The apocalyptic horsemen of drug discovery and development

The pharmaceutical industry should consider an 'evolutionary disease management' approach based on homeostasis, irreversibility, biological alinearity, "pseudo-N-of-1' health and disease states' and narrative medicine best practices in order to help secure a successful drug development future

By Dr Gary J. Keil

The issues discussed in this article have defined the success, and failure, of pharmaceutical research and development, and disease management more widely. Each area contributes individually to the low success rates across R&D, but they need to be addressed in aggregate if long-term changes are to be brought about. Because most biological systems are based on the characteristics described and they are not readily amenable to external forces, a new R&D paradigm is likely required. While the primary areas of focus are discussed in philosophical terms in the current perspective, concrete steps can be initiated in order to address them and processes altered to embrace them, helping to make the areas discussed the means to improve novel drug development and improve clinical outcomes. The points here are also paralleled within organisations, and can be used to help improve not just what is done within companies and research labs, but how. Research and clinical entities should consider how they operate as 'living organisms' with similar constraints (resistance to change, etc) of the individual employees, patients, departments and processes. Embracing an 'evolutionary organisational management' paradigm would be expected to maximise individual employee development, and help secure a place for them, and their employers, in the ever-changing future environment.

Background

Discussions by those involved in pharmaceutical research and development (R&D), as well as the beneficiaries of the collective work, often include asking what processes need to be further refined in order to improve the success rates and decrease the timelines behind the delivery of vitally-needed novel medications. Perhaps appropriate to the scientific foundation of the industry, many have supported the contention that similar scientific approaches would highlight high priority areas and guide process improvement activities. This approach has solid footing in that reductionistic sciences to understand the human body have led to dramatic understandings of how the individual parts work. By certain metrics the combination of traditional scientific-based 'trial and error' approaches and lean sigma/process improvement approaches have led to significant improvements in pharmaceutical R&D[1-4].

These activities, however, have failed to produce dramatic improvements in the key metric for the industry: the continued delivery of novel new medications to patients[5,6]. Perhaps the well-intentioned questions that have been asked, and multiple analyses subsequently conducted, represent subsets of higher-level issues deserving attention. Perhaps the reductionistic approach to R&D process analysis, ie continued dissection of the parts into the smallest fractions describable to our work, has provided minute details that must now be woven back into the overall tapestry of the industry's fabric. Perhaps it is an appropriate time to add higher-level debates and to begin revisiting the 'basics' of biology that may have been forgotten among the significant scientific and technological advances in the past few

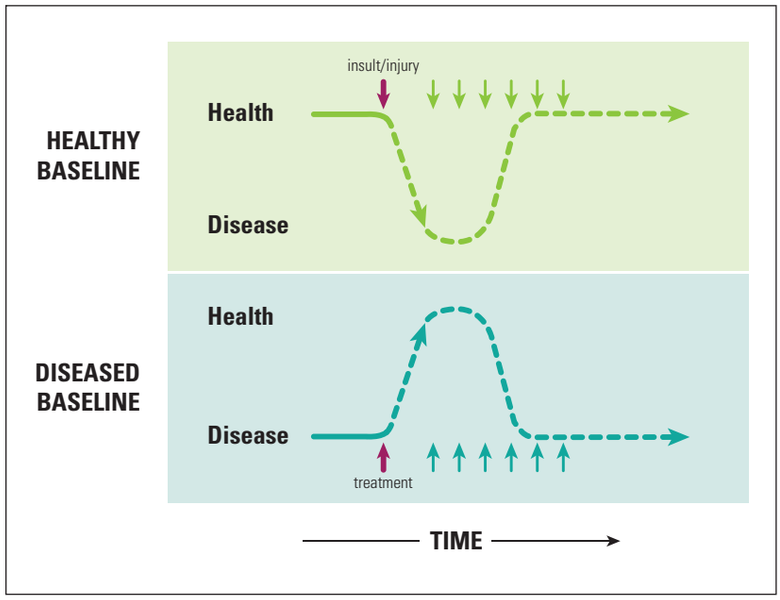

Figure 1
Homeostasis: The propensity of most biological systems to return to a pre-set value, regardless if baseline is one of health (upper section) or disease (lower section). For example, when a healthy person is exposed to an insult or injury (maroon arrow) the deviation towards 'disease' is reversed over time; importantly, too, even if subsequent insults/injuries continue (green arrows). The ultimate return to 'health' may not occur fully but the propensity to return to the healthy baseline fortunately exists. Unfortunately, a similar propensity exists for systems in a diseased baseline state such that treatments (singly or over time) will be fought by the system

decades. And if these basics are brought back to the forefront of our discussions, perhaps it may be appropriate to begin asking if there needs to be more radical shifts in our worldview and practices in order to get us to a new world only dreamt of before.

