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Shedding Light on Immunological Research in Lyon, France. IRCI2022 Brings the Scientific World to Lyon and Bridges the Latest Immunological Findings in Cancer and Infection

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1 Title: **Shedding light on Immunological research in Lyon, France. IRCI 2022 brings**
2 **the scientific world to Lyon and bridges the latest immunological findings in cancer**
3 **and infection.**

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10 **Running title: Immunological research in Lyon, France IRCI2022**

11 Abstract/About:

12 At the heart of Lyon, France exists the Centre International de Recherche en Infectiologie
13 (CIRI) and the Cancer Research Center of Lyon (CRCL). Both institutes were created in
14 the early 2010s and have departments with solidified poles in immunological research.
15 The first Immune Responses in Cancer and Infection (IRCI) meeting was co-organized
16 by CIRI and CRCL and held in Lyon, France in February 2017. Over two and half days,
17 world-renowned experts in the field of immunology in cancer and/or infection came to
18 Lyon and discussed their findings with PIs, students, and postdocs from the CIRI and
19 CRCL as well as other research centers. The huge local success and international
20 recognition of IRCI2017 mobilized the CIRI and CRCL to host another meeting 3 years
21 later. With the advent of COVID-19, the second IRCI in 2020 was cancelled, yet leaders
22 of the scientific organizing committee, Julien Marie (CRCL) and Uzma Hasan (CIRI),
23 persisted to host an in-person meeting on June 15th-17th 2022 at the ENS, Lyon, France
24 (<https://irci2022.insight-outside.fr>, [twitter#IRCI2022](https://twitter.com/IRCI2022)).

25

26 The meeting centered on six sessions in innate immunity, immune metabolism,
27 immunotherapy and clinical immunology, microbiota, genetics and epigenetics, and
28 infection. IRCI2022 brought together prominent international scientists and clinicians to
29 discuss their recent immunological findings in fundamental and clinical research. The
30 number of participants was limited to increase discussion between leaders in the field and
31 attendees, thus strengthening as well as defining immunological research and therapies
32 in the future. Funding from grant calls, as well as institutional and corporate sponsors
33 reduced the registration cost. The scientific committee promoted maximal participation of
34 students and postdocs based on abstract selection for short talks, poster sessions and
35 teasers. Prizes were awarded for best poster and judged by committees of invited
36 speakers and scientific committee members. The meeting was sold out prior to the early
37 registration deadline with over 400 participants of which 30% came from outside of
38 France. The organization incorporated complete parity for male and female international
39 invited scientists embedded with locally selected Lyonnais speakers from the CIRI or

40 CRCL to exemplify Lyon research. Highly appreciated by all participants was the 6
41 sessions of interactive invited and selected scientific talks, 3 poster sessions with comical
42 poster teasers, and networking cocktail mixer and gala dinner. Keynote talks were given
43 on each day by **Yasmine Belkaid, Antonio Bertoletti and Ruslan Medzhitov.**
44 Furthermore, Editors from Cell and Nature Immunology Reviews' participated in a meet
45 the editors session.

46
47 The three days increased the visibility of Lyon's excellence in immunology and stimulated
48 discussion between local, junior cancer or infection immunologists and international
49 senior experts. Most importantly the low cost of registration and 'local' organization
50 permitted Lyonnais students and postdocs to meet prominent scientists. IRCI2022 was
51 more successful than IRCI2017 and was well received by participants and invited
52 speakers. The call for another meeting has solidified the position of IRCI as a key
53 international immunological symposium. Shown in table 1 a summary of all the speakers
54 and below, we highlight the events and significant scientific takeaways from the three
55 days.

56

57 **Innate immunity**

58

59 The innate immune and DNA repair systems can induce cell death and tissue injury in
60 some disorders, such as infections and cancers. DNA damage from cellular stress are detected by
61 DNA sensors (such as cGAS and ALRs) and constitutes an intrinsic danger signal (1)(2).
62 Under homeostatic conditions, low levels of cytoplasmic DNA prime the innate immune
63 system via DNA sensors. However, excessive DNA damage increases cytosolic DNA,
64 constituting a false alarm to the immune system and leading to an enhanced constitutive
65 expression of IFN-I.

66

67 **Nelson O. Gekara** (Umeå University, Sweden) reported the role of DNA binding proteins
68 in immune priming, genome stability and microbiota-host interactions. The Ataxia
69 Telangiectasia (AT) disease model is caused by the loss of function of the DNA repair
70 kinase ATM. This was used to identify the impact of genomic stress on innate immunity.
71 Already published data showed that AT patients exhibit a basal inflammation
72 characterized by an elevated IFN-I response and anti-viral activity that significantly
73 decreases viral replication. Consistent with these patient observations, ATM-deficient
74 mice display a primed-innate immune system that can protect against Vesicular Stomatitis
75 Virus (VSV) infection (3). However, ATM-KO mice are also more susceptible to LPS-
76 induced sepsis, with an increase of interferon- β (IFN-B) and a decrease in survival as
77 compared to WT mice (4). Thus, a hyperactive innate immune system primed by
78 mutations in ATM provides a protective boost against viruses but remains a pathological
79 condition resulting from neurological defects. Gekara also described the microbiota as a
80 major extrinsic signal of the innate immune system. The human body contains 100 trillion

81 microbes, mostly composed of commensal bacteria (5). In addition to maintaining
82 homeostasis and providing a competitive barrier to bacterial and fungal pathogens, the
83 commensal microbiota also controls viral infections. Oral administration of antibiotics
84 negatively impacts the microbiota and promotes systemic infection by HSV-1 in WT
85 C57BL/6 mice. (4, 5). Thus, commensal bacteria prime innate immunity *via* the cGAS-
86 STING pathway, protecting against viruses. Activation of innate DNA sensors have been
87 described to be restricted to the cytoplasm under stress conditions. Yet DNA sensors can
88 also chromatin bound nuclear proteins (6, 7). Indeed, innate DNA sensors have distinct
89 functions according to their localization. Gekara showed that the nuclear DNA sensors
90 cGAS and ALR potentiate anti-tumor effects of DNA damage-based chemotherapy and
91 radiotherapy. He demonstrated that cGAS or ALR deficient mice are more resistant to
92 bone marrow depletion upon irradiation. In humans, lower expression of cGAS and ALRs
93 correlates with poor survival following chemotherapy(7). Finally, Gekara suggested that
94 DNA sensors could be potential biomarkers or therapeutic targets for radio/chemotherapy
95 responses.

