IMMUTRAIN - Immunotherapy of Cancer

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Innovative Training Network (ITN)
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IMMUTRAIN position paper

Report on the experience for future networks

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End of project: 30.11.2019

Work package 7

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Content

1. Executive summary

Progress has been significant in the last four years. In view of scientific results, the Early Stage Researchers of IMMUTRAIN could better understand mechanisms of immune suppression and generate antibodies against new targets. This led to thirteen co-authored original papers, among others in *Science*, and *Nature,* two patents and more than 20 outreach events. IMMUTRAIN organised ten European conferences and workshops with focus of knowledge of immunologic combinations of antibodies and therapies, scientific methods, transferable skills and career development. With the aim of ensuring excellence and independency, we paid a specific attention to the supervision using the opportunities of the network to broaden the learning effect.
In terms of implementation, we could count on a strong network which has brought tireless inputs for ten years of work, from the first application to the last funding balance. Based on our experience, we would like to make following recommendations to the scientific community, stakeholders, the European Commission, national and international funders.

- Although therapeutic progresses have been considerable in last decades, challenges remain in terms of therapeutic efficiency and side effects. Efforts are still needed to better target the individual immune responses of patients. For this we urgently need to increase investments in translational research in immunotherapy: if IMMUTRAIN stepped forward to a better understanding of tumor-derived immune suppression we still do not understand the complex interactions between cancer associated inflammation and tumor promoted immune suppression.

- Further observations are needed from basic understanding to clinical trials as well as from assessment of therapeutic impact in patients back to research. This understanding will be facilitated, if we can develop standardised process especially for cellular products. Nowadays, each trial or sponsor utilizes different production procedures which result in a different cellular product without proper understanding of the implications for the therapeutic outcome. This might vary from smaller alterations, such as closed versus open systems up to different types of virus, vectors and expansion protocols. The impact is unknown but this variability enhances the complexity of these therapies and thereby the time and resources needed for translation. Uniformisation of such process would save significant time and resources.

- Another promising way of scientific progress will also be the development of organ on-a-chip as an alternative for animal testing allows high-through-put screening of novel therapies.

- In view of project management, we encourage to reduce administrative burden. This concerns especially the updates of the scientific work during the funding period. They should be considered as usual and advisable and should not conduct to any amendment of the grant agreement.

- We also recommend to establish supplementary European funding schemes to prolong successful Innovative Training Networks in order to support long-term development of European training structures and scientific cooperation.

- Finally, from the geographic perspective of drug development, 47% of immuno-oncology active agents are developed in the US and 16% in China[1]. This underlines the need for EU countries to join forces, to intensify collaborations and to set common standards.

[1] Jia Xin Yu, Vanessa M. Hubbard-Lucey, Jun Tang. Immuno-oncology drug development goes global. Nature Reviews, 2019, doi: 10.1038/d41573-019-00090-z; ISSN 1474-1784 (online)

2. Overview and achievements of IMMUTRAIN

2.1. Key facts

- The Innovative Training Network of IMMUTRAIN started on 1st of December 2015 and will end on 30th of November 2019.
- 15 positions as Early Stage Researchers (ESR) are funded with a grant of 3.6 million euros by the European Union's Horizon2020 research and innovation program under the Marie Skłodowska-Curie actions.
- Eleven academic partners and six industrial partners from nine European countries have been involved.

2.2. Network and scientific expertise

Beneficiaries: Ludwig-Maximilians-Universität (LMU), Germany (coordinator); Radboud University Medical Center (RadboudU), Netherlands; Roche Diagnostics GmbH, Germany; Nottingham Trent University (NTU), UK; Istituto Europeo di Oncologia (IEO), Italy; Medical University Innsbruck (MUI), Austria; Spanish National Cancer Research Center (CNIO), Spain; University Hospital Herlev, Denmark; Institut Gustave Roussy (IGR), France; Humanitas University (HUNIMED), Italy.

Associated partners: 4SC Discovery GmbH, Germany; Bioncotech Therapeutics, Spain; CompanDX ltd., UK; Université de Fribourg, Switzerland; Roche Glycart AG, Switzerland; Friedrich-Alexander-Universität Erlangen, Germany; BioNTech Small Molecules GmbH, Germany; Université de Genève (UniGe), Switzerland.