The utility of myth, metaphor and allegory

Myths, metaphors and allegories are simply means to help frame the discussion of certain topics, and to help them be understood in ways that are meaningful as well as transcendental (beyond the specific topic at hand)[7]. A rather well-known story of the Four Horsemen of the Apocalypse will be adopted for the current perspective. The broadest sense of the apocalyptic story revolves around the end of the previous (historical) world, the 'battle' of the components of the current story and the ultimate establishment of a new world order. The four horsemen are harbingers (omens) sent to set a divine apocalypse upon the world, serving as vital links between the old and new worlds[8]. The myth/allegory approach also allows us to frame the discussion points in ways slightly different than in typical scientific discourse, an approach congruent with the thought that: "We can't solve problems by using the same kind of thinking we used when we created them" (Albert Einstein).

The timelines (pre- versus post-apocalypse), the players (horsemen) and the outcome (a new way of working) in the final judgment story can be applied here with a major exception: the current apocalyptic horsemen represent distinct areas amenable to our discussion and attention, and we are ultimately in charge of our own destiny.

The apocalyptic horsemen of the pharma industry

The following areas represent a rather familiar set of issues inherent to pharmaceutical R&D efforts and issues that are taught to students at very early educational times. Their description is not meant to offend any intellect, but to highlight salient points that may have been forgotten or 'sent to pasture' because of their simplistic and fundamental nature. Their importance, however, cannot be underscored and they represent not only the harbingers of our own world but, perhaps, the means to create a world more paradisiacal than the current one.

Horseman #1: Homeostasis

Homeostasis is the propensity of any biological system to maintain its current state, regardless if this state is healthy, predisposed to disease or acutely or chronically diseased. Moreover, homeostasis must be thought of as a non-static integral: biological status as a function of time. In a 'healthy' person, this is a continued and predictable trajectory of their biological system. A person in a 'prediseased' state is healthy but on a trajectory heading toward disease, while a diseased person has exceeded a certain threshold. All of these populations, however, have an established 'homeostatic set point.' Biological systems are designed by nature to fight pressures to change from their homeostatic set point (whatever the current set point is) and will recruit massively redundant systems to thwart any deviations greater than normal background variations. Importantly, homeostasis helps a healthy system to be healthy just as much as it does a diseased system to be diseased. 'Resetting the homeostatic bar' is the ultimate end-goal of disease mitigation, so biological systems must be completely reprogrammed if long-term changes are to ever be realised; treatment of symptoms, therefore, will fail unconditionally in the end. An additional but critical point to keep in mind is that human health and disease in developed countries are, metaphorically, 'already at war' with their environment, ie our physiological and genetic make-up are evolutionarily hundreds of thousands of years old, but we have been living in 'non-native' environments for generations, being exposed to 'non-native' pathogens or removing pathogens from our evolutionarily 'native' environment, and are living in altered diurnal and seasonal light/dark cycles due to artificial lighting, eg[9,10]. Even when we are 'healthy' we are, in effect, already living in

conditions that run counter to true (or evolutionarily-based) homeostatic set points.

Horseman #2: Irreversibility

Biochemical processes are frequently irreversible in nature and manipulations that attempt to 'undo what has already been done' might be considered futile activities. Differences between irreversible processes and dynamic, reversible homeostatic maintenance processes exist[11,12], but must not be confused. For example, phosphorylation and dephosphorylation of target moieties can represent one or the other, or both. Moreover, trying to reverse the primary steps of a multiple step process should be viewed with much caution – using an equine analogy, shutting the gate once the horse is out of the pen does nothing to get the horse back in. Blocking additional damage by inhibiting the primary cause(s) (ie shutting the gate to prevent more horses from escaping) is an obvious first step, but if irreversible changes have happened, attempts to reset the system by concentrating on those same systems must not be pursued. Manoeuvres to correct the sequelae of the original changes, therefore, may represent the best strategies. To put it differently, the causative agents of disease (genes, aberrant protein processing, etc) may not be the same as the curative or restorative agents of disease mitigation.