96
97 **Clara Taffoni** (IGH, France) discussed the role of the cGAS-STING pathways in tumor
98 responses. Tumor-derived DNA accesses the cytoplasm of innate immune cells, such as
99 dendritic cells (DCs), a key cell for anti-tumor responses. As DNA sensors, cGAS and
100 STING are expressed at low levels in cancers (8). Taffoni suggests the discovery of
101 alternatives to target inflammation in a cancer context. Interestingly, she clarified that
102 dsDNA-dependent IFN-I responses were not restricted to DNA sensors and showed the
103 cooperation between cGAS-STING and DNA-PK pathways in cancer. The activation of
104 DNA-PK complex (DNA-PKcs), allowed DNA repair by NHEJ, inhibits cGAS, and
105 activates IRF3 (9, 10), leading to the expression of IFN-I stimulated genes. Taffoni
106 confirmed that the addition of dsDNA in the glioblastoma cell line (T98G), which does not
107 express cGAS, increased phosphorylation of DNA-PK and IRF7 and expression of pro-
108 inflammatory cytokines (IFN- β and CXCL10). The addition of a DNA-PK inhibitor
109 (NU7441) in the presence of dsDNA in cGAS-deficient cells led to the downregulation of
110 phosphorylated IRF3 and decreased expression of cGAMP, IFN β , and CXCL10,
111 implicating DNA-PKcs in innate immune responses. However, no evidence is known for
112 a role of the DNA-PKcs in inducing inflammatory responses upon genotoxic stress.
113 Taffoni demonstrated that the addition of camptothecin, a topoisomerase inhibitor leading
114 to genotoxic stress, on the T98G glioblastoma cell line induces the same effects (i.e. the
115 upregulation of pIRF3, IFN β , STING and CXCL10) but the DNA-PK inhibitor reversed the
116 effects. Thus, DNA-PKcs induces IFN-I in cGAS-deficient cells and controls IRF3, STING
117 and cGAMP activation. Taffoni then focused on the role of cGAS in tumorigenesis. The
118 cGAS expressing-glioblastoma volume is significantly reduced across 90 days as
119 compared to non-expressing cGAS glioblastoma tumors. Also, macrophage type 1
120 markers (TNF α and CXCL11) increased, showing the cooperation between cGAS cancer-
121 cell expression and macrophage recruitment. Surprisingly, the high expression of PRKDC
122 (DNA-PK) and MB21D1 (cGAS) gene expression in a long-time course induces the
123 upregulation of macrophages markers (CD68 and ITGAM) and chemokine production

124 (CXCL10, CCL2, CCL5), leading to the reduction of survival rate
125 (<https://doi.org/10.1101/2022.06.08.495278>, submitted article). Thus, cGAS expression
126 exhibits anti-tumor functions early in tumorigenesis through anti-tumor macrophage
127 recruitment; however, DNA-PKcs and cGAS cooperation sustains inflammation and thus
128 promotes tumorigenesis in the long term.

129
130 Other cooperative immune cells present in the tumor microenvironment have a central
131 role in cancer-related inflammation and responses. **Jonathan C. Kagan** (Harvard
132 University, USA) highlighted the importance of DC hyperactivators in the activation of
133 anti-tumor immunity. In particular, the lipid 1-palmitoyl-2-glutaryl-sn-glycero-3-phosphocholine
134 (PGPC), an agonist of DC hyperactivation, drives higher DC migration to the lymph node
135 than other FDA-like adjuvants, such as LPS and Alum (11). Surprisingly, the combination
136 of LPS and PGPC increased the survival rate of B16OVA-injected mice with durable
137 protective immunity against cancer as compared to pyroptosis adjuvants (Aluminum or
138 LPS). Kagan also mentioned the first evidence of anti-tumor effect of DC inflammasomes
139 upon hyperactivation by an experiment with NLRP3-, Casp1/11- or CCR7-deficient mice,
140 showing no benefit of the hyperactivation adjuvant in the survival rate. Finally, he
141 concluded that immunizations with DC hyper activators are the most potent stimulators
142 of antigen specific CD8+ T cells. However, many defects in immunity occur in the elderly
143 population(12) and Kagan underlined the absence of their treatment on cancer therapies.
144 He showed that old mice lose their naïve CD8+ T cell repertoire and the absence of CD8+
145 T cells in young mice reduces their survival rate. Protective immunity against cancer rises
146 from CD4+ T cells in old mice whereas CD8+ T cells are responsible for anti-tumor
147 immunity in young mice. Remarkably, DC hyperactivation rearranges the CD4+ T cell
148 repertoire in the tumor microenvironment of old mice and generates memory T cells that
149 last into old age, demonstrating that DC hyper activators like LPS in combination with
150 PGPC induce protective immunity through memory T cells. In conclusion, DC
151 inflammasomes induce durable and protective CD4+ and CD8+ T cell responses and DC
152 hyper activators can correct age-associated defects in anti-tumor immunity.

153
154 The role of NK cells in tumors was discussed by **Nathalie Bendriss-Vermare** (CRCL).
155 She reminded the audience about the role of NK functions in immune surveillance at early
156 cancer stages and how cancer cells escape NK cell surveillance during tumorigenesis.
157 Bendriss-Vermare illustrated the importance of the DC/NK cross-talk. Precisely, TLR-
158 activated DC secrete IL-12 that engages STAT4 signaling in human CD56^{dim} NK cells,
159 driving the ST2 expression. The addition of anti-IL-12 antibody prevents the emergence
160 of ST2+ NK cell subpopulation. Furthermore, ST2⁺CD56^{dim} NK cells were shown to
161 display a unique transcriptional signature compared to conventional CD56^{bright} and
162 CD56^{dim} NK cells. Interestingly, IL-33 synergizes with IL-12 to trigger polyfunctionality
163 (cytokine production, proliferation, and cytotoxicity) of human ST2⁺CD56^{dim} NK cells.
164 Interestingly, ST2⁺ NK cells are also found in human tumors and respond to IL-33 and IL-
165 12 stimulation by producing IFN- γ . Using the mouse mammary E0771 tumor model,
166 Bendriss-Vermare demonstrated the NK-dependent anti-tumor effect and systemic IFN-

167 g production induced by IL-33 and IL-12 peritumor administration. Thus, IL-33 drives the
168 polyfunctionality of a unique ST2⁺ NK cell state with anti-tumor activities, infiltrating
169 tumors, and inducing tumor rejection. Finally, a strong NK/IL33/IFN γ signature is
170 associated with improved patient survival in breast cancer (Eberhardt et al., submitted).
171 Bendriss-Vermare and her team aim to i) identify the DC subset involved in ST2⁺ NK cell
172 emergence, ii) evaluate the potential of IL-33 to induce memory-like NK cells for adoptive
173 cell transfer approaches, and iii) demonstrate the role of the NK/IL-33/DC axis in tumor
174 control in therapeutic settings as well as in immune surveillance.

