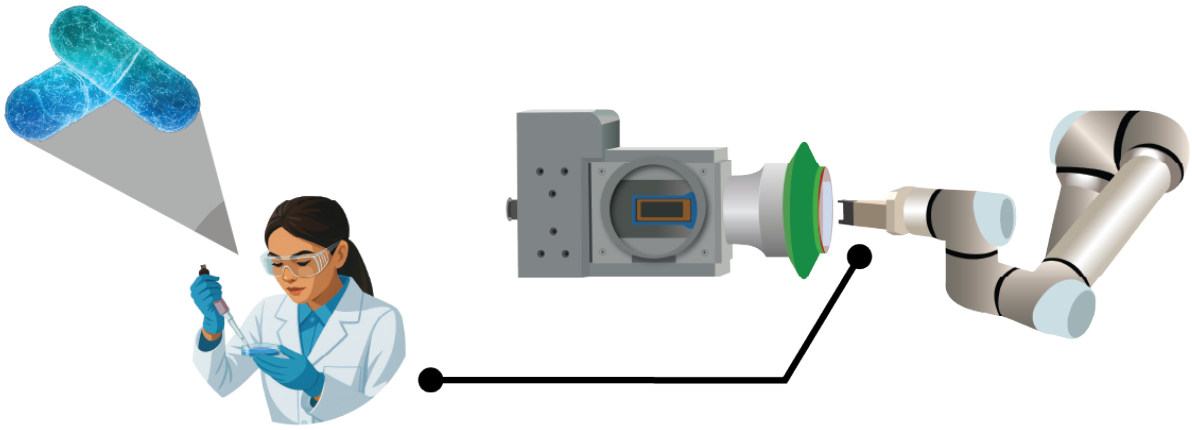
Hi ACTS | Helmholtz Innovation Platform for Accelerator-based Technologies and Solutions

IMPACT STUDY OF THE SOCIO-ECONOMIC BENEFITS FROM THE HI-ACTS USE CASE INITIATIVE

High-throughput pharmaceutical screening at room temperature



FINAL REPORT

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ACCELERATING EARLY-STAGE DRUG DEVELOPMENT...

Public health resilience depends on our ability to respond rapidly to emerging and re-emerging diseases, as highlighted during the COVID-19 pandemic. There is an urgent need for faster development of drugs, especially for underfunded or neglected infectious diseases[i]. Structural insights into protein-ligand interactions are crucial for drug discovery, with macromolecular X-ray crystallography remaining a cornerstone technique in identifying and optimising potential therapeutics.

The High-throughput Pharmaceutical X-ray screening instrument (HiPhaX) was developed at DESY[1] in 2021 to meet the growing demand for high-throughput pharmaceutical screening. It is located at the PO9 beamline at DESY PETRA III[2]. HiPhaX is a valuable tool for drug discovery, helping scientists quickly test thousands of potential medicines against disease-related proteins. Unlike traditional methods, it does not just confirm whether a drug binds, but shows exactly how it interacts at the atomic level, making it easier to design more effective treatments. Designed for full automation, HiPhaX aims to deliver over 1,000 structure determinations per day and ultimately provide fully autonomous data collection and analysis, speeding up early-stage drug development. It can operate at both ultra-cold and room temperatures, allowing for a wide range of experiments.

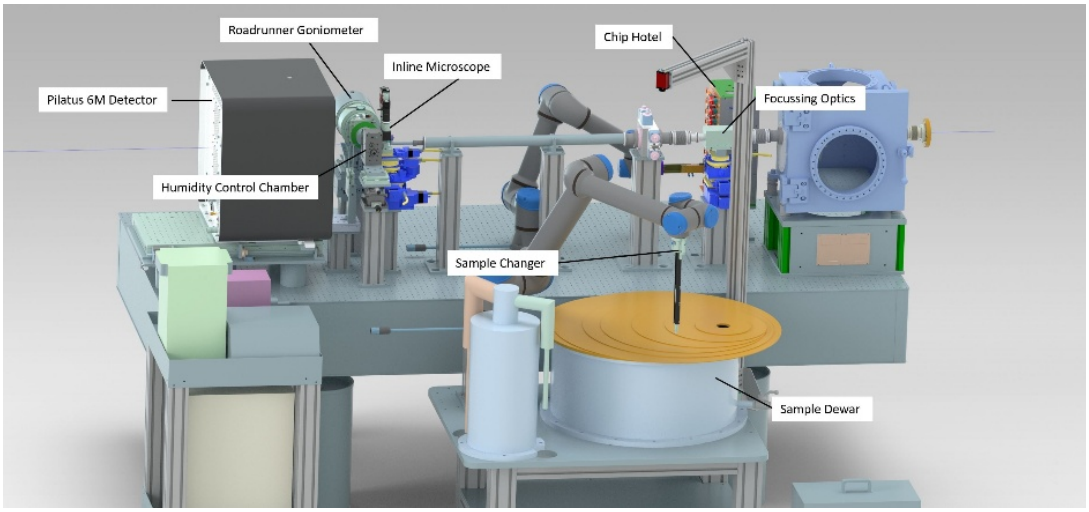
... THROUGH UCI-FUNDED HARDWARE ENABLING HIGH-THROUGHPUT ROOM TEMPERATURE SCREENING, A GLOBALLY UNIQUE CAPABILITY

