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The Role of the Chemical Biology Core Facility at EMBL: A Vision for a European Roadmap

Joe D. Lewis*

EMBL Chemical Biology Core Facility, Meyerhofstrasse 1, 69117 Heidelberg, Germany

Small-molecule tool compounds, or "biotools", that specifically modulate biological processes have played a crucial role in the elucidation of biological questions. Compounds such as α-amanitin in mammalian transcription and nocodazole in cell biology have become standard tools.

The discovery, characterization, and utilization of novel small molecules have always been the domain of both academia and the pharmaceutical industry. However, the latter has driven the development of hardware, detection chemistries, and software improvements to make screening assays against hundreds of thousands to millions of compounds within incredibly short time frames a reality. In recent years, with the cost of the technology decreasing, academia has also moved to acquire the technology and know-how to discover and develop biotool compounds independently from the pharmaceutical industry.

How the Chemical Biology Core Facility Supports Research at EMBL. The facility supports the research groups in all aspects of small-molecule screening, from assay development through screening to compound characterization and the elucidation of structure–activity relationships (see Table 1). The six staff members of the facility, which is jointly funded by the European Molecular Biology Laboratory (EMBL) and the German Cancer Research Center (DKFZ), have the necessary expertise and experience to guide research groups through the trials and tribulations of finding and characterizing biotools. Most of the projects are fairly long term, with a typical duration of 6–12 months, depending on a project's complexity. These joint activities involve a close interaction with respective research groups, and our current capacity is ~10–12 projects per year. The other core facilities at EMBL (shown in Table 2) have an indispensable role in supporting the entire process: from the early stages involving target protein expression to facilitating screening to conducting flow cytometry, and DNA microarrays and proteomics for characterizing and elucidating the effects of biotools discovered through screening.

We have successfully completed a significant number of screening campaigns against cell-based and biochemical assays that are helping to provide insights into complex biological questions. An example of one of those projects, undertaken with George Reid from the Gannon research group, has been to identify tool compounds that can be used to dissect the complexity of estrogen receptor (ER)-mediated transcription. The ER and its cognate ligand, estradiol, have an essential role in the development of breast and ovarian cancer. Recent work using kinetic chromatin immunoprecipitation assays has demonstrated a dynamic, temporally regulated interplay of factors on the promoters of ER-responsive genes (*1*, *2*).

A cell-based assay that quantitatively evaluates ER transcriptional activity was modified for high-throughput screening (HTS) and screened against our in-house

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***Corresponding author, lewis@embl.de.**

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TABLE 1. Services offered by the Chemical Biology Core Facility

Support for multilabel plate readers and HTS detection technologies
Assay development and validation
HTS of compound libraries
Computational data evaluation and structure–activity relationship analysis
Advice on secondary assay development and design
Cytotoxicity profiling of compounds against tumor cell lines
Medicinal chemistry optimization (currently outsourced)

libraries to discover agonists and antagonists of ER-mediated transcription. Several compound classes were identified that either activated (agonists) or inhibited (antagonists) estrogen signaling. The challenge then became to identify the cellular target and the molecular mechanism through which the compounds act. A combination of hard work and a comprehensive knowledge base built up in the lab allows educated guesses to be made; in one case, Reid identified the target of one of the series as topoisomerase II, an enzyme that is targeted by many anticancer agents. Further characterization of compounds has demonstrated that they inhibit the topoisomerase by a novel mechanism of action compared with drugs such as etoposide. Topoisomerase II is intimately involved in estrogen signaling, and Ju *et al.* have recently described its specific involvement in ER-mediated transcription (*3*).

These novel tool compounds, together with etoposide, will allow the dissection of the role of topoisomerase II at different stages of its catalytic cycle in ER-mediated transcription.

The Future of Chemical Biology. The future development of chemical biology faces three major challenges: integration, education, and training and infrastructure access.

