

BTCure activity report for People with Rheumatic and Musculoskeletal Diseases, April 2014

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History

In the beginning of 2013 a first comprehensive introduction

- to the public-private initiative IMI (Innovative Medicine Initiative), which is aiming to increase the research output in Europe and to speed up the development of better and safer medications, and
- to our IMI-funded research project BTCure (**BeTheCure**)

was forwarded to the national organizations of people with arthritis/rheumatism in Europe.

In April 2013 BTCure was further featured in the EULAR Standing Committee of PARE newsletter by our EULAR contacts, Marios Kouloumas and Florian Klett. Since then BTCure has even grown into a larger organization, based on a total budget of 35 million Euros and is currently including 38 industrial and academic partners from 15 European countries (<http://btcure.eu>).

BTCure`s goals

BTCure aims to establish a European harmonization and standardization platform for the improved reproducibility and comparison of experimental and clinical research results and to increase the predictability of preclinical drugs before they are tested in humans.

Examples for the harmonization approaches by BTCure so far are first available protocols and guidelines for the use of animal models, state of the art techniques, analytical assays, bioinformatics analysis, as well as common guidelines for the way we collate and handle patient information and samples and informed patient consent.

Scientifically, BTCure is using part of this established infrastructure, its unique network and expertise for the investigation of the role of adaptive immunity in the development and progression of rheumatic diseases as Rheumatoid Arthritis (RA). To better understand the role of the different immune pathways involved in rheumatic disease, it is important to systematically compare clinical symptoms with the underlying molecular and cellular disease characteristics. This strategy combined with the access to large patient cohorts all over Europe and aligned multi-center analysis will help to better understand the diverse picture of this type of diseases. Thereby BTCure holds a potential tool in hands to sub-classify complex diseases as RA into subgroups in order to significantly progress the development of more targeted and safer treatments. The identification of molecular features for the differentiation of patient subgroups and disease stages will further lead to the development of new biomarkers for better diagnosis and disease progression. Most importantly, researchers of the BTCure consortium not only have access to clinical information for patients with advanced disease. BTCure groups also actively assemble and study cohorts of people at risk of developing disease. These activities bear great potential to improve our understanding of disease drivers, as well as an option for early diagnosis, early intervention and treatment.

Dissemination strategy and patients` areas of interest

Outlined by Prof. Steffen Gay (UZH), in collaboration with BTCure`s Patient Advisors, Marteen de Wit, Marios Kouloumas and Florian Klett, EULAR Executive Secretariat

- It is imperative to acknowledge the work developed during BTCure. Materials and strategies developed in BTCure need to be published and shared with the scientific community. BTCure is doing exceptionally well here, with 160 scientific articles published since its start in April 2011.
- However, to highlight the key achievements and for the legacy of BTCure it is crucial to inform and reach a broader audience and in particular our most important stakeholder the people with RMDs. Thus, it is important to maintain current dissemination activities to inform about BTCure`s achievements of impact. This should be done in continuous collaboration with the EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (PARE). Specifically, to disseminate the obtained data via the **Newsletter – EULAR Standing Committee of PARE**, that is shared with all the member organizations.
- Thereby it needs to be stressed that biomedical research results provided by BTCure will in the future benefit the wider community of people with rheumatic disease, including people at risk of developing these conditions.
- As suggested by the EULAR SC of PARE, a session on patient issues in scientific research should be considered at the **EULAR Congress 2015** to highlight for example, the:
 - importance of basic and translational research for people with rheumatic disease
 - scope of early diagnosis or even prevention of rheumatic disease
 - need to think about the future ways of supporting more research and translational research, including the need to find out effective ways for inclusion of the patients perspectives
 - awareness for current and future ways of informed consent
- Moreover, BTCure activities should be streamlined with the work of EULAR study groups and Scientific Committees
- Other EU projects as for rare diseases can be reported in these dissemination activities.

Patient relations and dissemination activities in 2013

Marios Kouloumas and Florian Klett have been participating in BTCure`s annual meeting since 2011 and have been involved in first dissemination activities. In 2013 patient research partner, Lena Andersen and Maarten de Wit, expert for patient-research-partner questions, joined BTCure`s annual meeting, and an official Patient Advisory Board was founded.

Maarten de Wit shared his personal experience from many years of working with patients involved in research with BTCure`s Principal Investigators. According to Maarten the most important thing being is to involve the right patients from the beginning and the thorough planning and training of patients. Maarten de Wit further outlined that future large projects of the size of BTCure are advised to have governance structure and budget for patient involvement, and if possible it should be considered involving patients already at the stage of filing research proposals. More important points to consider in research patient collaborations has been summarized in EULAR information set cards produced to this topic. This information has been forwarded to all BTCure researchers:

[http://www.EULAR.org/myUploadData/files/EULAR Reference cards 25-04-13 1.pdf](http://www.EULAR.org/myUploadData/files/EULAR_Reference_cards_25-04-13_1.pdf)

[http://www.EULAR.org/myUploadData/files/Reference cards explained Booklet pages 23-08-13 1.pdf](http://www.EULAR.org/myUploadData/files/Reference_cards_explained_Booklet_pages_23-08-13_1.pdf)

During last year`s Annual Meeting, BTCure projects with previous or planned patient engagement were outlined and discussed. In 2012 patients were e.g. involved in:

- defining the terminology for different RA risk patients groups (*Gerlag D et al. 2012*)
- giving feedback to a personalized medicine questionnaire to evaluate their understanding of this topic (Frederique Ponchel, University of Leeds).

