NSLS-II Beamline Development Proposal Type I ☐ Type II ☒

NYSBC Microdiffraction Beamline (NYX)

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Science Case

Knowledge of biological structure at the atomic level has informed, indeed formed, modern biology since the discovery of the double helical structure of DNA. Nearly all enzymology is now structural enzymology, how transcription factors recognize their DNA targets is understood in considerable detail, fundamental processes of replication, transcription and translation are now all richly founded in atomic-level descriptions, there are structures for impressively large and often pathogenic viruses, several ribozymes are structurally characterized, the new biology of micro RNAs has quickly succumbed to structural analysis, structure often leads the way in the study of kinases and other signaling molecules, structure is well integrated into drug development, and membrane channels and receptors are increasingly amenable to structural analysis. These developments derive predominantly from x-ray crystallography (84% of the 66,000 current PDB entries). This science is vibrant; over half of the known structures were determined in the past five years, and increasing numbers of these more recent structures are challenging subjects – mammalian proteins, large multi-component complexes, integral membrane proteins. Synchrotron radiation plays a huge part now (81.0 % of crystal structures recorded into the PDB after 2005), and we anticipate that enhancements at NSLS-II will provide new advantages for structural analyses in increasing numbers and at ever increasing complexity.

The focus of attention for the proposed NYX undulator beamline NYX is on users from the ten member institutions of the New York Structural Biology Center (NYSBC),[1] but the beamline will also meet needs of NSLS-II General Users. NYSBC scientists and their research themes are identified in a

[1] Albert Einstein College of Medicine
Columbia University
City University of New York
Memorial Sloan-Kettering Cancer Center
Mount Sinai School of Medicine
New York University
The Rockefeller University
State University of New York
Wadsworth Center, New York State Department of Health
Weill Medical College of Cornell University

Table 3 below. It is beyond the limited scope of this proposal description to elaborate on even a representative sample of the research projects that would be enabled by the proposed instrumentation. Investigators from the NYSBC community include many pre-eminent structural biologists working on challenging problems at the forefront of the field. Challenges come from the size and complexity of systems under study. Moreover, as technology advances to make it possible to deal with new challenges, such as those that come from very small samples, demand grows for the technical capability to meet these challenges, such as can come from micron-sized x-ray beams. To achieve the desired brilliant x-ray microbeams, it is essential to take advantage of the interference enhancements that come only from undulator sources.

The microdiffraction beamline proposed here for NSLS-II is an intellectual successor to NSLS beamline X4A (discussed below), which was designed in part for the testing of multiwavelength anomalous diffraction (MAD). While moving to incorporate microbeams, we also want to preserve the versatility of optimized anomalous scattering experiments across a broad spectrum of options and we propose to capitalize on the intrinsic brightness of NSLS-II to optimize anomalous signals by improving energy resolution. At the same time, recognizing that many problems may not require *de novo* phase evaluation, we would not want to compromise generic performance. With these considerations in mind, we focus on the kind of science that will benefit from three attributes that have motivated our proposed beamline design. We aim to provide stable, high brightness beams at the level from 50-micron down to 5-micron cross section; we aim to preserve the inherent spectral flux from a monochromator crystal (typically Si 111) within a bandpass down to energy resolution of $\Delta E/E = 5x10^{-5}$; and we aim to support efficient diffraction experiments in the range of x-ray energies from the uranium L_{III} edge (17.2 KeV) down to the uranium M_V edge (3.5 KeV), with expected emphasis on the Se K edge (12.6 KeV).

Undulator characteristics have an important impact on the achievable energy range. The spectrum computed for a device that we consider appropriate for this proposed beamline is shown in Figure 1. This device will provide x-rays across the range specified above, but there is a gap in coverage between the first and third harmonics near 4-5 KeV. This gap proves difficult (and/or expensive) to fill without sacrifices in other parts of the spectrum. In any case, many special factors complicate diffraction experiments at low energy (< 6 KeV); thus, we propose to focus our attention with this NYX beamline into the energy range of 6 – 17.5 KeV. We do anticipate, however, that a companion beamline dedicated to low-energy experiments could be constructed on this same straight section with a canted undulator mate as its source. This companion beamline would be optimized for the energy range from 3 – 6.5 KeV. It likely would require development work to produce a most appropriate undulator. Incidentally, because samples need to be small to mitigate absorption, microbeams are essential for optimization in low-energy diffraction experiments.

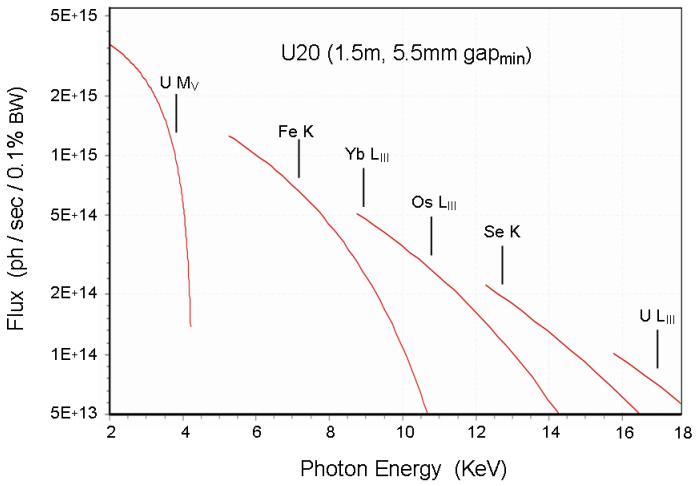

Figure 1. Undulator spectrum. The spectrum of peak photon fluxes upon gap variation is calculated for a U20 device (20mm period, B_{peak} = 0.91T at 5.5mm gap) of length 1.5m operated to a minimal gap of 5.5 mm. Selected absorption edge positions are identified.

