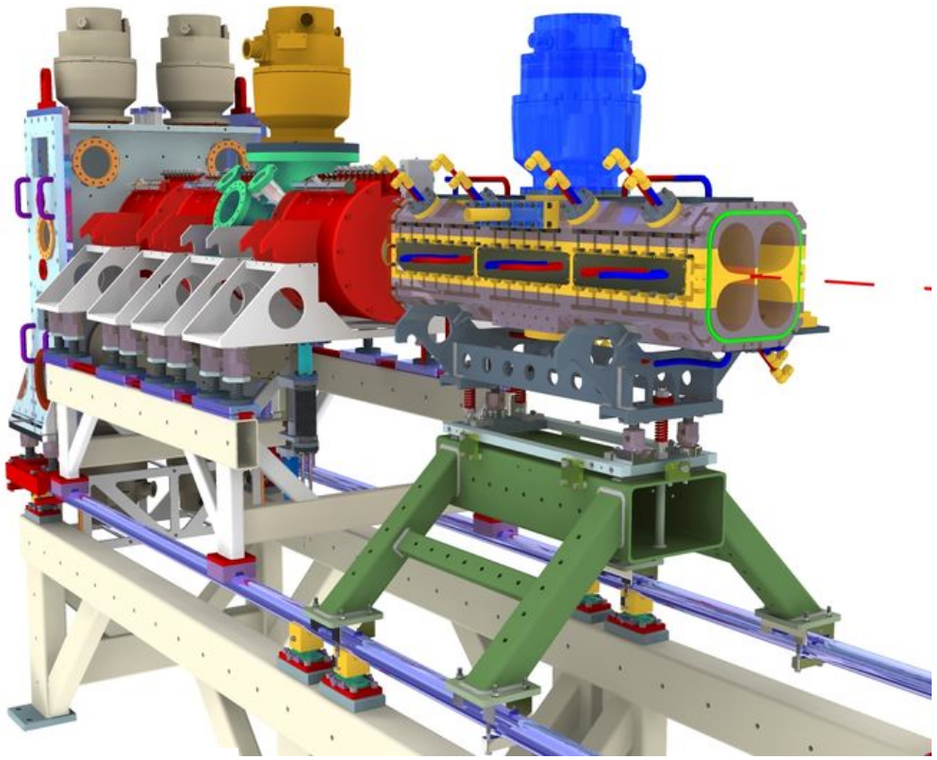
Science & Technology Facilities Council



Outline

- ISIS facility and medical research
- FETS overview and capability
- FFAGs for low energy neutrons
- HiPSTER: material irradiation
- Boron neutron capture therapy
- Isotope production

Applications of FETS

*Stephen Gibson**
on behalf of FETS with thanks to Alan Letchford, Juergen Pozimski, John Thomason, Chris Prior and Chris Densham.

Proton Accelerators for Science and Innovation Workshop
11-13th November 2015
Fermi National Accelerator Laboratory

* *stephen.gibson@rhul.ac.uk*

Some caveats

- This talk might better be entitled "Potential applications of FETS".
- We have received much interest in the high power beam that will be produced by FETS and several interested experts have offered proposals in recent years.
- The definitive plan has yet to be hatched: we are currently exploring the options to exploit the unique FETS facility in future, after the project to complete and commission the accelerator ends in 2017.
- The aim of this talk is to present a selection of the various options to stimulate discussion, collaboration, perhaps further ideas…
- Given the topic of this WG3 session, the emphasis will be on medical applications, with a briefer overview of others.

ISIS facility and medical research

- The ISIS pulsed neutron and muon source is a world-leading centre for research in the physical and life sciences.
  - Supports an international community of >3000 scientists from many fields.
  - Neutron scattering is a vital tool for nanoscale materials research.
- ISIS facility today:
  - 70 MeV H- linac
  - 800 MeV RCS
  - 0.2-0.25 ms pulse length
  - 20mA peak, 50 Hz rep rate.
  - <20 kW. Avg beam power

Medical research at ISIS

- A brief skim through the highlights in the last few ISIS annual reviews indicates the breadth of research into biomedicine and pharmaceuticals:

Polymorphism in cisplatin anticancer drug

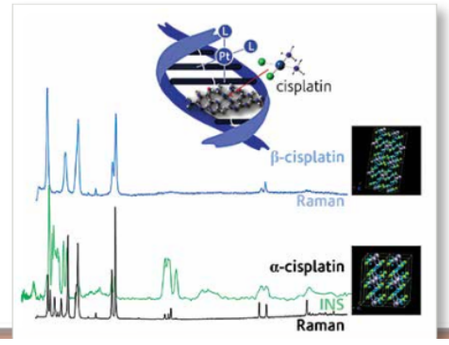
MPM Marques, R Valero (University of Coimbra, Portugal), SF Parker, J Tomkinson (ISIS) and LAE Batista de Carvalho (University of Coimbra, Portugal).

Instrument: Tosca **Support**: Portuguese Foundation for Science and Technology– PEst-OE/QUI/UI0070/2011, European Commission under the 7th Framework Programme through the Key Action: Strengthening the European Research Area, Research Infrastructures – Contract nº: CP-CSA_INFRA-2008-1.1.1 Number 226507-NMI3.

Cisplatin (cis-$(NH_3)_2PtCl_2$) is one of the most widely used anticancer agents, particularly towards testicular, head and neck tumours. Polymorphism, the ability to exist in more than one crystal form, is a key issue in pharmaceutical science since equilibrium between distinct polymorphs may affect the drug´s properties and therapeutic effect. Cisplatin´s polymorphic equilibrium between the two known alpha and beta species was elucidated by simultaneous Raman and INS spectroscopies, coupled to theoretical approaches. Alpha is predominant at very low temperatures (below ca. –170ºC), while beta occurs at room temperature and higher. Both species coexist at intermediate temperatures, their relative population depending on the sample´s history and follows a marked hysteresis. Simultaneous INS and Raman experiments, under exactly the same conditions, allowed a clear picture of cisplatin´s polymorphic behaviour to be attained. Elucidation of the polymorphic equilibrium of this extensively used chemotherapy drug is paramount for optimising its pharmaceutical preparation, as well as transport and storage conditions.

Contact: pmc@ci.uc.pt
Further Reading: MPM Marques *et al.*, J.Phys.Chem. B **117** (2013) 6421.

Alpha and beta cisplatin polymorphs (INS and Raman spectra) and cisplatin-DNA interaction.



Tumours and time of flight: a promising bio-nanocomposite for the treatment of breast cancer

ML Martins (University of Copenhagen), MJ Saeki (UNESP), MTF Telling (ISIS), JPRLL Parra (UNESP), RI Smith (ISIS), HN Bordallo (University of Copenhagen).

Instrument: Polaris **Support**: CAPES, FAPESP, DanScatt and the Science Without Borders

Breast cancer is the most common cancer in women in the UK. It tends to spread to different parts of the body, in particular the bones. By developing a bio-nanocomposite – formed by first encapsulating magnetic nanoparticles in a polymeric shell and then impregnating the surface with apatite nanocrystals (a main component of bone tissue) – this affinity can be used to fight the disease. Antitumour drugs can be further incorporated onto the carrier. The benefit of this magnetic delivery technique is that the drug carrier can be guided directly to the breast cancer site by external magnetic fields. It will then bind to tumour cells alone, due to apatite inclusions, leading to increased uptake of the drug at the target site, with reduced side effects. The properties of this magnetic nanoparticle-based targeting system, such as particle size and amount of apatite modification, can all be probed using neutron techniques, the results of which will lead to further device optimisation and, ultimately, more efficient drug delivery.

Contact: bordallo@nbi.ku.dk
Further Reading: Martins, M.L. *et al.*, Journal of Alloys and Compounds **584** (2014) 514–519.

Penicillin's auto-catalytic self-activation

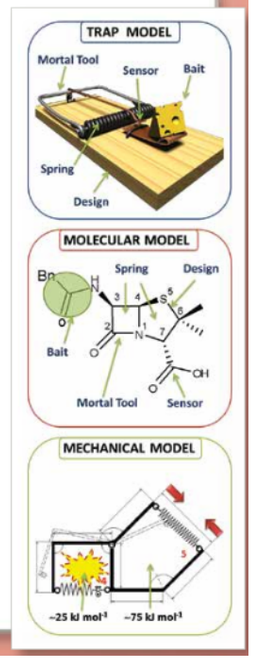
Z Mucsi (University of Toronto), GA Chass (Queen Mary University of London), P Ábrányi-Balogh (University of Szeged), B Jójárt (University of Szeged), DC Fang (Beijing Normal University), AJ Ramirez-Cuesta (ISIS), B Viskolcz (University of Szeged) and IG Csizmadia (University of Toronto).

Instrument: Tosca **Support**: EPSRC, UK (EP/H030077/1 & EP/H030077/2), Royal Society, UK (IE120096), National Natural Science Foundation of China (21073016), TÁMOP-4.2.2.A-11/1/ KONV-2012-0047, Hungary

Although penicillin is recognised as one of the great discoveries of the 2nd millennium, the appearance of resistant bacteria has significantly reduced its utility and viability. Continued characterisation of its structure and mechanism aids in the understanding and design of novel antibiotics with desired effects and great precision. Since its discovery by Fleming in 1928 and subsequent mass production, it has remained a mystery as to how penicillin escapes the body's hydrolytic effects, while maintaining its ability to hone-in on and disable the bacterial transpeptidase enzyme, efficiently blocking cell wall synthesis. To resolve this ability to switch from a non-active to a highly-reactive form, the dynamic structure-activity relationship of penicillin has been investigated by inelastic neutron spectroscopy, reaction kinetics, NMR and multi-scale theoretical modeling (QM/MM, DFT and post-HF ab initio). Results show that by a self-activating physiological pH-dependent two-step proton-mediated process, penicillin changes geometry to activate its irreversibly reactive acylation, facilitated by systemic intramolecular energy management and cooperative vibrations. This dynamic mechanism is confirmed by the 1st characterisation of a natural antibiotic by neutrons.

Contact: g.chass@qmul.ac.uk
Further Reading: Z Mucsi, *et al.*, Phys. Chem. Chem. Phys., **15** (2013) 20447-20455.

Trap composed of bait (to entice prey), sensor (detect prey), spring (energy reservoir) and mortal tool (kill prey). Components and systemic aspects are analogously reflected in penicillin's molecular structure.



