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Conference Report

Olten Meeting 2012: Highlight the Potential of Drug Development November 28, 2012

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Abstract: How can the full potential of drug development be exploited? This question was in the focus of attention at the annual Olten Meeting of the Swiss biotech branch held on November 28, 2012. Renowned scientists from research institutions and industry gave us a glimpse behind the scenes and reflected on the current state of research in the field.

Keywords: Biotechnet · Biotechnology · Drug development

The development of new drugs with therapeutic potential is one of the most complex and difficult undertakings in the pharmaceutical industry, swallowing millions of dollars and man-hours. What makes the discovery of new therapeutic agents so difficult is the fact that the activity of a drug is the result of different factors such as bioavailability, toxicity and metabolism.

Tracking Drug-like Bioactive Compounds

At the ETH Zurich, ***Gisbert Schneider***, professor of computer-assisted drug design breaks new ground with a computational method for the reaction-based *de novo* design of drug-like molecules. The software DOGS (Design of Genuine Structures) he developed aims at the automated generation of new bioactive compounds. To have the computer come up with suggestions for potentially isofunctional molecules, there is only a single known reference compound required to start the molecular design cycle (Fig. 1). The algorithm additionally proposes a potential synthesis plan for each designed compound, based on a large set of readily available molecular building blocks and established reaction protocols. DOGS features a ligand-based strategy for automated *in silico* assembly of potentially novel bioactive compounds. "We implemented a deterministic compound construction procedure that explicitly considers compound synthesizability, based on a compilation of 25'144 readily available synthetic building blocks and 58 established reaction principles", explains the biochemist and computer scientist. The proof of the pudding was highly potent *de novo* designed ligand candidates blocking human Polo-like kinase I, an anti-cancer drug target, which were synthesized by his group as suggested by the software. The computational approach proved to be suitable for scaffold-hopping from known ligands to novel chemotypes, and for generating bioactive molecules with drug-like properties. "Our *de novo* design software gives rapid access to tool compounds and starting points for the development of a lead candidate structure", Gisbert Schneider draws a positive balance. "Both theoretical analysis and prospective case studies prove its ability to propose bioactive, plausible and chemically accessible compounds." *http://www.modlab.ethz.ch*

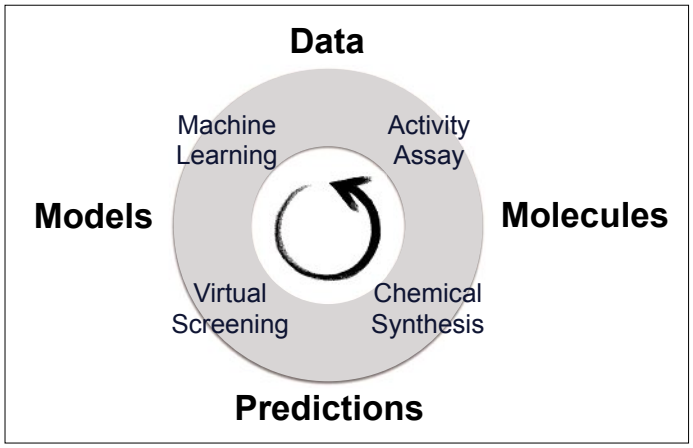

Fig. 1. A molecular design cycle that combines computational and 'wet' chemistry. In *de novo* design software like DOGS, all parts of the cycle are performed 'in silico', so that chemically feasible druglike candidate compounds emerge after a few virtual synthesis-and-test cycles. (Copyright Modlab ETHZ)

Bacterial Resistance to Antibiotics: An Evolutionary Change?

Antibiotics are losing their effectiveness at a rate that is alarming and seems to be irreversible. "In Europe alone, mortality rates are increasing and old diseases like tuberculosis re-emerge", states Dr. ***Marcel Tigges***, Co-Founder and CSO of BIOVERSYS AG. Especially high is the percentage of hospital-acquired infections caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). The dynamic young company has set itself the goal of switching off bacterial resistance with their proprietary technology enabling multi-level screening for TRIC (Transcription Repressor Inhibitory Compounds) that block the transcription of resistance-enabling genes, thus switching off bacterial resistance. Recent studies have shown the potential of compounds that inhibit the action of the repressor protein implicated in ethionamide resistance, thus stimulating activation of the drug and thereby restoring the activity of the antibiotic for treatment of *Mycobacterium tuberculosis*. MtB exhibits a very high level of intrinsic resistance to most antibiotics and all current treatments prove to be dramatically inefficient. "But such specific interference with regulators or signal transduction mechanisms involved in antibiotic resistance or virulence provides a new toolbox for novel combination of antimicrobial drugs with adjuvant molecules lacking intrinsic antibiotic activity", explains Marcel Tigges. Based on the successful application of its lead-compounds BV6481, the BIOVERSYS team is expanding its screening and compound portfolio to nosocomial bacterial strains (*e.g. Pseudomonas aeruginosa*, *Enterococcus faecium* or *Acinetobacter baumannii*) which claim many victims each year around the globe. The strategy of restoring or potentiating the activity of existing antibiotics may help – together with the development of new antibiotics and vaccination initiatives – to guarantee an efficient use of antibiotics for the medium-term future. *http://www.bioversys.com*

