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Screening-Based Translation of Public Research Encounters Painful Problems

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ABSTRACT: Whether identified through high throughput screening or in silico screening, and whether target-based or phenotypic, sets of hits will contain chemical con artists. Such pan-assay interference compounds (PAINS) and other subversive compounds continue to pollute the scientific literature. There are several angles of attack to aid identification of such nonprogressable molecules. One of these rules above all, and this is a demonstration of genuine structure−activity relationships. Recognition of this, which will require a greater effort in medicinal chemistry, will be of general benefit.

Without experienced handling, screening can wreak havoc. Do not get me wrong—I am a big fan of screening, in particular high throughput screening (HTS) to identify small molecule ligands of proteins. HTS is established as a successful technology that continues to rapidly evolve.[1] When fed into a sufficiently resourced medicinal chemistry engine, HTS remains one of the best ways to kick start the discovery of valuable tool compounds to help unravel the roles of proteins or of new drug classes for the treatment of diseases with unmet medical needs.

However, in uncritical or inexperienced hands, large amounts of misinformation can be generated and wrong directions taken. I would like to think, perhaps a little vainly but hopefully not in vain, that most readers of this journal will have heard of a big problem associated with HTS: that is, its ability to efficiently discover PAINS, or pan-assay interference compounds. These are classes of compounds that can chelate metals, alter redox cycle, covalently label − both reversibly and irreversibly − and photoreact. They may exhibit one or more of these behaviors in a single molecule. In this way they can signal in biochemical assays and then also in cellular assays designed to support mechanism of action, even though the signal in the former may not be causative of the signal in the latter. Even desired activity in vivo may be observed without necessarily coupling to either of these upstream readouts, but the apparent links can be convincing enough to enable publication in high impact factor journals, an irony exacerbated when medicinal chemistry-savvy reviewers may be overlooked in these more biologically focused journals. The higher the impact factor journal that PAINS appear in, the more likely they will be picked up by vendors who on-sell these misleading and dangerous compounds as useful probes to other researchers. Thus, a destructive cycle is set in motion. Adding insult to injury, costly patent streams protecting valueless compounds are readily initiated through University tech transfer offices keen to demonstrate research translation. While the focus in this article is on academic research, it is important to realize that equivalent problems arise in less HTS-experienced drug companies too.

Concerned with the collective resource waste, we have verged on being strident in our calls for more attention to be paid to this issue[2−5] and are pleased that the prevalence of these nuisance compounds in sets of screening hits is increasingly acknowledged.[6]

However, PAINS publications continue to issue forth. So how can readers recognize likely PAINS publications?

Their hallmarks typically comprise the following: little or no medicinal chemistry optimization, unconvincing structure−activity relationships (SAR), relative lack of improvement in biological activity to meaningful levels that often hover around the micromolar mark, and molecular modeling described as though it is an experimental observation of relevant binding sites. Also, the literature is frequently ignored as an important SAR source of evidence that similar compounds appear to be hitting different targets and could be promiscuous.

To counter this lack of information, speculative details on binding interactions and excessive focus on downstream biological interrogation on unoptimized screening hits is rife. In vivo data may be presented to support target validation in the absence of any PK/PD evidence that there is sufficient exposure to plausibly construct such a link. Conclusions of compound utility are unfounded and the question "are these compounds demonstrably useful?" remains without an answer based on data provided. For the reader's edification, a selection of recent representative publications that have been brought to my attention by PAINS converts and which to some extent have been discussed in the social media can be readily provided.[7−11] Medicinal chemistry centric journals are not without guilt, and in the interests of fair play, I have included an example from this journal in this selection. However, with more medicinal chemistry, compound utility can be judged to be firmly in the positive based on clear SAR and optimization to low or mid nanomolar levels of activity.[12−15]

So why is it that PAINS publications continue to appear?

