MassBiologics
The Monthly Dose
UMASS MEDICAL SCHOOL
Medicine for Better Lives

MassBiologics and other University News

December 1, 2012 Volume 1, Issue 4

Inside this issue:

December Happenings:

- December 4th: Breakfast with Dr. Klempner 8-9am
- December 7th: Last day to enroll in Flex Spending Account and apply for CCAP
- December 12th: Leaders in Innovation seminar with Dr. Celia Schiffer
- December 18th: Breakfast with Dr. Klempner 8-9am
- December 24th & 25th: Christmas Holiday

"New" Use for Tetanus Toxoid: Carrier Protein in Conjugate Vaccines

By Roger Anderson, PhD and Paul Casaz, PhD

People don't normally produce antibodies to very small molecules like drugs or simple structures like polysaccharides. However, inducing antibodies to these types of molecules could result in effective therapeutics. Antibodies that bind to small molecules such drugs of abuse could be used to treat an overdose, for instance. Some protective antigens such as bacterial sugars do not normally induce responses in people. Vaccine developers can improve the vaccine responses to these antigens by connecting them to carrier proteins in a process called conjugation. The combination of the carrier protein and the small molecule or hapten attached to the surface results in a conjugate vaccine capable of inducing antibodies to the carrier protein as well as the small molecule. Carrier proteins can come from a variety of sources but conjugate vaccines for humans primarily use well known safe vaccine proteins like Tetanus or Diphtheria toxoid.

Vaccines containing tetanus toxoid (TT) are effective at preventing tetanus and have been safely used in people for decades so there are fewer safety concerns compared to a new carrier protein. Haptens can be conjugated to TT with several chemical approach-

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Orphan Drug Status

By Brett A. Leav, MD

While the word "orphan" carries a significant amount of emotional baggage in the vernacular, it has a significantly different meaning to the pharmaceutical and medical device industry. In 1983, the U.S. Congress passed the Orphan Drug Act to promote the development of medicines to treat rare diseases. The law has several important components: 1) it created a pathway for designating orphan status to a drug, defined as treating a disease affecting less than 200,000 patients in the United States; 2) it provided a seven year period of market exclusivity for a drug that received orphan designation; and 3) it created a funding mechanism for the development of orphan products. Additional incentives include waiver of the prescription drug user fee at the time of application and a 50% tax credit applied to costs of clinical development.

This Act essentially created the FDA Office of Orphan Products Development. This office is responsible for reviewing applications for orphan product designation and for reviewing Orphan Products grant applications. A Sponsor can apply for

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From the Desk of Dr. Mark Klempner

The recent outbreak of fungal meningitis cases, attributed to contaminated injectable steroids compounded by the New England Compounding Center (NECC), contrasts with how much attention and how many regulations are devoted to the safety of MassBiologics licensed vaccine and IND biologics. This personal tragedy for so many families and public health fiasco also reminds me how outrageously different were the operating procedures and oversight of NECC. In many ways NECC was functioning as a drug manufacturer under regulatory rules designed for a local pharmacy to compound mostly non-sterile, hard to find medicines for an individual patient. Everything we do is ultimately directed at producing safe and effective medicines; from validating the purity of every ingredient that goes into our manufactured products to a visual inspection of each and every one of the millions of vials of medicines that we produce, and all the highly regulated steps in between to assure the safety and sterility of our products and the safety of the environment in which they are manufactured. Under the "watchful eye" of FDA regulations, which we embrace, we have delivered millions of doses of medicines to the American public without a single question of product safety or product liability. In fact MassBiologics was one of the first manufacturers of biologics to be compliant with federal oversight. In 1901, 13 children in St. Louis, MO and 9 children in Camden NJ died from tetanus contaminated equine diphtheria antitoxin and tainted smallpox vaccine which prompted passage of the Biologics Control Act of 1902. This was the beginning of federal regulations governing the production of vaccines and antisera. Many manufacturers, including city and state departments of health, were unable to comply with the strict safety regulations leading all but a few to cease making these vital medicines. In fact, we are the only former state department of health laboratory that has continued to make vaccines and biologicals, now for over 100 years.