Targeting Cancer Cells and Tumor Stroma – A Weapon against Cancer?

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths in 2008. According to the World Cancer

Report, cancer rates could further increase by 50% to 15 million new cases by 2020. Although highly heralded 'targeted therapies' are used in clinical practice and show significant efficacy in some cancers, the overall survival rate of patients with the most frequent tumors remains extremely poor. Targeted therapies often produce favorable therapeutic responses only in a fraction of patients with a particular tumor type, some tumors regress and later recur and continue to grow in a state of heightened malignancy. That is why researchers like Dr. ***Urs Regenass***, Senior Director Oncology at Actelion Pharmaceutical Ltd. focus on the fact that cancer is heterogeneous regarding cancer cells and the interacting tumor stroma. The cancer cell–stroma interactions and the heterogeneity evolve during disease progression. "Cancer can only arise and enter a malignant state when cancer cells interact with the microenvironment, the stroma", states the scientist. Therefore it is necessary, despite the success of so-called 'targeted therapies' with a focus on cancer cells, to treat in addition the tumor stroma to make therapy more efficacious. As Urs Regenass explains, the model systems we use today to find and develop new drugs often only partially reflect the biology of human disease and often insufficiently reflect the interaction of cancer cells with the tumor stroma. That is why it is not surprising that many new anticancer medicines may be lost in clinical development although they were active in preclinical models. It is hence very important that preclinical models are checked for relevance and consistency with the clinical situation. "As an example I would mention Macitentan, a novel dual endothelia receptor antagonist that resulted from a tailored drug discovery process, identified by Actelion and tested in cancer therapy", explains Urs Regenass. "In models of ovarian carcinoma we found that endothelin and its receptors are relatively weakly expressed in cell culture but much more pronounced in animal tumors and in human disease. The therapeutic use in preclinical models of metastatic ovarian carcinoma in mice shows that Macitentan in combination with chemotherapy causes simultaneously the death of cancer cells and vascular endothelian cells and thereby slows tumor growth."

In vitro models are indispensible for drug discovery but "it is essential that the *in vitro* test systems express the therapeutic target structures and that those have physiologically the same impact as in the tumor of the patient", says Urs Regenass. "Moreover, test systems may need to reflect the cancer cell-stroma interactions, as exemplified by the glioblastoma cell-astrocyte interaction, similar to clinical situations, since the key to more successful treatment is to have a therapeutic effect on the cancer cells and the tumor stroma at the same time." This opens up a wide spectrum of new therapeutic approaches and drug combinations. *www.actelion.ch*

Assessing Drug Safety with 3D Cell Models

Today, safety assessment of novel drug candidates to a significant extent is based on *in vivo* testing as required by regulatory authorities. With the ambition to reduce the use of animals in drug development and the need to predict potential adverse effects at early stages before gross expenditure of resources, cellular systems to address drug effects have become increasingly important. But there is a hitch: Until today, conventional *in vitro* systems, *i.e.* single cell-type monolayer cultures, cannot represent the cellular and structural complexity of tissues and organs as interactions between different cell types which may influence the toxic response are not present. Furthermore, cell types often used in *in vitro* toxicology such as hepatocytes from liver have a very limited life span and thus toxicities developing over time may escape detection in short term experiments. But there is a silver lining on the horizon with nanotechnology, enabling engineers to create extremely small, but defined structures. The so created 3D scaffolds can not only maintain liver function during longer periods, the structures also provide cues for adhesion and growth of specific cell types in defined patterns for a long time (Fig. 2). "It is true that these *in vitro* systems with primary liver cells stay fully functioning over an extended period of time", states Dr. ***Adrian Roth***, Global Head Mechanistic Safety at Pharma Research Hoffmann-La Roche AG in Basel. "As the 3D liver systems also include non-parenchymal cells such as stellate and kupffer cells, they make it possible now

