TOSOH

TOSOH
THE CUSTOMER
MAGAZINE

NO. #02 2017

PEOPLE/PASSION/PORTRAITS

TOSOH BIOSCIENCE

02
EDITORIAL
DEAR READER

Dear reader, welcome to the autumn 2017 issue of the Tosoh Bioscience customer magazine. This issue is dedicated to the people working with our chromatography products. Exemplarily we present some research groups and laboratories and their work. As you also might be interested in the people behind Tosoh, we introduce Patrick Endres to you, a colleague who recently joined our Technical Support team.

ENJOY READING AND STAY INFORMED.

REGINA ROEMLING I SENIOR MARKETING MANAGER
TOSOH BIOSCIENCE GMBH

THE SUPER-T - COMIC #6

CONTENT

IMPRESSUM

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03 EXPERT INSIGHTS

MAX-PLANK-INSTITUTE OF BIOCHEMISTRY

THE MAX-PLANCK-INSTITUTE OF BIOCHEMISTRY, LOCATED IN MARTINSRIED NEAR MUNICH, GERMANY, FOCUSES ON BASIC RESEARCH IN BIOCHEMISTRY, STRUCTURAL BIOLOGY AND BIOPHYSICS, THE BIGGEST STRENGTH BEING THE GREAT METHODOLOGICAL EXPERTISE IN ALL OF ITS RESEARCH AREAS. WITH APPROXIMATELY 850 EMPLOYEES COMING FROM 45 DIFFERENT NATIONS, THE MPIB IS ONE OF THE LARGEST INSTITUTES WITHIN THE MAX PLANCK SOCIETY. WE MET LEOPOLD URICH OF THE CORE FACILITY, RECOMBINANT PROTE-IN PRODUCTION.

Tosoh Bioscience (TB): What is the function of your department?
Leopold Urich (LU): Our Group is working in the Institute's Core Facility, one of many Service Facilities devoted to supporting the scientists during their work. Among the many areas of expertise we are working in the field of "Recombinant Protein Production". Meaning we are developing strategies for protein expression and purification.

TB: Which projects using chromatography are you working on?
LU: Almost all of our projects require some form of chromatography, since we are solely working with proteins.

TB: You mentioned that the two salt-tolerant ion-exchange chromatography media from Tosoh* are a breakthrough for your work. Could you elaborate on this?
LU: Ion-Exchange has been something we've been struggling with for a while now. The biggest issue has always been the binding conditions with other ion-exchange resins, meaning very low salt concentrations. Most of the material we are working with simply can't withstand such low amounts of salt. This problem has since been eliminated and on top of that, we're seeing some great separation results in our testing, even with simple linear gradients especially with the Toyopearl anion exchange columns.

TB: Would you see further application of these resins for other purposes?
LU: It's clear to say, with the testing complete and all of us being really content with the results, the resins, and ion-exchange in general, will play a much bigger role in our regular workflow.

*** TOYOPEARL SULFATE-650F AND TOYOPEARL NH2-750F**

04 EXPERT INSIGHTS

PHARMA TECHNICAL DEVELOPMENT ANALYTICS AT ROCHE DIAGNOSTICS GMBH

ROCHE IS THE WORLD'S LARGEST BIOTECH COMPANY AND DEVELOPS MEDICINES FOR VARIOUS DISEASE AREAS, INCLUDING ONCOLOGY, IMMUNOLOGY, INFECTIOUS DISEASES, OPHTHALMOLOGY AND NEUROSCIENCE. THE ROCHE DIAGNOSTICS GMBH SITE IN PENZBERG, GERMANY, IS ONE OF THE LARGEST BIOTECHNOLOGY CENTERS IN EUROPE. WITH APPROXIMATELY 5,800 EMPLOYEES FROM OVER 50 COUNTRIES, IT IS AN IMPORTANT CENTER FOR THE RESEARCH, DEVELOPMENT, AND PRODUCTION OF DIAGNOSTIC TESTS AND BIOPHARMACEUTICALS SUCH AS ANTIBODIES AND OTHER THERAPEUTIC PROTEINS. WE TALKED TO DR. RAPHAEL RUPPERT FROM THE PHARMA TECHNICAL DEVELOPMENT ANALYTICS DEPARTMENT ABOUT A POSTER HIS GROUP PRESENTED AT THE CASSS ANALYTICAL TECHNOLOGIES EUROPE CONFERENCE IN BRUSSELS THIS SPRING.

