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Tierversuche, Versuche mit und am Menschen: Grenzen und Möglichkeiten

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Do We Need a "Chair of Alternative Methods", and Where?*

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Summary

During the last two decades, the field of in vitro technology has been successfully developed and its use is continuously growing. Advanced tests avoiding animal experiments will be increasingly required for routine industrial applications e.g. for pharmacological high-throughput screening. Moreover and even more importantly, the availability of human cell based methods is essential for future quality assurance and risk assessment in the fields of health and consumer protection as well as environmental protection. Thereby, the potential of such advanced in vitro methods extends far beyond the mere replacement of regulated tests.

In practice, the introduction and expansion of this technology has been achieved predominantly by offering funding and awards to the scientific community. After this initiation phase, the next consequent step to exploit this knowledge clearly consists in academic promotion of this new scientific culture in an institutionalised form. The tasks of such a chair focussed on advanced in vitro tests – most probably the first of its kind world-wide - would cover in addition to (a) research and (b) teaching, (c) the sharpening of social conscience for the topic.

(a) While the validation of alternative methods was formally established by founding institutions like ZEBET in Berlin on the national and ECVAM in Ispra on the European level, the development of further new and more sophisticated in vitro methods to date emerge predominantly as a by-product of basic research. A considerable push might now be given by the structured search for new methods with a spill-over for research-based up-to-date teaching.

(b) The field of alternative methods is more than a panel of advanced in vitro techniques: A culture of systematic evaluation and validation of in vitro tests has been developed, which has bearing far beyond the replacement of animal experiments. In vitro systems inherently prone to artefacts require the

Zusammenfassung: Brauchen wir einen Lehrstuhl für Alternativmethoden? Und wenn ja: wo?

In den letzten zwei Jahrzehnten hat sich die in vitro Technologie sehr erfolgreich entwickelt und die Anwendungsmöglichkeiten nehmen kontinuierlich zu. Moderne Testmethoden, welche Tierexperimente ersetzen, werden zunehmend für Routineanwendungen in der Industrie gebraucht, z.B. für pharmakologisches High-Throughput Screening. Außerdem, und noch bedeutender, ist die Entwicklung von Methoden, die auf menschlichen Zellen beruhen, notwendig für zukünftige Qualitätsprüfungen und Risikoabschätzungen im Gesundheits- und Verbraucherschutz sowie im Umweltschutz. So geht das Potential solcher fortschrittlicher Methoden weit über den Ersatz von vorgeschriebenen Tierversuchen hinaus.

Praktisch wurde die Einführung und Verbreitung dieser Technologien vorrangig durch die Ausschreibung von Forschungsgeldern und Preisen für die Forschung erreicht. Nach dieser Einführungsphase ist der nächste Schritt konsequenterweise der Einsatz dieses Wissens in der akademischen Förderung dieser neuen wissenschaftlichen Kultur in einer institutionalisierten Form. Die Aufgabe eines solchen Lehrstuhls, der sich auf fortschrittliche in vitro Tests fokussiert – wahrscheinlich weltweit der Erste seiner Art – würde sich erstrecken auf (a) Forschung, (b) Lehre und (c) die Schärfung des sozialen Gewissens für dieses Thema.

(a) Während die Validierung von alternativen Methoden durch die Gründung von Institutionen wie ZEBET in Berlin auf der nationalen und ECVAM in Ispra auf der europäischen Ebene formell etabliert wurde, erfolgt die Entwicklung von neuen und ausgefeilten in vitro Methoden bislang vorrangig als Nebenprodukt der Grundlagenforschung. Ein beträchtlicher Anstoß könnte jetzt durch die strukturierte Suche nach neuen Methoden mit einem zusätzlichen Gewinn für forschungsbasierte topaktuelle Lehre entstehen.

highest level of quality control and assurance. A successful initiative to establish a Good Cell Culture Practice (GCCP) in analogy to Good Laboratory Practice (GLP) has evolved out of the field of in vitro alternatives. The concept of validating the relevance of an in vitro test in comparison to the respective in vivo situation represents a consequent translation of evidence-based medicine into in vitro biomedicine. In other words: It does no longer suffice that an in vitro model is plausible – it has to prove its suitability and quality.

