Biannual newsletter
September 2023

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Annual consortium meeting

On 8 September, a year after establishing the consortium, members from all 11 DARE-NL institutions gathered for the first time to network and exchange ideas. The meeting was attended by 125 participants, including the scientific advisory board, the patient organisations constituting the patient advisory board and patient participation review committee and representatives from regulatory institutes, research infrastructures and various companies. Thirteen companies sponsored the meeting and attended in person, with a booth or a presentation.

Excellent presentations were followed by very interactive panel discussions between the speakers, patient and scientific advisory board members and audience. In the first session, insights in the costs of ATMP production were shared and the strategy to setup GMP facilities was discussed. The focus in session 2 was on virus production in academia

with the aim to treat patients and more strategic choices were discussed. Several key messages in session 3 were to include regulators early in the process, costs involved and the role for academia as well as the role for patients. These insights and action points are compiled in a report which will soon be shared with all attendees and members.

The meeting has brought the field together, provided insight on the status of the DARE-NL project and trajectory from here and gave renewed energy to connect and continue to shape the future of ATMP development in the Netherlands. Excited about the synergy the DARE-NL meeting has empowered, preparations have already started for the meeting next year. Let us know if you have ideas or would like to contribute to the setup in any way!

Importance of DARE-NL for the patient

By the patient advisory board (PAB)

The first annual meeting has shown that all parties involved in the consortium are highly motivated to make the DARE-NL project a success. Patients and the DARE-NL project team are invaluable for each other. Eventually the main goal, for everybody involved, is to bring new advanced therapies to patients in a timely and sustainable manner. The focus should include the patients that may have less access to ATMPs due to the rarity of their disease.

Patients require and deserve the highest quality treatment available, meaning the given treatment has the most positive impact on their chances survival and quality of life. The value of DARE-NL for patients consists of several key points.

The first and most obvious one is the timely access to ATMPs for patients. However, it is crucial that development does not only focus on getting the treatments available as fast as possible, but also on treatments which will increase the patients' quality of life and chances

of survival most. Patients and by extension the PAB are therefore very invested in helping projects such as DARE-NL from the start to achieve the best results.

Another key point is that DARE-NL also serves as a source of valuable information for patients. Acquiring information relevant for patients about the latest research insights and involvement in discussions about scientific developments does not only help patients in providing high quality input for the consortium, but also allows patients(organizations) to better represent their interests elsewhere.

Finally, the information regarding ATMP development received by patient organizations through DARE-NL helps us educate patients about the progress within the project and ATMPs in general. The development and implementation of ATMPs could benefit from patients being well informed as it may raise their involvement in trials and other research.

To achieve highest impact for patients in the future the PAB hopes that the already well-established collaboration with the researchers and project leaders will continue and extend even further.

DARE-NL progress highlights

WP1: Setup of DARE-NL data, training and valorization platform

Lead: Emma de Pater, Erasmus Medical Center

Two employees have been appointed to manage WP1, welcome Soura Mardpour and Susette Lauwen!
The website (www.dare-nl.nl) is fully operational and the Zenya application has been implemented. All members can access Zenya and provide documents for access and authorization. The setup and content are in continuous progress. This means that the first milestone has been achieved:

✓ *1.1: Implementation of IT infrastructure for document, data and knowledge exchange*

The interviews with all partners to construct a detailed inventory of educational content and needs are ongoing. The first two members have followed the Market Approval course by Paul Janssen Futurelab and two additional members have registered for the course later this year. Continuation of the Regulatory Affairs program will commence early next year, which will involve the working out of themes relevant to multiple members, eventually resulting in a roadmap.
The first draft of the valorization framework has been assessed by all WP leaders and is further developed by the IPMC.

WP2: Harmonizing GMP processes for the manufacturing of cancer-specific ATMPs

Lead: Trudy Straetemans, University Medical Center Utrecht

An overview of materials approved to be used in ATMP manufacturing has been finalized and will be shared in Zenya. Supplier information has been organized in a 'kaartenbak' in Zenya. The SOP for supplier audits has been reviewed by DARE-NL and ATMP working group members and will soon be implemented in Zenya. Common procedures on risk policies are inventoried per center, based on which an overview of common denominators will be made. The end result will be a document detailing minimum requirements that all partners agree on and may use for their own documentation.