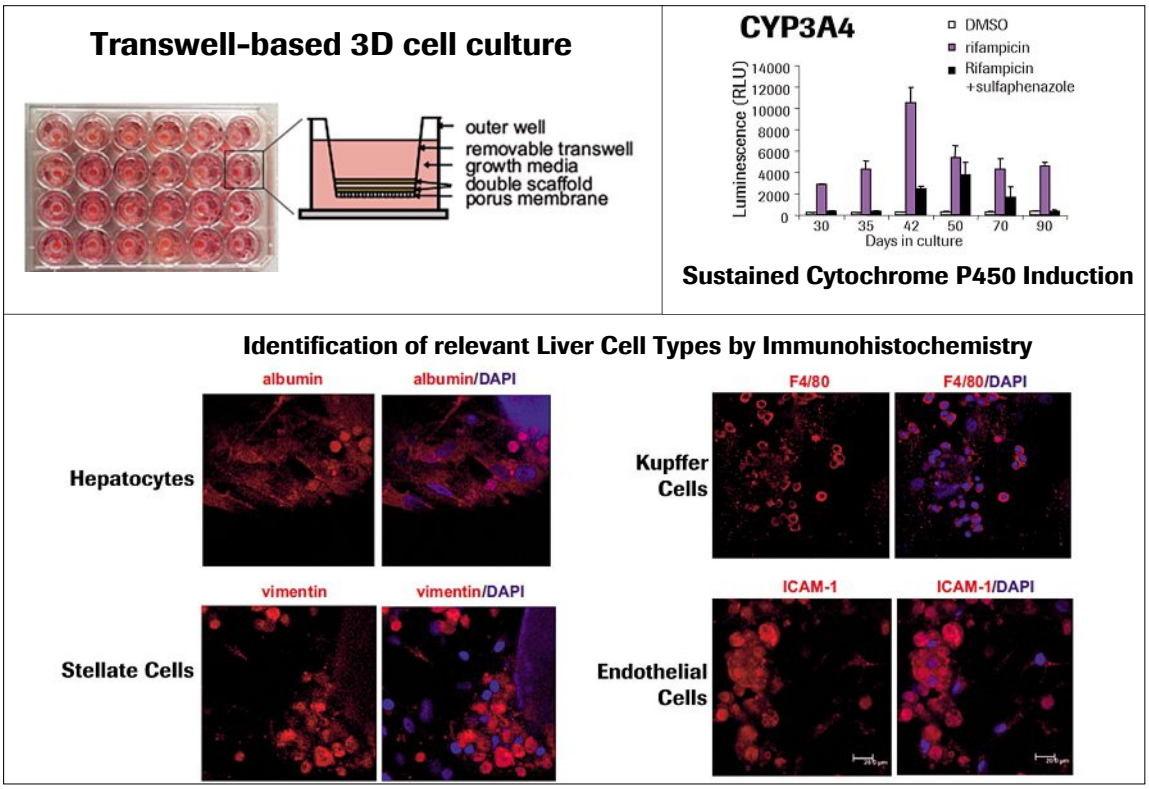

Fig. 2. (Copyright Hoffmann-La Roche AG)

to study inflammatory processes which are relevant for drug-toxicity *in vivo*".

The scientist predicts for the near future the combination of 3D models with – for example – stem cell-derived hepatocytes offering the potential to introduce human diversity into early pharmacology and toxicology screening systems. He is convinced that the possibility to have more human-like liver physiology in a small-scale *in vitro* system opens up new opportunities to investigate biomarkers for clinical purposes and to bridge preclinical markers and support efforts in favor of a personalized healthcare. And last, but not least can more targeted *in vitro* tools improve the predictivity of drug-safety assessment for humans, minimize the attrition rate of drug candidate and reduce the need for animal testing during drug development. *www.roche-pharma.ch*

How to Succeed with Biopharmaceuticals

'High price of failure drives drug development costs into the stratosphere', to quote a headline in a recent US magazine. It's all over town: The formulation of biopharmaceuticals should be made very early in their development: Consisting mainly of proteins or peptides, it is advisable to stabilize them in their active, native form until administration. Aspects like the protein structure, chemical degradation and aggregation studies in different aqueous solutions at different pH values and temperatures provide the experimental bases for the development of formulations and help to find conditions to stabilize the molecule", explains Professor Dr. ***Tudor Arvinte***, University of Geneva and Chairman and CEO of Therapeomic Inc. in Basel. High-throughput formulation (HTF) and high-throughput analysis (HTA) platforms permit in-depth physico-chemical characterization studies and allow investigation of hundreds of formulations for their stabilizing effects on the protein.

