Scientific Report ESF Exploratory Workshop Challenges for experimental and theoretical immunology Leeds, United Kingdom, 1 – 3 September 2008 convened by

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Local organising committee: Grant Lythe, Carmen Molina-París and Emily Stirk

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1 Executive summary

The workshop was held from Monday, September 1st until Wednesday, September 3rd, 2008 at the University of Leeds, Leeds, United Kingdom. The exploratory workshop was attended by 22 participants: 19 participants from 7 European countries (Finland, France, Germany, Netherlands, Portugal, Spain, United Kingdom), 1 participant from Australia and 2 participants from the United States and covered key issues related to current challenges for experimental and theoretical immunology.

Cell labelling techniques and imaging techniques are opening new perspectives in immunology by providing real time data. The ability to track parasites and cells *in vivo* using these techniques enables important and challenging questions to be addressed. Theoretical and computational modelling are essential to go beyond qualitative descriptions and quantify the cellular immune response. A cross-disciplinary approach is required to quantify the host-pathogen interactions of the cellular immune system. This exploratory workshop bridges the gap between immunological research and mathematical modelling. This will allow the participants to generate new models with predictive character and that can produce experimentally testable hypothesis. This workshop brought together key researchers, mainly based in Europe, from different communities involved in both experimental and theoretical immunology to discuss key issues related to achieving the aims of (i) developing the links and a common language between immunologists, mathematicians, computer scientists and physicists to address this new challenge in systems biology, (ii) developing a theoretical and computational framework to model the behaviour of cellular immune responses, in different immunological conditions, learning from advances in stochastic methods, and (iii) transferring ideas, experimental techniques, models and insight between the biological, mathematical, physical and computational communities.

The workshop has increased communication with and between the different communities and marked the start of a coordinated European effort to bring together experimental and theoretical immunology to address the current scientific challenges facing Quantitative Immunology. The outcome of the workshop is an agreement to work closely together and a strategy to form a network of scientists. We have taken the following steps:

- The development of a Marie Curie Initial Training Network (ITN) under the 7th Framework Programme of the European Union (a proposal submitted on the 2nd of September 2008). This network – called 2PM – will bring together for the first time known expertise in fundamentally different experimental and modelling approaches/techniques spread throughout Europe. Communication and cooperation between the different communities will be enhanced and the combined expertise will be employed to train a new generation of quantitative immunologists, fully capable of integrating state-of-the-art experimental and/or modelling techniques.

- The development of a Marie Curie International Research Staff Exchange Scheme (IRSES) under the 7th Framework Programme of the European Union (a proposal submitted on the 28th of March 2008). This network – called INTI – will provide European scientists with links to research institutions outside Europe: Australia, Canada, India, New Zealand and the USA.

- The preparation of a book (contract with Springer) provisionally entitled *Current mathematical models in lymphocyte biology*. The book will have both experimental and modelling chapters, so that it has a wider audience: scientists involved in modelling immunology, research fellows and post-graduate students in the field. This book will be of potential use for systems biologists, computational biologists and bio-informaticians. The book's aim will be to present current mathematical/computational models (both deterministic and stochastic) of different processes of the immune system. The immune systems involves a wide range of scales, from the gene level (evolution of the genes encoding molecules involved in immune recognition) to the molecular (how surface molecules of different immune cells interact), from the

single cell (T cell activation and differentiation) to the population level (how the immune system maintains a diverse and functional T and B cell repertoire). The models introduced in the book are generic and are, therefore, applicable to other biological scenarios, not just the immune system. Thus, both computational biologists and bio-informaticians will find in the book models and/or methods that are useful to them. The book is expected to be finished by December 2009.

- The preparation of a parallel application for an ESF Research Networking Programme to further develop and fully integrate the experimental and theoretical immunology communities in Europe. This network will provide long-term collaboration between the participants and the wider scientific community. The possibility of this collaboration hinges on our ability to provide theoretical and computational models of the relevant immunology considered and, in particular, the new experimental evidence provided by novel *in vivo* imaging techniques.

