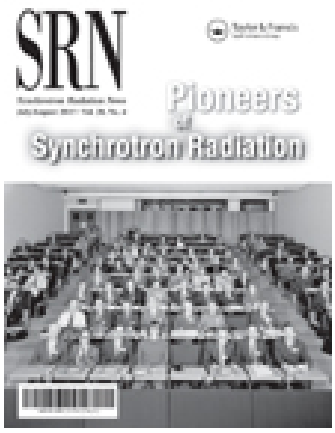

Synchrotron Radiation News
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrn20

First Protein Crystallography Experiments on a Synchrotron

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Published online: 14 Aug 2015.

To cite this article: Alexander Wlodawer (2015) First Protein Crystallography Experiments on a Synchrotron, Synchrotron Radiation News, 28:4, 28-29, DOI: 10.1080/08940886.2015.1059235

To link to this article: http://dx.doi.org/10.1080/08940886.2015.1059235

First Protein Crystallography Experiments on a Synchrotron

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My story started in the winter of 1973/1974. I was a graduate student at UCLA, my thesis work was going nowhere, and my wife was expecting a baby in the early summer, while we had no health insurance that would pay for this happy event. It was clearly time to find a place other than Los Angeles to continue work in protein crystallography. Since I wanted to study crystal structure of the nerve growth factor (NGF), and the West Coast expert in that field was Eric Shooter at Stanford, I asked him if he would be willing to accept me as a postdoc. He was, but had no funds. However, somehow he contacted Keith Hodgson and the two of them managed to find some money, to the best of my recollection in the Department of Psychiatry. Although Keith agreed to let me work on the structure of NGF and a few other proteins, he stipulated that my primary objective should be to help in setting up the first in the world beamline devoted to the use of synchrotron radiation for single-crystal diffraction from protein crystals. To tell the truth, I initially had some problems understanding what exactly he had in mind—somehow my undergraduate degree in physics did not cover that particular subject. Thus, in the late spring of 1974, the team was established—Keith at the lead, two postdocs (Margueritte Yevitz Bernheim and myself) and a graduate student, James Phillips. We were joined by Julia Goodfellow (now Dame Julia) a year later. And the Stanford Synchrotron Radiation Project also officially commenced at about the same time.

To say that our facilities were primitive is to overestimate the true state of affairs. Our only detector was an Enraf-Nonius precession camera that could be used with Polaroid films for alignment, or with multiple packs of radiology films for "data collection." The latter films could be later scanned in order to provide some numerical data, but usually we just looked at them in order to extrapolate the speed of data collection to the future when everything would work perfectly (it never did at that time). As is often the case in protein crystallography experiments, we started with the crystals of hen egg-white lysozyme (they are easy to grow and diffract very well). We were very happy when a precession photograph could be obtained in as little as two hours (that was, actually, the length of a single fill). However, we could not develop these pictures on site for the lack of a darkroom—that step required driving to the main campus in a Korean-war vintage armored personnel carrier, our official vehicle. Returning from one of our photography trips, we found the ring dark—a major fire in another location shut it down for several weeks. And the fact that psi particles that were studied by Burton Richter and his colleagues (and gave him the Nobel Prize) were found at the energy

Working on SSRL beamline 1-5 (left to right), Marguerite Yevitz, Keith Hodgson, Alex Wlodawer, and James Philips did a series of experiments that demonstrated the value of synchrotron radiation for protein crystallography measurements. The group, including Julia Goodfellow, Paul Phizackerley, and Ethan Merrit, also exploited the variable wavelength nature of synchrotron radiation.

of 1.55 GeV, while hardly any hard X-rays were generated below 2 GeV, also did not help in speeding up the rate of progress.

We used this first beamline to collect some diffraction data on proteins such as NGF, L-asparaginase, azurin, and rubredoxin. Most of these crystals were too small to provide measurable diffraction with standard laboratory X-ray sources, so we could consider the use of synchrotron to be quite successful. Experiments involving rubredoxin were particularly important, since we tuned the wavelength to match the absorption edge of iron, thus maximizing the anomalous signal. We were quite pleased to see the differences between the intensities of the Friedel mates by eye (the central projection in the space group *R*3 is non-centrosymmetric). Even these very early experiments proved that the tunability and high intensity of the synchrotron beam would ultimately revolutionize protein crystallography.

Running the experiments was quite exhausting, since the beam was down every two hours and it was necessary to adjust the camera after every fill. The longest single experiment took six nights and five days, with sleep possible in at most two-hour increments (on the floor, under a table). We felt pressure to get some positive results before others would beat us to it and, by mid-1976, we finally published the preliminary results in the *Proceedings of the National Academy of Sciences*. Just in time, since the results from DESY in Hamburg came out soon thereafter, and another group in Novosibirsk was also developing a protein crystallography beamline.

By the time I left Stanford in late 1976, the work on instrumenting the beamline for more practical work was already underway and I missed the subsequent developments, returning to the use of synchrotron radiation only a decade later. However, my experience at SSRL led to an offer of a position to develop a station for neutron protein crystallography, another big challenge. And the birth of my daughter cost us only $60 due to the excellent health insurance plan at Stanford. ■