A consequence of NECC producing tainted medicines is a loss of trust by the pubic in the makers of medicines to provide them with safe products. Patients coming to see their doctors worry as much or more about not having something bad happen to them as they do about getting better. As makers of sterile, injectable medicines MassBiologics gets smeared with the same brush that paints an accurate picture of how deviant NECC was in their disregard for the safety of their products. At MassBiologics we have a sacred obligation to "first, do no harm" and a responsibility to contribute to restoring the public's trust. Through our attention to all the details that have made our products safe we must continue to demonstrate the highest regard for safety and compliance with regulatory rules. And each of us can be ambassadors explaining how MassBiologics, like other licensed pharmaceutical manufacturers, operates under "safety first" policies, procedures and regulations that differ so markedly from rogues like NECC.

Antibody Expression Using MassBiologics Vectors and CHO Cells

By Yang Wang, Ph.D:

Achieving high production yield of recombinant antibodies from CHO cells requires the combination of many factors, including the expression vector, cell line, media and feeds. All aspects of this production require intensive testing and optimization. Many commercial technology platforms have been described for this application. For years, our production of CHO-derived antibody products has been subject to development constraints imposed by these intellectual property restrictions, which adversely impact our ability to deliver therapeutic antibodies to patients in a cost effective way.

Over the past two years, the Product Discovery team has been on a mission to develop our own technology platform for antibody production that will enable us to be free of licensing fees to outside corporations. One of the central dogmas of

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Antibody Expression Using MassBiologics Vectors and CHO Cells contd

improving antibody expression is to manipulate the efficiency of protein expression and colony selection, which could be achieved by well designed expression vectors and fully adapted suspension CHO cells suitable for cGMP antibody production. After months of DNA sequence compiling, vector construction, cell adaption and colony screening, we have generated our own antibody expression vectors and cell lines with promising antibody expression levels in small scale shaker experiments. This expression platform is currently being further optimized and we expect to achieve higher production yield with in-house media and feeds developed by the Process Development department.

The amazing team performing this work includes Yang Wang, Brian Booth, Leila Sevigny, Stuart Nelson and Andrew Crowley. After long hours of hard work electronically compiling sequences, designing new iterations of vectors, picking colonies in the cell culture hood, and expanding literally hundreds of transfectants, we are all excited to see how much further we can develop this new expression system and we are all looking forward to applying this new system to our future antibody production.

Confidentiality: Loose Lips Sink ~~Sh~~IP~~s~~

By Sardiaa Leney:

Communications and information shared between companies are often protected by a Confidential Disclosure Agreement, a.k.a. a "CDA". These agreements are also commonly referred to as Confidentiality Agreements and Non-Disclosure Agreements (NDAs). The idea behind them is simple: when parties need to exchange ideas, data or know-how, and do not want that information shared, the parties enter into an agreement that legally binds them to keep it secret. There are many reasons why this can be important. One common reason is the protection of intellectual property rights, such as trade secrets or patent rights. When information slips into the public domain, rights to exclude others from using it can diminish or be permanently lost.

Confidentiality agreements have many variations and are tailored to meet the needs of each relationship, though there are some common threads. First, they identify the parties bound by the agreement, and always define what counts as "confidential information". They also specify how the information can and cannot be used by the parties, how long the agreement will last, and what happens to the confidential information after the agreement expires.

So what is confidential information? In short, it is whatever the agreement says it is. The definition changes to meet the needs of each relationship. Here is an example:

"*Confidential Information means any information relating directly or indirectly to the Technology not generally known to the public provided to the RECIPIENT by FOUNDATION or its assignors/inventors and conveyed in written, graphic, oral or physical form including but not limited to, scientific knowledge, know-how, processes, inventions, techniques, formulae, products, business operations, customer requirements, data, plans or other records, biological materials, and or software.*" The scope is different for each business or academic relationship we have.

Here are some rules to live by:

1) Every employee should know that information they have could be confidential. Sometimes, even the name of the company you are working with is confidential information.

2) Always err on the side of caution and do not discuss your work with individuals outside of MassBiologics.