Horseman #3: Biological alinearity

Biological systems are complicated networks that do not generally operate via simple linear input-output processing mechanics or algorithms. Receptor reserve, asynchronous and synchronous neuronal circuits, retrograde signalling, polymorphic and partial protein expression, cell, tissue, organ and circadian supercycles and stochiastic gene and protein expressions[13-21] are just a few examples of biological complexity that underlie the massively dynamic ranges observed. These also critically determine the ranges of fluctuations of physiological phenomena in health and disease. Transient dynamics of signal transduction pathways are inherent to physiological systems, but

Figure 2
Irreversibility: An equine analogy illustrating that irreversible outcomes can result from external influences on biological systems, and that targeting the primary cause of disease may limit further disease but may not represent the same target(s) to reverse disease. Simply put, if an event occurs opening a pen gate and allowing a horse to escape, shutting the gate does limit other horses from escaping (ie, limiting disease progression) but does nothing to get (or even prevents getting) the escaped horse back in. A completely different gate may need to be designed

changes including cell differentiation and apoptosis can be initiated when even small and transient deviations exceed certain thresholds[22,23]. Preclinical or clinical studies optimised on linear input-output formats may provide flawed data that do not adequately represent what happens on a systems-wide level. Attempts to address alterations in single or multiple system points (via selective- or non-selective-pharmacological agents, respectively) in timeframes that do not adequately allow the full system to 'respond' need to be seriously reconsidered as they would also not likely provide data that represent long-term outcomes.

Horseman #4: "Pseudo-N-of-1' health and disease states'

Human health and disease populations have been traditionally defined according to blunt and grossly simplified population segments (eg anatomical pathology). Studies showing that significantly different genetic and phenotypic states of monozygotic twins are the exception and not the rule, that variations up to hundreds-fold of certain copy number variants can result in similar physiological states where variation of only a few percent from basal levels of other systems result in disease, and that individuals can significantly alter their own physiological states by simply altering their routine diet over time or are exposed to novel environmental agents[24-27] are just a few examples that help explain the finding that experimental power is not necessarily gained solely by increases in numbers of test subjects reviewed in, for example, the use of meta-analysis[28]. Significant variation of the timelines behind the progression of health to predisease, to acute disease, to chronic disease and through disease mitigation most likely exists. Indeed, many genome-wide association studies are identifying scores of previously unknown susceptibility loci[29] that suggest multiple forms of disease states likely exist. Experimental protocols which maximise the individual situation while providing aggregate information (ie 'pseudo-N-of-1' testing protocols) should, thus, be considered as the only tenable protocols to use in R&D and treatment settings.

Horseman #5: Narrative medicine best practices

'Narrative medicine' is defined as the validation of the experience of the patient, and the encouragement of creativity and self-reflection in the patient and physician through holistic (eg physical, emotional, societal, etc) descriptions of the patient's life. Narrative medicine is experiencing resurgence in ever-widening circles, but major shortcomings in the type and quality of care of patients remain[30]. Critics have decried the industrialisation and 'professionalism' (versus 'personalisation') of medicine for decades, emphatically contending that medical training and practice settings have all but removed the human touch from what has historically been medicine's primary focus: the treatment of an individual's whole life story and how it relates to the person's health. Indeed, concentrating not just on their medical history, but their individual story that includes ancestors and friends, interests and spiritual orientation were the cornerstones of the medical profession. Clinical trial designs and practice settings that treat medical problems merely as problems to be solved, without taking into account the specific psychological and personal history of the patient, will most likely fail; narrative medicine, on the other hand, will most likely succeed. This is not to say that narrative medicine best practice is not without potential 'downsides'. For example, appropriate care and attention to a person's suffering and concerns leads to extremely high 'placebo responses' – responses that indicate the power of the human mind, not its limitations. Indeed, it has been suggested the 'placebo response' should be redefined as the 'meaning response': the physiologic or psychological effects of meaning on the origins or treatment of illness[31-33]. Clinical trial design must be altered, therefore, to accommodate, not mitigate, such high 'meaning response rates' and pharmaceutical companies might do well to only conduct their trials at sites that practice narrative medicine approaches.