To enable room-temperature capability in the HiPhaX instrument, the 'High-throughput pharmaceutical screening at room temperature' activity received €60,000 in funding from Hi-Acts' Use Case Initiative (UCI). This was used to develop a measurement chamber with humidity and temperature control and a robotic arm for automatic sample exchange. The project sought to design a fragment screening beamline for rapid screening at physiologically-relevant conditions with applications in structure-based drug development. The 8-month long activity was led by DESY (specifically by the FS-CFEL-1-BMX research group, which focuses on advancing automated, high-throughput methods for structural biology and drug discovery), with Suna-Precision GmbH (a DESY spin-out organisation supplying hardware for serial crystallography, imaging systems and sample environments and handling) as an industry partner, concluding in late 2023.

The UCI-funded hardware developed enables faster, more cost-effective investigation of biologically relevant protein crystals (e.g., from viruses or bacteria) in combination with potential drug compounds. As room temperature more closely reflects physiological conditions, it may reveal biologically-relevant structural states obscured at cryogenic temperatures – an area still at the cutting edge of structural biology. The instrument's fully automated operation supports high-throughput screening, while room-temperature capability simplifies sample handling compared to cryogenic methods. All planned technical developments have successfully been completed, with next steps focusing on refining the software to enhance automation capabilities and AI-supported analysis.

Figure 1: HiPhaX experimental hutch overview

[1] Deutsches Elektronen-Synchrotron (DESY) is a premier German research institute specialising in particle accelerator technology and fundamental investigations into the structure and behaviour of matter.
[2] PETRA III is a high-brilliance synchrotron X-ray source at DESY in Hamburg, used for cutting-edge research in fields like materials science and biology. In this context, a beamline is the path along which synchrotron-generated X-rays travel to experimental stations for scientific investigation.



Source: DESY

Further developments to the HiPhaX instrument are planned. The addition of a sample dewar[3] holding up to 860 samples will enable near-continuous 24-hour data collection for cryogenic samples. A SampleDB-based database (developed by Helmholtz Center FZ Jülich) is also being implemented to support full automation.

The performance of the HiPhaX instrument is influenced by the frame rate of the Pilatus 6M detector, which affects fast X-ray centring and high-speed serial data collection. Enhancing its capabilities would involve incorporating a faster detector and refining X-ray optics to increase flux at the sample, though implementing these improvements would require additional funding beyond the original UCI support.

This activity supported by Hi-Acts UCI has already resulted in benefits for the organisations involved, and is anticipated to contribute to industry- and society-level impacts, as explored in the following sections.

