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# Meeting Report: Teaching Signal Transduction

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In July, 2005, the European Institute of Chemistry and Biology at the campus of the University of Bordeaux, France, hosted a focused week of seminars, workshops, and discussions around the theme of "teaching signal transduction." The purpose of the summer school was to offer both junior and senior university instructors a chance to reflect on the development and delivery of their teaching activities in this area. This was achieved by combining open seminars with restricted access workshops and discussion events. The results suggest ways in which systems biology, information and communication technology, Web-based investigations, and high standard illustrations might be more effectively and efficiently incorporated into modern cell biology courses.

## INTRODUCTION

The European Institute of Chemistry and Biology (IECB; http://www.iecb.u-bordeaux.fr) at the campus of the University of Bordeaux hosted a very intense week (July 04–09, 2005) of seminars, workshops, and discussions around the theme of "teaching signal transduction." This text is a report of that week. The purpose of the summer school was to offer junior lecturers a good basis for reflection on the development of their teaching program and to offer experienced, established lecturers/professors an opportunity to rethink their teaching subjects and methods. Such events are common in the world of research but rare in the realm of university teaching. The week had a double character: three days of limited access workshops, providing hands-on experience with bioinformatics, systems simulation, and cellular and molecular illustrations, and two days of open access seminars around the themes of "systems biology" and "information and communication technology (ICT) for blended learning in university courses." The workshops were attended by 12 participants from various European countries and the open access seminars attracted 25 teacher-scientists (see Figure 1). For more information please consult: http://www.cellbiol.net (section "summer schools"). Not all participants currently run their own signal transduction course; many taught or were going to teach signal transduction as part of courses in cell biology, biochemistry, or pharmacology.

## CONSTRUCTIVE THEORY AS A GUIDELINE FOR THE WEEK

The general paradigm, acting as a reference for discussions during the week, was provided by the launch presentation (IJ.K.), about "constructive theory" (http://www.cellbiol.net/docs/Constructive_teachingKramer.pdf). The presentation elaborated four main principles of constructive teaching: 1) learning involves the active construction of a conceptual knowledge base; 2) learning is reflective and builds on, and consolidates, existing knowledge; 3) learning benefits from multiple views of a subject area; and 4) learning is facilitated by authentic activity, authentic resources, experiences, and sharing.

The general observation was made that universities apply constructive teaching to only a limited extent. Curricula often have a progressive approach, starting with the basics and building from existing knowledge toward more complex understanding, but there is no built-in mechanism to consolidate the acquired knowledge. Many basic subjects (basic theories, key ideas, and even important molecules) do not get a second mention in the curriculum; teachers do not return to these subjects in any explicit way. For example, it is a revealing exercise to underline or highlight keywords in textbooks or lecture handouts on basic subjects ((bio)chemistry, mathematics and physics) and then screen for second mentions in more advanced modules in the biology or medicine curriculum (i.e., cross-referencing). Ideally, these keywords should return every year because recall is a fundamental step in the consolidation of any knowledge. In practice, a lack of repetition means that much of the knowledge acquired in the basic courses is no longer operational in later stages of the curriculum. All too frequently teaching staff blames such lack of retention on a lack of interest or intelligence among students, or some blame it on their colleagues. The following point was raised: "How would teaching or research staff score if they sat for first-year exams in chemistry, physics, and mathematics?" It was anticipated that such an experiment would not provide evidence for the common belief that "you first need the bricks in order to build the house." In other words, little of the so-called "basic

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**Figure 1.** Participants in the workshops and the speakers at open access seminars.

knowledge" routinely forced into undergraduates across Europe is actually used day-to-day by scientific professionals.

At a much more subtle level, evidence was provided that even classic cell biology textbooks fail in some ways to apply the principle of consolidation of knowledge or the inclusion of multiple views. Many subjects are treated in an almost anecdotal way, reflecting the way cutting-edge research advances. For example, ribosomes are shown synthesizing nonexistent proteins; the signal or destination peptides of specific proteins are shown, yet these proteins are never revisited in a meaningful context; transport through the ER and Golgi is described using irrelevant viral proteins; glycosylation is explained as the decoration of an object (a nondescript particle) rather than a specific, biologically relevant (glyco)protein. These weaknesses are then propagated unquestioningly in the classroom. With respect to gene expression, we work on general principles but without mentioning genes coding for proteins visited earlier or yet to be seen. Trying to "work through" the different aspects of cell biology using a smaller number of functionally important proteins would help students to create an integrated view of increasingly complex cellular events.

