ATP-based Chemosensitivity Testing: a New Direction for Chemotherapy

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This introduction to the ATP-TCA is intended for doctors, healthcare professionals, and others with some background knowledge.

Introduction

While some types of cancer remain localised for many years or virtually never spread to other organs, others can be regarded as a systemic disease at the time the patient first becomes aware of the primary tumour. While localised tumours can be dealt with by surgeons with increasingly successful results, tumours which have spread (metastasised) to other organs are often impossible to remove and will ultimately kill the patient unless they respond to systemic treatment. This usually means chemotherapy with drugs designed to kill tumour cells, although immunotherapy (persuading the patient's immune system to kill the tumour) and anti-angiogenic therapy (targeting the blood vessels needed by the tumour to grow) are now viable options for some tumours. The much-hyped possibility of gene therapy is as yet just that - a possibility for the future.

However, the causes of cancer are now understood. Cancer arises when cells lose the molecular mechanisms that control their growth and death - the result is that they proliferate out of control and form tumours. These molecular mechanisms are controlled by genes encoded in the DNA of the cell, and acquired mutations or other changes in these genes lead to loss of control. Cancers are therefore genetic diseases, but only rarely familial. Each individual tumour, even those of the same general type (e.g. breast cancer) will have different mutations, the consequences of which may be altered by the tissue environment, which can in turn be influenced by the external environment. The result is that cancers are even more different from each other than the individuals affected. This heterogeneity means that a particular drug will rarely be effective against all tumours of a particular type, and that the degree of efficacy will vary between patients too. Not only that, but as a result of their original mutations, many tumour cells acquire the ability to adapt rapidly to changes in their environment, sometimes by further mutation, often by molecular changes which induce resistance to the drugs used to treat them. Further courses of chemotherapy then select for resistant cells, and the treatment eventually fails to control the tumour.

The Challenge

It has long been the goal of oncologists to be able to tailor chemotherapy to individual patients, to overcome the problems of heterogeneity and prevent rapid cellular adaptation. This can theoretically be done by testing the tumour cells to see if they are susceptible to particular drugs before giving them to the patient. The concept is widely acknowledged to be sound, but the development of such tests has proved difficult and many oncologists have given up hope that this idea will ever succeed. Many hope that molecular tests may hold the key to success, particularly as more specific drugs are designed to hit the molecular changes that are responsible for the uncontrolled growth of cancer cells in the first place. There are some indications that this approach may work - testing breast cancer for the presence of hormone receptors and more recently over-expression of growth factor receptors is of proven benefit to patients. However, most drugs cannot be looked at in this way, and even the tests that are in use have limited predictive accuracy (usually around 65%).

