The roads and bridges of science

Research infrastructures are key components of Europe's future research, but their funding is not guaranteed

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The development of recombinant gene technology in the 1970s heralded a new era of application-oriented research for molecular biology, with a huge economic impact. During the decades that have followed, biological research and development have become a major enterprise, with an increasing demand for sophisticated technologies, databases, tissue banks and other tools that range from microscopes and DNA sequencers to bioinformatics services and mutant collections. Biology has followed in the footsteps of physics and astronomy, which share costly instrumentation such as particle accelerators, observatories and satellites. A key difference is that biological research infrastructures are often distributed across several sites and are less costly to establish. Nevertheless, they are expensive to operate and maintain, and need long-term financial support.

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The European Union (EU) regards biomedical research as an important component of its future economic and social development as part of its 'Innovation Union' strategy (EC, 2010), but the necessary creation and operation of research infrastructures is not keeping pace. European biologists have been highlighting the problem for years (van Dyck, 2005), to the effect that some pan-European infrastructures for biomedical research and the life sciences have been created, such as the European Bioinformatics Institute (EBI; Hinxton, UK). The European Commission (EC) also established the European Strategy Forum on Research Infrastructures (ESFRI) in 2002, to define the infrastructures required

for international research (ESFRI, 2006, 2011). However, most of the planned projects for the biomedical and life sciences (Table 1) do not yet exist, and the existing ones are of limited use in the absence of long-term funding.

As part of the ongoing discussion about the EC's next framework programme for research, a hearing took place on 5 May at the European Parliament (EP) in Brussels, Belgium, to discuss the long-term future of biomedical research infrastructures in Europe. A few members of the EP and their staff, and scientists and representatives from the EC, debated models of how to develop and support global research infrastructure projects. Predictably, the most important questions were about who would pay the bills. "We need conditions to provide stable funding and support, particularly in economically difficult times," said Antonio Correia de Campos, MEP and vice

Table 1 | Biomedical research infrastructures in the ESFRI roadmap (ESFRI, 2011)

Project	Construction costs (million €)	Operation costs (million €)
Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)	170	3
European Advanced Translational Research Infrastructure in Medicine (EATRIS)	20–100	3–8
European Clinical Research Infrastructures Network (ECRIN)	0	3.5
European Life Science Infrastructure for Biological Information (ELIXIR)	470	100
European Marine Biology Resource Centre (EMBRC)	100	60
European Infrastructure of Open Screening Platforms for Chemical Biology (EU-OPENSOURCE)	40	40
European Biomedical Imaging Infrastructure (Euro-Bioimaging)	600	160
European Research Infrastructure on Highly Pathogenic Agents (ERINHA)	174	24
European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes (Infrafrontier)	180	80
An Integrated Structural Biology Infrastructure for Europe (INSTRUCT)	300	25
Infrastructure for Analysis and Experimentation on Ecosystems (ANAE)	210	12
Infrastructure for Systems Biology-Europe (ISBE)	300	100
Microbial Resource Research Infrastructure (MIRRI)	190	10.5

chairman of the EP's Science and Technology Options Assessment.

There is no doubt among scientists that research infrastructures are essential for biomedicine and the life sciences. Janet Thornton, Director of the EBI, explained that centrally managed infrastructures have a crucial role at all levels, from basic to translational

research to product development. Ivan Baines, Chief Operating Officer at the Max Planck Institutes in Dresden, Germany, and Miami, USA, stressed that infrastructures make research more efficient by giving scientists access to sophisticated services, tools and technology that no research institute or university would be able to afford alone. Globally shared research infrastructures are therefore more cost-efficient because they reduce redundancy and enable more-efficient use of data and tools—a clear 'economy of scale' effect. In general, as Baines commented, well-funded research infrastructures with sophisticated equipment and experienced staff generate a huge return on investment.

Not surprisingly, research infrastructures are set to play a central role in the EU's Innovation Union. The overall rationale is to create a European research landscape clustered around shared research infrastructures in order to meet major challenges, such as tackling global climate change, the health issues of an ageing population, clean and sustainable

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energy and water production, sustainable food supplies and the risk of disease pandemics. Moreover, the infrastructures themselves would be linked to each other to share data and expertise so as to form a network of pan-European institutions and facilities that support scientists at every step of their research. The proposed Euro-Bioimaging project, for example, would include research institutes, universities and commercial partners that provide state-of-the-art imaging technology to the scientific community and promote standardization, best practice and coordination of research, in addition to researching and developing new imaging technologies.

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In their 2006 roadmap, the ESFRI recommended creating six biomedical research infrastructures—a number expanded to 10 in their 2008 roadmap (Table 1; ESFRI, 2006). In addition, the roadmap proposes the creation of e-infrastructures to connect and support increasingly diverse and distributed sites. Just two days before the hearing, the ESFRI published its 2010 roadmap, which lists three more projects and strongly reiterates the important role for pan-European research infrastructures (ESFRI, 2011).

