In support of the BMRB

The Biological Magnetic Resonance Bank (BMRB) is facing the threat of having its funding discontinued. Concerned about this situation, the editors of *Nature Structural & Molecular Biology* have asked the community why it is important to continue to support the BMRB. We have also asked John Markley, head of the BMRB, to present his case.

A word from the BMRB

Stable funding is essential for a data bank such as the BMRB. Ideally, the funding should support maintenance activities (data deposition, storage and dissemination), growth of the data bank to track the emergence of new types of data, and development of improved technology to reduce costs and improve the impact of the data bank. The BMRB has played a key part in developing standards for the representation of biomolecular NMR data, and continued efforts in this area are needed as new kinds of data, such as those for small-angle X-ray (or neutron) scattering and cryo-EM, are reported and need to be archived. The BMRB, through its association with the Worldwide Protein Data Bank (wwPDB), is participating in the development of new standards and software for the validation of structures determined by NMR spectroscopy. Opportunities exist for expediting the creation of (more extensive) BMRB depositions through collaboration with instrument manufacturers and software developers. Such developments can facilitate the deposition of peak lists associated with assignments and structure determination, as recommended by our advisory-board members. The challenge of the future will be in linking information across different data banks. The wwPDB is leading the way in demonstrating how this can be done.

Most grant regulations now require the timely deposition of experimental results, and an increasing number of journals have data deposition as a requirement for publication. Several growing areas of research are making extensive use of the BMRB. These include investigations of intrinsically disordered proteins, development of automated analysis of NMR data, solid-state NMR and NMR-based metabolomics.

With the budget cuts that the BMRB has suffered (reduced by 40%, compared to the previous operating budget), we currently are at the minimal level of keeping up with depositions, data validation and data-dictionary development. In addition, the BMRB is barely managing to meet its obligations as a partner in the wwPDB. We have had to lay off people who were developing new software and functionality. The wwPDB advisory-committee meeting, held at Rutgers University on 1 October 2010, had a session on funding, which enabled us to inform members of the US granting agencies about the impending expiration of remaining funding from the National Library of Medicine in September 2014. To date, no plan has been advanced to keep the BMRB functioning. None of the three agencies has expressed an interest in funding more than a part of the needed budget, so a multiagency approach appears to be needed. To stimulate this, BMRB staff members prepared a 'white paper' (see **Supplementary Note**), which was approved by its advisory board and then sent to representatives of the US grant agencies (National Institutes of Health (NIH), Department of Energy and National Science Foundation). Given the lead time for applications and review, it appears critical that a funding plan be developed within the coming year.

John L. Markley, University of Wisconsin–Madison, Madison, Wisconsin, USA

Note: Supplementary information is available at http://www.nature.com/doifinder/10.1038/nsmb.2371

Voices from the community

The BMRB is playing a very important part in determining structures and elucidating functions and interactions between biological molecules by NMR. The BMRB unit of Protein Data Bank Japan (BMRB-PDBj) has collected more than 600 chemical-shift data sets produced by RIKEN in the Protein 3000 project. Even if some of the structures themselves might not be that important, the chemical shift data can be used for drug discovery and to understand how they relate to secondary and tertiary structures. That relationship is used in many software tools for NMR data analysis, such as TALOS, SHIFTX and SPARTA. Thus, the chemical shift data are an important outcome of the structural proteomics effort, and this is the reason why the BMRB is a member of the wwPDB. The software programs mentioned above are commonly used by biological NMR researchers around the world. Personally, I am also using the database and software tools in my own research. I think they are indispensable in biological NMR and related fields.

The BMRB was established by John Markley at the University of Wisconsin–Madison. Now, a network with BMRB-PDBj and the European Bioinformatics Institute (EBI) has been formed, and the BMRB has an essential role in the development and management of the database. To provide a high-quality NMR database to researchers in the life sciences and related fields, the activity at the BMRB should be kept in full swing.

Hideo Akutsu, Institute for Protein Research, Osaka University, Osaka, Japan

Scientists in the Japanese NMR community greatly benefit from the data in the BMRB. Experimental NMR parameters, such as chemical shifts, are very important for improving NMR biomolecular structures and methods for NMR analyses. Many tools for NMR data analysis, such as TALOS, SHIFTX and SPARTA, are derived from the high-quality NMR data archived in the BMRB. These tools are commonly used in biological NMR applications in Japan. Experimental NMR data produced by Japanese scientists are also stored and available at the BMRB.

The NMR parameters deposited in the BMRB are useful for evaluating the accuracy of published structures and for studying intermolecular interactions. These molecular structures and functions are the subject of basic molecular sciences and their applications. Thus, these data contribute to many branches of science, such as biochemistry, biophysics and medicine, in addition to NMR spectroscopy.

