

TITLE: MULTIDRUG EFFLUX SYSTEMS

FIELD OR DIVISION OF SUBJECT:

Biological Sciences

ORGANISING COMMITTEE:

Dr Richard Callaghan (Corresponding Chair)

Prof Eitan Bibi (Co-Chair)

Prof Olga Lomovskaya (Vice-Chair)

Dr Anthony George (Vice-Chair)

KEYWORDS:

Membrane transport

Antibiotic resistance

Cancer chemotherapy

ABC transporters

Secondary active transporters

Multidrug resistance

Drug development

Structural biology

CONFERENCE DESCRIPTION:

Background: The phenomenon of resistance to chemotherapy continues to plague treatment of cancer as well as parasitic and bacterial infections. Whilst drug resistance should be considered a multi-factorial process the original "Multidrug Efflux Systems" GRC in 2003 highlighted the prominence and impact of drug efflux pumps in the phenotype. The long-term mission statement of the scientific community at this GRC was to provide a molecular description of the multidrug efflux process and to design inhibitors to overcome the actions of the pumps responsible for the phenomenon. The second GRC in 2005 focussed on molecular aspects of resistance to chemotherapy including regulation and bioenergetics. In addition, there was considerable discussion of the clinical relevance and the wider biological impact of multidrug efflux pumps. Efforts to understand the mechanism of multidrug efflux has advanced steadily with significant input from active participants of the previous GRCs.

2009 Meeting: The plenary session on day 1 comprised two lectures provided by world leaders in the two primary classes of multidrug efflux systems. These presentations related to pumps in either prokaryotic or eukaryotic systems. The first full day of the meeting examined the various classes of efflux pumps, their main roles in resistance and disease. In addition, a number of novel roles for these pumps in human disease were discussed in a lively session. The next day focussed on the molecular mechanisms of efflux pumps, how they are regulated and the bioenergetics of their function.

However, a complete understanding of mechanism obviously requires the input of structural data and unfortunately this remains a difficult task for membrane proteins. Provision of structural data has begun in earnest and advances in expression systems and extraction techniques have brought us to the cusp for many efflux pumps. This aspect of research was a strong focus for the "Multidrug Efflux Systems" GRC in 2009. The third day of the meeting was completely devoted to structural studies and relating structural information with biochemical data on drug-protein interaction and chemical synthesis of inhibitors. The emerging structural information heralds an exciting period in the quest to circumvent multidrug resistance in bacterial infections and cancer. The delegates were given a number of highly informative and pre-publication seminars on structures of various multidrug efflux pumps. Many positive comments on these sessions were provided by the delegates.

On the final day of the conference the focus shifted towards generating inhibitors of these troublesome transport systems. A number of eminent medicinal chemists

and pharmacologists provided insight into this long process and illuminated the delegates as to considerations required. This session led neatly into the final clinically based series of talks. These provided information on the current state of play with inhibition of multidrug efflux systems for bacterial, parasitic and neoplastic diseases. The delegates were left with a clear insight into the magnitude of the problem we deal with and the difficult task to circumvent this key resistance pathway.

The conference therefore contained interface between numerous scientific disciplines, the pharmaceutical sector and clinicians. A number of controversies were discussed and collaborations arose. The movement along the clichéd path of “bench-to-bedside” was highly regarded by the delegates in their comments.

CONFERENCE FREQUENCY:

Biennial. Two previous meetings were held in 2003 and 2005 whilst the recently completed meeting saw a rebirth. The delegates overwhelmingly voted for the conference to continue in the same 2 year cycle. The next meeting is likely to be held in Tuscany, Italy in 2011. We await confirmation from the GRC regarding finalised venue.

ATTENDANCE:

A total of 134 delegates were present at the meeting, which surpasses the previous figures of 101 in 2003 and 108 in 2005.

There were 34 invited speakers at the conference and 9 discussion leaders. Furthermore, the organising committee invited a further 12 early stage researchers (i.e. PhD students and post-doctoral fellows) to present their work to the conference. A total of 75 of the conference delegates provided posters for presentation on four days of the meeting.

Attendees gathered from Nth America, Europe, South East Asia, Australasia and the sub-continent. This added an international and cosmopolitan flavour to the conference and every effort was made to provide those from far-flung (e.g. Australia) or economically disadvantaged (e.g. India) regions some financial assistance towards registration and travel.

