feature

# Accelerating pharmaceutical structure-guided drug design: a successful model

**Lisa J. Keefe**[1,2] **and Vincent S. Stoll**[3], vincent.stoll@abbvie.com

**The impact and value of structure-based drug design to pharmaceutical discovery across the industry are now undeniable, with many break-through therapies on the market that are structure based in nature. Enabling the structural research is the Industrial Macromolecular Crystallography Association-Collaborative Access Team (IMCA-CAT), formed over 25 years ago as a world-class research facility at the synchrotron at Argonne National Laboratory. What makes IMCA-CAT unique is the strategy of the founding consortium to comprehensively provide for the evolving needs of industry in one facility. This includes year-round high-quality data, capabilities that match target portfolios, throughput and capacity that are never limiting, and unfailing security. Here, we illuminate the unique capabilities offered by IMCA-CAT and instruct how all industrial organizations can access this facility.**

## Why structure matters

Drug discovery and the ensuing process of developing a candidate ultimately into a drug on the market are among the most challenging and expensive of human endeavors. Over the past decade, numerous articles have been published detailing the decreasing productivity of the pharmaceutical industry and the sky rocketing costs of research and development (R&D) [1–4]. Although there are many ways in which the industry continually addresses long timelines, high costs, and slow success rates, here we focus on the impact of structure on accelerating drug design. The technique of protein X-ray crystallography has a crucial role in determining structures and, with the use of synchrotrons, in accelerating throughput and broadening capabilities for drug design. The impact of structural insights in driving clinical success is clear from the collective industry breakthrough in taking HIV/AIDS from a guaranteed death sentence to a long-term manageable disease [5–7]. This was accomplished over the course of 10–15 years of intense, prolonged R&D for which protein structure had a key role [8–12]. In numerous cases, structure-based drug design has been instrumental in drug discovery to drive success, either by reducing timelines or enabling drug discovery on targets thought to be undruggable. Synchrotron beamlines, such as the one at the IMCA-CAT facility have enabled structure-based drug discovery for more than 25 years. One example from the IMCA-CAT beamline is Bcl-2 and the approved Venclexta from AbbVie, the 2017 Prix Galien award winner [13]. Venclexta is the poster child of both fragment-based drug discovery and structure-based optimization of a previously deemed undruggable target, resulting in a breakthrough therapy for patients [13]. Another notable example of fragment or structure-based drug design developed from research conducted at IMCA-CAT is Kisqali from Novartis, a CDK4/6 inhibitor approved for metastatic breast cancer [14,15]. Examples of the impact of structure-guided drug design on drug discovery abound across the industry.

From the 1970s through to the early 2000s, in-house X-ray generators were the dominant source of X-rays for structure determination in most companies. Over the past 25 years or more, the use of protein crystal structures in structure-based drug design (SBDD) has evolved from retrospective rationalization of structure–activity relationship data (SAR) to driving real-time impact on drug discovery. This evolution of the impact and value of SBDD has gone hand-in-hand with a technology revolution. It was only 15–20 years ago, using in-house X-ray generators, that it would take 24–72 h to collect data

1359-6446/© 2018 Elsevier Ltd. All rights reserved.
https://doi.org/10.1016/j.drudis.2018.11.008

for a single structure. With current technology, a single data set can be collected in less than 1 min. Crystal structures of potential drug leads now can be requested and delivered in near real-time. This has transformed the value and impact of structural information on drug discovery.

The evolution in X-ray crystallography covers advances in construct design, protein preparation, crystallization technology and robotics, data collection technology and data-processing strategies, refinement, and interpretive computation. The explosion in access to high-resolution crystal structures has empowered a dramatic expansion of computational tools and improvements in algorithms for molecular modeling, modeling predictions, and virtual ligand-screening capabilities. When obtainable, chemists seize upon the opportunity to learn exactly how their compound binds, the nature of the binding site, and where the prospects are for optimization. It is reasonable that this type of insight alone would have significant impact on the speed of drug discovery. Furthermore, there is the discovery of the unexpected, such as a contaminant or intermediate that is more potent than the target molecule, a novel binding mode, unexpected protein movement, or crystal-packing artifacts, that frequently leads to transformational impact on a project, as encountered in the discovery of Venclexta [13]. The successes in solving increasingly difficult target structures, such as G-protein-coupled receptors (GPCRs), large protein complexes, and novel biologics is revolutionizing the role of structure in enabling drug discovery on increasingly challenging targets.