Construction and physiochemical characterisation of a multi-composite, potential oral vaccine delivery system (VDS)

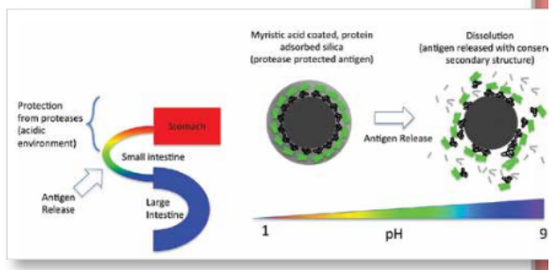
MW Pettit, PDR Dyer, PC Griffiths, F Pullen, B Alexander, B Cattoz (University of Greenwich), RK Heenan, SM King, (ISIS), UKR Schweins (Institut Laue - Langevin), SR Wicks, JC Mitchell, SCW Richardson (University of Greenwich).

Instruments: Sandals and LOQ **Support**: University of Greenwich and STFC

This prize-winning, interdisciplinary research highlights small angle neutron scattering studies undertaken at ISIS, characterising a potential oral vaccine delivery system. This system was initially proposed for use in livestock, impacting upon food security. Through careful design, there exists the potential for this technology to also translate into an oral vaccination system for people. This technology has the capacity to make an impact through the application of synthetic biology, that is, designing antigens that can be delivered to different compartments within the body, with world-class analytics (such as neutron scattering). This high degree of analytical precision helps tell us, at the nano-scale, if what we have made is what we think it is, a process critical for success! Surprisingly, the protein stabilisation involved in the vaccine delivery system may also have the capacity to reduce the cost of vaccination, as it may help negate the need for vaccines to be stored and shipped at ultra-low temperatures.

Contact: S.C.W.Richardson@Greenwich.ac.uk
Further Reading: Pettit *et al.*, International Journal of Pharmaceutics **468** (2014) 264–271.

Myristic acid coated, antigen-adsorbed silica was stable at low pH (i.e. in the stomach). At a higher pH the antigen was released (distal to the stomach).



Medical research at ISIS

Tackling the Great Wall of *E. Coli*

Instrument: INTER

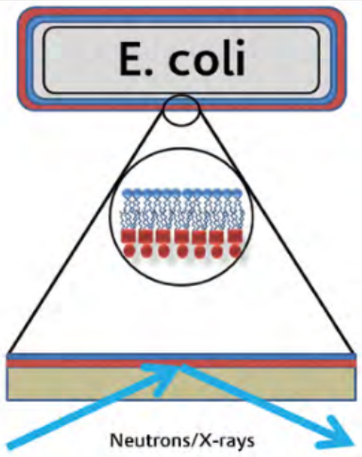
LA Clifton (ISIS) , AP Le Brun, SA Holt, (ANSTO) JH Lakey (Newcastle)

Support for research: Wellcome Trust

E. coli & Salmonella food poisoning, bubonic plague, bacterial meningitis, and Legionnaires' disease are all caused by Gram negative bacteria (GNB) which possess a characteristic 'outer' membrane. This outer membrane is a 5 nm thick bilayer with different molecules in each layer making it unusually asymmetric. The outer layer contains a molecule unique to GNB called LPS which presents a formidable barrier and an additional way to develop antibiotic resistance. Neutrons and X-rays can be used to investigate this structure but individual bacteria are too small to give a good signal in either technique. Model outer membranes can be built in the laboratory which can then be tested with antibiotics and other drugs. This study has shown that suitable asymmetric layers necessary for a useful model can be constructed and their molecular structure determined accurately. It is now possible to understand how this barrier to antibiotics is stabilised and how we might overcome it in the clinic.

Further reading: AP Le Brun, *et al*, Biomacromolecules 2013 Jun 10;14(6):2014-22.

Contact: JH Lakey, Jeremy.Lakey@ncl.ac.uk



By creating accurate models of bacterial outer membranes we can make them accessible to structural techniques and understand how they interact with antibiotics.

Finding the bacterial Achilles' heel

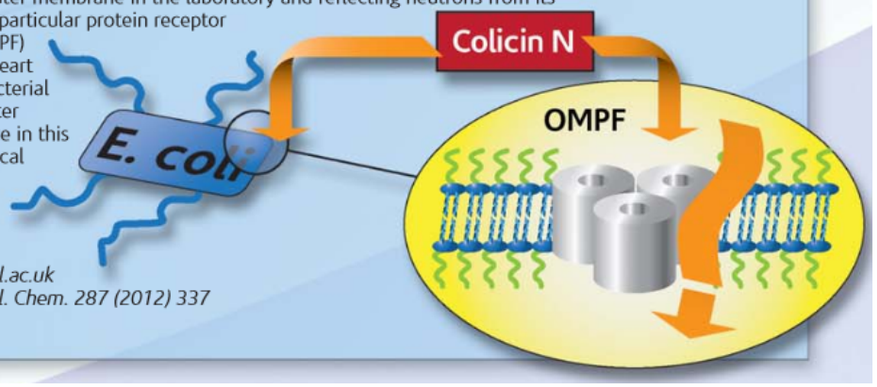
CL Johnson, AS Solovyova, H Ridley, JH Lakey, (Newcastle University), LA Clifton, JRP Webster, CJ Kinane (ISIS), P Callow (ILL), KL Weiss (ORNL), AP Le Brun, SA Holt (ANSTO)

Support for research: The Wellcome Trust

In the search for new antibiotics, we are studying the toxic molecules deployed by bacteria against each other in their battle for resources. Colicins are proteins used by *Escherichia coli* to kill closely related competing bacteria. They have the amazing ability to evade the host defences which consist of a robust and normally impenetrable outer membrane.

To follow the journey of the colicin across this barrier, which is only 5 nm thick (~30,000 times thinner than a sheet of A4 paper), we needed special techniques and neutron scattering gave us critical insights. By recreating the bacterial outer membrane in the laboratory and reflecting neutrons from its surface, we were able to show that a particular protein receptor called Outer membrane protein F (OMPF) allowed the colicin to penetrate the heart of the membrane. This may be the bacterial Achilles' heel – a weak spot in the outer membrane barrier. Neutrons are unique in this ability to see through complex biological structures and differentiate between their components.

The E. coli outer membrane is a complex mixture of lipids and proteins. Neutron scattering showed that colicin N penetrates at the OmpF-Lipid boundary.



***Contact**: Prof J Lakey, jeremy.lakey@ncl.ac.uk*
***Further reading**: LA Clifton et al., J. Biol. Chem. 287 (2012) 337*

Damage to lung surfactant following exposure to the environmental pollutant ozone

Instrument: SURF INTER

KC Thompson, JM Hemming, J Szyroka (Birkbeck), AR Rennie (Uppsala), T Arnold (Diamond Light Source), M Skoda (ISIS)

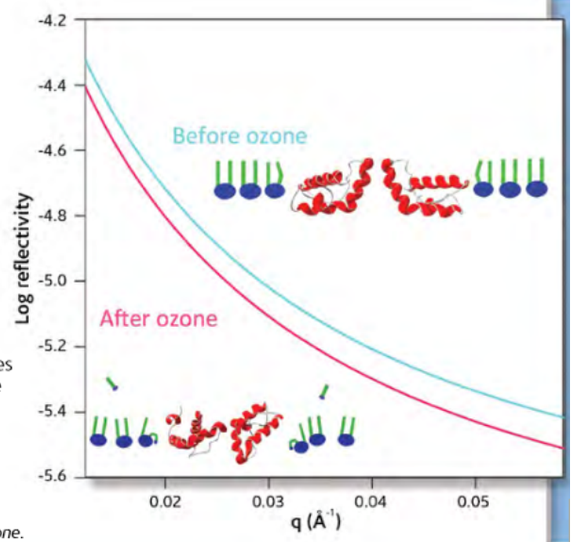
Support for research: Wellcome Trust

The interface of the lung with inhaled air is wet, with the presence of a layer of surfactant containing a mixture of both lipids and proteins on the wet surface, which are essential to maintain a low surface tension. This prevents acute respiratory distress, a potentially fatal condition.

The surfactant layer is directly exposed to atmospheric air and pollutants such as ozone. During episodes of high pollution on sunny days in city centres, ambient ozone levels frequently exceed air-quality limits. These ozone levels are directly linked to significantly increased death rates from respiratory failure. This study has exposed natural pig and sheep lung surfactant to low ozone levels and used neutron and x-ray reflection to follow changes to the structure of the air-water interface. The results show that the surfactant reacts rapidly with the ozone leading to a change in the surface tension, a slight reduction in the amount of material at the interface and a significant thinning of the surfactant layer.

Further reading: KC Thompson *et al*., Langmuir 29 (2013) 4594.

Contact: KC Thompson, k.thompson@bbk.ac.uk



Neutron reflection profiles before and after lung surfactant is exposed to ozone. Some lipid material is lost from the interface and the damaged film rearranges.

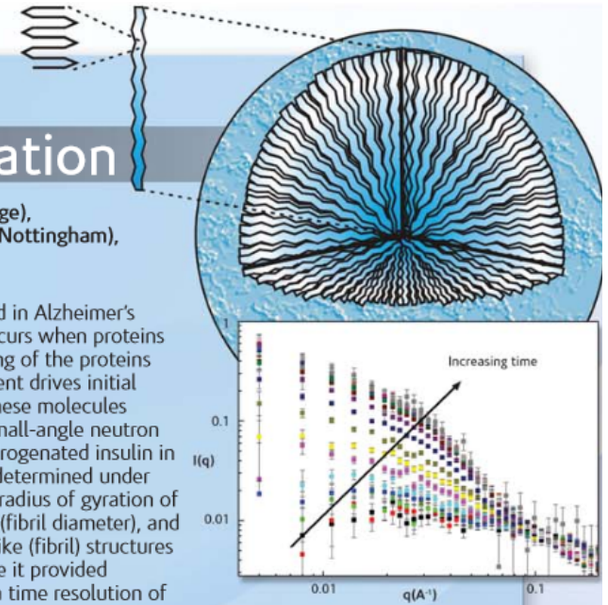
Early-stage kinetics of amyloid aggregate formation

MI Smith (University of Nottingham), V Fodera (University of Cambridge), AJ Parnell (University of Sheffield), JS Sharp, CJ Roberts (University of Nottingham), AM Donald (University of Cambridge), S Rogers (ISIS)

Support for research: EPSRC Grant EP/H004939/1

Amyloid fibrils and spherulites are protein aggregates that are implicated in Alzheimer's disease, Parkinson's disease, and Type-II diabetes. Amyloid formation occurs when proteins denature under certain protein-specific solution conditions. The unfolding of the proteins and exposure of hydrophobic molecular cores to the aqueous environment drives initial aggregation. Internal structural rearrangements can then occur within these molecules resulting in the formation of ß-sheet-rich fibrils. This experiment used small-angle neutron scattering (SANS) to study the early-stage kinetics of aggregation of hydrogenated insulin in D_2O-based solvents. Changes in the size and shape of aggregates were determined under conditions where fibrils and spherulites form. The results show that the radius of gyration of scatterers varies from ~1.5 nm (protein-molecule dimensions) to ~7 nm (fibril diameter), and that the shape of the growing aggregates changes from spheres to rod-like (fibril) structures on time scales of a few hours. SANS was an excellent technique because it provided information about aggregates over a broad range of length scales with a time resolution of minutes, and eliminated potential concerns regarding radiation damage to the samples.

