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MARIE SKŁODOWSKA-CURIE ACTIONS

Innovative Training Networks (ITN)
Call: H2020-MSCA-ITN-2020

PART B1

"**SystemicR**"

Systems-level understanding of innate immune influence on cancer therapeutic resistance

This proposal is to be evaluated as:

ETN

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LIST OF PARTICIPATING ORGANIZATIONS

Consortium Member	Legal Entity Short Name	Academic	Non-academic	Awards Doctoral Degrees	Country	Dept./ Division / Laboratory	Scientist-in-Charge	Role of Partner Organisation
Beneficiaries								
Fundació Institut d'Investigacio Biomedica de Bellvitge (B1) *Institut Catala d'Oncologia (entity with legal link)*	IDIBELL	√			ES	Cancer Risk and Systems-Biology Laboratory	Miquel A Pujana	
Università degli Studi della Campania Luigi Vanvitelli (B2)	UniCampania	√		√	IT	Department of Precision Medicine	Lucia Altucci	
Consorci Centre de Recerca Matematica (B3)	CRM	√			ES	Stochastic Processes Laboratory	Isabel Serra and Tomas Alarcón	
Prinses Máxima Centrum voor Kinderoncologie (B4)	PMC	√			NL	Developmental Biology Laboratory	Henk Stunnenberg	
Kobenhauvns Universitet (B5)	BRIC	√		√	DK	Tumor Microenvironment Laboratory	Janine Erler	
German Cancer Research Center (B6) *University of Heidelbertg (entity with legal link)*	DKFZ	√			DE	Division of Proteomics of Stem Cells and Cancer	Jeroen Krijgsveld	
Semmelweis University Egyetem (B7)	SU	√		√	HU	Bioinformatics	Balázs Győrffy	
geneXplain (B8)	geneXplain		√		DE	Bioinformatics and Systems Biology	Alexander Kel	
leadXpro (B9)	leadXpro		√		CH	Drug Discovery and Development	Michael Hennig	
Partner Organizations								
city2science (P1)	city2science		√		DE	Science Dissemination and Public Engagement	Annette Klinkert	Partner delivering specialized training and soft-skills, leads WP8.
European Cancer Patient Coalition (P2)	ECPC		√		BL	Patient Advocacy	Antonella Cardone	Partner delivering specialized training and soft-skills, leads WP9.
Universitat de Barcelona	UB	√		√	ES	Biomedicine	Francesc Viñals	Award Doctoral

								Degree for IDIBELL
Universitat Autonoma de Barcelona	UAB	√		√	ES	Mathematics	Angel Calsina	Award Doctoral Degree for CRM
Stichting Katholieke Universiteit (Radboud Universiteit)	RADBOUD	√		√	NL	Faculty of Science	L.M.C. Buydens	Award Doctoral Degree for PMC
UniversitätsMedizin Göttingen	UMG	√		√	DE	Medical Informatics	Tim Beissbarth	Award Doctoral Degree for GENEXPLAIN
University of Basel	UNIVERSITAT BASEL	√		√	CH	Structural Biology	Timm Maier	Award Doctoral Degree for LEADXPRO

Data for non-academic beneficiaries:

Name	Location (city/ country)	Type of R&D activities	No. of full-time employees	No. of employees in R&D	Web site	Annual turnover[1] (in Euro)	Enterprise status (Yes/No)	SME status[2] (Yes/No)
leadXpro	Villigen, Switzerland	Drug discovery, screening platform, target modeling	16	15	https://leadxpro.ch/	2 M €	Yes	Yes
geneXplain	Wolfenbüttel, Germany	Bioinformatics and systems biology tools/algorithms	12	8	http://genexplain.com	0.99 M €	Yes	Yes

Declarations:

Name (institution / individual)	Nature of inter-relationship
leadXpro	Prof. Michael Hennig is the beneficiary of the proposal, chief scientific officer, chairman of the board, structural biologist and senior pharma drug discovery executive. He is also professor in structural biology at the University of Basel. **There are not inter-relationships with other participants.**
geneXplain	Dr. Alexander Kel is the beneficiary of the proposal, founder and chief scientific officer. **There are not inter-relationships with other participants.**
IDIBELL	IDIBELL is a biomedical institute associated with the Faculty of Medicine of the University of Barcelona (UB).

[1] Defined as the total value of sales of goods and services during the last accounting period.
[2] As defined in Commission Recommendation 2003/361/EC.

1. Excellence

During the past years there has been substantial progress in our knowledge of the genetic determinants of **cancer progression** and **therapeutic response**. However, global cancer survival is still around 50% and there are few examples of implementation of clinical protocols to predict resistance to a given therapy. Critically, **cancer therapeutic resistance (CaRes)** is the main cause of failure of disease care. The complete set of biological factors that influence therapeutic response in a given setting is generally unknown. Since the activity of genes and proteins is precisely coordinated to execute cellular functions, the result of a therapy depends on the activity of a multitude of potential modifying factors. In this scenario, European academic, small-medium enterprises (SMEs), science communication, and patient advocacy experts have joined efforts to propose a **CaRes** and **Systems Biology** network for training a new generation of **interdisciplinary cancer researchers and professionals**. The training program is focused on the interplay between **innate immune and cancer cells** to prevent and inhibit CaRes (**SystemicR**).

The specific objectives are:

- To develop an excellent and innovative PhD program that provides comprehensive training and advanced supervision on cancer biology and therapeutic response/resistance research;
- To integrate education on methods, models, strategies and policies for translation of preclinical data into clinical activity and SMEs;
- To incorporate advanced learning for communication and dissemination of scientific results, public engagement, health care policies, and patient advocacy.

SystemicR will train **early stage researchers (ESRs)** to become **multidisciplinary and excellent first-class cancer researchers and professionals** that will decisively contribute to **improve cancer care by comprehensively tackling CaRes**.

1.1. Quality, innovative aspects and credibility of the research programme

1.1.1 Introduction, objectives and overview of the research programme

There were approximately **3.9 and 1.9 million cases of new diagnoses and deaths, respectively, from cancer in Europe in 2018**[3]. Critically, these figures are continuously increasing as consequence of extension of life expectancy. These facts indicate that one in two men and one in three women will suffer cancer throughout their lives. Balancing incidence, approximately **50% of the cases are alive after five years of diagnosis**. This is undoubtedly due to the implementation of screening and prevention programs, improvement of clinical care as a whole, and development of new therapies. In other words, substantial progress has been made in caring cancer globally. However, the same statistics reveal that major efforts are still required to increase rates of complete curation for many cancer types.

The percentage of women survivors at 5-year after the diagnosis of breast cancer is 85-90%[4]. However, the proportion of survivors is significantly lower in other types of cancer where development of precise therapies has been relatively limited for years. Colorectal cancer is the neoplasm with the second highest incidence in Europe (~500,000 annual diagnoses), but survival at 5-year is restricted to ~60% of cases. Even in breast cancer, where overall cure has been greatly improved, there are subtypes of relative poor prognosis that accumulate the highest mortality taking into account the number of incident cases (e.g., so called «triple-negative» subtype, TNBC). A relatively low survival rate in this setting occurs despite the fact that the majority of cases exhibit remarkable pathological responses to first-line chemotherapy. These limitations are also observed in non-solid cancers, being acute myeloid leukemia (AML) the most common type of aggressive leukemia diagnosed in European adults (~18,000 annual diagnoses). The complete remission rate to the first-line chemotherapy of AML in older adults is of 40%-60%, which limits 5-year survival rate to less than 30%[5]. That is, among the factors that require further efforts **to improve cancer care**, there is a leading role for **studying the mechanisms that influence response to current therapies**[6].

The existence or emergence of CaRes (i.e. intrinsic, innate or primary; or acquired, evasive or secondary) is the most frequent cause of failure of care[6,8]. Commonly, if a given patient shows no benefit from a standard first-line treatment, other therapeutic options are offered with the assumption these additional strategies are independent from the initial. However, the pressure applied by a therapy frequently produces the appearance of genetic and/or phenotypic heterogeneity that promotes rapid adaptation to new therapeutic disturbances and, in many cases, greater aggressiveness of cancer cells. In this context, there are few predictive, sensitive and specific markers of CaRes[7]. Beyond the pharmacokinetics of each drug and the inter-individual variability, different general mechanisms of CaRes have been defined[8]. These range from genetic and molecular adaptation at the level of the given drug target, to cellular adaptation to damage caused by therapy. In recent years, thanks to the development of massive genetic sequencing technologies, the focus of the research has been directed towards the identification of somatic mutations that **balance response/resistance**[9]. However, the translation of the results of the basic knowledge of resistance is not in the majority of cases immediate due to the lack of precise knowledge of the functional consequences of genetic alterations. The list of

[3] Ferlay J et al. *Eur J Cancer*. 2018;103:356-387.
[4] Allemani C et al. *Lancet*. 2015;385:977–1010.
[5] Kantarjian H et al. *Blood*. 2010;116:4422–4429.
[6] Vasan N, Baselga J, & Hyman DM. *Nature*. 2019;575:299-309.
[7] Bono JS & Ashworth A. *Nature*. 2010:467;543– 549.
[8] Holohan C et al. *Nat Rev Cancer*. 2013;13:714–726.
[9] Hyman, DM, Taylor BS & Baselga J. *Cell*. 2017;168:584–599.

human "**cancer gene drivers**" (i.e., genes that when altered promote cancer) includes hundreds of them[10]. These represent the fundamental framework for improving cancer care through development of novel targeted therapies; however, current clinical prediction of the progression of a particular patient and/or its therapeutic response based solely on the information of a given driver is often incomplete. In fact, all too often selected patients based on a specific target or driver show an insufficient benefit of the indicated therapy.

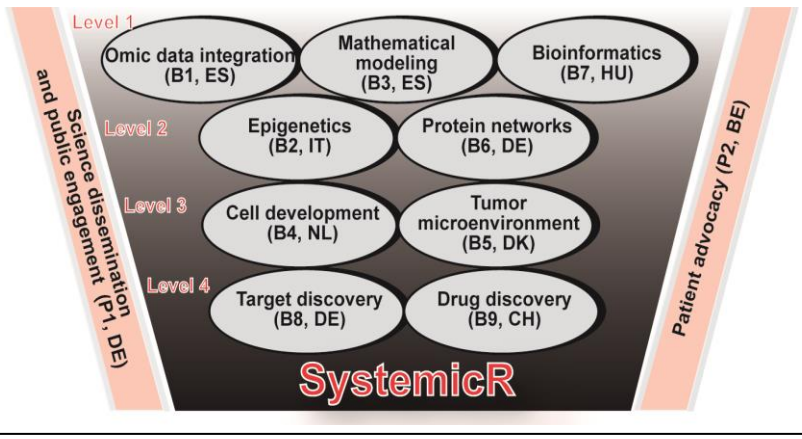
Every molecular process and signaling pathway involves the coordinated activity of groups of genes and/or proteins (genes/proteins) in **complex networks to achieve cellular functions**[11]. Coordinated gene/protein activity can be represented by different types of functional relationships or interactions, such as gene co-expression and protein complex membership. Therefore, the function of a given driver or therapeutic target can be modulated through each of its molecular relationships. This complexity is illustrated for example by the existence of >1,000 direct and/or indirect interactions of EGFR[12]. In this context, the role of any driver or target can potentially influence cancer progression and/or therapeutic response, defining hundreds of potential cancer modulators in molecular networks active within cancer cells. Therefore, beyond candidate gene/protein studies, **comprehensive understanding of CaRes requires integrative analyses of multiple biological levels**.

In addition to the above limitations, cellular interactions in the **tumor microenvironment (TME)** also play a crucial role on determining the balance of response/resistance[13]. In normal tissue repair and remodeling, and in inflammation, immune cells act in coordination with platelets and fibroblasts, among other cell types[14]. In cancer, tumor-associated fibroblasts can recruit immune cells and influence their behavior to promote cancer progression and metastasis[15]. Thus, different types of **immune and stromal cells** influence cancer immunological surveillance and tolerance, and precise coordination of cell activities determines the outcome in a given therapeutic setting and patient. Therefore, in addition to studying multiple biological data levels in cancer cells, **comprehensive understanding of CaRes also requires analyzing different cell types and their functional relationships within the TME**. The depicted scenario highlights that **cross-disciplinary collaborations have the potential of revolutionizing oncology**[16]. Thus, there is a need of fostering interdisciplinary alliances that ultimately will benefit patients, improve health care policies, and economic wellness. Some of these aspects are exemplified at the basic research level of large collaborative projects, such as those of The Cancer Genome Atlas (TCGA)[17] and International Cancer Genome Consortium (ICGC)[18], but there is a fundamental limitation at the root of these paradigms: **lack of a wide-ranging training programme for cancer researchers and professionals**.

SystemicR is a European multi-disciplinary and cross-sectorial research, educational, business and patient-advocacy network aiming at solving the depicted limitations to improve cancer care. The consortium includes research projects and training skills in mathematical modeling, bioinformatics, cell development, single-cell analyses, genetics, epigenetics, proteomics, mouse models, immunology and TME. On the top of this interdisciplinarity, the training programme includes gaining new mandatory skills on target and drug discovery and development, science dissemination and public engagement, and patient advocacy. Successful execution of this programme across **11 academic/non-academic entities from eight European countries** will deliver a new generation of cancer researchers and professionals with a holistic view to improve cancer care by tackling CaRes.

The **overarching Objectives** of **SystemicR** towards advanced training of **ESRs** are: **1)** *to educate a new generation of researchers with comprehensive, systems-level understanding of CaRes;* **2)** *in addition, to educate on how to protect and translate research findings towards higher patient, social, and economical benefits; and* **3)** *to complement advanced knowledge with education on how appropriately to communicate and disseminate science in the current era, how to attend and integrate patient needs and advocacy, and how these aspects should, in turn, orientate research.* These objectives will be met by gathering a range of expertise and research projects in an interdisciplinary consortium directed to **defeating CaRes, from a bottom-up approach and expertise (Fig. 1)**. In parallel to firm scientific goals, education and training in soft-skills will be ensured by a series of complementary actions and activities provided by beneficiary and partner organizations, and by external organizations, as defined in subsequent sections.

Fig. 1. Bottom-up organization of SystemicR.

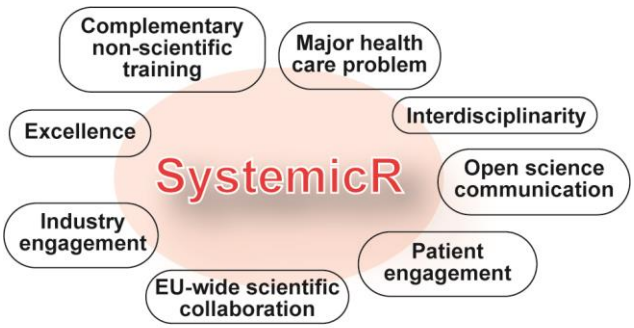


[10] Data from the COSMIC and IntOGen databases. Retrieved on December 2019.
[11] Vidal M, Cusick ME & Barabási A-L. *Cell*. 2011;144:986–998.
[12] BioGRID data retrieved on December 2019.
[13] Maman S & Witz IP. *Nat Rev Cancer.* 2018;18:359-376.
[14] Nowarski R, Jackson R & Flavell RA. *Cell*. 2017;168:362–375.
[15] LeBleu VS & Kalluri R. *Dis Model Mech* 2018;11.
[16] ESMO 2015 letter from Profs. D Lacombe, E Voest & J Tabernero (SAB member): "How are cross-disciplinary collaborations revolutionizing the field of oncology? What are the challenges that lie ahead?"
[17] TCGA, a landmark cancer genomics program, studying over 20,000 primary cancer and matched normal samples spanning 33 cancer types.
[18] ICGC project: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes.

Based on research experience and resources of the participants, the **SystemicR** research projects will be directed at better understanding and tackling the **signaling interplay between innate immune and cancer cells, and the influence of these interactions in therapeutic resistance of acute myeloid leukemia (AML), breast and colorectal cancer** (TNBC and microsatellite stable (MSS) subtypes, respectively).

Therapies based on immune system functions are transforming cancer care[19,20]. Agents targeting immune checkpoints have been approved in monotherapy or combined with other drugs in several cancer settings. These approaches are mainly directed at releasing effector T cells that trigger anti-tumor activities following presentation of cancer antigens. However, T cells do not function in isolation in the TME and, thus, their functional responses and long-lasting protective effects also depend on the activity of **innate immune cells**[21]. These cells, which include dendritic, mast, monocytes, macrophages, natural killer (NK) cells, natural killer T, and γδ T cells, are therefore the focus of many complementary therapeutic approaches to those centered on checkpoint inhibitors. These strategies exploit features of antimicrobial immunity, induction and amplification of immune responses, effector responses, and immune suppression[22]. However, **how these immune cell types interact among them and with cancer cells remains poorly understood**[23]. The complexity of gene/protein profiles within and between the different cell types, the heterogeneity of cell phenotypes, the intricacy of molecular and cell-cell interactions in the TME, **requires cross-disciplinary collaborations and training**. The groups in **SystemicR provide an appropriated framework to ultimately predict and inhibit resistance from immune-cancer cell studies (Fig. 2).**

Fig. 2. Innovative training qualities of SystemicR.



While the scientific focus of the **SystemicR** innovative training program is to obtain a systems-level biological understanding of immune-cancer cell interactions influencing CaRes, the overall aim is to establish **a new, internationally-recognized educational approach to train ESRs in a highly relevant health care issue, providing complementary non-scientific skills towards increasing the impact and benefit of their prospect actions.** The proposal is ***timely*** given the complexity of the health problem and the ***interdisciplinarity*** of the participating teams. The ***urgency*** resides on the need to educate ESRs with advanced skills to tackle a major health problem, CaRes. The new professionals will feed the academia, industry and/or patients organizations to improve cancer care in the near future.

1.1.2 Research methodology and approach

The work is divided into eight interconnected work packages (WPs; **Table 1.1**). The individual ESR projects are listed in **Table 3.1b**. **Table 1.1: WP themes, leaders, duration/type, and ESR projects involved:**

WP No.	Title	Start Month	End Month	Activity Type	Lead Beneficiary Short Name (No)	ESR involvement
1	**Scientific and Network Management**	1	48	M	IDIBELL (B1)	All
2	**Coordination of Research Training**	1	48	T	UniCampania (B2)	All
3	**Theoretical Modeling and Data Analysis (Level 1)**	6	48	R	CRM (B3)	1,2,3,6,7,8,11,13,15 (n=9)
4	**Cell-Autonomous and Single-Cell System Studies (Level 2)**	6	48	R	PMC (B4)	2,3,6,7,8,10,11,13,15 (n=9)
5	**Tumor System Studies (Level 3)**	6	48	R	BRIC (B5)	1,3,4,9,10,12,13,15 (n=8)
6	**Target Discovery (Level 4)**	6	48	R	geneXplain (B8)	1,2,5,6,8,12 (n=5)
7	**Drug Discovery (Level 4)**	6	48	R	leadXpro (B9)	1,4,6,7,9,11 (n=6)
8	**Science Dissemination and Public Engagement**	1	48	D	city2science (P1)	All
9	**Patient Advocacy**	6	48	D	ECPC (P2)	All

[19] Ribas A. *N Engl J Med.* 2015;373:1490-1492.
[20] Sharma P & Allison JP. *Cell.* 201;161:205-14.
[21] Demaria O et al. *Nature*. 2019;574:45-56.
[22] Corrales L et al. *Cell Res*. 2017;27:96–108.
[23] Jenkins RW, Barbie DA & Flaherty KT. *Br J Cancer*. 2018;118:9-16.

Overall design. The WP organization of the **SystemicR** network is designed to implement advanced ESR training through a **bottom-up approach** that will provide comprehensive understanding of CaRes, as well as education on science communication and dissemination, development and exploitation of biomarkers and therapies, clinical translation, and patient advocacy. These complementary facets of training are detailed as follows:

A. Scientific goals and deliverables. The bottom-up approach is supported by genetic, molecular, cellular, and tissue analyses focused on CaRes. These data will in turn feed new theoretical models, data integration and analysis algorithms, and complex network studies. Systems-level models will be completed from further data integration from TME, single-cell transcriptome and proteome profiling in heterogeneous CaRes samples. From single-factor evidence, and from validated model and network features, there will be identified biomarkers and therapeutic targets. Newly identified biomarkers will be assessed across public datasets and in clinical data from the participating groups affiliated to **oncology hospitals** (**B1-IDIBELL**, **B2-UniCampania**, **B4-PMC, B5-BRIC**, and **B7-SU**). Drug discovery and development will be based on newly identified targets, as well as on signaling constraints from validated theoretical models and from identified network fragilities. The neoplasms of study will be based on established expertise and resources of the participating groups, and include three prevalent cancer types (AML, breast and colorectal cancer subtypes). The participants with affiliated **oncology hospitals** are in turn linked to institutional biobanks including clinically annotated germline and somatic samples for these types of cancers. **Specimens, materials and models**: The **B1-IDIBELL** campus comprises a biobank approved in 2009 by the Spanish Ministry of Health and that nowadays include large collections of germline and somatic blood and tissue samples, respectively, of breast and colorectal cancer, which have been the basis of previous studies by the coordinator[24,25,26] and/or other IDIBELL PIs (e.g.[27]); **B2-UniCampania** is affiliated to the University of Campania Luigi Vanvitelli (Naples, IT) and offers collections of >200 frozen tumor samples for each AML, breast and colon cancer types, and using these resource **B2-UniCampania** and **B4-PMC** have successfully completed European collaborative projects (e.g., Blueprint Epigenome project[28]); and **B4-PMC** comprises a biobank that contains >500 primary AML patient materials (tissue, blood, bone marrow, etc.) and derivatives thereof (DNA, RNA, etc.), as well as research-derived organoid cultures and patient-derived xenograft (PDX) models. In addition to these resources, **B5-BRIC**, **B6-DKFZ** and **B7-SU** are actively involved in applying systems-medicine approaches to investigate cancer recurrence (e.g.[29,30,31]). **B5-BRIC** runs a **Precision Medicine Program** for patients with metastatic cancer at Denmark's main hospital (Rigshospitalet) in collaboration with her clinical partner Prof Ulrik Lassen, who is Head of Oncology. This program has generated organoids cultures from patients with diverse cancer types, but the majority are breast (33%) and colorectal (33%). These organoids can be implanted as tumors in mice to undertake studies. Preclinical mouse models will also be based on PDXs (**B1-IDBELL** (TNBC), **B2-UniCampania** and **B5-BRIC** (breast and colorectal cancer), and **B4-PMC** (AML)) and genetically modified animals. The later include a *Brca1*-null model (*Trp53*^{tm1Brd} *Brca1*^{tm1Aash} Tg-*LGB-Cre*; **B1-IDIBELL**), *PyMT* and *MMTV-Neu*, and *Vil-Cre-ER Apc*$^{fl/fl}$ *Kras*$^{G12D/+}$ *Trp53*$^{fl/R172H}$ *Tgfbrl*$^{fl/fl}$ (**B5-BRIC**)). Subsequently, intellectual data protection and business development training will be coordinated with results from the identification of biomarkers and therapeutic targets, and from subsequent drug discovery processes, which are provided by SMEs leading **WP6 (B8-geneXplain)** and **WP7 (B9-leadXpro)**. Therefore, the program includes the study of a cancer type that mainly affects women (i.e., breast cancer), and female mice will be mainly studied on this regard. For AML and colorectal cancer, both mouse genders will be analyzed.

B. Comprehensive ESR training. In addition to the above scientific aims, a major theme of the **SystemicR** programme will be centered on providing soft-skills on science communication and dissemination directed at the European general populations (**WP8**). The fact that this network is focused on a major health care problem (i.e., CaRes) will be a key feature for dissemination and public engagement, thus aiming at influencing future decision-making processes and health care policies. Critically, the social and economic impact of CaRes remains poorly quantified in most European countries. Therefore, **SystemicR** also aims to communicate and disseminate towards national and European-wide health care representatives (**WP9**, **ECPC**). Thus, the program also gives voice to patient needs and advocacy, which is generally missing in nowadays research activities.

Having a complementary training, the **ESRs will undertake experimental research, integrative data analysis and modeling, and preclinical studies**. In parallel, they will be educated in science communication and dissemination, intellectual protection and business development, and patient advocacy. Additional training courses and advanced workshops are depicted in subsequent sections and integrated in the overall program.

- **Scientific and Network Management (WP1; B1-IDIBELL).** This package focuses on **implementing the structures, processes and tools** for a successful execution of **SystemicR**. The network management structure will consist of a: 1) **Supervisory Board (SB)** chaired by the coordinator B1-Pujana, and including B4-Stunnenberg and B5-Erler; 2) **Training Committee (TC)** chaired by B3-Altucci, and including B6-Krijgsveld and B9-Hennig; and 3) **ESR committee (EC)** chaired by B2-Alarcon/Sierra, including B7-Győrffy, B8-Kel, and **two ESRs selected by the**

[24] Heyn H et al. *Cell Rep*. 2014;7:331-338.
[25] Mateo F et al. *Oncogene*. 2017;36:2737-2749.
[26] Ruiz de Garibay G et al. *Dis Model Mech*. 2018;11(5).
[27] Salazar R et al. *J Clin Oncol*. 2011;29:17-24.
[28] Stunnenberg H et al. *Cell*. 2016;167:1145-1149.
[29] Cox TR et al. *Nature*. 2015;522:106-110.
[30] Raffel S et al. *Nature*. 2017;551:384-388.
[31] Győrffy B et al. *Br J Cancer*. 2018;118:1107-1114.

fellows. The two first board/committees will be formally established and operative by the kick-off meeting (month 2), and the third one (EC) will be fulfilled with the inclusion of two ESRs from different sites (approximately month 8). **WP1** will be supported by the European Project Management Grant Offices of both the IDIBELL's and Catalan

Institute of Oncology (ICO, within the IDIBELL campus). Together, these bodies will establish a governance structure and consortium agreement, and will communicate with European Commission (EC) and ITN officers. They will also implement the processes for decision-making, risk management, progress reporting, recruitment, financial management and gender/equality monitoring. All beneficiaries have agreed to dedicate the necessary salary for a project manager to be hired at IDIBELL and that will oversee all aspects of **SystemicR**. An external **Scientific Advisory Board (SAB)** that will provide continuous advice on the program is also included in the structure, and is comprised by independent ITN holders, and recognized academic and industrial leaders in cancer research and treatment (section 3.2.2).

- **Coordination of Research Training (WP2; B2-UniCampania).** This package will be responsible for the **training programme** implementation and coordination, and meetings, workshops and courses organization within the consortium. A personal career plan (section 1.2.1) will be established by this package for each ESR. The fundamental pillars will be: 1) training with ***integrity***, being the foundation of education and supervision of any researcher and professional; 2) training according to the ***scientific method***, which will solidify a mature scientific character; 3) training ***interdisciplinary***, providing a comprehensive understanding of a major health problem, and broad knowledge and capacities to approach it from different angles; 4) training with ***continuous supervision*** dedicated to research, education, soft-skills and goals, which will be fundamental for embracing the ESRs in the overall project; and 5) training with ***innovation*** on scientific, experimental, and educational methods. The package tasks will also include strategies for managing stress and problem resolution.
- **Theoretical Modeling and Data Analysis (WP3, Experimental Level 1; B3-CRM).** This package focuses on coordination of training and research projects across **mathematics, bioinformatics, and data integration/modeling**, which are represented by several participating groups/SMEs (level 1, Fig. 1). The research activities will focus on the following points, from the bottom-up: i) gene/protein/cellular correlations associated with CaRes phenotypes; ii) theoretically analysis of signaling pathways and molecular interactions determining CaRes; iii) building and analyzing the structure and topology of CaRes molecular and gene regulatory networks; and iv) using i-iii results to predict CaRes biomarkers and therapeutic targets for subsequent preclinical validations (next **WPs**). According to these objectives, this package will design a sub-plan of training on *in silico* studies, which will be delivered to WP2 and integrated in the overall programme. Consortium intranet (**WP1**) and public webpages (**WP8**) will be implemented for data sharing and dissemination.
- **Cell-Autonomous and Single-Cell System Studies (WP4, Experimental Level 2; B4-PMC).** This package focuses on coordination of training and research projects focused on **molecular-level analyses**, from gene/protein characterizations in CaRes cell models, to **single-cell transcriptome and proteome profiling** in immune and cancer cells. Research activities will centered on the following points: i) measurements of gene/protein/signaling levels in cells and their associations with CaRes phenotypes; ii) integration of empirical measures with *in silico* models, and redefinition of predictions in coordination with **WP3**; iii) testing *in silico* predictions for biomarkers of CaRes using cell/tumor models, and clinical-pathological data from public repositories and participating oncology hospitals; and iv) preclinical cell-based assessment of predictions for therapeutic targets, in coordination with subsequent **WP5-7**. This package will also design a sub-plan of training for molecular and cell studies, which will be delivered to **WP2** and integrated in the programme.
- **Tumor System Studies (WP5, Experimental Level 3; B5-BRIC).** This package will be responsible for coordination of training and research projects focused on **tumor tissue-level analyses**, including ***in situ* single-cell profiling** and **multimarker studies**. Research activities will be centered on the following points: i) *in situ* measurements of gene/protein/signaling levels in tumor specimens and their association with CaRes; ii) integration of empirical measures with *in silico* models, and redefinition of predictions in coordination with **WP3** and **WP4**; iii) testing *in silico* predictions for biomarkers of CaRes in tumors from clinical-pathological public repositories and participating oncology hospitals; and iv) preclinical *in vivo* assessment of predictions for therapeutic targets, in coordination with **WP6** and **WP7**. This package will also design a sub-plan of training for TME-centered studies.
- **Target Discovery (WP6 Experimental Level 4; B8-geneXplain).** Following on the results obtained by **WP3-5**, this package will be responsible for coordination of training and research focused on **target discovery** and **SME activities**. Research activities will be centered on the following points: i) to exploit previous results (**WP3-5**) to identify valuable therapeutic targets and biomarkers; ii) to develop novel algorithms for target/biomarker identification; iii) to build and characterize gene regulatory networks linked to CaRes; and iv) to develop web-based tools to examine cell- and tissue-centered systems-level models of CaRes. Build on the interdisciplinary of **SystemicR**, this package will also be co-responsible of organization of a **workshop on intellectual data protection and business development**[32] (3rd SystemicR meeting, month 27). This workshop will be performed in coordination with leadXpro (**WP7**) and city2science (**WP8**). A training sub-plan including these objectives will be integrated in the overall programme.
- **Drug Discovery (WP7, Experimental Level 4; B9-leadXpro).** Following on the results obtained by **WP3-6**, this package will be responsible for coordination of training and research focused on **drug discovery**. Research activities will be centered on the following points: i) protein structure modeling towards prediction of targetable sites; ii) high-throughput *in silico* and/or experimental screens (depending on each molecular

[32] "Value Intellectual Property for SMEs (VIP4SME)" project funded by the EC to enhance Intellectual Property support to SMEs.

candidate) for drugs and small compounds targeting a given nominee; iii) *in vitro* characterization of initially effective drugs/compounds targeting CaRes; and iv) in cooperation with **WP3-5**, *in vivo* preclinical assays using relevant mouse models for tumor and/or metastasis inhibition studies. As above, a training sub-plan will be integrated.

