Meeting Report
Highlights of the Society for Medicines Research Symposium held September 29th, 2011, in London.

Oncology

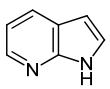
By Diane Coe, Neil Hales and Mark Searcey

On September 29th, 2011, the Society for Medicines Research held a one-day meeting entitled *Oncology*. Although a number of new treatments and new approaches to therapy have been devised in recent years cancer remains a major disease, with one in four of us likely to suffer during our lifetime. This SMR symposium brought together a panel of international speakers across the breadth of research and development in the field, to present and discuss new advances and results from early research to clinical data.

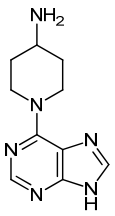
Cancer Drug Discovery: From concept to clinic

The meeting was started by a presentation from Dr. Michelle Garrett (The Institute of Cancer Research) on the development of inhibitors of the serine / threonine kinase AKT, also known as PKB. This protein regulates a number of key cellular activities including proliferation and survival and is an important component of the PI3 Kinase signalling pathway (see below). Disregulation and overexpression of AKT has been demonstrated in a number of human malignancies, so the discovery and development of inhibitors has, therefore, been proposed as a therapeutic strategy for the treatment of disease.

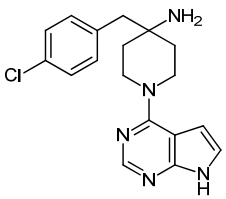
The drug discovery programme was run in collaboration with Astex™ using a fragment based approach.[1] A virtual screen of approximately 300 000 fragments (MW <250) followed by validation in a bioassay and crystallography afforded a number of ATP-competitve fragments with IC_{50} 15 - 100μM. The 7-azaindole **1** was a fragment found to occupy the ATP-binding site interacting via bidentate hydrogen bonding on the heterocyclic N and N-H to the hinge region of the kinase. Replacement of the azaindole core with a chemically more tractable purine and elaboration of the fragment through structure-based design afforded a 6-(4-aminopiperidinyl)purine **2**, which showed increased potency in the AKT enzyme assay: IC_{50} 270nM.[2] An important motif of amino derivative **2** was the basic amine, which forms an additional hydrogen bond in the ribose pocket. A key feature of the screening cascade incorporated a specific pharmacodynamic readout of AKT inhibition in cancer cells, the inhibition of phosphorylation of the downstream substrate GSK3β using a cell based system.[3]



1 IC_{50} >100μM



2 IC_{50} 270nM



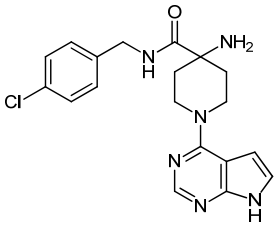
3 IC_{50} 6nM
CCT128930

Additional optimisation, incorporating a lipophilic group capable of binding to the P-loop pocket, resulted in the CCT128930 **3**, which had nanomolar activity in the AKT enzyme assay. Comparison of the structures of **3** bound to PKA and PKA-PKB chimera (a well established surrogate for PKB) showed significant differences in the position of the 4-chlorobenzyl motif. These differences arise

because of the change Met173 (PKB) → Leu (PKA) and effect the interaction of the 4-chlorobenzyl substituent with the P-loop pocket.

The preclinical pharmacology of CCT128930 was presented, showing decreased phosphorylation of direct substrates or downstream targets on treatment with increasing concentrations of the compound on PTEN-null U87MG human glioblastoma cells after 1 hour treatment.[4] In addition, the compound caused G_1 cell-cycle arrest in the same cell line, which is consistent with blockage of the AKT pathway. Evaluation of the pharmacokinetics of CCT128930 showed the compounds had low oral bioavailability, however i.p. administration at 50 mg/kg for 4 days resulted in pharmacologically active concentrations in tumour tissue. The effects on several AKT biomarkers in the U87MG xenografts harvested 2 and 6 hours after the last dose were consistent with the AKT inhibition *in vivo*. Antitumor activity was observed with the compound in both U87MG and HER2-positive PIKC3A-mutant BT474 human breast cancer xenografts.

