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Thiol-Mediated Uptake (TMU, TIMEUP)

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Abstract: This account briefly summarizes objectives and progress made so far with the Swiss-ERC AdG entitled Translational Dynamic Covalent Exchange Cascades (TIMEUP).

Keywords: Thiol-mediated uptake · Swiss-ERC AdG

Aufsteigt der Strahl und fallend giesst
Er voll der Marmorschale Rund,
Die, sich verschleiernd, überfliesst
In einer zweiten Schale Grund;
Die zweite gibt, sie wird zu reich,
Der dritten wallend ihre Flut,
Und jede nimmt und gibt zugleich
Und strömt und ruht.
Conrad Ferdinand Meyer (1825–1898)

Long before we started thinking about the process of thiol-mediated uptake (TMU), the Swiss poet *C. F. Meyer*, through his description of water flowing, beautifully described the nature and the challenge of dynamic covalent cascade exchange chemistry in 'The Roman Fountain'.[1] It is directional and off-equilibrium in a strange way, dynamically exchanging on the one hand while featuring robust covalent bonds at the same time, thus 'streaming and staying'. The Swiss-ERC AdG (Advanced Grant) 'TIMEUP' argues that this enigmatic nature of cascade exchange chemistry is the reason why thiol-mediated uptake (TMU) is not better understood and utilised more. Molecular structures become somewhat fuzzy, and covalent bonds start to move around, making it impossible to capture images like the one in Fig. 1 at the molecular level, let alone videos. For a long time, we thought this was acceptable as long as it worked well. However, recent results from various directions suggest that TMU might be much more important than first anticipated. It now seems that the 'time is up' to understand TMU.

Fig. 1. A fountain in Paris, Place des Vosges. (Photo credit, S. Matile)

TMU stands for the emergence of cell-penetrating activity with the attachment of a cascade exchanger (CAX) to a substrate of interest (SOI); inhibition with thiol-reactive agents is commonly accepted as evidence for the occurrence of TMU (Fig. 2).[2] Upon dynamic-covalent exchange with thiolates or disulfides of a cellular exchange partner, CAXs offer another tethered exchanger to continue dynamic covalent exchange. The simplest, oldest and most popular CAXs are strained cyclic disulfides derived from asparagusic acid (AspA) such as **1**.[3,4] The high activity of CAXs directly implies that TMU operates with cascade exchange with membrane-bound, extra- and intracellular partners. Following the imagery of *C. F. Meyer*, this is why TMU is so poorly understood.

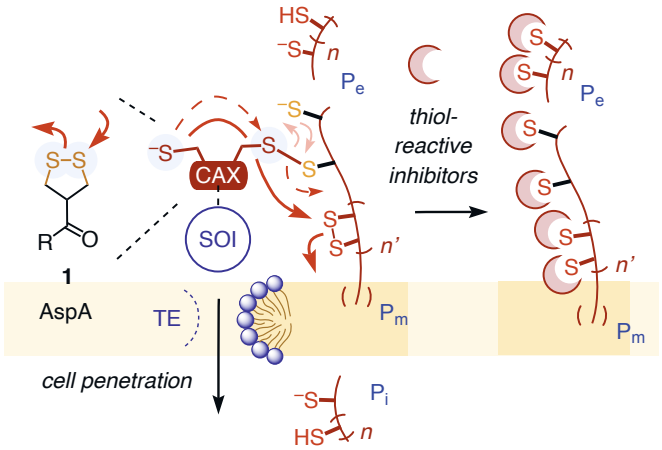

Fig. 2. Graphical summary of thiol-mediated uptake (TMU). Cascade exchangers (CAXs) like AspA **1** deliver substrates of interest (SOIs) into cells, thiol-reactive agents act as inhibitors. It is increasingly clear that a complex network of exchange cascades between CAXs and extracellular (P_e), membrane-related (P_m) and intracellular exchange partners (P_i) encodes for TMU, while the direct translocation is achieved through toroidal elastics (TEs, normal/reverse micellar defects that can be stretched by large SOIs to let them pass through without leakage).

In striking contrast to its enigmatic nature, there is no doubt that TMU is very powerful. Arguably, it was observed first by Hugues Ryser, a Swiss virologist, born in the Jura, educated at the University of Berne, active all his life in the US (Fig. 3).[5] In the context of the HIV crisis, he showed in the 1990s that Ellman's reagent **2** (DTNB) can function as an antiviral, inhibiting cellular entry of HIV.[6] Since then, TMU has been observed by