Microdiffraction is the defining capability of the new beamline, and this is a property in high demand by NYSBC scientists and other biological crystallographers. It is clear, both in principle and now demonstrated in practice (Moukhametzianov, et al. 2008), that even one-micron sized illuminations of protein crystals can suffice for structure determination. This makes it possible to contemplate structure determinations from exceedingly small crystals. Indeed, structure determinations with micron-sized beams has become routine for amyloid peptides (Sawaya et al., 2007) and microdiffraction experiments have been critical in recent structural advances for G-protein coupled receptors (Rasmussen et al., 2007; Cherezov et al., 2007; Warne et al., 2008). Moreover, structure

determinations from very fine needles or very thin plates are now commonplace. For example, we determined the structure of a complex between follicle-stimulating hormone and its receptor from 10-micron plates (Fan and Hendrickson, 2005). Even when it may ultimately be possible to obtain larger crystals, a precious sample will first yield only microcrystals and it is crucial to characterize the diffraction properties of these crystals to decide on a course of action. Moreover, oftentimes crystal perfection varies across a large crystal and the rastering of a microbeam across the crystal can reveal portions that can produce better diffraction (Cherezov et al., 2009). Radiation damage ultimately limits the amount of diffraction that can be observed from a given sample (Ravelli and Garman, 2006), and this limit will be reached sooner from smaller samples. Thus, strategies for the merger of data from multiple crystals or from multiple locations along single crystals are indispensable in microdiffraction crystallography. Ultimately, however, microbeams may provide some relief from radiation damage. Since much of the damage is done by photoelectrons as they travel several microns from the site of radiation (Nave and Hill, 2005), by appropriately rastering of a micron-sized beam it may be possible to realize greater lifetimes. Although we do not plan to implement 1μm focus at the NYX beamline, this will be feasible at NSLS-II and in the design for the FMX beamline.

Optimization of energy resolution is a major innovation for the proposed beamline. Our design is motivated by our interests in the use of anomalous scattering for phase determination in macromolecular crystallography. Resonant features at the absorption edges of phasing elements can be quite sharp, as seen notably at the L_{III} edges lanthanide complexes (Lye et al., 1980; Weis et al., 1991) and as we observed for the Se K edge in selenomethionyl proteins (Hendrickson et al., 1990). The strength of anomalous scattering signals depends on the values of scattering factors at the resonant edges (Hendrickson, 1990), and realized anomalous scattering factors depend on the energy resolution – higher resolution increases signals. For many beamlines, energy resolution is limited by beam divergences from the source rather than by the monochromator rocking curve ($\Delta E/E = 1.4 \times 10^{-4}$ for Si111 at CuKα) and intrinsic edge features are spoiled. Theoretically, line widths of resonant features in anomalous scattering factors are determined by lifetimes of the relevant electronic transitions, but as these transitions are into molecular orbitals the theoretical framework is not always sound. Conventional wisdom has it that resolution at the limit of Si111 bandpass suffices, but this has not been properly tested experimentally. Moreover, it is essential to assure that beamline optics should at least preserve the intrinsic line widths, which rarely happens at current beamlines. We have studied energy resolution from monochromators in our optimization of the horizontally bent, asymmetrically cut monochromator crystal of our beamline X4C (Lidestri and Hendrickson, 2009), and this forms the basis for the design that we propose here for undulator beamline NYX. In a similar manner, here we will bend to match the much more limited vertical divergence and use an asymmetric cut to limit acceptance to a defined energy bandbass; then for the double-crystal geometry we reverse the asymmetric cut on the second crystal to accept fully the resulting convergent beam. Thus, the monochromator system is optimized to preserve the full spectral bandpass defined by the asymmetric cut. We have verified by ray tracing that we can achieve optimized energy resolutions of $\Delta E/E \leq 5 \times 10^{-5}$ in microfocused beams with this instrument. Exceptional energy resolution would certainly be essential for exploiting the anisotropy in anomalous scattering for phase evaluation (Fanchon and Hendrickson, 1991; Schilz and Bricogne, 2008), and it could provide appreciable enhancement over current standards for selenomethionyl MAD and SAD phasing and for other important phasing elements such as the lanthanides, tungsten, tantalum and osmium.

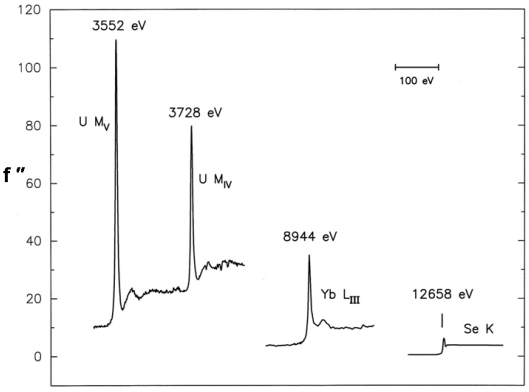

Figure 2. Selected f″ scattering factors. Experimentally measured spectra are shown from resonant transitions at U M-edges, a lanthanide L_{III}-edge and the SeMet K-edge.

Efficient operation across a broad energy span is a third special characteristic of the beamline design. Broad coverage is desirable in order to assure access to the fullest possible range of elements for anomalous phasing experiments. The predominant phasing experiment (~2/3 of MAD and SAD

applications) uses the Se K edge of selenomethionyl proteins; however, diverse absorption edges, including all of those shown if Figure 1, have proved effective in macromolecular phasing experiments (Hendrickson, 1999). The importance of anomalous diffraction in macromolecular crystallography has steadily increased over time; whereas from statistics of PDB deposits in 1997 only 17% of *de novo* structures were determined by MAD and 80% were from MIR or SIR, in 2007 the share of MAD and SAD structures combined had risen to 89% (unpublished results). Moreover, SAD determinations have come to predominate (48% overall; 54% of MAD + SAD). SAD experiments are conducted optimally at the absorption edge peak of f″, and thus access to these edges is needed. The K edges for sulfur and phosphorous are impractical for diffraction; however, but off-edge sulfur anomalous scattering can be very useful in SAD experiments as shown first with crambin (Hendrickson and Teeter, 1981) and as enhanced at lower energy with obelin (Liu et al., 2000). The f″ Bijvoet signals increase as energy is lowered, and effectiveness improves provided that absorption is kept in check. Low-energy sulfur SAD structure determinations are increasing (Lakomek et al., 2009; Guy et al., 2009; Bian et al., 2010), but there is much room for optimization of instrumentation and methods. We propose to build the NYX beamline for facile experiments down to 6 KeV ($\lambda \approx 2$Å), where from our experience sulfur SAD works well. We will also avoid optical impediments to exceptional experiments at 4 KeV or below, as for Ca K or U M_V. This latter capability could be important in the interim until a dedicated low-energy beamline is built. In any case, microdiffraction is advantageous for low energy applications since sample absorption is a major factor, both for reducing diffracted output and for causing radiation damage.

Ultimately, we would hope to complement the NYX beamline with one optimized for the energy range of 3 - 6.5 KeV. The motivation for going to low energies for phasing experiments is to access certain electron-rich L and M shells of heavier atoms as well as to further optimize sulfur and phosphorous SAD experiments. In general, anomalous scattering strengths increase from K to L to M edges, and for those with so-called 'white lines' the effect is even more striking (Fig. 2). We completed a successful MAD experiment on uranyl elastase at the U M_{IV} edge, and we showed that within just a 4eV span at the M_V edge one could conduct a 3λ MAD experiment with f″ = 110 e and $|\Delta f'|$ = 105 e (Liu et al., 2001). Moreover, L edges of potentially interesting mid-range elements such as Xe and I are in the uncovered gap of the current U20 design.

