REPORT

CARPEM SCIENTIFIC ADVISORY BOARD MEETING

Meeting dates: February 20-21 2020

Centre de Recherche des Cordeliers
15 rue de l'Ecole de Medecine
75006 Paris

Executive Summary: Overall Evaluation

A meeting of the CARPEM scientific advisory board meeting was held on February 20 & 21 2020 at Centre de Recherche des Cordeliers in Paris. In attendance were 8 of the 9 advisory board members consisting of Drs. Ana Anderson, Lucy Godley, Michael Karin, Josef Penninger, Alain Puisieux, Arnaud Roth, Robert Schreiber, Franck Sinicrope. Dr. Ma'n Zawati was not able to attend. Our report with executive summary follows.

CARPEM Paris is a terrific program overall. Superb faculty. Outstanding leadership. Great science Extremely productive. Highly collaborative. Great integration of the individual areas of expertise. It is clear, that the synergy that one would hope would come from bringing these various groups together, has been achieved and has led to the firm establishment of this program as one of the world-wide leaders in the fields of cancer and cancer immunotherapy. Our evaluation is that this is an exceptional program and we unanimously recommend its continuation and even consideration for additional support with our highest degree of enthusiasm.

Introduction: Presentation of the SIRIC Program and General Presentation of CARPEM
Presenter: Dr. Pierre Laurent-Puig

Dr. Laurent-Puig presented separate comprehensive and insightful overviews of the SIRIC system from its initiation in 2012-2013 to the current status after renewal of 6 of the 8 original units (including CARPEM) and the addition of 2 new units. Included was a charge by the National Cancer Institute for increased collaboration between the various SIRICs. In his second presentation, Dr. Laurent-Puig went into substantial detail about CARPEM and explained the procedure how CARPEM selects the projects to be supported by the program. It was clear to the committee that Dr. Laurent-Puig is a talented, well-informed leader who is extremely well respected by the program members and is obviously highly qualified to lead this innovative and productive program.

PROGRAM 1: Integrated Research Program- Metabolism, Genetics, Immunity & Environment
Presenters: Drs. Jessica Zucman-Rossi, Theo Hirsch, Romain Donne, Guido Kroemer

This program is very strong. The science is both diverse and impressive and reflects the partnerships built. The group of **Dr. Zucman-Rossi** has made impressive progress. Dr. Zucman-Rossi is a leader in liver cancer (HCC) genomics and has dedicated her effort to the identification of new initiating mutations, as well as mutations that affect metastatic progression and response to therapy. Dr. Zucman-Rossi had also invested a great deal of effort in establishing a well annotated liver cancer cell line database that will help the entire community. In recent years, she has characterized telomerase and cyclin A2 and E1 genetic alterations and defined a novel HCC subtype-macrotrabecular HCC. Another major effort is the correlation of HCC mutations with

environmental exposure and the classification of hepatic adenomas Dr. Zucman-Rossi is a key and highly dynamic member of the CARPEM group. **Dr. Teo Hirsch** presented interesting work on a BAP1 mutation in a subset of HCCs that mainly occurs in females. He also reported a very interesting linkage of BAP1 mutations to PKA upregulation, which may offer new avenues for therapeutic intervention. A particularly attractive component of his program is the large collection of tumors that his team has amassed. **Dr. Romain Donne** is investigating the role of polyploidy in liver development and cancer. Some of his work also focuses on the role of p38α in liver regeneration. The committee was highly supportive of Dr. Donne's plan to develop preclinical models of liver regeneration. This effort fits well with that of Dr. Zucman-Rossi. **Dr. Guido Kroemer** has continued to be as productive as ever. His work on starvation mimics and their effects on tumor metabolism and immune response is trailblazing and original. The committee found this work to be particularly interesting and of potential use in future cancer therapy. The cell biology screening platform created by Dr. Kroemer is a valuable resource and could be leveraged to benefit the individual research programs of scientists in CARPEM. Specifically, this platform could be adapted to study different cells of interest. Dr Kroemer also discussed a bacterial metabolite library. This is another valuable resource that could also be leveraged in conjunction with the screening platform to accelerate discovery. A priority will be to ascertain that these resources be made available to CARPEM investigators.