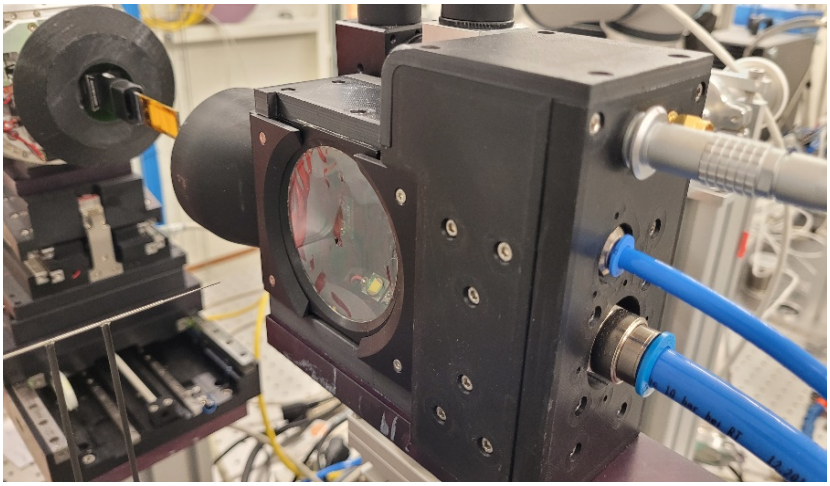
TECHNOLOGY MATURITY PROGRESSION

Hi-Acts UCI funding has enabled the technology maturity progression of critical hardware of the HiPhaX instrument, from Technology Readiness Level (TRL) 7 to TRL 9, with the equipment now operational.

Hi-Acts UCI funding has enabled technology maturity progression, from an estimated TRL 7 to TRL 9. The hardware is now fully integrated into the operation of the beamline, along with a room temperature storage container (funded by an alternative source). The science team highlighted that the equipment is operational, used regularly, and is working reliably.

Figure 2: Sample and environmentally controlled measurement chamber

[3] A dewar is a container designed to maintain the temperature of its contents, in this case, at cryogenic temperatures.



Source: DESY

Temperature and humidity stability and accuracy exceed the baseline requirements (+/- 0.5 % rH and +/- 0.1°C), which is critical to producing relevant and reliable measurement results. This allows multi-dimensional crystallography experiments to be conducted, to study protein flexibility and conformational space under varying external conditions. Fully remote and automated operations are also now possible, which is particularly beneficial, as it enables high throughput. The science team highlighted that one sample can now be measured in 1 to 2 minutes, significantly faster than the 10 to 15 minutes required prior to automation. This represents a reduction in measurement time of up to 93% (i.e., up to 15 times faster). The development of this technology thus presents an opportunity for significant benefits to DESY and the German industry, the magnitude of which will depend on user uptake. Room-temperature crystallography is a globally unique capability, positioning DESY as a leader and establishing German sovereignty in this field.

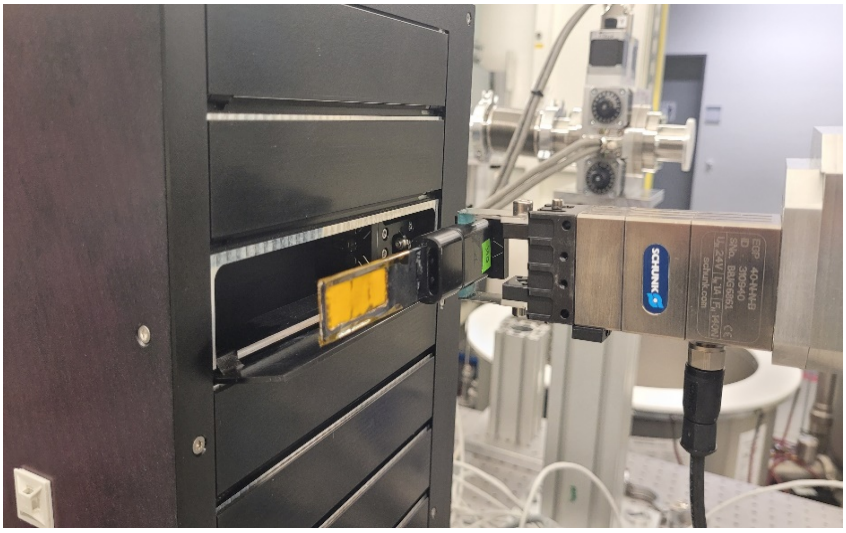
SCIENTIFIC BREAKTHROUGHS

HiPhaX, equipped with UCI-funded hardware, has already delivered key scientific breakthroughs, contributing to building public health resilience by accelerating drug development and reducing costs.