With respect to the teaching of signal transduction, the same principles apply; whenever possible one should make reference to past and to parallel modules. For example, when teachers explore the binding of ligands to receptors, they should make reference to the lectures that treated molecular bonds (electrostatic, hydrogen, or van der Waals). Ideally speaking, those chemists who teach bonding theories should work around real examples, e.g., adrenaline binding to its receptor. As another example, one may refer to pharmacology lectures and repeat terms like agonists, antagonists, or $K_d$. This way one subject reinforces the other and a more integrated view is obtained. A further example is the Wnt pathway: when the Wnt pathway is treated, one could take the opportunity to come back to the cytoskeleton and show that $\beta$-catenin has both a structural role, holding cadherins and the actin cytoskeleton together, and a signaling role. From a constructive theory point of view, teachers should, if the subject has been treated in earlier modules, return to the cell cycle and refer to cyclin D, cell cycle phases, and replication in order to convincingly explain to students why the arrival of $\beta$-catenin in the nucleus can drive the cell cycle. When the Wnt pathway is taught in the context of colon cancer, a review of the characteristics of intestinal epithelia (first-year histology lectures?) and of stem cells and cell differentiation would be appropriate. With respect to insulin signaling, one has a good opportunity to return to biochemistry and repeat glucose metabolism and glycogen synthesis; one should also mention the opposite actions of adrenalin and glucagon. A revision of protein synthesis would not be out of place in order to explain the anabolic effect of insulin. One can also return to physiology and review the endocrine function of the pancreas. Finally, it is a good idea to make reference to any lectures about membrane transporters and revise how glucose traverses the plasma membrane.

The use of constructive theory in practice means that teachers either come back to these subjects in the lecture (teaching intracellular junctions, glucose transporters, etc.) or give reading assignments with precise indications of which book and which pages to read. In a more active approach, students can be asked to write a 300-word abstract on, or make a detailed drawing of, the role of $\beta$-catenin in the assembly of cellular junctions. Coupling such assignments to integration of knowledge across the curriculum strengthens students' grasp of key concepts in signal transduction.

## HOW TO TEACH SIGNAL TRANSDUCTION: PROVIDING A CONTEXT WITH MULTIPLE VIEWS AND AVOIDING COMPREHENSIVENESS

Because of the complexity of signal transduction pathways, putting various signal transduction pathways in a clear physiological or pathological context is almost a necessity. Teaching signal transduction in a "catalogue-of-pathways" manner does not do justice to this complex and beautiful subject or to biology as a whole. Neither does the "catalogue" help that fraction (at least 50%) of the students who

need to see the "larger picture" before they can commit signaling cascades to memory. Many curricula still take the view that the subject should be covered, almost exhaustively, to ensure that at least it has been "said once and for all." Such an approach may serve as a means to discriminate between excellent and poor first-year students but it will not favor comprehension or an appreciation of how cells deal with extracellular cues. It will not contribute to a conceptual knowledge base.

There are numerous contexts that could serve as "coat hangers" from which to hang facts and perspectives while treating various signal transduction pathways. If the choice is with the teacher, it is recommended to choose a context that is closely related to his or her research area, because students like to discover that their teachers are not merely translating textbooks into lectures and that teachers can be scientific role models. Examples that easily come to mind are "fear, flight, or fight", insulin and diabetes, cell transformation, cell differentiation (e.g., hematopoiesis), muscle contraction (smooth and striated), vision, olfaction, apoptosis, inflammation and immunity, or mechanisms of development. These different physiological or pathological contexts should also include practical aspects. Examples include the treatment of diabetes or its detection, why some people are color blind, how we treat cancer, how signal transduction knowledge is applied to the development of new drugs, how we block the clonal expansion of T-cells in order to prevent rejection of transplanted organs, etc. The general message that the organizers wished to convey is that teachers should try to be restrictive, not exhaustive: restrictive in the sense that teachers should search for a comfortable context that allows the exploration of two or three signal transduction pathways.

