International Agency for Research on Cancer

World Health Organization

Scientific Council **SC/46/WP4**
Forty-sixth Session 25/11/2009

Lyon, 27–29 January 2010
Princess Takamatsu Hall

SCIENTIFIC REPORT OF THE SECTION OF INFECTIONS (INF) REVIEW

A. BACKGROUND INFORMATION

Working papers

The written submissions from the Section of Infections (INF), presenting a comprehensive overview of the work performed during the last five years (2005–2009) and the future research directions of the Groups, form the framework for the review.

The following submissions from the INF Section were sent to the Review Panel on 7 September 2009:

- ✓ Provisional Agenda (dated 27 May 2009)
- ✓ Provisional List of Participants (dated 2 September 2009)
- ✓ Guidelines for Reviewers (dated June 2009)
- ✓ SC/46/WP1 General Introduction to the work of INF
- ✓ SC/46/WP2 Group Review 1: Infections and Cancer Biology Group (ICB) – Head, Dr Massimo Tommasino
- ✓ SC/46/WP3 Group Review 2: Infections and Cancer Epidemiology Group (ICE) – Head, Dr Silvia Franceschi
- ✓ Key publications for ICB and ICE

Oral presentations

The presentations gave a short overview of the written material and focused on topics related to the Groups' future plans and directions, during the Review Panel meeting held at IARC on 4–6 November 2009.

Membership of the INF Review Panel has been established as follows:

External Reviewers:

- Dr Lawrence Banks (International Centre for Genetic Engineering and Biotechnology, Trieste, Italy)
- Dr Matthias Egger (Institute for Social and Preventive Medicine, Bern, Switzerland) – ***unable to attend***
- Dr Anna R. Giuliano (H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA)
- Dr Paul F. Lambert (School of Medicine and Public Health, University of Wisconsin, USA)

Scientific Council members:

- Dr Ian Frazer (University of Queensland, Diamantina Institute, Australia)
- Dr Bart Kiemeney **(Review Panel Chair)** (Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, The Netherlands)
- Dr Marina Pollán Santamaria (Centre Nacional de Epidemiologia, Instituto de Salud Carlos III, Madrid, Spain)

Their assessments and recommendations follow.

B. REVIEW OF THE INDIVIDUAL GROUPS WITHIN THE SECTION OF INFECTIONS (INF)

Group Review 1: Infections and Cancer Biology Group (ICB) – Head, Dr Massimo Tommasino (see document SC/46/WP2)

1. ICB's past work:

1.1/1.2 Overview and critical appraisal of ICB's work in the last five years

The work over the last five years has focused on two distinct areas, both of which have been highly productive.

The first area of research has been the development of a novel sensitive platform assay system for detection of known pathogens that might be relevant to cancer risk, particularly human papillomaviruses (HPVs). This work has been used effectively to support epidemiology studies conducted by ICE and other research groups worldwide.

The second area of research has examined molecular mechanisms of pathogenesis of cancer. Most work has examined aspects of HPV associated cancer. Some has focused on a tumour suppressor gene, Dok1.

The two senior scientists in the ICB group have published very well during this period. Massimo Tommasino, the Group Head, has published 39 papers, across a range of topics. He is senior author on 12. Of these, most describe studies on the biology of HPVs, with emphasis on the oncogenic properties of cutaneous HPVs in tissue culture and in transgenic mice. Other senior-author studies describe the development and utilization of a multiplex PCR/Luminex based HPV detection system. It is clear from the publication list, that Dr Tommasino has established many productive interactions with scientists around the world (e.g. from Canada, India, Israel, Italy, Germany, Mexico, and the US) both on basic and epidemiological studies. Dr Sylla has published 13 papers over the period. His two senior author papers relate to the Dok1 tumour suppressor gene. Most of the work is well-cited and highly regarded.

Project review

1) Dr Tommasino's major research focus has been on the β-papillomaviruses associated with skin cancer, and their potential contribution to oncogenesis. He has developed a range of assays which define functionally the relative oncogenicity of skin HPVs. These include E7 induced inhibition of p53 transcription, genomic instability, and more recently altered keratinocyte growth characteristics in vitro and in vivo animal models of skin carcinogenesis. This work is world leading and addresses a critical issue in defining the oncogenic potential of β-papillomaviruses in skin. A strong group of students and postdocs are working with him on this topic, which he clearly regards as his area of greatest interest and research strength.