The HiPhaX instrument, leveraging the hardware developed through this UCI-funded activity, has already enabled several scientific breakthroughs in its first three years. The science team advanced fixed-target serial crystallography to enable high-throughput fragment screening at room temperature (RT), systematically comparing results with conventional cryogenic single-crystal data for 'FosAKP', an antibiotic resistance-related enzyme. RT serial crystallography achieved 1.5 Å resolution[4], comparable to cryogenic methods and significantly better than RT single-crystal data (1.9 Å). This approach revealed a previously unobserved active-site conformation, offering new starting points for drug design. By uncovering structural features that are likely to be functionally relevant under physiological conditions, this work provides critical insight into how resistant enzymes adapt, and opens a path to developing inhibitors capable of overcoming antibiotic resistance in high-priority pathogens. For the seven ligands identified at both temperatures, binding modes remained unchanged. While more binders were detected at cryogenic temperatures, these were mostly at physiologically less-relevant sites. The ability to access alternative protein conformations through RT serial crystallography, especially when combined with HiPhaX automation, can enhance drug development by expanding the conformational space available for screening.

[4] Ångström (Å): A unit of length used to express molecular dimensions. 1 Ångström equals 10^{-10} metres or 0.1 nanometres.

Figure 3: Gripper tool moving sample from the room temperature storage container



Source: DESY

The science team also conducted experiments focusing on protein dynamics. They investigated protein conformational changes through controlled modulation of relative humidity and temperature. Lysozyme data at 1.4 Å resolution revealed water network changes and an active-site peptide flip. Additionally, user experiments explored the effects of relative humidity on the 2'-5'-Oligoadenylate synthetase 1 (OAS1) enzyme, which belongs to a family of essential proteins involved in the innate immune response to viral infections. Findings revealed the significant role of hydrodynamic effects in modulating enzymatic function under conditions of changing relative humidity. These experiments provide critical insight on protein flexibility in crystal structures, essential for the effective development of drugs.

The scientific breakthroughs enabled by the HiPhaX instrument can play a pivotal role in enhancing resilience to (re-) emerging diseases[5], ultimately driving down costs and saving lives[6] by accelerating drug development and improving therapeutic outcomes [ii,iii,iv].

NEW SKILLS, KNOWLEDGE, AND TECHNOLOGY TRANSFER

Developing the environment-controlled chamber and robotic arm has built new skills within the science team, while also facilitating knowledge and technology transfer across DESY and to international partners.

The UCI-funded activity has enabled the upskilling of all three senior individuals involved as part of the scientific team. They acquired valuable technical skills associated with the development of innovative precise temperature control processes to meet the demanding requirements of the technology.

The knowledge and experience acquired in room temperature fixed-target serial crystallography is being transferred to other parts of DESY and US-based SLAC National Accelerator Laboratory (SLAC), as part of a Helmholtz Institute-funded activity focusing on serial-femtosecond crystallography (SFX) experiments. This work, carried out at the European XFEL (X-Ray Free-

[5] The World Health Organization (WHO) released an updated list of (re-) emerging pathogens with epidemic and/or pandemic potential in 2024. It can be consulted here.

[6] For example, the indirect costs associated to the COVID-19 pandemic constituted 10.53% of the global GDP. The WHO highlights that over 7 million COVID-19 deaths were reported globally.

Electron Laser Facility) and SLAC, depends on competitive beamtime access. The technological developments and pre-tests conducted with HiPhaX have been crucial in enabling this follow-on activity, particularly due to the instrument's high-throughput capability. Future plans include expanding collaboration with XFEL facilities to support sample pre-testing, delivery, and training for users and beamline staff.

Additionally, the UCI-funded hardware is also being leveraged for the experiments ran under a follow-on international collaboration (explored in more detail below) and in the field of catalysis. The robotic arm device drivers have been transferred to PETRA III Beamline 65, which uses the same robot, and will be extended to additional beamlines in the future.

Hi-Acts UCI funding has fostered the development of new skills, valuable knowledge, and technology transfers within DESY and beyond, both nationally and internationally. This highlights that the funding's impact footprint reaches beyond the direct contractors and application domains. It also strengthens the science team and DESY's technological leadership in the field.

VISIBILITY AND REPUTATION

The UCI-funded activity has raised the profile of the hardware and highlighted the advantages of the room-temperature screening technique.

While DESY and the research team are already well-recognised globally, the UCI-funded activity has significantly increased visibility for the hardware developed and the benefits of room-temperature macromolecular synchrotron X-ray crystallography. Presentations at numerous conferences have raised awareness of these innovations and the new capability now available.