Integration. Chemistry, biology, physics, and engineering components of chemical biology must work together more closely. The establishment of regional and national networks is in part addressing this. In Germany, we have been part of an effort called ChemBioNet to build up an academic network of chemists and biologists (Table 3). The aim of this network is to further promote chemical biology research and especially to create a platform on which chemists and biologists can find common ground for collaborations. In this regard, it has been a success; the annual ChemBioNet conference in Frankfurt was very well attended.

Education and Training. Cross-discipline education and training are crucially important for the next generation of chemical biologists. The recent articles in *ACS Chemical Biology* exemplified by Arndt and colleagues (*4*) emphasized the crucial role that education plays and how institutions such as Dortmund are addressing this issue and implementing integrated programs. EMBL has also underscored its commitment to chemical biology and is actively recruiting new group leaders in this area.

The pharmaceutical industry could, and should, play an important role by collaborating with their academic colleagues. If academic centers can learn from their industry colleagues and *vice versa*, then unnecessary reinvention of the wheel can be avoided. Organizations such as the Society for Biomolecular Sciences should continue to support exchanges and forums between industry and academia.

Infrastructure. The infrastructure required for chemical biology, especially HTS, is very expensive and requires a significant investment in time and resources to enable optimal productivity. Such infrastructure cannot realistically be duplicated in every laboratory or institute that wishes to carry out chemical biology. Eventually, funding for equipment and compound libraries will run out. Funding agencies want to see tangible results from their investment, whether as papers in journals or as patents. Because of these significant hurdles, I believe solutions at a European level are required, and I have outlined them below.

Vision for an Integrated Future. The future of chemical biology seems to be secure. Despite this, many challenges must be overcome for chemical biology to continue to flourish in Europe and provide a viable counterpart to the National Institutes of Health (NIH) Roadmap for Medical Research. To date, no coherent European initiative can augment the NIH Roadmap initiative, either in funding or in ambition (*5*). To enable industrial-scale HTS on hundreds of thousands of compounds, large infrastructure investments and expertise are needed. In addition to financial constraints, the availability of experienced people who can undertake this highly specialized type of work remains limited.

One rational approach to address these issues in Europe is to fund a centralized HTS center equipped with state-of-the-art equipment and resourced with high-quality, diverse compound libraries for identification of hits and their initial characterization. In support of a centralized screening facility, national screening centers, responsible for development of assays and their validation, would present projects to the central screening center. Projects would be evaluated and

TABLE 2. Core facilities at EMBL

Advanced light microscopy
Chemical biology
Electron microscopy
Flow cytometry
Genomics
Monoclonal antibody
Protein expression and purification
Proteomic

TABLE 3. A selection of academic screening laboratories and networks in Europe

Germany	
EMBL/DKFZ	www-db.embl.de/jss/EmblGroupsHD/g_248
ChemBioNet	www.chembionet.org
Chemical Genomics Centre	www.cgc.mpg.de
France	
National Screening Network	http://ifr85.u-strasbg.fr/project/rnc
Switzerland	
Biomolecular Screening Facility	http://bsf.epfl.ch
U.K.	
Institute of Cancer Research	www.icr.ac.uk
Medical Research Council Technology	www.mrctechnology.org
University of Dundee	www.dundee.ac.uk

prioritized on a competitive basis for access to centralized screening. In turn, the scale of activities offered, namely, access to hundreds of thousands of high-quality compounds, would be beyond the reach of most national academic research programs. Active compounds would be returned to the investigators for in-depth characterization in their areas of expertise. This would ensure that investment would be directed to funding projects that can deliver novel biotools for researchers and not in duplicating expensive infrastructure.

It is my strong belief that the above scenario would not only result in the provision of novel tool compounds for basic science but also, where appropriate, be subject to patent protection, which would further encourage the progression of hit compounds into new drugs by the pharmaceutical and biotech industries. Collectively, the advantages of a pan-European screening facility would create a win–win scenario in which scientists, industry, and society would benefit from discoveries and progress in chemical biology.

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