2) Another significant research area has been the association of infection of keratinocytes with high risk genital HPV infection with down regulation of TLR-9 expression. Dr Tommasino has defined molecular mechanisms by which HPV non structural proteins E6 and E7 of HPV16 induce this down regulation in cultured keratinocytes. There is a plausible hypothesis that this finding may

in part explain the propensity of HPV16 to persist and therefore to be of particular oncogenic potential. An important development in this project was the demonstration that certain potentially oncogenic cutaneous HPV types can also downregulate TLR-9 expression. This provides evidence of conserved mechanisms of virus host interactions existing between cutaneous and mucosal HPV types. In vivo data developed to date are limited, although preliminary data support a downregulation of TLR-9 expression during the development of cervical malignancies.

3) Dr Sylla has assumed a significant responsibility in the supervision of the research work of the Group. He has continued working on the Dok1 tumour suppressor gene, work commenced before Dr Tommasino's arrival at IARC. The observation that nuclear sequestration of Dok1 may be associated with HPV infection is very exciting and provides further evidence of novel ways in which HPV oncoproteins inhibit cellular tumour suppressor function.

4) Epidemiological studies on the oncogenicity of HPV16 E6 sequence variants have been diligently pursued, however the molecular basis for the apparent differences in cancer risk between these HPV variants is proving to be extremely elusive.

5) The ICB Group has developed powerful new methods for virus detection and genotyping which have been used by other Groups within IARC and may be also of future use to the ICE Group.

In summary, the strength of ICB lies clearly in the area of mechanisms of oncogenesis of the cutaneous HPV infections. They are, and have the potential to remain, world leaders in this field, despite not having had sufficient institutional support in the past.

2. ICB's future plans:

2.1/2.2 Overview and critical appraisal of ICB's future plans and strategic vision

Future plans largely (in Dr Tommasino's opinion >60%) comprise a continuation of the stronger and more productive parts of the current work on skin associated HPVs. Specifically, further work on the mechanisms of oncogenicity of the β-papillomaviruses in skin, and on TLR-9 suppression by HPV16 and HPV38 early proteins, were given as the major focus.

Several other areas of endeavour were also proposed, including a search for known oncogenic agents in breast cancer (HPV) and bladder cancer (polyomavirus), and a search for unknown agents in body fluids from cancer patients. Dr Tommasino's answers however when asked about priority areas indicate that he wishes to continue to focus his work on skin related oncogenic viruses. Discussion indicated that he will continue to use biological assays to better understand the hierarchy of oncogenicity of the various β-HPV types and the reasons for this. This work has become highly competitive on an international level, and of considerable practical interest, and the Review Panel agreed that it should be given a high priority and be adequately resourced.

Work on TLR-9 inhibition was also given a high priority, and was agreed to be of considerably potential practical utility. The mechanistic studies proposed were held to be important. The Review Panel felt that it was equally important to look at the clinical relevance of TLR-9 downregulation to persistence of high risk HPVs in the setting of both mucosal and cutaneous types. This study will

be an ongoing collaboration with Uzma Hasan in her new position at INSERM, which should ensure sufficient critical mass for progress.

Much was made of potential detection of new infectious agents responsible for cancer, without a clear or competitive strategy, and of detection of known oncogenic infectious agents in cancers other than those with which they are known to be associated. While there was a clear methodological approach to this work, it was not clear how the field of research would be focused to give the Group a competitive edge in a very competitive space. However it was felt that additional input from ICE on which tumour types and tissues to investigate might help in this aspect.

The Dok1 studies proposed are aimed at finding a mechanism by which Dok1 is sequestered in the nucleus in cervical cancer, and merits further investigation. The role of Dok1 methylation and down regulation in other tumours has no champion at present and the Review Panel felt that it might logically be seen as a continuation of Dr Sylla's previous work. An understanding of the mechanism by which HPV causes nuclear localization of Dok1 would seem to be a logical focus for future research.

