

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title: Competence Network Malignant Lymphoma

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Part A – General Statements about the Project

A.1 Subject

Integrated network of the reference panel for lymph node pathology

A.2 Co-investigators

Name of scientists:

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Prof. Dr. P. Möller, Ulm ³
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Institutions:

- ¹ Medizinische Universität, Pathologisches Institut
- ² Universität Frankfurt, Senckenbergisches Institut für Pathologie
- ³ Universitätsklinikum, Institut für Pathologie und Rechtsmedizin
- ⁴ Universität Würzburg, Institut für Pathologie
- ⁵ Christian-Albrechts-Universität zu Kiel, Institut für Hämatopathologie und Lymphknotenregister Kiel
- ⁶ Universitätsklinikum Benjamin Franklin, Institut für Pathologie

Part B – Results from the First Funding Period

B.1 Summary

The aim of this project was to establish a computer network that enables a fast and reliable exchange of patient information (e.g. histo-pathological diagnosis) enrolled in clinical trials between the six pathology reference centres and the coordination centres for clinical trials. To achieve this, each pathology reference centre has been equipped with a local database containing all relevant patient information. Each local database is connected via Internet or ISDN with a central pathology server located in Leipzig, where the data from all pathology reference centres will be collected. Finally, the central pathology server were linked to the clinical trial coordination centres to enable an exchange of information in both directions.

B.2 Original aims of the project

The primary task of this project was the generation of a communication infrastructure, which enables an exchange of data between the six reference centres for lymph node pathology and clinical trial coordination centres. For this purpose, the definition and the establishment of a central pathology database and of local databases within each reference centre was necessary. To identify those patients enrolled in clinical trials from the local pathology databases in each reference centre, frequent matching of both data sets with a minimal data set is required. After having identified the corresponding patients, the pathology reference centres are provided with the clinical trial, and its branch; the coordination centre for the clinical trial will then receive the final reference diagnosis and the results of further analysis, such as immunohistochemistry.

Another assignment of this project was the introduction of a common lymphoma classification and agreement on a common set of supplementary analyses required to reach final reference diagnoses. This common “language” is vital for the automated IT-based exchange of patient data.

B.3 Scientific results

A prerequisite for the exchange of patient data is the establishment of a communication infrastructure between the reference centres for lymph node pathology and the clinical trial coordination centres. Initially, the plan was to facilitate this communication by peer-to-peer ISDN lines, however, it later became clear that this could be achieved via Internet. Internet communication requires the use of an encryption process and the consent of the data protection authorities. Encryption is based on the SKIP tool from SUN Microsystems which meets the recommendations of the TMF and is incorporated in the local, as well as central database. In cooperation with the sub-project 2, a security policy was developed and has been implemented.

Communication via Internet between the central pathology server (IMISE, Leipzig) and the local databases of all reference centres for lymph node pathology has already been established and is now working. Consent from the data protection authorities was given and is available for inspection; encryption of the patient data is incorporated.

The identification of patients enrolled in clinical trials is possible by the application of four basic parameters (minimal data set): family name, forename, date of birth and sex. These parameters, which are provided by the clinical trial coordination centres, will be used to screen the local pathology systems for matching patients. Matched patient data will then be transferred to and stored in the local database and complemented with additional information such as clinical trial, the branch of the trial, and the date the patient was randomised.

Furthermore, the data set in the central pathology server will be assigned the ID of the reference centre involved in the reference diagnosis of the patient, and the date of material admission. After the completion of reference diagnosis, the data set for each patient will be completed with the final diagnosis, the date of diagnosis, the ID of the reference centre, and any further data necessary for the corresponding clinical trial (e.g. immunophenotype etc.). The complete set of information will then be transferred from the local data server to the central pathology server and then on to the coordination centres for the clinical trials.

The exchange of data between the pathology reference centres and the central pathology server and between the central pathology server and the coordination centres for clinical trials has now been established, and is currently running a test phase in parallel to the conventional exchange of data by standard mail.