## TEACHING SIGNAL TRANSDUCTION IN "FIXED" CURRICULA

Many teachers felt, however, that the content of their lectures was determined by the faculty and that there was no alternative to "cataloguing," principally because of time constraints. This is particularly true for those teaching in medical courses, where curricula have very clear benchmarks (things physicians should know and those skills that should be mastered). Not every teacher or student is unhappy with this state of affairs. Others feel that the constructive approach is perhaps too cumbersome; they would have to work day and night in order to manage hundreds of students and fulfill all of the criteria of constructive teaching (with no time left for research). Recognizing these constraints, the organizers and participants nevertheless felt that changes have to occur when lecturers and/or students show signs of "wear and tear," even when this would cause a gap in the curriculum content. However, it was felt that the constructive learning approach might reduce the "learning fatigue" often experienced by (medical) students that results from studying several broad disciplines either in rapid succession, or simultaneously, but in very little depth. Making time for more focused, highly integrated, cross-referenced exercises in a comfortable teaching context would reduce the burden on students and, equally important, provide a much more rewarding teaching experience for teachers. The message to faculty deans or course tutors is that there is room for such changes. To give an example, we conducted the following experiment: All students at the European Molecular Biology Organization (EMBO) Receptor Mechanisms and Signal Transduction course of 2004, held in Bordeaux, had attended signal transduction lectures during their education in a variety of disciplines (biochemistry, pharmacology, cell biology, or in specialized signaling courses). The majority felt that their university had done a satisfying job, all of them were actively involved in signal transduction research, and yet only 13% passed a spot test (with a 5/10 pass grade) at the start of the course (details of this test are found in the Appendix). We feel that this experiment makes the point that the knowledge teachers have transmitted (and assessed) does not necessarily remain operational.

## DOES SYSTEMS BIOLOGY PROVIDE A NEW DIMENSION TO UNDERSTANDING AND TEACHING SIGNAL TRANSDUCTION?

The day of seminars on systems biology illustrated that the progress in molecular biology, particularly in genome sequencing and high-throughput measurements, might enable the collection of comprehensive data sets on the components of cellular systems. However, this "molecular botanizing" provides little information on system performance. Although an understanding of genes and proteins continues to be important, systems biologists focus on understanding a system's structure and dynamics. Hans Westerhoff gave a very good introduction to the subject of systems biology and focused on the power of the insights obtained during the development of metabolic control analysis. He clearly illustrated that there are no "key" enzymes in pathways; pathway control is distributed among all of its components. This, he suggested, means that targeting oncogenes in signal transduction cascades does not necessarily mean that the pathway is going to be effectively inhibited. One should also consider targeting an upstream or downstream component (which feeds forward or backward on the oncogenes). With these insights he set the scene for Reinhart Heinrich, who demonstrated that kinases play an important role in the amplitudes of signals, whereas phosphatases control their duration. He demonstrated that kinases act in a logarithmic mode, whereas phosphatases act in a linear mode. As to the question "why are signal transduction pathways often composed of three to four kinases?", Heinrich showed that multikinase pathways conduct the signal much faster than two-component cascades, with the optimum at four kinases in a row (on average cells employ three kinases in a cascade). Ursula Klingmüller showed that the STAT pathway, resulting in the expression of Sis, could be best described as a circular pathway of phosphorylated STATs entering and unphosphorylated STAT leaving the nucleus. The IL-6R acts as a remote sensor that influences the entry/exit rate of STATs and thus Sis expression. She also showed that there is considerable variation within and between experiments due to simple technical difficulties that must be understood and then adjusted for before reliable signaling system modeling can even start. Denis Noble took what Sidney Brenner had dubbed a "middle out" approach to understanding the functioning of the heart. The model is based on experimental data on the behavior of most of the major ionic currents: the

fast sodium, L-type calcium, transient outward, rapid and slow delayed rectifier, and inward rectifier current. The model also includes basic calcium dynamics. Using this model he studied the cause of re-entrant arrhythmias by changing the characteristics of ion channels that conduct the above-mentioned major ionic currents.

A clear message of all speakers was that systems biology often provides "counterintuitive" insights and therefore acts as an excellent supplementary source of inspiration for the design of molecular biology experiments. New data sets on system performance and on the molecules involved would, in turn, provide new parameters for improved modeling of signal transduction systems.