The proposed search for known oncogenic agents in breast cancer (HPV) and bladder cancer (polyomavirus), and for unknown agents in body fluids from cancer patients, was held to be a potential distractor from the main focus of the proposed research, and was also an area in which the Group did not appear to have an obvious competitive edge. While the asset of the IARC Biobank could potentially facilitate such work, the likely return on time and effort were not judged to warrant specific effort.

3. ICB's assessment (SWOT):

3.1 Assessment of ICB's Strengths

- Talented and enthusiastic students and postdoctoral scientists;
- World leading research output that provides fundamental insights into the mechanisms of cutaneous and mucosal HPV associated oncogenesis.

3.2 Assessment of ICB's Weaknesses

- Potential distracting effect of the focus on developing new assay methodologies and viral discovery;
- Lack of support for laboratory science by the past administration has left the Group vulnerable to competition.

3.3 Assessment of ICB's Opportunities

- To make fundamental inroads in our understanding of skin cancer and to provide mechanisms on how diverse HPV types contribute to cancer.

3.4 Assessment of ICB's Threats

- Structural issues within IARC including short term tenure of postdoctoral scientists, inadequate laboratory support, and lack of animal facilities;
- Potential difficulty in retaining staff and attracting new students given the lack of stability. This could be remedied were the IARC to provide additional staffing support so as to provide continuity in staffing of the laboratory;
- Competition on any work related to human polyoma viruses and viral discovery will be intense.

4. Evaluation of ICB

The **past performance** and **future plans** should be scored independently for **quality** and **relevance**, as follows:

a. Assessment of scientific quality (using the four-point scale below)[1]

Past: Outstanding

Future: Outstanding

b. Assessment of the relevance of the work to the mission of IARC[2]

Past: Perfect fit

Future: Perfect fit

[1] A single score should be assigned for the work of each Research Group, the Section as a whole, and separately for the performance of each Group and Section Head. The following classification will be used:

1: **Outstanding**: Work of the highest international calibre, pioneering and trend-setting.

2: **Satisfactory**: Work that is internationally competitive and will make a significant contribution to science or public health.

3: **Questionable**: Work which is not of a high scientific standard, but which could be improved.

4: **Unsatisfactory**: Work which is of poor scientific standard and is unlikely to make a contribution to science or public health.

[2] This should include how well the proposed work benefits from IARC's unique position, how well it appears to fit with the IARC strategy and how it might impact on public health. A single score should be assigned for the work of each Research Group and for the Section as a whole. The following classification will be used:

1: **Perfect fit**: This type of work is ideally suited to the mission of IARC.

2: **Good fit**: This type of work is suited to the mission of the Agency.

3: **Questionable fit**: Uncertain.

4: **Poor fit**: Work which should not continue.

5. Overall recommendations for ICB

- This Group should be provided with sufficient resources to enable their considerable potential for contribution to the field of skin oncogenesis to be realized.
- Group structure should take into account the need to allow continuity of supervision of research.
- The major focus of future work should be on HPV oncogenic mechanisms rather than on a hunt for novel oncogenic pathogens.
- The Review Panel supports the plans to initiate training in low and medium resource countries and notes that Dr Sylla may have an important role in this effort.

Group Review 2: Infections and Cancer Epidemiology Group (ICE) – Head, Dr Silvia Franceschi (see document SC/46/WP3)

1. ICE's past work:

1.1 Overview of ICE's work in the last five years

ICE is a multidisciplinary epidemiology group focused on understanding infection as a cause of cancer. The Group consists of four scientists, one shared scientist with the Quality Assurance Group (QAS), two visiting scientists, three post-doctoral fellows, and two students, as well as support staff.

Over the past five years, a major focus of ICE has been studies of HPV. This includes:

1. Studies of HPV prevalence in developing countries, data are now available for 25 countries, of which 11 where data collection was completed in the last five years;

2. Pooled analyses of prevalence study data to assess HPV infection risk factors and differences in HPV type distribution by world regions;

3. Meta analyses of HPV prevalence and type distribution in neoplastic diseases;

4. Pooled analyses of cervical cancer case control studies;

5. Studies of HPV/HIV co-infection in Africa;

6. Development of statistical approaches that support analyses of prospectively collected HPV data.

In addition to work in HPV, ICE has focused on understanding cancer risk among HIV infected individuals, continued studies on H. pylori and gastric cancer, and undertaken work to elucidate associations between HBV, HCV, and hepatocellular carcinoma.