## Meeting the research needs of a changing industry

Structure is of maximum benefit to drug discovery primarily if the structural information is provided both in real time and on all the targets of interest to continually evolving pharmaceutical pipelines. To effectively incorporate structure into the drug discovery process and meet the needs for quality data and real-time results, it is crucial that technology be cutting-edge. This can be a significant financial and technically challenging burden for any individual company to sustain on their own. With this in mind, a group of companies [Abbott (now AbbVie), Lilly, Merck, Monsanto, Proctor & Gamble, Bristol-Myers Squibb (BMS), and Upjohn] recognized the potential value of collaborating together and, thus, in 1990, founded IMCA to establish a shared research facility optimized for structural biology supporting drug discovery. The IMCA consortium, responding effectively to shifting tides within the pharmaceutical industry and unwavering in its commitment to the shared resource for over 25 years, now includes AbbVie, BMS, Merck, Novartis, and Pfizer. The research facility, maintained and operated by IMCA-CAT, was built in 1992 at the Advanced Photon Source, a high-energy synchrotron X-ray source at Argonne National Laboratory. The pillar of IMCA-CAT is the state-of-the-art structural biology beamline technically designed for high-throughput protein X-ray crystallography yielding high-quality structural information.

The success of IMCA-CAT and, thus, the sustained value of the IMCA industrial collaboration, can be attributed to the laser focus on accelerating drug discovery by adhering to five core values: outstanding quality in capabilities that match the company portfolios (e.g., soluble and membrane proteins); high throughput; reasonable cost; utmost security; and exceptional reliability. IMCA-CAT is unique in its longevity, industrial collaboration and funding, strategies for meeting the needs of member-driven drug discovery, and in the opportunities offered to nonmembers for access. To understand how IMCA-CAT continues to provide significant value to the pharmaceutical industry at large and offers a competitive advantage over other synchrotron beamlines world-wide, here we provide perspective on the organizational strategies, operational model, and future plans in meeting the needs of industrial users.

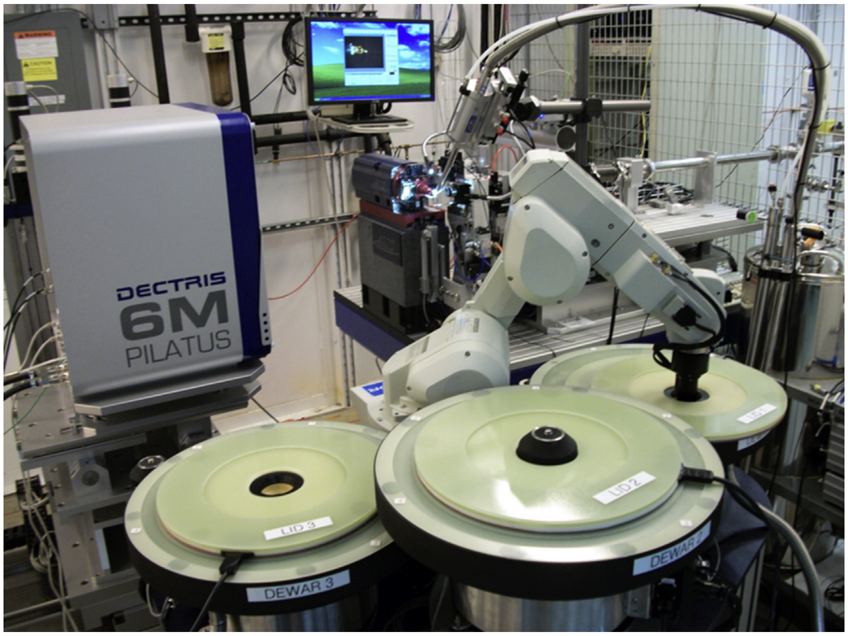
## Key elements of a shared research facility

Many beamlines at synchrotrons worldwide offer industrial access for pharmaceutical drug discovery research, but the key attractors for IMCA-CAT are quality, productivity, security, reliability, and guaranteed frequent and routine access. IMCA-CAT provides all of these elements along with never-limiting capacity. From its inception, the overarching approach of IMCA-CAT in meeting the needs of the industry has been to increase capacity ahead of increasing industry need. Toward this end, IMCA-CAT has embraced new technologies and innovation, and continually invests in upgrading the facility.