Communication between the local databases and the local pathology systems (DC Pathos [Berlin, Frankfurt, Ulm] and PAS [Kiel, Lübeck, Würzburg]) was achieved by the installation of an ODBC interface in both systems. In use, first a request is released from the local database (ORACLE; see annex) to the local pathology system to compare the minimal data set (see above) of all new patients (since the last request) for matches. These matches will then be transferred to the local database, and finally to the central pathology server and to the coordination centres of the clinical trials. This allows the reference centre for lymph node pathology to identify patients enrolled in clinical trials (including trial ID, branch and date of randomisation) and enables the coordination centres to localise the reference centre responsible. In a second request the local pathology systems are asked via the ODBC interface whether the diagnosis for the matched patients is completed. The completion of the diagnosis is identifiable by an archive flag in local pathology system. The completed reference diagnosis, including the results of the immunohistochemistry, is subsequently transferred to the local database, to the central pathology server and finally to the coordination centres.

The exchange of data between the local pathology systems and the local databases has been established and is now functioning.

The use of a common lymphoma classification is a prerequisite for automatic data exchange. This is now possible because of the introduction of the recently officially released WHO classification. To include the WHO classification in the local pathology systems, the database structure of PAS systems in Kiel, Lübeck and Würzburg have been extended accordingly whereas the database structure of DC-Pathos systems in Berlin, Frankfurt and Ulm allow for the introduction of additional classifications by default. The same holds true for inclusion of the results of immunohistochemical stainings. In the new release of the PAS system these data can be raised and retrieved via ODBC communication. The DC-Pathos database system allows for the introduction of immunohistochemical results for the first time since 1996.

The possibility of introducing additional information such as diagnosis or immunohistochemical results is now realised in all local pathology systems and these data are retrievable via the ODBC interface.

B.4 Publications and patents

Speer R., Hummel M., Heller B.: Vernetzung der Referenzpathologien für Lymphknotendiagnostik und Aufbau einer virtuellen Materialdatenbank. Informatik, Biometrie und Epidemiologie in Medizin und Biologie. 2001; Band 32: 300-301

Stein H.: Vernetzung des Referenzpanels für Lymphknotenpathologie. Vortrag: 108. Kongresses der Deutschen Gesellschaft für Innere Medizin am 22.04.2001 in Wiesbaden

B.5 Networking

The major partner in the first period of the funding was sub-project 2. This very close cooperation was necessary to establish the databases and the communication between the various partners (coordination centres for clinical trials; reference centres for lymph node pathology; IMISE Leipzig). This firm cooperation is further underscored by the fact that one co-worker of sub-project 3 was located in Leipzig to allow an easy integration of sub-project 3 in the entire competence network.

Part C – Follow-Up Proposal

C.1 Aims

The aim of the first period of this project was to establish a communication platform and database for the rapid exchange of patient data between the reference centres for lymph node pathology, and the coordination centres for clinical trials. Although this project started relatively late (due to the late release of the funding), we were able to realise all the major aims of the first period.

The aims of the first period are still relevant and achievable. For the second period, we are planning to continue, optimise and expand the existing communication platform and pathology database to integrate additional clinical trials enrolled in the Competence Network Malignant Lymphoma. Furthermore, we will establish an online and offline discussion forum (“digital microscope”) for difficult cases. Finally, a central database covering all tissue materials from patients enrolled in clinical trials will be established.

Online and offline discussion of difficult cases

The images for online discussion will be made accessible by the application of a digital camera or video camera placed on a remote microscope; the images for offline discussion will be acquired by a high-resolution digital camera and scanning at low microscope magnification. After storage on a ZOOM-server, the latter approach allows the visualisation of microscopical slides on a computer screen comparable to a normal microscope (e.g. different magnifications, various areas, etc.) and can be designated as a “digital microscope”. This enables high quality consultation independent of time and location.

Central database for tissue materials

A second major undertaking for the forthcoming period of this project is the establishment of a database for all tissue materials. The inclusion of this material database has already been prepared in the first phase of our project. In this current phase, we would like to integrate this part of the database in the pathology database and link this information to all available patient data. This will allow a very precise retrieval of tissue for quality control and research projects and to correlate the results obtained to the available patient information. Access to the new tissue database is not restricted to pathologists but is also available to other members in the lymphoma network.

Continuation, extension and optimisation of the established communication platform

In continuation of the work of the first period, the optimisation and the integration of further clinical trials into the pathology database (local databases and central pathology server) is planned to adapt our system for future requirements.

