Toward the Safe Use of Lentivirus and Retrovirus Vector Systems

Takaomi Sanda, MD, PhD

Principal Investigator, Cancer Science Institute Singapore; Assistant Professor, Department of Medicine, National University of Singapore
Outline of Today’s Presentation

1. Introduction
   - Why am I interested in lentivirus and retrovirus vector systems?

2. Lentivirus and other retrovirus vector systems
   - Basic virology and HIV-1 genome
   - Old generation virus vector system: potential risks
   - New generation virus vector systems: safety features

3. Proper understanding of risks involved in the virus work
   - Potential bias: is the risk overestimated or underestimated?

4. Attempts toward the safe use of virus vector systems
   - Safety and health management system in CSI
   - Lentivirus safety training
1. Introduction
Takaomi Sanda:
Current Position and Research Interest

**Current Position:**
- Principal Investigator, Cancer Science Institute (CSI) of Singapore
- Assistant Professor, Department of Medicine, National University of Singapore (NUS)

**Committee Assignments:**
- Chair, CSI Safety Committee
- Manager, CSI virus room
- Member, NUS Institutional Biosafety Committee (IBC)

**Research Interests:**
- Molecular abnormalities in T-cell leukemia
Young children with immunodeficiency received gene therapy to repair the defective gene.

- The normal gene was delivered using a retrovirus vector system into the genome of blood stem cells.
- Immune function was significantly improved after 2.5 years.
Correspondence after 8 months

(Hacein-Bey-Abina et al, NEJM, 2002)

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SUSTAINED CORRECTION OF X-LINKED SEVERE COMBINED IMMUNODEFICIENCY BY EX VIVO GENE THERAPY

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ABSTRACT

Background: X-linked severe combined immunodeficiency due to mutation in the gene encoding the common γ (γc) chain is a lethal condition that can be cured by autologous hematopoietic stem-cell transplantation. We investigated whether infusion of autologous hematopoietic stem cells that had been transduced in vitro with the γc gene can restore the immune system in patients with severe combined immunodeficiency.

Methods: CD34+ bone marrow cells from five boys with X-linked severe combined immunodeficiency were transduced ex vivo with the use of a defective retroviral vector. Integration-site expression of the γc gene and development of lymphocyte subgroups and their functions were sequentially analyzed over a period of up to 2.5 years after gene transfer.

Results: No adverse events resulted from the procedure. Transduced T cells and natural killer cells appeared in the blood of four of the five patients within four months. The numbers and phenotypes of T cells, the repertoire of T-cell receptors, and the in vitro proliferative responses of T cells to several antigens after immunization were nearly normal up to two years after treatment. Thymopoiesis was documented by the presence of naïve T cells and T cell antigen-receptor-epitope-specific T cells, and the development of a normal-sized thymic gland. The frequency of transduced B cells was low, but serum immunoglobulin levels and antibody production after immunization were sufficient to avoid the need for intravenous immunoglobulin. Correction of the immunodeficiency eradicated established infections and allowed patients to have a normal life.

Conclusions: Ex vivo gene therapy with γc can safely correct the immune deficiency of patients with X-linked severe combined immunodeficiency. (Hacein-Bey-Abina et al, NEJM, 2003)

A Serious Adverse Event after Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency

To the Editor: We recently reported (April 18 issue) the sustained correction of X-linked severe combined immunodeficiency disease by ex vivo, retrovirally meditated transfer of the γc gene into CD34+ cells in four of five patients with the disease. These results have since been confirmed in four additional patients with typical X-linked severe combined immunodeficiency. Of the first four successfully treated patients, three continue to do well up to 3.6 years after gene therapy, whereas a serious adverse event occurred in the fourth patient. At a routine checkup 18 months after gene therapy, lymphocytoysis consisting of a mononuclear population of VVγ9V1.6 T cells of mature phenotype was detected. The proliferaion-site integration site was found, located on the short arm of chromosome 11 within the LMO2 locus, as determined by the use of a linear amplification-mediated polymerase-chain-reaction analysis. This integration within the LMO2 locus was associated with abberant expression of the LMO2 transcript in the mononuclear T-cell population. Abberant expression of LMO2 has been reported in acute lymphoblastic leukemia arising from T cells with γc or T-cell receptors, usually with the chromosomal translocation t(11;14). Tests for replication-compotent retrovirus were repeatedly negative in our patient’s lymphocytes.

