ACGT is a European Commission co-funded project supported by grant FP6-IST-026996.

NEWSLETTER

ACGT on Cancer

Advancing Clinico Genomic Trials

EDITORIAL

ACGT is working onto an integrated approach over Clinical Trials on clinic-Genomics, proposing models for defining the protocols, preparing the ground for vast possibilities for clinicians to assess diagnosis and treatment results against already existing data repositories.

As the number of clinical trials sees a general decline in Europe due to the heavy costs and legal constraints, ACGT can assist oncologists into getting out of isolation, assisting in increasing the number of collaborations between practitioners.

ACGT provides a platform for the patients to enter their data on a daily base so that practitioners can make a daily monitoring. These advances in telemedicine available in the ACGT platform will enhance the capacity of the oncology community in getting further into trials, allowing therefore the patients to receive the most adapted treatments, care and attentions.

We wish you a pleasant reading through the articles.

Samuel Keuchkerian

Newsletter Edition
Edition 5. Summer 2009
5

Editor-in-Chief
Samuel Keuchkerian
samuel.keuchkerian@healthgrid.org

Editorial Board
Prof. Dr. Norbert Graf
Norbert.Graf@uniklinikum-saarland.de
Mr. Stelios Sfakianakis
ssfak@ics.forth.gr
Ms. Ana Lucia Da Costa
ana.dacosta@healthgrid.org

Contact ACGT
Web: www.eu-acgt.org
Scientific Director:
Dr. Manolis Tsiknakis
tsiknaki@ics.forth.gr
Administrative Manager:
Mr. Remi Ronchaud
remi.ronchaud@ercim.org

Newsletter Design
HealthGrid
www.healthgrid.org

European Commission
Information Society and Media

Clinical Trials News

Latest developments in the world of clinical trials in cancer

Gene signatures identifies breast cancer patients who will respond to chemotherapy

Finding ways to tailor therapy to the characteristics of individual patients is an important area of cancer research. The recent results from the TOP trial, one of the clinico-genomic trials serving as a pilot trial in ACGT, shows that this goal can be achieved by developing more sophisticated ways to use older drugs.

Led by the Institut Jules Bordet, researchers in Belgium, France, Luxembourg and Italy collaborated to study 149 women with breast cancer who were being treated with epirubicin, an anthracycline drug with a long history of use in many tumour types, but especially in breast cancer.

Although anthracycline drugs are among the most effective chemotherapies in breast cancer, a small proportion of women suffer severe side-effects that include congestive heart failure. By identifying those women who are most likely to benefit from treatment, doctors may be able to ensure fewer women are unnecessarily exposed to that risk.

We studied gene signatures that could identify those tumours which completely disappeared in response to treatment with the drug. We identified two distinct signatures for tumours that over-expressed the HER2 gene (which tend to by more aggressive) and those which did not. Both signatures consisted of several hundred different genes expressed by the tumour cells. Importantly, the predictive performance of these gene signatures was validated in an external cohort of patients also treated with pre-operative anthracyclines.

Interestingly, the TOP trial avoided any possible confusion by including only women being treated with single-agent epirubicin. We also limited their patient population to women whose tumours did not over-express the oestrogen receptor. This is because for these women, chemotherapy can stop the ovaries from working, offering an additional benefit that may confuse the results.

These results were presented recently as an oral presentation at the annual meeting of the American Association for Cancer Research which took place in April in Denver and at the IMPAKT breast cancer conference which took place in Brussels in May.

Christine DESMEDT,
Jules Bordet Institute

Products and Services

News on the latest products or services in our area of interest

Secure integration of third party services into ACGT platform

Introduction – Legal and Security requirements

One of the most important constraints for the management of personal clinical and genomic data is the compliance to the ethical and legal data protection requirements. In ACGT a generic data protection framework has been defined which is based on a technical security infrastructure as well as on organizational measures and contractual obligations. Most of the technical requirements are dealt with the Grid infrastructure layer (GSI), which supports user authentication through digital signatures and also the delegation of user privileges to a service so that it can retrieve data or perform an action on the user's behalf and without the user's intervention.

