DEPARTMENT OF VIRAL ONCOLOGY
LABORATORY OF CELL REGULATION

I. Sugita group

Full attention of the recently set up Sugita's laboratory has been directed to a novel lineage of antigen-presenting molecules, CD1. Unlike conventional MHC molecules that present protein-derived peptide antigens, molecules of the human group 1 CD1 family (CD1a, CD1b, CD1c) mediate presentation of lipid antigens to specific T lymphocytes. By taking cell biological and immunological approaches, this group wishes to establish a molecular and cellular basis for CD1-dependent immunity and determine how CD1 has been evolved to function critically in host defense. An important extension of this study is a challenge for developing a new type of lipid-based vaccines against cancer and microbial infection.

I-1) Reconstitution of the human CD1 system in mice: I. MATSUNAGA, H. FUKUI, A. MORIMOTO, A. OTSUKA, T. SHIINA* and M. SUGITA (*Tokai Univ.)

Mice and rats are useful animals for many immunological studies, but important exceptions exist. These animals have deleted genes for group 1 CD1 family, and thus, lack the lipid recognition system that is comparable to that in humans. Given the necessity of appropriate small animal models for monitoring CD1-mediated immune responses *in vivo*, we have developed two distinct, but complementary animal systems; namely, guinea pigs and CD1 transgenic mice. We have recently found that guinea pigs have evolved the CD1 system equivalent to that in humans, and, as discussed below, are capable of mounting the CD1-restricted T cell response upon mycobacterial infection. On the other hand, the paucity of critical guinea pig reagents often hampers the thoroughgoing in vivo evaluation of the CD1 system *in vivo*.

As an alternative animal model, we now have established CD1 transgenic mice in which the CD1-dependent immunity is reconstituted. CD1c transgenic mice carrying the human *CD1C* genome were generated and analyzed for CD1c expression. Similar to human myeloid dendritic cells (DCs), bone marrow-derived DCs from CD1c transgenic mice prominently expressed CD1c. Splenic macrophages did not express CD1c in naive CD1c transgenic mice, but upon infection with BCG, at least a subset of macrophages now acquired its expression most likely via TLR-dependent pathways. Thus, the two major host cell types for mycobacterial infection, namely macrophages and DCs, are able to express CD1c in infected hosts. It remains to be established whether a full range of "positive selection" for CD1c-restricted T cells may have occurred in these CD1c transgenic mice, our pilot studies readily detected the presence of CD1c-restricted autoreactive T cells in these mice. We also generated CD1a and CD1b transgenic mice, now allowing us to comparatively analyze functions of each CD1 component.

I-2) CD1-dependent immunity against *Mycobacterium avium* complex (MAC) and HIV-I: I. MATSUNAGA, A. OTSUKA, K. TOMITA, A. OCHI, D. MORITA, I. YANO* and M. SUGITA (*Japan BCG Central Laboratory.)

After moving to this Institute, the Sugita's laboratory has set out to study lipid-specific immune responses against MAC. Following infection with MAC, guinea pigs mounted significant cell-mediated and humoral immune responses directed against cell wall lipid components of MAC. In the follow-up studies, we have identified a certain species of mycolyl glycolipids as the major target antigen for the protective immunity against MAC infection. Infection with MAC is clinically important because of its resistance to treatment of antibiotics, and often critical in prognosis of AIDS patients. Thus, one of the goals of this study is to determine if these glycolipids to which host immune responses are targeted may function as a new class of subunit vaccines against mycobacterial infection.

As in mycobacteria-infected cells, lipid-containing molecules are also produced in cells infected with viruses that can potentially serve as antigens recognized by the CD1 system. We have made extensive search for such candidate antigens in HIV-1 infection, using newly developed CD1 binding assays. We now focus on a couple of HIV-1-related antigens and see if these are capable of activating CD1-restricted cytotoxic T cells.

I-3) Demonstration of lipid-specific allergic reactions: N. MORI*, I. MATSUNAGA, A. OTSUKA, D. MORITA, and M. SUGITA (*Div. of Applied Life Science, Kyoto Univ.)

