After 25 years in operation, the Advanced Photon Source (APS) is about to undergo a massive upgrade, one that will increase the brightness of its X-ray beams by up to 500 times. At the heart of this upgrade is a new multi-bend achromat electron storage ring, which will completely replace the original storage ring.
Welcome to the APS-U Structural Biology Townhall Meeting

Laurent Chapon is Argonne’s Associate Laboratory Director for Photon Sciences, and director of the U.S. Department of Energy Office of Science’s Advanced Photon Source (APS).
# APS-U Structural Biology Townhall Agenda

<table>
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<th>Start</th>
<th>Duration</th>
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<th>Presentation</th>
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<td>Welcome - Laurent Chapon,</td>
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<td>APS-U Overview and Life Sciences at the APS, Bob Fischetti</td>
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<td>SBC/eBERLight, Andrzej Joachimiak and Karolina Michalska</td>
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<td>Roundtable Q&amp;A</td>
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<td>Adjourn</td>
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Each APS CAT or Light Source has 15 minutes (10 min. presentation, 5 min. Q&A)

Speakers, please remember to say next slide

A 10-minute notice will be given. After 15 minutes we will move to the next speaker.

Participants can enter questions in the CHAT (your microphone will be disabled)

Speakers can address questions from the CHAT during their Q&A

Argonne staff will monitor the CHAT for unanswered questions which may be addressed during the Roundtable

During the Roundtable participants may use the RAISE HAND function and use their microphone when called on
OVERVIEW OF LIFE SCIENCES AT THE APS AND THE APS-UPGRADE

Bob Fischetti
Life Sciences Advisor to the APS Director
and GM/CA@APS Group Leader
Advanced Photon Source
Structural Biology Townhall
June 21, 2019
Outline

- Structural Biology at the Advanced Photon Source
- APS Upgrade (APS-U)
- Radiation damage
Argonne’s Advanced Photon Source (APS) a DOE Office of Science User Facility

- The APS provides high-energy, high-brightness X-ray beams that are ideal for studying the arrangements of molecules and atoms.
- Use of the APS (and other Office of Science user facilities) is free for open research intended for publication.
- There are 68 beamlines at the APS where over 5300 researchers do their work every year.
- Scientists use 15 of these specialized beamlines for macromolecular crystallography, to examine molecular structures and interactions that could yield lifesaving medicines for various diseases.
- Biological & Life Sciences accounts for $\sim\frac{1}{3}$ of APS users.
- Users have studied many diseases and drugs – cancer, influenza, Type 2 diabetes, HIV/AIDS, Ebola, Zika, COVID-19.
## Beamlines That Fully or Partially Support Life Sciences Research

**MX beamlines were built and are operated by CATS**

8 Sectors - 15 MX beamlines → 11.8 IDs - 2 BMs

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### MAPPING OF APS BEAMLINE CAPABILITIES TO DOE FACILITIES

#### APS > APS-U > Comparable Beamline Options for Users

Denny Mills and Managers from other Light Sources

<table>
<thead>
<tr>
<th>APS Beelines</th>
<th>NSLS-II Beams</th>
<th>SSRL Beams</th>
<th>ALS Beams</th>
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[Image of the table and chart showing beamline mappings]
# MAPPING OF APS LIFE SCIENCE CAPABILITIES TO OTHER FACILITIES

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*Notes:*
- NSLS-II: National Synchrotron Light Source II
- SSRL: Stanford Synchrotron Radiation Lightsource
- ALS: Advanced Light Source
- CHESS: Center for High Energy Synchrotron Science

*Beamlines and stations are represented with blue squares.*
The SARS CoV-2 virus is ~120 nm in diameter (1/1000 of a human hair)

It is composed of 28 unique proteins

Potentially all of the proteins are antiviral or vaccine targets

Important protein targets include:
- NSP3 (papain-like protease): involved in replication and may interfere with immune response
- NSP5 (main protease, 3CLpro): involved in replication
- Spike: initiates infection by binding to the cell receptor

Prior to the COVID-19 pandemic, researchers utilizing the APS determined 70 coronavirus protein structures

APS beamlines rank 3rd in the number of SARS CoV-2 structures (>280)

APS beamlines provided the most diverse coverage of the 28 unique proteins

PAXLOVID™ was developed using IMCA-CAT beamline

Viruses. Family Coronaviridae.
DOI: http://dx.doi.org/10.1016/B978-0-12-803109-4.00017-9
COVID-19 Vaccine & Antibody Development

2009-2013

2013: Respiratory Syncytial Virus (RSV) Fusion Glycoprotein (F). Early vaccines generated ineffective antibodies against F in the post-fusion state (left). Human antibody D25 stabilizing metastable F in the pre-fusion state (right). APS 22-ID

McLellan, Graham, et al.

2013-2017

2015: Middle East respiratory syndrome coronavirus (MERS-CoV) receptor binding domain with spike protein trimers (one up) stabilized in the prefusion state with the 2-proline mutation.

2020: This has been incorporated in SARS-CoV-2 mRNA vaccines. Cryo-EM, APS 19-ID, SSRL

2020

2020: SARS CoV-2 RBD (green) with multivalent neutralizing nanobody NB20 (brown) which may be more effective and resistant to mutations. APS 23-ID
Adenovirus deliver vehicle for COVID-19 vaccines

• Largest biomolecule structure determined to atomic resolution with X-rays
• Modified adenovirus delivers DNA for cells to produce stabilized SARS CoV-2 spike protein used in Janssen’s (Johnson & Johnson) and AstraZeneca’s vaccines

Vijay Reddy
Glen Nemerow

### Myoglobin (2W6X)

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Users of US light sources have contributed over 25% of the structures.
Nobel-Prize winning RESEARCH AT THE APS

Important discoveries about human physiology and clues to new pharmaceuticals to combat disease

Ada Yonath
Weizmann Institute of Science, Israel

Thomas Steitz
Yale University, U.S.

Venkatraman Ramakrishnan
MRC Laboratory of Molecular Biology, U.K.

2009 Nobel Prize in Chemistry
Structure and function of the ribosome

2012 Nobel Prize in Chemistry
Studies of G-protein-coupled receptors (GPCRs)

Brian K. Kobilka
Stanford University, U.S.

Robert J. Lefkowitz
Duke University, U.S.
**APS-U: THE ULTIMATE 3D MICROSCOPE**

**High Energy**
- Penetrating bulk materials and operating systems
  - World’s brightest source of hard x-rays
  - 3D mapping deep inside samples
  - X-ray cinematography in previously inaccessible regimes

**Brightness**
- Providing macroscopic fields of view with nm-scale resolution
  - Multi-scale imaging connecting nanometer features across macroscopic dimensions
  - Fast sampling with chemical, magnetic, electronic sensitivity

**Coherence**
- Enabling highest spatial resolution even in non-periodic materials
  - Extends lens-less imaging to hard x-ray domain, with resolution down to <1 nm, localizing atoms
  - Increases phase contrast for fast full-field imaging
  - Correlation methods improve by 10,000x-1,000,000x
The APS accelerator complex and beamlines

- **LINAC** - electric field accelerates the electrons to 450 million electronvolts (MeV).
- **Booster Synchrotron** – radio frequency cavities accelerate electrons from 450 MeV to 7 billion electron volts (7 GeV). (Speed >99.999999% of the speed of light.)
- **Storage Ring** - The 7-GeV electrons are injected into the 1104-m-circumference storage ring, a circle of more than 1,000 electromagnets and associated equipment, located in a radiation-proof concrete enclosure inside the experiment hall, which is large enough to encircle Chicago's Wrigley Field.
- **Insertion Devices** – APS is a "third-generation" light sources optimized to produce insertion device radiation in the hard (highly penetrating)
- **Beamlines** - comprise crystal and/or mirror optics designed to tailor the X-ray beam for specific types of experiments. The beam is delivered to a radiation-proof experiment station that contains the sample under investigation; additional optics that may be needed to analyze and characterize the scattering, absorption, or imaging process; and detectors to collect data from the interaction of x-ray beam and sample.
APS Upgrade multi-bend achromat lattice concept

