

Technology Transfer Success Story: BNL-Developed Cell-Labeling Kit Hits the Market

UltraTag® RBC is the high-tech name of a blood cell-labeling kit invented at BNL that hit the medical marketplace this June. During the first quarter of sales, over 500 hospitals and nuclear medicine centers have placed their orders for this easy-to-use kit.

Priced at \$28 per patient, UltraTag® RBC is expected to earn its place in nuclear medicine by being used in many of the over 500,000 blood-pool studies done in the U.S. each year to diagnose heart disease. The kit may also be used in a large percentage of the procedures performed in this country a year to investigate gastrointestinal bleeding.

UltraTag® RBC is used to tag red blood cells (RBCs) with technetium-99m (^{99m}Tc) — the radioactive tracer used in 85 percent of all diagnostic procedures in nuclear medicine worldwide, which was also developed at BNL about three decades ago.

While tagging RBCs with ^{99m}Tc could require a chemistry lab to carry out all the steps, BNL's patented method has been consolidated into a single vial and two syringes packaged into an off-the-shelf kit. All that needs to be added is a small sample of the patient's blood and ^{99m}Tc. In all, the hands-on use of the kit takes

less than five minutes.

UltraTag® RBC is the first commercial kit for preparing in vitro technetium-labeled RBCs for human use to receive approval from the federal Food & Drug Administration (FDA).

The invention was patented in July 1988 by Senior Scientist Suresh Srivastava, former Technical Collaborator John Babich of Massachusetts General Hospital, Medical Associate Rita Straub and Powell Richards, who retired from BNL's Medical Department in 1983 as Head of the Radionuclide & Radiopharmaceutical Research Division, which since then has been led by Srivastava. Prior to its patenting, the invention earned an I-R 100 award, as one of the 100 top technological achievements of 1986.

While this is one of 12 BNL inventions to be licensed to industry, it is the first Lab invention to be licensed exclusively to one private company. The company is Mallinckrodt Medical, Inc., a pharmaceutical firm that is located in St. Louis, Missouri, and is a leader in the nuclear medicine field.

Interested in the kit because of its convenience and labeling efficiency, and the great stability of the labeled cells within the human body, Mal-

Margaret Bogosian, Deputy Manager of BNL's Office of Technology Transfer, reviews the product literature on UltraTag® RBC, while Suresh Srivastava, Head of the Radionuclide & Radiopharmaceutical Research Division of the Medical Department, examines the kit's packaging.



Photos on this page by Roger Stoutenburgh.

linckrodt obtained an exclusive license for the invention in 1989. After further refining the invention for market, successfully concluding clinical trials and obtaining FDA approval for human use, Mallinckrodt announced its new product at this year's annual meeting of the Society of Nuclear Medicine.

"This kit is the best there is on the market, so we have great clinical expectations for this product," says Mallinckrodt's Patrick Hastings, the product manager for UltraTag® RBC.

As per the patent policy of Associated Universities, Inc. (AUI), net royalties received by AUI from Mallinckrodt's sales of UltraTag® RBC will be shared with the BNL inventors of the kit.

In Vitro vs. In Vivo

"Given the advantages that our kit method has, I wouldn't be surprised if UltraTag® RBC replaces the other existing techniques for labeling red

blood cells with technetium-99m — including BNL's original in vitro method," comments Srivastava.

Before UltraTag® RBC, there were three primary techniques for tagging RBCs: an in vivo method, a combined in vivo-in vitro procedure called modified in vitro, and an in vitro process, which was developed earlier at BNL and has been used in about 1 percent of cases.

Though easiest to carry out, the in vivo method has many drawbacks, including limited incorporation of technetium into the cells, instability within the body and lack of reliable results. The modified in vitro method produces better labeling and stability but is long and cumbersome. The earlier BNL technique presented two problems: the need for manipulating and centrifuging the patient's blood, and the fact that it had not received FDA approval, so it was available only experimentally.

(continued on page 2)

Licensing BNL Technology

Once their inventions work, most scientific inventors are more interested in starting new research than in marketing a new technology. But this can mean that valuable ideas reach the marketplace only after inordinate delay, if ever.

To help prevent this situation, BNL's Office of Technology Transfer (OTT) has added a licensing specialist, Eugene Cooper, to find and license the right firms to develop BNL-invented technology that can be of benefit to the public. Cooper, who came to the Lab last March, joins fellow licensing and patent attorneys Margaret Bogosian and Vale Myles in the patent-licensing program that OTT conducts for Associated Universities, Inc. (AUI).