3) If you need to discuss work with an outside party, check with your supervisor. Maybe they will know or maybe they will need to check with someone else, but don't just guess.

Is there anything we *can* discuss? Sure. The contents of this newsletter, anything on the MassBiologics public website or anything published in a journal article or a press release has already been deemed non-confidential. That's material that's already in the public domain and you can feel free to talk about that as much as you like, in fact, it's even encouraged.

News from Around Campus

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Gov. Cellucci receives Chancellor's Medal for 'selfless service'

Award given at reception to benefit the UMass ALS Champion Fund

By Brian Goodchild
UMass Medical School Communications
November 15, 2012

Chancellor Michael F. Collins awarded former Gov. Paul Cellucci a Chancellor's Medal at a reception to benefit the UMass ALS Champion Fund on Wednesday, Nov. 14.

"With deep gratitude for all your years of selfless service and in recognition of your political acumen, professional skills and personable manner that you have exercised to such great effect, we recognize and honor you," said Chancellor Collins in awarding the medal.

Cellucci announced in May of 2011 that he is raising money for an endowment at UMMS that will fund research into the causes of and treatments for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, a progressive neurodegenerative disorder affecting the motor neurons in the central nervous system. The UMass ALS Champion Fund supports the groundbreaking research of Robert H. Brown Jr., DPhil, MD, the *Leo P. and Theresa M. LaChance Chair in Medical Research* and chair and professor of neurology.

To see a video please go to this link: http://youtu.be/tFeysXTzcKI

14th Annual Walk To Cure Cancer: A Beautiful Day-A Great Cause

By Jim Fessenden
UMass Medical School Communications
December 3, 2012

Sarah H. Cheeseman, MD, professor of medicine, microbiology & physiological systems and pediatrics and Shan Lu, MD, PhD, professor of medicine and biochemistry & molecular pharmacology, were interviewed by the Worcester *Telegram and Gazette* for an article on World AIDS Day. World AIDS Day, held on Dec. 1 each year, is an opportunity for people worldwide to unite in the fight against HIV, show their support for people living with HIV and to commemorate people who have died. World AIDS Day was the first-ever global health day and was first held in 1988.

In the article, Dr. Cheeseman, an infectious disease expert who has been treating patients with HIV for more than 20 years, talks about how treatments for HIV have improved. Despite these improvements, she says a diagnosis of HIV is still a tremendous burden for patients.

Dr. Lu, an HIV researcher, explains that the quest to find a vaccine is making progress. Recent studies, including those made by his lab, suggest a "prime and boost" strategy, in which a genetically-engineered virus is injected and "boosted" with recombinant-DNA protein, may have potential.

Read the full story: 25 million AIDS deaths, but the fight goes on or http://www.telegram.com/article/20111202NEWS/112029699/1052

umass med NOW

News from Around Campus

National Grid awards UMMS $1.6M for Sherman Center efficiencies

Newest facility will use 25 percent less energy than a similar building of standard design

By Jim Fessenden
UMass Medical School Communications
December 3, 2012

UMass Medical School has been awarded a $1.6 million incentive payment from National Grid Massachusetts for a wide range of energy-efficient features designed and built into the Albert Sherman Center, a 500,000-square-foot research and education facility nearing completion on the Medical School's Worcester campus.

The combination of efficient design and advanced technologies at the ASC will result in the new facility operating 25 percent more efficiently than a similar building of standard design, resulting in consumption of 4.1 million fewer kilowatt hours of electricity, and an annual 4.5 million pound reduction in carbon dioxide emissions.

"Public health is tied to the health of our environment. That is why sustainability and energy efficiency are objectives we embrace," said Chancellor Michael F. Collins. "We value our partnership with National Grid. Incentive programs like this enable us to invest in design and advanced technologies that ease the environmental impact of our campus, and save money over the long term."

"Once again, we're pleased to be partnering with the UMass Medical School and supporting their ongoing efforts to introduce cleaner technologies in their campus buildings," said Marcy L. Reed, president of National Grid Massachusetts. "It's because of the aggressive energy-efficiency legislation by the Patrick Administration and our strong commitment to delivering innovative efficiency programs that we can empower customers like UMass Medical School to maximize energy savings while protecting the environment."