One reason is that HTS output may be disconnected with experienced hit-to-lead medicinal chemists. In fact, the whole process from protein expression to publication may be undertaken by people not in the habit of reading medicinal chemistry journals. Structural red flags may not be sought or recognized. It may not be realized that PAINS are likely to

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outnumber progressable hits, may appear to be more potent, and can appear to be selective.[16] However, when we were discovering PAINS about a decade ago, it never once crossed our minds to portray and publish them as genuine and progressable hits. It was clear to us that SAR showed that they were not. It is hard to understand how research groups appear to think otherwise. Some may not want to know or to understand. Worse − and unconscionably − there may be instances where the pressure to publish overrides lingering concerns or even a firm belief that disclosed compounds may not be useful ("my student has spent a year on this screening hit, so they have to get a paper out of this effort, regardless").

Inexperienced reviewers and editors may serve the role of unwitting accomplices or in some sense wittingly, in that pressured editors, in the face of proliferating journal competition, may treat critical reviews more leniently than they should. I have experienced this very recently with a well-established journal that should have known better and I will not be reviewing for that journal again.

Screening too few compounds, perhaps even as small a number as several thousand, is a contributory problem. An understandable attraction to academic researcher with a tight budget is the relative affordability and that such an exercise may not even require access to robotics but just the services of an on-site research assistant. However, screening too small a library of unbiased commercially available compounds may not return a progressable hit. In contrast, it will certainly produce artifacts that are then more likely to attract unwarranted further attention. This problem is exacerbated in Australia, which has no dedicated fund for HTS despite its somewhat frustrating status of, in my view, having some of the highest quality publicly accessible HTS libraries available.[16] Rather than "catching every fish in the ocean and only keeping the good ones", inexperienced grant review panels tend to think of HTS as a "fishing exercise", a term that if mentioned instantaneously dooms the proposal to failure in this sadly risk-averse funding environment. However, a proposal with a small screen as a cheap component may attract less scrutiny and elicit fewer objections.

A relevant question then is how many compounds should one screen to find worthwhile starting points for optimization? I believe that even screens of 30,000 compounds are suboptimal, especially for difficult targets. For highly druggable targets, some progressable hits will plausibly be unearthed, but why not screen 150,000−250,000 compounds to find better hits that could potentially save years of medicinal chemistry optimization? A good deal of the cost of such an undertaking, which does not scale linearly, would have already been borne in screening 30,000 compounds. For certain applications, such as kinase orthosteric inhibitor discovery (luciferase interference aside in reporter gene assays) focused library screening can be useful. Otherwise, there is a reason why pharma favor screening deck sizes of 250,000 compounds or more (or 100,000 for phenotypic screening). There are examples where 1 M or even 2 M compounds were screened to obtain suitable starting points for drug discovery.[17,18] This sort of effort is less common now and likely to be beyond the scope of most academic sites but nevertheless serves as an important message about the inadequacy of screening too few compounds for difficult targets.

Of course, the appropriate library size to screen is dependent on compound and assay design, screening concentration, cutoff criteria, and nature of target. By way of example, the main Australian HTS libraries were designed on lead-likeness (such as mw 150−400) with exclusion of highly similar compounds to result in good coverage of available chemical diversity space. One of our most successful protein−protein interaction inhibitor programs was derived from such a library of 100,000 compounds that yielded, among numerous time-wasting PAINS, just a single progressable hit (this was our first, stage 1 library[16] and hence contained PAINS because we had not learned what they were then). There was no cell-based activity, as to be expected from a target-based screening hit,[4] but with around 5−10 years worth of medicinal chemistry optimization, this has gone on to furnish a globally unique and valuable tool to probe Bcl-XL pharmacology.[12−14] Worryingly − or amusingly, depending upon your point of view − the screening hit responsible for all this was one of the last compounds purchased for our first library (100,308 to be precise) and had we stopped library expansion at exactly 100,000 compounds, no useful outcome would have resulted from all our effort. The importance of this issue for difficult targets cannot be underestimated especially when the foundation for such a program might comprise decades worth of effort in biological research by the host institute, as it was in this case, which can then reap the rewards associated with having control over a unique pharmacological tool. A small, so-called PPI focused library − available off-the-shelf from many vendors − would not have been useful here nor would an unbiased library of 30,000 compounds or a phenotypic screen.

Some believe that screening fewer compounds is more acceptable, and for obvious reasons, even desirable, when those compounds are FDA-approved drugs. However, not only is such an exercise fraught with seldom realized limitations,[19] but some drugs can form aggregates that signal promiscuously in biochemical assays at micromolar concentrations,[20] while others contain PAINS moieties that will do the same.