The best-quality hig- resolution diffraction data from microcrystalline samples are collected at synchrotron beamlines where the X-rays are highly intense and focused. The IMCA-CAT beamline (Fig. 1) is optimized and automated to generate quality X-ray diffraction data from ever smaller samples at high-throughput rates. The beamline uses cutting-edge mirror optics to tightly focus the X-ray beam followed by apertures to deliver beams as small as 5 μm. Over the years, structural biologists have steadily pushed the limits of data-collection capabilities by presenting crystalline samples of progressively smaller size. This has been driven predominantly by technology enabling high-quality data from smaller crystals, accelerated drug discovery timelines that prioritize efficiency and resource savings, and the increased complexity of the molecules that limit the growth size of crystals. The need for quality data from these crystals that typically are $<10$ μm has effectively sparked innovation in a range of technologies for protein crystallography.

An area of significant innovation has been the development of detectors for use at synchrotron beamlines. Starting during the 1990s, the detector of choice was the charge-coupled device (CCD) area X-ray detectors, which were deployed at synchrotron beamlines for protein crystallography. During the early 2000s, the introduction of the hybrid photon counting (HPC) pixel array detector for protein crystallography radically transformed strategies for data collection. HPC detectors have: (i) no readout noise, thus yielding exceptionally high signal:noise ratios, which enables experiments on weakly diffracting crystals; and (ii) extremely fast readout, thereby enabling shutterless continuous-rotation data collection, which minimizes errors. Indeed, shutterless data collection makes it feasible to diffraction raster across the sample mount for highly accurate sample centering (key for automated data collection), and utilize novel data-acquisition strategies, such as helical or vector data collection, which is instrumental for measuring data from radiation-sensitive samples. By 2010, when IMCA-CAT deployed one of the first pixel array detectors, throughput and productivity immediately increased sevenfold and the experiment envelope expanded to enable data collection on challenging samples, including membrane proteins and RNA complexes. Overall, the advanced features of these new detectors inspired the development of new strategies for experiment design (Fig. 2), yielding better-quality data collected faster.

Pharmaceutical companies have had a significant role in contributing to innovation that has revolutionized structural biology at synchrotrons. In 2002, 'Abbott Laboratories and Rigaku/MSC received *R&D Magazine*'s 2002 R&D 100 Award for their invention and refinement of the world's first commercial robotic system for automated pharmaceutical drug sample handling' [16]. Robotics have been in routine use at the IMCA-CAT beamline for over 10 years. The impact on efficiency has been profound. With the synchrotron operating round the clock,



Drug Discovery Today

**FIGURE 1**

The Industrial Macromolecular Crystallography Association-Collaborative Access Team (IMCA-CAT) insertion device beamline 17-ID at the Advanced Photon Source, Argonne National Laboratory, is optimized for high throughput. With the current detector, the Dectris Pilatus 6M, a data set is collected in 60 s. In 2019, the detector will be upgraded to the Eiger2 X 9M, thus enabling the collection of a data set in 10 s. The robot, Rikagu ACTOR, is custom integrated to the beamline and is essential for a variety of data-collection strategies, automated data collection for unattended overnight data collection, and remote access.

conducting experiments throughout every night presented challenges in both endurance and accuracy for researchers. With robotics for automated data collection, fatigue is no longer a concern and data collection can proceed unattended at sustainable throughput rates of at least 18.5 data sets per hour (Fig. 3).

The fast rate of data generation necessitates secure, efficient, and reliable data-management protocols for the protection of proprietary data. Data are processed on-the-fly with specialized software developed by Global Phasing Ltd (www.globalphasing.com), another consortium of which the companies are members [17]. High-speed, secure, and encrypted data transfer to off-site company locations directs the flow of images and processed data for integration into company-based pipelines. Samples are shipped overnight to the facility and inventoried upon receipt. Barcodes on the sample packs serve for tracking both samples and data. Access to data is strictly and securely limited to the company that owns the sample. Since its founding 25 years ago, IMCA-CAT has a flawless record of protecting the confidentiality of proprietary samples and data.