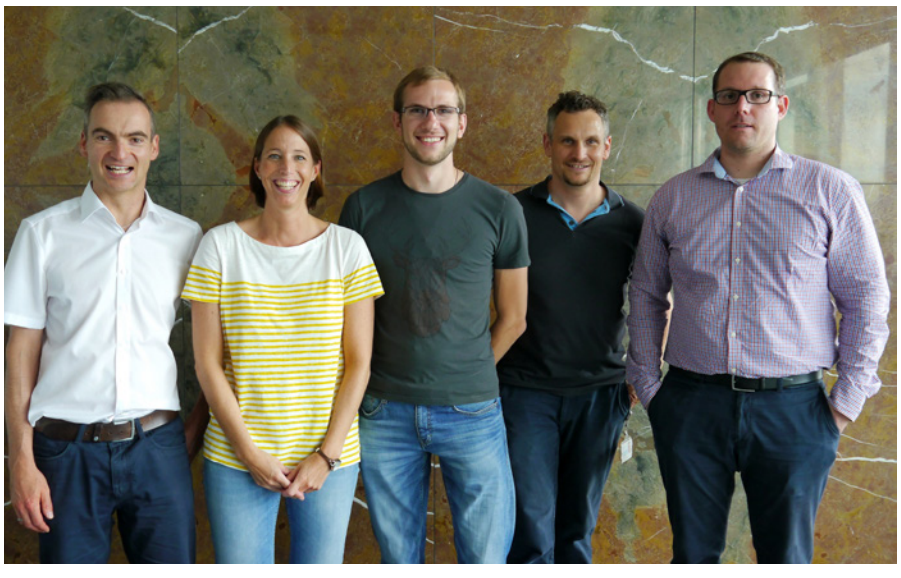
Tosoh Bioscience (TB): Dr. Ruppert could you give us a short summary of your activities within the Roche Group?
Dr. Ruppert (RR): Our group is responsible for release analytics, stability testing and extended characterization for biologics tox and clinical supply. Another important focus area of our work is the evaluation of new technologies as well as implementation and validation of new methods for Quality Control and extended characterization.

TB: You presented a poster at the CASSS 2017 about UHPLC analysis of bi-specific antibodies [1]. What was the key driving force to develop a UHPLC method for this target molecule?
To ensure high safety standards of our products, it is of absolute importance to reliably monitor product related impurities. As our product pipeline contains more and more advanced and complex antibody formats, there is a need to constantly improve our repertoire of methods to assess potential new product related impurities with highest possible resolution and sensitivity. Our new SE-UHPLC method is exemplary for this approach, enabling us to increase the sensitivity for detection of product related impurities during quality control while providing shorter run time and increased robustness.

TB: You evaluated two UHPLC columns for this project: a TSKgel UP-SW3000 column and an UHPLC column from another supplier. Why did you end up selecting the Tosoh column as your standard UHPLC column?
We were testing several columns from different vendors with a variety of our pipeline products. Although, several columns showed a comparable resolution, the Tosoh TSKgel UP-SW3000 column (2 µm, 4.6 x 30 mm) convinced us in terms of robustness, especially the high lot-to-lot stability (see Figure below), an absolute requirement for quality control under GMP conditions.

TB: What do you think will be the key challenges for analytics of biomolecules in the future?
1. The need for increased analytical throughput: automated solutions for the entire analytical workflow (from sample preparation to data evaluation), shortened run time.
2. Requirement for increased sensitivity and resolution to enable separation of product variants and impurities with subtle molecular differences.
3. High effort to screen the constantly increasing market for bioanalytical solutions meeting the above mentioned requirements.