***Contact**: Dr JS Sharp, james.sharp@nottingham.ac.uk*
***Further reading**: MI Smith et al., Colloid Surface B 89 (2012) 216; Soft Matter 8 (2012) 3751*



***Top**: Amyloid spherulites are formed when ß-sheet-rich amyloid fibrils grow radially from a central core.*

***Bottom**: SANS data taken during aggregation.*

Medical research at ISIS

How neutrons can improve orthopaedic implants

R Ahmed (Heriot-Watt University), **AM Paradowska** (STFC), **M Fitzpatrick** (Open University)

Contact:

Dr R Ahmed,
R.Ahmed@hw.ac.uk

Further reading:

R Ahmed et al., Mater Sci Forum 652 (2010) 309

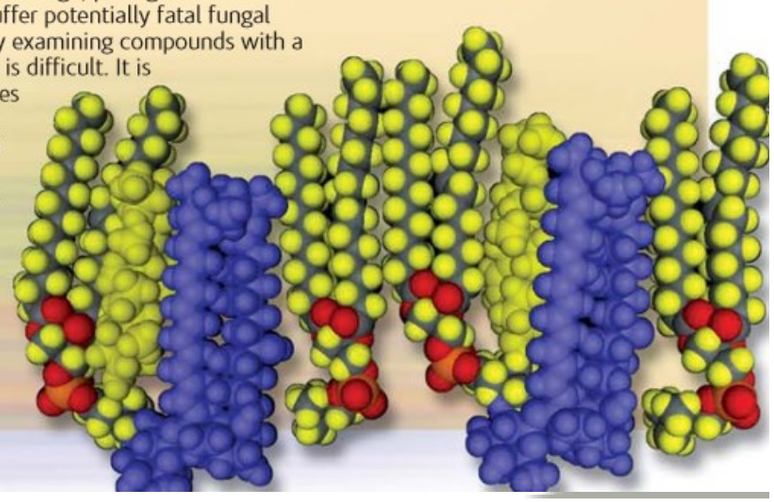
The use of surface coatings in orthopaedic and dental implants has significantly improved the quality of human life. Modern implants provide improved recovery times and lower implant rejection rates. Early implants were expensive, and often failed because the bonding between the implant and the bone, a process known as osteo-integration, was poor. Several designs have been formulated to date but many failed to achieve a strong enough bond. A solution involves coating the metal with a layer of hydroxyapatite (HA). Hydroxyapatite forms almost three-quarters of natural bone. Coating the metal first with HA gives a stronger metal-bone bond. Even with this improvement, one in five implants can still fail. One of the main reasons of failure is the residual stress developed at the metal-HA interface. Neutrons offer significant advantages to analyse this critical interface, enabling measurements to be made in-depth and non-destructively. This unique capability enables us to improve our understanding of how HA bonds to the metal and bone.

How does the antibiotic amphotericin work?

F Foglia, A Dabkowska, MJ Lawrence, DJ Barlow (King's College London), R Barker (University of Bath), AE Terry, SE Rogers, AV Hughes, JRP Webster (ISIS)

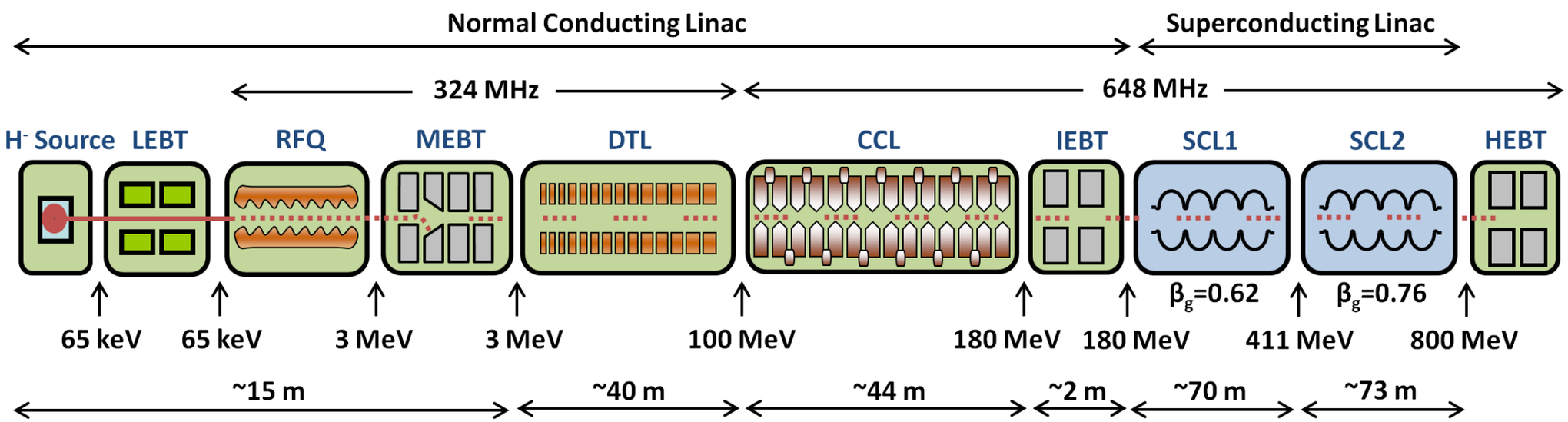
Contact: Dr DJ Barlow, dave.Barlow@kcl.ac.uk
Further reading: F Foglia et al., Biochim. Biophys. Acta 1808 (2011) 1574

Amphotericin has been the first line of defence against fungal infections since the mid-1950s. Unfortunately, resistance to this drug is beginning to emerge, posing serious problems for AIDS and chemotherapy patients who often suffer potentially fatal fungal infections. Normally, replacement drugs would be sought by examining compounds with a similar mechanism of action. For amphotericin, though, this is difficult. It is established that the drug punches holes in cells, which makes them leaky and so causes them to die, but how it does this, and why it causes more damage to fungal cells than human cells remains unclear. Neutron reflectivity and small-angle scattering studies have been performed to study the effects of amphotericin on model human and fungal cell membranes, to find out why the drug is so selective. Rather surprisingly, the drug is found to insert into both fungal and human cell membranes but the neutron studies also clearly show that it perturbs these two types of membranes in markedly different ways.



Molecular model of a lipid monolayer showing the fungal sterol ergosterol (yellow) interacting with the inserted antibiotic amphotericin (blue).

Motivation for FETS



- FETS was original conceived as a test stand for the front end of an ISIS upgrade, to demonstrate the technologies required for a high power proton driver. Main objectives:
  - Generation of 3 MeV high-power H- beam, with perfect chopping:
  - High power means 20 kW @ 3MeV, or 1 MW at 180 MeV.
- FETS is at RAL due to the infrastructure available, but the technology is generic with many potential applications.

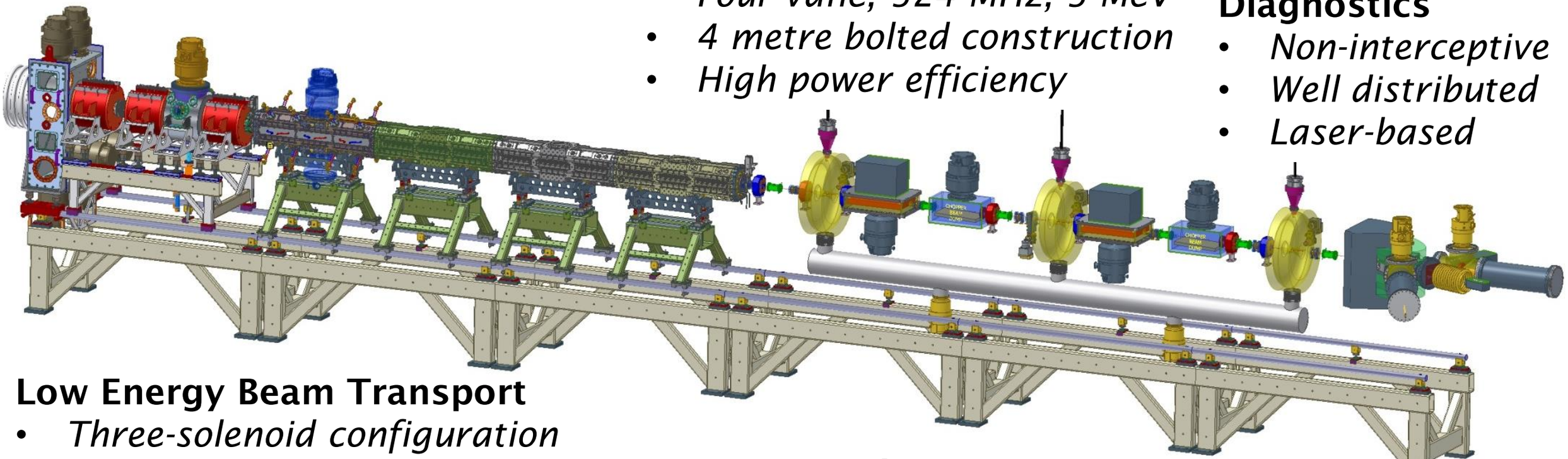
FETS overview

For a full overview please see Alan Letchford's talk in WG1

High brightness H^- ion source
- *4 kW peak-power arc discharge*
- *60 mA, 0.25 π mm mrad beam*
- *2 ms, 50 Hz pulsed operation*

