Minimum information about a protein affinity reagent (MIAPAR)

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(2007).
3. de Godoy, L.M. *et al. Nature* **455**, 1251–1254 (2008).
4. Nesvizhskii, A.I. & Aebersold, R. *Mol. Cell. Proteomics* **4**, 1419–1440 (2005).
5. Nesvizhskii, A.I., Keller, A., Kolker, E. & Aebersold, R. *Anal. Chem.* **75**, 4646–4658 (2003).
6. Carr, S. *et al. Mol. Cell. Proteomics* **3**, 531–533 (2004).
7. Nesvizhskii, A.I., Vitek, O. & Aebersold, R. *Nat. Methods* **4**, 787–797 (2007).
8. Grobei, M.A. *et al. Genome Res.* **19**, 1786–1800 (2009).
9. Resing, K.A. *et al. Anal. Chem.* **76**, 3556–3568 (2004).
10. Searle, B.C., Turner, M. & Nesvizhskii, A.I. *J. Proteome Res.* **7**, 245–253 (2008).
11. Ma, Z.Q. *et al. J. Proteome Res.* **8**, 3872–3881 (2009).
12. Elias, J.E. & Gygi, S.P. *Nat. Methods* **4**, 207–214 (2007).
13. Gupta, N. & Pevzner, P.A. *J. Proteome Res.* **8**, 4173–4181 (2009).
14. Ahrens, C.H., Brunner, E., Hafen, E., Aebersold, R. & Basler, K. *Fly* **1**, 182–186 (2007).
15. Anderson, N.L. *et al. Mol. Cell. Proteomics* **8**, 883–886 (2009).

Minimum information about a protein affinity reagent (MIAPAR)

To the Editor:

We wish to alert your readers to MIAPAR, the minimum information about a protein affinity reagent. This is a proposal developed within the community as an important first step in formalizing standards in reporting the production and properties of protein binding reagents, such as antibodies, developed and sold for the identification and detection of specific proteins present in biological samples. It defines a checklist of required information, intended for use by producers of affinity reagents, quality-control laboratories, users and databases (**Supplementary Table 1**). We envision that both commercial and freely available affinity reagents, as well as published studies using these reagents, could include a MIAPAR-compliant document describing the product's properties with every available binding partner. This would enable the user or reader to make a fully informed evaluation of the validity of conclusions drawn using this reagent (**Fig. 1**).

Supplementary Table 2 shows an example of a MIAPAR-compliant document, which could be derived from the information supplied in a single publication using the workflow summarized in **Supplementary Figure 1**.

Affinity reagents serve various roles in experimental studies. These include protein sample identification and detection; protein capture for isolation, purification and quantification; and functional studies. The choice of an applicable molecular tool is conditioned by the experimental objectives and the chosen approaches and methods. This has led to a widening of the range of molecules being used as affinity reagents (**Table 1** and ref. 1). The best established are 'natural' polyclonal and monoclonal antibodies; however, an expanding range of recombinant constructs are now available, including single-chain variable fragments (scFvs), single-domain antibody fragments and diabodies. More recently, alternative affinity reagents have been developed, the biophysical properties of which present advantages in specific applications. They include protein scaffolds, such as fibronectin, lipocalins and ankyrin and armadillo repeat domains, and nucleic acid aptamers. These reagents are used in a growing range of experimental methods, including enzyme-linked immunosorbent assay (ELISA), western blotting, immunohistochemistry, affinity chromatography and immunoprecipitation (**Table 2**).

At the same time, the systematic characterization of complete proteomes has led to an increase in the scale on which affinity reagents are produced. Several ambitious projects aim to develop systematic affinity-reagent collections. In Europe, they include the EU ProteomeBinders consortium[1], the Human Protein Resource and Human Protein Atlas[2] and the Antibody Factory[3]. In the United States, the National Cancer Institute (Bethesda, MD) has initiated the Clinical Proteomic Reagents Resource within the Clinical Proteomic Technologies Initiative for Cancer[4]. Globally, the Human Proteome Organization (HUPO) Human Antibody Initiative aims to promote and facilitate the use of antibodies for proteomics research, which embraces many of these activities (http://www.hupo.org/research/hai), and the HUPO Proteomics Standards Initiative has developed PSI-PAR, a global community standard format for the representation and exchange of protein affinity-reagent data[5].

