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Advancing the Integration of 'Basic/Fundamental' and Translational Cellular and Gene Therapy Science within the EBMT: Accelerating the Pathway to Progress

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Introduction

The mission statement of the EBMT is to function as 'a community of healthcare professionals focused on innovation, research and the advancement of cellular and stem cell-based therapies to save and improve the lives of patients with blood-related disorders'. Since the establishment of the EBMT society in 1974, facilitated by true pioneers within the field, rapid and dynamic progress has been observed across the breadth of haematopoietic cell transplantation (HCT) and cellular/gene therapy practice. Currently we represent a large, diverse, and vibrant community of clinicians (physicians, nursing, and allied health professionals), cellular/gene therapy research scientists, data specialists, statisticians/ bioinformaticians and patient advocates. We must not forget that none of this would have been possible without the foresight, drive and determination of the founding members, which included Eliane Gluckman, Jon Van Rood and Bruno Speck[1]. For a number of years, it has been recognized by the wider community that there needs to be more comprehensive inclusion of basic/fundamental and translational science embedded within core EBMT activities, educational offerings, and overall strategic goals of the society. Such enhanced interaction will ultimately accelerate future success within our field. There are many examples of translational work impacting immensely on clinical practice for patient benefit over the six decades that HCT has been evolving and in the more recent arenas of chimeric antigen receptor (CAR) T cell and Natural Killer (NK) cell programs and gene therapy. Examples include the pioneering work of Jon van Rood and Els Goulmy on Human Leukocyte Antigens (HLA). Van Rood was, in the 1960's, one of the first to understand the importance of HLA in transplantation science and Goulmy and colleagues amongst the pioneers who demonstrated that killing of donor cells was HLA-restricted in humans[2–5]. In the 1980's, the group of Metcalf and colleagues successfully isolated and cloned G-CSF[6], ultimately leading to use of cytokines as pharmacological agents. More recently, work from many, including Nobel Prize winners Charpentier and Doudna, paved the way for current and future developments in genome editing/CRISPR technology, which have significantly impacted on the entire clinical arena[7]. In the early

'2000s', retroviral and lentiviral gene transfer into T cells and autologous haematopoietic stem cells (HSC) was developed, including members of the EBMT and European Society of Immunodeficiencies (ESID) amongst others, and established novel treatments potentially available as marketing-authorised advanced therapy medicinal products (ATMPs) for patients with Inborn Errors of Immunity (IEI), Inborn Errors of Metabolism (IEM) and hemoglobinopathies. These studies established wider community leadership in T-cell and HSCs biology and *ex-vivo* manipulation and paved the way to a bench-to-bedside infrastructure within and around EBMT transplant centers as the successful model for translational medicine[8,9]. Without such leaps in basic science and rapid translation into clinical practice by these pioneering leaders, transplantation would not have advanced to where we are today.

Within this short perspective article, we briefly discuss the 'headlines' of the short-, medium- and longer-term goals of the EBMT to foster enhanced interaction between the basic/translational scientific and clinical communities within the cellular and gene therapy fields. This is a dynamic piece of work, that we are excited to share, and the wider community will be kept regularly up to date via the EBMT annual general meeting (AGM), working party events, newsletters and dedicated webinars on progress of all such aspects.

Aims of the Perspective

The overall aim of this perspective is to highlight EBMT's integrative scientific strategy to the wider community. We strive for the EBMT to become the 'place to go' for basic and translational researchers in the field of HCT and cellular/gene therapy, irrespective of career stage and background. There are a number of inter-connected core streams, as discussed in turn below, through which these aims can be achieved. These goals include re-defining current and future educational event structure and content to incorporate more topics that are 'cross cutting' across clinical and basic/translational science, increased grant opportunities for scientists, establishment of an enhanced bioinformatic support network (ideally with machine learning approaches) to aid integration and interpretation of

large scale clinico-biological data sets, and a future desire to have an EBMT-labelled biobanking strategy systematically linked to prospective collection of clinical data on patients and donors. Lastly, there is a need to drive forward prospective HCT and cellular/gene therapy trials coupled with correlative translational studies under the auspices of the EBMT **(Figure 1**). We acknowledge that many of these goals could be challenging to meet yet, in our view, will be essential for the future success of the society.