Radio Frequency Quadrupole
- *Four-vane, 324 MHz, 3 MeV*
- *4 metre bolted construction*
- *High power efficiency*

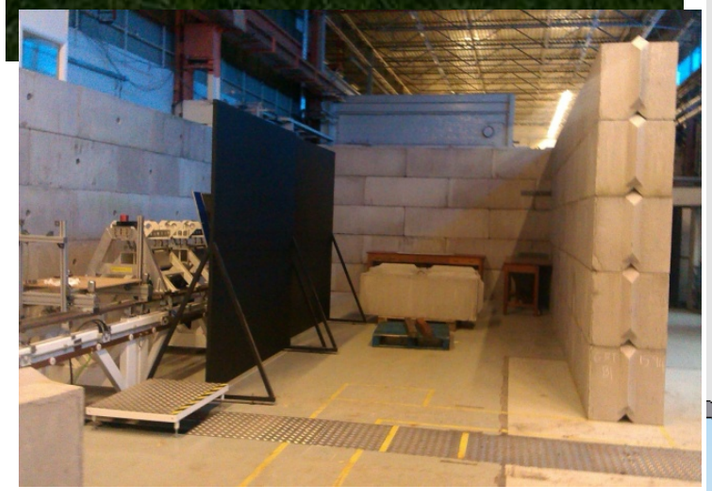
Diagnostics
- *Non-interceptive*
- *Well distributed*
- *Laser-based*

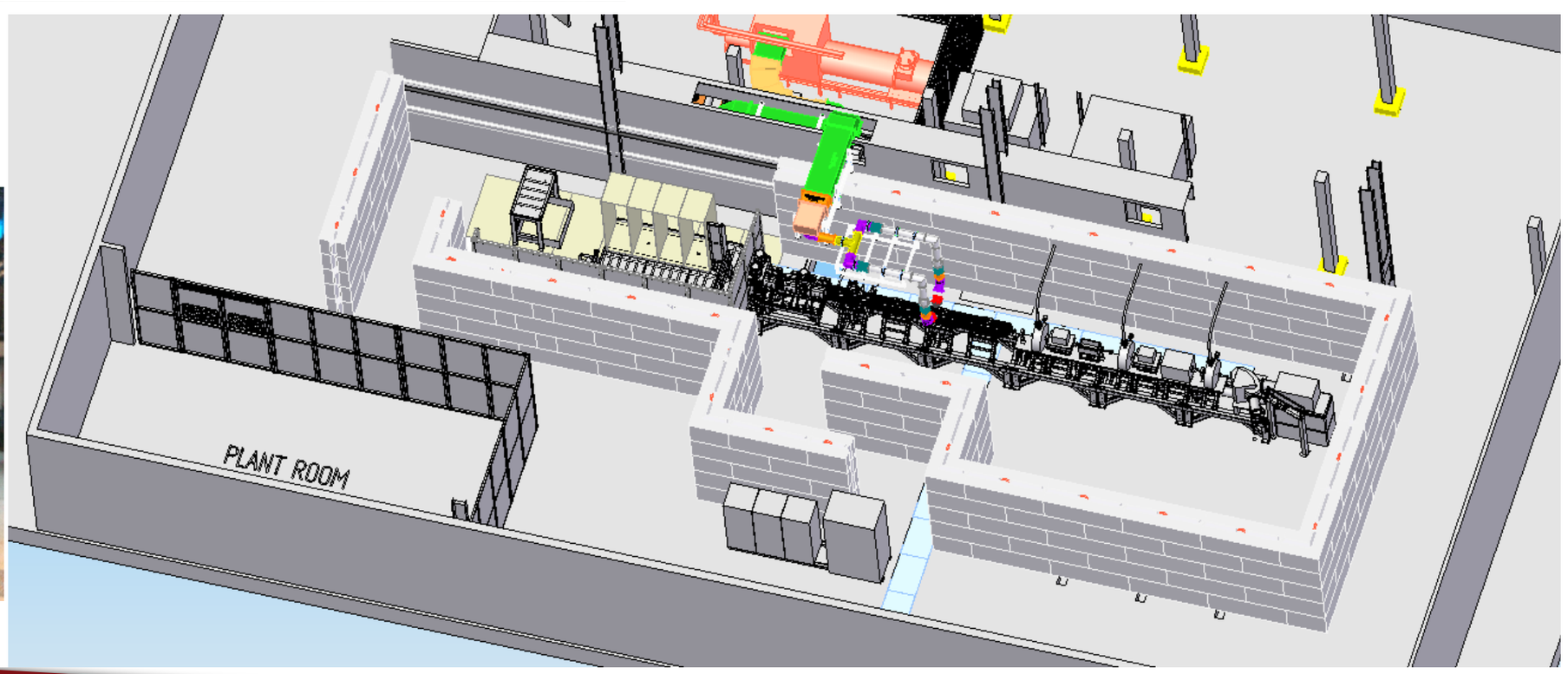


Low Energy Beam Transport
- *Three-solenoid configuration*
- *Space-charge neutralisation*
- *5600 Ls^{-1} total pumping speed*

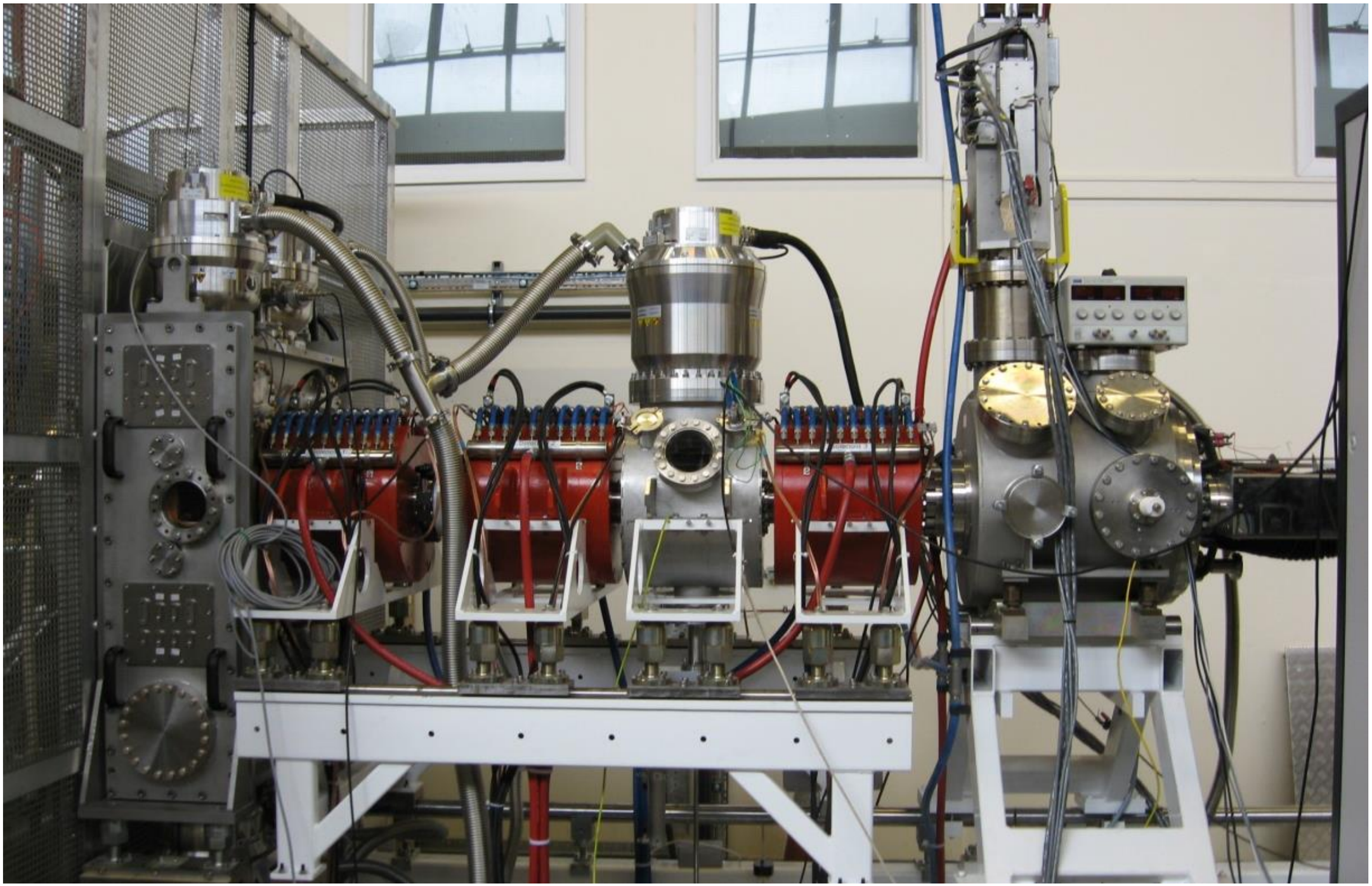
Medium Energy Beam Transport
- *Re-buncher cavities and EM quads*
- *Novel 'fast-slow' perfect chopping*
- *Low emittance growth*