Between 30 and 34 months after gene therapy, the patient’s lymphocyte count rose to 300,000 per cubic millimeter, and hypoplasmenogosity developed. Further investigations showed the presence of a t(6;15) translocation, which has not been detected 30 months after the therapy. Treatment with a chemotherapy regimen based on a high-risk protocol for acute lymphocytic leukemia (a protocol of the Dutch Childhood Leukemia Study Group) was initiated and has resulted, to date, in a dramatic reduction in the abnormal cells.

We interpret these findings as the consequence of the insertional mutagenesis event, a risk that is potentially associated with retrovirally mediated gene transfer and that has previously been considered to be very low in humans. For this reason, a thorough reassessment of the potential risk of retrovirally mediated gene therapy is warranted. It is likely that additional factors may have contributed to the adverse event in our patient, including a virus–virus vector infection five months before clinical detectable lymphoproliferation, which may have stimulated immature activity of the 8V γc T-cell clone, or a selective growth advantage conferred by γc expression in the transduced cells. Genetic predisposing factors for childhood cancer are also possible, since medioloblastomas have developed in the proband’s sister and a first-degree relative.

We have proposed to the French regulatory authorities a halt to our trial until further evaluation of the causes of this adverse event and a careful re-assessment of the risks and benefits of continuing our study of gene therapy in patients with X-linked severe combined immunodeficiency can be completed. The latter will include a comparison with the outcome of the available alternative therapy, haploidentical stem-cell transplantation.

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Gene Therapy-related Adverse Event: Development of T-cell Leukemia

(LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1)

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- After 3 years, T-cell (T-lymphocyte) leukemia occurred in 2 out of 10 patients. Later, 2 other patients also developed leukemia.

- In these patients, retrovirus was inserted near the cancer causative gene (LMO2) and induced abnormal expression.
T-cell Leukemia:
Serious Risk Involved in the Use of Retrovirus Vector

Key Points:
- T-cell leukemia was possibly caused by an integration of retrovirus.
- This induced abnormal expression of a cancer causative gene.
- The whole process is very rapid (< 3 years).

Scientific Questions (my research interest as a investigator):
- Why did leukemia develop so quickly?
- What is the mechanism?

Safety-related Questions (my role as the CSI virus room manager):
- Was this risk properly estimated?
- How can we reduce such risk?
2. Lentivirus and other retrovirus vector systems
- **Retrovirus** is a type of virus.
- Retrovirus was named for a viral protein known as “reverse transcriptase” which can synthesize DNA from the viral RNA.
- Viral DNA can integrate into the host genome.

- **Lentivirus** is one of subgroups of retrovirus that can cause chronic and deadly diseases.
- HIV-1 was discovered in 1983 as a human lentivirus.
- The HIV-1 genome is very compact and highly efficient, as it contains all essential components that mediate virus infection and integration processes.
- HIV-1 primarily infects T-cells (T-lymphocytes) which helps to activate and coordinates other cells of the immune system in the body.
- HIV-1 can be replicated in infected T-cells and further transmitted to other T-cells, leading to the disruption of immune system: acquired immune deficiency syndrome (AIDS).
The Earliest Virus Vector System for the Analysis of Viral Replication in Culture System

Virologists tried to experimentally produce lentivirus to track viral infection process and to use as a platform to test therapeutic drugs.

In the earliest system, the Env gene was deleted from the viral genome and was separately expressed.

Infective virus can be produced but cannot be replicated after the 1st round of infection.

Lacks an essential gene. Cannot produce virus by alone.

