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The University of Manchester

Centre for Excellence in Enquiry-Based Learning

Project Case Study

3D: An Enquiry-Based Approach to Drug Discovery and Development

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Abstract

Drug discovery and development is an important topic for students of pharmacology, neuroscience and other allied biomedical subjects. It is, however, a challenging topic to teach because the range and scope of practicals that can be offered in university teaching laboratories are limited to relatively simple experimental and analytical methods. Thus students often find it hard to relate theoretical teaching about the complex techniques and decision making processes used in the pharmaceutical industry to their own experiences in the laboratory.

In an attempt to bridge the gap between our theory and practical teaching we have developed a group-based interactive Enquiry-Based Learning (EBL) exercise simulating the process of drug discovery and development (called 3D). In the 3D simulation students select a drug target and then pass through a series of eight data analysis, experimental design and decision making steps that allow them to refine an initial library of 65,000 compounds to a few candidate drugs. The exercise culminates in a reflective poster presentation in which the students are required to describe and justify the decisions they made at each step. Forty students, primarily from the honours schools of pharmacology and biomedical sciences, took part in the first trial of the 3D exercise. Apart from minor issues concerning group composition and intra-group communication, feedback solicited by post-exercise questionnaire was very positive with students citing improved knowledge of the drug discovery process and improved data handling skills as benefits.

Background

In its industrial setting, drug discovery and development is a multistage decision-making process driven by stringent financial, legal and experimental pressures. Beginning with a library of perhaps hundreds of thousands of compounds, drug development can be regarded essentially as an evolutionary process in which repeated rounds of testing eliminate unsuitable compounds until perhaps only one or two candidate drugs are left at the stage of clinical testing. At each stage of this process, pharmaceutical companies must analyse large and complex sets of experimental data in order to make decisions as to which candidate compounds have the characteristics required for further consideration. Drug discovery and development is a core topic for level two Pharmacology and joint honours Pharmacology/Physiology students and an important optional subsidiary topic for students in related disciplines. The subject is taught via a second semester 10-credit lecture unit (BL2792, Drug Discovery and Development) which had an enrolment of 75 students in the 2005-2006 session. Students on this unit came largely from the degree programmes of Pharmacology, Pharmacology/Physiology, Neuroscience, Biochemistry and Biomedical sciences. In addition, 34 of the students taking BL2792 (primarily in the degree programmes of Pharmacology, Pharmacology/Physiology and Biomedical Sciences) also took the second semester 10-credit Pharmacology Research Skills Module (RSM) practical unit (BL2932). Although independent from the BL2792 lecture unit, the Pharmacology RSM exposes the students to experimental techniques such as radioligand binding, organ bath studies and human volunteer experiments that are important in the screening and evaluation of new drugs.

Rationale

In the Life Sciences, teaching has traditionally followed a model of lecture-based teaching linked to laboratory practical classes. The rationale behind this model is that students learn best when theory is reinforced by practical experience (Katajavuori *et al.* 2006). For drug discovery and development, however, our opportunities to apply this model are limited. Many methods used routinely in the pharmaceutical industry, such as animal toxicology

studies, are clearly beyond the scope of university teaching. Further, the large and complex datasets that drive the drug discovery process, not to mention the stringent financial and regulatory pressures governing the pharmaceutical industry, are beyond anything students will experience in the teaching laboratory. Indeed, our practical teaching via the BL2932 Pharmacology RSM can only provide students with a small sample of the experimental and analytical techniques used in drug discovery. To bridge the gap between our theory teaching and the students' practical experience we therefore decided to develop an EBL activity based on drug discovery and development. Unlike previous EBL activities in this area that have focussed on the financial and market aspects of drug discovery (*Zeneca Teaching Day* 1997), our aims in designing this activity were to improve student understanding of the drug discovery process by:

- providing experience of handling large datasets;
- extended practice of data analysis techniques;
- stimulating research of techniques not encountered in the laboratory;
- providing experience of designing experiments that comply with regulatory requirements.

In addition, we aimed to incorporate features that would improve the students' transferable skills in:

- decision making;
- group working;
- presentation and communication.

Approach

The drug discovery and development (3D) exercise is an e-mail based interactive simulation in which students work in randomly assigned groups of 2-4 and play the part of project managers in a pharmaceutical company. Divided into nine stages, the exercise runs over a total of five weeks and culminates in a reflective poster presentation event.