[1]: R. RUPPERT, G. HAFENMAIR, A. KNAUPP, F. WINKHAUS, M. LEISS & M. HAINDL; DEVELOPMENT OF A RAPID SE-UHPLC METHOD FOR THE DETERMINATION OF PRODUCT-RELATED IMPURITIES IN BISPECIFIC ANTIBODY FORMATS; CASSS ANALYTICAL TECHNOLOGIES EUROPE 2017, BRUSSELS, BELGIUM, MARCH 14 -17



MEMBERS OF THE TEAM INVOLVED IN THE PROJECT: FROM LEFT TO RIGHT: ALEXANDER KNAUPP, DR. FRIEDERIKE WINKHAUS, GEORG HAFENMAIR, DR. MICHAEL LEISS, DR. RAPHAEL RUPPERT

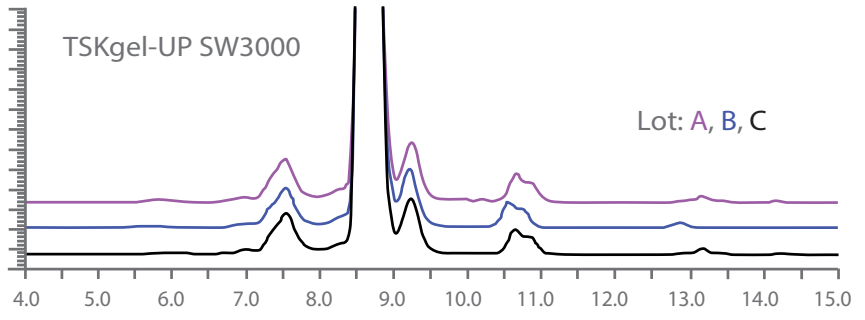


FIGURE: LOT-TO-LOT VARIATION OF TSKgel-UP-SW3000 [1]

05 EXPERT INSIGHTS

INSTITUTE FOR BIOENGINEERING AND BIOSCIENCES, UNIVERSITY OF LISBON, PORTUGAL

THE INSTITUTE FOR BIOENGINEERING AND BIOSCIENCES (IBB) IS A NEW RESEARCH UNIT CREATED IN 2013 AT THE UNIVERSIDADE DE LISBOA, PORTUGAL. THE INSTITUTE AIMS TO EXCEL IN RESEARCH AND ADVANCED EDUCATION IN BIOTECHNOLOGY, TO RESPOND TO THE CHALLENGES OF EXPLORING INNOVATIVE APPROACHES IN BIOSCIENCES AND BIOENGINEERING. WE MET ANA AZEVEDO AT THE RECENT HIC/RPC CONFERENCE, WHERE SHE PRESENTED MICROFLUIDIC APPROACHES FOR HIGH-THROUGHPUT SCREENING OF CHROMATOGRAPHY MEDIA AND RAPID METHOD OPTIMIZATION. WE USED THAT OPPORTUNITY TO TALK WITH ANA ABOUT THE RESEARCH PROJECTS OF HER GROUP IN LISBON.

Tosoh Bioscience (TB): Ana, at the recent HIC/RPC conference you gave an impressive introduction to the use of microfluidic devices in high throughput downstream processing development. What other research topics is your group at the IBB working on?
Anan Azevedo (AA): The research activities of our lab are essentially directed towards the design and development of novel purification processes in order to intensify and optimize the downstream processing of proteins and biopharmaceuticals, with special emphasis on antibody-based molecules (mAbs and Fabs), plasmid DNA and viruses. Several alternatives to the currently established downstream processing platforms of recombinant proteins are being explored, with main focus on aqueous two-phase extraction, nanomagnetic separation and of course chromatography, from a nano-scale to process scale.