- **Science Dissemination and Public Engagement (WP8; P1-city2science).** This package will be responsible of implementing, maintaining, and reviewing the **Communication Dissemination and Exploitation Plan**. This plan consists of: i) development of corporate design, logo, related documents and CD Handbook; ii) public website including connections to social media platforms; iii) online newsletter coinciding with each of the consortium meetings detailed in **Table 1.2b** (including major media/press release at middle term); iv) other press conferences alongside meetings and accomplishments of Milestones; v) communication of results to European stakeholders and decision makers (policy briefs 1-3); vi) development of a project YouTube channel documenting activities, results, training and beneficial/partner collaborations; and vii) participation in international scientific, science communication and patient advocacy conferences as panels, instructors, and/or presenting project progress and results. The effectiveness of the plan will be monitored through measurable goals, e.g. Google Analytics. In collaboration with ECPC (**WP9**), this package will provide a **workshop on Public Engagement and Society Dialogues**[33] (1st meeting, month 9), following methodologies of Responsible Research and Innovation, and a **course on Building Trust on Research(ers)**[34].
- **Patient Advocacy (WP9; P2-ECPC).** This package will provide education and training on **patient needs and advocacy**, and how these should be coordinated with research goals and results. A specific **workshop**[35] (2nd meeting, month 18) on this topic will be organized for all ESRs. In addition, a study will be conducted to provide indications for measuring the current social and economical impact of CaRes in European countries. This effort will be coordinated between the national patient association members and representatives of ECPC and the participating oncology centers. The expected deliverables include **CaRes quantification guidelines and workshop report**. Overall population awareness of patient needs will be a key outcome.

The scientific facet of **SystemicR** is contained in **five WPs (3-7)** aimed at **comprehensive understanding of CaRes, from gene/protein analyses to systems-level models, and target and drug discoveries —being all these studies centered on innate immune-cancer cell interactions**. The program will deliver: i) new mechanisms of CaRes; ii) new biomarkers and target candidates to impair CaRes; and iii) drugs and/or small compounds able to reduce or impair CaRes. The ESR research projects are thus designed to tackle a major health care problem from academic and non-academic angles, and from basic, to translational to preclinical levels. Last, but not least, this **innovative programme provides education on translation of findings to SMEs (WP6-7), dissemination and public engagement (WP8), and valorization of patient needs (WP9).** This education is complemented by several local and network-wide courses and workshops (subsequent sections).

1.1.3 Originality and innovative aspects of the research programme

For the first time in the early-training scenario, the established European network will pool relevant expertise, technologies, data and tools of leading researchers and industrial partners to address what is currently the most challenging aspect to improve cancer care: comprehensive biological understanding of CaRes and, as a consequence, finding new ways to prevent this care-limiting phenomenon. The members of the consortium are complementary, ranging from theoretical to preclinical studies, and include balancing academic groups and SMEs. Therefore, substantial ***originality*** of this proposal is based on its ***interdisciplinary*** nature to tackle a ***major health care problem***. Compared to other educational programs, such the "High-Impact Cancer Research Program" of the Harvard University[36], the current proposal overlaps in providing cutting-edge knowledge on cancer biology and therapies, but goes much beyond these topics by offering mathematical, bioinformatics and systems-biology projects, and by providing advanced education on how to translate findings for patient and economic benefits. To fill the training gap towards intellectual protection and business development, **SystemicR** also proposes specific training on this regard (**WP6-7**, **Table 1.2b**). Relative to the currently active ITN CANCERPREV network[37], our proposal also includes expertise on cancer risk studies, but this topic is not the main focus of **SystemicR, so both networks are complementary**. In parallel, **SystemicR** goals and strategy do not overlap with ITN CONTRA, which aims to train ESRs on novel data types and software development[38]; **SystemicR will invite representatives of both ITNs to the first annual meeting (month 9, Table 1.2b) to discuss collaborations and common education.**

The above observations support the ***excellence*** of the current ERS training proposal beyond the current state-of-the-art programs. In addition, we consider **SystemicR** as highly ***innovative*** based on the inclusion of specific training and dedicated WPs to provide the ERSs specialized education on **Public Engagement (WP8) and Patient Advocacy (WP9)**. Patients and advocates have a growing voice in clinical research, trial design and approvals, as well as in funding decisions, following a patient-centered approach; however, their role in the continuum of research activities is still very scarce, which hampers complete understanding and prioritization of patient and population needs. This gap is being approached by, for example, the Scientist-Survivor AACR

[33] Public Engagement Masterclass, 8-10 July, 2019, Wellcome Genome Campus, UK.
[34] Ruhr University of Bochum Research School, BUILDING TRUST IN RESEARCH(ERS), 3 July, 2018.
[35] ECPC-ESO Masterclass in Cancer Patient Advocacy 2018, 23-25 February 2018, Lisbon, Portugal.
[36] High-Impact Cancer Research Program, Harvard Medical School, Boston, MA, USA.
[37] The International Cancer Prevention Institute (ICPI), ITN CANCERPREV.
[38] CONTRA (Computational ONcology TRaining Alliance) ITN Network.

Program[39] and Disease-Oriented Education sessions organized in key conferences (e.g. San Antonio Breast Cancer Conference[40]) or, locally, by the **OpenLab**[41] program by the ICO-IDIBELL. However, none of these approaches provide fundamental training for ERSs that, in turn, will represent the future research and decision-making leaders in the field. To fill this gap, **SystemicR** proposes a specific **WP** (**#9**) lead by a major European patient organization, ECPC[42]. On the top of the limitations by other programs, ERSs and many researchers at different stages do not currently receive or have the opportunity to be trained in Science Dissemination and Public Engagement. The **Public Attitudes to Science 2014 Report**[43] from the UK Ministry of Science highlighted the fundamental dissociation between public interest for science and how science is communicated. This limitation is exemplified by topics like climate change, but noticeably also involves weaknesses in communicating preclinical and clinical cancer research advances. Critically, these limitations influence health care policy makers and funding bodies, which, in turn, may be biasing scientific projects and efforts. In our opinion, and coherent with the WPs design, researchers have a responsibility to clearly explain results and their consequences not only in science conferences and basic media (i.e., tweeting their publications), but also in appropriated channels towards the patients and general population. To fill this gap, **SystemicR** proposes a specific **WP** (**#8**) lead by a relevant expert partner in the corresponding themes, **city2science**[44]. In addition, **SystemicR** includes a course for all ESRs on **Open Science** (month 27), which will provide them with the necessary tools for transparency, reproducibility, dissemination and transfer of obtained results. **SystemicR** aims to enroll an expert in this field to teach this key topic, being the European participatory initiative **OpenAIRE**[45] a reference.

1.2. Quality and innovative aspects of the training programme

SystemicR is an interdisciplinary and cross-sectional program directed at implementing novel and advanced ESR training in a fundamental phenomenon that largely limits cancer care. The ESRs will learn skills in mathematical modeling, statistics, bioinformatics, molecular and cell biology, immunology, developmental biology, human genetics, cancer biology, and clinical oncology via the creation of an accurate combination of local and network-driven research training. Despite these skills might represent a common target for other programs, the **SystemicR** consortium will create an **International & Interdisciplinary PhD Program** dedicated to different university degrees. The students will develop complementary and transferable skills, but also will be trained in entrepreneurship via exposure to SMEs that apply systems-biology approaches for target/drug discovery. The connection among ESRs coming from different disciplines will develop a rich framework, increasing collaborations and synergism. These features will enhance future employability in academic and non-academic environments. The training will be implemented through scientific excellence, reflected in the international reputation of the program members. Further ensuring the viability and promise of **SystemicR**, **several members have participated in successful ITN actions (EpiPredict[46] SAB, B4; GLIOTRAIN[47], B8; TubInTrain[48], B9; and PREDICT[49], P2).** The ***interdisciplinarity*** (**Fig. 1**) integrated into a novel training program is detailed as follows:

- **Level 1 ("in silico"):**
  1. **Cancer omic data integration** with application on determining **macrophage** influence on CaRes and **immune/stromal** associations with tumorigenesis (B1-IDIBELL).
  2. **Theoretical and stochastic/multiscale data modeling** with application on analyzing tumorigenesis and **immune responses** (B3-CRM).
  3. **Cancer genetic/genomic** data analyses with application on **biomarker identification** and associations with **immune cell signatures/phenotypes** (B7-SU).
- **Level 2 (genes/proteins):**
  4. **Epigenetic deregulation** with application on cancer **immune surveillance/evasion** (B2-UniCampania).
  5. **Protein expression, interaction and secretion** with applications in cancer and **immune cell profiling** (B6-DKFZ).
- **Level 3 (cells and tissue):**
  6. **Cell development** studies with application on **innate immune cell function** (B4-PMC).
  7. **TME** studies with application on **immune and stromal cell profiling** (B5-BRIC).
- **Level 4 (transferability, targets/drugs):**
  8. **Target discovery** and development of **bioinformatics and systems-biology tools** (B8-geneXplain).
  9. **Drug discovery** and protein structure modeling and drug screening platform (B9-leadXpro).

The following partners complement the research teams:

10. **Science Dissemination and Public Engagement** (P1-city2science).
11. **Patient advocacy** (P2-ECPC).

[39] AACR's Survivor and Patient Advocacy Program fostering partnerships with survivor advocates.
[40] Patient Advocate Mentor Sessions and Advocate Program at the San Antonio Breast Cancer Symposium (SABCS) 2019.
[41] ICO-IDIBELL organized visits to research laboratories in collaboration with the Catalan Federation of Entities Against Cancer (FECEC).
[42] European Cancer Patient Coalition (ECPC), largest European cancer patients' umbrella organization.
[43] Research and analysis, Public attitudes to science 2014, Department for Business, Innovation & Skills, UK Government.
[44] city2science: Science Communication and Strategy Consulting SME, Germany.
[45] OpenAIRE e-infrastructure, in operation since 2010, ensures availability of Europe's research publications, data and other outputs in an open way.
[46] EpiPredict ITN to train a multidisciplinary cohort of ESRs in a new approach to fully exploit the epigenetics of complex diseases.
[47] Exploiting GLIOblastoma intractability to address European research TRAINing needs in translational brain tumour research, cancer systems medicine and integrative multi-omics, ITN GLIOTRAIN.
[48] TubInTrain ITN on chemistry and biology and focused on the microtubules breakdown associated to neurodegenerative diseases and neurotoxicity.
[49] ECPC takes part in PREDICT as a partner organization involved in courses and offering expertise in patient involvement and advocacy.

The program addresses the **EC goals for superior education, advanced skills, interdisciplinary, networking, innovation, and wide international mobility**. The ESRs will witness first-hand how innovation occurs beyond academia, and how patient, scientific community, and public engagement is accomplished towards positively influencing interests, opinions and policies. While **SystemicR** focuses on a specific topic of CaRes —which otherwise is very broad— we anticipate that our **scheme will be applicable** to other settings for advanced biomedical research training.

1.2.1. Overview and content structure of the training

The **SystemicR** program includes state-of-the-art to development of new methods in genomics and epigenomics (single- and bulk-cell bisulfite-seq), genomic (single and bulk-cell chromatin immunoprecipitation-seq), transcriptomic (single and bulk-cell RNA-seq), proteomic, target and drug discovery, and computational analyses. In addition, the network features expertise in methods for genome and epigenome editing, culture and differentiation of mouse and human cancer stem cells, and RNA fluorescence *in situ* hybridization. Furthermore, the network provides know-how and facilities for advanced **experimentation with disease models in mice** (PDXs and genetically-modified models detailed above). Moreover, the network is embraced in institutes leading **clinical trials and with extensive clinical oncology expertise** (**phase-I clinical unit at B1-ICO-IDIBELL**[50]; in addition to similar units/facilities in **B2-UniCampania** and **B4-PMC**[51]). The Directors of these facilities and key professionals leading clinical trials in these three institutes will be invited to the kick-off and middle term **SystemicR** meetings (other actions may also be engaged depending on collaborations and secondments). The network is also equipped with **unique advanced technologies** enabling recruited fellows to conduct frontline research: **single-cell RNAseq** (B4-PMC), **tumor *in situ* marker analysis** (B5-BRIC), **click-chemistry to study secretory proteins, affinity-enrichment to study protein complexes, and mass spectrometric analyses** (B6-DKFZ).

The **ESRs will be able to learn**: i) fundamental concepts of CaRes; ii) a broad variety of intellectual and analytical approaches build on an interdisciplinary program; iii) a broad variety of techniques, e.g. vast data analyses, integration and modeling, proteomic analyses, single-cell profiling, *in situ* and multimarker tissue analyses, high-throughput phenotypic and drug screening strategies, mouse models, and *ex vivo* assays; iv) connecting *in vitro* and *in vivo* preclinical data towards target and drug discovery; v) intellectual property management, human and animal ethical issues, project management, and entrepreneurship; vi) scientific communication; and vii) responsiveness relative to patient needs and research priorities.

Main soft-skills will be acquired through inter-program mobility and **four mandatory workshops**; additional **soft-skills** will be learned through local training programs (subsequent sections). In agreement with the seven principles of **Innovative Doctoral Training defined by the EU policies** in research career and training, the **SystemicR** programme will be composed of: i) local training; ii) network-wide training; and iii) complementary skills training. The cross-disciplinary nature of the programme will prepare the trainees for careers in different settings, improving scientific non-scientific excellence, and enhancing **employability** and **entrepreneurship**.

Personal Career Development Plan (PCDP). Each ESR will define her/his PCDP (month 2 after recruitment) with **TC** and **supervisors** guidance (section 1.3.2). The PCDP will include periodical assessment and re-setting of goals. In the first step of the PCDP, the initial goals will be set and the trainees, their supervisors and TC will plan how these goals will be met and will identify training needs in accordance with the plan, in which **secondment** in partner-labs will be an essential feature to receive training and gain skills. All goals, training and research progress will be documented and will be reviewed every six months (section 1.3.2). The training program developed from the PCDP will include a balance of training in scientific/technological, transferable and soft-skills. Formal assessments will be made at network meetings through mandatory presentations. For each **secondment**, there will be a preliminary supervising meeting between the beneficiaries, biweekly meetings between the groups, and a final report, which will be evaluated by the supervisors and TC, with the advice of the SAB, and finally approved by the SB (section 1.3.2).

Local training. This will ensure: i) training in scientific methodology, integrity and rigor of thinking, and applying this education to research decisions; ii) developing the ability to critically evaluate scientific evidence; iii) acquiring knowledge of the power of different disciplines to address complex questions; iv) instructing on continuous supervision; and v) learning ethical research guidelines and protocols regarding animals and human studies. Each participating academic institute has in place:

Laboratory meetings, journal clubs, and seminar series. Each academic laboratory runs weekly lab meetings in which the members report progress, joint lab meetings with other groups working on related topics, and regular literature reviews to present and discuss important novel findings in the field. These local forums will expose ESRs to excellent laboratories and offer them intellectual stimulus for collaborations between researchers with different backgrounds.

Courses. Three central themes will be the focus of local courses: **i) research techniques and experimental design; ii) advanced statistics, R software and data analysis; and iii) animal research practices and ethics**. These courses will be provided by the local PhD programs in which they are enrolled and/or by the corresponding host

[50] Functional Phase I ICO Unit aims to contribute to improve cancer therapies and to offer the best therapeutic alternatives.
[51] Trial and Data Center of the PCM.

institutes. In line with specific needs of each fellow, academic institutions will also provide courses in language,

job application training, scientific writing and/or management skills (career development, communication and other advanced trainings are included in the annual meeting programs; Table 1.2b).
Local communication and patient association interactions. Each PI will coordinate their Institutional Communication Officers with the partners responsible of Dissemination and Public Engagement (**WP8**) and Patient Advocacy (**WP9**) to implement the corresponding training. This includes communication with local media and ESR presentations at local patient associations (e.g., **B1-IDIBELL** interaction with the **Catalan Federation of Entities Against Cancer**[52]), which in turn will feed the objectives of the network at the European level.

Network-wide training. Access to a full range of different methodologies and tools being applied to CaRes studies is not available at any single local institution within **SystemicR**. To ensure and supervise the novel opportunities, several mechanisms have been planned and, among them, **Secondments constitute the essential program backbone**. **Each fellow will make at least one secondment (1 (several) – 12 (single) months/each)** in one of the other participants to execute a project on an innate immune-cancer interaction subject. Each secondment has been carefully chosen based on partner discussions and the needs of each individual project, as detailed in Table 3.1d. However, secondment might need to be modified based on parallel scientific advances and/or unanticipated subjects; in these cases, the TC will have to approve the changes agreed between a given ESR and her/his supervisors, always considering the advice of the SAB, and coordinated with the SB and EC.
Public website. Instrument focused on providing programme information, opportunities, and dissemination. This tool will include the following fields: i) PhD program overview; ii) description of consortium structure, laboratories and research projects; iii) application instructions and portal; iv) detailed explanation of visits and scholars program; v) outreach and publications; vi) organized workshops and courses; vii) communication and public engagement stories; and viii) patient advocacy forum and news. This webpage will be constructed by **WP8** and hosted at the coordinating institution, B1-IDIBELL (delivery month 3).
Intranet. The intranet will serve for program coordination and continuous ESR supervision, being private to each student-supervisor. It will also assist on SAB coordination, and will be key for unpublished data sharing, wiki-methods, protocols, troubleshooting, and scientific network discussions. The intranet will be constructed in coordination by **WP1** (B1-IDIBELL) and **WP8** (P1-city2science), and hosted in B1-IDIBELL linked to the public website (delivery month 3).
Consortium meetings. PIs and fellows of the same WP and/or linked by secondments will have regular monthly teleconferences to discuss plans, progress and/or share data and results. **Six consortium meetings** have been agreed with mandatory participation for all network members (including **SAB**). Each meeting is planned to be of **four days with the following sections** (**Fig. 3**):

1. **Scientific training**: Presentation of all individual ESR projects and lectures by **SystemicR** PIs from a bottom-up research order (Fig. 1).
2. **Invited speakers**: at least on academic keynote on a relevant research topic and one private/non-profit expert on a non-scientific topic/training included in **SystemicR**.
3. **Workshop**: one per meeting (full/half-day) addressing a major topic of **SystemicR**. The following workshops and their organizers are planned in this order:
   - *Science Communication and Public Engagement (P1-city2science, month 9)*
   - *Patient Needs, Advocacy, Health Care Policies and Research Priorities (P2-ECPC, month 18)*
   - *Intellectual Data Protection and Business Development (SMEs and external[53], month 27)*
   - *Bridging the Preclinical-Clinical Boundary; Essentials of Clinical Studies and Trials (external, SystemicR aims to contract the European Centre for Clinical Research Training to provide this workshop[54], month 36)*
4. **Courses**: two courses per meeting (2-4 hours/each) have been planed as follows:
   - *Big Data Oncology (B1-IDIBELL, B3-CRM, B7-SU, month 9)*
   - *Planning and Managing your Career (external[55], month 9)*
   - *Single-Cell Genomic and Proteomic Profiling (B4-PCM, B6-DKFZ, month 18)*
   - *Building Trust on Research(ers) (P1-city2science, , month 18)*
   - *Tumor Heterogeneity and Cancer Therapy (B5-BRIC and external, month 27)*
   - *Open Science (external, OpenAIRE[56], month 27)*
   - *Current and Novel Immunotherapies (B2-UniCampania, month 36)*
   - *Academic and Non-Academic Career Orientation (external[57], month 36)*

Fig. 3. Annual meetings (2nd-5th) schedule. *This schedule may be modified depending on duration of each specific workshop/course, keynotes, etc.*

Day 1	Day 2	Day 3	Day 4
Governance, updates, committees meetings	*Private*	*Private*	*Public*
Invited Keynotes: 1 academic 1 non-academic	ESR presentations PI presentations	ESR presentations PI presentations	1 scientific course 1 soft-skills course
Public			*Private*
Workshop (half-day)	ESR presentations PI presentations	ESR presentations PI presentations	Challenge

[52] ProCURE ICO-IDBELL research program presentation through the FECEC.
[53] "Intellectual property in H2020: The research and innovation currency", RTDS group publication, EU funding consulting and services.
[54] European Centre for Clinical Research Training (ECCRT) training courses.
[55] "Planning and Managing your Research and your Career", Trinity Careers Service, Dublin, Ireland.
[56] OpenAIRE e-infrastructure, in operation since 2010, ensures availability of Europe's research publications, data and other outputs in an open way.
[57] "Career Guidance for PhD's and Postdocs", VIB Life Sciences Research Institute, Leuven, Belgium.

5. Challenges: At the end of each the 2nd-5th meetings, the ESRs will prove the knowledge acquired by facing real-case based tests that they will need to solve in groups. Each group will collaboratively work on, propose and present a solution to the problem exposed, and a jury composed by PIs (2) and ESRs (2) will proclaim a winner. The **four Challenges** will cover: 1st, *integration of omic data to uncover immune-cancer cell interactions*; 2nd, *heterogeneity and relevance of single-cell phenotypes*; 3rd, *targeted CaRes therapeutic approaches based on immune-cancer cell interactions*; and 4th, *novel immunotherapies based on the acquired knowledge through the program.* Therefore, **the designed Challenges are centered on the aims of the program and will prove ESRs capabilities for problem analyzing and solving, teamwork and presentation skills.**

A **kick-off meeting** with all 11 group/organization representatives plus the **SAB** and **Clinical Trial Unit Directors/Representatives** (3 included) will take place in month 2, and will include a course for ***Mentoring and Coaching Researchers***[58] **for PIs** (external provider). A **final symposium** (month 45) will be co-organized with an **International Conference on CaRes** and will include a **public debate** on CaRes, analogous to previously co-organized by B1-IDIBELL and Biocat[59]. The costs of the meetings will be covered by the overheads of all of the beneficiaries according to the number of fellows (**Table 1.2a**), but independent resources will fund the conference.
Complementary training. As introduced above, there are defined a minimum of **three topics for local courses** and all ESRs will be encouraged to consider these common themes in their PCDPs. The consortium is aware that career success may require further specific training. Thus, SystemicR partners have agreed to dedicate a percentage (10%) of the training budget to **specific ESR interests** that may arise during execution of the program. Each ESR will have access to at least one of such specific training during her/his PhD, in agreement with the TC, supervisors, and her/his PCDP.

1.2.2. Role of non-academic sector in the training programme

The **SystemicR** scheme includes **four non-academic contributors**, two of them being beneficiaries. The expertise, projects, and training tasks assigned to the non-academic SMEs/organizations are fundamental for a successful interdisciplinary education in **SystemicR**.
geneXplain (B8, WP6, Level 4) is a company that offers a **platform for bioinformatics, cheminformatics and systems-biology studies in biomedicine**. The goal is to assist translational research in the context of personalized medicine and pharmacogenomics. The company has developed tools that are widely used (e.g., TRANSFAC[60]). It has also established collaborative agreements with numerous academic and pharma partners and is involved in several EU projects[61]. **SystemicR** will benefit from the expertise obtained in COLOSSUS[62] (precision medicine for metastatic colorectal cancer), OxidoCurin[63] (targets and biomarkers of novel anticancer compounds inducing cancer oxidative stress), miRCol[64] (identification of miRNA-TF network motifs for drug repurposing to treat colorectal liver metastasis) and MyPathSem[65] (data integration platform to generate patient-specific signaling pathways for personalized medicine). It will host **ESR14** (see **Table 3.1b** for individual project and secondments).
leadXpro (B9, WP7, Level 4) is a drug discovery company specialized in membrane proteins, such as G protein-coupled receptors, ion-channels, and transporters. **It develops and applies biophysical and structure-based methods for the discovery and optimization of compounds with unmet efficacy and specificity**. Its technology is funded on expert knowledge and is accompanied by external collaborations providing assays on the synchrotron, X-ray free electron laser, and cryo-electron microscopy. Additional technologies include a variety of biophysical methods (ligand affinity binding, binding kinetics, and stoichiometry), production of membrane proteins for structural and biochemical studies, serial X-ray crystallography, computational chemistry, and antibody/nanobody discovery. Strategic to provide training on entrepreneurship, leadXpro also has numerous pharma collaborations[66] (e.g., BASF, Bayer, Boehringer Ingelheim, and Sanofi). It will host **ESR15** (**Table 3.1b**).
city2science (P1, WP8) is a company dedicated to science communication, strategy consulting and public engagement. It develops strategic alliances between cities, individuals and institutions, and develops innovative formats of science communication and engagement. The CEO is Executive Director of the **European Science Engagement Association** (**EUSEA**)[67], which organizes Researchers' Meetings, Science Parliaments, and Public Debates connecting scientists, populations and policy makers. In cooperation with EURIDA, city2science also

[58] "European Network of Mentoring Programmes for the Advancement of Equal Opportunities and Cultural and Institutional Change in Academia and Research", Heinrich-Heine-University Dusseldorf, Germany.
[59] "B·Debate: Cancer Therapeutic Resistance: Progress and Perspectives", 7-8 April, 2016, Barcelona, Spain.
[60] TRANSFAC® is a database of eukaryotic transcription factors, their genomic binding sites and DNA-binding profiles.
[61] Partners of geneXplain research projects and business development.
[62] COLOSSUS, EU-funded H2020 project to study new and more effective ways to classify colorectal cancer patients and to develop better treatments.
[63] OxidoCurin, Eurostars, SME-driven project for "Targets and biomarkers of novel anticancer compounds inducing oxidative stress in cancer cells".
[64] miRCol, German-Russian Funding Competition in the Area of Industry-Oriented Applied Research and Cooperation of Innovative SMEs 2016, "Identification of miRNA-transcription factor network motifs to search for drug repurposing candidates in the treatment of colorectal liver metastasis".
[65] MyPathSem project: "A data integration platform for generating patient-specific signaling pathways for personalized treatment decisions in clinical applications".
[66] leadXpro industrial and pharmaceutical partners.
[67] EUSEA is an international knowledge-sharing platform and accelerator of innovation in the fields of public engagement.
[67] "HORIZON 2020: Project Impact through Science Communication and Stakeholder Engagement", and "HORIZON 2020 and its Impact on Science Communication and Policy Making in Europe", January and April 2014, Berlin.
[67] ECPC works for a Europe of equality, where all European cancer patients have timely and affordable access to the best treatment and care available, throughout their life.

organizes strategy workshops within the HORIZON 2020 framework[68]. Therefore, the expertise of city2science stands as a perfect balance in **SystemicR**, including organization of workshops and courses (**Table 1.2b**).
ECPC (P2, WP9) is the major voice of cancer patients in Europe. With over 450 members, it is the largest patients' association umbrella, covering all 28 EU member states. ECPC represents patients affected by all types of cancers. Thus, the ECPC Missions[69] are in fully accordance with **SystemicR** goals: to empower European cancer patients through dissemination of information, to make cancer a priority for action in the European health policy agenda, and to foster patients voice in cancer research. ECPC and the consortium believe that cancer patients are the most important partners in the fight against cancer, so the corresponding training is fundamental for all ESRs.

Table 1.2a. Recruitment deliverables per beneficiary.