Further work is needed to enhance industry's understanding of the added value of this measurement technique, though the science team anticipates that their upcoming high-profile publications in *Nature Communications* and *Science* will help demonstrate the hardware and concept, building confidence for commercial end users, and fostering uptake.

FOLLOW-ON COLLABORATION

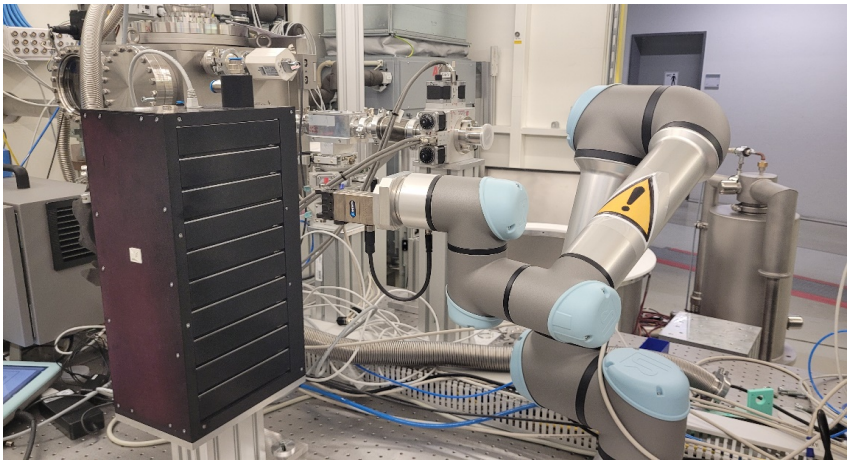
The development of the enabling hardware has resulted in follow-on international collaboration, driving innovation in structure-based drug discovery to enhance resilience against outbreaks, saving lives and reducing costs.

Hi-Acts UCI funding has directly led to a follow-on international collaboration with eight partners (through a Block Allocation Group, BAG), including the University of Hamburg (Germany), DESY (Germany), the Centre for Structural Systems Biology (Germany), the University of São Paulo (Brazil), the Hanover Medical School (Germany), and the Brazilian Synchrotron Light Laboratory (Brazil). The science team had worked with some of these organisations before, though around half of them were new partners. This work is funded by the German Federal Ministry of Research, Technology and Space (BMFTR) and leverages the equipment developed for structure-based drug discovery, focusing on emerging diseases as well as existing diseases that scientists regard as being underfunded in pharmaceutical research.

Sub-projects within this framework target diverse scientific goals. Three explore new starting points for antiviral drug development against influenza A (i.e., H5N1, a highly virulent strain with pandemic potential). Others focus on fundamental research into magnetoreception and pathogen defence mechanisms in humans and bacteria. Additional efforts aim to establish a Ca^{2+}-dependent enzyme as a benchmark for time-resolved mix-and-diffuse serial crystallography and to extend basic room-

temperature measurements at HiPhaX to time-resolved studies. Under this framework, one experiment has successfully been concluded to date (with Prof. Dr. Matthias Rarey's group of the University of Hamburg), targeting the Lassa virus (LASV), an arenavirus that causes Lassa haemorrhagic fever in humans and primates.

Figure 4: Robotic arm approaching the sample container



Source: DESY

The science team is also collaborating with the Centre for Bioinformatics at the University of Hamburg on a joint BMFTR-funded project focused on developing AI-based software for automated ligand hit identification and position refinement from electron density maps. In addition to full automation, this will save the time typically spent manually identifying ligands across hundreds or thousands of datasets, increasing the speed of screening.

As an enabling equipment of these follow-on collaborations, the UCI-funded hardware is contributing to cutting-edge research in structure-based drug discovery, which could enhance resilience to future outbreaks, saving lives and minimising economic costs. Being able to collaborate with leading research institutes globally is also an opportunity to build new partnerships, strengthen existing ones, and benefit from knowledge transfers, overall fostering innovation.

COMMERCIAL POTENTIAL

The HiPhaX instrument, equipped with UCI-funded hardware, offers significant value for research and industry, with strong revenue potential. High uptake could lead to the creation of a spin-out organisation to support commercialisation.

The HiPhaX instrument can be valuable for both research and industry customers, and is now accepting users for pharmaceutical screening experiments with both conventional cryo-crystallography and room temperature serial-crystallography. Several research institutions, especially based in Germany, have already been using the UCI-funded hardware, notably as part of the follow-on international collaboration highlighted earlier. Members of the BioMAX group at the MAX IV Laboratory (Sweden) have also been conducting humidity studies at room temperature using the equipment developed. This is helping build heritage for this capability and demonstrate its effectiveness and benefits to a wider customer base.