(TB): Where do you apply chromatographic methods?
(AA): We apply chromatographic methods for both preparative and analytical proposes. Their high selectivity makes them the ideal method for the purification of high-value molecules. We are currently looking at multimodal chromatography (MMC) as the key to unlock current downstream bottlenecks. As multimodal resins bind proteins through multiple interactions, in contrast to conventional resins (e.g. IEX and HIC) that utilize a single binding mode, they can offer unique selectivity windows for biomolecules separation. However, the development of an optimized MMC process is not straightforward, and typically requires time-consuming optimization on a case-by-case basis. To overcome this drawback, we have developed a versatile and inexpensive method to expedite chromatography screening studies, based on micro-columns fabricated in-house by soft lithography. This platform allows the measurement of binding and elution kinetics in real time, at resin level, in a wide range of operating conditions, using reduced amounts of reagents (50 µL), target biomolecule (25 µg) and resin (70 nL), in less than 3 min.

Chromatography is also a powerful analytical method that can be used to quantify and determine the purity of our preparations. In the case of antibodies, we are using protein A affinity HPLC for quantification and SEC to determine aggregates levels. We have recently tested the new TSKgel UltraSW Aggregate and we were very happy with its performance.

(TB): Your group is very open to cooperations with industrial partners. Where do you see the values in this type of projects?
(AA): I believe we only have to gain from collaborations with industrial partners: the ideas arise after a fruitful discussion; the possibility of testing new materials or alternative materials to the ones we typically use; better understanding the needs of industry and the role that academia can play in addressing some industry challenges...

(TB): What do you think will be the key future challenges with regard to purification and analysis of biologics?
(AA): The challenge remains to develop ever more efficient and effective methods that are able to selectively separate the target molecule from all the remaining impurities with a high productivity, low cost and using a minimal number of steps. This will definitely require developing new or improved materials and processes; adapt traditional batch process to continuous processing and take advantage of single-use devices.

(TB): Ana, you are also involved in the organization of the 12th European Symposium on Biochemical Engineering Sciences – ESBES 2018 – taking place in Lisbon in September 2018. We are looking forward to meeting you there.

ANA AZEVEDO AND HER GROUP AT THE IBB

06
PEOPLE
BEHIND TOSOH

PATRICK ENDRES, TOSOH BIOSCIENCE GMBH

THE TECHNICAL SUPPORT GROUP AT TOSOH BIOSCIENCE GMBH IS LOCATED IN GRIESHEIM, GERMANY, AND OFFERS TECHNICAL SUPPORT BY PHONE, BY MAIL, IN WORKSHOPS OR ON CUSTOMER SITE. HEAD OF THE GROUP IS P.D. DR. EGBERT MUELLER, WELL KNOWN IN THE SCIENTIFIC COMMUNITY FOR HIS WORK IN THE FIELD OF SEPARATION TECHNOLOGY. FIVE TECHNICAL SPECIALISTS ARE COVERING THE TECHNICAL SUPPORT FOR GPC INSTRUMENTS, (U)HPLC COLUMNS AND PROCESS RESINS. WE ASKED PATRICK ENDRES, THE ROOKIE OF THE GROUP, TO DISCLOSE A LITTLE BIT ABOUT HIMSELF AND HIS JOB AT TOSOH.

Tosoh Bioscience (TB): Patrick, you joined Tosoh Bioscience some months ago. How did you get to know about Tosoh?
Patrick Endres (PE): In 2014, in the 5th semester of my bachelor studies, Egbert Müller (Technical Director at Tosoh Bioscience GmbH) gave a lecture about chromatography at my university. He also mentioned the possibility of internships and bachelor or master theses at Tosoh. As I really liked the topic, I applied and got the job. From June 2014 until March 2015, I did my bachelor thesis and an internship at Tosoh. Afterwards I went back to university to get a master's degree.

Tosoh seemed to be very happy with my performance and we kept contact throughout my master studies. During summer 2016 our contact got closer again, as we discussed the possibility of doing my master thesis at Tosoh and afterwards starting as a full-time employee. Everything went well and I started at Tosoh in November 2016 with my master thesis.