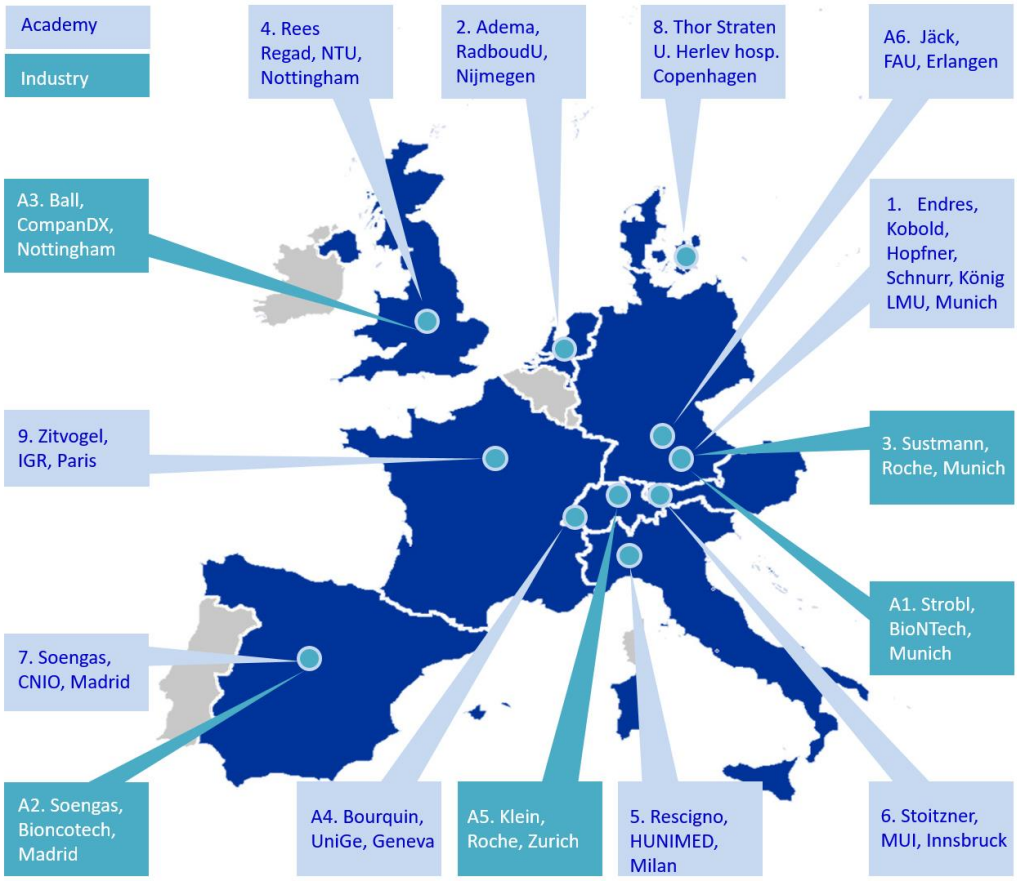

Figure 1: The network of IMMUTRAIN in 2019

IMMUTRAIN is the first European training in immunotherapy of cancer for doctoral researchers, so called Early Stage Researchers. Particular focus was placed on combinatorial therapies and on the field of bispecific antibodies used to target both the tumor and the patient´s immune system. 15 ESR, reinforced by the project leaders, investigated innovative therapeutic strategies to provide the rationales for future clinical trials. The training program represents a high interdisciplinary approach at the interface of industrial and academic research. Besides cutting-edge scientific projects, the ESR benefit from a broad range of training opportunities sharpening experimental and transferable skills. Therefore, the network builds a unique platform of expertise in the fields of monoclonal antibodies, dendritic cells, T cells and immunomodulatory nucleic acids with a considerable industrial involvement.