Produced separately

Infect into T-cells
Additional Application: Lentivirus/Retrovirus Vector System as a “Tool” for Stable Gene Delivery

- Researchers realized that this system would be also useful as a “tool” to deliver a gene of interest.
- The gene can be inserted into the human genome and stably expressed like a real human gene.
- The inserted gene can be also transferred to “daughter cells” after cell division.
The viral attachment protein “VsVg” was used instead of the HIV-1 Env protein.

- VsVg protein can bind the cell membrane, thus allowing researchers to deliver a gene of interest to a wider set of cells, including non-mammalian cells.

Lacks an essential gene.
Cannot produce virus by alone.

- Produced separately

Wide variety of human cells
Potential Risks Involved in the Use of Lentivirus and Other Retrovirus Vector Systems

- Virus can enter the body through injured skin or wounds or by infecting mucosal surfaces.

- Risk of generating “replication competent virus” through recombination.

- Integrate into genome (randomly) so there is an unpredictable risk associated with gene disruption.

- Additional operational precautions if the gene of interest encodes a biological toxin or a cancer gene.
Potential Risks Involved in the Use of Lentivirus and Other Retrovirus Vector Systems

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Generation of New Virus Species Through Viral DNA Recombination

- New virus may be generated by “DNA recombination”, if the sequences are conserved.
- The generated virus can be “replication competent” and may also acquire an unexpected ability.
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Improvement of Safety Features: Reduction of Accidental Viral Production and Recombination

Viral genes were separated into several parts to reduce the conserved sequences and to prevent accidental production of the virus.

In the 3rd generation system, the packaging plasmid was further divided into 2 parts.

The Tat protein that facilitates HIV-1 replication has been removed.

Many recent vectors are “self-inactivating (SIN)” system which prevents virus replication.
Potential Risks Involved in the Use of Lentivirus and Other Retrovirus Vector Systems

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- Integrate into genome (randomly) so there is an unpredictable risk associated with gene disruption.

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Is the likelihood of virus integration at the cancer gene locus low or high?

- The total length of the human genome is over 3 billion base pairs.
- Only 1.5% of the genome encode protein-coding genes. The vast majority of human genome are “non-coding” elements.
- Among protein-coding genes, only a small fraction of genes can cause cancer by alone.
- If the virus integration is truly random, the likelihood to induce cancer should be extremely low.
SUSTAINED CORRECTION OF X-LINKED SEVERE COMBINED IMMUNODEFICIENCY BY EX VIVO GENE THERAPY

SALIMA HACEIN-BEY-ABINA, Ph.D., FRANÇOISE LE DEST, M.D., PH.D., FREDERIQUE CARLER, B.S., CECILE BOUMAUG, Ph.D., CHRISTOPHE HUE, B.S., JEAN-PIERRE DE VELAYST, Ph.D., ADRIAN J. THURSDAY, M.D., PH.D., NICOLA MACPRAIRON, M.D., RICARDO SOUZA, M.D., SOPHIE DUPUIS-GRIOB, M.D., ALAIN FISCHER, M.D., PH.D., AND MARINA CAVAZANZA-CALVO, M.D., PH.D.

ABSTRACT

Background X-linked severe combined immunodeficiency due to a mutation in the gene encoding the common γ (γc) chain is a lethal condition that can be cured by autologous hematopoietic stem cell transplantation. We investigated whether infusion of autologous hematopoietic stem cells that had been transduced in vitro with the γc gene can restore the immune system in patients with severe combined immunodeficiency.

Methods CD34+ bone marrow cells from five boys with X-linked severe combined immunodeficiency were transduced ex vivo with a self-retroviral vector, and the expression of the γc and β2m transgene and development of lymphocyte subgroups and their functions were sequentially analyzed over a period of up to 2.5 years after gene transfer.

Results No adverse effects resulted from the procedure. Transduced T cells and natural killer cells appeared in the blood of four of the five patients within four months. The numbers and phenotypes of T cells, the repertoire of T-cell receptors, and the in vitro proliferative responses of T cells to several antigens after immunization were nearly normal up to two years after treatment. Thymopoiesis was documented by the presence of naïve T cells and T-cell antigen receptor-negative and CD4-CD8- double-negative thymocytes. The frequency of transduced B cells was low, but serum immunoglobulin levels and antibody production after immunization were sufficient to avoid the need for intravenous immunoglobulin. Correction of the immunodeficiency eradicated infections and allowed patients to have a near-normal life.

