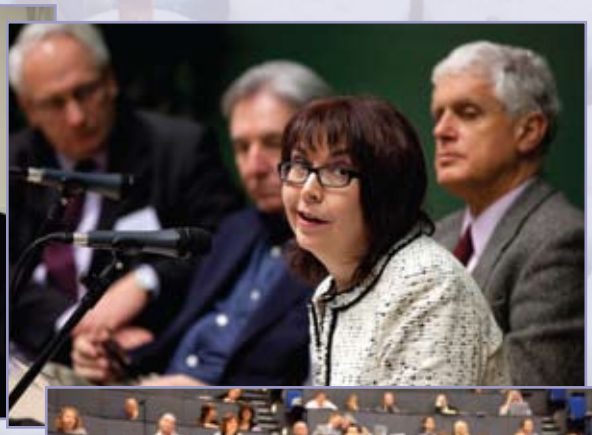
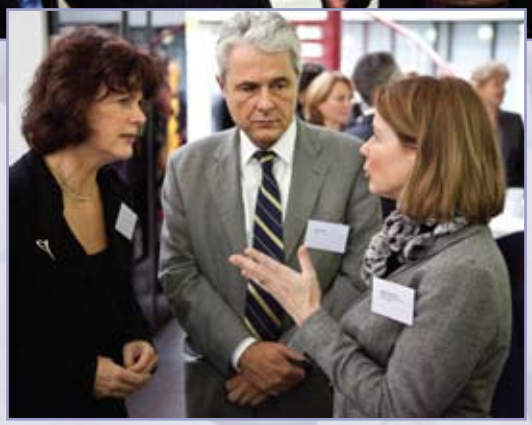
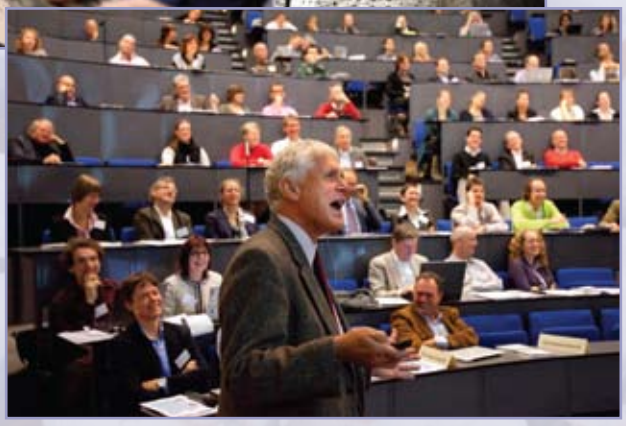
Hub 2

