BACR Interview #2: KuDOS Pharmaceuticals

In the second of a series of interviews with key personnel from companies founded by BACR members, Nick Miller chatted to Professor Steve Jackson from Cambridge University's Gurdon Institute (Wellcome Trust / Cancer Research UK), whose research formed the basis of KuDOS Pharmaceuticals Limited.

NM: As background to this discussion, perhaps we should remind readers that radiotherapy and chemotherapy often achieve their therapeutic effects by damaging DNA, the specificity of the effect being related to the relative sensitivity of cancer cells to such damage. However, DNA damage may trigger mechanisms of DNA repair, allowing a proportion of malignant cells to survive the therapy. So, in summary, the main element of the KuDOS thesis is that inhibition of DNA repair pathways should facilitate many existing and future therapeutic strategies for cancer.

SJ: Yes, that's a reasonable summary. But I think it is also worth pointing out that KuDOS was formed as an oncology-focussed drug discovery company, not a "DNA-repair-inhibitor" company. Hence, some of our drug candidates are not DNA repair inhibitors, although they are conceptually complementary to DNA repair inhibitors in that they also target cells which tend to be resistant to radio- and chemotherapy. For example, AQ4N, which KuDOS, and our North American partner Novacea are evaluating in multiple phase I trials is a hypoxia-induced anthroquinone prodrug and therefore would be expected to target quiescent cells in hypoxic tumour regions, ie cells which avoid therapies based on DNA damage. However, it's true to say that at present most of the KuDOS drug candidates are inhibitors of DNA repair.

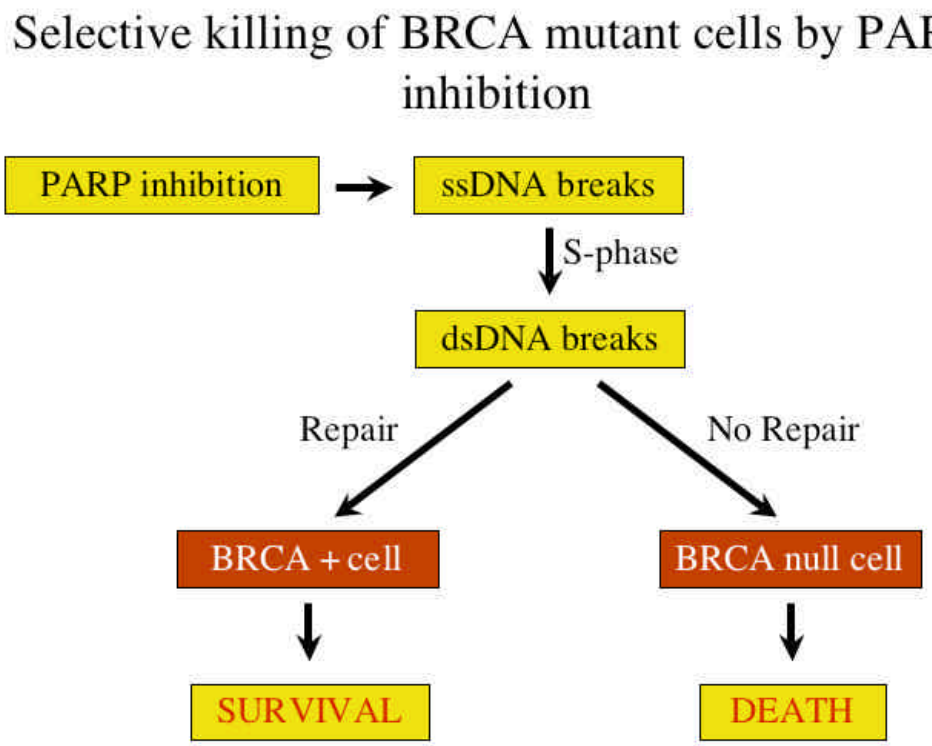
NM: I think Patrin is the most advanced of your repair inhibition products, and is now in Phase II for melanoma, in conjunction with temozolomide. Is there anything you can tell us about the progress of this trial?

SJ: On the basis of results to date, we have chosen to extend Phase II evaluation in additional patients and we have modified the dose and schedule. We expect to evaluate the data within six months along with the results for phase I trials in the USA of Patrin in combination with decarbazine (another alkylating agent). It's an exciting time, and if we get the results we hope for, this could add significantly to the company and provide the basis for its further development.

NM: You must often get asked about the possibility of side effects with the drugs that you are developing. For example, existing chemotherapies are known for their deleterious effects on normal cell types that are rapidly dividing, and have been associated with mutations which can themselves lead to secondary cancers, particularly leukaemia. Would inhibition of DNA repair exacerbate these types of effect?

