The evolution of microarrayed compound screening

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This review describes recent developments in the evolutionary process of microarrayed compound screening (µARCS™) to become a robust and efficient ultra-high-throughput screening technology. Improvements in compound spotting (including new quality-control methods), gel casting and imaging, together with software capable of automatic analysis and deconvolution of images, have helped to streamline the screening process. A variety of screening projects using cell-based and non-cell-based approaches have been successfully concluded using µARCS. Comparison of hits derived from standard microtitre-plate-based screening and from µARCS reveals excellent overlap. Furthermore, there seems to be no bias towards finding compounds within a particular range of log P values, even though compounds are solubilized from a dry state during the course of the assay.

Gel-based microarrayed compound screening assays have evolved from antimicrobial screening regimens where compounds are usually spotted directly onto a thin agarose matrix containing the appropriate cells [6]. The compounds diffuse into the gel and interact with the cells. Zones of inhibition correspond to lack of cell growth and indicate the presence of compounds with potential antimicrobial activity. This basic principle was later extended to the use of yeast strains and Xenopus melanophores [7] to screen for compounds that act on specific G-protein-coupled receptors (GPCRs). A further development used mammalian cell lines growing in agar [8] to screen combinatorial chemical libraries in the search for anticancer agents. The history of well-less gel-permeation screening formats has been nicely described by Burns et al. [6].

Abbott Laboratories (http://www.abbott.com) pioneered the development of a system based on arrayed chemical compounds (microarrayed compound screening, µARCS™) in combination with a well-less, gel-based assay format [6]. µARCS technology provides an ultra-high-throughput screening (uHTS) capability by using compounds that are placed on smooth, homogeneous sheets (ChemCards™) for screening. This is unlike traditional technologies, which use plates with discrete wells in which compounds are placed and assays are performed. The cards for µARCS are the size of a conventional 96- or 384-well microplate but can accommodate densities of 9200+ compounds per card. The card format is significantly different from the traditional plate-based approach. Only minute amounts (20 nl per spot) of compound are used to spot a set of cards; this is especially useful for compounds for which only small amounts are available for screening. After the spotting process, the cards are dried and sealed under an inert
atmosphere. Until required for a particular biological assay, the compounds are maintained under favourable conditions: dry, cold, dark, oxygen-free, dimethylsulphoxide (DMSO)-free. An advantage of this methodology over traditional plate screening is the ability to stockpile the compound collection in a ‘ready-to-screen’ format. Compound retrieval, biological assay and data evaluation can be done on the same day. With µARCS, compounds are immediately fed into the screening process from their dry state, thus eliminating exposure of compounds to solvents such as DMSO and the potential deleterious effects of predilution with buffer.

All assay components are embedded in agarose gels and the assembly of gel layers to form an ‘assay sandwich’ is analogous to the pipetting step in a traditional plate-based assay. ARCS gels can be formed using a specially designed device where the final gel is surrounded by a plastic frame and protected by a plastic layer on both sides, or, more simply, by using a standard sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS–PAGE) gel-casting chamber where the final gel can be released onto a suitable surface. Gels can be manipulated by washing or soaking reagents into them, and additional materials, such as membranes with special coatings (e.g. streptavidin) or plastics, can be introduced throughout the assay.

This review focuses on recent developments in the evolutionary process of µARCS becoming a robust and efficient uHTS technology.

**ChemCards™ and GelCards**

The current best practice in µARCS entails the spotting and analysis of each compound in duplicate. To achieve this, Abbott established the screening of two identical sets of compounds on two separate cards [6]. Some of the advantages of the high-density format were sacrificed with this format since the individual analysis of two separate experiments added to the variability of the results. To screen duplicate compound sets on a single card, a special compound-spotting pattern was developed, thereby avoiding identical nearest neighbours to each of the duplicate compound spots. This spotting pattern permits the screening of 4608 individual compounds in duplicate on a single card under identical biological conditions. Since a standard printing head with 12 solenoid valves in a row is not capable of printing this pattern, the printing head has to be modified to achieve a 3×4 configuration of the 12 solenoid valves and needles. We use two Gilson Constellation® 1200 devices (http://www.gilson.com) that have been modified in-house to meet our specific requirements. One spotting run generates nine identical cards with the full set of compounds. With the currently available system, spotting of 4608 individual compounds onto ChemCards takes 16 h.

