Continuous Flow Production and Purification of Malaria Medications

Artemisinin combination therapies (ACTs) are currently the most effective drugs to combat malaria. Artemisinin was discovered in the 1970's as a promising anti-malarial candidate in an extract of *Artemisia annua*. Artemisinin derivatives with improved uptake and activity can clear most parasites in a few hours. Artemisinin is used in combination with other long-lasting malaria drugs in so called artemisinin combination therapies (ACTs).

The total synthesis of artemisinin, due to the molecular complexity is commercially not viable. Therefore, artemisinin is still almost exclusively obtained by extraction from the plant that is cultivated just for this purpose. An unstable supply, variation in the quality of the harvest and speculation have resulted in heavily fluctuating artemisinin prices. Due to the price of artemisinin ***up to 50% of the ACT drugs sold in Africa and Asia are fake and useless or harmful.*** To ensure sufficient supplies of high quality medication, access to ACTs at prices that are low enough for all in need, require reliable and inexpensive access to artemisinin derivatives.

Today, the key active pharmaceutical ingredients (APIs) of all ACT anti-malarials are produced in one or two chemical steps from artemisinin (**3**) (Fig. 1). ***The majority of artemisinin (~ 200 tons / year) is extracted*** and prices fluctuate with harvest yields. The plant produces dihydroartemisinic acid (DHAA) and its dehydrogenated precursor artemisinic acid (AA). Both AA and DHAA are potential starting materials for a semi-syntheses. The key step in the chemical semi-synthesis of artemisinin from DHAA involves singlet oxygen that can be produced photochemically from oxygen using a sensitizer. The scale-up of photochemical batch reactors that ensure uniform irradiation is not possible as light intensity decays quickly with increasing distance from the light source. Continuous flow chemistry offers a simple solution to overcome this serious challenge: ***by wrapping transparent tubing around a light source short residence times and convenient scale-up of photochemical reactions can be achieved.*** Thereby, high specific phase interfacial areas improve the mass transport of oxygen from the gas into the liquid phase. ***Prof. Seeberger initially developed the photochemical continuous synthesis of artemisinin from DHAA in 40% yield on 200 g scale per day*** (*Angew. Chem. Int. Ed.* **2012**, *51*, 1706). ***Careful optimization*** of the reaction parameters of the continuous flow semi-synthesis ***resulted in a greatly simplified process (residence time less than 12 minutes) and a significantly improved yield*** (69%). The continuous flow reaction requires now just one pump and an oxygen supply (*Chem Eur. J.* **2013**, 19, 5450). This process can be combined with continuous purification methods to obtain artemisinin of greater than 99.9% purity.