Conclusions Ex vivo gene therapy with γc can safely correct the immune deficiency of patients with X-linked severe combined immunodeficiency. (N Engl J Med 2002;346:1185-93.)

DEFICIENCY of the common γ (γc) chain, an X-linked disorder, causes the most frequent form of severe combined immunodeficiency disease. The γc is an essential component of five cytokine receptors, all of which are necessary for the development of T and natural killer cells. Without the γc chain, there is a complete absence of mature T and natural killer cells, whereas B cells are usually present in normal or increased numbers. Severe combined immunodeficiency is fatal during the first year of life because of severe, recurrent infections, unless transplantation of hematopoietic stem cells restores T-cell function.1,2 The survival rate after transplantation of HLA-identical hematopoietic stem cells is more than 90 percent, whereas with haploidentical stem cells it is 70 to 78 percent.3 In most patients, deficient B-cell function persists after transplantation and requires lifelong immunoglobulin–replacement therapy.4 Some patients also have persistent deficiencies of T-cell function after stem-cell transplantation.5 Assessment of an allogeneic hematopoietic stem-cell transplant in a patient with X-linked severe combined immunodeficiency disease (XLCID) (without a human leukocyte antigen–matched sibling donor) shows promise for this approach.6

HACEIN-BEY-ABINA ET AL. • N Engl J Med • 2002

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What did we learn from this incident?

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(Hacein-Bey-Abina et al, NEJM, 2002)

(NEJM) What did we learn from this incident?

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TO THE EDITOR: We recently reported (April 18 issue) the sustained correction of X-linked severe combined immunodeficiency disease by ex vivo, retrovirally mediated transfer of the γc gene into CD34+ cells in four of five patients with the disease. These results have since been confirmed in four additional patients with typical X-linked severe combined immunodeficiency. Of the first four successfully treated patients, three continue to do well up to 3.6 years after gene therapy, whereas a serious adverse event occurred in the fourth patient. At a routine checkup 30 months after gene therapy, lymphoproliferosis consisting of a monoclonal population of Vγ9Vα1.6 T cells of mature phenotype was detected. Our proviral integration site was found, located on the short arm of chromosome 11 within the LMO2 locus, as determined with the use of linear amplification mediated polymerase-chain reaction analysis.7 This proviral integration within the LMO2 locus was associated with aberrant expression of the LMO2-transcript in the monoclonal T-cell population. Aberrant expression of LMO2 has been reported to induce lymphoblastic leukemia arising from T cells with a γδ receptor, usually with the chromosomal translocation t(11;14).8 Tests for replication-competent retrovirus were repeatedly negative in our patient’s lymphocytes.

Between 30 and 34 months after gene therapy, the patient’s lymphocyte count rose to 300,000 per cubic millimeter, and hepatosplenomegaly developed. Further investigations showed the presence of t(11;14) translocation, which had not been detected 30 months after the therapy. Treatment with chemotherapy resulted in a high-risk protocol treatment for acute lymphoblastic leukemia (a protocol of the Dutch Childhood Leukemia Study Group was initiated but has resulted, to date, in a dramatic reduction in the abnormal cells).

We interpret these findings as the consequence of the insertion mutagenesis event, a risk that is potentially associated with retrovirally mediated gene transfer and that has previously been considered to be very low in humans.9 For this reason, a thorough reassessment of the potential risk of retrovirally mediated gene therapy is warranted. It is likely that additional factors may have contributed to the adverse event in our patient, including a virus–carrier virus infection five months before clinical detectable lymphoproliferation, which may have stimulated immune reactivity of the γc T-cell clone, or a selective growth advantage conferred by γc expression in the transduced cells. Genetic predisposing factors for childhood cancer are also possible, since medulloblastomas have developed in the proband’s sister and a first-degree relative.