(c) The broad implementation of advanced in vitro technology into curricula implies development of lectures, courses and other teaching materials including virtual education offers. Such a basis will allow efficient spreading of knowledge and ease transnational acceptance. Last but not least, taking over the leadership for erecting a chair for alternative methods represents a major political signal that demonstrates to the public the willingness to adapt academic education to modern social awareness. A location for such an initiative needs to be found that is in the centre of Europe, has the necessary infrastructure of surrounding biomedical research, international networks for the evaluation and validation of tests, technology transfer to industrial use and access to relevant publication organs.

The unequivocal answer to the question in the heading is therefore: we need a chair for in vitro alternatives because (i) the patient is our primary concern but the animal is not just secondary (ii) man's responsibility for the integrity of all creatures including the own species makes it mandatory.

(b) Das Feld von Alternativmethoden ist mehr als eine Ansammlung von fortschrittlichen in vitro Techniken: Eine Kultur der systematischen Evaluierung und Validierung von in vitro Tests ist entstanden, die viel weiter reicht, als nur zum Ersatz von Tierexperimenten. In vitro Systeme, welche inhärent zu Artefakten neigen, erfordern das höchste Maß an Qualitätskontrolle und –sicherung. Eine erfolgreiche Initiative zur Etablierung einer Good Cell Culture Practice (GCCP) analog zur Good Laboratory Practice (GLP) entstand deshalb gerade aus dem Feld der in vitro Alternativen. Das Konzept der Validierung der Relevanz eines in vitro Tests im Vergleich mit der entsprechenden in vivo Situation repräsentiert eine konsequente Übertragung von beweisbasierter Medizin (evidence-based medicine) in die in vitro Biomedizin. In anderen Worten: Es ist nicht mehr ausreichend, dass ein in vitro Modell plausibel erscheint – es muss Eignung und Qualität unter Beweis stellen.

(c) Die breite Implementierung von fortschrittlicher in vitro Technologie in Lehrpläne impliziert die Entwicklung von Vorlesungen, Kursen und weiteren Lehrmaterialien, inklusive Angeboten der virtuellen Lehre. Eine solche Basis wird die effiziente Verbreitung von Wissen ermöglichen und die transnationale Akzeptanz fördern. Nicht zuletzt stellt die Initiative für die Einrichtung eines Lehrstuhls für Alternative Methoden ein bedeutendes politisches Signal dar, das der Öffentlichkeit die Bereitschaft demonstriert, akademische Lehre an modernes soziales Bewusstsein zu adaptieren. Eine solche Einrichtung sollte im Zentrum Europas erfolgen, an einem Ort, der die notwendige Infrastruktur umgebender biomedizinischer Forschung, internationaler Netzwerke für die Evaluierung und Validierung von Tests, Technologietransfer für industrielle Anwendungen und Zugang zu den relevanten Publikationsorganen aufweist.

Die eindeutige Antwort auf die Frage des Titels ist daher: Wir brauchen einen Lehrstuhl für in vitro Alternativen, weil (i) der Patient unser primäres Anliegen darstellt, aber das Tier nicht nur sekundär ist und (ii) die Verantwortung des Menschen für alle Kreaturen inklusive der eigenen Spezies gilt.

Keywords: professorship, research, commentary, alternative methods, humane science

1 Introduction

The ethical principle that *in vitro* alternatives to experiments in live animals should be used whenever possible has become a central issue in biomedical research. A differentiated basis for the concept of alternatives was laid by Russell and Burch in their book, The Principles of Humane Animal Experimental Techniques, Charles Thomas, Springfield, IL, 1959. They promote a definition of alternatives as "the three R's – replacement, reduction, and refinement" which has become a pervasive theme in biomedical research today. In most countries, a form legally required in an application for animal experimentation asks for the strategies used to search for alternatives to procedures that may cause more than slight pain or distress to animals. The OECD guidelines now contain regulations that animal experiments are not allowed when a validated *in vitro* method is available to answer the question under consideration. This regulation acknowledges the progress made in the development of alternatives, but also takes into account that *in vitro* models are always dependent on pre-existing *in vivo* information, i.e. comparison to *in vivo* experimentation and preferably clinical correlates. Since all of the variables in physiology and pathology in the complexity of a live organism are not known, any research on biological processes must be confirmed in a living organism at some point. Without any doubt or compromise, however, this final

'reality check' must be kept to a minimum and, if inevitable, must be done with respect and care to avoid or at least relieve pain and distress of the living animal.

