| ESRF | **Experiment title:** Ion Channels and Diseases of electrically excitable cells | **Experiment number**: WT-57 |
|---|---|---|
| **Beamline**: ID23-2 | **Date of experiment**: from: 24 nov 2007 to: 25 nov 2007 | **Date of report**: |
| **Shifts:** 3 | **Local contact(s)**: Dr. Joanne Mccarthy | *Received at ESRF:* |

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## Report:

The ATP-sensitive potassium ($K_{ATP}$) channel is a eukaryotic plasma membrane protein that links cellular metabolism to electrical excitability in numerous cell types (1). Opening of the channel inhibits, and closure of the channel stimulates, cellular responses. In pancreatic beta-cells, $K_{ATP}$ channels have a key role in insulin secretion. Thus, glucose metabolism closes $K_{ATP}$ channels, so inducing beta-cell depolarization, opening of voltage-gated calcium channels, calcium influx and insulin release. Conversely, opening of $K_{ATP}$ channels prevents insulin secretion. Indeed, gain-of-function mutations in the genes encoding the $K_{ATP}$ channel cause neonatal diabetes (2)

$K_{ATP}$ channels consist of two subunits that assemble as an octameric (4:4) complex (1). Four Kir6.2 subunits form a central tetrameric pore, which is surrounded by four regulatory sulphonylurea receptor (SUR) subunits. ATP binding to Kir6.2 shuts the channel while interaction of Mg-nucleotides with SUR opens the channel. The SUR subunit composition varies between tissues, being SUR1 in pancreatic beta-cells and many neurones, SUR2A in cardiac and skeletal muscle, and SUR2B in smooth muscle and some neurones. This variability accounts for the different sensitivities of $K_{ATP}$ channels in these tissues to metabolism and drugs. SUR1 subunit is the binding site for the sulphonylurea drugs that are commonly used to treat both type 2 diabetes and neonatal diabetes (3).

They act by causing closure of the $K_{ATP}$ channel.

Our current studies focus on obtaining an atomic structure of SUR. We have succeeded in growing small and very thin plate-like crystals of SUR (maximum dimension 50μm, minimum dimension 2μm). Fifty of these crystals were tested on ESRF beamline ID23-2 during 24th November 2007. These crystals diffracted to 10Å in one direction, with one crystal reaching a resolution of about 5Å. The most common diffraction pattern was somewhat fiber-like (Fig.1). Improvement of the crystals is currently underway.

## References


1. Ashcroft FM (2007) The Walter B Cannon Lecture. ATP-sensitive K-channels and disease: from molecule to malady. *American Journal of Physiology: Endocrinology and Metabolism* 293, E880-9
2. Hattersley AT, Ashcroft FM (2005) Activating Mutations in Kir6.2 and neonatal diabetes: New clinical syndromes, new scientific insights and new therapy. *Diabetes* 54, 2503-13.
3. Gribble FM, Reimann F (2003) Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 46: 875-91


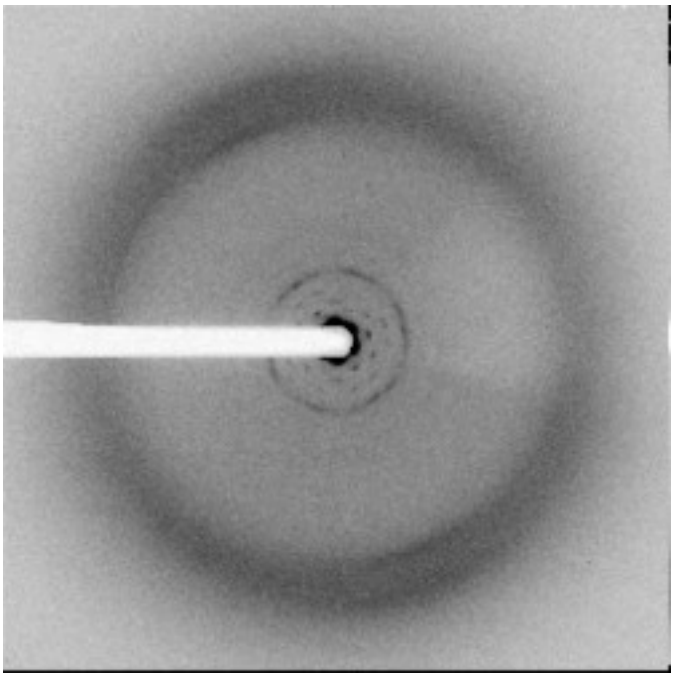

**Fig. 1 .**
**X-ray diffraction pattern of SUR1 microcrystals at microfocus beamline ID23-2.**