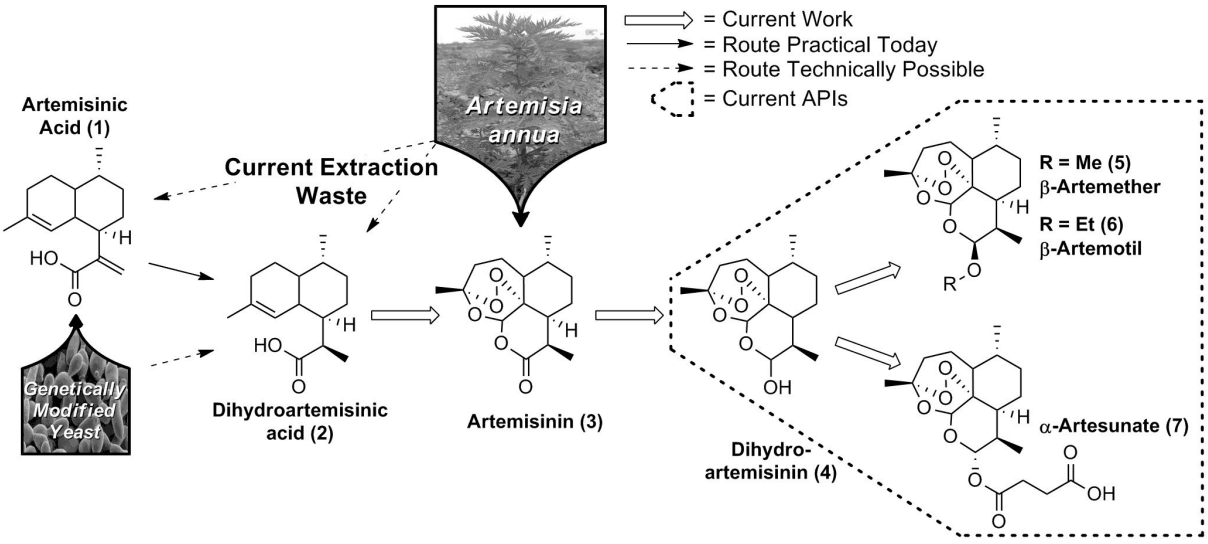

Figure 1. Production scheme of anti-malaria APIs from artemisinin obtained by extraction from *Artemisia annua* and genetically modified yeast combined with chemical modification. Dihydroartemisinin (**4,** combined with piperaquine in Eurartesim, Artekin and Duo-Cotecxin), β-artemether (**5**, combined with lumefantrine in Coartem), β-arteether (**6**, Artemotil), and α-artesunate (**7**, combined with amodiaquine in Coarsucam and ASAQ-Winthrop).

Critical to the cost of ACT medications is not just the procurement of artemsinin, but also its conversion to the corresponding APIs **4**-**7**. While API synthesis requires just one or two chemical steps, the reduction of artemisinin **3** to dihydroartemisinin (DHA) **4** posed a practical challenge due to the exothermicity of sodium borohydride ($NaBH_4$) reductions. The final modification of DHA **4** by esterification or etherification to furnish the APIs **5**-**7** is followed by batch-wise purification.

To demonstrate the power of the fully continuous synthesis/purification regime, Seeberger and Seidel-Morgenstern developed a continuous three-stage, multi-column chromatographic/crystallographic purification method for α-artesunate 7 (Figure 2). The continuous synthesis of artemisinin **3** from DHAA **2** (Fig. 2, module 1) was followed by a continuous process using a packed-bed column containing $NaBH_4$, Celite®, Li_2CO_3, and LiCl for the complete and clean reduction of crude artemisinin **3** to **4**. By combining modules 1 and 2, the first API **4** is produced from DHAA **2**. β-Artemether **5**, the API of the drug Coartem, was obtained in 25% overall yield from DHAA **2** by combining artemisinin reduction and methyl ether formation (modules 2 and 3). Artemotil **6** was obtained in 22% yield from **2**. Artesunate **7**, the active ingredient in Coarsucam, was continuously prepared from DHAA **2** in 28% yield using a succinic anhydride solution (*Chem. Comm.* **2014**, *50*, 12652)

Continuous monitoring using infrared spectroscopy (FlowIR) at the outflow of every module ***was introduced***. When a "lamp failure" was simulated, the result is observed approximately 11 minutes later (Figure 2c). The continuous synthesis of malaria APIs was complemented by ***continuous purification to yield pure APIs that meet the standards set by the FDA*** or WHO. A continuous three-stage, multi-column chromatographic/crystallographic purification method was developed for α-artesunate **7**. The first stage dilutes the stream exiting module 3 with *n*-hexanes, which decreases the solvent strength and precipitates polar byproducts. The recovery yield of **7** after dilution and filtration of the reaction mixture is 65%. Following filtration, the artesunate-containing stream can enter a separator consisting of five identical

chromatography columns participating in the following steps: loading, elution, rinsing, and equilibration. The artesunate fraction is subsequently fed directly into a continuous crystallizer to remove the remaining impurities. With 73% of **7** recovered from the crystallizer, the overall recovery yield of α-artesunate from the crude exit stream of module 3 is 48% with an HPLC purity of greater than 99.5%, exceeding the requirements set by the WHO.