Emittance is a measure of the average spread of particle coordinates in position-and-momentum phase space.

\[ \varepsilon_x = C_L \frac{E^2}{N_D^3} \]

- \( C_L \) = Ring circumference
- \( E \) = Beam energy (\( E = 6 \) GeV for APS MBA)
- \( N_D \) = Number of dipoles per sector (\( N_d = 7 \) for APS MBA)

APS-U / APS emittance \( \sim 40 - 50 : 1 \)
APS Upgrade (APS-U) Multi Bend Achromat (MBA) Lattice

Brightness vs. x-ray energy at top beamlines among U.S. DOE synchrotron facilities

Curves for APS, ESRF, and SPB upgrades based on present designs, assuming identical undulators
APS Upgrade Project

- New storage ring, 42 pm emittance @ 6 GeV, 200 mA
- New and updated insertion devices, including SCUs
- Combined result in brightness increases of up to 500x
- 9 new feature beamlines + Long Beamline Building
- 15 enhanced and improved beamlines
- Realign 17 bending magnet beamlines
- Exploit high performance computing, AI
New Schedule – Announced May 10, 2021

- Original June 2022 shutdown schedule impacted by pandemic
- Start of the storage ring installation period shifted by 10 months to **April 17, 2023**
- No change in duration of 1-year installation period (key deliverable)
- Resume x-ray operations in April 2024

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**Milestones**

- Storage Ring & Mezzanine Removal Complete (7/22/22)
- Integrated System Test Without Beam Complete (8/24/24)
- Integrated System Test With Beam Complete (4/25/24)
- Threshold KPPs Complete (10/7/24)
- Objective KPPs Complete (9/6/24)

**Accelerator**

- R&D
- Design
- Procurement
- Assembly/Test
- Installation/Test

**Front Ends & Insertion Devices (FE&IDs)**

- R&D
- Design
- Procurement
- Assembly/Test
- Installation/Test

**Experimental Facilities (Beamlines)**

- R&D
- Design
- Procurement
- Assembly/Test
- Installation/Test
- Commissioning

**Original Start of Dark Period**
The Impact of the APS dark period on structural biology

Assessment began in 2017

<table>
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<tr>
<th>Facility</th>
<th>Life Sciences Representatives</th>
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<tbody>
<tr>
<td>ALS</td>
<td>Paul Adams and Corie Ralston</td>
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<td>APS</td>
<td>Bob Fischetti</td>
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<td>CHESS</td>
<td>Rick Cerione, Marian Szebenyi and Richard Gillilan</td>
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</table>
APS structural biology beamlines examine about 300,000 samples annually resulting in more than 1800 PDB depositions and in over 850 peer reviewed publications.
APS-U storage ring replacement is scheduled to take 12 months. MX beamline capacity will be reduced by 37% during that period.
Protein data bank deposits based on X-ray data

Total from all X-ray sources: 163,819
Total from all synchrotron sources: 135,481
APS beamlines have contributed: 28,603 deposits (21.1%)

APS beamlines are contributing over 60% of US output

These numbers do include pharma research!

Data as of February 15, 2022
Time to Garman Limit with 4th generation synchrotron sources – <100 µsec!

Garman limit\(^1\) \(\sim 3.0 \times 10^7\) Gray (35% intensity loss)

Data complied by Bob Fischetti, updated and plotted by Sean McSweeney

Interaction of X-rays and mater - briefly

- **Photoelectric effect**
- **Thompson scattering - elastic**
- **Compton scattering - inelastic**

“Typical protein”
C: 1818; H: 7286; N: 420; O: 2673; S: 25.
This corresponds to a 50% solvent content.
Crystal decay (intensity loss) vs. beam size and dose

Damage decreases 3-fold with beam size

Detector Quantum (QE) efficiency vs energy

The QE of Si-sensors of 450- and 1000-micron thickness (Data courtesy of Dectris).

The QE of a CdTe sensor for three pixel sizes and sensor thicknesses on an Eiger2 ASIC as measured (dots) and simulated (continuous lines). The CdTe sensor thickness is indicated in parentheses. (Zambon et. al. 2017).
Quantitating radiation damage vs X-ray energy and beam size

- Repetitive data collection over the same 0-1 degree
- For a given energy and Dose radiation damage is reduced with decreasing beam size
- For the same beam size radiation damage is reduced with increasing X-ray energy
Beamlines Townhalls & Workshops

Targeted communications with specific user communities

- Structural Science Workshop Jan. 11-15
- ASL & Timing (25-ID) Sept. 1
- XPCS (8-ID) Sept. 20
- CSSI (9-ID) Oct. 6
- HEXM (20-ID) Oct. 25
- Polar (4-ID) Nov. 12
- Spectromicro/Bionanoprobe (2-ID) Nov. 30
- ISN(19-ID)/Ptycho (33-ID) Dec. 2
- Atomic/3DMN (34-ID) Dec. 6
- Structural Biology Jun. 21
Other resources

https://www.aps.anl.gov/APS-Upgrade/Meetings-Workshops

**Science Workshops for the APS-U: 2018/2019/2020**

1. Biological Science Opportunities Provided by the APS Upgrade, August 20-21, 2018
2. Opportunities in Biological and Environmental Research Uniquely Enabled by the APS Upgrade, August 28-29, 2018 (tentative)
3. Condensed matter physics, x-ray scattering and x-ray spectroscopy at the APS-U, September 25-26, 2018
4. Discovery, synthesis and development of emerging materials and the role of the APS-U, September 27-28, 2018
5. Time resolved chemistry at the APS-U, October 1-2, 2019
6. Catalysis research, x-rays and the APS-U, October 3-4, 2019
7. Industrial processes and the role of APS-U, September 21-22, 2020
8. Materials under extreme conditions at the APS-U, September 23-24, 2020
Thank you for your attention!
## APS-U Structural Biology Townhall Agenda

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is a structural biology resource for IMCA and the broader community of pharma companies.
IMCA-CAT’s mission is to accelerate pharma drug discovery
IMCA-CAT is highly optimized for delivering **quality diffraction data** at **high-throughput** with **routine frequency** and **reliability**.
IMCA-CAT operations are optimized for industry

**Auto Mode**

Reliable and Fast

- quality data
- >400 data sets daily
- robot reliability: 99.99%
- auto processing by Global Phasing

**Mail-In**

Routine and Efficient

- expert data collection
- weekly flow of data
- trusted data security

**Flexible**

Predictable for Continuous Flow of Data

- data when needed
- prompt queueing
- fast turnaround (within a few days)
During APS-U, data will be collected for industry for:

- >41,000 samples per year
- >26,000 data sets per year
During APS-U, IMCA-CAT will collect data for industry.
IMCA-CAT beamline will be upgraded to deliver a small and highly intense beam during the APS-U Beamline Optics Upgrade:

- state-of-art monochromator
- highest quality focusing mirrors
- high precision goniometer

focused to 5 μm x 5 μm
IMCA-CAT is critical for shortening pharma drug discovery pipelines.
A Structure-Based Drug Design Success

PAXLOVID™

Binds to SARS-CoV-2 main protease

SCIENCE • 2 Nov 2021
DOI: 10.1126/science.abl4784
IMCA-CAT
Industrial Macromolecular Crystallography Association
Collaborative Access Team

**INDUSTRY**
IMCA Members
- abbvie
- Bristol Myers Squibb
- evotec
- janssen
- MERCK
- NOVARTIS
- Pfizer
- RELAY

IMCA-CAT Subscribers

**EXPERIMENT**
Beamline 17-ID @ APS
- focused, intense beam
- mini beam 5-50 µm
- pucks: Unipuck, ACTOR, ALS

**CAPABILITIES**
- diffraction rastering
- collect-along-vector
- auto collect & process
- proprietary
- rapid & frequent access
- mail-in, remote, on-site

**PRODUCTIVITY**
41,000+
samples annually
- high-throughput
- fast, encrypted data transfer
- real-time integration to company pipelines