C.2 Methodological approach

Online discussion of difficult cases

Despite much progress over the last decade, the diagnosis of lymphoproliferative diseases is still a challenging task, which should be performed in specialised reference centres with long established experience in the field of lymph node pathology. This principle is practiced for lymphoma patients in most clinical trials in Germany. In addition, approximately 25% of all cases are reviewed by the reference pathology panel as an additional quality control. This constant dialogue ensures that the same diagnostic criteria are applied in all reference centres, however, in daily routine diagnostic work difficult cases can arise, which require a rapid second opinion from another reference centre to reach a final consensus. For this

purpose, the establishment of online discussion of live microscopical pictures is to be established. In each reference centre for lymph node pathology at least one microscope will be equipped with a video camera or a digital camera, connected either to high speed INTERNET (provided by the DFN) or to bundled DSL or ISDN lines. The microscopical live picture will then be transferred to a computer screen. The application window will be made available for remote users by remote access programs (e.g. MS Netmeeting or AVT Horn), which allows a remote access in true color quality. The usability and practicability of this approach has already been tested and is working with sufficient quality. A separate second window will be used for online communication (chat/voice) to discuss the corresponding lymphoma cases. Plans are currently not underway to install a fully remote controlled microscope enabling the inquiring pathologist to demonstrate the case under discussion to his colleague in another reference centre.

At least one qualified pathologists would be available for consultation – in addition to his routine work – during working hours. This would ensure an immediate response to inquiries from other reference centres and rapid consensus diagnosis.

This simple transfer of live images has several drawbacks but offers the possibility of establishing an online discussion at short notice. In addition, most reference centres have suitable hardware (microscopes, PCs, camera) at their disposal, which can easily be used for online discussion. The drawbacks of this communication system (limited functions, online availability of the qualified pathologists on both sides, very high network traffic, etc.), however, point to the necessity to develop an alternative way for the on/offline discussion of difficult cases. This new approach, the “digital microscope”, is described below.

“Digital microscope”

The development of a “digital microscope” is planned to overcome the drawbacks of current on- and offline microscopical images. This new approach offers the advantage of exchanging high quality images of difficult lymphoma cases, which can be reviewed by the remote pathologists in any desired magnification and in any area of the section. This can be achieved by scanning the selected histological/immunohistological section into an automated microscope, which then creates a high-resolution image of the slide. After completion of the automated scanning process, the image(s) will be stored in the flashpix format on a central ZOOM-server together with all relevant patient information.

The remote pathologists will be informed by email that a new case is available on the central server to be reviewed. Independent from time and location, the remote pathologist can login to the ZOOM-server (MGI Software Corp.) and can review the histological/immunohistological images in any desired magnification at any point of the histological section. This viewing will be very comparable to traditional viewing at a conventional microscope. We therefore chose the term “digital microscope” to describe this kind of viewing of histological images.

The “remote” pathologists are able to open the digital files including all relevant information and to give their differential diagnosis. If additional information or analysis (e.g. further immunohistochemical stainings) are needed, a request can be released to the sending reference centre, the additional data will then also be transferred and stored on the ZOOM server, and the consulting pathologists will likewise be informed by email about availability of this new information. After the collection of all second opinions, the originating pathologist will make a final diagnosis, which would then automatically be released via the local and central pathology database to the coordination centre of the corresponding clinical trial and to the colleagues involved in the generation of the final reference diagnosis.

The “digital microscope” offers several advantages over conventional online discussion possibilities. Firstly, the remote pathologist can – independent from time and place – access

the ZOOM-server to review the available cases. Secondly, the quality of each image will be very high. Thirdly, the network traffic raised by accessioning to the ZOOM-server will be very low because only the necessary parts of the image will be transmitted on request. This will allow for a very fast image formation (real-time) and thus enable very efficient and rapid review of cases. Fourthly, in those cases where an online live discussion of one or more pathologists is necessary, the ZOOM-server offers the possibility of simultaneous access to the case under discussion. Finally, the access to the ZOOM-server can simply be facilitated by most up-to-date Internet browsers (e.g. MS Internet Explorer 6.x; Netscape 6.x).

The introduction of the "digital microscope" for the reference-pathological diagnostic requires significant developmental efforts. There is currently no "ready-for-use" system available, which can be directly used for our purpose although all major components are accessible. Therefore, in a first step, we will establish a prototype system at the pathology of the university in Lübeck, which is equipped with an atomised microscope for scanning of histological sections. The ZOOM-server, however, on which the images are stored in the Flashpix format will be accessible from all reference centres and can be used to review the scanned cases. After successful establishment of the prototype, all reference centres will be equipped with the same or comparable atomised microscope scanning systems. The funding for this additional hardware is already in preparation.