Apart from the security requirements, the need in ACGT for a standard workflow definition language lead to BPEL, from the business process management world, as the most prominent and well supported technology. Nevertheless, the choice of BPEL gave rise to more requirements and challenges. The first one is the provision of a user friendly workflow authoring environment. The second relates to the need for an infrastructure that would make possible the invocation of the ACGT secure grid services from inside the BPEL-based workflows, since BPEL and the Web Services standard security specifications do not deal with such requirements. Another major challenge comes from the wish to integrate into BPEL workflows non-ACGT services, which is by itself a complex technological task in many aspects, let alone the challenges due to the legal and security requirements.

Proxy Services for credential delegation

The design methodology that was chosen to overcome the incompatibilities between the BPEL processes and the GSI secured ACGT services was to introduce a "layer of indirection": the Proxy Services. The proxies, or wrapper services, provide BPEL friendly "facades" of the original, real ACGT services, effectively working as call transformation bridges between the two worlds (Figure). The core idea behind wrapper services is that we transform the interface of the underlying service and we pass extra pieces of

information, which empowers us to detour the usual flow of credential delegation and bypass the Enactor but also at the same time to maintain all the required information so that we keep track of the "chain of responsibility". All credential delegations are performed automatically inside a secure sandbox and are also logged in a database, thus we have also an effective mechanism for monitoring the whole process.

Proxy Services as interface adapters

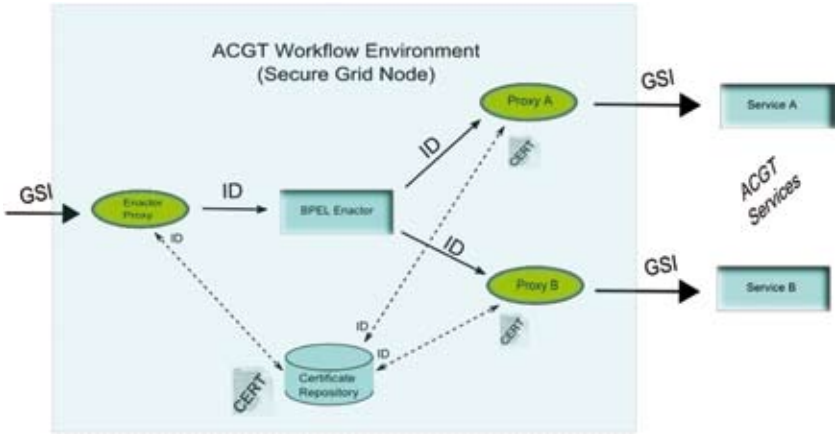
The proxy service mechanism can also be used to provide higher level abstractions. An example of this is to remodel the interface of a service in order to simplify it and hide some technical details, thus aid in user friendliness of services. This wrapping technique has been applied to provide secure access to WSRF OGSA-DAI resources and simplify the connection to them by enclosing and hiding the technical hindrances of OGSA-DAI, like perform documents and stateful resources.

Another example is to provide access to many services through one proxy service which functions as a gateway, by dynamically creating custom interfaces. In the case of the "GridR Proxy Service", by using this technique we were able to encapsulate the underlying "GridR Service" and hide its technical details, but also to support the notion of "Scripts as Services", in which a different web service interface is exposed from the same single proxy service, depending on the actual R-script that is being "proxied".

Proxy Services as gateways to 3rd party services

A major challenge in the ACGT workflow environment is to allow the integration not only of ACGT services. The integration into ACGT platform also of 3rd party services will greatly expand the abilities and the potentials of the platform and will provide to the end-users numerous helpful tools, far more than we could implement ourselves. The most prominent methodology to achieve this desirable augmentation is, again, through the proxy services mechanism.

First of all, it is a major challenge to integrate services which are heterogeneous, both syntactically and semantically, and enable them to interact while they use different protocols, data types and semantics. The use of proxy services can facilitate the required transformations and interpretations between the interacting parties and assist the mapping between different se-



mantics or data types. One example where this technique has been applied with success is the integration of BioMoby services into ACGT workflows. The usage of a proxy service has been used in order to bridge the gap between the different semantics and transform the syntax of the messages exchanged between ACGT services and BioMoby services.