As evidence by the studies described above, it is now clear that CD1 mediates a critical pathway for host defense. On the other hand, undesirable immune responses to lipids may result in tissue damage and autoimmunity. In collaboration with Dr. Naoki Mori, who successfully isolated α- and β-acaridial, representing monoterpenes from astigmatid mite *Tyrophagus putrescentiae*, we addressed the possibility that these mite-derived lipids may function as allergens and induce contact dermatitis. Using *in vivo* systems, we showed that immune sensitization with these compounds indeed occurred effectively, and subsequent challenges with the same antigens induced allergic reactions, typically observed as the form of contact dermatitis in the skin.

I-4) Identification of cancer-related lipid antigens: H. TAKABA, A. OTSUKA, I. MATSUNAGA and M. SUGITA

Self and "altered" self lipids are often found to be the target for CD1-restricted cytotoxic T cells. Since aberrant expression of group 1 CD1 molecules is noted in certain types of cancer cells, we

reasoned that lipids, besides peptides, may constitute a new entity of tumor antigens and induce specific cytotoxic T cell responses that control tumor cell survival directly. This project, which can potentially create a new field of cancer immunology, has been undertaken in this laboratory. Although the project is still at the immature stage, we have candidate antigens in hand that can bind group 1 CD1 molecules. By taking advantage of both immunological approaches with specific antibodies and TLC-based chemical approaches, we monitor their expression in various types of cancer cells. At the same time, specific CD1-restricted T cell lines are being obtained.

II. Murakami group

Murakami's group is interested in the regulation of higher order chromatin structure and its role in various chromosome functions. Currently this group mainly focuses on the dynamic organization of heterochromatin that is important constituent of chromosome using fission yeast *Schizosaccharomyces pombe* as a model organism. In addition, this group analyzes the regulation of DNA replication and DNA damage repair during S phase.

II-1）Role of RNA polymerase II in the RNAi-dependent Heterochromatin Formation: Y. MURAKAMI, H. KATO*, A. SHIMADA, M. NAKAMA, F. BÜHLER, D. MOAZED** and K. TANAKA**** (*Shimane Univ., **Harvard Medical School, ***Kansei-Gakuin Univ.)

In centromeric heterochromatin formation in fission yeast, the RNA interference (RNAi) machinery converts pericentromeric non-coding RNAs (ncRNA) into small interfering RNAs (siRNAs) and the siRNA is required for the assembly of heterochromatin. Specially, association of RNA induced transcriptional silencing (RITS) complex, which contains the siRNA and Argonaute homologue, to ncRNA appears to be a key step for RNAi-dependent heterochromatin formation, because artificial tethering of RITS complex to *ura4* RNA by a specific RNA binding protein induces *ura4*-siRNA formation and heterochromatin formation at *ura4* locus (Bühler et al, Cell, 125, 873-886, 2006). Previously we isolated a mutation of the second subunit of RNA polymerase II (*rpb2-m203*) that specifically inhibit RNAi-dependent heterochormatin formation but does not affect general transcription. Detailed analysis of this mutant indicated that RNA polymerase transcribes the ncRNA at centromeric repeats and couples transcription and subsequent siRNA formation (Kato et al. Science, 309, 467-469, 2005). Interestingly, We found that *rpb2-m203* did not affect the heterochromatin formation or siRNA formation induced by the artifictial RITS tethering system. This indicates RNA polymerase II is involved in the siRNA-dependent binding of RITS complex to the non-coding RNA. Recently, RNA polymerase II in plant cells was shown to interact with one of the plant Argonaute homologues. Thus, direct recruitment of RITS complex to ncRNA by RNA polymerase II might be a basis for the coupling of transcription and siRNA processing. Now we are examining the interaction between RNA polymerase II and RITS complex in fission

yeast.