2 Scientific content of the event

The workshop started on Monday 1st of September 2008 with introductory talks on the organisation of ESF (M. Röllinghoff) and expectations of the workshop (C. Molina-París). The first talk (experimental) introduced the participants to current challenges for *in vivo* imaging in immunology, particularly to T cell-antigen presenting cell (APC) interactions in the lymph nodes, and of modelling T cell search strategies and effector cell output. In particular M. Miller described current limitations of *in vivo* imaging, such as time constraints (continuous imaging does not last longer than one hour, one only sees what is labelled, etc.) The second talk of the morning session provided the participants with state-of-the-art knowledge of quantitative immunology, with a focus on: (i) quantify HIV CD4-T cells death rates, (ii) cytotoxic (CTL) responses and (iii) two-photon microscopy in immunology. The last talk of the morning session (experimental/theoretical) focused on experimental techniques for estimating T lymphocyte turnover and a comparison of naive T cell dynamics of mice and humans. Both afternoon presentations were experimental talks: the first talk focused on memory T cells and, in particular, competition between different T cell memory populations. The second focused on the molecular details of T cell receptor triggering and the importance of the size of the different molecules involved.

The Monday afternoon discussion focused on T cell modelling, in particular how mathematical/computational modelling can help T cell immunology. The T cell repertoire is comprised of at least 25 million receptors each with different antigen specificity. During the immune response, only a small fraction of the T cells will recognise foreign antigen, activate and undergo proliferation. In the lymph nodes, these antigen-specific T cells face the daunting task of first finding a dendritic cell presenting their cognate antigen. This seems specially difficult because the lymph nodes are densely packed with millions of competing T cells having irrelevant specificity, dendritic cells presenting non-cognate peptide-MHC complexes, and many solid obstacles, such as the reticular network. Recently, it has become possible to visualise the *in vivo* motility of different immune cells. The resulting vivid movies and measurements of the events occurring in the lymph nodes suggest that T cells achieve their aim by moving around at high velocities, greater than one cell diameter per minute. They may move in a consistent direction for several minutes but follow random trajectories in the long term. A "stop-and-go" fashion of walking has been suggested. However, these studies reveal neither the underlying mechanism of the observed behaviours nor the influences of the densely-packed lymph node environment on T cell motility. The visualisation of dynamic processes in lymphoid tissues by confocal laser scanning microscopy and multi-photon excitation laser scanning microscopy opens up possibilities for combined modelling and experimental efforts.

The participants concluded that

- The interaction of T cells with APCs is a key event in the control of self-tolerance. There is currently intense research effort that aims to understand the way lymphocytes collect signals from their environment. For example, a T cell might decide its activation state upon a single interaction with an antigen-presenting cell (APC) via the development of an immunological synapse. Alternatively, T cells might collect signals from short encounters with APCs that are then subject to an intracellular integration. Understanding the process of lymphocyte activation is the pre-requisite to finding suitable targets that control the state of the immune system.

- In recent years cell-cell contacts and cell migration in lymphoid tissues has become accessible *in vivo* by the technique of intravital two-photon microscopy (2PM). With the advent of such novel imaging techniques, it is now possible to visualise the movements, as well as the physical interactions, relevant to cell activation in the natural environment of secondary lymphoid organs. This method permits observation of cells in living tissues of anaesthetised animals, with minimal alteration of natural conditions. A quantitative evaluation of the tracked cells and cellular interaction data is now possible and most suitable as a basis for modelling. However, a

fully automated tracking software is still lacking and will be one subject of research within the proposed ITN network.

- Currently-generated two-photon (2PM) imaging data sets remain widely descriptive and lack functional context and interpretation. *This situation calls for the combination of 2PM experimental methodology with mathematical tools that are adapted to include the quantitative data sets and to set them into a dynamical context.* In particular, there is a need to understand the clustering of CD8 T cells that are formed in the lymph node during infection.

- A functional understanding of the dynamics of adaptive immunity will only be possible by exploiting the synergies of high-end imaging techniques and advanced modelling approaches. Modelling approaches that combine (1) cell motility and interaction data with (2) immune repertoire, lymphocyte homeostasis, and the maintenance of self-tolerance, do not yet exist. *Such a comprehensive understanding of immune processes will help to develop new treatment strategies and will lead to novel and targeted drug developments in the pharmaceutical industry and in medical research.* However, this step is only possible in a multi-disciplinary network of academic and industrial/medical researchers.