The next generation of spotters will be designed to increase the output by a factor of three, thereby adding 1–2 h to the spotting time. The accuracy of the spotting process is currently monitored by sacrificing one position on the spotting deck to load a quality control (QC) card. This QC card monitors the accurate positioning of the 20 nl droplet (Figure 1). Missing spots (if one needle has been clogged by a compound precipitate) can be easily detected within minutes after the spotting has been concluded and the missing compound is re-spotted, resulting in a fully accurate card. The coefficient of variation is in the range of 5% (at 20 nl) and the current spotting accuracy is 99.5%.

Previously, assay gels were created using standard SDS–PAGE gel-casting equipment. The recent development of a fully temperature-controlled horizontal gel-casting device renders this process more robust and reproducible [9]. The new device allows two 0.75-mm-thick agarose gels to be cast on a plastic support, which improves gel handling. The temperature control feature also improves the embedding of cells and SPA (scintillation proximity assay) beads in agarose gels.

**Storage of compounds and preparation for screening**

Conventional MTP screens typically make use of collections of compounds stored in DMSO [10]. The plates are usually sealed and stored below ambient temperature.
Repeated use of such plates requires several freeze–thaw cycles, which can lead to decomposition and partial precipitation of the compounds. Because of the hygroscopic nature of DMSO, repeated pipetting onto the plates leads to increased water content, which again can lead to further precipitation of the compounds. Compound stability studies performed in our laboratories indicate that precipitation is the major reason for loss of compound during the first 6 months of frequent plate usage. After 6 months of usage, compound decomposition starts to be detectable and becomes the major cause of compound loss. Finally, during pipetting steps, compound solutions are repeatedly exposed to the atmosphere and light, which also contribute to compound degradation.

Storage of compounds on ChemCards™ avoids all the above problems since the compounds are dried immediately after spotting onto the cards which are sealed in gas-tight, light-proof pouches in an inert atmosphere. No plate-preparation steps are required before running the assays since cards are taken from the storage device and used directly in the assay. The associated savings in time and resources are significant.

**Improvements in software for spot identification**

During the past 2 years, new software (ChemCardExpress™) has been developed which automatically analyses and processes image files from µARCS gels (Figure 2). Spots are identified by applying a series of gaussian functions to characterize each spot. The series of ink spots (alignment spots) that are present on every card are used to map the identified spots to the underlying compound grid. With the current version of the software this alignment has to be done manually.

In order to deconvolute the spots and identify the corresponding compounds, all spots are analysed with respect to their amplitude, flatness and shape. Twin spots representing the same compound should have matching or similar intensity and shape. Additionally, the ‘ownership’ of a spot is also taken into account to construct the final hit score (the more compounds that are covered by a spot the lower the ownership of this spot to a particular compound will be).

Image files in the most common formats (bitmap, TIFF, JPEG) can be processed automatically. Depending on the image quality, the image file can be processed within minutes and a whole series of pre-aligned images can be processed in an unattended batch mode.

**Assays compatible with the µARCS platform**

One of the key advantages of µARCS-based assays is that, unlike other high-density formats, a 96-well plate-based bioassay can be transferred to the µARCS format without any further modifications. This allows for a very convenient and efficient transfer between assay formats. Assays are generally developed in the MTP format because this allows matrix experiments to be set up (e.g. to determine the correct enzyme and substrate pairs) and it also allows for accurate determination of $K_d$ and $K_m$ values. Once the optimal assay parameters have been determined, the assay is transferred to the µARCS format without the need to change reagent concentrations [9]. Primary HTS is accomplished in the µARCS format, whereas follow-up verification and IC$_{50}$ determination are performed in microplates. This strategy efficiently capitalizes on the
major advantages of both systems. Microplate assays have advantages in the assay development phase (matrix experiments) and IC_{50} determination (serial dilution of test compounds), whereas µARCS has major advantages in the massive parallel screening of targets in uHTS screening regimens.

