

ILAE TRANSLATIONAL RESEARCH TASK FORCE



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The goals of this task force are to optimize and accelerate preclinical anti-epileptic therapy (AET) development by:

- (a) Formulating precise terminology and identifying optimal methods and strategies for the discovery, validation, and translation of new therapies into the clinics;
- (b) Recommending infrastructure developments that optimize the utilization of resources that can accelerate the discovery and validation of AETs and their clinically relevant biomarkers.

Since 2011, the work of this ILAE Task Force has been a partnership with the American Epilepsy Society (AES) Translational Research Working Group Chaired by Aristea Galanopoulou and Jackie French.

The motivation for the formation of this task force is the concern that, despite the significant advances and introduction of many anti-seizure drugs into the clinical practice, there has been minimal impact on several key unmet therapeutic needs for people with epilepsy. In particular these unmet needs are drug-resistant seizures and anti-epileptogenic/disease-modifying therapies for epilepsies and their comorbidities. It is recognized that changes in traditional pre-clinical development pathways for anti-epileptic therapies are needed if truly transformational new therapies, that address these unmet needs, are to successfully be developed for clinical use. The significant activities of the Translational Research Task Force from July 2012 through June 2013 are outlined below:

1. Joint ILAE/AES London Workshop to optimize preclinical epilepsy therapy discovery

This workshop was held 27 - 29 September 2012 in London, UK, prior to the European Congress of Epileptology. The purpose of the workshop was to identify and recommend optimal methodologies, strategies and infrastructure developments to accelerate and de-risk the discovery, validation, and translation of preclinical discoveries into clinically successful therapies for seizures, epilepsies and their comorbidities. The workshop was organized by Drs French, Galanopoulou, O'Brien, and Simonato, attended by 49 international investigators, and was made possible through the generous co-sponsorship by the ILAE, AES, CURE, Epilepsy Therapy Project, and Autism Speaks. The active participation of Drs Whittemore, Fureman, and Ranganathan was also valuable in interfacing with the parallel initiatives from NINDS. Other contributors included: Alexis Arzimanoglou, Kevin Bath, Elinor Ben-Menachem, Ann Berg, Edward H. Bertram III, Amy Brooks-Kayal, Jim Cloyd, Andrew Cole,

Stephen Collins, Mark Dichter, Tracy Dixon-Salazar, Ed Dudek, Jerome Engel Jr, Dan Friedman, Brandy Fureman, Greg Holmes, John Huguenard, Frances Jensen, Rafal Kaminski, Andres Kanner, Jaideep Kapur, Henrik Klitgaard, Merab Kokaia, Holger Lerche, Jeffrey Loeb, Wolfgang Loescher, John Messenheimer, Istvan Mody, Solomon L Moshé, Astrid Nehlig, Jeffrey L Noebels, Manisha Patel, Emilio Perucca, Asla Pitkänen, Roger Porter, Michael Privitera, Jong Rho, Robert Ring, Michael Rogawski, Dieter Schmidt, Graeme Sills, Daniel Smith, Helen Scharfman, Kevin Staley, Eugene Trinko, Elisabetta Vaudano, Annamaria Vezzani, Matthew Walker, Steve H White, Samuel Wiebe, and Karen S Wilcox.

The participants had been organized into seven working groups which had prepared background discussion documents prior to the conference. At the conference each working subgroup presented its summary presentation and proposal followed by group discussions. The working groups were:

1. Defining the clinical "gaps to care" and the "opportunities" to develop new treatment approaches for epilepsy (Chair: J French).
2. General technical and methodological issues in AET development (Chair: A Galanopoulou).
3. Issues related to development of new anti-seizure treatments (Chair: Karen S Wilcox).
4. Issues related to development of anti-epileptogenic therapies (Chair: A Pitkänen).
5. Issues related to symptomatic and disease modifying treatments affecting comorbidities (Chair: A Brooks-Kayal).
6. Issues related biomarkers and surrogate endpoints (Chair: J Engel).
7. Issues related to "Stage II pre-clinical trials" and criteria to propose candidates for clinical trials (Chairs: M Simonato and T O'Brien).

Incorporating the inputs from the general discussion, following the workshop each working group wrote a position paper which were published in a dedicated supplement of *Epilepsia* in 2013 (see below).

Invited speakers from the pharmaceutical industry and funding agencies were also incorporated in the program. Henrik Klitgaard (UCB S.A.) discussed the expectations of the pharmaceutical industry as well as strategies to de-risk the anti-epilepsy drug discovery for seizures and epilepsy syndromes in need of better therapies. Elisabetta Vaudano (Innovative Medicine Initiative (IMI)) presented an overview of the IMI model of public-private partnerships to support drug development. Rajesh Ranganathan (National Institute of

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Neurological Disorders and Stroke [NINDS]) gave an overview of the current state of funding of translational studies in epilepsy, as well as the history and future goals for the Anticonvulsant Screening Program of the NINDS.

After a general panel discussion, the workshop agreed on the following vision for translational research in epilepsy: *To develop transformational new treatments for people with epilepsy that address the current major clinical gaps in care by 2025, in particular:*

1. *Anti-epileptogenic and disease-modifying treatments*
2. *Drug resistant seizures*
3. *Therapies for comorbidities.*

Five primary next steps were identified to achieve this vision:

1. Develop standards for seizure and comorbidity classifications in animal models.
2. Undertake a systematic review of data from specific animal model data for particular clinical syndromes, including treatments, biomarkers and comorbidities through a Cochrane collaboration.
3. Develop a central database of EEG recordings and interpretation from animal models.
4. Formulate a system for publishing results of negative pre-clinical studies.
5. Work with government funding organizations (NIH and EC) to fund the establishment of a central infrastructure for undertaking multicenter pre-clinical studies to produce higher quality evidence of efficacy of new treatments and targets. This is likely to require the involvement of industry and philanthropic foundations in a partnership with academia and government.

