell line.

When it comes to metal ion receptors, nitrogen holds a near monopoly,\(^{28}\) in spite of its known pH sensitivity. Finney, Deiters and their team\(^{37}\) introduce sulfur-based thiourea 8 as a monoply breaker, which fits a PET switch design. Here, the thiourea serves as PET donor to the naphthalimide fluorophore across the dimethylene spacer. The pyridyl groups are too remote from the fluorophore to the Cu\(^{2+}\) centre, if we go by the conclusions of Gunnlaugsson’s previous Zn\(^{2+}\) sensor,\(^{50}\) where attention is paid to parameters such as wet storage which only hardened industrialists would realize. The fluorescence at 550 nm, when excited at 470 nm, gives FE\(_{Zn^{2+}}\) = 50 (Log\(_{FE_{Zn^{2+}}} = 4.6\)). The glutamate side chain aids cell permeability in its diester form and later in its dicarboxylic form, helps retention in the cytosol of HeLa cells. Gunnlaugsson’s design components of the aminonaphthalimide fluorophore, the N-phenyliminodiacetate receptor and the PET switching mechanism itself are maintained.

Though equipped with only pyridyl and alcohol units as potential receptors, the fluorescence of 13\(^{31}\) at 375 nm gives FE\(_{Ag^{+}}\) = 0.06 (Log\(_{FE_{Ag^{+}}} = 3.2\)) when excited at 272 nm in water, with PET and/or EET from the fluorophore to the bound Fe\(^{3+}\) being responsible. Like Ihmels’ sensing of DNA-bounded Hg\(^{2+}\),\(^{52}\) Zeng et al measure Ag\(^{+}\) near DNA with 14.\(^{14}\) 14’s fluorescence at 590 nm, when excited at 455 nm, gives FE\(_{Ag^{+}}\) = 28 (Log\(_{FE_{Ag^{+}}} = 4.6\)). Like Finney’s 8,\(^{37}\) the PET donor of 14 is based on sulfur. The polyamionic nature of DNA concentrates Ag\(^{+}\) in 14’s vicinity. Although, the intercalation of cationic 14 within DNA suppresses rotation around the styryl alkene linkage, the drop of fluorescence intensity indicates that PET is accelerated at this stage.

6. Anion targets

This review would be lacking unless some reports on anion targets are considered from the past year. Like 1.\(^{22}\) 7\(^{35}\) and 9.\(^{41}\) Madhu and Ravikanth’s 15\(^{53}\) focuses on the BODIPY fluorophore. However, 15 has an appended benzimidazole which engages in N-H...F hydrogen bonding with the two fluorines on the boron centre. X-ray crystallography shows that this hydrogen bonding also leads to planarization of the entire structure (except the two fluorines). There is a large F\(^{-}\)-induced alteration in the absorption spectrum which causes a pink-to-blue colour change. The fluorescence at 592 nm in MeCN, when excited at 530 nm, gives FE\(_{F^{-}}\) = 0.11 (Log\(_{FE_{F^{-}}} = 6.4, 1.2\) (F-P)), though the absorbance changes need to be borne in mind. The F\(^{-}\)-induced
fluorescence quenching is caused by deprotonation of the benzimidazole so that the latter anionic unit can rotate out of the BODIPY plane. Now PET can take place from the benzimidazole anion to the BODIPY unit. The HF side-product picks up an additional F⁻ to give FHF⁻. Addition of H² reverses the above effects.