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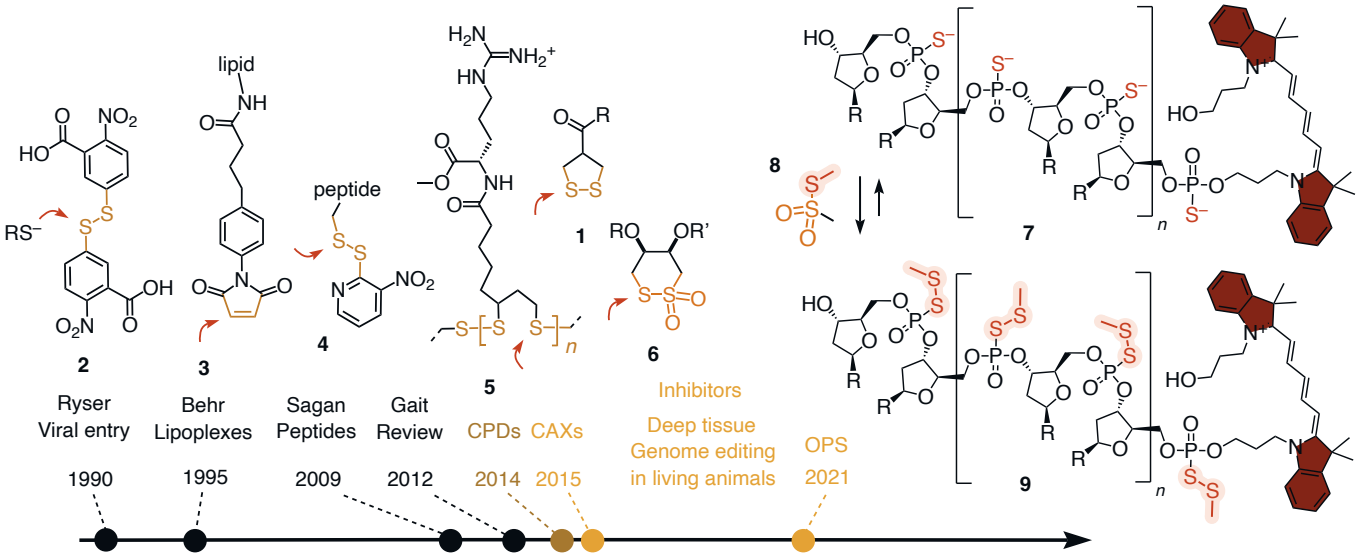

Fig. 3. Timeline with milestones for the emergence of thiol-mediated uptake.

many, but it has never been followed up with more serious studies. Important early contributions were made by the French giants Jean-Paul Behr, Strasbourg, who observed partial TMU first with lipoplexes **3**[7] and Sandrine Sagan, Sorbonne, who observed partial TMU for peptides **4**, supported by inhibition with DTNB **2**.[8] The practical benefits of integrating disulfides in polymer-based delivery systems has long been recognized.[9,10] Mike Gait, MRC of Cambridge, summarized the many eclectic observations beyond polymer chemistry in 2012, insisting that there is something potentially important we do not understand.[11]

We entered the topic in 2014, when we thought to detoxify arginine-rich cell-penetrating peptides (CPPs) by replacing the peptide backbones with degradable poly(disulfide)s.[12,13] The resulting cell-penetrating poly(disulfide)s (CPDs) like **5** worked beautifully. However, mechanistic analysis implied that the guanidinium cations of CPPs are much less important for cell penetration than the poly(disulfide) backbone. This was interesting because CPPs, operating by non-covalent repulsion-driven ion-pair hopping along lipids rather than proteins and toroidal elastics to translocate,[14] remain most popular for delivery. Although, these CPPs can suffer from toxicity, endosomal capture, inactivity in deep tissue, and more.[15,16] Learning that they are less important than expected, we quickly removed the guanidinium cations in CPD **5**. Next we realized that also poly(disulfide)s are not essential and cyclic disulfide monomers like AspA **1** suffice to penetrate cells.[3] Since then, we and a growing number of other groups[17–57] have enjoyed introducing new CAXs and delivering a wide variety of SOIs without understanding the mechanism of TMU.[2] This seemed acceptable until the appearance of reports suggesting that TMU might be much more important than expected. For instance, among several *in vivo* studies performed mainly in China, TMU was shown to be compatible with genome editing in living animals.[20,22] Along the same line, we found that TMU excels in spheroids, delivery into deep tissue, where CPP alternatives mostly fail to penetrate.[15,16,58] Additionally, when the pandemic began, we recalled the early results from the Ryser group but had also learned by then that Ellman's reagent is a poor and unreliable TMU inhibitor. We thus started to screen our CAX collection for inhibition of TMU and found inhibitors more than 5000 times more active than DTNB.[59,60] Some of the CAXs were also tested as inhibitors of the cellular entry of SARS-COV-2 lentivectors.[61,62] Cyclic thiosulfonates **6**, a mostly unexplored motif in dynamic covalent chemistry, were most promising,[61] together with pnictogen-centered CAXs, arsenic and bismuth,[62] similar to Ehrlich's magic bullet against syphilis, the first rationally developed drug, later on identified as an adaptive dynamic covalent network.[63]

Finally, the same CAX collection was applied to solve the 'mystery' of phosphorothioate oligonucleotides (OPS) like **7**. OPS are antisense oligonucleotides that really work in practice, in part also because they spontaneously penetrate cells. Somehow the oligonucleotide counterpart of CPPs, the emergence of this cell-penetrating activity upon replacement of one oxygen by one sulfur *per* monomer has remained mostly mysterious. The identification of CAXs as inhibitors implies that the explanation, at least in part, is TMU.[64] Interestingly, the dynamic covalent chemistry of phosphorothioates has been mostly ignored until now. It turns out that they can act like *pseudo*-thiolates. Exchange with CAXs like MMTS **8** affords *pseudo*-disulfides in the backbone of OPS **9** *in situ*, which could be of interest to enhance TMU.

Taken together, all these recent results suggested that TMU might be more important than expected, and exists as a dynamic network in place to bring matter into cells in a general way, thus central not only for drug delivery but also for drug discovery. TMU is compatible with CAXs beyond disulfides, many of which are waiting to be discovered, and also of interest as dynamers[65] in the materials sciences. This emerging importance suggested that it was time to crack TMU. To do so, we first needed to better understand CAX chemistry and map out the CAX universe. This required the synthesis of many new CAXs, which was good news for us because, as synthetic organic chemists, we enjoy nothing more than creating new molecules.