The BMRB is the chief NMR database in the United States, and it collaborates with the EBI in Europe and the BMRB unit of the PDBj in Japan. The BMRB makes great efforts not only to collect data but also to maintain their high quality by data annotation. Such database activity is essential for enhancing NMR studies internationally. On behalf of the Nuclear Magnetic Resonance Society of Japan, I would like to support the BMRB at the University of Wisconsin–Madison.

Tetsuo Asakura, Tokyo University of Agriculture and Technology, Tokyo

We are writing to express our strong support for the continuation of funding of the BMRB. The role of the BMRB as the only public-domain repository for NMR spectroscopic data has become stronger and more important for the NMR community over the years. It started as an archive for chemical shift data, and, although this is still a very important activity, its scope has now broadened to encompass all NMR-related spectroscopic data. Assigned chemical shift data have also grown in importance. For instance, they are now generally used as restraints in structure calculations, and it has even been shown that complete 3D structures can be obtained based solely on chemical shifts. Also, many protein-ligand interaction studies are based on chemical shift perturbations, and the BMRB has become an essential resource in the field of biological solid-state NMR. Presently, the submission of NMR restraints (nuclear Overhauser effects, residual dipolar couplings, and so on) to the PDB is mandatory with NMR-derived macromolecular structures, and the BMRB plays a crucial part in the validation of these data.

Also, our research at Utrecht University has strongly benefitted from the existence of the BMRB and will require the continuation of this invaluable resource. Given the BMRB's central and unique role in making NMR data publicly available, it would be no less than a disaster for the NMR field, but also for the structural biology community as a whole, if this database were to cease to exist. We therefore strongly support the plea for continued support of this vital activity for NMR.

Marc Baldus, Rolf Boelens, Alexandre Bonvin & Robert Kaptein, Bijvoet Center for Biomolecular Research, Utrecht University, Utrecht, The Netherlands

Over the past 15 years, the BMRB has played, and continues to play, a pivotal part in protein NMR. This database contains many of the experimental parameters that underlie protein structural studies, and therefore it is infinitely richer than simply the atomic coordinates that often are considered the primary goal of such endeavors. By building the framework for collecting and archiving the numerous parameters that have such important roles in NMR analysis of biological macromolecules, the BMRB has become an invaluable treasure trove in terms of fundamental parameters related to biomolecular structure and dynamics. Of the numerous types of data now stored in the BMRB in a readily retrievable format, I will briefly comment on perhaps its largest component, chemical shifts, which have been of central importance in our own work.

By collecting, validating and pruning heteronuclear chemical shift data, available for nearly all proteins whose structure has been determined by NMR and frequently also by X-ray crystallography, the BMRB offers a unique, large and reliable repository of such data, which can be directly related to structural details. Work in my group has exploited this database to develop empirical tools, such as TALOS and TALOS+, which now can identify protein backbone torsion angles from just chemical shift data, at a level of accuracy that continues to improve with further growth of the BMRB. Similarly, on the basis of BMRB-archived data, programs such as SPARTA allow prediction of chemical shifts for proteins of known structure, again at an accuracy that continues to improve with the size of the data deposits. Such data are playing a key part not only in accelerating the determination of protein structures, by programs such as CHESHIRE, CS-Rosetta and CS23D, but also in starting to enable modeling of more challenging structures not easily amenable to classical protocols for protein structure determination. It is clear that the BMRB, with its wealth of deposited data, is playing a fundamental part in the future development of protein NMR as a key tool in structural and mechanistic studies. By making those data accessible to the entire community, the BMRB effectively leverages the value of a wide array of different types of data collected for diverse sets of biologically important systems. It is key to the future of biomolecular NMR that this incredible resource remains healthy and continues to grow.

Ad Bax, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

The BMRB is frequently described as a repository for biomolecular NMR data, but this short description masks its true significance. A filing cabinet is also a data repository. More importantly, the BMRB is a high-capacity data dispensary. The data model that the BMRB has developed to regularize protein chemical shifts, which it is extending for other types of biomolecular NMR data, forms the interface that launched a thousand applications. Rapid, automatic access to these data enabled the computational surveys that opened new scientific vistas, most notably structural insights on fluxional or transiently populated species such as protein folding intermediates and transition states of enzymes—detailed insights that cannot be gained by any other way. Prediction is always risky, especially when predicting the future, but we would not be surprised to see novel and important applications of the BMRB involving biomolecular associations, whether protein-protein or drug-target. Metabolomics is also a likely bet. As important as the BMRB has been for enabling novel biomedical applications of NMR, we have little doubt that equally important applications enabled by the BMRB are yet to come. Conversely, without a continuing and robust BMRB, harnessing the collective efforts of hundreds of biomolecular NMR laboratories worldwide would be a distant vision, a costly lost opportunity, rather than a modern-day engine of discovery.