While I have deliberately focused on target-based HTS, PAINS are discovered just as readily by other techniques, such as fragment-based screening and screening in silico, and indeed the latter technique dominates the problematic screening papers cited earlier. Phenotypic screening may allow for some leniency, both in terms of library size and structural scrutiny, but in most cases one would not progress a PAINS-containing phenotypic screening hit unless there is clear and genuine SAR.[3,4] Further, it is possible that some amphiphilic phenotypic screening hits may simply be signaling through membrane perturbation.[21−25] While this may be common knowledge among experienced scientists, on the basis of some recent exchanges, we anticipate a new wave of phenotypic screening publications and patents unintentionally reporting on HTS hits or drugs that are actually signaling amphiphilically and not specifically (Figure 1).

So what can we collectively do as a drug discovery community to reduce such wastage of the precious research dollar?

One thing to do is to exclude PAINS when establishing new HTS libraries, although it may be difficult to implement PAINS filters to accurately achieve this. This is what we have chosen to do with our more recent library expansions[16] because it alleviates the awkward situation of having to dissuade colleagues insistent on pushing unprogressable hits. Why pay money for a PAIN that takes the place of a better compound? It can take an extraordinary amount of meticulous investigation to reveal PAINS behavior,[26] so why allow for this possibility in the first place by having such compounds in your screening deck?

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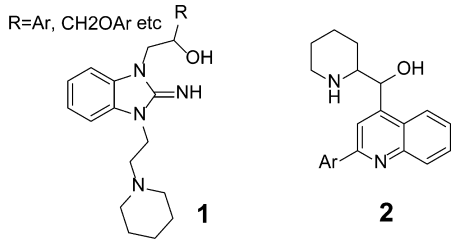

Figure 1. While cationic amphiphilic drugs (CADs) are well-known to be membrane active, screening hits (CASH) are more likely to fly under the radar. We have reported on iminobenzimidazoles **1** as trypanothione reductase inhibitors, but believe these and quinolone methanols **2** have additional membrane-active properties that are causing them both to appear throughout the screening literature (including many patents), particularly **2**. There will be many other compounds with these properties.

It is consequently logical to suggest that vendors expunge PAINS from their collections, but on this matter I am less certain because it is conceivable that PAINS may have utilities unrelated to in vivo applications. In respect to the latter and as discussed later, even here there are circumstances where a PAIN can be a valid starting point, so it may be convenient should such a compound or set of compounds be available for purchase.

If your HTS library already contains PAINS, which it will if they were not excluded during purchase, one could potentially go to the effort of cherry-picking these out from your library. However, this may not always be feasible or economical, and it may be easier to accept the fact that they will appear as screening hits and to triage accordingly. There are published assays for chelation, redox activity, covalent labeling, and amphiphilicity to aid this endeavor (watch out for an April/May 2015 Assay Artifacts Chapter in the NIH/NCATS Assay Guidance Manual). In some ways it seems messy for every lab to set these up, and it makes a certain sense for a battery of such assays to be centralized, perhaps in designated centers in Europe, Asia, and the US to serve as one-stop-shops to return standardized assessments.

Another way to recognize PAINS is structurally,[27] including the use of electronic filters[28,29] (care has to be taken here as poorly converted filters are in widespread use and while the SLN-based Sybyl implementation is accurate, most SMARTS-based implementations including our own in KNIME[29] are less so and can inappropriately filter out non-PAINS cores, except for the FAF-Drugs2/3 implementation and this performs well).

Apart from desisting in screening too few compounds, we also need to collectively change our attitude. We need to acknowledge how easy is it to find compounds that signal in assays in unexpected ways. If you find curcumin or an alkylidene rhodanine as a hit in your assay, you should not be excited, you should run for cover after having performed a literature search that reveals unworkable promiscuity. Your PAIN may not have a name for convenient searching, so you need to perform a structural search. This needs to be a substructure search. Nonchemists tend to only perform similarity searches, and this is inadequate.[16] I am not saying it is easy to drop a compound based on the information derived at this point. My experience is that one almost has to have been burnt by PAINS in hit-to-lead optimization to be able to do so. Fiscal pressure also influences judgment. Does one refuse financial support from a successful grant proposal to support a post-doc in your lab to work on compounds of doubtful merit? To what extent should optimistic pragmatism yield to ruthless realism with the result being to be cash poor? As an academic, I am not immune to these pressures. The life of the academic research is tough, and correspondingly these are tough questions to address.