Hub is the official newsletter of BBMRI-NL

State secretary launches BBMRI-NL



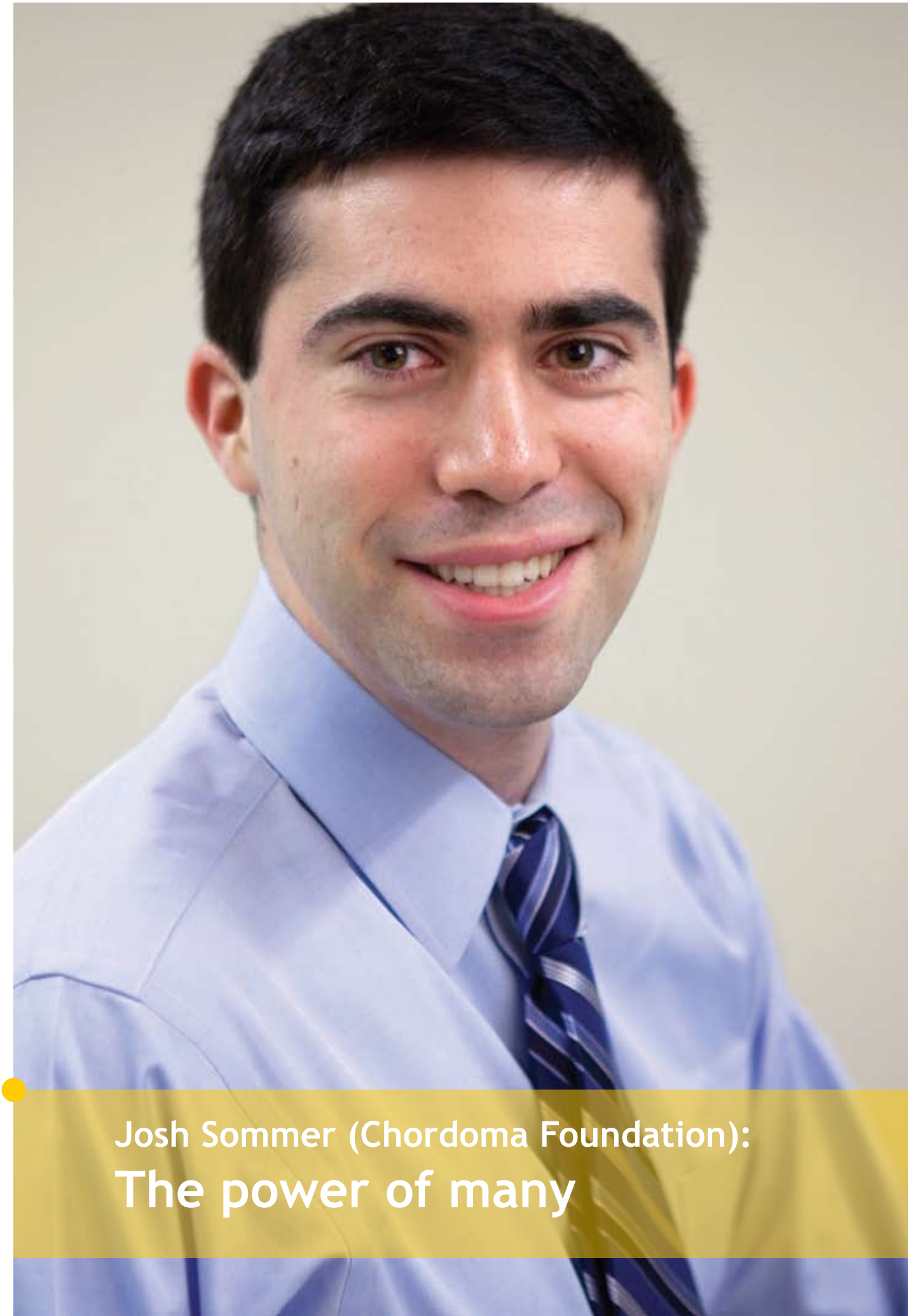




Top left: Dr. Ruben Kok (NBIC), State secretary Halbe Zijlstra and Professor Gert-Jan van Ommen (BBMRI-NL). Top right: Professor Carole Goble (School of Computer Science, University of Manchester) during the forum debate. Bottom left: Dr. Jeannette Ridder-Numan (Ministry of Education, Culture and Science), Dr. Colja Laane (Netherlands Genomics Initiative) and Margot Scheltema (Taskforce Stimulation Large Infrastructures). Bottom right: Professor Nick Martin (Queensland Institute of Medical Research, Australia) during his presentation on the Australian Twin Registry. (Photos: Thijs Rooimans)

State secretary of Education, Culture and Science Halbe Zijlstra performed the official launch for BBMRI-NL during the conference 'Connecting Biobanks' on November 22. In his speech, Zijlstra called collaboration between biobanks a necessity: "Biobanks are the key to the future", he stressed. After his speech the State secretary pushed a symbolic red button to signal the official start of BBMRI-NL. Unofficially, BBMRI-NL has been active for almost a year and a half, as scientific director Professor Gert-Jan van Ommen pointed out. "We have been busy", he said. "Good examples are the forty-three Complementation projects which are underway, plus the two Rainbow projects."

During the conference, which was co-hosted by BBMRI-NL, the Netherlands Bioinformatics Centre (NBIC) and the Concept Web Alliance (CWA), many international speakers commented on the forerunner position the Netherlands have when it comes to scientific research collaboration.



Josh Sommer (Chordoma Foundation):
The power of many

To understand what causes a disease and in order to find a cure, access to as many patients' data and biomatter as possible is invaluable. This is even more true for rare diseases, such as the rare bone cancer chordoma. But patients can play an even more active part in research, trials and treatment, says founder of the Chordoma Foundation Josh Sommer.

Sommer should know: he is himself a chordoma patient. Diagnosed with the disease four years ago, he changed his Duke College major from environmental engineering to a self-designed bioengineering curriculum and set up the foundation together with his mother, Dr. Simone Sommer. Ever since, he has been doing battle with chordoma by bringing together patients and researchers from all over the world, connecting specialists with biobanks, promoting awareness amongst physicians, and doing research in the lab of Dr. Michael Kelley, a Duke oncologist studying the genetic basis of chordoma.