Irina Bezsonova, Michael R. Gryk, Jeffrey C. Hoch, Dmitry M. Korzhnev & Mark W. Maciejewski, University of Connecticut Health Center, Farmington, Connecticut, USA

I am pleased to provide some personal comments on the utility of the BMRB. My group began analyzing chemical shift patterns in proteins in the late 1980s, when the BMRB hardly existed. At that point, collecting data from the literature involved finding original articles and retyping data found there by hand. What worked for a dozen proteins then would not

be remotely possible today without having a sustained effort to organize and curate such data and having the authors themselves create the entries.

The systematic analysis of chemical shifts in proteins, made possible by the BMRB, has had a major impact, allowing structures to be determined with minimal input (sometimes with chemical shifts alone), providing secure secondary-structure information and improving the quality of structures in general. In addition, persistent uncertainties in chemical shift referencing were uncovered (and essentially solved) by careful analysis of large data sets. There is a need to continue the collection and preservation of these data.

Recent work has shown that protein shifts can be used to detect protein flexibility and to provide surprisingly detailed information about residual structure in nominally disordered regions, and the benefits of such database analyses are just beginning to be felt for nucleic acids and carbohydrates. Relatively newer initiatives from the BMRB to help organize other types of NMR data, such as restraints and coupling constants, are also beginning to pay real dividends. The close collaboration between the BMRB and the PDB helps both organizations provide better service to our community.

Dave Case, BioMaPS Institute, Rutgers University, New Brunswick, New Jersey, USA

As *the* repository for data, the BMRB has a critical role in support of NMR scientists performing biomedical research. The centralization and organization of the various parameters derived from NMR experiments comprise an invaluable service because these data are used by a large majority of the scientists performing NMR experiments on a biological macromolecule. The most prominent application is the direct analysis of perturbations to the NMR chemical shift to directly assess the effects of mutation(s) or titration of a ligand and to assign these to specific regions of the structure. Versions of this approach are used in hundreds of publications each year, from laboratories around the world, and the application of this approach continues to increase over time as the structural and biochemical communities realize its wide applicability and value for characterizing intermolecular interactions. The BMRB greatly facilitates such studies by placing the baseline sequence-specific resonance assignments, under standard conditions, at the user's fingertips. The BMRB also provides a gold mine of information for the expert biomolecular NMR spectroscopist. The compilation of parameters has allowed members of our community to perform highly valuable secondary data analyses of NMR parameters. For example, the similarity in backbone chemical shifts in homologous proteins recognized and analyzed over the past ~25 years provided the foundation for the development of today's powerful chemical shift–based approaches to the generation of protein structures. Finally, I note the critical part the BMRB plays in organizing the NMR community, for example in assembling the data structures needed to enable the generation of an NMR interface to the PDB. There is no doubt that the BMRB merits continued support, as it has, and continues to have, a central role in the biomolecular NMR community in the United States and throughout the world.

Walter J. Chazin, Center for Structural Biology, Vanderbilt University, Nashville, Tennessee, USA

I have submitted datasets to the BMRB and use the database not only for our solution NMR research but also for our work on the solid-state NMR spectroscopy of membrane proteins. Without the careful validation and correction of the chemical shifts deposited, the valuable statistics generated by the database would be useless. Chemical shifts are increasingly used as important structural restraints, and without an accurate database, this would not be possible. The community is constantly demanding more information from such structural databases, including the BMRB. Without proper staffing (always the most important resource), the BMRB will not be able to do what the community needs for its biomedical research. The close working relationship between the PDB and the BMRB is very important for the future of protein structural biology.

Timothy A. Cross, National High Magnetic Field Laboratory, Florida State University, Tallahassee, Florida, USA

We would like to express our strongest appreciation and support for the BMRB. We sincerely hope that this essential resource for biomolecular NMR and structural biology will continue to flourish and will be supported by appropriate funding.

The BMRB fulfils a very valuable function in supporting the biological NMR community. It is the only public-domain repository for NMR-related spectroscopic data derived from biological macromolecules: The journal *Biomolecular NMR Assignments* requests NMR data deposition to the BMRB for publications, and NMR structures deposited in the PDB are linked to corresponding entries in the BMRB, illustrating the unique role of the BMRB repository for the international NMR community.

The BMRB stores curated and assigned chemical shifts but also various other types of NMR data, including raw time-domain spectroscopic data, which are crucial for derivation of information about the structure and dynamics of biological macromolecules. These data are essential for statistical and theoretical studies of NMR parameters and for the development of new software. Examples are the widely used program TALOS and the use of NMR chemical shift information combined with ROSETTA for structural modeling. NMR chemical shifts are also useful for the validation of NMR-derived protein and nucleic acid structures.

Were the BMRB to disappear, we in the NMR community would face substantial difficulties in almost all areas of our research. A unique worldwide facility for the storage of biological NMR data would be lost and with it the continuing efforts for standardized curation. Efficient and curated data storage of biological NMR data is absolutely essential. A discontinuation or even reduction of the activities of the BMRB would be a big step backwards in the development of biological NMR as a field.