Furthermore, with the inclusion of 3rd party services into ACGT workflows, many legal and security aspects arise since we could potentially give access to sensitive data. By using proxy services, we ensure that this is done through a controlled sandbox and that we can enforce specific access policies. The proxy service can allow the access based on certain conditions and restrict the authorization to specific data resources, something which could otherwise be difficult to monitor.

Conclusion

The integration of 3rd party services into the ACGT platform is a complex technological task in many aspects, let alone also the need to comply with specific legal and security constraints. In order to accomplish this, the design methodology that has been chosen is the use of "proxy services"; mediator services that transform the interfaces, messages and the semantics of the interacting software components in order to bridge the gap between them. The major benefit drawn from the proxy services is the application of the security model that has been chosen for the ACGT platform and the enforcement of the legal requirements. This versatile approach has enabled us to integrate many heterogeneous tools into the ACGT platform and we still aim for the integration of many more. Note that some of the above-mentioned tools are still under development; nevertheless, prototypes are currently operating inside the ACGT platform.

This article is based on the following publication:

S. Sfakianakis, L. Koumakis, G. Zacharioudakis, M. Tsiknakis, «Web-based Authoring and Secure Enactment of Bioinformatics Workflows», 4th International Workshop on Workflow Management (ICWM 2009), 4-8 May 2009, Geneva, Switzerland

Giorgios Zacharioudakis,
FORTH

Grid News

Latest developments in the world of computer grid research

Cancer Knowledge Cloud for a new generation of medicine

Thinking BIG

Ken Buetow thinks BIG. He envisions what he calls a Cancer Knowledge Cloud — an IT environment designed to foster information connectivity among cancer patients, cancer researchers and clinical care providers. This environment, powered by caBIG ((cancer Biomedical Informatics Grid)) tools and infrastructure, would enable a continuous and accelerated cycle of discovery, diagnostic and pharmaceutical product development, and improved clinical care.

Cancer care and research still operate on a linear, slow and cost-ineffective 20th-century model that fails to capture the value of clinical data, according to Buetow. He outlined the traditional model's four sequential steps as discovery, product development, clinical care and outcomes. The discovery phase, he says, suffers from difficulty in accessing clinical outcomes data as well as high quality biospecimens. "Siloed" information and a lack of standing infrastructure for clinical trials hamper product development, and actual clinical outcomes are not captured systematically to further inform discovery research processes.

Buetow wants to move to a 21st century, continuous-loop model in which an "analysis and learning" phase connects from "outcomes" back to "discovery" (see figure below). This would allow clinical experience to figure into the mix for product development and then into the next iteration of clinical care. This model of a "learning healthcare system" cannot be achieved without IT connectivity.

Knowledge cloud for biomedical connectivity

Buetow describes the Cancer Knowledge Cloud as a virtual biomedical capability that uses caBIG to integrate distributed individual and organizational data, software applications, and computational capacity through the Internet. This capability requires standards to be established in order to exchange information. Comprised of tools, grid infrastructure, data standards, and policies, caBIG can furnish the semantic middleware infrastructure that binds the components together in a flexible way, as standards solidify and domains expand.

Because the biomedical community has not traditionally seen connectivity and data-sharing as desired objectives, Buetow and the NCI are also pioneering a new model of collaboration for academiae, government and industry. Called the BIG Health Consortium, this initiative is fostering an integrated and interactive ecosystem (or "mega-community") of previously-unlinked sectors within life sciences and health care. They would work collaboratively to make a new generation of medicine — personalized, predictive, preemptive and participatory — a reality.

The stars are aligning

The time is right for the Cancer Knowledge Cloud, according to Buetow, due to a convergence of factors. The caBIG software deployment is mature enough, with software packaged in easy-to-install bundles that include online tutorials, videos and documentations, he says. Then there's the availability of the software's knowledge centers and support service providers that underpin a viable user community. At the same time, the rate of scientific discovery is accelerating to unprecedented levels, and a shift is underway towards the development of molecularly-based diagnostics

and therapeutics. Overall, there is growing recognition of the urgent need for change within biomedicine.