Among newly added CAXs, highlights include dynamic phosphorus[66] and reversible Michael acceptors[67] (Fig. 4). Dynamic covalent phosphorothioate chemistry attracted our attention first when we addressed the mystery of antisense oligonucleotides **7** and showed how they can be further activated as p*seudo*-disulfides **9** (Fig. 3).[64] Although unorthodox and underexplored, this exchange chemistry of phosphorothioates operates still with the sulfur as the exchange center. However, with phosphorotri- and -tetrathioates, the phosphorous atom itself turns dynamic.[66] Phosphorotri- and -tetrathioates were readily accessible from the trichloride and the thiol/ates of interest. The exchange with other thiol/ates was detectable by ^{31}P NMR spectroscopy. It occurred also in micelles in water, with multifaceted pH dependence (Fig. 4a, left). Cascade exchange of *p*-bromothiophenol/ates (green, **10**) as substituents in phosphorotrithioate **11** first, with *p*-fluorothiophenol/ates (blue, **12**) and then *p*-methoxythiophenol/ates (brown, **13**) provided impressive examples for virtual walking along a Hammett gradient, which also passed through the chiral central

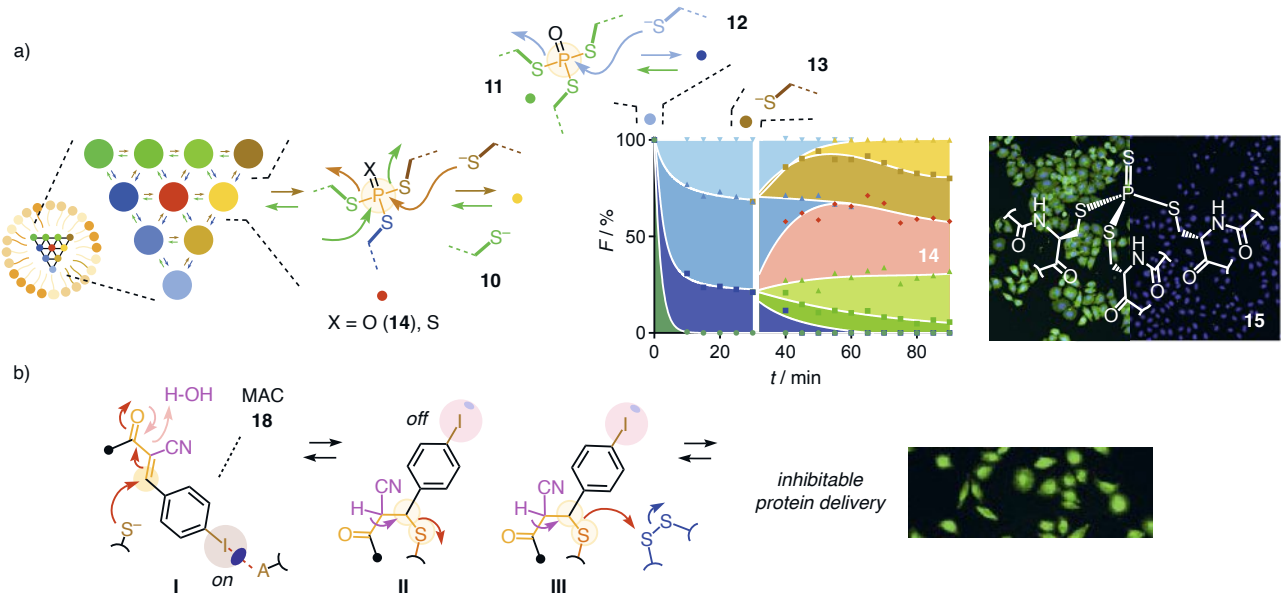

Fig. 4. Charismatic new CAXs for TMU and beyond: (a) Dynamic phosphorus and (b) reversible Michael acceptors. (a) Phosphorus-centered dynamic covalent exchange cascades with tri/tetraphosphorothioates in micellar water, with virtual walking along a Hammett gradient (green: *p*-bromothiophenol/ate **10**, blue: *p*-fluorothiophenol/ate **12**, brown: *p*-methoxythiophenol/ate **13**) and inhibition of TMU with cysteine exchanged tri/tetraphosphorothioates such as **15**. (b) Reversible Michael acceptors **18** as '*pseudo*-CAX' supported by halogen-bonding switches, strong before (**I**) and weak after conjugate addition (**II**), capable of inhibitable cytosolic protein delivery. Adapted from refs. [66,67].

phosphorothioate **14** with three exchangers on the phosphorous exchange center (Fig. 4a, middle). Loaded with cysteine exchangers, covalent dynamic phosphorotri- and -tetrathioates such as **15** were not toxic and efficiently inhibited TMU into living cells (Fig. 4a, right). Dynamic covalent phosphorus is unprecedented as an exchange center in cascades (dcP, Fig. 5). It is remarkable that this has not been explored before, given its impressive potential spanning from biology to materials science.

Moving down in the pnictogen series, arsenic (AsC, **16**) and bismuth (BiC, **17**) were explored recently as exchange centers in TMU (Fig. 5).[62] Contrary to dynamic phosphorus, pnictogen-centered cascade exchange with these elements is anything but new. AsC and BiC emerged as interesting lead compounds because they do not only inhibit TMU but also the entry of SARS-CoV-2 lentivectors.