To enhance this process and identify common priorities across disciplines, the first one-day, in-person 'ideation' meeting convened in March 2024, bringing together 20 European experts from across the fields of interest. This was the first in a series of planned meetings across a diverse range of stakeholders. **Table 1** outlines the first set of scientific proposals discussed, highlighting the initial arenas discussed. As the program develops, there will be wider work streams developed and prioritization with deadlines for key deliverables. Financial constraints of such forward-thinking approaches will naturally require a 'fresh look' at funding/program grant opportunities and discussions with the relevant European Union agencies.

Goal 1: Educational Activities: Refinement of current program and Enhanced Opportunities

The established EBMT educational program plays a pivotal role in the development and standardization of contemporary and relevant educational content focused on HCT and cellular/ gene therapy for a global audience. Promotion of best practice and standards in the field is encouraged through the already established diverse 'Flagship' educational initiatives, the AGM and the International Transplantation and Cellular Therapy Course (ITCTC), in addition to the multiple disease specific working party, nursing and EBMT trainee committee educational events. Recognizing the growing necessity to enhance 'cross disciplinary integration,' there is an absolute need to include more basic and translational science across the existing educational program to accelerate knowledge sharing. This will be achieved via incorporation across the breadth of the existing educational structure

and platforms rather than generation of multiple new and competing meetings. Such a multifaceted approach aims to generate both excitement and enthusiasm amongst clinicians for basic and translational science and increase bi-directional collaboration. In addition, it should help foster the next generation of clinician-scientists and scientists whose research themes will benefit from linkage to clinical data/ registries and the wider clinical HCT and cellular/gene therapy community. Additional immediate goals of the EBMT scientific council are enhancement of the AGM program by more inclusive incorporation of basic and translational science across appropriate themes and to include workshops highlighting wider applicability of novel technologies (e.g., single cell transcriptomics, 'immunome' assessment by multicolor flow/mass cytometry, imagine mass cytometry or proteomic platforms; CRISPR/Cas9) which should ultimately encourage broader collaborations. Key leaders in basic and translational science applicable to the EBMT scope will hence be included in the program organizational committee and abstract review panels moving forward. Moreover, a number have been asked to refine the current abstract topic categorization to encourage more basic/ translational science relevance and better reflect emerging areas of interest. Disseminating learning from other disease-areas, such as the rapid precision science developments in solid tumor oncology, will be included where appropriate. Coupled with AGM changes, a dedicated basic/ translational science track will be developed in the annual ITCTC. It is important to highlight that there is an existing recurring meeting already in place, 'The American Society of Transplantation and Cellular Therapy (ASTCT)-EBMT 'Basic and Translational Scientific Meeting', focused on unpublished innovative science. This occurs annually with alternate geographical location (USA versus Europe). Moreover, there is an annual meeting focused on the biology and prevention of relapse after HCT and cellular therapy. Momentum for these meetings is growing and the meeting styles, limited to around 100-120 attendees, facilitates collaboration, networking, and focused discussion between junior and senior attendees. There is a focus from the organizing boards in future proofing such meetings and ensuring continuity, whilst in parallel obtaining regular feedback to help improve further meeting style and content.

Potential challenges could be that members of both the clinical and basic and translational science community may not immediately appreciate the relevance of such educational meetings to their field and missed opportunities for collaboration may occur. We will promote our planned activities through our networks and other relevant scientific societies and ensure early involvement of basic/ translational scientists in agenda setting and meeting design which will be key for success. We will develop a multi-year roadmap looking at a 'pipeline' for both themes and speakers with a focus on basic/translational science and establish representation on the EBMT Educational Task Force to carry this work forward. As these educational activities are occurring in established meetings, there is less financial burden, but we will additionally seek sponsorship from industry and diagnostic laboratory partners who focus on emerging technologies. We expect to see the initial steps towards successful enhancement of the programs by 2026 onwards. The success of integration will be monitored through the Educational Task Force and an annual comparison to ensure we are meeting growth in these areas. Moreover, we will feedback to the community in the annual report.