Modification of the linker between the piperidine and lipophilic group addressed the issues of high clearance and low oral bioavailability and resulted in CCT129254 **4**.[5] This compound showed a significant inhibition of tumor growth in mice with U87MG human glioblastoma xenografts when dosing 200mg/kg p.o. five times a week. The programme was licensed to AstraZeneca and further developments delivered AZD5363 which is currently being evaluated in Phase I clinical studies.

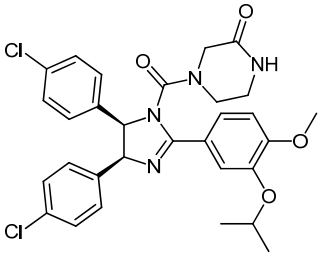


4 CCT129254

Dr. Garrett also described the work of the Clinical PD Biomarker group which has responsibility for the development, validation and implementation of assays for the evaluation of PD biomarkers in Phase I clinical trials. The PD biomarkers developed for the Phase I studies of an AKT inhibitor included detection of phosphor-GSK3β in platelet rich plasma or tumour tissues / cells from patients using Meso Scale Discovery (MSD™) technology. A semi-quantitative assay of the hair follicle PRAS40 biomarker assay was also described, *ex vivo* treatment of human hair (eyebrow) with CCT128930 at 18.9 mM (3 x GI_{50} (U87MG) showed a significant decrease in the pThr246 pRAS40 signal versus total PRAS40. This data supported the potential use of hair follicle measurements in clinical trials of AKT inhibitors.

Dr. Ian Hardcastle (Newcastle Cancer Centre, University of Newcastle) presented work on isoindolinone-base inhibitors of the MDM2-p53 protein-protein interaction. The p53 tumor suppressor has been described as the guardian of the genome, as cellular stress, such as hypoxia or DNA damage, activates p53 resulting in gene transcription. The activity of p53 is regulated by the MDM2 protein by binding to and inactivation of the p53 transactivation domain, export of the complex from the nucleus and subsequent ubiquitylation of the MDM2-p53 complex to target it for proteosomal degradation. Inhibitors of MDM2-p53 binding interaction are expected to restore normal p53 activity in MDM2-overexpressing cells and to exert an antitumor effect.

A number of small molecule inhibitors of the MDM2-p53 interaction are known, which include Nutlin-3 **5**, benzodiazepinedione **6** and the spirooxindoles MI-63 **7**.[6,7] The X-ray structures of Nutlin-3 **5** and MI-63 **7** have been reported indicating the key shape-filling and hydrophobic interactions.



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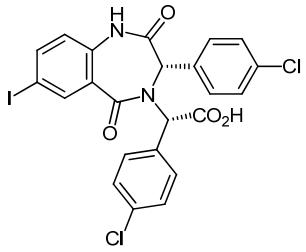

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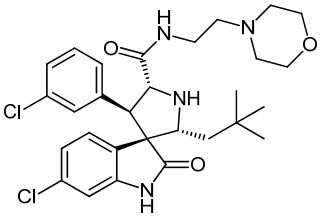

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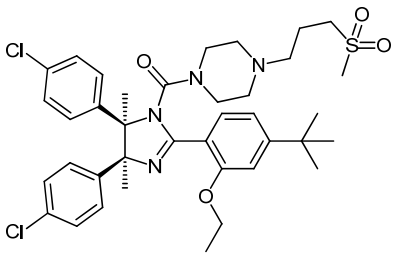

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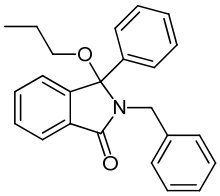
A molecule from the Nutlin series, RG 7112 **8** has been progressed into Phase I clinical studies.