With the broadening availability of tools and methods, researchers have to define the most efficient binder applicable to the method and approach they have selected. These applications are carried out under different experimental conditions, which affect the choice of affinity reagent used. For example, binders can be either in solution or immobilized to a solid phase, and target proteins may be present either in a native, conformationally folded form or in a denatured state. To compare affinity reagents and decide upon the most appropriate one, users need comprehensive information regarding each reagent. Currently, multiple sources of information exist, including commercial catalogs of antibodies, portals centralizing affinity-reagent properties from various sources and experimental results published in the literature describing the successful use of a binder in a specific application. Large-scale production initiatives also add other sources such as validation and quality-control results from production centers and independent quality assessment laboratories (such as the Antibodypedia portal; http://www.antibodypedia.org/). Even so, the available information may be incomplete; for example, the identification of a protein belonging to a particular family using a given antibody may be reported with no information concerning the assessment of possible cross-reactivity of the antibody with other family members. Existing information may also be biased by unsubstantiated reports from a commercial producer. Furthermore, data may appear contradictory at first glance, owing to a lack of precision in target or sample descriptions.

The purpose of MIAPAR is to permit the reliable identification of affinity reagent–target–application triples. A binder is designed and produced for the detection of a particular target protein or peptide, often within a complex mixture. For maximum benefit of potential users, reporting of data about such a protein binder must describe (or reference) both its intended target and its qualities as a molecular tool. Ideally, such a description should include: (i) affinity reagent (and target) production processes, which may influence the characteristics of the binder and permit the unambiguous identification of the molecules; (ii) properties of the reagent as a binding tool, including its specificity, affinity, binding kinetics and cross-reactivity; (iii) the use of the reagent in applications (that is, compatibility with experimental

techniques and methods); and (iv) links to standardized protocols or experimental records that support the production process, the qualities of the binder as a tool and the claimed applications.

MIAPAR-compliant descriptions need to be kept up to date and relevant to the batch of material being made available. This may require a new document with every batch in the case of potentially variable reagents, such as polyclonal antibodies.

The underlying principle in MIAPAR is similar to that of other reporting guidelines developed as part of the HUPO Proteomics Standards Initiative (HUPO-PSI)[6]. Required information is structured so as to allow entry into databases and enable useful querying and automated data analysis. This structure is designed to achieve comprehensive coverage and clarity. To provide unambiguous reports, MIAPAR recommends the use of standard naming conventions, such as database accession numbers, controlled vocabularies and the like, to describe entities and processes. Other important criteria in MIAPAR are sufficiency, meaning that a reader should be able to understand and evaluate the conclusions and their experimental corroboration, interpret the validity of the project and its outcome, and perform comparisons with similar projects; and practicality, meaning that the guidelines should not be so burdensome as to prohibit their widespread use.

The objective is not to describe in detail experimental results that will typically be recorded in databases or laboratory information management systems; nor is MIAPAR intended as a substitute for production protocols and procedures that are documented elsewhere, and its minimal information will not be sufficient to reproduce binder and target production or synthesis. Finally, the guidelines are not expected to be static. They have been assembled through consultations with a large number of experts and will evolve according to community requirements in the context of a rapidly developing technological framework. The MIAPAR document displayed on the HUPO-PSI website describes the most up-to-date version of the standard (http://www.psidev.info/index.php?q=node/281); the content at the time of this publication can be found in the **Supplementary Note**.