175

176 Post-translational modifications, such as linear ubiquitination by OTULIN (OTU
177 deubiquitinase with linear ubiquitin chains cleaving activity), and their implication on
178 chronic inflammation and diseases were described by **Geert Van Loo** (Ghent University,
179 Belgium). He reported the regulation of LUBAC (linear Ub chain assembly complex) -
180 mediated inflammatory signaling by OTULIN using a mouse model (OTULIN-AlfpCre) of
181 ORAS (Otulin-related autoinflammatory syndrome). The LUBAC complex is active in
182 inflammatory signaling and cell death and regulated by the cytotoxic TNF, which promotes
183 apoptosis or necroptosis (13). Hepatocyte-specific OTULIN-deficient mice develop liver
184 cancer and hepatitis, dependent on FADD and RIPK. Indeed, the absence of OTULIN
185 increases AST, ALT and ALP levels, inducing a liver pathology, whereas genetic ablation
186 of FADD and RIPK reverses this phenotype. Thus, OTULIN prevents liver inflammation
187 and hepatocellular carcinoma by inhibiting FADD and RIPK1 kinase mediated hepatocyte
188 apoptosis (14). These observations are also demonstrated in skin inflammation and
189 lesions when OTULIN expression is removed specifically from skin. Interestingly, OTULIN
190 deficient mouse skin shows enhanced keratinocyte cell death that drives inflammation
191 and skin lesions. The deletion of *FADD* and *MLKL* genes in keratinocytes rescues the
192 observed defects (15). Thus, OTULIN maintains skin homeostasis by inhibiting RIPK1
193 kinase-mediated keratinocyte death. In an unpublished study, Van Loo showed that
194 OTULIN controls intestinal homeostasis by preventing intestinal epithelial cell apoptosis.
195 In conclusion, OTULIN controls LUBAC-mediated inflammatory signaling pathways, such
196 as TNF, and plays a critical role in inhibiting cells from death and preventing chronic tissue
197 inflammation and cancer.

198

199 **Immunometabolism**

200

201 Several speakers discussed the importance of metabolism in controlling immune
202 responses and tumor proliferation. Immune and tumor cells are both highly activated and
203 characterized by high energy and nutrient demands. To sustain their proliferation and
204 functions, these cells engage in anaerobic glycolysis, which is characterized by high
205 glycolysis whereby the pyruvate produced from glucose is converted to lactate instead of
206 being funneled into the mitochondria (Warburg effect) (16). Even though anaerobic
207 glycolysis has been described as a hallmark of tumor cells, **Ping-Chih Ho** (University of
208 Lausanne, Switzerland) opened this session by reminding the audience that cancer cells

209 utilize a broad range of metabolic programs, at least *in vitro* (17), suggesting that
210 uncharacterized mechanisms force tumor cells into anaerobic glycolysis. He postulated
211 that this driving force is the selection pressure exerted by the immune cells on the
212 developing tumor, a process called immunoediting (18). To test the importance of
213 immunoediting on tumor cell metabolism, Ping-Chih Ho and his team used melanoma
214 cells coming from either WT mice (edited tumor cells) or Rag KO mice (non-edited tumor
215 cells). Using both Seahorse and metabolomic analysis, they showed that non-edited
216 tumor cells relied more on oxidative metabolism than their edited counterpart while
217 producing the same amount of ATP. Furthermore, using T cell depleting antibodies at
218 different time points, they showed that this phenotype is observed only if the T cells are
219 present at early time points (between 2 and 5 weeks after tumor injection). This study
220 highlights the importance of immunoediting in governing the tumor metabolic switch to
221 aerobic glycolysis, which allows tumor cells to support cell division while promoting an
222 immunosuppressive environment through glucose depletion within the tumor
223 microenvironment. The suspected mechanism relies on IFN γ production by T cells, which
224 drives STAT3-cMyc activation and promotes metabolic reprogramming in tumor cells.

225

226 Upon activation, immune cells also experience metabolic reprogramming to meet their
227 energy needs. Signaling hubs allow the cell to integrate multiple signals such as nutrient
228 availability or immune signals to dictate a cell fate that matches the environmental
229 stimulus. The mTOR pathway, which was first described to regulate cell growth and
230 metabolism, is among the essential signaling pathways for metabolic reprogramming (19)
231 . However, a large body of recent evidence shows that mTOR signaling is also
232 fundamental in cell fate decisions. Indeed, several reports show the importance of mTOR
233 in lymphocyte development and function (review in (20)), yet the mechanisms are still
234 poorly characterized. Local speaker **Antoine Marçais** (CIRI) presented data on mTOR
235 regulation in NK cells by cytokines. He showed that mTOR is activated synergistically by
236 both IL-15 and IL-18, two cytokines used to generate activated NK cells for
237 immunotherapy (21, 22). The combination of IL-15 and IL-18 treatment increased NK cell
238 proliferation and metabolism in an mTOR-dependent manner. Deciphering the pathway
239 involved, he demonstrated that these cytokines activate mTOR through non-canonical
240 pathways, relying on PI3K-AKT and ERK for IL-15 and p38 MAPK for IL-18. **Leonid**
241 **Pobezinsky** (University of Massachusetts, USA) presented another unconventional
242 mechanism of mTOR regulation in T cells. He showed that inhibition of miRNA let-7 in
243 CD8 $^+$ T cells promotes a T cell exhausted signature characterized, among others, by an
244 increase in PD-1 expression and poor tumor growth control. On the contrary, an increase
245 in let-7 expression leads to a memory signature with decreased PD-1 expression and
246 better control of tumor growth. Comparative transcriptomic analysis of these mutants
247 revealed dysregulation of the mTOR pathway, echoing several reports suggesting a role
248 of miRNA in mTOR regulation (23–25) . He provided evidence that let-7 inhibits the mTOR
249 pathway, which in turn controls ROS production, an essential factor in terminal effector T
250 cell differentiation (18, 26). Treatment of Let-7 deficient cells with rapamycin, an inhibitor
251 of mTOR, or a ROS inhibitor rescued the T cell memory phenotype. These two studies

252 highlight the importance of multiple layers of regulation to control mTOR pathway activity,
253 a key determinant of both NK and T cell fate decisions.

