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Careful selection of physicians is required to allay public fears in clinical trials

I read the recent editorial by Kathleen Drennan in *Drug Discovery Today*[1] with great interest. One of the problems with clinical trials is that Phase I studies, by their nature, can be rigorously controlled and audited. This is because smaller numbers of volunteers are used, and the studies are normally performed 'in-house' by pharmaceutical companies or outsourced to specialist clinical research organizations. However, most of the notable catastrophes in clinical trials have occurred in the much larger Phase II and III studies. These are much harder to control as they are usually done in hospital settings and are usually multicentre, or even multinational, studies. The physicians responsible for these studies often complete them in combination with their main clinical workload and, therefore, the study is not their sole, or even primary, focus.

Study monitors and auditors often find it difficult to actually meet the physician who is the principal investigator responsible for the study (often because of their clinical workload) and even when they do, it quickly becomes apparent that they have often delegated the running of the study to subordinates, and that they have limited understanding of the logistics of the study. Furthermore, auditors do not audit to the same level in Phase II and III studies as they do in Phase I studies. Instead, the audit emphasis in Phase II and III studies has often been switched to data rescue. This is partly a result of the larger number of volunteer patients used in these studies and because these studies are spread over several sites.

However, the selection of physicians to run studies should, in my opinion, be performed with greater care. Just because a physician is a world leader in their particular field does not imply that they have either the necessary skills or the inclination to run, what are often, highly complex clinical studies. Another worry is that some physicians who run Phase II and III studies do not appear to have a grasp of the International Conference of Harmonization of Good Clinical Practice (ICH GCP), the international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of volunteer human subjects.

I am probably doing a disservice to the large majority of physicians who do take care in the running of clinical studies but, unfortunately, all too often a blind eye is turned to the inadequate minority, particularly as they often hold positions of power and influence. Another factor in the adverse reporting of clinical trials is that, in the eyes of the media the large numbers of trials that are done well and pass off without incident, are not newsworthy items.

For all clinical studies it is extremely important that none of us lose sight of our prime directive that the volunteers' safety is paramount. The easiest way to allay public fears surrounding clinical trials is simply to ensure that studies are run to the guidelines and laws that are currently in place.

Reference

1 Drennan, K.B. (2001) Have the ultimate benefits of clinical trials been maligned beyond repair? *Drug Discov. Today* 6, 597–599

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Virogenomics: the future looks bright

The article by Früh *et al.* in a recent issue of *Drug Discovery Today*[1] assesses an emerging trend in the field of antiviral drug discovery. The authors outline the preliminary evidence that human genomics is providing an under-appreciated benefit to antiviral researchers. Most antiviral drug research has centered on the relatively small number of non-structural protein targets in the viral genome; for instance, there are less than ten such targets in HIV, and the hepatitis C (HCV) and human papilloma (HPV) viruses. By contrast, viruses use the host-cell systems throughout their life cycle to infect, replicate and re-infect. If the host proteins that are intimately involved in the viral life-cycle could be inhibited without impairing the host, a broader array of targets for combating viral infections would become available. In addition, the inhibition of host proteins will avoid the hypermutability of

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viral-protein targets. With the deciphering of the human genome, this approach becomes viable if the viral and/or host pathways can be determined. A potential way to do this would be to use DNA-array technology to analyze virus-induced gene expression in host cells. Taken together, these processes have been termed 'virogenomics'.

Unraveling the host-cell pathways that are essential for viral infection using DNA arrays is not trivial and understanding the functional consequences further complicates the picture. Are changes in gene expression during viral challenge a cellular-defense mechanism, a virally induced response necessary for the virus, or a functional, but not therapeutically relevant, byproduct of viral infection?

Despite this complexity, meaningful results are starting to appear. Human cytomegalovirus (HCMV) is one of the most complex viruses, with >200 genes. A DNA-microarray experiment indicated that, *inter alia*, HCMV strongly regulated the interferon (IFN) pathway in the host[2]. One of the IFN pathways involves the upregulation of cyclooxygenase-2 (COX-2) and concomitant increases in the inflammatory prostaglandin E2. This pathway was shown to be crucial to HCMV: using the clinically effective COX-2 inhibitors a reversible dose-related inhibition of HCMV growth in tissue culture was observed[3].

A similar DNA-microarray experiment with Kaposi sarcoma-associated virus (KSV) demonstrated that the stem-cell factor receptor, c-kit, was upregulated[4,5]. Small-molecule inhibition of c-kit inhibited virus-induced cellular changes. The results of both of these experiments demonstrate that virogenomics is a new approach to discovering therapeutically useful antiviral agents. In addition, without the use of DNA microarrays and knowledge of the host and viral genomes, it is unlikely that these pathways would have been discovered as easily.

The initial successes achieved by applying global host-gene expression analysis to the identification of novel targets for antiviral drug discovery suggest that other systematic approaches might also provide complementary sets of novel antiviral targets. For example, single nucleotide polymorphism (SNP) analyses of sensitive and resistant human populations could help to identify gene products that are essential for viral infection or replication, but whose expression *per se* is unaltered during infection (e.g. the CCR5 coreceptor for HIV). Similarly, the application of proteomics technologies could accelerate the discovery of host proteins that interact functionally with viral proteins during infection or replication. Some of these interacting partners might be host proteins that aid infection; other interacting partners might be host antiviral proteins whose activity is suppressed by the binding of a viral protein. In both cases, the expression levels of interacting host proteins might be upregulated, downregulated or unchanged during infection, and these host proteins would represent excellent drug targets if their function or interaction with the viral protein could be disrupted in a specific manner.

In the future, investigators pursuing virogenomics and other global, systematic strategies for antiviral drug-target discovery will want to refine these approaches to further distinguish between molecular causes and effects of viral infections. The cross-referencing of data sets from the study of multiple human-viral-infections will identify virus-specific human proteins, and these proteins might be more likely drug-target candidates. In addition, the cross-referencing of virally induced pathway data with gene-expression analyses of approved or emerging drugs, might also provide clues towards novel drug intervention strategies. These hypotheses are easily testable, as shown by the successful application of COX-2 inhibitors to inhibit HCMV replication.

The pioneering concept of virogenomics could add substantially to both the approaches for attacking viral infections and the identification of new antiviral therapeutic agents.

References

1 Früh, K. *et al.* (2001) Virogenomics: a novel approach to antiviral drug discovery. *Drug Discov. Today* 6, 621–627

2 Zhu, H. *et al.* (1998) Cellular gene expression altered by human cytomegalovirus: global monitoring with oligonucleotide arrays. *Proc. Natl. Acad. Sci. U. S. A.* 95, 14470–14475

3 Shenk, T.E. (2000) Use of microarrays to probe the replication and pathogenesis of human cytomegalovirus. *25th International Herpesvirus Workshop*, 29 July–4 August 2000, Portland, OR, USA, Oral presentation

4 Luukkonen, B.G.M. *et al.* (2000) DNA microarrays reveal molecular events of KSHV transformation. *25th International Herpesvirus Workshop*, 29 July–4 August 2000, Portland, OR, USA (Abstract 10.22)

5 Moses, A.V. *et al.* (2000) HHV8 infection and growth regulation of dermal microvascular endothelial cells. *J. Acquired Immune Defic. Syndr.* 23, S12

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