Researcher No.	Recruiting Participant	PhD awarding entities	Planned Start Month	Duration (months)
1	IDIBELL (a)	Univ. Barcelona	6	36
2	IDIBELL (b)	Univ. Barcelona	6	36
3	UniCampania (a)	Univ.Campania Luigi Vanvitelli	6	36
4	UniCampania (b)	Univ.Campania Luigi Vanvitelli	6	36
5	CRM (a)	Univ. Autonomous Barcelona	6	36
6	CRM (b)	Univ. Autonomous Barcelona	6	36
7	PMC (a)	Radboud Univ.	6	36
8	PMC (b)	Radboud Univ.	6	36
9	BRIC (a)	Univ. Copenhagen (UCPH)	6	36
10	BRIC (b)	Univ. Copenhagen (UCPH)	6	36
11	DKFZ (a)	Univ. Heidelberg	6	36
12	DKFZ (b)	Univ. Heidelberg	6	36
13	SU	Semmelweis Univ.	6	36
14	geneXplain	Univ. Goettingen	6	36
15	leadXpro	Univ. Basel	6	36
Total: 15				

Table 1.2b. Main training events, conference, and contribution of beneficiaries (*Typically 1 ECTS/20 hours, but specific equivalences will be defined by each PhD awarding institution).

Event	Main Training Events & Conferences	ECTS (*if any*)	Lead Institution	Action Month (*estimated*)
1	**KICK-OFF MEETING** - SB and TC presentations, and SAB introduction. - TC leading discussion and agreement on PCDP protocol. - Presentation of **all research projects** and **press release (WP8)**. **Course for all PIs:** - Mentoring and Coaching Researchers (**external**).	*	IDIBELL (ES)	1
2	**1st SystemicR meeting:** **1A. Scientific training**: Presentation of ALL individual ESR projects and lectures by initial bottom-up project PIs: **B1, B3, B7**. **1B. Invited speakers:** 1) **academic keynote on innate and adaptive immune response in CaRes**; 2) leaders of **ITN CANCERPREV** and **ITN CONTRA**. **1C. Workshop:** Science Communication and Public Engagement (**P1**). **1D. Courses:** - Big Data Oncology (**B1, B3, B7**). - Planning and Managing your Career (**external**). **1E. 1st SystemicR CHALLENGE.** **1F. Voting of ESRs to establish and initiate the EC.**	*	UniCampania (IT)	9

3	**2nd SystemicR meeting:** **2A. Scientific training***:* Presentation of ALL individual ESR projects and lectures by subsequent bottom-up projects: **B2, B6**. ***Middle term major press release and conference.*** **2B. Invited speakers:** 1) **academic keynote** on **integrative genomics and cancer systems biology in CaRes**; 2) **EU representative** on cancer care policy and research strategy. **2C. Workshop:** Patient Needs, Advocacy, Health Care Policies and Research Priorities (**P2**). **2D. Courses:** - Single-Cell Genomic and Proteomic Profiling (**B4, B6**). - Building Trust on Research(ers) (**P1**). **2E. 2nd SystemicR CHALLENGE.**	*	PMC (NL)	18
4	**3rd SystemicR meeting:** **3A. Scientific training***:* Presentation of ALL individual ESR projects and lectures by subsequent bottom-up projects: **B4, B5**. **3B. Invited speakers:** 1) **academic keynote** on **TME influence on CaRes**; 2) leader on science communication (**SCi25**). **3C. Workshop:** Intellectual Data Protection and Business Development (**B8, B9** and **external**). **3D. Courses:** - Tumor Heterogeneity and Cancer Therapy (**B5** and **external**). - Open Science (**external, OpenAIRE**). **3E. 3rd SystemicR CHALLENGE.**	*	BRIC (DK)	27
5	**4th SystemicR meeting:** **4A. Scientific training***:* Presentation of ALL individual ESR projects and lectures by subsequent bottom-up project: **B8, B9**. **4B. Invited speakers: 1) academic keynote** on **drug discovery targeting CaRes**; and 2) leader from the **private sector (e.g., Bristol-Myers Squibb)**. **4C. Workshop:** Bridging the Preclinical-Clinical Boundary: Essentials of Clinical Studies and Trials (**external, ECCRT**). **4D. Courses:** - Current and Novel Immunotherapies (**B2**) - Academic and Non-Academic Career Orientation (**external**) **4E. 4th SystemicR CHALLENGE.**	*	leadXpro (CH)	36
6	**FINAL REVIEW SystemicR:** Presentation of ALL individual ESR projects, **SystemicR** results and outcomes from each WP. It will open to the public and scientific community. • **SystemicR organization in parallel with an International Conference on CaRes (expected ~300 attendees)** • To include an **open debate** including researchers, policy makers, SMEs and patient representatives: "**Collective European Battle Against CaRes**".	*	IDIBELL (ES)	45

1.3 Quality of the supervision

1.3.1 Qualifications and supervision experience of supervisors

All **SystemicR** institutions have PIs with the appropriate expertise in supervision and training of ESRs (**Table 1.3**), and several have been actively involved in EU-funded research and training projects, as detailed above. **The nine beneficiary groups encompass experience as supervisors of >100 PhD theses and >100 Master' students. Several of them also teach in PhD/MSc programs and/or have major responsibilities directing research departments.**

Table 1.3. Supervisors' experience.

Group B1	**Miquel Angel Pujana**
Outputs: supervisor of 6 completed PhD theses and 12 Master' projects; 2 active PhD projects. **Other relevant information**: Interdisciplinary theses as supervisor combining bioinformatics and cancer biology studies (e.g., "Molecular Networks and Cancer", J Serra-Musach, 2018 PhD degree Mathematics). Director a ProCURE research program including 55 researchers, ~70% ESRs.	
Group B2	**Lucia Altucci**
Outputs: supervisor of >20 PhD theses and >20 Master' projects; 8 active PhD projects. **Other relevant information**: director/supervision/teaching five PhD programs with interdisciplinary (medical students, sanitary professions, and biologists).	

Group B3 (a)	Tomas Alarcón
Outputs: supervisor of 6 PhD theses and 5 Master' projects; 1 active PhD project. **Other relevant information:** co-supervisor of one Industrial Doctorate (ongoing), one PhD co-supervised with a PI ICO-IDIBELL under the LaCaixa-CRM Collaborative Mathematics interdisciplinary programme. Teaching a MSc course on Applied Stochastic Processes for the last five years (70 students approx.)	
Group B3 (b)	**Isabel Serra**
Outputs: supervisor of 5 Master' projects and 3 active PhD students. **Other relevant information:** Teaching MSc courses at the Univ. Autonomous of Barcelona (awarding PhD entitity) on Mathematics in Big data and Statistical Modeling.	
Group B4	**Henk Stunnenberg**
Outputs: supervisor of >50 PhD thesis, >30 Master projects; 5 active PhD projects. **Other relevant information:** research and training collaborations in imaging (Anne Rios at PMC and Peter Friedl at Radboud UMC), *in situ* sequencing (Mats Nilsson, SciLifeLab), mass spectrometry (Michiel Vermeulen, Radboud UMC), immunology (Mihai Netea, Radboud UMC).	
Group B5	**Janine Erler**
Outputs: supervisor of 6 completed PhD theses (plus 4 as co-supervisor) and 12 Masters projects; 3 active PhD projects. **Other relevant information:** Yearly teaching on Matrix Biology PhD course. Organizer of EU-Life PhD course "Tumor Microenvironment and Metastasis" (2016 to 2019).	
Group B6	**Jeroen Krijgsveld**
Outputs: supervisor of 8 completed PhD theses and 14 Master/Bachelor projects; 5 active PhD projects. **Other relevant information:** teaching in two PhD programs, of Systems biology and Cancer biology. Coordinator of EMBO course in proteomics.	
Group B7	**Balázs Győrffy**
Outputs: supervisor of 7 completed PhD theses and 29 Master' projects; 3 active PhD projects. **Other relevant information**: Teaching pathology, pediatrics, bioinformatics at degree level, and all projects are based on the simultaneous studies of medicine and bioinformatics.	
Group B8	**Alexander Kel**
Outputs: supervisor of 3 PhD theses and 6 Master' projects; 2 active PhD projects. **Other relevant information:** research and training collaborations in bioinformatics education (with Dr. Pedro Fernandes, Gulbenkian, Portugal). Supervision of software development on promoter and pathway analysis (biosoft.ru, Novosibirsk, Russia).	
Group B9	**Michael Hennig**
Outputs: supervisor of 5 PhD theses and 3 Master' projects; 1 active PhD project. **Other relevant information:** teaching as guest professor at the University of Basel in Structural Biology for the Master and PhD programs. The PI and leadXpro also participate in the training of a PhD student within the ITN TubInTrain.	

1.3.2 Quality of the joint supervision arrangements

Supervision scheme. Each ESR is assigned a well-identified supervisor at the employing organization (**Beneficiary Supervisor** (**BS**)). Co-supervision with a PI (**Co-Supervisor** (**CS**)) from a different beneficiary is implemented for all projects prior to the starting of each project, and the **CSs are selected among the corresponding secondments** to facilitate training coordination and research synergies. The **BS** and **CS** are detailed in the individual ESR research projects (**Table 3.1d**); **CSs** have been agreed among the **principal or final term secondments** to provide supervision over the complete training period. In addition to this dual coordination and continuous supervision, each ESR will also have a **University Supervisor** (**US**) affiliated to the corresponding PhD programme of the PhD awarding entity (**Table 1.2a**).

The **TC** (committees/boards defined in section 1.1.2, WP1) has a key role in the overall supervision scheme and is chaired by a renowned scientist (**L Altucci, B2**) with extensive experience in PhD management, teaching and participation in EU projects. Cutting-edge technology training and industrial participation are also integrated into the **TC** (i.e., B6-Krijgsveld and B9-Hennig). The **TC** will set the training standards as well as plan, coordinate and monitor them. The **TC** will also promote continuous communication and exchange of best practice among the network participants to optimize and maximize the benefits of the partnership. The **SystemicR** framework also implements strategies for managing stress and problem resolution between ESRs and between ESRs-supervisors (**WP2**). On this regard, in addition to local and network-wide courses, each ESR will provide feedback concerning training and supervision quality at institute and at network-wide level by filling up **questionnaires once every six months**. The **TC** and **EC** will evaluate these questionnaires, and if subsequent actions are required, they will be discussed with the **ESR** and **BS-CS-US**, with **TC-EC** acting as mediators.

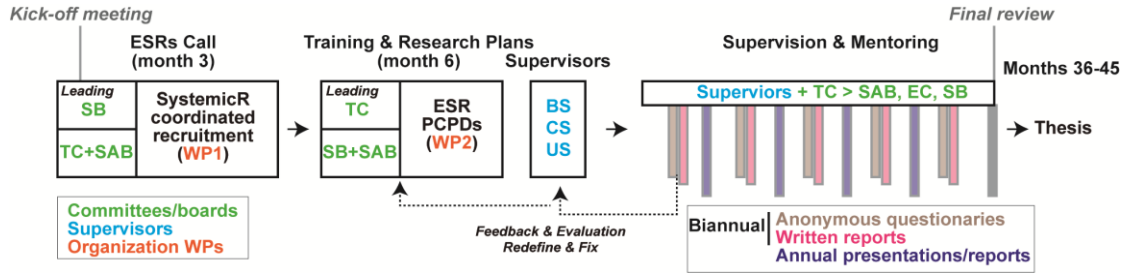
Supervision and mentoring. This process will take place at two levels. A **first level** involves ESR mentoring by the direct supervisors (**BS**, **CS**, and **US**), who will be the responsible for guiding the execution of the research plan and to ensure that the aims of the training and scientific project are met. All doctoral schools will provide PhD tuition to the incoming ESRs according to their regulations. In general, tuition includes at least 120 hours of compulsory training in science and complementary skills within the 3-year PhD course. The **TC** and **EC** will make sure that the local training is as much as possible complementary and non-overlapping with the network training. The **TC** will also ensure that all ESRs obtain approximately equal exposure to appropriate local and network-wide courses. Depending on each doctoral school, a university committee may also assess progress once a year and will definitively evaluate the final thesis defense to award the doctoral degree. All academic participant and partner institutions have the infrastructure required for teaching and research. On a **second level**, the **ESR and supervisors will report progress biannually to the TC** (subsequent section details the mechanisms). In turn, the **TC** in coordination with the supervisors will issue recommendations and advice to the ESR and will, if necessary,

mediate between the ESR and supervisor(s) at the request of either side. Upon recruitment, the TC will guide ESRs through the spectrum of training opportunities, and drafting the PCDP will coordinate this. All ESRs will be encouraged to complete their doctoral thesis within the project duration; if needed, the beneficiaries will grant access to the infrastructures on a best effort basis beyond the initial ESR appointment to complete the thesis.

Training quality will be monitored using **quantitative** (questionnaire) and **qualitative** (presentations, publications) indicators, as well as **verbal feedback** from fellows (**Fig. 4**). For each ESR, three mechanisms of progress recording have been be established:

1) **PCDP** (drafted within first two months of recruitment) will be defined in cooperation with the supervisors and **TC**, and based on EU-ITN normalized template. It includes supervision agreement between employer and university, scientific and training objectives, course selection and milestones. Each plan is provided to the **SB** and should be approved by the **SAB**. It will be updated on a biannual schedule by the ESR, supervisors and TC.
2) **6-month written reports and questionnaires** to the **supervisors** and **TC,** and then to the **SB** and **SAB**.
3) **Research project status report (annual)**, doctoral study progress review, risk identification and mitigation are fixed items on the **supervisory** and **SAB** agenda, coordinated with the annual meetings and questionnaires mentioned above.

Fig. 4. Supervision and mentoring scheme of SystmicR.



1.4 Quality of the proposed interaction between the participating organizations

1.4.1. Contribution of all participating organizations to the research and training programme

All participants will actively contribute to the **SystemicR** research and training program: as defined, through complementary **WPs** (**Table 1.1**), **committees** (**section 1.1.2**), **workshops/courses** (**Table 1.2b**), and **supervision** and **secondments** (**Table 3.1d**). All beneficiaries including the SMEs will recruit ESRs and will train them in their groups/institutions and during secondments by collaborative research projects (**Table 3.1d**). Furthermore, all academic beneficiaries and the **partner** organizations will contribute to annual workshops and/or courses (**Table 1.2b**). On this foundation, the anticipated success of **SystemicR** also lies on the intellectual and technological ***interdisciplinarity*** of the groups, which are putting together training expertise to study a ***timely*** health care problem. The activities are conducted in a bottom-up workflow with feedback loops within and between the groups/WPs to ensure the ultimate goals of each project are achieved; which are commonly directed at deciphering the influence of innate immune-cancer cell interactions on CaRes, and to impair this phenomenon though therapeutic target and drug discovery.

1.4.2. Synergies between participants

The network's training extends beyond the capacities of any single group:

- The PIs from IDIBELL (**B1**), CRM (**B3, WP coordinator**), SU (**B7**), and geneXplain (**B8**) will contribute to **WP2** through their expertise in mathematics, statistics, bioinformatics and systems biology.
- The PIs from UniCampania (**B2**), PMC (**B4, WP coordinator**), and DKFZ (**B6**) will contribute to **WP3** through their expertise in epigenetics, proteomics and cellular profiling.
- The PIs from BRIC (**B5, WP coordinator**), IDIBELL (**B1**), UniCampania (**B2**), and PMC (**B4**) will contribute to **WP4** through their expertise in tumor and animal studies.
- The PIs from geneXplain (**B8, WP coordinator**), IDIBELL (**B1**), DKFZ (**B6**), SU (**B7**), and leadXpro (**B9**) will contribute to **WP5** through their expertise in target identification and characterization.
- The PIs from and leadXpro (**B9, WP coordinator**), UniCampania (**B2**), PMC (**B4**), DKFZ (**B6**), and geneXplain (**B8**) will contribute to **WP6** through their expertise in target-drug screens, drug discovery and development.

1.4.3. Exposure of recruited researchers to different research environments, and the complementarity thereof

SystemicR is designed to get maximum value from existing resources within the network; from *in silico* modeling to *in vivo* mouse preclinical studies, and from molecular/target modeling to drug discovery and development. This innovative training will be possible by **secondments** that have been carefully defined to combine expertise and technologies (**Table 3.1d**). **Each ESR will undertake at least one research secondment**. The **supervisors**, in coordination with the **TC** and with advice of the **SAB**, will ensure that successful synergies are established to enhance the collaborative spirit amongst the fellows and research groups, institutions and non-profit organizations. On the top of advanced scientific training, **SystemicR** comprises at least four network-wide workshops and eight courses combining unique scientific and soft-skills relevant to the overall program. These workshops and courses will be complemented with local and on-demand specific training (section 1.2.1).

2. IMPACT

2.1 Enhancing the career perspectives and employability of researchers and contribution to their skills development

SystemicR is designed to create an environment of international and multidisciplinary research that provides much needed training to improve cancer care. Thus, **SystemicR** will produce a cohort of **top-ranked researchers (Impact #1)** who should be able to make a significant contribution to EU competitiveness **(Impact #2)** by applying their advanced skills in the academic, industrial and/or non-profit sectors. Their unique qualities will enhance ESR employability (**Impact #3**), and SystemicR laboratories have demonstrated capability on this regard (UniCampania ITN Ocean Medicine PhDs). In parallel, the program, and further collaborative actions expected to be developed among the partners, will improve and harmonize training standards, and create a unique European collaborative and research background in the field of CaRes **(Impact #4)**. No other training program offers these benefits focused on improving disease care, at the same time that integrates social awareness and patient needs.

The depicted **secondments are central to the above impacts** and will contribute to considerably enrich the ESR technical and scientific curriculums, while also improve the research activities and outputs of the corresponding groups and SMEs. Thus, the **skills acquired by the fellows will be**:

- **Integrity, mature scientific character, and inspiration** on dedicated **continuous supervision** and **mentoring**, which in turn will build a culture of long-term support (*alumni* generations);
- **Holistic thinking to confront complex disease questions**, being able to integrate different approaches and methodologies, and therefore making the fellows highly competitive for prestigious subsequent career moves in both academia and industry;
- **Translational knowledge towards the private and clinical scenarios**, combined with expected high-impact publications that will help the fellows in seeking career development;
- **Influence on public opinion and policy makers**, with recognition gained across the network and widely via interactions with key professionals and by high-impact dissemination and communication of results;
- **Awareness of patients' priorities and needs**, largely thanks to interplay and training with key European patient representatives and associations.

The depicted **impacts** are reinforced by the organization of an **international conference on CaRes** coinciding with the **final network meeting** (month 45). This will be a unique opportunity for presenting results, benefits from the interdisciplinary training and technological collaborations, as well as a matchmaking opportunity for **SystemicR** ESRs for their future career moves.

The partners also envisage relevant benefits at the European social (**Impact #4**) and health care policy (**Impact #5**) levels. Tasks contributed by **WP8** and **WP9** are directed towards achieving these benefits. They include newsletters coinciding with each of the consortium meetings, press conferences alongside these meetings and accomplishments, direct communication with national and EU policy makers, active participation in scientific and patient conferences, and recommendations to evaluate CaRes in Europe. As **key actions**, there will be major press releases at the **first, middle and final terms of the program** (organized by P1-city2science). Regarding influence on policy-making, there will be **direct contacts with national** (i.e., health care government secretaries) and **EU representatives** (i.e., Health Commissioner Stella Kyriakides), as well as joint scientific-ECPC presentations at two key European conferences, ESMO[70] and EARC[71] (initial presentation planned in the 2021 meetings). The contacts and invitations to target national and EU representatives will be initiated by P2-ECPC, and a EU keynote speaker will be invited at the middle meeting term (month 18).

The **impact** of **SystemicR** will be achieved by: i) yielding top-ranked PhDs employability; ii) enhancing EU academic and industrial competitiveness; iii) establishing a unique interdisciplinary and collaborative cancer research network; iv) enhancing population engagement and awareness on cancer care and patient needs; and v) influencing policy makers towards the relevance of the problem and the benefit of interdisciplinary European actions.

2.2. Contribution to structuring doctoral/ESR training at the European level and to strengthening European innovation capacity

Biomedical research in human disease is increasingly multidisciplinary and researchers require awareness on a wide portfolio of advanced techniques. Despite a universal recognition of this reality, current practices provide training that is fragmented and based around single disciplines and sectors. This does not capture the complexity of what happens in diseased tissue and, therefore, such a narrow perspective harms researchers' international competitiveness. **SystemicR** brings together diverse, but complementary expertise and techniques from both academia and industry to provide training that crosses traditional boundaries, hence producing researchers **'ready for the future' (contribution #1)**. Through an integrated approach and employing state-of-the-art technologies, the network aims to characterize the cellular and tissue systems underlying CaRes and their impact on disease treatment. This approach will establish an **innovative training model applicable to other biomedical areas** and particularly relevant to complex polygenic human diseases **(contribution #2)**. Thus, **SystemicR** will train students coming from diverse degrees, including Biology, Computer Engineering, Chemistry, Mathematics,

[70] ESMO Patient Advocates Working Group, 2019.
[71] EACR Cancer Conference Hub and Calendar.

Medicine, Physics, among others. This interdisciplinarity will in turn enhance collaborations, and methodological and technological developments, which should contribute to make **Europe a greater competitive and dynamic knowledge-based economy (contribution #3)**.

Some partners have had previous successful PhD exchanges, leading to joint publications[72,73], which provides a solid base for the successful development of new ones. Improved working relationships will promote the shearing of **best practices in research and strengthen individual teams**, while interdisciplinary interaction will **broaden research agendas**, facilitating the cross-application of techniques and the integration of approaches **(contribution #4)**. **SystemicR** will therefore contribute to increase group sizes and training volume, promoting further collaborative applications. It is also anticipated that the approach will have a **significant impact on training practices (contribution #5)**. Interactions with more experienced colleagues will have a positive impact on the less experienced ones, who will learn the highest professional standards for supervision. Longer-term benefits are expected as fellows advance through their careers and become supervisors, when the structured **SystemicR** experience will provide a model for their own practice. The network also aims at educating fellows on shared standards for **Open Data** and exploitation. This effort will spread seeds in Europe for tomorrow's optimized research collaborations on e-resources and registries. This mutual recognition will again improve career prospects and employability of the ESRs. Moreover, it will promote common education standards in a trans-European network, which is prerequisite for harmonizing ESR programs across the EU and increasing the attractiveness of Europe as a destination for obtaining the highest standards of training.

SystemicR will contribute to structure European ESR training by delivering: i) interdisciplinary PhDs; ii) proved practices and supervision within a broad program applicable "beyond-cancer"; iii) enhanced economic competitiveness and translation innovation; iv) reinforcement of research groups; and v) improvement of training practices, sharing and exploiting open data in the context of multidisciplinary collaborations.

2.2.1 Meaningful contribution of the non-academic sector to the doctoral/research training (as appropriate to the implementation mode and research field)

SystemicR considers critical to establish and strength long-lasting strategic academic-non-academic partnerships to finally benefit the European economy and educational system. The WPs, research projects and secondments, and workshop/courses offer real potential to remove barriers between both worlds. To accomplish this, the non-academic beneficiary and partner institutions will play active roles in the training program; for example, organization and teaching of workshops (Science Communication and Public Engagement, P1-city2sciece; Patient Needs, Advocacy, Health Care Policies and Research Priorities, P2-ECPC; and Intellectual Data Protection and Business Development, SMEs B8 and B9) and courses (Building Trust on Research(ers), P1-city2science). The non-academic partners will also have a major role on communicating the program features, results and achievements at the European level, in addition to embracing patients and associations, and influencing local and EU decision and policy makers.

In parallel to the above responsibilities, the role of the private sector is key on many ESR projects: **11 secondments include an SME** (**Tables 3.1d**). The SMEs are willing to invest in the network as they see benefit of the defined interactions. *First*, they will gain access and become associated with scientific leaders in CaRes. *Second*, they will establish collaborative research endeavors beyond their specific expertise that will help them to enhance their industrial impact. *Third*, they will be able to network with ESRs that they have helped develop entrepreneurially and may be suitable for positions in their companies. *Finally*, they will have direct and early access to findings with potential for commercial exploitation (deliverables summary 6 and 7, **Table 3.1b**). The foreseen exploitable results by the non-academic beneficiaries and partners are:

- ✓ **B8-geneXplain**: i) gene regulatory and molecular network models of CaRes exploitable through development of new bioinformatic tools for custom-based analyses and exploration; ii) models at the single-cell and cancer tissue levels, including interactions between immune and cancer cells, and development of new tools for analyses and exploration; and iii) identification of targets to impair CaRes from the previous i-ii developments.
- ✓ **B9-leadXpro**: i) drug discovery from cell-based, PDX and/or genetically modified mouse studies; ii) identification of drugs impairing cancer progression mediated by immune cells; and iii) synergistic drug combinations based on molecular interaction networks and immune-cancer cell interactions.
- ✓ **P1-city2science**: it will benefit from the implementation and probing of new strategies for population, patients and scientists engagement. These include organization of courses (Table 1.2b), YouTube channel, press releases/coordination, and collaboration with P2-ECPC for diffusion, influencing and lobbying on a relevant health care problem, patient needs and research priorities.
- ✓ **P2-ECPC**: this non-profit organization will benefit from the continuous interplay between researchers-SMEs and patients, foundations, populations and policy makers all centered on improving cancer care and giving voice to patients. It will help to define strategies for research and funding priorities, health care deficiencies and necessary policies based on patient needs.

[72] Dell'Aversana C et al. *Leukemia*. 2018;32:573.
[73] Carafa V et al. *Clin Cancer Res*. 2018;24:2886-2900.

2.3 Quality of the proposed measures to exploit and disseminate the results

2.3.1 Dissemination of the research results

In coordination with their **supervisors** and **TC** (i.e., Personal Career Development Plans), as well as **WP8** and **WP9** leaders, the ESRs will participate and present their results in national and international conferences relevant to the program (as mentioned above, two key European will be ESMO and EACR). In parallel, the **SystemicR** meetings will be hosted trying to overlap with other major conferences at the sites, enabling the presence of key invited speakers and other relevant professionals that will be personally invited to the private two-day sessions. The invitations will be executed following indications from the PIs (B1-B9) and P1-P2. In addition, dissemination of research results will follow a plan coordinated by **WP8**:

- **Each network meeting (1-6th) will generate a press release** highlighting key results/information; a press conference may be also organized depending on results relevance and press demands. Major press communication actions are WP8/P1-planned for the kick-off, middle ad final meetings (months 2, 18 and 45).
- **Each network publication will also generate a press release** and, eventually, conference.
- Parallel diffusion for the general audience (adjusting language and information included) will be completed through the **website, social media, and a newly dedicated YouTube channel**.
- **Periodic reports (one month deadline after each meeting: months 2, 10, 19, 28, 37, and 46) to EU and ITN representatives** with a **Specific Section** for scientific results and their innovative/translation relevance will be provided (WP1 tasks).
- **Joint presence of beneficiaries and ECPC in international scientific and patient conferences**: first presentation in ESMO and EARC, and ECPC Annual 2021 congresses. Subsequent presentations in all annual ECPC congresses, and in the ESMO/EARC conferences within the last year of **SystemicR**.
- **Final international CaRes conference** with presentation of major results by all projects, and coordinated with previous points.
- **Scientific pee-review publications that will be openly deposited as preprints** following **Open Data** and **Intellectual Property Rights (IPR)** guidelines[74] (subsequent sections). As a minimum, one top-ranked publication is expected from each research project.

2.3.2 Exploitation of results and intellectual property

Prior to results publication or public presentation in any format, **relevant data will be screened for Intellectual Property Rights (IPR) by the SB with support of the ICO-IDIBELL Innovation and Technology Transfer Officers, in addition to the corresponding analogous Officers in the corresponding institution B2-B9**. This ITN has agreed to adopt the DESCA 2020 Model[75] of Consortium Agreement (CA) with respect to IPR. In accordance, each ESR will sign a Non-Disclosure Agreement (NDA) upon appointment. The network activities will require a strict and considered handling of IPR that fulfills the needs of all participants, and this will be ensured by **WP1**. Each proposal may lead to joint ownership stemming from the collaborative research and the coordinator will monitor and promote filing of patents. This process forms the basis to establish additional agreements between participants and industrial partners after consultation with the involved Officers. All ESRs will receive training in IP management and patent creation, to learn how to formulate research results in a way that permits exploitation (workshop month 27). Related teaching is already implemented in the some host institutions[76]. The industrial partners can directly profit from the openly accessible research results to improve their products and services offered worldwide, as detailed in the previous section. In case of joint developments, institutions will retain the IP jointly and will develop a dedicated exploitation agreement. In the course of secondments, researchers may be requested to sign a Partnership Agreement or additional Non-Disclosure Agreement. Beneficiaries or Partners requiring this practice will communicate it before submitting the request. In order to ease the establishment of a CA, all Beneficiaries and Partners will agree with a specific form prior to the start of the research projects (deadline month 6). The goals of **SystemicR** anticipate the identification of molecular mechanisms, targets and drugs with potential patent applications in cancer care. These deliverables will be the basis of subsequent grant applications through EU calls of FET OPEN or SME Technology Development, which will expand the original network and reinforce European innovation.