254

255 Key pathways like the mTOR pathway are also largely controlled by nutrients and
256 metabolites in the environment. **Helene Poinot** (Institute of Pharmaceutical Sciences of
257 Western Switzerland) presented a study on the role of endogenous glucocorticoids in
258 renal cancer. Glucocorticoids are molecules known for their anti-inflammatory properties
259 and their role in glucose metabolism. Data from The Cancer Genome Atlas reveals that
260 glucocorticoid pathway enzyme expression correlates with the clinical outcome in renal
261 cancer patients. More precisely, HSD11B1 (11 β -Hydroxysteroid dehydrogenase type 1)
262 expression, an enzyme that reduces cortisone into its active hormone cortisol, was
263 associated with poor clinical outcome and an immune repression signature. In patients,
264 HSD11B1 is expressed by macrophages in the tumor microenvironment. Using both
265 murine models and human samples, she showed that HSD11B1 decreases antigen-
266 specific T cell activation, inhibiting the immune control of the tumor. Inhibition of HSD11B1
267 in myeloid immune cells restores the immune activation.

268

269 The speakers agreed on the importance of immunometabolic studies for immunotherapy
270 design. Indeed, a better understanding of immune cell metabolism will improve cell culture
271 and activation techniques for adoptive cell therapy. This line of research can also be used
272 to enhance immunotherapy efficiency. In this regard, Helene Poinot concluded with data
273 revealing that HSD11B1 inhibitors increase the efficacy of anti-PD-1 and TLR agonist
274 treatments in a renal tumor model, supporting the idea of combined treatments in
275 immunotherapy.

276

277

278 Immunotherapy in the clinic

279 Immunotherapies have revolutionized cancer care and treatment of infections by
280 reactivating neutralized immune responses (27, 28). In cancer, anti-PD1/PD-L1 and anti-
281 CTLA-4 antibodies (Ab), which are known as Immune Checkpoint Blockade (ICB)
282 therapies, have completely changed the prognosis of several malignancies, such as
283 melanoma, and are now used as first line treatments (27–29). Yet we still do not
284 completely understand the function of ICB therapies on the immune response.

285 **Ido Amit** (Weizmann Institute of Science) discussed how the complexity of the immune
286 system has prevented a full understanding of ICB mechanisms of action. For example,
287 the cell types that are targeted by ICB therapies remain unknown. **John Wherry**
288 (Perelman School of Medicine, University of Pennsylvania) gave a talk on CD8 T cell
289 exhaustion and addressed some of these questions. He demonstrated that exhausted
290 CD8⁺ T cells (T_{EX}), which are supposedly anergic cells, can respond quickly to anti-PD1
291 antibody. T_{EX} are composed of four intermediate states: T_{EX}^{prog1} , T_{EX}^{prog2} , T_{EX}^{int} , T_{EX}^{term}
292 (30). In mice infected with Lymphocytic Choriomeningitis virus (LCMV), T_{EX}^{prog1} and

293 T_{EX}^{prog2} respond to the anti-PD1 treatment. However, prolonged treatment leads to
294 terminally exhausted cells (T_{EX}^{term}) and defective clearance of virus. Interestingly,
295 intermittent treatment avoided this pitfall, resulting in better immune responses to LCMV.
296 Therefore, he concluded by stating that one should be cautious about the
297 pharmacodynamic of anti-PD1 treatment on T_{EX} because the current prolonged anti-PD1
298 treatment might be suboptimal and induce terminal exhaustion of T cells.

299 In the context of cancer, **Ido Amit** argued for another anti-PD1 target cell population.
300 Using PIC-seq technology (RNAseq of Physically Interacting Cells) on human non-small
301 cell lung carcinoma samples, a tumor specific CD4⁺ T helper cell population was identified
302 in the tumor microenvironment (TME). These Tht (T-helper tumor) cells are primed in
303 tumor-draining lymph nodes and are required for harnessing antitumor response following
304 aPD-1 treatment (31). **Lucas Blanchard** (Institut de Pharmacologie et Biologie
305 Structurale) discussed the role of tumor-associated high endothelial venules (TA-HEVs)
306 in response to anti-PD-1/anti-CTLA-4 combination therapy. TA-HEVs were identified as
307 major sites of lymphocyte entry into tumors both at baseline and during treatment with
308 combined anti-PD-1/anti-CTLA-4 combination therapy (32). Following the combination
309 therapy, HEVs are increased in the tumor bed, suggesting a crosstalk between T cells
310 and TA-HECs. Therapeutically modulating TA-HEVs with an agonist of Lymphotoxin β
311 Receptor ameliorates the efficacy of combined ICB. TA-HEVs were identified as
312 predictors of response and survival of melanoma patients treated with combined ICB.
313 **Mariana Diniz** (Division of Infection and Immunity, University College London, UK)
314 showed that NK cells limit T cell responses to therapeutic vaccination in mouse models
315 of persistent Hepatitis B virus (HBV) infection. She identified a population of liver resident
316 NK cells with high PD-L1 surface expression that inhibit therapeutic vaccine-induced
317 virus-specific CD8 T cells. Blocking PD-L1 on cytokine-activated NK cells allows them to
318 help virus-specific T cells to control HBV infection (33).