The 3D simulation began with the premise that garden gnomes (*Homo smallus*) have received entitlement to National Health Service treatment and that this has sparked interest from pharmaceutical companies in

developing drugs for gnomes. Students were provided with descriptions of four gnome diseases and were told the current treatment for each disorder (Table 1). Students were also informed that gnomes have a broadly similar

Gnome Disease	Main Symptoms	Current Treatment	Human Parallel Disease
Barometric Paralysis	Panic attacks when atmospheric pressure falls	Flunitrazepam	Panic attacks/anxiety
Zwergmann's Syndrome	Hearing voices from garden statues	Haloperidol	Schizophrenia
Kleindicker's Mania	Excessive time spent counting toadstool spots	Paroxetine	Obsessive - compulsive disorder
Rod Wilt	Inability to keep an erect fishing rod	Sildenafil (Viagra)	Erectile dysfunction

Table 1 Diseases of the gnome. Students selected one of four clinical targets for drug development. Each gnome disease has a parallel disorder in humans that can be deduced from the clinical description provided to the students and from the drug currently used to treat the disease.

physiology to humans but can differ markedly from humans in terms of drug metabolism and side effects. We adopted the "gnome approach" because we have previously found that humour is an effective way of engaging students' interest in an EBL topic. Further, a fictional drug target allowed us a certain amount of licence when describing drugs' unwanted effects and prevented students from short circuiting the EBL process by making use of literature on human drug studies.

Data for the simulation were produced in Microsoft Excel using the Random Number Generation tool available via the Data Analysis Add In. The spreadsheet produced contained 65,000 rows, each corresponding to a hypothetical compound identified only by a serial number. Compounds were grouped into 6,500 series, each notionally containing a base compound and nine derivatives. In order to simplify the generation of data, chemical structures and names were not provided. Each of the 28 columns in the spreadsheet corresponded to a pharmacological or physico-chemical property of the compound. The parameters in each column were initially set to values that were undesirable for drug activity. Next, a subset of compounds was manually assigned values concordant with high potency and efficacy. The data were structured such that in subsequent stages of the simulation, fewer and fewer compounds exhibited the desired

properties: for each disease, the initial screening step yielded approximately 1,000 ‘good’ compounds (100 series) with choice narrowed to 2-3 compounds by the penultimate stage of the exercise.

In vitro pharmacological data were generally provided in the form of summary parameters e.g. pKi, pEC50, maximum effect. However, for some compounds students were provided with concentration-response data and were required to determine the summary parameters themselves. For toxicology studies the students were simply told whether or not the compounds exhibited toxicity, and for animal disease model studies, they were informed whether the effects of the drugs were significantly different from the placebo.

The data were revealed stepwise to the students over the nine stages of the exercise (summarised in Table 2). At each stage they were required to analyse the data presented to them and then select a subset of compounds they believed exhibited the correct properties to merit further investigation. They then requested data for the next stage of the exercise for their chosen compounds. Contact with the students was via e-mail with data sent as attached Excel spreadsheets.

Inevitably, some students found aspects of the exercise challenging and made errors in the decision making processes e.g. choosing the wrong assay, or in the analysis of data. Where decision-making errors occurred we adopted an approach of initially asking the students to justify their choice. In many cases this prompted a swift reappraisal of the data and a more judicious decision. Where students persisted with their error they were allowed to proceed unhindered and attempt the next stage of the exercise before further intervention. A different approach was adopted with numerical errors in data analysis. When this type of error occurred students were immediately told that they had made a mistake and were invited to re-examine the data. If they could not resolve the problem, help was offered in the form of worked examples or short face-to-face tutorial sessions.

Stage	Data provided	Task
1. Select assay	List of 15 drug screening assays	Identify correct assay for clinical target selected
2. Identify hit compounds	Screening assay results for 6,500 base compounds	Calculate pKi values and select 100 best compounds
3. Validate hit compounds	Second screening assay results for 100 chosen compounds	Select compounds showing activity in both assays
4. Hit to lead phase	Physico-chemical properties of validated hit compounds and their derivatives	Select compounds with good solubility and that obey Lipinski's Rule of Fives
5. Lead optimisation	Selectivity and in vitro drug metabolism and pharmaco-kinetic (DMPK) data	Identify compounds with good selectivity profile. Interpret DMPK data to identify compounds with good stability and bioavailability
6. Animal model testing	Results of animal model	Students required to identify a suitable animal model for the selected disease prior to data being released.
7. Toxicology testing	Results of toxicity screen.	Deselect toxic compounds. Describe the chronic toxicity tests that would be required for drug licensing
8. Phase I clinical trials	Adverse effect data from clinical trial	Students asked to identify 1 drug and 1 reserve compound to submit for phase I clinical trials. On the basis of adverse effect data, asked for decision on whether to proceed to phase II trials
9. Poster session		Poster presentation reflecting on the decision making processes during the exercise

Table 2 Stages of the 3D simulation.

Experience

Participation

Initially the 3D exercise was offered as a voluntary, non-assessed supplement to the BL2792 Drug Discovery and Development lecture unit. Students were sent information about the exercise by e-mail and were encouraged to volunteer during the first lecture of the unit. As an incentive to participate, we offered a £500 prize to the group producing the best poster. However, despite this generous bait, only six students volunteered to take part. To circumvent this apparent lack of enthusiasm on the part of the students we decided to make the exercise a compulsory component of the BL2932 Pharmacology RSM practical unit. In order to reflect the 'real-world' situation in industry we randomly assigned students to groups rather than allowing them to self-select membership.

