

SCIENCE & TECHNOLOGY COUNCIL [STC]

Minutes of the Meeting held on 19th September 2001 - CTL

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R&T SCIENCE AND TECHNOLOGY COUNCIL**Minutes of Meeting held on
Wednesday 19th September 2001****CTL****STC 01/04****1. PARAQUAT TOXICOLOGY RESEARCH** (Mike Clapp, Jon Heylings, Nick Sturgess)

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STC01_14a.ppt



STC01_14b.ppt

Paraquat (PQ) is the example of successful PLCM. A new sales target of \$1bn by 2010 has been set. Activities at CTL are focussed on:

- Vigorous defence of all registrations and uses
- Development and introduction of innovative low toxicity products by 2005, principally through the “Prometheus Project” lead by Jon Heylings.

1.1 Prometheus Project

The objective is to deliver a new 200g/l formulation with a 10x reduction in acute oral toxicity (relative to Gramoxone) for first sales in 2005. The product design spec has been agreed with the business. Cost is critical – the target is <15% increase in cost cf. Gramoxone. The preferred technical approach to turn a mobile pH 7-8 liquid formulation into a gel at pH 3 in the stomach. This buys time by delaying emptying of the stomach and reduces absorption by the gut, thereby reducing peak and total PQ in the blood stream. Selected gelling agents are all water soluble, contrasting with the earlier Magnoxone approach. The alignate-based Manutex-containing formulation looks most promising. The emetic remains an important component, which must be delivered to the blood stream in sufficient amount to be effective. The preferred formulation reduces emetic plasma concentrations cf. Gramoxone, but is still acceptable. A patent was filed in March 2001. Five candidates have been selected for field trials, with animal and human trials expected 2002 and 2002/3 respectively.

There is a parallel project on Alerting Agents (= stenchers) to find reduced irritancy versions and these are being incorporated into new gels.

In discussion :

- **The STC was concerned about adding cost to the product given that the new formulation must ethically be sold in all outlets. Those territories with the tightest margins will determine the bearable price increase. 15% sounds high without some improvement in weed control, although our strategy to exploit PQ uniqueness and not compete with other NSH may make price increases more acceptable.**
- **Business sign-on needs to be tested thoroughly via the DevCo. Wider exposure of the issues may help manage expectations.**

Action : Dave Lawrence and Lewis Smith to take to DevCo.**1.2 Parkinson's Disease issues**

Perceptions linking PQ with Parkinson's Disease are growing due to academic reports. The starting point seems to be a claimed similarity between PQ and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a Parkinsonism-inducing agent. In reality MPTP and PQ are entirely different, especially in their physical properties. This means MPTP crosses the blood-brain barrier where it is known to be activated to MPP⁺ by monoamine oxidase before affecting dopaminergic neurones. PQ does not cross the blood-brain barrier. Studies at CTL has shown no evidence for any neurotoxic effects of PQ by all relevant routes of exposure. However, intracerebral injection, an unconventional route of exposure, does result in neurotoxicity and this has triggered academic interest.

Ca 5 publications per week are appearing, so monitoring this activity is important. Most recently, an apparent synergy with Maneb is claimed in the literature using i.p. administration.

Regardless of the quality/relevance of the science, it is likely that regulatory authorities will take an increasing interest in the academic findings and may request neurotoxicity studies. A series of activities are in place to actively manage the situation, including in-house studies to refute literature claims and counter the perceptions being propagated by academia.

The STC congratulated the team on its patience and forbearance in the face of some poor academic science. Several ideas emerged in discussion eg. what happens with bipyridyl, the non-quaternised version of PQ?, what is the purity of the samples used by academics?, is the manganese in Maneb significant?.

The team's strategy was fully supported.

2. PROTEIN ALLERGENICITY RESEARCH AND TEST METHOD DEVELOPMENT AND VALIDATION (Ian Kimber)

The item followed-up the July 2001 STC discussion, when we agreed that the development of a widely-accepted validated animal model test was a high priority for HAES.

Three options for future allergenicity animal model were discussed :

- Brown Norway rat ip. injection
- " " " oral exposure
- BALB/c mouse systemic exposure

The atopic dog is not considered a suitable method, but access to the current test should be maintained as a back-up.