MIAPAR is designed to be used for the reporting of several processes. The first is the production of new affinity reagents. This can be part of a large-scale activity performed by academic or commercial producers or by systematic initiatives. In this case, a MIAPAR-compliant document could be used in the producer's catalog or in public databases and repositories to describe accurately and unambiguously the qualities of such reagents as molecular tools. Alternatively, a laboratory may produce one specific affinity reagent, either to develop a new production process or to meet research goals when there is no suitable commercial binder. In such a case,

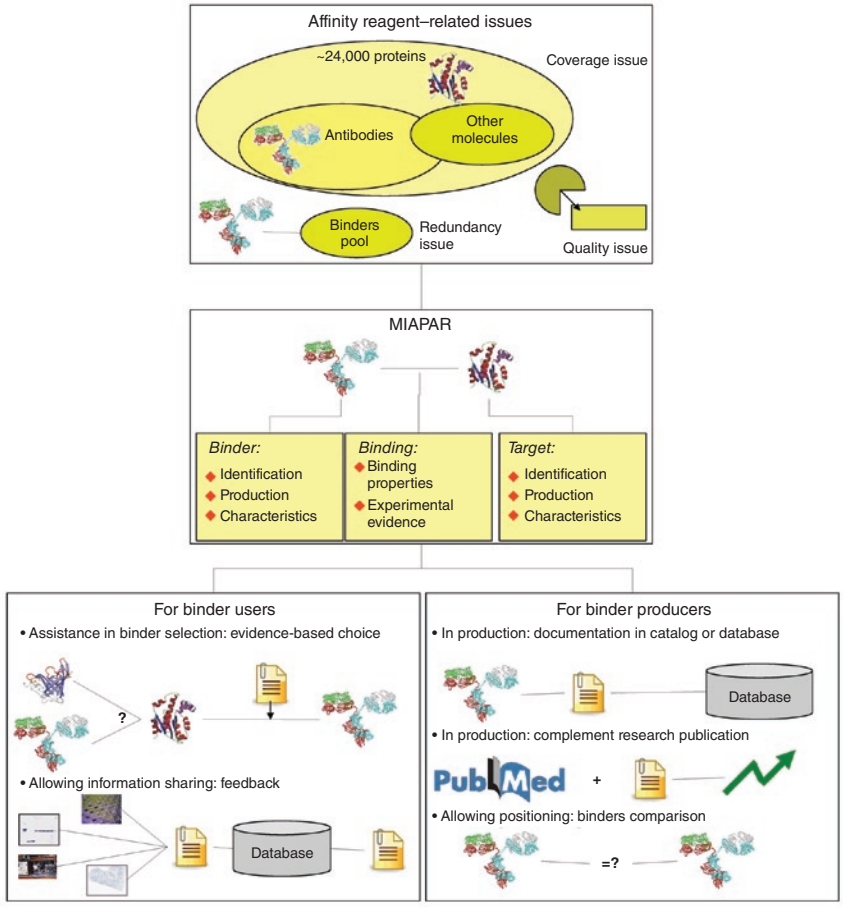

Figure 1 The scope of MIAPAR. MIAPAR-compliant reports will enable users to make informed choices when selecting from catalogs, databases or publications the binder best suited to a particular application.

Table 1 Affinity-reagent types

Affinity reagent category	Example
Immunoglobulin	Full-length antibody (monoclonal or polyclonal)
	Antibody fragment (e.g., Fab, scFv and related constructs including minibodies, diabodies, single V_H or V_L domains or nanobodies)
Protein scaffold	Fibronectin
	Ankyrin repeat
	Armadillo repeat
	Lipocalin (anticalin)
	Affibody
Peptide ligand	Natural peptide
	Synthetic peptide
	Peptidomimetic
Nucleic acid aptamer	DNA aptamer
	RNA aptamer
Small chemical entities	Natural product (secondary metabolite)
	Synthetic product