Goal 2: Establishment of a Dedicated Grants Scheme for Basic/ Translational Science Themes and a Virtual Network for Collaboration

Our next key goal is to launch a dedicated grants scheme from the EBMT science fund for translational HCT immunology, cellular and gene therapy study applications with a rotating theme annually focused on emerging scientific priorities. The aim would be to advertise between 1-3 research grants per annum through open calls, akin to the EBMT-EHA 'GOCART' alliance, ensuring high visibility. The EBMT website will be updated to become a more attractive organization to the basic and translational science community by highlighting funding opportunities, enhanced virtual networking prospects and 'an ask' for direct involvement within the society. This work has already commenced and changes to the website will be more visible in the later stages of 2025 and beyond. Furthermore, we want to establish a network of translational groups and ideally, through mentorship style schemes, facilitate global exchange opportunities for PhD students and Postdoctoral scientists within the fields. This will

aid multi-institutional educational opportunities. Dynamic surveying of participants across grant applications etc. will let us understand the need and how best to adapt. Underpinning these activities is the EBMT's mission for Equality, Diversity and Inclusion which will apply across all such basic/ translational science activities, including appraisal of representation within associated scientific and educational outputs[10]. Lastly, the 'success' of integration will be objectively collated annually through a review of the number and academic caliber of grant applications and outcomes and surveys requesting feedback on networking opportunities and academic collaboration that has arisen.

Goal 3: Driving Innovation through Future-Thinking Bioinformatics within the EBMT

Enhanced bioinformatics capacity within the wider EBMT organization, involving clinical biostatisticians and machine learning specialists, is a fundamental and cross-sectional theme required for future proofing our scientific output. Integrative data analyses are now essential given the increasing complexity and size of the clinical, genomic, and cellular therapy data sets that are collected under the auspices of the unique EBMT registry. This can tackle the heterogeneity associated with missing values and mixed variable types seen across registry style data. Although widely applicable across the registry, this is particularly relevant to the emerging CAR-T registry where novel data sets are being collated rapidly, frequently with robust clinico-genomic and, in some cases, immunological data held at centres, that will require enhanced integrative analysis to harness the most valuable output for patient benefit such as predictive response scores etc. An ability to gather dynamic datasets by direct and secure linkage to Electronic Health Records (EHR) at centres, where both structured and unstructured data components would be analyzed, could be ground-breaking but currently has inherent limitations due to the massive computational requirements, a current lack of available machine learning scientists in this arena and data protection/ language variances across nations. This concept has been explored for many years without success hence alternative approaches are required. Here, so-called fully, partial or hybrid synthetic datasets or synthetically-augmented datasets have potential to accelerate hypothesis driven questions across the cellular/gene therapy arena whilst

preserving patient confidentiality[11,12]. Moreover, leveraging synthetic data may enable the execution of virtual randomized trials, optimizing efficiency by reducing the need to enroll additional physical patients or assigning them to active therapy arms. Consequently, resource utilization is optimized, and the attainment of results is expedited[13]. Ideally, a robust data sharing structure will be developed to foster collaborative research. These goals can initially be addressed through enhancing the current statistical committee to include a broader Bioinformatics and Artificial intelligence Task Force in 2025 to cultivate internal expertise and drive educational and training opportunities. Leaders in these areas will be asked to join the EBMT community and the first areas of future development should focus on improved integrative data analysis with a work plan developed thereafter.

Goal 4: Development of an EBMT Biobanking Strategy for the Future

The EBMT recognizes the critical requirement of a clear and strategic focus on development of EBMT-associated/ labelled biobanks and 'virtual' biorepositories that can systematically cross—link with longitudinally clinical data collection within the EBMT Registry. We need to remain cognizant, however, of previous unsuccessful attempts and the absolute need for robust funding to ensure set up and sustainability. Looking globally, the Center for International Blood & Marrow Transplant Research (CIBMTR) have successfully established a CIBMTR research sample repository which contains 'approximately three million sample aliquots from more than 60,000 first allogeneic related and unrelated transplant recipient/donor (or cord blood) pairs with complete, validated clinical outcome data from CIBMTR's Research Database. The majority of the paired samples have complete high-resolution data available for HLA-A, B, C, DRB1/3/4/5, DQ and DP loci.' This massive biobank facilitates applications for access to annotated samples for validated research requests and there is a requirement for the information derived from such analyses to be fed back to the National Marrow Donor Program (NMDP). Other examples of the many current successful biobanks include the French national CRYOSTEM and the biorepository associated with the Mount Sinai Acute GVHD International Consortium (MAGIC)[14]