FETS housed at RAL



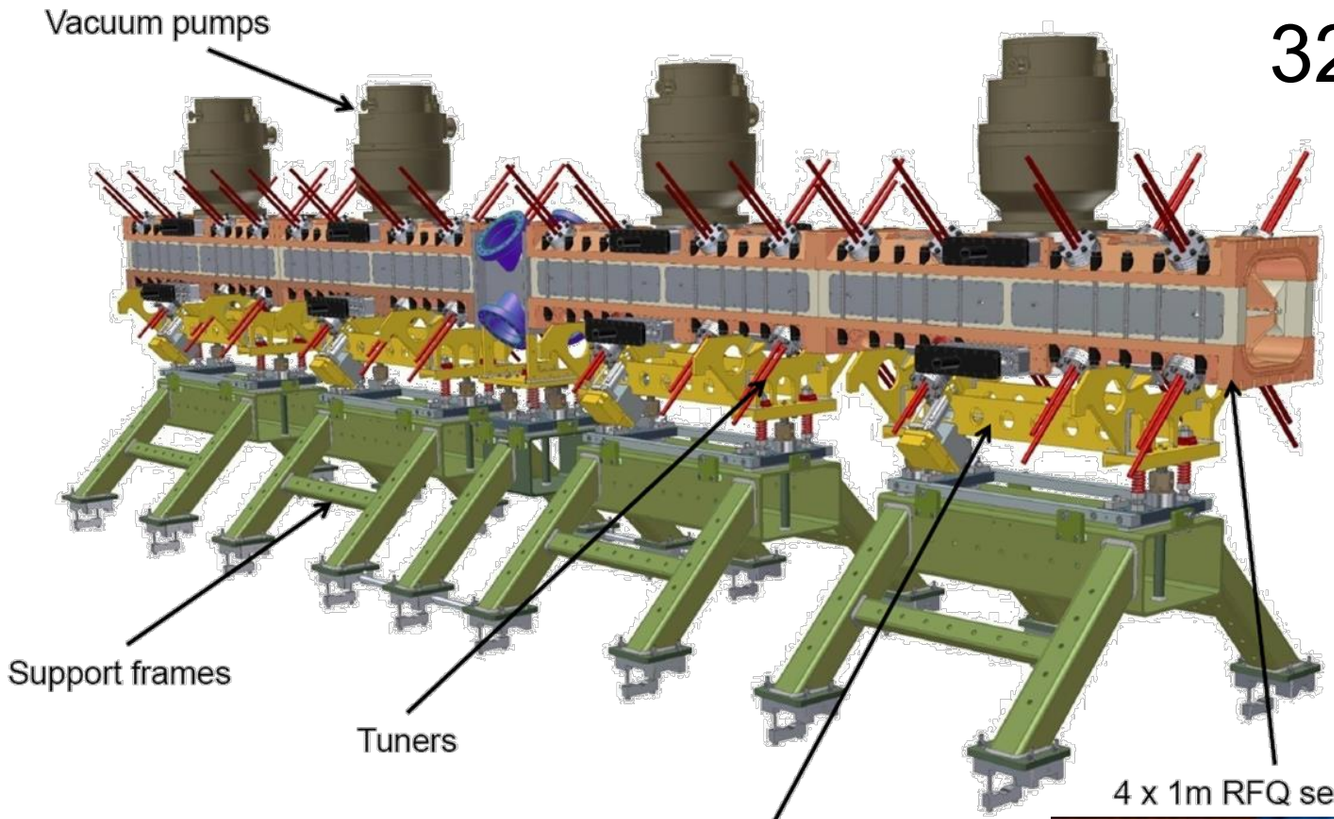


Low Energy Beam Transport

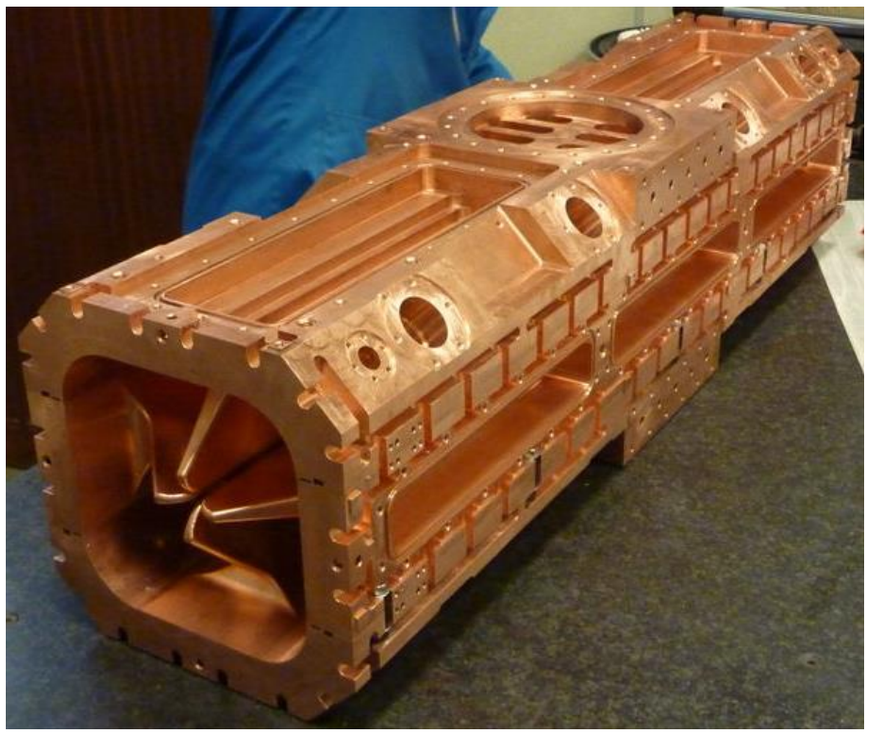


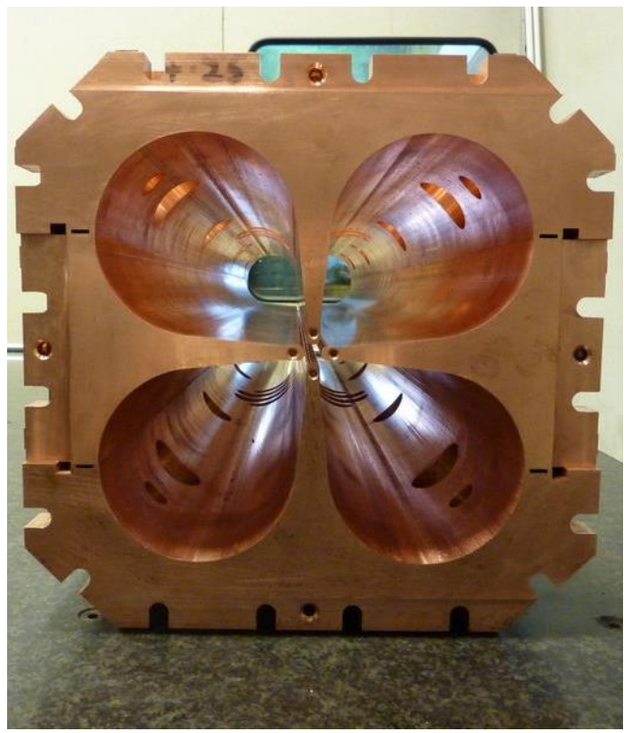
The FETS RFQ

324 MHz, 3 MeV, 4 vane, 4m long



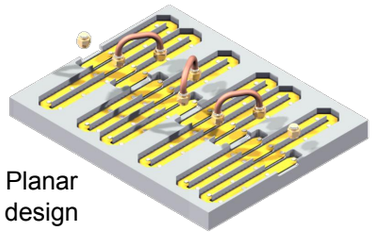
4 x 1m RFQ sections





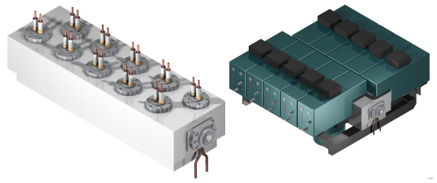
MEBT Elements

3 rebunching cavities



Planar design

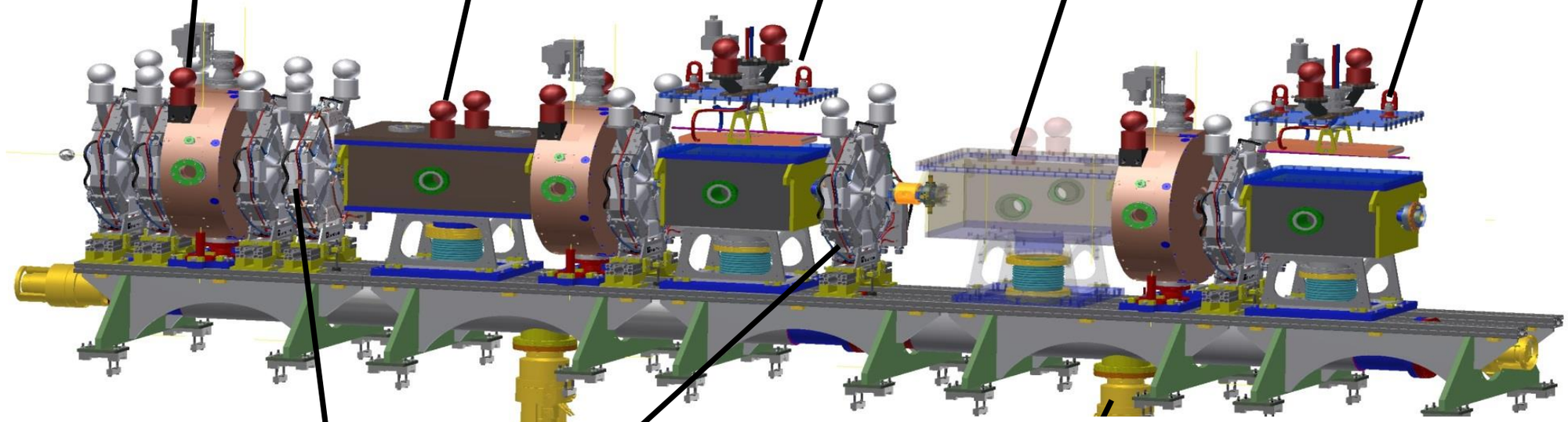
Fast chopper



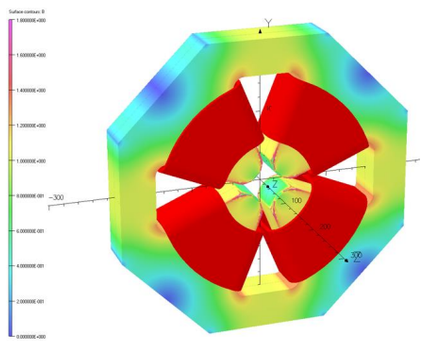
Fast chopper beam dump

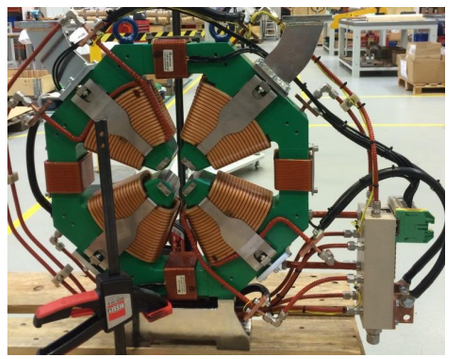
Slow chopper

Slow chopper beam dump

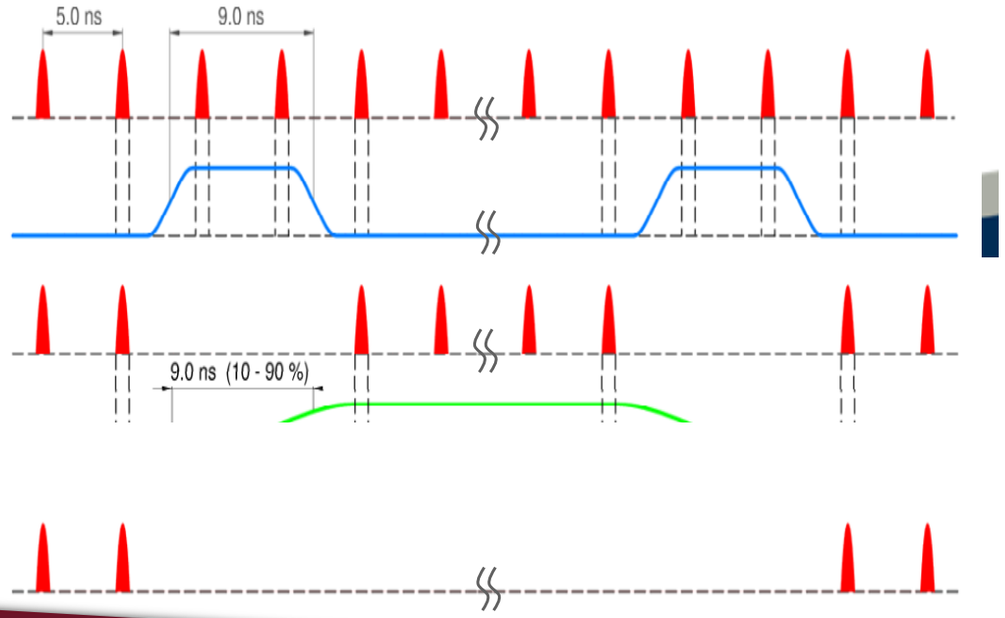


7 small bore quads

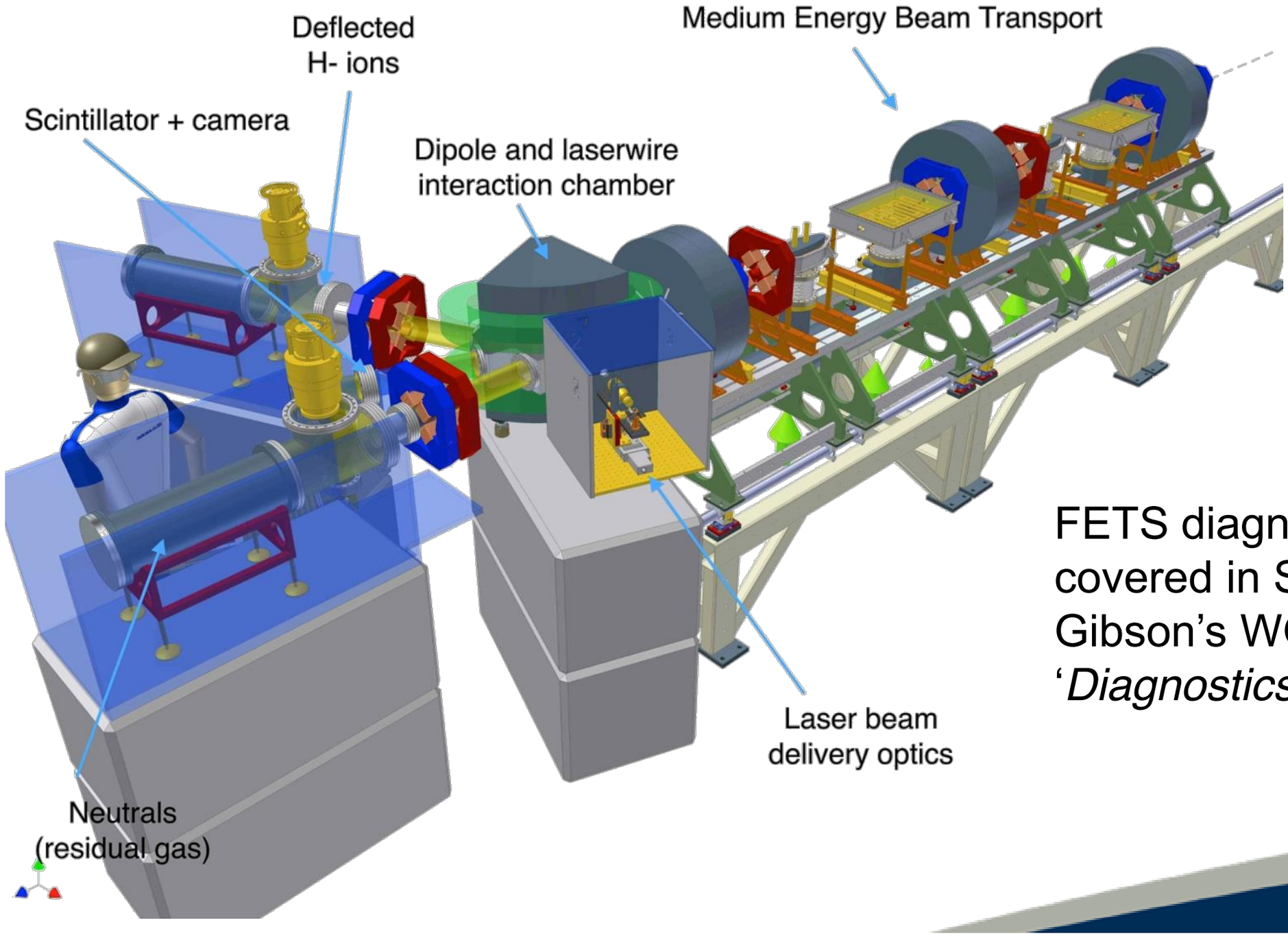




‘Fast-slow’ chopping scheme:



Laserwire diagnostics



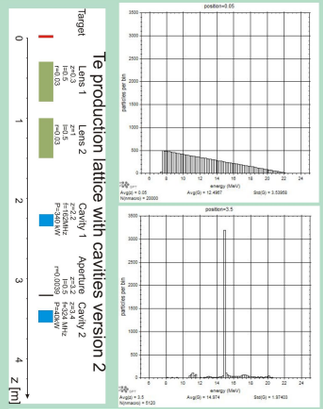
FETS diagnostics is covered in Stephen Gibson's WG1 talk '*Diagnostics in FETS*'