Beamline Concept and Feasibility

The unique brilliance of the NSLS-II storage ring provides us with great opportunities to address the science needs in macromolecular crystallography that we identify above. NSLS-II is designed to produce electron beams without precedence for controlled emittance. Both a small source size and low divergences contribute to an extraordinarily confined phase space, and both properties contribute to produce photon beams with exceptional opportunities for focus into microbeams and also exceptional opportunities for energy resolution. We have designed x-ray optics that will capture the full spectral brilliance passed by a Si111 monochromator but focused into a beam of ~10 micron cross-section and while achieving an energy resolution under 5×10^{-5} in ΔE/E (0.5 eV at 10 KeV). Beams can readily be defocused to 50 micron cross section, and they can be further focused to 5 micron cross section at the cost of a 50% decrease in flux. The monochromator is the heart of the system and its novel design will define the energy resolution (independent of x-ray energy), pre-focus the beam vertically, and focus the beam horizontally. A downstream vertical mirror will complete the vertical focus (also independent of x-ray energy) and provide for harmonic rejections. Conventional vacuum transports will contain the beam path between optical elements and into the experimental end station. The end station will feature a precision six-axis table and an air-bearing goniometer system. A dual mode integrating and counting pixel-array detector will be implemented to cope with exceptionally high count-rate densities at low angles from microdiffraction at NSLS-II while assuring accurate measurement of the weak high-angle data. Control systems will include automatic beam alignment and automated sample control. This is our beamline development plan in outline; details follow:

Undulator source and beamline configuration. The source for the NYX beamline in our notional design is a 1.5m U20 undulator positioned in a low-β straight section. This undulator would be one of a canted pair sharing this straight section. The proposed device (U2 in Figure 1) is canted -1

mrad from the center line and positioned downstream from a somewhat shorter device (U1) that is canted +1 mrad from the centerline. The inbound (+1) beam would be diffracted horizontally across the outbound (-1) beam by monochromator (Mo1) to separate the outbound (-1) beam, which proceeds downstream to the NYX monochromator (Mo2), mirror assembly (Mi) and sample goniometer (G).

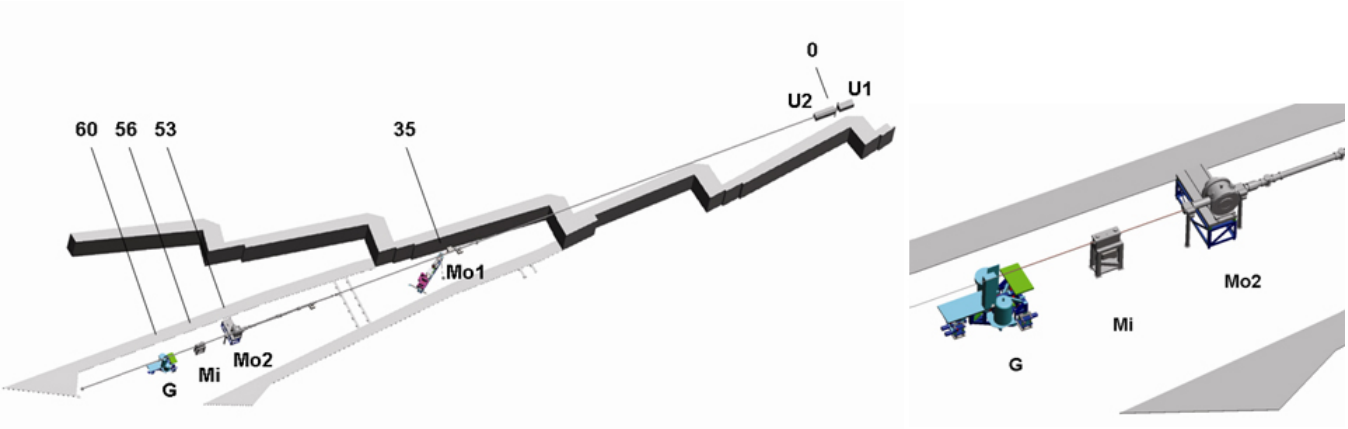

Figure 3. Beamline configuraton. (Left) CAD layout of a prospective beamline configuration. (Left) This notional design is based on a canted undulator pair serving NYX and a companion beamline for future development. Undulator U1 (1.0m in this layout) and monochomator Mo2 serve the companion beamline for low-energy experiments. A candidate monochromator, mirror and end station scheme are laid out for compatibility as shown. Elements of NYX x-ray optics include the monochormator (Mo2), mirror (Mi) and sample goniometer (G) as shown. The positions of optics elements are indicated as distances in meters from the center of the straight section. **(Right)** Enlargement of the NYX elements from lower left.

Monochromator development. Although energy resolution is not intrinsic to synchrotron radiation, the contracted phase space resulting from relativistic effects at synchrotron light sources does make high-energy resolution achievable, and with low emittance as for NSLS-II this is more readily accomplished. Typically, the monochromator is configured to exploit that the smallest phase plane to achieve satisfactory energy resolution. A defined energy resolution can be realized by matching the angular acceptance of the monochromator to the Darwin width of the monochromator crystal. A common monochromator geometry at synchrotron beamlines uses a flat, unbent crystal oriented to diffract in the vertical plane. The vertical plane is chosen most often because of its much smaller phase plane relative to the horizontal; nevertheless, as the incident beam divergence typically exceeds the monochromator rocking curve width, usually this still requires reduction of angular acceptance by limiting slits or a collimating mirror. The use of slits necessarily results in an overall reduction of flux; pre-monochromator collimation may not achieve perfection and, depending on mirror slope errors, there may be degradation in this approach as well. Alternatively, without such conditioning of the incident beam, the energy resolution intrinsic to a given monochromator will be spoiled. A perfect and perfectly matched Si111 monochromator will produce an energy resolution of $\Delta E/E = \Delta\lambda/\lambda = 1.4 \times 10^{-4}$, but typical incident beam divergences are larger and these blur resolution.