"We live in extraordinary times," notes Buetow. "And the Cancer Knowledge Cloud is a natural evolutionary step for boosting the biomedical enterprise into the 21st century knowledge economy."

This article originally appeared in the 1 July 2009 of International Science Grid this Week.

Anne Heavey,
iSGTW

Feature Article

Clinical need for exploitation of ACGT

Clinical trials are essential to achieve better treatments for patients. As a result of the Clinical Trials Directive 2001/20/EC the conduct of clinical trials throughout Europe has changed[1,2]. The directive, aimed largely at holding pharmaceutical companies to higher standards, has tied up academic clinical research, particularly large trials, with redundant paperwork, liability tangles and unending bureaucracy[1].

Scenarios and structures that help to run more clinical trials and to bridge the gab between clinical and basic research is of utmost importance. The following problems in clinical care of patients do exist today:

- There is a time lack for physicians being kept informed about all the new developments in medicine, even in their specialized field. Every week hundreds of new papers are published. To find the most relevant, to read them all and to judge them as important for the own work is impossible.
- Today teamwork is of utmost importance. Physicians have to work in a collaborative environment to treat a patient with cancer. He always has to communicate and work together with other specialists in medicine. As a result a lot of so-called Cancer Comprehensive Centres are established to facilitate the interdisciplinary work. But up to now no IT infrastructure is supporting this by storing all relevant data in a database, so that every treating physician will have immediate access to the history, diagnosis, treatment and other relevant data of patients in an anonymous and secure way.
- Physicians face some difficulties to get feedback of how efficient they are working. Indeed, there is a lack of information concerning the survival of given patients compared to the survival of all patients with that kind of cancer. Such benchmarking would help health experts to guide their work.
- Physicians do not know enough about the possibilities of modern IT technologies that could help them to support them in daily care of patients, or in developing new clinical trials. The

lack of this knowledge leads to a lack of requests and requirements to IT people for the creation of new and user friendly tools in this respect.

- Only a minority of patients is enrolled in prospective clinical trials. The reason for this is manifold.
- There exists no database for clinical trials with an easy way of access for physicians or patients in Europe. This is twofold unacceptable:
  - A physician is not able to find the best trial that fits the need for his patient
  - A trial chairman might build a new trial that is still running by another physician
- Today patients do use the Internet to get information about their disease. There is no way how a patient can trust such information. Often information is contrary and alienates patients.
- Even if patients do find relevant information, they may not understand the medical language used in these information.
- More patients are asking for second opinions regarding their disease. This is time consuming for physicians, expensive for the health care system and often unsatisfying for patients. They often get different and contrary answers resulting in the question: "And what shall I do now?"

A part of these problems are already faced and solved in ACGT. Main tasks for the future can be summarized in simplification of the clinical trial process and patient empowerment. By seamless integration of clinical, imaging and basic research data in single patients and cohorts of patients personalized medicine will get reality. In this respect ACGT provides an IT platform for the integration of largely distributed and heterogeneous data, a legal framework guaranteeing data security and patient privacy and tools for conducting and running trials as well as tools for querying and analyzing such integrated databases. To introduce this platform in the daily clinical care an organizational structure has to be built up mainly dealing with requests from clinicians and other stakeholders. Such a support is needed to coordinate the necessary cooperation of all stakeholders including clinicians, basic researchers, IT and legal people as well as pharmaceutical companies and at the end patients. For that purpose a Study, Trial and Research Centre (STaRC) is founded. This approach aims to build, run and analyze more clinico-genomic trials faster and more efficient. In addition training modules will help physicians and others to use the IT-infrastructure in an efficient way. To foster the acceptance and use of such an integrated platform with its tools in daily clinical practice the curricula of medical schools have to be changed in a long term. Increased knowledge of IT will benefit clinicians most and allow them to critically use data and tools of such a platform for the sake of their patients.