- Other current challenges are: (i) modelling the dynamics of leukocyte flow in blood vessels (how these cells escape the laminar flow) and adhere to epithelial cells, (ii) how do cells "make decisions" about which chemokine gradient to follow? and (iii) understand the rate limiting step for the entry and exit of T cells in the lymph node, what happens when the observed lymph node does not have the "right" T cell receptor to generate an immune response?

- There are time and spatial scales that limit current *in vivo* imaging experiments. Modelling can help to push current space and time resolution.

On Tuesday 2nd of September the focus shifted from T cells to B cells. M. Meyer-Hermann introduced and compared different modelling approaches to B cell motility in germinal centres, O. Lassila gave an experimental approach to transcriptional control of plasma cell differentiation and J. Faro focused on alternative models of germinal centre dynamics. The last talk of the morning was a beautiful experimental review of B cell homeostasis by A. Freitas. The first afternoon talk provided both an experimental and a modelling perspective to measuring heterogeneous B cell behaviour. J. Carneiro presented different modelling approaches to cell cooperation mechanisms and peripheral T cell repertoire selection.

The Tuesday afternoon discussion focused on modelling B cell responses. B lymphocytes are central to all adaptive immune responses, producing and secreting antibodies. These molecules, also known as immunoglobulins, specifically recognise and bind to a particular target protein: antigen. The antigen may be a protein expressed on the surface of a pathogen or tumour cell, or a secreted protein, such as a toxin. Specific binding of the antibody to the antigen initiates a cascade of events which lead to the destruction of the target cell and an increase in the immunogenicity towards the antigen by facilitating its uptake and presentation by other cells of the immune system. Therefore, understanding how to enhance the production of specific antibodies has the potential to constitute an important tool for the cancer treatment and diagnosis. The fate of developing and mature B cells is determined by antigen binding to the antigen receptor on the B cell surface. At the immature stage, encounter with high-affinity antigen leads to cell death (a way of preventing the production of auto-reactive cells). In contrast, at the mature B cell stage, the immune system specifically selects for B cells that recognise the antigen with high affinity, as production of high affinity antibodies is essential for protective immunity to viruses and other foreign antigens.

The participants concluded that

- A key challenge is understanding how B cell fate is determined by antigen, both in regard to the affinity of the antigen and the way in which it is encountered. No other receptor system needs

to give a graded (and qualitatively modulated) response to ligand that is dependent on ligand affinity over such a wide range.

- Experimental models together with the latest imaging techniques are essential to understand the cellular and molecular mechanisms leading to B cell activation. In particular, a first step in this direction is to explore how the kinetics of synapse formation and receptor compartmentalisation will be affected by the density, affinity and the context in which antigen is seen.

- Modelling can help identify cellular and molecular mechanisms by which B cell activation is controlled, identify cellular and molecular mechanisms by which B cell fate is controlled, understand how the fate of a B cell can be regulated and develop models of B cell activation that include the kinetics of synapse formation and the clustering of receptors.

- Modelling the interactions of T cells, B cells and APCs in the lymph node is one of the great challenges. In particular, it is essential to understand the time scales of these interactions. For T cells: what are the time scales to find a cognate APC, for T cell-APC interaction and to exit the lymph node? For B cells: what are the times scales to meet TCR in the T zone, to express antibody, to meet a follicular dendritic cell, to meet a T cell and to exit the lymph node?

On Wednesday 3rd September the focus shifted to understanding immunity and infections. B. Asquith presented modelling techniques to quantifying the impact of HIV escape from cytotoxic T cells (CTLs). M. Gunzer gave an experimental account of how *in vivo* imaging can help analyse the cellular dynamics and functional plasticity of innate and adaptive immunity (T cell and infection) and finally J. Brewer presented recent experimental work on T cell and dendritic cell behaviour in tolerance and immunity, and how T cell behaviour changes in the presence of infection (malaria).