Sonja Dames, Horst Kessler, Oliver Lange, Tobias Madl, Bernd Reif & Michael Sattler, Bayerisches NMR Zentrum, Technische Universität München and Helmholtz Zentrum München, Munich

The BMRB is the primary NMR chemical shift repository in the world and, as such, represents the only viable location to deposit and access such data. Its existence enables academic journals, their editors and their reviewers to demand the deposition of chemical shift data in a publicly accessible location and format. Accessibility of such data is critical to numerous scientific endeavors involving NMR spectroscopy, including reanalysis of published data and results as well as interpretation of new experimental results using previously reported assignments, without the need to repeat the laborious assignment process or to contact the original assignment authors or rely on their goodwill or timely action to obtain those assignments. Just as important, the data in the BMRB enable many different statistical analyses of chemical shift data for a large number of proteins. In the context of our own work, such analyses can be used to obtain database-derived random-coil chemical shifts, which are critical for the analysis of residual structure in disordered proteins, a class of proteins that is only just becoming fully appreciated for its ubiquity and importance. Such proteins are not amenable to crystallographic analyses, leaving solution NMR as the primary high-resolution technique for their characterization, and access to large amounts of chemical shift data, for

both folded and disordered proteins, is critical to allow us to advance our understanding of the structure-function relationships of such proteins.

David Eliezer, Weill Medical College at Cornell University, New York

As *Nature Structural & Molecular Biology* gets somewhere between $5,000–$10,000 of page and library subscription charges for each NMR paper published in the journal, it would be a most fitting encouragement for it to make a donation to the BMRB, especially as *Nature Structural & Molecular Biology* relies so heavily on the publicly funded databases.

Alan Fersht, University of Cambridge, Cambridge

We would like to add our strong voice of support for the continued funding of the BMRB database for NMR data. The chemical shift data, in particular, are extremely valuable information for the entire structural-biology community. For small proteins, chemical shifts on their own can define tertiary structure, so they could be viewed as a proxy for coordinates. The availability of chemical shifts in this database has provided the main source of data to enable the development of the methodologies used to derive structural information from chemical shifts. In addition, the rapid development of approaches to characterize transient structure within disordered states of proteins, including work from one of our labs, has also relied on the chemical shifts in the BMRB. Many labs, including ours, take advantage of the deposited chemical shifts for specific proteins to enable analysis of NMR spectra for these proteins (including effects of binding or other modifications) without having to reassign, an incredibly time-consuming process and one that is wasteful of the scarce resources available to the scientific community, particularly now. NMR techniques and approaches are still in a rapidly growing phase, and the availability of a database containing various kinds of NMR information will be critical for the continued creative methodological developments in the field. In particular, relaxation data have already been used to provide general insights into the structure and dynamics of proteins, and its utility will certainly grow if a well-curated source of such data remains available. The importance of this resource for the NMR community cannot be overstated.

Julie Forman-Kay & Lewis E. Kay, Hospital for Sick Children, University of Toronto, Toronto

The BMRB stores the past achievements of NMR spectroscopists and enables future breakthroughs in computational structural biology. Safeguarding experimental data allows for retrospective improvements in structural ensemble calculations from improved computational protocols. The large database of chemical shift assignments in the BMRB can now be combined with computational methods to calculate ensembles from proteins with sparse assignments or distance constraints. Additionally, the BMRB is an essential resource for computational structural biologists seeking to leverage the unique ability of NMR to characterize protein dynamics. Based on constraints from deposited ground-state chemical shifts, excited-state structures can now be calculated. Structural insight into these rare states has the potential to elucidate new allosteric and catalytic mechanisms. The efforts of the BMRB in standardizing data formats and deposition policies for NMR-dynamics measures is likely to spur new computational developments that will increase our understanding of the evolution and biological function of macromolecular motions.

James Fraser, John Gross, Tanja Kortemme & Andrej Sali, University of California San Francisco, San Francisco

Experimental NMR parameters such as chemical shifts are very important for improving NMR biomolecular structures and methods for NMR analysis. The NMR parameters deposited in the BMRB are also useful for evaluating the accuracy of the structures published. Thus NMR databases such as the BMRB should be supported worldwide. The BMRB at Wisconsin is a key NMR database and should be sustained mainly by US funding agencies.

Toshimichi Fujiwara, Institute for Protein Research, Osaka University, Osaka, Japan

We are writing today to express our strong support for the BMRB and our concern for the impending stoppage of its funding from the National Library of Medicine. As detailed below, the BMRB has had an important role in our groups' research, providing us and the structural community at large with a much-needed central repository for many types of NMR data and tools. We wholeheartedly encourage continued funding of this valuable resource.