A post-apocalyptic world: The need to move beyond the current approaches

Although presented in very simplistic terms, the apocalyptic horsemen of the pharma industry are areas that contribute individually and in aggregate to the current low success rates across pharma R&D. For the present discussion, the current pharmaceutical R&D and clinical disease management processes can be roughly grouped together as the 'current paradigms'. While they represent the current way(s) of working, these paradigms are fraught with limitations:

Current paradigms that attempt to produce system-wide changes beyond 'biological tolerance limits' or on time scales that 'overwhelm' the system will be more strongly resisted and possibly limited by biological adaptations designed to keep the system 'as was'.

Current paradigms that attempt to reverse irreversible processes will not likely work, as 'resetting the system' to initial states (ie prediseased) is impossible.

Current paradigms that are based on simple linear readouts will likely not adequately predict systems-wide and alinear outcomes. Moreover, current paradigms that attempt to 'change too much, too quickly' will nearly always produce additional and unwanted effects (toxicities or other secondary pharmacological effects).

Current paradigms that presume intra-patient variability is small enough to generalise and those that assume simple and linear dosage adjustments (ie varying treatment doses two- to 10-fold) are all that are needed to treat large enough segments of the intended disease population will likely fail to address the significant uniqueness of the individual patient. Moreover, these will fail to address how the individual's physiology and disease-load, and thus therapy-requirements, change over time.

Current paradigms that are perceived by patients or trial subjects to operate, or that actually do operate, in an 'industrial/professional' manner, or those that do not espouse narrative medicine approaches, will not successfully engage subjects at all levels and will ultimately compromise drug development and post-approval utility.

Because the primary areas of focus in this paper will not be impacted by any extrinsic means and are likely to be rather resistant to fluctuations in other development environments (eg regulatory, political, payer, etc), a radically different approach away from the current paradigms is required.

On towards an 'evolutionary disease management' future?

Current paradigms predominantly consist of one or a handful of highly-selective and potent pharmacological agents with relatively long pharmacological half lives. The push of the industry during at least the last half-century has been to identify the most potent, longest-lasting selective agents possible, with a very prescriptive set of criterion desired (eg Lipinski's 'rule of five')[34,35]. Although this has been challenged by some[36], in general 'dirty' (ie nonselective) and low potency agents requiring multiple daily dosing usually do not progress further than early drug discovery[5]. High potency, selective and long-duration attributes have certainly contributed to increased convenience and dosing frequency-related compliance, and have helped mitigate the risks inherent to agents with diverse sets of actions and higher dose-related limitations (manufacturing, doses required, etc). They may have, however, concurrently brought on significant limitations. For example, although there are correlations there are distinct differences between ligand affinity, potency and efficacy[37-39]. In addition, barring some exceptions, for many systems higher-efficacy ligands are associated with a more rapid and extensive development of tolerance and desensitisation (including receptor internalisation and degradation)[40], thus leading to higher subsequent dosing requirements and the manifestation of withdrawal reactions after ligand administration ceases.

Historically, the pharmaceutical industry has depended primarily on selective manipulation of critical nodal point targets that were thought to singly 'reset' a diseased system back to normal or to prevent further development of disease, ie, low-hanging, but critical, 'fruit' (targets). This interpretation is now believed to be based on overly simplistic hypotheses that have needed extensive revisions in order to reconcile the hypotheses with experimental data. For example:

- β-adrenergic blockade in the long-term maintenance of hypertension may result less in the direct prevention of G-protein coupled receptor (GPCR) activation by endogenous ligands than it does receptor internalisation, sequestration and interactions with other proteins like RGS and GIRK family members and subsequent heterologous/heterogenous/pleiotropic effects[41,42].