We need to recognize the astonishingly limiting bottleneck created by the pace with which hit discovery through HTS so overwhelms the subsequent and necessary medicinal chemistry optimization. Impatient biologists may find it hard to understand that HTS heralds just the start of a multiyear journey of medicinal chemistry optimization. In this context, the medicinal chemists among us could do a better job explaining to biologists that drugs are not discovered through screening or design, but principally through medicinal chemistry. Zelboraf (vemurafenib/PLX4032) was not principally discovered through FBDD nor Navitoclax (ABT-263) through SAR-by-NMR. The principal science of their discovery was medicinal chemistry. Also, even though we medicinal chemists love structural biology, too often we are party to overplaying its role in order to appease reviewers and publishers, or even team managers.

We need to adopt a fact-driven and evidence-driven behavior rather than that which is progression-seeking and to recognize that this is as relevant to academia as it is to industry.[30] We also need to realize that lead-like chemical diversity space is so poorly represented that a target based screening hit will almost certainly never be topographically optimum for its target: significant medicinal chemistry optimization will be necessary to obtain a better and more useful compound, and this should take place initially within the volume of the scaffold.

However, HTS libraries cleansed of PAINS will still likely harbor new chemotypes capable of finding new ways to be promiscuous. Further, it may not always be obvious when counter assays – if and when they are centrally established – designed to detect PAINS behavior in vitro will be predictive of intracellular promiscuity. Cultural, structural, and behavioral change takes time. New and inexperienced research groups will continue to take up HTS. In short, reviewers will continue to receive PAINS manuscripts for the foreseeable future.

"PAINS-shaming" is borne of exasperation and has the potential to be quite effective in making researchers (and publishers) think twice about attempting to publish around poor quality compounds.[31] I am a little uneasy about this tactic because of linguistic connotations with the potential to be culturally insensitive. There is no suggestion that the science is fraudulent. Also, it can be hard to identify scientific flaws without reproducing and perhaps elaborating the research in question. It is possible that author intentions are honorable and reviewers merely unaware. Granted, among the exemplary papers selected earlier, there is disappointing science necessarily accompanied by sloppy editorial and reviewing efforts.[32,33] However, there is also better science, such as analysis of binding kinetics by SPR. In some cases compounds are only PAINS-like, but not actually recognized by the PAINS filters, and so there may be less certainty about how problematic such compounds are. Also, in some cases, sets of analogues are constructed in an attempt to demonstrate SAR. Nevertheless, in none of these examples cited is the extent of medicinal chemistry adequate to produce sufficiently optimized offspring and SAR that proves the compounds are in any way truly useful. Given the propensity for screening to find compounds that falsely signal, the logical conclusion is that these compounds are very unlikely to be genuinely useful tools,

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especially considering their generally problematic structures. Coupled with the potential for damage such papers can instill, I think it is useful for the drug discovery community to have papers with conclusions of questionable merit identified. Some may be concerned enough to be comfortable with the term "PAINS-shaming" when doing so. Either way, I find it reasonable to iterate[2] that such publications constitute pollution of the scientific literature.

Let me take a moment to relay an anecdote. One of my sons, who is studying psychology at University, recently came up to me after a Facebook session with his Aunt, who is privately employed outside of the biomedical research sector. He asked me whether it was true what his Aunt said; that published academic research is not to be trusted. I was about to respond strongly in the negative, then paused. I felt compelled to outline Amgen's and Bayer's now well-known inability to reproduce but a small proportion of published public biomedical research. A lengthy and robust discourse ensued that, among a variety of issues, touched on the fact that the complexities of scientific research and its reporting does not mean irreproducible research from one laboratory to another constitutes scientific fraud. Nevertheless, while we could not quantify the sums involved, we both agreed that significant taxpayer's monies were, in effect, wasted. I left the conversation feeling uncomfortable. Why I raise this anecdote is that while most PAINS publications will neither be fraudulent nor irreproducible, if they are not of value then the common theme here is accountability of the precious public research dollar. We are all members of the same club. Social media's reach is wide and long and could be a powerfully negative force none of us would want to reckon with.