Utilisation of pre-existing knowledge for teaching, application and transferal of known principles to new systems to look for similarities, and use of advanced *in vitro* methods to screen large numbers of agents, e.g. for toxicity or mutagenicity, requires awareness of the progress in the scientific world, as well as orientation in the growing jungle of regulatory affairs. It is therefore of great necessity to reflect whether and to which extent this progressive change in our scientific culture is reflected in academic education, research and implementation in industry by technology transfer.

As the author himself is active in research as a professor of pharmacology, is currently university vice president and on the board of executives of the German Society of Experimental and Clinical Pharmacology and Toxicology (DGPT), it makes sense to address the question in the heading from the viewpoints of these three positions. Most probably, an unequivocal, objective answer will emerge from the congruency area of the overlaps of these three roles, with complimentary support from common sense in the individual fields.

On a structural-analytical level, the question to be addressed first is: What is driving the development and use of alternative methods and would a newly installed chair add to this over-all goal? To find an answer, it is helpful first to consider the genesis of a novel method and its passage through different stages, i.e. the development, the validation, the regulatory acceptance and the commercial application. In the following small sections, this question will be reiterated step-by-step and answered point-by-point as illustrated schematically in Figure 1.

2 Development of alternatives – what is driving it and will a chair contribute?

Developer: The educated mind, i.e. the researcher aware of the needs and opportunities in the field of alternatives, needs trained personnel and financial resources currently restricted to funding in this field. An institutionalised facility, such as a chair, will not only add a budget but will definitively increase awareness of the field among other scientists and create a commitment to proper education of students and postgraduates, e.g. in state-of-the-art *in vitro* techniques.

Pharmacology/Toxicology: Two main forces have been driving the application of *in vitro* methods in these scientific disciplines, i.e. high-throughput drug development and the need for human-based risk assessment. In line with public pressure as well as acceptance (depending on the country), the overall number of animal experiments is permanently declining, while advanced cellular models are taking over. Except in some veterinary faculties, the panel of techniques that has emerged has only rarely been formally included into curricula for e.g. post-graduate education and specialisation of future users in biomedical research. A chair on alternatives will therefore allow the implementation of appropriate study programs and thus provide the necessary training.

University: A new field of quality control and quality assurance of experimental models has emerged from the validation of *in vitro* alternatives, which has influenced the entire spectrum of biomedical research greatly: to the best of the author's knowledge, a similarly thorough effort for validation of models has not been and is not undertaken in any other field. Millions of Euro are spent in order to assess the properties of assays in collaborative studies and to validate them in comparison to the respective *in vivo*