Sommer is a staunch believer in intensive patient involvement: "First and foremost, patients can help advance research by donating their biospecimens. Since every single rare cancer specimen is a precious resource and many hospitals do not routinely collect and preserve these tumors, it's up to patients to advocate for their tumor to be saved. Patients can also ask whether their physicians are involved in research for their respective disease, and encourage them to work with organizations like the Chordoma Foundation that are uniting and supporting teams of researchers from around the world."

He adds: "Participating in clinical trials is critical for developing new and improved treatments for chordoma, or any cancer. Currently only a small fraction of patients participate in clinical trials, often because they are unaware that trials are available."

"Aside from donating biospecimens and participating in clinical research, I believe that every patient has something of value to contribute to the search for a cure, whether it is donating money, raising money from friends and family, or volunteering professional expertise in marketing, finance, or medicine."

Josh Sommer: "Institutions can accomplish more than they would ever be able to do alone by pooling resources together." (Photo: Thijs Rooimans)

Biobanks

Biobanks are an essential resource for research, and collaboration and exchange between biobanks is particularly important where rare diseases such as chordoma are concerned, says Sommer. "Collaboration between biobanks, such as BBMRI is promoting, is vital to finding causes and remedies for any number of diseases. But when you talk about a rare disease, the importance is even more evident. Because chordoma is so rare, no single institution sees more than 10-15 cases per year, and no single institution has banked large numbers of chordoma tumors. By pooling resources together, institutions can accomplish more than they would ever be able to do alone."

"For example, the Chordoma Foundation has made numerous research projects possible by distributing a chordoma cell line to 27 different labs, and by brokering sharing of tumor samples among labs in the US, Canada, and the UK.

In Europe, there is a bone tumor consortium called EuroBoNeT (see inset, ed.) which has pooled over 180 chordomas from hospitals across Europe, and members of this consortium have collaborated to publish some of the most seminal research on chordoma to date. It is the best example I've seen of an organic collaboration between institutions in different countries."

Breakthrough

So far, the research and trials carried out have not resulted in a cure, but Sommer firmly believes a breakthrough is not far away. "If I did not wholeheartedly believe that a cure for chordoma is within reach, I wouldn't dedicate my life to this pursuit", he says. "Over the past few years the field of chordoma research has grown from just a handful of isolated researchers to a vibrant community of over

Members of the Chordoma Foundation during its second Community Conference in 2009. “The Chordoma Foundation is the vehicle by which patients can increase the odds of finding a cure”, claims Sommer.

170 scientists and physicians across the world. During this time, several promising therapeutic targets have been discovered, and one of these discoveries has resulted in a new treatment option for chordoma patients with advanced disease.” He goes on with hopeful news. “Recently, the cause of familial chordoma was uncovered, and this gene, called brachyury, was discovered to play a very important role in sporadic chordomas as well. Perphaps most encouraging of all, we’ve had every single drug approved by the FDA and EMEA screened against two chordoma cell lines, which has resulted in a number of hits. Now we are raising money to begin screening these hits in recently-developed chordoma animal models to determine whether any of these already-approved drugs could shrink chordoma tumors, and potentially benefit chordoma patients.”

Foundation

The Chordoma Foundation, founded in 2007, has been an active and resourceful catalyst of chordoma research during its short existence. The foundation is also a place where patients can meet, exchange experiences, and find out about current developments. “For any patient in need of a cure, supporting the Chordoma Foundation is the best way to speed the development of potentially life-saving treatments. Simply put, the Chordoma Foundation is the vehicle by which patients can increase the odds of finding a cure”, claims Sommer.

EuroBoNeT: distributed biobanking works

Primary bone tumours account for only 0.2 percent of the cancer burden. In the Netherlands, only 350 to 400 new cases are diagnosed each year. Still, researchers in the EU trying to find the genetic causes of these tumours, of which chordoma is one, have access to over 17,000 samples of DNA/RNA and data. The source is a virtual biobank created by EuroBoNeT, a project initiated by LUMC professor of Pathology Pancras Hogendoorn.

Hogendoorn: "There is simply too much legislation involved in setting up a physical biobank with access for researchers from all over Europe. That is why when EuroBoNeT first started in 2006, one of our first deliverables was setting up what we call a virtual biobank, a catalogue that tells researchers where they can find the data they want, complete with email addresses of the person in charge, and how to access it."