**DISCOVERY**
- micro crystals
- membrane proteins
- MAD / SAD
- in situ

www.imca-cat.org
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19-ID/19-BM Beamlines, Sector 84 Facilities

**PILATUS3 6M**
Detector - 30 images/sec
ACTOR robot nano xyz-head
SSX capabilities
19-BM fast sample exchange robot

**Sample centering**

**Diffraction data**
Electron density

**Microcrystals and mini-beams**

**Protein purification and crystallization**

**Structure**

**Highly flexible beam size**
from 5 x 5 μm to 200 x 200 μm

**Remote access**

**SBCollect loop auto-centering**
Crystal “point-and-click” centering

6,260 PDB deposits
2,616 publications
219,355 total citations
214 H-index

47 Microcrystals and mini-beams

19-ID/19-BM Beamlines, Sector 84 Facilities
New 19-ID Capabilities

- Modular goniostat was installed at SBC 19-ID with new magnetic mount.
- This goniostat can accommodate variety sample holders designed and 3D printed at the SBC:
  - Compound Refractive Lens increased the x-ray flux at the sample 8 times, enabling serial crystallography with smaller crystals experiments.
  - ALEX holder for SSX
  - Plate scanner
  - Capillary holder for microfluidics experiments (ice formation, chemical reactions etc.)
- These sample holders and their controllers can be ported on other APS beamlines.
19-ID Set up for Serial Crystallography

- Dynamic crystallography implemented at 19-ID and available to users.
- Rapid data collection for serial crystallography.
- Visualizing chemical reaction in the crystal of enzyme.
- Sector 19 is linked to Argonne Leadership Computing Facility to rapidly process diffraction images and provide near real time feedback to diffraction experiments.
SBC – User Support During “Dark” Period

• SBC will continue support of MX user operations till APS “dark” period, starting ~ April 17, 2023

• SBC conducted survey how we can help users to go through the APS “dark” period?

• Users expressed interest and SBC will apply for beamtime at several light sources:
  • BNL/NSLS-II, SSRL/SLAC MX and LBNL/ALS MX Beamlines

• SBC will help to coordinate user success and SBC staff will provide limited user support.

• Sector 84 (APCF) molecular biology capabilities will stay open
Structural Biology Center Transitioning to eBERlight

Current status
- SBC is funded by DOE Biological and Environmental Research
- Operates 2 MX beamlines (19-ID, 19-BM) for the general user community

Need for change
- BER community needs access to other techniques
- APS-U brings new opportunities
- 19-ID will host In Situ Nanoprobe

Future program
- eBERlight will serve as a liaison between BER researchers and the APS
- Leverage additional ANL resources
- Integrate with other DOE/BER facilities
# Multimodal Approach to BER Science at APS-U

## APS-U Techniques

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<th>Solution SAXS</th>
<th>Point Probe XFM / XAS</th>
<th>Crystallographic MX</th>
<th>Full-field Imaging XMIC</th>
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eBERlight Capabilities for Biological and Environmental Science

- **Crystallography**
  - 21-ID (LS-CAT)

- **Full-field imaging**
  - 2-BM
  - 32-ID

- **X-ray microscopy**
  - 2-ID-D
  - 2-ID-E (ISN, 25-ID-D,E)

- **Electron microscopy**
  - Center for Nanoscale Materials Picoprobe

- **X-ray absorption spectroscopy**
  - 9-BM
  - 20-BM
  - 25-ID-D,E
  - 10-ID, BM

- **Small-angle X-ray scattering**
  - 9-ID
  - 12-ID
  - 12-BM

- **Molecular biology**
  - Advanced Protein Characterization Facility

- **Microfluidics**
  - Advanced Protein Characterization Facility

- **Sample preparation**
  - Cryolab at APS Lab infrastructure in bid. 203

- **Computing**
  - Argonne Leadership Computing Facility
Comprehensive program for BER community starting FY24

Virtual Collaborative Access Team (CAT) managed by X-ray Science Division

Guaranteed beamtime across several beamlines (max. 2 beamlines equivalent)

Effort distribution:
   25% crystallography (LS-CAT)
   65% microscopy & imaging (XSD)
   10% X-ray absorption spectroscopy & SAXS (XSD)

50% of the eBERlight guaranteed beamtime to support CAT members (BER researchers), 50% to support General User Program
## APS-U Structural Biology Townhall Agenda

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LS-CAT Upgrade

Spencer Anderson
Operations Manager, LS-CAT
6/21/2022
Sector 21 Component Layout

- Kohzu Monochromator
- Power-Limiting Aperture
- Side-Bounce Monochromators
- Power-Limiting Aperture
- Fixed Apertures
- Be Lens Assemblies
ID-F/G Side Stations

- fixed energy above Se peak
  - ID-F 12.668 keV
  - ID-G 12.670 keV

- current beam 50µm
  - poorly focused/relatively low flux
  - 1-3s per image exposure
  - CCD limited to ~30 frames per minute
21-ID-D

- tunable from 6-20 keV
- bimorph mirrors focus to ~25µm

- MD2 microdiffractometer
- MD3-UP microdiffractometer

- Dectris Eiger 9M PAD
- Eiger2 X 16M PAD

- Compound Refractive Lens Transfocator
- new sample changer
NEVER FINISHED

- needs monochromator
- original designed to be tunable:
  - 12.5 – 12.8 keV
  - 13.4 – 13.6 keV
- bimorph mirror
- CCD detector
- CATS sample changer
Post Upgrade Crystallography

• Microcrystallography
  • MD3-UP designed for small samples
  • detector readout 130Hz or faster

• Serial crystallography
  • plates
  • chips
  • capillaries

• Dynamic crystallography
  • redox sensitive proteins
  • caged compounds
  • ID-D designed for white beam


On Site Clinics

Start up again if pandemic ever ends…

- crystallographic theory
- data collection and analysis
- **increase focus on sample preparation**
- room temperature vs frozen
- cryo protection
- freezing method
- humidity manipulation

![Arinax REX Rapid Nozzle Exchanger](image1)

![Mitegen Watershed Workstation](image2)
Summary

• LS-CAT designed for high flux and already compatible with post APS-U beam

• continue routine single crystal experiments on side stations, but with a huge improvement in flux

• ID-D (and ID-E) designed for more challenging serial and dynamic crystallography experiments

• ID-D in great shape with new microdiffractometer and PAD

• prioritize finishing ID-E since challenging experiments take lots of beamtime
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APS Structural Biology Virtual Town Hall Meeting

SER-CAT
SouthEast Regional Collaborative Access Team

B.C. Wang, John Rose, John Chrzas and
SER-CAT Team

June 21, 2022
SER-CAT’s Vision/Goals and Future Challenges

Vision/Goals

• The construction of SER-CAT’s two synchrotron beamlines at the APS was initiated in 1997 with a grant from the Georgia Research Alliance (GRA) as an enabling technology for research and education for the institutions in the State of Georgia.

• The first (22ID) of the two beamlines was commissioned in 2002 when it started providing “Light When You Need it” as a virtual home synchrotron source.

• SER-CAT has since become a shared Research Resource for institutions, mostly in the Southeast, in promoting structural biology programs and faculty recruiting. A SER-CAT Trust Estate fund was also established at UGA in 2001 to assist SER-CAT’s future operations and upgrade.

• SER-CAT has now grown into a consortium of 23 institutions.
SER-CAT Program’s Response to the APS-U

1. SER-CAT VALUES ITS USERS – Working with several facilities in the U.S. to find beam time for SER-CAT users during APS dark period.

2. SER-CAT VIEWS THE APS DARK PERIOD AN OPORTUNITY – To optimize and upgrade SER-CAT Operation and Equipment to support future structure-based new science enabled by the 4th generation storage ring at the APS, first of its kind in the U.S.

- APS generates over half of all PDB entries coming from U.S. facilities (2008 – 2018)
- Other US facilities do not have the extra capacity (or undulator beamlines) required to address this need
- APS Users will have to make GU applications at other facilities – the lines will be long

Will discuss the plans in later slides
SER-CAT Response to the APS Dark Period

SER-CAT VALUES ITS USERS

• SER-CAT will serve as the central hub for the scheduling and management of SER-CAT’s beamtime at these collaborative facilities.