319 Besides ICB, other immunotherapies are emerging and hold great promise. One exciting
320 area of cancer research seeks to identify immunogenic tumor neoantigens that can be
321 used to prime lymphocytes and induce an adaptive immune response. Local selected
322 speaker **Stephane Depil** (CRCL), founder of the ErVaccine Technologies, characterized
323 Human Endogenous Retroviruses (HERV)-derived epitopes that induce adaptive immune
324 responses and used them as therapeutic strategies
325 (<https://www.ervaccinetechnologies.com/>). Using *in silico* studies to explore the TCGA
326 Database, ErVaccine Technologies found HERV epitopes that are shared between
327 different solid tumors and Acute Myeloid Leukemia (AML). These HERV epitopes are
328 immunogenic and induce polyfunctional CD8⁺ T cells that can kill tumor cells (34). HERV
329 specific CD8⁺ T cells can be found in samples from Triple Negative Breast Cancer
330 (TNBC), ovarian cancer, and AML. Thus, HERV epitopes are alternative tumor-specific
331 antigens, which are shared between patients with the same disease, and these epitopes
332 are therapeutic targets for off-the-shelf cancer vaccines and T-cell based therapies,
333 especially for tumors with a low/moderate tumor mutational burden (TMB), which
334 ErVaccine Technologies is trying to develop.

335 The potential of adoptive transfer of gamma-delta ($\gamma\delta$) T cells to treat both cancer and
336 cytomegalovirus (CMV) infection was discussed by **Julie Dechanet-Merville**
337 (ImmunoConcEpT, Bordeaux University). She showed that $\gamma\delta$ T cells can recognize
338 common stress-induced self-antigens on tumor and CMV-infected cells. She presented
339 unpublished results demonstrating that HLA-I heavy chains free of β 2-microglobulin
340 (B2M) or peptides known as "open conformers" can be targeted by $\gamma\delta$ T cells. Open
341 conformers are upregulated during CMV infection, and she hypothesizes that $\gamma\delta$ T cells
342 recognize them as stress signals. Encouraging preliminary data suggest that *in vitro*
343 amplified V δ 2^{neg} $\gamma\delta$ T cells may be used as adoptive cell therapy to fight CMV infection
344 and glioblastoma. **Mansun Law** (The Scripps Research Institute) is studying the
345 neutralizing face (NF) of a conserved antigenic surface on the E2 envelope glycoprotein
346 of the hepatitis C virus (HCV). E2 NF is frequently targeted by broad neutralizing Abs
347 utilizing the human antibody heavy chain variable gene IGHV1-69 in HCV patients (35).
348 Structural data of E2:VH1-69 bnAbs complexes presented by Mansun Law demonstrate
349 that it is an excellent opportunity for HCV rational vaccine design and testing.

350 Effective immunotherapies are saving the lives of many patients. As we have seen during
351 this session of IRCI 2022, immunologists are currently developing a better understanding
352 of their mechanisms of action, especially at the cellular level. However, we still cannot
353 predict the patients who will respond to the treatment. Single-cell (sc) genomics and
354 transcriptomics will likely characterize how molecules and clinical targets interact in a
355 complex immune response. During Ido Amit's talk, he presented novel technologies such
356 as spatial transcriptomics, PIC-seq, MARS-seq and Ins-seq, which allowed him to localize
357 transcriptomic data, identify interactions between cells, and study the intracellular protein
358 activity of cells. Their use in studies on infection, autoimmunity, and cancer have already
359 accelerated our understanding of the immune system and even resulted in clinical trials
360 (36) Ido Amit concluded that in the future, we will be able to create a detailed blueprint of
361 immunity in disease by combining population-scale sc genomics with patient records and
362 artificial intelligence.

363 Microbiota

364 The alliance between the immune system and the microbiota plays a fundamental role in
365 the maintenance of a symbiotic functional relationship of the host with commensal
366 microbes. More importantly, the microbiota composition and density can modulate
367 immune and inflammatory responses locally and at distal sites in physiological and
368 pathological conditions. This session of the IRCI2022 highlighted the latest findings on
369 the role of the microbiota in anti-tumor immunity, immunotherapy responses, cancer
370 development, and metabolic disorders.

371

372 **Thomas Gajewski** (University of Chicago Medicine, USA) opened the session by
373 investigating the factors that influence the immune infiltration of the tumor
374 microenvironment (TME) as sources of inter-patient heterogeneity. His previous work
375 showed that the activity of anti-PD-1 in multiple cancers is associated with T cell-inflamed
376 TME signature at baseline(37). These factors include tumor cell-intrinsic oncogenic
377 events, such as the Wnt/ β -catenin pathway that failed to recruit Batf3-lineage dendritic
378 cells into the tumor site when activated, the composition of the gut microbiota, and
379 polymorphisms in immune regulatory genes. Regarding the commensal microbiota,
380 previous analyses in metastatic melanoma patients revealed that the gut microbiome
381 composition is associated with anti-PD-1 efficacy (38). The establishment of stable
382 colonies of germfree mice (GFM) reconstituted with responder or non-responder
383 microbiota has confirmed a causal role for the gut microbiota in regulating immunotherapy
384 efficacy. Moreover, scRNAseq analysis of the TME of GFM reconstituted with non-
385 responder microbiota showed a shift to M2 macrophages and Granulocyte-like Myeloid
386 Derived Suppressor Cells (G-MDSCs), and a low M1/M2 gene signature ratio is
387 associated with lack of anti-PD-1 efficiency in melanoma patients (*unpublished data*).
388 Regarding germline variants, loss of function variants of the PKC δ gene were associated
389 with greater immune gene signature score, and an improved tumor control was observed
390 in mice engineered with PKC δ -KO bone marrow. Finally, scRNAseq of tumor-infiltrating
391 immune cells revealed a shift from M2 to M1 macrophage phenotype in PKC δ -KO mice
392 (*unpublished data*).

393
394 A post-doctoral fellow in the lab of Pr Bertrand Routy, **Meriem Messaoudene** (M.M.,
395 University of Montreal, Canada), first mentioned that the gut microbiome is now part of
396 the “hallmarks of cancer” and represents a novel biomarker of response to
397 immunotherapies. Hence, antibiotherapy (ATB) can blunt the efficacy of anti-PD-1 and
398 strategies to overcome ATB-related dysbiosis are needed. M.M. showed the positive
399 preclinical results in immuno-oncology associated with the clinical trial DAV132-CL-1006
400 (*NCT03710694*), that is based on the use of a charcoal adsorbent-based product
401 (DAV132, DaVolterra $\text{\textcircled{O}}$) that sequesters ATB and prevents microbiota destruction. The
402 results showed that the gut microbiome of healthy human volunteers treated with
403 DAV132+ATB (ceftazidime-avibactam) restores the anti-tumor response to anti-PD-1
404 when transferred to tumor-bearing GFM, compared to ATB treatment alone. Then M.M.
405 presented his recent work published last April in *Cancer Discovery* (39) wherein they
406 identified the anti-tumor activity of the natural polyphenol castalagin, which promoted CD8
407 T cell infiltration within the TME in mice, as well as its prebiotic potential to circumvent
408 anti-PD-1 resistance in GFM reconstituted with non-responder microbiota.