Eugene Cooper

As in the past, a BNL employee who invents a new device, material or process is encouraged to send a description of the invention to OTT. There, the attorneys assemble information on the invention's patentability and commercial potential, then send it to AUI.

On this basis, AUI decides whether to take title to the new technology. If AUI does take title, OTT staff and the inventor prepare and file the U.S. patent application.

While the patent application is pending, Cooper and the other licensing specialists evaluate the invention's commercial potential. They look for companies that are interested and have the funding and expertise necessary to develop a new marketable product.

Said OTT Deputy Manager Margaret Bogosian, "Having Gene devote the majority of his effort to licensing allows us to put more emphasis on getting inventions into the marketplace."

And Cooper elaborated, "Some new technologies are ready for marketing with little additional development, and they are easier to place. But others are new discoveries or recent results of basic research, as happens most often in laboratories like Brookhaven. A company must be willing to develop these inventions quite extensively before they are marketable."

Cooper's background as an attorney and licensing executive with such companies as RCA, CBS and University Science is valuable in his evaluating and licensing marketable BNL inventions. "We're building up a network of companies, both locally and elsewhere, that are willing to expand and want new technologies to develop," said Cooper. "With all the worth-while ideas coming out of the Lab, we should be able to keep them busy. And in the process, we may help improve America's economic security."

— Liz Seubert

Coming Up

A panel discussion of highlights of the 22nd National Training Program sponsored last July by the organization Federally Employed Women will be presented on Tuesday, September 24, by BNL's three representatives to the conference. Attending with the support of the Personnel Division were Virginia Brown, Personnel, BNL's Women's Program Coordinator Patricia Durcan, a senior secretary in the Department of Nuclear Energy who is also corresponding secretary of the Upton Chapter of Professional Secretaries International (PSI); and Mary Wood, BNL's Health Promotion Specialist in the Medical Department and an executive board member of Brookhaven Women in Science (BWIS).

Sponsored by BWIS, PSI and the Women's Program Coordinator, the panel will begin at

12:15 p.m., in Berkner Hall, Room A, and will be preceded by a brief business meeting of BWIS members at noon. Coffee and cookies will be served, and everyone is invited to attend.

Lynn R. Sykes, who holds the Higgins Chair in Geological Sciences at Columbia University, will present the next AUI Distinguished Lecture on "Earthquake Prediction," on Thursday, September 26, at 4:30 p.m. in Berkner Hall.

In addition to his earthquake expertise, Sykes is an authority on the use of seismology to evaluate nuclear tests. As such, he will deliver a second talk the next morning. "Verification of Nuclear Test Ban Treaties" will take place on Friday, September 27, at 9:30 a.m., in the Hamilton Seminar Room, Chemistry, Bldg. 555.

BWIS Seminar

The Amazing Maize Maze of Transposable Elements

Like the one student who can disrupt an otherwise orderly line of his peers by jumping from place to place, "jumping" genes break out of their normal linear arrangement in a chromosome and move to different positions in the DNA. But because DNA carries genetic information, these jumping genes — also known as transposable elements — can seriously affect the genetic message.

Though transposable elements were originally discovered in maize, or corn plants, these kinds of genes have been found to be ubiquitous to all life forms, raising questions about their role in evolution, genetic engineering, agriculture and human genetics. For answers, researchers have looked at the molecular structure of these jumping genes.

Nina Fedoroff, a plant molecular



Nina Fedoroff

biologist with Carnegie Institution of Washington's (CIW) Department of Embryology, will share some insights in this area when she talks about "Molecular Biology of Maize Transposable Elements" in the next Brookhaven Women in Science (BWIS) Seminar. Her talk will begin at 3:45 p.m., on Thursday, September 19, in the Biology Department Seminar Room in Bldg. 463.

While an undergraduate at Syracuse University, Fedoroff was also a flutist with the Syracuse Symphony and did Russian-English translations. After earning her B.S. in biology and chemistry in 1966, she did graduate work at Rockefeller University, obtaining her Ph.D. in molecular biology in 1972.

Fedoroff joined the faculty of the University of California at Los

Angeles in 1972, leaving in 1978 to take her present position as staff scientist at CIW. She is also a professor in the Biology Department of The Johns Hopkins University and a member of the National Academy of Sciences.