1.2 Critical appraisal of ICE's work in the last five years

Overall this is an outstanding group of investigators who have and continue to contribute significantly to the scientific literature and our understanding of infection and cancer.

The ICE Group has been very productive over the past five years (through Sept. 2, 2009), with a listing of approximately 300 peer reviewed publications and book chapters in this time period. Over the last five years, in the area of "cervical cancer and HPV" the Group published 68 manuscripts and list an additional six In Press. Eighteen manuscripts have been published in the area of "Cancer and HIV" with four additional manuscripts In Press. There are fourteen publications focused on "liver cancer and hepatitis viruses", with an additional two In Press, and 17 publications focused on "cancer and other infections", with an additional two In Press. Five publications are listed related to "statistical methods" with one additional manuscript In Press. Twenty-four publications are listed related to "cancers of the head and neck" and ~96 publications are listed related to "other", although these publications appear not to be related to infections and cancer. However, many of those represent completed research with other IARC Sections. The majority of the publications are in highly regarded peer reviewed journals, and several have made

a significant impact to our knowledge of a global understanding of infection and cancer. In addition, Dr Plummer is an active participant in the development group of the R software that is freely available to the research community.

Outside financial support for the projects listed within the ICE Group has been strong. In particular, the large grant from the Bill and Melinda Gates Foundation has enabled the Group to conduct outstanding research focused on HPV and related disease in numerous countries. Each project listed has received external funding. The Group should be commended for their efforts in securing extramural funding for their research, and should be encouraged to continue to seek extramural funding to support their current and planned research efforts. There is a risk to the Group in depending and focusing almost exclusively on one funding agency (e.g. Bill and Melinda Gates Foundation). There may be several grant opportunities that should be explored to test the hypotheses that the Group has put forward in their future plans.

In addition to the work directly related to grants and publications, ICE has contributed significantly to the teaching mission of IARC. However, it is surprising that the Group is not teaching courses in Infection and Cancer or supervising more graduate students. ICE has also made significant contributions to the dissemination of information internationally through their participation in the IARC Monograph series and through participation in key expert groups that are making policy decisions regarding HPV screening and immunization (e.g. WHO's Strategic Advisory Group of Experts).

HPV Related Projects: The Group lists seven projects focused on HPV infection. This work has spanned numerous countries with the resulting data contributing importantly to our understanding of differences in infection prevalence and disease associations by country and world region. These data serve to inform what we can expect to see relative to HPV vaccine effectiveness in different world regions. Of particular importance to the field have been the studies of Drs Franceschi, Clifford, Plummer and Vaccarella: Pro2-1 "Prevalence of genital HPV infection worldwide", Pro2-4 "Meta-analysis of HPV prevalence and type distribution in neoplastic diseases", Pro2-5 "Prevalence of HPV in men", Pro2-6 "International collaboration of epidemiological studies of cervical cancer", Pro2-8 "HPV and HIV co-infection in Africa", and Pro2-10 "Bayesian modelling applied to HPV and cancer". Among the HPV studies conducted, those focused on HPV prevalence risk factors (Pro2-2) and cross-sectional studies of HPV serum antibodies and risk of disease (Pro2-3) were of less scientific significance.

HIV Related Projects: An important area of research ICE has focused on is Pro2-7 which examines risk of cancer in persons with HIV/AIDS in southern Europe. More work is needed, not only to describe cancers caused by HPV, but also cancers caused by other infections.

H pylori and Gastric Cancer Project: ICE conducted a nutrient supplementation trial to reduce the progression of pre-cancerous gastric lesions in Venezuela (Pro2-9). Although there was a null outcome of the intervention trial, there were important findings related to variants of H pylori and severity of pre-cancerous lesions that may be useful in future studies for gastric cancer risk assessment.

2. ICE's future plans:

2.1 Overview of ICE's future plans and strategic vision

The strategic plan proposed for ICE includes continuation of research with a focus on HPV related carcinogenesis, cancers occurring in HIV/AIDS populations, hepatitis C (HCV) research, and other cancers suspected to be associated with infectious agents, such as gallbladder and biliary tract cancers.