The participants in the summer school considered how this information could be introduced into signal transduction teaching. The introduction of a simple model would help students to see the relationships and patterns between the components of signaling systems, how they feed forward or backward and influence each other. Some students might find it challenging to try to understand the systems of differential equations often required to construct systems biological models. However, new interfaces that hide the intimidating formal rate laws behind friendly interfaces or mathematical approaches that do not routinely use difficult rational functions, e.g., the power functions seen in biochemical systems theory, are becoming more widely available and popular (see below). The advantage of the inclusion of a model in the teaching is the same as the inclusion of a physiological context. Models help students to see the "relatedness" of molecular events. The model could also serve as a starting point to let students design a wet-lab experiment that might provide them with data to verify the model. However, there are limits to what is currently achievable. Virtually all established researchers and teachers of signal transduction have been raised and have prospered in the "reductionist school" and so have little appreciation for the complex behavior that can emerge from even the simplest of biological systems subject to feedback control.

## ILLUSTRATING A SIGNAL TRANSDUCTION LECTURE COURSE

We all know that a good illustration is worth a thousand words, but why should teachers need to know how to make these illustrations? Why should they not leave it to professional illustrators? The very first reason is because teachers are keen students of their own subject discipline and they need to make the illustrations to clarify matters in their own mind. Second, teachers often have their own points of view and these are not always shared by existing illustrations. Third, some teachers fear to breach copyright rules if they use pictures from books or Web sites. Lastly, and importantly, personal illustrations may serve to illustrate the teaching (and research) skills of the teacher (teachers as role models).

As one example of the illustration process, Oliver Hantschel, from the Centre of Molecular Medicine in Vienna, Austria, gave a superb overview, with excellent molecular animations, of what protein tyrosine kinases look like. In particular he focused on c-Abl (and its oncogenic variant Bcr-Abl) and its inhibition by the novel anticancer drug Gleevec (Glivec or Imatinib). His seminar was a very good example of how molecular structure helps us to understand and communicate the mechanisms of regulation of protein kinases. His seminar also illustrated the descriptive power of molecular illustrations and animations. The summer school participants then spent the rest of the day creating diverse representations of both c-Abl and any protein of their choice, using the coordinates obtained from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/) and the program PyMOL (http://pymol.sourceforge.net/).

Graham Johnson, a professional biomedical illustrator (http://www.fivth.com/) and now a Ph.D. student at the Scripps Research Institute, La Jolla, CA, gave a wonderful description of how an artist has turned into a leading biomedical illustrator who has revolutionized the molecular illustration in cell biology. He gave brief instructions on the composition of lecture slides, of how to give direction to the flow of events that one wishes to illustrate, and how to focus attention on visual aspects of the presented material. The participants then moved to their laptops and worked hard with Adobe Illustrator and Photoshop, under Graham's tutelage, to draw their own lipid membranes and proteins, and, in line with constructive theory, c-Abl.

## ORGANIZING AUTHENTIC ACTIVITIES IN SIGNAL TRANSDUCTION COURSES

"Authentic activities" are an essential aspect of learning and teachers should include these in their signal transduction courses (for our definition of authentic activities, see Table 2 on p. 565 of an article by Reeves *et al.*, 2002; see Higher Education Research & Development Society of Australasia, http://elrond.scam.ecu.edu.au/oliver/2002/Reeves.pdf). Below, we will highlight three aspects of how authentic activities could function within signal transduction courses.

### *Coordinating Activities with a Web-based Learning Support System*

Betty Collis, Shell professor at the Faculty of Behavioral Sciences, University of Twente, The Netherlands, gave an impressive presentation on the use of ICT in support of blended learning courses (http://www.cellbiol.net/docs/ICT_for_blended_learning_Collis.pdf). The term "blended learning" refers to different types of resources, different types of learning activities, different places and times where activities take place, and different ways that people interact with each other. The process is coordinated in an efficient way via a Web-based learning support system that she, and her team at Twente, has developed (TeleTOP, http://www.teletop.nl). The trainees can choose between a predominant Web environment (working at home) and a predominant classroom environment. Instructive teaching elements occur in both settings. We highlight two aspects of her presentation here.

She and her colleague Jef Moonen (who contributed to the workshop session in the afternoon) have published extensively on active learning. The success of Betty and Jef's courses relied on a meticulous design of complex activities. Apart from assessment and feedback, the main contribution of the organizer/instructor to courses consists of discover-

ing where instructions are ambiguous, where course material is incomplete or insufficient, where objectives are not clearly defined, or where deadlines are unrealistic. With respect to course design, Betty suggests the following preparation cycle: first, design the learning activities and their supports; second, design the assessment procedure; third, choose the Web environment to support the approach; and finally prepare your lectures and all the rest.