Given the initial significant costs, regulatory and legal issues of setting up a bespoke 'stand-alone' facility for samples from multiple countries, better integrative pathways between existing biobanking facilities could be the first aim. The goal of such an 'EBMT-labelled' biobank network could be multiple: transparent and equitable access to samples for specific, innovative principal investigator led basic & translational research questions, to act as a repository for clinical trial samples, enhance sample collection in rare disease/ novel technologies (e.g. IEI/IEM) and additionally facilitate an adjunct for dynamic sample collection for long-term follow up safety evaluations. Many European centers have established small- medium sized biobanks and an EBMT-labelled umbrella linkage could be helpful for fostering collaboration. Of course, challenges will be multiple including funding, differing sample collection, processing and distribution practices, regulatory and legal issues with sharing samples between nations and ethical issues concerning robust data sharing and how potentially clinically relevant findings could be 'fed back' to clinical teams and patients.

Practical considerations required to bring this goal to fruition will be establishment of an EBMT biobank strategic task force which will be formed in late 2025, incorporating key stakeholders including representatives of the EBMT scientific council, statisticians, experts in bio-banking, patient advocates and legal representatives and, ultimately, generation of a business plan and time line that evaluates initial 'prime' funding opportunities to prioritize enhancement of existing biobank linkage and limited yet focused sample collection. Such a virtual bio-repository scheme could ideally aid information flow to the clinical registry and enhance impact of future studies, but this will of course be a challenging process.

The project will start in a focused manner with time-dependent goal posts in place and prioritization of key disease areas/ technologies. It is pivotal that a stratified approach is taken; focused samples are collated initially with a view to further expansion only once the process has become embedded and funding established. If such a virtual scheme is successful, a universal sample access management system application could be put in place, with scientific committee review for approval and a standard

material transfer agreement in place. Close monitoring for productivity will ensue. Access fees may be required to cover the costs of facilitating the specimen request application, ideally this can be reduced for applications from Low- and Middle-Income Countries (LMIC). The EBMT will strive to link further with the CIBMTR sample repository, CRYOSTEM, MAGIC biorepository etc. so that sample type, annotation and time points could be aligned across disease types/ platforms and technologies as much as is feasible. A strong policy to address the multiple ethical issues that may arise from new findings will be required. Involvement of patients and caregivers will be paramount. Risks and potential mitigation strategies by the EBMT for this workstream are summarized in **Table 2.** The timeline for first steps of an EBMT-labelled network would be 2027 onwards,

Goal 5: Prospective EBMT-labelled and sponsored clinical trials.

There is a medium-long term goal to facilitate prospective EBMT-labelled HCT, cellular and gene-therapy trials that have 'built-in' robust translational science components. This activity is not actually novel for the EBMT, since it has already been very successfully explored, such as in the RACE trial coordinated by the EBMT Severe Aplastic Anaemia (AA) Working Party - the largest global phase 3, randomized trial for this condition[15]. The RACE study additionally included a cutting-edge translational science project to complement the clinical component, highlighting that the goals of biobanking and correlative translational science can be achieved with both drive and determination. Whether this will be a 'stand-alone', comprehensive clinical trials unit (CTU) or collaborative work with an existing multinational provider remains to be decided and established. Clearly, such an overall clinical trial mission is a massive undertaking but is the only way to comprehensively address, with sufficient power, optimization of HCT and cellular-therapy intervention in rare diseases, refine and improve current management and systematically approach the numerous unanswered questions within the field. Furthermore, establishment of an overarching structure will ultimately be less cumbersome for future trial set up, have a legal and regulatory component that facilitates common regulation approaches that can, at least in part, address the specific requirements and nuances of national

authority approval, strive to increase geographic representation and patient recruitment from under-represented groups and will act as a valuable resource for investigators at large. Lobbying from the EBMT to 'simplify' the multiple bureaucratic steps involved at an EU level is required to ease the many 'roadblocks' to clinical trial success and develop streamlined trial approval processes. This will require comprehensive legal, logistical, and regulatory frameworks. Patient and caregiver involvement will also be encouraged at all points in development of such a strategy.