We have proposed to the French regulatory authorities a halt to our trial until further evaluation of the causes of this adverse event and a careful reassessment of the risks and benefits of continuing our study of gene therapy in patients with X-linked severe combined immunodeficiency can be conducted. The latter will include a comparison with the outcome of the only available alternative therapy, hypoplastic stem-cell transplantation.10

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3. Proper understanding of risks involved in the virus work
Is “2 out of 10” cases still considered “Random”?

(Hacein-Bey-Abina et al, Science, 2003)

**LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1**

- After 3 years, **T-cell (T-lymphocyte) leukemia** occurred in 2 out of 10 patients. Later, 2 other patients also developed leukemia.

- In these patients, **retrovirus was inserted near the cancer causative gene (LMO2)** and induced abnormal expression.

This strongly suggested that there would be a preference in the virus integration sites.
Recent Research Demonstrated a Possible Bias

- Recent genome-wide studies revealed that there are “hot spots” where retrovirus integrations are more frequently found.

- “Hot spots” are also different among cell types. For example, the \textit{LMO2} gene locus is one of hotspots of some types of retrovirus in blood stem cells.

- Additionally, \textit{LMO2} serves as a cancer causative gene in the context of T-cell leukemia (but not in other cancers).

- Lentivirus can integrate more “randomly” as compared to other retrovirus, although there are still preferential elements.

- Risks can be different depending on virus types and target cells.
Is the Risk Overestimated or Underestimated?

(Hacein-Bey-Abina et al, Science, 2003)

**LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1**


- This gene therapy-related incident has been long cited when considering the risks involved in using retrovirus and lentivirus vector systems.
- In the original trial, this risk might be underestimated.
- But, the risk may be also overestimated, if we apply this for all virus work.
- More accurate assessment would be:
  “The risk of using retrovirus in blood stem cells is high”.
  “The risk of using lentivirus in other tissues is relatively low”.

T-cell Acute Lymphoblastic Leukemia
Potential Risks Involved in the Use of Lentivirus and Other Retrovirus Vector Systems

- Virus can enter the body through injured skin or wounds or by infecting mucosal surfaces.
  > The likelihood can be reduced by general risk controls.

- Risk of generating “replication competent virus” through recombination.
  > The likelihood can be reduced by general risk controls and improvement of the virus vector system

- Integrate into genome (randomly) so there is an unpredictable risk associated with gene disruption.
  > Proper risk assessment is needed.

- Additional operational precautions if the gene of interest encodes a biological toxin or a cancer gene.
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- Additional operational precautions if the gene of interest encodes a biological toxin or a cancer gene.

*We are working at the cancer institute. Many of us are trying to overexpress the real cancer gene. What other risk controls are needed?*
4. Attempts toward the safe use of lentivirus and other retrovirus vector systems in Cancer Science Institute
Cancer Science Institute (CSI) Singapore

Transforming hopes to reality
Who we are. What we do.

Our mission is to be a major centre for cancer studies in Asia with a global presence.

- Established in October 2008.
- One of the Research Centre of Excellences.
- Funded by NRF and MOE.
- Director Prof. Daniel G. Tenen.
- Basic and translational cancer studies.
- Approximately 30 laboratories.
- Over 300 research staffs and students.
The CSI “Core” Safety Staffs in 2017/2018

Prof Daniel Tenen (Director) and Dr Ruby Huang (Vice Chair)
Ms Liy Sim Low (Safety Coordinator)
Ms Priscilla Fernandez (Safety Officer)

Prof Daniel Tenen (Director)
Dr. Takaomi Sanda (Chair; virus room manager)
Dr. Ruby Huang (Deputy chair)
Ms. Priscilla Fernandez (Safety officer)
Ms. Liy Sim Low (Safety coordinator)
Mr. Swee Siang (Rex) Ng (Lab manager)
Ms. Fiona Chia (Microscope facility manager)
Ms. Michelle Mok (FACS facility manager)
Ms. Selena Gan (Administrative director)
The CSI Safety & Health Management System (SMS)

CSI Director
Prof. Daniel G. Tenen

CSI Safety Committee

Establishment, implementation, review

Keep and update original documents

Documentation, document control

Upload

Communication, participation, consultation

Internal audits, monitoring

Institutional trainings

CSI internal server

CSI staffs and students

Download

CSI safety policy, SOPs, RAs, Legal register, Objectives & Programmes, R&R register and ERP
The Use of Lentivirus and Retrovirus Vectors in CSI

More than 50% of laboratories in CSI are using retrovirus and lentivirus vectors.