A workshop to inventory generic procedures to harmonies resulted in a shortlist of the six most wanted procedures to align in the Dutch academic ATMP facilities:

1. Environmental monitoring → procedure for the assessment of results (results of the facility, process, personnel)
2. Validation master plan and IQ/OQ/PQ procedure for automated, closed culture systems
3. Policy document APS/media fill (including bracketing)
4. Procedure for segregation of productions in place & time (future proof, bonus cleaning)
5. Comparability procedure (QC?) between sites (tech transfer)

6. Electroporation procedure (and other new SOPs)

Representatives from each center will write and review at least one procedure. A working group of writers and reviewers has been assembled and started with the first procedure of environmental monitoring. Members have shared existing environmental monitoring procedures and determined to focus on microbiology, GMP grades A, B and C both in operation and in rest. Writing and reviewing is ongoing and the approach will serve as a template for the harmonization design process. A working group will discuss the sharing of harmonized procedures with IGJ on 23 October.

A structure for sharing inspection results has been drafted.

WP3: QC harmonization and assay development

Lead: Inge Jedema, NKI/AVL

A flow cytometry panel for T-cell product composition has been validated by the NKI/AVL. A draft template for validation of flow cytometry-based identity and purity assessments will be based on this.

The NKI/AVL will start the dialogue on the requirements of characterization and potency assays for their TIL product with the EMA later this year. The outcome of this will be shared within DARE-NL.

WP4: Setup of a Dutch academic GMP vector manufacturing platform

Lead: Edwin Bremer, University Medical Center Groningen

An informal FTO analysis by Ian Bell (Oncode Institute) indicated that the lentiviral vector pRRL is most likely in the public domain. The process for in-house production of the MCB/WCB has been established and upscaling of GMP-like lentivirus batches has been completed. The pDARE-NL vector has been designed, the transfection process established and the purification process identified.

The in-house physical and functional titer assays have been established and all requisite QCs have been identified.

WP5: Identification and implementation of new technologies for the development and GMP-compliant manufacturing of ATMPs

Lead: Harry Dolstra, Radboud University Medical Center

The inventorization of current technologies has been completed through carrying out a questionnaire and holding a symposium (January 2023). Most centers are working on CRISPR/Cas9, as this is the most-used non-viral engineering approach right now. We are currently gaining information from companies like IDT, Aldevron, Synthego and GenScript in order to get a clear idea on the cost of joint outsourcing of production of common CRISPR reagents such as Cas9 protein, gRNAs and HDR templates. Alternatively, we would produce these reagents in-house in a centralized manner following the paths for viral vector production in WP4.

In addition, transfection procedures such as electroporation and nanoparticle mediated delivery are being discussed for various ATMPs.

The WP5 coordinators (Dolstra & Hagemans) have also paid site visits to Sanquin, LUMC, UMCG and NKI. Next on the list is UMCU.

You can now find the agenda for WP5 meetings on SharePoint: follow this link.

WP6: Regulation, health economics, health technology assessment and patient access

Lead: Pauline Meij, Leiden University Medical Center

An overview of regulations is in development. A database of approved oncological ATMPs under HE or in trials is under development and incorporation of ATMP trials in the Dutch trial register are under discussion with the CCMO.

The costing tool is ready and currently undergoing updating.

A list of topics for discussion in the stakeholder sandbox is under development.

A registry setup for the development characteristics, HE and clinical trials of oncological ATMPs is under development and in discussion with CCMO and IKNL.

A patient engagement plan to define the way of working of and with the patient advisory board has been setup and reviewed by the patient advisory board. Further review by the WP leaders follows.