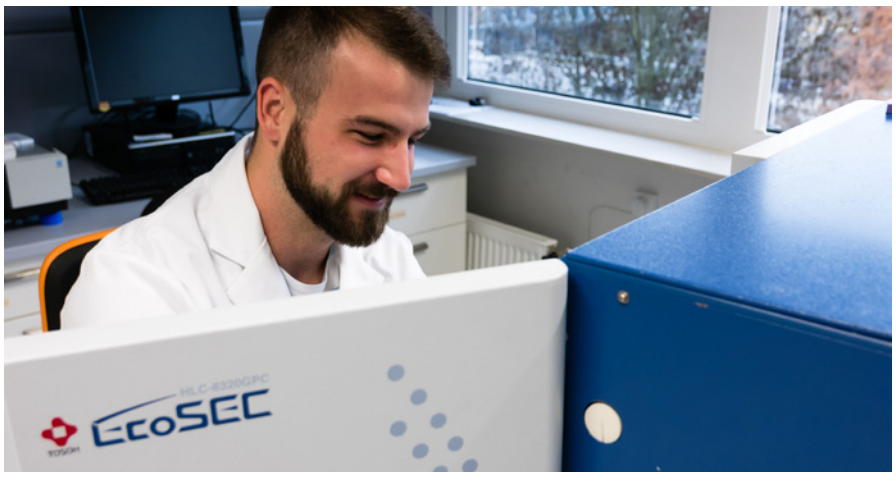
TB: What was the topic of your thesis?
PE: The title of my thesis was "Development and Evaluation of a Continuous Chromatography Process for the Purification of monoclonal Antibodies". I developed a batch protocol for a Protein A step and an aggregate removal step with cation exchange chromatography. Based on this process I developed and optimized a continuous process with TOYOPEARL resins. I presented the results of the cation exchange step during the PREP Symposium in Philadelphia in July. For the Protein A results, we are currently working on a publication.

TB: Could you please tell our readers a little bit about yourself and what you do for Tosoh?
PE: With the beginning of my thesis, I started my job induction and after I got confident, I helped our customers with application support via phone and e-mail. I finished my thesis in May 2017 and I am now testing prototype resins and doing application development in our lab in Griesheim, Germany. Additionally, I attend scientific conferences to present our new developments and assist our sales team at customer visits with hands-on experience of our products, which I gathered during my time in the lab.

TB: What part of the work do you like most?
PE: The best part is the variety of my job and the working environment. I really like the family-like atmosphere in our small team in Griesheim. Also, no day is like the day before. I encounter new challenges in method development, and also when talking to our customers via phone or e-mail.

TB: What were the highlights during your first months at Tosoh?
PE: The first small highlight was in December, when I did my first case of e-mail support and could help a customer. It was a very basic request, but it was the first thing I did on my own and I was really proud of it. Of course, the best feeling so far was when I handed in my thesis and successfully defended it in front of the scientific audience at my university.

TB: What are your interests besides Chromatography?
PE: I do a lot of sports and recently developed an interest for bouldering, which is climbing without a rope, with maximum height of around four to five meters. But my passion is motorsports and ever since I was a little kid I wanted to have my own racecar. During my time as a student I lacked the financial possibilities to pursue this hobby, but since February I got my own car to go racing on racetracks across Germany. Additionally I try to go karting at least once a month and could also get some of my colleagues of the technical department to join me at the karting track. But they have to learn a lot… :-D



PATRICK AT WORK …

… AND ON THE RACE TRACK.

07 GPC KUNSTSTOFF-INSTITUT

SEC – DEFINING DEGRADATION

THE KUNSTSTOFF-INSTITUT LÜDENSCHEID – ESTABLISHED IN 1988, DIN EN ISO 9001 CERTIFIED AND EQUIPPED WITH AN ACCREDITED TEST LAB ACCORDING TO DIN EN ISO/IEC 17025 STANDARD SINCE 2000 – COMBINES TOMORROW'S SCIENTIFIC KNOWLEDGE WITH TODAY'S MANUFACTURING PROCESSES. ITS MAIN FOCUS LIES ON QUALITY AND THE PROFITABILITY OF COMPANIES FROM THE PLASTICS INDUSTRY, ESPECIALLY IN THE AREA OF INJECTION-MOLDED PARTS MADE OF THERMOPLASTIC AND THERMOSET MATERIALS. IN THE FAILURE ANALYSIS LAB SIZE EXCLUSION CHROMATOGRAPHY IS BEING USED ON A REGULAR BASIS FOR THE DETERMINATION OF A POSSIBLE MATERIAL DEGRADATION OR MATERIAL DEVIATION.