409

410 **Jonathan Schertzer** (J.S., McMaster University, Canada) aimed to understand the
411 connection between how blood glucose may interact with host-microbe symbiosis in the
412 context of metabolic diseases. The blood glucose level is part of the emerging risk factors
413 of death in several pathological contexts, such as cancer and vascular diseases, and is
414 regulated by postbiotics such as lipopolysaccharide (LPS). Interestingly, his lab
415 discovered that metabolic endotoxemia (low-level LPS increase in the blood during
416 metabolic disease) may be beneficial or detrimental depending on the acylation status of
417 lipid A in LPS that dictated changes in blood glucose control in obese mice (40). Under-
418 acylated LPS can antagonize other LPS forms, setting up the potential use of different
419 types of LPS as postbiotics to mitigate metabolic inflammation. Independent of obesity,
420 J.S. showed that hyperglycaemia is necessary and sufficient to promote death from
421 enteric infection by *Citrobacter rodentium* in mice. Mechanistically, hyperglycemia
422 increased activation of the Wnt/ β -catenin in the distal gut leading to diarrhea death, and
423 treatment with Wnt pathway inhibitor improved survival during enteric infection.

424
425 **Giorgio Trinchieri** (Center of Cancer Research, NCI, NIH, USA) gave an overview
426 of the different studies that identified bacterial species correlating with a favorable clinical
427 response to anti-PD-1. Data from 5 different US melanoma cohorts, batch correction, and
428 meta-analysis allowed G.T. to reveal shared taxonomic patterns associated with
429 favorable and unfavorable response to anti-PD-1(41). Machine learning approaches
430 trained on the same melanoma patients' microbiota composition can predict the ability of
431 patients to respond to anti-PD-1 with some accuracy. Regarding underlying mechanisms,
432 a high Neutrophil to Lymphocyte Ratio (NLR) was associated with poor survival after anti-
433 PD-1 and with a fecal microbiota enriched for detrimental taxa, largely Gram negative.
434 Interestingly, the host (human) fecal transcriptome showed in progressor patients a pro-
435 inflammatory gene signature from shed myeloid cells (dendritic cells, macrophages,
436 neutrophils) in part dependent on LPS, NF κ B activation, myeloid cell attracting
437 chemokines (CCL2, CCL4, CXCL8) and ROS production (41). Giorgio ended his
438 presentation by showing results of clinical proof of concept studies in anti-PD-1-treated
439 melanoma patients demonstrating that fecal microbiota transplant DOI:
440 10.1126/science.abf3363 (42) (*NCT03341143*) or diet alteration (43) may be utilized clinically
441 to improve cancer immunotherapy's success rate.

442

443 **Lars Vereecke** (L.V., VIB Center for Inflammation Research, Ghent, Belgium) was the
444 last short-talk of the microbiota session and discussed the role of host-microbiota
445 interactions during colorectal cancer (CRC) development. Using an original murine model
446 of spontaneous microbiota-dependent invasive CRC (Zeb2^{IEC-Tg/+} mice, PMID 35121975),
447 L.V. lab identified the adherent-invasive *Escherichia coli* pathobiont bacteria (pks+ *E. coli*
448 CCR20 strain, a human CRC isolate) accelerates CRC disease development, and that
449 loss of the bacterial type 1 pilus adhesins FimH and FmlH prevented such aggravation.
450 Interestingly, in monocolonized Zeb2^{IEC-Tg/+} mice, or in a minimal microbiota setting,
451 CCR20 did not promote CRC progression, suggesting that CCR20 requires a complex
452 bacterial ecosystem and adhesion-mediated tissue binding to promote CRC progression.
453 The genotoxic effect of CCR20 was highlighted by an increase of DNA damage
454 responses (γH2AX positive cells within crypts) in Zeb2^{IEC-Tg/+} mice. Finally, L.V. identified
455 that goblet cell deficient mice develop spontaneous CRC, suggesting a major role of this
456 population in CRC carcinogenesis.

457

458

459 Genetics and Epigenetics

460

461 The Genetics/Epigenetics session showcased speakers presenting data on the COVID-
462 19 pandemic, especially exploring the genetics of individual susceptibility, which is a
463 major risk factor.

464 Data suggests that the SARS-CoV2 pandemic originated from *Rhinolophus* bats in China
465 (44) however, bats do not show pathogenic symptoms from infection. Locally selected
466 speaker **Lucie Etienne** (CIRI) presented studies on the evolutionary history of SARS-
467 CoV-2 protein molecular interactome in bats and primates containing a human genetic
468 history. Identifying common molecular features and differences of the SARS-CoV-2
469 interactome between bats and primates might explain the pathogenicity in humans. Using
470 the Detection of Genetic INNovation (DGINN) pipeline, which infers the speed of evolution
471 of a given gene, the evolution of 334 SARS-CoV-2 interacting proteins was studied.
472 Twenty proteins were identified as being positively selected during evolution specifically
473 in bats, 64 specifically in primates, and 17 in both organisms. Three genes captured the
474 attention of Lucie Etienne. Tmprss2, which is required for the fusion of the viral particle
475 to the cell, evolved quickly in primates but not in bats, suggesting marks of ancient CoV
476 epidemics and lesser involvement of Tmprss2 in bats. Fyco1 (FYVE and coiled-coil
477 domain Autophagy Adaptor protein 1) is a protein involved in vesicle formation and
478 autophagy. It evolved under positive selection in primates, but not in bats. Fyco1
479 polymorphism is associated with severe COVID-19 (45) and may be involved in viral
480 egress and/or in inflammation/pathogenesis. Finally, Ripk1 has been under positive
481 selection in bats but not in humans. This protein is essential for inflammation and cell
482 death/survival. Ripk1 is activated by TNF receptor engagement and can switch between
483 activating the NFκB pathway or trigger apoptosis (46). Therefore, it can regulate pro-
484 survival or death activities in bats but also induce tolerance to viruses and inflammation.

