J. Steroid Biochem. Molec. Biol. Vol. 37, No. 6, pp. 1089–1095, 1990
Printed in Great Britain.

0960-0760/90 $3.00 + 0.00

GROWTH FACTOR-RECEPTOR PATHWAY INTERFERING TREATMENT BY SOMATOSTATIN ANALOGS AND SURAMIN: PRECLINICAL AND CLINICAL STUDIES

J. G. M. KLIJN,* B. SETYONO-HAN, G. H. BAKKER, M. E. L. VAN DER BURG, M. BONTENBAL, H. A. PETERS, A. M. SIEUWERTS, P. M. J. J. BERNS and J. A. FOEKENS

Division of Endocrine Oncology (Department of Medical Oncology), Dr Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

Summary—Interference in growth factor mediated pathways is a new strategy in the treatment of cancer. Somatostatin analogs can inhibit hormone and growth factor secretion, while suramin can block the binding of several growth factors to their receptors. In addition, somatostatin analogs can cause direct growth inhibitory effects after binding to tumoral somatostatin receptors. We tested the efficacy and endocrine effects of chronic treatment with three somatostatin analogs (Sandostatin,® RC-160 and CGP 15-425) or suramin in several tumor models and in patients with various types of cancer. Treatment with somatostatin analogs caused growth inhibition of breast cancer cells (MCF-7) *in vitro*, and of rat transplantable pancreatic (50–70% inhibition) and prostatic Dunning tumors (12% inhibition). No tumor growth inhibition was observed with respect to DMBA-induced rat mammary tumors, a transplantable colon tumor and a rhabdomyosarcoma in rats. In 34 patients with metastatic pancreatic or gastrointestinal adenocarcinomas chronic Sandostatin treatment caused stable disease in 27% of the patients, but no objective remissions. Somatostatin receptors were found in the responding MCF-7 mammary tumor cells, rat pancreatic tumors and in 20–45% of human breast cancer specimens [*J. Steroid Biochem. Molec. Biol.* **37** (1990) 1073–1077], but not in rat DMBA-mammary tumors or in 10 human pancreatic adenocarcinomas. Suramin caused significant dose-dependent growth inhibition of human breast cancer cells *in vitro* and of rat pancreatic tumors *in vivo* in the presence of plasma levels up to 150 μg/ml. In a preliminary clinical study concerning 11 patients with various tumor types we observed significant hematological, biochemical, endocrine and clinical side effects, but no objective remissions in spite of relevant peak plasma suramin concentrations of 270–330 μg/ml. In conclusion: somatostatin analogs and suramin can cause growth inhibition of various experimental tumors *in vitro* and *in vivo*, but the clinical value has to be established for several types of cancer, especially with respect to suramin and suramin-like compounds.

INTRODUCTION

Blocking growth factor mediated pathways is a new strategy in the treatment of cancer. In principle, there are several possibilities for using knowledge on growth factors and their respective receptors in the choice of cancer therapy (Table 1). To date, a few treatment modalities are available in clinical practice. The secretion of hormones and growth factors, especially growth hormone (GH) and insulin-like growth factor 1 (IGF-1), can be decreased by administration of somatostatin analogs (Table 2) [1–3]. In addition, somatostatin analogs can inhibit tumor growth by direct antiproliferative effects via somatostatin receptors being present in several tumor types [4–7] (see also sections in Refs [5, 7]). Another strategy is to block the binding of circulating or autocrine/paracrine growth factors to their

Table 1. Possible strategies for intervention in growth factor mediated pathways

1.	Identification of patient subgroups with different prognoses based on growth factor receptor status.
2.	Withdrawal of growth stimulatory growth factors (e.g. TGF-α, EGF, IGF-1).
3.	Administration of growth inhibitory growth factors (TGF-β).
4.	Growth factor analogs.
5.	Growth factor antagonists: suramin; alkyl lysophospholipid derivatives.
6(a).	Cytostatic drugs linked to growth factors or growth factor antibodies.
6(b).	Radiolabeled growth factors (^{131}I).
7.	Antibodies against growth factor receptors (anti-EGFR).
8.	Growth factor receptor tyrosine kinase inhibitors.
9.	Gene therapy.