Moving from pnictogens to tetrels as exchange centers, reversible Michael acceptors (MACs, **18**) were interesting to enable and inhibit TMU (Fig. 4).[67,68] For reversibility, a cyano group is added in α-position of **18** to increase the acidity of the added hydrogen sufficiently, to enable elimination together with the Michael donor.[69,70] The highest TMU activity of MAC **18** with a *p*-iodo substituent implied contributions from a halogen-bonding switch, with strong bonds before (**I**) and weak bonds after Michael addition (**II**, Fig. 4b, left). This halogen-bonding switch might help to move reversible Michael acceptors along exchange cascades (**III**), affording a '*pseudo*-CAX' that is capable of inhibitable cytosolic protein delivery. This finding was quite enjoyable, who would have predicted to deliver proteins with reversible Michael acceptors? (Fig. 4b, right).

The tetrel-centered series was expanded with a dimeric MAC, dMAC **19**, better as TMU inhibitors than as transporters, the presumably irreversible 'super-spice' SS **20** and the definitely irreversible thiol-reactive agent EBX **21** with elegant hypervalent iodine chemistry from the Waser group (Fig. 5). Moreover, thiolactones, including TL **22**, and their polythioesters have been considered as possible tetrel-centered CAXs, with limited success.[68]

Despite this progress with pnictogen- and tetrel-centered CAXs, chalcogens, particularly sulfurs, remain the best explored and best performing exchange centers for TMU. The discovery of CPDs **5** in 2014 and the introduction of AspA **1** as the first primary CAX one year later have already been highlighted (Figs. 3 and 5).[3] A second primary CAX was discovered with ETP **23**, a bioinspired motif that drives disulfide ring tension to the maximum.[71] BPS **24** was introduced one year later as the third primary CAX known today.[72] Found in marine natural products, BPS was an early target in total synthesis, emerged as a surprise hit from an array of libraries, and acts as a dynamic adaptive network of oligomers. Oxidation of cyclic disulfides leads over thiosulfinates to cyclic thiosulfonates (CTOs) **6**, with interesting antiviral potential and nearly unexplored cascade exchange chemistry characterized by ultrafast ring opening and proticity dependent continuation.[61]

Selenium-centered CAXs have been introduced early on with diselenolipoic acid **25**.[73,74] DSe **25** shows distinct cascade exchange chemistry, characterized by ultrafast exchange with preferred ring closure due to reduced ring tension and selenophilicity, and interesting activity to deliver a wide variety of SOIs into the cytosol. Cyclic selenenylsulfides **26** (SeS) are currently explored in the Thorn-Seshold group for cascade exchange chemistry along polarized dynamic covalent bonds.[75] The selenium-centered exchange chemistry of ebselen **27** (EBS) has received much attention in many groups and is thus maintained although it does not explicitly qualify as CAXs.[62]

This emerging and still expanding CAXs universe was mapped out to decode TMU networks because if different pathways exist with different cellular partners, then their access should be controlled by different cascade exchange chemistry (Fig. 5). Early proteomics studies in the Adibekian group have revealed the transferrin receptor as exchange partner 1 (P1) of AspA **1**[76] but not of ETP **23**[71] (Fig. 5). Results have been validated by knockdown, overexpression and specific Cys mutations.[76] This finding was interesting because the transferrin receptor is involved in many drug delivery and viral entry systems, and efficient transcytosis is compatible with the power of TMU to deliver into deep tissue.[15,58] Many other candidates were observed,[76] but the meaning of conventional proteomics results is unclear considering the dynamic nature of exchange cascades accounting for TMU. Besides more specific proteomics methods,[77] the use of functional feedback