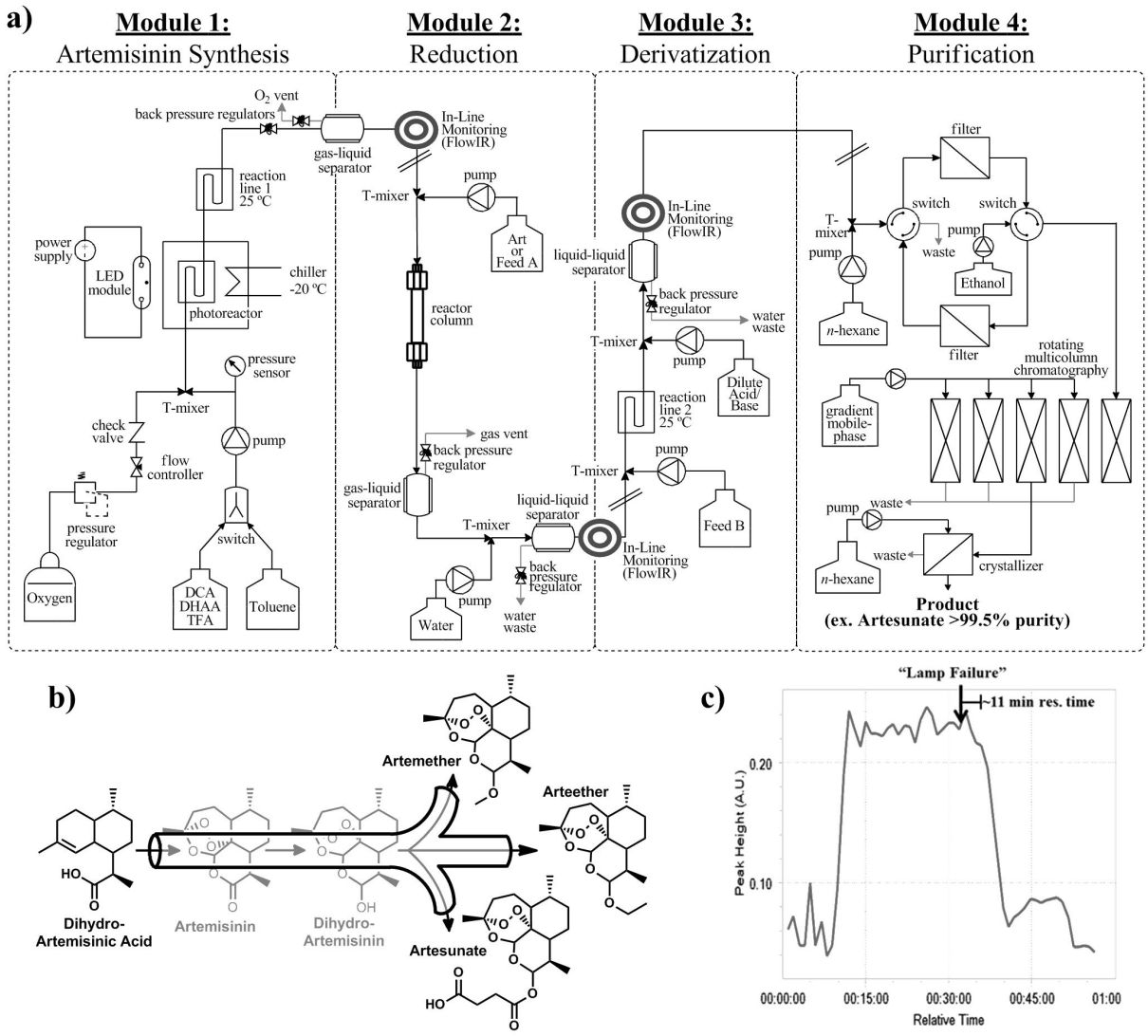

Figure 2. (a) Four module chemical assembly line system for the continuous synthesis and purification of artemisinin APIs. DCA: 9,10-dicyanoanthracene, DHAA: dihydroartemisinic acid, TFA: trifluoroacetic acid, Art: artemisinin. (b) The conceptualized synthesis of artemisinin APIs from the plant waste material dihydroartemisinic acid. (c) The system includes three in-line monitoring points using FlowIR, module 1 shown here with detection of a "lamp failure" by loss of signal at 1033 cm^{-1}.

The process Seeberger and Seidel-Morgenstern developed is currently implemented in a pilot plant in Vietnam to enable the production of less expensive anti-malaria medications and increase participation of developing nations in the value chain of drug production.

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Berlin, December 4, 2014

Nomination of Professors Peter H. Seeberger and Andreas Seidel-Morgenstern for the "Humanity in Science Award"

Dear Members of the Selection Committee,

I am hereby nominating Professors Dr. Peter H. Seeberger and Andreas Seidel-Morgenstern of the Max-Planck Institutes in Potsdam and Magdeburg for the "Humanity in Science Award". The two chemists and engineers have used a **combination of flow chemistry and advanced chromatography methods to produce Artemisinin Combination Therapies (ACTs) the most important malaria medications extremely efficiently from a plant waste material, air and light**. This process is currently being applied in Asia and Africa to provide access to the drugs to those most in need in Africa and South East Asia. As such, the nominees are a perfect match for this award and provide a glowing example of what advanced chemical and analytical methods are capable of today and how these methods can make a difference to people in need.

The work of the nominees over the past three years has provided a very simple, new method to produce ACT drugs using flow chemistry and chromatography in a high yielding and scalable manner. Until today, artemisinin, the core compound present in all ACTs is extracted from a plant primarily grown in China and Vietnam. This extract is converted to the APIs artemether and artesunate via two further chemical reactions. The difficulties associated with the process along with the mark ups of each resale render the drugs expensive.