Proceedings of the 2nd International EORTC Symposium on "Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti-)Steroidal Agents", Rotterdam, The Netherlands, 9–11 April 1990.

*To whom correspondence should be addressed.

Table 2. Mechanism of action of the tumor growth inhibitory effects of somatostatin analogs

1. Inhibition of the secretion of GH, insulin and/or other gastrointestinal hormones?
2. Inhibition of IGF-1 production and/or other tumor growth factors?
3. Inhibition of angiogenesis?
4. Direct antimitotic effect on the tumor cells?

receptors by suramin [8–11], a polyanionic agent which also dissociates growth factors from their receptors (Table 3). Therefore we have tested the effects of treatment with somatostatin analogs or suramin in different experimental models and in patients with various types of cancer (Tables 4A and 4B).

SOMATOSTATIN ANALOGS

As indicated in Tables 4A and 4B we have used three different somatostatin analogs, but in most studies we used the analog Sandostatin.

Breast cancer

Direct growth inhibitory effects were demonstrated by the natural hormone somatostatin-14 and two analogs (Sandostatin and CGP 15-425) on MCF-7 human breast cancer cells (Fig. 1). Previously we demonstrated the presence of specific somatostatin receptors on MCF-7 cells [12]. With respect to the dose–response relationship a bell-shaped curve was observed with the maximal inhibition of tumor cell growth at a sharply defined amount of these agents (10 nM) [12].

In vivo we tested the efficacy of Sandostatin treatment in rats with DMBA-induced mammary tumors. In this tumor model we observed no (direct or indirect) growth inhibitory effect due to the absence of somatostatin receptors in these mammary tumors and insufficient suppression of plasma hormone levels [13]. However, Szende *et al.* [14] demonstrated clear

Table 3. Mechanism of action of suramin

1(a). Blocks binding of several growth factors to their receptors: PDGF, EGF, IGF-1, bFGF (HBGF-2), TGF-β.
1(b). Dissociates bound growth factors from their receptors.
2. Inhibition of enzymes—DNA polymerases —other enzyme systems.
3(a). Inhibition of (adrenal) hormone secretion.
3(b). Blocks binding of several peptide hormones to cell membranes.

Table 4a. (Pre)clinical investigations with somatostatin analogs

	Analog(s)
Experimental models	
1(a). Human breast cancer cells (*in vitro*)	Sandostatin, CGP 15-425
1(b). DMBA-induced rat mammary tumors	Sandostatin
2. Dunning rat prostate tumors	Sandostatin
3. Transplantable rhabdomyosarcoma in rats	Sandostatin
4. Transplantable rat colon tumors	Sandostatin
5(a). Transplantable rat pancreatic tumors	Sandostatin, CGP15-425/RC-160
5(b). Carcinogen-induced (pre)neoplastic pancreatic lesions in rats and hamsters	Sandostatin
Clinical studies	
1. Pancreatic and gastrointestinal adenocarcinomas	Sandostatin
2. Breast cancer	Sandostatin

Table 4b. (Pre)clinical investigations with suramin

Experimental models
In vitro: human breast cancer cell lines
In vitro: human androgen-responsive cell lines (prostate, DDT-1)
In vivo: rats with transplantable pancreatic tumors
rats with transplantable colon tumors
Dunning rat prostate tumors
Clinical study
A broad phase II study concerning patients with different tumor types