As ACGT is based on the principles of 'Open Source' future concepts of exploitation will follow these principles. From the perspective of ACGT a lot of components and tools will and have to be maintained. This includes the legal framework, the Portal, the Workflow generator, the ACGT Master Ontology, the mediator, ObTiMA and others. In the near future two clinical trials (the SIOP 2001/GOH for nephroblastoma and the EU-RHAB for Rhabdoidumour) will prospectively collect data by using the ACGT platform and tools like ObTiMA to evaluate the usability of ACGT and corresponding tools in the clinical setting. Nevertheless there is a long way to go from research tools to productive tools with certification for the daily clinical practice. This task has to be taken over and solved. It will be one other duty of STaRC.

Norbert Graf, USAAR - Andreas Persidis, BIOVISTA - Nikolaus Forgó, LUH - Manolis Tsiknakis, FORTH

[1] *Keim B: Tied up in red tape, European trials shut down. Nature Medicine 13:110, 2007*

[2] *Pritchard-Jones K: Clinical trials for children with cancer in Europe – Still a long way from harmonisation: A report from SIOP Europe. European Journal of Cancer 44:2106-2111, 2008*

Community View

Invited contributions from non-ACGT members of the wider research community

HOPE (HOspital Platform for E-health)

The goal was to deploy a web platform using grid technolgies to support broad access to rapid, cost-effective and high quality healthcare. Such platform, named HOPE, create an environment where data of medical interest can be stored, processed and made easily available to the different actors of healthcare: physicians, medical physicists, healthcare administrations and, of course, citizens.

The HOPE prototype platform was designed to enable telemedicine and calculations in a grid environment. The sharing of knowledge and the exchange of diagnosis between physicians contribute to the improvement of the standard of medical knowledge, particularly in developing countries. Special care has been given to the design of a user-friendly interface dedicated to any medical speciality on the basis of feedback from healthcare professionals. The goal was to create a natural workflow that will enable easy searching, adding, updating, sharing and discussing clinical exams and their attached images.

In addition, with the objective of making Monte Carlo dose computations become standard for radiotherapy quality assurance, planning and plan optimisation, the international collaboration OpenGATE (http://www.opengatecollaboration.org) participate to the development of a Monte Carlo platform dedicated to SPECT, TEP, radiotherapy and brachytherapy simulations. As the grid showed a significant added value in reducing the computing time of GATE simulations, the next step was to develop adequate functionalities on the HOPE platform to enable medical physicists, physicians and researchers to compute GATE treatment planning using grid facilities.

Medical data management demands high level standards in terms of security and data privacy both concerning data access policy and data security on the grid.

To guarantee this high-level of security, we developed our platform keeping in mind some main requirements:

- User authentication using both grid certificates and professional smart card,
- Local and inter-hospital communications encrypted using SSL,
- Fine-grained user authorization policy based on AMGA ACL mechanism,
- Medical images stored anonymized and encrypted on the grid.

As a consequence, the web platform HOPE was designed to offer a complete, transparent and secure way to manage medical data files containing images, physician's prescription and treatment plans.

As an objective, the conviviality of the web portal and the Grid performances could enable, in a near future, the usage of HOPE in clinical routine.

Lydia Maigne,
Université Blaise Pascal

Events

Information on upcoming events of interest

CABIG Annual Meeting, Solving Basic and Clinical Research Challenges in Cancer and Beyond

caBIG® cancer Biomedical Informatics Grid®

July 20-22, Washington, D. C.

Attendees will hear how caBIG® is accelerating biomedical research through interoperable tools, infrastructure, standards, and policies that enable data-sharing and collaborations that transcend institutional, geographical, and disciplinary boundaries.

The meeting will feature:

- Case studies and best practices in clinical trials management, in vivo imaging, molecular analysis, tissue banking and pathology, and data-sharing and security
- Tips on implementing, adapting, and customizing caBIG® tools and infrastructure
- Presentations on caBIG®-enabled translational research projects in cancer and beyond
- Opportunities for future collaborations and partnerships

https://cabig.nci.nih.gov/2009AnnualMeeting

MICCAI, International Conference on Medical Image Computing and Computer Assisted Intervention

September 20-24, London

MICCAI 2009, the 12th International Conference on Medical Image Computing and Computer Assisted Intervention, will be held from 20th to 24th September 2009 in London, UK. MICCAI attracts annually world leading scientists, engineers and clinicians from a wide range of disciplines associated with medical imaging and computer assisted surgery.