Conclusions

This position paper highlights the drive of the EBMT to foster enhanced integration of basic and translational cellular and gene therapy science with our organization and across the breadth of our activities. Laying of the required foundation blocks is underway and already pivotal components of the required programs discussed above have been implemented and will be under regular EBMT board review. Furter stakeholder meetings, with wider and inclusive participation, are planned later in 2025 to both accelerate momentum and assess progress. We are certain that our wider EBMT community will ultimately benefit by this enhanced clinical and scientific integration policy, which will drive forward more innovative science and 'state-of-the -art' care for our patients.

References

1 Gluckman E, Sureda A. Half a century of healing: celebrating the 50th anniversary of EBMT. *Bone Marrow Transplant* 2024; **59**: 1341–1348.

2 van Rood JJ. The detection of transplantation antigens in leukocytes. *Semin Hematol* 1968; **5**: 187–214.

3 Van Rood JJ. Tissue typing and organ transplantation. *Lancet Lond Engl* 1969; **1**: 1142–1146.

4 van Rood JJ, van Leeuwen A, Bruning JW, Porter KA. The importance of leukocyte antigens in renal transplantation. *Folia Med Neerl* 1968; **11**: 4–11.

5 Goulmy E, Termijtelen A, Bradley BA, Van Rood JJ. Y-antigen killing by T cells of women is restricted by HLA. *Nature* 1977; **266**: 544–545.

6 Nicola NA, Metcalf D, Matsumoto M, Johnson GR. Purification of a factor inducing differentiation in murine myelomonocytic leukemia cells. Identification as granulocyte colony-stimulating factor. *J Biol Chem* 1983; **258**: 9017–9023.

7 Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science* 2012; **337**: 816–821.

8 Bonini C, Ferrari G, Verzeletti S, Servida P, Zappone E, Ruggieri L *et al.* HSV-TK Gene Transfer into Donor Lymphocytes for Control of Allogeneic Graft-Versus-Leukemia. *Science* 1997; **276**: 1719–1724.

9 Aiuti A, Pasinelli F, Naldini L. Ensuring a future for gene therapy for rare diseases. *Nat Med* 2022; **28**: 1985–1988.

10 Montoto S, Snowden JA, Chabannon C, Corbacioglu S, De La Camara R, Dolstra H *et al.* The first steps towards a diverse and inclusive EBMT: a position paper. *Bone Marrow Transplant* 2022; **57**: 343–346.

11 Gonzales A, Guruswamy G, Smith SR. Synthetic data in health care: A narrative review. *PLOS Digit Health* 2023; **2**: e0000082.

12 D'Amico S, Dall'Olio D, Sala C, Dall'Olio L, Sauta E, Zampini M *et al.* Synthetic Data Generation by Artificial Intelligence to Accelerate Research and Precision Medicine in Hematology. *JCO Clin Cancer Inform* 2023; : e2300021.

13 Piciocchi A, Cipriani M, Messina M, Marconi G, Arena V, Soddu S *et al.* Unlocking the potential of synthetic patients for accelerating clinical trials: Results of the first GIMEMA experience on acute myeloid leukemia patients. *eJHaem* 2024; **5**: 353–359.

14 Robert E, Fontenille C, Dalle J-H, De Latour RP, Calmels B. "CRYOSTEM Biobank: A National Prospective, Standardized Collection to Better Characterize Allogeneic Hematopoietic Stem Cell Transplantation Complications". *Open J Bioresour* 2020; **7**: 4.

15 Peffault De Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M *et al.* Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia. *N Engl J Med* 2022; **386**: 11–23.