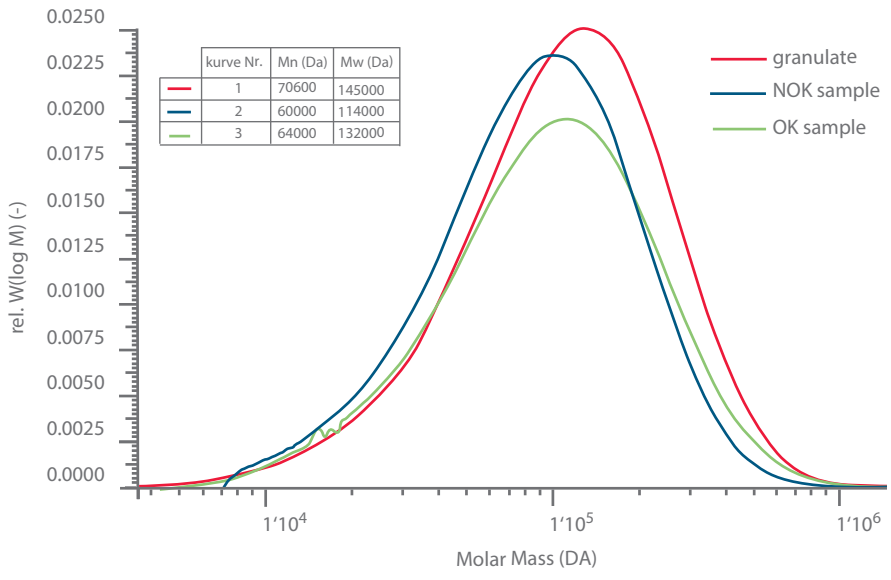
There are many parameters like granulate drying, holding time, mass and mold wall temperature, trapped air/burner and many more which influence the quality of an injection-molded article. Since the mechanical properties are directly linked to the molecular weight distribution of the polymer chains, size exclusion chromatography can help to resolve the question of suspected polymer degradation even in the final product. For this purpose the molecular weight distribution of good and bad samples are being compared with the corresponding granulate batch.

To evaluate the production process in detail, samples can be taken at various steps of the process. Is the main degradation taking place in the dryer or the hot-runner for example? Depending on the type of polymer, certain deviations are tolerable while others negatively affect the properties. For the measurement only a small sample is sufficient making this method ideal for small articles were the determination of the viscosity number or the melt flow index are not realizable. The polymer solution is being filtered to get rid of the filler content and being injected into our EcoSEC and compared to a polystyrene standard calibration curve. Consequently the measurements do not provide the absolute value, but permit a direct comparison between the samples. An example is illustrated in the figure below.

Here the NOK article demonstrates a significantly lower weight average compared to the granulate. However the OK sample also shows some degradation which reveals that a certain amount of degradation is normal for this kind of thermoplastic processing. But the focus is not always on the production process itself. A failure in the field can have multiple root causes. Degradation induced by heat, UV-light, chemicals and erosion can also be investigated using this method. Especially in the field of failure analysis the sample preparation is an essential aspect which is often underestimated. Sewing, sonicating, heating and uncooled grinding can lead to degradation and falsify the results. Degradation can be local therefore the sample must be taken out of the damaged area with respect to the correct preparation.