Topics to be addressed in MICCAI 2009 include, but are not limited to:

- General Medical Image Computing
- Computer Assisted Interventional Systems and Robotics
- Visualisation and Interaction
- General Biological and Neuroscience Image Computing
- Computational Anatomy (statistics on anatomy)
- Computational Physiology (virtual organs)
- Innovative Clinical/Biological Applications and Surgical Procedures

http://www.miccai2009.org/

Legal and ethical

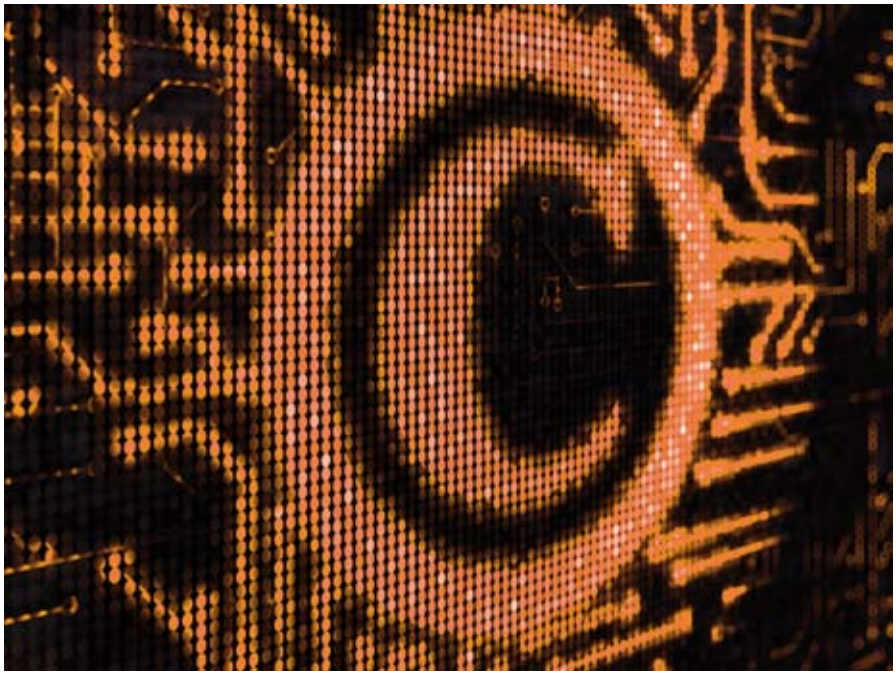
The latest thinking on legal, ethical and data security issues surrounding clinical trials

Intellectual property rights, mainly copyrights and patents are an important success factor for ACGT. They can be relevant incentives for research but might also hinder technical developments and patient commitment. They are of specific importance as ACGT sees itself as an open source/open content initiative.

Copyrights are the most relevant legal tools to protect components of ACGT such as computer software developed and the GRID-infrastructure. They grant, generally speaking, protection for the expression of a work from moment of its creation for 70 years based on the assessment of the originality criteria.

In ACGT the partners have been developping a number of computer software (applications). It is often said that computer software posses a "hybrid" nature which means they have some elements of expression and others of functionality. Their means of protection lies under the copyright framework, thus, the originality and creativity criteria in their creation or adaptation is the decisive factor to determine their protection. The GRID infrastructure developed in ACGT is made of a cluster of different interconnected resources networks which allow the users to execute a variety of applications such as those useful for scientific research or data management. They contain a number of layers, therefore the way they are selected and arranged on The GRID may also be subject to copyright protection.

The question whether computer software is also protected



by patents revolves within the wordings of Art 52 European Patent Convention (EPC) giving (in principle) a negative answer on the patentability of software. Unfortunately the answer may no longer be that clear due to current developments: As a consequence of a recent case (the so called Symbian case) the President of the European Patent Office (EPO) referred four questions to the Enlarged Board of Appeal of the EPO which aim at harmonizing and clarifying the circumstances under which individual features can contribute to the technical character of a patent claim and make computer implemented inventions patentable. It is important to highlight that due to the fact that the EPO referred four questions to the Enlarged Board of Appeal, patent applications in this context may remain unclear until the answers are made. The situation will have to be closely monitored within ACGT.