Reliability and efficiency are notable features that differentiate the IMCA-CAT facility as an outstanding resource for the pharmaceutical industry. Effective risk management, such as sufficient spare components to mitigate equipment failures, minimizes down time to near 0%. The entire data acquisition process, including sample mounting, centering, and data collection and processing, is automated, thus enabling unattended operation, which has proven efficient for the success of both remote data collection and mail-in service. Pharmaceutical companies ship samples weekly and most data are collected by staff as mail-in service. The turnaround time from start of beam time or receipt of samples to delivery of processed data (Fig. 3) is within 1 day (for >90% of the samples) and, for many samples, the same day (~60–65% of the samples). A vital benefit of investing in the facility is the guaranteed access for frequent and routine data collection. The reliably and frequency of data flow smoothly integrate with pharmaceutical work flows.

## Opportunities for access

The estimated budget to build a state-of-the-art synchrotron beamline today is projected at US $14 million, admittedly too costly for a single company to burden. Yet, with the IMCA-CAT throughput of >20 000 data sets annually and a beamline lifetime of 10 years before upgrading, the cost, including operations and maintenance, is <US $150 per data set. IMCA-CAT is a highly powerful and productive research facility and, at an economical price, provides ample capacity to meet the demands of each member company. The goal of IMCA of a shared industrial synchrotron beamline is visionary: competitors working together to provide for the common need of frequent, routine, and reliable access to synchrotron radiation for proprietary crystallography supporting drug discovery.

Access to the IMCA-CAT facility is available to nonmember companies, either through IMCA membership or via IMCA-CAT subscription that is modeled on full cost recovery. Benefits for both include frequent and rapid access, security for confidential and proprietary data collection and processing, and full access to the experiment capabilities of the beamline. Members receive additional benefits and services not available to subscribers. Subscribers can request mail-in data collection service as an additional cost option. The subscription program, having grown substantially in recent years, is a valuable strategic opportunity to advance SBDD for the pharmaceutical industry.

## A bright future

Weekly flow of data is crucial for industrial SBDD. The APS synchrotron facility pauses operations