If the monochromator is bent to satisfy the Rowland condition, whereby all rays from the x-ray source can match the Bragg condition, one obviates the need for slitting or a collimating mirror. When such bending is coupled with the condensing effect of an asymmetric cut, as introduced by Fankuchen (1937), then energy resolution can also be improved. This can be accomplished with a cylindrically bent asymmetric crystal as implemented for horizontally diffracted monochromators (Lemonnier et al., 1978; Schildkamp, 1988). We have used such a crystal at NSLS beamline X4C, and we recently analyzed the energy resolution properties of this monochromator (Lidestri & Hendrickson, 2009). Here we plan to implement such bending in the vertical plane. We have developed a novel geometry double-crystal geometry in which the first crystal is bent tangentially and second crystal is bent sagittally. This geometry can only be made to work efficiently by using an asymmetric cut crystal in the second position with its orientation reversed to favor increasing the acceptance angle facing the first crystal. The energy band pass is definable by selection of the asymmetric angle, α. Here, emergence of the diffracted beam at the 17.5 KeV extreme constrains α to 6º. This double-crystal configuration is illustrated in Fig. 4, and the rocking curves generated for crystals with α = 6º is shown in Fig. 5.

From the rocking curves (Fig. 5) one notices the narrowing and broadening of the rocking curves when compared to the symmetric case. The narrowed rocking curve at +6º defines the improved energy resolution and the broadened curve at -6 º provides increased angular acceptance in the second crystal. This increased acceptance is essential. Since diffracted rays from the bent first crystal are convergent, the second crystal must have an asymmetric cut oriented in oppositely to permit full acceptance. The dominant feature of this novel monochromator geometry is the monochromatic match to the finite angular divergence of the x-ray beam while still allowing the second crystal to be sagittally bent for horizontal focusing.

With the low emittance of NSLS-II, the source divergence is dominated by that from the undulator emission. The component due to electron beam divergence, σ'^{e}_{x} = 2.7μrad, is small compared to that due to the undulator, σ'^{U}_{x}. The relevant overall divergence seen by the monochromator is then $\sigma'^{overall}_{x} = (2\pi [(\sigma'^{e}_{x})^2 + (\sigma'^{U}_{x})^2])^{1/2}$, which we have computed for selected energies including extremes of the NYX design and used to evaluate energy resolution performance (Table 1).

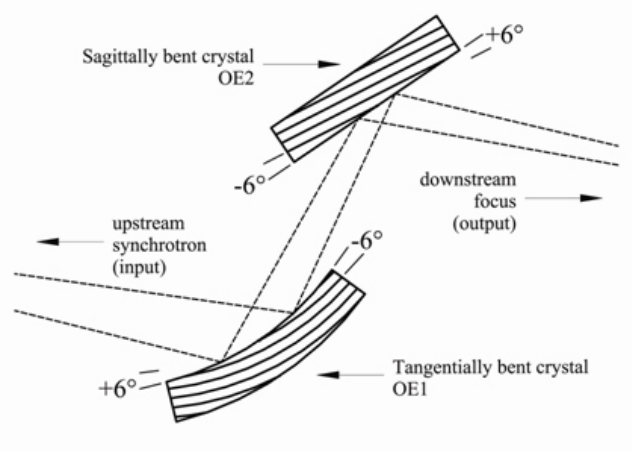

Figure 4. Monochromator schematic. The bent asymmetrically cut first crystal defines the energy resolution. The sagittally bent second crystal focuses horizontally and has a reversed asymmetric cut to fully accept the convergent beam from the first crystal.

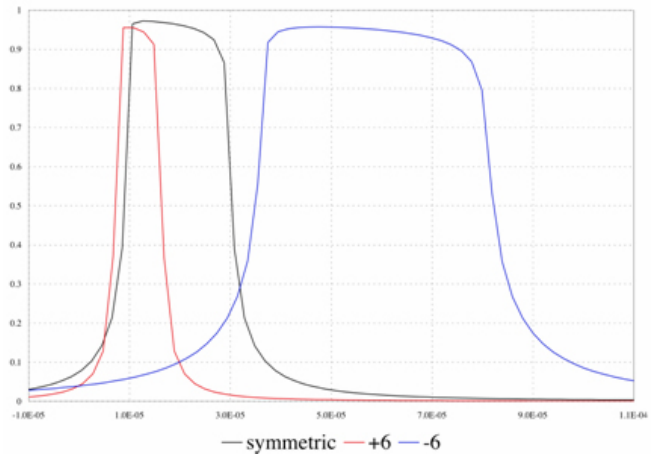

Figure 5. Rocking curves. Profiles are shown for Si(111) crystals at the Se K-edge (12658 eV), including the case for symmetric geometry (black) and for asymmetric cuts of both +6º (red) -6º (blue).

Table 1. Monochromator Parameters at Selected Relevant Energies

Energy (eV)		Source $\sigma'^{overall}_{x}$ (μrad)	Si111 Darwin Width α=0 (μrad)	Si111 Darwin Width α=6º (μrad)	Energy Resolution Si111 α=0 flat (ΔE/E)	Energy Resolution Si111 α=0 flat (ΔE)	Energy Resolution Si111 α=6º bent (ΔE/E)	Energy Resolution Si111 α=6º bent (ΔE)	Flux (ph/s/0.1%)
3552	($U M_V$)	39.07	33.63	28.81	7.9×10^{-5}	0.27	4.3×10^{-5}	0.15	1.7×10^{18}
6000		30.07	37.07	27.17	1.4×10^{-4}	0.84	7.8×10^{-5}	0.47	1.4×10^{15}
12658	(Se K)	21.42	20.00	8.98	1.9×10^{-4}	2.34	5.7×10^{-5}	0.72	2.2×10^{15}
17500		18.49	14.65	2.90	2.1×10^{-4}	3.62	2.5×10^{-5}	0.43	1.4×10^{14}

Heat load analysis. The primary technical challenge to be addressed in realizing the increased energy resolution of the NYX monochromator (Table 1) is associated with minimizing the effects of local heating of the crystal surface. It has been shown (Zaeper et al., 2001) that crystal bending is effective in compensating for the broadening of a rocking width from the thermal bump induced from local beam heating (Zaeper et al., 2001), which could be an ancillary benefit of our bending design. Cryogenic cooling will be required, but existing technology should suffice. Monochromator development work at APS (Mills, 1996) has demonstrated that intrinsic Darwin widths of silicon can be maintain by cryogenic cooling at power loads as high as 3.8kW with an associated power density of 140W/mm^2 @ 8KeV (APS undulator A). The calculated total power for the proposed 1.5m U20 undulator is comparable: maximum strength of 2.9kW and corresponding power density of 164W/mm^2 @ 17.5keV. Thus, the

primary issues associated with achieving improved energy resolution will come in combining the designs for cryogenic cooling with those for crystal bending. Shastri et al. (2002) have shown at APS that cryogenic cooling is compatible with the bending of a silicon crystal.