The number of isoindolinones (**9**, **10**) were identified of inhibitors of MDM2-p53 interaction using an *in vitro* binding assay, IC_{50} 200μM.[8] These compounds also displayed modest growth inhibitory activity in NCI 60 cell line screen and were rated COMPARE negative with respect to known classes of antitumor agents. A hit-to-lead programme was initiated using virtual screening to guide the synthesis of focused library synthesis; this work resulted in the compounds NU8231 **11** and NU8165 **12** which have modest *in vitro* activity.



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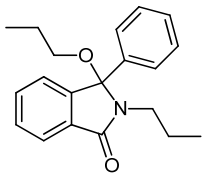

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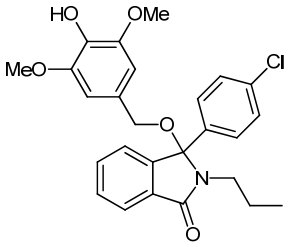

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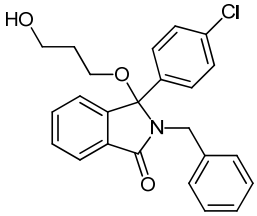

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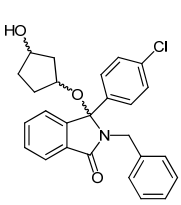
A number of potential binding modes were identified using some elegant NMR studies comparing the ^{1}H-^{15}N HSQC-NMR shift changes associated with compound **12** and p53.[9] Although complete assignment was not possible the work indicated that additional potency may be gained by introduction of a conformational constraint in the 3-alkoxy group.

Preparation of the 3-hydroxycyclopentoxy derivative **13** as mixture of *cis* and *trans* isomers showed a 5-fold improvement in potency, IC_{50} 3μM.[10] Introduction of a 4-nitrobenzyl group, NU8261 **14**, also resulted in an increase of potency. The SAR around the 3-alkoxy substituent was explored further, retaining the 4-nitrobenzyl group. The best molecule identified was the 2-(1,1-cyclopropane)dimethanol derivative **15** IC_{50} 225nM. The racemic mixture was separated into single enantiomers via chiral HPLC and the MDM2-p53 activity was shown to reside in the (+)-R-enantiomer NU 8354A **16**.



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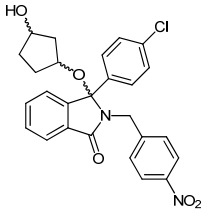

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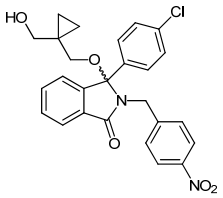

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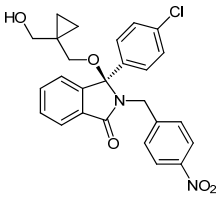

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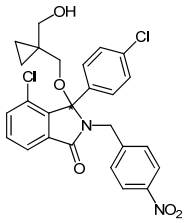

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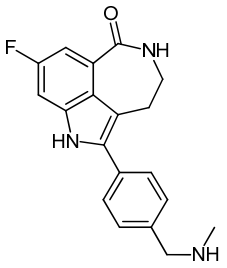
The compound NU8354A **16** was evaluated in a range of cell lines with defined p53 and MDM2 status and demonstrated a similar profile to Nutlin-3, thus demonstrating the potential of the isoindolines as promising class of compounds.

Attempts to replace the undesirable nitro group using a both classical and nonclassical isosteres failed to produce a compound with comparable potency. However, introduction of a 4-chloro substituent onto the aromatic-ring of the isoindolinone ring afforded a compound, NU8406A **17**, with increased potency and cellular activity consistent with activation of p53.[11]

The final talk of the first session was given by Professor Hilary Calvert (UCL Cancer Institute) on poly(ADP-ribose)polymerase (PARP) inhibitors as an approach to selective cancer therapeutics. PARP-1 is the best characterised of the 17 isoforms and is present in high activity in most tissues. PARP-1 is activated by DNA strand breaks and is involved with single strand break repair by binding to DNA breaks and attracting DNA repair proteins to the site of damage.

