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Meeting Report

Signal Transduction Modulators for Cancer Therapy: From Promise to Practice?

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Cancer cells receive signals from their environment, stimulating them to grow and to proliferate. These signals are carried by autocrine, paracrine, and endocrine growth factors that activate surface receptors on the outside of cells. To translate activation of a membrane-bound receptor into a biological response, the signal generated by receptor activation needs to be carried to the nucleus to trigger protein synthesis. This is achieved by the activation of a cascade of intracellular biochemical reactions, the so-called signal transduction pathways. In cancer cells, elements of signal transduction pathways are often mutated or overexpressed compared with normal cells. Oncogenic gene mutations frequently lead to constitutive activation of signal transduction elements, such as growth factor receptor tyrosine kinases, mimicking a situation of continuous activation of the receptor, even in the absence of the relevant growth factor. Also, more downstream signal transduction elements may be mutated or overexpressed, contributing to the malignant phenotype.

The elucidation of signal transduction pathways in cancer cells, both at the proteomic and the genomic levels, has fueled the design of drug molecules intended to act at specific proteins of the signal transduction cascade, often referred to as signal transduction modulators (STMs). STMs may interfere with signal transduction processes by blocking cell surface receptors, inhibiting growth factor receptor tyrosine kinases, or inhibiting the effects of further downstream genes, such as the mitogen-activated protein kinases. Many drug molecules directed against a wide range of signal transduction elements are being evaluated worldwide as potential anticancer therapies (Table 1). Several STMs are currently in clinical trials; others are still in preclinical research and development. Two anticancer drugs, trastuzumab and imatinib, which can be considered STMs, have already received worldwide regulatory approval in several cancer indications. Thus, the area of signal transduction modulation in cancer therapy has reached a state of maturity warranting a dedicated international scientific meeting.

The Amsterdam-based NDDO Research Foundation and a number of academic key opinion leaders, including *Drs. Bob Pinedo, John Mendelsohn, Jose Baselga,* and *Bruce Chabner*, have joined forces to initiate a series of meetings under the title: International Symposium on Signal Transduction Modulators in Cancer Therapy. The first meeting in this series was held in Amsterdam, September 23-25, 2002, and was very successful in bringing together the world's leading experts from academia, governmental agencies, and industry [1, 2]. About 350 delegates, representing over 25 countries, attended the two-and-a-half day meeting at the intimate venue of the "Vrije Universiteit" in Amsterdam. They reviewed various aspects of STMs in (experimental) cancer therapy including:

- Identification of new drug targets in signal transduction pathways
- STM drug design strategies

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Figure 1. **Dr. John Mendelsohn** *(left), Director, M.D. Anderson Cancer Center, receiving the NDDO Honorary Lecture Diploma from* **Dr. Coenraad van Kalken** *(right), Director, NDDO Research Foundation.*

- Preclinical data on novel STMs
- Recent clinical and translational data on STMs in clinical development
- Methodological and regulatory issues in the development of STMs

One of the many highlights was the presentation of the NDDO Honorary Lecture, *Targeting the EGF Receptor in Cancer Therapy*, by *Dr. John Mendelsohn*, Director of the M.D. Anderson Cancer Center, Houston, TX. *Dr. Mendelsohn* was awarded the NDDO Honorary Lecture (Fig. 1) for his pioneering research on the role of growth factors and growth factor receptors in tumor cell proliferation. The focus of his work has been on the epidermal growth factor receptor (EGFR) and its signaling mechanisms. EGRF is expressed at high levels in about one-third of epithelial cancers. Autocrine activation of the EGFR appears to be critical for tumor growth. Nowadays, EGFR and its tyrosine kinase are targeted by a range of STMs in clinical development (Table 1). *Dr. Mendelsohn* and his group developed a murine antibody, the human:murine chimeric version which is now being investigated in phase III clinical studies. This drug is known as C225 or cetuximab. Another EGFR blocking agent is EMD72000, a humanized monoclonal antibody. Interim results of a phase I pharmacokinetic/pharmacodynamic study with this drug, conducted by the group of symposium co-chair *Dr. Jose Baselga* (Barcelona, Spain), were reported during the meeting.

Dr. Baselga could not attend the symposium in Amsterdam for a very good reason—he was presenting clinical data on ZD1839 (gefitinib) to the U.S. Food and Drug Administration Oncology Drug Advisory Committee (ODAC), which met simultaneously to formulate a recommendation on this small-molecule EGFR tyrosine kinase inhibitor. ODAC recommended ZD1839 for expedited approval as a third-line treatment for non-small cell lung cancer (NSCLC), mainly on the basis of international phase II studies. The results of two of these studies, IDEAL 1 and 2, were presented in poster form in Amsterdam.