Database for histological pictures

In addition to the microscopical images described above, which will be used for the direct diagnosis of lymphoma cases, a database collection of microscopical pictures will also be established for qualification and education purposes. This collection of pictures will also be available to other members of the lymphoma network. These pictures will cover all lymphoma entities and will include the most typical morphological and immunophenotypical features as a database of examples.

The morphological and immunohistological images for this database will be provided by all participating reference centres and will be categorised in accordance to the new WHO classification. It is planned to present the pictures in a web page embedded in a structure compatible with the WHO classification. The platform for this presentation will be based on the Internet presentation of the Competence Network Malignant Lymphoma.

The inclusion of histological/immunohistological images is also planned as an extension of the already established central pathology database. However, not all cases will be documented and only in cases with unusual morphology and/or immunophenotype, the most relevant (immuno)histological stainings will be stored in the central pathology database. This will allow other pathologists, not initially involved in the original diagnosis, to comprehensibly reconstruct and understand the reasons for the final diagnosis at any stages in the patient's history.

Central database for tissue materials

The lymphoma network is not only seen as a communication platform, but also envisaged as a means of initiating and supporting basic research projects. Many of these projects require tissue material from the corresponding lymphoma entity/entities for their investigations. Nowadays, the retrieval of tissue material in sufficient quantity and quality is a major challenge since there is no common database covering all relevant patient data, including final reference diagnosis and the type and number of tissue blocks available in each case. Furthermore, there is currently no information on where tissue blocks are stored.

To overcome these limitations, the installation of a central database for tissue material is one further important task of this sub-project. This database will be linked to the central pathology database and to the patient information at the coordination centres of the clinical trials. Whereas the database itself will be centralised, the tissue blocks will be stored at the

reference centre for lymph node pathology, which obtained the tissue for establishing the reference-pathological diagnosis.

To make the central tissue database most effective, the following information will be collated with each case: type of material (frozen, paraffin), type of tissue (lymph node, bone marrow, skin, etc.), number of blocks, place of storage (reference centre ID, exact location within the reference centre) and availability (no material left, enough material, currently not available, etc.). All these data will be linked to all other patient data available in the central pathology database. In addition, there will be a reminder system, which will limit the loan time and will provide information about the type of investigation (project) being undertaken, and the principle investigator responsible for returning (in a designated time and in the right quality) the loaned blocks.