II-2) Isolation of Novel Mutants of RNA polymerase II that Disrupt RNAi-Dependent Heterochromatin Formation: SATORU TSUNEMINE AND YOTA MURAKAMI

As mentioned in II-1), a mutation of the second largest subunit of RNA polymerase II in fission yeast, *rpb2-m203*, disrupts coupling between transcription and siRNA processing in RNAi-dependent heterochromatin formation. The mutation converts asparagine 44 in the "protruding domain" of Rpb2 to tyrosine. This domain is well conserved from fission yeast to higher eukaryote but no interacting protein has been reported. We speculate that the domain interacts with the RNAi-related factor(s) such as RITS comples (see II-1)). To confirm our speculation, we have been trying to isolate novel mutant alleles in this domain that show the same phenotype as *rpb2-m203* using site-directed mutagenesis and preliminary results suggest that such mutation can be isolated. Since it is unknown yet if similar system operates in higher eukaryote, we are planning to introduce the isolated mutations including *rpb2-m203* into vertebrate cells and to analyze function of RNAPII in heterochromatin formation as well as other non-coding RNA-mediated and higher eukaryote specific phenomena, such as micro RNA formation and X chromosome inactivation.

II-3) Non-Coding RNAs Associate with Chromatin in Heterochromatin-Mediated Silencing: M. NAKAMA, H. KATO*, T. URANO, K. FURUKAWA**, Y. MURAKAMI** (*Shimane Univ., **Nagoya Univ.)

The RNAi-dependent heterochromatin formation model (See II-1)) suggests centromeric non-coding RNA (ncRNA) may play multiple roles in RNAi-mediated chromatin assembly, including the production of dsRNA and siRNA, siRNA-directed localization of RITS, and the recruitment of chromatin-modifying complexes. Specially, the model predicted that ncRNA associates with chromatin and functions as a platform for RNAi-dependent heterochromatin formation but the direct evidence for the prediction is missing. We tried to RNA-IP (RNA-immunoprecipitation) to detect the interaction between non-coding RNA and chromatin, using antibodies against C-terminal region of histone H3, histone dimetyl-histone H3(Lys9) (H3K9-me) and dimethyl-histone H3(Lys4) (H3K4-me), which represents whole chromatin, heterochromatin and euchrhomatin respectively. We found that centromeric non-coding RNA associated with histone H3 and H3K9-me but not to H3K4-me. In contrast, general transcripts, like mRNA encoding actin, do not associate with histone H3. The analysis using various kinds of heterochromatin mutants indicates that there is good correlation between ncRNA-chromatin association and heterochromatin formation. This result supported the functional link between

ncRNA associated histone and heterochromatin assembly. We are now trying to understand the mechanism and the functional significance of the ncRNA-heterochormatin association.

II-4) RNA Metyltransferase Tgs1 is Required for Pericentromeric Heterochromatin Assembly: A.SHIMADA, Y. MURAKAMI

In the effort to identify genes involved in the RNAi-dependent heterochromatin formation, we found *tgs1*, which encods RNA methyltransferase, as a candidate gene. *tgs1* null mutant showed the phenotype similar to RNAi mutants, the loss of heterochromatin specific histone modifications and the accumulation of pericentromeric non-coding RNAs. The point mutation of Tgs1, W153A, which loses the methyltransferase activity, also showed the same phenotype, indicating that the methyltranserase activity is necessary for RNAi-depenedent heterochromatin formation. Tgs1 is known as snRNA (small nuclear RNA) trimethylguanosine synthase and converts the cap structure from m7G to m3G. The modification is important for the intra-nuclear localization of snRNA. Therefore, Tgs1 may modify the pericentromeric non-coding RNAs and help their intra-nuclear localization that is important for RNAi-dependent heterochromatin formation.

II-5) Role of Histone Deactylace Clr3 in the Formation of Heterochromatin: S. TSUNEMINE, M. NAKAMA, A. SHIMADA, H. NAKAGAWA*, M. HATTA, K. DOHKE, M. YOKOYAMA AND Y. MURAKAMI** (*presently Ohita Univ., **presently Graduate School of Medicine, Kyoto Univ.)