Over the years, Fedoroff has done research with a number of different biological systems, including: the replication apparatus of the bacterial virus $\phi 2$, *Xenopus* 5S DNA, HeLa cell heterogeneous nuclear RNA, mouse myeloma tumor polysomes and messenger RNA, and, finally, control elements and transposable elements in maize.

Anyone interested in joining the speaker for dinner following the lecture should call Jane Setlow, Ext. 3420.

Cell-Labeling Kit (cont'd)

In addition to its many advantages, UltraTag® RBC has none of the above-mentioned drawbacks.

One to three milliliters of anticoagulated whole blood are simply injected into the small vial of powdered reagents supplied as part of the kit. After five minutes, the contents of the kit's first syringe are added to the vial and mixed, and then the second syringe's contents are added and mixed. Finally, ^{99m}Tc is added, and the vial's contents are occasionally mixed while being incubated for 20 minutes.

With the chemical reactions completed, the whole blood containing the technetium-tagged red blood cells can be reinjected into the patient up to six hours after labeling.

After reinjection, the technetium tracer emits gamma rays that can then be imaged and quantified using either a planar camera or SPECT, single photon emission computed tomography.

Forefathers of UltraTag

The lineage of UltraTag® RBC can be traced back to the first patent for a kit to label RBCs with ^{99m}Tc , which was awarded to Powell Richards and former BNL Associate Chemist Terry Smith in 1976. And its genealogy goes even further back — to the development of ^{99m}Tc at BNL in the late 1950s by the late Walter Tucker, Margaret Greene, Powell Richards and others.

As part of the division's efforts to find medical applications for the radionuclides that it developed, Richards and Smith came up with that first RBC-tagging kit. After Srivastava, Straub and others revised the concept, a second-generation version of that original kit came into being.

Under FDA approval as an investigational new drug (IND), BNL supplied about 20,000 second-generation kits to hospitals through the early 1980s. In the mid-1980s, after the IND approval was transferred non-exclusively from BNL to Cadema Medical Products in Watertown, New York, that firm took over the manufacture and distribution of the second-generation kit.

"The second-generation kit was used in the U.S. and abroad, so obviously the approach was accepted and the technology was needed — but the technology was not transferred exclusively to industry because the patent rights rested with DOE," comments Margaret Bogosian, Deputy Manager of BNL's Office of Technology Transfer.

Prior to 1980, the patent policy adopted by many federal agencies, including the U.S. Department of Energy (DOE), called for the U.S. government to take title to inventions developed with public funding. Although this policy did place this

new technology in the public domain, thereby making it available to all, it did not foster the commercialization of new products.

Explains Bogosian, "In the technology fields where significant investment is needed to bring a new product to market, such as the pharmaceutical field, industry has been reluctant to make such an investment unless they have exclusive rights to commercialize the product."

This outcome prompted the U.S. Congress to pass the Bayh-Dole statute in 1980, giving universities, nonprofit organizations and small businesses the option to take title to inventions developed with federal funding. This statute was amended several years later in Public Law 98-620, to extend this option to the DOE national laboratories including Brookhaven. As of January 1, 1988, this change was reflected in AUI's prime contract with the DOE to manage BNL.

Recalls Bogosian, "When the new and improved kit was developed, which was before 1988, AUI requested that DOE waive its rights to title to

AUI. In the spirit of Public Law 98-620, DOE granted with waiver. Since that time, AUI has been obtaining title to inventions of commercial value and licensing its patented inventions to industry for commercial use." (See sidebar.)

New & Improved

Continues Bogosian, "There are only a handful of U.S. radiopharmaceutical companies, so my office knew which to contact to see if any were interested in obtaining a license for the 'new and improved' blood-labeling kit."

Around the same time, during a meeting of the American Chemical Society, Srivastava supped with an acquaintance who was in an upper echelon at Mallinckrodt. This acquaintance was interested when Srivastava informed him that the new and improved method of tagging RBCs with technetium being developed at BNL showed great promise.

As it turned out, Mallinckrodt took interest in the kit. Exclusive license in hand, the company first carried out further development work at BNL in 1987-88, under a proprietary research agreement for which the full cost was recovered.

Involving five patients, the first phase of clinical trials necessary for FDA approval began at BNL in the fall of 1988, in collaboration with BNL Research Collaborator Harold Atkins of the Nuclear Medicine Division of the State University of New York at Stony Brook. Phase II and III clinical trials included 200 patients at six medical centers in the U.S. and Canada.