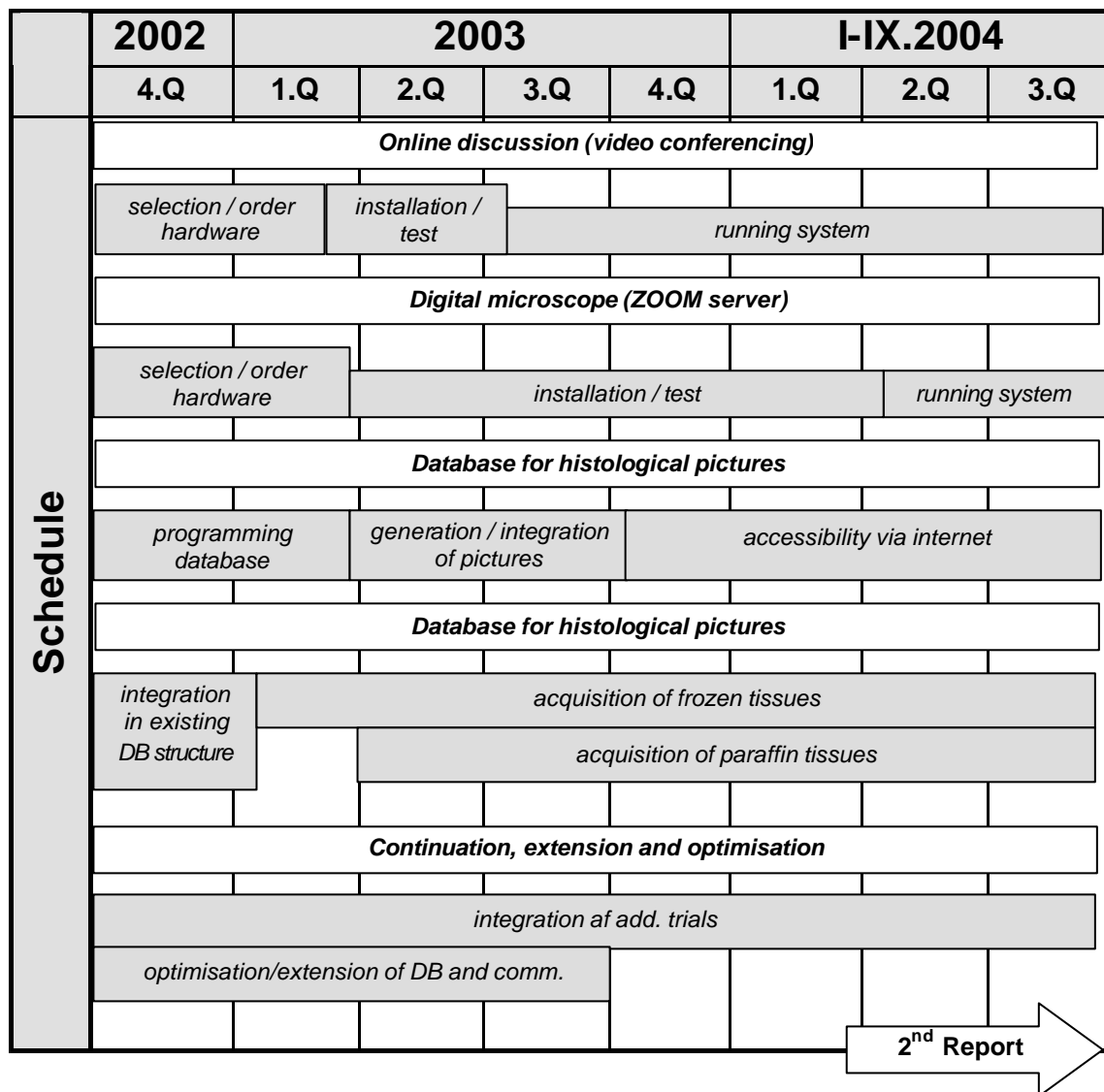
The material bank of the reference centres of the lymph node pathology will, in principle, be open to all researchers in the lymphoma network. However, there will be a central organisational (steering) committee, which will rule on applications for tissue material to be released. It will not be possible to give material to any investigation initiated. Duplicate investigations, projects lacking specific detail, or a research plan etc. will unfortunately not be supported with tissue materials.

Continuation, extension and optimisation of communication platform

The continuation and optimisation of the established communication structure of the first period is planned to continue for the second period. Furthermore, the integration of additional clinical trials requires the extension of our database and communication structure (between the reference centres, the central pathology server, and the coordination centres for the newly included clinical trials). This will have an influence on all aspects of our previous work, including database, communication structure, local databases, input and output possibilities etc.

C.3 Work plan

Most tasks of the sub-project have to start immediately after the release of the funding. Whereas the establishment of the online discussion and the generation of images for database of histological pictures will be initiated at each centre, the work for the ZOOM server and for modification of the database will be performed in Lübeck and Leipzig, respectively. The work for the establishment of the online discussion will be divided into several parts, which will be performed in parallel in all reference centres. For the generation of the database for histological pictures of the various lymphoma entities, from which images are required, the workload will be distributed among the different centres. These images will be continuously integrated into the database. The establishment and expansion of the central database for tissue materials is also a permanent task for all centres throughout the entire funding period. The entire IT structure of the sub-project 3 will be held and coordinated in Leipzig. This also includes further modifications and extensions of database as well as the communication with additional coordination centres for clinical trials. The development of the ZOOM server will be done in Lübeck; the testing of the ZOOM server technology with the help of the other reference centres is planned at a very early stage. The results of these tests are the major basis for improvement and practicability of the “digital microscope”.



C.4 Networking

The reference centres for lymph node pathology represent an integral part of the whole competence network. However, the closest cooperation will be with sub-project 2, which is reflected by the fact that one coworker (BAT IIa/2) of our sub-project is located and permanently working at the IMISE in Leipzig (SP2). A very close cooperation is also planned with sub-project 5 and TMF.