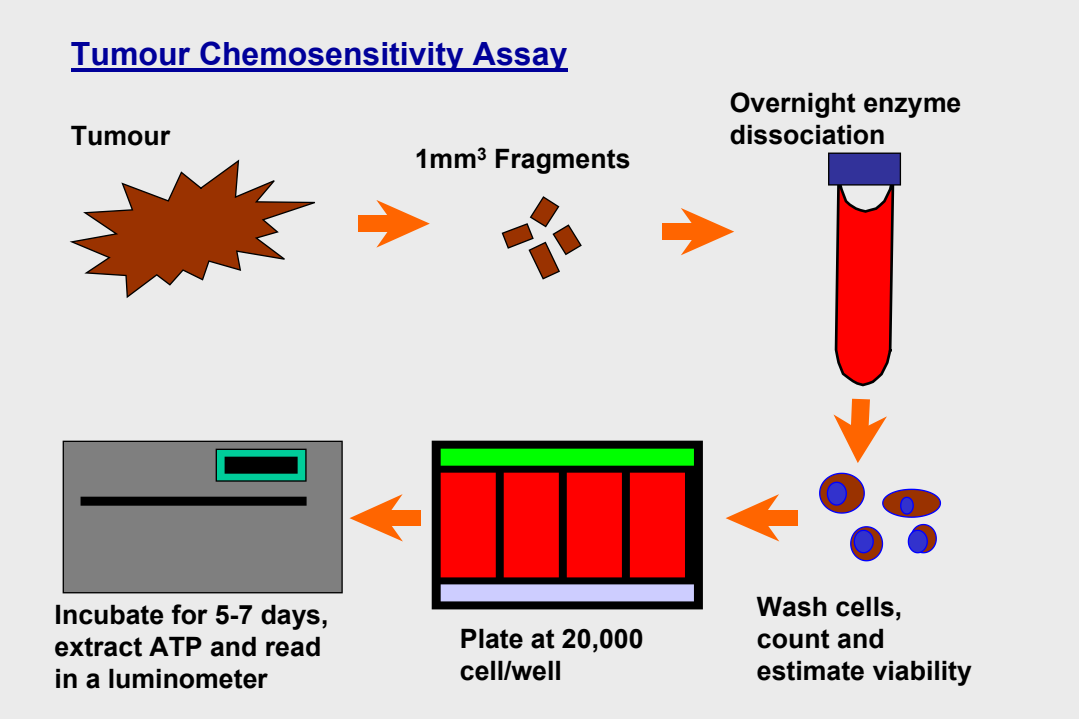
The Solution

So how about exposing cancer cells to the drug and testing their effect? Previous tests (assays) failed for a number of technical reasons, mainly because they needed large amounts of tumour material and could not determine whether all of the cells present were killed. In the early 1990s, Peter Andreotti and I started working with a new assay based on our knowledge of luminescence, the production of light from biochemical reactions. We were excited by the potential of ATP assays based on the firefly luciferin-luciferase reaction to measure the presence of very small numbers of bacterial cells in fluids, on surfaces and even in milk. Dead cells contain no ATP (it is used up in seconds following cell lysis by enzymatic degradation).

It was a small step to design a chemosensitivity assay using an ATP endpoint (fig 1), but we also had to find a way of exposing the cancer cells to the drugs without altering their behaviour from the original tumour. It is not possible to remove the non-cancer cells from the tumour without doing this. We therefore developed a selective culture method to get rid of the non-cancer cells before the end of the 6-day culture period used in the assay, as we just want to measure the degree to which the cancer cells themselves survive. Clinically achievable drug concentrations in tumours are rarely known with any accuracy, so we have used achievable plasma concentrations for most of the drugs we test, altered to take account of protein-binding and tissue distribution data. The result is an assay with the following characteristics:

- Needs relatively small amounts of tumour material (allowing histological and molecular analysis), though needle biopsies are not suitable.
- Measure multiple drugs and combinations.
- Measures 6 concentrations of 4 drugs in triplicate on one 96 well microplate.
- High evaluability rate (>95%).
- Clearly defined endpoint with criteria for analysis of results and interpretation.
- Good relevance to the clinical situation.

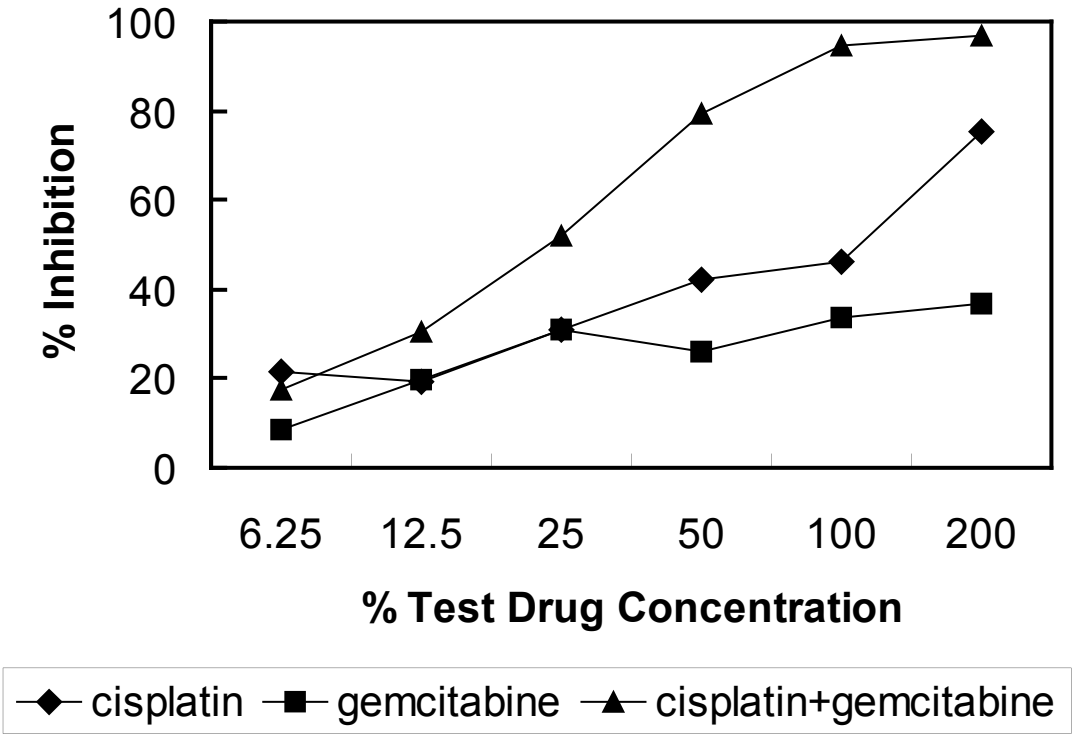
Figure 1: The ATP-based chemosensitivity assay measures the degree of cell death that occurs following short-term cell culture of tumour-derived cells with cytotoxic drugs.