### *Using Bioinformatics to Bring a Sense of Insight and Discovery*

Geraint Thomas, of the Physiology Department, University College London, United Kingdom, gave a demonstration of the use of bioinformatics in signal transduction teaching courses. Over the last six years he has developed a second-year course in which students explore proteins, at the level of sequence, structure, and domain composition, in the context of signal transduction. The students learn to build signaling cascades based on the interactive properties of proteins. The increasing number of databases, many now containing extensive annotation and numerous hyperlinks, has provided staff and students with an overwhelming repository of information. In the past, a student or teacher had to work extremely hard to track down articles for sequences, structures, or annotations. The Internet now offers all of this in a splendid and efficient way; nevertheless, there is far too much information for a student to explore blindly. Luckily, cell signaling can provide an excellent starting point and rationale for approaching this vast resource, because much is known about signaling elements, their structure, and how it relates to their function, and their roles in health and disease. By using signal transduction as a gateway subject, students with only modest molecular and structural biological backgrounds can undertake detailed molecular explorations in silico.

Geraint made the point that many protein analysis programs do not necessarily provide a user with accurate biological prediction, e.g., the number or orientation of transmembrane spans, and that verification at different levels is necessary to reach increasingly sound conclusions. To make students explore these databases, teachers have to provide a framework comprising a set of relevant "entry level" questions and a "toolbox" portal of URLs to different useful databases and processing servers. These are easily constructed in a modular form that allows additions and deletions to be used to tailor teaching materials to any class. An example is available through http://www.cellbiol.net/MRindex.htm (section "active learning projects"). Using this approach, the participants spent the afternoon collecting and analyzing sequences, extracting and rendering molecular models, searching for phosphorylation sites, and predicting potential protein kinases and other protein–protein interactions. Ideally, as a part of signal transduction course, students would follow up this introductory material by applying the same tools and resources to their own individual (or group) studies of key signaling proteins or cascades.

Geraint reported that this process works particularly well if students are asked to submit small project reports (individual or group efforts) or make public presentations. Here the students are only allowed to describe the results of their de novo investigations into their target molecules. All of the data should be obtained from the analysis of primary bioinformatics sources. A class can rapidly build for itself a good annotated database on the structure-function properties of many components of signaling systems. Database searches and analysis are authentic activities: they have a high level of relevance to the professional situation, they are open-ended because one can always find more, and they provide many opportunities for fruitful interaction between students. Searches could be complemented by visualization of proteins and domains using PDB coordinates and appropriate rendering software. Many curricula still reserve these activities for postgraduate courses, but experience has shown Geraint that second- or third-year undergraduates are perfectly able to assimilate this kind of information and enjoy the challenge. Indeed, student efforts often supersede recently published authoritative reviews in front-rank journals (shortest time to "obsolescence" is currently three weeks), uncover putative new members of signaling protein families, or even find powerful counterexamples to well-publicized hypotheses or relationships.

### *Modeling Signal Transduction Pathways*

When signal transduction pathways are taught, students will inevitably ask whether they have to learn it all and why cascades are so long and so complicated. Standard answers include hand waving and mention of "amplification" or "signal integration." The answer is certainly not based on experimental proof. For example, astute students may ask, "Why do cells respond to minute concentrations of TGF$\beta$1 without an apparent production of second messengers or the inclusion of long amplification cascades?" In contrast, "Why does EGF, acting at similar concentrations, need so many intermediates before its signal reaches the nucleus?" "Why is all the attention focused on protein kinases and not on protein phosphatases, because they too must play an important role if signaling cascades are regulated by phosphorylation?"

Certain students would like to find answers to these questions by modeling the pathway they are studying. To do so, they must insert the different components, second messengers, kinetic equations, and dissociation constants into a model. Such an activity would give an idea of the scale and amplitude of a process (e.g., Does the ligand act in the fM or $\mu$M range? How many receptors do cells actually have?) and what the effects are if parameters are changed (e.g., inclusion of a protein kinase inhibitor or modifying the activity of a protein phosphatase). This activity also has relevance for professional settings. For example, pharmaceutical researchers have turned to modeling in order to better select the targets for therapeutic intervention, biochemists now require systems insights, and cell biologists need to tackle the complexity of responses observed in single cells as opposed to populations.

Two software programs were presented and explored by the summer school participants during the meeting and these might be suitable for teaching activities.