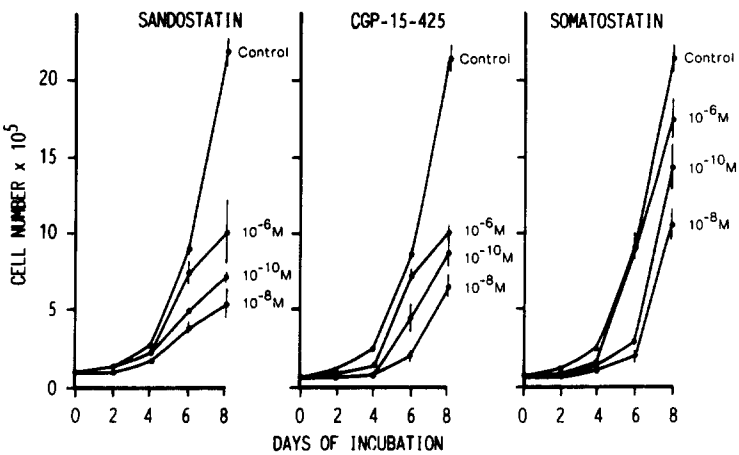

Fig. 1. Growth inhibitory effects of somatostatin-14 and the two somatostatin analogs Sandostatin and CGP 15–425 on the growth of MCF-7 human breast cancer cells *in vitro*.

growth inhibitory effects in MXT mice mammary adenocarcinoma using a depotpreparation of the somatostatin analog RC-160.

In view of the presence of somatostatin receptors in about 8–46% of human primary breast cancers [4, 5, 15–17], with a higher incidence (46%) when determined in large fresh tumor samples [17], the application of somatostatin analogs in the treatment of metastatic breast cancer might be useful. However, so far there is little clinical data showing limited efficacy in heavily pretreated patients [18–20]. At present we are carrying out a large randomized study in previously untreated patients.

Prostate cancer

In the Dunning prostate tumor model we found only limited growth inhibitory effects (12%) of treatment with Sandostatin, when used as single agent or in combination with an LHRH agonist in comparison to the respective controls without treatment or with only single treatment with buserelin depot. These results are comparable with those reported by other investigators [21, 22]. We have observed no additive antitumor effects of Sandostatin treatment when combined with surgical castration or the antiandrogen cyproterone acetate (CPA).

In a small series of patients with metastatic prostate cancer resistant to first-line endocrine therapy, Dupont *et al.* [23] observed no significant antitumor effects by somatostatin analog treatment.

Sarcomas

Schally [1] showed antiproliferative effects of somatostatin analog treatment in experimental chondrosarcomas in rats. In rats with transplantable rhabdomyosarcomas we did not observe any tumor growth inhibitory effect [24]. In the past we applied Sandostatin in the treatment of one patient with a very large chondrosarcoma resistant to chemotherapy, but without success. To our knowledge no other clinical data are available with respect to results in patients with sarcomas.

Colon cancer

In a rat transplantable colon tumor model we were unable to demonstrate growth inhibitory effects of Sandostatin treatment [24]. In 16 patients with metastatic colorectal cancer we observed only stable disease in 4 of 13 evaluable patients [25]. All died within 2 years.

Pancreatic cancer

In cooperation with the TNO-CIVO Toxicology and Nutrition Institute we demonstrated inhibition of the development of carcinogen-(BOP)-induced ductular pancreatic lesions in male hamsters by the somatostatin analog Sandostatin [26]. Such an inhibitory effect was not observed with respect to preneoplastic acinar lesions in the pancreas of azaserine-treated rats. Zalatnai and Schally [27] demonstrated growth inhibitory effects of another analog, i.e. RC-160, in hamsters with chemically-induced ductal pancreatic adenocarcinomas.

In rats with transplantable pancreatic tumors containing specific somatostatin receptors, treatment with the somatostatin analogs Sandostatin, CGP 15–425 and RC-160 during 6 weeks caused 50–70% inhibition of tumor growth when compared with untreated controls [24, 28, 29]. We found no difference in efficacy between these three analogs when administered by daily s.c. injections. When administered by Alzet minipumps the antitumor effects of Sandostatin tended to be better than daily s.c. injections. Growth inhibitory effects of somatostatin analogs in this tumor model have also been described by Schally [1].

In a clinical study concerning 14 patients with metastatic pancreatic cancer treated by Sandostatin we observed only stable disease in 3 out of 13 evaluable patients [25]. These relatively poor results of treatment with Sandostatin might be explained by a number of different reasons: (1) insensitivity of human tumors *per se*; (2) lack of somatostatin receptors [30]; (3) lack of indirect tumor growth inhibition caused by insufficient long-term suppression of hormone or growth factor secretion; (4) pretreatment with chemotherapy and the presence of extensive disease at the start of Sandostatin therapy; and (5) lack of clinical availability of a depotpreparation in order to reach better suppressive endocrine effects.