The ATP-based tumour chemosensitivity assay (ATP-TCA) has now been tested in a large variety of different solid cancers and has a remarkable track record. Within two years, the assay had produced evidence of heterogeneity similar to that seen in patients for both ovarian and breast cancer. Correlation with outcome proved to be 70-80% in both breast and ovarian cancer, leading to trials of assay-directed treatment in ovarian cancer, breast cancer, and melanoma. The results in recurrent ovarian cancer are mature and were recently published, showing an increase in both progression-free survival and response rate. This has recently been confirmed in a second laboratory in a group of patients from multiple centres. A randomised phase II trial comparing assay-directed drug selection with physician's choice from the same panel tested in the assay is complete and preliminary analysis of the data is encouraging.

The ATP-TCA has also shown itself to be capable of improving current therapy by aiding the development of new regimens and the assessment of new drugs (Kurbacher et al., 1994; Cree & Kurbacher, 1999). Many tumours are treated with combinations rather than single agents, and the ATP-TCA data on single agents has already proved invaluable for studies of the molecular basis of both resistance and sensitivity.

Figure 2. Assay results for the combination of cisplatin and gemcitabine in a recurrent ovarian carcinoma. There is resistance to cisplatin, with just 40% inhibition at the 100 test drug concentration, which equates to the maximum clinically achievable concentration. There is also resistance to gemcitabine, but in combination there is considerable synergy, and the result indicates likely activity of the combination.



The Future

The ATP-TCA has already established itself as the most promising chemosensitivityassay for clinical use in breast and ovarian cancer, and is being used a variety of other settings. It is particularly appropriate for patients with rare tumours, or tumours of unknown type, for which there is little or no trial-based data available. In these instances, it has produced some spectacular results with regimens the oncologist would not otherwise have considered. The contribution of this assay to new drug and regimen development is set to grow considerably in the next few years. It has already contributed to the molecular understanding of chemosensitivity and resistance, and this too is likely to become even more important.