Leiden, for instance, holds materials and data for over 3,000 primary bone tumour cases. All the data is stored according to a common standard and there are protocols in place for freezing, storing and fixing samples. "All cases have a unique tracking number, which is used in every publication about research that uses that sample", explains Hogendoorn. "The system works a treat. And yet, outsiders are often skeptical. They seem to think a virtual biobank cannot work. I always tell them, look, it is working, so why question it?" Chordoma is a good example of how and why the biobank works. Hogendoorn: "We just published a joint study on chordoma in which the Netherlands, the UK, Austria, and Switzerland collaborated. We were able to use the best resources and technologies of all participating institutions."

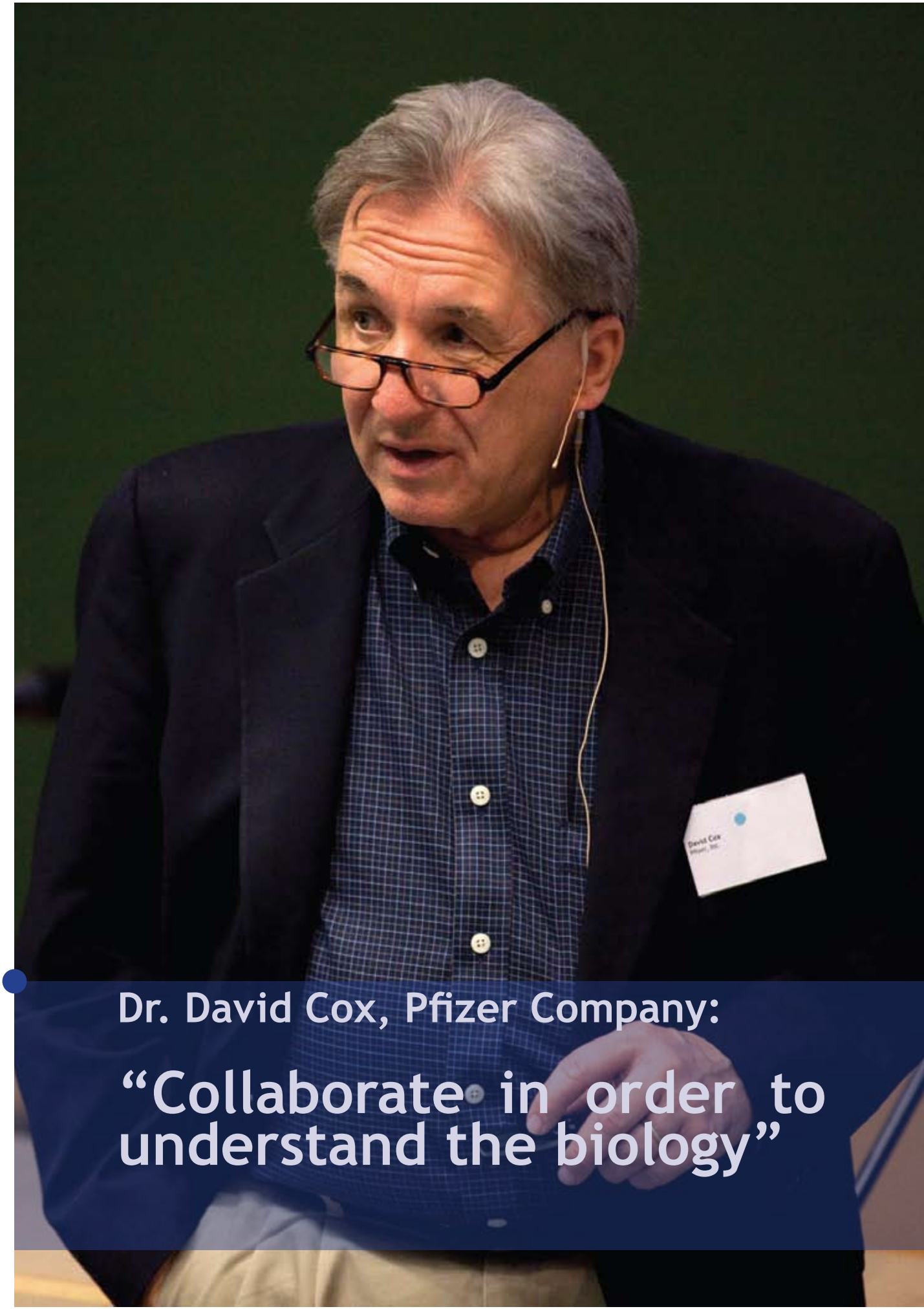
The distributed biobank holds samples and data of various types of bone tumours. "That is important", Hogendoorn stresses. "You have to be able to place your research in the context of related diseases."

