MassBiologics
The Monthly Dose
UMASS MEDICAL SCHOOL
Medicine for Better Lives

March 2013 Volume 2, Issue 3

MassBiologics and other University News

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Upcoming Happenings

- Friday March 22nd: Leaders in Innovation Seminar - Dr. Zhiping Weng from UMMS
- Wednesday March 20th: First Day of Spring
- Sunday March 23rd : Easter Sunday
- Monday March 25th: Passover Begins
- Monday April 12th: Leaders in Innovation Seminar - Dr. Chris Sassetti from UMMS

The Animal Rule

Heidi Smith, MD, PhD

On December 14 2012, the FDA approved an anti-anthrax monoclonal antibody, raxibacumab, utilizing "The Animal Rule" as the regulatory strategy. Raxibacumab was approved for treatment of inhalation anthrax (the disease that killed several patients exposed to anthrax spore-laced letters mailed in 2002) and for the prevention of inhalation anthrax in exposed individuals.

This approval was noteworthy for two reasons: 1) raxibacumab is only the second monoclonal antibody approved to treat or prevent an infectious disease; and 2) raxibacumab is the first monoclonal antibody to be licensed based on the FDA's Animal Rule.

The FDA requires new drugs to demonstrate both safety and efficacy in carefully controlled human clinical trials before licensure. However, there are certain medical conditions for which such human clinical trials are not ethical or feasible. Inhalation anthrax is a rare disease and is often fatal, despite antibiotic treatment and aggressive care. These disease characteristics make intentional human exposure to anthrax unethical.

The Animal Rule is found in the Code of Federal Regulations (21 CFR) for drugs (21 CFR 314 Subpart I) and for biologics (21 CFR 601 Subpart H). It allows the FDA to grant marketing approval if a drug is effective when studied in adequate and well-controlled animal experiments. The Animal Rule is only used if it is not possible to apply for licensure using human efficacy data and strict criteria must be met, based on the recognition that some treatments which appeared to be effective in animal experiments have not subsequently been shown to be effective in humans.

In the animal model to address efficacy under the Animal Rule, animals must become sick in the same way people with the disease become sick and the way the drug would prevent illness must be reasonably well-understood. The effect of the drug must, in most cases, be demonstrated in more than one species of animal. The endpoint studied must be clearly related to the desired effect in humans (like prevention of death) and researchers must obtain data that allows for the selection of an effective dose in humans.

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Monoclonal Antibody Purification: Cell Removal

By Lauren Roth

At MassBiologics, mAbs are produced using large-scale, Chinese Hamster Ovary (CHO) cell cultures. MAbs are secreted by CHO cells and then purified from cell-free harvest material, therefore the first step in purification involves removing cells, membrane fragments and other particulates. This cell clarification stage commonly involves a combination of centrifugation and filtration. We use a series of single-use, large-pore, depth filters for cell clarification of CHO cultures here at MassBiologics. A typical culture harvest involves two filtration stages. First, cell culture is pushed through a large-pore, course filter which removes whole cells and large particulates. Harvest material is then further clarified us-

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Diphtheria Monoclonal Antibody

By Leila Sevigny, PhD

While diphtheria is preventable by vaccination, the disease persists because of variations in vaccine compliance and inadequate booster regimens. The current standard of care for diphtheria is an anti-toxin that is produced from horses. This equine diphtheria anti-toxin (DAT) is not licensed by the FDA, but distributed by the CDC through an active IND. This treatment has serious side effects associated with the administration of equine antibodies. A bigger problem is that DAT is in short supply throughout the world and the stockpile that many countries hold has passed its expiration date. A safe effective human monoclonal antibody for diphtheria could replace the precious equine antitoxin.

Over the past two years, the Product Discovery department has been working on a project to develop human monoclonal antibodies for tetanus and diphtheria derived directly from the B cells of healthy volunteers immunized with Td. After cloning, screening and initial characterization, a lead candidate diphtheria antibody, S315 has been selected and tested. The candidate strongly neutralizes diphtheria toxin in cytotoxicity assays in-vitro and can protect guinea pigs from toxin challenge.