1) PLAS (Power Law Analysis and Simulation, http://www.dqb.fc.ul.pt/docentes/aferreira/plas.html), a program created and demonstrated during the week by Antonio Ferreira of the Department of Chemistry and Biochemistry at the University of Lisbon, Portugal. It was

designed specifically to aid in the modeling of biological systems and handles either power law formulations or the more familiar rate differential equations of undergraduate biochemistry. It is freely available for download and is particularly attractive for use in an educational environment because all of the equations can be seen and manipulated.

2) PathwayLab, created by InNetics (http://innetics.com/), a commercial product not freely available. The program was demonstrated by one of the participants, Elie Järnmark from the University of Skövde, Sweden. A useful feature of this program is the side-by-side presentation of the pathway diagram (e.g., a typical signal transduction cascade scheme) and the pathway analysis (production of intermediate products of the pathway). The program has a useful palette of common reaction mechanisms to "drag and drop" that masks the complexities of their corresponding algebraic formulations.

## A REMARK ON COURSE ASSESSMENT

What students learn is greatly determined by what teachers assess and how they assess it. Assessment, other than multiple-choice questions (MCQ), is time consuming and fatiguing (in particular when student numbers become large). European universities have a tendency to assess at the very end of semesters (two sessions a year), leaving it entirely to students to organize their study time. Strong students have no problem with this approach but average students may lose out because they cannot manage their time or prioritize their activities properly.

In the workshop that followed Betty Collis' seminar, the participants came back to the subject of assessment because statistical analysis revealed that certain subjects always scored badly in their respective end-of-term exams, regardless of the teaching effort that had been put in. Although not all examples could be drawn from signal transduction courses or materials, what emerged is that students may avoid certain subjects entirely, because they are difficult or uninteresting. This practice allows them to focus on subjects they can master more easily and increases their chance of a good mark. Two examples: Jamie Weiss reported that the subject of the bacteriophage Lambda's lytic versus lysogenic pathways, as part of her first-year course on the Principles of Molecular Biology, always scored badly in the MCQ exam, despite her efforts to link the molecular subject to important issues such as the latency phase in HIV infection. Another example was provided by Ediz Demirpence, who reported that medical students repeatedly failed to memorize the enzymes involved in the synthesis pathway of steroids. They were unable to integrate this material to create useful hypotheses describing the likely physiological outcomes of medically relevant enzyme deficiencies. The use of "in course" or "just-in-time" assessments was felt to be one way to stimulate students to tackle the difficult subjects that teachers find important. It might prove extremely useful to target the main assessment of the student's ability to handle complicated materials in this way, rather than wait for final assessments where students are under pressure to be selective about their coverage.

## SOME REMARKS ON THE EVENT

The event brought together outstanding speakers, workshop facilitators, and a small group of teachers eager to work hard, discuss, and discover more about teaching. The format, a mixed program of seminars, workshops, and presentations by participants, worked extremely well. A computer cluster room with good ambience and a multimedia projector with full access to the Internet was found to be vital. The improvement in working conditions and the flexibility achieved by having a competent and interested informatics engineer at hand should also be noted. Lastly, many teachers found it difficult to raise funds for attending this type of event. Forward-looking universities should perhaps earmark some resources for this purpose.

## ACKNOWLEDGMENTS

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# Appendix

The following spot test has been employed at the start and the end of an EMBO lecture course on "Receptor Mechanisms and Signal Transduction" organized by Alasdair Gibb, IJsbrand Kramer, and Geraint Thomas, held at the University of Bordeaux in 2004 (for more information about the event, consult http://www.cellbiol.net, section "Summer Schools").

We developed this test for two reasons:

1) We wanted to immediately assess the heterogeneity of knowledge among the course participants at the onset of the week. This information was used to tailor both the design and execution of the immediate course and also to more accurately plan future events. 2) We wanted to assess whether or not the lecture course actually delivered a measurable increment in student knowledge.

Notably, the students were not warned that there would be a spot test at the start of the week and they were also not told that the test would be repeated at the end of the course. We believe that this element of surprise helped us to make a more accurate assessment of the class.

## *Spot test EMBO 2004*

Correct answers in bold.