The ASC includes numerous, integrated systems that reduce energy consumption. Among the key technologies that helped earn the incentive payment are: occupancy sensors for lighting, heating and cooling of offices and conference rooms; heat recovery wheels that allow the building to exhaust stale air and draw in fresh air while retaining most of the heat in the building; variable speed fans, with sash sensors, on the fume hoods in the laboratories; daylight harvesting sensors that adjust interior lights based on the available sunlight; and a sophisticated building automation system that monitors building operations every 15 minutes and adjusts systems for maximum efficiency.

Additionally, the physical orientation of the Sherman Center on the site and the exterior materials used contribute significantly to the building's efficiency. On the north side of the building, where the laboratories are located, the façade is mostly glass, with long windows designed to allow in as much natural light as possible. On the south side of the building, the windows have external baffles or sun-shades designed to block much of the heat energy of the sun's rays, and also to bounce some of the light up to the interior ceilings of the offices and educational spaces on that side of the building. The glass on the south side is also slightly more reflective than the rest of the building, again to limit solar glare and heat gain. The building's roof is white, and the exterior terracotta lightly colored, so they reflect rather than absorb heat. The result is the exterior envelope of the ASC helps reduce the need for electric lighting, heating and cooling of the facility.

This new incentive payment was awarded for the efficiencies of the ASC building itself. On April 9, 2012, UMass Medical School received a $5.6 million incentive payment from National Grid—the largest rebate given by the utility company in the commonwealth—for an energy-efficient 14,000-square-foot expansion of the Worcester campus power plant built to help meet the demands of the growing institution. That project included installation of a high-efficiency, 7.5-megawatt, gas-fired combustion turbine and an associated heat recovery system that will boost UMass Medical School's capacity to generate electricity to serve the ASC. The new gas turbine replaces one of the plant's original gas and oil-fired steam boilers, which will be taken off-line and kept in reserve as an emergency back-up. Since natural gas burns cleaner than oil, and the new jet turbine is highly efficient, the expanded power plant will actually have lower green-house gas emissions, despite its added energy capacity. Producing electricity on-site is approximately 30-percent more efficient than using electricity from the regional distribution network, because of the losses that occur when electricity travels long distances on distribution lines.

"New" Use for Tetanus Toxoid contd.

Bill Latham in Tetanus incubator in the 1960's

es to produce vaccines capable of inducing good immune responses. Polysaccharide-toxoid conjugate vaccines are now routinely used to prevent bacterial meningitis and pneumonia. Examples are the capsular polysaccharides of pathogenic organisms such as *Haemophilus influenzea* type b, *Streptococcus pneumoniae*, and four strains of Neisseria meningitidis . Conjugate vaccines can also be made by attaching small molecules like nicotine to protein carriers to induce anti-nicotine antibodies to help smokers quit. Clinical trials with a nicotine-TT conjugate found that volunteers with higher anti-nicotine antibodies had a better chance of quitting. There are many examples of effective conjugate vaccines.

As you are aware, TT produced by MassBiologics is one of the main components of MBL's Td vaccine but our TT can also be used as a potent carrier protein. MassBiologics has prior history in manufacturing conjugate vaccines. In the 1990's MassBiologics prepared a *Haemophilus influenzea* polysaccharide TT conjugate vaccine that was effective when tested in clinical trials. Our TT also has an advantage as a carrier protein since it has been produced to GMP standards and has been safely used in millions of people. MassBiologics is taking advantage of this by actively pursuing opportunities to use TT produced by our vaccines department in conjugate vaccine programs at other universities and companies. These relationships could provide the foundation for increased demand for our toxoid products.