With no adverse effects and excellent images as a result of the kit's use, Mallinckrodt applied to the FDA for its final approval in September 1989, and was given the green light to introduce the product in the marketplace this June.

Sharing the Wealth

Under AUI's patent policy, the first \$100,000 of net royalties is divided 50-50 between the inventors and AUI. Of the next net \$400,000, the inventors receive 25 percent and AUI 75 percent. The inventors will receive 15 percent of the next \$2 million, while AUI will get 85 percent. Finally, inventors share 10 percent and the AUI share is 90 percent of net royalty income in excess of \$2.5 million.

According to its policy, AUI is required to distribute its percentage of net royalty income from its patent licensing agreements "in a manner that recognizes the best interests of the facility which developed the technology which is the source of such income."

Funds for developing the licensed RBC-tagging kit, as well as other projects within the Radionuclide & Radiopharmaceutical Research Group, have come from what is now



Roger Stoutenburgh

With Suresh Srivastava looking on, Medical Associate Rita Straub demonstrates how easy UltraTag® RBC is to use.

DOE's Medical Applications & Biophysical Research Division (MABRD) headed by Acting Director Robert Wood. This division is within DOE's Office of Health & Environmental Research, which is a part of the DOE Office of Energy Research.

Concludes MABRD's John Maddox, "After years of funding the research and development of this kit, it is gratifying that the beneficiaries are not only the private sector and the kit's inventors, but also patients in need across this country and around the world."

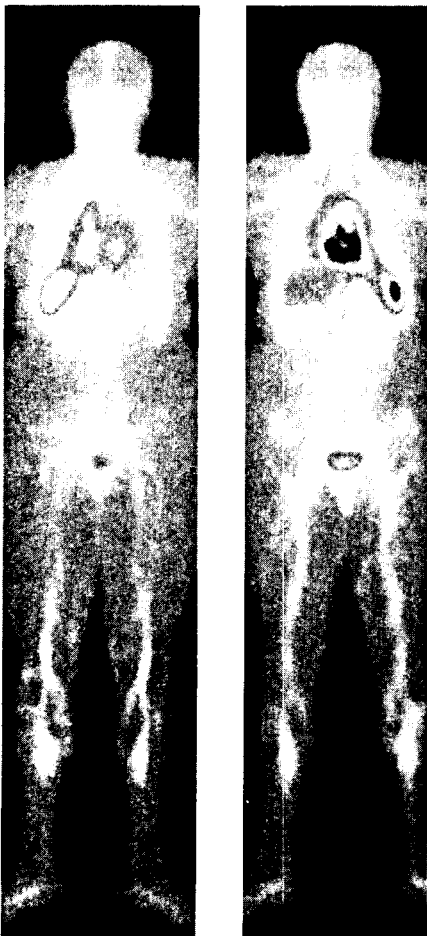
— Marsha Belford

In Addition

Last week's story about the BNL Lecture on "Reducing Bone Pain in Cancer Patients Using Radioactive Tin," explained how BNL researchers hope to develop an effective radionuclide therapy for the severe bone pain associated with some cancers by using tin compounds that exhibit high uptake in bone and bone tumors, without localization in any other organs. Inadvertently omitted from that story was the fact that a patent on the composition of these compounds and their potential use in therapy was issued in 1985 to Suresh Srivastava, George Meinken and Powell Richards, all of the Medical Department.

Hospitality News

The Parent/Toddler Group, which is sponsored by the BNL Hospitality Committee, meets every Wednesday morning, from 9:30 to 11:30 a.m., at the Recreation Building in the apartment area. Everyone is welcome, especially those with young children. Please join us.



Anterior (left) and posterior whole-body images obtained one hour after a patient was injected with red blood cells (RBCs) that were tagged with technetium- ^{99m}Tc using UltraTag® RBC, a labeling kit developed at BNL and commercialized by Mallinckrodt Medical, Inc. With a half-life of only six hours, technetium-labeled RBCs give a radiation dose equivalent to one-fifth of a chest x-ray.

Tai Chi Club

Members of the BERA Tai Chi Club enjoy the benefits of practicing the art of Tai Chi, a gentle, flowing exercise developed centuries ago to promote physical and mental health, longevity and stamina.

Practiced by enthusiasts from a wide range of BNL working backgrounds, the art offers a restful way to balance energy, reduce stress, heighten awareness and concentration, and gain flexibility and grace.