2.4 Quality of the proposed measures to communicate the activities to different target audiences

2.4.1 Communication and public engagement strategy

SystemicR will follow a strategic **Dissemination and Exploitation Plan**[77] (**Table 2.4,** P1-city2science) to inform potential users about the expertise, good practice, and outcomes obtained from the program. The plan will ensure a wide exploitation of the results at local, regional, national and European levels. The plan will be refined during the initial phase of the project in collaboration with **WP1** and **WP9**.

[74] "Open Access & Data Management", H2020 Online Manual.
[75] DESCA 2020 Model Consortium Agreement, v1.2.
[76] "EU Intellectual Property Law and Policy in an International Context", University of Copenhagen course, 2016.
[77] "Dissemination and Exploitation in Horizon 2020", Mrs. Kirsti Ala-Mutka, European Commission, H2020 Common Support Centre/J5.

Table 2.4: Communication activities, targets, results and methods.

SystemicR activities/outputs	Target Groups / Users (No.)	Desired Result	Exploitation Method	Dissemination Method
Development of corporate design, logo, related documents and CD Handbook	Consortium (11) plus affiliated institutes/univ/organizations (>20), media (general public)	Clear attractive presentation for non/academic	Uptake by all partners involved in the project	Shared consortium documents
Public website connected to social media: Facebook, Instagram, Twitter, YouTube (specific channel)	Same as above plus any early career researchers, established researchers and research schools	Accessible collection, presentation and discussion	Distribution via EU and National Publications, stakeholder groups, etc.	Open Access URL
Online newsletters at consortium meetings Table 1.2b	Relevant stakeholders at national and EU levels (foundations, ministries/secretaries, representatives)	Sharing of results	Via partners, EU and national publications, stakeholders, etc.	Open Access via website
Press releases alongside meetings, publications and Milestones (major press months 2,18,45)	Media (general public)	Sharing of results	Via partners, EU and national publications, stakeholders, etc.	Mailings via consortium partners
Policy Briefs 1-3 to communicate results to European stakeholders and decision makers	European Commission, European University Research Schools, Medical Stakeholders	Maximization of Impact and uptake of results	Distribution via EC Policy Officers	Impact Assessment
Project YouTube channel documenting activities, results, training and beneficial/partner collaborations	Consortium (11) plus affiliated institutes/univ/organizations (>20), media (general public)	Sharing of project results to younger target groups	Dissemination Report	Website and Social Media platforms, Open Access

3. Quality and Efficiency of the Implementation

3.1 Coherence and effectiveness of the work plan, including appropriateness of the allocation of tasks and resources (including awarding of the doctoral degrees for EID and EJD)

SystemicR is based on nine interconnected WPs that sustain a bottom-up scientific and educational program to deliver top-ranked ESRs with advanced multidisciplinary skills.

3.1.1. Table 3.1a: Description of Work Packages.

WP Number	**1**	**Start Month 1 – End Month 48**
WP Title	**Scientific and Network Management**	
Lead Beneficiary	**IDIBELL (B1, ES)**	
Objectives. To **coordinate the project and manage the administrative, research and training activities of the consortium**. **1:** Coordination and management. To establish key governance and decision-making structures and processes. To ensure risk and dependencies across participants and WPs are managed effectively. **2:** Project planning and reporting. To manage the progress of WPs and ensure the timely release of deliverables and Milestones. **3:** Project administration and communication. To organize and facilitate meetings of the consortium and manage communication both with the EC and between consortium members. To collate and deliver all required scientific and financial reporting in a timely manner.		
Description of Work and Role of Specific Beneficiaries / Partner Organizations This WP will focus on implementing specific bodies of the organization structure of the project: SAB, SB, TC, EC, and WPs. The coordinator at IDIBELL will lead this work with support of a full-time project manager, SB, dedicated ICO-IDIBELL Project Management Units, and SAB. It will also implement processes for decision-making, risk management, progress reporting, Open Data, recruitment, financial management and reporting, intellectual data protection, and gender and equality monitoring.		
Description of Deliverables. **Deliverable 1:** Signed Consortium Agreement (month 1). **2:** Recruit of a full-time project officer (month 2). **3:** Management of network meetings (months 2,10,17,23,31,45). **4**: Advertisement of ESR positions at national and European-wide portals (month 3). **5**: Approval of PCDPs, Research Declaration, and Secondments (months 6,12). **6**: Coordination of SAB, TC, EC, Quality Questionnaire, and Evaluation and Yearly Survey administration (months 9,18,27,36,45). **7**: Reports to EU (months 2,10,19,28,37,46).		
WP Number	**2**	**Start Month 1 – End Month 48**
WP Title	**Coordination of Research Training**	
Lead Beneficiary	**UniCampania (B2, IT)**	
Objectives. To implement, coordinate, and supervise **ESR training**. These include definition and agreement of each PCDP in coordination with the supervisors, the corresponding universities, with advice of SAB, lead by the TC and confirmed by the SB. It also includes supervision of training, evaluation and reporting ESR questionnaires, reports and presentations, and coordination of secondments.		
Description of Work and Role of Specific Beneficiaries / Partner Organizations *A fundamental piece of this WP is the TC, constituted by B3-Altucci, B6-Krijgsveld and B9-leadXpro/Hennig.* **Task 1:** Definition and supervision of each PCDP. **2:** Continuous supervision of local and network-wide training, environment, and project results. **3:** Definition and supervision of ESR secondments, their results and reports. **4:** Ensure complementary ESR training and education with an appreciation of intellectual property, innovation and entrepreneurship. Also to consider and integrate specific training requests.		
Description of Deliverables. **Deliverable 1:** PCDP handed to the SB (deadline month 10). **2:** Secondments plan scheduled (deadline month 12). **3:** Workshops and courses at network meetings (months 10,17,23,31,45). **4:** ESR questionnaires, written reports and presentations, provided to SAB and SB (biannually and major reports/presentations in months 9, 18, 27, 36, and 45). **5:** Doctoral degrees (month 45 with potential extensions).		

WP Number	3	Start Month 6 – End Month 48
WP Title	Theoretical Modeling and Data Analysis	
Lead Beneficiary	CRM (B3, ES)	

Objectives. To coordinate ***in silico* consortium research**, to produce **quantitative methodology and software** to inform decision-making regarding therapeutic approaches to overcome CaRes, and **to provide training for big data studies**. **1:** Coordination of project-centered *in silico* analyses performed mainly by academic groups B1-IDIBELL, B3-CRM, and B7-SU, in addition to B8-geneXplain. **2:** Analytical support and training to consortium members, including organization of **Big Data in Oncology course** (month 9). **3:** Development and implementation of clustering and machine learning techniques for high-throughput data allowing for dimensional reduction of CaRes systems. **4:** Development and evaluation of CaRes pathway models in coordination with results obtained from **WPs 4-7**.

Description of Work and Role of Specific Beneficiaries / Partner Organizations
Task 1. To establish and coordinate periodic (expected to be **every 3 months**) virtual meetings among the consortium members focused on *in silico* analyses and projects. **Task 2.** To develop and support new methods to uncover clusters of gene expression influencing CaRes phenotypes. **Task 3.** To apply and develop analytical techniques for stochastic systems to provide dynamic models of CaRes pathways. **Task 4.** To revisit methodologies for survival analysis and re-evaluate their efficiency regarding capability to identify genes that act as modulators of CaRes in the context of the interaction with the immune system. **Task 5.** To organize training course at annual meeting (month 9).

Description of Deliverables. **Deliverable 1.** Minute reports of each periodic virtual meeting, to be provided to **SB**. **2:** Reports of analytical and training support to groups, to be provided to **SB** and **TC**. **3:** Computational results based on survival and risk analyses. **4:** To establish methodology (by publications) for detecting complex dependences and classify them to identify molecular/cellular interactions influencing CaRes. **5:** Computational results (by publications) regarding the coarse-grained dynamics of the transition to CaRes/differentiated phenotypes. **6:** Identification of genes that act as modulators of CaRes and/or influence immune-cancer cell interactions. **7:** PhD theses whose methods and results are based on this **WP** tasks (Table 1.1).

WP Number	4	Start Month 6 – End Month 48
WP Title	Cell-Autonomous and Single-Cell System Studies	
Lead Beneficiary	PMC (B4, NL)	

Objectives. To **coordinate cell-centered studies** within the consortium, to produce **gene/molecular data and experimental models linked to CaRes, and to provide training for cell-system level studies**. **1:** Coordination of project-centered genetic, transcriptome and proteomic analyses in immune and cancer cells. **2:** Analytical support and training to consortium members, including organization of **Single-Cell Genomic and Proteomic Profiling** course (month 18). **3:** Development and implementation of single-cell protocols in coordination with **WP3**. **4:** To produce data and models of single-cell immune-cancer cell interactions influencing CaRes.

Description of Work and Role of Specific Beneficiaries / Partner Organizations
Task 1. To establish and coordinate periodic (expected to be **every 3 months**) virtual meetings among the consortium members (including **WP3** leader) focused on cell autonomous and single-cell analyses and projects. **Task 2.** To co-develop (**WP3**) and assess new methods to uncover single-cell phenotypes associated with CaRes. **Task 3.** To produce data and experimental models of immune-cancer cell interactions influencing CaRes. **Task 4.** To organize training course (month 18).

Description of Deliverables. **Deliverable 1.** Minute reports of each periodic meeting, to be provided to **SB. 2:** Reports of analytical and training support to groups, to be provided to **SB** and **TC**. **3:** To deliver methodology and results (by publications) for detecting single-cell CaRes phenotypes. **4:** To deliver methodology and results (by publications) of immune-cancer cell interactions influencing CaRes. **5:** Identification of interactions that influence CaRes. **6:** PhD theses whose methods and results are based on this **WP** tasks (Table 1.1).

WP Number	5	Start Month 6 – End Month 48
WP Title	Tissue System Studies	
Lead Beneficiary	BRIC (B5, DK)	

Objectives. To **coordinate cancer tissue-centered studies** within the consortium, to produce **cell/tissue heterogeneous data and experimental models, and to provide training for tissue-system level studies**. **1:** Coordination of project-centered tissue analyses including studies of immune and cancer cells in tissue samples. **2:** Coordination of mouse model therapeutic studies. **3:** Analytical support and training to consortium members, including organization of **Tumor Heterogeneity and Cancer Therapy** course (month 27). **4:** To produce data and models at the tissue and organismal levels linked to CaRes.

Description of Work and Role of Specific Beneficiaries / Partner Organizations
Task 1. To establish and coordinate periodic (expected to be **every 3 months**) virtual meetings among the consortium members (including **WP3,4** leaders) focused on tissue and *in vivo* analyses and projects. **Task 2.** To develop and assess methods to uncover immune-cancer cell interactions in heterogeneous samples. **Task 3.** To produce data and experimental tissue models of immune-cancer cell interactions influencing CaRes. **Task 4.** To organize training course (month 27).

Description of Deliverables. **Deliverable 1.** Minute reports of each periodic meeting, to be provided to **SB**. **2:** Reports of analytical and training support to groups, to be provided to **SB** and **TC**. **3:** To deliver methodology and results (by publications) for detecting tissue-context immune-cancer cell, molecular and functional interactions. **4:** To deliver methodology/results (by publications) of immune-cancer cell interactions influencing CaRes. **5:** Identification of tissue-level features influencing CaRes. **6:** PhD theses whose methods and results are based on this **WP** tasks (Table 1.1).

WP Number	6	Start Month 6 – End Month 48
WP Title	Target Discovery	
Lead Beneficiary	geneXplain (B8, DE)	

Objectives: The objectives are to **coordinate target identification studies** within the consortium, to produce **data and experimental models for subsequent drug discovery, and to provide training for translation of findings and entrepreneurship**. **1:** To build and characterize gene regulatory networks linked to CaRes. Results of theoretical modeling (**WP3**), single-cell (**WP4**) and tissue (**WP5**) studies will be applied for analysis of signaling pathways and molecular interactions. **2:** To develop novel algorithms for CaRes target/biomarker identification, also in coordination with previous **WPs**. **3:** To identify valuable CaRes therapeutic targets and biomarkers. **4:** To develop web-based tools to examine cell- and tissue-centered systems-level models of CaRes. **GeneXplain platform on-line tool integrated with Galaxy system will be used for the software development**. **5:** To co-organize workshop **Intellectual Data Protection and Business Development** (month 27).

Description of Work and Role of Specific Beneficiaries / Partner Organizations

Task 1. To establish and coordinate periodic (expected to be **every 3 months**) virtual meetings among the consortium members (including **WP3-5** leaders) focused on CaRes target analyses. **Task 2.** To develop and assess bioinformatic methods to uncover targets from heterogeneous data types. **Task 3.** To produce data and experimental models of molecules and interactions influencing CaRes. **Task 4.** To organize training workshop (month 27).

Description of Deliverables. Deliverable 1. Minute reports of each periodic meeting, to be provided to **SB**. **2:** Reports of analytical and training support to groups, to be provided to **SB** and **TC**. **3:** To deliver methodology and results (by publications) for identification of CaRes targets. **4:** To deliver methodology and results (by publications) of immune-cancer co-targets. **5:** PhD theses whose methods and results are centered on this **WP** tasks (Table 1.1).

WP Number	**7**	**Start Month 6 – End Month 48**
WP Title	**Drug Discovery**	
Lead Beneficiary	**leadXpro (B9, CH)**	

Objectives: To **coordinate drug discovery studies** within the consortium, **training for target-drug studies, and drug development and entrepreneurship**. **1:** To identify (coordination with **WP6**) and preclinically assess (coordination with **WP5**) drugs targeting CaRes. **2:** To delineate target-drug interactions. **3:** To coordinate *in vitro* drug screens and contribute to *in vivo* assays. **4:** To provide training and support for target biochemical studies and drug property analyses. **5:** To co-organize workshop **Intellectual Data Protection and Business Development** (month 27).

Description of Work and Role of Specific Beneficiaries / Partner Organizations

Using results obtained by **WP3-6**, this WP will be responsible of the following tasks. **1:** To establish and coordinate periodic (expected to be **every 3 months**) virtual meetings among the consortium members (including **WP6** leader) focused on drug discovery. **2:** To develop and assess expression and purification of CaRes proteins, biophysical assays, structure determination by computational or experimental methods, prediction of drug targetable sites, high-throughput i*n silico* and/or experimental screens for drug-like small compounds, hit and lead generation by *in vitro* methods. **3:** In cooperation with **WP5**, to test drugs/compounds though *in vivo* assays using mouse models.

Description of Deliverables. Deliverable 1. Minute reports of each periodic meeting, to be provided to **SB**. **2:** Reports of analytical and training support to groups, to be provided to **SB** and **TC**. **3:** To deliver methodology and results (by publications) for identification of drugs targeting CaRes. **4:** To deliver methodology and results (by publications) of synergistic drug combinations based on immune-cancer cell interactions. **5:** PhD theses whose methods and results are centered on the objectives of this **WP** (Table 1.1).

WP Number	**8**	**Start Month 6 – End Month 48**
WP Title	**Science Dissemination and Public Engagement**	
Lead Beneficiary	**city2science (P1, DE)**	

Objectives: To define and execute the **Dissemination and Exploitation Plan** (**Table 2.4**) to inform potential users, stakeholders, populations, patients, policy makers, etc. about the potential, expertise, good practices, and outcomes obtained from the program, and to provide **key soft-skills training and education**. The plan will be defined during the initial phase of the project in coordination with **WP1** (**SB**, **SAB)** and **WP9**. **1:** To make the relevant methodologies and evidence-based outcomes of the project available and accessible to the European and global research communities, thus contributing to making an impact in its scientific and social meanings. **2:** To reach out to a significant number of stakeholders in the European cancer care and research communities, and also including national and EU policy-makers, and other relevant representatives and practitioners. **3:** To promote and share advanced learning modules for the communication and dissemination of the project results. **4:** To inform non-academic users about the **SystemicR** results and outcomes (i.e., via training toolkits, science education methodologies) to ensure its further exploitation and the sustainability of the project's results. **5:** To organize workshop (**Science Communication and Public Engagement**, month 9) and course (**Building Trust on Research(ers)**, month 18).

Description of Work and Role of Specific Beneficiaries / Partner Organizations

Task 1. To establish and coordinate periodic (expected to be **every 6 months**) virtual meetings among the consortium members focused on communication and public engagement, including **WP1,9** leaders and their **Institutional Communication Officers**. **Task 2.** To develop and execute the Plan, including media releases and three major program press conferences defined above. **Task 3.** To organize training workshop (month 9) and course (month 18). **Task 3.** To design and develop webpage, media diffusion, and YouTube channel.

Description of Deliverables. Deliverable 1. Annual Dissemination Reports including CD Handbook, Website, Online Newsletters, Social Media Reports (months 12,24,36,48). **2:** Annual Policy Briefs summarizing project results for stakeholders (months 2,24,36,48). **3:** Public Engagement Training Toolkit/Handbook (month 45).

WP Number	**9**	**Start Month 6 – End Month 48**
WP Title	**Patient Advocacy**	
Lead Beneficiary	**ECPC (P2, BL)**	

Objectives: To **coordinate consortium goals and activities towards patient needs, influencing decision and policy makers**, and to provide **education on these topics**. These objectives will be coordinated with **WP1** (communication of health care problem and consortium goals) and **WP2,8** (training and education, and lobbying). **1:** To engage scientist, professionals, populations, and stakeholders in the European community, including policy-makers, and other relevant representatives and practitioners, in patient's needs and advocacy. **2:** To communicate relevant national and EU representatives regarding needs/limitations of research, care and policy. **3:** To organize presentations of consortium members in patient conferences, and patient-centered debates including the final International CaRes Conference. **4:** To organize workshop (**Patient Needs, Advocacy, Health Care Policies and Research Priorities,** month 18). **5:** To provide report of recommendations for measuring and evaluating CaRes in the European scenario (month 36).

Description of Work and Role of Specific Beneficiaries / Partner Organizations

Task 1. To establish and coordinate periodic (expected to be **every 6 months**) virtual meetings among the consortium members focused on engagement of patient needs and advocacy, including **WP1,8** leaders. **Task 2.** To contact, present and discuss with key national and

EU representatives the current impact of CaRes and program goals/results. **Task 3.** To provide recommendations to measure CaRes and current limitations to reduce its individual, clinical and population impacts. **Task 4.** To organize training workshop (month 18).
Description of Deliverables. Deliverable 1. Annual Reports, Communications and News (months 12,24,36). **2:** CaRes briefs summarizing current status in participants oncology Institutions (months 12,24,36). **3:** Patient Advocacy Training Toolkit/Handbook (month 45).

3.1.2 List of major deliverables

The nine coordinated **SystemicR** WPs will provide the following major deliverables. **Table 3.1b.**

Scientific Deliverables						
Deliverable Number	**Deliverable Title**	**WP No.**	**Lead Beneficiary Short Name**	**Type**	**Dissemination Level**	**Due Date**
1	Molecular circuits and pathways influencing CaRes	3	CRM	PDE	PU	36
2	Biomarkers of CaRes	3	IDIBELL & SU	PDE	PU	36
3	Molecular networks influencing CaRes	4	IDIBELL & DKFZ	PDE	PU	36
4	Immune-cancer cell interactions influencing CaRes	4	UniCampania & PMC	PDE	PU	36
5	TME features influencing CaRes	5	PMC & BRIC	PDE	PU	36
6	Potential targets to impair CaRes	6	geneXplain	PDE	PU	36
7	Candidate drugs to impair CaRes	7	leadXpro	PDE	PU	36
Management, Training, Recruitment and Dissemination Deliverables						
Deliverable Number	**Deliverable Title**	**WP No.**	**Lead Beneficiary Short Name**	**Type**	**Dissemination Level**	**Due Date**
1	Signed Consortium Agreement	1	IDIBELL (ALL)	ADM	CO	1
2	Recruit of a full-time network administrator-PO	1	IDIBELL	ADM	PU	2
3	Network meetings	1	IDIBELL (ALL)	PDE	CO	2,9,18,27,36,45
4	Committees/boards coordination (SAB,BC,TC,EC)	1	IDIBELL	OTHER	CO	2,9,18,27,36,45
5	Advertisement of ESR positions at national and European-wide portals and program website	1	IDIBELL (ALL)	ADM	PU	3
6	Communication plan	8	city2science (ECPC)	ADM	CO	3
7	Website and social media presence built, maintained and operated	8	city2science (IDIBELL)	ADM	PU	3
8	Intranet maintained and operated	1	IDIBELL (city2science)	ADM	CO	6
9	All ESRs recruited	1	IDIBELL (ALL)	ADM	CO	6-9
10	PCDPs	2	UniCampania	PDE	PU	6,12
11	Workshop reports	1	IDIBELL (city2science, ECPC, geneXplain, leadXpro)	R	PU	9,18,27,36,45
12	Patient advocacy and conference interactions	9	ECPC (city2science)	OTHER	CO	9,18,27,36,45
13	Questionnaire evaluation and supervision	2	UniCampania	OTHER	CO	9,18,27,36,45
14	Reports to EU	1	IDIBELL	R	CO	10,19,28,37,46
15	Secondments and supervision	2	UniCampania (ALL)	OTHER	CO	12,45
16	Career development plans	2	UniCampania	PDE	CO	36
17	Guidelines, policies and recommendations to evaluate CaRes	9	ECPC (ALL)	R	PU	45
18	Identification of potential targets of CaRes	6	geneXplain (ALL)	R	CO	45
19	Proposal of drugs targeting CaRes	7	leadXpro (ALL)	R	CO	45
20	PhD awards	2	UniCampania (ALL)	ADM	PU	45 (extendable)

Among the depicted deliverables, the following Milestones have been defined for successful execution of **SystemicR**:

3.1.3 List of major milestones:

Table 3.1c. Milestones.

No.	Title	Related WPs	Lead Beneficiary	Due Date	Means of Verification
1	Consortium Agreement (CA)	1	IDIBELL	1	CA signed
2	Public and intranet website	1 & 8	IDIBELL & city2science	6 (3 for public)	Website live and running
3	ESR recruitment finalized	1	IDIBELL	12	Appointed fellows validated by SB and TC
4	PCDPs, projects and secondments	2	UniCampania	12	TC, SAB and SB approvals
5	Enhanced communication, dissemination & engagement	8	city2science & ECPC	18	Press releases, conferences and news impact, to be detailed in annual report
6	Theoretical molecular models validated though experiments	3	CRM	36	Dynamic pathways associated with CaRes: publications and annual report
7	Single-cell phenotypes associated with CaRes	4	PMC	36	Unique transcriptomic/proteomic profiles linked to CaRes: publications and annual report
8	Immune-cancer cell interactions and tissue-level evidence associated with CaRes	5	BRIC	36	Cell interactions and tissue distributions associated with CaRes: publications and annual report
9	Novel targets and drugs (preclinical) to impair CaRes	6,7	geneXplain & leadXpro	36	Publications and annual report
10	Multidisciplinary top-ranked educated ESRs	2	UniCampania	45	Report including results of research, training and the four Challenges
11	Increased awareness of needs & priorities	9	ECPC	45	Contacts, conferences and news detailed in annual report, and recommendations summary
12	Doctoral degrees	2	2 (ALL)	45 (extendable)	University document degrees

Funded in the overall scientific goal of **SystemicR** —to better understand the interplay between innate immune and cancer cells in CaRes— the following **individual research projects** and their **secondments** have been agreed:

3.1.4 Fellow's Individual Research Projects

Table 3.1d. Individual projects, secondments, and supervisors (BS and CS, section 1.3.2).

ESR 1	B1, IDIBELL (a) Pujana (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,3,4,6,7
Project Title/ Work Package: Integrative omics analysis of modulators of immune-breast cancer cell signaling (WP3,5,7).					
Objectives: To integrate multiomics cancer data to build models of molecular and functional interactions between macrophages and TNBC cells, and to assess these interactions (e.g., gene-gene expression interactions) influencing cancer progression. The goal of this project is to predict key molecular and functional interactions between both types of cells that can subsequently be targeted to impair cancer progression. The group has experience on analyzing macrophages profiles in breast cancer[78].					
Expected Results: (1) Identification of functional interactions between immune (focus on macrophages) and cancer cells. (2) Identification of small compounds and/or drugs that can impair these interactions in co-culture cell assays and *in vivo* models. **Contingency plan:** There might not be specific and/or available compounds/drugs targeting the identified functional/cellular interactions; if this is the case, validations will be based on deletion (CRISPR-based) of defined key genes in the corresponding cell type. These genetic validations will open the path for developing missing drug-targeted approaches.					
Planned secondment(s): Year 1: B3-CRM (3 months, data analyses and integration). Year 2: B5-BRIC (3 months, tumor cell studies). Year 3: B9-leadXpro (6 months, compound/drug screens). CS: B9-Hennig.					
ESR 2	**B1, IDIBELL (b) Pujana (BS)**	**PhD enrolment Y**	**Start date Month 6**	**Duration 36 months**	**Deliverables: 2,3,4**
Project Title/ Work Package: Identification of cancer gene drivers influencing innate immune cell content in breast cancer (WP3, 4,6).					
Objectives: To analyze multiomics cancer data to identify cancer gene drivers that are associated with differences in innate cell content and/or profiles in TNBC, and to assess if these associations influence progression. The goal of this project is to detect cancer drivers whose status differentiates innate cell content and/or profiles based on gene expression deconvolution analyses and biomarker analyses.					
Expected Results: (1) Identification of cancer gene drivers influencing innate cell content in tumors. (2) Defining a molecular mechanism by which cancer gene drivers alter immune surveillance/tolerance to cancer. **Contingency plan:** The effects of cancer gene drivers may be indirect and/or complex to be captured by regular regression analyses; if this is the case, multifactor and stochastic approaches will be applied using large omic datasets with support of B3-CRM.					
Planned secondment(s): Year 1-2: B4-PMC (6 months, single-cell RNA profiling of TNBC with different driver mutations). Year 3: B7-SU (6 months, gene expression and biomarkers influencing driver-immune interplay). CS: B7-Győrffy.					
ESR 3	**B2 UniCampania (a), Altucci (BS)**	**PhD enrolment Y**	**Start date Month 6**	**Duration 36 months**	**Deliverables: 2,4,5**
Project Title/ Work Package: Identification of myeloid-derived suppressor cells (MDSC) in CaRes (WP3-5).					
Objectives: MDSC consist of two large groups of cells termed granulocytic or polymorphonuclear (PMN-MDSC), which are phenotypically and morphologically similar to neutrophils, and monocytic (M-MDSC), which are phenotypically and morphologically similar to monocytes. MDSC are normally present at very low numbers in healthy individuals, but may accumulate					

[78] Roux C et al., *PNAS.* 2019;116:4326-4335; Kubli SP et al., *PNAS.* 2019;116:3604-3613.

under inflammation and cancer conditions. Recently, MDSC have become an important part of the tumor immunology field because their role of immune suppression, in particular targeting T-cells. The objective is to define if MDSC are linked to resistance phenomena in breast cancer and AML. In addition, by eliminating MDSCs via compound/drug the ability of host's immune system to attack the cancer will be evaluated, providing the rational to combine conventional targeting therapy with immunotherapy.

Expected results: (1) Identification of immune-tumor crosstalk and (2) of a subset of MDSC suppressive activities that can be linked to CaRes. (3) Identification of compounds or drugs able to specifically target MDSC subpopulation to restore immune system surveillance against cancer. **Contingency Plan:** MDSCs are difficult to isolate because their phenotypic signature includes multiple surface markers. If this is the case, a multi-parametric approach will be applied to distinguish cell populations coupled with single-cell analysis.

Planned secondment(s): Year 1: B4-PMC (6 months, MDSC and single-cell transcriptome and proteome profiling). Year 2: B5-BRIC (3 months, MDSC crosstalk with solid cancers). Year 3: B3-CRM (3 months, data analysis). CS: B4-Stunnenberg.

ESR 4	B2, UniCampania (b), Altucci (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,4,5,6,7

Project Title/ Work Package: Identification of tumor microenvironment in AML (WP5,7).

Objectives: Immunotherapies strategies using bispecific antibodies represent a promising tool for AML treatment. Given the strong crosstalk between tumor and immune microenvironment, experiments will be performed to define the best antigen useful for the realization of the project. Experiments will be performed in *ex vivo* AML patient's blasts at different stage of treatment. Bispecific antibodies will combine the capability of the antigen recognition and the induction of immune and death cellular response by the delivery of a selected epigenetic drug. The aim of this project is to define the TME and cellular pathways activated in AML systems, providing a new therapeutic strategy.

Expected results: The project will aim to gain more insight into knowledge about TME in AML, still little known, and the characterization of the cell response to the combined action between an antibody and epi-drug. Data obtained will give useful information about the restoration of immune system and leukemia cell death induction. **Contingency Plan:** Our lab has a long-standing expertise in drug characterization and in the identification of cellular responses. We envisage a potential problem on the functionality of bispecific antibody concerning the antigens expression. In this scenario will be applied different technical strategies to identify and enrich the specific cell population with the selected antigen.

Planned secondment(s): Year 1: B9-leadXpro (6 months, drug discovery and protein structure modeling). Year 2: B5-BRIC (6 months, study of tumor microenvironment). CS: B5-Erler.

ESR 5	B3, CRM (a), Serra (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 1,2,6

Project Title/ Work Package: Survival analysis applied to identify modulators of resistance in cancer cells (WP3).

