The new generation of patch-clamp equipment

During the past few years there has been increasing interest in ion channels as drug targets. The respective therapeutic areas include cardiovascular-, CNS- or metabolic-diseases, cancer, allergy and asthma. However, some interactions with ion channels have been shown to cause side effects, for example, blocking HERG potassium channels might cause drug-induced QT-prolongation. For these reasons there is an increasing need to test compounds on ion-channel targets.

Until today, the technologies that have been used to investigate the effect of compounds on ion channels are either precise but low throughput (e.g. the patch-clamp technique [1]), or high throughput but with limitations in the correlations to physiology (e.g. binding experiments). Recently, several companies have developed new systems to automate the patch clamp technique and to increase the throughput of this technology.

A recent article [2] described the different technologies of specialized companies in detail and compared positive and negative aspects of each. The technologies were compared with respect to throughput, success rate of the experiments, physical parameters of the access to the cell, usability for different ion channels (e.g. voltage-gated or transmitter-gated) and cost. The review provides a very good and comprehensive overview of the literature, concluding that the current automated patch technologies are still not to be seen as high-throughput techniques and that a large number of improvements still have to be made. A clear evaluation of the anticipated projects of the individual pharmaceutical or biotech company has to be done to select the right technology for the individual needs.

For modern drug discovery and development, a combination of different technologies might serve best as a useful strategy to perform screening campaigns. For a variety of ion channels, HTS of 30,000, 100,000 or 500,000 compounds, using either binding-, flux- or fluorescence-based assays [3, 4] can be used for the initial detection of hits. The selected compounds (e.g. 1–2% of the total screened) and those synthesized afterwards in medicinal chemistry can be investigated using automated patch-clamp devices. For this part of the ion-channel drug discovery projects, reliable systems with moderate throughput have to be developed for the market. It is likely that some of the available systems could be optimized within the near future to meet this goal.

References

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Imaging in oncology

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SMi's *Imaging in Oncology* conference, held in London 17–18 March 2004, assembled drug developers, academics, informaticians and data managers, together with the specialist imaging CROs whose expertise is so often essential in delivering usable data from multicentre imaging studies. The meeting covered all aspects of imaging in cancer, including animal models, clinical trials and diagnostics, but the main focus was on biomarkers to support Phase II and III clinical trials. Imaging in oncology is a field of rapidly advancing technology, and as Ellen Feigal from the National Cancer Institute (NCI; http://www.nci.nih.gov) pointed out, received US$170 m in US grant funding in 2003, a fourfold increase since 1996.

Molecular imaging

No imaging meeting is complete without something new on the hot topic of molecular imaging, and delegates were treated to a tantalising glimpse of the future. Willy Eidsaunet from Amersham (http://www.amersham.com) showed beautiful SPECT (single photon emission computed tomography) images in breast cancer using their angiogenesis imaging agent ^{99m}Tc-NC100692, currently in Phase II trials, while Padmaja Yalamanchili [Bristol-Myers Squibb (BMS) http://www.bms.com] described new gamma-emitting imaging agents

targetted at matrix metalloproteinases (RP782, RP805) and at $\alpha_v\beta_3$ (RP593). Agents of this type might help patient selection, or might provide biomarkers for Phase I/II proof-of-principle in oncology drug development. Unfortunately, it is unlikely that every diagnostic imaging agent will be commercially viable. Frustratingly, there appear to be almost insurmountable regulatory hurdles in combining an investigational diagnostic in the same trial as an investigational therapeutic, so it could be many years, if ever, before we can use these exciting molecular imaging technologies in trials of new anti-cancer therapeutic drugs.

Morphology

Imaging of tumour size seems dull in comparison. The unidimensional measurements beloved by the regulators, encapsulated in the WHO and RECIST (Response Evaluation Criteria In Solid Tumors) guidelines, are based on 50-year-old imaging technology, but remain embedded in most Phase III trials. Klaus Noever from BioImaging (http://www.bioimaging.com) reminded us of the FDA's view that 'for many cancer therapies it is appropriate to utilise objective evidence of tumor shrinkage as a basis of approval'. This is indeed reflected in recent drug approvals, where 14 agents have been granted accelerated approval based on objective response rate (although with requirement for post-approval confirmation of clinical benefit). Despite reflecting established technology, measurements made according to the RECIST and WHO guidelines still often show poor reproducibility, especially outside the controlled environment of a core laboratory. Moreover, the guidelines lack detail and sometimes give perverse results, for example, when necrosis or fluid are measured as 'tumour'. For this reason, the guidelines often require modification (and the image analysis protocol must be discussed prospectively with the FDA). Oliver Bohnsack from Perceptive Informatics (http://www.perceptive.com) pointed out that in 2002 every single oncology submission included 'modifications' to RECIST. Indeed a theme of the whole meeting was the need for centralized monitoring and review by specialist core labs in anything but the simplest single-centre imaging study.

Translational science and proof-of-principle

Halfway between the high science of molecular imaging, hot from the pages of *Nature* but years away from application, and the carefully regulated informatics and data management in Phase III, lies the world of translational science and proof-of-principle. Can we use imaging to pick the winners, at the right dose, and to kill the losers? The two leading imaging technologies here are Dynamic-Contrast-Enhanced Magnetic Resonance Imaging (DCEMRI), and Positron Emission Tomography using [18]Fluorodeoxyglucose as a tracer (FDG PET). Several speakers reminded us of the FDG PET images showing a dramatic response to Glivec published recently in the *New England Journal of Medicine* [1].

FDG PET, reviewed by Helen Young from AstraZeneca, is now quite widely available, and its head-to-toe scanning capabilities make it ideal in the typical heterogeneous Phase I population. The signal depends on trapping of FDG in tumour cells, which have high levels of Glut-1 and hexokinase. One limitation of FDG PET in the past was the difficulty in verifying the anatomic origin of the FDG signal, although now that combined PET-CT scanners are widely available this problem is much diminished.

DCEMRI, reviewed by Anwar Padhani (Mount Vernon Cancer Treatment Centre; http://www.mountvernoncancercentre.nhs.uk), has also been widely used, especially with anti-angiogenic and vascular targeting compounds, and has contributed to several proof-of-principle decisions. The technique relies on the standard, clinically available gadolinium-based contrast agents, which perfuse into the tumour and cross the leaky endothelium. The signal therefore depends in a complex way on endothelial permeability, flow, vascular volume and interstitial space, although compartmental models are available to help quantitate the data. John Waterton (AstraZeneca) discussed the evaluation of imaging biomarkers. We need to know not only reproducibility and robustness in the trial setting, but also about the correlation of the imaging biomarker with histopathology, and with outcome. Also, crucially for any statistical power calculation, we need to have some idea of the likely magnitude and duration of the effect of the drug treatment, and for novel targets this is best addressed by animal experiments. Here PET and MRI have the distinct advantage of a sophisticated and vigorous translational science community, with wide availability of excellent animal scanners, especially for MRI.

Future technologies

Both FDG PET and DCEMRI are complex technologies, and difficult to incorporate into multicentre trials. Several speakers reviewed less familiar imaging technologies that might have real advantages in the future. Ken Miles (Professor of Imaging at Brighton & Sussex Medical School; http://www.bsms.ac.uk) made a powerful case for Dynamic Computed Tomography, a technology that is widely available and offers high speed and high resolution, as well as being apparently easy to quantitate. Other PET ligands for protein synthesis and proliferation were discussed, as well as magnetic resonance spectroscopy, and diffusion-weighted MRI. Perhaps in a few years these techniques will also join the armamentarium of the drug developer.

Reference

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