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ScienceDirect
Nuclear Instruments and Methods in Physics Research B 260 (2007) 97–100
NIM B
Beam Interactions with Materials & Atoms
www.elsevier.com/locate/nimb

A scanning focussed vertical ion nanobeam: A new UK facility for cell irradiation and analysis

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Available online 14 February 2007

Abstract

A new initiative to build a vertical scanning focussed nanobeam is outlined. This is a collaboration between the Gray Cancer Institute and the University of Surrey. The new beam line will operate in both single ion and full current modes and will enable the irradiation of single cells *in vitro* with precisely counted numbers of ions, it will also enable the analysis of cells *in vitro*. The beam will be focussed and scanned and should be capable of irradiating 100,000 cells per hour. A new end station will enable the cells to be irradiated in an environmentally controlled environment and will enable the cells to be imaged both on-line and off-line. The beam line will be housed in its own purpose built building, with the area around the end station comprising a biological clean room.

Keywords: Vertical nanobeam; Cell irradiation; Ion beam analysis

1. Introduction

The Gray Cancer Institute (GCI) has been actively involved in the development and application of ion and focussed X-ray microbeams for radiobiological research since the early 1990s. The Surrey Ion Beam Centre (IBC) is a UK national centre for research using ion beams and has been actively involved in the development of ion beam analysis techniques since the late 1970s. In 2002 this expertise was strengthened when Dr. Geoffrey Grime joined the IBC from the University of Oxford and brought with him a wealth of experience in the design of focused scanning ion microbeam systems.

In this paper we describe an ambitious new collaborative research programme between Surrey and GCI which seeks to build a vertical, focused, scanning, nano-irradiation and analysis facility. This radically new technology will be used to challenge and characterize living biological materials, with clear applications in cancer treatment, understanding the risks associated with occupational and environmental exposure to radiation and probing the internal working of cells and how they respond to external and internal stimuli such as stress, toxins, drugs, nutrition and radiation.

The specific objectives of this project are to:

- Develop and build a horizontal nanobeam system to act as a test bed for the development of a vertical nanobeam.
- Design, build, commission and use a vertical focused scanning ion nanobeam for applications such as radiation biology, (i.e. radiation induced cell signalling, DNA damage and repair), using a range of ions; hydrogen to argon.
- Within the same facility, develop *in vitro* elemental ion beam analysis of living cells.

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0168-583X/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.nimb.2007.01.281

- Using data from nanobeam studies develop further a comprehensive mechanistic mathematical model of the response of cells and tissues to ionising radiation for the design and optimization of individualised radiotherapy treatment schedules [1].

2. Vertical beam line

The current GCI system uses collimation. The new Surrey/GCI vertical nanobeam will be focused and steered using electromagnetic fields so we can precisely target areas of <10 nm with single ions (*in vacuo*). The system will be designed so that it can run in either single ion or full current modes.

- The full current mode will be used for ion beam analysis, where a beam spot of typically ~100 nm will be employed to give a capability for trace element mapping.
- The single ion mode will allow the ions to be precisely positioned and targeted with a spatial resolution of <10 nm.