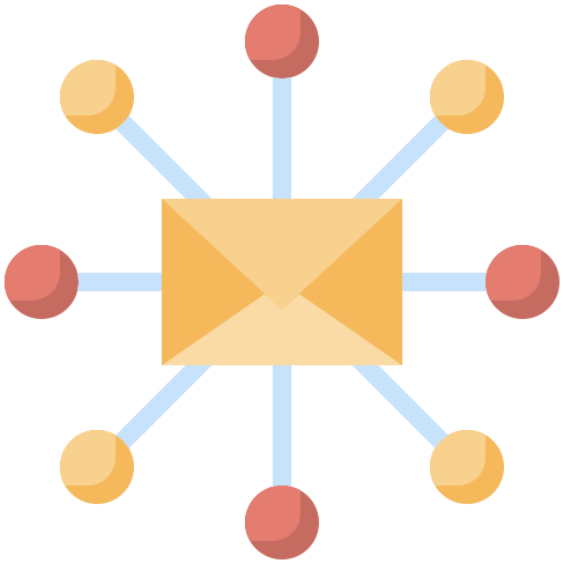
WP7: Project management

Lead: Trudy Straetemans, University Medical Center Utrecht

New milestones to define harmonization and impact have been formulated.
The annual progress reports were sent to the steering committee end of August. With this, the next milestone has been achieved:

✓ *7.2: First interim report of technical, infrastructural and financial progression*

The second steering committee meeting is scheduled on 12 September and the second KWF progress meeting on 17 October.



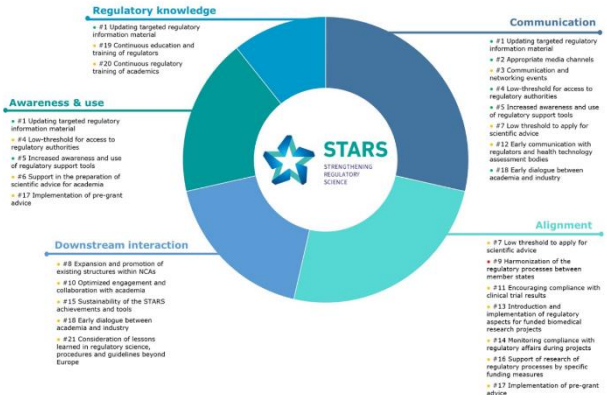
DARE-NL distribution lists

In the process of setting up a centralized oncological ATMP infrastructure, we are setting up communication channels based on the DARE-NL topics. These channels are meant to provide timely information focused on the topics of interest. When you leave your e-mail address and topics of interest here, we will keep you informed of developments in the selected fields of interest. Of course, you can opt out at any time by contacting info@dare-nl.nl.

Do not miss out on the latest information - sign up for topic-specific distribution channels

Research highlights: what is new in the field of ATMPs

Recommendations to improve the interaction and knowledge exchange between academics and regulators, and thereby advance academic drug development (Nature Reviews Drug Discovery, February 2023).



www.nature.com/bmt

PERSPECTIVE

A guide to the collection of T-cells by apheresis for ATM manufacturing—recommendations of the GoCART coaliti apheresis working group

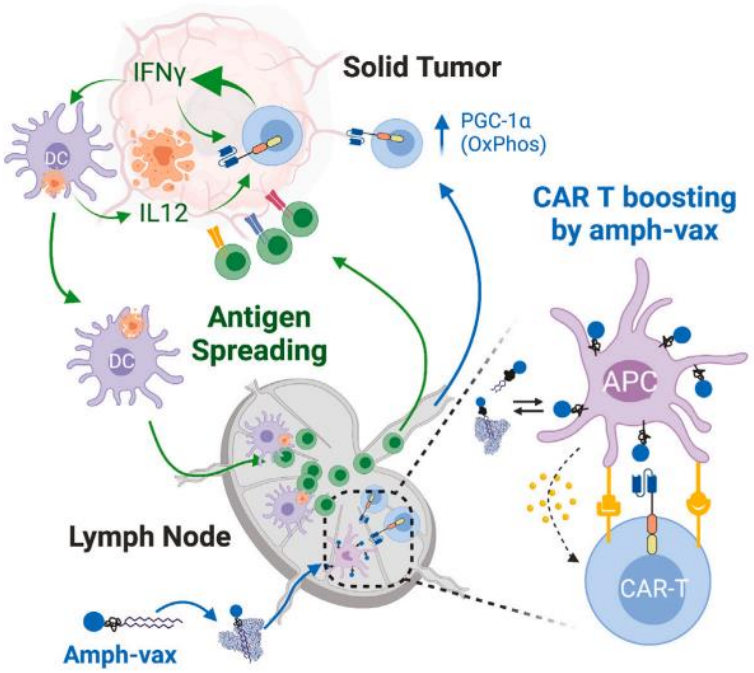
Nina Worel[1✉], Andreas Holbro[2,3,4], Hans Vrielink[5], Claudia Ootjers[6], Kaatje Le Poole[5], Ingrid Beer-Wekking[6], Tuula Rin Miquel Lozano[8] and Halvard Bonig[9,10]

Initial suggestions for patient's apheresis readiness and performance to collect starting material by the GoCART coalition (Bone Marrow Transplantation, April 2023).