Focusing and harmonic rejection. The downstream focal point in the vertical plane, due to the bent first crystal, is constrained by the asymmetric crystal angles. Therefore, an additional vertical mirror is required for practical positioning of the focus. This grazing incident mirror is also needed for rejection of the unwanted high order harmonics diffracted by the monochromator, notably Si(333). In our current configuration (Fig. 3), we have a total source to focus distance of 60m. Given these long distances, the length of a grazing incident mirror becomes long due to the finite beam divergence of the source. One of the added benefits of using a bent first crystal in the above geometry is the vertical focusing that tends to control the beam divergence, allowing the vertical mirror to be kept to a minimum. By placing the vertical mirror 3m downstream from the monochromator, the length required for 12658 eV x-rays is estimated to be 0.6m long. To reduce the dominant horizontal source size, the monochromator is placed 6.5m from the focus to before the vertical mirror to achieve 8:1 demagnification in the sagittal plane.

Ray tracing analysis. The synchrotron optics program SHADOW (Lai & Cerrina, 1986) has been used to simulate the over all performance of the proposed beamline. The source parameters used in the computer model were computed form the actual electron beam parameters in a low-β straight section at NSLS-II (electron beam sizes σ_x=31μm and σ_y=3.0μm; electron beam divergences σ'_x=17.5μrad and σ'_y=2.7μrad). The x-ray source characteristics are derived from undulator parameters in NSLS-II source documents. Based on these parameters, we obtain B = 0.63T at a gap = 7.8mm (K=1.18) from which radiation from the 5th harmonic for the Se K-edge (12658eV) yields a flux of 2.2x10^{14} (photons/sec/0.1%BW), a brightness of 1.5x10^{20} (photons/sec/mm^2/mr^2/0.1%BW), and photon beam horizontal and vertical divergences of σ'_H = 19.3 μrad σ'_V = 8.5 μrad. We have propagated ray tracing analyses for some relevant Se K-edge conditions (Figure 6). Here, the first crystal is tangentially bent to meet the Rowland condition at 12658 eV for an asymmetric cut of α=6º, the vertical mirror is bent to complete the resulting the vertical focus at the sample, and the second crystal is bent sagittally for horizontal focus at the sample. In the event that a larger beam would be desired, curvatures of the mirror and sagittal crystal would be relaxed to the desired degree.

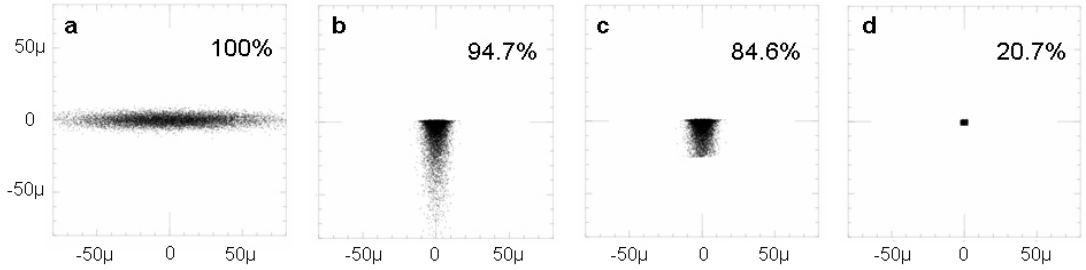

Figure 6. Ray tracings for NYX undulator beams at the Se K-edge energy. SHADOW (Lai & Cerrina, 1986) scatter plots are shown comparing the expected Se K-edge photon beam profiles at the sample position (60m) under four different conditions: (**a**) an unimpeded undulator beam without optics, (**b**) a fully focused beam from the described optical configuration, (**c**) the focused beam through a 25μ x 25μ aperture, and (**d**) the focused beam through a 5μ x 5μ aperture. Monochromator efficiencies, including crystal transmission factors, are indicated as percentages.

Vacuum beam path and radiation enclosures. Although we will need to specify and develop crystals and benders for our monochromator design, we expect to use a commercial monochromator tank and axial control system, similar to the one from Kohzu that we introduced into the US when we constructed X4A. Similarly, we expect to use a commercial mirror tank. Standard vacuum pumps and will be used to evacuate the beam pathes between optical elements. All windows will be kept to a minimum or elimated by the use of differential pumping. Radiation enclosures will be developed to house the NYX experimental station and possibly to house the monochromator and mirror assembly, although these devices could be appropriately shielded on the floor (Fig. 3). If a first optical enclosure is constructed to accommodate eventual beam separation from a prospective companion low-energy beamline, this will need to anticipate the footprint of that design.

Microdiffractometer. A precision goniometer will be developed to specification for microdiffraction control. We have a quote from CrystalLogic for a 1-micron sphere of confusion, with <0.002 degree reproducibility and <0.01 degree accuracy at speeds up to 180 degrees/sec. A six-axis kinematic support table is quoted at two micron resolution in translation and bidirectional reproducibility of 0.001 degree in yaw and pitch and 0.002 degrees in roll. CrystalLogic have also quoted an assembly of shutters, slits, ionization monitors, motorized beam stop, fluorescence detector mount, microscope and illumination system designed to support automatic beam aligment. We also have an alternative quote for an MD2 microdiffractometer of a design developed at the European Synchrotron Radiation Laboratory (ESRF) and implemented at other sites including the Northeast Collaborative Access Team (NE-CAT) beamlines at the Advanced Photon Source of Argonne National Laboratory. Sample crystals will be cryogenically cooled with a liquid nitrogen system and exchangeable with a robotically controlled cryogenic sample exchanger.

Pixel array detector. In order to cope with data rates expected from the high performance designed into the new beamline, we anticipate that need for a pixel array detector system. We are engaged in discussions with ADSC about the development of an appropriate pixel array detector. With the exceptionally high pixel densities from microdiffraction at low angles, integrating performance is needed; on the other hand, weak high-angle data will benefit from counting. A Pilatus system is an alternative option.

Required Technical Advances

Most of the required technology for the proposed beamline is already in hand. Some technical considerations have not been fully analyzed as yet, including vibration-free monochromator cooling, cryogenic monochromator bending, and high precision goniometer motions. It is possible that some elements of the associated designs may require technical advances. Further development work is also required by ADSC for the pixel array detector system that we intend to adopt.