Objectives: To revisit methodologies of analysis of survival and risk to identify modulators or modifiers of cancer driver genes. To describe the genetic patterns discovered using unified techniques such that can be exploited with machine learning approaches. To apply this methodology to describe the characteristics of cancer gene modulators and their nonlinear dynamics and patterns of gene expression.

Expected results: (1) To understand the dynamic interactions of both cancer gene drivers and modulators. (2) To predict possible causality schemes through analyses of patterns of gene/protein associations. (3) To predict causal dynamics from the interaction patterns. **Contingency Plan:** Several analytical approaches are going to be considered in the field of artificial intelligence. In patterns of causality are not clearly identified, Bayesian techniques will b applied for examining uncertainty on this point.

Planned secondment(s): Year 1: B1-IDIBELL (3 months, cancer data interpretation). Year 2: B8-geneXplain (6 months, regulatory networks defining CaRes causality). CS: B1-Pujana.

ESR 6	B3, CRM (b), Alarcon (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 1,2,3,4,5,6

Project Title/ WP: Quantifying cell-fate decision landscapes for the interaction between cancer and the immune systems (WP3,4,7).

Objectives: To use single-cell transcriptome data to determine in a quantitative way the corresponding Waddington landscape, thus providing (1) information on the most likely transition paths, and (2) to infer the pseudo-time of cells in their evolution towards the corresponding phenotype. To determine how different patterns of cell interactions and environmental cues affect the most likely cell-fate decision pathway.

Expected results: The development of novel analytical and computational techniques regarding clustering and stochastic modeling of single-cell gene expression data. Specifically, we expect that topological data analysis (TDA) outcompetes other techniques to cluster the raw genomic data into groups corresponding to (meta)stable cell states. **Contingency Plan:** If TDA does not work, we will (i) resort to other clustering techniques (such as k-means, random walks, optimization techniques, etc.) and (ii) investigate ways to improve the current TDA methodologies.

Planned secondment(s): Year 1: B1-IDIBELL (3 months, cancer data interpretation). Year 2: B4-PCM (3 months, single-cell analyses). Year 3: B8-geneXplain (3 months, evaluation of novel algorithms). CS: B8-Kel.

ESR 7	B4, PMC (a), Stunnenberg (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 1,2,3,4,6,7

Project Title/ WP: Single cell analysis of the pediatric AML heterogeneity and treatment resistance (WP3,4,7,8)

Objectives: To perform single-cell transcriptome (scRNA-seq), epigenome (scATAC-seq and exome sequencing of pediatric AML bone marrow taken at diagnosis, at the end of the treatment and at relapse. The resource data will provide critical information and novel insight into tumor heterogeneity, clonality and treatment response and improve our understanding of changes in the leukaemic immune-environment under treatment. Identified cellular interactions will feed complementary studies in breast and colorectal cancer.

Expected results: A comprehensive resource for the community; insight into the effect of treatment on tumor heterogeneity and clonality as well as the identification of pathways affected/altered in response to treatment. The data will be the basis to explore new patient specific treatment strategies. **Contingency Plan:** Contingency plan is not required as the Princess Maxima Center treats about 25 pediatric patients with AML. The single cell technologies are running optimally using the 10X Chromium equipment and FACS facilities.

Planned secondment(s): Year 1: B8-geneXplain (1 month for gene regulatory analyses). Year 2: B3-CRM (2 month for statistical analyses of single-cell data). Year 3: B9-leadXpro (1 month for drug target predictions). CS: B3-Alarcon.

ESR 8	B4, PMC (b), Stunnenberg (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 4,5,6

Project Title/ WP: Single cell and imaging-based analysis of colorectal tumor tissue (WP3,4,6)

Objectives: In phase one, single cell transcriptome (scRNA-seq) and epigenome (scATAC-seq) profiling will be performed on microsatellite stable colorectal cancer samples (~15-20) providing detailed information about the cell types and cell states within the tumor tissue. Imaging-based technologies and targeted *in situ* RNA sequencing of cell type/state specific transcripts will unveil tumor tissue organization and presumed interactions between tumor and infiltrated immune cells with emphasis on infiltrated and re-programmed macrophages. Well-characterized tumor samples will be provided by CS-Altucci (B2-UniCampania).

Expected results: Insight into the factors and mechanisms of this tumor-innate immune cell interaction and the reprogramming of macrophages. The project will also provide critical information of tumor tissue organization and likely uncover novel druggable targets pathways in our war against cancer. **Contingency Plan:** Pilot experiments have shown the feasibility of 2D analysis of tumor slices using *in situ* sequencing (developed by Mats Nilsson lab, Sweden) and with help of this external collaborator have been established in the Stunnenberg team. Critical expertise in imaging (team of Anne Rio) and a state-of-the-art imaging facility is available at the PMC.

Planned secondment(s): Year 1: B2-Unicampania (2 months for colorectal cancer sample analyses). Year 2: B1-IDIBELL (2 months for cancer data integration). Year 3: B8-geneXplain (1 months for regulatory network analyses). CS: B2-Altucci.

ESR 9	B5, BRIC (a), Erler (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,4,5,6,7

Project Title/ Work Package: Influence of CD11b+ cells on drug response (WP5,7).

Objectives: To test how CD11b+ cells impact on drug response. We have previously shown that CD11b+ cells are critical for the formation of breast cancer metastases (Erler et al., *Cancer Cell*, 2009). In order to test their impact on drug response, we will co-culture CD11b+ cells isolated from FVB mice with organoids grown from the PyMT transgenic mouse model of breast cancer. The ESR will develop the set up at BRIC in collaboration with leadXpro, and will then perform a 6-month secondment at leadXpro to undertake screening of their chemical compound library. We seek to identify compounds effective against cancer cells when CD11b+ cells are present. These will then be tested in further co-culture experiments and *in vivo* in the Erler lab at BRIC. We will focus on 3D invasion assays, and tumor studies using PyMT cells injected orthotopically in the first instance, and then in the transgenic model. We will then test the same drugs against patient-derived organoids from breast cancer patients, and in corresponding PDX mice.

Expected results: We expect to find that CD11b+ cells provide cancer cells with resistance against chemical compounds. We will identify drugs that are effective against cancer cells in the presence of CD11b+ cells. We expect to confirm efficacy in 3D co-culture models of invasion, and in mouse models of breast cancer. We also expect validation in patient-derived samples. **Contingency Plan:** The set-up allows the possibility to study other immune cells other than CD11b+ cells. We can therefore adjust the immune cell type of interest based on initial findings. We also have experience in culturing neutrophils, macrophages and T cells.

Planned secondment: Year 1: 6 months at leadXpro for compound screening. CS: B8-Hennig.

ESR 10	B5, BRIC (b), Erler (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,4,5,6,7

Project Title/ WP: Influence of macrophage secretome on cancer cell signaling (WP4,5).

Objectives: To study how proteins secreted from macrophages impact on cancer cell kinase activation, with the aim to identify new therapeutic targeting strategies. We have previous experience in studying the hypoxic secretome (Cox et al, Nature, 2015). Macrophages are known to secrete pro-cancer proteins and play a major role in hypoxia-driven metastasis. Here, we will assess the impact of the secretome from macrophages isolated from FVB mice on the growth and invasiveness of organoids isolated from tumors from the PyMT transgenic mouse model of breast cancer and/or a colorectal cancer model. The macrophages will be grown in normoxia and hypoxia (2% oxygen). In parallel, we will perform Pamgene kinase array profiling on the cancer organoids to assess changing in signaling. Once initial studies have been performed in the Erler lab, the ESR will have a 12-month secondment in the Krijgsveld lab where state-of-the-art technologies will be used to analyze the macrophage secretome. The ESR will then return to the Erler lab and test strategies to interfere with this cell-cell communication *in vitro* and *in vivo* (orthotopic and transgenic mouse models). The ESR will validate findings on patient-derived organoids from breast cancer patients, and corresponding PDXs.

Expected results: To understand how the macrophage secretome in normoxia and hypoxia affects cancer cell growth, invasion and metastasis through kinase activation. To identify and test therapeutic strategies that could be translated into the clinic to benefit cancer patients. **Contingency Plan:** The set-up allows the possibility to study other immune cells other than macrophages. We can therefore adjust the immune cell type of interest based on initial findings. We have experience in culturing neutrophils, CD11b+ and T cells.

Planned secondment(s): Year 2: 12 months at B6-DKFZ for secretome analysis by proteomics. CS: B6-Krijgsveld.

ESR 11	B6, DKFZ (a), Krijgsveld (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,3,6,7

Project Title/ WP: Cytokine and oncogene-induced signaling networks in the onco-proteome (WP3,4,7).

Objectives: It is incompletely understood how upstream oncogenic events instruct downstream responses in the proteome that eventually execute a cellular function. Moreover, in the TME, it is unknown how immuno-modulatory factors originating from immune or other cells intersect with intrinsic oncogenic signaling pathways. Therefore, we will here apply nascent proteome analyses to investigate the proteomic response induced by various cytokines/chemokines (e.g., TNFα, IFNγ, TGFβ, IL6, MCSF, GMCSF) in a panel of cancer cell lines with diverse driver mutations in the main signaling pathways (EGFR-MEK-ERK, PI3K-AKT-mTOR). In addition, we will perform these studies in the presence and absence of drugs that target kinases in these pathways to infer how oncogene and cytokine-induced signaling intersect, and how this depends on sensitivity or resistance to the respective drugs. Collectively, we aim to derive context-dependent signaling networks, defined by the reach of drugs, mutations and cytokines in onco-proteomes.

Expected results: 1) identification of proteomic programs that operate downstream of oncogenic drivers to execute a cellular response; 2) identify how cytokines and chemokines reshape the cancer proteome, and vice versa 3) network-view of cancer signaling at a proteome-wide scale, illuminating functional crosstalk between kinases and cytokine-dependent pathways in a cell type-specific manner. **Contingency plan:** We may not be able to cover the space of all representative cell types, kinases and cytokines, and will therefore initially focus on selected cancer types (breast, colon), and on main oncogenic drivers and cytokine classes, and expand from there.

Planned secondment(s): Year 1: leadXpro (3 months to select drugs). Year 2: SU (6 months, to derive relationships between mutations, drugs, and cytokines). CS: B7-Győrffy.

ESR 12	B6, DKFZ (b), Krijgsveld (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,3,4,5,6

Project Title/ WP: Proteomic and secretory crosstalk between cancer and immune cells (WP5,6).

Objectives: To characterize bi-directional communication routes between cancer (breast cancer (BRCA), colorectal cancer (COAD) and AML) and immune cells (macrophages, neutrophils), and to determine how this is intersected by anti-cancer drugs. The goal of this project is to use nascent proteome analysis to characterize the proteins that are secreted by cancer and immune cells, both in mono- and co-culture systems to characterize bi-directional interaction routes. This will be primarily done in 2D cell culture, but in select cases (breast cancer) we will set this up for organoids (together with BRIC). We also aim to identify how secretory proteins from immune cells reshape the cancer proteome, and vice versa. Finally, it will be investigated how anti-cancer drugs (primarily in the MAPK and PI3K pathways) modulate these secretory landscapes, to collectively gain molecular insight at the interface of cancer/immune cell interaction and drug sensitivity.

Expected results: 1) Identification of proteins whose secretion from cancer cells depends on the presence of immune cells, and vice versa; 2) understand what proteomic programs in cancer cells are controlled/induced by immune cells, and vice versa; and 3) understand 1 and 2 in a cancer and immune cell-specific manner. **Contingency Plan:** Co-culture in trans-well systems may not be possible/practical for all cancer/immune cell combinations. In that case we will use mono-cultures and transfer supernatants to the recipient cells.

Planned secondment(s): Year 1: B5-BRIC (6 months for co-culture and 3D cell-based assays). Year 3: B8-geneXplain (4 months for data integration and interaction networks). CS: B5-Erler.

ESR 13	B7, SU, Győrffy (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 1,2,3,4,5

Project Title/ WP: Investigation of high prevalence of mutations in large and inactive genes not necessary for cell proliferation (WP3-5).

Objectives: The major objective is to uncover whether there is a systematic and predictable feature(s) behind therapeutic effects mediated by immune cells. In the last decade, whole genome analyses of cancer genomes show an increasing proportion of new mutations within tumor cells in genes not related to proliferation. A major hypothesis behind the project is that function loss not related to proliferation will be favored by natural selection in the tumor cells. Such mutations are either silent, or lead to a loss of a function in a generally inactive gene. The first task of the project is to connect mutation probabilities to functions necessary for cell survival in case of external stimuli. Such stimuli can come in form a drug treatment, a radiation or a physical force. Then, the best hits are investigated in cell culture systems. Finally, a link to the TME will be established.

Expected results: 1) Ranked list of proteins based on gene size and necessity of the protein for survival after a non-lethal effect. 2) Assessment of these effects after an experimental treatment using the top five best possible combinations. 3) Investigation of the prevalence in actual tumor tissues in relation to TME. **Contingency Plan:** Tumor heterogeneity might pose as a significant bias for the identification of such a target. To overcome this limitation, the combination of multiple simultaneous therapies will be evaluated.

Planned secondment(s): Year 1: B6-DKFZ (6 months for protein network analyses). Year 2: B2-UniCampania (3 months for new strategies to investigate best hits). Year 3: B5-BRIC (3 months for tumor context analysis). CS: B6-Krijgsveld.

ESR 14	B9, geneXplain, Kel (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 1,2,3,6

Project Title/ WP: Upstream analysis of signaling and regulatory network of cancer cells in immune system microenvironment (WP3).

Objectives: Complex interaction between cancer cells and their microenvironment consisting of various cells of immune system plays an important role carcinogenesis and in response to anti-cancer therapy. Modeling of these interactions is an important task for development of the effective drugs and drug combinations. The goal of this project is development of computational methods of analysis of multi-omics data, balk as well as single cell resolution, that will help to delineate the signal transduction networks acting in the cancer cells and in interacting with them immune cells. The novel methods will be developed for analysis of signal transduction and gene regulatory networks communicating between different cells in the tumor microenvironment. These methods will help to identify master regulators of these networks governing gene expression in each cell type and propose the drug combinations potentially effective in different cancer sub types. We will apply these methods to various data sets available in the project for breast cancer, colorectal cancer and AML and will build the corresponding network models and identify master-regulators. Finally, the developed models will be validated by the data of cancer treatment by various anti-cancer targeted drugs in combinations with drugs modulating immune system.

Expected results: (1) Construction of reference signal transduction network of various cancer cells and cells of immune system as well as collecting information on tumor-innate immune cell interaction and the reprogramming of macrophages. Reference network will include information from such databases as TRANSPATH, Reactome, KEGG, Disease maps and other databases. (2) Developing upstream analysis algorithm for reconstructing of interacting signaling and gene regulatory (using TRANSFAC, Hocomoco, Jasper databases) networks of cancer cells and other cells in the microenvironment. The networks are interacting via secreted peptides and proteins that will be studies in the other sub-projects of this project. The algorithm will help to identify master regulators of these networks governing gene expression in each cell type and propose the drug combinations potentially effective in different cancer sub types. (3) Application of these methods to various data sets available in the project for breast cancer, colorectal cancer and AML and will build the corresponding network models and identify master-regulators. (4) Validation of the developed models by the data of cancer treatment by various anti-cancer targeted drugs in combinations with drugs modulating immune system. **Contingency Plan:** Existing knowledge on signal transduction networks and their interacting factors is still not full. This may hinder the results of the modeling. We will use various bioinformatics algorithms and text mining tools to get or predict missing interactions in the networks.

Planned secondment(s): Year 1: B3-CRM (3 months for learning statistical methods). Year 2: B1-IDIBELL (3 months for data analysis). CS: B1-Pujana.

ESR 15	B10, leadXpro, Hennig (BS)	PhD enrolment Y	Start date Month 6	Duration 36 months	Deliverables: 2,6,7

Project Title/ WP: Chemical biology for proton sensing receptors as drug targets (WP6,7)

Objectives: Acidosis is considered a defining hallmark of the tumor microenvironment protecting the cancer cells from immune response. Acid-sensing ion channels (ASICs), transient receptor potential channel vanilloid subfamily (TRPV), and proton-sensing

GPCRs are some of the potential drug targets and are highly upregulated in numerous types of cancer. In particular, emerging evidence has revealed that proton sensing receptors such as GPR65, GPR68 may play crucial roles in tumor biology, including tumorigenesis, tumor growth, and metastasis. By identification of chemical tool compounds by structure based drug discovery, chemical biology will contribute to a better understanding of the role of these targets and open opportunities for drug discovery.
Expected results: Setup of structures and assays for the identification of compounds to investigate the mode of action of proton sensing proteins with respect to the interaction of innate immune response and tumor cells and their environment. We will identify small molecule modulators of proton sensing proteins. **Contingency Plan:** In order to establish biophysical assays as well as structural information, expression, solubilization and purification of the proteins needs to be established. We will focus on the proteins identified with greatest confidence. In case these proteins are not feasible, other candidate proteins can be followed up on. In particular the ASIC and TRPV channel proteins have shown good feasibility.
Planned secondment(s): Year 1: B1-IDIBELL (3 month, cancer data analysis and integration). Year 2: B5-BRIC (3 month, tumor studies), Year 3: B6-DKFZ (3 month for impact of drugs to secretory crosstalk). CS: B6-Krijgsveld.

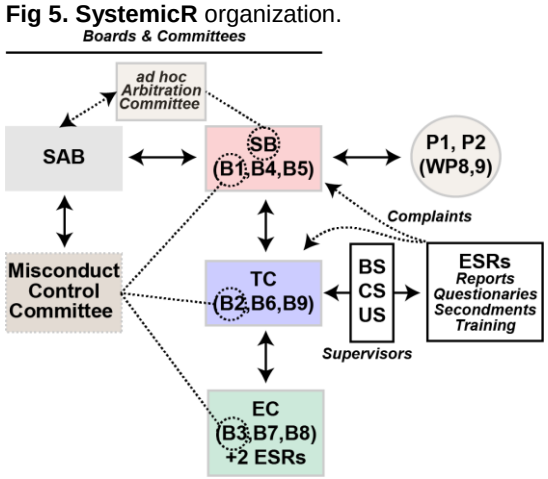
3.2 Appropriateness of the management structures and procedures

3.2.1 Network organization and management structure.

SystemicR is based on the training experience, research activity, involvement of beneficiaries in EU projects, and on lessons learned and the exploitation of methods and tools. Dr. Pujana is the coordinator and will manage all activities with the support of a full-time Project Officer that will be hired at B1-IDIBELL. The funds (**financial and administrative tasks**) will be managed centrally by IDIBELL that has extensive experience with coordination of EU consortia, including two active ITN networks. The funds will be managed in accordance with EU-ITN rules and distributed to network members to cover the costs of providing training at the network-wide meetings, workshops, courses, as well as material required for program diffusion and events. This is particularly relevant for P1 and P2, which have projected specific budgets. All expenditure will be reported at 6-month intervals via the coordinator to all beneficiaries and partners.

The **strategy for dealing with scientific misconduct** will be steered by the **TC** with the advice of the **SAB** and will be reported to the **SB** and **EC** (detailed committees in section 1.1.2). The rules will be included in each PCDP and in the **Consortium Agreement (CA)**[79]. Each group leader will be responsible for evaluating the quality of raw experimental data. Should scientific misconduct be identified, the PI or ESR will notify to the TC or SB or EC (to avoid difficulties regarding misconduct origin and notification), and then the three committee chairs (**B1-Pujana**, **B2-Altucci**, and **B3-Alarcon**; **Misconduct Control Committee**) will coordinate subsequent actions, which will first follow the rules of the involved institution(s). In parallel, all consortia members will be notified by the **SB** and each situation will be evaluated according to the **European Code of conduct for Research Integrity**[80]. Governance and executive bodies will base their decision making on the principle of consensus finding and simple majority votes. If necessary, the coordinator shall call for a conflict resolution meeting, as will be specified in the CA. The decision-making process will also be outlined in the CA. Conflict resolution will be performed in increasing order of authority, the last step being the creation of an ***ad hoc*** **Arbitration Committee** by the **SB** with the supervision of the **SAB**.

Fig 5. SystemicR organization.



3.2.2 Supervisory board. The **SB** oversees and is the executive body of the program, being constituted by the coordinator **B1-Pujana**, **B4-Stunnenberg** and **B5-Erler**. The SB is critically supported by the **SAB**, constituted by five internationally reputed scientists/professionals in cancer research and treatment, translation of preclinical findings and/or clinical research:

- **Dr. Mariona Graupera** (ES), expert in PI3K signaling and angiogenesis, and coordinator of an active ITN[81].
- **Prof. Marianne Rots** (NL), Professor of Molecular Epigenetics at the University of Groningen and member of another active ITN consortium[82].
- **Prof. Saverio Minucci** (IT), Division Director at the European Institute of Oncology, and Associate Professor of Pathology at the University of Milan, with research activity centered on the deregulation of chromatin structure/function in cancer.
- **Prof. Josep Tabernero** (ES), Director of the Vall d'Hebron Institute of Oncology (VHIO)[83], ESMO past-president, and principal Investigator of several clinical trials assessing novel therapeutic approaches for cancer.
- **Prof. Marion Wiesmann** (CH), Director Oncology Drug Discovery Novartis Institutes for Biomedical Research with renowned expertise in target and drug discovery, and translation of preclinical results.

The **SAB** will provide strategic guidance and an independent review of program activities, including quality of the deliverables, corrective measures to ensure progress if necessary, and exploitation of research results and input on leadership. They will advise on project strategies, and oversee any ethical or miscount issue. They will be

[79] "How to draw up your H2020 consortium agreement" v2.2, EC Directorate-General for Research & Innovation.
[80] "The European Code of Conduct for Research Integrity", 2017, ALLELA, Germany.
[81] ITN "PhD - PI3K Biology in Health and Disease".
[82] EpiPredict ITN to train a multidisciplinary cohort of ESRs in a new approach to fully exploit the epigenetics of complex diseases.
[83] Vall d'Hebron Institute of Oncology (VHIO) Director and Program.

invited to attend to each network meeting to advise and provide objective assessment of the scientific and innovation/exploitation-related findings.

3.2.3 Recruitment strategy

The strategy will follow the **MSCA mobility rules**[84] and the principles defined by the **European Charter for Researchers and Code of Conduct for the Recruitment of Researchers**[85]. To efficiently implement the process, a **joint call by all beneficiaries** (B1-B9) will be published by month 2 and followed by: i) initial selection of best curriculums (call open for at least 2 months); ii) evaluation/contact to referees; iii) virtual interviews and, when possible, face-to-face interviews (by the corresponding supervisors (BS and CS), secondment PI (if different from CS) and with participation of at least one SB and TC members); iii) panel virtual discussion among the beneficiaries; iv) initial selection communicated to the SAB for advice; v) decision notifications; and vi) signature of contracts, preferably prior to month 6. The call will be advertised by **WP1** at the program website, through social media, and at the **EURAXESS** platform. Efforts will be made to identify qualified women and minorities as applicants, in parallel of diverse discipline degrees. The assessment of candidates will include academic qualifications, academic/non-academic experience, achievements, communication skills, mobility, interest in dissemination and exploitation, interest in disease care and social needs, and the will and potential to grow through multidisciplinary training. Prior to the selection, best practices for recruitment and mentoring will be reminded and exposed to all beneficiary PIs at the course of **Mentoring and Coaching Researchers** (month 1).

3.2.4 Progress monitoring and evaluation of individual projects

Each ESR research project and BS-CS supervisors are already identified at the time of the proposal submission (**Table 3.1d**). A **project written report** will be produced by the ESR every six months, corrected/discussed/agreed by supervisors, and then provided first to the TC, and subsequently to the SB and SAB for evaluation/advice. Feedback comments, recommendations, and/or approvals/rejections to the reports will be provided to the ESR and supervisors within the subsequent month. **If serious concerns are raised** that hamper continuation of the project as it was originally defined, the ESR and supervisors will redefine the study following the indications of the **SAB and in coordination with a committee composed by the program coordinator (B1-Pujana) and TC chair (B2-Altucci)**. The changes should then be approved by the SAB, TC and SB. Yearly reviews will be based on the reports and on mandatory oral presentations for all ESRs at each network meeting. The above reports, presentations, in addition to the biannual questionnaires will be administered and assessed through the program intranet, providing a rapid and efficient platform for reviews and feedbacks. Each year, the SB will complete a detailed written evaluation of the entire program, including evaluations/recommendations for research projects, which will be delivered to EU-ITN representatives, all consortium members and SAB.

3.2.5 Risk management

The contingency plans for each ESR project have been defined in **Table 3.1d** and the implementation risks are detailed in subsequent **Table 3.2a**. **SystemicR** has established measures at the following **critical levels: recruitment, ESR motivation/drop off, interdisciplinary alignment, and delivery of Milestones**.

Risk No.	Description of Risk	WP No.	Proposed mitigation measures
1	Delay in recruitment	1	City2science and external support for posting diffusion, including websites Nature jobs, Science Careers and Academic Positions. Enhance diffusion through national research networks where beneficiaries participate
2	Conflicts among beneficiaries	1	In case of a conflict of interest between academic and/or non-academic participants (leading to compromised science/dissemination/innovation) the SB will enforce a decision supported by the SAB and with eventual *ad hoc* Arbitration Committee (section 3.2.1), keeping with the CA
3	Poor supervision of ESR	1-2	SB will call a meeting with the TC and the supervisor to evaluate the situation; provide suggestions and monitor improvement and if necessary, assigned a co-mentor (additional CS) within the same WP and ideally from one of the secondment laboratories
4	PCDP incomplete	2	TC will get advice from the SAB to complete it
5	Website/intranet delayed	1-8	Refocus design to finalize the project and get external-contracted support
6	Keynote speaker or course cancelled last minute	1	Recruit new speaker/course or PIs will replace the speaker/course teaching masterclass on a relevant theme for the network and based on their expertise
7	Insufficient outreach	8	Involve the SAB and further WP9 for support and improvement advice
8	Drop-out of PI (e.g. due to change appointment)	1-2	Keep collaboration within the network and/or adapt research and training plan, if necessary
9	ESR poor motivation and/or drop-off from program before completion of PhD	2	**SystemicR** is aware of ITN challenges might increase PhD drop-off in some settings; all beneficiary PIs are aware of this relevant issue and will carefully monitor any sign of lack of motivation, disconformity or related. If noticed, a Supervisors-TC meeting will be held to subsequently approach the ESR for improving the situation. In parallel, the biannual questionnaires will include specific questions directed to detect the level of motivation and likelihood of drop-off
10	Insufficient data and collaborative results	4-7	Strict management and coordination by each WP leader will be required using the defined periodic virtual meetings, with specific invitations to SAB members and other key scientists to provide advice for enhancing data/results

[84] Guide for Applicants, Marie Skłodowska-Curie Actions Individual Fellowships, v. 1.3, July 2019, H2020 Programme.
[85] "The European Charter for Researchers, The Code of Conduct for the Recruitment of Researchers", 2005, EC Directorate-General for Research.

11	Technical difficulties/limitations with preclinical cell and mouse models	4,5	Should any beneficiary encounters difficulties or limitations, issues will be resolved through communication within the network looking for alternative models through collaborators
12	Inefficient integration between biology and informatics	3	To ensure seamless cross-disciplinary supervision, each ESR will be assigned two different mentors, one for biology and one for informatics disciplines. Enhanced participation of WP3 leader and other bioinformatics PIs in the periodic virtual meetings of the WPs 4-7
13	ESR does not perform at an adequate standard to progress	2	Redefinition of PCDP goals according to his/her capabilities and secondments. If no resolution is feasible and hampers project goals, the ESR will submit the work for an MSc (by research)/MPhil instead of a PhD
14	Delay or fail to deliver specific Milestones	1	The SB will monitor timing and if potential delays or delivery issues are predicted, the SAB will be contacted for obtaining advice to avoid these problems. If no resolution, related Milestones will be adjusted to embrace results for the delayed/failed one

3.2.6. Intellectual Property Rights

SystemicR embraces the **DESCA model CA with respect to IPR** (section 2.3.2): *Existing background remains with the current holder and foreground developed in the scope of this project belongs to creator of this foreground*. Particularly protected background that is required to perform the research will be identified in the course of the CA preparation and will be made available through a dedicated bi-lateral agreement between provider and recipient, such as an NDA that needs to be signed by each ESR upon appointment. Any other background is excluded from project use. A Beneficiary or Partner has at any point in time the option to add background. Foreground created in the scope of this project shall be owned by the developing organization. In case of joint developments, institutions will retain the IP jointly and the institutions will develop a dedicated **Exploitation Agreement**. In the course of secondments, researchers may be requested to sign a Partnership Agreement or NDA. Beneficiaries or Partners requiring this practice will communicate the need for such practice at month 1 before CA signature. In parallel, **SystemicR** will train ESRs via these topics (workshop month 27).