A traditional clinical trial to measure efficacy for the diphtheria MAb is not possible due to the small number of cases of diphtheria. However, an IND could be used to treat affected people with S315, if we could adequately demonstrate the antibody's efficacy in animal studies. We have currently been testing our antibody in guinea pig models and comparing it directly to DAT. We have been able to prevent guinea pig intoxication with S315 and have been able to treat diphtheria in some animals by giving antibody after they have been challenged with a lethal dose of toxin. Using this preliminary data, we will propose efficacy studies to the FDA that would be required for filing an IND submission so the MAb can be given to people suffering from diphtheria. Hopefully soon this safer, more readily available alternative to DAT will be available for human use.

Monoclonal Antibody Purification contd.

ing a smaller pore, fine filter which reduces turbidity and removes contaminating host cell proteins (HCPs) and DNA.

Using disposable depth filters for clarification has many advantages including a wide range of capacity, easy validation, minimal cleaning, easy set up and consistent mAb recoveries. However, depth filter capacity, or the filter area required to clarify a given culture volume, is highly dependent on culture parameters such as cell density and % viabilty. Extensive experimental testing during development for each new cell line is done to be sure to size filters adequately to maximize recovery and avoid catastrophic clogging during manufacturing. In Process Development, depth filters are sized by performing several, small-scale test filtrations, but filter capacity can still vary considerably from culture to culture. Therefore, we recommend a filter area to the manufacturing group that is 50% greater than the experimentally determined capacity to reduce the risk of filter clogging and subsequent loss of valuable cell culture. Taken together, considerable development testing and necessary over-sizing of expensive, single-use filters can make utilizing depth filtration for clarificaiton a costly process in terms of both time and money.

In order to minimize the expense and time expenditure inherent in depth filtration, Process Development is working to develop a predictive model for filter capacity that could effectively eliminate scale-down testing and reduce uncertainty in filter sizing. Downstream Processing is currently designing a study based on Design of Experiments statistical principals (DOE) to evaluate depth filter performance as compared to cell culture paramters such as % viability, cell density, packed cell volume and contaminant concentration. Our goal is to use the information gained in this study to establish a model that can accurately predict necessary filter area based soley on measurable parameters for any given cell culture. Such a model will enable us to size depth filters without experimental testing and inevitably save us money once a process is implemented at the manufacturing scale.

The Animal Rule contd.

These studies must be carried out under GLP and comply with the Animal Welfare Act. In addition, the safety of the drug must still be demonstrated by studying whether the drug causes any side effects in otherwise healthy humans.

For raxibacumab, studies were performed in rabbits and macaques to obtain approval under the Animal Rule. The animals were exposed to anthrax spores by inhalation, similar to human exposure, and developed many of the same symptoms that humans with inhalation anthrax develop. The MAb was shown to help protect animals when given prior to exposure to anthrax spores and to improve survival when given to animals that became sick from the spores. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125349Orig1s000SumR.pdf

In addition to the anti-anthrax monoclonal antibody, there have been only two other products approved to date using the Animal Rule - pyridostigmine bromide for pre-treatment before possible exposure to nerve gas and Cyanokit to treat cyanide poisoning. However, several products in development are moving towards approval through this mechanism. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/UCM110322

The History of Where the Mattapan Campus Has Been Built

By Mark Leney, PhD

As MassBiologics moves towards a final winding down of operations at the historic Jamaica Plain campus I wanted to write something about the Mattapan campus. As the subject of turkeys appears to have been dealt with at length, I decided to look at the history of the site. As best as can be determined, the site on which our buildings now stand was under agricultural use as the Pierce Farm when it was purchased in 1892 by the Boston Insane Hospital. Since the early 1880s the city had been operating an institution housing 200 "unfortunate women" on a "poor farm" on the other side of Morton Street, formerly known as the "Austin Farm" It's inmates were transferred elsewhere in 1894 paving the way for the establishment of the hospital on the site. Parcels of land were purchased around the Pierce Farm up to about 1903 when the current area bounded by Harvard, Walk Hill, American Legion and Morton Streets had been assembled into the West Campus of the Insane Hospital, dedicated to male patients, females being kept on the other side of Morton St.