• SER-CAT will provide a second layer of user support during data collection - answering questions and providing suggestions as they currently do.

• SER-CAT will also assist users in data processing and analysis - including tackling “Problem data sets”

• SER-CAT will also help users apply for GU time at other U.S. facilities - providing links and other materials

Goal

The user ships their crystals to the beamline and uses familiar software for mounting, centering & data collection to collect the best possible data from the crystal.
The SER-CAT - BCSB/ALS Collaboration

• In preparation for the APS “dark” period, we established a Partnership program with ALS-BCSB in 2020

• We held a virtual training workshop using BCSB beamlines on March 18, 2021, the day before SER-CAT’s 2021 Annual Symposium

• In addition, we provided hands-on remote data collection training runs to individual SER-CAT users during May – June 2021 & 2022 on ALS Beamlines 501 and 502

• SER-CAT Users are now ready to use ALS 501 & 502 during APS-U

A standard Test Run on ALS 502
Extreme S-SAD phasing test using bovine a trypsin crystal and data collected using 1.0 Å X-rays ($\Delta F” = 0.24$)
New York Structural Biology Center

SER-CAT is in negotiations with the New York Structural Biology Center to come on as an additional member using their NYX beamline (19ID) at NSLS-II.
SER-CAT Upgrade

• Sector 22 will have a canted front-end installed to enable a second undulator resource 22ID-E to replace 22BM.

• The first priority is to ensure 22ID-D comes out of the upgrade fully operational.

• The user program on 22ID-D must be established as soon as possible once the APS provides X-rays.

• The new beamline (22ID-E) will come online 6-12 months after 22ID-D is operational.
22ID-D Upgrade

- New FMB-Oxford Monochromator to replace the current one.
  - 2 sets of crystals pairs, Si(111) and Si(220), in vacuum tank
  - Provide large energy range 5-24 keV
  - Provide improved energy resolution option with Si(220) crystals
- IDT K-B mirror system
  - Currently installed with the horizontal mirror in service
- New MD3 diffractometer with new sample robot
- Full automation of routine sample screening and data collection
- Upgrade all motion control and vacuum systems
- Network upgraded in 2020
- Equipment Protection System (EPS) upgraded in 2020
- Upgrade to Generation 4 Personnel Safety System (PSS)
22ID-E Upgrade

Bringing 2nd ID X-ray Beam from Station 22ID-A to the Future Station 22ID-E (currently 22BM-C)

• Side Bounce single crystal monochromator  
  ▪ Si (220)
• MD2 diffractometer with sample robot
• CRL focusing  
  ▪ Multiple lens stacks for range of focus options
• Full automation of routine sample screening and data collection
Acknowledgements

**UGA & GRA**
Lars Ljungdahl
Mike Cassidy
Susan Shows
Joe Key
Karen Holbrook

**BCSB/ALS**
Marc Allaire
Corie Ralston
Stacey Ortega

**SER-CAT**
John P. Rose
Zheng-Qing (Albert) Fu
Gerold Rosenbaum
Jim Fait
Unmesh Chinte
Norma Duke
Rod Salazar
Lily Li
Larry DeLucas (UAB)

**APS**
Gopal Shenoy
Denny Mills
Susan Barr Strasser
J. Murray Gibson
Stephen Streiffer
Robert Fischetti

**NIGMS/NIH**
SER-CAT Institutions, APS/ANL
Ramsay - Georgia Research Alliance Endowment Fund
University of Georgia Research Foundation
# APS-U Structural Biology Townhall Agenda

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GM/CA @APS

Nagarajan Venugopalan (Naga)

APS Upgrade Structural Biology Town Hall
21 June 2022
GM/CA Dual-canted Undulator beamlines layout

Rapid energy tunability – High intensity and positional stability – Low convergence optics

23-ID-D

Pilatus3 6M
5-20 keV
21 x 20 μm²
1 μm with CRLs

Eiger 16M
3.5-20 keV
20 x 80 μm²

23-ID-B

3.0 cm device optimized for Se SAD/MAD phasing
GM/CA-Hardware Upgrades: 23-IDD

New end station table and sample environment

CRL Transfocator

New focusing mirrors

Exciting new frontier!

A crystal will survive <1 msec → need rapid beam delivery and detector framing
GM/CA-Hardware Upgrades: 23-IDB

Installation during the dark period

CRL Transfocator  New focusing mirrors

New Horizontal Deflecting mirrors

23-IDA
Increased Dewar capacity

Current Robot Dewar
18 pucks, 288 Samples

Double the capacity, 2 dewars side-by-side
36 pucks, 576 Samples
Serial Synchrotron Crystallography: LCP Injector

Fixed target Serial Crystallography

PyBluluce: Data collection software upgrades

Serial Crystallography
- Injector collect
- Mesh collect
- Large cell count raster

Sustained HDR (High data rate)
- Full detector speed
- Faster spot finding

Automation
- Auto-raster
- Multiple modes of data collection

Scriptability
- Modular approach
Beamline Computing upgrades:

• 1 Petabyte size storage array network for ID lines, additional 0.5 Petabyte size storage will be merged from BM
• 8 computers with 100 Gig connectivity
• Network switch with dual 100 Gig connectivity to ALCF (Argonne Leadership Computing Facility)
• Working with Nicholas Schwarz group at APS, arranging for real time data transfer and data processing at ALCF
• Merged 2 Globus servers, increasing Globus online data transfer speeds
• Procure faster computers

Computing Access During Dark Period:

Requirements:

• Registered APS Users
• ESAF submission
• Completed Training
The future is bright!

- Upgraded X-ray focusing optics will deliver an intense beam as small as 1-µm
- Routine Serial Synchrotron Crystallography
  - LCP Injector
  - Fixed Target
- New software tools for routine serial crystallography, High Data rate and Automation
- Computing upgrades: large storage and real time data transfer and processing

- Exciting times are ahead!
Thank You
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# APS-U Structural Biology Townhall Agenda

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Improvements at NE-CAT
Driven by APSU

Malcolm Capel
NE-CAT Deputy Director
Dept. Chemistry and Chemical Biology,
Cornell University
Sector 24 Beamline Schematic
Common Endstation

1) Eiger 1/2 16M

2) A-Frame Detector Positioner

3) Arinax MD2 Microdiffactometer

4) Locally Designed 14 Puck ALS robot
APSU-Related Upgrades
FMB-Oxford Dual Channel Cut Monochromator

Dual Channel cut of differing channel widths optimized to reduce overall vertical shift of beam to less than ±0.35 mm over the spectral range of 6 to 20 KeV.

Channel cut selection via horizontal translation of entire vacuum chamber.

Minimize LN2 flow-related monochromatic beam position instabilities ...mechanically more simple than existing system.

2nd leaflet detune for 3rd harmonic rejection or flux compensation for thermal drift.
Channel Cut Design and Roll Configuration

Roll Arc

Detune Flexure Drives

Flexure Drive Engagement

Flexure Relief

LN2 Flow Channels

Detune Flexure Drives

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<tr>
<th>Crystal</th>
<th>A</th>
<th>B</th>
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<tr>
<td>Cut</td>
<td>Si&lt;111&gt;</td>
<td>Si&lt;111&gt;</td>
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<tr>
<td>Energy Range</td>
<td>6-8 keV</td>
<td>8-20 keV</td>
</tr>
<tr>
<td>Channel width</td>
<td>13.1mm</td>
<td>12.7mm</td>
</tr>
<tr>
<td>Beam Offset</td>
<td>24.7 – 25.4mm</td>
<td>24.6 – 25.3mm</td>
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Replacement of Aging Arinax MD2 microdiffractometers: MD3UP

- Vertical omega axis eliminates gravitational effects on sphere of confusion (< 200 nm).
- New high precision mini-kappa head.
- Greatly improved sample / beam visualization & illumination (high resolution /speed digital cameras).
- x,y,z beam stop.
- Fast magnetic levitation data shutter.
- Extensive control API for beam line integration
  - Motion control
  - Visualization
- Both units delivered and cold-commissioned
  - Nov 2021 – Jan 2022
  - Software integration in process
- C-Line & new robot MD3 installed during dark period,
  E-Line MD3, robot installed after C-Line recommissioning
New 30 Puck (480 sample)  
MD3-Compatible, ALS-Style Autoloader
Extant Sample Mounter: 14 (ALS/Uni) Pucks, 224 Samples
1) Large vertical pneumatic stage

2) Voice-coil linear drive stage

3) Horizontal pneumatic stage

4) Sample gripper

5) Horizontal linear magnetic pulse motor stage.