Program 2: Cancer Heterogeneity: A Challenge for Patient Management

Presenters: Drs. Eric Tartour, Florent Petitprez, Franck Pages, Olivier Kosmider, Stephane Oudard, Jerome Galon

Dr. Wolf Fridman's group has achieved a major insight into defining an important immune-stimulatory role for B cells in soft tissue sarcomas. Their results suggest that the presence of B cell-rich tertiary lymphoid structures in sarcomas can guide decision making and treatment choice. The committee felt strongly that this is a major fundamental achievement in tumor immunology. **Dr. Eric Tartour** set the stage nicely for this program by outlining the complexity of cancer heterogeneity and the challenges that it presents. He presented a convincing argument for a link between the presence of B cells in human sarcoma and survival. Perhaps equally surprising was the observation that survival was not linked to the presence of CD8+ T cells in sarcoma. The committee felt that these observations could be followed up in two experimental directions: (1) development of a prognostic clinical test and (2) a deep investigative approach to define the molecular and cellular mechanisms underlying the observations. We have no doubts that these approaches and others will be put into place by this highly innovative, well-informed team. **Drs. Franck Pages** and **Olivier Kosmider** then reported on their studies using state-of-the-art technologies (circulating tumor cells and single cell approaches, respectively) to gain further insights into both tumor heterogeneity as well as heterogeneity of host anti-tumor responses. These efforts thus bring the major advances made in experimental analysis of complex biological systems such as cancer to identify potential new ways to treat this disease. For these reasons, the committee felt extremely positive about the use of these forward-looking approaches, although such technologies are rapidly developing and so it will be important to remain flexible as new approaches are brought online. **Dr. Stephane Oudard** presented very interesting information about the BIONIKK and sarcoma projects. These are superb clinically oriented

projects that will very likely provide new insights into novel therapies. Perhaps oner issue that should be additionally considered here is that as Dr. Oudard points out, is very heterogeneous. So, would it be preferable to treat samples with combinatorial therapy rather than monotherapies. Finally, **Drs. Jerome Galon** and **Franck Pages** continue to improve on defining the contextual considerations for tumors and immune infiltrates. There have been very impressive advances made in the Immunoscore technology and it is particularly interesting that this approach is now being used to study cancer immunoediting and its impact on patient care. The committee is extremely excited to see that Dr. Galon is now applying the remarkably informative protocols he has developed to both primary and metastatic tumor sites. Dr. Galon unequivocally continues to be a major contributor to the entire fields of cancer immunology and immunotherapy and has been, continues to be and will be a major contributor to the success of the CARPEM program. This will likely be an area that will benefit most from the introduction of single cell characterization approaches.

Program 3: Dynamic Consent and Health Democracy

Presenters: Marie-France Mamzer, Anita Burgun, Gaelle Wendeu-Foyet

This program recognizes that, with current information technologies and the need for fluidity of data and sample flow within broad research networks, the consenting process is complex. Dynamic consenting allows for updating of research participants on the latest efforts in translational research. As such, the methods for involving participants must be adapted while respecting the autonomy of research participants. In this aspect, this program is particularly innovative and forward-thinking. The program seeks to explore the acceptance and the feasibility of the implementation of a dynamic consent (DC) and is implemented as a personalized digital communication interface between researchers and patients, allowing mutual communications in both directions [researcher to patient and patient to researcher], guaranteed data security, and transparency through tracking of communications regarding ongoing research projects. Program 3 maintains two chat rooms for its Expert Committee and its Patient Committee. They jointly hold an Advisory Translational Ethics Board (ATEB), which reviews questions such as: How do we to collect samples ethically for retrospective studies? How do we inform patients about the need to reuse their samples? These questions led to the idea of the dynamic consent. Research participants put their report into the system, and they give consent project by project, which can be updated. The review committee asked how this was done in practice. It was not clear how the system knew when participants moved or died. These issues would seem to challenge the integrity of the dynamic consent process. In a traditional consent process, there is no expectation that participants would be asked in the future about their degree of participation, so these issues are less relevant. Program 3 addresses the legal, ethical, and human barriers encountered in modern translational research, which they term 'ethical vigilance'. The consensus of their field work was that consideration of patients' opinions was extremely important and that researchers needed to uphold their responsibility and accountability. Program 3 recognizes that current legal and regulatory texts are changing to adapt to precision medicine and new translational practices. For example, in France doctors are not allowed to reveal incidental findings from clinical testing. Overall, the reviewers were highly impressed by Program 3. CARPEM was commended for having this