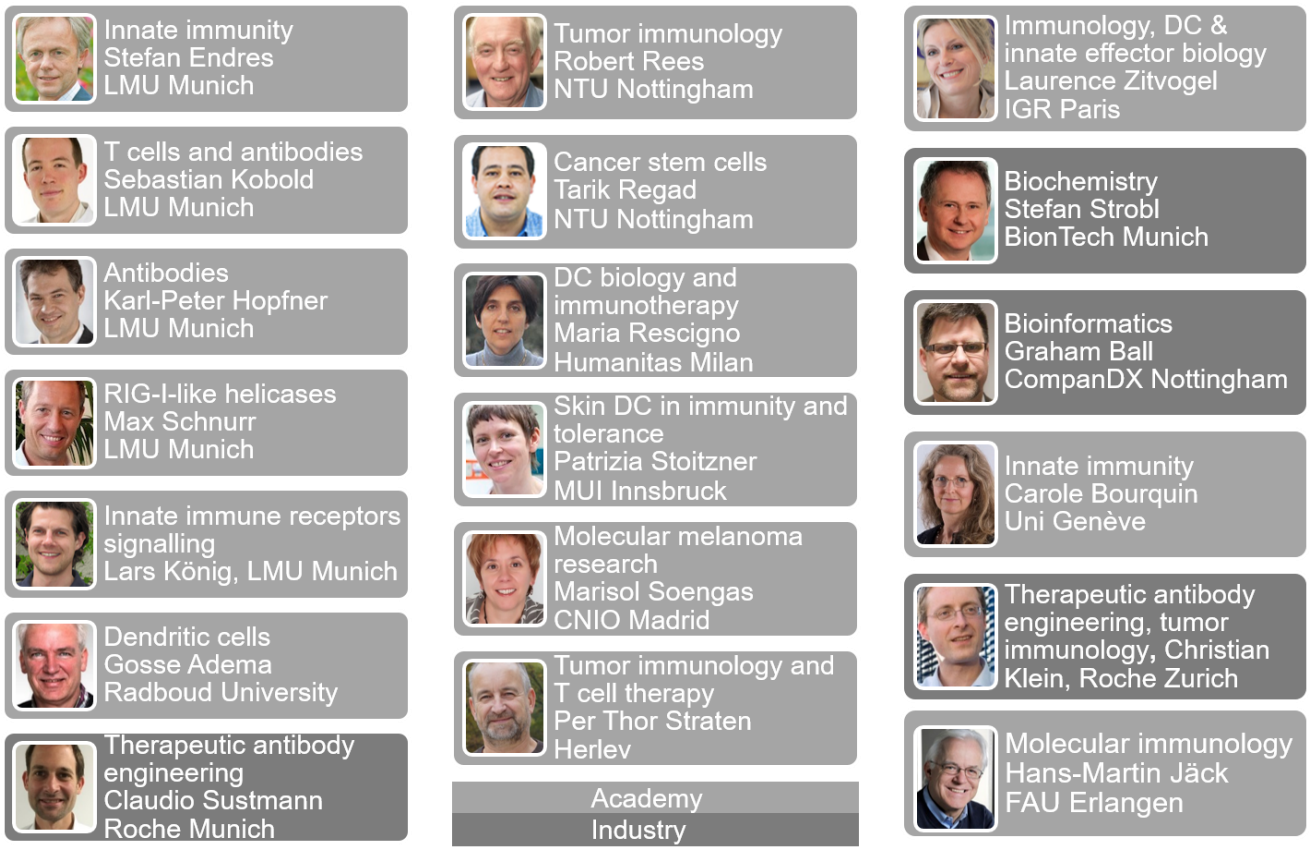

Figure 2: Scientific expertise of the project leaders of IMMUTRAIN

2.3. Main achievements

Progress has been remarkable in these few years. Work by the Early Stage Researchers (ESR) has been able to identify tumor-secreted factors that favor immune suppression, uncover immune checkpoints, generate antibodies against new targets and ultimately, devise strategies to reactivate the immune system and reduce cancer growth and metastasis. Our main achievements are:

- Thirteen co-authored original papers, among others in *Science*, and *Nature*
- Two patents
- Six training workshops and four international conferences
- Fifteen ESR are completing a PhD degree
- More than 20 outreach events, for scientists, stakeholders and general audience

have taken place during the project. It ranged from lab visits and open gates to the participation in international scientific conferences like ITOC or Miltenyi Biotec Scientific Days.

- Social media presence on LinkedIn: IMMUTRAIN has gained 180 followers from the fields of research, biotechnology, academy, healthcare, human medicine, human resources and professional training.

Website of IMMUTRAIN: www.immutrain.eu

3. Research

3.1. Research objectives

IMMUTRAIN aims at tackling major challenges of immunotherapy of cancer: the incomplete understanding on the mechanisms by which tumors evade immune surveillance, and the improvement of the efficacy of the antibody-based therapies. Although significant progress has been made, only a fraction of the patients responds to treatment. Resistance development to classical antibody therapies arise from local immune effector suppression, from loss of tumor antigen or from inhibitory effects on signalling pathways. To avoid or bypass these resistance mechanisms, the scientists of IMMUTRAIN have combined antibodies with several immunotherapeutic approaches: adoptive T cell therapy, immune cell activation, dendritic cell therapy and nucleic acids. These therapeutic antibodies have emerged with alternative immunostimulatory agents to ultimately increase antitumor efficacy by enhancing specificity and decreasing secondary toxicities. To this end, the work packages of IMMUTRAIN were set in an ambitious manner to address the four most promising strategies to enhance the clinical efficacy of antibodies:

- **Work package 1**, "Combination of antibodies with adoptive T cell transfer", to increase the infiltration and activation of tumor-specific T cells to tumor sites.
- **Work package 2**, "New formulations and combinations of antibodies to activate immune cells", with the objective of restoring immune activating mechanisms.
- **Work package 3**, "Combination of antibodies with dendritic cell therapy", to unleash dendritic cell-induced immune responses.
- **Work package 4**, "Target discovery and validation for antibody combination therapies", designed to improve the delivery and efficacy of immunostimulatory nucleic acids.