From our perspective, the BMRB has achieved this success by expertly pursuing several interlinked aims. At its core, the BMRB is an independent, well-validated and expert resource to hold chemical shift assignments and other data. We have all benefitted from this in the archiving of our own research results, ensuring the utility of our work in novel directions in labs beyond our own. Similarly, the widespread contribution of data from labs around the world to the BMRB has allowed us to initiate work in new areas with confidence in data obtained from this resource (for example, R. Akella *et al.*, *Structure* **18**, 1571–1578, 2010). Finally, BMRB resources have been essential for the development of novel software tools for NMR and structural analysis, both in Madison and throughout the community, that take advantage of the uniquely comprehensive collection of data gathered there.

As we look ahead to the future—where NMR tackles even more complex systems, with greater challenges for chemical shift assignment and restraint measurement—we argue that the BMRB will play an even more important part in leveraging these data for the benefit of all of the structural-biology community. We strongly encourage the continued funding of the BMRB to allow for its full and active participation in this exciting period ahead.

Kevin Gardner, Xuelian Luo, Jose Rizo-Rey & Michael Rosen, University of Texas Southwestern Medical Center, Dallas, Texas, USA

The BMRB is an extremely valuable repository for biomolecular NMR data, in particular protein chemical shifts and also, increasingly, other types of biomolecular NMR data. This represents an immensely important resource for a plethora of researchers, both with respect to methods development and for answering specific biological questions. Providing rapid and easy access to this type of data is the BMRB's hallmark, not simply its collection. Without the BMRB, the past collective efforts of numerous biomolecular NMR laboratories worldwide would go to waste, and future novel opportunities would never bear fruit.

Roberto R. Gil, Chien Ho & Gordon Rule, Carnegie Mellon University, Pittsburgh; Angela M. Gronenborn, Rieko Ishima, Judith Klein-Seetharaman, Pei Tang, Patrick van der Wel & Yan Xu, University of Pittsburgh, Pittsburgh

We are gravely concerned about the serious threat that the BMRB faces of losing its funding from the NIH National Library of Medicine. This matter is of utmost importance to the international community of NMR spectroscopists working on biological molecules. The BMRB provides an absolutely vital service to this community by storing,

curating and making easily available all data that are necessary for successful analysis of biomolecules, spanning the wide range from structure determination to dynamic and functional analysis of single molecules to the statistical analysis of large biomolecular ensembles. The tremendous progress that our field has seen over the last 25 years would not have been possible without this resource. A particularly striking example is the recent development of obtaining structures from chemical shifts alone. As a matter of fact, our groups use the services of the BMRB almost daily, and data analysis using the BMRB resources is an integral part of our very successful European Molecular Biology Organization (EMBO) practical courses on NMR spectroscopy, which have been attended by hundreds of students since 1999.

Worldwide, many tens of millions of dollars are invested yearly in new NMR hardware for biomolecular analysis. Compared to these investments, the costs for the BMRB appear small; yet they create tremendous returns by helping us to make the best use of this equipment. A discontinuation or even significant reduction of the BMRB would be a disaster for our field, as data could no longer be shared and very likely would also be lost if the storage responsibility were left to the individual investigators.

For these reasons, we sincerely hope that a solution for the continued funding of the BMRB can be found. We also want to take this opportunity to express our heartfelt, personal thanks to the people running the BMRB for all their efforts of providing such a superb and flawless service to our community.

Stephan Grzesiek, Sebastian Hiller & Joachim Seelig, Biozentrum, University of Basel, Basel, Switzerland

The BMRB functions as an absolutely essential repository for the curation and dissemination of experimental NMR data in the biological and medical sciences. Consequently, it is a great worry to learn that they are faced with the threat of losing their funding from the NIH National Library of Medicine.

The need for, and benefits of, proper curation and dissemination of research data are ever more clear. In the UK, the research councils, the Wellcome Trust and the major journals have all decided that research must result in the deposition of the resulting data in publicly available resources, for the benefit of the wider community. This has been highlighted by two recent reports by the Royal Society and the UK government. Similar trends are evident in many other countries, and it is likely that this will be followed worldwide. It therefore seems very counterproductive to terminate the funding of a repository that serves exactly this purpose.

In the Collaborative Computing Project for NMR (CCPN), we have worked for many years with the BMRB and the wwPDB to develop improved software for NMR data deposition and remediation. This has resulted in the development of streamlined software and procedures for the deposition and curation of NMR-derived research data for use by the worldwide scientific community. The ready accessibility of previously derived experimental data on medically important systems is an important factor in reducing the cost of future work on those systems and allowing rapid progress to be made. Importantly, the long-term preservation of experimentally derived data enables its re-evaluation using new and improved analysis protocols (for example, for structure determination) as they are developed.

We could imagine that the NIH feels that it should not have to fund the entire cost of the BMRB alone, and indeed the costs of supporting the wwPDB, which curates and disseminates both structures and experimental X-ray crystallographic data, are shared between the United States and other countries. However, it is also worth noting that researchers in the United States are among the beneficiaries of the BMRB's collection of data resulting from research funded by other countries worldwide.