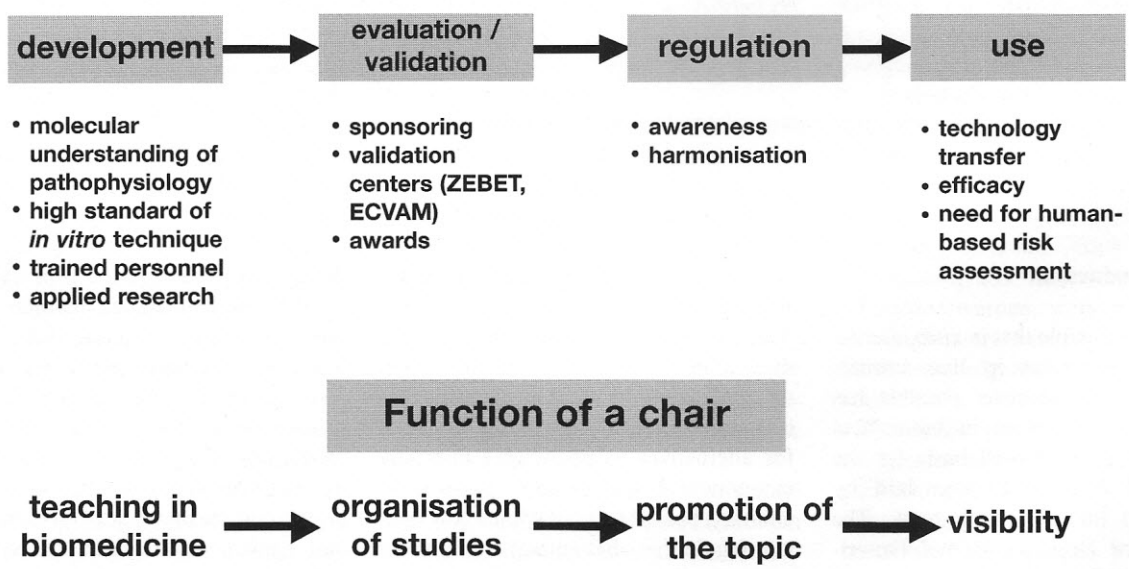

Fig. 1: The genesis of a novel method and its passage through different stages.

models. What we are currently experiencing is the fascinating development of evidence-based medical findings in the form of evidence-based *in vitro* models. Therefore, it was a logical development that movements towards quality control emerged from this field, such as the adoption of Good Laboratory Practice for alternative methods and the current development of an independent Good Cell Culture Practice, both initiatives hosted and pursued by the European Center for the Validation of Alternative Methods (ECVAM) with respective task-forces. A chair of alternative methods could incorporate this "culture of validation" into scientific education and practice. In the firm belief that education has to be research-driven, active research in this field is required at the site of education, a prerequisite for optimal training. It will be a genuine core task of a chair of alternative methods to develop, implement and execute suitable education programs.

3 Validation of alternatives – what is driving it and will a chair contribute?

Developer: While the development of novel tests is a self-fulfilling comfortable aspect of academic research, their validation represents the major obstacle, for some researchers even a nightmare: First of all, validation is a long-term and laborious effort, e.g. the average time from development to administrative acceptance by the European Pharmacopoeia of new tests is currently 12 years. In a field where in a three-year rhythm every generation of Ph.D. students calls for new exciting projects, only the focused commitment of the researcher to bring an own development into application makes it possible to endure this long period and finally succeed. No doubt, however, a continuous feed-back with the developing laboratory is mandatory during validation in order to optimise the models and enable technology transfer of the adaptations made. It has to be credited to the various national and EU-wide campaigns which motivated applications for funding, and to the increasing number and prestige of awards in this field, that basic researchers were encouraged to endure this stage with their *in vitro* models. The second, similarly serious obstacle is that almost all basic researchers are unfamiliar with the complicated process of validation and acceptance. A chair of alternative methods represents a facility that is able to transport not only the technological aspects but also the necessary knowledge of the formal requirements into a broader scientific community.

Pharmacology/Toxicology: The validation of *in vitro* tests represents the threshold to meaningful risk assessment and efficient drug development. Therefore, the limiting step for technology transfer from academia to commercial use is usually the visibility of available methods. Public databases have contributed substantial material improvement here, on top of which a chair of alternative methods might provide access to details on identification and recognition of availability of alternative advanced methods.

University: Admittedly, validation studies cannot be a core activity of universities. Nevertheless, the participation in collaborative studies, which are typically performed on an international level, represents a unique opportunity for international research feedback and exchange of education systems. Since a chair on alternatives has the potential to participate or even organise such collaborative studies, this means a further chance for a university to gain access to such programs and the respective international networking.

4 Regulatory acceptance of alternatives – what is driving it and will a chair contribute?

Developer: The final goal of validation is regulatory acceptance of advanced methods. The developer's initial euphoric expectations for the progress of the project are frequently dashed when the length and obscure complexity of the process becomes clear. The reason for this is as obvious as frustrating: the constraints of safety and consumer protection force regulators to be conservative and reluctant to any change from established test methods to novel assays. The only feasible resolution of the conflict of interests is mutual understanding which eventually may result in identification of a common goal. If a chair of alternative methods can give initial help with the prospects of the enterprise and continuous guidance during the project, academic researchers can enter this stage with realistic anticipation of the duration and the chances of success and thus proceed through it with confidence.