Peter Seeberger invented a flow chemistry approach to convert dihydroartesinic acid, a plant waste product that is obtained during the extraction of sweet wormwood in the same amounts as the desired artemisinin and is currently being discarded. The photochemical flow process uses a reactor that is illuminated with a LED lamp and produces artemisinin in 65% yield from DHAA.

Collaboration with the Max-Planck colleague Prof. A. Seidel-Morgenstern resulted in the combination of continuous flow chemistry with simulated moving bed (SMB) chromatography produced completely pure artemisinin that meets WHO criteria of purity. Seeberger and Seidel-Morgenstern developed a continuous synthesis process that converted DHAA via artemisinin all the way to the APIs artemether or artesunate The APIs that are produced by flow chemistry are purified by SMB. Currently, this invention is being translated to a real life application via the spin-off company ArtemiFlow that is in the process of setting up a continuous flow synthesis and purification facility in Asia to produce ACTs at greatly reduced prizes.

I believe that Professors Peter H. Seeberger and Andreas Seidel-Morgenstern from the Max-Planck Institutes are most deserving candidates for the "Humanity in Science Award" since they have demonstrated that continuous chemistry coupled with continuous chromatography can impact the life of millions of people by making the most important anti-malaria drugs via a continuous process. By translating the scientific accomplishments to real-life application via the Spin-off company ArtemiFlow, they stand to lower the cost of life-saving medicines and push faked medicines from the African and Asian markets.

Sincerely,

A. Knauer

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Brief CVs of the Main Nominees

Peter H. Seeberger studied chemistry and biochemistry in Erlangen (Germany) and Boulder (USA). After completing his PhD and performing research at the Sloan-Kettering Cancer Center Research in New York he built an independent research program at MIT where he was promoted to Firmenich Associate Professor of Chemistry with tenure after just four years. After six years as Professor at the Swiss Federal Institute of Technology (ETH) Zurich he assumed positions as Director at the Max-Planck Institute for Colloids and Surfaces in Potsdam and Professor at the Free University of Berlin. In addition he serves as Affiliate Professor at the Sanford-Burnham Institute for Medical Research (La Jolla, USA) and honorary Professor at the University of Potsdam.