The Wednesday morning discussion focused on modelling immunity and infections. For some microbes virulence is linked to increase motility and trans-epithelial migration, which may be due to their being taken up by dendritic cells. The effectiveness of the host at restricting microbial invasion and dissemination from the site of infection is, therefore, crucial to determining the outcome of infection. Furthermore, in the case of per-oral infection, the interactions of the microbe with cells in the intestine are key to the success or failure of parasitism. There are still many unclear aspects of microbial infection, *e.g.,* how quickly after per-oral infection the parasite invades host tissues, the route(s) of trans-epithelial migration, the identity of cellular targets of infection and the impact parasite virulence and host resistance has on these parameters. Once the parasites have crossed the intestinal barrier they must enter the circulation, either in dendritic cells or other infected leukocytes or free.

The participants concluded that

- One should make use of new *in vivo* imaging techniques to identify the cellular targets of different microbes and to track the migration of the parasites, either free or in infected cells. This will enable us to determine how dendritic cell migration is affected by parasite virulence and host resistance (whether resistant or susceptible host).

- Modelling can help identify pathways of microbial invasion in the gut, identify the kinetics and targets of infection, track dissemination *in vivo* and develop a stochastic models of parasite infection that will take into account the different strains of the parasite, the infections dose of parasites and the mouse strain differences (susceptible versus resistant host).

The Wednesday afternoon summary focused over three long-term directions that are envisaged to make immunology more quantitative:

1. To develop stochastic models for the motion of pathogens and of cells of the immune system, validated by comparing with experiments that track parasites, T cells, B cells and dendritic cells *in vivo* using dynamic real time imaging.

2. To build a model of the immune system as a whole using stochastic dynamics of interacting populations. We aim to understand how the system maintains its diversity of millions of lymphocyte populations, how populations of naive and memory cells are maintained, to determine the turnover rates of various lymphocyte populations, and to understand the possible homeostatic mechanisms regulating lymphocyte population sizes.

3. To develop stochastic models of T cell and B cell maturation. In the case of T cells, maturation is a life-long saga, opening with generation in the bone marrow, continuing to thymic selection and then to peripheral repertoire maintenance and homeostatic equilibrium.

3 Assessment of the results, contribution to the future direction of the field

A good way to assess the short-term results of this Exploratory Workshop is by getting feedback directly from the participants. Here are some of the comments provided:

- **Feedback from participant A** *The meeting was excellent, especially novel bio-imaging technology and its applications in the immune system are challenging and these topics were well covered during the meeting and during the discussions also practical hints for modelling systems were covered. The meeting was truly cross-disciplinary and gained the objectives of the workshop.*

- **Feedback from participant B** *The assistance to the ESF Exploratory workshop "Challenges for experimental and theoretical Immunology" held in September 08 at the University of Leeds, was very productive on the understanding of new developing strategies related with mathematically models on immunological responses. Particularly, I found quite challenging the discussions and talks related with the motility and the dynamics in germinal centers, and also the talks and discussions related with B cell homeostasis. These discussions can bring new ideas and interactions with some of the groups represented in the meeting, in terms of scientific collaborations and discussions with researchers that are directly involved in the mathematical modelling and have the experience to teach me what are the difficulties and advantages to incorporate some of these strategies in the current knowledge of the laboratory.*

- **Feedback from participant C** *I very much liked the meeting, the fact that it was so focused on a few topics, very interactive, lots of discussions thanks to the small size of the group, just positive!*

- **Feedback from participant D** *The ESF exploratory workshop on mathematical modelling held in Leeds, September 2008 was a very fruitful meeting. Experts from diverse fields such as mathematical modelling, basic computer science and biology/immunology met, presented their data and discussed intensively about implications of their findings/methods for the development of the field. The ample time reserved for interaction during the coffee/lunch breaks as well as the dinners was very effective in fostering the discussion. A number of potential co-operations as well as plans for a cooperative grant application have been installed and should be come to life in the following years.*

- **Feedback from participant E** *I thought this was an excellent meeting during which there was considerable interaction between biologists and mathematicians. There was frank, open and enjoyable discussion which raised interesting challenges relating to image analysis and testing and refining mathematical models when contextualising them with the "real" biology.*