In 1899, Edward Lane writing in the Roxbury Magazine sketched the life of the institution where between five and six hundred insane patients "appreciated the beautiful surroundings" while spending "between five and fifty years" in the care of the state. It was also "a haven for the most distressing cases" who must be cared for while they lead a mere animal existence… until death releases them". The Commonwealth assumed responsibility for the institution in 1908 and it was renamed the Boston State Hospital. Perhaps unsurprisingly with at least one patient being added to the population each day, that a program of building expansion occurred between around 1912 and 1920 and again around the early 1930's (under depression era stimulus spending) until there were approximately 24 buildings, totaling almost a million square feet, on the West Campus that we currently occupy together, with gardens and orchards cultivated by the inmates. The essentially Victorian institution continued its rather closeted existence until the 1960s when there are believed to have been around 3000 patients resident in the facility.

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News from Around Campus

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Discovery prompts new hope for pediatric HIV cure at UMMS

By Lisa M. Larson and Bryan Goodchild

UMass Medical School Communications

January 30, 2013

Fresh off the dramatic discovery of the first functional HIV cure in an infant, UMass Medical School researchers are refocusing their studies toward replicating the results.

“We never thought this was possible,” said Katherine Luzuriaga, MD, professor of pediatrics and molecular medicine, who worked with doctors from the Johns Hopkins Children’s Center and the University of Mississippi Medical Center on the stunning case of a Mississippi baby who, given very early and aggressive antiretroviral therapy, appears to have cleared most traces of HIV.

The breakthrough, announced March 3 at the 2013 Conference on Retroviruses and Opportunistic Infections in Atlanta, received international attention as only the second well-documented case of a cure, out of the more than 70 million cumulative HIV infections. It is the first time the infection was cleared with currently available medications.

"Up to this point, we believed that all children who were treated for HIV were sentenced to a lifetime of treatment,” said Dr. Luzuriaga, a nationally known pediatric HIV specialist who has spent more than two decades studying the disease at UMMS. “This case suggests that if we can treat early enough, we may be able to reduce the size and the extent of those viral reservoirs to the point that we may someday spare children a lifetime of therapy."

The baby in this case, born to an HIV-infected mother who did not have prenatal care, received therapeutic antiretroviral treatment beginning 30 hours after birth. That therapy continued until about 18 months of age, when the child was lost to follow-up and off the drugs. Months later, the child returned to the hospital and underwent repeated standard blood tests, none of which detected HIV presence in the blood. Test for HIV-specific antibodies—the standard clinical indicator of HIV infection—also remained negative throughout.

Deborah Persaud, MD, of Johns Hopkins Children’s Center, and Luzuriaga headed a team of laboratory researchers on the case, funded by the National Institutes of Health and the American Foundation for AIDS Research (amfAR). Hannah Gay, MD, of the University of Mississippi Medical Center, treated the baby. The investigators say the prompt administration of antiviral treatment likely led to the infant’s cure by halting the formation of hard-to-treat viral reservoirs—dormant cells responsible for reigniting the infection in most HIV patients within weeks of stopping therapy.

Currently, high-risk newborns—those born to mothers with poorly controlled infections or whose mothers’ HIV status is discovered around the time of delivery—receive a combination of antivirals at prophylactic doses to prevent infection for six weeks and start therapeutic doses if and once infection is diagnosed. But this particular case, the investigators say, may change the current practice because it highlights the curative potential of very early ART.