The GRC also provides a number of minority fellowships to encourage participation from under-represented communities and the conference was successful in attaining two of these:

(i) Carl Storm Underrepresented Minority Fellowship

Eligible candidates must be: a graduate student, post doc, faculty, or research scientist; African American, Hispanic American or Native American; a U.S. citizen or permanent resident; working at a U.S. institution; a first-time attendee of a Gordon Research Conference. The amount of the fellowship award is \$600.

This was provided to *Alexandra Mercante* (Hispanic American)

(ii) Eastern European / Former Soviet Union Fund (EEF/FSU)

The Conference Chair must submit a request for support from the EEF/FSU Fund for a qualifying candidate. The EEF/FSU award (\$600) is available for one (1) qualified scientist who is part of the research establishment of his/her native country per conference.

This was awarded to *Rimantas Daugelavicius* (Lithuania)

BUDGET:

Total Revenues:	
Gordon Research Conferences	\$17,500
GRC Carl Storm Fellowship	\$ 600
AstraZeneca	\$ 3,000
British Society for Antimicrobial Chemotherapeutics	\$ 2,037
National Institutes of Health	\$ 5,000
Prof William Shafer (donation)	\$ 2,000
Prof Richard Brennan (donation)	\$ 1,000
GlaxoSmith Kline	\$ 1,000
MPEX Pharmaceuticals	\$ 2,500
NIH-Office of Rare Diseases	\$10,000
Center for Cancer Research	\$10,000
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Total Revenue	\$54,637
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Final Expenditures:	
Speakers & Discussion Leaders	\$38,830
Early Stage Researcher Talks	\$ 9,877
Financial need (early researchers)	\$ 4,580
Social Activity	\$ 1,350
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Total Expenditure	\$54,637

The budget figures are detailed in the two tables above and indicate sources of income and the expenditures. Registration was paid for all eligible invited speakers and discussion leaders. Those from India and Sth East Asia (including Australia) were given further assistance towards travel costs. All of the early stage researchers asked to provide an oral presentation were given a partial offset of the registration fees. A number of delegates specifically requested financial assistance to enable participation and we were able to meet their needs – at least partially. Social activity refers to the provision of beverages at each of the poster presentation sessions. GRC regulations specify that none of the budget could be carried forward to the 2011 meeting. All expenditures were ratified by the GRC to ensure compliance with funding source regulations.

BUSINESS MEETING:

On the Thursday evening of the conference the conferees were asked to evaluate the conference and provide recommendations for future meetings. The format of the evaluation was through the GRC Evaluation Questionnaire, which covered both scientific and non-scientific concerns. The current and future Chair and Co-Chair solicited verbal comments during the meeting to discuss venue, timing and focus of next conference. Finally the delegates were asked to vote for the Vice Chairs of the 2011 meeting. The current organising committee solicited volunteers from the delegation and candidates were chosen equally between the prokaryotic and eukaryotic sections of the community. Vice-Chairs assist with the organisation of the next conference and assume the roles of Chairs for the subsequent meeting. The new organising committee for the 2011 meeting are:

Prof Olga Lomovskaya (Corresponding Chair)
Dr Anthony George (Co-Chair)
Dr Martin Plos (Vice-Chair)
Dr Susan Bates (Vice Chair)

The following pages provide a summary of the delegates' questionnaire responses.

Meeting Comments

Hotel Galvez (3/22/2009 - 3/27/2009)