- **Feedback from participant F** *The meeting was very well organised and run. There was a good combination of experimental and theoretical work which provided me with valuable insight into what modellers were working on and the approaches that they used. What was clear was that there were large gaps in our understanding which limit the ability of models to emulate the systems under study. However models help identify which gaps we should focus on. There is quite a divide between those working at the molecular/cellular level, like me, and those at the cellular/systems levels. Paradoxically, complexity is greatest in the former. More work needs to be done at the molecular/cellular level and at linking the two levels.*

The long-term outcome of the ESF Exploratory Workshop is that we intend to set-up an international network of immunologists and modellers. As a first step in this direction, two proposals have been submitted to FP7:

- The development of a Marie Curie Initial Training Network (ITN) under the 7th Framework Programme of the European Union (a proposal submitted 2nd September 2008). This network – called 2PM – will bring together for the first time known expertise in fundamentally different experimental and modelling approaches/techniques spread throughout Europe. Communication and cooperation between the different communities will be enhanced and the combined expertise will be employed to train a new generation of quantitative immunologists, fully capable of integrating state-of-the-art experimental and/or modelling techniques.

- The development of a Marie Curie International Research Staff Exchange Scheme (IRSES) under the 7th Framework Programme of the European Union (a proposal submitted 28th March 2008). This network – called INTI – will provide European scientists with links to research institutions outside Europe: Australia, Canada, India, New Zealand and the USA.

The convenors of this workshop form the core group around which both the ITN and IRSES networks are organised. The proposed 2PM ITN will be the first of its kind in Europe. We will build upon successful ongoing efforts in the international community (MATSYB BBSRC network and multi-disciplinary workshops). The remarkably strong European expertise in the field of quantitative immunology (theoretical and modelling), combined with established expertise in *in vivo* imaging offers a unique opportunity to train the new generation of quantitative immunologists. This research effort is timely, as understanding how immune responses are regulated is essential for developing vaccines and immune therapies. Recent advances in tracking and imaging antigen specific immune responses in real time *in vivo* have begun to revolutionise our understanding of how these processes occur. However, the theoretical and computational modelling of these processes lags behind their imaging. The novelty of both the ITN and IRSES networks is that we will apply state-of-the-art analytical and modelling techniques to immune responses for the first time, exploiting the unique set of resources and expertise provided by the participants of the Exploratory Workshop. The mathematical tools available are very suitable for cross-fertilisation into the health care sector. This Exploratory Workshop has provided a unique and excellent opportunity to use these tools in a completely different scientific area and it will set the European scientific community at the forefront in the field of imaging and modelling in immunology.

We also plan to prepare of a parallel application for an ESF Research Networking Programme to further develop and fully integrate the experimental and theoretical immunology communities in Europe. This network will provide long-term collaboration between the participants and the wider scientific community. The possibility of this collaboration hinges on our ability to provide theoretical and computational models of the relevant immunology considered and, in particular, the new experimental evidence provided by novel *in vivo* imaging techniques.

4 Final programme

Monday – T cell immunology Location: Centenary Gallery, Parkinson Building, University of Leeds

- 9:30-9:40 Welcome (Dr. Molina-París)
- 9:40-10:00 Presentation of the European Science Foundation (ESF) (Prof. Röllinghoff, Medical Sciences (EMRC))
- 10:00-10:45 Talk 1, Mark Miller, **Modelling T cell search strategies and effector cell output**
- 10:45-11:30 Talk 2, Rob de Boer, **Towards a more quantitative immunology**
- 11:30-11:45 Coffee break
- 11:45-12:30 Talk 3, José Borghans, **Estimating T lymphocyte turnover by stable isotope labelling**
- 12:30-14:00 Lunch (Centenary Gallery, Parkinson Building)
- 14:00-14:45 Talk 4, Ananda Goldrath, **Making good T cell memories: competition between memory populations**
- 14:45-15:30 Talk 5, Anton van der Merwe, **The importance of size in TCR triggering**
- 15:30-15:45 Coffee break
- 15:45-17:00 Discussion: **Challenges for T cell immunology: how can modelling be of help?**
- 20:00 Dinner at Leeds Seventeen (transport from hotel to venue)