More details to SEC, especially in the case of re-granulate and recycled materials also compared to methods like melt flow index and viscosity number are part of the joint research project "Reliable quality control for the use of recyclates" which starts in beginning of 2018. Our labs as well as over 20 exhibitors can also be visited within the first Polymer Analytic Exhibition at the Kunststoff-Institut Lüdenscheid on 29th and 30th of November 2017. Listen to the lectures, discuss your applications with the experts and test the instruments in the hands-on sessions.

AUTHOR: **ANDREAS BERTZ, KUNSTSTOFF-INSTITUT LÜDENSCHEID; WWW.KUNSTSTOFF-INSTITUT.DE**



kurve Nr.	Mn (Da)	Mw (Da)
1	70600	145000
2	60000	114000
3	64000	132000

FIGURE: **COMPARISON OF OK-, NOK-SAMPLE AND GRANULATE**

QR CODE: **POLYMER ANALYTIC EXHIBITION**

08
WHAT'S HAPPENING TOSOH CORPORATION

TOSOH CORPORATION EXPANDS R&D CAPABILITIES

IN THE PREVIOUS ISSUE OF THIS MAGAZINE WE REPORTED ON THE ANNOUNCEMENT OF TOSOH CORPORATION, OUR PARENT COMPANY, THAT PRODUCTION CAPACITY FOR CHROMATOGRAPHY MEDIA WILL BE INCREASED IN RESPONSE TO THE GROWING GLOBAL DEMAND FOR PURIFICATION MEDIA. NOW, TOSOH CORPORATION HAS STARTED ANOTHER PROJECT AT ITS MAIN MANUFACTURING AND R&D COMPLEX IN NANYO, JAPAN. THE INVESTMENT OF ABOUT 85 MILLION EUROS WILL INCLUDE NEW RESEARCH FACILITIES AND A MODERNIZED MAIN GATE AREA, INCLUDING THE CONSTRUCTION OF A NEW MAIN BUILDING.

ARTIST'S RENDERING

Nanyo Complex is Tosoh Corporation's main manufacturing hub. This complex is nothing less than a self-contained city with its own power generation plants and port and shipping and, of course, manufacturing facilities. It is also the R&D center for Tosoh's specialty products business. The construction of new research laboratories will consolidate in one location laboratories that to date are dispersed in four locations. This will heighten the efficiency of the complex's R&D, chiefly by improving the functionality of its laboratories through proximity and the better leveraging of the synergies among the technologies being worked on at the various laboratories.

These and the other new laboratories at Nanyo Complex will increase coordination between technology themes through functional consolidation and will serve as development bases for the mid- to long-term growth of the Tosoh's specialty products business. The improved R&D will be further advanced through expanded bench test facilities and clean rooms and the introduction of other state-of-the-art R&D-related facilities.

NEWS & EVENTS | MEET TOSOH BIOSCIENCE

MEET TOSOH AT TRADESHOWS AND CONFERENCES

UPCOMING EVENTS

NOV. 7	2017	BIOSEPARATION FORUM DOWNSTREAM PROCESSING	COLOGNE [GERMANY]
NOV. 8	2017	BIOSEPARATION FORUM BIOANALYSIS	COLOGNE [GERMANY]
NOV. 29 - 30	2017	KUNSTSTOFFANALYTIK	KUNSTSTOFF-INSTITUT LÜDENSCHEID [GERMANY]
NOV. 29 - 30	2017	BIOPROCESS UK	CARDIFF [ENGLAND]
DEC. 6	2017	BIOSEPARATION FORUM	BASEL [SWITZERLAND]
FEB. 7 - 8	2018	11TH BIOINNOVATION LEADERS SUMMIT, BILS 2018	BERLIN [GERMANY]
MAR. 18 - 21	2018	ARABLAB	DUBAI [UAE]
APRIL 10 - 13	2018	ANALYTICA 2018	MUNICH [GERMANY]

TRAININGS | WORKSHOPS

NOV. 22 - 23	2017	CHROMATOGRAPHY IN PROCESS DEVELOPMENT & PRODUCTION BASIC COURSE IN ENGLISH | GRIESHEIM | [GERMANY]

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