485 The positive selection of these genes could represent important evolutionary virus-host
486 determinants of symbiosis. Lucie concluded her talk presenting clues that explain the
487 resistance and/or susceptibility of severe COVID-19 illness. A higher virus tolerance and
488 less inflammation in combination with host specific determinants (such as RIPK1) could
489 be the key to understanding variable immune responses in COVID-19.

490 **Esteban Ballestar** (Josep Carreras Institute) and **Anne Puel** (Imagine, Laboratory of
491 Human Genetics of Infectious Diseases) linked inborn errors of immune related genes to
492 increased susceptibility to severe forms of COVID-19. Esteban Ballestar presented data
493 on patients with common variable immunodeficiency (CVID), the most frequent
494 symptomatic Primary Antibody Deficiency that is characterized by severe deficiency of
495 switched memory B cells (47). CVID are mostly sporadic, and patients develop recurrent
496 and chronic respiratory infections. Because CVID patients do not mobilize neutralizing
497 immune responses to SARS-CoV2 vaccines, Ballestar examined the consequences of
498 COVID-19 in CVID patients. Droplet-based single cell RNA sequencing analysis was
499 performed on CVID patients and healthy donors before, during and after the SARS-CoV2
500 infection. Impaired IFN- γ and TNF- α production in both T cell and NK cell subsets and
501 impaired activation of BCR-associated NF- κ B pathway in naïve B cells was observed in
502 CVID patients as compared to healthy donors. Additionally, an enrichment in type I
503 interferon (IFN-I) responses of the monocyte compartment, which is similarly found in
504 severe COVID-19 cases, and persistent hyperactivation of several inflammasome
505 complexes was also observed during convalescence in CVID patients as compared to
506 healthy patients. Future studies will validate and explore the epigenetic dysregulation for
507 the hyperactivation of the inflammasome in SARS-CoV2 patients.

508 As a member of the international consortium « Covid Human genetic effort », Anne Puel
509 aims to discover the human genetic and immunological basis of the various clinical forms
510 of SARS-CoV-2 infection. Indeed, severe COVID-19 is associated with epidemiologic
511 factors (48). Analysis of large cohorts of severe and benign COVID-19 patients revealed
512 that about 3.5% of them carry inborn errors in IFN-I response pathway, which are known
513 mechanisms of susceptibility to severe viral infections (34). Autoantibodies neutralizing
514 specific cytokines, such as IFN- $\alpha/\beta/\omega/\gamma$, IL-6 or IL-17A/F, induce Autoimmune
515 Phenocopies of Inborn Errors of Immunity (49). Exploring the potential role of
516 Autoimmune Phenocopies of Inborn Errors of Immunity in susceptibility to severe COVID-
517 19, Anne found that 10% of severe COVID-19 patients display higher titers of IFN-I
518 neutralizing auto-antibodies that block the viral protective effect of IFN- α (Bastard P et al.
519 Science 2020). Moreover, neutralizing auto-antibodies against IFN- $\alpha/\beta/\omega$ were found in
520 approximately 15-20% of patients with critical pneumonia following SARS-CoV2
521 infection(50). Interestingly, anti-IFN-I autoantibodies sharply increase in patients older
522 than 70 and are highly present in patients with genetic variants that impair thymic
523 development or thymic T cell selection, such as IPEX (*FoxP3* mutation) or APS-1 (*AIRE*
524 mutation) (51). Therefore, severe COVID-19 appears to be tightly linked with defective
525 thymus T cell selection. Additionally, 80% of patients with NF- κ B2 variants presented
526 neutralizing anti-IFN-I autoantibodies and approximately 40% of these patients suffered

527 from various viral diseases. Five patients with NF- κ B2 mutations were reported to suffer
528 from severe or critical COVID-19 disease.

529 In addition to the COVID-19 studies, the role of epigenetics in the control of immune cells
530 and pathologies was assessed. Esteban Ballestar presented interesting data on a pair of
531 identical twins, one healthy and the other one presenting CVID. They had no identified
532 pathogenic gene variants. Interestingly, defective demethylation occurred during the
533 naïve-to-memory B-cell transition in CVID, which disrupted B cell function and germinal
534 center reactions, leading to clinical symptoms. Indeed, the dynamics of DNA
535 methylation/demethylation controls the differentiation of B cells, particularly the transition
536 from naïve to memory B cells (52). Ballestar demonstrated that CVID patients show
537 impaired DNA demethylation during the naïve to memory B cell transition and present
538 hypermethylation in B cells as compared to healthy subjects (53). Consequently, CVID
539 patients display a highly heterogeneous memory B cell compartment. Using whole exome
540 sequencing, **Laurent Genestier** (CIRI) and his team identified a recurrent *Jarid2*
541 depletion in NKT cells in 6 patients with PTCL (Peripheral T Cell Lymphoma). Conditional
542 deletion of *Jarid2* in mouse T cells (*CD4cre⁺Jarid2^{fl/fl}p53^{-/-}* mice) expanded peripheral NKT
543 cells and rearrangement of the epigenome. Interestingly, the conditional deletion of *Jarid2*
544 in mouse T cells increased incidences of T and NKT cell lymphomas, suggesting that
545 *Jarid2* is a tumor suppressor gene for T and NKT cells. *Jarid2* induced hypermethylation
546 of DNA and closed conformation of the chromatin to control specific-related genes such
547 as IGF2BP genes.

548 **Julien Marie** (CRCL) presented the role of TGF β in TH17 cell program maintenance with
549 consequences on the development of inflammation-induced cancer. This work revealed
550 that TGF β , known to play a key role in the differentiation of TH0 cells to TH17 cells, also
551 functions in differentiated TH17 cells. Using mouse models with loss and gain of TGF β
552 mutations selectively in TH17 cells, this work demonstrated that differentiated TH17 cells
553 need continuous TGF β signaling to sustain their TH17 program. TGF β in the gut
554 conditions TH17 cells at an epigenetic level and in a reversible manner. Subsequently, in
555 the absence of TGF β provided by the gut, TH17 cells lose their TH17 program to become
556 pathogenic cells and promote spontaneous intestinal adenocarcinoma development.