References

1 Cuatrecasas, P. J. Clin. Invest. 2006; 116:2837-42.
2 Johnstone, C, Pairaudeau, G, Pettersson, JA. Drug Discov. Today 2010; doi:10.1016/j.drudis.2010.11.005.
3 Paul, SM et al. Nat. Rev. Drug Discov. 2010; 9:203-14.
4 Wehling, M. Nat. Rev. Drug Discov. 2009; 8:541-546.
5 Hopkins, AL. Nat. Chem. Biol. 2008; 4:682-690.
6 Mullard, A. Nat. Rev. Drug Discov 2011; 10:82-85.
7 Campbell, J. http://www.jcf.org/new/index.php.
8 Four Apocalyptic Horsemen. http://en.wikipedia.org/wiki/Four_Horsemen_of_the_Apocalypse
9 Elliott, DE, Urban Jr, JF, Argo, CK, Weinstock, JV. FASEB J. 2000; 14:1848-1855.
10 Grant, B. The Scientist 2011; 25:42-47.
11 Citri, A, Malenka, RC. Neuropsychopharm. 2008; 33:18-41.
12 Füllgrabe, J, Hajji, N, Joseph, B. Cell Death and Diff. 2010; 17:1238-1243.
13 Aron, L, Klein, R. Trends NeuroSci. 2011; 34:88-100.
14 Cai, L, Friedman, N, Xie, XS. Nature 2006; 440:358-362.
15 Houle, D, Govindaraju, DR, Omholt, S. Nat. Rev. Gen. 2010; 11:855-866.
16 Kar, G, Keskin, O, Gursoy, A, Nussinov, R. Curr. Opin. Pharmacol. 2010; 10:715-722.
17 Raj, A, van Oudenaarden, A. Cell 2008; 135:216-226.
18 Renart, A et al. Science 2010; 327:587-590.
19 Silver, RA. Nat. Rev. Neurosci. 2010; 11:474-489.
20 Snijder, B, Pelkmans, L. Nat. Rev. Mol. Cell Biol. 2011; 12:119-125.
21 Thurmond, RL, Gelfand, EW, Dunford, PJ. Nat. Rev. Drug Discov. 2008; 7:41-53.
22 Dodge, ME, Lum, L. Ann. Rev. Pharmacol. Toxicol. 2011; 51:289-310.
23 Rateitschak, K, Wolkenhauer, O. J. Theor. Bio. 2010; 264:334-346.
24 Bruder, CEG et al. Amer. J. Human Genet. 2008; 82:1-9.

Continued on page 16

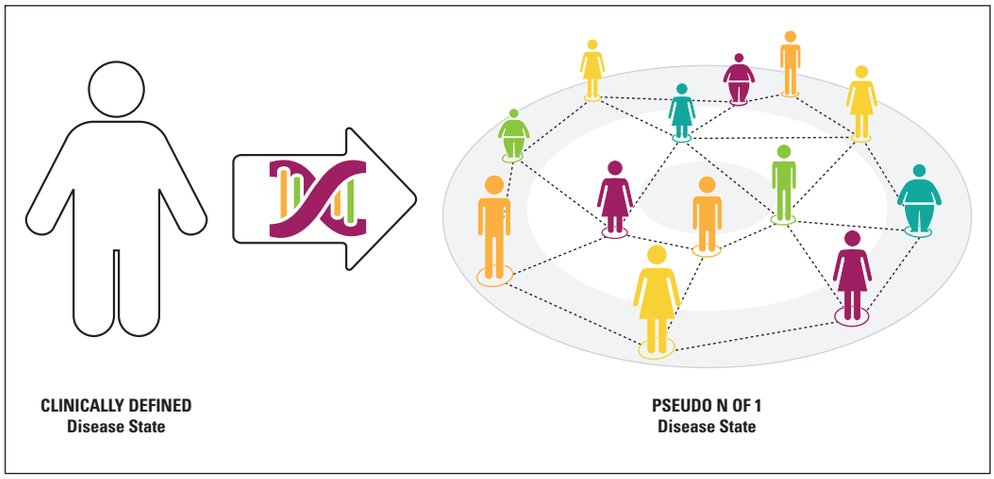

Figure 3
'Pseudo-N-of-1' disease states: Diseases have historically been categorised, and thus researched and treatments designed, along blunt clinical characteristics. Advances in our understanding of the genetic origins of disease and the slow but positive progression of personalised medicine (pharmacogenetics) are helping redefine how diseases may be better approached. Unfortunately, pure 'n of 1' research, defined as the deep analysis of a single individual and their disease, does not necessarily equate to an overall advancement in understanding diseases of populations more broadly. Protocols that link an individual and their disease with the myriad of other people and their own, but slightly different, diseases (ie, 'pseudo-N-of-1') will help expand our understanding and power to treat all disease variants

- Protein kinase inhibition prevents the phosphorylation of cognate targets which can lead to simple changes in phosphoprotein levels, but alterations in phosphorylation/dephosphorylation levels induce massive changes in multicomponent complexes that ultimately underlie their efficacy; moreover, data in certain systems have shown phosphatases may control rates and duration of signaling while signal amplifications are controlled primarily by kinases (thus, simple 'on/off' phosphoprotein switching does not normally happen)[43].
- Ligands acting at GPCRs can activate their cognate G-proteins in a monomeric form, but they can also assemble into dimers or larger oligomers; moreover, 'asymmetric' organisation of some dimers may lead to activation of certain signalling cascades while 'symmetric' organisation may activate other cascades[44].
- 'Conformational ensembles' of GPCRs exist and various conformations in the ensemble can produce functional selectivity for signalling pathways[45].
- Genetic buffering (ie the activation or deactivation of certain gene products following physiological stimuli) can mask phenotypic consequences, and at least three completely different relationships (mixed epistasis, complete redundancy and quantitative redundancy) underlie the functional overlap and regulatory links between signalling pathways[46].