3.2.7. Gender aspects

All partners in this network are committed to promote and actively pursue gender balance. Five women are groups/organization leaders in the consortium; four are WP leaders; and the SAB includes three women among five members. Initial ESR selection will carefully consider gender balance and the ESRs will be educated in this topic by local training courses or workshops, such the one implemented at B1-IDIBELL[86]. The WP1-Project Manager and the corresponding Human Resources Units will provide and explain the H2020 goals on "Promoting Gender Equality in Research and Innovation"[87] at the moment of each appointment. Hiring will also be instructed to find solutions for ESR applicants with children and partners, fully avoiding that these conditions prejudice selection. Once hired, the consortium will establish common fund from the institutional costs for gender equality support in, for example, secondments and assistance to conferences, on a case-by-case basis. Support will also be offered to any ESR wishing to pursue a complaint, which will be dealt with in a sensitive manner by the SB. Importantly, **each female ESR will be assigned a reference from one of the three female PIs (B2-Altucci, B3-Serra, B5-Erler) to provide a model, support and/or counseling related to women empowering in science**. Finally, the network will strive for equal representation of genders at the meetings and the final conference will follow the "positive discrimination" approach used in the Frontiers in Cancer Research DKFZ-organized meeting[88].

3.2.8. Data management plan

WP1 will define a **Data Management Plan** following EC recommendations[89]. This plan will be then presented to all consortium members at the kick-off meeting (month 1), provided to the **SAB** for advice, and approved. The plan should in turn be based on the **FAIR Data Management Principles** to make data findable, accessible, interoperable and reusable[90]. Given the multidisciplinary of the network, it will operate as an **Open Data** working group that gradually develops the most appropriate approaches and formats of data gathering, sharing, analysis and publication. There will be using commercial and proprietary (**WP3,6**) strategies for quality control (QC), public repositories (principally **GitHub**[91]) for software deposition and automated versioning, and for raw and metadata/processed genetic/molecular data (principally at the European Bioinformatics Institute (EBI), **ArrayExpress**[92] and **PRIDE**[93]). Most groups have experience in depositing data in these sites (**B1**, **B4-B9**). The data will be initially collected and stored at the storage/servers of respective project leaders and exchange between partners will be following the guidelines provided by the IT Services avoiding public repositories, but centered on the dedicated network intranet. All human data will be anonymized in the intranet and exchanges, and ID reversion would only possible according to the instructions of the corresponding Institutional Ethics Committee that evaluated a given project. All the data will be stored and backed up on the network storage provided by the

[86] "Empowering women in science: A workshop for women and men", February 2020, IDIBELL.
[87] "Promoting Gender Equality in Research and Innovation", Horizon2020 Work Programme.
[88] Vogel G, *Science* 2018 doi:10.1126/science.aav5694.
[89] Data Management, EC H2020 Online Manual.
[90] Wilkinson MD et al., *Sci Data*. 2016;3:160018.
[91] GitHub development platform, open source to business, host and review code, manage projects, and build software.
[92] ArrayExpress stores data from high-throughput functional genomics experiments and provides these data for reuse to the research community.
[93] Proteomics Identification Database.

IT Services of the respective project partners according to the national regulations. The data will undergo regular backup (daily, weekly, monthly) according to the setup workflows of the respective Services. The selected private data will be stored for at least five years after duration of the project using the storage facilities provided by the Services of the respective partners. The data will be made publicly accessible though the aforementioned repositories at acceptance of publications or when collaborations may foster results, and preprints will also be deposited in public repositories (mainly **bioRxiv**[94]). Besides, **SystemicR** is committed to ensuring that biomedical research resources, including cell and mouse models, are made readily available in a timely fashion to the research community in compliance with the guidelines of the **NIH Model Organisms Sharing Policy**[95].

3.3 Appropriateness of the infrastructure of the participating Organizations

The proposed work combines advanced **mathematical, epi/genetic, transcriptomic, proteomic, biochemical, cellular, histopathological, and animal studies** that require specialized equipment and facilities, all of which are available network-wide. **Cutting-edge** facilities are available to study single-cells, proteomes, molecular structures and drug mechanisms of action, and fully meet the requirements necessary for the execution of the proposed project. In those cases that the host-institute is not equipped with a particular facility, ESRs will have access to the technology via secondment at another laboratory within the network. **Level 1**: IT equipments for large data processing, analysis and storage; **Level 2**: equipments for single cell genetic, transcriptomic and proteomic profiling, including mass spectrometry-based assays and determinations of protein-protein interactions; **Level 3**: *in situ* gene and protein expression, tissue cellular distributions and interactions; and **Level 4**: integrative platforms (e.g. Galaxy, B8-geneXplain), and biophysical and structure-based methods, and drug screen platforms for the discovery and optimization of drugs/small compounds (B9-leadXpro).

3.4 Competences, experience and complementarity of the participating organizations and their commitment to the programme

3.4.1 Consortium composition and exploitation of participating Organizations' complementarities

SystemicR has been originally defined to study CaRes from a systems-biology perspective centered on the interplay between innate immune and cancer cells. Thus, it is rooted on the complementarity of its members *and not in circumstantial conditions*. There is key participation of academic, private and non-profit organizations, which overall provide the research and training expertise required for bench-to-bedside cancer research. Not only the network represents a wide spectrum of complementary expertise and skills (including cutting-edge technologies (e.g., single and *in situ* cell profiling (**B4-PMC** and **B5-BRIC**), and proteome analyses (**B6-DKFZ**)), it also provides access to clinical resources though several institutional **biobanks** (section 1.1.2) and **clinical trial units** (section 1.2.1). Prior, at the analytical basis of the consortium, there is unique expertise in data integration and interpretation (**B1-IDIBELL**), mathematical modeling (**B3-CRM**), and omic data meta-analyses (**B7-SU**). On the top of these academic opportunities, the consortium is complemented with two companies that provide unique technologies and expertise for exploitation of therapeutic targets, drug discovery and development. None of the academic groups in the consortium, and barely outside it, has the recognized potential to foster target discovery (**B8-geneXplain**) and drug discovery (**B9-leadXpro**) through the depicted comprehensive approach. This key features are aligned to the composition of the **SAB** and, in particular, with the renowned expertise of **Profs. Wiesmann** and **Tabernero** in novel therapeutic approaches and clinical translation. In turn, these features will be key for a complete training of the ESRs including innovation, business development and entrepreneurship.

3.4.2 Commitment of beneficiaries and partner Organizations to the programme

The consortium members are driven by the need to improve **cancer care** by training ESRs with multidisciplinary scientific and soft skills. Thus, full commitment is demonstrated by the **agreed leadership in key aspects of the program, including both beneficiaries and partners:** i) **WPs** (B1-IDIBELL, B2-UniCampania, B3-CRM, B4-PMC, B5-BRIC, B8-geneXplain, B9-leadXpro, P1-city2Science, and P2-ECPC); **committees** (**SB**, B1-Pujana, B4-Stunnenberg, and B5-Erler; **TC**, B3-Altucci, B6-Krijgsveld and B9-Hennig; **EC**, B3-Alarcon/Sierra, B7-Győrffy, and B8-Kel; and Misconduct control committee, B1-Pujana, B2-Altucci, and B3-Alarcon); **workshops** (P1-city2Science and P2-ECPC); and **courses** (several beneficiaries and both partners). Commitment is further endorsed by **co-supervision** of the ESRs (depicted in Table 3.1d), organization of the **annual meetings** at different sites, innovative organization of ESR **Challenges**, and of an **International Conference** as conclusion of the program. Thus, it can be anticipated that this collaborations and relationships will fund new applications and joint research projects far beyond this period. All organizations have confirmed their commitment by means of their letters of support.

As further shared commitment, the coordinator center will retain 19,4 % of Research Training and Networking Costs to finance the training organized for all ESRs of the consortium (workshops, courses, invited speakers, etc.) and associated reservation of venues, catering and travel and accommodation of the speakers. From this proportion, it will be also paid a part of the research-associated costs related to mice work, especially for the secondments. The 33,3 % of Management and Indirect Costs will be retained by the coordinator center in order to hire a Project Manager during the whole project duration, travel and accommodation for project manager and coordinator to the annual consortium meetings, cost for yearly management meetings, as well as web and logo design. Travel and accommodation of ESRs will be covered from individual beneficiaries' budget.

[94] Free online archive and distribution service for unpublished preprints in the life sciences (Cold Spring Harbor Laboratory).
[95] NIH Model Organism Sharing Policy, NIH Guide 2004.

i) Funding of non-associated third countries: Not applicable.

ii) Partner Organizations: The role of partner organizations and their active contribution to the research and training activities has been described in WPs 8-9 (page 6), and sections 1.2.2, 2.2.1, 2.4.1 (Table 2.4), and 3.1 (WP descriptions and Table 3.1a). Letters of commitment are provided in section 7.

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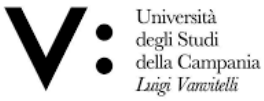
4. Participating Organisations

Beneficiary Legal Name: Institut D'Investigació Biomèdica de Bellvitge (IDIBELL), Miquel Àngel Pujana (MAP)	
General Description	Bellvitge Biomedical Research Institute (IDIBELL) is one of the most dynamic health research institutes in Spain with more than 800 researchers in the fields of basic, clinical and epidemiological research striving to attain significant improvements in human health. IDIBELL manages the research activities of Bellvitge University Hospital, the Catalan Institute of Oncology (Hospitalet), the University of Barcelona (Bellvitge Campus) and its own researchers. Research is structured into three thematic areas (cancer, neurosciences and translational medicine) with a total of 9 research programs. IDIBELL is currently merging with the Center of Regenerative Medicine of Barcelona. The project will be developed within the Catalan Institute of Oncology (ICO), entity will legal link to IDIBELL (www.iconcologia.net), which is a public non-profit center working exclusively in the field of cancer. ICO is a leader in cancer care in Catalonia. Its approach to the disease is comprehensive, combining, all in one organization, prevention, care, specialized training and research. IDIBELL's vision is turning Bellvitge Health Area into a health hub of excellence, thanks to its combination of comprehensive medical care, research experience and unique economic environment. Dr. MA Pujana (MAP) is the head of the Breast Cancer & Systems Biology research group at the ICO-IDIBELL and Director of the ICO Research Program Against Cancer Therapeutic Resistance (ProCURE). ProCURE consists of 10 research groups that have produced >800 peer-review publications, >40 patents and three spin-off companies. In this context, MAP's group combines experimental, bioinformatic and systems-level analyses to better understand cancer risk, the emergence of subtypes, and their therapeutic response/resistance. The group has recognized expertise in data integration and modeling and, thus, has produced seminal observations in the context of BRCA1-mutant breast cancer risk and development, and resistance to endocrine therapies and mTOR inhibition. MAP is author of more than 120 peer-review publications.
Role and Commitment of key persons (including supervisor)	• MAP laboratory is composed of 2 Postdoctoral fellows (E. Blommaert, hired 1 Feb 2020; F. Mateo, Research Assistant, group staff), 2 PhD students (C. Herranz (experimental biologist) and R. Espin (computer engineering), and 1 Research Technician (A. Extremera). F. Mateo will devote 25% time; E. Blommaert will devote 15% time; C. Herranz and R. Espin will devote 15% time; A. Extremera will devote 50% time; and **MAP will devote 25% time**. • The team is complementary with campus collaborations with the University Hospital Bellvitge, Department of Pathology, and IDIBELL Biobank (Drs. A Petit and T. Soler), Director of Phase I ICO Clinical Trials Unit (Dr. R. Salazar), Director of Molecular Diagnosis Unit ICO-IDIBELL (Dr. C. Lázaro), and Head of Breast Cancer Clinical Unit (Dr. S. Pernas).
Key Research facilities, infrastructure and Equipment	IDIBELL has all the facilities, infrastructure and equipment necessary to promote and support innovative, cutting edge research. IDIBELL has a total laboratory area of 5,000m2, including shared facility areas such as rooms for cell culture, licensed radioisotope use, histology, microscopy (including confocal and time-lapse), PCRs, flow cytometry, sequencing services, an animal house, pathology unit, bioinformatics unit, proteomic unit, etc. It also has a set of centralized platforms dedicated to developing and providing research resources to assist the campus' biomedical researchers.
Status of Research Premises	IDIBELL is an independent entity with wholly independent research premises. All infrastructures described above are owned by IDIBELL.
Previous Involvement in Research and Training Programmes, including ITN	IDIBELL has a longstanding track-record in the participation in and successful coordination of European projects, including Marie Skłodowska-Curie Actions (MSCA). The International Projects Unit in the Research Support Office managed 38 projects in FP7 and H2020, 15 of which are from the MSCA programme (7 MSCA-ITNs and 8 MSCA-IFs), 6 ERCs and 14 coordinated projects, 2 of them financed by IMI. 18 projects funded under H2020 projects are still active: 8 MSCA, 1 IMI project, 9 EU coordinated projects. IDIBELL is also managing 8 projects financed by prestigious international organizations, including the National Institutes of Health (NIH) and Worldwide Cancer Research, Ciência sem Fronteiras. Also, IDIBELL manages over 300 national grants.
Current Involvement in Research and Training Programmes, including ITN	• IDIBELL is currently leading 1 MSCA-ITN projects which are still active: META-CAN (2017-2021). IDIBELL is also participating in another MSCA-ITN as beneficiary: TRAIN-ERS (2015-2019), Phd (2015-2019) and 5 MSCA-Individual Fellowships: PORTAL (2018-2020), MECoCAM (2018-2020), M-LYSOSOMES (2019-2021), MEsHH (2018-2020); PI3K-Vas (2018-2020). • MAP is a group leader with expertise in human genetics, cancer biology, bioinformatics, and systems biology. MAP laboratory is composed of 2 Postdoctoral fellows (E. Eline Blommaert, hired 1 Feb 2020; F Mateo, Research Assistant, group staff), 2 PhD students (C. Herranz (experimental) and R. Espin (computational biology), and 1 Technician (A. Extremera). • MAP is the leader of the OpenLab educational program of the ICO-IDIBELL for the patients and general public. He also teaches annually at the PhD program on Biomedicine by the University of Barcelona-Bellvitge campus with the topic "Cancer Target Therapies and Resistance" (Dr. F. Viñals coordinator), and at the "Translational Molecular Oncology Planning" MSc program of the Autonomous University of Madrid, School of Medicine (Dr. G. Moreno coordinator).
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	None
Relevant Publications and/or research/innovation product	• Decapping protein EDC4 regulates DNA repair and phenocopies BRCA1. ***Nature Communications*** 2018 Mar 6;9(1):967. • Stem cell-like transcriptional reprogramming mediates metastatic resistance to mTOR inhibition. ***Oncogene*** 2017. May 11;36(19):2737-2749 • Cancer network activity associated with therapeutic response and synergism. ***Genome Medicine*** 2016. Aug 24;8(1):88. • Integrating germline and somatic data towards a personalized cancer medicine. ***Trends in Molecular Medicine*** 2014. 20(8):413-5. • Interplay between BRCA1 and RHAMM regulates epithelial apicobasal polarization and may influence risk of breast cancer. ***PLoS Biology*** 2011. Nov;9(11):e1001199.

Beneficiary Legal Name: UNIVERSITÀ DEGLI STUDI DELLA CAMPANIA LUIGI VANVITELLI (UNICAMPANIA)	
General Description 	The University of Campania "Luigi Vanvitelli", formerly Second University of Naples, with its 16 departments located in 5 territorial areas between Naples and Caserta, promotes a vocational training offer integrated with the territory, supports quality research, and promotes the creation of business initiatives from research groups, in a constant perspective of internationalization and cultural exchange with other universities. The Department of Precision Medicine responds to the need to develop a knowledge that integrates the precision of new biomolecular technologies for diagnosis, prognosis & prevention of pathologies with the clinical approach, contact with the patient. It intends to make concrete the will to bring "to the patient's bed" the precision of the new diagnostic and therapeutic resources.
Role and Commitment of key persons (including supervisors)	**Lucia Altucci MD, PhD, specialist in Medical Oncology** 35%, full Professor of General Pathology studies the deregulation of epigenome as a key element in pathologies. The objective of research is the characterization of i) new biomarkers for the diagnosis of pathologies and ii) new drugs for the treatment of tumors, based on interference with epigenetic signaling mechanisms. **Fortunato Ciardiello, Oncologist & President of the school of Medicine** (35%). He published nearly 400 research articles, H-index 87. In the project he will follow the preclinical and clinical phases. **Rosaria Benedetti, PhD, Assistant professor,** specialised in Clinical pathology **(**Involvement 50%**).** She will be devoted to follow directly ESR3's project on the identification of MDSC in cares. **Vincenzo Carafa, senjor assistant professor,** specialized in genetics and expert of cell death deregulation in AML. Involvement 50%. He will be devoted to follow directly ESR4's project on the identification of tumor microenvironment role in AML. **Giovanna Marmo** (PhD program manager & project assistant) **50%.** She will be the contact point for all PhD students enrolled in this ITN to the PhD program.
Key Research Facilities, Infrastructure and Equipment	Novaseq6000 Illumina coupled with ddSEQ Single-Cell Isolator, xCELLigence RTCA DP instrument, ACEA; Bio-rad QX200 droplet digital PCR; PerkinElmer EnSpire plate reader; BioTek Cytation imaging reader; 3 Tesla MRI Scanner, TECAN-EVO robotic station. A large animal house and cell sorter facilities are also on the premises. High Technological facilities are: The Sequencing & Synthesis Facility. The Proteomics Resource Facility equipped with mass spectrometers, robotics for mass spectrometry sample preparation, high-throughput two-dimensional gel electrophoresis units, and an automated chromatography station for multi-dimensional chromatography. There is also an NMR station for structure analysis and a confocal microscope. The Functional Genomics Resources Facility. CGA, a multifunctional structure dedicated to biotechnological processes with operational capacities up to the pilot scale. The laboratory obtained the UNI EN ISO 9001-2008 accreditation for multidisciplinary design and services applied to research. In addition, for MD, there is access to the facilities of the Universitary Hospital where Ciardiello leads the Oncology program and Altucci the Medical Epigenetics program. For more info: http://www.policliniconapoli.it
Status of Research Premises	Research facilities are available for beneficiaries in full; they are owned by the Department and University.
Previous Involvement in Research and Training Programmes, including ITN	-Programma Operativo Nazionale "Ricerca e Competitività" PON01_01227: Development of Sirtuin modulators as a novel therapeutic approach in neurodegenerative, oncology and cardiovascular disease. Acronym: 'SIRT-IN'; -Programma Operativo Nazionale "Ricerca e Competitività" PON01_02782: Novel nanotech strategies for development of drugs and diagnostics for targeting of circulating cancer cells; -H2020 COST action: Epigenetic Chemical Biology – Action CM1406H2020 –RISE 'Ocean Medicines', on-going, GA n° 690944.
Current Involvement in Research and Training Programmes, including ITN	-H2020 –RISE 'Ocean Medicines', GA n° 690944. -POR FSE Campania 2014-2020 (DOTTORATI DI RICERCA CON CARATTERIZZAZIONE INDUSTRIALE" - DGR N. 156 DEL 21/03/2017-DD N. 155 DEL 17/05/2018 - A VALERE SUL POR CAMPANIA FSE 2014/2020 - OBIETTIVO SPECIFICO 14- AZIONE 10.4.5. - MODIFICA DD N. 321 DEL 27/09/2018):training for industrial PhD programs PhD in Traslational medicine DOT1349104 -Programma Operativo Nazionale FSE-FESR "Ricerca Innovazione 2014-2020" Azione I.1 "Dottorati innovativi con caratterizzazione industriale" del PON R&I 2014-2020, finalizzate al sostegno dei percorsi di dottorato di ricerca
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	I declare that I have not submitted similar proposals
Relevant Publications and/or Research / Innovation Product	BRD9 binds cell type-specific chromatin regions regulating leukemic cell survival via STAT5 inhibition. **PMID: 31000698** *I BET* on anti-FGFR to fight cancer resistance. **PMID: 30610114** RIP1-HAT1-SIRT Complex Identification and Targeting in Treatment and Prevention of Cancer. **PMID: 29535128** miR-194-5p/BCLAF1 deregulation in AML tumorigenesis. **PMID: 29271969** Distinct Trends of DNA Methylation Patterning in the Innate and Adaptive Immune Systems. **PMID: 27851971**

Consorci Centre de Recerca Matematica (CRM) / T. Alarcon (TA), I.Serra (IS)	
General description 	The Centre de Recerca Matematica (Centre for Mathematical Research, CRM) is part of the CERCA network of catalan research centres. Its purvue include conducting research in Collaborative and Applied Mathematics and doing transfer of state-of-the-art mathematical knowledge to industry. Currently, CRM is composed of 10 research groups organised in four general topics of applied mathematics, namely, Complex Systems, Computational & Mathematical Biology, Computational Neuroscience, and Industrial Mathematics, and an office of Knowledge and Technology Transfer.
Role and Commitment of key persons (including supervisor)	TA will lead the Theoretical Modelling work package. TA has ample experience in stochastic/multiscale modelling in Integrative Systems Biology. IS is an expert in statistics and data science, including machine learning. Both TA and IS will co-supervise the PhD students hosted by CRM.
Key Research facilities, infrastructure and Equipment	CRM runs a computational cluster consisting of 7 DELL computing servers and 1 storage server (15TB). CRM also has facilities and dedicated staff for organisation of conferences and workshops.
Status of Research Premises	The CRM has its premises in the UAB Faculty of Sciences with a total floor space of 2.125 m2, including administration and direction offices, office space for up to 60 researchers, three meeting rooms, three lecture rooms with capacity for 40 people and an auditorium with capacity for 100 people. All lecture and meeting rooms are equipped with overhead projectors and streaming facilities. The CRM computer equipment is based on a LAN Ethernet net of, approximately, eighty workstations structured under a Windows/Linux domain. Among other services, the net includes an e-mail server, a printer server (managing the tasks of five printers), a file server and a Firewall/Router that linked it to the UAB infrastructure by means of a 1 Gb connection. Wi-Fi connection is available in all rooms. There is an experimental lab in Microfluidics and Rheology.
Previous Involvement in Research and Training Programmes	Participation in Research Training Networks “Using Mathematical Modelling and Computer Simulation to Improve Cancer Therapy” (RTN-2000-00105) and “Modelling, Mathematical Methods and Computer Simulation of Tumour Growth and Therapy” (MRTN-2004-503661).
Current Involvement in Research and Training Programmes	CRM is the coordinator node of the H2020 ITN “Climate Advanced Forecasting of sub-seasonal Extremes (CAFE)”, MSCA ITN 2018 H2020, Grant Agreement number 813844. It is also the coordinating institution of the Maria de Maeztu Unit of Excellence “BGSMath”, MDM2014-0445
Relevant Publications and/or research/innovation product	1.- J.A. Menendez, E. Cuyas, N. Folguera-Blasco, S. Verdura, B. Martin-Castillo, T. Alarcon. In silico clinical trials for anti-aging therapies. Aging. 11, 6591-6601 (2019) 2.- N. Folguera-Blasco, R. Perez-Carrasco, E. Cuyas, J.A. Menendez, T. Alarcon. A multiscale model of epigenetic heterogeneity reveals the kinetic routes of pathological cell fate reprogramming. PLos Comp. Biol. 15, e1006592 (2019) 3.- N. Folguera-Blasco, E. Cuyas, J.A. Menendez, T. Alarcon. Epigenetic regulation of cell fate reprogramming in aging and disease: A predictive computational model. PLoS Comp. Biol. 14, e1006052 (2018). 4.- J.A. Menendez, B. Corominas-Faja, E. Cuyas, M.G. García, S. Fernandez-Arroyo, A.F. Fernandez, J. Joven, M.F. Fraga, T. Alarcon. Oncometabolic nuclear reprogramming of cancer stemness. Stem Cell Reports. 6, 273-283 (2016) 5.- L. Willis, T. Alarcon, G. Elia, J.L. Jones, N. Wright, T.A. Graham, I.P.M. Tomlinson, K.M. Page. Breast cancer dormancy can be maintained by a small number of micrometastases. Cancer Research. 70, 4310-4317 (2010).

Beneficiary Legal Name: Prinses Maxima Centrum Voor Kinderonkologie BV (PMC)	
General Description 	The Princess Maxima Center is with 600 patients per year it is the largest European cancer center for children. It is a unique center that has centralized all care and research for children with cancer of the whole Netherlands. Its mission is to bring the best possible patient care and scientific research together to cure every child with cancer and to provide them with optimum quality of life. Researchers and clinicians work together within one institute, allowing a very close connection and optimal setting to translate fundamental research into the clinics. Within the Maxima Center we have access to state-of-the-art facilities including; Biobank, FACS, Genomics, organoid technology, mouse facilities, epidemiology and a phase I/II trial center.
Role and Commitment of key persons (including supervisors)	**Hendrik G. Stunnenberg (male) PhD**: is senior PI at the Princess Maxima Centre for Pediatric Oncology and Professor at the Radboud University, Nijmegen, The Netherlands. He is a member of EMBO since 1993. He has supervised more than 50 PhD students in the course of his career. He will act as the supervisor and promoter of the ESRs. He will dedicate 20% of his time to this task.Stunnenberg laboratory is deeply involved in the study of the mechanisms underlying gene transcription and the role that chromatin plays in these processes. His team has very extensive experience in determining the chromatin structure (3D organisation) and histone profiling in various model systems. His lab has performed an extensive, systems biology approach on embryonal stem cells in the context of an ERC advanced grant. Furthermore, his lab has performed epigenetic profiling of all human blood cell types and blood cancers as part of the BLUEPRINT EC FP8 High Impact Project of which Stunnenberg was the coordinator. This work has opened up new avenues and new concepts. The collaborative work at unraveling innate immune response in infection has caused a paradigm shift in innate immunology showing that in contrast to current believes, innate immune cells do have a memory of previous exposures to pathogens. More recently, team has gone into the stud of single cells using single cell (sc)RNA- and ATAC-seq. The efforts are focused on pediatric (brain tumors and Acute Myeloid leukemia)and adult cancers (colorectal cancer). Single cell technology implies that tissues are dissociated into single cells which implies that the spatial organization of tissues and tumors is lost. The team has started to employ state-of-the-art spatial transcriptomics, in situ sequencing and imaging approaches **Dr Wout Megchelenbrink** (male), assistant professor will provide daily supervison and support in particular in bioinformatic analysis. He has supervised many PhD and master students. **Dr Peter Brazda** (male), senior post-doc who will provide, daily supervison of the ESR in particular at the level of experimental approaches. He has ample experience in single cell analysis as well as in imaging approaches. He will spend 20% of his time.
Key Research Facilities, Infrastructure and Equipment	The standard single cell RNA-seq platform is a modification of the SORT-Seq approach involveing FACS sorting of cells (in the onsite facility) into 384-well plates. Alternative, the Chromium 10X equipment can be used when higher throughput is essential to be able to detect rare subpopulations of cells. The center has set up bioinformatics infrastructures with a state-of-the-art imaging, High-Performance Computing facility, workflow management systems, and data sharing facilities.
Status of Research Premises	The standard single cell RNA-seq platform is a modification of the SORT-Seq approach involving FACS sorting of cells (in the onsite facility) into 384-well plates. A Chromium 10X equipment for higher throughput is part of the facilities capable to detect rare subpopulations of cells. The center has set up bioinformatics infrastructures with a High-Performance Computing facility, workflow management systems and data sharing facilities. All necessary equipment and facilities are property of the PMC Center.
Previous Involvement in Research and Training Programmes, including ITN	Prof **Stunnenberg** has been involved in Research and Training Programs from the early start of the EU Framework Programmes, especially in FP6 (e.g. EPITRON, X-TRA-NET, BioMalPar, HEROIC (coordinator) and FP7 (ATLAS, Cancer DIP, BASIS, SYSCOL, GENCODYS, ParaMet, BLUEPRINT (coordinator)). Moreover, he was the founder and main organizer of the biennial EMBL meeting on transcription (participation of > 200-250 young researchers) from 1994-2012. He has supervised >50 PhD students and 40 post-docs.
Current Involvement in Research and Training Programmes, including ITN	Stunnenberg is currently involved in several research and training programs, and currently supervises one ESR (male) from the AipBand ITN and 3 others ESRs (3 female): · Dutch Cancer Foundation grant: The molecular signature of ETS factors in Acute Myeloid Leukemia · Dutch Cancer Foundation grant: Loss of hydroxy-methylcytosine and its role in tumorigenesis through epigenetic deregulation . ZonMW: Epigenetic targeting for prevention of sepsis-induced macrophage tolerance in humans · NWO-ALW-open: Programming human macrophages . EU ITN AipBand
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	*none*
Relevant Publications and/or Research / Innovation Product	• Atlasy N., Bujko A., Brazda P.B., Janssen-Megens E. , Bækkevold E-S. , Jahnsen F.L., Stunnenberg H.G. **Single cell transcriptome atlas of immune cells in human small intestine and in celiac disease. BioRxiv** August 01, 2019. • Atlasi Y, Megchelenbrink W, Peng T, Habibi E, Joshi O, Wang SY, Wang C, Logie C, Poser I, Marks H, Stunnenberg HG. Epigenetic modulation of a hardwired 3D chromatin landscape in two naive states of pluripotency. Nat Cell Biol. 2019 May;21(5):568-578. doi: 10.1038/s41556-019-0310-9. Epub 2019 Apr 29. • **Stunnenberg HG**; International Human Epigenome Consortium., Hirst M. The International Human Epigenome Consortium: A Blueprint for Scientific Collaboration and Discovery. ***Cell*****.** 2016; 167(5):1145-1149. • Novakovic B, Habibi E, Wang SY, Arts RJ, Davar R, Megchelenbrink W, Kim B, Kuznetsova T, Kox M, Zwaag J, Matarese F,van Heeringen SJ, Janssen-Megens EM, Sharifi N, Wang C, Keramati F, Schoonenberg V, Flicek P, Clarke L, Pickkers P, Heath S, Gut I, Netea MG, Martens JH, Logie C, **Stunnenberg HG**. β-Glucan Reverses the Epigenetic State of LPS-Induced Immunological Tolerance. ***Cell***. 2016; 167(5):1354-1368.e14. • Saeed S, Quintin J, Kerstens HH, Rao NA, Aghajanirefah A, Matarese F, Cheng SC, Ratter J, Berentsen K, van der Ent MA, Sharifi N, Janssen-Megens EM, Ter Huurne M, Mandoli A, van Schaik T, Ng A, Burden F, Downes K, Frontini M, Kumar V, Giamarellos-Bourboulis EJ, Ouwehand WH, van der Meer JW, Joosten LA, Wijmenga C, Martens JH, Xavier RJ, Logie C, Netea MG, **Stunnenberg** HG. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science.* 2014; 345: 1251086.