SURAMIN

Suramin, 8,8′-{carbonylbis[imino-3,1-phenylenecarbonyl-imino(4-methyl-3,1-phenylene)-carbonyl-imino]}bis-1,3,5-naphthalenetrisulfonic acid hexasodium salt (Germanin), is a polyanionic compound with a molecular weight of 1429 ($C_{51}H_{34}N_6Na_6O_{23}S_6$). The drug was discovered in 1917 by O. Dressel, R. Kothe and B. Heymann, and has been used for over

55 years as the treatment of choice for Trypanosomiasis and Onchocerciasis. In the last 5 years suramin has also been applied as an antiviral agent in the treatment of AIDS in light of the *in vitro* inhibition of the reverse transcriptase of retroviruses. Suramin can display many actions (Table 3) and is of potential interest for the treatment of cancer [8, 9]. Therefore, we have investigated the various effects of suramin *in vitro* on tumor cell lines, in experimental animal models and in patients with different types of metastatic cancer.

In vitro studies

We have investigated the effects of suramin on the proliferation of human breast cancer cells, the binding of EGF and IGF-1 to its receptor, and on cell cycle kinetics [31, 32]. In complete growth medium, suramin ($>250\ \mu g$/ml) inhibited the proliferation of MCF-7, ZR 75.1 and MDA-MB 231 cells in a dose-dependent manner. Proliferation of ZR 75.1 cells was stimulated at dosages of suramin $<250\ \mu g$/ml. The effects of suramin were reversible and cytostatic rather than cytotoxic, since washing out of the suramin after 3 days of culture restored cell proliferation. In serum-free medium the basal and the stimulated (E_2/IGF-1) proliferation of MCF-7 cells were inhibited by suramin. The net inhibitory effect at low dosages could be partly overruled by the addition of E_2 and/or IGF-1. In experiments with human placental membranes suramin more effectively interfered in the binding for IGF-1 (50% reduction at $\pm 400\ \mu g$ suramin/ml) to its receptor than of EGF to its receptor. Under all culture conditions studied, the presence of suramin caused an accumulation of MCF-7 cells in the G_2M-phase of the cell cycle.

Previously we reported that suramin also inhibits proliferation of androgen-dependent tumor cells in a dose-dependent way [33]. Growth of LNCaP prostate cancer cells was inhibited by suramin, but resumed after removal of suramin. Suramin inhibited PDGF- and bFGF-stimulated growth of DDT-1 hamster ductus deferens tumor cells. However, in the presence of testosterone, suramin showed a biphasic effect: stimulatory at low doses (0.01 mM) and inhibitory above 0.01 mM.

In vivo studies

The effects of suramin treatment were studied in rats with transplantable pancreatic tumors, with transplantable colon tumors and in the Dunning prostate tumor model. Suramin showed significant antitumor effects on the pancreatic tumor [34], but not on the experimental colon and prostate tumor. Healthy rats, as well as rats bearing the transplanted pancreatic tumor (EGFR+, IGF-1-R+, somatostatin receptor+), were treated with suramin (0.5, 2.5 and 5 mg twice weekly s.c.). Rats were divided into groups of 18 rats each. Three rats from each group were sacrificed weekly. The plasma suramin concentration measured by HPLC, hematological parameters and the influence of suramin treatment on organ weights were examined. Plasma suramin concentrations reached a plateau level after about 5 weeks with concentrations between 40–150 μg/ml. Doses of 2.5 and 5 mg suramin twice weekly resulted in significant tumor growth inhibition within 4–5 weeks, postinoculation of tumor cells. The highest dose of suramin also resulted in reduced body weight; nonsignificant effects could be detected on the weights of various organs. However, kidney weight was exceptionally increased in some rats. The weight of mesenteric lymph nodes was often reduced. The most pronounced effect of suramin was on the spleen weight, which was increased from the second week of treatment.