2.2 Critical appraisal of ICE's future plans

Overall, the Review Panel agreed with the strategic vision proposed by the Group. This includes the four proposed *essential* projects on HPV and HIV and the three proposed *desirable* projects on HPV, HCV, and *Helicobacter* species.

A lack of plans for collaboration across projects and Sections in the submitted Working Papers was noted and was of concern. Discussions suggest that efforts were underway to develop research collaborations across projects and Sections. Achieving synergy across projects and Sections should be pursued and continued to be promoted wherever possible, e.g. shared appointments across Sections.

Proposed HPV Studies

Pro3-1 – Follow-up studies of HPV infection in populations with high HPV prevalence in middle-aged women: The Group is proposing to focus on two representative areas from Asia and Africa to pursue long term projects that allow for a prospective evaluation of HPV natural history and associations with age. While there is a strong need for prospective studies conducted among communities where the patterning of HPV infection and disease appears to be different from the US and EU, there are concerns with the methodological approach proposed for these studies. The Group proposes to build on the prevalence studies conducted in the past five years, forming the baseline evaluation for a prospective analysis. The Group should consider a plan to re-interview and exam women more frequently than only every five years. With such a change it will be possible to address more effectively some of the stated goals.

Pro3-2 – Oncogenicity of high-risk HPV variants: This proposed project has received external funding, builds on the tissue archive from the numerous HPV prevalence studies previously conducted by IARC, and will answer important questions related to intra-typic HPV gene variants that may help to elucidate the different patterns of disease risk observed internationally. Depending on the findings of future planned prospective studies, these data may be able to assist in distinguishing HPV persistence from re-infection.

Pro3-3 – Concurrent infection with multiple HPV types: The purpose of this proposed project is to study the pattern of multiple HPV type infections utilizing pooled data from the large prevalence studies conducted by IARC. As indicated, IARC is uniquely positioned to conduct such an analysis given the large sample size pooling of the completed prevalence studies offers.

Pro3-5 – HPV type distribution in cervical cancer and screening and treatment of pre-cancerous lesions among HIV-positive women in Africa: How to effectively screen HIV positive women for cervical cancer remains an unanswered question. This proposed project is designed to assess HPV type distribution among HIV positive cervical cancer cases and to conduct a screening trial to evaluate the sensitivity and specificity of single and combination screening modalities in detecting CIN2+ among HIV positive women.

The Group has identified a need to monitor the long-term impact of vaccination on incidence of HPV infection and pre-cancerous lesions in low and medium-resource countries. This indeed is an important area of research. However, no project was proposed that addresses this area of research.

Proposed HIV Studies

Pro3-4 – Trends of and risk factors for cancer among PWHA in the era of HAART: The overall goal of this study is to assess the cancer burden among individuals with HIV. Data from this study will likely inform which cancers should be targeted for prevention and management, associations with known onco-viruses, and the effect of HAART on cancer incidence. The Group has access to a unique European cohort that allows them to efficiently address these questions. To expand the sample size and power, the Group is encouraged to collaborate with other existing HIV cohorts in the western communities. If the anticipated results are confirmed, it will enable further studies in a population experiencing a very high prevalence of HIV/AIDS – e.g. southern and eastern Africa.

Proposed Hepatocellular Carcinoma and Helicobacter Studies

Pro3-6 – HCV: a growing threat in less developed countries: The Review Panel has the opinion that this is an interesting area of research based on the preliminary data presented.

Pro3-7 – Helicobacter species and cancers of the gall bladder and biliary tract: The Review Panel has the opinion that this is an interesting area of research. However, caution should be taken in devoting extensive resources to this project until additional information supports this project moving forward.

3. ICE's assessment (SWOT):

3.1 Assessment of ICE's Strengths

- The scientific and managerial expertise and experience of the Group Head Dr Franceschi is outstanding;
- The team of scientists has a strong publication record and is highly regarded internationally;
- The collaborations established enable recruitment to studies in multiple low resource countries and collection of specimens for analyses from large populations.

3.2 Assessment of ICE's Weaknesses

- The possibilities for productive collaborations with other Sections within IARC have not yet been fully exploited;
- Current dependency on a limited number of external funding agencies to support their research.