Even though the µARCS platform is capable of maintaining optimal assay conditions equivalent to those in 96- or 384-well microtitre plates (MTPs), it achieves major savings in reagents. Consumption of chemical test compounds is minimized since a typical compound spot is made up of ~200 pmol of compound (20-nl spots from a 10-mM compound stock solution in duplicate). Consumption of biological reagents is minimized due to the large number of compounds screened per gel. A standard µARCS gel holds ~9 ml of reagent. Since a typical ChemCard holds more than 9200 compounds (4600 compounds in duplicate), the amount of reagent used to assess the biological activity of a single compound is on average 1 µl per compound. In this respect, µARCS technology accomplishes a significant reduction in reagent usage, thus eliminating the (error-prone) repeated addition of submicrolitre volumes in current high-density microplate platforms. We have easily achieved 20–50-fold reductions in enzyme usage per data point generated.

The constantly increasing pressure in drug discovery to decrease the consumption of chemical compounds and assay reagents and overall screening times led to the development of ever-more miniaturized assays and, as a consequence, to a high demand for efficient high-resolution readout systems. Standard photomultiplier-based readers have proven to be efficient and sensitive readout systems for 96-well plates and, by manually moving the plate under the detector, also for 384-well plates. The advent of high-density microplates and the boom in the usage of microarrays triggered the development of high-resolution imagers (Table 1). Today, we are looking at the third or even fourth generation of some of the imaging devices. The readouts that are available cover the full spectrum that is required for drug discovery projects: i.e. fluorescence (intensity, time-resolved fluorescence and fluorescence polarization), luminescence, colorimetric and isotopic readout. µARCS has capitalized on these developments since the gel-based screening format is amenable to almost any mode of detection. This led to the development of an ever-increasing portfolio of assays making good use of the newly available detectors. Most notably, the development of charge coupled device (CCD)-based imagers with the capability to monitor time-resolved fluorescence led to the development of several assays using LANCE™ (http://www.perkinelmer.com) and HTRF™ (CisBio; http://www.HTRF.com) technology.

The assay portfolio of current HTS operations is dominated by three classes of drug targets: kinases, proteases

<table>
<thead>
<tr>
<th>Device</th>
<th>Detection principle</th>
<th>Detection modes</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViewLux™</td>
<td>CCD camera</td>
<td>Fluorescence (intensity, time-resolved, fluorescence polarization), luminescence, colorimetric</td>
<td>Perkin Elmer (<a href="http://www.perkinelmer.com">http://www.perkinelmer.com</a>)</td>
</tr>
<tr>
<td>LeadSeeker™</td>
<td>CCD camera</td>
<td>Fluorescence (intensity, time-resolved, fluorescence polarization), luminescence, colorimetric</td>
<td>Amersham Biosciences (<a href="http://www.amershambiosciences.com">http://www.amershambiosciences.com</a>)</td>
</tr>
<tr>
<td>Acumen Explorer™</td>
<td>Scanner</td>
<td>Fluorescence</td>
<td>TTP LabTech (<a href="http://www.ttlabtech.com">http://www.ttlabtech.com</a>)</td>
</tr>
<tr>
<td>CLIPR™</td>
<td>CCD camera</td>
<td>Luminescence</td>
<td>Molecular Devices (<a href="http://www.moleculardevices.com">http://www.moleculardevices.com</a>)</td>
</tr>
<tr>
<td>Cyclone™</td>
<td>Scanner</td>
<td>Isotopic</td>
<td>Perkin Elmer (<a href="http://www.perkinelmer.com">http://www.perkinelmer.com</a>)</td>
</tr>
<tr>
<td>FluorChem™</td>
<td>CCD camera</td>
<td>Fluorescence, luminescence, colorimetric</td>
<td>Alpha Innotech (<a href="http://www.alphainnotech.com">http://www.alphainnotech.com</a>)</td>
</tr>
<tr>
<td>Cybi™-Lumax</td>
<td>CCD camera</td>
<td>Luminescence</td>
<td>CyBio AG (<a href="http://www.cybio-ag.com">http://www.cybio-ag.com</a>)</td>
</tr>
<tr>
<td>Typhoon™</td>
<td>Scanner</td>
<td>Fluorescence, luminescence, isotopic</td>
<td>Amersham Biosciences (<a href="http://www.amershambiosciences.com">http://www.amershambiosciences.com</a>)</td>
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</tbody>
</table>