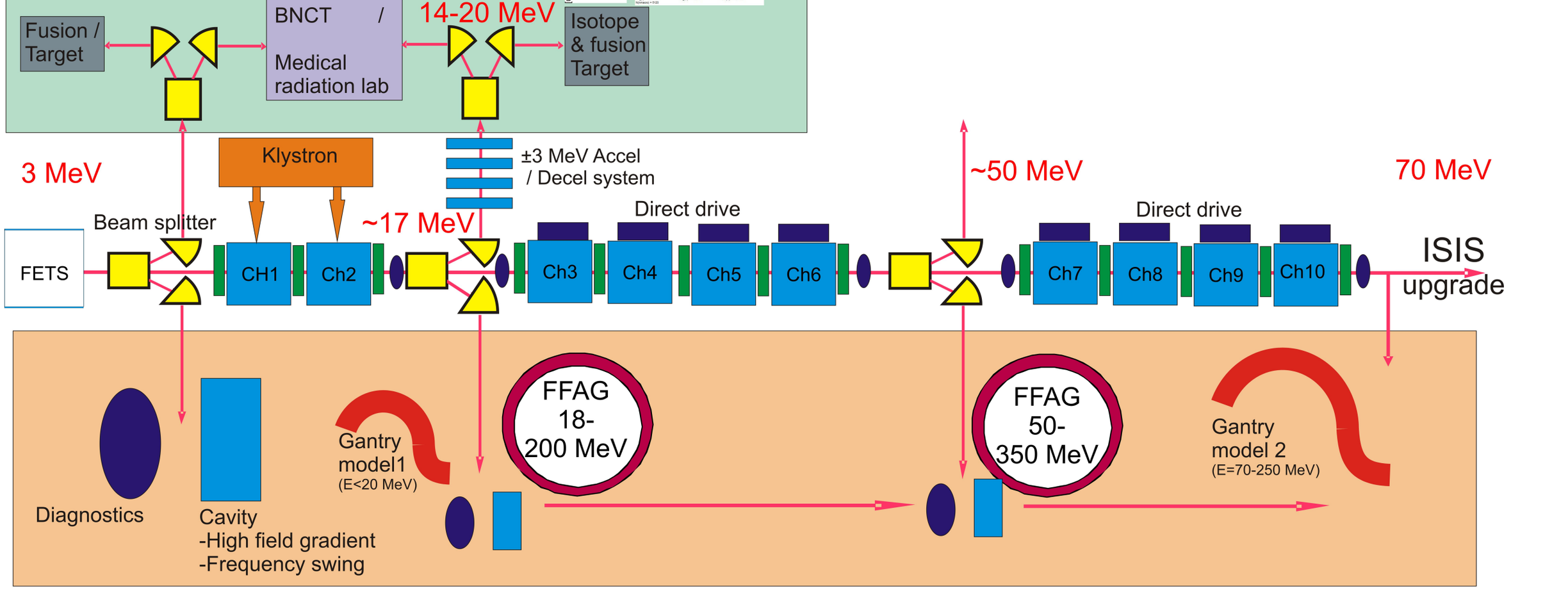
Previous proposals

- After commissioning FETS will offer a unique facility producing a low-energy high power proton beam, which could be interesting for a series of experiments and applications. Several topics considered so far:
  - Test of novel direct-drive cavity set-ups (solid state klystron – Siemens) on FETS;
  - High-power beam test of a CH cavity linac module reusing the available RF and delivering a 5-6 MeV beam;
  - High power target tests for BNCT, isotope and slow neutron production (at 5-6 MeV);
  - Extension of FETS to a 20 MeV linac and injection into a low energy proton FFAG to investigate injection and acceleration of space charge dominated proton beams as required for ADSR and other applications; and
  - Extension of FETS to 70 MeV (or above) using CH and SC spokes cavities as a replacement for the ISIS linac.