1. Engineering control (physical means to limit the hazard).
   - Lentivirus work are conducted in designated area (4 cores).
   - Equipment designated for virus work (centrifuge, incubator, autoclave) are provided by CSI for each core.

2. Administrative measures (adherence to procedures and instructions)
   - Review of safety protocols (by OSHE) and GMAC applications (by IBC)
   - CSI-specific standard operating procedure (SOP)
   - CSI-specific risk assessment (RA)
   - CSI lentivirus safety training
   - Update user list.

3. Personal protection equipment (PPE) and disinfectant
   - Lab coat, gloves (double), covered shoes and eye google.
   - Disposable gowns are provided by CSI
   - Virkon (disinfectant) are provided by CSI
CSI Lentivirus Safety Training

- Mandatory for all virus users in CSI.
- Conduct every 3 months.
- A total of 30 sessions were conducted in 2013-2017.
- Over 200 staffs and students attended.
- 1 hour session including 30 min presentation and 30 min on-site training (waste management and biological spill response).

**Step 1: Decontamination with Disinfectant**

- De-contaminate all wastes (virus media, dish, flasks, serological pipettes) with disinfectant before disposal.

**Step 2: Autoclave**

- Please autoclave all biohazard materials immediately after use.
- Use an autoclave tape and write the date, PI's initial and "CSI".
- Autoclaved bags should be collected in biohazard trash bins.
How can we make training programs more efficient?

- Documents and training programs are complementary.
- Training program is useful to clarify and emphasize critical points written in SOPs and RAs.
- On-site hands-on training is particularly useful to demonstrate specific situations and risks in the institute or department.
- Interesting topics (or scary images) are useful to explain risks. But, should not mislead attendees!
- Users must understand reasons behind each step of safety practices.

Make it interesting (or scary) to attendees

Let them think why we need risk controls
Closing Remarks:

Lentivirus and Retrovirus Vector System as a Prime Example of Risk Management

- In the past few decades, the efficacy and safety of retrovirus and lentivirus vector systems have been significantly improved.
- This is one of the most successful examples of application of biotechnology to basic and clinical researches.
- This is also one of the most important lessons we learned.

- Likelihood of many risks involved in the virus work can be reduced by general risk controls (engineering control, administrative measures and PPE).
- Additional risks should be assessed based on the vector systems, cell types and activities in the institute.
- Training program is useful to clarify critical points and specific situations/risks in the institute.
Extra slides
CSI is very “Dynamic”:
How can we make a better SMS?

“5 Rs” to improve our SMS:
1. Research
2. Review
3. Revise
4. Refine
5. Reduce
Research:
Make a SMS fit better to the institute/department

In addition to the general planning:

1. Research the institute/department
   - What are the scope, vision and policy of your institute/department?
   - SMS must help and promote them.
   - Safety and research are not exclusive – can synergize.

2. Research the people
   - How many students? How many graduates?
   - How many non-native English speakers?

3. Research the activities
   - What activities are done in the same area?
   - Do the staffs/students know other lab’s activities?
Review and Revise:
Improve the SMS

- Keep monitoring the situation.

- Review your SMS periodically. Annual management review is very important.

- Revise timely. Incorporate feedbacks.

- Do not hesitate to report incidents or accidents. Transparency is very important.
Refine and Reduce:
Make it More Efficient and Productive

- Meetings and guidelines can promote the productivity.
- But, too many meetings or guidelines may reduce the productivity.

Need to determine the cut-offs!!