assessment—for example the requirement for sequential recruitment in phase 1 trials and the requirement to study every dose that will be applied to humans in animals first. The classic principle that the highest dose is the most relevant dose for determination of safety and the safety margin might not apply for future immunomodulators, for which, in theory, lower doses could have a divergent effect (and even enhanced potency) compared with higher doses.

We have proposed above three criteria for identifying mAb molecules that would warrant more stringent regulatory oversight. An intensive discussion among scientists in academia, in industry and at regulatory authorities must now be initiated to refine these principles and find mutually acceptable criteria for defining 'high-risk' mAbs. Without doubt, the TGN1412 trial has highlighted the fact that the production of new animal models and the identification of surrogate markers that are more predictive of risk factors in human volunteers should now become a priority for biopharmaceutical research and development.

Christian K. Schneider, Ulrich Kalinke and Johannes Löwer

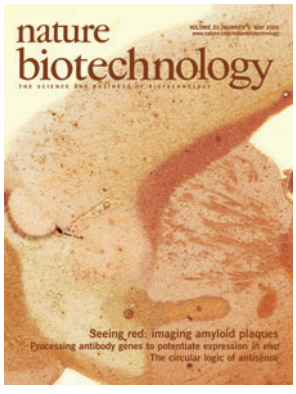
Paul-Ehrlich-Institut, Division of Immunology, Paul-Ehrlich-Str. 51-59, Langen 63225, Germany
e-mail: kalul@pei.de

1. European Medicines Agency. *Xolair European Public Assessment Report* (EMEA, London, 2005). (http://www.emea.eu.int/humandocs/Humans/EPAR/xolair/xolair.htm)
2. Jiang, H. & Chess, L. *N. Engl. J. Med.* **354**, 1166–1167 (2006).
3. Lenschow, D.J., Walunas, T.L., Bluestone, J.A. *Annu. Rev. Immunol.* **14,** 233–258 (1996).
4. Phan, G.Q. *et al. Proc. Natl. Acad. Sci. USA.* **100,** 8372–8377 (2003).
5. Lühder, F. *et al. J. Exp. Med.* **197,** 955–966 (2003).
6. Beyersdorf, N. *et al. J. Exp. Med.* **202**, 445–455 (2005).
7. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals S6* (ICH, Geneva, Switzerland,1997). (http://www.ich.org/LOB/media/MEDIA503.pdf)
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline General Considerations for Clinical Trials E8* (ICH, Geneva, 1997). (http://www.ich.org/LOB/media/MEDIA484.pdf)
9. Committee for Medicinal Products for Human Use. *Position Paper on the Non-Clinical Safety Studies to Support Clinical Trials, with a Single Low Dose of a Compound* (EMEA, London, 2002). (http://www.emea.eu.int/pdfs/human/swp/259902en.pdf)
10. Reichert, J.M. *et al. Nat. Biotechnol.* **23,** 1073–1078 (2005).

Human tissue bank regulations

To the editor:

I read with interest the article by Karen Maschke on human gene banks in your May issue (*Nat. Biotechnol.* **23**, 539–545, 2005). However, I would like to draw the attention of your readers to several inaccuracies in the text that require correction and other points that require clarification.



The first major problem is that the article fails to distinguish between the two different types of tissue stored by tissue banks. One type, 'residual tissue,' is collected from patients either during treatment (for example, tissues extracted on suspicion of malignancy) or in the course of a diagnostic procedure. It can be used in research, but only under certain circumstances, and represents the majority of tissue samples presently held in biological repositories. The other type of tissue is collected explicitly for the purpose of research. From a regulatory (and also ethical) standpoint, there is a huge difference between the former, exemplified by the type of tissues stored in pathology laboratories, and the latter, exemplified by the tissues in stored in the UK Wellcome Trust Biobank (http://www.ukbiobank.ac.uk), which started recruiting volunteer donors in March. By conflating residual tissues with tissue collected explicitly for research (and the respective banks that store them), Maschke is guilty of comparing apples and oranges both in the text and Table 1 of her article.