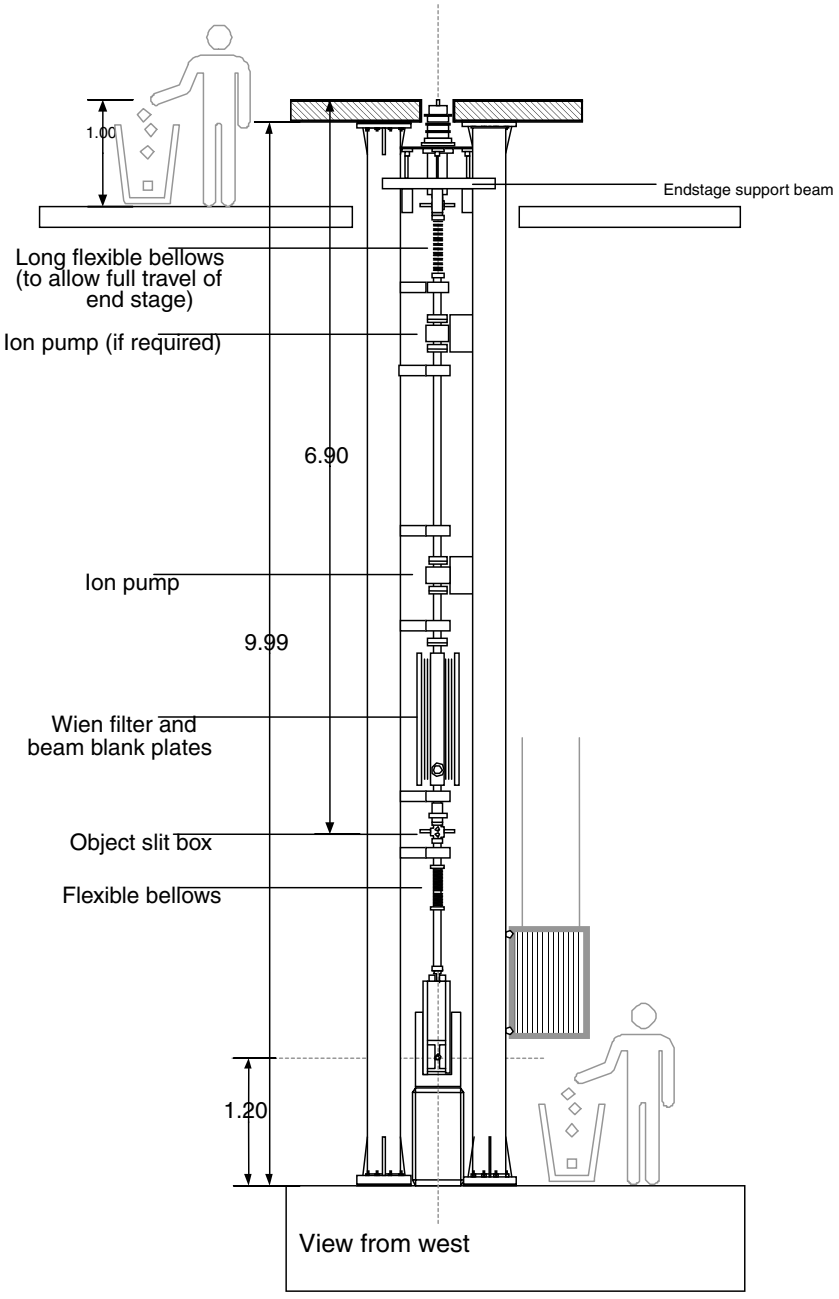

Fig. 1. Design of vertical beam line.

- Single ions will also be used to target cells outside the vacuum system, i.e. where they are maintained in appropriate physiological conditions. Here a reduced spatial resolution, will be available, limited by the inevitable 'beam scattering'.

Rapid targeted single ion positioning will enable the number of cells irradiated per second to be greatly increased. We estimate that, when fully developed, the facility will be capable of irradiating ~100,000 cells per hour. Complementary sample imaging techniques will of course need to be developed, but the intention is to operate under conditions where the beam positioning is not the limiting factor in achieving high throughput targeting accuracy. Ultimately three-dimensional and functional (i.e. molecular) imaging methods will be necessary to fully utilise the performance achievable with this type of nanobeam.

The design for the new vertical nanobeam is shown in Fig. 1. The nanobeam will use the state of the art 2 MV high voltage tandetron accelerator which was installed at the University of Surrey in 2001. In addition to protons and helium, this machine is also capable of supplying heavy ion beams (e.g. O, F, C, Ne, Ar, Xe and Au) and ions up to the mass of Ar are expected to be available for the vertical nanobeam. There is a compromise here between the size of the bending magnet (bending radius 0.75 m) at the base of the tower, the height of the tower and therefore the cost of the tower and the anticipated use for heavier ion species. The maximum ion rigidity in the vertical column will be around 20 MeVamu/q^2, which assuming that we can strip to at least a charge state of 5 will allow us to use ions of the full energy available from our 2 MV tandem up to an atomic mass of around 40 (e.g. 12 MeV $^{40}Ca^{5+}$).