Clinical studies

In a broad phase II study we are treating patients with various types of metastatic carcinomas, for which no other satisfactory form of treatment exists. Preliminary data on the first 11 patients are available [35]. The patients were treated by 24-h infusions with suramin for 10 days (350 mg/m^2/day). In view of the possible occurrence of adrenal insufficiency, corticosteroids were added 5–10 days after the start of treatment with suramin. During the first 10 days, and thereafter weekly, blood samples were taken for measurement of plasma suramin concentrations. Suramin levels were measured by HPLC. When plasma suramin concentrations decreased below $50\ \mu g$/ml in the absence of tumor progression, patients were treated with the next suramin infusion. In the first 11 patients (6 women, 5 men; mean age 56 yr, range 48–69 yr), we have evaluated the hematological, biochemical, endocrine and pharmacokinetic effects.

Mean plasma suramin levels ($\pm$SD) increased gradually to $203 \pm 51\ \mu g$/ml after 5 days and to $278 \pm 36\ \mu g$/ml (range 199–327 μg/ml) after 10 days of treatment, followed by a decrease to

90 ± 41 μg/ml ($n = 6$) 4 weeks after the start of the 10-day treatment period (Table 5).

Hematological side effects were a decrease in their platelets count from 387 ± 103 to $245 \pm 172 \times 10^9$/l ($P < 0.005$) in 3 out of 11 patients, resulting in thrombopenia ($< 100 \times 10^9$/l). Furthermore, we observed lymphopenia (mean value decreased from 20 to 9%; $P < 0.005$), eosinophilia (mean value increased from 3 to 6%; $P < 0.02$) and a coagulopathy (mean INR increased from 1.0 to 1.5; $P < 0.005$) during treatment.

Biochemical side effects were a significant decrease in plasma Na^+ and K^+ concentrations (from 138 to 134 and from 4.3 to 3.3 mmol/l, respectively; both $P < 0.05$) and hypoproteinemia (mean decrease from 67 to 57 g/l; $P < 0.05$) in the absence of proteinuria.

Endocrinological effects were: (1) a significant decrease in both mean T_4 (from 94 to 64 nmol/l; $P < 0.01$) and TSH response to TRH (from 8.2 to 4.3 mU/l; $P < 0.05$); (2) in men, an increase in mean plasma estradiol levels (from 61 to 105 pmol/l; $P < 0.005$) and a decrease in testosterone; and (3) an increase in plasma ACTH concentrations (from 22 to 36 ng/ml; $P < 0.02$), accompanied by a significant increase in basal cortisol levels (from 470 to 690 pmol/l; $P = 0.05$), without a change in cortisol response to ACTH during a single suramin treatment. In spite of an intact pituitary–adrenal axis within the first 5–10 days, the patients showed a striking subjective improvement after the addition of corticosteroid treatment. Clinical side effects were exanthema and fever (×6, especially from day 8 onwards), swelling of reactive lymph nodes (×2), strange metallic taste (×4), tiredness (×2) and neuropathy (×1). One patient died from internal bleeding in the presence of severe thrombopenia (13×10^9/l) and coagulopathy (INR = 1.9). When corticosteroid treatment was started on day 6, generally, less side effects were observed than when this treatment began on day 10.

With respect to antitumor effects 1 patient showed stable disease, the other 10 patients showed tumor progression.

Table 5. Pharmacokinetics of suramin

	Mean plasma suramin levels (μg/ml)			
	Mean	SD	*n*	Range
Stages of treatment				
1 day	72	35	11	43–172
2 days	107	39	11	61–206
3 days	142	48	10	103–230
4 days	176	40	10	120–246
5 days	203	51	8	142–259
6 days	216	44	8	141–274
7 days	224	39	10	173–286
8 days	241	47	9	177–337
9 days	281	47	7	196–331
10 days	278	36	9	199–327
End of treatment				
2 weeks	167	59	7	116–270
3 weeks	132	40	6	89–179
4 weeks	90	41	6	46–132
5 weeks	76	37	4	42–128