Abbreviation: CCD, charge coupled device.
and, most of all, GPCRs. Naturally, these targets were among the first to be addressed in the ‘second wave’ of µARCS assays taking advantage of the newly established imaging capabilities. Kinase assays have been developed on isotopic and nonisotopic platforms [6,9,11]. If a tagged substrate for any given protein kinase is available and if the phosphorylation event is detectable by a phosphorylation site-specific antibody, the assay can most conveniently be formatted using LANCE or HTRF technology. The sensitivity of such assays is in general very high and the overlap of hits between plate-based screening and µARCS screening is excellent [12] (see below). The combination of µARCS with antibody-based time-resolved fluorescence (TRF) assays is especially advantageous since it reduces the amount of labelled monoclonal antibody used for detection of the phosphorylation event compared with plate-based screening by a factor of 10–100. In the event that a kinase substrate is not recognized by a suitable antibody, the use of a heterogenous isotopic assay format using capture membranes (SAM™ Membranes, Promega; http://www.promega.com) has delivered good results [13].

Traditionally, protease activity has been monitored by the increase in fluorescence of quenched peptides upon cleavage. AMC-coupled peptides (AMC; 7-amino-4-methylcoumarin) were abundantly used, but, due to the unfavourable emission spectrum that overlaps with the fluorescence emission of some test compounds, more rhodamine-coupled peptides are now in use, allowing a ‘red shift’ in detection and thus eliminating much of the compound interference. Both labels have been successfully established for µARCS protease assays. Recently, a homogeneous time-resolved fluorescence quenching assay for protease activity has been developed based on LANCE technology [14]. This assay uses a peptide labelled with both a luminescent europium chelate and a quencher. Cleavage of the peptide by caspase-3 separates the quencher from the chelate and thus recovers europium fluorescence. When transferred to the µARCS format, this assay showed excellent sensitivity and was actually able to identify inhibitors with significantly lower affinities compared with a mixed-compound plate-screening format [15].

To address the functional status of a GPCR in a cellular assay, the most common detection principle is the release of intracellular calcium, which subsequently triggers a transient fluorescent response from an indicator dye that can be quantitated using a fluorescence imaging plate reader (FLIPR™; Molecular Devices; http://www.moleculardevices.com). The transient nature of the fluorescent response requires that a GPCR agonist is actually added to the cells during the course of the detection to capture the signal. Since µARCS is a nonautomated technology that relies on the manual application of gels onto a compound card and subsequent imaging, this process takes ~4–5 s. In this respect, µARCS cannot compete with FLIPR technology. However, since the agarose gel acts as a diffusion barrier to the GPCR agonist, its diffusion is significantly reduced (0.5 mm/min on average), thus prolonging the window for observation to up to 5 min until the signal fades away due to increased dilution of the agonist. The GPCR agonist triggers a fluorescent (or luminescent [16]) response at the cellular level while it diffuses radially in the agarose gel from the point where it has been spotted on the compound card. Receptor desensitization eliminates the fluorescence (or luminescence), thus producing a fluorescent (or luminescent) ring-like structure, indicating the presence of a GPCR agonist [17]. An additional advantage of the ring-like signal triggered by a GPCR agonist is the possibility of distinguishing between real receptor agonists and fluorescent test compounds, which produce a fluorescent spot. FLIPR does not allow this possibility. It thus turns out that µARCS is a convenient, entirely manual uHTS method for functional screening of GPCR agonists (Figure 3). The overall throughput and reagent savings compared with traditional screening formats makes µARCS highly attractive for GPCR de-orphaning. Functional screening of 500,000
compounds against a large panel of GPCRs using standard MTP-based technology is currently prohibitively expensive.