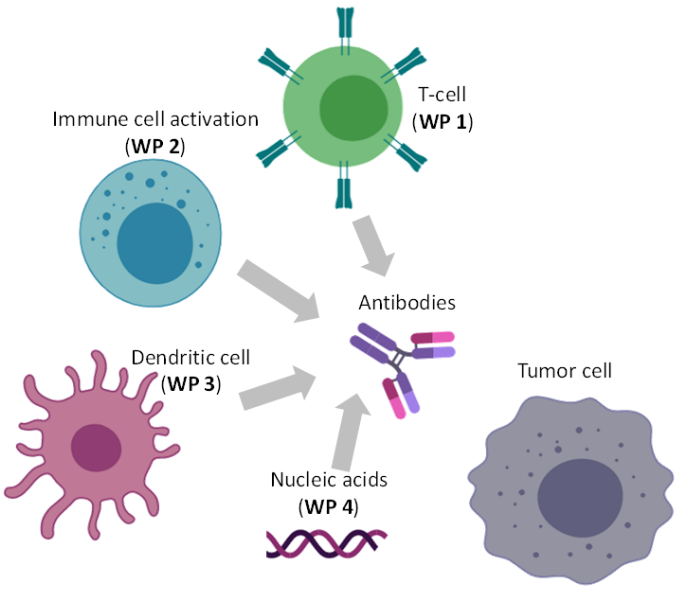

Figure 3: The four work packages of IMMUTRAIN

3.2. Main conclusions

IMMUTRAIN has set out to probe the combination of antibodies with other immunotherapeutic modalities. As a main take home message from the work conducted, it is plain that antibodies can be efficiently combined with T cell therapy, dendritic cell therapeutics or other immune stimulators. Similarly, IMMUTRAIN has also pioneered novel targets and antibody formats. In preclinical studies, ESR of IMMUTRAIN could demonstrate additive and synergistic activities of the later, providing the basis for further investigations and preclinical testing which might lead to clinical trials. At the same time the efforts of IMMUTRAIN have also deepened our mechanistic understanding of tumor-derived immune suppression in general and in the context of antibody therapy. The complex nature and at time redundant functions of immune suppressive mechanisms clearly indicate that we have yet to understand their interplay as a cornerstone to their therapeutic exploitation.

3.3. Recommendations for further scientific orientations

Stefan Endres, coordinator, Ludwig-Maximilians-Universität Munich: "It is not a breakthrough, it's a revolution" this is how an oncologist termed cancer immunotherapy opening a conference in Munich last year. Indeed, the advances of targeting the immune system for the benefit of patients suffering from cancer have been breathtaking: the number of tumor entities with proven prolonged – and sometimes long-term – survival upon treatment with checkpoint inhibitors is steadily growing. We are also bettering our understanding of the mechanisms of adoptive CAR T cell therapy which might lay the foundations to extend its success to non-hematological malignancies.

Yet, major challenges remain: First, most patients will not benefit on the long run or relapse after an initial response. Next, the unwanted effects of immunotherapy – cytokine release syndrome, neurological toxicity and autoimmune complications – require highly specialized and interdisciplinary patient care, sometimes including intensive care medicine. The high costs – both in treatment burden and in financial terms – make the identification of predictive biomarkers paramount; they are necessary to identify those patients suffering from tumors that will respond to a given tumor immunotherapy with reasonable probability. And lastly, society and public health policy will need to identify policies to best allocate these costly therapies to the appropriate patients.

With these challenges, world-wide efforts are on the way: just for the example of CAR T cell-based therapies, at least thirty-fold more clinical studies are currently ongoing both in the US and in East Asian countries compared to all European countries together. This underlines the need for EU countries to join forces, to intensify collaborations and to set common standards.

Sebastian Kobold, scientific coordinator, Ludwig-Maximilians-Universität Munich: As a consequence of IMMUTRAINs pioneering work there is now a major need not only to fully map and understand tumor-promoted immune suppression and cancer-associated inflammation but also to decipher the complex interplay of these mechanisms. This will be of crucial importance to future immunotherapeutic implementations, as it is becoming increasingly clear that immunological effects by novel therapeutics is not sufficient to validate them as prime candidates for clinical trials. In fact, redundant functions of other pathways might blunt therapeutic effects, leading to failures in clinical trials as recently observed for IDO inhibitors or LAG3-specific antibodies. Importantly, the success of immunological targets such as

checkpoint inhibitory molecules PD1 and CTLA-4 as such might be more of an exception rather than a therapeutic rule. As a further consequence, this might even differ from one tumor entity to another, as exemplified by CTLA-4 which yielded convincing results so far just for melanoma.

Future efforts and network will need to address the burning questions of how to best translate basic research into the clinics.
Further observations are needed from basic understanding to clinical trials as well as from assessment of therapeutic impact in patients back to research. This understanding will be facilitated, if we can develop standardised process especially for cellular products. Nowadays, each trial or sponsor utilizes different production procedures which result in a different cellular product without proper understanding of the implications for the therapeutic outcome. This might vary from smaller alterations, such as closed versus open systems up to different types of virus, vectors and expansion protocols. The impact is unknown but this variability enhances the complexity of these therapies and thereby the time and resources needed for translation. Uniformisation of such process would save significant time and resources.

Patrizia Stoitzner, project leader, Medical University of Innsbruck: Combination therapy will be the future of cancer treatment, as single therapy only works in a certain percentage of patients and opens the door for resistance development. Preclinical testing of promising combination therapies in mouse models is the first step to evaluate the potential of the novel approach. The development of organ-on-a-chip as an alternative for animal testing allows high-through-put screening of novel therapies. Bioprinting of human tissue is a fast developing research area that should soon allow the design of more sophisticated organ-on-a-chip systems. For example, to investigate tumor-immune cell interactions in organ-on-a-chip approaches we require novel in vitro 3D-systems that connect tumor organoids to artificial lymphoid organs. Thus, the biomedical engineering research of organ-on-a-chip constitutes a huge potential for future therapeutic developments.