ZD1839 and several other small-molecule EGFR inhibitors under development were reviewed in an excellent comprehensive overview by *Dr. Giaccone* (VU Medical Center, Amsterdam, The Netherlands). The most advanced in development after ZD1839 is OSI-774 (erlotinib), another EGFR tyrosine kinase inhibitor. OSI-774 has a high degree of similarity with ZD1839 in its preclinical profile

Table 1. Selection* of antitumor and antivascular STMs under investigation for cancer therapy

Drug name	Molecular target
17-AAG, 17-DMAG	Heat shock protein-90
AP23451	Src protein kinase
BAY 43-9006	Raf kinase
Bevacizumab	VEGFR
2C4 monoclonal antibody	ErbB2 receptor
C225, cetuximab	EGFR
CCI-779	m-TOR
CI-1033	HER receptors
CI-1040	MEK1/MEK2
COXIBs	cyclooxygenase-2 (COX-2)
Cpd5	Cdc25 dual specific phosphatases
CT-32228	LPAAT-beta
CT53518	Flt3 tyrosine kinase
EMD72000	EGFR
Flavopiridol	Cyclin-dependent kinases, VEGF, P-TEFb
GW211	EGFR and HER2
IMC-1C11, IMC-2C6	VEGFR2
OSI-774, erlotinib	EGFR tyrosine kinase
PKI 166	EGFR tyrosine kinase
PS-341, bortezomib	Proteasome
R115777, tipifarnib	Farnesyl transferase
STI571, imatinib	Bcr-abl, PDGF, kit receptor tyrosine kinases
SU11248	Multiple receptor tyrosine kinases
SU5416	VEGFR tyrosine kinase
Trastuzumab	HER2
U0126	Janus kinase-2
UCN-01	Protein kinase C
ZD1839, gefitinib	EGFR tyrosine kinase
ZD6126	Endothelial cell tubulin cytoskeleton
ZD6474	VEGFR and EGFR tyrosine kinases

*Noncomprehensive list; selection based on *Proceedings of the 1st International Symposium on Signal Transduction Modulators in Cancer Therapy* [2].

and is developed clinically much the same way as ZD1839. OSI-774 has shown clinical activity in pretreated NSCLC patients and is currently being evaluated in randomized phase III studies in combination with chemotherapy as first-line treatment. The results of these studies are awaited anxiously, since the results of very similar studies with ZD1839 reportedly have failed in demonstrating a survival benefit for the EGFR tyrosine kinase inhibitor. Other growth factor tyrosine kinase inhibitors are slightly different from ZD1839 and OSI-774 in that they inhibit other receptors of the (HER) family at similar concentrations as the EGFR tyrosine kinase. Examples are CI-1033, which can inhibit all four HER receptors, and GW211, which inhibits both EGFR and HER2 equally well. Both drugs are being evaluated in phase II clinical studies in various tumor types. A prominent feature of the toxicity profile of all these receptor tyrosine kinase inhibitors is skin toxicity in the form of rash and acneic reactions. However, their overall toxicity profiles are relatively mild, allowing their chronic daily administration, also in combination with standard chemotherapy.

In his keynote lecture, *Dr. Axel Ullrich* (Martinsried, Germany) reviewed the exploitation of genetic alterations in tumor cells as the basis for anticancer drug design and development. This concept was employed successfully in the design of the humanized anti-HER2 monoclonal antibody trastuzumab, the first oncogene-based therapeutic for breast cancer. Along the same lines of research, Flk-1/vascular endothelial growth factor receptor-2 (VEGFR2) has recently been identified as a critical signaling element in tumor angiogenesis and a potential target for novel antiangiogenic agents.

The (developing) tumor vasculature has become the target of a range of experimental anticancer agents, many of which are STMs interfering with the process of angiogenesis. The recombinant humanized anti-VEGF antibody bevacizumab is capable of neutralizing all VEGF isoforms and has demonstrated clinical activity in pretreated patients with metastatic breast cancer (monotherapy) and in metastatic colorectal cancer (in combination with 5-fluorouracil/leucovorin). The drug is currently being evaluated in phase III trials (*Dr. Eric Hedrick*, San Francisco, CA).

Exciting data on a synthetic small-molecule antiangiogenic STM were reported by *Dr. Jerry McMahon* (San Francisco, CA). SU11248 is an orally active inhibitor of multiple receptor tyrosine kinases. The drug is active against four different tyrosine kinases in the nanomolar concentration range. Although the results of an ongoing phase I study at Institut Gustave Roussy (Villejuif, France) were reported in a condensed form, they clearly impressed the audience by reports on a few impressive clinical responses. A later report on the same study, presented at the European Organization for the Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research Conference on Molecular Targets and Cancer Therapeutics (Frankfurt, November 2002), confirmed the relatively high response rate in this study in patients with advanced cancer.