A similar PET process from a deprotonated receptor to a BODIPY fluorophore is implicated in the case of Rurack and coworkers. In this case, F⁻-induced deprotonation of a N-(4-nitrophenyl)thiourea is involved. The fluorescence of 16 at 513 nm gives FE(⁺) = 0.47 (LogP⁻ = 4.7) when excited at 482 nm in 1:1, DMSO/water at pH 6.8. Test strips containing 16 can be used to measure F⁻ in lateral-flow readers, which augurs well for the future. Older F⁻ sensors which share some structural features and operate in mixed aqueous solution are known.56,57

### 7. Reactive oxygen targets
The fluorescent PET sensor/switch principle can also be applied in the form of fluorescent PET reagents when the target reacts irreversibly as in the case of various thiol58-63. Some of these improve selectivity towards cases like glutathione versus simpler thiols by cleverly employing AND logic involving connected chemical inputs. However, we choose to focus on reactive oxygen species (ROS) at this time.65-68 Due to Xu, Qian and colleagues, PET from the aminophenoxy moiety to the naphthalimide which renders 17 non-emissive.65 Hypochlorite oxidizes the aminophenoxy unit to a separate quinoneimine and leaves a naphthalimide with a carbamate in the 3-position which emits at 460 nm when excited at 340 nm (FE(⁺) = 71). This partly decarboxylates to yield a 3-Aminonaphthalimide which emits at 570 nm (FE(⁺) = 63). Only the 460 nm component of this dual emission is found when peroxynitrite is the ROS. Other ROS like hydrogen peroxide produce no emission at all. Even 7x10⁻⁷ M hypochlorite can be detected in this way, even inside HeLa cells.

Kim and Kim’s 18 is non-fluorescent because of PET from the catechol moiety to the BODIPY unit.64 Hypochlorite oxidizes the catechol moiety to a o-quinone. Apparently, the possible PET to the latter group from the BODIPY unit does not occur. Though further analysis of this issue would be welcome, the experimental upshot is a rather selective FE(⁺) value of 80 with a limit of detection of 3x10⁻⁷ M.

### 8. Physicochemical property targets
A consortium of Xu, Cui, Qian, Spring and colleagues utilise the flailing rotatory motion inherent in the generation of twisted intramolecular charge transfer (TICT) excited states and the conformation-dependent PET to develop the viscosity sensor 19 and apply it to intracellular microscopy studies. Fluorescence intensity and lifetime are both put to use. Nice viscosity maps with organelle-level resolution are produced. The thermodynamics of TICT states² and PET processes are very similar since a radical ion pair is produced in each case, though there are subtle differences in a sensor context. Structurally, 19 contains two fluorophores - aminonaphthalimide and anthracene - and an electron donor aniline. The latter shows no metal binding ability and displays a pKₐ value of 3.1. So, protonation-based interference would not be expected even in some of the most acidic regions, i.e. lysosomes with pH values around 5. However, a word of caution would be advised here since organelle membranes can easily concentrate H⁺ at nanometric distances near them by several orders of magnitude, thus encroaching on 19’s pKₐ value of 3.1. Such effects are known from model membrane studies.23,24 Classical optical microscopy images would not be able to resolve such effects. The presence of two fluorophores leads to electronic energy transfer (EET) effects too, and almost exactly this pair has been studied in a ratiometric PET/EET-based pH sensor context before.74 The presence of the anthracene emission serves as an internal reference for the viscosity-dependent emission of the aminonaphthalimide moiety.

As seen in other PET sensors,75,76 the fluorescence of 19 has a substantial polarity effect, i.e. the total quantum yield goes from 0.004 in water to 0.14 in toluene, though the viscosity effect is clearly present too, as seen in the corresponding value of 0.36 in glycerol. Therefore, another word of caution would be that organellar membranes can have polarities at least as low as toluene, so that environments nearby (which are unresolvable by conventional optics) would cause switching ‘on’ at whatever pH value. Jets of an aniline electron donor is also found in Tsien’s PET sensor 20 for membrane potential77,78 in live cells. The relatively large fluorescence intensity response shown by 20 when cells are depolarized allows it to produce images of membrane potential with submicrometer and microsecond resolution. Thus it forms a nice complement to classical electrophysiology. 20 positions itself in cell membranes owing to its hydrocarbon chains and general hydrophobicity. The oligoalkene section acts as a molecular wire to facilitate the PET process. However, the hydrophilic ionized fluorescein fluorophore sticks out into the aqueous environment. Because of its depth of penetration of the membrane, 20 can respond to the electric field caused by a large fraction of the membrane potential. Molecular-scale electric fields are known to control PET rates very strongly.79