Publications

1. Hunter EM, Sutherland LA, Cree IA, Dewar JA, Preece PE, Andreotti PE. Heterogeneity of chemosensitivity in human breast carcinoma: use of an adenosine triphosphate (ATP) chemiluminescence assay. European Journal of Surgical Oncology 1993; **19**: 242-249.
2. Cree IA, Hunter EM, Sutherland LA, Subedi AMC, Dewar JA, Preece PE, Andreotti PE. Breast cancer chemosensitivity testing by ATP luminescence assay. In: Chemiluminescence and Bioluminescence. Status Report, eds. Szalay A, Kricka LJ, Stanley PE. John Wiley & Sons, Chichester, 1993: 276-280.
3. Andreotti PE, Linder D, Hartmann DM, Becker K, Herbst K, Cree IA, Bruckner HW. ATP tumor chemosensitivity assay application for solid tumors and leukaemias. In: Chemiluminescence and Bioluminescence. Status Report, eds. Szalay A, Kricka LJ, Stanley PE. John Wiley & Sons, Chichester, 1993: 271-275.
4. Andreotti PE, Linder D, Hartmann DM, Cree IA, Pazzagli M, Bruckner HW. TCA-100 Tumor Chemosensitivity Assay: differences in sensitivity between cultured tumor cell lines and clinical studies. Journal of Bioluminescence and Chemiluminescence 1994; **9**: 373-378.
5. Petty RD, Cree IA, Sutherland LA, Hunter EM, Lane DP, Preece PE, Andreotti PE. Expression of the p53 tumour suppressor gene product is a determinant of chemosensitivity. Biophysical and Biochemical Research Communications 1994; **199**: 264-270.
6. Hunter EM, Sutherland LA, Cree IA, Subedi AMC, Hartmann D, Linder D, Andreotti PE. The influence of storage on cytotoxic drug activity in an ATP-based chemosensitivity assay. Anti-Cancer Drugs 1994; **5**: 171-176.
7. Cree IA, Petty RD, Sutherland LA, Hunter EMM, Subedi AMC, James EA, Andreotti PE, Harrison DJ. Elucidation of molecular determinants of tumour chemosensitivity by ATP-based luminescence assay. In: Chemluminescence and Bioluminescence. eds. Campbell AC, Stanley PE, Kricka LJ. John Wiley & Sons, Chichester 1994; 407-410.
8. Kurbacher CM, Mallmann P, Kurbacher JA, Sass G, Andreotti PE, Rahmun A, Hübner H, Krebs D. In vitro activity of titanocenedichloride versus cisplatin and doxorubicin in primary and recurrent epithelial ovarian cancer. Anticancer Res 1994; 14: 1961-5.
9. Kurbacher CM, Nagel W, Mallmann P, Kurbacher JA, Sass G, Hübner H, Andreotti PE, Krebs D. In vitro activity of titanocenedichloride in human renal cell carcinoma compared to conventional antineoplastic agents. Anticancer Res 1994; 14: 1529-33.
10. Andreotti PE, Cree IA, Kurbacher CM, Hartmann DM, Linder D, Harel G, Gleiberman I, Caruso PA, Ricks SH, Bruckner HW. Sensitivity testing of human tumors using a microplate ATP assay. In: Chemluminescence and Bioluminescence. eds. Campbell AC, Stanley PE, Kricka LJ. John Wiley & Sons, Chichester 1994; 403-406.
11. Petty RD, Sutherland LA, Hunter EM, Cree IA. Comparison of MTT and ATP-based assays for the measurement of viable cell number. Journal of Bioluminescence and Chemiluminescence 1995; **10**: 29-34.
12. Cree IA, Pazzagli M, Mini E, Mazzei T, Hunter EMM, Sutherland LA, Pinzani P, Gerli A, Andreotti PE. Methotrexate chemosensitivity by ATP luminescence in human leukaemia cell lines and in breast cancer primary cultures: conparison of the TCA-100 assay with a clonogenic assay. Anti-Cancer Drugs 1995; **6**: 398-404.