However, back to PAINS: for sure, complexities abound, and that some of these features are present in known drugs, may cause inexperienced scientists to question the relevance of PAINS to drug discovery; but, it is only a small percentage (6−7%) of drugs and restricted mainly to a few, generally quirky, narrow and unattractive classes: tricyclic neuroleptics, catechols, quinones, and azo dyes.[2] Many of the catechols are substrate mimetics based on catecholamines and administered intravenously. The quinones are cytotoxic DNA intercalaters derived from natural products and are highly toxic. The azo is group is a prodrug that is bioreductively cleaved in the gut. Tricyclic neuroleptics are pharmacologically promiscuous and also nonspecifically membrane active at screening concentrations. Above all, these drugs were discovered through traditional means, not target-based unbiased HTS of vendor-supplied synthetics. Granted, it is possible that a tricyclic neuroleptic could form the basis of target-based progression if you really wanted to go down that path. However, catechols and quinones are moieties clearly associated with nonspecific reactivities.[2−5] To justify progression of a catechol or quinone target-based screening hit for, example, on the basis that such moieties are "present in known drugs" is not sensible for the reasons just outlined, yet commonplace.[34]

Certainly, other apparent anomalies can be confusing. Consider eltrombopag, a drug with a name as ugly as its structure but is nevertheless an effective thrombopoietin receptor agonist approved by the FDA in 2008 for chronic idiopathic thrombocytopaenic purpura (this may be a case where higher potency allows for lower doses that clearance mechanisms can handle to circumvent potential toxicity). This compound started with an azonaphthalene screening hit in a cell-based luciferase reporter assay,[1] recognized as a PAIN by virtue of the azo group. We know less about azo group interference than we do for the rhodanines, for example, and so already an azo hit may warrant further attention in certain circumstances. Nonetheless, a library purged of PAINS would not have led to this hit. There are sporadic other cases of a PAIN progressing through hit-to-lead that we have discussed elsewhere.[2−4] Further, while one would not recommend such a route, one could not rule out fortuitous discovery of a drug starting with a target-based PAIN that through undetected off-target polypharmacology accessed during what would normally be considered to be premature escalation successfully progresses all the way.

What a shame there is no single, simple, universal way to separate the wheat from chaff!

Well, actually, there is. There is a simple and complete solution to trap all publications describing compounds of limited utility, and this solution has been a theme throughout this viewpoint. To some readers this theme will already be clear, to others it will be obvious in hindsight. The solution is first predicated on reviewer expertise. We have previously described certain points that reviewers need to look for, such as orthogonal assays, binding kinetics, literature substructure searching and discussion, convincing SAR, cellular activity typically much weaker than biochemical activity and only kicking in with biochemical IC_{50} values of say less than 500 nM (if activities are similar, then suspect off-target cellular activity), biomarker responses in both biochemical and intracellular assays, and logical PK/PD.

There is, however, one of these that rules above all, and it is as simple as A−B−C, or should I say SAR; that is right, SAR, convincing hit-to-lead SAR, whether phenotypic or target-based. As simple as that. Not SAR by catalogue − that will always be insufficient − but focused SAR derived from medicinal chemistry optimization. SAR typically starting with truncations to show that all parts of a hit are important, then modification within the core as well as Topliss-like substituent SAR, then, if required, expansion SAR. SAR where, for example, optimization from micromolar to nanomolar levels of activity is demonstrated. SAR with activity cliffs, where relatively similar analogues display sharp variances in activity of at least 100-fold. Even if your compound acts covalently, this may still be acceptable with clear SAR elsewhere in the molecule as just described. While generally ≫100 analogues is necessary, typically requiring ≫1FTE years, on occasion a few dozen analogues, may be sufficient to demonstrate this SAR. That is, it may not be an insurmountable task to undertake in an academic setting.