The PARP inhibitor programme was initiated in Newcastle in 1990 with the objective of generating high affinity compounds for *in vivo* and clinical use. Inhibition of PARP-1 is known to potentiate specific cytotoxic agents such as monomethylating agents (temozolomide, nitrosoureas) and topoisomerase 1 inhibitors (topotecan, irinotecan) or radiation therapy. A collaboration between Newcastle and Agouron resulted in AG014699 **18** Ki <5nM which was taken into clinical development by Pfizer.[12]



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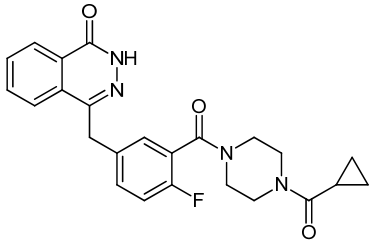

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In a Phase 0/1 trial involving a Day 1-5 schedule with temozolomide substantial PARP inhibition was seen in peripheral blood mononuclear cells in tumor biopsies. There was no significant toxicity attributable to the PARP inhibitor as a single agent and encouraging evidence of clinical activity were seen.

BRCA1 and BRCA2 are involved in the repair of double strand breaks by the homologous recombination (HR) pathway. Mutations in these genes predispose the carrier to breast, ovarian, prostate and other cancers. BRCA1 and BRCA2 deficient cells are hypersensitive to PARP inhibitors; inhibitors have been shown to selectively kill breast cancer type 1 susceptibility protein BRCA1 or BRCA2 deficient tumor cells while having minimal effects on normal cells with intact BRCA pathways and as such represents a specific approach in cancer treatment.[13, 14]

Olaparib **19** (Kudos / AstraZeneca) is an orally active PARP inhibitor, a Phase I study demonstrated that olaparib was well tolerated and had satisfactory pharmacokinetic and pharmacodynamic profile.[15]

Olaparib was administered 400mg bid in two Phase II studies involving BRCA1 and BRCA2 mutation carriers with breast or ovarian cancer: both studies provided positive proof of concept for the efficacy and tolerability of treatment.[16, 17]

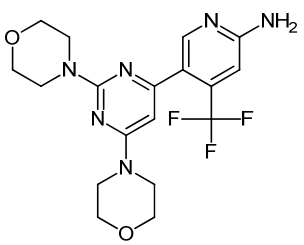
It was clear from the presentation that significant progress has been made in recent years in this area and there is potential to further develop the synthetic lethality between tumor-specific defects and PARP dependent pathways.

The second session was started by a presentation from Dr. Frederic Stauffer (Novartis) on the PI3 Kinase/mTOR signalling pathway and its relevance to cancer treatments. There are at least 14 proteins in the family that *inter alia* regulates the AKT pathway (*vide supra*) both upstream (mTORC2 and PI3K) and downstream (mTORC1). Novartis has a clinical portfolio of inhibitors with different selectivity profiles that provide an insight into the role in oncology of different parts of the pathway.

The clinical role of the downstream regulator mTORC1 has been established by the registration of the selective inhibitor RAD001 as Affinitor® (Everolimus).

The selective PI3Kα inhibitor NVP-BYL719 is at Phase I but its role remains unclear. It seems unlikely that PI3K inhibition alone will be an effective cancer therapy and stratification of the patient cohort for mutant PI3KCA (the PI3Kα gene) should address this question.