KOBENHAVNS UNIVERSITEIT /BIOTECH RESEARCH & INNOVATION CENTRE (BRIC)	
General description	Biotech Research & Innovation Centre (BRIC) was established in 2003 by the Danish Ministry of Science, Technology and Innovation to form an elite centre in biomedical research. Our aims are to: • perform interdisciplinary, cutting-edge research • establish a strong research education programme • attract funding and new research projects • ensure that research results are used for the development of commercial products • promote exchange of ideas within the Danish biotech research community
Role and Commitment of key persons (including supervisor)	Prof Janine Erler, leader of WP7, supervisor of ESR
Key Research facilities, infrastructure and Equipment	*In vivo* mouse models including patient-derived xenografts and transgenic mouse models. ESRs at BRIC will be enrolled in the MoMed Program, which offers a wide range of training courses to PhD students plus an annual retreat. There are also weekly BRIC internal and external seminar series that PhD students can benefit from.
Status of Research Premises	Mice are kept in the animal facility in the basement of the BRIC building. This facility is run independently from BRIC. Thus cage and service charges exist, and appropriate training is required for Access.
Previous Involvement in Research and Training Programmes	Prof Erler runs a PhD program on the "Tumor Microenvironment and Metastasis" (2016+2019)
Current Involvement in Research and Training Programmes	Prof Erler teaches once a year on a PhD course "Matrix Biology".
Relevant Publications and/or research/innovation product	Cox TR, Rumney RMH, Schoof EM, Perryman L, Høye AM, Agrawal A, Bird D, Latif NA, Forrest H, Evans HR, Huggins ID, Lang G, Linding R, Gartland A#, **Erler JT#.** The hypoxic cancer secretome induces pre-metastatic bone lesions through lysyl oxidase; Nature 522 (2015), pp. 106-10. (#co-corresponding) Madsen CD#, Pedersen JT, Venning FA, Singh LB, Moeendarbary E, Charras G, Cox TR, Sahai E#, **Erler JT#.** Hypoxia and loss of PHD2 inactivate stromal fibroblasts to decrease tumour stiffness and metastasis. EMBO Reports 16 (2015), pp.1394-408. (#co-corresponding) Miller BW, Morton JP, Pinese M, Saturno G, Jamieson NB, McGhee E, Timpson P, Leach J, McGarry L, Shanks E, Bailey P, Chang D, Oien K, Karim S, Au A, Steele C, Carter CR, McKay C, Anderson K, Evans TR, Marais R, Springer C, Biankin A, **Erler JT#**, Sansom OJ#. Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: Inhibition of LOX abrogates metastasis and enhances drug efficacy; EMBO Molecular Medicine 7 (2015), pp.1063-76. (#co-corresponding) Baker AM, Bird D, Welti JC, Gourlaouen M, Lang G, Murray GI, Reynolds AR, Cox TR, **Erler JT.** Lysyl oxidase plays a critical role in endothelial cell stimulation to drive tumor angiogenesis; Cancer Research 73 (2013), pp. 583-94. Baker AM, Cox TR, Bird D, Lang G, Murray GI, Sun XF, Southall SM, Wilson JR, **Erler JT.** The Role of lysyl oxidase in SRC-dependent proliferation and metastasis of colorectal cancer; Journal of the National Cancer Institute 103 (2011), pp. 407-24.

Beneficiary Legal Name: Deutsches Krebsforschungszentrum / German Cancer Research Center (DKFZ)

General Description 	DKFZ is the Germany's largest biomedical research center with a worldwide reputation of excellence in basic and translational cancer research. Established in 1964 as a foundation under public law, the DKFZ today has a staff of about 3070 (whereof 632 employees come from 80 foreign countries), including nearly 949 scientists and 1362 employees providing administrative and technical support. The DKFZ is a member of the Helmholtz Association of German Research Centres – Germany's largest research organization. The strategic goals of the DKFZ are to contribute towards a better understanding of fundamental processes in cancer and to develop innovative methods of cancer diagnostics and therapy. Research at the DKFZ is divided into seven main research programs: Cell Biology and Tumor Biology; Structural and Functional Genomics; Cancer Risk Factors and Prevention; Tumour Immunology; Imaging and Radio-oncology; Infection, Inflammation, and Cancer; and Translational Cancer Research. All research programs are reviewed and evaluated every 5 years by an international panel of experts. Collaborations with many clinics and hospitals in the area provide opportunities to link basic and clinical research. To support "bench-to-bedside-and-back" translational research, the DKFZ and the Medical Center of Heidelberg University founded the first "Comprehensive Cancer Center" in Germany (National Center for Tumor Diseases, NCT) together with German Cancer Aid, providing an exceptional environment for translational biomedical research with state-of-the-art infrastructure and expertise. The impact of research at the DKFZ is highlighted by the Nobel prize for Medicine awarded to Prof. Harald zur Hausen in 2008 and the Nobel Prize for Chemistry awarded in 2014 to Prof. Stefan W. Hell DKFZ is member of the Helmholtz international Graduate School for Cancer Research. Helmholtz Graduate School doctoral students are registered with a university faculty, primarily the Biosciences, Medical or Physical Science Faculty of the University of Heidelberg - with whom the Helmholtz Graduate School has long-standing close ties and collaboration agreements - who award the doctorate degree (typically Dr. rer. nat. or Dr. sc. hum.) upon successful completion of the Graduate School program and submission and oral defense of their doctoral research dissertation. Therefore, University of Heidelberg is DKFZ's entity with a capital or legal link, awarding thedoctorate to its ESRs. Many DKFZ scientists are professors or lecturers at the University of Heidelberg and University faculty members act as Thesis Advisory Committee (TAC) members for DKFZ students. Further close ties to the Faculty of Biosciences in the area of graduate education exist through the Master Program in Molecular Biosciences, one arm of which, the "Major in Cancer Biology", is entirely organized and taught by DKFZ scientists. As a requirement of the Helmholtz Graduate School, doctoral students are supported by a Thesis Advisory Committee (TAC), consisting of their supervisor and at least two other senior scientists, one of whom is external to the DKFZ, and one of whom is their University Faculty Examiner. This committee meets annually to assess progress and set goals for the next period.
Role and Commitment of key persons (including supervisors)	Jeroen Krijgsveld will be responsible for the daily supervision of students recruited to the project. This includes planning of experiments, facilitating internal and external training/courses, chairing thesis advisory committees, and guiding publication of ensuing research work.
Key Research Facilities, Infrastructure and Equipment	Key Research Facilities: Center for Preclinical Research, Chemical Biology Core Facility, Genomics and Proteomics Core Facility, Imaging and Cytometry Core Facility, Information Technology Core Facility Infrastructure: Modern laboratories and equipment, technologies for high-throughput analyses in proteome and genome research, IT Core Facility, Advanced Education and Training program, Library Services, e-journals.
Status of Research Premises	The Krijgsveld lab houses a complete and state-of-the-art proteomic infrastructure, including Orbitrap Fusion and QE-HF mass spectrometers, nano-flow liquid chromatography systems, an ultra-sonicator, a robotic liquid handling system, a cell culture lab, an S1 lab for molecular biology, and a suite of software tools for bioinformatic data analysis.
Previous Involvement in Research and Training Programmes, including ITN	The DKFZ has long-standing experience with EU Framework Programs. Fifty-eight projects (comprising approximately 30 million euros) were conducted at DKFZ within FP7. DKFZ has had numerous structured graduate training programs for early-stage researchers and experienced researchers: EU: Initial Training Networks, Intra-European Fellowship and International Reintegration Grant. National: Graduate School, several National Postdoc Programs; International: Multiple DAAD and International Postdoc Programs. All Programs include diverse complementary skills training and opportunities for placements in other institutions.
Current Involvement in Research and Training Programmes, including ITN	Since several years, Jeroen Krijgsveld is a coordinator of various EMBL- and EMBO-funded post-graduate courses in the area of proteomics, including courses entitled 'Quantitative proteomics: strategies and tools to probe biology' and 'Analysis and Integration of Transcriptome and Proteome Data'.
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	none
Relevant Publications and/or Research / Innovation Product	The Krijgsveld lab is highly active in the development and application of novel proteomic technologies, e.g. on protein-RNA interactions (Castello et al, Cell 2012; Trendel et al, Cell 2019), chromatin proteomics (Rafiee et al, Mol Cell 2016), miniaturized and streamlined proteomic sample preparation (Hughes et al, Mol Syst Biol 2014; Hughes et al, Nature Protocols 2019), and protein secretome analysis (Eichelbaum et al, Nature Biotechnology 2012).

Beneficiary Legal Name: Semmelweis Egyetem (SU)	
General Description	The Semmelweis University is the largest medical university in Central and Eastern Europe and the only Hungarian University listed in the Times Higher Education index. The Department of Bioinformatics performs the teaching of bioinformatics, serves as a core facility and leads bioinformatic research projects. The main focus in on cancer related studies including discovery and validation of prognostic and predictive biomarkers using genomic, transcriptomic, and proteomic analyses. The Department is home of several widely used web-based tools like the KM-plotter and the Recurrence Online platforms.
Role and Commitment of key persons (including supervisors)	Prof. Dr. Balázs Győrffy, supervision of the PhD fellows, 20% Dr. Ádam Nagy, assistance with deep learning algorithms, 25% Dr. Janos Fekete, assistance with predictive makers, 25% Boglárka Weltz, MSC, web-interface programming, 10%
Key Research Facilities, Infrastructure and Equipment	The Department of Bioinformatics primarily uses computing infrastructure including five web-servers. Installation of a Galaxy central server is currently in progress. A cell culture lab with standard cell culture equipment, a zebrafish lab and a next generation sequencing lab are also operated by the Department and as such it provides core facility services throughout the university. Currently, the set-up of a large biobank facility with four deep freezer containers and a barcode-based sample catalogue system is also in progress. Recruited early-stage researchers will receive their private workstations and will have access to all infrastructures in the Department.
Status of Research Premises	Semmelweis University acts as the legal owner of the entire Department and as such it is independent of external companies or third party academic centers. The research premises are independent from other beneficiaries or partner organizations in the consortium.
Previous Involvement in Research and Training Programmes, including ITN	No previous involvement in other ITN project by the Department of Bioinformatics.
Current Involvement in Research and Training Programmes, including ITN	The Department participates in graduate and postgraduate teaching at the Semmelweis University. The department director is also head of Elixir Hungary (Elixir is the bioinformatic life science infrastructure in the EU), and as such it is involved in national training programmes organized by Elixir.
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	No other proposal submitted.
Relevant Publications and/or Research / Innovation Product	1. Fekete JT and Győrffy B*. ROCplot.org: Validating predictive biomarkers of chemotherapy/hormonal therapy/anti-HER2 therapy using transcriptomic data of 3,104 breast cancer patients. **Int J Cancer.** 2019 Apr 24. doi: 10.1002/ijc.32369. 2. Fernando TM, Győrffy B, et al. BCL6 Evolved to Enable Stress Tolerance in Vertebrates and Is Broadly Required by Cancer Cells to Adapt to Stress. **Cancer Discov**. 2019 May;9(5):662-679. 3. *Győrffy B, et al. An integrative bioinformatics approach reveals coding and non-coding gene variants associated with gene expression profiles and outcome in breast cancer molecular subtypes. **Br J Cancer.** 2018 Apr;118(8):1107-1114. 4. Patten DK, Győrffy B, et al. Enhancer mapping uncovers phenotypic heterogeneity and evolution in patients with luminal breast cancer. **Nat Med**. 2018 Sep;24(9):1469-1480. 5. Nagy Á, Győrffy B*, et al. KRAS driven expression signature has prognostic power superior to mutation status in non-small cell lung cancer. **Int J Cancer**. 2017 Feb 15;140(4):930-937.

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<tr><th colspan="2">Beneficiary Legal Name GeneXplain GmbH (GENEXPLAIN)</th></tr>
<tr><td>General Description</td><td>GeneXplain GmbH (GENEXPLAIN) was founded in April, 2010. It has been set up by Edgar Wingender, the creator of the TRANSFAC® database, and Alexander Kel, a renowned expert in bioinformatic algorithms together with an international team of experts in software development and chemoinformatics. The company has developed a comprehensive platform for statistical, bioinformatic and systems biological tools. The geneXplain platform integrates statistical, bioinformatics, and systems biological modules with the access to the manually curated knowledge base on transcription factors and their binding sites (TRANSFAC® - gold standard in the field), and the most detailed database on signal transduction (TRANSPATH™), both of which are maintained and distributed exclusively by geneXplain. The business activity of GENEXPLAIN is mainly in offering access to the geneXplain platform as “software as a service (SaaS)” to academic research organisations, core facilities, biotech and pharmaceutical companies. GENEXPLAIN also offers data analysis and interpretation services as well as complex research project consulting that are performed by a dedicated multidisciplinary team of 10 persons.</td></tr>
<tr><td>Role and Commitment of key persons (including supervisors)</td><td>Dr. Alexander Kel, (15% involvement), supervision of the research and training activities.
Mr. Philip Stegmaier (30% involvement), research and training
Dr. Jeannette Koschmann (20% involvement), training</td></tr>
<tr><td>Key Research Facilities, Infrastructure and Equipment</td><td>GeneXplain is located in a rented office building on the Ostfalia University of Applied Sciences campus. Offices are equipped with state of art IT hardware, server space is mainly cloud-based (Hetzner Online GmbH, Germany).</td></tr>
<tr><td>Status of Research Premises</td><td>Rented office space, 308.34 m^2.</td></tr>
<tr><td>Previous Involvement in Research and Training Programmes, including ITN</td><td>
<table>
<tr><th>Acronym</th><th>Call</th><th>Program</th><th>Number</th></tr>
<tr><td>miRNA-DisEASY</td><td>H2020-MSCA-RISE-2015</td><td>H2020</td><td>690866</td></tr>
<tr><td>RESOLVE</td><td>FP7-HEALTH-2012-INNOVATION-1</td><td>FP7</td><td>305707</td></tr>
<tr><td>SysmedIBD</td><td>FP7-HEALTH-2012-INNOVATION-1</td><td>FP7</td><td>305564</td></tr>
<tr><td>SYSCOL</td><td>FP7-HEALTH-2010-two-stage</td><td>FP7</td><td>258236</td></tr>
<tr><td>GLIOTRAIN</td><td>H2020-MSCA-ITN-2017</td><td>H2020</td><td>766069</td></tr>
<tr><td>PD-MitoQUANT</td><td>H2020-JTI-IMI2-2017-13-two-stage</td><td>H2020</td><td>821522</td></tr>
<tr><td>COLOSSUS</td><td>H2020-SC1-2017-Two-Stage-RTD</td><td>H2020</td><td>754923</td></tr>
<tr><td>MIMOmics</td><td>FP7-HEALTH-2012-INNOVATION-1</td><td>FP7</td><td>305280</td></tr>
<tr><td>OPTOGENERAPY</td><td>H2020-NMBP-2016-two-stage</td><td>H2020</td><td>720694</td></tr>
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</td></tr>
<tr><td>Current involvement in Research and Training Programmes, including ITN.</td><td>1. Gliotrain, Exploiting GLIOblastoma intractability to address European research TRAINing needs in translational brain tumour research, cancer systems medicine and integrative multi-omics, Type: MSCA-ITN-ETN, Project ID: 766069, Call: H2020-MSCA-ITN-2017.
2. miRNA-DisEASY, microRNA biomarkers in an innovative biophotonic sensor kit for high-specific diagnosis, Type: MSCA-RISE, Project ID: 690866, Call: H2020-MSCA-RISE-2015.</td></tr>
<tr><td>Submission of similar proposals under the same H2020-MSCA-ITN-2020 call</td><td>None.</td></tr>
<tr><td>Relevant Publications and/or research/innovation products</td><td>1. Kel, A., Boyarskikh, U., Stegmaier, P., Leskov, L. S., Sokolov, A. V., Yevshin, I., Mandrik, N., Stelmashenko, D., Koschmann, J., Kel-Margoulis, O., Krull, M., Martínez-Cardús, A., Moran, S., Esteller, M., Kolpakov, F., Filipenko, M. and Wingender, E. (2019) Walking pathways with positive feedback loops reveal DNA methylation biomarkers of colorectal cancer. BMC Bioinformatics 20 (Suppl 4), 119.
2. Kel, A. E., Stegmaier, P., Valeev, T., Koschmann, J., Poroikov, V., Kel-Margoulis, O. V. and Wingender, E. (2016) Multi-omics “upstream analysis” of regulatory genomic regions helps identifying targets against methotrexate resistance of colon cancer. EuPA Open Proteomics 13, 1-13. German Cancer Research Center German Cancer Research Center
3. Koschmann, J., Bhar, A., Stegmaier,P., Kel, A. E. and Wingender, E. (2015) “Upstream Analysis”: An integrated promoter-pathway analysis approach to causal interpretation of microarray data. Microarrays 4, 270-286. doi:10.3390/microarrays4020270.
4. Shi, Y., Nikulenkov, F., Zawacka-Pankau, J., Li, H., Gabdoulline, R., Xu, J., Eriksson, S., Hedström, E., Issaeva, N., Kel, A., Arnér, E.S., Selivanova, G. (2014) ROS-dependent activation of JNK converts p53 into an efficient inhibitor of oncogenes leading to robust apoptosis. Cell Death Differ. 21, 612-623. doi:10.1038/cdd.2013.186.
5. Stegmaier P, Voss N, Meier T, Kel A, Wingender E, Borlak J (2011) Advanced Computational Biology Methods Identify Molecular Switches for Malignancy in an EGF Mouse Model of Liver Cancer, PLoS ONE 6(3):e17738. doi:10.1371/journal.pone.0017738.</td></tr>
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Beneficiary Legal Name: LeadXpro AG	
General Description 	**leadXpro** is a lead discovery company focusing on membrane protein drug targets (GPCR's, channels and transporters) and committed to the application of biophysical and structure based methods for the discovery and optimization of next generation lead compounds. leadXpro enjoys premium access to the synchrotron (Swiss Light Source - SLS) and the Free Electron Laser (SwissFEL). Core expertise beyond X-ray includes single particle electron microscopy (cryo-EM). leadXpro team consists of about 18 colleagues.
Role and Commitment of key persons (including supervisors)	**Michael Hennig** (PhD) (m) (coordination of the leadXpro activities, WP leader, 10%, daily co-supervisor ESR15). Guest professor of structural biology at the University of Basel, Biozentrum. 20 years post PhD pharmaceutical industry experience in drug discovery at F. Hoffmann- La Roche, worked on numerous projects in drug discovery and development like Tamiflu, Fortovase, Xenical, Carmegliptin, Aleglitazar etc.; Author of more than 80 articles and 8 patents, Co-founder and CEO of leadXpro AG. **Nicolas Bocquet** (PhD) (m) (30%, co-supervisor ESR15), Structural biologist, studied Biochemistry Pierre et Marie Curie University, obtained PhD at the Institute Pasteur Paris working on structural and functional characterization of proton gated ion channels. Postdoctoral research at F. Hoffmann La Roche, Basel working on several GPCR's and biophysical studies. Joined leadXpro 2017, head of Biophysics, project leader for GPCR drug discovery collaboration with a big pharmaceutical company. **Robert Cheng** (PhD) (m) (30%, daily co-supervisor ESR15), Structural biologist, DPhil from the University of Oxford on the structure and regulatory mechanism of mitotic kinases. Formerly principal scientist at Heptares therapeutics working on the purification, crystallisation and solving multiple GPCR targets structures; Previous experience with fragment-based drug discovery at Evotec and Astex therapeutics. Joined leadXpro in 2016 and worked on multiple GPCR structural biology projects with emphasis on the use of serial crystallography and XFEL. >50 publications in peer-reviewed journals. **Denis Bucher** (PhD) (m) (30%, daily co-supervisor ESR15) computational chemist, bioinformatics. DPhil from the EPFL Lausanne, postdocs in diverse computational methods at the University of California and Sydney, 4 years of experience at Galapagos pharmaceuticals France for project support for medicinal chemistry, joined leadXpro 2018 and works on several drug discovery projects
Key Research Facilities, Infrastructure and Equipment	leadXpro has access to state-of-the-art facilities for gene to lead capabilities, protein purification, detergent screening, assessment of membrane protein stability, ITC, SPR-like based ligand characterization (GCI, Creoptix), fragment screening by biophysical methods, LCP crystallisation, serial crystallography at synchrotron (SLS) and Free Electron Laser (SwissFEL), single particle cryo-electron microscopy. leadXpro is part of the SLS PXII consortium (with Roche, Novartis, MPI) for synchrotron radiation, SwissFEL access of 150h of beamtime/year from 2020.
Status of Research Premises	leadXpro offices and laboratories at PARK INNOVAARE, 5234 Villigen, Switzerland
Previous Involvement in Research and Training Programmes, including ITN	**Previous and Current Involvement in Research and Training Programmes** 1) Eurostars!170301, A novel structure based discovery platform to translate orphan GPCR into new drug targets. 1.680 Mio €, 2 years 2017-2019. 2) Non-beneficiary organization, ITN "TubinTrain" Tuning Tubulin Dynamics and Interactions to Face Neurotoxicity: a Multidisciplinary Approach for Training and Research. HORIZON MSCA ITN EJD 2019 Project n. 860070. 3) CTI project 18726.1, Development of X-ray diffraction instrument using ultrasound acoustic levitation, with PSI scientists Jörg Standfuss, Takashi Tomizaki, Soichiro Tsujino, project 1.3 Mio over 2.5 years, 2016-2019 4) CTI project 25864.1, Swissbodies for antibiotics drug discovery, CHF 530'000, 2 years 2017-2019
Current Involvement in Research and Training programmes including ITN	Non-beneficiary organization, ITN "TubinTrain" Tuning Tubulin Dynamics and Interactions to Face Neurotoxicity: A Multidisciplinary Approach for Training and Research. HORIZON MSCA ITN EJD 2019 Project n. 860070
Submission of similar proposals under the same H2020-MSCA-ITN-2020 call	We intend to submit another proposal under the same H2020-MSCA-ITN-2020 call as beneficiary entitled "GPCRNET".
Relevant Publications and/or Research / Innovation Product	1) Apel, A-K., Cheng, R.K.Y.Tautermann, CS., Brauchle, M., Huang, C-Y., Pautsch, A., Hennig, M., Nar, H., Schnapp, G. Crystal Structure of CC Chemokine Receptor 2A in complex with an orthosteric antagonist provides insights for the design of selective antagonists. **Structure**, 27 (2019) 2) Cheng, R.K.Y., Abela, R., Hennig, M. X-ray free electron laser: opportunities for drug discovery, **Essays in Biochemistry** 61, 529-542 (2017) 3) Weinert, T, Olieric, N., Cheng, R. et al. Serial millisecond crystallography for routine room-temperature structure determination at synchrotrons. **Nature Communications** 8, 542-553 (2017) 4) Cheng, R.K.Y., Fiez-Vandal, C., Schlenker, O., Edman, K., et al. Structural insight into allosteric modulation of protease-activated receptor 2. **Nature** 545, 112-115 (2017) 5) Renaud, J.-P., Chung, C-w., Danielson, H., Egner, U., Hennig, M., Hubbard, R.E., Nar, H., Biophysics in drug discovery: impact, challenges and opportunities, **Nature Reviews Drug Discovery** 15, 679-698 (2016)

Partner Organisation Legal Name: City2science GmbH	
General description	City2science is a German company for science communication and strategic consulting, founded in 2012 by CEO Dr. Annette Klinkert. Based on 20 years of leadership experience in the fields of city-management and science communication, city2science supports local stakeholders, policy makers, universities and scientific institutions by providing strategic consulting and innovative communication strategies connecting science, city and society. City2science offers trainings, assistance, individual consultancy, workshops and lectures on science communication and public engagement to German and European partners from universities, public institutions, cities and regions.
Key Persons and Expertise	Dr. Annette Klinkert is an internationally experienced workshop facilitator, trainer and science communicator. Since 2012 she is CEO of city2science, a German company developing innovative communication approaches connecting scientific institutions with urban and regional development strategies. Over the last 10 years Annette Klinkert has initiated and conceptualized a number of large-scale science communication formats across Germany,
Key Research Facilities, Inf.+Equip.	**None**
Previous and Current Involvement in Research and Training Programmes	city2science and/or EUSEA have participated in many FP7 and SwafS calls, such as e.g. • NUCLEUS, New Understanding of Communication, Learning and Engagement in Universities and Scientific Institutions (H2020-ISSI-2014-1). 2015-2019 • PERFORM, Participatory Engagement with Scientific and Technological Research through Performance. 2015-2018 (H2020-SEAC-2014-1 • PLACES, Platform of Local Authorities and Cities Engaged in Science, 2010-2014 (FP7-SCIENCE-IN-SOCIETY-2009-1):
Relevant Publications and/or Research / Innovation Product	*Concept Design and Organisation of large-scale dialogue-oriented Science Engagement Festivals:* • *GENIALE – macht Euch schlau!* http://www.geniale-bielefeld.de/ • *Science Night Ruhr* https://www.wissensnacht.ruhr/home/ • *Maker Faire Ruhr* https://www.makerfaire-ruhr.com/

Partner Organisation Legal Name: European Cancer Patient Coalition (ECPC), Antonella Cardone (AC) & Max Schravendeel (MS)	
General description	ECPC is the voice of the European cancer patient and represents almost 450 patient organizations in 47 countries. Having the ECPC on board would enable your project to engage directly with patients and caregivers. The European Cancer Patient Coalition has expertise in participating in steering committee and advisory boards to ensure the patient-centricity of the project, reviewing patient information and informed consent forms, and leading the communication and dissemination of results and recommendations.
Key Persons and Expertise	Antonella Cardone (F) is the Director of the European Cancer Patient Coalition. She has over twenty years of international activity in health, social and employment sectors. Prior to ECPC, Antonella was the Executive Director of the Fit for Work Global Alliance and Director of the Global Smoke free Partnership of the American Cancer Society. Antonella has managed over 40 large EU co-funded projects across all EU member states. She holds a Master's in Business Administration. Max Schravendeel (M) is the Health and Research Officer at the European Cancer Patient Coalition. He holds a Bachelor of Science in Medical Imaging and Radiation Therapy and a Master of Science in European Public Health. Max is responsible for maintaining various scientific partnerships and ECPC contributions to several research projects.
Key Research facilities, infrastructure and Equipment	ECPC is physically based next to the European Parliament and the European Commission. It has a meeting room with videoconferencing facilities that can hold up to ten people. ECPC links the project to over 400 patient organizations in 46 countries. Additionally, ECPC has partnerships with CDDF, EAPM, EAU, ECC, ECCO, EMA, EORTC, ESMO, ESSO, OECI, UICC and the WIN Consortium.
Previous and current involvement in research and training programmes	1. BD4BO DO-IT [http://bd4bo.eu/] H2020 IMI, 2017 – 2019 2. JARC [http://www.jointactiononrarecancers.eu/] 3HP, 2016 – 2019 3. CanCon [https://cancercontrol.eu/] 3HP, 2014 – 2017 4. EPAAC [http://www.epaac.eu/] 3HP, 2009 – 2014 5. iPAAC [https://www.ipaac.eu/] 3HP, 2018 – 2021 6. PREFER [https://www.imi-prefer.eu/] H2020 IMI, 2016 – 2021 7. BD4BO PIONEER [https://prostate-pioneer.eu/] H2020 IMI, 2018 – 2023 8. DIAdIC [http://diadic.eu/] H2020, 2018 – 2023 9. LEGACy [http://legacy-h2020.eu/] H2020, 2018 – 2022
Relevant Publications and/or research/innovation product	1. Lorenzo, F., & Apostolidis, K. (2019). The European Cancer Patient Coalition and its central role in connecting stakeholders to advance patient-centric solutions in the mission on cancer. Molecular Oncology. doi: 10.1002/1878-0261.12448 2. Lagergren, P., Schandl, A., Aaronson, N. K., Adami, H. O., de Lorenzo, F., Denis, L., ... & European Academy of Cancer Sciences. (2018). Cancer survivorship: an integral part of Europe's research agenda. Molecular oncology. doi; 10.1002/1878-0261.12428 PMID: 30552794 3. Calvo, F., Apolone, G., Baumann, M., Caldas, C., Celis, J. E., de Lorenzo, F., ... & Voest, E. (2018). Cancer Core Europe: A European cancer research alliance realizing a research infrastructure with critical mass and programmatic approach to cure cancer in the 21st century. European Journal of Cancer, 103, 155-159.