Transcriptionally silent heterochromatin is characterized by deacetylated histones. Histone H3 is deacetylated at Lys 9 and Lys 14 (H3K9 and H3K14), and methylated on Lys 9 (H3K9), which is bound by a chromo-domain protein HP1. It is still unclear how histone tail modifications are orchestrated, and what the role of HP1 is in the formation of silent chromatin. We found that neither Clr3 nor H3K14 deacetylation was absolutely required for methylation of H3K9 or the subsequent binding of the fission yeast HP1 homologue, Swi6 at centromeric RNAi-dependent heterochromatin. Instead, Swi6 was required for recruitment of Clr3, to deacetylate H3K14, and both Swi6 and Clr3 were required for deacetylation of histone H4. Since gene silencing was partially disrupted in the absence of Clr3, one of the roles of HP1/Swi6 in transcriptional gene silencing would be enhancement of histone tail deacetylation by recruiting HDACs such as Clr3. In contrast to centromeric heterochromatin, lack of Clr3 causes the dislocalization of Swi6 and increase of phosphorylation of histone H3S10 that inhibits Swi6 binding to methylated H3K9 at mating locus heterochromatin (Yamada et al. Curr. Biol, **20**, 173-186, 2005). Interestingly, we found that loss of Clr3 does not cause the increase of H3S10 phosphorylation at centromeric heterochromatin indicating that some features of centromeric heterochromatin is different from mating type

heterochromatin.

II-6) Chromatin Assembly Factors in Fission Yeast Contributes to the Stable Maintenance of heterochromatin.: K. DOHKE, S.I.S. GREWAL[1], K. TANAKA[2], S. KATAYAMA[3], T. URANO[4], Y. MURAKAMI ([1]National Institutes of Health, USA, [2]Shimane Univ., [3]Saga Univ., [4]Nagoya Univ.)

Higher order structure of chromatin plays an essential role in various nuclear processes. Once established, the higher order structure need to be maintained through cell divisions. The molecular mechanism for the maintenance of the chromatin structure is not well understood yet. Chromatin assembly factor-1 (CAF-1) is three subunits (p150, p60, and p48) complex and loads histone H3-H4 complex onto newly synthesized DNA through interaction with a replication factor, PCNA *in vitro*.

We identified fission yeast genes (*pcf1, pcf2, pcf3*) showing significant homology to CAF-1 p150, p60 and p48 subunits. We found that Pcf1, Pcf2 and Pcf3 form a complex that interacts with PCNA like human CAF1. We also showed that *pcf1, 2* and *3* are required for maintenance of heterochromatin rather than establishment. It is known that human CAF-1 p150 interacts directly heterochromatin protein HP1. In *S. pombe*, fission yeast CAF-1 interacts heterochromatin protein Swi6 in S phase specifically. In the mutant analysis, we found that CAF-1 is required for the heterochromatin-specific modifications of histone H3 tail and localization of Swi6. Therefore, CAF-1 may play an important role in "the exact inheritance of heterochromatin structure."

Disruption of CAF-1, however, does not affect cell growth significantly, indicating that other chromatin assembly factor(s) exist. Asf1 (anti-silencing function 1) is thought to be a histone chaperon working cooperatively with CAF-1. We have used the temperature sensitive mutant of fission yeast *asf1* to analyze its role of heterochromatin formation and relationship to CAF-1, since *asf1* is essential for cell growth. Our results indicated that CAF-1 and ASF1 function independently to maintain heterochromatin. These date suggested that both chromatin assembly factors does participate in "the exact inheritance of heterochromatin structure" in fission yeast.

II-7) The Novel Gene *mus7*$^+$ Is Involved in the Repair of Replication-Associated DNA Damage in Fission Yeast : M. YOKOYAMA , H. INOUE*, C. ISHII* and Y. MURAKAMI (*Saitama University)