These and many other drug molecules discussed during the symposium illustrate the wealth of the signal transduction machinery as a source of molecular anticancer drug targets. So, to come back to the question posed by the title of this report, the 1st International Symposium on Signal Transduction Modulators has definitely confirmed the promise that signal transduction pathways and STMs hold for the future of cancer therapy. However, the translation of these promises into the reality of superior drugs for use in daily practice may be harder than anticipated when the first STMs received regulatory approval in cancer indications. The recently reported disappointing results for ZD1839 in first-line treatment of NSCLC may not remain the only disappointment surrounding STMs.

An important question is whether the lack of efficacy in these pivotal trials was due to failure of the STM concept or failure of the methods employed to test the drug in patients. It cannot be denied that ZD1839 and other STMs in advanced clinical development are being subjected to conventional drug development methodology, which worked for cytotoxic chemotherapy in the past. However, being relatively nontoxic, molecularly targeted agents directed against tumor-specific aberrations, these drugs may require innovative drug development strategies and trial designs in order to reveal their true potential.

Dr. Elizabeth Eisenhauer of the National Cancer Institute of Canada Clinical Trials Group (Kingston, Canada) presented an excellent review of the challenges facing those involved in the clinical development of STMs and the lessons already learned from ongoing programs. The challenges are multiple and related to the issues of dose-effect relationships for efficacy and toxicity, the type of effect expected at the tumor level (shrinkage, growth delay), the effects on the molecular target in patients (not to be confused with clinical efficacy, which remains to be demonstrated by survival end points), the way of administering STMs (on a continuous or cyclical basis like the conventional chemotherapeutic agents), and the selection of clinical trial populations (metastatic disease, adjuvant setting, or "enriched" populations in terms of target expression). From the clinical trials of STMs completed or ongoing to date, a number of lessons can be learned:

- The selection of doses of STMs for phase II/III evaluation has been achieved with a reasonable degree of success by the use of toxicity and drug blood level criteria rather than tumor target information.

- Conventional phase II studies looking at tumor regression in response to single-agent STM administration have been relatively predictive for efficacy in phase III studies. Of the six agents inducing tumor regression in phase II, four have yielded positive results in phase III thus far.
- Chronic dosing is widely used in ongoing STM drug development programs, but there is no evidence that this is the preferred strategy.
- Current evidence speaks against the use of STMs in combination with conventional chemotherapy as the only approach for a successful outcome. An alternative strategy that may be considered is to combine different STMs.
- Little information has been collected thus far on tumor target effects. It is advisable to collect this type of information in future trials as it may teach us, in case a new STM fails in clinical trials, whether the drug was inappropriate and did not affect the tumor target or the selected target was irrelevant for efficacy.
- Also, little information has been collected on tumor characteristics in terms of target mutation and amplification levels (which tumors are more vulnerable) or molecular patterns (what patterns in tumors lead to efficacy).
- Study populations in STM clinical development programs have all been patients with recurrent metastatic disease thus far. By putting these agents in the worst possible scenario first, their real impact may have been underestimated so far. According to *Dr. Eisenhauer*, STMs should not only be tested in advanced disease, but also in the adjuvant setting.

Only properly designed drug development programs and clinical trials will be able to provide more definitive answers about the potential of STMs in cancer indications. Also, the selection of STMs as candidates for clinical development may need revision. In view of the complexity of intracellular signaling cascades, highly selective STMs may not be the best clinical candidates. Instead, agents blocking multiple signal transduction pathways simultaneously may be required for meaningful clinical activity (*Dr. S. Grant*, Richmond, VA).

The lively plenary discussion on these methodological and regulatory themes at the end of the Amsterdam symposium, with *Dr. Eric Rowinsky* (San Antonio, TX) as an inspiring moderator, made it clear that more questions than answers will be around for the time being. Hopefully, some of these questions will be answered by the time of the next symposium in this series [3].

References

1 The 1st International Symposium on Signal Transduction Modulators in Cancer Therapy. Abstracts. NDDO Research Foundation. Available from the NDDO website at: http://www.parthen-impact.com/pco/7_0214/public/.

2 Proceedings of the 1st International Symposium on Signal Transduction Modulators in Cancer Therapy (hard copy). NDDO Research Foundation. Available via e-mail to: congress@nddo.org.

3 The 2nd International Symposium on Signal Transduction Modulators in Cancer Therapy. Amsterdam, October 23-25, 2003. Information requests by e-mail to: congress@nddo.org (re. STM-2003).