In addition, taking into account that ACGT owes its existence to the participation of patients through clinical trials, an important question is 'Who owns the patient's data?' This question has to be answered not only legally but also ethically. Regarding the donation of biological material and data, the gift model has been established in clinical research without delineating the rights of ownership.

We propose in our current work for ACGT a model slightly modifying the donorship-paradigme: In this respect, patients are asked to sign an informed consent form concerning the processing of their data for further research within ACGT. The Center for Data Protection (CDP) is empowered to conclude legally binding contracts. It provides security and trust to the framework. For this reason, the CDP could also act as a "Trusted Party" and could define property rights on the biological material and the data coming out of this material as a "common" In order to find a balance between the interests of patients, doctors and researchers, CDP as the "Trust" could hold a percentage of the net profits and re-distribute the revenues to the community of patients.

Further research will be done to clarify whether such an approach, trying to indirectly let patients participate at the value of "their" data, is legally and ethically feasible. In any case the work already done has two major outcomes: First, the CDP is an invention that might be important not only in the data protection field but as a basic tool for pending ethical and legal issues in the IP-area as well. ACGT could establish a best practice here for other projects. Second, IP-issues in the area of biological data/information are important factor in convincing patients to participate and give their consent. Understanding their motives and rights is an important success factor for the whole project.

Eva Egermann,
Nikolaus Forgó,
Institute of Legal Informatics
University of Hanover

Life in ACGT

ACGT annual review

The Annual ACGT project review took place in Bohn, Germany with the presence of most ACGT partners, the EC desk officer (Sweden) and 3 reviewers. The review, while being a formal assessment of the projects developments, was the opportunity to confront the project strategies and technological developments to the views of the EC onto clinical research onto Cancer and onto large health related infrastructures related to the grid technologies. Project members demonstrated the different services and tools that were developed to date, showing the potential of the different tools that will assist the oncology community in developing treatment protocols, follow up patients and patient related data, development of the ACGT ontology MO. We thank all the persons who participated and made sure that the demonstrations could be ready on time to discuss with the representatives of the EC but special thanks goes to the persons who organized the event, allowing us to work in a very favorable environment.

ACGT PEOPLE

Remi Ronchaud

In his role of ACGT Coordinator on behalf of ERCIM, Rémi is responsible for the project as a whole and supervises the administrative and financial coordination of activities in this large scale Integrated Project.

Rémi Ronchaud graduated in 1997 at E.S.S.E.C. (Ecole Superieure des Sciences Economiques et Commerciales) in Paris, France. He obtained his MBA in Strategy and Management while studying in Warwick University in 1998. He joined ERCIM in June 2000, and has successfully managed several IST initiatives across European Framework Programmes 5, 6 and 7. He also acts as ERCIM's European Relations Manager while coordinating ACGT in cooperation with Manolis Tsiknakis (FORTH) who ensures scientific coordination of the project.

Nikolaus Forgó

Prof. Dr. Nikolaus Forgó studied law, philosophy and linguistics in Vienna and Paris. In 1997 he finished his Dr. iur. (Dissertation in legal theory). Between the years 1990-2000 he was Assistant Professor at the University of Vienna (Austria). Since 2000 he is full Professor for Legal Informatics and IT-Law at the University of Hanover and since 2007 co-head of the IRI. He publishes, teaches and consults on national and international level in all fields of IT-law, mainly data protection, data security and copyright.

JOIN ACGT

Membership in ACGT is open to all. Here are some benefits you enjoy as an ACGT member:

- Access to all member resources
- Support in solving problems in the areas of interest of ACGT
- Direct contact with ACGT experts in a variety of fields including clinical trials, cancer research, advanced software development, Grid implementations, legal, ethical and data security issues and much more
- Ability to contribute to the ACGT infrastructure and receive support for it.

Join us at: www.eu-acgt.org

SUBSCRIBE!

Subscribe today and be among the first to learn of all the latest developments in ACGT and post-genomic clinical trials research on Cancer

3 EASY STEPS

1. Visit us at www.eu-acgt.org
2. Type in your name and email
3. Press the Subscribe button