The sample dewar is located 35 cm below the midline of the linear magnetic pulse stage. MD3 situated to the left of the field of this figure.

The figure shows the configuration immediately before installation on the MD3 omega stage.
1) Design & fabricate dewar components:
   Dewar seal assemblies
   Puck support plates
   Dewar rotary stage
   Lexan dewar cover.
   Support structure

2) Software revision
   optimization of duty cycle
   (30 second dismount/mount cycle time).

3) Cryofab Dewars on hand.
Additional Upgrades

1) Replacement of both monochromator cryopumps (FMB-Oxford Cryopump-XV).

2) Replacement of both sample cryocoolers (Oxford Cryosystems Cryostream-800)

3) Sydor photoresistive diamond BPMS: post monochromator, endstation.

4) Replacement of entire motion control system: mcu, drivers.

5) Replacement of all UHV components: gate valves, ion pumps, pump controllers.

6) Software:
   - Development of fully-automated unattended crystal survey system (snaps & runs)
   - Improved grid and vector (helix) scan speed
Computing Cluster and Storage

• Computer cluster built in three phases
  • Phase 1: 32 x Intel Xeon X5520 4C/8T 2.3 GHz processors 576GB RAM
  • Phase 2: 8 x Intel Xeon E5-2687W 8C/16T 3.1 GHz processors 256GB RAM
  • Phase 3: 10 x Intel Xeon E5-2687W4 12C/24T 3.1 GHz processors 1.28TB RAM

100 GBS Infiniband interconnect: cpu interconnect & shared memory backplane

• Total formatted disk storage space is 0.92 PB
  • 1 x Nexsan SATABeast storage arrays (total 30TB)
  • 2 x Nexsan SATABeast2 storage arrays (total 120TB)
  • 1 x Nexsan E48 plus 2 expansion units (total 340TB)
  • 1 x Nexsan Beast P (total 430TB)

Cluster and Storage Facilities will remain available to users during APSU dark period.
## APS-U Structural Biology Townhall Agenda

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LRL-CAT: NEW CAPABILITIES AFTER APS-U

Jordi Benach, Ph.D.
Sr. Director-Chemistry & Head of Operations, LRL-CAT, DCRT
Eli Lilly and Company
Advanced Photon Source, Argonne National Laboratory, Lemont, IL, USA

APS-U Structural Biology Townhall
June 7, 2022
<table>
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<tr>
<th>Year</th>
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<tr>
<td>2017</td>
<td><strong>LRL-CAT network</strong>, NAS, archive and backup systems, fiber connectivity to Lilly HQ, ethernet connectivity to APS.</td>
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<tr>
<td>2018</td>
<td><strong>Pilatus3 S 6M</strong> (DECTRIS, Switzerland).</td>
</tr>
<tr>
<td>2020</td>
<td>Si (111) cryogenically cooled <strong>Double Crystal Monochromator</strong> (Kohzu, Japan) + UPS system.</td>
</tr>
<tr>
<td>2023-2024</td>
<td><strong>Dark period data collection plan</strong>: Lilly only crystals, off-site data collection at domestic and overseas synchrotrons.</td>
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<tr>
<td>2024</td>
<td><strong>[TENTATIVE]</strong> June-September: commissioning with beam, October: Data collection tests (internal), November: Open to all users.</td>
</tr>
<tr>
<td>2025</td>
<td>Regular operations and <strong>surveys to be sent out to users</strong>.</td>
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</table>
Crystal harvested
Shipment created
Dewar received
Samples loaded
Screening images 18-24 h after harvest
Datasets available 18-32 h after harvest
LRL-CAT ~ in-house X-ray diffractometer
4 x frames
Scored, center-verified, resolution estimated
Datasets available
18-32 h after harvest
900-1800 frames x 0.2°

Mail-in - High-throughput - Automation - Unscheduled - Fast data turnaround
A human-derived antibody targeting amyloid-β (Aβ)
Crystal structures of Aducanumab complexed with a small piece of this amyloid were determined from data collected at LRL-CAT
Aducanumab selectively targets the **aggregated species of Aβ**
Aducanumab was approved for medical use in the FDA in June 2021

Structural and kinetic basis for the selectivity of aducanumab for aggregated forms of amyloid-[beta]
LRL-CAT SCIENCE : Hepatitis C Virus (NIH/NIAID)

- Hep C virus: chronic liver disease, cirrhosis and hepatocellular carcinoma in humans, and afflicts more than 70 million people worldwide

- Better understanding the binding of hepatitis C virus to the host cells

- Acidification and receptor binding result in a conformational change in E2 in preparation for membrane fusion

Structural insights into hepatitis C virus receptor binding and entry Kumar, A. et al. Nature 598, 521-525 (2021)
Bamlanivimab is a monoclonal antibody developed by AbCellera Biologics and Eli Lilly as a treatment for COVID-19

LY-CoV555 antibody blocks the interaction between SARS-CoV2 and human ACE2 receptor

The medication was granted an emergency use authorization (EUA) by the FDA in November 2020, and the EUA was revoked in April 2021

The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates

APS WILL DELIVER A MUCH SMALLER SOURCE

Electron Beam/Machine Parameters

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<td>Ring Current [A]</td>
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Electron Beam Properties

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<td>Horizontal Beam Divergence dx [rad]</td>
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<td>Vertical Beam Divergence dy [rad]</td>
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ID Parameters

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<td>Horizontal K</td>
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<td>Vertical K</td>
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<tr>
<td>Number of Periods</td>
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Photon Source Size (µm)

Simulations and slide provided by Luca Rebuffi (APS)

E = 21 KeV
LRL-CAT CHOSE THE BEST FOCUSING MIRRORS

Figure error rms: ~5-10 nm  
Slope error rms: ~0.15 µrad

Figure error rms: ~4 nm  
Slope error rms: ~0.1 µrad

Figure error rms: < 0.5 nm  
Slope error rms: < 0.5 µrad  
(IRELEC/JTEC)

Pictures provided by Luca Rebuffi (APS)

HIGH THROUGHPUT MODE
beam size range ~25x25 to 100x100 µm² (HxV)

SBDD, fragment screening, established projects

- Fast
- Improved loop and X-ray centering routines
- Improved strategy data collection routines
- Automated data processing

MICRO-FOCUS MODE
beam size ~7x2 µm² (HxV)

Mem. prot, macromolecular interactions, micro-crystals

- Very fine X-ray crystal centering & cartography
- Iterative automated data collection to:
  - Improve resolution, completeness, multiplicity, anomalous signal
  - Achieve or improve de novo phasing
  - Optimize macromolecule/ligand e-density maps
Thank you!
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MX at the Advanced Light Source

Marc Allaire
Head of BCSB

Overview
The Advanced Light Source

- ALS at Lawrence Berkeley National Laboratory
- (DOE/BES supported synchrotron facility
- Specialized in soft X-ray science, but spans UV to hard X-rays
- 40+ experimental stations (beamlines)
- More than 2000 users, 1000 publications per year
## Biosciences at the ALS

### Macromolecular X-ray Crystallography
- Provides atomic resolution insight into biomolecules
- 7 Beamlines
- Funded by HHMI, Industry, Universities, NIH
- 15 Staff

### Soft X-ray Tomography
- Unique to ALS
- Rapid 3-dimensional reconstructions of biological samples (cell biology)
- Funded by NIH & DOE/BER
- Lead - Carolyn Larabell
- 7 Staff