CONCLUSION

Somatostatin analogs and suramin can inhibit the proliferation of different tumor types in experimental models and in cancer patients. Somatostatin analogs are especially effective in patients having pituitary tumors (acromegaly), carcinoids or endocrine gastroenteropancreatic tumors, while in experimental models antitumor effects have been demonstrated on breast cancer, prostate cancer, pancreatic cancer, chondrosarcomas and meningiomas [1–3]. A series of recent reports showed antiproliferative effects of suramin on many tumor cell lines of different origin *in vitro* [8, 10, 11, 31–33]. However, there are only a few data available of studies on animal models and on cancer patients. We observed growth inhibitory effects of suramin on a transplantable pancreatic tumor, but the results in patients are less promising than in experimental models. In the clinic suramin is mainly active in (a minority of) patients with metastatic hormone-independent prostate cancer, adrenal cancer or (heavily pretreated) lymphomas [9, 11, 35–37]. For the future, the development and availability of more specific growth factor antagonists is needed, and can be expected in due course.

Acknowledgements—We would like to thank S. F. Sliwa for preparing the figure, R. Kalkman for typing the manuscript, Sandoz, Ciba-Geigy and Bristol-Meyers for supply of Sandostatin, CGP 15-425 and RC-160, respectively, and The Dutch Cancer Society (KWF) for financial support (Project RRTI 86-5).

REFERENCES

1. Schally A. V.: Oncological applications of somatostatin analogs. *Cancer Res.* **48** (1988) 6977–6985.
2. Lamberts S. W. J., Krenning E. P., Klijn J. G. M. and Reubi J.-C.: The clinical use of somatostatin analogues in the treatment of cancer. In *Endocrine Aspects of Malignancy* (Edited by S. M. Shalet). *Baillière's Clin. Endocr. Metab.* **4** (1990) 29–49.
3. Lamberts S. W. J., Krenning E. P., Klijn J. G. M. and Reubi J.-C.: Clinical applications of somatostatin analogs. *Trends Endocr. Metab.* **1** (1990) 139–144.
4. Reubi J.-C., Maurer R., Werder K. von, Torhorst J., Klijn J. G. M. and Lamberts S. W. J.: Somatostatin receptors in human endocrine tumors. *Cancer Res.* **47** (1987) 551–558.