Figure and Table Legends

Figure 1: Fundamentals of enhanced integration of Basic and Translational Science into the EBMT structure

Legend: HCT=Haematopoietic Cell Transplant, AGM=Annual General Meeting, ITCTC=International Transplantation and Cellular Therapy Course

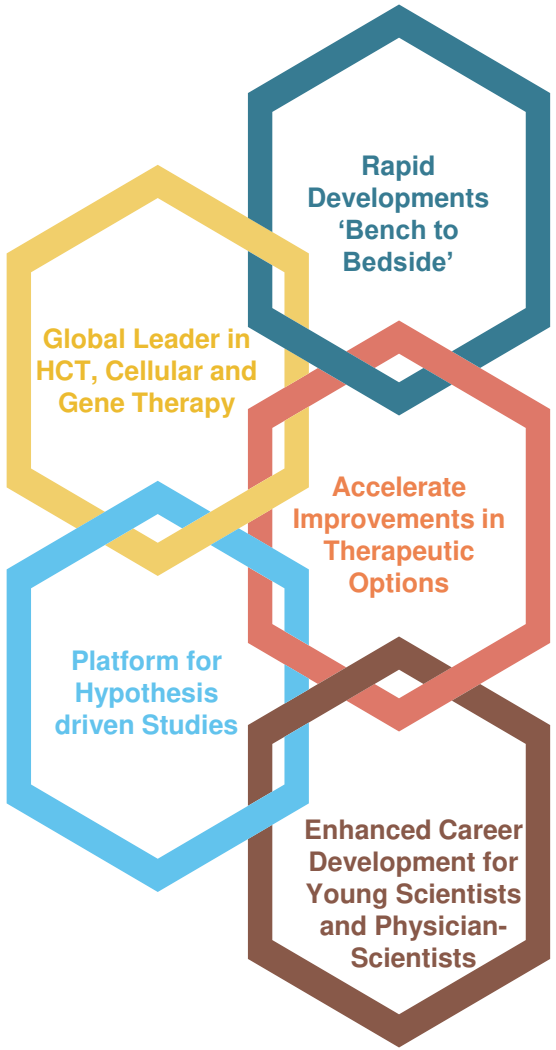
Table 1: Summary of the initial scientific concepts discussed at the 1st Stakeholder Meeting

Legend: GvHD = Graft Versus Host Disease, allo-HCT=allogeneic haematopoietic cell transplantation, MRD=measurable residual disease, HSC= haematopoietic stem cell, AI=artificial intelligence, ICANs=immune effector cell associated neurotoxicity, CRS=Cytokine release syndrome.

Table 2: Risks and Mitigation Strategies for Biobanking Work stream

Initial Scientific Topics	Proposals
GvHD	● Assess onset, severity, duration, and steroid resistance mechanisms. ● Analyze the role of minor histocompatibility antigens in GvHD onset and maintenance. ● Analyze clinical and other exploratory biomarkers for routine clinical use: accelerate development
Infections and vaccination	● Creation of a' biobank' to analyze biomarkers and as a rapid response platform for potential emerging pathogens. ● Focus on vaccine immunogenicity in immunocompromised recipients. ● Donor vaccinations prior to allo-HCT. ● Study of rare infections and emerging pathogens.
Graft *versus* leukemia	● Bone marrow microenvironment at time of AML diagnosis and how this affects post allo-HCT immune responses. ● Biobanking of timed samples for aiding refinement of the definition of MRD, relapse and for interventions after relapse. ● Prospective interventional studies on AML relapse after allo-HCT. ● Interventional trials on underlying biology of relapse using AI and whole exome sequencing or similar approaches.
CAR T cells	● Gamma delta CAR T-cells and relation to 'tumor free' outcome. ● Pathophysiology of cytopenia after CAR T-cell therapy. ● CAR T-cell therapy for non-malignant indications. ● Biology of ICANS and CRS. ● Toxicity of checkpoint inhibitors when used as a bridge to CAR T-cell therapy. ● Harmonization of outcome definitions and biomarkers. ● Novel CAR T point of care investigator-initiated studies and product availability.
Gene therapy	● Biobanking to investigate long term safety of gene therapies. ● Studies on mutagenesis and clonal hematopoiesis related to conditioning and HCT. ● Novel and safer CRISPR/Cas9 based technology development. ● Role of *in vivo* HSC targeting as an alternative to HCT ● Evaluation of influence of bone marrow microenvironment on engraftment and efficacy of gene therapy approaches ● Comparison to allo-HCT as regards efficacy, safety and costs