MassBiologics HRDI Calendar:

December 2012

Tuesday December 4th: Jim Mack, Talent

Thursday December 6th: Ben Moorghen, Employee Relations

Tuesday December 11th: Jim Mack, Talent

Wednesday December 12th: Karin Fitch-Urbano, Employee Relations

Tuesday December 18th: Michelle Jones-Johnson, Talent

Thursday December 20th: Jodie Nosiglia, Employee Relations

Friday December 28th: Ben Moorghen, Employee Relations

Monday December 31st: Jim Mack, Talent

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
ONLINE: www.umassmed.edu/hr/benefits

Boiler Operations:

People Behind the Scenes

By Ken Hill:

While many of our Facilities Maintenance personnel are very visible throughout our buildings our Boiler Plant Operators are largely unknown. Our Boiler Chief Bob Jasper and boiler technicians Isam Alzaben, Tom Dewar, and Dave Hamlin are located in the boiler plant in the Mattapan 1 Central Utility Building (CUB).They provide around the clock services to MassBiologics 7 days a week, 365 days a year. They operate, monitor, and maintain the three 500 HP Cleaver Brooks boilers which provide the 125 psi of plant steam required to heat both Mattapan 1 and Mattapan 2. The plant steam is also used to power several of our process utilities including clean steam for autoclaves and SIP, water for injection, and hot glycol used for process temperature maintenance. They also monitor our Buildings, process equipment and manufacturing equipment by monitoring the PCS and BMS alarm systems around the clock. They are our first line of defense when alarms occur outside of normal business hours.

The boiler operators are here around the clock making sure that the whole MassBiologics community is kept warm and comfortable and provide the steam for drive our mission of Making Medicines for Better Lives.

Compounding Errors

By Mark Leney, PhD:

Over the past couple of months many people have asked me if I knew anything about the fungal meningitis outbreak reported to have been caused by contaminated injectable drugs produced by New England Compounding Center (NECC). While it is easy to say that this has nothing to do with MassBiologics, except in the sense that we happen to operate in the same state as NECC, at a more fundamental level this does concern us. What NECC was attempting to do – put a preservative free single dose injectable into vials for use in human patients, is also the most critical aspect of our GMP manufacturing. Five hundred patients have been impacted following treatment with the NECC product implicated. To date 36 have died. Is there anything we can learn from this? How is what we do, different from what they did?

NECC operated at as a compounding pharmacy, that is to say their business included making final dosage form drugs from active ingredients, excipients, carriers, containers and closures – under the supervision of a licensed pharmacist and subject to the provision that doses produced were made in fulfillment of a proper prescription or medical practitioner's order. The filling of such a prescription or order creates a distinctive relationship between the pharmacist, the patient and the clinician. The compounding of sterile doses is one of the most critical activities in pharmacy but it has been recognized as a legitimate mode of producing and providing small numbers of doses for specialized or unique needs and it is governed by the USP as well as the regulations promulgated by the States, typically State Boards of Pharmacy. Like any aseptic procedure, compounding sterile doses carries some risk, risk that is traditionally mitigated by small scale, brief, operations each relating to just a single patient, or perhaps a small group of patients, so that the cycle of follow-up should there be an adverse event is extremely tight. The mass production of final doses is, as you all know, regulated by the Federal Government, and our friends at the FDA have a clear mandate in this regard, codified in the 21 CFR regulations and the Food Drug and Cosmetics Act. It appears from records in the public domain that whatever NECC were doing it was not approved by the FDA.

MassBiologics' aseptic manufacturing, whether we are producing Td vaccine or sterile investigational drugs, is regulated and overseen by the FDA, and follows the FDA's published guidance for the manufacture of drugs by aseptic processing. Our processes assuring product sterility are qualified and validated; that is to say that we have demonstrated that these processes, assuring this most critical quality attribute, work consistently as we expect them to. We demonstrate this before we release any doses. We demonstrate this when we make any change that impacts sterility assurance. We continue to demonstrate this through simulations on a regular basis (multiple events each year). We also have written procedures in place to ensure that we manufacture in an effective and consistent fashion. We have an independent quality unit that assures that these procedures are followed and which documents and investigates any departures from such procedures. Every lot of drug product is sampled and tested to ensure that it passes the requirements of the compendial (USP) sterility test. While many vials are tested, the total number subject to testing is a small fraction of the total number of doses produced. As such the validation, the periodic requalification, the following and documentation of standard procedures and independent oversight and review each contribute as necessary pillars of sterility assurance upon which the sterility test itself is merely a capstone.