The BALB/c option is recommended as the one most likely to meet future needs and the team's progress was reported. Evidence of a good correlation between exposure to a limited number of known allergens and the mouse IgE responses was shown, together with a demonstration that not all stable proteins (to simulated gastric fluid) are allergens, nor do they elicit IgE responses.

Requirements for further test development are substantial, starting first with in-house evaluation, followed by well-managed and selective national and international collaborative trails. The target is to have the method recognised as a valid approach to protein sensitivity testing within a period of 3 years, although further management after initial acceptable will be needed. The STC was advised to regard this as a 5-year programme. People resource and protein availability are both constraints on progress.

The STC very strongly supported the approach recommended and the investment of appropriate resource. The project is critical to furthering biotech products. Protein structural SAR is likely to become important as understanding develops and the involvement of Tim Hawkes (for eg.) may be helpful. Protein modelling may also be useful (eg. involving Mafalda Nina). We may also need to bring some new skills in – eg. on protein glycosylation. The STC agreed the recommendation to maintain support for the atopic dog population, but asked to be advised should the model become discredited. We agreed the project should be formally recognised within the biotech project portfolio (c/o S Rees). Ian Kimber was confirmed as Project Leader.

3. **PATENTING OF TARGETS** (Edouard Lebel)



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Hundreds of essential genes have already been claimed as targets in over 30 patent applications and more invention disclosures are in-hand. Patent Offices are requesting splitting of such joint applications to one target per granted patent (at ~ \$50k per patent), with the potential for vast expense and resource demand. This item therefore addresses the need for a strategy to provide optimal protection in a cost effective manner. The paper and presentation are the result of considerable consultation within IP department and with scientist stakeholders.

The options are :

- Keep the targets as trade secrets
- Publication only
- US-filing only
- PCT filing, with the national phase in the US and EU only

Following careful analysis and consultation, the IP group recommended all novel targets be filed in the US to provide FTO and maintain our options. Foreign filing via PCT should be considered only for targets which are, or are planned to be, used in assays at JH (or used in Syngenta biotech products). At the national phase, EU and US filings only were recommended, and at prosecution stage we should review the level of continuing interest before progressing.

The STC congratulated the presenter and the team on the quality of the thinking and the clarity of the recommendations. The recommendations were accepted in full and the STC advised that two key questions should be used when reviewing applications : Is there a good reason for keeping it? Is there a good reason for not disclosing it? The default should be publication if not interested.

We separately discussed mode-of-action claims based on the inhibition of a particular function, and agreed that data supporting such an application would probably come as part of the normal research process in the hunt for new products, and we should consider filing broad claims in such cases.

The STC also requested that more active consideration be given to obtaining IP on assays that indicate toxicity cf. peroxisome proliferation.

4. CONTAINMENT OF PROTEINS PRODUCED IN PLANTS (John Steffens)



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The team reviewed options for containing non-food proteins that cannot be allowed to enter the generic food chain, in a range of potential target crops. Three overlapping & interacting components have to be considered :

- Crop production strategy
- Containment strategy
- End-product production strategy

Within containment, the key issues that require consideration are : gene flow, product flow and residue flow. No one potential solution addresses all – so a combinatorial approach will be needed. One attractive approach favoured by the team is viral expression. The team has addressed the ideal criteria for a plant production host and examined a range of crop classes. The options are:

- Tubers (mainly potatoes)
- Fruit (mainly tomato)
- Leafy species (eg. tobacco or alfalfa)
- Seeds – which is preferred by the team, and lead to further analysis of maize and rice (which looks attractive).

Since different products are likely to have different containment & production needs, the team has begun to look at potential Syngenta products (phytase, feed antibodies, oral tolerance antigens). Recommendations for further work, particularly about assessing the cost of the various options, are included in the slide set above.

Discussion points :

- **Zeneca had looked some time ago at the use of transient virus expression, but felt that establishing an infection was a problem. DKL agreed to send the background to John Steffens. Action : Dave Lawrence**
- **Orynova has stated publicly that it has an interest in hybrid rice. There may be some relevant technology that we could licence.**
- **Male sterile hybrids are clearly attractive, but how easy it is to produce them compared to male-sterile in-breds? The team believed that some serious seed breeding would be required.**
- **The STC questioned whether we should be trying to select one system now – or be opportunistic? The team believes we need to be opportunistic and until we**

get some real examples to work on case-by-case.