Receptor Mechanisms

1. The simplest possible model for the interaction between a ligand, A, and its binding site on a receptor, R, is:

$$A + R \underset{k-1}{\overset{k+1}{\leftrightarrows}} AR$$

$k_{+1}$ is the
- (a) association equilibrium constant
- (b) affinity constant
- **(c) association rate constant**
- (d) activation constant

2. Is $K_A = k_{-1}/k_{+1}$ the:
- (a) association equilibrium constant
- (b) affinity constant
- (c) association constant
- **(d) dissociation equilibrium constant**

3. The dissociation equilibrium constant for the interaction between a ligand, A, and its binding site on a receptor, R,

$$K_A = \frac{[A][R]}{[AR]}$$

has dimensions:
- (a) $M^{-1}$
- **(b) M**
- (c) $s^{-1}$
- (d) $Ms^{-1}$

4. The del Castillo-Katz model of receptor activation:

$$A + R \leftrightarrow AR \leftrightarrow AR^*$$

supposes that when an agonist combines with its receptor, an inactive complex, AR, is formed. The receptor then undergoes a conformational change that results in an active form of the receptor, AR*. For an agonist with relatively poor ability to activate the receptor, a very high agonist concentration would cause the proportion of receptors in the active state to be:
- (a) 1.0
- (b) close to 1.0
- (c) exactly 0.5
- **(d) much less than 1.0**

5. If a receptor has constitutive activity (so the receptor can sometime isomerise to the active state in the absence of agonist) an *inverse* agonist would:
- (a) inhibit the receptor activity
- (b) increase the proportion of receptors in the AR (inactive) state
- **(c) decrease the proportion of receptors in the AR* state**
- (d) not affect the proportion of receptors in the unliganded (R) state

6. An antibody has an equilibrium constant of 1.0 nM. In order to occupy more than 90% of antibody binding sites, the antibody concentration should be at least:
- (a) 1.0 nM
- (b) 5.0 nM
- **(c) 10.0 nM**
- (d) 90.0 nM

Signal Transduction

7. GTP binding proteins
- are activated through phosphorylation on serine residues
- **are characterized by 5 highly conserved GTP binding regions**
- **are usually active in a GTP-bound state and inactive in a GDP-bound state**
- have the capacity to hydrolyze ATP

8. Cadherin
- is involved in tight junctions
- **is involved in desmosomes and adherens junctions**
- is linked to actin via desmoplakine
- **is linked to actin via β-catenin**

9. TGFβ
- **binds two different receptor proteins with one molecule**
- binds two different receptors with two molecules (dimer)
- **binds, in most cases, first with a type II receptor and then with a type I receptor**
- activates a tyrosine protein kinase

10. PKB has anabolic effects
- by directly stimulating PKA
- **by facilitating ribosomal initiation and translocation**
- **by facilitating phosphorylating of 4E-BP**
- by stimulating phosphorylase *a*

11. PI 3-kinase is
**- both a protein kinase and an inositol lipid kinase**
- a lipid kinase that phosphorylates diacyglycerol into phosphatidic acid
**- an essential component of the PKB signal transduction pathway**
- the immediate intracellular kinase associated with the insulin receptor

12. Members of the Rho family of GTPases are involved in
- vesicle transport
**- cell cycle regulation**
- nuclear import and export
**- cytoskeletal organization**

13. Ras activators are
**- hSos**
**- ras-GRF2**
- neurofibromin
- PI 3-kinase

14. A GTPase effector loop
- has to be phosphorylated in order to allow access of substrate
**- is a short stretch of amino acids that interacts with downstream effectors**
**- changes conformation when GDP is replaced by GTP**
- interacts with the GTPase activating protein (GAP)

15. GSK3$\beta$
- dephosphorylates and inactivates glycogen synthase
- protects $\beta$-catenin against its destruction by the S26 proteasome
**- is "inhibited" by the Wnt/Dsh signaling pathway**
**- interacts with axin/APC**

16. Gleevec™
- binds the EGF receptor and prevents ligand binding
**- competes with ATP to bind the Abl protein kinase**
**- holds Abl in an inactive conformation**
- is used for lung cancer treatment

17. Chromosome translocation can contribute to cancer because of
- an increased number of copies of genes
**- a loss of regulation of activity of novel fusion proteins.**
**- an elevated expression of certain genes (change of locus)**
- an unbalance in chromosomal length

18. The SH2 domain
- mediates SMAD oligomerization (SMAD2/4 complexes)
**- is a conserved domain first identified in Src**
**- contains two pockets, one that binds phosphotyrosine and one that binds a "specificity" amino acid(s)**
**- plays an essential role in some receptor signaling complex formations**

More than one completion (answer) may be correct
Zero mistake 4 points, 1 mistake 2 points, 2 mistakes 1 point, more than 2 no points