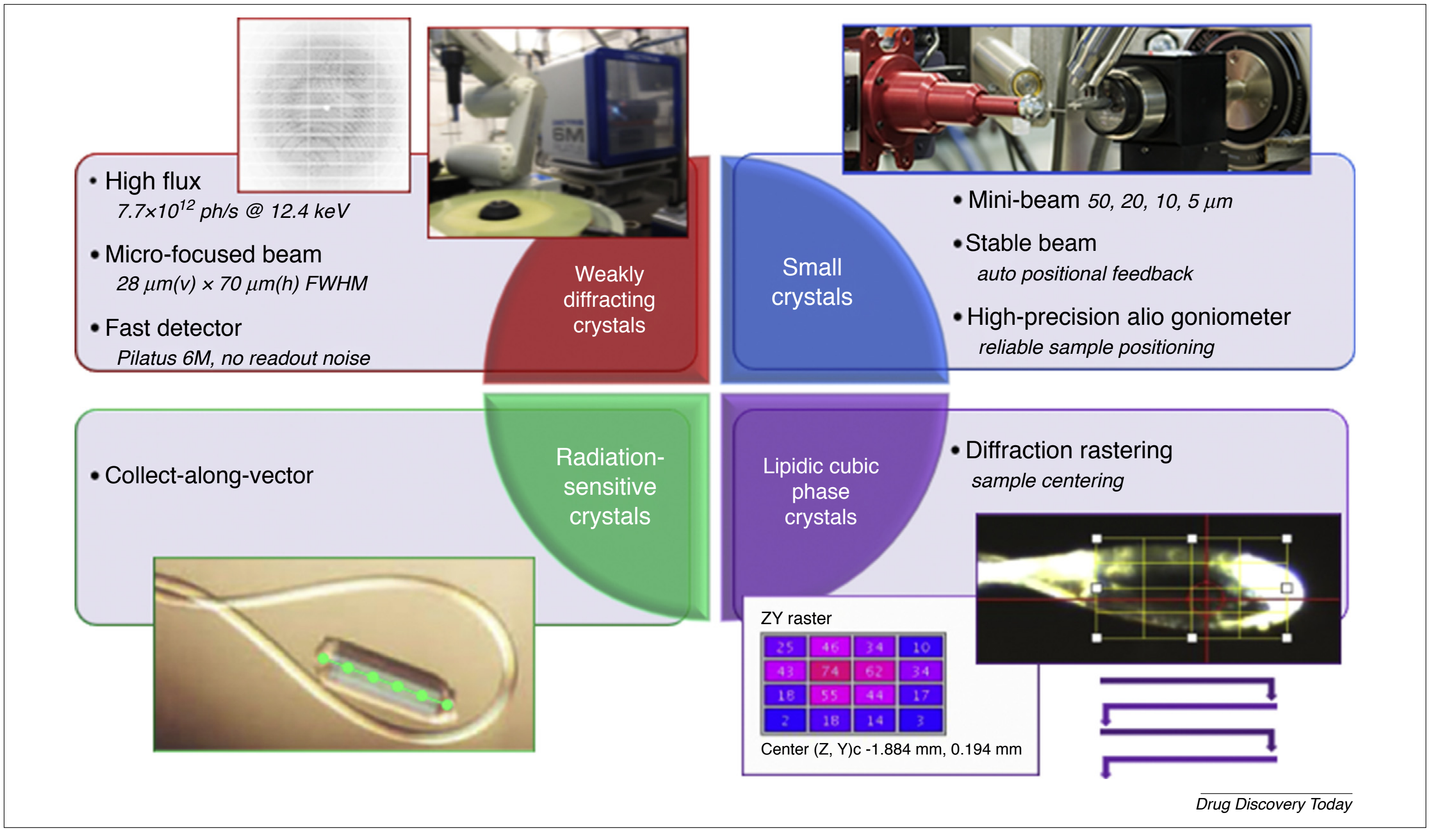


**FIGURE 2**

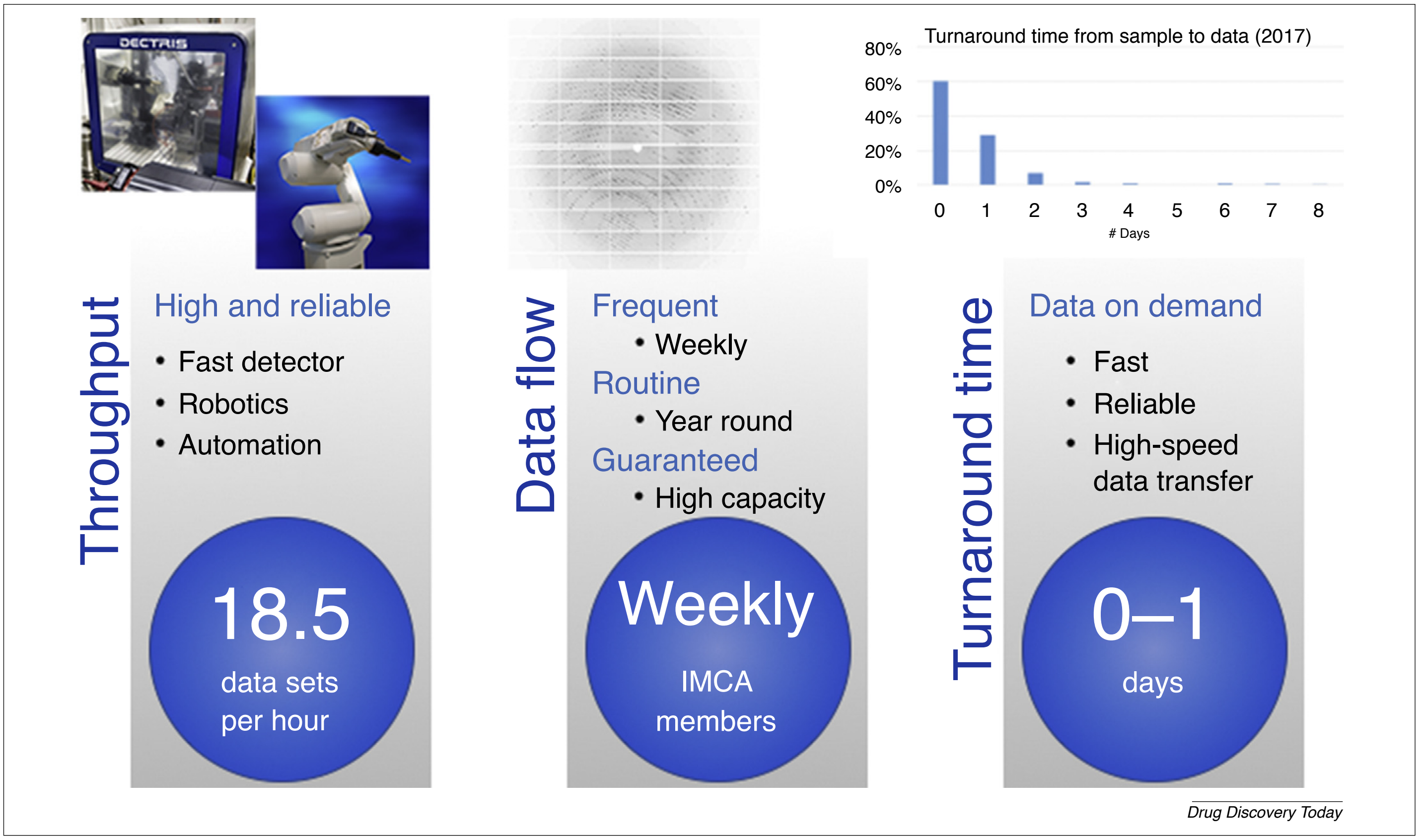
Challenging experiments are enabled at Industrial Macromolecular Crystallography Association-Collaborative Access Team (IMCA-CAT). The synchrotron beamline delivers a focused, intense, and stable X-ray beam for protein crystallography. The intense X-ray beam, high-precision goniometer, and fast detector sparked the development of new strategies that enable high-quality data to be collected on very small samples. These small samples, often not visible in camera images, are accurately centered in the X-ray beam via fully automated diffraction rastering, thus overcoming the challenges of collecting quality data on membrane protein crystals in lipidic cubic phase. Data-collection strategies, such as collecting data on a sample as the sample is translated through the beam (collect-along-vector), enable data to be collected on challenging samples, such as those that are radiation sensitive.