What the 2010 roadmap does not say is who is going to pay. Initial funding from the EC runs out in 2011 and has been earmarked to support the preparatory phase, but not the creation of infrastructure projects, let alone their maintenance and operation. The main problem is that most EU member states alone

cannot fund and support even a medium-sized research infrastructure. Unlike the US federal government, which, with the sheer size of its budget, can finance globally shared research institutes or facilities such as the NIH, NASA and the Public Library of Science, even the largest EU member states would be overwhelmed by such costly enterprises.

Hervé Pero from the EC's Directorate Generale for Research and Executive Secretary of the ESFRI identified the major problems for internationally shared research infrastructures: insufficient funding, complex management of diverse and distributed enterprises, insufficient policy tools including validation, legal issues and guaranteeing access for all scientists from the 27 EU member states. Moreover, some national

governments are reluctant to finance globally used research institutions that do not directly provide tangible benefits to their economies. "Sometimes it is easy to convince a research minister because he's a scientist; it's not so easy to convince financial ministers," Pero said.

The EC therefore proposes to use funding models already used by CERN and the European Molecular Biology Laboratory, in which interested parties—states, philanthropists, charities or funding organizations—commit to supporting research infrastructure such as databases, bio-informatics services, tissue banks or microscope facilities. "Member states are the key partners for this initiative," de Campo said. The EC would organize and coordinate support, and create the legal and political framework. The ambitious aim, according to the ESFRI, is that by 2015 the most important research infrastructures should be up and running and freely accessible to the scientific community.

It is not clear, however, whether and to what extent EU member states will fund pan-European infrastructures: the UK, Finland and Poland, among others, have earmarked some money for the establishment of ELIXIR—the infrastructure for biological information—and other projects, but this is far from what is needed and does not address the problem of long-term operation and maintenance, particularly in these difficult economic times. Moreover, coordinating support for the 13 projects recommended by the ESFRI remains a major challenge. “It is unprecedented to coordinate all these activities across 27 countries,” Baines remarked.

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Mere coordination by the EC to organize support from individual member states might, therefore, not be enough. Bernd Pulverer, head of publications for EMBO, who moderated the hearing, enquired whether a European agency similar to the European Research Council (ERC), which funds basic research, would be a solution to the problem of guaranteeing long-term stability. Pero agreed that an agency that identifies needs and funds the establishment, maintenance and operation of pan-European infrastructures would be a viable solution, but he was not optimistic. “It would be the way forward to create a body at the EU level to coordinate funds and actions. Unfortunately, the time is not right,” he said. Given the economic crisis, various member states are not keen to contribute more money to the EU. Moreover, the ERC has not existed for long enough to convince the EP and ministers that additional funding for another agency for research would benefit the whole EU. Nevertheless, the EC is aware of the problem of long-term financial support, and has therefore included research infrastructures in its proposal for the next research framework.

Some MEPs at the hearing share the concerns of scientists about the viability of long-term funding. Vittorio Prodi expressed concern over nationalistic reflexes that would be an impediment to international research. Instead, he said the EU should focus on the added value of pan-European

research infrastructures and their potential for development. Even so, economic and other factors may well force the EU to take a more proactive role. “In times of global challenges, the best answer for the EU is to pull together and not go for nationalistic solutions,” Prodi said, “[and to] give the EU directly the resources that are needed.”

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Published online 10 June 2011

EMBO reports (2011) 12, 641–643.
doi:10.1038/embor.2011.113

New optics sheds light on biology

Advances in microscopy, genetics and biochemistry are together increasingly enabling scientists to watch molecules in action

Philip Hunter

Advances in light microscopy are about to transform molecular biology by enabling biologists to observe molecular processes *in vivo*. Although biochemical analysis or genomic sequencing, along with imaging techniques such as X-ray diffraction and electron microscopy, can provide detailed information about cellular structures and the products of particular processes, it is light microscopy that allows scientists to capture dynamic events in the cell. Basic research is not the only enterprise that benefits from improvements in microscopy; new optical techniques also have an increasing role in diagnosis and surgery—in particular for some cancers—to analyse tissue in real time.

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For decades, light microscopy was regarded as the poor relative of electron microscopy and X-ray crystallography, both of which enable much greater resolutions, down to atomic scales around 0.1 nm. Yet both techniques come at the expense of the object because they can only analyse fixed samples—crystals in the case of

X-ray crystallography and thin sections for electron microscopy. This has always been the advantage of light microscopy: to capture events in living systems. Now, various developments over the past two decades have come together to introduce real-time imaging. “Revolutionary improvements in laser light sources, detectors, or cameras, and the advent of computerized digital light and fluorescence microscopy have been essential for enabling real-time imaging and micro-endoscopy in living systems,” said Frank Chuang, associate director of research and education at the Centre for Biophotonics and Research at the University of California, Davis in Sacramento, USA.

The first major step for real-time light microscopy was the development of fluorescence methods for labelling proteins *in vivo*. These methods exploit the fact that fluorescent compounds absorb electromagnetic radiation at one wavelength and emit light at a different wavelength. A sample can be illuminated by electromagnetic radiation at the prescribed wavelength, and only the fluorescent components of the sample, as well as areas very close to them, are observed. Using fluorophores as markers for specific