4. Training and supervision

4.1. Training

The training program has combined several schemes to foster scientific and interpersonal skills. Actions have been implemented at two levels: (i) locally, each ESR has been enrolled in a graduate school and has conducted a PhD project in a partner lab and (ii) at the European level. Twice a year, the Early Stage Researchers participated in the common European training program to present their work-progress to the members of the network; to organise and participate in conferences with international guest speakers; to improve their skills and methods within workshops.

The European training remains built around five thematic axes:

1. Overview of immunologic combination partners for antibodies
2. How to develop new therapies: target validation, drug discovery and development
3. Methodological know-how in the field of immunotherapy like methods of bio imaging, diagnostics, therapies and bioinformatics for data analysis.
4. Transferable skills: scientific writing, how to communicate science, science and diversity, work life balance, intellectual property and patent filing, transfer of technology and oral and poster presentation.

5. To improve chances of cooperation and employment in industry and academy: mentoring program with members of IMMUTRAIN and meetings and pitches with external experts from the fields of scientific media, patent, technology transfer, investment and biotech.

Besides the training program organized at European level, each ESR benefited from the opportunity of interdisciplinary and international cooperation by conducting research at another member laboratory. Four of these secondments took place at an industrial partner, 11 at an academic lab.

4.2. Supervision

The main objective of supervision has been to ensure excellence and independency. For this the ESR had a broad range of opportunities to become feedbacks on the work performed.

a) Supervision of the scientific work and Career Development Plan
Each ESR has been supervised by a senior project leader on site and had the opportunity to select a co-supervisor at another member lab. They all have participated in a doctoral school from the recruiting institution or of an academic partner based in the same region. The supervision of the Early Stage Researchers was framed by an individual Career Development Plan (CDP). This document paved the way to independency as it established the short and long term career objectives in terms of as examples, research results, attendance to conferences, participation in publications, trainings of soft skills and networking opportunities.

b) Mentoring
Besides the scientific support, the project leaders have mentored the ESR along the project and greatly contributed to their career development. The mentoring program was implemented at the first training event in Munich 2016, setting up objectives, features and timeline.

c) Interdisciplinary perspectives and different point of views from different professions to foster individual scientific and research development
With the aim of cross-fertilizing the expertise of the network and increasing the learning effect, data presentations have taken place from 2017 during the European meetings. At these occasions, the ESR presented their results and got feedbacks from the project leaders of the network. Each ESR was also assigned to a team of one experienced researcher and one doctoral researcher to comment in an informal and confidential way on the content and the form of the presentation.

Finally, to gain more insides of career opportunities and to enhance personal network, IMMUTRAIN organized from 2018 on three times exchanges with external experts like editors, funding experts, scientists of private companies, investors and patent lawyers. The guest speakers presented their professional experience, evaluated presentations in pitch sessions and exchanges with the ESR in small groups as well as in one-to-one meetings. They could then join the network on LinkedIn and keep on following the progress of work.

4.3. Main achievements

- **10 international training events driven by ESR**. Since December 2015, six workshops and four conferences have taken place in Munich, Milan, Copenhagen, Paris, Nijmegen and Madrid to cross-fertilize the know-how gained in the network.

At these occasions, the doctoral researchers met more than 100 guest-speakers and took part in more than 20 sessions on methods, soft-skills and career development at the interface of academy and industry. Although the outline of the training events was set up, the Early Stage Researchers could define contents and have actively participated in the organisation.

- **Widened learning effect by exploiting the opportunities of the network**. These events combined several types of meetings, which greatly increased the learning effect and the exchange of experiences: lectures and discussions with international experts of the field, pitches and feedbacks in small groups, one-to-one meetings between young researchers, scientists and experts and the numerous casual exchanges.

- **Development of transferable skills with a focus on communication**. A broad range of training modules aimed on the one hand at improving professionalism in scientific communication. On the other hand, the ESRs trained to present science to different audiences like journalists, stakeholders from funding agency and researchers. We used several types of training: classical workshop with a trainer; individual presentations in front of scientists and experts like poster, data presentations and pitches; individual feedbacks with a team of one experienced scientists and one Early Stage Researcher.
Besides these trainings, the ESRs had the opportunity to participate in dissemination activities of the network by conducting lab visits and writing articles for the website and for the social forum on LinkedIn.

- **Awareness of career opportunities for ESR and of the training value for potential employers**: IMMUTRAIN involved around 50 experts from academic and non-academic sector in the training sessions on one side and the ESR presented their work and profile at many occasion on the other. The LinkedIn website has been a further way to keep on informing about IMMUTRAIN and to offer the opportunities of individual exchanges.