Another anticipated customer group is the measurement service providers for pharmaceutical companies. Pharmaceutical companies directly could also constitute a customer segment, though service providers are more likely. Cryogenic macromolecular synchrotron X-ray crystallography is the

current status quo, meaning that the benefits of the room temperature equipment developed will have to be convincingly demonstrated to trigger a change in processes for these customers. As highlighted previously, the science team anticipates that this will be achieved through the dissemination of the three articles currently in the publication process for prestigious journals. However, as highlighted earlier, while the Pilatus 6M detector used in the equipment developed still offers high performance, it is not state-of-the-art, which could potentially deter some industry customers.

There is a notable revenue potential for this equipment. According to the science team, the market rate price to measure one cryogenic sample at a synchrotron facility in Europe is around €50. To encourage a shift toward room-temperature macromolecular synchrotron X-ray crystallography and increase adoption, we explored, for illustrative purposes, a cost-competitive pricing model of €35 per sample. Under this conservative hypothetical scenario, processing 1,000 samples (i.e., in 1 day with this new equipment) would generate €35,000 in revenue. However, due to high operating costs, profit margins are expected to remain low – estimated at only a few percent. Assuming a conservative 3% margin, the resulting profit would be approximately €1,050 per day. The science team indicated that if uptake is high, a spin-out organisation could be created to support commercialisation endeavours.

PUBLIC HEALTH RESILIENCE

The UCI-funded HiPhaX hardware helps accelerate drug development for high-risk and underfunded diseases, contributing to saving lives and reducing the considerable economic burden of future pandemics.

By enabling high throughput screening at room temperature, the hardware developed with UCI funding is contributing to speeding up the development of effective drugs. As noted, follow-on projects leveraging the equipment are principally focused on (re-) emerging and underfunded diseases, areas where rapid therapeutic development is critical for global health preparedness and resilience.

These diseases, such as pandemic-prone viruses or neglected tropical infections, can place significant strain on healthcare systems and economies. For example, in Germany alone, the COVID-19 pandemic[7] resulted in economic losses amounting to €330 billion over 2020 and 2021, representing approximately 10% of the country's 2019 GDP[v]. Across the European Union, the pandemic led to a 6.1% contraction in GDP in 2020[vi]. The ability to accelerate early-stage drug development not only helps save lives but also reduces the long-term economic burden associated with delayed treatments, containment efforts, and healthcare costs. In this way, the HiPhaX instrument, and its UCI-funded hardware, support both public health and economic resilience, contributing to the United Nations' Sustainable Development Goals[8].

ATTRIBUTABILITY OF THESE BENEFITS TO HI-ACTS FUNDING

Hi-Acts UCI funding was critical in enabling the development of the measurement chamber with controlled temperature and humidity, as well as the robotic arm for automatic sample exchange as part of the HiPhaX instrument. The science team noted that securing funding for this hardware elsewhere would have been challenging, although they did obtain alternative DESY internal funding for the room temperature storage container, which was initially included in the UCI proposal but ultimately not funded. They highlighted that they could have accessed resources through a larger

[7] DESY's PETRA III X-ray source contributed to research on improving RNA vaccines, specifically supporting BioNTech's development efforts for the BioNTech-Pfizer COVID-19 vaccine. Further details can be found here.