13. Andreotti PE, Cree IA, Kurbacher CM, Hartmann DM, Linder D, Harel G, Gleiberman I, Caruso PA, Ricks SH, Untch M, Sartori C, Bruckner HW. Chemosensitivity testing of human tumors using a microplate adenosine triphosphate luminescence assay: Clinical Correlation for Cisplatin Resistance of Ovarian Carcinoma. Cancer Research 1995; **55**: 5276-5282.
14. Kurbacher CM, Bruckner HW, Andreotti PE, Kurbacher JA, Sass G, Krebs D. In vitro activity of titanocenedichloride versus cisplatin in four ovarian carcinoma cell lines evaluated by a microtiter plate ATP bioluminescence assay. Anticancer Drugs 1995; 6: 697-704.
15. Lee JM, Bruckner HW, Szrajer L, Brenne U, Schindelheim G, Andreotti PE. Taxol inhibits growth of mesothelioma xenografts. Anticancer Res 1995; 15: 693-6.
16. Kurbacher CM, Cree IA, Brenne U, Bruckner HW, Kurbacher JA, Mallmann P, Andreotti PE, Krebs D. Heterogeneity of in vitro chemosensitivity in perioperative breast cancer cells to mitoxantrone versus doxorubicin evaluated by microplate ATP bioluminescence assay. Breast Cancer Research and Treatment 1996; 41: 161-70.
17. Cree IA, Kurbacher CM, Untch M, Sutherland LA, Hunter EMM, Subedi AMC, James EA, Dewar JA, Preece PE, Andreotti PE, Bruckner HW. Correlation of the clinical response to chemotherapy in breast cancer with ex vivo chemosensitivity. Anti-Cancer Drugs 1996; 7: 630-5.
18. Cree IA, Petty RD, Kurbacher CM, Untch M. Comments on Tumor Chemosensitivity and Chemoresistance Assays. Cancer 1996; 78: 2031-2.
19. Kurbacher CM, Brenne U, Kurbacher JA, Mallmann P, Krebs D[Comparison of the cytostatic effect of epirubicin and mitoxantrone on native breast carcinoma cells using the ATP tumor chemosensitivity assay]. Zentralbl Gynakol 1996; 118: 271-8.
20. Kurbacher CM, Mallmann P, Kurbacher JA, Hübner H, Krebs D. Chemosensitivity testing in gynecologic oncology. Experiences with an ATP bioluminescence assay. Geburtshilfe Frauenheilkd 1996; 56: 70-8.
21. Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D, Bruckner HW. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996; 103: 183-9.
22. Cree IA, Andreotti PE. Measurement of cytotoxicity by ATP-based luminescence assay in primary cell cultures and cell lines. Toxicology In Vitro 1997; 11: 553-6.
23. Kurbacher CM, Bruckner HW, Cree IA, Kurbacher JA, Wilhelm L, Poch G, Indefrei D, Mallman P, Krebs D, Andreotti PE. Mitoxantrone combined with paclitaxel as salvage therapy for platinum-refractory ovarian cancer: laboratory study and clinical pilot trial. Clinical Cancer Research 1997; 3: 1527-33.
24. Cree IA, Kurbacher CM. Individualising chemotherapy for solid tumours - is there any alternative? Anti-Cancer Drugs 1997; 8: 541-8.
25. Kurbacher CM, Untch M, Cree IA. A randomised trial of chemotherapy directed by a tumour chemosensitivity assay versus physician's choice in patients with recurrent platinum-resistant ovarian adenocarcinoma. Lancet Internet publication 1997: http://www.thelancet.com/newlancet/sub/author//menu_NOD7.html
26. Myatt N, Cree IA, Kurbacher CM, Foss AJE, Hungerford JL, Plowman PN. The ex vivo chemosensitivity profile of choroidal melanoma. Anti-Cancer Drugs 1997; 8: 756-62.
27. Kurbacher CM, Cree IA, Bruckner HW, Mallmann P, Andreotti PE. Use of an ex vivo ATP luminescence assay to direct chemotherapy for recurrent ovarian cancer. Anti-Cancer Drugs 1998; 9: 51-7.
28. Cree IA. Luminescence-based cell viability testing. In: Bioluminescence Methods and Protocols, ed RA LaRossa, Humana Press, Methods in Molecular Biology 1998; 102: 169 -177.