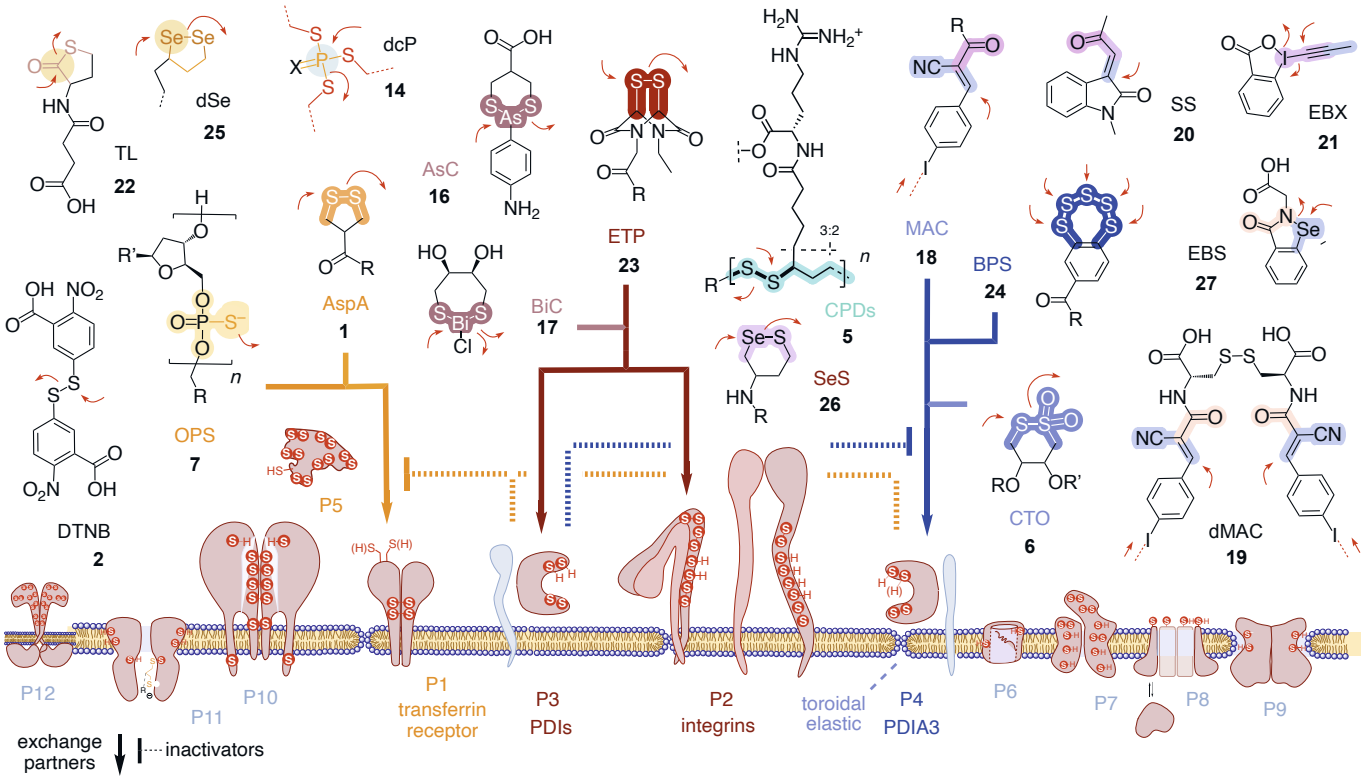

Fig. 5. The expanding CAX universe with cellular exchange partners (P) as well as AspA (gold), ETP (dark red) and BPS pathways (blue). Bold: Productive exchange partners, TMU inactivated by knockdown (KD) or alternative inhibitor (AI) of P; dashed: Inactivators, KD or AI of P enhance TMU.

loops seemed unavoidable to decode TMU, identify distinct uptake pathways and the exchange partners involved.

With this objective, the most important CAXs were equipped with a fluorophore as formal SOI to be delivered into cells.[78] The TMU of these Fl-CAXs was quantified by the fluorescent intensity of the cells in automated high-content high-throughput (AHCHT) fluorescence imaging, which can also report on cytotoxicity and remove false positives from endosomal capture and plasma membrane binding in one and the same measurement.[78] Then the inhibition of Fl-CAXs uptake by the same and other non-fluorescent CAXs was determined by the same AHCHT imaging method. The results were arranged in a heatmap, showing strong inhibition in strong colors and weak inhibition in weak colors (Fig. 6a).[78] Activities were described as IC_{50} (top) and MIC, equivalent to IC_{15} (bottom). These values were determined under co-incubation conditions (right) and pre-incubation conditions, where the inhibitor is removed before the transporter is added (left). Columns and rows were labeled in a chess player's notation, which allows each combination to be precisely pinpointed. The self-inhibition diagonal from J12 for BPS to N8 for MAC is highlighted with cyan circles.

The central heatmap comparing CAX transporters and inhibitors without additional modifications covers the area from J12 for BPS to O1 for DTNB inhibiting OPS uptake.[78] The rich, far from uniform pattern generated by this central heatmap supports that it is not simple dynamic covalent exchange that accounts for TMU but distinct networks with distinct characteristics originating necessarily from different cellular exchange partners with different selectivities at work. Also immediately visible was the poor performance of DTNB **2** (J1-O1). This result confirms all concerns with DTNB as the standard probe in biology and explains all the confusion caused in the field. Every inhibitor listed in Fig. 6a would be preferable over DTNB, although most are not commercially available, and none detects every CAXs tested. Excluding availability concerns, BPS or ETP would probably be the best choice (A11-W12), EBS **27** could be the best more practical alternative (A3-O3).

To use these patterns to identify uptake pathways with specific cellular exchange partners, integrins were considered first.[79] Integrins are a family of 24 dimers composed of α and β-monomers, involved in cell adhesion and motility, signaling, and viral entry. They were selected as TMU candidates because they feature one of the most impressive disulfide tracks which, *inter alia*, controls the conformational change from inactive bent to active straight conformers (Fig. 7a and b). Genetic knockdown of β-subunits had little impact on TMU except for ETPs, which lost about half of their activity (Fig. 6b, J13-O13). This selectivity was important because it identified integrins as exclusive exchange partners of ETP (Fig. 5). Among CAXs that are available only as inhibitors but not as fluorescent transporters, comparable patterns in the inclusive heatmap implied that the pnictogen-centered AsC **16** and BiC **17** also use the ETP pathway. For BiC **17** and ETP, this includes a meaningful loss in inhibitory activity against ETP transporters upon removal of their common primary exchange partner (G4-I4, G11-I11). In contrast, they better inhibit TMU of BPS because they are not occupied with their primary partner anymore (F4, F11).

Uptake pathway identification by chemical rather than genetic exchange partner removal was probed with protein disulfide isomerases (PDIs).[80–85] This is a family with 21 members that catalyzes thiol/ate/disulfide exchange mostly to assist protein folding in the ER. However, they occur throughout the cells and on their surfaces with many different functions, including signaling, viral entry and protein activation, also integrins, caveolin or the gp120 mediating HIV entry. They have a U-shaped structure with two active sites at both ends, binding protein substrates in-between and protein partners often on the other side. The active disulfide **28** is in *N*-capping position of an α-helix that controls ring tension in disulfide **28** and the acidity of the thiols in the reduced **29** (Fig. 7d). This interesting, underexplored motif is