On behalf of the undersigned, and representing the CCPN and UK NMR community, we appeal to the NIH to continue the funding of the BMRB and, if necessary, to discuss an equitable sharing of the costs with other funding bodies internationally.

Ernest D. Laue, Helen Mott & Daniel Nietlispach, University of Cambridge, Cambridge

Igor Barsukov, Lu-Yun Lian & David Middleton, University of Liverpool, Liverpool, UK

Tharin Blumenschein & Geoffrey Moore, University of East Anglia, Norwich, UK

Iain Campbell, Jason Schnell, Ioannis (John) Vakonakis & Anthony Watts, University of Oxford, Oxford

Maria R. Conte, James Mason, Mark Pfuhl & Mark R. Sanderson, King's College, London

Jeremy Craven & Michael Williamson, University of Sheffield, Sheffield, UK

Cyril Dominguez & Gordon Roberts, University of Leicester, Leicester, UK

Ulrich Günther & Michael Overduin, University of Birmingham, Birmingham, UK

Joern Werner & Philip Williamson, University of Southampton, Southampton, UK

Claudia Blindauer, University of Warwick, Coventry, UK

Matthew Crump, University of Bristol, Bristol, UK

Paul Driscoll, Medical Research Council National Institute for Medical Research, London

Tom Frenkiel, Medical Research Council Biomedical NMR Centre, London

Alexander Golovanov, University of Manchester, Manchester, UK

Steve Matthews, Imperial College London, London

John Parkinson, University of Strathclyde, Glasgow, UK

Dusan Uhrin, University of Edinburgh, Edinburgh

Mark Williams, Birkbeck College London, London

I am writing to express my strongest possible support for the efforts to find a funding source for the BMRB. In my view, the activities of the BMRB are hugely important to all those who, like me, work in the area of NMR structure determination of proteins and their complexes. The BMRB is the only public-domain repository for the underlying experimental data that are generated by all such studies, most significantly the chemical shift assignments, but also many other data forms such as dynamics and relaxation data, coupling constants, raw time-domain data and others. I see it as a sign of the maturity of the technique that deposition of chemical shift assignment data at the BMRB is now mandatory before a PDB code can be issued for an NMR-derived structure, and that deposition of NMR data is a requirement of many funding bodies and for publication in many journals. It is entirely as it should be that such requirements now exist, as such data are of central importance in the structure-determination process, and they should therefore be made transparently available to the community, both for validation and for use in follow-up studies. Also, the standardized curation of assignment data at the BMRB provides authors with an extremely valuable check on their results, which, I am sure, has caught and corrected many errors. Such analysis can really only be provided by a team of NMR experts dedicated to the task.

Were the BMRB to be forced to close, the structural biology NMR community would presumably find itself back in the unsatisfactory situation where responsibility for the maintenance and distribution of NMR data would again become the sole responsibility of the originating authors, and there would no longer be any standardized curation and

analysis of such data. I think this would be, quite simply, a disaster that would represent a massive step backwards for the whole field.

I very much hope that a funding source will be found that will allow this vital resource to continue its activities for the benefit of the worldwide NMR structural biology community.

David Neuhaus, Medical Research Council Laboratory of Molecular Biology, Cambridge

Structural biology is at a point where the PDB is well filled with structures of globular proteins or domains, and some RNA and DNA, but the pressing question is still how they act and interact together in their native context. It is foreseeable that NMR will have an even larger role in the future in characterizing large-scale rearrangements in extended, full-length multidomain proteins and their (transient) complexes, capitalizing on the particular ability of this technique to determine transient interactions and dynamics at various time scales. It has become standard to use NMR for initial interaction studies—and to retrieve chemical shifts for this purpose from the BMRB. And it is expected that the structural investigation on nondissected biomolecules in a 'cellular structural biology' context will require crucial contributions from NMR with regards to the characterization of mobility—and of mobility changes—in individual sections of these holoproteins. In the past 10 years, NMR has further matured and is now in a position to deliver such information on very large systems.

Any doubt around the financing of the BMRB must be alarming for the NMR community, as the database is the harbor for its most specific results, chemical shifts, and it has the potential to also be the place for routine deposition of dynamics data. Chemical shifts are useful for binding studies and bear information with regard to secondary or tertiary structure; dynamics data may be important in the course of designing or interpreting biological experiments. If a database like the BMRB is not available and further developed, it will be more difficult for biological NMR to make its point. Keeping in mind that more than 30% of all protein sequences form dynamic structures, with individual sections involved in transient interactions, it can be assumed that the BMRB contains information relevant to a large fraction of the proteome, by providing a representation of protein structural properties through chemical shifts and dynamics data. Only such a database makes a comprehensive structural characterization of proteins easily accessible.