The ion focusing system will be based on a compact triplet of magnetic quadrupoles using the proven OM-52 quadrupoles [2,3]. These lenses have a small physical size and mass, making them suitable for mounting in a vertical orientation yet achieve a high focusing strength through the use of a small (8 mm) bore diameter and a pole extension. The overall length of the final focusing system (object to sample) is 6 m and the image plane is approximately 10 m above the ground. The focusing system is standard apart from the provision to insert a high resolution Wien filter after the object apertures in order to deflect slit scattered particles with reduced energy and so improve the halo on the final beam spot. This component will be prototyped as part of the ongoing development of the horizontal nanobeam at Surrey. The Wien filter will also contain the plates for fast single ion switching.

The challenge of suspending a high resolution microbeam system in this orientation will be met by supporting the final optical table on a tripod of sand-filled steel columns firmly attached to the massive piled concrete foundation slab of the new building. Vibration surveys carried out on the site suggest that this will attenuate the majority of external ground vibration. The tripod and the optical table will be completely isolated from the rest of the building structure so that internally generated vibrations will not be transmitted to the beam. The components of the beam tube will be suspended from brackets attached to one of the columns and the final lens will be mounted on precision motorised jacks permitting easy adjustment of the lens to sample position.

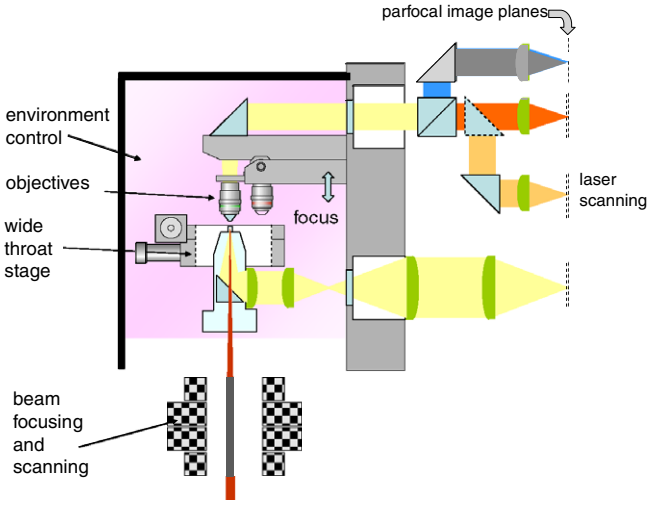

Fig. 2. Design of optical detection end station.

The beam line will incorporate a high degree of automation in order to minimise the need for frequent access to the components on the column. Installation and non-routine access will be provided by a cradle which can be suspended from any of the columns and will allow access to all parts of the beam line.

3. The cell irradiation 'end-station'

The development of an end-station to support, find and align cells at the correct location for irradiation will build on the experience of the GCI Group, who have already established robust methods in their facility [4].

The GCI group are also in the final stages of commissioning a second X-ray microprobe which takes full advantage of recent developments in the performance of desktop computers and electronic imaging hardware and we would anticipate implementing similar state-of-the-art capability on the new facility at Surrey. Particular attention will be given to environmental control and to enabling off-line (trans-illuminating) cell imaging. Fig. 2 shows a schematic of the optical detection end station.

4. Models and applications

We anticipate many research applications for this new facility. For instance, precise data can be acquired concerning mechanisms of radiation induced cell death and DNA damage and repair which can be used to inform and validate mathematical models. Such models can be used to

optimise radiotherapy planning using both conventional photon as well as, eventually light ions. Experimental data on normal tissue and tumour cell response may eventually be incorporated with imaging systems to maximise both normal tumour killing and normal tissue sparing.

5. Concluding comments

A new vertical nanobeam is to be built at the Ion Beam Centre at the University of Surrey in a new collaborative venture with GCI. The beam will be focussed and scanned into an end station system capable of both internal, *in vacuo* and externalised operation. Detectors for ion beam analysis will be present as well as microscopy and imaging for precise positioning of the ions in both full current and single ion modes. The system is primarily designed to irradiate and analyse biological samples, but other exciting applications are also possible.

Acknowledgements

The authors would like to thank the Wolfson Foundation, the UK Engineering and Physical Sciences Research Council and the European Union (Marie Curie Research Training Network Cellion MCRTN-CT-2003-503923) for their support of this work.

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