In 2013, BTCure Patient Advisors were further introduced to the following BTCure projects:

- BTCure`s harmonization approach for performing animal experiments in Europe and our strategy for strengthening patient perspectives on this sensitive issue. Work Package Leader, Prof. Rikard Holmdahl (KI), recently filed a report for patients on this topic in collaboration with our BTCure`s Patient Advisory Board. Upon recommendation the report will be forwarded, together with this activity up-date, to EULAR`s Standing Committee of People with Arthritis/Rheumatism in Europe (PARE) and national PARE organizations.
- The concept and concerns associated with biobanking (the large-scale, structured and governed collection and storage of human samples and data for research purposes)
- BTCure`s guidelines to achieve informed patient consent, that are aligned to the needs of patients, researchers and industry. A stakeholder conference with patient groups being one of the central stakeholders took place in Brussels Oct 17-18 2013 to identify and solve problems related to consent and data sharing (organized by Deborah Mascalonzi, Uppsala, Centre for Research Ethics & Bioethics). Although this conference focused on rare diseases, the consent questions are similar in rheumatic disease and thus BTCure patient advisors have been invited to this meeting. With the input of patients Uppsala CRB developed a draft model for electronic informed consent to be developed into an electronic tool. The current model comprises the major ethical and legal information that need to be included in an informed consent for research with bio-specimens/patient samples. It can be filled in and tailored for different projects and collections. This general draft is the basis to develop an electronic version to be filled in via a website. The planned tool will fulfil two major goals: a) Help scientists in more easily shaping an electronic informed consent for their project b) Allow patients to access and control their consent online via a personal webpage.

Generally BTCure results have been more and more present and acknowledged at international RA conferences, as at conferences of the American College of Rheumatology (ACR), the EULAR and at the European Workshop for Rheumatology Research (EWRR). BTCure work and results play a considerable role in some representative EULAR or EWRR Standing Committees and study groups as e.g. our approaches with regard to clinical data harmonization, harmonization of animal work and corresponding ethical aspects, innovative cell therapy studies, our experiences with regard to the reliability, usefulness and unmet needs of current diagnostics, as well as our studies related to early disease diagnosis and RA risk groups, etc.

An Outlook

In response to recommendations of BTCure`s independent Ethics Board Susanne Karlfeldt (administrative project management) will exercise a Public Relation strategy for Sweden, as

well as organize the translation of existing reports in order to distribute information material to the respective languages of national patient organizations and clinics.

Important research results of 2013

Research to understand disease development, to enable early diagnosis and intervention

BTCure groups in Sweden, the Netherlands and in Austria have made great progress in the assembly of cohorts and samples from people at risk for developing RA. Some of these cohorts include samples that were taken from healthy donors who later developed rheumatic disease, representing important material for the analysis of factors driving the development of disease. Ethical approvals for the assembly of cohorts and related studies could be obtained and interesting work has already been published 2013 in this context, as to environmental factors versus genetics risks and their relation to RA development (Haj Hensvold A et al 2013), familial risk (Frisell T et al 2013), features of the synovium (the tissue surrounding our joints) in risk patients (de Hair MJ et al 2013, Shanker R et al 2013), smoking and overweight as risk factors (de Hair MJ et al 2013), genetic risk scores and the role for vitamin D in the pathogenesis of RA (Yarwood A et al 2013, McAllister K et al 2013), auto-(self)-antibodies profiles prior to RA development and association of auto-antibodies with genetics and smoking (Mikael Brink et al. 2013, Heidi Kokkonen et al 2013), antibody enrichment in the lungs detected early in RA (Reynisdottir G et al 2014), the association of microRNAs (molecules influencing the activity of our genes) with the disease activity in patients with early rheumatoid arthritis (Filkova M et al 2013), etc. Many more studies are currently ongoing in this context and a laymen report of the main outcomes of this work can be provided in next year's activity report and at the end of the project.

Translational research and innovative therapies

BTCure has also made significant advance in investigating certain auto-antibodies and other potential biomarkers associated with rheumatic disease and added respective counterparts on a multiplex antibody chip. First large BTCure sample cohorts have been analysed on this chip and current analysis is ongoing. Preliminary results indicate that some markers may have an advantage over current diagnostic testing, and are able to detect people with rheumatic disease, that have been tested negative beforehand. This will contribute to earlier diagnosis and treatment of a considerable proportion of people with rheumatic conditions. Markers on this chip are currently further investigated for their potential to stratify people into disease subgroups and for their prognostic value, as to predict the patient's response to certain medications, which will lead to targeted and safer drug prescriptions. However, BTCure is not only translating first findings into potential diagnostic tools and procedures. Most importantly, we could recently gather a lot of knowledge and information about auto-immunity, the regulation/deregulation of the immune system and about factors contributing to the break of immune tolerance for the bodies' own components. This will result in efforts to identify targets for new innovative drug development and treatment approaches that may even be able to cure RA in the long term. We will soon have a workshop with key opinion leaders from all over the world to initiate strategic discussions with industry partners on potential strategies for drug developments aimed at re-establishing self-tolerance.