In addition to the homogeneous cell-based and non-cell-based assays mentioned above, several heterogeneous assays have been described, most of them using capture membranes. Xuei et al. [18] described the use of a streptavidin-coated membrane (SAM2©, Promega) in the development of two viral nucleic acid polymerization assays: an HIV reverse transcription assay and an E1 helicase-dependent human papillomavirus replication assay that uses cell-free extract as an enzyme source for DNA polymerization. In both assays, the nucleic acid polymerization reaction occurs on the surface of the membrane. Here, the µARCS format allowed the integration and flexible handling of various washing steps to remove unincorporated nucleotides and other nonspecific materials. The associated reagent savings were threefold, and the time savings fivefold, compared with the standard plate-based assay. The most complex µARCS assay known to date has been described by David et al. [19]. The HIV integrase assay described requires 11 steps, with five transfers of gels or membranes. Despite its complexity, an excellent correlation exists between the results of the primary (µARCS) screen and potencies measured in the equivalent 96-well format. The assay is also very sensitive, detecting compounds with IC_{50} values higher than 100 µM. After screening 250 000 compounds in duplicate, David et al. [19] were able to demonstrate that the intensity and size of the inhibition spots on the agarose gel appeared to correlate well with the potency of the compound. Of the 648 highest-quality spots, 86% were confirmed when re-tested, and compounds from at least seven structural classes were identified as novel inhibitors of integrase.

The growing list of cell-based and recombinant assays that have been transferred to the gel format is given in Table 2.

### Problematic assays and detection principles

Even at the standard agarose concentration generally used for a µARCS gel (usually only 1%), it nevertheless represents a porous environment. This has an impact on a particular molecule’s ability to rotate freely in an aqueous environment. As a consequence, fluorescence polarization assays have not to date been established on the µARCS platform. Even if the impact of agarose gels on the rotational freedom of small molecules is not strong, there is still the unresolved issue of how to visualize the reaction in a suitable format.

### Table 2. Assays that have been established in gel format

<table>
<thead>
<tr>
<th>Target</th>
<th>Assay principle</th>
<th>Readout</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>Recombinant targets</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Protein kinase</td>
<td>Substrate phosphorylation</td>
<td>LANCE™, isotopic</td>
<td>[6,9,11]</td>
</tr>
<tr>
<td>Protein phosphatase</td>
<td>Substrate dephosphorylation</td>
<td>LANCE, isotopic</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Protease</td>
<td>Substrate cleavage</td>
<td>UV excitation (AMC), red-shifted dyes, LANCE</td>
<td>[6,15,17,22]</td>
</tr>
<tr>
<td>β-Galactosidase</td>
<td>Substrate conversion</td>
<td>Colorimetric, luminescent</td>
<td>Unpublished</td>
</tr>
<tr>
<td>HIV integrase</td>
<td>Strand transfer</td>
<td>Colorimetric</td>
<td>[19]</td>
</tr>
<tr>
<td>HIV reverse transcriptase</td>
<td>Incorporation of nucleotides</td>
<td>Isotopic</td>
<td>[18]</td>
</tr>
<tr>
<td>DNA helicase</td>
<td>Incorporation of nucleotides</td>
<td>Isotopic</td>
<td>[18]</td>
</tr>
<tr>
<td>Neuraminidase</td>
<td>Substrate cleavage</td>
<td>Fluorescent</td>
<td>[6,8]</td>
</tr>
<tr>
<td>Phosphodiesterase</td>
<td>SPA beads</td>
<td>Isotopic</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Cell-based assays</td>
<td></td>
<td></td>
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<tr>
<td>Cytotoxicity in bacteria, yeast, mammalian cells</td>
<td>Growth inhibition</td>
<td>Colorimetric, fluorescent</td>
<td>[6,8]</td>
</tr>
<tr>
<td>GPCRs</td>
<td></td>
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<tr>
<td>Membrane potential</td>
<td>Ca^{2+} mobilization</td>
<td>Fluorescent ring, luminescent ring</td>
<td>[6]</td>
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<tr>
<td>Receptor binding</td>
<td>DiBAC₄, distribution</td>
<td>Fluorescent</td>
<td>[6]</td>
</tr>
<tr>
<td>GPCR antagonist</td>
<td>Binding of labelled ligand</td>
<td>Isotopic, ELISA</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td>Melanin dispersion in Xenopus melanophores</td>
<td>Colorimetric</td>
<td>[6,7]</td>
</tr>
</tbody>
</table>