EuroBoNet aims to facilitate research and promote knowledge about primary bone tumours, amongst others by exchanging staff and data, organizing training courses for specialists, and by standardizing work methods. Institutions from twelve countries participate in EuroBoNeT (www.eurobonet.eu), but newcomers are always welcome, says Hogendoorn: "Connecting to EuroBoNeT is relatively easy, provided you comply with our technological standards and operating protocols. For many countries, this actually means a surge upwards in know-how and technology."

"Beyond catalyzing research, the Chordoma Foundation is committed to helping patients get the best care possible by providing information about treatment options, experienced physicians, and relevant clinical trials. We provide this information through our website, and through one-on-one patients support. We also host international community conferences to connect chordoma patients and family members with one another, and with the researchers who are working to save their lives."

The Chordoma Foundation has certainly demonstrated itself to be efficient and effective. But will the cure come in time? Sommer: "I am convinced that we have the capacity to develop new treatments in time to save the lives of patients living with chordoma today. So it's full steam ahead at the Chordoma Foundation!"

Visit www.chordomafoundation.org for more information. For a complete list of all clinical trials open to chordoma patients, see www.chordomafoundation.org/treatment/clinicaltrials.aspx.



Dr. David Cox, Pfizer Company:

“Collaborate in order to understand the biology”

With the evolution of research methods in genetics and the growing possibilities for collaboration, the entire landscape surrounding diseases and their treatment is changing. The pharmaceutical industry is no longer at the end of the line throwing money at researchers for clinical trials, based on preliminary findings. It becomes more and more involved in the process from the outset, as do the participating patients. "We are evolving from a linear process to a circular one", says Dr. David Cox, Chief Scientific Officer for the Applied Quantitative Genotherapeutics Unit of Pfizer's Worldwide Research & Development.

Dr. David Cox tells the same story wherever he goes: that global collaboration and partnerships between scientists, industry and participants—whether they be patients or so-called 'population' donors—are the way to go instead of competition. "I am met with skepticism sometimes", he admits. "People have this image of pharmaceutical companies as a highly competitive industry, out to make money, and that's about it."

"Of course we aim to keep our shareholders happy, but in my opinion that does not have to involve cutthroat competition. I advocate public availability for results from genomics research, clinical trials, etc. This will lead to a better overall understanding of biology and will actually save companies a lot of money that they now spend on supporting clinical trials that are really based on what I would call raw materials, because it is not linked to the biology."

The possibility, inherent to the information age, to communicate with people and companies across the globe plays a key role in the changes that are taking place today, says Dr. Cox. "Previously, communication was limited to institutions, even to departments within institutions. A clinical scientist did not co-operate with a geneticist, although really, they were working on two aspects of the same problem. The scientific research community has been picking up on what global communications methods such as the internet can offer, I'm pleased to notice."

Dr. David Cox: "I believe research information should be publicly available so that everyone involved can benefit from it." (Photo: Thijs Rooimans)

Human Genome Project

"A second essential component of the change I see is that the empirical value of research is simply going up. Projects like the Human Genome Project (Dr. Cox is a HUGO Council member - *ed.*) present both the scientific community and the pharmaceutical industry with a formidable amount of detailed information. Whoever holds that information, has access to the world."

"Genetics can become the glue between scientists and the pharmaceutical industry. Together they are going to change the relationship from a linear one to a circular process, where the industry is much more involved in the health sector from the outset: from thinking about, what is it that we should be looking at?, to supporting research, to supporting clinical trials based on the outcome of that research, and ultimately to developing drugs."

And all this in the public domain. "Yes, I believe the information should be publicly available so that everyone involved can benefit from it", says Dr. Cox. "This will lead to closer collaboration and faster results. Public access will provide the substrates required for economic development by a variety of commercial and public organizations, leading to new therapeutics and diagnostics."

"Call me a dreamer, but I think if you look at the people who participate in trials, or contribute to population or clinical biobanks, what they ultimately want, the reason they participate, is an altruistic one: they want to help improve society by providing the materials and data that will help scientists and companies to improve the quality of peoples' lives. This is what we, also, ultimately work for."

Protection?

Several initiatives are currently underway to encrypt and shield off participants' data from prying eyes, such as DataSHIELD. But protecting

the privacy of participants if research results are made publicly available would be a huge problem. So how does Dr. Cox propose to go about this?
"I think we have to change our attitude towards participants altogether. These are people who want to know to what use you are putting their materials, because they care about the outcome. I think if you communicate openly to them that their data may be traced back to them, they have the choice. And I think they will choose to co-operate. It's all about trust and transparency: if the scientists are open about what they are doing and how, and share the results with the participants, the participants will trust them. If you 'protect' them by anonymising their data, you not only hamper science but effectively cut them out of the equation."