5. Reubi J.-C., Krenning E., Lamberts S. W. J. and Kvols L.: Somatostatin receptors in malignant tissues. *J. Steroid Biochem. Molec. Biol.* **37** (1990) 1073–1077.
6. Srkalovic G., Cai R.-Z. and Schally A. V.: Evaluation of receptors for somatostatin in various tumors using different analogs. *J. Clin. Endocr. Metab.* **70** (1990) 661–669.
7. Schally A. V., Srkalovic G., Szende B., Redding T. W., Janaky T., Juhasz A., Korkut E., Cai R.-Z., Szepeshazi K., Radulovic S., Bokser L., Groot K., Serfozo P. and Comaru-Schally A. M.: Antitumor effects of LH-RH and somatostatin: experimental and clinical studies. *J. Steroid Biochem. Molec. Biol.* **37** (1990) 1061–1067.
8. Coffey R. J., Leof E., Shipley G. D. and Moses H. L.: Suramin inhibition of growth factor receptor binding and mitogenicity in AKR-2B cells. *J. Cell. Physiol.* **132** (1987) 143–148.
9. Stein C. A., La Rocca R. V., Thomas R., McAtee N. and Myers C. E.: Suramin: an anticancer drug with a unique mechanism of action. *J. Clin. Oncol.* **7** (1989) 499–508.
10. Marzouk H. F. A. I., Zuyderwijk J., Uiterlinden P., Jong F. H. de and Lamberts S. W. J.: Suramin prevents ACTH-stimulated corticosterone release by dispersed adrenocortical cells. *Endocrinology* **126** (1990) 666–669.
11. La Rocca R. V., Stein C. A., Danesi R. and Myers C. E.: Suramin, a novel antitumor compound. *J. Steroid Biochem. Molec. Biol.* **37** (1990) 893–898.
12. Setyono-Han B., Henkelman M. S., Foekens J. A. and Klijn J. G. M.: Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. *Cancer Res.* **47** (1987) 1566–1570.
13. Bakker G. H., Setyono-Han B., Foekens J. A., Portengen H., Jong F. H. de, Lamberts S. W. J., Reubi J.-C. and Klijn J. G. M.: Effects of tumor growth and endocrine parameters by somatostatin analogue (Sandostatin, SMS 201–995) treatment of rats bearing mammary tumors. *Breast Cancer Res. Treat.* **17** (1991) 23–32.
14. Szende B., Lapis K., Redding T. W., Srkalovic G. and Schally A. V.: Growth inhibition of MXT mammary carcinoma by enhancing programmed cell death (apoptosis) with analogs of LH-RH and somatostatin. *Breast Cancer Res. Treat.* **14** (1989) 307–314.
15. Foekens J. A., Portengen H., Putten W. L. J. van, Trapman A. M. A. C., Reubi J.-C., Alexieva-Figusch J. and Klijn J. G. M.: Prognostic value of receptors for insulin-like growth factor I, somatostatin, and epidermal growth factor in human breast cancer. *Cancer Res.* **49** (1989) 7002–7009.
16. Fekete M., Wittliff J. C. and Schally A. V.: Characteristics and distribution of receptors for [D-Trp^6]-luteinizing hormone-releasing hormone, somatostatin, epidermal growth factor, and sex steroids in 500 biopsy samples of human breast cancer. *J. Clin. Lab. Anal.* **3** (1989) 137–147.
17. Reubi J.-C., Waser B., Foekens J. A., Klijn J. G. M., Lamberts S. W. J. and Laissue J.: Somatostatin receptor incidence and distribution in breast cancer using receptor autoradiography: relationship to EGF receptors. *Int. J. Cancer* **46** (1990) 416–420.
18. Manni A., Boucher A. E., Demers L. M., Harvey H. A., Lipton A., Simmonds M. A. and Bartholomew M.: Endocrine effects of combined somatostatin analog and bromocriptine therapy in women with advanced breast cancer. *Breast Cancer Res. Treat.* **14** (1989) 289–298.
19. Vennin P. H., Peyrat J. P., Bonneterre J., Louchez M. M., Harris A. G. and Demaille A.: Effect of the long-acting somatostatin analogue SMS 201-995 (Sandostatin) in advanced breast cancer. *Anticancer Res.* **9** (1989) 153–156.
20. Holtkamp W. and Nagel G. A.: Remission of metastatic breast cancer after combined somatostatin and antiprolactin treatment. *Eur. J. Cancer* **26** (1990) 177 (Abstr. 122).
21. Schally A. V. and Redding T. W.: Somatostatin analogs as adjuncts to agonists of luteinizing hormone-releasing hormone in the treatment of experimental prostate cancer. *Proc. Natn. Acad. Sci. U.S.A.* **84** (1987) 7275–7279.
22. Siegel R. A., Tolcsvai L. and Rudin M.: Partial inhibition of the growth of transplanted Dunning rat prostate tumors with the long-acting somatostatin analogue Sandostatin (SMS 201–995). *Cancer Res.* **48** (1988) 4651–4655.
23. Dupont A., Bouche H., Cusan L., Lacourciere Y., Emond J. and Labrie F.: Octreotide and bromocriptine in patients with stage D2 prostate cancer who relapsed during treatment with flutamide and castration. *Eur. J. Cancer* **26** (1990) 770–771.
24. Klijn J. G. M., Setyono-Han B., Bakker G. H., Henkelman M. S., Portengen H. and Foekens J. A.: Effects of somatostatin analogue (Sandostatin) treatment in experimental and human cancer. In *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)Steroidal Agents* (Edited by J. G. M. Klijn, R. Paridaens and J. A. Foekens). *EORTC Monogr. Ser.* Raven Press, New York **18** (1987) pp. 459–468.
25. Klijn J. G. M., Hoff A. M., Planting A. S. Th., Verwey J., Kok T., Lamberts S. W. J., Portengen H. and Foekens J. A.: Treatment of patients with metastatic pancreatic and gastrointestinal tumours with the somatostatin analogue Sandostatin: a phase II study including endocrine effects. *Br. J. Cancer* **62** (1990) 627–630.
26. Meijers M., Garderen-Hoetmer A. van, Foekens J. A., Bakker G. H., Klijn J. G. M. and Woutersen R. A.: Modulation of development of dietary fat-promoted (pre)neoplastic pancreatic lesions in BOP-treated hamsters by (anti)hormones. *Eur. J. Cancer* **26** (1990) 192 (Abstr. 182).
27. Zalatnai A. and Schally A. V.: Treatment of *N*-nitrosobis(2-oxopropyl)amine-induced pancreatic cancer in Syrian Golden hamsters with D-Trp-6-LH-RH and somatostatin analogue RC-160. *Cancer Res.* **49** (1989) 1810–1815.
28. Klijn J. G. M., Setyono-Han B., Bakker G. H., Portengen H. and Foekens J. A.: Prophylactic neuropeptide-analog treatment of a transplantable pancreatic tumor in rats. In *Hormones and Cancer 3; Proceedings of the 3rd International Congress on Hormones and Cancer* (Edited by F. Bresciani, R. J. B. King, M. E. Lippman and J. P. Raynaud). Raven Press, New York (1988) pp. 550–554.
29. Klijn J. G. M., Setyono-Han B., Bakker G. H. and Foekens J. A.: Dose–effect finding studies on endocrine parameters and tumor growth by the somatostatin analog RC-160 in rat pancreatic tumors. In *Book of Abstracts 6th NCI–EORTC Symposium on New Drugs in Cancer Therapy* (1989) (Abstr. 241).
30. Reubi J.-C., Horisberger U., Essed C. E., Jeekel J., Klijn J. G. M. and Lamberts S. W. J.: Pancreatic adenocarcinomas: lack of somatostatin receptors in human but not in rat tumors. *Gastroenterology* **95** (1988) 760–763.
31. Foekens J. A., Stuurman-Smeets E. M. J., Groenenboom-de Munter I. K., Berns P. M. J. J., Dorssers L. C. J. and Klijn J. G. M.: Effects of suramin on proliferation of human breast cancer cells *in vitro*. In *Book of Abstracts 3rd Joint NCI/IST Symposium on Biology and Therapy of Breast Cancer, Genoa* (1989) (Abstr. 54).
32. Foekens J. A., Stuurman-Smeets E. M. J., Groenenboom-de Munter I. K., Peters H. A., Trapman A. M. A. C., Berns P. M. J. J., Dorssers L. C. J.