The pharmaceutical industry's pursuit to find 'magic bullet ligands' – agonists or antagonists with ultra-selective qualities – has, by and large, failed. This is not to say that selective agents are not without merit in that they can produce much more limited changes in biological systems that can minimise secondary pharmacological actions and produce unwanted side-effects. Multiple lines of evidence, however, suggest that single-point pharmacological agents either do not exist, or that there are very few biological targets that are involved in single and self-limiting processes within the human body. And even when there are genetic defects in single biological systems (eg β-hexosaminidase in Sandhoff disease, α-galactosidase A in Fabry's disease, glucocerebrosidase enzyme mutations in Gaucher's disease), recombinant human enzyme replacement (rhEnzyme replacement) can offset many of the disease symptoms, but not all of them and not without, for example, enzyme production at 'non-native' sites and at levels beyond normal physiological levels[47]. Moreover, rhEnzyme replacement can result in non-native enzyme-protein or enzyme-lipid complexes, as well as the disruption of native enzyme complexes, and may well be subjected to pharmacogenetic differences in the target and signalling cascades similar to those of small molecule approaches[48,49], all of which can produce unwanted effects. Finally, a recent review has shown that only 885 of the 1,204 approved non-biological drugs satisfy the widely adopted 'rule-of-5' drug-likeness criteria, with only 619 of the 885 being available in oral formulations[36]. It appears, then, that only half of the successful marketed products match the desired attributes that govern drug discovery and development paradigms, prompting some to propose novel paradigms in drug discovery[5].

The degree which pharmacological agents mimic the actions of endogenous substances can also dramatically affect their overall actions in the body. For example, while not corroborated by decades-worth of clinical data, some have suggested that compounds synthesised from endogenite

Continued from page 13

25 Eichler, EE et al. Nat. Rev. Gen. 2010; 11:446-450.
26 Nadeau, JH, Lee, C. Nature 2006; 439:798-799.
27 Stranger, BE et al. Science 2007; 315:848-853.
28 Cohn, LD, Becker, BJ. Psychol. Meth. 2003; 8:243-253.
29 Barrett, JC et al. Nat. Gen. 2008; 40:955-962.
30 Myers, KR, Green, MJ. Ann. Int. Med. 2011; 154:129-130.
31 Moerman, DE, Jonas, WB. Ann. Intern. Med. 2002; 136:471-476.
32 Silberman, S. PLoS BLOGS December 22, 2010: http://blogs.plos.org/neurotribes/2010/12/22/meet-the-ethical-placebo-a-story-that-heals/.
33 Tracey, I. Nat. Med. 2010; 16:1277-1283.
34 Hill, AP, Young, RJ. Drug Discov. Today 2010; 15:648-655.
35 Lipinski, CA, Lombardo, F, Dominy, BW, Feeney, PJ. Adv. Drug Deliv. Rev. 2001; 46: 3-26.
36 Zhang, M-Q. Drug Discov. Today: Technologies 2010; 7:e95-96.
37 Broadley, KJl, Sykes, SC, Davies, RH. Biochem. Pharmacol. 2010; 80: 1537-1545.
38 Colquhoun, D. Br. J. Pharmacol. 1988; 125:923-947.
39 Kenakin, T, Onaran, O. Trends Pharmacol. Scil 2002; 23:275-280.
40 Lopez-Gimenez, JF, Milligan, G. CNS & Neurol. Disorders – Drug Targets 2010; 9:616-626.
41 Whalen, EJ, Rajagopal, S, Lefkowitz, RJ. Trends in Mol. Med. 2010; doi:10.1016/j.molmed.2010.11.004.
42 Wieland, T, Lutz, S, Chidiac, P. Curr. Opin. Pharmacol. 2007; 7:201-207.
43 Heinrich, R, Neel, BG, Rapoport, TA. Mol. Cell 2002; 9:957-970.
44 Rovira, X, Pin, J-P, Giraldo, J. Trends Pharmacol. Sci. 2009; 31:15-21.
45 Vaidehi, N, Kenakin, T. Curr. Opin. Pharmacol. 2010; 10:775-781.
46 van Wageningen, S et al. Cell 2010; 143:991-1004.