- As we bring proteins forward, we will need to decide whether the risk is acceptable, given proposed containment measures. The STC started to debate possible policies that will require further debate eg. zero gene flow for a human gene (a likely requirement from regulators?). What about an animal gene?
- The STC agreed that we should start working case-by-case on current “real” projects – and then develop policy statements as the issues emerge.
- Agreed Steve Evola and Lewis Smith would work with John Steffens and his team to exemplify the principles presented to the STC with three projects :
 - Animal antibodies
 - Thioredoxin
 - Phytase
- Two page analysis and recommendations were requested for 1st November discussion at next R&T LT in Atlanta describing :
 - Benefits and risks
 - Regulatory status
 - How we propose to contain risk
 - Technical probability of success

Action : Steve Evola, Lewis Smith and John Steffens

5. RICE GENOMICS (Steve Goff)



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Steve Goff overviewed the progress with the rice genome project to date in some detail, as background (sees slides). Next steps were recommended as follows :

- Publish Results before GBI Disclosure
- Continue IP Filings
- Support Cereal Functional Genomics Effort
- Establish External Collaborations
- Finish Rice in Collaborative EffortExtend Rice
- Genomics to All Cereals
- Protect Future Use of Genes via IP Access

STC discussion centred on what Syngenta needs to do to extract maximum benefit for us? and....what's getting in the way? A large number of legitimate stakeholders exist all of whom have the potential to slow progress. However, the Agribusiness Council has already agreed in principle to publication, and the concepts of collaboration. Actions were agreed as follows :

- DAE will write to David Jones and Michael Pragnell outlining the plans for publication and collaborative access to the data and advise them of our intention to proceed unless overwhelming difficulties are raised.

Action : Dave Lawrence to draft, David Evans to send

- Publication should be sent to Marian Flattery to operate the publication approval process, involving stakeholders.

Action : Steve Briggs & Marian Flattery

- Agreements for access to sequence by collaborators are in place and need publishing on the internet as soon as David Jones and Michael Pragnell have had time to comment.

Action : Steve Briggs

6. PYRROLNITRIN PROJECT (John Steffens)



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The projects aims to express pyrrolnitrin in crops for fungal control. Spectacular technical success has been achieved with the expression of the four-gene pathway in Arabidopsis, plus the demonstration of pyrrolnitrin accumulation sufficient to confer strong resistance to *Sclerotinia* and *Botrytis* in planta. Given the known broad anti-fungal spectrum of pyrrolnitrin, broad application in crops is expected.

The remainder of the presentation focussed on toxicology, environmental and regulatory issues. Toxicology judgements are based on Eli Lilley work showing a relatively benign profile. Mutagenicity testing has not been completed. Dietary Safety is judged unlikely to be a critical issue – but requires specific work to confirm. Both fludioxonil and fenpiclonil have significant aquatic toxicity, but aquatic exposure is likely to be low, so aquatic risk is also unlikely to be critical. Again, specific data will be needed.

We do not know about the metabolites of pyrrolnitrin and their fate. Pyrrolnitrin itself autoxidises in light, which will go some way to reduce exposure to parent.

The registration of pyrrolnitrin as a biological will be attempted, although the team reported that project can support full chemical registration, if required. Each protein will also require biotech registration, but none are stable in simulated gastric fluid.

The potential value is significant based both on the value of fludioxonil in relevant crop targets and on the business estimates for relevant disease resistance effects.

The availability of sufficient biologically-produced pyrrolnitrin was noted as a concern.

The STC was comforted by the preliminary data and the thinking around toxicological, environmental and regulatory issues, and was fully supportive of the

project going ahead. DKL requested more data on target diseases and crops and expressed a concern that root diseases are difficult to test for in the field (although those that attach seedlings are easier). Tom Hohn was confirmed as Project Leader and will provide the project definition for the portfolio add-up process.

Action : Tom Hohn

Next Meeting is October 18th at Jealott's Hill. The meeting will be run by tele and/or video conference.

Distribution:

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