Hartmut Oschkinat, Leibniz-Institut für Molekulare Pharmakologie, Berlin

The BMRB is an important tool in our studies and a great resource for the NMR community. My lab's work in the field of RNA biology and in the molecular and structural analysis of protein-RNA interactions relies on the availability of up-to-date methods for efficient structure determination. The availability of a large, curated database of chemical shifts is essential to the implementation of such methodologies (for example, CS-Rosetta or TALOS) in protein structural studies. Although the use of CS in RNA structure determination is not as advanced, consistent progress is being made in this direction, and we can expect that similar tools for RNA analysis will become available in the next few years. The availability of an open-access database such as the BMRB prevents duplication of efforts in specific investigations, and we find that it represents a unique on-the-job reference and teaching tool.

The threat of the BMRB losing its funding is a great worry to my own research and to the community at large, and I welcome the opportunity to write in support of what I consider a key tool for biomedical research.

Andres Ramos, Medical Research Council National Institute for Medical Research, London

The BMRB is a valuable resource that supports both the simulation and experimental communities. Data of the type deposited at the BMRB—order parameters, for instance—are used by computational chemists to test and validate the force fields that govern the motion of macromolecules in molecular dynamics (MD) simulations. By serving as important touchstones that tie simulation to experiment, these data have enabled widespread efforts to improve MD force fields. In addition, the coordinate data hosted by the wwPDB partner organizations, including the BMRB, are critical starting points for simulations (for example, MD, MD-quantum mechanics, Monte Carlo and Brownian dynamics) focused on understanding the functional mechanisms that underlie macromolecules of biomedical interest (such as receptors, enzymes and nucleic acids, to name just a few). Continuing the community's collaborative efforts to encourage, support, strengthen and fund resources such as the BMRB is vital.

David E. Shaw, D. E. Shaw Research, New York

The MetaboLights database, the EBI's metabolomics database, will be closely collaborating with the BMRB on NMR data exchange in metabolomics. The BMRB hosts a unique collection of NMR data for metabolites, and it would be very unfortunate if the BMRB's expertise and data were lost to the community.

Christoph Steinbeck, European Bioinformatics Institute, Cambridge

The BMRB is leading a quiet revolution in NMR spectroscopy. Before the BMRB came into existence, NMR data on proteins and nucleic acids tended to be available only on an individual basis, often requiring an exchange of messages with the authors or the access to supplementary tables in published papers. As a consequence, it was very challenging to develop methods for analysis of NMR measurements that could fully exploit the knowledge accumulated from the thousands of NMR studies of biological macromolecules. This situation was not helpful for NMR spectroscopy, whereas other areas of structural and molecular biology were showing how great advances can be made by creating extensive and readily accessible repositories of data.

To illustrate the importance of the BMRB's role in extending the scope of NMR spectroscopy, I would like to discuss the use of chemical shifts for protein structure determination, an area in which I am very interested. Until not that long ago, the complexity of the mapping between chemical shifts and protein structures had largely prevented the direct use of these NMR observables for structural studies. Only relatively recently, with the availability of large amounts of chemical shift data, has this mapping started to become better understood, thus opening the possibility of determining the structures of proteins in states that are very challenging to study, in which essentially no other observable NMR can be measured. Without the BMRB, these types of advances, which are based on the analysis of large databases, would be much more difficult.

Michele Vendruscolo, University of Cambridge, Cambridge

It is greatly worrisome that the BMRB in Madison, Wisconsin, is currently facing the threat of losing its funding from the NIH National Library of Medicine. The BMRB serves as an absolutely essential repository for the curation of experimental data that underpin the structural and dynamics studies by NMR spectroscopy.

The preservation of experimental data is crucial for validation of the resulting NMR-derived structures. As a member of the wwPDB NMR-validation taskforce, I have stressed and do recommend a proper validation analysis of both experimental and structural data together. Our own validation server iCing (http://nmr.cmbi.ru.nl/iCing) is performing

such joint analysis and relies, among other things, on BMRB-derived statistics. We have also combined structural data and NMR data from the BMRB repository, to conduct longitudinal searches into structure quality, for the design of optimized NMR experiments. Well-curated and well-documented research data also allow the testing and re-evaluation of the data using newer and improved protocols, once available. Finally, the preservation of research data into publicly available repositories is a requirement put forward by the UK research councils, and all publically funded research will have to adhere to the standard of data disclosure.

Over the years, the BMRB has served as an example of the value of data preservation and has explored the proper procedures and implementation for curation of NMR-derived research data. It is unimaginable that they would have to terminate this scientific task because of the lack of funding.