Professor Seeberger's research on the chemistry and biology of carbohydrates, continuous flow chemistry and automation of chemistry, carbohydrate vaccine development and a broad range of topics from engineering to immunology has been documented in over 370 peer-reviewed journal articles, two books, more than 35 patents, over 150 published abstracts and more than 670 invited lectures. This work was recognized with more than 25 international awards from the US (*e.g.* Arthur C. Cope Young Scholar Award, Horace B. Isbell Award, Claude S. Hudson Award from the American Chemical Society), Germany (*e.g.* Körber Prize for European Sciences), Holland (Havinga Medal), Israel (Honorary Lifetime Member Israel Chemical Society), Japan (Yoshimasa Hirata Gold Medal), Switzerland ("The 100 Most Important Swiss") and international organizations (Whistler Award 2012, International Carbohydrate Society). In 2013 he was elected to the Berlin-Brandenburg Academy of Sciences.

Peter H. Seeberger served the scientific community in many functions. He greatly supports the idea of open access publishing as the Editor-in-Chief of the *Beilstein Journal of Organic Chemistry*, was the Editor of the *Journal of Carbohydrate Chemistry* and serves on the editorial advisory boards of many other journals.

Through his work in the area of neglected diseases, Peter Seeberger has become involved in philanthropic causes. He is a co-founder of the *Tesfa-Ilg "Hope for Africa" Foundation* that aims at improving health care in Ethiopia that recently helped to build a bed-net factory and established an IT training center.

The research in the Seeberger laboratory has given rise to several spin-off companies in the USA and Germany.

Andreas Seidel-Morgenstern graduated from Technische Hochschule Leuna-Merseburg and received a Ph.D. from the Institute of Physical Chemistry of the Academy of Sciences in Berlin. After working as a postdoctoral fellow at the University of Tennessee in Knoxville he defended a Habilitation at the Technical University Berlin. Subsequently he worked for Schering AG in Berlin, before becoming in 1995 Professor of Chemical Process Engineering at the Otto von Guericke University in Magdeburg. In 2002 he was appointed as a Director at the Max Planck Institute for Dynamics of Complex Technical Systems, where he is head of the "Physical and Chemical Foundations of Process Engineering" group.

The research interests of Andreas Seidel-Morgenstern include heterogeneous catalysis, the development of new reactor concepts, crystallization, adsorption and

preparative chromatography. The results of his work are published in almost 400 research papers.

Andreas Seidel-Morgenstern received the Max Buchner Award of Dechema (2000), holds Honorary Doctorates of the University of Southern Denmark (Odense, Denmark) and the Lappeenranta University of Technology (Finland). He is Member of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) and the German National Academy of Science and Engineering (Acatech).

Full citations of papers published by the nominees that describe the work

1. Levesque, F.; Seeberger, P.H.; Continuous flow synthesis of the antimalarial drug artemisinin; *Angew. Chem. Int. Ed.* **2012**, *51*, 1706-1709.
2. Kopetzki, D.; Lévesque, F.; Seeberger, P.H.; A Continuous Flow Synthesis of Artemisinin; *Chem Eur. J.* **2013**, 19, 5450-5456.
3. Gilmore, K.; Kopetzki, D.; Lee, J.W.; Horvath, Z.; Horosanskaia, E.; McQuade, D.T.; Lorenz, H.; Seidel-Morgenstern, A.; Seeberger, P.H.; Continuous Synthesis of Artemisinin-Based Medicines; *Chem. Comm.* **2014**, *50*, 12652-12655.