Abbreviations: AMC, 7-Amino-4-methcoumarin; SPA, scintillation proximity assay; GPCR, G-protein-coupled receptor; DiBAC₄, bis(1,3-dibutylbarbituric acid)trimethine oxonol.
The crosslinked environment of a µARCS gel might have a negative impact on the rotational freedom of molecules, although it is not crosslinked enough to significantly slow down the diffusion of highly mobile reagents [6]. A standard phosphatase assay using malachite green detection is a good example of an assay that works well in plates but has problems in the gel format. An active phosphatase releases a phosphate group from its substrate that is subsequently captured by malachite green reagent resulting in a colour change of the phosphomolybdate complex. Both the reaction intermediates and the final product are highly soluble and diffuse rapidly. This is not a problem for a microtitre plate assay with its discrete reaction chambers, but it significantly reduces the sensitivity in gel-based assays. This drawback can be overcome in two ways, either by using a reagent that precipitates upon binding and hence ‘freezes’ the reaction product until the image has been acquired, or, alternatively, formatting the phosphatase assay to detect the residual peptide substrate rather than the liberated phosphate.

Since the gel-casting process requires that all reagents are temporarily exposed to elevated temperatures (~35°C), some heat-labile reagents or temperature-sensitive enzymes might be negatively affected. A convenient solution to this problem is to use membranes instead of gels [20]. Alternatively, the reagent solution (e.g. substrate or developing agent) can be sprayed onto a gel surface [21]. Other potential problems are associated with heavy metal contaminants, particularly in agarose preparations, and the difficulty of working with low turnover enzymes since they require prolonged incubation, thus facilitating unwanted dilution of test compounds. In addition, we have not been able to identify a convenient assay design to run GPCR antagonist assays in ARCS. In conclusion, ARCS assays work nicely for several major drug discovery targets, but the suitability of ARCS has to be determined for each individual assay. Fortunately, ARCS assays run with identical reagent concentrations to plate-based assays, so evaluation is straightforward.

Comparison of µARCS screening hits with hits derived from standard MTP-based screening

As outlined in the epidermal growth factor receptor (EGFR) kinase screen (Figure 4), hit overlap between µARCS and conventional MTP screens is typically very high. However, there seems to be no direct correlation between the spot intensity and some physicochemical parameters (e.g. log P) [12]. The size and intensity of an inhibitory spot in an ARCS assay is based on a combination of compound solubility and potency towards a specific target. Thus, a very
potent but poorly soluble compound will generate a very intensive small spot. A compound of identical potency and increased solubility will generate an equally intensive, but larger, spot. The inability of certain compounds to exert a measurable effect can be attributed to poor solubilization from the dry state. Thus, the compound is not present in the gel. During the course of the EGFR kinase µARCS versus plate screen, two compounds were identified for which the solubilization rate was too slow to yield a detectable inhibitory spot for these moderate EGFR kinase inhibitors. Experiments with various solubilization enhancer formulations (e.g. cyclodextrins, nanoparticles) showed that the solubilization rate of these compounds could be substantially increased, resulting in a positive identification of those compounds and leading to a 100% overlap with the plate data [12].

Conclusion and outlook

During the course of the past 2 years there have been numerous improvements in µARCS hardware, software and assay design. As a result, this gel-based screening technology has become a robust and reliable tool for a variety of screening projects. µARCS will prove to be especially useful in applications such as GPCR de-orphaning using combinatorial libraries, as well as for screening natural compounds for which only very small amounts are available. Both tasks involve screening a potentially high number of compounds to identify the starting point for a more focused approach to address a particular drug target. Other future applications might be the detection of protein expression or pathway induction. A cell gel, after being exposed to small molecule compounds, can be blotted onto a suitable membrane and probed with a variety of, for example, phosphorylation-specific antibodies to assess the activation state of certain signalling proteins. Very recent data point to the possibility to simplify the µARCS screening protocol even further by using paper or membranes instead of gels [22,2]. One group [21] has even eliminated all but the first gel and used a spraying device to apply assay reagents. The future will provide further applications for µARCS.

Acknowledgements

We thank Dave Burns, Jim Kofron, Caroline David, Sujatha Gopalakrishnan and Usha Warrior at Abbott Laboratories for sharing their insights and experience with gel-based assays; Christoph Joesch for his skilful work in transferring plate-based assays to the µARCS format; Riccardo Pigliucci, Urs Regenass, John Lillig, Rhett Affleck, Bill Ewing, Rob Neper, Hansueli Wehner, Frithjof Tegtmeier, Andreas Topp and Serge Parel for very productive discussions and for finishing several ambitious tasks.

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