Expert centers

Collaboration between all the stakeholders involved in finding causes and cures for diseases sounds like a fine idea, but national laws and regulations make international exchange of data and especially biomatter a cumbersome process. "There is no need for that", says Dr. Cox. "Why move around samples? Focus on the experts, set up expertise centers where the experts are in control and use local resources from across the field."
"Of course, you need to harmonise those resources, and that is why what BBMRI does is so important. Making sure everyone uses the same datasets, enriching biobank content so that scientists can access the same type of data in the same way, everywhere in Europe. And hopefully, one day America will catch up too!"

From BBMRI Europe: ERIC explained

The application for the ERIC status is underway, but what does it entail? What advantages does it offer BBMRI? Jeannette Ridder-Numan, representative for the Netherlands in the ERIC committee and BBMRI-NL steering committee member, explains.


Photo: Thijs Rooimans

What is an ERIC?
"A European Research Infrastructure Consortium is a legal entity that operates internationally to set up research infrastructures such as telescopes and synchrotrons, but also collections of biobanks. Because it is a legal entity in its own right, it can do business in the same way that a foundation or person could: apply for a loan, set up offices, apply for project funding, etc. The concept of ERIC was especially devised by the European Committee, to accommodate and facilitate cross-border research infrastructures. It can be set up by a minimum of three European member states."

Why does BBMRI want to become an ERIC?
"There are several advantages. Most importantly, the level of commitment on the part of the participating countries is high. Then there is the application process itself, which in potential is much faster than the application process for an international organization, which is a treaty between countries. An ERIC involves the ministry in charge of Science; there are agreements in place with the tax office and the Ministry of Finance, but they are not a part of the ERIC. Another major advantage is that an ERIC, as a legal entity and ruled by European legislation, is exempt from paying VAT and duty taxes. So for instance, if the Dutch national BBMRI hub wants to set up office, it can do so as a legal entity once BBMRI is an ERIC, plus renting the space will be 19 per cent cheaper."

So how fast can BBMRI-ERIC be a fact?
"Right now, the countries interested in participating are working very hard on the

statutes and the technical description, the business plan if you like, in the ERIC committee. Halfway through December we hope to be able to present these documents to the intended member states. In January, we expect to receive all the responses and be able to sign a Memorandum of Understanding, after which a sort of intermediary phase will start and the statutes and technical description can be discussed in detail before any country commits itself unequivocally."
"At a certain moment the application has to be sent by the host country via the Permanent Representation to the European Commission. They will check if everything is in order and will ask a scientific panel if they believe this is a real infrastructure serving the goal of the European Research Area. If this is all in order, it will come to the ERIC Committee and the delegates will vote. This whole process takes at least three months." "If all goes well, the first half of 2011 will serve to finalize matters as well as for the organization to sort out all kinds of logistical and organizational questions: where will the central offices be, will we set up a separate center of excellence for legal matters, what is the procedure if we want to hire an intermediary CEO? These are all just examples of course, but you get the idea."

Once BBMRI becomes BBMRI-ERIC, will the exchange of samples be free?
"No. Although the ERIC itself falls under European legislation, the shipping of bio matter for cross-border research is still subject to the national laws of the countries involved. Right now a pilot is taking place in Nijmegen on behalf of BBMRI EU, as part of the String of Pearls hereditary colorectal cancer research, to assess the consequences of conducting cross-border research, both on a legal and an ethical scale. Perhaps the results will one day lead to a proposal to alter the EU procedures, but for now that is still in the future."

Jeannette Ridder - Numan is Deputy head Science & Humanities at the Ministry of Education, Culture and Science, Dept for Research and Science Policy.