CAT quarterly highlights and approved A

May 2023

Quarterly highlights and approved ATMPs by the Committee for Advanced Therapies



CAR-T-cell-derived IFN-γ plays a critical role in promoting antigen spreading, and vaccine boosting provides a clinically translatable strategy to drive such responses against solid tumors (Cell, July 2023).

CBG MEB MEDICINES EVALUATION BOARD

Towards Tomorrow

A status update on the Medicines Evaluation Board Science Policy 2020 - 2024

Chapter 4.2 Advanced therapy medicinal products (ATMPs)

The MEB invests in setting up projects and building a network of expertise with the scientific community to follow and support the development of safe and effective ATMPs to aid the patient (MEB Wetenschapsbrochure, April 2023).

ATMP landscape: what happens in the network

An innovation mission was organized by Health~Holland, RVO, the Dutch ambassy and the Switzerland Innovation Park in Basel on 19-21 March. This mission had the aim to connect the Dutch and Swiss cell and gene therapy innovation ecosystems from academia to pharma and every stakeholder in

between. Trudy and Edwin presented the hurdles in academic ATMP development in a strategic round table. The Cell and Gene Therapy theme was a starting point for subjects that fall under the preconditions for a well-functioning ecosystem, such as research and development, valorization, legislation/regulation, investments, production and financing of innovative therapies.

Connections are established with the Future Affordable Sustainable Therapies (FAST), the initiative that monitors the balance between entrepreneurship and accessible novel therapies. The (IT) infrastructures in DARE-NL and FAST are discussed in a meeting between the two initiatives in October. A workshop on this topic organized by FAST in July was attended by DARE-NL members Mara and Susette.

Following the publication by Maria Themeli *et al.*, the Amsterdam UMC Cancer Center received €16 million private funding to establish the Life Science Made Better-foundation (announcement). The team of Sonja Zweegman, Maria Themeli, Richard Groen and DARE-NL members Tuna Mutis and Dirk Geerts set out to develop a CCR-CAR T therapy to treat multiple myeloma without the help of the pharmaceutical industry.

In the field of regenerative medicine, the RegMed XB 1st Annual Conference focused on collaborative research efforts, cutting-edge technologies, ethical and regulatory considerations and challenges and future directions. Read more here. ICAT, part of the RegMed XB Pilot Factory infrastructure, was presented together with DARE-NL by Trudy at the Advanced Therapies summer course in Los Alcáres, Spain in July. The course featured the therapeutic potential of advanced therapies in oncology, genetic diseases and regenerative medicine, also highlighting the Spanish TERAV and European GoCART initiatives.

Emma de Pater and Reno Debets are involved in JOIN4ATMP, a Horizon Health application and collaboration with groups in Germany, Italy, Denmark,

France, Sweden, Belgium, Austria, Spain and the UK to accelerate ATMP development and transition to the clinic and increase access to ATMPs.

DARE-NL was (re)presented at these events:

- CBG ATMP committee meeting (13 March) - *Inge presented DARE-NL*
- Innovation mission to connect the Dutch-Swiss Life Sciences Ecosystems, focus on Cell and Gene therapy (19-21 March) - *Trudy and Edwin represented DARE-NL*
- European Parliament (22 March) - *Pauline provided CGT update*
- FAST workshop on 'wegwijsloket' (6 July) – *Mara and Susette represented DARE-NL*
- Advanced Therapies – scientific basis and clinical uses (14 July) - *Trudy presented DARE-NL*
- **DARE-NL annual consortium meeting** (8 September)

Calendar

SEP 12 **DARE-NL SC meeting**

SEP 19 **DARE-NL IPMC meeting**

OCT 17 **DARE-NL KWF progress meeting**

OCT 23 **CBG ATMP committee meeting**

APR 14-17 **EBMT annual meeting**

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