29. Neale MH, Myatt N, Cree IA, Kurbacher CM, Foss AJE, Hungerford JL, Plowman PN. Combination chemotherapy for chroroidal melanoma: ex vivo sensitivity to treosulfan with gemcitabine or cytosine arabinoside. British Journal of Cancer 1999; 79: 1487-93.
30. Cree IA, Kurbacher CM. ATP based tumour chemosensitivity testing: assisting new agent development. Anti-Cancer Drugs 1999; 10: 431-5.
31. Cree IA, Neale MH, Myatt NE, de Takats PG, Hall P, Grant JG, Kurbacher CM, Reinhold U, Neuber K, MacKie RM, Chana J, Weaver PC, Khoury GG, Sartori C, Andreotti PE. Heterogeneity of chemosensitivity of metastatic cutaneous melanoma. Anti-Cancer Drugs 1999; 10: 437-44.
32. Satherley K, De Souza L, Neale MH, Alexander RA, Myatt N, Foss AJE, Hungerford JL, Hickson ID, Cree IA. Relationship between expression of topoisomerase II isoforms and chemosensitivity in choroidal melanoma. Journal of Pathology 2000; 192: 174-81.
33. Konecny G, Crohns C, Pegram M, Felber M, Lude S, Kurbacher C, Cree IA, Hepp H, Untch M. Correlation of drug response with the ATP tumorchemosensitivity assay in primary FIGO stage III ovarian cancer. Gynecol Oncol 2000; 77:258-63.
34. Neale MH, Charlton PA, Cree IA. Ex vivo activity of XR5000 against solid tumours. Anti-Cancer Drugs 2000; 11: 471-8.
35. Myatt N, Aristodemou P, Neale MH, Foss AJE, Hungerford JL, Bhattacharya S, Cree IA. A role for the transforming growth factor-beta pathway in choroidal melanoma. Journal of Pathology 2000; 192: 511-18.
36. Boabang P, Kurbacher CM, Kohlhagen H, Waida A, Amo-Takyi BK. Anti-neoplastic activity of topotecan versus cisplatin, etoposide and paclitaxel in four squamous cell cancer cell lines of the female genital tract using an ATP-Tumor Chemosensitivity Assay. Anticancer Drugs 2000; 11: 843-8.
37. Breidenbach M, Rein D, Schmidt T, Heindel W, Kolhagen H, Mallmann P, Kurbacher CM. Intra-arterial mitoxantrone and paclitaxel in a patient with Stewart-Treves syndrome: selection of chemotherapy by an ex vivo ATP-based chemosensitivity assay. Anticancer Drugs 2000; 11: 269-73.
38. Schondorf T, Becker M, Kolhagen H, Kurbacher CM, Gohring UJ. Ex vivo assays to evaluate the role of protein kinase C in tumor cells of patients with breast cancer. Anticancer Res 2000; 20: 5073-6.
39. Neale MH, Lamont A, Hindley A, Kurbacher CM, Cree IA. The ex vivo effect of high concentrations of doxorubicin on recurrent ovarian carcinoma. Anti-Cancer Drugs 2000; 11: 865-71.
40. Rein DT, Schondorf T, Breidenbach M, Janat MM, Weikelt A, Gohring UJ, Becker M, Mallmann P, Kurbacher CM. Lack of correlation between P53 expression, BCL-2 expression, apoptosis and ex vivo chemosensitivity in advanced human breast cancer. Anticancer Res 2000; 20: 5069-72.
41. Geerling G, Daniels JT, Dart JK, Cree IA, Khaw PT. Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. Invest Ophthalmol Vis Sci. 2001; 42: 948-56.
42. Neale MH, Myatt NE, Ghassan G Khoury GG, Weaver P, Lamont A, Hungerford JL, Kurbacher CM, Hall P, Corrie PG, Cree IA. Comparison of the *ex vivo* chemosensitivity of uveal and cutaneous melanoma. Melanoma Res 2001; 11: 601-9.
43. Boyd SR, Tan DS, de Souza L, Neale MH, Myatt NE, Alexander RA, Robb M, Hungerford JL, Cree IA. Uveal melanomas express vascular endothelial growth factor and basic fibroblast growth factor and support endothelial cell growth. Br J Ophthalmol 2002; 86: 440-447.