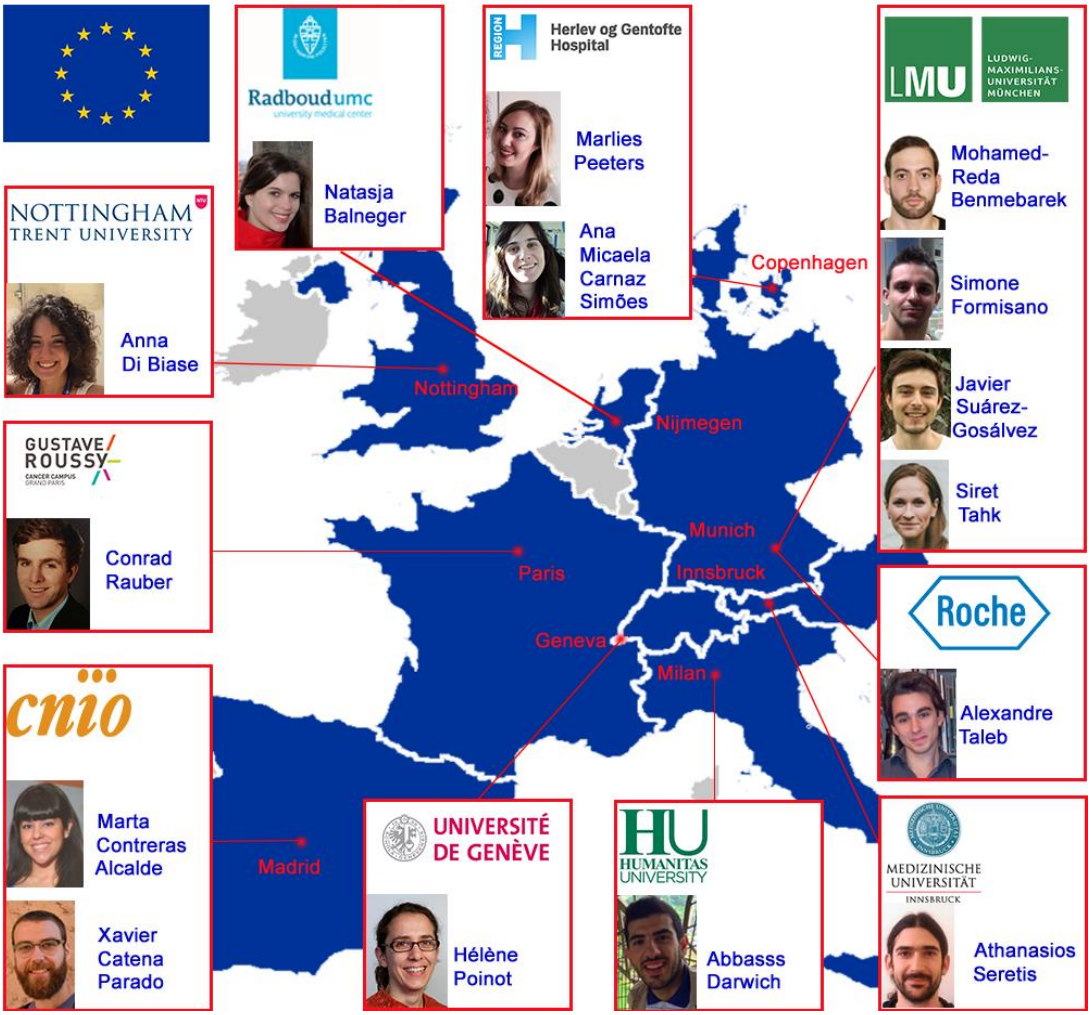

Figure 4: Early Stage Researchers of IMMUTRAIN in 2019

5. Recruitment, agreements, implementation and decision making

5.1. Recruitment

Key facts

- Almost 450 applicants from around 70 countries worldwide
- Six calls for positions from Jan. 2016 to Jun. 2018
- International advertising campaigns
- 17 recruitments
- Two steps evaluation procedure
- 53% of applicants and 47% of the ESR are women

Good practices

- **Central application tool for the network**. The Graduate Center of LMU offered a management tool for recruitment. The coordinator had access to an electronic platform where the applicants could post their documents in a standardised form complying with the requirements of the project. The project leaders accessed the applications and proceeded to the first step of evaluation online.

- **Common selection criteria and process of evaluation**. At the occasion of the first supervisory board meeting, the network agreed on a common way to evaluate the candidates and to communicate the results.

- **Integration in attractive research environment**. As an example, one lab at LMU developed a "welcome package" with practical information about the working place and all the administrative procedures for installation, visit of lab and introduction to the support services. The ESR have been fully integrated in their teams and had the opportunity to participate in the trainings and information events of the host institution like language courses and trainings for PhD students or taking part in scientific conferences.

Recommendations to the recruiters

- The coordinator should inform the partners on the EU regulation related to employment contracts. Examples: during the supervisory board meetings, by organising a meeting for administrative staff, by posting "information letters" per E-Mail or on the intranet of the project website.

- Each host institution should use the support of the national contact points to verify the compliance of the employment contract of ESR with the EU regulation. https://europa.eu/youreurope/citizens/national-contact-points/index_en.htm

- Advertising: The way of advertising the ESR positions is strictly regulated. Centralised advertising campaigns benefit from the attention of one responsible and experienced person. In the case of decentralised advertising, the partners should agree with the coordinator on the content of the call and the way to advertise before starting.