557

558

559 Infections and Immune Responses

560

561 The regulatory importance of CD8⁺ T cells in fighting infection was highlighted by
562 both **Lion Uhl** (University of Oxford), who presented how paracrine signaling of interferon-
563 gamma (IFN- γ) mediates T-T cell interaction upon infection, and **Carlson Tsui** (University
564 of Melbourne), who presented unpublished data on the role of c-Myb in regulating CD8⁺
565 T cell exhaustion in chronic LCMV infection.

566

567 The original conception of this meeting in 2020 was for the speakers of this session
568 to highlight the crosstalk between viruses and cancer immunology. However, the
569 conversation quickly turned to a discussion of the SARS-CoV-2 pandemic. Even as the
570 global campaign to contain the SARS-CoV-2 outbreak focused on antibody mediated
571 vaccine technology, a theme of this session highlighted the often-overlooked T cell
572 response to COVID-19. Departing from her work investigating the role of Hepatitis B virus
573 and hepatocarcinoma, **Mala Maini** (University College London) described how she
574 pivoted her research into pandemic response as one of the lead investigators in a
575 longitudinal study of London healthcare workers (HCW), who underwent weekly SARS-
576 CoV-2 PCR testing, serum collection for antibody titration, and health questionnaires for
577 self-reported COVID symptoms during the lockdown prior to vaccine distribution. Maini
578 and colleagues were particularly interested in seronegative individuals testing negative
579 via PCR, postulating that these individuals had been exposed to the virus but were
580 clearing the infection sub clinically by memory T cell responses to cognate antigen. T cells
581 from seronegative HCWs exhibited strong memory T cell response to replication-
582 transcription complex (RTC) compared to infected cohort peers, who mounted a reduced
583 memory T cell response that was comparable to control PBMCs collected prior to the start
584 of the COVID19 pandemic (54). Furthermore, these RTC-specific T cells coincided with
585 an upregulation of the blood biomarker *IFI27*, an early identifier of SARS-CoV-2. These
586 results indicate the presence of an “abortive infection” in seronegative HCW, suggesting
587 this cohort of T cells were primed by prior infection by other coronaviruses. Dr. Maini
588 emphasized the benefit of expanding cross-reactive T cells targeting the highly conserved early
589 expressed RTC proteins and suggested that a mucosal vaccination strategy expanding RTC-
590 specific T Cells could be a useful therapeutic in anticipating future coronavirus outbreaks.

591
592 In the context of T cell biology, the answer to how the immune system fine tunes
593 the effector response to non-self-threats may lie in $\gamma\delta$ T cells, or tissue resident
594 lymphocytes that recognize and present single antigen in an MHC-independent manner.
595 These $\gamma\delta$ T cells play a crucial role in maintaining tissue homeostasis through novel
596 mechanisms of immunosurveillance. One of the pioneers in the field of $\gamma\delta$ T cell biology,
597 who founded Gamma Delta Therapeutics, and who recently introduced a novel concept of
598 "normality sensing", **Adrian Hayday** (King's College London, Francis Crick Institute)
599 presented his study of the mouse epidermis, where $V\gamma 5V\delta 1+$ dendritic epidermal T cell
600 (DETC) sensory activity was dependent upon the expression of PD-L1-like protein Skint1
601 by keratinocytes in steady state (55). Additionally, Adrian underscored how the capacity of
602 tissue-resident $\gamma\delta$ T cells to distinguish normality from pathology extends beyond the mouse
603 model and into human clinical relevance where tissue resident $\gamma\delta$ T cells occupy an anti-
604 tumoral niche within the tumor microenvironment, with promising prognosis in both breast
605 and lung cancer. His group found an enrichment of $V\delta 1$ T cells in human breast
606 epithelium, which contain an increased signature for anti-tumoral cytokines like IFN- γ ,

607 (56), and non-small cell lung cancers (NSCLCs), which is notably resistant to immune
608 checkpoint inhibitors (57). In each case there was a clear and significant association with
609 positive clinical outcomes. Adrian emphasized how $\gamma\delta$ T cells' innate-like, non-MHC restricted
610 effector functions, including cytotoxicity, offer the opportunity (now being realized) of using them
611 as allogeneic therapies derived from healthy donors, as opposed to autologous grafts of $\alpha\beta$ T cells
612 from patients themselves. Furthermore, Adrian placed the importance of $\gamma\delta$ T cell biology in
613 the context of the COVID-19 infection wherein a longitudinal COVID immunophenotyping
614 study of seropositive patients found an increase in adaptive V δ 1 T cell responses that
615 positively correlated with viral titer. This finding accompanies an overall loss of T cell
616 function (particularly amongst IFN-I and IFN-II producing subsets), alongside a marked
617 increase in IFN γ -induced protein 10 kDa (IP-10), a chemokine induced upon viral
618 infection, in COVID-19 seropositive patients as compared to healthy donors(58). These
619 phenotypes in COVID-19 patients not only offer key insights into the innate-T cell
620 crosstalk, emphasizing the importance of $\gamma\delta$ T cells that function as intermediates
621 between the two systems, but also introduce a clinical diagnostic tool for estimating the
622 severity of COVID-19 disease.

623 Interestingly, a key factor in the diagnosis and prevention of severe COVID-19
624 disease burden is the IFN-I response. Local speaker **Sophie Trouillet-Assant** (CIRI)
625 highlighted that reduced IFN-I was found in 20% of patients hospitalized with severe
626 COVID-19 clinical presentation. She postulated that the IFN-I response in the nasal
627 mucosa may predict clinical outcomes of infection. Using Nanostring RNA-seq technology
628 from blood samples in parallel with FilmArray nested-PCR on nasal swabs from patients
629 tested for SARS-CoV2, her group found a positive correlation between IFN-I signature
630 and nasal viral load (59). Emphasizing the data presented earlier in the meeting by Anne
631 Puel, her group observed neutralizing autoantibodies against IFN-I in both blood and
632 nasopharyngeal mucosa (51), suggesting autoantibodies against both IFN- α_2 and IFN- ω
633 may compromise intranasal antiviral immunity in the primary stages of infection. This
634 hypothesis was supported by work in a model of SARS-CoV-2 infection in human airway
635 epithelium (HAE) cells where autoantibody blockage of IFN-I led to increases in viral
636 replication *in vitro* (59). Sophie's findings suggested that a patient's intranasal IFN-I/III
637 autoantibody signature may serve as a useful diagnostic in predicting SARS-CoV-2 case
638 severity.

639

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641

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