Possible layout of a proton centre

Application R&D
(partly) external funded





Accelerator R&D
(Proton Accelerator Alliance)

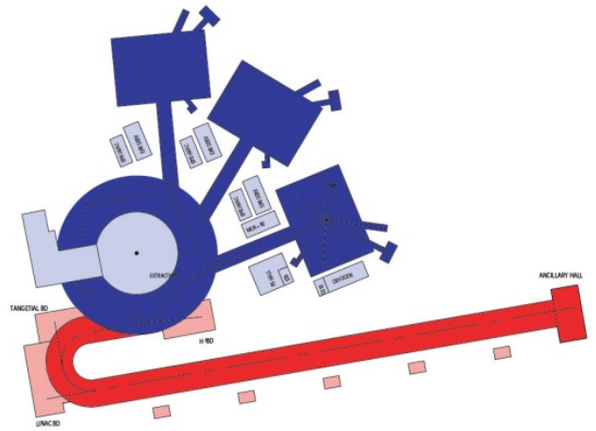
FFAG development for ISIS upgrade

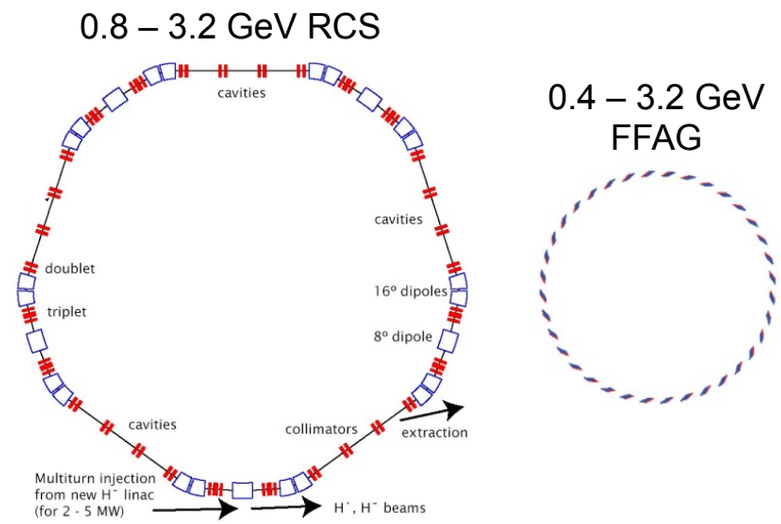
Please see J. Thomason's UK Vision & Capabilities talk, Wednesday's Plenary session

- Scenarios to upgrade the ISIS facility are being explored:

1) 1 – 2 MW upgrade, higher power option

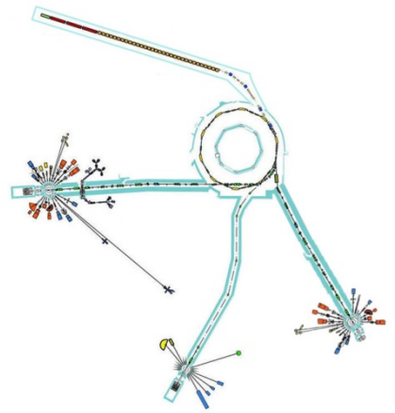
   - 0.8 GeV superconducting linac + 0.8 – 3.2 GeV RCS baseline.
   - FFAG may be a compact alternative (ASTeC intense beams group), lower injection energy, high efficiency & reliability – will it work at high intensity?
   - High energy linac + accumulator ring





2) 0.5 – 1 MW medium power option.

   - 180 MeV linac replacement.
   - Or house new accelerator in existing complex: might an FFAG be viable?



Compact neutron source (not ISIS-II)

Please see J. Thomason's UK Vision & Capabilities talk, Wednesday's Plenary session

A Fixed Field Alternating Gradient prototype for ISIS ?

- Recent interest in a compact short pulse option with a proton energy in the 14- 20 MeV range.
- Could be an extension of FETS in R8 at RAL, which is likely to be handed over to ISIS at the end of Programmes Office funding in 2017.
- A small <5m diameter FFAG has been designed by the ASTeC Intense Beams Group, that could accelerate FETS 3 MeV protons to the 14 - 20 MeV range.
  - Study high intensity beam dynamics to establish whether FFAGs are really a possibility for ISIS-II.
  - Prototype relevant components.
- Potential to demonstrate technology readiness for an ISIS upgrade.

HiPSTER: material irradiation

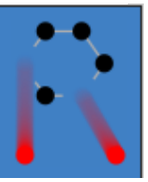
High Intensity Proton Source for Testing Effects of Radiation

Chris Densham, Tristan Davenne, Alan Letchford, Juergen Pozimski, Steve Roberts (Oxford/CCFE)

- Extension of FETS could provide a high-intensity (6mA, 3 MeV) materials irradiation facility.
- HIPSTER would be capable of studying:
  - Irradiation induced microstructural changes
  - – 'deep' (~25 micron), near-uniform radiation damage to moderate levels within reasonable timescales (up to ~100 dpa per annum)
  - High heat flux source (ref fusion divertor)
- Pulsed beam is good for accelerator materials testing, though a potential limitation for fusion / fission materials testing.
- Requires remote handling facilities and transfer of samples ot post-irradiation examination to e.g., the NNUF irradiation materials test facility at CCFE (Culham Centre for Fusion Energy).

RaDIATE Collaboration

Radiation Damage In Accelerator Target Environments



HiPSTER: material irradiation

Proposal submitted to UK National Nuclear Users Facility

High-Flux Proton Irradiation Facility

Proforma for additional equipment for the National Nuclear Users Facility.

FETS-HIPSTER- A High-Flux Proton Irradiation Facility

Names: Steve Roberts (Oxford/CCFE), Chris Densham (RAL), Alan Letchford (RAL), Juergen Pozimski (Imperial College/RAL)

Institution: University of Oxford, Department of Materials; STFC Rutherford Appleton Lab

High Intensity Proton Source for Testing Effects of Radiation (HIPSTER). Extension of the Front End Test Stand (FETS) proton source already funded and currently being commissioned at Rutherford Appleton Laboratory to provide a world-unique high-intensity (6mA, 3MeV / 18MeV) materials irradiation facility. FETS-HIPSTER would be capable of delivering deep (~25 micron), near-uniform radiation damage to moderate levels within reasonable timescales (up to ~100 dpa per annum) , enabling studies of irradiation induced microstructural changes and mechanical properties including hardening, embrittlement, creep, fatigue and stress-corrosion cracking, and thermal property changes such as thermal conductivity. The facility would also have applications in verifying and developing nucleonics codes and in thermal shock loading tests.

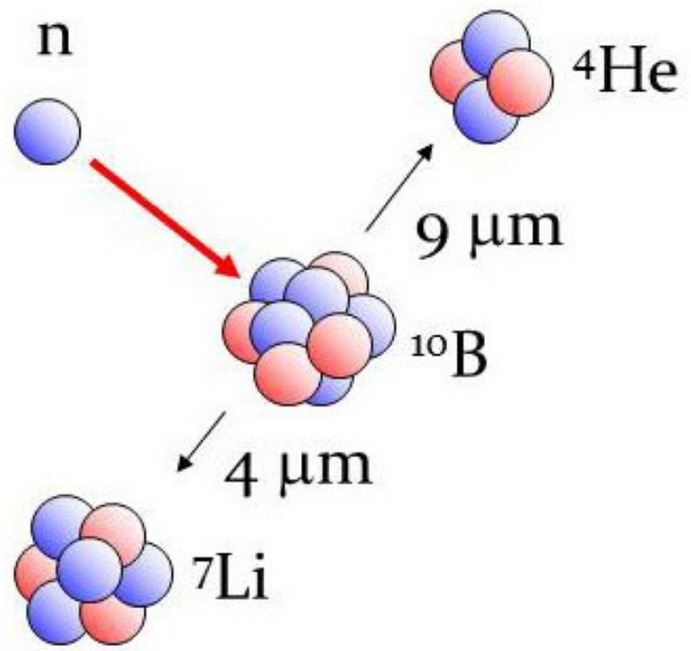
HiPSTER: material irradiation

Comparison with other proton facilities:

	Energy	Proton current	Target area	T-range	Readiness	Notes
FETS-HIPSTER	**3 MeV fixed: upgradable to 15-18 MeV**	**6mA average (60mA pulses, 10% duty cycle)**	**undecided, but up to 300mm diameter**	**300 – 1000C likely**	**Accelerator being commissioned, target area to be designed & commissioned**	**protons only.**
DCF	variable, <1 MeV – 10 MeV	0.1mA	~5cm diameter	Under development	Single beam now, dual beam in late 2015	part of dual – beam facility. Can deliver any ion at micro-Amp current
Birmingham cyclotron	11-39 MeV	60 μA	Several cm?		Under construction	Max run time 6-10 hours – shared with isotope production.
Birmingham dynamitron	**Up to 3MeV**	**1 mA**	**Several cm?**		**Under construction**	**Long run times?**
UK IBC, Surrey	up to 2 MeV	3 μA (2x10^13 H/s) / 30 μA	Up to ~40cm diameter	Up to 900C	Operational	
JaNNUS	up to 4 MeV (typically 2.5MeV on *Yvette* for H^+)	40 μA (2.5×10^{14} ions/s)	~2.5cm diameter	up to 800C	Operational	Part of triple – beam facility.
HZDR	up to 6 MeV	0.001 - 100 μA	Up to 10cm diameter?	up to 800C	Operational	
IMBL, Michigan	400 kV – 3 MeV	1 nA – 50 μA	~5cm diameter		late 2014.	Part of triple – beam facility.
MIAMI Huddersfield	**2- 100 kV**	**10^{10} – 10^{14} ions/cm^2/s**	**TEM foil**		**Operational**	**In-situ irradiation TEM**