three times per year for a month-long maintenance shutdown. To maintain the flow of industrial data during this time, IMCA-CAT conducts experiments remotely at other synchrotrons. Several synchrotron beamlines comprise the portfolio of alternate sources, and the portfolio is growing.

Crystallography provides the bulk of structure data for industry, yet there are important projects that do not lend themselves to producing diffraction-quality crystals. These projects are aided by the structural insights garnered from other biophysical techniques, such as small-angle X-ray scattering (SAXS), cryo-electron microscopy, and cryo-electron diffraction. Combining structure information from different types of experiment in an integrative approach is becoming a necessity for dynamic macromolecular complexes. Meeting the emerging need for comprehensive approaches to structural biology, IMCA-CAT is expanding its scope of partnerships with complementary synchrotron beamlines and laboratories to provide access to these integrative biophysical techniques for proprietary drug discovery projects.

With a strategic vision for the future, IMCA-CAT is committed to the continued investment and growth in enhancing capabilities and increasing productivity. Emerging interests in large complexes and challenging projects are driving the development for enhanced capabilities. IMCA-CAT is working on the challenging goal of expanding the experiment envelope to develop effective strategies and successfully automate data collection for membrane proteins in lipidic cubic phase. Long-term sustainability is driving the growth in productivity. IMCA-CAT is aiming for the ambitious goal of collecting 1000 data sets per day. Although maintaining excess capacity for pharmaceutical drug discovery has always been a high priority, this goal of ultra-high-throughput effectively doubles the current capacity. Meeting this goal requires entirely different methodologies for sample handling and delivery to the beamline. Indeed, IMCA-CAT has already embarked on this R&D path by actively exploring new techniques, including serial crystallography, *in situ* plate-based data collection, and other developments emanating from the BioXFEL project [18]. Additionally, plans are underway to deploy a new detector that will shorten the data collection time to 10 s, expand the computing capability to manage the marked increase in volume of data, and, for the interim until new sample delivery protocols are developed, upgrade the robotics system to achieve faster sample exchanges.