On p. 542 of her Feature, Maschke is also wrong when she states that Iceland is "unique in that it permits presumed consent (that is, consent is assumed unless otherwise indicated) to govern the storage of samples in a biobank if they were obtained for the purpose of clinical tests or treatment." Denmark also permits presumed consent for research on tissue samples—whether they are anonymized or anonymized with a code that enables linkage to other medical data associated with the donor[1]. The text of the UK Human Tissue Act, after a governmental amendment[2], even allows no consent at all for the use of such tissue[3]. However, the recent of Code Practice of the UK's Human Tissue Authority proposes consent as best practice for more complex tissue-banking projects[4]. In France, Article 1235-2 of the Code de la Santé Publique (CSP) states that anonymized or coded anonymized tissue may be used in research as long as the donor has not opted out, though admittedly other provisions of the CSP and of the French Data Protection Act complicate this considerably. For tissue banking, one needs the approval of at least two authorities[5], and for research using tissue banks that include residual tissue that is not fully anonymized, one needs both specific consent from the donor and an authorization from the French Data Protection Authority[6].

In Box 2 of her article, Maschke commits another error by conflating research on human subjects with research on residual tissue. In the United States, research using human data and human tissue is considered human subjects research. In Europe, however, only interventional research is considered as human subjects research. Research with data and residual tissue is considered observational research, which is subjected to different regimes[7], as seen in the case of Denmark, the United Kingdom and France. The same holds true for the Netherlands. Thus, Maschke's article is inaccurate when it states: "In the Netherlands, consent must be obtained from both parents or legal representatives for children less than 12 years old; children between the ages of 12 and 18 must give consent, along with both of their parents or legal representatives." In fact, this age limit refers to the Dutch Act on Medical Research with Human Subjects[8], which does not apply to work on residual tissue. In this case, the legislation Maschke should have referred to is the Dutch Act on the Medical Treatment Contract[9] and the Dutch Data Protection Act[10], both of which consider minors competent to make decisions from the age of 16 (not 18).

Research with tissue always means research with data. As Maschke briefly outlines in Box 3 of her article, the ways in which data are associated with residual tissue profoundly influence whether or not donor consent is needed as well as other regulatory aspects, such as the applicable provisions in the data protection legislation.

In Europe, use of personal data is covered by Directive 95/46 EC. This Directive

did not achieve harmonization for the use of data for medical research. In fact, there are even substantial differences in what constitute personal data depending on national jurisdiction. In the United Kingdom and the Netherlands, for example, research using coded data or samples, for which investigators do not have access to the code, is not considered to be research involving personal data[11,12]; in contrast, the majority of other European countries do consider such research as involving personal data. Although a European Commission report on the implementation of data protection in member states did not decide whether such data are personal or not, it did state that the definition in Directive 95/46/EC should be applied with (in my words) common sense[13]. There are also differences in the kind of authorization required to use data, and therefore tissue, for research. In the Danish case, if data or tissue are not fully anonymized, an investigator must have permission from the Danish Data Protection Authority to use the associated data[14]. No such authorization is needed for the use of coded data and tissue in, for example, the United Kingdom, Austria or the Netherlands[7]. Nuances such as these are lost in Maschke's description.

In the United States, Maschke also oversimplifies the situation by referring to the US Health Insurance Portability and Accountability Act (HIPAA), but neglecting to mention the applicable part of the Code of Federal Regulations(the so-called common rule)[14] and to comment on the role of the US Office on Human Research Protections. The latter stated in a guidance that research with data and tissue that, though coded, are unidentifiable at the level of the researcher is not considered human subject research[15]. Therefore, although research on anonymized tissue, even if it is coded, lies outside the common rule, it may contain protected health information according to HIPAA, which is subject to restrictions on use and disclosure. The US situation is further complicated at the state level by the impact of 'genetic privacy' legislation in several states that may apply to research on residual tissue[16].

To sum up, then, by failing to differentiate between the two fundamental types of tissue collected by tissue banks—residual tissue and tissue specifically acquired for research purposes—Maschke creates confusion about relevant regulations. For tissue-banking projects using residual tissues, a distinction could also have been made between those that involve retrospective studies and those that involve prospective studies. All of these differences are relevant to the regulatory regime and ethical considerations.

By heaping together and conflating issues, perhaps owing to lack of space, Maschke oversimplifies and muddies the legal situation with regard to research on human tissues in several national jurisdictions. As suggested by the article's title, human gene banks do present an "ethical patchwork" and legal comparisons between regulations in different countries are laborious and defy generalizations. Any article that suggests the contrary should be read with caution.