In every suspected PAINS paper I have ever seen, in every publication describing compounds of uncertain utility, a genuine medicinal chemistry effort and genuine SAR like this has been absent. Apparent anomalies such as eltrombopag and others[4] are no longer anomalies with recognition of the clear antecedent SAR. While evidence of pathway selectivity may usefully support the value of such compounds, I do not believe exhaustive selectivity profiling is a prerequisite because obtaining this and in any case knowing exactly what this means may be nontrivial and more suited to subsequent investigation.[35] The main thing is the SAR to show that the activity is real in the first place. I do not mean to be glib. The concept sounds simple, but it took me more years than it should have to truly appreciate how important SAR depth is in this context.

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When journals recognize how easy it is to discover false hits and leads and enforce this requirement of genuine SAR, admittedly usually hard won, then this problem of valueless publications – and this is the main problem – would largely have been solved. There is a trend for the leading paper in a biologically focused journal to contain only chemistry snippets with the bulk reported in specialist medicinal chemistry journals. This is quite workable as reviewers of the leading paper can be supplied with evidence of the depth of SAR during review.

We need to be careful of knee-jerk reactions. So while one would seldom recommend progressing a target-based PAIN, and while a reviewer should view any such manuscript (or grant proposal!) with extreme caution and anticipate rejection of a vast majority, there may be occasional redemption if true SAR as described above is demonstrated and especially with successful morphing onto a non-PAINS scaffold. We need to stick to evidence-based decision-making and not dismiss a compound on the grounds that it is ugly or resembles a PAIN. There is confusion in the literature here, and some are recognizing compounds as PAINS when they are not. Indeed, one of our most successful hit-to-lead programs[12−14] was based on just a single hit that could be called ugly and contained a carboxylic acid, a furan, a hydrazone, and a 2-amino-benzothiazole, with a cLogP of 5.2, no cell-based activity, and no in vitro biomarker activity.[4]

To facilitate this change in publication culture, those with oversight of screening projects must recognize the need to engage sufficient medicinal chemistry. This behavioral change may take time. At odds with its utility and value-adding potential, public medicinal chemistry is globally under-resourced, so capacity is also an issue. However, there are promising signs. Look at NCATS. Though I speak as an outsider from another country, an initiative like this looks to me like a move in the right direction to start to widen this translational bottleneck. Excellence is already being practiced in several academic settings around the globe. To select just a couple of examples, look at the work emanating from the Frye group at the Center for Integrative Chemical Biology and Drug Discovery in the UNC Eshelman School of Pharmacy, or Pollastri's group at NEU. We still desperately need better global funding in this space but it is reassuring that some sites - albeit generally led by medicinal chemists - not only recognize the need for medicinal chemistry optimization but importantly, have found ways to support sufficient medicinal chemistry to enable publications around higher quality compounds. Of course, major roles will continue for medicinal chemistry both outsourced with an upstream focus and within industry with a downstream focus, but, and subject to better resourcing, there promises to be a special and much greater role for University-based medicinal chemistry, particularly in higher risk projects: challenging chemistry to validate risky biology, higher in innovation.[36] Successful public hit-to-lead derisking with increased likelihood of licensing a more valuable product – the creation a valuable bridge between University biology and pharma lead optimization, for example – sounds like a win–win translational situation to me. An internal hit-to-lead program can allow for creative and interdisciplinary information exchanges with breakthrough results in a manner that simply would not happen if this was outsourced. Universities need to better occupy this space and showcase their successful medicinal chemistry. This will help to keep biologists on-side as well as performing a valuable educational role. It will also undermine the notion readily seeded in some University Departments that medicinal chemistry-led drug discovery belongs in pharma and not the public arena. In contrast to the tarnish applied to target-based HTS by those with bad experiences imposed by inadequate hit-to-lead prosecution, successful outcomes will support current thinking that this approach is one of the best ways to discover new chemotypes for new biology.[37]

OK, so some journals may become starved of a previously lucrative source of publications. Correspondingly, the proportion of publications reporting useful compounds will surely increase. Less time will be wasted on propagation of poor research fueled by inadequate tool compounds. The low regard in which much academic drug discovery research is held by many within industry – perhaps to an unfair degree that at times in some chemistry blogs seems close to an impasse – will shift upward. Fewer dollars will be spent on protecting disingenuous intellectual property and allow for more to be spent on that of real value.

For every medicinal chemist at the public–private interface, would such outcomes not be the realization of his or her every dream?

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Notes

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