Agenda

Dutch Life Sciences & Health Conference
Beurs van Berlage Amsterdam, 8 december 2010
The central theme of the 6th Dutch Life Sciences & Health Conference is 'From Innovation to Commercialisation'. The conference features plenary presentations, dedicated workshops, an investors forum, and exhibition, networking and partnering opportunities.
See www.dutchlshconference.com

Registries for Rare Disorders
Brussels, Belgium, 25 and 26 January 2011
What are the advantages of setting up registries for patients with rare disorders? This is the question addressed by EPPOSI, the European patient-led collaboration between patient organizations, industry and science on January 25 and 26. All stakeholders are invited to discuss the perspective viewpoints in interactive workshops.
See www.epposi.org

Genetica Retraite
Conference Centre Rolduc, 24 and 25 February 2011
The Genetica Retraite enables (young) researchers from the Dutch universities to get acquainted with the research that is going on in other Dutch centres and new developments in the field of genetics. It is organized by the Academic Medical Centre of Maastricht.
See www.azm.nl/zorgcentra/zorgcentra/Erfelijkheid/retraite/retraite2011

VSOP symposium: biomedical research
Location t.b.a., 17 June 2011
VSOP is a clustered patient organization representing (parents of) patients suffering from rare diseases. In June 2011, VSOP hosts a symposium on the ways forward for biomedical research through biobanks, medical databanks and patient registries.
See www.vsop.nl

Photo: Thijs Rooimans

Building the tools to harvest biobank data

By Pieter van Megchelen

Astronomical amounts of new molecular data will be generated from large projects like the Genome of the Netherlands project and other nationwide BBMRI-NL 'enrichment' projects. This bounty of raw materials for scientific exploration requires bio-informatics tools that are flexible, scalable and usable. The bioinformatics Rainbow project, 'Dynamic bioinformatics infrastructures for biobank enrichment' aims to deliver such a tool set, and more. Project leader Dr. Morris Swertz (Groningen) talks about his efforts.

Recent efforts within biobanking generate an unprecedented data stream of several terabytes per week. Within this stream, future breakthroughs in medicine and biology are hiding. But first the quality of these data has to be checked, their position within the large picture established and they have to be analysed and compared with relevant data from other sources. Bioinformatics is there to provide biologists with the tools they need to do all these things. So when there is an increase in scale in biological research, like BBMRI-NL is currently organising, there has to be a matching effort in bioinformatics. Swertz: "We need to address the questions arising from the two major goals of BBMRI-NL, enrichment and harmonisation. For enrichment we need to establish suitable protocols to analyze, organise, process and manage data coming from both small and large scale data collection efforts: like the Genome of the Netherlands project, where 750 individuals will be fully sequenced and circa 100.000 GWAS sets 'imputed' (enriched). And we need harmonization to be able to combine data from multiple biobanks to achieve sufficient statistical power to actually find something."

"Our efforts for now are focused mainly on the bioinformatics of the former, but we also address some questions concerning the latter. This Rainbow project will not focus on the Babylonian challenges that arise when you try to combine phenotype data from independently collected biobanks. That challenge, hopefully, will be tackled by a future project. But the first groundwork will be included in this one: for instance, a first catalogue of the BBMRI-NL biobanks and an exploration of smart search

techniques. It will not contain all the data, but it will show what kind of data are where, like a telephone directory."

Clever tools

There are many tools we can build on and standard data formats to connect them. But tools also need to be tailored, for every project has its own specifics that standards don't cater to. The time needed to tailor software tools can become a bottleneck for large-scale research projects like the Genome of the Netherlands project, and even more so for smaller scale local efforts where there is no staff and no budget to build software from scratch. In a paper in Nature Reviews Genetics (2007) Swertz and his colleague Professor Ritsert Jansen describe a clever approach to re-use modules and rapidly combine them into new tools and pipelines: "We believe that it is time to move bioinformatics from expensive, almost one-at-a-time, 'cottage-industry' towards twenty-first-century engineering practice. (…) We must go beyond standards as they focus only on commonalities and not on variations. We need a minimal computer language that can be used by systems biologists and their bioinformaticists to adapt software components to the biological details of their particular system, and a software tool, called a generator, that automatically produces a customized software infrastructure using reusable assets. This would reduce the number of hand-written lines of software code to a level at which one can much more efficiently maintain and evolve such software infrastructures" (Swertz and Jansen, 2007).

'Deliverables'

The MOLGENIS software is such a 'generator' (Swertz also calls it 'our factory') and is at the core of the many bioinformatics tools the project will deliver in the years to come. Some of them have to be ready quite soon, as the data from the Genome of the Netherlands project are already coming back from BGI in China, where the main sequencing is being done. Swertz: "The raw sequencing data consist of hundreds of millions of 'short reads', sequences of about a hundred DNA bases for each of the 750 individuals. Together we develop workflows, we call them pipelines, to check quality and identify known and new genetic variants. That will result in a catalogue containing the specific variations in the Dutch population. We are also building a database and user interfaces for biobankers to collect and trace all this data, so progress can be monitored and results can be annotated and compared with the reference human genome and other data."

