

## COMMENTARY

# In Search of System-Wide Productivity Gains - The Role of Global Collaborations in Preclinical Translation

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## INTRODUCTION

Given the increasing complexity of the biomedical innovation pipeline, collaboration across organizational, sectoral and national boundaries is an increasingly important means of leveraging resources and mitigating risk. The need to jointly tackle systemic bottlenecks is particularly acute. Using examples from EATRIS European infrastructure for translational medicine, we advocate for actors in all domains related to preclinical translational research to expand their collaborative horizons to tackle the long-term systemic risks that hamper drug development.

## GOOD NEWS, BAD NEWS

From the perspective of biomedical innovation we are clearly in exciting times, with the horizons of therapeutic feasibility expanding into truly wondrous territory, albeit in fits and starts. Driven in part by ever more sensitive analytical technologies increasing our mechanistic understanding of underlying pathologies, we're shifting from populations to the  $n = 1$  indication<sup>1</sup>, from a phenotypical description of disease to a molecularly-based taxonomy<sup>2</sup>, and all the while the number of new therapeutic strategies increases steadily. It is heartening to witness these - and many other - mini revolutions in the making.

On the other hand, in the shadow of 2016's disappointing and abrupt end to the recent uptick in new drug authorizations,<sup>3</sup> cause for optimism is somewhat blunted. Moreover with the late stage clinical failure rates remaining stubbornly high<sup>4</sup>, pipeline productivity is clearly sorely in need of efficiency gains.

The development pathway remains littered with systemic bottlenecks acting as a drag on the process. As increasingly complex products enter the pipeline, with each novel strategy bringing with it technical and regulatory uncertainties, many bottlenecks will stagnate into systemic risks that affect all similar projects in the pipeline. In the highly fragmented biomedical research eco-system, these systemic bottlenecks are often addressed with project-specific solutions that may never be shared or are not applicable to the

wider risk. This leaves a patchwork approach to innovation that does little to improve system-wide efficiency, and can lead to undesired duplication of efforts. Furthermore, as negative results are rarely published, we will never know the full extent to which resources are being thrown at dead-end tracks by multiple parties at the same time. This tragedy of the biomedical commons must be tackled with greater urgency and combined firepower if we are to have any hope of reducing the cost and duration of drug development.

## COMPLEX NETWORK, VALUABLE OUTCOMES

In Europe and abroad we are witnessing a growing number of initiatives, both public-private and public-public, that seek to address the systemic deficiencies dogging the pipeline, which is a welcome development. Not only the quantity, but the scope and breadth of these collaborations seem to be expanding, implying that the cost and complexity of highly networked, multi-sectoral collaboration is dropping such that the benefits outweigh the risks. A good example is the Innovative Medicines Initiative (IMI), involving Europe's pharma partners in EFPIA, the European Commission and Europe's academia, as well as regulators and patients. The second cycle, started in 2014, has a combined budget of over €3.2 billion and aims to build on the success of the first round.<sup>5</sup>

Europe's regulators, too, have in recent years become much more open and collaborative in their stance, while naturally remaining cautious to prevent conflicts of interest. In acknowledgment of the increasing complexity of medicinal products and the need for evidence-based regulatory transparency to stimulate innovation, the European Medicines Agency's recently published framework for engagement with academia includes an objective "to ensure that the best scientific expertise and academic research are available to support timely and effective evidence generation".<sup>6</sup> This would entail a tripartite initiative requiring regulators, independent research labs and non-commercial funders working in unison to answer emerging regulatory science questions - a very exciting development, particularly for the advanced therapy field.

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At EATRIS ERIC, the European Infrastructure for Translational Medicine, working on pipeline productivity is a critical part of their strategy. Important activities to this end seek solutions to some of those aforementioned systemic bottlenecks, such as identifying and validating tools to better predict the likelihood of proof of concept, reduction of variability through harmonization and standardization exercises, and validation of biology to support precision medicine. A key initiative for EATRIS involves collaborators from around the globe, including Therapeutic Innovation Australia, the Center for Drug Research and Development (CDRD) in Canada, LifeArc (formerly MRC Technology) in the UK, and NIH's National Center for Advancing Translational Sciences (NCATS). The logistical challenges of such a geographically spread initiative, including holding monthly teleconferences spanning 14 time-zones, have been far outweighed by the advantages of bringing together likeminded experts in the field<sup>7</sup>. Structured as a modular, light collaboration, the group identifies joint advocacy, educational, technical and harmonization projects in a bottom-up manner, with operational teams formed on a voluntary basis.

One of their recently launched projects serves as an excellent example of the simple, yet vitally important exercises that such collaborations permit. A high-throughput screening (HTS) system ring-testing project being piloted by NIH NCATS and EATRIS member institute IMTM in Olomouc, Czech Republic, is under development in order to identify drivers of variability in HTS, as well as to provide feedback to HTS sites on potential sources of variability in their systems. Once piloted successfully, the initiative will be opened to wider collaboration (see "EATRIS Inside" in **Supplementary Information**).

Within the cancer therapeutics field, the alarming rate of failure among clinical trials is a major issue that partly results from the use of inadequately predictive 2D *in vitro* tumor models for the screening of promising hits and leads in pre-clinical studies. Within EATRIS, several institutes focus on the utilization of novel 3D *in vitro* tumor models that reproduce *in vivo* tumor complexities for effective drug selection in the preclinical stages of drug development.