The pan class 1 PI3K inhibitor NVP-BKM120 (**20**) is at Phase II: the compound arose from a potent screening hit (**21**) by optimisation of physicochemical and pharmacokinetic properties at a cost of 1 log unit of potency followed by optimisation to recover the lost potency and then add a further log units of potency (**22**). Finally a second round of optimisation of pharmacokinetics and *in vivo* efficacy gave (**20**), which has excellent pharmacokinetics and high exposure. Because of the high exposure some concern about adverse effects was expressed: 24% of patients showed hyperglycemia – PI3K is downstream of the insulin receptor - and CNS effects were also seen in 20% (anxiety) and 18% (depression) of patients - probably because the free brain concentrations are the same as the free plasma concentrations. CT Evaluation of 24 patients with heavily pre-treated and advanced tumors showed some useful changes in tumor size but no clear pattern of efficacy against a single tumor type emerged. Again, a more detailed stratification of the patient population is underway to characterise the responsive patient sub-group more accurately. The picture is further complicated by the fact that although NVP-BKM120 (**20**) is a relatively selective PI3K inhibitor, it also acts as a tubulin destabiliser similar to Nocodazole and some of its anti-tumor activity may a due to this off-target pharmacology.



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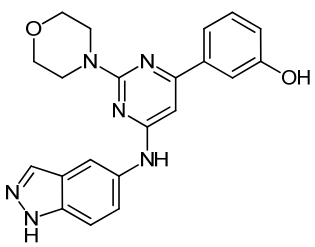

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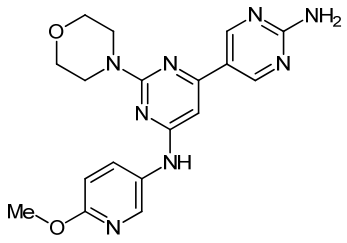

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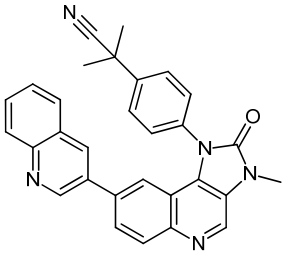
The pan class 1 PI3K inhibitor with broad catalytic mTOR inhibitory activity NVP-BEZ235 (**23**) is also at Phase II. NVP-BEZ235 (**23**) arose from a privileged kinase inhibitor scaffold (**24**) selected by structure based design as AKT inhibitor. Modification of this structure led to the observation that the derivative (**25**) was a dual PDK1/pan Class 1 PI3K inhibitor. Optimisation of *in vivo* activity provided NVP-BEZ235 (**23**), which is a potent compound, but which has only limited solubility. NVP-BEZ235 (**23**) strongly inhibits the PI3K pathway and either induces apoptosis or is cytostatic against a wide variety of breast cancer cell lines depending on the genetic status of the cell. In a MDA-MB361 breast cancer cell line (Her2 amplified and E545K PI3KCA mutated) NVP-BEZ235

(**23**) induces apoptosis and inhibits proliferation (IC_{50} *ca* 10 nM). A similar profile of activity is shown by the combination of GDC0941 (pan Class 1 PI3K inhibitor) and AZD8055 (catalytic mTOR inhibitor), but not by either alone. The antiproliferative effect of NVP-BEZ235 (**23**) is associated with G1 arrest. In the breast cancer cell line BT474 xenograft – BT474 also exhibits Her2 and PI3KCA changes – a combination of Herceptin and NVP-BEZ235 (**23**) completely supressed tumor growth for the duration of the 42 day experiment, and was more effective than either agent alone. CT evaluation of a similar treatment of human breast cancer with Herceptin and NVP-BEZ235 (400 mg daily) showed regression of tumor size. Even at efficacious doses NVP-BEZ235 (**23**) showed few significant effects on glucose levels in rats and those small changes normalised on chronic dosing. Overall, PI3K/mTOR pathway inhibitors do not seem to offer a magic bullet against cancer, but appear to be an effective treatment against certain type of cancers with defined genetic changes, and they are well tolerated in clinic. There is a clear need for stratification and better trial design, and there may be further niche indications of allosteric mTOR inhibition. PI3K/mTOR pathway inhibitors may be good candidates for combination therapy with cytotoxic or targeted drugs.