Table 2 Assay types and associated reagent states

Assay class	Assay type	Affinity reagent state	Target state
Gels and blots	Immunoblot (western blot)	In solution	Denatured
Purification	Affinity chromatography	Bound to solid phase	In solution, native folding
	Immunoprecipitation	In solution	In solution, native folding
Staining	Immunohistochemistry	In solution	Fixed (cross-linked)
	Live cell imaging	In solution	Native folding
Sorting and counting	Fluorescence activated cell sorting	In solution	Membrane bound, native folding
	Magnetic cell sorting	In solution	Membrane bound, native folding
Assays	Radioimmunoassay	Capture binder: in solution Detection: in solution	Native folding (sometimes denatured)
	Sandwich ELISA-type	Capture binder: solid phase Detection: in solution	Native folding (sometimes denatured)
	Competitive ELISA-type	Various configurations	In solution, native folding
	Affinity determination (SPR, QCM, etc.)	In solution or bound to surface	Bound to surface or in solution
Arrays	Protein arrays	No binder	Bait: bound to surface Prey: in solution
	Antibody arrays	Capture: solid phase	In solution, native folding
	Antibody arrays with sandwich	Capture: solid phase Detection: in solution with other binders	In solution, native folding
	Reverse phase arrays	In solution	Surface immobilized
Bead assays	Single bead assays	Capture: solid phase, bound to bead Detection: in solution	In solution, native folding
	Multiplex bead assays	Capture: solid phase, bound to bead Detection: in solution with other binders	In solution, native folding
Therapeutics	Tumor therapy: tumor targeting	Administered to mammalia	Cell surface receptor, native folding
	Tumor therapy: toxin neutralization	Administered to mammalia	Native folding

the MIAPAR document can complement the scientific publication describing the binder and provide a checklist for the author to work with during manuscript preparation. As reagents pass through quality-control procedures, an initial MIAPAR document could be updated with the corresponding reagent quality reports produced by laboratories charged with independent characterization and evaluation of available affinity reagents. Finally, when the binder is used in a specific experiment, such as protein identification in tissue samples, a reference to the corresponding MIAPAR document in the paper reporting the experiment would allow unique identification of the binder used and a clear understanding of both the strengths and the limitations of that protein identification. This process could also lead to an update of the MIAPAR document with the report of a successful experimental use of the binder in a particular application.

Whereas MIAPAR provides a list of descriptive items to document a binder uniquely and unambiguously, it does not define terms to be used to fill in the descriptions. Use of database accession numbers, controlled vocabularies and ontologies for describing entities, processes and conditions is strongly recommended for MIAPAR documents. Regarding molecules, they may be identified by a database accession number from a public database, such as UniProtKB (http://www.uniprot.org) for proteins and Ensembl (http://www.ensembl.org) or Entrez Gene (http://www.ncbi.nlm.nih.gov/gene/) for genes. The PSI-PAR controlled vocabulary under development (see below) provides a list of recommended databases and unified names for these resources.

A number of controlled vocabularies are available in the Open Biomedical Ontologies Foundry (http://www.obofoundry.org/)[7] and may be used to describe proteins, tissues, diseases and molecular interactions, including protein affinity interactions. A controlled vocabulary is currently being developed (PAR) to cover specifically protein affinity reagents, including terms not described in existing controlled vocabularies[5]. This is based on the molecular interactions vocabulary (MI) maintained as part of the HUPO-PSI. A draft version is available online through the European Bionformatics Institute ontology lookup service (http://www.ebi.ac.uk/ontology-lookup/browse.do?ontName=PAR)[8]. The ontology may also be downloaded from the HUPO-PSI website (www.psidev.info/index.php?q=node/281#cv). The use of a structured format and ontology to describe experiments and reagents has already aided the development of tools for selecting epitopes to raise affinity reagents[9].

The MIAPAR guidelines have been developed within the affinity-reagent community in close collaboration with the HUPO-PSI work group on molecular interactions. As a standard for representation of affinity reagent–target interactions, MIAPAR extends the MIMIx guidelines for molecular interactions[10] with specific principles and practices appropriate for affinity reagents and their target molecules. As a standard to describe molecular tools, MIAPAR complements MIMIx with further characterization of the molecules involved, their method of production and their binding properties, and it further documents the use of the binders in experimental applications.