“Complete viral eradication on a large scale is our long-term goal but, for now, remains out of reach, and our best chance may come from aggressive, timely and precisely targeted use of antiviral therapies in high-risk newborns as a way to achieve functional cure,” said Luzuriaga.

umass med NOW

News from Around Campus

National ranking again puts UMMS in top 10 for primary care

By Jim Fessenden
UMass Medical School Communications
March 12, 2013

UMass Medical School was ranked ninth in primary care education among 126 medical schools and 23 schools of osteopathic medicine surveyed by weekly news magazine *U.S. News & World Report* in its 2014 edition of the "Best Graduate Schools" issue, released Tuesday, March 12. UMMS has been listed near the top of the category since 1994 when the magazine began publishing the much-anticipated rankings. Of note, UMMS is the only school in the top 50 that accepts only in-state students into its medical degree program. *U.S. News* also ranked UMMS 46 among top research schools and 46 in the biological sciences.

"UMass Medical School's consistently high ranking is a reflection of our dedication to our mission and the faculty's unwavering commitment to providing an outstanding education to our students," said Chancellor Michael F. Collins. "As we enter a period of unprecedented change in health care, the part our medical school, faculty and students play in shaping this future has never been more essential."

"A national leader in primary care education and in biomedical research, UMass Medical School continues to garner national and worldwide recognition for its quality program in these and other areas," said University of Massachusetts President Robert L. Caret, PhD. "The accomplishments of the students, faculty and alumni at UMass Medical School are a testament to the vision that created our system of public higher education 150 years ago, and that is a vision of service to individuals, to communities, to our nation and the world."

The School of Medicine, which had accepted just 100 students per year since the 1970s, recently expanded the class size to 125 to help increase the pool of physicians, particularly primary care providers, trained to meet the needs of the commonwealth and the nation. Traditionally, more than 50 percent of each year's graduates enter a primary care residency program. In addition, more than half of each class stays in the state for residency, totaling 260 new residents in the last five years alone. Graduates of UMMS are poised to excel in their medical careers, and at noon on Friday, March 15—Match Day across the nation—all fourth-year medical students will discover where they will begin their medical careers.

"The medical school's standings are a point of pride for our faculty, administration and students, many of whom are matching into primary care residencies this week," said Terence R. Flotte, MD, executive deputy chancellor, provost, and dean of the School of Medicine. "The importance of our mission has never been clearer and these accolades are validation of the rich education our students

Pediatric HIV discovery contd.

UMMS is designing and preparing to launch additional lab studies and clinical trials to test the effectiveness of early and aggressive treatment of HIV in newborns.

"UMass has a long history of working in pediatric HIV infection," Luzuriaga said. "One of the drugs that is a mainstay for either prevention of mother-to-child transmission or treatment of women and children—which is call neviraparine—was discovered in this lab and was brought into very early clinical trials here at UMass."

In 1995, UMMS started some of the first early treatment trials of children with HIV.

"The oldest of those children are now approaching their 18th birthdays," she said. "I think we have been able to make a major impact on pediatric HIV infection. We have benefited from the very strong research environment here, including the Center for Clinical and Translational Science."

Employee Recognition and New Awards at the 2013 Winter Social

By Jeffrey Way

On Friday February 22nd, MassBiologics celebrated not only the achievements of the organization but also the accomplishments of its employees. While there had been a two year intermission from the last recognition event, this event overwhelmingly succeeded in delivering a blueprint to future events, easily surpassing its predecessors. The uniqueness of the Liberty Hotel and the museum like style was a great backdrop for showcasing the long history of MassBiologics. The fourth floor balcony was where staff and family gathered to socialize while also being able to view one of the 20 photos of years gone by.

This year's Winter Social proved once again that MassBiologics has a dedicated staff that takes pride in the mission of the organization. Longevity is something we all strive for in many aspects of our life and employment is near the top of that list. We currently have 185 employees and 77% of them have been here for 5 years or more and 40% have been here for more than 10 years. What's most impressive is the fact that we current have 21 employees that have been here since before the merger with UMMS on May 11, 1997.