The formulation should not only be based on physical-chemical stability data but also reply to other needs like an easy application procedure, optimal release of the protein at the application site, optimal activity of the molecule at the target site, minimum side effects and realistic scale up and robust manufacture of the formulation. "The analysis of protein properties in formulations and drug delivery systems often require tailor-made analytical methods", states Tudor Arvinte. "These methods should be adapted to the necessities of the formulation and not to the requirements of the analytical techniques!" In his opinion, the analytical methods for the formulations should be able to detect small differences against a complex background and, if necessary, provide information on the protein structure in heterogeneous formulations such as aggregated slow-release formulations or proteins adsorbed onto adjuvants in vaccines.

"The investment in a good proof-of-concept, enabling formulation is minimal compared with the risk that companies are taking in performing human studies with non-optimized formulations", the researcher comments, referring to his own experiences. "The success of the medical proof of concept of the phase II and phase III clinical trials and the final market success all depend upon the quality of protein formulation."

Persistently Tracking the Mysterious FAP for Heart Attack Prevention

In Switzerland alone, 30'000 people every year are the victim of an acute coronary event, *i.e.* a heart attack or Angina Pectoris. Myocardial infarction is the number one cause of death worldwide. Regarding patients with cardiovascular risk factors, the clinician generally asks two questions: Who is at risk of a heart attack? How should they be treated? Heart attacks are caused by atherosclerosis, the development of so-called 'plaques' in blood vessels. Dr. ***Chad Brokopp***, working in the Regenerative Medicine Program at the University Hospital Zurich found out that the enzyme called 'Fibroplast Activation Protein FAP' previously observed in cancer and arthritis, also contributes to the inflammatory mechanisms of atherosclerosis. While studying FAP he found evidence that the enzyme contributes to plaque destabilization, the main cause of heart attack and stroke. "When plaques rupture open, blood clots form which block the vital flow of oxygen in a dangerous process known as atherothrombosis", explains the scientist. The research finding show that FAP clearly contributes to atherothrombosis in patients suffering a heart attack (Fig. 3).

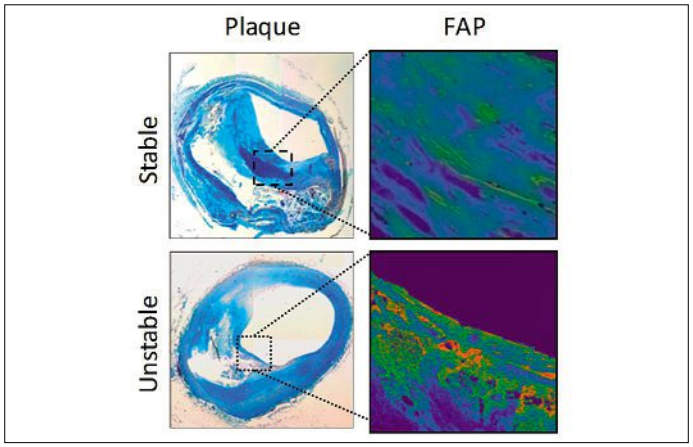

Fig. 3. FAP is increased in life-threatening unstable plaques. FAP (in red) is increased in benign 'stable' vs. life-threatening stable human coronary atherosclerotic plaques. (Copyright mabimmune)

That was the hour of birth of InfarctPrevent. This is a clinical theranostic package with a blood test to identify the patients to treat and a human antibody-based medication to reduce the risk of heart attack by blocking the negative effects of FAP. The aim is to prevent casualties thanks to an early diagnosis and a targeted treatment. The innovative infarct package consists of an FAP blood test to identify patients who will benefit from FlowMab – an antibody-based therapeutic for stabilizing life-threatening plaques to prevent infarction. "The FAP blood test and FlowMab are combined into a clinical package to identify high-risk patients expected to benefit from FAP-blocking therapy to prevent heart attacks", concludes Chad Brokopp. To bring this technology to the clinic he founded Mabimmune Cardiology AG in August 2011 (Schlieren, Switzerland) with a team of medical professors from the University Hospital Zurich. *www.mabimmune.com*

There is much work to do for the biotechnet partners from academia and industry to develop strategies taking advantage of the full potential biotechnology offers to bring onto the market safe, effective and commercially viable drugs which achieve the regulatory approval within a short period of time. The world-class scientific expertise and the great commitment of the biotechnet partners provide a basis to jointly realize the ambitious objectives for the future. *www.biotechnet.ch*

For further information, please contact Dr. Daniel Gygax, Professor of Bioanalytics at the FHNW School of Life Sciences and President of biotechnet. *www.biotechnet.ch*

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