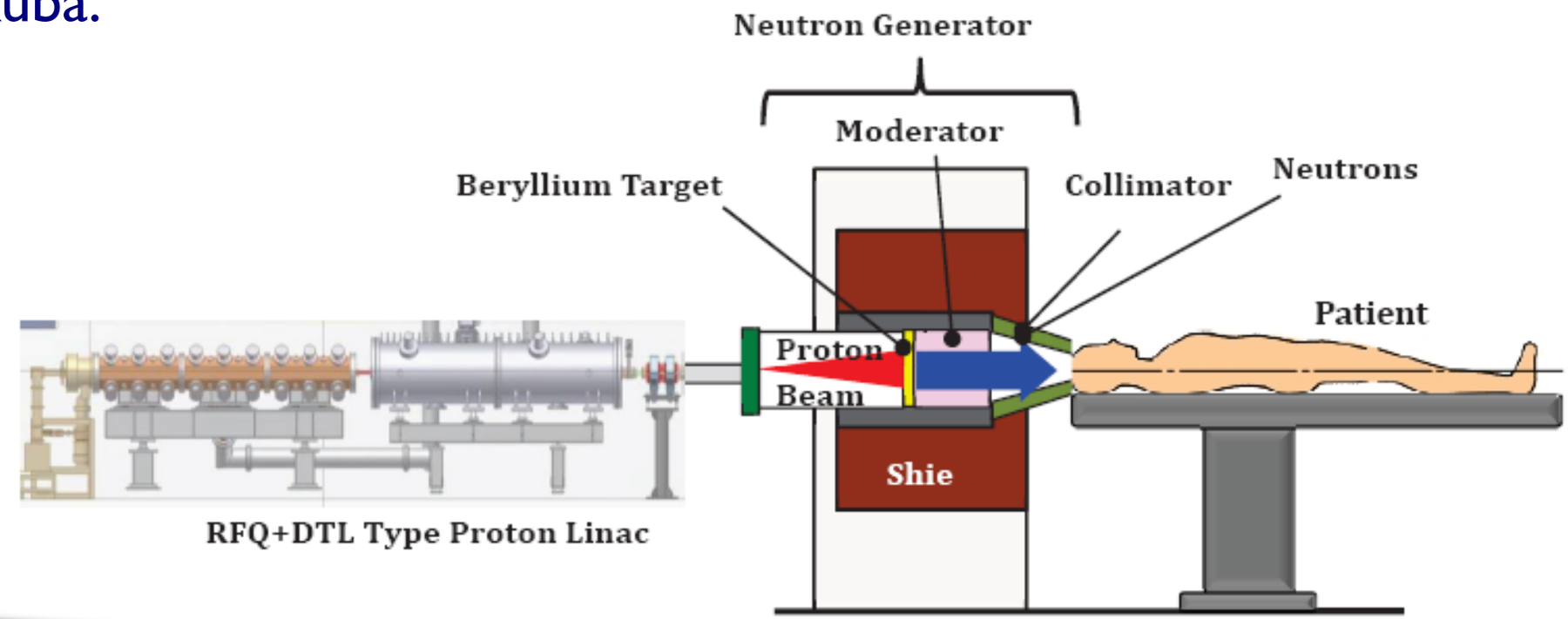
Boron Neutron Capture Therapy

- BNCT uses the neutron capture properties of Boron to deliver a lethal radiation dose to a tumour with little or no dose to the surrounding tissue.
- A Boron compound which selectively accumulates in the tumour is administered to the patient. A neutron beam is then administered to the patient.
- ^{10}B has a very large neutron capture cross section compared to normal tissue.
- ^{11}B is formed which quickly decays to He and Li ions with high kinetic energy.
- The ion range is of the order of a few cells at most, limiting the ionization damage to the vicinity of the cells containing Boron.



Boron Neutron Capture Therapy

- All clinical use of BNCT to date has been limited to nuclear reactors as the neutron source.
- For treatment at a hospital or therapy centre a nuclear reactor is not a viable solution. An accelerator based neutron source (ABNS) using a proton beam and Lithium or Beryllium target is ideally suited.
- The first clinical trials of ABNS for BNCT are beginning most notably in Japan.
- With a suitable target a facility based on the linac technology being developed at FETS would be readily achievable. Such a system is already under investigation in Tsukuba.



Isotope production

- Technetium-99m is a metastable nuclear isomer of technetium-99 that is used in tens of millions of medical diagnostic procedures annually, making it the most commonly used medical radioisotope. It's gamma ray energy of 140.5 keV is convenient for detection.

- ^{99m}Tc is the result of the nuclear decay of its parent nuclide ^{99}Mo. ^{99}Mo is a fission product resulting from the bombardment of ^{235}U by neutrons in a reactor.

- With the reactors used to produce most of the ^{99m}Tc aging a world shortage emerged in the late 2000s. As building new reactors is politically sensitive, alternative routes to ^{99m}Tc production are being sought.

Isotope production

- 99mTc can be produced directly by bombarding a 100Mo target with protons at an energy of 22 MeV through the reaction $^{100}Mo(p,2n)^{99m}Tc$.

- However the short half life of ^{99m}Tc of only 6 hours makes its storage impossible and timely transport to medical facilities possibly very expensive. Instead the parent nuclide, ^{99}Mo, is supplied to hospitals in Technetium generators where the 99mTc is chemically extracted as the ^{99}Mo decays.

- An alternative and possibly more attractive route to 99mTc generation is the direct production of ^{99}Mo in an accelerator based neutron source through the $^{100}Mo(n,2n)^{99}Mo$ reaction or an accelerator based gamma source by the $^{100}Mo(\gamma,n)^{99}Mo$ reaction.

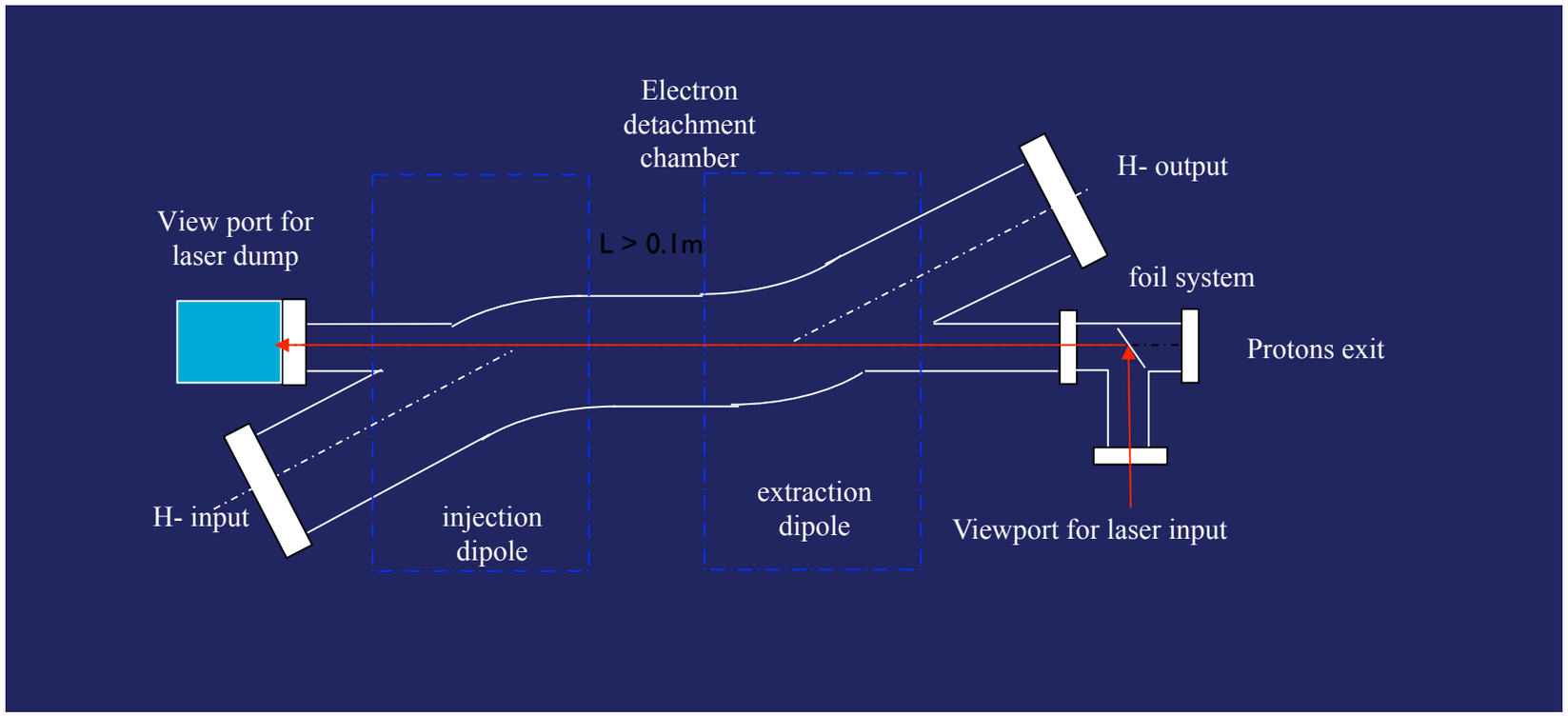
- Technologies very similar to those being developed at FETS could be adapted to produce a neutron or gamma source for radioisotope production.

Novel Diagnostic Development

- A non-destructive laserwire emittance scanner based on H- photo-detachment has been recently demonstrated by FETS-CERN collaboration at Linac4 at multiple beam energies.
  - Profile and transverse emittance measurements are now routinely achieved.
  - Lasers pulse widths of 1-300ns typically cover many bunches: bunch current within a macro pulse can be followed, but not bunch by bunch.
- However, there is interest in developing longitudinal laserwires, based on short pulse width lasers.
  - A dedicated area for novel diagnostics development at FETS could benefit several international groups developing laserwires.
  - E.g. Potential for collaboration on developments of longitundinal laserwire for PIP-II

Laser controlled proton beams?

- Potential to further investigate the laser based control of proton beam for medical applications, following earlier work by Dr. Carol Johnstone and Dave Johnson (FNAL) and Prof. Shaoul Ezekiel (MIT). [As mentioned in Dave's talk on Thursday]
  - Fast raster scanning of laser
  - Generate neutralized beamlet then stripped by foil.



LASER-ON:

- Enters vacuum chamber through viewport perpendicular to "axis"
- Reflects off 45 deg mirror/stripper
- Single passes thru dipole B to interact (head-on) with H-beam then pass through dipole A thru a viewport to a laser dump.
- The head on collision length > 0.1m gives 100% detachment in area covered by laser creating neutral H0.
- Neutral H0 passes thru dipole B unaffected (while H- gets swept to the dump)
- Neutral H0 passes through Al foil stripping remaining electron and converting to proton.

2009 FFAG workshop, D. Johnson

Summary

- On completion and commissioning of the accelerator in 2017, FETS will offer a unique low energy, high power beam.
- Many options to exploit this facility are being explored and several are relevant to medical applications:
- Potential applications:
  - Recent interest in a compact neutron source to demonstrate FFAG technology for ISIS.
  - HiPSTER: iradiation facility for fusion material research.
  - Boron Neutron Capture Therapy
  - Isotope production
  - Novel diagnostics / laser controlled proton beam for medical imaging.
  - … Your suggestion?

Thank you – questions, suggestions?