IMCA-CAT, tailor-made for quality data and high productivity, provides an outstanding research environment for confidential and proprietary structural biology programs in the pharmaceutical industry. Pharmaceutical companies, via IMCA membership or IMCA-CAT subscription, value the guaranteed, frequent, and routine access to the beamline for X-ray diffraction data collection. By partnering with the pharmaceutical industry members of IMCA to both drive innovation and sustain cutting-edge operations, the IMCA-CAT beamline is distinguished as a cost-effective and world-class facility for pharmaceutical research.



*Drug Discovery Today*

**FIGURE 3**

At Industrial Macromolecular Crystallography Association-Collaborative Access Team (IMCA-CAT) in 2017, the throughput rate was 18.5 data sets per hour, and data flowed year-round with weekly data collection for each company. With its fast sample-to-data turnaround time, with most data collected within 1 day, and high-speed data transfer to company sites and pipelines, the IMCA-CAT facility serves as an integral element of the pharmaceutical research laboratory for structure-based drug design.

## References

1 Kuntz, I.D. (1992) Structure-based strategies for drug design and discovery. *Science* 257, 1078–1082
2 Anderson, A.C. (2003) The process of structure-based drug design. *Chem. Biol.* 10, 787–797
3 Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–716
4 Mullin, R. (2014) Tufts study finds big rise in cost of drug development. *Chem. Eng. News* 92, 6
5 Egger, M. *et al.* (2002) Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 360, 119–129
6 Boule, A. *et al.* (2014) Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: a collaborative analysis of prospective studies. *PLoS Med.* 11, e1001718
7 CDC (2016) *Today's HIV/AIDS Epidemic*. CDC
8 Fitzgerald, P.M. *et al.* (1990) Crystallographic analysis of a complex between human immunodeficiency virus type 1 protease and acetyl-pepstatin at 2.0 Å resolution. *J. Biol. Chem.* 265, 14209–14219
9 Erickson, J. *et al.* (1990) Design, activity and 2.8 Å crystal structure of a C2 symmetric inhibitor complexed to HIV-1 protease. *Science* 249, 527–533
10 Jaskolski, M. *et al.* (1991) Structure at 2.5 Å resolution of chemically synthesized human immunodeficiency virus type 1 protease complexed with a hydroxyethylene-based inhibitor. *Biochemistry* 30, 1600–1609
11 Pettit, S.C. *et al.* (1993) The specificity of the HIV-1 protease. *Perspect. Drug Discov. Des.* 1, 69–83
12 Stoll, V.S. *et al.* (2002) X-ray crystallographi280c structure of ABT-378 (Lopinavir) bound to HIV-1 protease. *Bioorg. Med. Chem.* 10, 2803–2806
13 Souers, A.J. *et al.* (2013) ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat. Med.* 19, 202–208
14 Cho, Y.S. *et al.* (2010) 4-(Pyrazol-4-yl)-pyrimidines as selective inhibitors of cyclin-dependent kinase 4/6. *J. Med. Chem.* 53, 7938–7957
15 Cho, Y.S. *et al.* (2012) Fragment-based discovery of 7-azabenzimidazoles as potent, highly selective, and orally active CDK4/6 inhibitors. *ACS Med. Chem. Lett.* 3, 445–449
16 Muchmore, S.W. *et al.* (2000) Automated crystal mounting and data collection for protein crystallography. *Structure* 8, R243–R246
17 Vonrhein, C. *et al.* (2011) Data processing and analysis with the autoPROC toolbox. *Acta Cryst.* D67, 293–302
18 Johansson, L.C. *et al.* (2017) A bright future for serial femtosecond crystallography with XFELs. *Trends Biochem. Sci.* 42, 749–762

**Lisa J. Keefe**[1,2]
**Vincent S. Stoll**[3,*]

[1] *Hauptman-Woodward Medical Research Institute, Buffalo, NY 14203 USA*
[2] *Industrial Macromolecular Crystallography Association – Collaborative Access Team (IMCA-CAT), Advanced Photon Source, Argonne National Laboratory, 9700 S. Cass Avenue, Argonne, IL, 60439 USA*
[3] *AbbVie Inc. 1 North Waukegan Road, North Chicago, IL 60064-6098, USA*

**Corresponding author.*
vincent.stoll@abbvie.com