Potential Barrier	Mitigation Approaches
Initial High set up costs and Longer term sustainability Funding	Phased model for Biobank linkage development, with focus on well-established biobanks in first instance (3-4) as a pilot. Diversify funding streams such as through annual budget, grant opportunities (Horizon EU for example), national grant schemes, patient advocacy fund raising, philanthropy etc. Generate funding pipeline and do not plan growth too early.
Cross border variability in regulatory and compliance issues	Start with countries with already established protocols and regulatory networks, generate compliance tool kits to ensure consistency, establish robust material transfer agreements and have legal/ compliance expertise on the EBMT biobank Task Force. Legal and compliance platforms will require regular audit. Longer term goal to establish an online EBMT-labelled biobank portal to encompass education and 'kits' on these issues to ensure more rapid future set up for centres wishing to join an EBMT labelled biobank network.
Complexity of multiple disease and sample types	Focus on 1-2 specific areas in first year before further diversification to ensure robust processes are in place e.g. GVHD and longitudinal CAR-T patient samples, by way of example.
Governance Issues	Biobank Task Force will meet regularly to review issues and strategic goal achievement with clear performance management implementation. Standardise operational activities for access to samples.
Ethical Issues	Ethics board incorporating key scientific, operational and patient/ carer advocates to be established and oversee all developments. Online consent modules. Transparent communication strategy to all EBMT community and patients.

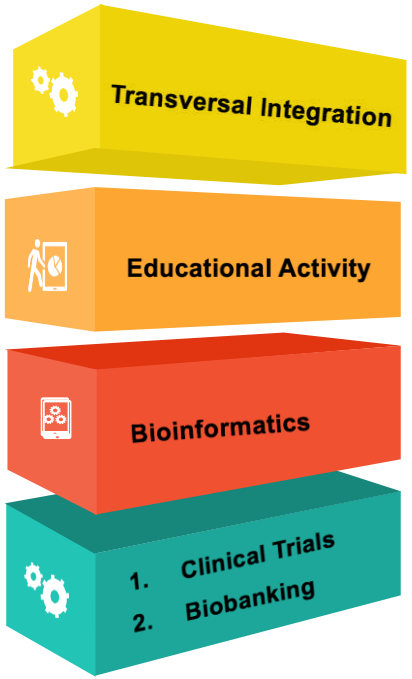


INTEGRATION ACROSS THE EBMT

- Integration of Basic and Translational Science into all aspects of EBMT Activity
- Representation in Working Parties, AGM Scientific Committee etc.
- Specific Meetings e.g. ASTCT-EBMT Basic and Translational Science and Relapse meetings
- Grant opportunities from EBMT
- Networking for young scientists

FUTURE-THINKING BIOINFORMATICS

- Integrative data analysis via Machine Learning approaches
- Enhanced Prognostic tools across HCT and CAR T/ gene therapy
- Fully, partial or hybrid 'synthetic' datasets or synthetically-augmented datasets
- Establishment of 'virtual' clinical trials to evaluate science-driven hypotheses quickly and safely



EDUCATIONAL ACTIVITIES

- Accelerate cross-disciplinary knowledge sharing
- Enhanced Integration of Basic and Translational Science in all Educational Activity: AGM, Working Party Events, ITCTC etc.
- Joint Clinical and Scientific Podcasts, webinars and 'online' peer to peer events

PROSPECTIVE CLINICAL TRIALS and BIOBANKING STRATEGIES

- EBMT 'labelled' prospective clinical trials unit
- Plan expanded physical biobanks
- Include 'virtual' biorepositories
- Dynamic sample collection from clinical HCT and CAR T/ Gene therapy trials
- Annotated samples; paired with Clinical Registry