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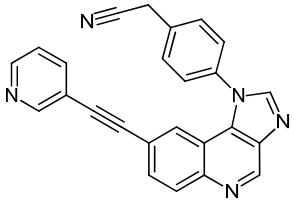

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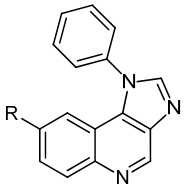

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Selectivity profile

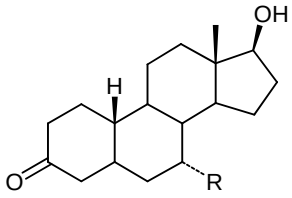
	IC_{50}/nM	
Protein	NVPBEZ235	NVP-BKM120
p100α	4 ± 2	52 ± 37
p110α H1047R	4.6 ± 0.8	58 ± 2
p110α E545K	5.7 ± 1	99 ± 6
p100β	75 ± 45	166 ± 29
p100δ	7 ± 6	116
p100α*	5 ± 4	262 ± 94
mTOR	20.7	4610 ± 1860

* Possibly p100γ

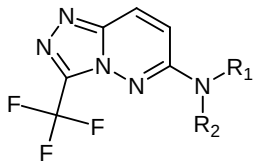
Graeme Walker (AstraZeneca) presented an overview of AstraZeneca research aimed at extending the range of therapeutic options for late-stage prostate cancer.[18] Prostate cancer is the second most common cause - after lung cancer - of cancer death in men. 37051 Men were diagnosed with prostate cancer in 2008 and 80-90% of these were androgen dependent. Such early stage tumors are usually well treated using LHRH agonists and/or androgen antagonists, but often progress to disease that is "castration-resistant" (androgen independent) although still driven by the androgen receptor (AR). It is at this stage that new and effective therapies are needed.[19]

A precedent in the analogous case of estrogen and estrogen receptor (ER) dependent cancers was provided by the conversion of the agonist estradiol into the ER downregulator Fulvestrant. Similar changes to the androgen agonist 19-nor-dihydro-testosterone (**26**) gave a weak AR downregulator (**27** IC_{50} 1μM), the discovery of which was facilitated by development of a cellular assay to measure AR downregulation in the LNCaP cell line by detecting cellular immunofluorescence on the Acumen platform. The potency of analogues of (**27**) was too low to permit development of a sustained release

depot formulation analogous to that of Fulvestrant. However, the availability of a reliable assay for AR downregulation made the search for a non-steroidal AR downregulator possible.



26 R = H
27 R = $(CH_2)_9S(=O)(CH_2)_3C_2F_5$

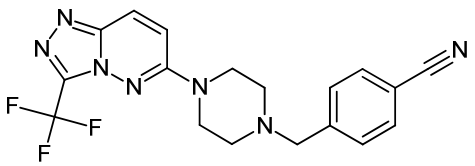


28 R_1, R_2 = e.g. optionally cyclic alkyl
29 R_1, R_2 = $(CH_2)_5$

A screen of 100,000 compounds, chosen with regard to their physico-chemical properties and the general features of size, shape, and hydrogen-bonding characteristics of the AR agonist pocket, was carried out using an Invitrogen 384 well Fluorescence Polarisation (FP) assay that measures compound binding indirectly by displacement of a red fluorescent dye. Similar assays established compound binding selectivity against other nuclear hormone receptors (NHR). The screening assays characterised a series of triazolopyridazines **(28**) as sub-micromolar AR ligands with selectivity against other NHR. Triazolopyridazines are ligand efficient and novel as AR ligands with good DMPK properties. The core is lead-like in size, simplicity, ease of synthesis, and hydrophobicity. However, as befits a compound found in this way, the compounds were also AR agonists and not AR downregulators.

The agonist 6-(1-piperidinyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (**29** LogD = 3, MW = 271) was an attractive chemical starting point. It seems likely that the triazolo-moiety binds at the heart of the AR-LBD, since (**29**) can be superimposed on the reference structure of hydroxyflutamide in its AR-hydroxyflutamide complex. The binding model suggested that side-chains attached to the amino-substituents on the pyridazine ring were most likely to confer AR downregulation, if such a change in activity profile could be induced at all.