Multi-Drug Efflux Systems

Meeting Best

- * The talks were very targeted and nice and short(20minutes). Also the great quality of the poster talks. The poster sessions were very well attended and very informative.
- * All speakers stayed within the allotted time allowing enough time for discussion.
- * The relevance to what I am studying.
- * The talks were excellent. this is my first GRC and I wonder why I haven't been here before. The talks were great. The quality was wonderful. I did enjoy also the shorter poster talks. It also provided an environment where I felt comfortable to talk to the leaders of the field - I could have coffee or eat with them - that couldn't happen at a bigger meeting.
- * New data, not just what's already published. The chance to meet people in the field and discuss science. Fantastic opportunity for a new PI just starting to get to talk over my data with senior investigators.
- * Unpublished data was presented.
- * Free exchange of ideas and integration of all aspects of the field into one program.
- * The organizers found a good equilibrium between the different communities working on efflux and transport as well as a balance between structural biology and biology or biophysical chemistry.
GRC people were excellent - office and room projection.
- * Exciting debate
- * New ideas, new techniques.
- * Openness of conferees to share information and thoughts.
- * Cutting edge presentations, good balance between prokaryotic and eukaryotic topics.
- * Presentation of Pgp structure prior to publication.
- * The diversity of relevance.
- * Introduced me to unfamiliar aspects in the field, advice given during poster sessions.
- * New high resolution structure.
Complimentary variety between mammal ABC transporters and bacterial non-ABC tranporters.
- * Two days of poster sessions for each group allowed for ample time for discussion. The poster sessions/"happy hour" was the best part of this meeting.
- * Quite interdisciplinary approaches. Very good cross feeling, very good science in most parts, outstanding structure talks!
- * Talks were great! Enjoyed hearing the leaders of the field. Richard did a great job.
- * 20-30 minute talks were a great idea.
- * The diversity of speakers - different nations and different levels of scientists. Also a great breadth of model systems - human, plant, animal and bacteria.
- * Wide diversity of talks.
Very nicely and logically organized. Excellent to have a big break in the middle.
- * Wide range of talks.
Excellent quality of speakers and posters.
- * Structure. Breadth of different systems.
The participants.
- * Variety of expertise; in-depth biology.
- * Mouse Pgp structure.
- * The scientific controversy - it's a field that's very much alive.

- * Length of sessions (and length of talks) has been excellent. Sufficient to communicate important data but also to sustain concentration throughout! All sessions have strictly kept to time.
- * To hear about new directions and advances in current research.
- * Topics at the forefront of science.
- * Good talks, speakers mostly stayed on time.
Good posters; informative, poster presenters available.
- * Exciting new structures, very interesting developments of efflux pump inhibitors.
- * Discussions with other investigators, post-doctoral fellows and graduate students.
- * Provided a good overview of the field.
Interesting talks that covered different topics.
Scheduling - length of sessions was really good.
Poster sessions: it was very interesting to talk to the other researchers, a good opportunity to discuss scientific topics and to network.
- * Being part of the discussion of people's work and being able to discuss the work prior to being published.

Hotel Galvez (3/22/2009 - 3/27/2009)

Multi-Drug Efflux Systems

Meeting Poorest

- * The layout of the seats.
- * There could be a microphone on a stand in the center of the room for people to walk up and ask questions after the presentation. It's a nuisance for people to run microphones to those who want to ask questions.
If possible, it would be nice to have a dinner-dance the last night.
- * Variable quality of the poster talks -some fantastic, some not as good.
- * Discussion tended to be question and answer format rather than open discussion led by chairs.
- * few personalities dominated some aspects of discussion.
- * Some talks spent too much time discussing published data.
- * Poster speakers at other GRC meetings were selected based on posters, not abstracts. This should be adopted by this GRC meeting.
- * Wish intro talks gave a little more background.
- * Unequal level of speakers.
- * Science very good BUT GRC administrators & representatives were unfriendly, impolite, moderate administration.
"Policing" is unacceptable. GRCs should not be run as boot-camps.
- * This conference was unfortunately quite unbalanced with respect to prokaryote vs. eukaryote talks. Personally, I was disappointed that "my" area of ABC transporter gained poor attention as more than 90% of the talks were dedicated to bacterial-drug efflux issues. I had hoped this would be more balanced.
- * Poster talks were of uneven quality with respect to content.
- * I would have liked to see more focus on the genetic regulation aspect as opposed to structure and function.
- * No informal discussions where young investigators can express their views, input more comfortably.
- * Need more chemistry, e.g. ePIs chemical approach to cancer / anti-infectives.
- * One attached mic on the chair is necessary, so the additional handheld mics can both be used for audience questions.
- * Late sessions are less effective, people are too tired already.
Let's make a shorter break in the middle of the day and finish the evening session early.
- * I would include a bit more sort talks, selected from abstracts.
- * cant think of any - this was really an ideal meeting.
- * No major deficiencies - it would be nice if there were abstracts available for the talks/posters.
- * Not enough time for discussion selections immediately proceeding some of the talks. Would have been nice to see Chris Tate and Shimon go at it for longer than 10 minutes.