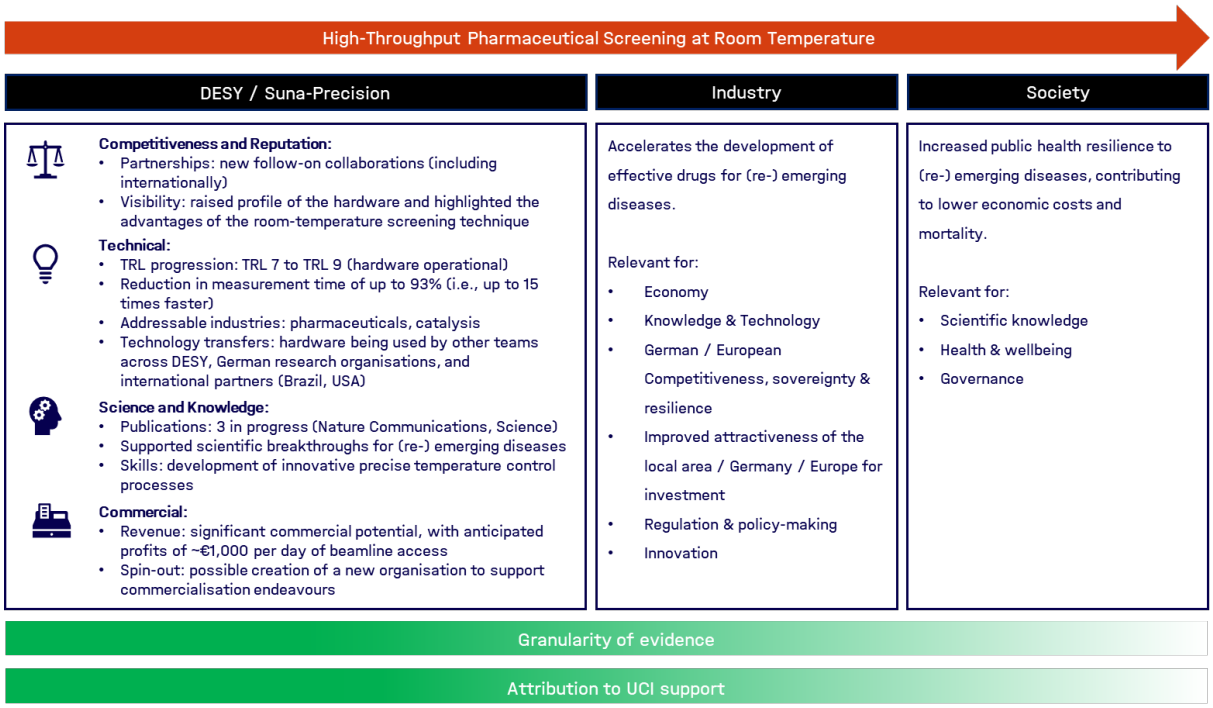
[8] Notably Goal 3 (Ensure healthy lives and promote well-being for all at all ages), Goal 8 (Promote sustained, inclusive and sustainable economic growth), and Goal 9 (Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation).

project, but those are more complex to design and more difficult to fund, as they typically require larger budgets.

UCI thus provided a rapid and flexible funding source to develop this enabling hardware. Most of the benefits outlined in the previous sections would consequently not have occurred without UCI support, notably the follow-on collaborations and scientific breakthroughs. Wider societal impact, such as accelerating the development of effective therapeutics (including those targeting antibiotic-resistant pathogens) and the subsequent strengthening of public health resilience, remain contingent on the broader uptake of room temperature measurement techniques, sustained research investment, and coordinated efforts across the drug development pipeline.

While the UCI-funded hardware represents an essential enabling step, it is important to note that realising its full impact will depend on many additional scientific, funding and policy factors.

IMPACT SUMMARY



[i] WHO (2025). *World Health Statistics 2025*. Available from: https://iris.who.int/bitstream/handle/10665/381418/9789240110496-eng.pdf?sequence=1

[ii] Faramarzi, et al. (2024). *The global economic burden of COVID-19 disease: a comprehensive systematic review and meta-analysis.* Systematic Reviews 13, 68. https://doi.org/10.1186/s13643-024-02476-6

[iii] WHO (2025). *Number of COVID-19 deaths reported to WHO (cumulative total).* Available from: https://data.who.int/dashboards/covid19/deaths

[iv] WHO (2024). *Pathogens Prioritization – A scientific framework for epidemic and pandemic research preparedness*. Available from: https://cdn.who.int/media/docs/default-source/consultation-rdb/prioritization-pathogens-v6final.pdf?sfvrsn=c98effa7_7&download=true

[v] ifo Institute (2022). *Coronavirus Pandemic Caused EUR 330 Billion in Economic Losses for Germany*. Available from: https://www.ifo.de/en/press-release/2022-02-17/coronavirus-pandemic-economic-losses-germany

[vi] European Parliament (2022). *How have major economies responded to the COVID-19 pandemic?*. Available from: https://www.europarl.europa.eu/RegData/etudes/STUD/2022/699531/IPOL_STU(2022)699531_EN.pdf