SJ: You have to remember that cancers resulting from chemotherapy take many years to materialise. We do not foresee the risk from KuDOS small molecule inhibitors that are associated with cytotoxic therapy, but nonetheless we envisage that our products will be used initially in advanced stage cancer patients, where the risk-benefit profile of our inhibitors can be better investigated. With regard to shorter-term toxicities, this may be an issue for some DNA repair inhibitors, but of course we will have to wait and see what the pre-clinical and Phase I trials tell us. However, there are good reasons to believe that certain classes of repair inhibitor will not suffer from the obvious side-effects. For example, we are developing drugs that inhibit PARP. Normal cells can survive PARP inhibition because lesions associated with such inhibition are normally repaired by the protein products of the *BRCA1* and *BRCA2*

genes; but cells that are deficient in the functional proteins BRCA1/2 are much more sensitive to PARP inhibition. This may be the basis of a specific treatment for tumours with *BRCA* mutations. Indeed, we believe that PARP inhibitors could be effective monotherapies for some cancers, ie they would not necessarily need to be used in conjunction with other chemotherapies or with radiotherapy. Most tumours have typically lost one or more mechanisms of DNA repair already, and therefore are *a priori* more susceptible than normal cells to any further reduction of DNA repair capacity. So we believe that there is a good basis for expecting products based upon our inhibitors to show selected toxicity in malignant cells as compared to normal cells.



NM: Perhaps we could talk a little about the beginnings of KuDOS. How did it start, and what made you want to commercialise your academic accomplishments?

SJ: Perhaps the fundamental driver was the desire to make a difference. You can do well in your career, get the post you want, and publish a string of good papers – but have you changed the world in any substantial way? So I founded KuDOS as a concept rather than a technology-based company as such, the concept being to develop the research from my laboratory into real products that, truly, make a difference to people's lives. We had already demonstrated the proof of principle in terms of showing that small-molecule inhibition of DNA repair can sensitise cells to radiotherapy. Hence, with the approval of the Cambridge University Technology Transfer Office, I approached the commercialisation arm of the Cancer Research Campaign. Coincidentally, I then learned that they were just about to approach me with a similar proposition. The next step was to raise some cash. We tried talking to big pharma but found that we were at too early a stage to capture their attention. So we ended up discussing our proposition with venture capital organisations, and eventually found some that we could work with, namely Advent, 3i and Schroders. A key development at that stage was Barrie Ward joining KuDOS as CEO, as he helped tremendously in finalising the shape of the Business Plan and then played a crucial role in getting the show on-the-road.

NM: I have spoken to several people who have expressed reservations regarding the utility of University Technology Transfer Offices, usually because of the lack of significant commercial

experience in most TTOs leading to a somewhat naïve view of the commercial terms that may be actually achievable. Did you find the TTO to be a help or a hindrance?

SJ: They were helpful, but this was a while ago, and they did not get too involved. I understand that they are a bit more proactive these days, and I can see that there could be both pros and cons to this.

NM: Do you have any advice for other BACR members who are thinking of taking a similar step in terms of forming a commercial vehicle to carry the results of their research to the market?

SJ: First of all, you should go with your gut feeling – if it feels right, then do it. You should also seek advice from numerous sources, by talking to people from academia who have gone down this route, and to people from commercial backgrounds. In particular, you should seek advice from individuals that have worked in big pharma and who can advise on the type of products that big pharma is likely to be interested in. Finally, you should be prepared for a hard slog, especially in the initial stages – it took us over a year to complete our first funding round from VCs.

NM: That seems to be a common experience, especially in the funding climate that has prevailed in the UK in recent years. Perhaps even the best gut feeling may become constipated in the current environment.

SJ: Only moral fibre can cure that condition – you just have to keep going!

NM: Apart from bad puns, do you have any regrets? What would you have done differently?

SJ: I think we did most things pretty much as well as we could, given all the circumstances. Perhaps we should have been a bit more focussed at the beginning, as our initial broad concept was a bit too vague for the tastes of most venture capital groups. Personally, I think I should have spoken up a bit more often and earlier about the organisation of the company, in terms of structure and shareholdings. These things ended up fine but the negotiations were more protracted than they needed to be. I had some regrets from time to time, particularly when trying to take the company forward at the same time as moving / renovating my house and helping my wife looking after our two young children, and at the same time keeping my lab going, as I ended up being very overstretched. But things have calmed down a bit now and I can't say that I regret having done it – in fact I am very glad I did.

NM: In the meantime, would you be interested in collaborating with other BACR members?

SJ: We would certainly be interested in collaborating with other groups with complementary clinically-oriented programmes, for example in the areas of DNA repair, cell cycle control and apoptosis. We would also contemplate in-licensing intellectual property and products relating to novel druggable targets relevant to cancer. This goes for other biotech companies as well as for other academic groups.

NM: Do you have any final words of advice for BACR members?

SJ: Only to say that I have tremendously enjoyed the experience of setting up and growing KuDOS. I have learnt a lot and met a whole variety of people that I would otherwise never have come into contact with, and I am tremendously excited by the prospect of our drugs making a difference in the real world. Also, for others thinking of going down this route, be aware that quality of personnel is critical at all levels – even the best technology in the world can be a commercial failure if it is not supported by a commercially experienced management team.