Assessment and completion

A total of 40 students participated in the 3D exercise. Of these, 34 were press-ganged by virtue of being enrolled on the Pharmacology RSM (BL2932) and a further six took part voluntarily. Marks for the exercise (which accounted for 20% of the overall mark for BL2932) were awarded on the basis of the number of stages completed, with all groups being encouraged to produce a poster even if they did not complete the exercise. Of the twelve groups beginning the 3D simulation, seven completed all stages, one group eight stages and two groups six stages, yielding an average mark of 93%. Two groups dropped out of the exercise at an early stage and did not complete a poster. Interestingly, both consisted of volunteer students.

Evaluation

Methods

Student opinion on the value of the exercise was solicited via a questionnaire at the poster session. The questionnaire consisted of 18 closed format questions using a 5-point Likert scale and 12 open format questions in which the students were requested to complete

an introductory statement. Out of the 34 students who completed the poster stage, 24 returned a questionnaire. All of these contained answers to the Likert scale questions and 18 had at least partially completed open format questions. Scores of the Likert scale questions were compared to the expected score (3) using Wilcoxon's Signed Rank Test.

After the questionnaire results had been analysed, some of the more interesting issues that emerged were followed up during informal interviews with 12 students. Quantitative evaluation was also attempted by comparing the examination results for the BL2792 lecture unit of participants and non-participants in the 3D exercise (Student's unpaired t-test).

Results and Conclusions

Three main themes emerged from the questionnaires and follow-up interviews:

1. **Data-handling skills and knowledge base**
   Students agreed that the 3D exercise improved their data handling abilities, increased their confidence in dealing with large datasets and improved their knowledge of the drug-discovery process. They also found the level of support provided to be appropriate and that it encouraged them to research and evaluate information rather than simply follow instructions. Student feedback suggested that the extended data-handling practice provided by the 3D exercise was a particularly valuable aspect of the simulation. Our personal experience is that Life Sciences students often find numerical exercises difficult and regard them as tedious and pointless. We suggest that incorporating such exercises into EBL may act as a 'sugar-coating' for data handling and allow students to appreciate its context within the panoply of experimental methods. Disappointingly, comparison of the BL2792 exam

results of students participating in the project with non-participants did not reveal any significant difference. However, the BL2792 examination focuses heavily on factual recall rather than problem-solving and thus is probably an inappropriate means of assessing the effects of the 3D exercise upon student learning.

2. **Team working**

   Students were ambivalent about the value of the exercise in building team-work skills. They commented that it was difficult to work with people they did not know and that they would have preferred to self-select their team members. Further, it was apparent from the questionnaire responses and from analysis of e-mail contacts that in, some teams, most of the work was carried out by a single person owing to poor communication between team members. Follow-up interviews revealed that in many cases the preferred team compositions reflect groupings established during level one tutorials. These groups tend to be maintained by a Faculty policy of placing students into practical classes on the basis of their tutorial groups, in order to facilitate timetabling. A consequence of this policy is that, whilst our students work effectively in their long-established and close-knit teams during practical classes, they have little experience of the skills required to form an effective team. Further, friendship-based teams tend to be homogeneous, and previous work on group-based EBL has emphasised the value of heterogeneous group compositions in order to develop group-working skills (Johnson and Johnson 1975). Combined with our present findings, this research suggests that it may be worthwhile re-appraising current Faculty practice regarding practical group composition.

3. **Participation and workload**

   The poor initial uptake of the exercise prompted us to ask the students whether, after completing the exercise, they would have participated voluntarily. Bearing in mind that none of the students surveyed volunteered initially, the 30% of students who indicated a retrospective willingness to volunteer represents a heartening figure. However, overall the students responded ambivalently to this question, indicating that some still retained a reluctance to participate voluntarily. We probed more deeply for the reasons underlying this attitude during informal interviews with students at the end of the 3D exercise. Their responses revealed that most feel pressured by high workloads during the second semester because this time is also when they are required to complete their dissertations. They are therefore unwilling to take on extra work that 'does not count for anything'.

Further Development

For the 2006-2007 academic year we will incorporate the 3D exercise in the BL2792 lecture unit as compulsory coursework contributing 5% to the unit mark. However, based on our experiences running the simulation this year we will make several changes to its assessment:

a. 50% of the marks will be allocated for completion of stages 1-8;
b. 50% will be awarded for the quality of the final poster presentation with a component of intra-group peer assessment based on level of individual contribution.

In the future we intend to retain the random assignment of students to groups as we believe that this method is an opportunity to develop team-building skills. To facilitate this process we will provide a set of guidelines regarding intra-group communication and will run a 'meet the team' icebreaker session.

References

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