Close to 200 guests were on hand to celebrate years of service for themselves and their co-workers, as well as to recognize their many other achievements. In addition to the traditional years of service awards, four new achievement awards were created and awarded. Dr. Mark Klempner declared, "these awards are now and forever a part of MassBiologics". The creation and goal of these recognition awards is to recognize and show appreciation for an employee's or groups' achievement in specific areas. These awards will memorialize to all employees our continued excellence and commitment to the mission of the organization.

The new awards, what they are for, and who they were awarded to this year, are as follows:

Above and Beyond Award: This award is for an individual or small group that went way above and beyond the call of their job to help achieve the mission. This year's winners were:

Jessica Sedan and David Rihan for their efforts to establish the grants administration and CMO function as a new division of our Business Development function.

Peter Cheslock who stepped up to take on the Animal Facility move, something that needed to get done but that was well beyond his previous experience or ordinary duties.

Derek Bursey stepped up and provided technical insight to a wide variety of contract manufacturing issues and he took a more prominent and significant role in the leadership and management of the labeling and packaging operations. Derek also assumed a leadership role in vaccine manufacturing and most recently added significant technical insight to performing some feasibility work with our automated visual inspection machine.

Medicine for Better Lives Award: This award is for an individual or small group that was instrumental in bringing forth a medicine for better lives- reflects on our core mission and value.

This year's award was given to Frank Fazio for identifying and executing a strategy to donate short dated vaccine to Project HOPE. This is significant for a variety of reasons. First, it puts important medicine into the hands of people who truly need it. Second, it avoids costs at MassBiologics. And, the significance is that it was not a theoretical solution, it was accomplished. An almost insurmountable amount of work and bureaucratic road blocks would have stopped most from pursuing this donation. Only through Frank's dogged dedication to the end game were we able to accomplish this mission driven goal.

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Employee Recognition contd.

Edwin Cohn Innovation Award is for an individual or small group who was responsible for an innovation that affected our ability to achieve the Mission of MassBiologics—named after an innovator that brought plasma fractionation to MassBiologics and beyond.

Kirk Rowley was this year's recipient for developing the b cell cloning assay enabling a *new generation* of human antibodies. Successfully cloning tetanus and diphtheria MAbs.

Theobald Smith Milestone Award is for an individual or small group that was key to achieving an organizational milestone for MassBiologics. This award is named after our founding director, who achieved the milestone of putting us on the map.

Marge Tucker was bestowed this award for her leadership and management of the compositing move. This was a mission critical milestone that was the first important step to leaving the Jamaica Plain campus thus consolidating all manufacture to the Mattapan campus.

These new and special awards were preceded by the years of service awards. Below are the employees that celebrated an anniversary in 2011, 2012 and 2013. Not everyone was mentioned at this year's Winter Social, so when you see any of these folk below please congratulate them on the hard work and commitment to their work and the mission of MassBiologics, Medicine For Better Live.

2011 Years of Service Awards

Five Years
Kellyann Barrow
Bryant Fay
Mark Leney
Melvin Maradiaga
Dennis McArthur
Stacey Mohamed
Ejaz Nasser
Truong Pham
Anne Roussell
Jen Royal
Heidi Smith
Mark Townsend
Harv Vij

Ten Years
Jennifer Brennan
Horacio Caneja
Daniel Cullins
Everett Erwinn
Aphuong Lai
Marie Manning
Michael Mena
Ying Xu

Fifteen Years
Sarith Phat
Guangping Wang
Rima Yeroshalmi

Twenty Years
Neal McNair

Thirty Years
Nancy Hall

2012 Years of Service Awards

Five Years
Scott Bertolami
Nain Bonilla
Brian Booth
Derek Bursey
Rossy Figuereo
Mike Marcel
Gleny Peralta
Marcia Steger
Yang Wang