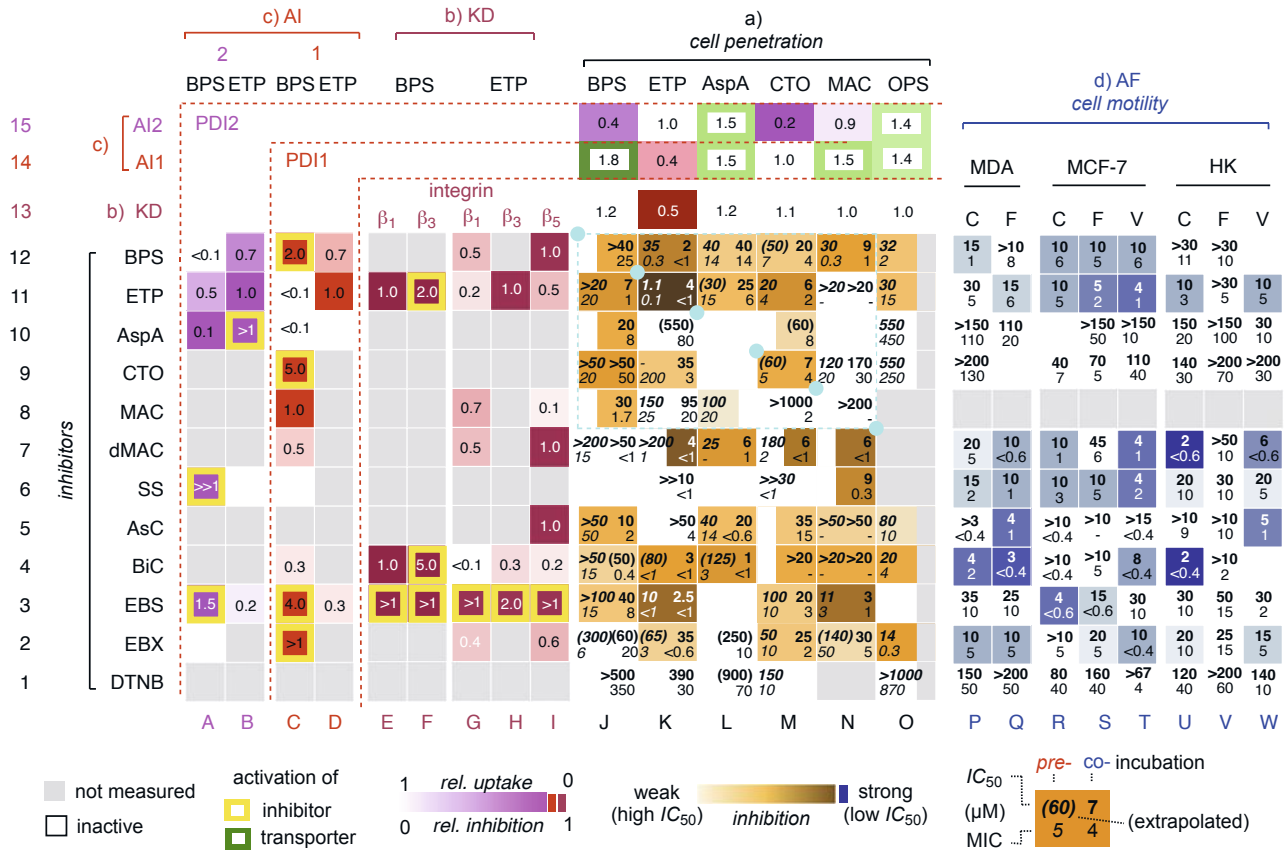

Fig. 6. Inclusive heatmap to decode TMU networks: (a) Central heatmap for CAX inhibitors (vertical, 1-12) of Fl-CAX transporters (horizontal, J-O), with impact of (b) knockdown (KD) and (c) alternative inhibitors (AI) on Fl-CAX transporters (13-15) and their inhibitors (A-I), and (d) inhibition of alternative function (AF). AI1 = 16F16, AI2 = LOC14, MDA = MDA-MB-231 cells, C = collagen I, F = fibronectin, V = vitronectin (V). Adapted from ref. [78].

shared with the related thioredoxins and glutaredoxins. It is reminiscent of the protein version of a CAX. For instance, the exchange of **29** with AspA **1** will produce **30**, which can continue to exchange to disulfide **28** and the opened AspA **31**, with the equilibrium between the two determined by their respective redox potential.

For chemical PDI removal, two inhibitors with different selectivity were considered, 16F16 **32** as alternative inhibitor 1 (AI1),[83,86–89] LOC14 **33** as AI2.[89,90] The results were surprisingly distinct. In the presence of the irreversible 16F16 **32**, TMU of ETP was strongly reduced (Figs. 7e and 6, K14). This suggested that the PDIs inhibited by AI1, referred to as PDI1 (Fig. 6) and P3 (Fig. 5), act as major exchange partners in the ETP pathway (bold dark red arrows, Fig. 5). In sharp contrast, TMU of BPS was strongly enhanced in the presence of AI1 (Figs. 7e and 6, J14). This result suggested that the same PDIs P3 that support TMU of ETP repress TMU of BPS (dashed lines, Fig. 5). The nature of P3 is unknown, similar structure and behavior of SDL3 suggest that GPX4 and TRX might be involved besides PDIs.