In the shade of tall pines at the Recreation Park picnic area, near the gazebo off the east end of Brookhaven Avenue, a new session will begin on Monday, September 16. The instructional fee for ten weeks of classes is \$30, payable at registration during the first class.

Classes are held on Monday and Wednesday, 12:15 to 12:45 p.m. At the new session, instruction in the Yang Long Form style of Tai Chi (88 postures) will continue, with the addition of instruction in Push Hands, an adjunct exercise form to Tai Chi.

Club instructors Dejun Xue, Ext. 2846, and Chuan-Zheng Yang, Ext. 5790, will teach parts 1 and 2 of Tai Chi and Push Hands on Monday, and part 3 of Tai Chi and Push Hands on Wednesday.

For more details, call either instructor or Jerry Tanguay, club secretary, Ext. 2198.



Tennis Champs

This year's Tennis Tournament produced many exciting moments and these 1991 champions: (photo below) Diana Mathabane, who won the women's singles contest; (photo at left) Om Singh (right), victor in men's singles; Rita Kito (center left) and Gail Williams (center right), the winning team in women's doubles; and Peter Vanier (left), who teamed with Williams to win the mixed doubles event and with Singh to take the men's doubles.



— Photos by Roger Stoutenburgh

Art, Antiques and Fall Foliage



On Saturday, October 19, come up the Hudson on a BERA Art Society trip to Boscobel, a beautifully restored Federal house with period furniture, china, silver and books. After a very quick lunch break at attractive Cold Spring village, visit Storm King Art Center where massive sculptures dominate the open hillside. All scenery will be glorious

and the leaves should be good, too!

The day's schedule will be:

- 7:30 a.m. — Depart BNL, from farmer's market parking lot.
- 10:30 a.m. — Visit Boscobel House, herb garden, orangerie, etc.
- noon — Stop in Cold Spring for coffee or quick lunch.
- 2:00 p.m. — See outdoor sculpture and museum at Storm King Sculpture Art Center.
- 3:45 p.m. — Leave for BNL, arriving around 6 p.m.

Bus and entry fees cost \$26 (\$24 for senior citizens). If 36 tickets are not sold by October 5, the trip will be canceled, so please decide quickly. To sign up or for more information, call Liz Seubert, Ext. 2346.

Softball Dinner

This year's Softball Dinner will be held on Friday, September 20, from 6 p.m. to midnight, at the Rock Hill Country Club. Tickets are \$15 per person with a cash bar. Purchase tickets through your league representative no later than Tuesday, September 17.

Cooking Exchange

At the BERA Cooking Exchange, members meet new people and experience dishes from all over the globe.

The season's first meeting will be held at noon on Wednesday, September 25, at the Recreation Building in the apartment area. This will be a business meeting; no dishes will be demonstrated, but coffee and cake will be served.

Please come to contribute your ideas for another successful season.

Call chairperson Barbara Kowalski, 744-3569, with any questions.

Arrivals & Departures

Arrivals

Mordechai Bordoley.....NSLS
 Robert M. Brugger.....Medical
 Romney B. Duffey.....Nuc. Energy
 Deborah L. Faivre.....Nuc. Energy
 Sean Gavin.....Physics
 Maya Paczuski.....Physics
 Jacob Rodnizki.....Nuc. Energy
 James A. Safranek.....NSLS
 Yue Shen.....Physics
 Appathurai Vairavamurthy.....DAS

Departures

This list includes all employees who were terminated from the Lab, including retirees:
 Dorothy-Jean Greco.....Con. & Proc.
 Charles F. Hayes.....Sfgrds. & Sec.
 Jialin Xie.....NSLS

Bowling

Red/Green League

J. Muller had a 246/627 scratch series, R. Larsen 244/603 scratch series, M. Palumbo 237/226/641 scratch, M. Guacci 233, R. Raynis 219, A. Warkentien 211.

White League

Sharon Smith had a 233/182, Gerry Riker 222, Skelly Frei 219, Dick Adams 206, Joe Sheehan 202, Tracy Ryan 201, Fern Simes 189, Terry Diaz converted the 4/10 split.

Purple League

Kevin Carney had a 220, Ginny Waterman 200, Mary Ellen Hubner 185, Dee Collins 184.