- Trial period: A trial period complying with the internal regulation of the recruiter should be systematically included to the employment contracts.

- Funding: The supervisors should envisage a supplementary funding in order to support an additional year of research needed for the completion of a doctoral degree. This has been the case in IMMUTRAIN, and all ESR who have wished to keep working on their projects to complete their doctoral degree, have got a position at their employing institute.

5.2. Consortium and grant agreements, decision making and evolution of the network

Key facts

- From Feb. 2016, consortium agreement has been signed by the beneficiaries and the associated partners.
- Eight supervisory board meetings have taken place.
- The management structure includes: one supervisory board; one coordination team with a coordinator, a scientific coordinator and a project manager for the daily management; one external advisory board; one ethical advisor; one ombudsman; two representatives of ESRs as members of the supervisory board; work package leaders for the coordinating of the scientific work within each work packages.
- The Grant Agreement has been amended with one update of the scientific content, one change of beneficiary, two changes of associated partners and one additional associated partner.

Good practices

- The Consortium Agreement of IMMUTRAIN adapted the template "DESCA Horizon2020 Model Consortium agreement" http://www.desca-2020.eu/

- The ESR have been actively involved in the decision making system: Each year, the ESR have elected two representatives to be members of the supervisory board meeting. The ESR also participated actively in the organisation of the training events and all of them met the project manager at least twice a year.

- The supervisory board meetings took place two times a year and the members could also participate remotely per video conference.

- We have benefited from a very supportive and excellent communication flow with the Research Executive Agency and the administrative staff of the consortium members. We would like to express our deep gratitude to all persons involved in the implementation of IMMUTRAIN.

5.3. Remarks and recommendations

- **Stamina and strong network are compulsory**

From the first application to the payment of the final funding balance, ten years will have passed. As we could count on a strong network, we have been able to resubmit and adapt the demand on the remarks of the referees. Each application could be improved by an intense work on content and form. We also have benefitted from the support of the European research office of LMU, the national contact points and the KOWI-Kooperationsstelle EU der Wissenschaftsorganisationen. We would like to express our gratitude at this occasion to all people who have actively contributed to the final success. (Figure 5)

Figure 5: Time line

Recommendations to the Research Executive Agency (REA)

- **Scientific development is rapid. Once funded, how much scalability do have scientists to adapt and to ensure research excellence along the project?**

Two years have separated the description of work submitted to the reviewers and included with the Grant Agreement from the start of scientific work. Once the Grant Agreement signed, the partners have to conduct every single action as described in this description (Annex I).

In order to offer to the ESR up to date scientific projects, ensuring research excellence, the project leaders of IMMUTRAIN have adapted the content to the state of the art. For this, the partners sent a detailed list with the rationales to the REA, the project was reviewed by a referee and then, the Grant Agreement amended.

Considering the high amount of supplementary work to justify the changes of content of scientific projects; Considering the long time from application to starting and the rapid development of scientific results – an intrinsic feature of research - we recommend to ensure higher flexibility in the implementation of the scientific projects, by focusing on the report rather than amending the grant agreement: changes in scientific projects should be regarded as usual - and advisable.

- **Long term funding**

Furthermore, we strongly recommend to develop a funding scheme to prolong the financing of ITN. This should be granted for the results and the plans for implementing long-term cooperation. In the field of immunotherapy, international and interdisciplinary cooperation are essential. This can be only achieved on European level.

Finally, we urgently need excellent, interdisciplinary PhD training in immunotherapy conducted by outstanding international experts and funded on a long term basis.

6. Acknowledgements of the coordination team

We would like to thank very warmly all members of Immutrain and all the co-workers from the scientific, technical and administrative teams who supported the implementation of the project.

Our particular thanks go to the project leaders who organized European training events at their institution: Marisol Soengas, Madrid, from 23rd to 26th July 2019; Gosse Adema, Nijmegen, from 26th February to 1st March 2019; Laurence Zitvogel, Paris, from 2nd to 6th July 2018; Per thor Straten, Copenhagen, from 2nd to 6th October 2017 and Maria Rescigno, Milan, from 8th to 10th February 2017.
We are very grateful to the European Commission which has funded this project and more specifically to the project officers who have supported the coordination: Bronius Goosens who actively helped to start, Patricia Rischitor and since October 2016, Riccardo Ricci who has provided us with precious advices and tireless support.

And last but not least, we thank very much the members of the External Advisory Board who sent us assessments on progress of work: Ulrich von Andrian, Harvard Medical School; Charles Dinarello, University of Colorado and Radboud University; Heiner Igel, Ludwig-Maximilians-Universität Munich; Eugene Maraskovsky, CSL Limited, Melbourne and Kai Wucherpfennig, Harvard Medical School.

Authors

Simone Gautier, Project Manager; Stefan Endres, Coordinator; Sebastian Kobold, Scientific Coordinator.