Pharmacology/Toxicology: Regulatory acceptance, e.g. by Pharmacopoeia or OECD, is the prerequisite that allows the broad commercial application of new tests. The concomitant international harmonisation has the positive consequence that the need to maintain *in vivo* tests in parallel is further reduced or abrogated. The relations developed by a successful chair of alternative methods with other institutions and departments are suitable instruments to advocate and promote such wide-spread acceptance.

University: The university is not only a preferential research site, but also the place where in different faculties, including and beyond biomedicine, future regulators are trained. An incorporation of alternatives into the curricula of its education units will promote awareness and willingness to assess and acknowledge progress towards the refinement, reduction and replacement of animal experiments.

5 Use of alternatives – what is driving it and will a chair contribute?

Developer: The gap between development and use is filled by either validation/regulatory acceptance or simply by technology transfer. Many applications of alternative methods do not require formal validation, e.g. in drug development any scientifically sound advanced method will easily replace animal experiments, especially for cost reasons. A chair on alternatives can contribute to this directly by offering training of end-users and transfer of methods directly or indirectly through the trained students

who take over responsibilities in industrial research.

Pharmacology/Toxicology: Both public interest and political opportunity are calling for the use of advanced *in vitro* methods; a very recent example is the EU White Book on the necessity of risk assessment for chemicals produced in large quantities. However, the limiting factors are availability and visibility, rather than willingness on the scientists' side. Thus, a chair on alternative methods which makes new tests available and increases awareness of as well as access to advanced methods is a platform to aid and spread their application.

University: The university can readily profit from the application of state-of-the-art methods which emerge from its basic research activities. On the one hand, this mechanism makes it more attractive and financially more potent to hire top scientists. On the other hand, it allows the interplay of academia and society to become less unidirectional, because the return of added value into the social system increases. As a total, the use of *in vitro* methodologies feeds back into research, making methods available in commercial, standardised forms for broader use.

6 Conclusion

The key roles of a chair of alternative methods in an academic surrounding are

- to complement teaching in biomedicine, promoting advanced methods and making students aware of the opportunities and requirements at an early stage, as well as training them for the future jobs at an advanced stage
- the participation in external organisation of internally coordinated validation studies
- promotion of the topic within scientific societies, national authorities and the public
- enhancing the visibility of alternatives and promoting technology transfer

Thus, the different points of view taken at the beginning of this treatise converge to a common viewpoint that unequivocally argues for installing a chair on alternative methods.

7 An intent as to its local placement

The University of Konstanz has decided to start an incentive to install the first chair of alternative methods because of

- its central location in Europe, with its vivid academic environment at Lake Constance as the intersection between Germany, Switzerland and Austria
- the biomedical focus of the faculty of biology, i.e. chairs in biochemical pharmacology, biological chemistry, molecular toxicology, ecotoxicology, genetics and immunology in the network of excellence-program supported research groups and a Graduate College "Biomedical drug development" of the German Research Council
- the lecture programs on alternatives to animal experiments for the past decade and a toxicology education network (ToxNet Baden-Württemberg)
- the high standard of animal welfare, e.g. state-of-the-art animal facilities
- the external recognition as highlighted by numerous awards for alternatives to animal experiments and advanced methods development
- a reputable Technology Transfer Center for "*In vitro* Pharmacology and Toxicology" (STZ InPuT) devoted to the development, validation and transfer of alternatives with experience in international contract studies as well as EU validation studies
- the German editorial office of *ALTEX*

The University of Konstanz is therefore confident it offers an attractive environment to accommodate and support a chair on alternative methods as a nucleus for numerous opportunities of transdisciplinary and transnational implementation of the "3R's principle" into target-oriented research, problem-oriented development, socio-ecological awareness, regulatory acceptance and commercial use for assuring the health and living comfort of animals and man.

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