Continued on page 17

(endogenous metabolite) chemical backbones may have more 'natural' physicochemical and pharmacological actions and are metabolised locally (intracellularly) at rates and by systems more similar to endogenous ligands[50,51]. The more traditional developmental pursuit, therefore, of ligands with extremely long half-lives and/or activation/deactivation/metabolism/excretion kinetics that allow for single daily or less frequent dosing requirements may serve a 'dosing convenience' purpose but at the expense of inappropriate physiological actions.

Finally, the cognitive-behavioural and somatophysiological changes that are necessary for long-term health/disease mitigation might best be thought of in more extended timeframes than previously. For example, significant caloric restriction diets can prompt overt conditions (hyperammonemia) leading to chronic changes (chronic inflammatory disorders and epimutations), sequelae that are not mirrored when more gradual, but even more extensive, restrictions are established[52,53]. Likewise and extremely important, abrupt initiation or withdrawal of therapeutic agents from nearly every disease area studied, can produce profound physical and psychiatric sequalae, while more gradual onset and withdrawal paradigms of the same agents are not necessarily observed.

Based on these lines of evidence, pharmacological manipulations with more subtle and directed pressures, primarily ones that offer full inclusion of the patient and their wider 'world,' might be expected to better guide diseased biological systems toward healthy or disease-managed states: a process that could be described as 'evolutionary disease management'. Similar to traditional evolutionary changes (Darwinian evolution), subtle pressures over more extended periods of time allow biological systems to not just adapt to new environments, but to eventually become quite radically changed. Moreover, if more salutatory (ie, step-jump) evolution is needed, subtle (but subacute) changes in a person could occur that en masse set up the person for a 'jump change' (from, say, disease to health). Changes brought on too strongly or too quickly tend to overwhelm the system and result in either systems-wide collapse or a concerted 'counter attack' by the system to keep it unchanged. Occasionally, strongly concerted efforts are precisely what are required to prevent a damaged part of the system from shutting down the entire system (eg systemic infection or outright ablation of aggressive cancer cells). More often, though, the biological system has been exposed to small but progressive changes over the course of years to decades and strong manoeuvres might be able to force the system out of its 'current state' (disease or pre-disease) but at great cost.

This approach would represent a dramatic shift in nearly every established part of drug discovery, development, marketing and business approach, as well as disease treatment paradigms, payer systems and regulatory best practices. All of which could be seen as threats to be fought.

Heading into paradise – or at least a more paradisiacal place – may require multiple battles?

The complete harmonisation of the areas (ie, the five horsemen) discussed, the evolutionary disease management paradigm and the current state and approach of the pharmaceutical industry seems to be quite difficult, if not outright impossible. For sure there are significant differences on both philosophical and practical levels among them. Any attempt to address them without an open and honest dialogue about their impact on the current paradigms would be ill-founded and would certainly be a recipe for failure. In fact, their impacts across the entire value chain would need to be evaluated and a deep understanding about how they are interconnected would be a required early step. These differences should not prevent us from confronting them head-on, battle-ready and prepared to struggle through a hard slog.

"So many of our dreams at first seem impossible, then they seem improbable, and then when we summon the will, they soon become inevitable."

Christopher Reeve

A preparatory (pre-battle) first step to be conducted may be to solidify the tenet that what was defined as impossible in the past may be now defined as only improbable or even commonplace in the future. The evolution from our past to our present may have been methodically carried out, or may have been due to a 'random' series of events. The cause is less important than the outcome for those factors leading us to our current state. The influencing of the future, however, should neither be left to providence nor chance, but as a consequence of conscious action based on experience and ingenuity.