### 9. Multiple targets
Given the molecular engineering backdrop to the fluorescent PET sensor/switch principle, chemical emulation of physical devices was an associated discipline from the early days. While logic devices receive a lot of airtime,80 some attention has to be given to their components. The triode82 which is one of those, is a three-electrode assembly where the input to one electrode influences the output from another. We arrange something similar by using a ‘fluorophore-spacer-receptor-spacer-receptor’ system 21,83 where receptor₁ and receptor₂ target H⁺ and Na⁺ respectively. However, only receptor₁ is PET-active. The upshot is that a sigmoidal fluorescence intensity – pH profile is tuned by altering Na⁺ concentration. Electrostatic repulsion between the receptor-bound H⁺ and receptor-bound Na⁺ is responsible for this tuning by influencing the pKₐ value of the sensor. It is only fair to note that Gust, Moore, Moore and their colleagues published an all-photic triode emulation in 2010.84 AND logic gate due to Farrugia and Magri, contains an...
amine moiety to interact with $H^+$ and a ferrocene moiety to respond to redox inputs. Both moiieties are PET-active and fluorescence is weakened as a result. Arrest of both these PET pathways by the provision of $H^+$ and an oxidizing equivalent leads to switching ‘on’ of fluorescence. However, there is a residual PET process from the fluorophore to the ferricinium moiety (in the oxidized form of 22), which puts an upper limit on the FEH+,redox value. 22 is logically extended to 23 by Magri and his colleagues. They do it by the addition of a PET-active benzocrown ether receptor to interact with Na’ inputs. A $H^+$, redox, Na’-driven AND gate is the result, which would become a ‘lab-on-a-molecule’ for direct detection of some cancers which possess elevated $H^+$, Na’ and free iron.

The original approach to a ‘lab-on-a-molecule’ exploited a small set of selective receptors which communicated intramolecularly with a fluorophore, which then provided a binary readout to a human observer. At least conceptually, this approach can be modified to contain a set of relatively nonselective receptors, e.g. phenylboronic acids to tackle a set of sugar-based drugs. In compensation, a set of fluorophores can be built into the supermolecule so that the fluorescence intensities at several wavelengths serve as readouts. The intensity patterns can be chemometrically analyzed for further sharpening of the results so that the drugs become distinguishable with confidence.

Margulis’ first successful case of this kind, showing that several of the imaginable pitfalls due to the complexity of the structures do not arise. Though the design is broad enough to embrace multiple photochemical mechanisms, PET remains at its heart since several arylmethylamine units are present within 24. The binding of sugar-based drugs to aminomethylphenylboronic receptors will then affect fluorescence intensities at a primary level. An internal charge transfer (ICT) mechanism also affects fluorescence intensities at some wavelengths at a primary level due to the presence of a fluorophore with push-pull groups. Electronic energy transfer (EET) between the different fluorophores serves to modulate the fluorescence intensity pattern at a second level.

As found in several cases within section 5, the bispicolylamine moiety also stars within Akkaya’s 25 where PET is arranged to occur from the bispicolylamine unit to the BODIPY fluorophore. However, the special feature of this work is that Zn2+ is supplied to 25 by a photo-uncaging procedure. Zn2+ is held within the ‘cage’ of 26 and is only released when a 360 nm light dose decomposes 26 to 27 and N-methylpicolylamine. The mechanism here is a rather classical bit of organic photochemistry. The $\pi$ triplet excited state of the nitroaryl unit causes an intramolecular hydrogen abstraction via a six-membered ring intermediate. This work has the wider vision of physically integrating molecular logic gates by using metal ions as the linker species. In this context, the 360 nm light dose is input. The powerful general complex ext EDTA is input. Since EDTA would swallow up any Zn2+ to prevent the fluorescence activation of 25, it serves as a disabling input. Thus 26 is a light dose, EDTA-driven INHIBIT (EDTA) gate where EDTA is the disabling input. Its output of Zn2+ then feeds the YES logic gate 25 whose own output is its fluorescence. Similar physical concatenation of logic gates aided by $H^+$ was known previously.