Ten Years
Rebecca Cannon
Paula Carlson
Teresa Donahue
Ghia Griess
Ken Hill
Robert Jenkins
John Rodrigues
Marge Tucker

Fifteen Years
Christine Strickland

Thirty Years
Larry O'Toole

2013 Years of Service Awards

Five Years
Emelia Ansu-Gyeabourh
Johanna Breeden
Peter Cheslock
Frank Guardabascio
Joel Perry
Jessica Sedan

Ten Years
Katherine Baptista
Naomi Boatright
Roxana Cosma
Bernie Creswick
John Finch
Michaelle Fleurissaint
Ephrem Gebretsadik
Larry Jadormio
Pauline Locke
Jane Lynch
Eneida Shkurti

Fifteen Years
Brian Abbott
Joanne Ash
Catherine Hay
Steven McCabe
Lisa McGonigle

Twenty Years
Paul Landolphi

Twenty Five Years
Lynne Farley

Thirty Years
Kelvin Claxton

MassBiologics News

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MEDICINE FOR BETTER LIVES

In Our Next Issue……

Our next issue will be released in early October.

Department News: Catch up on the latest developments across the organization with updates from your Deputy Directors.

Spring Open Enrollment Information

MassBiologics Archivist

Plus much more...

Upcoming HRDI Schedule

Wednesday March 20th: Ben Moorghen

Monday March 25th: Jodie Nosiglia

Wednesday April 3rd: Ben Moorghen

Wednesday April 10th: Jodie Nosiglia and Benefits Open Enrollment Session in Cafeteria

Note: HRDI staff will be onsite 10am-4pm in Room 2020 of MTP II. Staff substitutions may be made due to unforeseen circumstances. For immediate assistance please contact the Human Resources Benefits Service Center Team

PHONE: 508-856-2282 | Monday-Friday, 8:30a.m.-4:30p.m.
EMAIL: Benefits.UMMS@umassmed.edu

History of our Campus Site contd.

In the 1970s a program of deinstitutionalization saw the number of inmates dwindle to a few hundred with eventual closure in 1979. In 1981 the central power plant (providing steam to the buildings) was closed and in 1982 the Department of Mental Health eventually declared most of the land to be surplus. A review concluded that the facility was unlikely to be suitable for inclusion in the National Register of Historic Places. While most of the East Campus buildings were demolished in 1986, the shell of the hospital remained on this site (West Campus) well into the 1990s. Two buildings were in use in 1995, for campus security and a pre-release processing facility operated by the Department of Corrections, although neither of these building remains on the site today.

During the process of transferring responsibility for Massachusetts Biologic Laboratories from the Department of Public Health to the University of Massachusetts during 1996, the legislature provided that if MBL were to expand, that the Boston State Hospital parcel was the preferred location. In 1998 MBL reported that it was exploring the possibility, and in 2000 the legislature formally approved this location for MBL's expansion. Photographs from the Mattapan 1 construction show that several of the old state hospital structures survived as late as 2004, including two dating from the 1920's including the "Detention" building (where the gravel parking lot is now behind Mattapan 1) and a building latterly used for Occupational Therapy and Rehab that stood on what is now the cleared meadow behind Mattapan 2. The Mattapan 1 building itself stands on the site of the former "E" and "F" Wards (originally build as attendants' housing and dating to 1914). The Mattapan 2 building is built on the site of the later Johnson Building, constructed in 1956 as a hospital for those unfortunate enough to be both physically and mentally ill. Just four above-ground structures remain from the State Hospital – the three cottages, dating to about 1933 that stand a little to the west of Mattapan 2 and that once housed hospital staff and the oldest extant structure which stands half hidden in the scrub behind the Mattapan 1 building. This was, most recently, a recreational facility or "community lounge" although it's original function when it was built 99 years ago remains unknown.