In addition to the lamentable lack of standards in the field, a further major challenge facing translational scientists is a limited understanding of how disease in preclinical animal models translates to humans, which likely further contributes to the high attrition rate in phase II and III clinical trials<sup>8</sup>. Strategies to overcome this include not only development and validation of novel models with higher predictivity, but also efforts to overcome the current limitations in the experimental design and statistical analysis of studies utilizing current *in vivo* models<sup>9</sup>. In a collaboration of several Finnish member institutes of EATRIS, a computational algorithm has been made freely available that matches the animals based on all available baseline variables, and thus assists researchers in optimizing the study design and minimizing the number of animals needed to achieve statistically significant results (see **Supplementary Information**). This provides the researcher with a variety of options to conduct adequately powered and fully-randomized preclinical intervention studies.

Another EATRIS program that can impact systemic inefficiency is underway in collaboration with the European

Association of Nuclear Medicine (EANM), to enable multi-center clinical trials utilizing PET imaging tracers using zirconium-89 (<sup>89</sup>Zr), that finds increasing application in so-called "immuno-PET" studies of biologicals, nanomedicines, and cells. The <sup>89</sup>Zr-PET/CT accreditation programme will facilitate cross-calibration of PET/CT imaging devices and image reconstruction in a standardized manner, allowing data to be shared and pooled with sufficient quantitative accuracy.

System-wide improvements need not be limited to the technical bottlenecks affecting drug developers and research labs. There are a myriad of operational bottlenecks that plague the translational research system, such as efficient access to high-quality biological samples with associated clinical data, access to pre-competitive funding for the validation of promising tools such as imaging tracers, and reliability of the peer review system for selection of applied research projects. With regards to the latter EATRIS has been working with public and non-profit private funders for several years, collaborating with them to support their translational research portfolios, in the recognition that these entities are not uniformly aware of the differing requirements of funding and executing confirmatory research vs. exploratory research (see "EATRIS Inside" in **Supplementary Information**).<sup>10</sup>

## NOT ALL PLAIN SAILING

Developing and running initiatives involving multiple organizations, regions, and sectors brings with it the complexities and inefficiencies inherent to networked activities, with the added unknowns of foreign (organizational) cultures and mores waiting to entrap the uninitiated. It is thus important that the potential profit to be had from collaborating outweighs the additional burden. Regarding the former - in the case of multi-party collaborations - an important operational concept is that of modularity, whereby not all partners in the initiative are forced into each sub-project. This ensures that all partners can be satisfied contributing to activities that are important to them, choosing to pass on projects that are not aligned with their own priorities. Additionally, it is always wise to build in mechanisms whereby free-riders and non-performers can be censured and eventually ejected.

Sadly, not all collaborations deliver on their initial promise despite the good intentions of those involved. Common showstoppers include low organizational priority of "unsexy pre-competitive projects," cultural inertia preventing leading edge developments from taking hold, and unbalanced contributions or prioritization from partners leading to chagrin and eventual abandonment. In all of the above the adequate vetting of partners, gradual build-up of joint activities, and strong management of the initiative can go a long way to minimizing these risks.

## KEEP GOING GLOBAL

Given the increasing complexity of the biomedical innovation pipeline, collaboration across boundaries is an increasingly important means of leveraging resources and mitigating risk. Joint ventures have long been a bulwark of product

development in the truly global drug market; we believe that extending these types of relationships to the pre- and non-competitive space is logical, as long as the risks and inefficiencies associated with doing so are outweighed by the benefits. Our experience thus far certainly indicates so.

The benefits are clear - increasing quality in an age where the reproducibility of foundational research is under intense scrutiny, reducing variability in a pipeline with poor predictability of clinical success, and validating (biological) tools to increase confidence and reduce cycle time are all worthy outcomes. The huge number of bottlenecks, combined with the need for consensus when talking of standards and harmonization, leaves few alternatives to boundary spanning. By working together on the issues that bind us to a poorly performing pipeline, we can transform the tragic patchwork of competition into a more efficient innovation continuum. By better sharing the costs and risks of developing the tools that help us make better drugs, we can improve the cost-effectiveness of R&D without sacrificing competitiveness, thereby delivering more value to patients and payors.

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1. See for example Naipal, Kishan A. T. *et al.* - Tumor slice culture system to assess drug response of primary breast cancer. *BMC Cancer* **16**,78 (2016).
2. Garber K. Oncologists await historic first: a pan-tumor predictive marker, for immunotherapy. *Nat. Biotech.* **35**, 297–298 (2017).
3. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm>
4. Hay M. *et al.* Clinical development success rates for investigational drugs. *Nat. Biotech.* **32**, 40–51 (2014).
5. <https://www.imi.europa.eu/content/imi-2>
6. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2017/03/WC500224896.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224896.pdf)
7. Gilliland C.T. *et al.* Putting translational science on to a global stage. *Nat. Rev. Drug Disc.* **15**, 217–218 (2016).
8. Paul, S. M. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Rev. Drug Discov.* **9**, 203–214 (2010).
9. Aittokallio *et al.* Matched preclinical designs for improved translatability. *Science Translational Medicine* **9**, 389:4101 (2017).
10. Kimmelman *et al.* Distinguishing between exploratory and confirmatory preclinical research will improve translation. *PLoS Biology* **12**;5: 1001863 (2014).

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