Ben-Evert van Veen

Medlawconsult, Postbus 11500, 2502 AM, The Hague, The Netherlands e-mail: eb.vanveen@medlaw.nl

1. Art. 18 b of the Danish Act on Patient Rights, as amended in 2004.
2. Commons Hansard Debates for 28 June 2004 (pt. 31).
3. UK Human Tissue Act Chapter 30, part 1, subsections 8 and 9.
4. Draft Code of Practice Consent, Code 1. The Human Tissue Authority, Crown, 2006; Section 29 <http://www.hta.gov.uk/download/Code%20of%20Practice%201%20Consent.pdf> (last accessed February 2006).
5. Art. 1243-3 Code de la Santé Publique.
6. Chapter IX of French Data Protection Act as amended in 2004.
7. As explained at section 3 in van Veen E.B. Comments on the Draft CIOMS Guidelines for Ethical Review of Epidemiological Research, The Hague, 2005 <http://www.medlaw.nl/documenten/comments.pdf> (last accessed March 2006).
8. Dutch Act on Medical Research with Human Subjects <http://www.ccmo-online.nl/main.asp?pid=21&thid=7> (last accessed March 2006). For an English version of the Act, before the implementation of Directive 2001/20 EC, and a commentary see <http://www.healthlaw.nl/humsub.pdf> (last accessed March 2006).
9. Dutch Act on the Medical Treatment Contract <http://www.dutchdpa.nl/indexen/en_ind_wetten_wbp.shtml> (last accessed March 2006).
10. Art. 37.2 of the Dutch Data Protection Act, see http://www.dutchdpa.nl/indexen/en_ind_wetten_wbp.shtml (last accessed March 2006)
11. van Veen, E.B. *Privacy Informatie* **6**, 259–262 (2003).
12. van Quanthem, K. *Privacy Informatie* **8**, 155–161 (2005).
13. First Report on the Implementation of the Data Protection Directive (95/46/EC) (Commission of the European Communities, Brussels, 2003) <http://europa.eu.int/eur-lex/en/com/rpt/2003/com2003_0265en01.pdf> (last accessed February 2006).
14. Art. 45 and art. 50 of the Danish Data Protection Act.
15. Chapter 45 of the Code of Federal Regulations (CFR), part 46.
16. Guidance on Research Involving Coded Private Information or Biological Specimens (Office for Human Research Protection and Department of Health and Human Services, Bethesda, MD, USA, 2006) <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf> (last accessed February 2006).
17. Hakimian, R., Taube, S., Bledsoe, M. & Aamondt, R. *50-State Survey of Laws Regulating the Collection, Storage and Use of Human Tissue Specimens and Associated Data for Research* (U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, publication no.05.5628, November 2004).

Karen Maschke responds:

Although Evert-Ben van Veen provides some important clarifications in his letter, he raises several points with which I respectfully disagree.

He correctly points out that Iceland is not the only country permitting presumed consent in the tissue research context; however, my statement that the Act on Biobanks in Iceland is "unique in that it permits presumed consent. . .to govern the storage of samples in a biobank if they were obtained for the purpose of clinical tests or treatment" was made in the context of comparing the Icelandic Biobank project to the other population-based biobank projects listed in Table 1 of my article. Readers should be aware, though, that several countries have legislation governing a broader array of tissue research that includes presumed consent provisions. van Veen also points out that countries differ in how they regulate the use of personal data associated with human tissue and that in addition to the federal HIPAA privacy rule, many states in the United States have privacy legislation that may apply to data obtained from research with human tissue. The National Conference of State Legislatures provides a summary of state genetic privacy laws that is updated at least once a month[1].

van Veen's perspective on the ethical and regulatory issues involving tissue collected from patients in the clinical setting—what he refers to as 'residual tissue'—is not a perspective that I and others share. van Veen says that "from a regulatory (and also ethical) standpoint, there is a huge difference between residual tissue and tissue collected specifically for research." In the United States, this is not true from a regulatory perspective. Moreover, the vast literature on the ethics of research with human tissue suggests there is disagreement about constructing different ethical frameworks for residual tissue and for tissue collected specifically for research, as well as over whether tissue research constitutes human subjects research. As Weir and Olick[2] show in their book regarding research with stored tissue, the debate from the outset (in the United States at least) over the use of stored tissue centered on the fact that residual tissue had long been used for research purposes without explicit consent for such use. They and others challenge the claim that coding or anonymizing residual tissue obviates the need to obtain informed consent because doing so fails to take seriously the fact that some people have concerns and interests about how their residual tissue will be used. This concern also