With the kind contribution of the Project Leaders of IMMUTRAIN:

Karl-Peter Hopfner, LMU Munich; Max Schnurr, LMU Munich; Lars König, LMU Munich; Gosse, Adema, RadboudU, Nijmegen; Claudio Sustmann, Roche Diagnostics GmbH, Munich; Robert Rees, NTU, Nottingham; Tarik Regad, NTU, Nottingham; Maria Rescigno, HUNIMED, Milan; Patrizia Stoitzner, MUI, Innsbruck; Marisol Soengas, CNIO, Madrid; Per Thor Straten, Hospital Herlev; Laurence Zitvogel, IGR, Paris; Stefan Strobl, BioNTech Small Molecules GmbH, Munich; Graham Ball, CompanDX ltd., Nottingham; Carole Bourquin, UNIGE, Genève; Christian Klein, Roche Glycart AG, Zurich; Hans-Martin Jäck, FAU, Erlangen.

Annex 1 – Publications and patents

Current list of publications with contribution of ESRs and of patents
Early Stage Researchers as co-authors are marked in **blue** and Project Leaders in **black**

Original papers

2019

13. Darowski D, Jost C, Stubenrauch K, Wessels U, Benz J, Ehler A, Freimoser-Grundschober A, Brünker P, Mössner E, Umaña P, **Kobold S, Klein C**.
P329G-CAR-J: A novel Jurkat-NFAT-based CAR-T reporter system recognizing the P329G Fc mutation
Protein Engineering, Design & Selection (PEDS), 2019, (eJournal)
JIF 2.0

12. Bellmann L, Cappellano G, Schachtl-Riess J.F., Prokopi A, **Seretis A**, Ortner D, Tripp C.H., Brinckerhoff C.E., Mullins D.W., **Stoitzner P**.
A TLR7 agonist shapes the effector immune cells during BRAF-targeted therapy in a preclinical melanoma model.
In revision*, Int J Cancer*. 2019
JIF 5.0

11. **Peeters MJW**, Dulkeviciute D, Draghi A, Ritter C, Rahbech A, Skadborg SK, Seremet T, **Carnaz Simoes AM**, Martinenaite E, Halldórsdóttir HR, Andersen MH, Olofsson GH, Svane IM, Rasmussen LJ, Met O, Becker JC, Donia M, Desler C and **thor Straten P**.
MERTK acts as a costimulatory receptor on human CD8+ T cells
American Association for Cancer Research 2019
JIF 10.2

10. Karches CH, **Benmebarek MR**, Schmidbauer ML, Kurzay M, Klaus R, Geiger M, Rataj F, Cadilha BL, Lesch S, Heise C, Murr R, vom Berg J, Jastroch M, Lamp D, Ding J, **Duewell P**, Niederfellner G, **Sustmann C**, **Endres S**, **Klein C** and **Kobold S**.
Bispecific antibodies enable synthetic agonistic receptor-transduced T cells for tumor immunotherapy
Clinical Cancer Research 2019
JIF 10.2

9. Liu X, Li J, Cadilha B, Markota A, Voigt C, Huang Z, Lin P, Wang D, Juncheng D, Kranz G, Krandick A, Libl D, Zitzelsberger H, Zagorski I, Braselmann H, Pan M, Zhu S, Huang Y, Niedermeyer S, Reichel Ch, Uhl B, Briukhovetska D, **Suarez Gosalvez J**, **Kobold S**, Gires O, Wang H.
Epithelial-type systemic breast carcinoma cells with a restricted mesenchymal transition are a major source of metastasis.
Science Advances 2019
JIF 11.5

8. Heise T, Pijnenborg JFA, Büll C, van Hilten N, Kers-Rebel ED, **Balneger N**, Elferink H**, Adema GJ**, Boltje TJ.
Potent metabolic sialylation inhibitors based on C-5-modified fluorinated sialic acids.
Journal of Medicinal Chemistry 2019 24;62:1014-1021
JIF 6.3

2018

7. Büll C, Boltje TJ, **Balneger N**, Weischer SM, Wassink M, van Gemst JJ, Bloemendal VR, Boon L, van der Vlag J, Heise T, den Brok MH, **Adema GJ**.
Sialic acid blockade suppresses tumor growth by enhancing T-cell-mediated tumor immunity.
Cancer Research 2018; 78:3574-3588
JIF 9.1

6. Vadakekolathu J, Al-Juboori SIK, Johnson C, Schneider A, Buczek ME, **Di Biase A**, Pockley AG, Ball GR, Powe DG, **Regad T**.
MTSS1 and SCAMP1 cooperate to prevent invasion in breast cancer.
Cell Death Disease 2018; 9:344.
JIF 5.9

5. Rataj F, Kraus FBT, Chaloupka M, Grassmann S, Heise C, Cadilha B, Duewell P, Endres S, **Kobold S**.
PD1-CD28 fusion protein enables CD4+ T cell help for adoptive T cell therapy in models of pancreatic cancer and non-Hodgkin-lymphoma.
Frontiers in Immunology 2018; 9:1955.
JIF 5.5

4. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, **Rauber C**, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, **Zitvogel L**.
Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors.
Science 2018; 359:91-97.
JIF 41.0

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Application number: 18168195.8
Application date: 2018.