Geerten W. Vuister, University of Leicester, Leicester, UK

Since its inception, the BMRB has had a sustained impact on the field of biomolecular NMR. By disseminating reliable NMR data, it has prevented financial waste and duplication of efforts within our community. Its usage is likely to increase as more of us expand our studies to biomolecular complexes, many of which contain components that have been studied previously by NMR. In my lab, we routinely use the BMRB for data on individual components that we are studying in complex, and this application has saved us large sums of money. When we identify new protein interactions in cell-based experiments, we immediately check for chemical shift assignments of the putative binding partner in the BMRB. In cases in which these are available, our transition to NMR structural studies has been seamless and inexpensive. We use other aspects of the BMRB as well, including applications for reformatting data files. Equally important are that comparative studies that are feasible because of the NMR data accessible via the BMRB: for example, the behavior of specific proteins can be readily compared across multiple complexes. These tough economic times and reduced resources across the scientific community would suggest a greater urgency for a well-maintained database that rigorously archives the wealth of information that it has accrued and continues to acquire.

Kylie J. Walters, University of Minnesota, Minneapolis

What does the BMRB have in common with the recent announcement of a new science institute in New York City and with new initiatives announced by the NIH and the White House? The BMRB is a data bank, the institute is for data sciences, and the initiatives are termed 'big data'. Like the members of my own lab and of the Institute for Computational Biomedicine (ICB) that I direct at Weill Cornell Medical College, I am very excited and hopeful about the impact of these expressions of commitment to managing, using, applying and exploiting biological data of all kinds in the best possible way. Their aim, whose efficiency and feasibility is well documented, is to seek, achieve, organize and store the understanding inherent in intelligent collection and analysis of the data that are acquired through ever more incisive and powerful methods enabled by technological innovation, scientific progress and the sustained and hopeful support of the public. Data about molecular structure and dynamics are essential for the work of my colleagues in the lab and in the ICB, and NMR-generated data are key to allowing our computational work to extract fundamental understanding of the dynamics of the molecular systems that constitute human cells, tissues and organs. The structural templates obtained from crystallography are cornerstones of this understanding, but the essential role of dynamics, as measured by NMR and calculated computationally in simulations of functional processes, provides an even closer look into the time-dependent and space-specific mechanisms. The NMR data resulting from countless careful and rigorous evaluations, curated with care and scholarship by dedicated scientists, are the lifeline for this type of scientific investigation—and that's the role of the BMRB. It would be inconceivable for us, at this stage, not to have such data available; it would be unconscionable to allow such hard-earned treasures to disappear or to discontinue their accessibility in the age of data and the time of big-data initiatives. It is the responsibility of the custodians of the public trust to protect and enhance such resources—and by this I mean those who have led us all to believe that the treasure is safe. This is the public's ongoing mandate, to which all agreed when they accepted the budgets (the NIH, the NSF, the DOE), when they sought the responsibility (the NLM) and when they enjoyed the benefits (we, the scientific community, and the journal-publishing community). I hope we do not shortchange the public trust.

Harel Weinstein, Institute for Computational Biomedicine, Weill Cornell Medical College at Cornell University, New York

It is with anxiety that I follow the news about threats to an orderly future of the BMRB, due to funding considerations. The BMRB is the only readily accessible repository of NMR data on biological macromolecules. It has a key role in this highly active area of structural biology, both as a data repository for the worldwide community of teams working in biomolecular NMR and as a source of information that provides a platform for new research projects on a wide range of biological and biomedical themes. Downgrading the BMRB would be a catastrophe for a large community of scientists, which extends far beyond the circle of those directly involved in NMR structure determination of biological macromolecules.

Kurt Wüthrich, The Scripps Research Institute, La Jolla, California, USA and Eidgenössische Technische Hochschule Zürich, Zürich

The BMRB is an essential resource for the biological NMR community that accumulates and provides a variety of NMR data in suitable formats for the users. The data include the chemical shifts of proteins and peptides, nucleic acids and so on as well as their relaxation data. When we determine the solution structure of a protein, for example, and deposit the coordinates in the PDB, all these kinds of data for the protein are needed by scientists who want to study its biological functions, such as its interactions with other molecules, by NMR. Therefore, it is extremely important to have the BMRB to provide the data promptly when they are necessary. Between 2002 and 2007, the collaboration of the RIKEN Structural Genomics/Proteomics Initiative (RSGI) and the Japanese National Project on Protein Structural and Functional Analyses (Protein 3000) determined more than 1,300 solution structures of functional domains from human or mouse proteins by NMR. As we deposited all of their coordinates in the PDB, we then met with many requests for the NMR data. So, Takanori Kigawa and others at the RIKEN are collaborating with Hideo Akutsu at Osaka University in order to accelerate the process of NMR data deposition in the BMRB. Without the BMRB, we cannot fulfill our duty to provide valuable NMR data to the worldwide community. Furthermore, statistical analyses of NMR data are important to advance methods and techniques to determine NMR structures of biological macromolecules, and therefore bulk usage of NMR data in the BMRB is indispensible. All the dedicated efforts to construct and maintain the BMRB are enormously valuable not for only the community of NMR spectroscopists but also for a wide range of biological researchers who enjoy the structural and functional aspects elucidated by NMR. Therefore, the BMRB deserves continued funding.

Shigeyuki Yokoyama, RIKEN Systems and Structural Biology Center, Yokohama, Japan