44. Di Nicolantonio F, Neale MH, Knight LA, Lamont A, Skailes GE, Osborne RJ, Allerton R, Kurbacher CM, Cree IA. Use of an ATP-based chemosensitivity assay to design new combinations of high concentration doxorubicin with other drugs for recurrent ovarian cancer. Anti-Cancer Drugs 2002; 13: 1-7.
45. Breidenbach M, Rein DT, Mallmann P, Kurbacher CM. Individualized long-term chemotherapy for recurrent ovarian cancer after failing high-dose treatment. Anticancer Drugs 2002; 13: 173-6.
46. Kurbacher CM, Kurbacher JA, Cree IA, Wardelmann E, Stier U, Kolhagen H, Scharl A, Andreotti PE. Chemosensitivity of normal human trophoblasts evaluated by a newly developed ATP-based luminescence assay. Anti-Cancer Drugs 2002; 13: 701-8.
47. Cree IA, Knight L, Di Nicolantonio F, Sharma S, Gulliford T. Chemosensitization of solid tumors by modulation of resistance mechanisms. Curr Opin Invest Drugs 2002; 3: 634-640.
48. Cree IA, Knight L, Di Nicolantonio F, Sharma S, Gulliford T. Chemosensitization of solid tumor cells by alteration of their susceptibility to apoptosis. Curr Opin Invest Drugs 2002; 3: 641-647.
49. Di Nicolantonio F, Neale MH, Knight LA, Lamont A, Skailes GE, Osborne RJ, Allerton R, Kurbacher CM, Cree IA. Use of an ATP-based chemosensitivity assay to design new combinations of high concentration doxorubicin with other drugs for recurrent ovarian cancer. Anti-Cancer Drugs 2002; 13: 1-7.
50. Kurbacher CM, Kurbacher JA, Cree IA, Wardelmann E, Stier U, Kolhagen H, Scharl A, Andreotti PE. Chemosensitivity of normal human trophoblasts evaluated by a newly developed ATP-based luminescence assay. Anti-Cancer Drugs 2002; 13: 701-8.
51. Kurbacher CM, Grecu OM, Stier U, Gilster TJ, Janat MM, Untch M, Konecny G, Bruckner HW, Cree IA. ATP chemosensitivity testing in ovarian and breast cancer: early clinical trials. Recent Results in Cancer Research 2003;161:221-30.
52. Cree IA. Chemosensitivity testing as an aid to anti-cancer drug and regimen development. Recent Results in Cancer Research 2003 161: 119-25.
53. Di Nicolantonio F, Neale M, Onadim Z, Hungerford JL, Kingston JL, Cree IA. The chemosensitivity profile of retinoblastoma. Recent Results in Cancer Research 2003; 161: 73-80.
54. Whitehouse PA, Knight LA, Di Nicolantonio F, Mercer SJ, Sharma S, Cree IA. Heterogeneity of chemosensitivity of colorectal adenocarcinoma determined by a modified ex vivo ATP-tumour chemosensitivity assay (ATP-TCA). Anti-Cancer Drugs 2003; 14: 369-75.
55. Pfohler C, Cree IA, Ugurel S, Kuwert C, Haass N, Neuber K, Hengge U, Corrie PG, Zutt M, Tilgen W, Reinhold U. Treosulfan and gemcitabine in metastatic uveal melanoma patients: results of a multicenter feasibility study. Anti-Cancer Drugs 2003; 14: 337-40.
56. Mercer SJ, Somers SS, Knight LA, Whitehouse PA, Sharma S, Di Nicolantonio F, Glaysher S, Simon Toh S, Cree IA for the Portsmouth Upper GI Cancer Multi-Disciplinary Team. Heterogeneity of chemosensitivity of oesophageal and gastric carcinoma. Anti-Cancer Drugs 2003; 14: 397-403.
57. Sharma S, Neale MH, Di Nicolantonio F, Knight LA, Whitehouse PA, Mercer SJ, Higgins BR, Lamont A, Osbourne R, Hindley AC, Kurbacher CM, Cree IA. Outcome of ATP-based tumor chemosensitivity assay directed chemotherapy in heavily pre-treated recurrent ovarian carcinoma. BMC Cancer 2003; 3: 19.
58. Whitehouse PA, Mercer SJ, Knight LA, Di Nicolantonio F, O'Callaghan A, Cree IA, on behalf of the Portsmouth Upper GI and Colorectal Cancer Multidisciplinary

Teams. Combination chemotherapy in advanced gastrointestinal cancers: ex vivo sensitivity to gemcitabine and mitomycin C. British Journal of Cancer 2003; 89: 2299-304.
59. Srouji IA, Resouly A, Cree IA. Case of thymic parathyroid carcinoma in a haemodialysis patient: application of tumour chemosensitivity testing. Journal of Laryngology and Otology 2004; 118: 162-4.
60. Cree IA. Predictive Oncology-Second Conference of the International Society for Chemosensitivity Testing in Oncology. Anticancer Drugs 2004; 15: 301-302.
61. Tulley PN, Neale M, Jackson D, Chana JS, Grover R, Cree I, Grobbelaar AO, Wilson GD. The relation between c-myc expression and interferon sensitivity in uveal melanoma. British Journal of Ophthalmology 2004; 88: 1563-7.
62. Di Nicolantonio F, Knight LA, Di Palma S, Sharma S, Whitehouse PA, Stuart J Mercer SJ, Charlton PA, Norris D, Cree IA. Ex vivo characterisation of XR11576 (MLN576) against ovarian cancer and other solid tumours. Anti-Cancer Drugs 2004; 15: 849-860.
63. Di Nicolantonio F, Knight LA, Glaysher S, Whitehouse PA, Mercer SJ, Sharma S, Mills L, Prin A, Johnson P, Charlton PA, Norris D, Cree IA. Ex vivo reversal of chemoresistance by tariquidar (XR9576). Anti-Cancer Drugs 2004; 15: 861-869.
64. Di Nicolantonio F, Louise A Knight LA, Whitehouse PA, Mercer SJ, Sharma S, Charlton PA, Norris D, Cree IA. The ex vivo characterization of XR5944 (MLN944) against a panel of human clinical tumor samples. Molecular Cancer Therapeutics 2004; 3: 1631-7.
65. Knight LA, Di Nicolantonio F, Whitehouse P, Mercer S, Sharma S, Glaysher S, Johnson P, Cree IA. The in vitro effect of gefitinib ('Iressa') alone and in combination with cytotoxic chemotherapy on human solid tumours. BMC Cancer 2004; 4: 83.