### Small Angle X-ray Scattering
- Provides information about biomolecules in solution
- Combined of with crystallography and soft X-ray tomography
- Funded by NIH, DOE/BER
- Lead - Greg Hura
- 6 Staff

### X-ray Footprinting
- Probes interactions between proteins
- Funded by NIH
- Lead - Corie Ralston
- 1 Staff

### Synchrotron Infrared Spectroscopy
- Probes chemistry of live samples
- Funded by DOE/BER
- Lead - Hoi-Ying Holman
- 2 Staff (also ALS)
MX at the ALS

~1/4th ALS Usage is Biosciences

Quantum Materials (MAESTRO) 7.0.2
Coherent Scattering and Microscopy (COSMIC) 7.0.1
Calibration, Optics Testing, Spectroscopy 6.3.2
Magnetic Spectroscopy / Materials Science 6.3.1
Full-Field Transmission Soft X-Ray Microscopy 6.1.2
Energy, Catalytic, and Chemical Science (AMBER) 6.0.1
Double-DispersionRIXS(QERLIN) 6.0.2
Polymer STXM 5.3.2.2
STXM 5.3.2.1
Research and Development 5.3.1
Macromolecular Crystallography (BCSB) 5.0.3
Macromolecular Crystallography (BCSB) 5.0.2
Macromolecular Crystallography (BCSI) 5.0.1
Macromolecular Crystallography (MBC) 4.2.2
High-Resolution Spectroscopy (MERLIN) 4.0.3
Magnetic Spectroscopy and Scattering 4.0.2
General X-Ray Testing Station 3.3.2
X-Ray Footprinting 3.3.1
LIGA 3.2.1
National Center for X-Ray Tomography 2.1
Macromolecular Crystallography (GEMINI) 2.0.1
Infrared Nanospectroscopy and Imaging 2.4
IR Spectromicroscopy 1.4

KEY
Operational
Insertion Device Beamlines
Bend Magnet Beamlines
Superbend Beamlines
Under Development
SIBYLS—MX and SANS
Microdiffraction
### MX beamlines at the ALS

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<td>Allaire</td>
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<td>Allaire</td>
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<td>Holton</td>
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<td><strong>Detector</strong></td>
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<td>RDI CMOS 8M</td>
<td>Pilatus 2M</td>
<td>Pilatus 6M</td>
<td>Pilatus 2M</td>
<td>ADSC Q315r</td>
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<td>Undulator (IVID)</td>
<td>Super-Bend (5T)</td>
<td>56-pole 11.4 cm wiggler (1.9T)</td>
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<td></td>
<td>SUPERBEND (5T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary mirror RMS slope error (μRad)</strong></td>
<td>None</td>
<td>Silicon 0.2</td>
<td>Silicon 1.0</td>
<td>Silicon 1.0</td>
<td>Silicon 1.0</td>
<td>Silicon 0.2</td>
<td>Silicon 0.2</td>
<td>Silicon 0.2</td>
</tr>
<tr>
<td><strong>Energy range (keV)</strong></td>
<td>5 - 15</td>
<td>5.5 - 16</td>
<td>12.7</td>
<td>5 - 16</td>
<td>12.7</td>
<td>5 – 16</td>
<td>5 – 16</td>
<td>5 - 17</td>
</tr>
<tr>
<td><strong>Mono-chromator</strong></td>
<td>Cryo Si(111) 0.4% ML</td>
<td>Sagittal Si(111)</td>
<td>Si(220)</td>
<td>Cryo Si(111)</td>
<td>Si(220)</td>
<td>Cryo Si(111) 0.4% ML</td>
<td>Si(111)</td>
<td>Si(111)</td>
</tr>
<tr>
<td><strong>Flux (ph/s)</strong></td>
<td>2x10^{12} 100 μm dia. hole</td>
<td>1x10^{12}</td>
<td>3x10^{11}</td>
<td>1.5x10^{12}</td>
<td>5x10^{11}</td>
<td>6x10^{11} ML 2x10^{12}</td>
<td>6x10^{11}</td>
<td>1x10^{12}</td>
</tr>
<tr>
<td><strong>focus size (v x h; μm)</strong></td>
<td>15 x 15</td>
<td>85 x 55</td>
<td>350 x 150</td>
<td>350 x 150</td>
<td>350 x 150</td>
<td>100 x 50</td>
<td>75 x 40</td>
<td>80 x 60</td>
</tr>
<tr>
<td><strong>Collimation/defocus (μm)</strong></td>
<td>15 - 100</td>
<td>20 - 400</td>
<td>20 - 150</td>
<td>10 - 150</td>
<td>20 - 150</td>
<td>20 - 150</td>
<td>20 - 150</td>
<td>15 - 100</td>
</tr>
<tr>
<td><strong>Pin / puck compatibility</strong></td>
<td>SPINE ALS Unipuck</td>
<td>ALS Rigaku Unipuck</td>
<td>SPINE ALS Unipuck</td>
<td>SPINE ALS Unipuck</td>
<td>SPINE ALS Unipuck</td>
<td>SPINE ALS Rigaku Unipuck</td>
<td>SPINE ALS Rigaku Unipuck</td>
<td>All pins Staff unpacking</td>
</tr>
<tr>
<td><strong>Sample capacity</strong></td>
<td>24 x 16</td>
<td>5 x 16</td>
<td>12 x 16</td>
<td>12 x 16</td>
<td>6 x 16</td>
<td>5 x 16</td>
<td>5 x 16</td>
<td>52 pins + “infinite”</td>
</tr>
<tr>
<td><strong>GU fraction</strong></td>
<td>(25%)</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
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Gemini Microfocus Beamline

• The need to study smaller crystals requires smaller, brighter beams
• The new Gemini beamline will provide:
  – Brightness: 100-fold over current beamlines and additional 10-fold boost with multilayer when running at Se edge
  – Focus: 15 x 15 μm focused beam size
  – Spot separation: less than 1 mrad divergence allows large unit cells
  – Efficiency: 8 sec sample exchange with robotic sample mounting; large puck storage capacity; shutterless data collection; fully remote and automated options
• Successful collaboration between MBIB, ALS and LBNL Engineering
Gemini Microfocus Beamline

Leda Insertion Device

X-ray Optics

Light and Data
Recent development
ALS-ENABLE

- NIH P30 grant to support user access to ALS structural biology beamlines ([als-enable.lbl.gov](http://als-enable.lbl.gov))

- Mature Synchrotron Resource
- Supports general user access to MX, SAXS and X-Ray Footprinting beamlines
- Automated data collection
- Collaborative projects
- High throughput SAXS
- Room temperature data collection
- In plate data collection
User Access

- Non-peer reviewed access to Participating Research Teams (PRT), who support operations and beamline development
  - TomAlberTron (James Holton – jmolton@lbl.gov)
  - MBC (Jay Nix – jcnix@lbl.gov)
  - BCSB (Marc Allaire – mallaire@lbl.gov)

- Peer reviewed access through General User proposals (als.lbl.gov/users/user-guide)
  - Merit-based review
  - ALS administered (alsuser@lbl.gov)
  - 6-month and RAPIDD
    - Register as an ALS user
    - Apply for beamtime
    - Establish a user agreement
    - Proprietary research requires reimbursement for the cost of the photons
Preparing in view of the APS upgrade

- Mature Synchrotron Resource at the ALS
- GUI upgrade for ease of operations
- Down to 4-hour shift for rapid response
- Pixel-Array Detectors on 8.2.1/8.2.2
- Increased GU fraction (200% to 400%)
- Remote access on all beamlines
- Automated data collection
- Increase resource for collaborative projects
- Room-temperature data collection
- In-situ data collection from plates
- Remote training on beamline use
- Outreach at conferences

Dewars waiting to be shipped
### APS-U Structural Biology Townhall Agenda

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Cornell High Energy Synchrotron Source

*Marian Szebenyi for the CHESS team*
Located on Cornell’s central campus, CHESS hosts a wide range of X-ray experiments, with a focus on innovation.

2019 upgrade to storage ring and beamlines.