It is grimly instructive to see this issue unfold. It certainly points to why we take special care to ensure that there is no viable mold or fungus anywhere where it might compromise an aseptic process as some species are persistent as well as hard to reliably detect. Some of you will be interested to review the 2006 warning letter that NECC received from FDA and the 14 November 2012 testimony to Congress by FDA Commissioner Hamburg which briefly references that previous warning. However, what I'd like us to take away from this tragedy is this: we are regulated by FDA for a good reason and we follow the aseptic guidance to mitigate potentially lethal risks. One or more of those pillars of sterility assurance was absent or faulty at NECC and dozens of people are dead as a result. We have special and particular duties towards every aspect of sterility assurance and the NECC disaster is a sobering reminder of that.

MassBiologics and other University News

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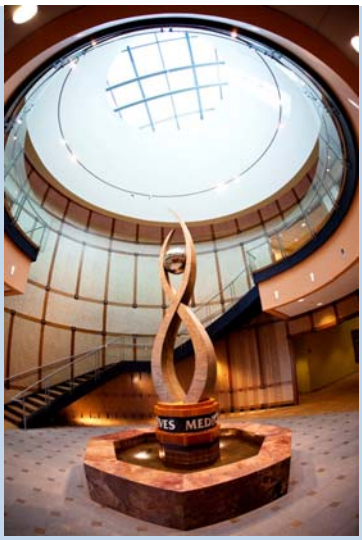
Letter to the Editor: Beginning next newsletter we would like to hear from you. We will be adding a 'Letter to the Editor' section. If there is something you would like to submit please send no more than 150 words to Jeffrey.Way@umassmed.edu. All submissions will be reviewed and one will be selected every month to be printed in the newsletter.



MEDICINE FOR BETTER LIVES

Orphan Drug Status *contd.*

Orphan product designation anytime during the development of the product. Since 1983, this Office has reviewed over 3700 applications and approved approximately 70%. Another important function of the Office is to provide funding for the clinical development of drugs, biologics and devices to treat rare diseases. National Institutes of Health (NIH)-type grants are used to provide funding of up to $200,000/year for phase 1 studies and up to 400,000/year for phase 2 and 3 studies. In 2012, the Office received 125 applications and funded 16 with a grant approval rate of 13%.

The Orphan Drug Act also appears to have achieved the goal of providing incentive for companies to develop drugs affecting small patient populations. According to a 2012 report from Thomson Reuters entitled "The Economic Power of Orphan Drugs," sales of orphan drugs currently account for 6% of the total pharmaceutical market and from 2001 to 2010, the growth rate of the orphan drug market exceeded that of "non-orphan" drugs. A major reason for the growth of this market is that despite treating only a small number of patients, the price of many orphan drugs is very high. For example, the monoclonal antibody eculizumab (Soliris™) to treat paroxysmal nocturnal hemoglobinuria, a very rare blood disorder, costs more than $409,000/year. Another factor, perhaps unforeseen during the initial drafting of the 1983 law, is that drugs which are licensed for a non-orphan indication can be given orphan designation for another indication. For example, rituximab (Rituxan™) which has non-orphan designation for the treatment of rheumatoid arthritis was also given orphan designation for four other conditions.

In 2011, Congress proposed an amendment to the Orphan Drug Act partly to help clarify the murkiness around defining "rare diseases." For example, while a prevalent disease like breast cancer is not rare, a subset of patients with a particular type of breast cancer who might benefit from a specific drug could support an orphan designation. This and other clarifications in the proposed amendment should help realign the Orphan designation process with the original intended goals of the Act.

While the results of the Orphan Drug Act may not necessarily reflect what Congress had intended when the Act was created nearly thirty years ago, it clearly has had a positive impact on domestic drug development. The Act has supported the development of therapies for rare diseases and has shown that this focus doesn't have to be a financially losing proposition. Given the mission of MassBiologics to develop biologics for public health or unmet medical needs, there are likely to be therapeutic candidates for which an orphan drug designation will facilitate further product development.