As is true for numerous issues in life, simply starting is more important than the actual starting point. The five horsemen highlight that nearly every aspect of drug discovery, development and business process is open to challenge, but is there a better first battle to be waged? There may, indeed,

be one. A main component of all five horsemen, and thus a logical target of first attack, is that of human capital. Much has been written around the importance of employee engagement, happiness and a sense of value, and how these underlie the success, innovation and longevity of business. To be sure, companies that learn, that use 'tools for foresight,' that have a persona (identity), that are able to continuously evolve, and that recognise that being brain-rich (versus capital-rich) are the most likely to survive[54,55]. These types of companies are termed 'living companies' – an appropriate metaphor to be considered in the current perspective. Individuals in the organisation could be considered the cells of the company, each operating individually, with their own 'genetic makeup' but intimately connected to the whole. The individuals, their local networks, and wider function in the business 'corpus' can be influenced dramatically, if not controlled outright, by the five horsemen. For example, people are usually rather resistant to change, they operate/act in irreversible and alinear manners, they nearly always consider their own point of view as important, and want their life's story to be heard. Guiding them individually (as a cell), as well as en masse (as a collective body), might best be done more along evolutionary (extended timelines with multiple small step changes) or along habit-inducing time lines suggested in de Geus' landmark book[54]?

How to expand the efforts beyond human resource battleground is less clear but should involve careful discussion before any action. Conversations should be held among previously identified key customer, stakeholder and content expert groups previously identified by others. For example, the pharmaceutical industry is among the most regulated of industries and national and international regulatory bodies (FDA, EMEA, etc) are well-known to be the major drivers of clinical trial design and interpretation. There is, thus, a tremendous opportunity for health authorities to establish a regulatory environment where the industry is able to adopt new value propositions in the drug development operating model (such as the use of drug prototypes[56]). Additional example areas that might serve as starting points include: novel drug research models to maximally incorporate network pharmacology/systems biology approaches that look beyond the 'one target one clinical endpoint' paradigm; regulatory authorities taking a more 'holistic' approach to study execution guidelines and regulatory approval processes; payer organisations approaching healthcare reimbursement from a 'narrative medicine' perspective; and a healthcare delivery system that addresses patient care differences based on their individual circumstances throughout their 'evolutionary disease management' lifetime.

In closing, this perspective is neither meant to be an exhaustive review of the five primary areas nor a comprehensive list of examples supporting the points. The apocalyptic horsemen myth analogy, moreover, should only be considered as one of many that could be used to help frame the necessary discussions around each area. Indeed, perhaps other philosophical or religious myths would help identify additional critical areas worthy of exploration. Regardless of the specific story chosen or characters identified, the power of futuristic stories lies not in the predicting of the eventual future, but in the crafting of multiple possible futures – a process referred to as a 'tool for foresight'[54]. Through the identification of possible futures, both leaders of business and science can enhance their awareness of previously 'unthinkable' movements in the world that might ultimately become the major driving factors of their eventual fate. It is hopefully a good use of our time to tell the tall tales that open our minds to the possible futures that might await us as an industry, especially if we remember there are always available options of the actions we can take to help them become a reality.

Acknowledgements

The author would like to thank the following colleagues for insightful discussion and criticism of the manuscript: James (Jim) Resch, Helen Dowden, William (Bill) Zinkand, Martin (Marty) DeBerardinis, Keith Russell and Neill H Carman.

Competing financial interest statement

The author is an employee of AstraZeneca Pharmaceuticals, LLC, and owns stock in the company. The author is solely responsible for the content of the article and the conclusions drawn. DDW

Dr Gary J. Keil *is a chronic pain neuropharmacologist and electrophysiologist and has worked in AstraZeneca's discovery and pan-R&D strategy groups for the past 14 years. This work has included strategic analyses of novel sciences and technologies, environmental impact assessments and organisational dynamics.*

Continued from page 16

47 Russell, CS, Clarke, LA. Clin. Genet. 1999; 55:389-394.
48 Gaide, O. Am. J. Med. Genet. 2009; 149A:2042-2044.
49 Krejsa, C, Rogge, M, Sadee, W. Nat. Rev. Drug Discov. 2006; 5:507-521.
50 Dobson, PD, Patel, Y, Kell, DB. Drug Discov. Today 2009; 14:31-40.
51 Khanna, V, Ranganathan, S. BMC Bioinformatics 2009; 10(Suppl 15):S10.
52 Clay, AS, Hainline, BE. Chest 2007; 132:1368-1378.
53 Szarc vel Szic, K, Ndlovu, MN, Haegeman, G, Berghe, WV. Biochem. Pharmacol. 2010; 80:1816-1832.
54 de Geus, AP. Harvard Business School Press 1997; ISBN 978-1-57851-820-3.
55 de Geus, AP. The Washington Quarterly 1998; 21:197-205.
56 Cohen, AF. Nat. Rev. Drug Discov. 2010; 9:856-865.