The Genome of the Netherlands project fits into a larger picture, enriching the information content of many existing genome wide association studies (GWAS) within Dutch biobanks. The bioinformaticians will deliver several essential tools for GWAS as well, from database and user interfaces to manage and query GWAS data to protocols and workflows that can be used to impute GWAS data, using the Dutch genome to find the rare variants that are the Holy Grail in population genetics. The list of 'deliverables' in Swertz' project proposal contains ten more of these highly useful tools for researchers, all of them made easily adaptable into the specific 'toolbox' a scientist may need for a particular research question.

In the course of our conversation, Swertz mentions how all these efforts are only possible via collaborations between many teams: LUMC, Erasmus MC, VU, UMCU, BGI/China and UMCG supported by the sequencing and biobank 'taskforces' of Netherlands Bioinformatics Centre (NBIC), CIT/Groningen and SARA/Amsterdam compute centres, the Broad institute of Harvard and MIT, and Sanger/European Bioinformatics Institute, to name a few. Swertz and his colleagues don't have to worry about their data storage capacity either: they cooperate with TARGET, a 10 petabyte (1015 bytes) storage facility—a quantity equal to a DVD pile of 2,91 kilometres—built for large biomedical data of the LifeLines biobank and radio telescope data sets from astronomy. Talk about astronomical amounts of data...

More information on www.bbmri.nl, www.bbmriwiki.nl, www.molgenis.org, www.nbic.nl, www.broadinstitute.org.

What future is there for privacy in genomics?

by Professor Ruth Chadwick

Privacy protection in genomics has always been at the centre of debate, but it is interesting to reflect why so much discussion has taken place here, while in other contexts there appears to be more acceptance of possible threats to individual privacy in exchange for benefits —both convenience, in the case of mobile phones, and greater security, as in the case of surveillance and airport procedures.

Professor Ruth Chadwick: is it time to rethink our concept of 'privacy'? (Photo: Gavin Dando)

It is tempting to think that genomics has unjustifiably had a bad press, but this may be due to historical legacies related to public (dis)trust of science. On the other hand, maybe the appropriate norms of information flow differ according to context, as Helen Nissenbaum has argued; maybe there is variation between different publics, e.g. generational differences in how much information we are willing to reveal about ourselves and in what arena. A social medium like Facebook appears to be challenging old conceptions of 'friendship' and 'privacy', but how people relate to their genetic information still gives rise to controversy.

The end of privacy?

Biobanking has brought with it new challenges, particularly in an era of data sharing and cross-border flow of samples and data. In this situation there are two broad types of response, not mutually exclusive. The first is to seek enhanced forms of data protection, at both a technological and regulatory level (such as P^{3}G's DataSHIELD, *ed.*). The other is to re-examine what our thinking about privacy is and should be. Some have argued that we should accept that privacy is no more, because reidentification is always, at least in principle, possible.
In that case it is misleading to ask people to consent to donate samples in exchange for a promise of privacy. A less strong view is that privacy as we knew it is no more. Mireille Hildebrandt has argued, for example, that privacy regarded as sovereignty over my data is not tenable, and this is particularly the case when the issues concern how conclusions may be drawn about me through data mining and profiling. Group privacy has become a real issue alongside individual privacy.

Towards a new concept

It seems right that there is a need to think differently about privacy in today's world and this is not necessarily a matter of surprise or regret. Values change and thinking about ethics develops, just as scientific paradigms shift. This makes it clear, however, that it is not sufficient just to focus on data protection, important though that is. Privacy is a richer and wider concept than data protection, including as it does spatial, physical and decisional aspects, in addition to informational. What is needed is a real sense of what interests (of different kinds) are at stake, and how the appropriate balances can be struck.

Literature references:

Profiling the European Citizen, Mireille Hildebrandt and Serge Gutworth eds., Springer Press (2008).
Privacy in Context, Helen Nissenbaum, Stanford University Press (2009).

About the author

Ruth Chadwick is Distinguished Research Professor at Cardiff University and Director of CESAGen (www.genomicsnetwork.ac.uk/cesagen). She holds a Cardiff University 'Link' Chair, held jointly between the School of English, Communication and Philosophy and the Cardiff Law School. She is also chair of the Human Genome Organisation (HUGO) Ethics Committee, co-editor of the journal Bioethics and editor of the online journal Genomics, Society and Policy.

Colophon
Hub year 1, issue 2, December 2010.

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