CESR now runs at 6 GeV, 100-200 mA. All beamlines are fed by insertion devices.
Beamlines

- **1A3**: Structural Materials (SMB)
- **2A**: Photon In-Photon Out spectroscopy (PIPOXS)
- **3A**: Forming & Shaping Technology (FAST)
- **3B**: Functional Materials (FMB)
- **4B**: Q-Mapping for Quantum Materials (<QM>)
- **7A**: Biological Small-Angle X-ray Scattering (BioSAXS)
- **7B2**: Flexible Macromolecular Crystallography (FlexX)

Beamlines are supported by a mix of funding agencies, for different purposes.

![Funding Agencies Logos]

Cornell University
Cornell Laboratory of Accelerator-based ScienceS and Education
BioSAXS standard features

- Tunable multilayer monochromator, 1.5% bandwidth, 7-14 KeV.
- Beam size 250 x 200 or 25 x 30 µm, q range 0.005-0.7 Å⁻¹.
- EIGER 4M detector, in vacuum tank. For most experiments, no air gap between sample and detector.
- Options for sample loading:
  - From trays using robot
  - Directly from size-exclusion (SEC-SAXS) or ion-exchange column
  - Manually (e.g. for loading high-pressure cell)
- In-line DLS/MALS
Most users come in person and make use of the wet lab facilities for final sample preparation.

For samples needing no special preparation, a mail-in option is available.

Support for this option is dependent on the availability of staff to run the samples; if funding is obtained for additional automation this will be less of a problem.

For a complex experiment where the user cannot come in person, a joint mode with communication over NoMachine and Zoom is possible.
BioSAXS for developing techniques

High pressure:
- Static cell for up to 4 kbar pressure.
- Chromatography system, pressurized throughout, to 1 kbar.

Non-standard samples:
- Anaerobic systems.
- Membranes mounted on a support; required installation of special equipment.
- Other examples: cell nuclei, nanoparticles (potential drug carriers).

Test for BioCAT:
- Good data collected from muscle fibers.
FlexX for standard MX

- Tunable multilayer monochromator: 9-14 KeV, 0.6% bandwidth.
- Beam diameter 100 μm using collimator or 10 μm using CRL, ~2x10^11 ph/sec on sample.
- EIGER2 16M detector, BAM-2 automounter (ALS, Unipuck, SPINE pins), Oxford cryosystem, annealer.
- ADX data collection GUI, automatic data reduction using fast_dp.
- Common crystallographic software installed.
- Remote experiment control using NoMachine, rapid data retrieval using Globus.
- High pressure cryocooling available.
**FlexX for developing techniques**

**High pressure:**
- VivoDAC cell allows precise control of pressure in 0-15 kbar range. Can mount 2-3 crystals per cell.
- Usable data sets can be obtained from <10 crystals.

**Serial MX (fixed-target):**
- Chips, tools, and humidity controlled enclosure for mounting crystals are available. **ADX** includes option for rastering across chip, collecting small oscillation at each point.
- Structures have been determined using serial data from CHESS.

**Other:**
- Unusual samples including frozen embryos have been examined.
- Tunable from 6-70 KeV, with 0.01% bandwidth.
- Has 4-circle diffractometer, Pilatus2 6M detector.
- Useful for crystallography (MAD, diffuse scattering experiments) requiring a narrow X-ray bandwidth.
- Caveat: MX not a priority, could be difficult to get time.
PIPOXS

- Provides absorption and emission X-ray spectroscopy, including EXAFS, HERFD-XANES, resonant and non-resonant XES.
- Helps determine geometric and electronic structure of catalysts, and relate structure to activity.
- Can be used to study active sites in metalloenzymes.
- Photon energy range 4 – 30 KeV with Si(111),
- 7 – 58 KeV with Si(311).
- Microfluidic system enables time-resolved observation of ongoing reactions.
Getting beamtime

- Typical running schedule is mid-Jan to mid-Mar, mid-Apr to late-Jun, late-Sep to Thanksgiving; 6 days per week, 24 hours per day.
- Submit a proposal application on-line; proposals are good for 2 years. For additional visits after the first, submit a beamtime request (BTR).
- For BioSAXS and MX, submit any time; response is usually rapid.
Summary

- CHESS BioSAXS and MX beamlines provide excellent routine service; in-person, mail-in and remote modes are supported.
- Non-standard experiments are welcome; we have special expertise in high pressure BioSAXS and MX, as well as fixed-target serial MX.

For more information:
- CHESS web site [www.chess.cornell.edu/](http://www.chess.cornell.edu/).
### APS-U Structural Biology Townhall Agenda

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Structural Biology Program beamlines

Are clustered near NSLS-II building 745.

- X-ray scattering: LIX
- Macromolecular Crystallography: AMX, FMX, NYX
- X-ray Footprinting: XFP
- Electron Microscopes: 745 & 748

Facility Beamlines: 100% of access through General User program,
Partner Beamlines: 50% access through General User Program.

**Premise:**

X-ray radiolysis of water gives OH radicals that react with *solvent accessible* regions of proteins and nucleic acids (“controlled radiation damage”). Map damage onto structure, observe effects from binding of a drug, etc. Complements MX, SAXS, CryoEM.

**Science example:** Evolution of virus structure

RNA-binding protein can assemble into a virus-like particle (capsid).

XFP used to show increasing protection of the nucleic acids

Model for how viruses evolved to protect their genetic code.
LIX  Solution scattering

The protein is in solution, with integrated chromatography units. Kinetics in different ways are possible – allowing study reactions or formation of complexes.

Scanning structural mapping

Visualize the spatial distribution of structural components in biological tissues based on their scattering signatures.

Brain myelin contents in normal and shiverer mice

Cellulose in physical (left) and virtual (right) sections of plants
NYX Protein Crystallography Beamline

- NYX is a partner user beamline funded and operated by the New York Structural Biology Center (NYSBC).
- Our objective is to provide high energy resolution x-rays to optimize the signal-to-noise ratio for anomalous scattering experiments.
- Spokesperson: Wayne Hendrickson.
- Staff
  - Kevin Battaile; LBS
  - Dieter Schneider; co-LBS
  - Randy Abramowitz; Mechanical Technician
  - Michael Skinner; Software Engineer
To enable the resources at CBMS:

- NIH/NIGMS P30 supports Structural biology at LiX, FMX and AMX
- DOE-BER supports structural biology and also bioimaging.

https://www.bnl.gov/ns1s2/lifesciences
**17ID-1 & 2: AMX and FMX – Automation and microfocus x-ray beams.**

**FMX and AMX: Two beamlines with overlapping and complementary capabilities**

<table>
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<th>5 – 30 keV</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Wavelength range</strong></td>
<td>0.4 – 2.5 Å</td>
<td>0.7 – 2.5 Å</td>
</tr>
<tr>
<td><strong>Flux at focus at 12.7 keV</strong></td>
<td>$3.5 \times 10^{12}$ ph/s</td>
<td>$5 \times 10^{12}$ ph/s</td>
</tr>
<tr>
<td><strong>Focal spot min (H×V)</strong></td>
<td>1 × 1.5 µm²</td>
<td>7 × 5 µm²</td>
</tr>
<tr>
<td><strong>Focal spot range</strong></td>
<td>1 – 10 µm</td>
<td>5 (– 20) µm</td>
</tr>
<tr>
<td><strong>Detector</strong></td>
<td>Eiger 16M</td>
<td>Eiger 9M</td>
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</table>

Sample changers using **unipuck bases** and **SPINE pins**. We find these are **essential for reliable high throughput automation**. >95% of experiments are remote access.
Access to NSLS-II

Three main forms:

• **General User** proposal: single PI, single beamline

• **Rapid Access** proposals: rolling call, beamtime usually within two to three weeks, if space in schedule

• **Block Allocation Groups**: multi-PI, multi project applications gaining access to all beamlines in the program from one application. Good for two years
Our suggestion to you if interested in access to NSLS-II

Block Allocation Group (BAG)

• **The BAG** may be science themed, or geographical, could be a APS-CAT

• **Lowers administrative overhead**: one application, essentially rapid access once active. Makes life easier for you and us.