Relatively conservative modification of the piperidine ring of agonist (**29**) provided a series of AR downregulators: the modest cellular potency of 4-(4-cyanobenzyl)piperazin-1-yl analogue (**30**) as an AR downregulator (IC_{50} 1μM) was fully compensated by good DMPK properties (9.2% free, clearance 13% LBF, and bioavailability 100% in rat) so that an *in vivo* estimate could be made of the properties of this series of AR downregulators. In the Herschberger rat, which measures androgen dependent tissue growth in castrated rats, downregulator (**30**) was able to reduce the testosterone propionate stimulated weight of seminal vesicles to the same extent as Bicalutamide, a therapeutically useful antiandrogen. More encouragingly, in a model of castration resistant prostate cancer developed by Dr Martin Gleave (Vancouver Prostate Centre, University of British Columbia), downregulator (**30** 100 mg bid po) was able to exert an essentially complete inhibition of tumour growth and clinical biomarker (PSA) secretion for the 8 weeks duration of the experiment.



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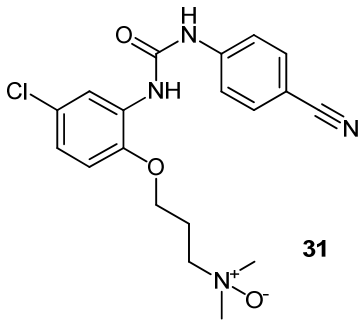

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In summary, Graeme Walker emphasised that the AR is a key target in hormone sensitive and castrate resistant prostate cancer, and reported the identification of compounds which selectively down-regulate the AR and block AR mediated signalling. Pre-clinical data with one of these compounds (**30**) shows that in validated *in vivo* models downregulator (**30**) modulates AR dependent growth of both normal tissue and of castrate resistant prostate cancer xenografts. Further work leading to a clinical candidate will be described in due course

Bob Boyle (Sentinel Oncology) discussed some of the problems and opportunities encountered in setting up a virtual drug company. Sentinel Oncology has been developing a pipeline of drugs since 2005 using a business model in which all of the practical work is outsourced as required, and in which all of the design and intellectual property is generated and retained within the company. The key driver behind this model is that it allows all of the necessary work to be resourced in a flexible and capital efficient manner. The initial funding was by the founders and private capital, with subsequent additional funds from the East of England Development Authority and Wellcome Trust before commercial partnerships were established with Ethical Oncology Science and Antisoma. Sentinel was able to develop projects with P70S6K (mTOR pathway), Chk1 (DNA repair), and Flt-3 (cell signalling).

The value of Chk1 inhibition lies in its role in the DNA Damage Response: DNA damage or errors of DNA synthesis are common and a cell must be held in stasis while the damage is corrected. Chk1 is activated by phosphorylation when DNA damage is detected by, for instance, ATR, and this leads to cell cycle arrest at the S phase and G2/M checkpoints. This property is illustrated by FS111 (**31** Chk1 IC_{50} < 10 nM, hERG IC_{50} = 16.3 μM, Bioavailability <5%), which produces at 3 μM a 14.3 fold increase in the sensitivity of p53 –ve HT29 cells to the DNA damaging agent SN38 (Irinotecan). In p53 +ve cells (HCT116) there is a viable G1 checkpoint that allows damage repair and undermines the activity of Chk1 inhibitors.

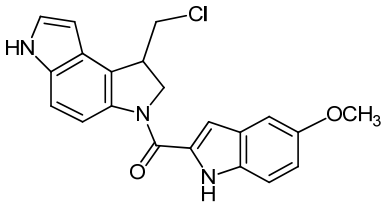
FS105 (Chk1 IC_{50} < 10 nM, Bioavailability 95%) shows a good degree of selectivity. It potentiates the cytotoxic effects of Gemcitabine in HT29 cells. Biochemically the effect is to inhibit Chk1 autophosphorylation and increase the amount of cleaved PARP indicative of increased apoptosis. Use of Gemcitabine in combination with FS105 produces a marked S phase cell cycle arrest. Although the role of Chk1 inhibitors seems clear in combination with DNA damaging agents, the DNA damage response has been shown to be constitutive in cases of acute myeloid leukemia (AML). Accordingly, FS106 (Chk1 IC_{50} < 1 nM) is potent in a range of AML cell lines, with IC_{50} = 70 nM in MOLM-13 cells.