3.3 Assessment of ICE's Opportunities

- Extension of existing laboratory collaborations to address ICE's proposed goals;
- Utilize existing international collaborations to address questions related to HPV infection and disease such as vaccine effectiveness, duration of vaccine protection, and factors associated with receipt of vaccine;
- Within IARC, develop new collaborations for research with the Early Detection and Prevention Section;
- The ability to extend existing collaborations with the ICB Group and with other investigators where the laboratory methods for detection of onco-viruses are available;
- There is an opportunity to conduct studies to discover infectious agents associated with cancer utilizing banked specimens available at IARC.

3.4 Assessment of ICE's Threats

- Lack of study infrastructure to conduct prospective HPV studies in less developed countries;
- Lack of cancer registry infrastructure in less developed countries;
- The lack of promotion and career progression opportunities for staff within the institution;
- The challenge in obtaining grants to support the proposed large scale research needed to address the proposed goals.

4. Evaluation of ICE

The **past performance** and **future plans** should be scored independently for **quality** and **relevance**, as follows:

a. Assessment of scientific quality (using the four-point scale below)[1]

Past: Outstanding

Future: Outstanding

b. Assessment of the relevance of the work to the mission of IARC[2]

Past: Perfect fit

Future: Perfect fit

5. Overall recommendations for ICE

- Develop a comprehensive plan that will support, with sufficient extramural funding, the broader goals of ICE in cervical cancer screening and HPV vaccine monitoring in low resource countries.
- The plans proposed would benefit from infrastructure development and long-term commitment by IARC in specific countries.
- Explore possibilities to attract more PhD students.

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4: **Poor fit**: Work which should not continue.

C. GENERAL OVERVIEW OF THE SECTION OF INFECTIONS (INF)

The Section of Infections (INF) comprises two Groups: the Infections and Cancer Epidemiology Group (ICE) and the Infections and Cancer Biology Group (ICB).

ICE, headed by Dr Silvia Franceschi, has carried out studies on the association between human papillomavirus (HPV), human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV, HCV), Kaposi sarcoma herpes virus and *Helicobacter pylori* and cancer risk. ICE strives to work in countries where little knowledge is available on the topic of infection and cancer, notably low-resource countries.

ICB, headed by Dr Massimo Tommasino, is engaged in biological studies, the aim of which is to characterize the oncogenic properties of specific HPV types, as well as other viruses. The ICB Group has greatly contributed to the elucidation of the cutaneous HPV types that can interfere with cellular machinery and has established comparisons with what is already well-known for oncogenic mucosal HPV types.

IARC has been a leader in studies of cancers associated, or suspected to be associated with infectious agents for 30 years, but the bulk of the research carried out on the topic was epidemiological in nature. The establishment of a Group focusing on mechanisms of the infection/cancer link, coupled with the creation of new laboratory facilities (including an L3 laboratory) enhanced the IARC's reputation enormously, especially on HPV-related cancers.

The close collaboration between ICE and ICB continued between 2004 and 2008 when they were assigned to the same Cluster (Epidemiology and Biology Cluster). The introduction of the new IARC scientific structure, which placed both Groups in INF, allowed this collaboration to continue in a broad range of activities (i.e. research, meetings, staff training, grant submission, budgetary issues).

From the discussion with the Group Heads, the staff, and the students the Review Panel has the impression that the atmosphere in the Groups is very positive which contributes significantly to the overall scientific productivity in the Section.

Overall evaluation of INF

The **past performance** and **future plans** should be scored independently for **quality** and **relevance**, as follows:

a. Assessment of scientific quality (using the four-point scale below)[1]

Past: Outstanding

Future: Outstanding

b. Assessment of the relevance of the work to the mission of IARC[2]

Past: Perfect fit

Future: Perfect fit

Overall recommendations for INF

- Group structure should take into account the need to allow continuity of supervision of research.
- Increase career promotion and progression opportunities for scientists.
- Conduct annual performance evaluation with students and post-doctoral fellows.
- Allow faculty to name non-permanent staff on research grants submitted for funding.
- Allow for collaborations with industry, which do not constitute conflict of interests, to facilitate timely and state of the art research studies.
- Develop and implement courses in infection and cancer.
- If INF wishes to identify novel infectious agents associated with individual cancer types, then the ICE and ICB Groups should harmonize their plans.

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