• Enables you to establish “mini-shifts” for each PI/group in the BAG.

• **Will need an active BNL user account**: changes in our cyber security policy make this a requirement for access to the IT infrastructure.

• **Next deadlines**: Sept 31 2022, for experiments to begin Jan 2023, Jan 31 2023, for experiments to begin May 2023.
Scheduling

• We try to run a hybrid system of user self-scheduling and us setting the schedule.
• Flexible and adapted through each NSLS-II operation cycle.
• Late availability shifts advertised.
• We are looking to roll out fully automated overnight data collection as our preferred way of using all the nighttime shifts.
• The aim is to maximize time available for experiments without staff burnout.
Macromolecular crystallography short term aims

- Further optimize use of micro-focus beamlines.
- Fully Automated data collection for most experiments.
- Guided automation for xtals < 20micron.
- Common user interface across all three MX beamlines. *(Done)*
- On the fly data analysis and merging of all data collected. *(Available)*
- Easy access to data, and experiment summaries through ispyb database. *(In process)*
- Integrated analysis workflows with SAXS, x-ray footprinting and cryo-em.
- Collaboration and optimization of instruments for room temperature and time-resolved measurements.
- Very high throughput automated fragment/ligand screening:
  - goal ~ 1000 samples / day (data collection to map)
- Dynamics through collection of many datasets from “similar” crystals.
Unfortunately not in the photo: Grace, John, Tom, Jun, Matt, Vijji, Tom, and Lonny.
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Macromolecular Crystallography at the Stanford Synchrotron Radiation Lightsource

APS Upgrade Structural Biology Virtual Townhall Meeting

Aina Cohen – ACohen@SLAC.Stanford.edu
June 21, 2022
Remote Access Program

- >98% of Users Collect Data Remotely
- You Control the Experiment
- Saves Time and Money
- Access to Cutting-edge Equipment
- Fosters Collaboration

SSRL:
- BL12-1 Undulator, Microcrystal
- BL12-2 Undulator, Microcrystal
- BL9-2 Wiggler Multi-wavelength
- BL14-1 Bend Multi-wavelength

Beamtime Inquiries Welcome
Aina Cohen: ACohen@SLAC.Stanford.edu
Lisa Dunn: Lisa@SLAC.Stanford.edu
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2004 – First Remote Control Experiments

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Improved Remote Access Facilities

Remote Access Program
- >97% of Users Collect Data Remotely
- You Control the Experiment
- Saves Time and Money
- Access to Cutting-edge Equipment
- Fosters Collaboration

Beamtime Inquiries Welcome
Aina: ACohen@SLAC.Stanford.edu
Lisa: Lisa@SLAC.Stanford.edu

Fully Autonomous Data Collection and Processing

User:
1. Ship Samples to SSRL in Uni-pucks or Cassettes
2. Use Blu-ice Screening Tab to choose parameters for automation

Automated Steps:
1. Robot mounts sample pin
2. Sample loop or mesh centering (video)
3. Low dose X-ray grid search to center the best crystal into the beam and to set the best beamsize.
4. Video snapshot of crystal
5. Shutterless X-ray diffraction data collection (or screening)
   – strategy coming soon

1. All data collected is automatically processed! (XDS, results in /data directory with diffraction images)
Repeat for next crystal…

15 seconds loop centering
73 seconds down to 18 seconds in shutterless mode (150 pts)

SSRL:
- BL12-1 Undulator Microcrystal
- BL12-2 Undulator, Microcrystal
- BL 9-2 Wiggler Multi-wavelength
- BL14-1 Bend Multi-wavelength

Faster robotic sample exchange (~25 s)
Faster automated loop centering (~15 s)
Shutterless data collection (EIGER or PILATUS)
Shutterless grid searches to locate crystals
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Fully Remote Access
UV-Visible Microspectrometry at BL9-2

Monitor the spectra as a function of X-ray dose (Gy)

Illumination and Collection Objectives
Fully Remote Access

UV-Visible Microspectrometry at BL9-2

Monitor the spectra as a function of X-ray dose (Gy)

Interleave microspec-snapshots with diffraction data collection
Real-time X-ray Dose Calculator Aids Experimental Strategy

- Feedback on the predicted total x-ray exposure based on the experimental Run definition
- Raddose3D is used to calculate the Average Weighted Dose

Real-time X-ray Dose Calculator Aids Experimental Strategy

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Microfocus Beam Line 12-1

Remote Access at Controlled Humidity and Physiological Temperatures

- Robotic Sample Mounting of Samples at Controlled Humidity
- First offered used at LCLS-MFX
- Based on a new in-situ crystallization plate
- 18 different user groups across the US so far

https://www-ssrl.slac.stanford.edu/smb-mc/content/users/manuals/remote-access-at-elevated-temperatures-and-controlled-humidity

- System will be duplicated on other SSRL MC beamlines
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Disposable silicone liner cups hold crystallization solutions and make cleaning and reuse of plates easy.

Soft foam insert prevents splashing or spilling of the well solutions during transport.

Commercially Available: www.crystalpositioningsystems.com
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**Tester for sample pins compatibility**

- Uses a magnetic sample base
- If sample on base fits inside the tester it is compatible with the SSRL robot
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- Maintains a 20 °C (+/- 5) environment for 7 days
- Gel packs further stabilize the temperature
- Foam inserts securely hold crystallization trays

Prototype plates and shipper tested between Buffalo, NY and Stanford, CA
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User-support inserts plates prior to beamtime

Humidity controlled enclosure holds 5 plates / 50 samples

Remote Control
SSRL Structural Molecular Biology Facilities

CryoEM Facilities at SLAC
part of the SSRL Directorate

SSRL SMB

CryoEM

• NIH National Service Center for Cryo-EM
Combined User Admin Software and Scheduling
Experimental Methods and Software Developments
LCLS X-ray Free Electron Laser (XFEL)

Hard X-rays at LCLS
- Photons/pulse: $10^{12}$ (9500 eV)
- Pulse duration: 40 fs
- Pulses/second: 120
- Diffraction before Destruction

- Very small crystals
- Room temperature
- Metalloenzymes
- Time resolved studies

1 km linac 3-15 GeV

Far Experimental Hall

Near Experimental Hall

Undulator Hall
electron motion in phase with field of emitted photons
LCLS X-ray Free Electron Laser (XFEL)

Crystallography Experiments at LCLS

- **CXI**
  - Coherent X-ray Imaging
  - In Vacuum environment
  - Beam size 100 nm to 4 µm
  - **Crystal injector experiments**
    - Crystal slurries (100 nm to 5 µm)
    - Difficult to crystallize
    - Time resolved studies

- **MFX**
  - Macromolecular Femtosecond Crystallography
  - In atmosphere (air or helium)
  - Beam size 3 µm (up to 50 µm)
  - Flexible sample environment
  - **Standard Goniometer Setup**
    - Target individual crystals (>5 µm)
    - Controlled temperature (RT to cryo)
    - Delicate samples or limited supply
    - High resolution (large complexes, metalloenzymes, RT - hydration)
    - Time-resolved studies

Operation, Support & Development
Collaboration of LCLS & SSRL-SMB

SSRL Far Experimental Hall
Near Experimental Hall

CryoEM

LCLS
Thank you for your attention

Talk to us about your ideas for new experiments.

Becoming an SSRL User: https://smb.slac.stanford.edu/forms/becominguser/
Lisa Dunn – user scheduling administrator – Lisa@SLAC.Stanford.edu
Aina Cohen – Acohen@SLAC.Stanford.edu

Learn more at a remote access training workshop!
# APS-U Structural Biology Townhall Agenda

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<th>Start</th>
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Participants may use the RAISE HAND function and use their microphone when called on. You can address your question to a specific speaker or to any of the speakers.

Questions not addressed during the individual Q&A can be raised here or Argonne staff may bring them to the table.

I would like to acknowledge All the speakers
Andre Salles, Beth Schlesinger and Jade Thomas
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