Results with AI2 were almost opposite to AI1. This inhibitor **33** did not support TMU of ETP (Figs. 7e and 6, K15). However, AI2 strongly inhibited TMU of BPS (Figs. 7e and 6, J15). This orthogonality implied that the target of AI2 is not involved in the ETP network (Fig. 5). Since LOC14 **33** is the only inhibitor that is active also against PDIA3, the observed selectivity identifies this intriguing PDI with many talents to act as a major exchange partner in the BPS uptake pathway (solid blue arrows, Fig. 5). Inhibition of CTO uptake by AI2 suggested that these CAXs penetrate cells along the BPS pathway (Fig. 6, M15, Fig. 5, blue solid arrows).

TMU of AspA increases in the presence of both AI1 and AI2 (Fig. 6, N14, N15). This suggested that the AspA pathway, with the transferrin receptor as the main exchange partner, is inhibited by both PDIs P3 and P4 (dotted golden lines, Fig. 5). The same double activation by AI1 and AI2 was found for OPS (Fig. 6, O14, O15). The interpretation that OPS exchange with the transferrin receptor to penetrate cells was supported by colocalization experiments. This result is of practical interest to understand and enhance the uptake of clinically relevant antisense oligonucleotide phosphorothioates **7** (Fig. 3).

The presence of strongly inhibiting cellular exchange partners in the AspA pathway nicely explains why self-inhibition is not effective. The inhibition of productive partners is compensated by activation through removal of inhibiting partners (Fig. 7, L10). At the other extreme, exceptionally powerful self-inhibition in the ETP pathway is understandable from the absence of inhibiting cellular exchange partners (Fig. 7, K11, Fig. 6).

Besides genetic and chemical partner removal, comparison of TMU inhibition with alternative functions of exchange partners was considered as the third strategy to expand the pattern generation in inclusive heatmaps (Fig. 6d). The dynamic covalent inhibition of cell motility with CAXs was of particular interest because of its potential for drug discovery, particularly thrombosis and tumor progression.[79] To efficiently screen through the CAX universe, an AHCHT wound healing assay was developed. Three different surfaces were covered with three different cell types, and 'healing' of a scratch in the presence of CAX inhibitors was automatically quantified. Consistent with ETP-independent TMU, BPS emerged as a comparably poor inhibitor of cell motility (Fig. 7c). In clear contrast, TMU of AsC along the ETP pathway coincided with efficient inhibition of cell motility. Such consistent trends were observed throughout the heatmap recorded for the dynamic covalent inhibition of cell motility (Fig. 6d). The pattern generated differs meaningfully with the pattern obtained for the inhibition of TMU, with, for instance, the integrin-independent BPS being overall less efficient to inhibit motility (J12-W12)