User Community and Demands

The focus of our attention is on users from the ten member institutions of the New York Structural Biology Center (NYSBC). NYX will also be available many other users, but we feel that NYSBC scientists provide an excellent cross section of challenging applications of relevance to the community at large. NYSBC currently operates two highly productive beamlines as a Participating Research Team (PRT) partner at the NSLS. Beamline X4A was developed with original support from the Howard Hughes Medical Institute (Staudenmann et al., 1989) with the aim of developing the newly devised multiwavelength anomalous diffraction (MAD) approach for phase evaluation (Hendrickson, 1991). MAD phasing proved its effectiveness in large measure through X4A experiments (Hendrickson, 1999), and X4A became the prototype for a new class of beamlines. Moreover, as measured by resulting publications and by deposits into the Protein Data Bank (PDB), X4A has been one of the most productive of beamlines worldwide throughout its history and it remains so to this day despite increasing popularity of the brighter insertion device (ID) beamlines (Table 2).

Table 2. Beamline Productivity in PDB Deposits

1995 – present				2009 – present			
Rank	Beamline		Number	Rank	Beamline		Number
1	APS	19-ID	2067	1	APS	19-ID	418
2	**NSLS**	**X4A**	**1066**	2	NSLS	X29	331
3	ESRF	ID14-4	1052	3	SSRL	9.2	233
4	ESRF	ID14-2	1044	4	SSRL	11.1	209
5	ESRF	ID14-1	1009	**5**	**NSLS**	**X4A**	**200**
6	APS	22-ID	1004	6	SLS	X06	184
7	NSLS	X29	840	7	SLS	X10	182
8	SSRL	9.2	831	8	APS	24-ID-C	179
9	ESRF	ID29	817	9	APS	22-ID	175
10	DESY	X-11	811	10	ESRF	ID23-1	160

http://biosync.rcsb.org/BiosyncStat.html 120 productive beamlines worldwide 15 June 2010

NYSBC beamlines X4A and X4C use radiation from a dipole bending magnet and cannot be focused to ultrafine spots while retaining high flux, as can be done with the radiation from undulators. Indeed all of the beamlines listed in Table 1 except for X4A and the venerable DESY X-11 are ID beamlines. Many diffraction studies by NYSBC scientists are conducted on undulator beamlines currently. Four NYSBC institutions (Columbia, Cornell, Rockefeller and Memorial Sloan Kettering) are

also members in NE-CAT, and their scientists also use those APS beamlines. In addition, NYSBC scientists also use other undulator beamlines, most importantly X29 at NSLS. Thus, we feel very confident that there will be high demand for the proposed undulator beamline by our community. We also take pride in the continued effectiveness of X4A, the only remaining highly productive bending-magnet beamline, and we submit this record as evidence for scientific demand from NYSBC scientists.

NYSBC users of x-ray diffraction come from many research groups and have diverse research interests (Table 3).

Proposal Team Expertise and Experience

Wayne A. Hendrickson is a structural biologist and biochemist who uses x-ray crystallography to study biological molecules. He has experience and expertise in diffraction methodology with contributions that include phase probability coefficients, stereochemically restrained refinement, multiwavelength anomalous diffraction (MAD), and selenomethionyl proteins. He tested MAD phasing in first experiments at SSRL, PF, CHESS, LURE, ESRF and APS, and he developed the X4 beamlines at NSLS for further optimization. He and his colleagues have determined atomic-level structures for numerous molecules of biological significance, including human CD4, HIV envelope glycoprotein gp120, human insulin receptor kinase, human follicle-stimulating hormone complexed with its receptor, Hsp70-family and other molecular chaperones, and a homolog of an anion channel that controls closing of stomata in plant leaves.

Joseph P. Lidestri has 23 years of professional experience primarily in the fields of pulse power, plasma physics, accelerator physics and x-ray optics. Since 1995, he has managed the technical development, maintenance and operation of an X-ray facility at Columbia University that is dedicated to macromolecular structure determination. He was also instrumental in commissioning of experiments on NYSBC beamline X4C at NSLS, and he is presently involved in directing the upgrades of X4A and X4C beamlines. His other activities include the design of a superconducting synchrotron for macromolecular structure determination, the development of novel X-ray multilayer systems for highly divergent X-ray sources, and a collaboration for development of a hadron synchrotron for particle-beam cancer therapy.

Xiaochun Yang is a computer programmer. He has over 20 years of beamline programming experience. He has designed and coded several motion control and data acquisition software which are used in the beamlines at APS and NSLS. His expertise includes real time data acquisition and motion control, device driver, multi-thread and EPICS programming. Extensive experience and knowledge in VME, GPIB, CAMAC, RS232, motor controller, counter/timers, A/D and D/A controllers, I/O controller, multi-channel analyzer, digital multi-meter, temperature controller and automounter.

Qun Liu has expertise in many aspects of macromolecular crystallography: low resolution envelope phasing, multi-crystal phasing, long-wavelength SAD phasing, low temperature crystallography, high pressure crystallography, multilayer crystallography, parallel scientific computing. He also has experience in management and operation of NSLS X4 beamlines: user community support, mail-in synchrotron crystallography, student training and NSLS X4 website development. He is gaining experience in beamline optics, beamline automation and membrane protein crystallography.

Randy Abramowitz has been associated with NSLS X4 beamlines since their inception in 1987. He was involved in all of the mechanical aspects of their construction, and he has been responsible for their maintenance and operation in later years.

John Schwanof oversees computing and software at the X4 beamlines, and he manages user access to these beamlines. He also has many years of previous experience at NSLS beamlines.

Funding and Management

Funding has been arranged from multiple sources: awarded grant from the National Science Foundation (NSF); NSF cost sharing committed from NYSBC itself and from the New York State Innovation Economy Matching Grants Program; committed funding from the Defense Threat Reduction Agency (DTRA) of the Department of Defense (DoD); and requested additional DoD funding. The project will be managed by NYSBC with appropriate work breakdown structures.