Golf Tournament

The fifth BGA tournament of 1991 will be held on Tuesday, September 24, at Rock Hill Golf and Country Club, under stroke play rules, as a "Red, White and Blue tournament." Call Mike Losquadro, Ext. 7594, to arrange a tee-off time or with questions about the format. Tee times run from 10:30 a.m. to approximately 12:30 p.m., depending on the number of people signed up.

Greens fees of \$37 include a mandatory cart. The sign-up deadline is Tuesday, September 17; all callers are encouraged to have a complete four-some prior to calling. If it rains, please direct any questions to the pro shop, at 878-2250.

Tournament standings as of the Swan Lake tournament are:

Gross Score Standings		
Rank	Name	Points
1	John Usher	28.616
2	Peter Bond	25.459
3	Les Lawrence	21.632
4	John Millener	19.820
5	Artie Dick	14.797
Net Score Standings		
1	Bill Cahill	22.296
2	Don Gates	17.339
3	Tom Dilgen	16.985
4	John Bennett	12.676
5	James Marsch	12.386
	Paul Poleski	12.386

Volleyball

The first Volleyball League captains' meeting will be held on Wednesday, September 18, at noon, in Room 300, on the third floor of Chemistry, Bldg. 555. Team captains or their representatives must attend. Team roster sheets are being sent to last year's captains and must be submitted at this meeting as they will not be accepted later.

Anyone not on a roster who wants to play and those interested in receiving a roster sheet should contact either Kathi Barkigia, Ext. 7661, or Nancy Ohlmann, Ext. 4440.

Reminder: The nights that Open League and League I matches will be played have changed. On Monday nights, Open League and League 2 will play. On Wednesday nights, Leagues 1 and 3 will play.



Remember!

Unravel your receipts from Finast and King Kullen and mail them to Carole Kerr, Bldg. 460, for 10 percent discounts from these stores on more shopping for the BNL Food Drive. Personal checks are also welcome.

Learn About OpenWindows

Jeff Soto, a representative of Sun Microsystems, will introduce OpenWindows, the graphical user interface for the Unix-based Sun workstation operating system, SunOS 4.1.1, on Thursday, September 19, from 9 a.m. until noon, in the CCD Seminar Room. He will discuss the Deskset, methods of designing the workspace to fit individual needs, and changing the Programs and Utilities menus, and present an overview of the X Window System.

For more information, call Ron Wittlock, Ext. 4112, and, to register for the course, send E-mail to wittlock@bnl.gov.

Cafeteria Menu

Luncheons

Monday, September 16

Soup: French onion	.75/.95
Entree: Sweet & sour pork w/1 veg.	3.10
Entree: Pizza	3.25
Fitness: Chef's choice	3.10
Carvery: Hot pastrami sandwich	2.85
Grill: Reuben w/cole slaw and pickle	2.85

Tuesday, September 17

SPICE: Baked Potato Challenge - make it great at our fixings bar (each)	1.50
Soup: Chunky chicken & rice	.75/.95
Entree: Meatloaf w/mushroom gravy & 1 veg.	3.10
Fitness: Baked fish amandine w/1 veg.	3.10
Carvery: Hot roast beef sandwich	2.85
Grill: Cheeseburger, fries & 32-oz. sports cup of soda	3.10

Wednesday, September 18

Soup: Hot & sour soup	.75/.95
Entree: Stir-fry beef & broccoli w/1 veg.	3.10
Entree: Stuffed peppers w/1 veg.	3.10
Fitness: Vegetable lasagna w/1 veg.	3.10
Carvery: Hot Black Forest ham sandwich	2.85
Grill: 2 Chili dogs w/fries & 32-oz. sports cup of soda	3.10

Thursday, September 19

Soup: Pork & cabbage w/dumplings	.75/.95
Entree: Chef's special	3.10
Entree: Salisbury steak w/gravy & 1 veg.	3.10
Fitness: Vegetarian plate - 5 veg. & roll	3.10
Carvery: Hot corned beef sandwich	2.85
Grill: Philly cheese steak, cole slaw & pickle	2.85

Friday, September 20

Soup: Manhattan clam chowder	.75/.95
Entree: Chef's choice	3.10
Entree: Pasta w/marinara sauce	3.10
Fitness: Long Island baked fillet of fish	3.10
Carvery: Hot turkey sandwich	2.85
Grill: Tuna melt w/French fries, cole slaw and pickle	2.85

BROOKHAVEN BULLETIN

Published weekly by the Public Affairs Office for the employees of BROOKHAVEN NATIONAL LABORATORY

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