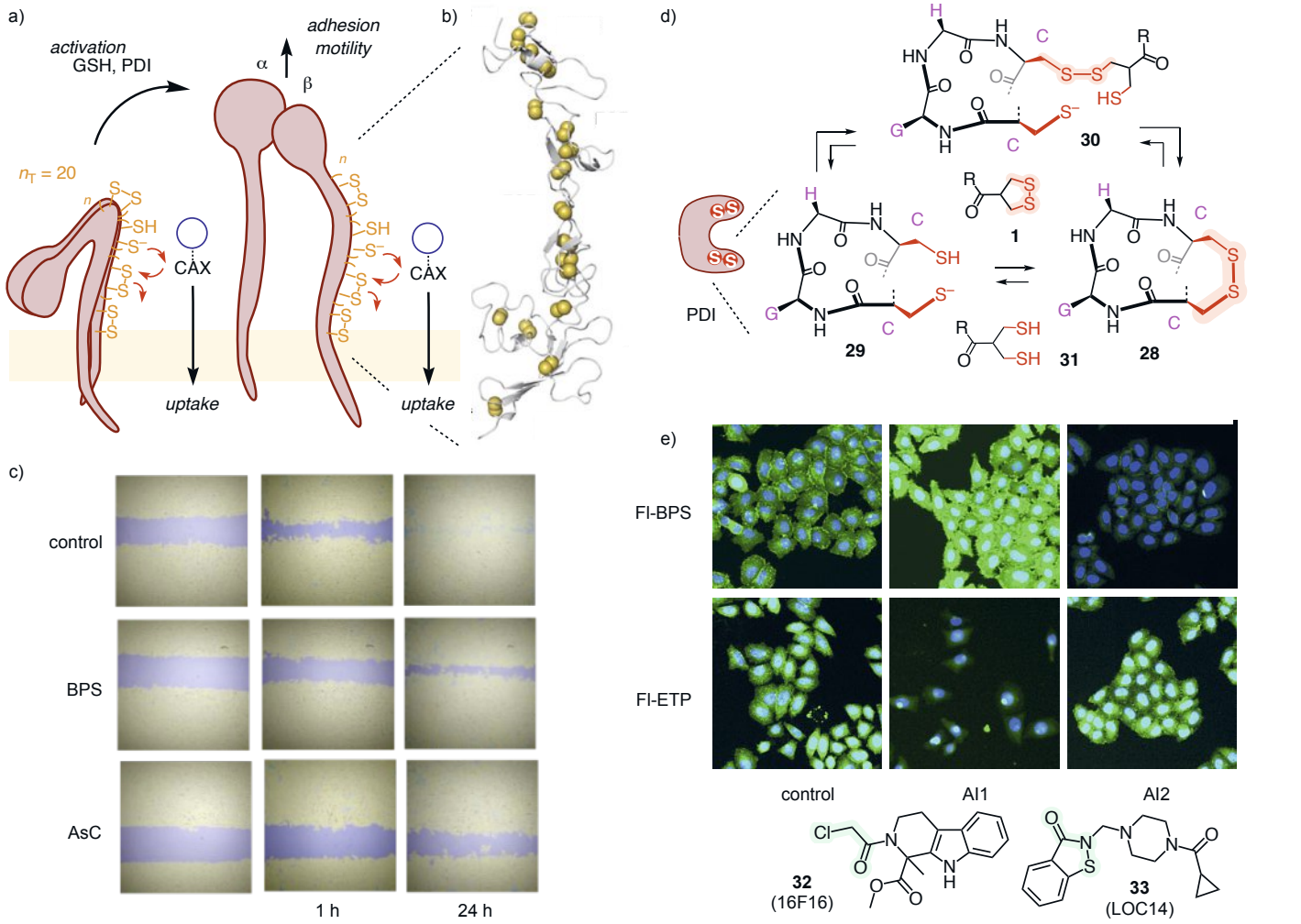

Fig. 7. Newly identified cellular exchange partners: Integrins (left) and PDIs (right). Integrins are a family of 24 heterodimers of α and β monomers, involved in cell adhesion and motility, signaling and viral entry. a) Activation from inactive, bent conformers into active, more linear conformers occurs by dynamic covalent exchange of GSH and PDIs with b) a beautiful track of 20 disulfides in the β-subunit. c) Inhibition of cell motility (yellow) to heal a scratch (blue) by BPS (middle) and AsC (bottom) as representative CAXs. d) The 21 known PDIs are involved in protein folding, signaling, cellular entry and more, operating with two disulfides at the *N*-terminus of an α-helix which controls ring tension and thiol acidity to generate the protein version **29** of a CAX like AspA **1**, capable of cascade exchange through intermediates like **30**. e) Dependence of cell penetration by Fl-BPS (top) and Fl-ETP (bottom, green) on PDI inhibitors **32** (AI1, middle) and **33** (AI2, right). Adapted from refs. [66,78,79].

than TMU when compared to the integrin-dependent ETP (J11-W11).

In summary, this ERC AdG grant suggests that time is up to crack thiol-mediated uptake. The key hypothesis is that a better understanding of the underlying dynamic covalent cascade exchange chemistry will be needed to succeed. In this spirit, new CAXs are being introduced, which in turn allow us to develop inclusive pattern generation methods and start to decode the dynamic exchange network that are suspected to be in place to bring matter into cells, in the broadest sense. Three almost orthogonal pathways have been identified so far. The AspA pathway has the transferrin receptor as the primary exchange partner, is inactivated by two types of PDI, and is used also by antisense oligonucleotide phosphorothioates. The ETP pathway has integrins and PDIs as primary exchange partners, is not inactivated by other exchange partners, and is used also by pnictogen-centered CAXs like BiC and AsC. The BPS pathway has PDIA3 as the primary exchange partner, is inactivated by other PDIs, and is used also by CTOs and, in part, MACs. The discovery of three orthogonal exchange networks accounting for TMU is of interest not only for drug delivery but also for drug discovery and the elucidation of similar networks involved in, for instance, biological redox homeostasis.

While different exchange networks account for what happens before and after, they do not explain how TMU moves SOIs across membranes. As for CPPs,[14] only the non-leaky passage through toroidal elastics can explain compatibility with giant substrates like polymersomes[91,92] or protein-covered quantum dots[74,93] (Fig. 5).[2] Although plausible, their existence in nature remains to be confirmed.

TMU has so far been inaccessible to the community because transporters are not commercially available, activities are not generalizable and poorly predictable, procedures on how to proceed with unknown SOIs are missing, and user-friendly kits are far from being ready. While a better understanding of the complex chemistry involved should generally improve predictability, several approaches toward traceless tags have been and are being explored to make TMU useful for the broader community.[58]

The identification of new exchange partners is attractive not only for drug delivery but also for dynamic covalent drug discovery and the decoding of related networks involved in, for instance, redox biology. Beyond antiviral potential, current examples relate to thrombosis and tumor migration, among others that are expected to emerge.[79] For TMU, the expectation is to decode the complete network in place to be ready to enable and inhibit cellular entry reliably on demand.

The discovery of new CAXs to map out cascade exchange chemistry is at the heart of the project. While dynamic phosphorus is the clear highlight so far,[66] the emerging cascade exchange chemistry of cyclic thiosulfonates[61] and oligonucleotide phosphorothioates,[64] TMU with reversible Michael acceptors[67] or cyclic selenenylsulfides under remote control[94] will attract future attention as well. Beyond TMU and other biological applications, new CAXs contribute to progress with fundamental principles in supramolecular chemistry and provide access to modern materials, dynamers[65] and beyond, with degradable, recyclable, adaptive and self-healing properties. Since we experienced the power of poly(disulfide)s first to grow ordered surface architectures for artificial photosystems,[95–97] we have emphasized the potential of CAX chemistry to access modern materials.[98] The current flurry of reports on polymerized lipoic acids,[99–103] progress with classical[104–106] and expansions toward new CAXs[49,54,107–109] start to illustrate well what will become possible when the entire emerging CAXs universe is considered seriously in the materials sciences.

Acknowledgments

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[1] C. F. Meyer, 'Sämtliche Werke, Band I, Gedichte', H. Zeller, Ed., Wallstein Verlag, Göttingen, Germany, **2014**, p 170.
Up springs the spout and, falling, fills
To brim the marble basin's round,
Which, under veiling, over spills
Into a second basin's ground;
The second one, too rich now, runs
Into the third its falling waves,
And each one takes and gives at once
And streams and stays.
Translation: R.-P. Wille, http://meyerbrunnen.blogspot.com/, accessed 25.7.2024.

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