Program. The construction of Program 3 and its goals were deemed highly innovative and extremely important to the ideals of informed consent. Recommendations for consideration included: consideration of placing a time limit on the re-analysis of genomic data for five years, given the rapid pace of medical knowledge. Without a time-limit, research participants might expect for updates on genomic data indefinitely. Reviewers also expect that the national policy on revealing incidental findings might change based on public opinion, which could be queried by Program 3. Considering the large amount of information which might be exchanged between doctors/scientists and patients, there is also a risk of giving too much and/or too detailed information. It is well known that "too much information kills the information" and could be a source of anxiety for the patients. In order to avoid this, the committee recommends development of a set of standardized tools (formulations) to make this information more understandable to the average patient. In addition, we suggest developing a scale regarding the level of detail transmitted going from the most basic info to the most detailed one. This could be an interesting side project which would allow the program to become more conscious about what is needed and what is unnecessary. Such a scale would be then useful in adapting the exchanges with each patient, some of them being satisfied with simple information while some others wanting more precise explanations. Finally, such a standardized scale could be also an excellent education tool to be discussed with ethical committees and students. In sum, the committee felt that is was a huge positive to have this type of program incorporating the novel and creative idea of patient participation and cooperation as part of the CARPEM program. We express our congratulations to the CARPEM team for successfully making the link between Nutrient-Sante and certain cancers and would like to express our encouragement to the plan to set up fecal microbiome analyses to cancer development and response to therapy.

Program 4: New Platforms: Where We Are, Where We Should Go

Presenters: Drs. Valerie Taly, Guillaume Andrieu, Eric Tartour, Aurelien de Reynies

Dr. Valerie Taly presented her approach to develop assays, e.g. organotypic cultures, that will help translate basic research findings. The microfluidics capabilities she is building are both incredible and valuable. Her talents are and will continue to be in great demand. For this reason, it will be important for her to prioritize her efforts carefully and hopefully, because CARPEM provides some support for her work, she will prioritize her collaborations to build microfluidics-based screening platforms within the CARPEM program. The committee felt that the potential for this program is incredible but that to achieve its full success, it will be important to separate the research development functions from the Core functions of this program. Dr. **Guillaume Andrieu** is studying targeted therapy for T-ALL. He has successfully established several patient derived tumor transplant (PTX) models in immunodeficient mice and is currently looking for effects of blocking various signaling pathways. He clearly has a great handle on his screen. However, the element that is missing from this approach is the use of the immune system to drive durable responses. Since this project is being presented in the context of CARPEM, it would seem reasonable that Dr. Andrieu should consider exploring the *combination* of targeted therapy with cellular immunotherapy, for example by employing dome form of adoptive T cell therapy. Perhaps this type of approach will provide insights into the likelihood of which tumors will escape therapy. **Dr. Eric Tartour** presented exciting data showing the remarkable success he has had in

combining various well-established imaging platforms to assess changes in tumor cells and immune cells during various forms of cancer therapy. The data presented was extremely impressive. A second advantage of the approaches being used is that it brings together scientists with various forms of expertise. The big question at this point is which of the new technologies that provide high dimensional profiling on a single cell basis while preserving the three-dimensional structures of the tumor microenvironment should be recruited into the program. The four most likely systems are Hyperion, CODEX, Nanostring and 10X Spatial Transcriptomics. There are pluses and minuses of each system and Dr. Tartour is well-aware of them. At the current time, Nanostring, CODEX and the 10X systems appear to be the most cost effective of the four approaches and several high-profile papers have begun to appear demonstrating their flexibility and sensitivity. Finally, **Dr. Aurelien de Reynies** discussed his work on single cell transcriptomics versus supervised deconvolution of gene expression profiles. It was clear to the committee that Dr. de Reynies is extremely talented and has a clear view of how interactions should be optimally setup between experimental biologists and bioinformaticians. Importantly, he will receive a full-time Professor appointment in CARPEM and intends to develop a unique PhD program in cancer Bioinformatics. This will be an important resource to the CARPEM program going forward.