Table 3. NYSBC Users of X-ray Diffraction

Institution / PI	Department / Unit	Research Interests
Albert Einstein College of Medicine		
Steve Almo	Biochemistry	Cytoskeleton / signal transduction
Alexander Fedorov	Biochemistry	Enzymatic reactions
Stephen Roderick	Biochemistry	Antibacterial drug targets
City University of New York (CCNY)		
Gary Quigley	Hunter College	DNA oligomers
Columbia University		
Qing R. Fan	Pharmacology	G-protein coupled receptors
Wayne A. Hendrickson	Biochemistry / Physiology	HIV, molecular chaperones, receptors
John F. Hunt	Biological Sciences	Protein machines
Filippo Mancia	Physiology	Membrane receptors
Lawrence Shapiro	Ophthamology / Biochemistry	Cell adhesions
Alexander I. Sobolevsky	Biochemistry	NMDA glutamate receptors
Liang Tong	Biological Sciences	Metabolism of fatty acids
Ming Zhao	Physiology	Ion Channels and Transporters
Memorial Sloan-Kettering Cancer Center		
Jonathan Goldberg	Structural Biology	Vesicular trafficking
Chris Lima	Structural Biology	Sumoylation / RNA stability
Stephen Long	Structural Biology	Membrane proteins
Dimitar Nikolov	Structural Biology	Receptor interactions
Nikola Pavletich	Structural Biology	Cancer biology
Dinshaw Patel	Structural Biology	RNA interactions
Mount Sinai School of Medicine		
Aneel Aggarwal	Structural & Chemical Biology	Protein-DNA recognition
Ming Ming Zhou	Structural & Chemical Biology	Epigenetic control
New York Structural Biology Center		
David Cowburn		Kinases
Joseph Lidestri		Instrumentation
Qun Liu		Methods / membrane proteins
James Love		NYCOMPS membrane proteins
New York University		
Stevan Hubbard	Pharmacology / Skirball	Receptor tyrosine kinases
Xiangpeng Kong	Biochemistry	HIV receptors
Moosa Mohammadi	Skirball	FGF signaling
Da-Neng Wang	Skirball	Membrane proteins
Nadrian Seeman	Chemistry	DNA engineering
Rockefeller University		
Günter Blobel	Cell Biology	Protein trafficking
Seth Darst	Molecular Biophysics	Bacterial transcription
Roderick MacKinnon	Molecular Neurobiology	Voltage-gated channels
Mike O'Donnell	DNA Replication	Replication
C. Erec Stebbins	Structural Microbiology	Infectious diseases
State University of New York (SUNY)		
Edward Berry	SUNY Upstate, Blochemistry	Mitochondrial respiratory proteins
Michael Malkowski	SUNY Buffalo / HWI	Membrane proteins
Wadsworth Center, Albany		
Joachim Jaeger	Computational & Structural Biology	DNA polymerase
Hongmin Li	Computational & Structural Biology	Superantigens / apoptosis
Patrick Van Roey	Computational & Structural Biology	Substrate-ligand recognition
Weill Medical College of Cornell University		
Olga Boudker	Physiology & Biophysics	Membrane proteins
Min Lu	Biochemistry	Viral membrane fusion
Crina Nimigean	Biochemistry	Ion channel structure & mechanism
Hao Wu	Biochemistry	Cellular recognition in signaling

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BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Wayne A. Hendrickson	University Professor
eRA COMMONS USER NAME hendricksonw	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Wisconsin at River Falls	B.A.	1963	Physics / Biology
Johns Hopkins University, Baltimore, MD	Ph.D.	1968	Biophysics
Johns Hopkins University, Baltimore, MD	Postdoc	1968-69	Biophysics
Naval Research Laboratory, Washington, DC	Postdoc	1969-71	Structure of Matter

A. Personal Statement:

Our laboratory works to advance diffraction methods for analyzing biological structure, and we use such technology together with biochemical and cellular analyses to study biological molecules in atomic detail. Our current emphasis is on membrane receptors and cellular signaling, on viral proteins and HIV infection, on molecular chaperones and protein folding, and on structural genomics of membrane proteins.

B. Positions and Honors:

1971 - 1984 Research Biophysicist, Naval Research Laboratory, Washington, DC
1984 - Professor of Biochemistry and Molecular Biophysics,
College of Physicians and Surgeons, Columbia University, New York, NY
1986 - Investigator, Howard Hughes Medical Institute
2001 - University Professor, Columbia University
2008 - Violin Family Professor of Physiology & Cellular Biophysics, Columbia University
2009 - Associate Director for Life Sciences, NSLS-II, Brookhaven National Laboratory
2010- Scientific Director, New York Structural Biology Center

Washington Academy of Sciences Award in Biological Sciences (1976)
Arthur S. Flemming Award for Outstanding Young Federal Employees (1979)
A.L. Patterson Award of the American Crystallographic Association (1981)
Distinguished Alumnus Award, University of Wisconsin at River Falls (1984)
Fellow of the American Association for the Advancement of Science (1984)
Johns Hopkins Society of Scholars (1986)
Fritz Lipmann Award of the American Society for Biochem. and Mol. Biol. (1991)
Fellow of the American Academy of Arts and Sciences (1992)
Stevens Triennial Prize, Columbia University, College of Physicians and Surgeons (1992)
Member of the National Academy of Sciences (1993)
Doctor of Philosophy *honoris causa*, Uppsala University (1995)
Aminoff Prize, Royal Swedish Academy of Sciences (1997)
Christian B. Anfinsen Award, Protein Society (1997)
Alexander Hollaender Award, National Academy of Sciences (1998)
Doctor of Science *honoris causa*, Mount Sinai School of Medicine (2000)
Fellow of the Biophysical Society (2001)
Compton Award, Advanced Photon Source of Argonne National Laboratory (2001)
Academy Medal, New York Academy of Medicine (2003)
Gairdner International Award (2003)
Paul Janssen Prize (with M.G. Rossmann), Rutgers University (2004)
Harvey Prize, Technion - Israel Institute of Technology (2004)
Mayor's Award for Excellence in Science & Technology, New York City (2005)
Kaj Linderstrøm-Lang Prize, Carlsberg Laboratory (2008)

BIOGRAPHICAL SKETCH

Joseph P. Lidestri

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(A) Professional Preparation

Texas Tech University, Lubbock, TX	B.S.	1985	Electrical Engineering
California State University, San Francisco/San Jose, CA		1994-95	Physics
Columbia University, New York, NY	M.S.	2003	Applied Physics

(B) Appointments

2004 - Present	Director of X-Ray Facilities and Instruments R&D, NYSBC
1999 - Present	Senior Staff Associate, Columbia University
1995 - Present	Research Specialist, Howard Hughes Medical Institute
1988 - 1995	Staff Physicist, Pulse Sciences Division of Titan Systems Corp. San Leandro, CA
1986 - 1988	Staff Engineer, Pulse Sciences Division of Titan Systems Corp. San Leandro, CA

(C) Selected peer-reviewed publications

1. Lidestri, J.P., Hendrickson W.A. "Optimization of x-ray energy resolution from a horizontally focused single-crystal monochromator." *Nucl. Instr. Meth.* A. 599, 289-300 (2009).
2. Lidestri, J.P. "A synchrotron design for marcromolecular structure determination." *Particle Accelerator Conference. PAC 2001. Proceedings of the 2001,* Volume: 4, Pages: 2772-2774 (2001).
3. Lidestri, J.P. "Hazardous emissions from a 2.5GeV synchrotron." *Internal Report, 2001.* Columbia University (2001).
4. Lidestri, J.P. **"**Production of fluorine-18 using high current proton accelerators." *Invention Report, 2000.* Columbia University (2000).
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10. Lidestri, J.P., Kares, R.J. "Plasma source characterization and development for the density controlled opening switch." *Pulsed Power Conference*, 1989. 7th, 1989, Page(s): 262 -267 (1989).