Partner Organisation Legal Name: Universitat de Barcelona	
General description	Universitat de Barcelona (UB) was founded in 1450. Today it boasts of a student body of 88.335 and a research staff of 5.696 members. Degrees are offered in 74 different areas of teaching with numerous postgraduate and doctorate programs as well as continuing education courses. Universitat de Barcelona (UB), ranked the first Spanish university, and the twenty third European institution in scientific quality and productivity, is the largest of the six universities of Barcelona and of the ten in Catalonia and manages an average of 150 European projects per year.
Key Persons and Expertise	UB has highly qualified investigators and professors involved in teaching activities of several bachelor, master and PhD Programmes. Dr. Viñals forms part of the Teaching Staff of the Master's Degree in Biomedicine of the University of Barcelona. He is the coordinator of the Course "Advances in Molecular Mechanisms of Cancer Progression and Dissemination" of the same Master's Degree in Biomedicine. Moreover, Dr. Viñals also participates in the Doctoral Programme in Biomedicine in the Faculty of Medicine of the University of Barcelona. He forms part of different Supervisory committees, commitees that are in charge of the follow up of the Ph.D. students in the faculty.
Key Research Facilities, Infrastructure and Equipment	The Scientific-Technical Services of the University of Barcelona provides research support in a coordinated and integral way. They are at the service of this educational institution and affiliated institutes, like IDIBELL. The UB Scientific and Technical Services include the following: Quality Assurance Unit , Genomics Unit, Magnetic Nuclear Resonance Unit, Peptide Synthesis Unit, Nanometric Techniques Unit, Confocal Microscopy and Cellular Micromanipulation Unit, Electron Microscopy and In situ Molecular Identification Unit , Separative Techniques Unit
Previous and Current Involvement in Research and Training Programmes	UB has coordinated several Research and Training Projects in previous Framework Programmes, being one of the Spanish leading institutions. During FP7 UB was involved in 59 MSCA Grants. Previous involvement in ITN projects during H2020: MiND 643051, PACE 642961, ARCADES 675789, DIAPHORA 675415, ELUSIVES 674896, EUROLEISH-NET 642609, FRAGNET 675899, NANOTRANS 674979, MOGLYNET 675527, HaemMetabolome 675790, TCCM 642294. Current involvement in ITN projects: Training4CRM 722779, ASCTN-Training 813851, Sweet CrossTalk 814102, PAVE 861190, GRAPES 860843, MANTEL 722518, TUBINTRAIN 860070.
Relevant Publications and/or Research / Innovation Product	**- Orthoxenografts of Testicular Germ Cell Tumors Demonstrate Genomic Changes Associated with Cisplatin Resistance and Identify PDMP as a Resensitizing Agent**." Clin Cancer Res. 2018 Aug 1;24(15):3755-3766. doi: 10.1158/1078-0432.CCR-17-1898. Epub 2018 Apr 4. - "A role for CXCR4 in peritoneal and hematogenous ovarian cancer dissemination". **Molecular Cancer Therapeutics** 17: 532-543, 2018. - The TGFβ pathway stimulates ovarian cancer cell proliferation by increasing IGF1R levels". **International Journal of Cancer** 139: 1894 -1903, 2016.

Partner Organisation Legal Name: Universitat Autonoma de Barcelona (UAB)	
General Description	The Universitat Autònoma de Barcelona is one of the major public universities in Spain, with roughly 40000 students and 4500 faculty staff. UAB portfolio covers a wide range of fields in humanities and arts, social sciences, health sciences, technology and physical sciences. The UAB offers more than 100 bachelor's degrees and 136 master's degrees, including 8 Erasmus Mundus master's degrees, such as MathMods (Mathematical Modelling in Engineering, http://www.mathmods.eu/). Finally, the UAB runs 68 doctoral programs and an average of 850 PhD thesis/ year. The UAB scored as the 2nd best Spanish University (2019), 69th in Europe and 157th worldwide in the Times Higher Education World University Ranking (2019), which reflects the excellent quality of its research and teaching. The UAB was awarded the HR Excellence in Research Logo in 2014.
Key persons and Expertise	The UAB is the PhD-awarding institution for the two ESRs hired by CRM, which will register at the Mathematics Doctoral Programme. Their mentor will be prof. Tomás Alarcón (ICREA/CRM; lecturer at the UAB Mathematics Department, see profile at CRM Form 5)
Key Research Facilities, Infrastructure and Equipment	Support from the International Welcome Point, International Office and Finance Department, Language Centre. Access to the Campus libraries and the DDD (Open Access repository). Computational support is available from the Department of Mathematics, which maintains a state-of-the-art HPC cluster.
Previous and Current Involvement in Research and Training Programmes	During the EC Framework Programme 7th period (2007-2013) the UAB has participated in more than 282 projects funded by external agencies. Regarding MSCA FP7, UAB participated in a total of 45 projects and hosted 51 fellows. Since the beginning of EC Horizon 2020 programme (1/1/2014) The UAB has been awarded more than 55M€ for 117 H2020 projects and 11M€ for 139 non H2020 projects, including 49 MSCA projects. Fourteen of them are ITNs, being the coordinator of two of them. Ongoing ITN projects are: ACO-811312; BeMAGIC-861145 (Coordinated by UAB); BIOREMIA-861046; CCIMC-860322; COUPLED-765408; INIA-859869; INSPiRE-MED-813120; LAST-JD-RIoE-814177; MANNA-765423; mCBEEs-764977; TeraApps-765426; WEGO-764908; RUNIN-722295.
Relevant Publications and/or Research / Innovation Product	Regarding the UAB's research activity in 2017, more than 4,200 articles published (Clarivate Analitics WOK); 677 research agreements; 161 national research projects; 64 patents filed, and ten new companies hosted at the UAB's Research Park (including 5 UAB spin-offs).

Partner Organisation Legal Name: Stichting Katholieke Universiteit / Radboud University	
General description 	Radboud University is a broad, internationally oriented university, combining excellent education (almost 20,000 students) with leading-edge research (resulting in almost 6700 scientific publications in 2015). Its academic expertise is closely related to important societal issues, both in the public and in the private domain and it plays an important role in transferring knowledge to society. The Department of Molecular Biology (Faculty of Science) is part of the Radboud Institute for Molecular Life Sciences (RIMLS) which is a leading multidisciplinary research institute within the domain of molecular mechanisms of disease and particularly in the fields of cell biology, molecular medicine, and translational research. The Radboud University has chosen Genetics & Epigenetics among their top scientific research areas. RU holds the Best Traditional University Award in Netherlands.
Key Persons and Expertise	**Hendrik G. Stunnenberg** (male), PhD, is full professor, head of the Department of Molecular Biology and a world-renowned scientific leader in the field of epigenetics. He is a member of EMBO since 1993. He was the coordinator of the EU FP7 High Impact Project BLUEPRINT (A Blueprint of Haematopoietic Epigenomes) and chair of the International Scientific Steering Committee of the International Human Epigenome Consortium (IHEC) from 2013-2016. In 2013, he received an ERC advanced grant for his project 'SysStemCell' on embryonic stem cells. He ranked 29th of most cited European Researcher in Cell Biology in the period 2007-2013. He has published >380 publications, with >30,000 citations and H-index 92. Prof. Stunnenberg will supervise two ESR's in WP4. His involvement in the supervision will be 10% FTE.
Key Research Facilities, Infrastructure and Equipment	The department of Molecular Biology has a complete Sequencing facility, including Hi-Seq and NextSeq500 equipment, servers and analysis pipelines. Single cell analysis (C1-machine, Fluidigm) is part of the equipment of the department as well as two state-of-the-art mass spectrometers. A nanodrop II liquid dispenser is being installed in the department for high throughput single cell RNA and DNA methylation analysis. Besides, the department has its own (extensive) team of bioinformaticians for data analysis, data integration and mining.
Previous and Current Involvement in Research and Training Programmes	Prof Stunnenberg has been involved in Research and Training Programs from the early start of the EU Framework Programmes, especially in FP6 (e.g. EPITRON, X-TRA-NET, BioMalPar, HEROIC (coordinator) and FP7 (ATLAS, Cancer DIP, BASIS, SYSCOL,GENCODYS, ParaMet, BLUEPRINT (coordinator) and AiPBand ITN). Moreover, he was the founder and main organizer of the biennial EMBL meeting on transcription (participation of > 200-250 young researchers) from 1994-2012. He is chairman of the Council of Scientist from the HFSP.
Relevant Publications and/or Research / Innovation Product	1. Nader Atlasy, Anna Bujko, Peter B Brazda, Eva Janssen-Megens, Espen S. Bækkevold, Jørgen Jahnsen, Frode L. Jahnsen, Hendrik G. Stunnenberg Single cell transcriptome atlas of immune cells in human small intestine and in celiac disease. bioRxiv 721258; doi: https://doi.org/10.1101/721258 2. Atlasi Y, Megchelenbrink W, Peng T, Habibi E, Joshi O, Wang SY, Wang C, Logie C, Poser I, Marks H, Stunnenberg HG. Epigenetic modulation of a hardwired 3D chromatin landscape in two naive states of pluripotency. Nat Cell Biol. 2019 May;21(5):568-578. doi: 10.1038/s41556-019-0310-9. *3.* Novakovic B, Habibi E, Wang SY, Arts RJ, Davar R, Megchelenbrink W, Kim B, Kuznetsova T, Kox M, Zwaag J, Matarese F,van Heeringen SJ, Janssen-Megens EM, Sharifi N, Wang C, Keramati F, Schoonenberg V, Flicek P, Clarke L, Pickkers P, Heath S, Gut I, Netea MG, Martens JH, Logie C, Stunnenberg HG. β-Glucan Reverses the Epigenetic State of LPS-Induced Immunological Tolerance. *Cell*. 2016; 167(5):1354-1368.e14.

Partner Organisation Legal Name: Universitätsmedizin Göttingen (UMG)	
General description UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG	The "Universitätsmedizin Göttingen (UMG)" of the Georg-August-Universität combines the "integration model" of the medical faculty and the university hospital in health care, teaching and research under one roof. With its centers and medical competence centers, the UMG is geared to modern requirements in health care, research and teaching. The UMG occupies a leading position nationwide, particularly in the research areas of neuroscience, cardiovascular research and oncology. With over 40 clinics and numerous special consultation hours, the UMG is the only regional maximum provider.
Key Persons and Expertise	**Prof. Dr. Tim Beißbarth**, Expertise in Medical Bioinformatics and Systems Medicine, High-dimensional data analysis, Machine Learning, Modelling of molekular Networks, Applications in Cancer.
Key Research Facilities, Infrastructure and Equipment	Institute for Medical Bioinformatics, Core-Facility for Medical Biometry and Statistical Bioinformatics.
Previous and Current Involvement in Research and Training Programmes	MSCA-ITN-ETN GLIOTRAIN (contract no. 766069), duration 48 months, start date 01 Sep 2017.
Relevant Publications and/or Research / Innovation Product	Chereda H, Bleckmann A, Kramer F, Leha A, **Beißbarth T** (2019). Utilizing Molecular Network Information via Graph Convolutional Neural Networks to Predict Metastatic Event in Breast Cancer. *Stud Health Technol Inform 267:181-186.* Wlochowitz D, Haubrock M, Arackal J, Bleckmann A, Wolff A, **Beißbarth T**, **Wingender E**, Gültas M (2016). Computational Identification of Key Regulators in Two Different Colorectal Cancer Cell Lines. *Front Genet 7:42.* Fuchs M, **Beißbarth T**, **Wingender E**, Jung K (2013). Connecting high-dimensional mRNA and miRNA expression data for binary medical classification problems. *Comput Methods Programs Biomed 111(3):592-601.*

Partner Organisation Legal Name: University of Basel	
General description 	The University of Basel has an international reputation of outstanding achievements in research and teaching. Founded in 1460, the University of Basel is the oldest university in Switzerland and has a history of success going back over 550 years.As a comprehensive university offering a wide range of high-quality educational opportunities, the University of Basel attracts students from Switzerland and the entire world, offering them outstanding studying conditions as they work towards their bachelor's, master's or PhD degrees. Today, the University of Basel has around 13,000 students from over a hundred nations, including 2,800 PhD students.The University of Basel has seven faculties covering a wide spectrum of academic disciplines. At the same time, the university has positioned itself amidst the international competition in the form of five strategic focal areas: Life Sciences, Visual Studies, Nanosciences, Sustainability and Energy Research and European and Global Studies. In international rankings, the University of Basel is regularly placed among the 100 top universities in the world thanks to its research achievements.
Key Persons and Expertise	Timm Maier, Professor for Structural Biology, Biozentrum. Timm Maier studied biochemistry at the University of Tübingen, Germany, and completed his doctorate in structural biology with Wolfram Saenger at Freie Universität, Berlin, Germany, in 2003. Timm Maier then moved as a Postdoc to the lab of Nenad Ban at ETH Zurich, Switzerland, where he was promoted to a team leader and lecturer position in 2006. In 2011, Timm Maier moved to the Biozentrum of the University of Basel as tenure track assistant professor and is associate professor at Biozentrum since 2016. He and his team are best known for structural studies on giant multienzymes in primary and secondary metabolism, in particular fatty acid and polyketide synthases, as well as on metabolic regulation and mTOR complexes.
Key Research Facilities, Infrastructure and Equipment	Protein production facility, Cryo-EM, analytical instruments, nano DSF, computing facility
Previous and Current Involvement in Research and Training Programmes	The University Basel worked on 6 MSCA-ITN's in the past 5 years.
Relevant Publications and/or Research / Innovation Product	• Herbst, Dominik A; Huitt-Roehl, Callie R; Jakob, Roman P; Kravetz, Jacob M; Storm, Philip A; Alley, Jamie R; Townsend, Craig A; Maier, Timm (2018). The structural organization of substrate loading in iterative polyketide synthases. Nature Chemical Biology, 14 (5), 474-479. • Aylett, C. H. S.; Sauer, E.; Imseng, S.; Boehringer, D.; Hall, M. N; Ban, N.; Maier, T. (2016). Architecture of human mTOR complex 1. Science, 351 (6268), 48-52. • Gruss, Fabian; Hiller, Sebastian; Maier, Timm (2015). Purification and Bicelle Crystallization for Structure Determination *of the E. coli Outer Membrane Protein TamA. Methods in Molecular Biology, 1329, 259-70.*

5. Ethics Issues

Each SystemicR **beneficiary and partner will fulfill the national and EU ethics regulations relative to research with human specimens, data, animals, modified organisms and agents. The projects will not research directly on patients or on human embryos or stem cell lines (the** SystemicR does not include research fields that are not eligible for funding under H2020[1]**). However, we will use human biological samples such as cancer tissues as well as animal models of disease. All beneficiaries will comply with the laboratory safety guidelines of the individual countries and will provide the ESRs, either from their scientific team or from their administrative department, with knowledge on ethical sciences. The ESRs will be kept well informed about the new ethical regulation concerning the project. The members aim to protect the human health and the environment for both the present and future generations.** All the partners will send the final version of the project to their Institutional Ethical Committee(s) (including research with human samples/tissue/data and animal experimentation, when required) and the research projects will not start before the coordinator-SB has received the definitive approvals. **The program, PIs, ESRs and groups will strictly comply with the international codes of practice including** Declaration of Helsinki[2]**, the** Principles of Good Practices[3]**, and the conventions of the** Council of Europe on Human Rights and Biomedicine[4]. Copies of approvals for the collection of personal data by the competent institutional Data protection Officer/National Data Protection authority will also be provided to the coordinator if the corresponding project includes these data and/or analyses. Individual data from large collaborative external studies (e.g, TCGA and ICGC) will be analyzed upon request and obtaining approval by the corresponding Data Access Committee, as mandatory defined in the original studies.

Animal models in research

All animal procedures will be governed by the Ethical and Animal protection procedures already in place within each country and center involved in the program. All animal experiments are subjected to power calculation where possible and the 3Rs are always integral to the design implementation of animal experiments. Mice will be kept in specific pathogen free (SPF) conditions (conventional, transgenic, knockout and immune depressed mice). Participants' animal's houses have obtained full accreditation from the AAALAC (Association for Assessment and accreditation of Laboratory Animal Care international). All experiments will be performed in accordance with the EU directive 2010/63/EU on the protection of animals used for scientific purposes. All participants secure: i) Evaluation and acceptance to use physiological and Pathological by local and national Animal Research Committee, ii) Strict regulation for the use of rodents for research and even more stringent regulations are applied to cancer models. They define the ethical limits on animal welfare including limits on tumour size, animal physiological conditions, pain suffering. To monitor for these ethical issues there are daily controls of animal welfare, with a mandatory weekly veterinarian inspection of all animals included in these types of protocols, iii) Evaluation one by one of specific procedures that have to be performed on live animals. In this case, the host Institute's Animal Research Committees review all the experimental procedures involved in the research project, including surgical manipulations in anesthetized animals and substance delivery to live animals. After careful evaluation, the Animal Research Committees emit an acceptance or non-acceptance resolution that decides whether the project is allowed to proceed, iv) All partners have already applied for the Animal Research Committee acceptance of the animal research protocols that include all the procedures and manipulations of each individual disease model described in the program and thus, they will be officially and legally in a position to perform all the animal experiments. Copies of training certificates/personal

[1] Human cloning and embryos, and genetic make-up (H2020 guidelines, v6.1, 4 February 2019).
[2] WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS.
[3] The European Charter & Code for Researchers, European Commission, 2005.
[4] Treaty No.164, Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.

licenses of staff involved in animal experiments will be provided to the coordinator; including general information must be provided in the nature of the experiments, the procedures to ensure the welfare of the animals, and how the principle of the 3Rs will be applied.

At the coordinator institute, all research projects involving the direct participation of human subject (patients or healthy volunteers), use of personal and/or clinical data, use of biological samples of human origin requires the evaluation and approval by the Ethics Committee for Clinical Research (CEIC) from Bellvitge University Hospital. If necessary, patients are informed and signed Informed Consent documents are obtained, and sample gathering goes together with an anonymization of personal and sensitive data from each patient in the studies to rigorously keep the confidentiality of each patient from the very beginning. Current research in cancer therapeutic resistance is approved by the Ethics Committee references PR120, PR235, PR187, and PR115. Animal experimentation protocol is approved as PI Research Assistant-Staff Dr. F. Mateo, Government of Catalonia, with reference 8469.

6. Letters of Commitment

UNIVERSITAT DE BARCELONA

Oficina de Projectes Internacionals de Recerca
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08028 Barcelona
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recerca.europea@ub.edu
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Commitment Letter for ITN partner organisations

I undersigned Dr **Francesc Xavier Roigé**, in my quality of **Vice-Rector for Doctoral Studies and Research Promotion at Universitat de Barcelona**, commit to set up all necessary provisions to participate as partner organisation in the proposal ***"Systems-level understanding of innate immune influence on cancer therapeutic resistance (SYSTEMICR)"*** submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of **Universitat de Barcelona**, I also confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, Universitat de Barcelona will be involved in and confirms that it has the legal capacity to award doctoral degrees, and will facilitate the enrollment for 2 Early Stage Researchers (ESR) hosted by the beneficiary IDIBELL, which offers an ideal environment for their training and for the achievement of the doctorate degree, as long as the 2 ESRs meet the corresponding admission and access requirements. The ESRs will have access to the Universitat de Barcelona facilities. Universitat de Barcelona assumes that costs related to doctoral degree fees or any other related expenses, will be covered by the ETN beneficiary IDIBELL.

I hereby declare that I am entitled to commit into this process the entity I represent.

Dr Francesc Xavier Roigé , 17/12/ 2019

Name, Date

ROIGE VENTURA FRANCESC XAVIER - 38061627P

Firmado digitalmente por ROIGE VENTURA FRANCESC XAVIER - 38061627P
Fecha: 2019.12.17 16:15:52 +01'00'

Signature

city2science
SCIENCE COMMUNICATION AND STRATEGY CONSULTING

CITY2SCIENCE GMBH
DR. ANNETTE KLINKERT // UNTER DEN LINDEN 31 // D-32052 HERFORD

Letter of Commitment to "SYSTEMICR" proposal. MSCA ITN-ETN-2020.

TO WHOM IT MAY CONCERN

I undersigned Dr. Annette Klinkert, in my quality of CEO of city2science GmbH, commit to set up all necessary provisions to participate as partner organisation in the proposal "**SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance**" submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of city2science GmbH, I also confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, city2science GmbH will be involved as Partner Organisation in delivering two trainings for early career researchers.

Training 1: "Science Communication in Practice: Face the Challenge, make a Difference!". Training 2: "Start the Dialogue, Open Up Science! Introduction to Engaged Research". The trainings will invite early career researchers from all disciplines to discover engaged research as a way to boost their academic careers and take up a responsible role in society. The courses will empower researchers through a mix of input, reflections and practical sessions. A major goal of the trainings is to enable participants to develop and test a public engagement and communications strategy related to their individual research topic.

I hereby declare that I am entitled to commit into this process the entity I represent. I will also be the contact person for this project.

Yours faithfully

Dr. Annette Klinkert
CEO city2science GmbH

2 January 2020

city2science GmbH
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European Cancer
Patient Coalition

Letter of Commitment to "SYSTEMICR" proposal. MSCA ITN-ETN-2020.

TO WHOM IT MAY CONCERN

I undersigned *Antonella Cardone*, in my quality of *Director,* commit to set up all necessary provisions to participate as partner organisation in the proposal **"SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance"** submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of the *European Cancer Patient Coalition*, I also confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, the *European Cancer Patient Coalition* will be involved as Partner Organisation by leading the Work Package on Patient Advocacy, providing education and training on understanding patient needs and advocacy, and how these should be coordinated with research needs, goals and results.

I hereby declare that I am entitled to commit into this process the entity I represent.

Yours faithfully,

Antonella Cardone
Director, European Cancer Patient Coalition
Brussels, 12 December 2019

European Cancer Patient Coalition
www.ecpc.org info@ecpc.org
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UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

Universitätsmedizin Göttingen, Institut für Medizinische Bioinformatik
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Institut d`Investigació
Biomèdica de Bellvitge
Hospital Universitari de Bellvitge
Edifici Unitat de Recerca - IDIBELL
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Zentrum für Informatik, Statistik und Epidemiologie
Institut für Medizinische Bioinformatik
Direktor: Prof. Dr. Tim Beißbarth

Sekretariat:
Yvonne Madlung

Goldschmidtstr. 1, D-37077 Göttingen **Adresse**
0551 / 39-14912 **Telefon**
0551 / 39-14914 **Fax**
office@bioinf.med.uni-goettingen.de **E-Mail**

09.01.2020 Datum

Betr.: Letter of Commitment SYSTEMICR

Dear Mrs. Blanco,

as Director of the Institute for Medical Bioinformatics I commit to set up all necessary provisions to participate as partner organisation in the proposal "SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance" submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of University Medical Center Göttingen, Institut for Medical Bioinformatics, I confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, our Institue for Medical Bioinformatics will be involved in training oft he ESR and joint research in the fields of medical statistics, machine learning and bioinformatics. Further, the University Medical Center Göttingen will be involved as partner organisation facilitating the enrollment for the SYSTEMICR Early Stage Researchers (ESRs) hosted in Genexplain in the PhD programs of this University, which offers an ideal environment for their training and for the achievement of the doctorate degree.
The University Medical Center Göttingen has the legal capacity to award doctoral degrees and, in case the application is successful and a suitable PhD candidate can be found, we commit ourselves to participate as a partner organisation in the consortium.

I hereby declare that I am entitled to commit into this process for the entity I represent.

Yours faithfully,

Prof. Dr. Tim Beißbarth

UNIVERSITÄTSMEDIZIN GÖTTINGEN
GEORG-AUGUST-UNIVERSITÄT
Institut für Medizinische Bioinformatik
Goldschmidtstr.1, D-37077 Göttingen

19EB002302

Letter of Commitment to "SYSTEMICR" proposal. MSCA ITN-ETN-2020.

TO WHOM IT MAY CONCERN

I undersigned Prof. L.M.C. Buydens, in my quality of Dean of the Faculty of Science of the Stichting Katholieke Universiteit, more particularly Radboud University Nijmegen ("SKU-RU"), commit to set up all necessary provisions to participate as partner organisation in the proposal "**SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance"** submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of SKU-RU, I also confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, RU will be involved as Partner Organisation facilitating the enrollment for the ***SYSTEMICR*** Early Stage Researchers (ESRs) hosted in PRINSES MAXIMA CENTRUM VOOR KINDERONCOLOGIE BV in the PhD Programs of this University, which offers an ideal environment for their training and for the achievement of the doctorate degree.

SKU-RU confirms that has the legal capacity to award doctoral degrees and, in case the application is successful, we commit ourselves to participate as a Partner Organisation in the Consortium.

I hereby declare that I am entitled to commit into this process the entity I represent.

Yours faithfully,

SIGNATURE + STAMP

Prof. dr. L.M.C. Buydens

Dean of the Faculty of Science

Place: Nijmegen

Date: 14/12/2019

Radboud Universiteit

FACULTY OF SCIENCE

Radboud University Nijmegen
The Netherlands

University of Basel
Vice President's Office
for Research

University of Basel, Vice President's Office for Research, P.O. Box 2148, 4001 Basel

Letter of Commitment

Proposal Acronym: **SYSTEMICR**
Call: H2020-MSCA-ITN-ETN-2020

The University of Basel and its principal investigator Prof. Timm Maier would like to confirm their full support to the application entitled 'SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance ', to be submitted within the MSCA Innovative Training Network (ITN) call of the Horizon 2020 Framework Programme.

Founded in 1460, the University of Basel is the oldest university in Switzerland and has a history of success going back over 550 years. Today, it has around 12,700 students from over a hundred nations (24% are international students), including 2,800 PhD students. It regularly ranks among the 100 top universities in the world in international rankings, thanks to its research achievements. The University of Basel is an experienced host institution regarding European research funding programmes and has been involved in more than 260 FP7 and H2020 projects including 47 ERC grants and 73 Marie Curie actions, of which 25 Marie Curie Training Networks (FP7 and H2020 ITN) and 43 individual Marie Curie Fellowship programs.

Prof. Dr. Timm Maier is at the University of Basel since 2011, leads a research group of 15 persons, has supervising experience for more than 10 PhD students and is an established figure with highest-level scientific output in the field of structural biology. Should this application receive funding, Prof. Timm Maier will act as the academic supervisor of the Early Stage Researcher (ESR) who will be hosted in leadXpro AG and will facilitate the enrolment of the ESR in the relevant PhD Program of the University, which offers an ideal environment for the training and the achievement of the doctorate degree.

Yours sincerely

Prof. Torsten Schwede
Vice-President for Research
University of Basel

Date: 10/01/2020

Prof. Timm Maier
Structural Biology, Dep. Biozentrum
University of Basel

Date: Jan. 10, 2020

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UAB
Universitat Autònoma de Barcelona

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Letter of Commitment to "SYSTEMICR" Proposal MSCA ITN-ETN-2020.

TO WHOM IT MAY CONCERN

We undersigned Dr. Francisco Javier Lafuente, in the quality of Vicerector for Innovation and Strategic Projects, and Dr. Àngel Calsina, in the quality of Coordinator of the PhD programme in Mathematics of the UAB, commit to set up all necessary provisions to participate as partner organisation in the proposal **"SYSTEMICR: Systems-level understanding of innate immune influence on cancer therapeutic resistance"** submitted within the call H2020-MSCA-ITN-2020 should the proposal be funded.

On behalf of Universitat Autònoma de Barcelona, I also confirm that we will participate and contribute to the research, innovation and training activities as planned in this project. In particular, Universitat Autònoma de Barcelona will be involved as Partner Organisation facilitating the enrolment for the ***SYSTEMICR*** Early Stage Researchers (ESRs) hosted in Centre de Recerca Matemàtica in the PhD Programs of this University, which offers an ideal environment for their training and for the achievement of the doctorate degree.
Universitat Autònoma de Barcelona confirms that has the legal capacity to award doctoral degrees and, in case, the application is successful; we commit ourselves to participate as a Partner Organisation in the Consortium.

I hereby declare that I am entitled to commit into this process the entity I represent.

Yours faithfully,

Dr. Francisco Javier Lafuente

UAB
Universitat Autònoma de Barcelona
Francisco Javier Lafuente Sancho
Vicerector d'Innovació
i de Projectes Estratègics

Vicerector for Innovation and Strategic Projects
Universitat Autònoma de Barcelona

Dr. Àngel Calsina

Universitat Autònoma de Barcelona
Departament de Matemàtiques

Coordinator PhD programme in Mathematics
Universitat Autònoma de Barcelona

Bellaterra, December 16th, 2019