Molecular keypad locks are interesting examples of logical molecules which are history-dependent, i.e. the output signal value depends on the order of addition of the inputs. One way of arranging this history-dependence is to exploit multivalent interactions so that the full disconnection of complexed species becomes sluggish. Then, several kinetically stable states may appear for a given system. Being replete with aminomethylphenylboronic acids, Margulis’ 24 can engage in such multivalent interactions with inputs chosen from a set of many sugars as well as the catechol derivative 28. Thus it can also serve as a molecular keypad lock with new features which are more reminiscent of semiconductor-based counterparts. One of these new features is that inputs can be repeated to result in passwords such as 333. In the present instance, this means that the intensity pattern obtained by reading at several wavelengths (following chemometric analysis, if necessary) is dependent on the input species concentration, i.e. when the latter is doubled or trebled. Another of these new features is that multiple passwords can be declared as being valid to open the lock. Of course, this requires a separate definition of ‘open’ and ‘closed’ states, which is best done from a Boolean standpoint.

10. Conclusions and perspectives for future research

The work surveyed above reveals several trends. One of these is that many fluorescent PET sensor/switch laboratories are augmenting their research with frontier orbital energy calculations conducted through general software. This move to appreciate the physicochemical design aspects is to be applauded, especially because the fluorescent PET sensor/switch principle started off as an exercise in molecular engineering. Dedicated papers on calculations are also being published so that additional insights can be gained. Another of these trends is that a large fraction of the publications are including intracellular evaluations. This move to be involved in the physiological application aspects is important because fluorescent PET sensors are tools. Tools are meant to be used so that they shed light on cellular processes involving the analytes. Tsien’s pioneering work along this line remains inspirational. Just as fluorescent PET sensors are being associated with cells, they can also be anchored on polymer particles of various kinds. Though there is no room for detailed discussion, we cite additional references to the fluorescent PET sensing/switching literature from 2014 where a few cases concerning mechanisms which closely related to PET are also included.

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As noted in the previous paragraph, Tsien’s work still has much to guide future developments in the field of fluorescent PET sensors and switches. For instance, he showed how real time analysis tools of this kind can revolutionize the understanding of intracellular signalling. A valuable lesson from this is that the fluorescent PET sensing community needs to conduct more fluorescence sensing studies in real time. Currently, most studies are reporting single fluorescence micrographs in the presence of the target species. If these can be extended to a set of images in time sequence as the cell goes about its business, the value of the results will be greatly enhanced. During this process, challenges with respect to sensor photostability, sensor survival in the face of cellular processes and calibration of target species concentrations will need to be faced.

Further exploitation of fluorescent PET sensors and switches in the future will also benefit if they can operate deeper within tissue. Such multi-cell monitoring can produce important information about cell-cell communication. Two-photon fluorescence versions of fluorescent PET sensors should be able to achieve this by employing red or near-infra red photons for excitation. Once the excited state is produced, the usual PET criteria and arguments would apply. It is a delight to note how much to guide future developments in the field of fluorescent science to be useful to others.

It is our hope that this review will provide added impetus to research on fluorescence PET sensors/switches. For instance, he showed how real time fluorescence versions of fluorescent PET sensors should be able to achieve this by employing red or near-infra red photons for excitation. Once the excited state is produced, the usual PET criteria and arguments would apply. It is a delight to note how much to guide future developments in the field of fluorescent science to be useful to others.

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Notes and references

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Fluorophores can be combined with receptors according to a molecular engineering design to yield fluorescent sensing and switching devices.

Group photograph

Biography

The authors came to study for their PhD at Queen’s University Belfast, Northern Ireland, from places as far apart as Zhenjiang, Belfast and Colombo. Besides the chemistry day jobs, Brian (left) brings up his two daughters, Jue (centre) plays basketball and AP (right) plays percussion with an Irish traditional band.