and Klijn J. G. M.: Reversible proliferative and antiproliferative effects of suramin on human breast cancer cells *in vitro*. *Proc. 81st A. Mtg AACR* **31** (1990) 50 (Abstr. 298).
33. Berns P. M. J. J., Schuurmans A. L. G., Bolt J., Lamb D. J., Foekens J. A. and Mulder E.: Antiproliferative effects of suramin on androgen responsive tumour cells. *Eur. J. Cancer* **26** (1990) 470–474.
34. Setyono-Han B., Bakker G. H., Peters H. A., Sieuwerts A. M., Eggermont A. M. M., Foekens J. A. and Klijn J. G. M.: Suramin: pharmacokinetic monitoring, haematological and antitumor effects on rats bearing transplantable pancreatic tumors. *Eur. J. Cancer* **26** (1990) 184 (Abstr. 184).
35. Klijn J. G. M., Burg M. E. L. van der, Seynaeve C., Hoff A., Peters H., Sieuwerts A., Oosterom R., Lamberts S. W. J. and Foekens J. A.: Hematological, biochemical, endocrine and pharmacokinetic effects of growth factor antagonist treatment with suramin. *Proc. 81st A. Mtg AACR* **31** (1990) 212 (Abstr. 1255).
36. Rijswijk R. E. N. van, Loenen A. C. van, Horenblas S., Wagstaff J. and Pinedo H. M.: Phase I/II study of suramin in hormone resistant metastatic prostate cancer. *Eur. J. Cancer* **26** (1990) 185 (Abstr. 155).
37. Oosterom A. T. van, De Smedt E. A., Denis L. J., Bruijn E. A. de and Mahler C.: Suramin for prostatic cancer; a phase I/II study in advanced extensively pretreated disease. *Eur. J. Cancer* **26** (1990) 422.