2. Epilepsia Supplement on joint AES/ILAE translational workshop to optimize preclinical epilepsy research (Epilepsia 2013; 54(Suppl. 4): 1-74)

The purpose of this supplement was to report the outcomes of the "London Workshop" and to provide discussion documents for the international epilepsy and drug development community on the critical aspects of translational research addressed by these working groups. The supplement consisted of an article by each of the working groups, and a cover article by the workshop organizers. Each article underwent peer-review prior to being accepted for publication:

1. *Joint AES/ILAE translational workshop to optimize preclinical epilepsy research.* Aristeia S Galanopoulou, Michele Simonato, Jacqueline A French, Terence J O'Brien.
2. *Development of new treatment approaches for epilepsy: Unmet needs and opportunities.*

Jacqueline A French, H Steve White, Henrik Klitgaard, Gregory L Holmes, Michael D Privitera, Andrew J Cole, Ellinor Quay, Samuel Wiebe, Dieter Schmidt, Roger J Porter, Alexis Arzimanoglou, Eugen Trinkka, Emilio Perucca.

3. *Epilepsy therapy development: Technical and methodologic issues in studies with animal models.* Aristeia S Galanopoulou, Merab Kokaia, Jeffrey A Loeb, Astrid Nehlig, Asla Pitkänen, Michael A Rogawski, Kevin J Staley, Vicky H Whittemore, F Edward Dudek.
4. *Issues related to development of new antiseizure treatments.* Karen S Wilcox, Tracy Dixon-Salazar, Graeme J Sills, Elinor Ben-Menachem, H Steve White, Roger J Porter, Marc A Dichter, Solomon L Moshé, Jeffrey L Noebels, Michael D Privitera, Michael A Rogawski.
5. *Issues related to development of antiepileptogenic therapies.* Asla Pitkänen, Astrid Nehlig, Amy R Brooks-Kayal, F Edward Dudek, Daniel Friedman, Aristeia S Galanopoulou, Frances E Jensen, Rafal M Kaminski, Jaideep Kapur, Henrik Klitgaard, Wolfgang Loscher, Istvan Mody, Dieter Schmidt.
6. *Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy.* Amy R Brooks-Kayal, Kevin G Bath, Anne T Berg, Aristeia S Galanopoulou, Gregory L Holmes, Frances E Jensen, Andres M Kanner, Terence J O'Brien, Vicky H Whittemore, Melodie R Winawer, Manisha Patel, Helen E Scharfman.
7. *Epilepsy biomarkers.* Jerome Engel Jr, Asla Pitkänen, Jeffrey A Loeb, F Edward Dudek, Edward H Bertram III, Andrew J Cole, Solomon L Moshé, Samuel Wiebe, Frances E Jensen, Istvan Mody, Astrid Nehlig, Annamaria Vezzani.
8. *Proposal for a "phase II" multicenter trial model for preclinical new anti-epilepsy therapy development.* Terence J O'Brien, Elinor Ben-Menachem, Edward H Bertram III, Stephen D Collins, Merab Kokaia, Holger Lerche, Henrik Klitgaard, Kevin J Staley, Elisabetta Vaudano, Matthew C Walker, Michele Simonato.

3. Other publications related to the work of the Task Force

Simonato M, French F, Galanopoulou AS, O'Brien TJ. Issues for new antiepilepsy drug development. *Current Opin in Neurology* 2013;26:195-200.

Michele Simonato, Amy R Brooks-Kayal, Jerome Engel Jr, Aristeia S Galanopoulou, Terence J O'Brien, Asla Pitkänen, Karen S Wilcox, Jacqueline A French. *The challenge and promise of*

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preclinical therapy development for epilepsy. Invited to resubmit to Lancet Neurology.

4. Liaison with UK NC3Rs Survey on Animal Models Used in Epilepsy Research

The National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3R) of the UK has begun an initiative to assess current practices using animal models for epilepsy research, and to formulate recommendations. It was recognized that there was potential for overlap with the work of the ILAE/AES Translational Research Task Force. In order to address this a teleconference was held between the Task Force chairs and the NC3R on August 29, 2013. The outcome of this meeting was a resolution to ensure there was communication between the work of the two groups. Michele Simonato was nominated to represent the Task Force on the NC3R committee.

5. Planning toward addressing the “Next Steps”

A meeting was held of the joint ILAE/AES Translational Task Force at the American Epilepsy Society Meeting in San Diego, December 2012, and at the International Epilepsy Conference in Montreal, June 2013 to begin formulating plans to address the next steps identified at the “London Conference” (see above). Working groups were nominated to address each step, but after discussion with the ILAE leadership it was decided that the final formation of these working groups should wait until the new Commissions and Task Forces were established after July 2013. The members of the new ILAE Task Force nominated are: Terence O’Brien, Michele Simonato (Co-chairs), Marco de Curtis (as Chair of Neurobiology), Akio Ikeda and Asla Pitkänen. It was also decided that the work of the Task Force should be done in partnership with the AES Translational Research Working Group, with Aristeia Galanopoulou and Jackie French nominated by the AES as chairs. The new joint ILAE/AES Task Force will meet at the American Epilepsy Society Meeting in Washington in December 2013.