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SUMMARY OF QUALIFICATIONS

Software developer with over 20 years of working experience. Recognized for initiative, problem solving skill and creativity in both software design and programming. Demonstrates expertise in real time data acquisition and motion control, device driver, multi-thread and EPICS programming. Complete software development life cycle.

EDUCATION

M.S. in Theoretical and Applied Mechanics (SUNY at Stony Brook, 1989); Research in Data acquisition Control System

B.S. in Modern Mechanics (University of Science and Technology of China and the Chinese Academy of Sciences, 1982)

SKILLS

GNU C/C++, Visual C++, Winsock, TCP/IP, Perl, Java, FORTRAN, Tcl/tk, Expect, Qt,STL EPICS, PLOT, GRAPHER, MYSQL, APACHE,TOMCAT

WORKING EXPERIENCE

Argonne National Lab, Argonne, Programmer (Sep. 2004 – May 2010)
Implemented and developed crystallographic data collection/motion control/analysis software Package BLU-ICE, Including designed and coded real time multithread Distributed Hardware Server (DHS), Interfacing motor controller, scalars, A/D D/A, counters etc.. Developed a robot DHS for auto mount system. Developed EPICS database and control for QBPM. Coded an automation program in Perl for auto data processing using XDS software package. Developed a web data publishing program.

Howard Hughes Medical Institute, at Brookhaven National Lab
Senior Programmer (Sep. 1992 – Aug. 2004)
Initiated, designed and coded a motion control and data acquisition software package XSCAN in Visual C++ for Window. It is highly integrated experiments control, real time data acquisition, data analyzing, plotting, server/client communications and user defined macro control. Developed a data acquisition software package in C under UNIX.

Brookhaven National Lab, Programmer (Sep. 1986 – Sep. 1992)
Designed and coded a menu driven X-ray scattering software in C under DOS .Tasks include real time motion control and data acquisition, microsecond resolution timing, nonlinear data modeling, numerical analysis and experimental data curve fitting. Developed portable CAMAC control software in C under DOS. It included a complete redesign of a set of CAMAC interface drivers in C. Developed a recursion technique to handle any dimensional motions and designed user defined motion functions for motion control.

A. BIOGRAPHICAL SKETCH

NAME Qun Liu	POSITION TITLE X-ray crystallographer

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Anhui University (Hefei, China)	B.S.	1994-1998	Physics
University of Science and Technology of China (Hefei, China)	M.S.	1998-2001	Biochemistry and Cell Biology
Cornell University (Ithaca, New York)	Ph.D.	2001-2006	Biophysics
Cornell University (Ithaca, New York)		2006-2009	Structural Biology

A. Positions and Employment

2006-2009 Postdoctoral Associate, Cornell High Energy Synchrotron Source, Cornell University
2009- X-ray Crystallographer, New York Structural Biology Center, NSLS X4, Brookhaven National Laboratory

B. Selected peer-reviewed publications (of 34)

1. Liu, Q., Huang, Q., Teng, M.K., Weeks, C.M., Jelsch, C., Zhang, R. and Niu, L.W. (2003). The crystal structure of a novel, inactive, lysine 49 PLA2 from Agkistrodon acutus venom: an ultrahigh resolution, AB initio structure determination. ***J. Biol. Chem.*** 278, 41400-41408.
2. Liu, Q., Weaver, A.J., Xiang, T., Thiel, D.J. and Hao, Q. (2003). Low-resolution molecular replacement using a six-dimensional search. ***Acta Cryst. D*** 59, 1016-1019.
3. Liu, Q., Huang, Q., Lei, X.G., and Hao, Q. (2004). Crystallographic snapshots of Aspergillus fumigatus phytase, revealing its enzymatic dynamics. ***Structure*** 12, 1575-1583.
4. Lou, X., Liu, Q., Tu, X., Wang, J., Teng, M.K., Niu, L.W, Schuller, D.J., Huang, Q., and Hao, Q. (2004). The atomic resolution crystal structure of atratoxin determined by SAD phasing. ***J. Biol. Chem.*** 279, 39094-39104.
5. Liu, Q., Kriksunov, I. A., Graeff, R., Munshi, C., Lee, H. C., and Hao, Q. (2005). Crystal structure of human CD38 extracellular domain. ***Structure*** 13, 1331-1339.
6. Yan, N., Chai, J.J., Lee, E.S., Gu, L.C., Liu, Q., He, J.Q., Wu, J.W., Kokel, D., Li, H.L., Hao, Q., Xue, D., and Shi, Y. (2005). Structure of the CED-4-CED-9 complex provides insights into programmed cell death in *Caenorhabditis elegans*. ***Nature***, 437, 831-837.
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9. Liu, Q., Kriksunov, I. A., Graeff, R., Lee, H.C. and Hao, Q. (2007). Structural basis for formation and hydrolysis of calcium messenger cyclic ADP-ribose by human CD38. ***J. Biol. Chem.*** 282, 5853-5861.
10. Xing, W., Zou, Y., Liu, Q., Liu, J., Luo, Xi., Huang, Q., Chen, S., Zhu, L., Bi, R., Hao, Q., Wu, J. W., Zhou, J. M. and Chai, J. (2007). The structural basis for activation of plant immunity by bacterial effector protein AvrPto. ***Nature*** 449, 243-247.
11. Liu, Q., Kriksunov, I.A., Moreau, C., Graeff, R., Potter, B.V.L. Lee, H.C., and Hao, Q (2007). Catalysis associated conformational changes revealed by human CD38 complexed with a non-hydrolyzable substrate analog. ***J. Biol. Chem.*** 282, 24825-24832.
12. Liu, Q., Kriksunov, I.A., Jiang, H., Graeff, R. Lin, H., Lee, H.C., and Hao, Q. (2008) Covalent and non-covalent intermediates of an NAD utilizing enzyme, human CD38. ***Chem. Biol.*** 15, 1068-1078.
13. Liu, Q., Kriksunov, I.A., Wang, Z., Graeff, R., Lee, H.C., and Hao, Q (2008) Hierarchical and helical self-assembly of ADP-ribosyl cyclase into large-scale protein microtubes. ***J. Phys. Chem. B*** 112, 14682-14686.
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