Within MIAPAR, information regarding experiments is limited to that which is essential for documenting the properties of the binder as a molecular tool. When required, more complete descriptions should be provided using

other relevant guidelines; for instance, the immunohistochemical application in our example MIAPAR document (**Supplementary Table 2**) could be described more fully using the 'minimum information specification for *in situ* hybridization and immunohistochemistry experiments' (MISFISHIE) guidelines[11]. The Minimum Information for Biological and Biomedical Investigations project[12] is working to manage all such guidelines through a central repository of standards, providing a single entry point for users of guidelines and ensuring that these standards are complementary and nonoverlapping.

MIAPAR has been developed to facilitate the sharing of data about affinity reagents within the scientific community. It does not dictate a specific format for reporting information but rather provides a checklist of the information which should be included somewhere within such a report. It is also a first stage toward the design of a data model and information infrastructure associated with the affinity-reagents field. In particular, an XML exchange format based on PSI-MI XML2.5 (refs. 6,13) and associated controlled vocabulary are now available[5], and MIAPAR-compliant data maps to the PSI-PAR XML schema. Plans have also been made to adapt the IntAct[14] database to support the management of affinity-reagent data. The current MIAPAR guidelines serve as a basis for the design of a more complete knowledge model to be used for information exploitation and inference.

We recognize that these reporting guidelines are addressed to a somewhat different audience than most, in that the majority of available agents, particularly antibodies, are produced and sold by commercial companies. It is hoped that researchers will use these guidelines as leverage to request that companies supply MIAPAR-compliant data with each purchase, thus providing clear and consistent information about the quality of binding agents. Although it is difficult to see how this could be anything other than a voluntary agreement, we hope that once this commitment is made by a critical mass of manufacturers, both commercial and nonprofit, it will become standard practice.

We anticipate that MIAPAR will be updated as other binder types, production methods and experimental applications of affinity reagents emerge. There is still considerable scope for discussion of which characteristics of binders should be documented to support their efficient use in a wide range of experimental settings. Suggestions from the community are encouraged and will be collected and published on the PSI-PAR HUPO-PSI website (http://www.psidev.info/index.php?q=node/281). We encourage binder producers and users to promote compliance with MIAPAR in the interests of the entire community.

Note: Supplementary information is available on the Nature Biotechnology website.

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1. Taussig, M.J. *et al. Nat. Methods* **4**, 13–17 (2007).
2. Ponten, F., Jirström, K. & Uhlen, M. *J. Pathol.* **216**, 387–393 (2008).
3. Mersmann, M. *et al. New Biotechnol.* **27**, 118–128 (2010).
4. Tao, F. *Expert Rev. Proteomics* **5**, 17–20 (2008).
5. Gloriam, D. *et al. Mol. Cell. Proteomics* **9**, 1–10 (2010).
6. Taylor, C. *et al. OMICS* **10**, 145–151 (2006).
7. Smith, B. *et al. Nat. Biotechnol.* **25**, 1251–1255 (2007).
8. Cote, R.G., Jones, P., Martens, L., Apweiler, R. & Hermjakob, H. *Nucleic Acids Res.* **36**, 372–376 (2008).
9. Haslam, N. & Gibson, T. EpiC: a resource for integrating information and analyses to enable selection of epitopes for antibody based experiments. in *Data Integration in the Life Sciences*, Paton, N.W., Missier, P. & Hedeler, C. (eds.) 173–181 (Springer, Berlin and Heidelberg, Germany, 2009)
10. Orchard, S. *et al. Nat. Biotechnol.* **25**, 894–898 (2007).
11. Deutsch, E.W. *et al. Nat. Biotechnol.* **26**, 305–312 (2008).
12. Taylor, C.F. *et al. Nat. Biotechnol.* **26**, 889–896 (2008).
13. Kerrien, S. *et al. BMC Biol.* **5**, 44–54 (2007).
14. Aranda, B. *et al. Nucleic Acids Res.* **38**, 525–531 (2010).