Tuesday – B cell immunology Location: Centenary Gallery, Parkinson Building, University of Leeds

- 9:15-10:00 Talk 6, Michael Meyer-Hermann, **Mathematical modelling of B cell motility in germinal centres**
- 10:00-10:45 Talk 7, Olli Lassila, **Transcriptional control of plasma cell differentiation**
- 10:45-11:30 Talk 8, José Faro, **Alternative models of germinal centre dynamics**
- 11:30-11:45 Coffee break
- 11:45-12:30 Talk 9, Antonio Freitas, **B cell homeostasis**
- 12:30-14:00 Lunch (Centenary Gallery, Parkinson Building)
- 14:00-14:45 Talk 10, Phil Hodgkin, **Modelling and measuring heterogeneous B cell behaviour**
- 14:45-15:30 Talk 11, Jorge Carneiro, **From cell cooperation mechanisms to peripheral T cell repertoire selection**
- 15:30-15:45 Coffee break
- 15:45-17:00 Discussion: **Challenges for B cell immunology: how can modelling be of help?**
- 20:00 Dinner at Arti Image (transport from hotel to venue)

Wednesday – Immunity and infections Location: MALL room, School of Mathematics, University of Leeds

- 9:15-10:00 Talk 12, Becca Asquith, **Quantifying the impact of HIV escape from CTL**

- 10:00-10:45 Talk 13, Matthias Gunzer, **Analysing the cellular dynamics and functional plasticity of innate and adaptive immunity (T cell and infection)**
- 10:45-11:30 Talk 14, James Brewer **Analysing T cell and dendritic cell behaviour in tolerance and immunity**
- 11:30-11:45 Coffee break
- 11:45-12:30 Discussion: **Immunity and infection: how can modelling be of help?**
- 12:30-14:00 Lunch at Thai Edge
- 14:00-14:30 Coffee
- 14:30-15:30 Summary
- 15:30-16:00 End of workshop and departure

5 Statistical information on participants

5.1 Names of participants

A total number of 22 participants attended the meeting. There were two last minute cancellations. A list of all attendees is given in the next Section. The names of participants are listed in alphabetical order: **Dr. Belén de Andrés Muguruza** (Madrid, Spain), **Dr. Rebecca Asquith** (London, UK), **Prof. Rob de Boer** (Utrecht, Netherlands), **Dr. José Borghans** (Utrecht, Netherlands), **Dr. James Brewer** (Glasgow, UK), **Dr. Jorge Carneiro** (Oeiras, Portugal), **Dr. Mario Castro Ponce** (Madrid, Spain), **Dr. José Faro** (Vigo, Spain), **Prof. Antonio Freitas** (Paris, France), **Prof. Paul Garside** (Glasgow, UK), **Dr. Ananda Goldrath** (San Diego, California, USA), **Prof. Matthias Gunzer** (Magdeburg, Germany), **Dr. Phil Hodgkin** (Melbourne, Australia), **Prof. Olli Lassila** (Turku, Finland), **Mr. Florian Lipsmeier** (Bielefeld, Germany), **Dr. Grant Lythe** (Leeds, UK), **Prof. Anton van der Merwe** (Oxford, UK), **Dr. Michael Meyer-Hermann** (Frankfurt, Germany), **Dr. Mark Miller** (St. Louis, Missouri, USA), **Dr. Carmen Molina-París** (Leeds, UK), **Ms. Emily Stirk** (Leeds, UK), and the ESF rapporteur **Prof. Martin Röllinghoff** (Erlangen-Nuremberg, Erlangen, Germany).

5.2 Age structure:

No specific age details were collected, but approximately 40% of the participants was younger than 40 years.

5.3 Gender repartition:

Participants: 6 female and 16 male.

5.4 Countries of origin:

Australia: 1
Finland: 1
France: 1
Germany: 4
Netherlands: 2
Portugal: 1
Spain: 3
United Kingdom: 7
USA: 2

5.5 Scientific background:

Participants: 11 experimental background and 11 theoretical (modelling) background.

6 Final list of participants

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22. **Ms. Emily Stirk**
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