A final approach adopted by Sentinel is "Targeted Synergy", a novel approach to targeting hypoxia and DNA repair. Nitro compounds (e.g. PR-104 from Proacta; TH-302 from Threshold) and azine N-oxides (e.g. Tirapazamine from TPZ-Sanofi) have already been targeted at hypoxic tissue. The aim of targeted synergy is to deliver in one drug an agent that will damage DNA in hypoxic tissue and then inhibit the DNA damage repair process. An example of this is provided by FS103, which is a potent Chk1 inhibitor (Chk1 IC_{50} = 11 nM) that selectively kills HCT116 cells under hypoxic conditions: (Cell killing potencies: normoxia IC_{50} >30 μM; hypoxia IC_{50} 0.055 μM). FS103 significantly enhances the ability of SN38 (Irinotecan) to kill HT-29, is more effective in p53 –ve cells, and increases the sensitivity to radiation of cells in hypoxic conditions.

Natural products and their analogues have formed the backbone of clinically utilised antitumour agents for many years and in the final talk Professor Mark Searcey (School of Pharmacy, UEA) highlighted the continuing utility of such agents and their potential for further development. The story behind the compound paclitaxel is well known, and while its mechanism of action was initially fairly unique, it has now been shown that several natural product compounds exert their effects through stabilising microtubules. Included among these are the epothilones, amongst which ixabepilone has been shown to be useful in the treatment of breast cancer.

Natural products can also be the starting point and the inspiration for new compounds. The anthracycline antibiotics such as doxorubicin and daunorubicin are well known clinically utilised agents that work through inhibiting topoisomerase II. Unfortunately, they also suffer the dose-limiting problem of cardiotoxicity. The mechanism of action of doxorubicin inspired medicinal chemists to simplify the anthraquinone-type structure and, ultimately, to generate the synthetic analogue mitoxantrone. Mitoxantrone in turn became the inspiration for further development. Such simple anthraquinones are potent topoisomerase II inhibitors, but such an anti-proliferative effect is toxic to all dividing cells, leading to associated side effects and a small therapeutic window. The development of prodrugs that could target the inhibitor to the tumour cell with some specificity would allow the development of much more selective non-toxic agents. Banoxantrone, an *N*-oxide derivative of a topoisomerase II inhibitor, is totally inactive as an antitumour agent until it reaches a reducing environment, such as the hypoxic region of a solid tumour. In this region, the *N*-oxide is reduced to the free amine, probably by the action of cytochrome P450 (CYP) enzymes, to generate the active antitumour agent.

Finally, Searcey described the ongoing work in his own laboratory and that of his collaborator Laurence Patterson of the University of Bradford Institute for Cancer Therapeutics. This project seeks to further exploit prodrugs through their activation by CYP enzymes, but in this case through a bio-oxidative approach. CYPs are known to activate prodrugs – the clinically utilised agent cyclophosphamide is one compound that is activated in this way. The research by Searcey and Patterson was focused on the idea that if one could identify particular enzymes that were over-expressed in the tumour but not in the liver or other systems, one could select antitumour agents that were specific for the tumour. Preliminary work in this area[20] has identified ultrapotent antitumour duocarmycins as candidates agents for cytochrome P450 bio-oxidative activation. A synthetic analogue of the natural product ICT2700 (**32**) that is entirely inactive in tumour cell lines was synthesised and shown to be selectively activated by the isoform CYP1A1. The antitumour activity of the compound against a cell line expressing the CYP and the DNA sequence selectivity of the compound both suggest that the active form of the compound is formed by the enzyme. This research demonstrates that natural products can still inspire the development of new small molecules with therapeutic potential.



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