The progression of replication forks is often impeded by obstacles that cause them to stall or collapse, and appropriate responses to replication-associated DNA damage are important for genome integrity. Here we identified a new gene, *mus7*$^+$, that is involved in the repair of replication-associated DNA damage in the fission yeast *Schizosaccharomyces pombe*. The Δ*mus7* mutant shows enhanced sensitivity to methyl methanesulfonate (MMS), camptothecin, and

hydroxyurea, agents that cause replication fork stalling or collapse, but not to ultraviolet light or X-rays. Epistasis analysis of MMS sensitivity indicates that Mus7 functions in the same pathway as Mus81, a subunit of the Mus81-Eme1 structure-specific endonuclease, which has been implicated in the repair of the replication-associated DNA damage. In Δ*mus7* and Δ*mus81* cells, the repair of MMS-induced DNA double-strand breaks (DSBs) is severely impaired. Moreover, some cells with either mutation are hyper-elongated or enlarged, and most of these cells accumulate in late G2 phase. Spontaneous Rad22 (recombination mediator protein RAD52 homolog) foci increase in S phase to late G2 phase in Δ*mus7* and Δ*mus81* cells. These results suggest that replication-associated DSBs accumulate in these cells and that Rad22 foci form in the absence of Mus7 or Mus81. We also found that the rate of spontaneous conversion-type recombination is reduced in mitotic Δ*mus7* cells, suggesting that Rhp51- (RAD51 homolog) dependent homologous recombination is disturbed in this mutant. From these data, we propose that Mus7 functions in the repair of replication-associated DSBs by promoting RAD51-dependent conversion-type recombination downstream of Rad22 and Mus81.

II-8) Drosophila ORC1 (DmORC1) Loads onto the Chromosomal DNA Replication Origin for Gene Amplification: H. KOHZAKI and Y. MURAKAMI

Others and we have been shown that transcription factors, including nuclear proto-oncogenes such as *c-jun* and *c-fos*, regulated DNA replication. This suggests that disturbance of the regulation of DNA replication by the nuclear oncogenes is one of the mechanisms for chromosomal abnormality including gene amplification, which leads to oncogenesis.

We chose *Drosophila* (Dm) chorion gene amplification as a model system to study the regulation of DNA replication by transcription factors. The chorion gene amplification is tightly regulated during development of follicle cells and utilizes a similar set of proteins to the normal chromosomal replication, such as origin recognition complex (ORC). The replication origin contains two essential elements ACE3 and ori-beta, where DmOrc2 binds. Interestingly, transcription factors, such as E2F and Myb, have been shown to regulate this amplification.

We first analyzed the behavior of DmORC1, because, unlike DmORC2, the level of DmORC1 is modulated during cell cycle and regulates origin utilization during development. We indicated that DmOrc1-GFP formed foci in the follicle cell nucleus, which may represent the amplifying loci. ChIP assay indicated that DmOrc1 bound to ACE3 and Ori-beta in the tissue in which chroion gene amplification takes place. Considering the regulatory role of DmORC1, we speculate that loading of DmORC1 is a major regulatory step for the gene amplification. We hypothesize that the transcription factors regulate the loading of DmORC1 and are now examining the loading of DmORC1 in the mutant flies of E2F and Myb. In addition, we also start to characterize DmCDC6

because of functional exchangeability between DmORC1 and DmCDC6 has been suggested.

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Laboratory of Cell Regulation

I. Sugita group

Watanabe Y, Watari E, Matsunaga I, Hiromatsu K, Dascher CC, Kawashima T, Norose Y, Shimizu K, Takahashi H, Yano I, Sugita M. BCG vaccine elicits both T-cell mediated and humoral immune responses directed against mycobacterial lipid components. Vaccine 24: 5700-5707, 2006.

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Murakami Y. RNA polymerase II plays an essential role in RNAi-dependent heterochromatin formation. The 13th East Asia Joint Symposium on Biomedical Research, Seoul Korea, July 17-19 2006,

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神崎　秀嗣、村上　洋太：ショウジョウバエ ORC1(DmORC1)の過剰発現はプログラムされた遺伝子増幅を乱す　第 18 回　DNA 複製・分配ワークショップ、熱海、平成 18 年 10 月

村上 洋太、横山 美佳, 井上 弘一, 石井 千津:DNA 複製時の DNA 二本鎖切断の修復に関与する新規遺伝子の解析 第 18 回　DNA 複製・分配ワークショップ、熱海、平成 18 年 10 月

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Ｉ．杉田グループ

松永勇助手とともにセットアップを進めてきた新しい研究室は、2006 年になってようやくその体裁を整えるに至り、4 月より初めて大学院生を受け入れ始めた。生命科学研究科修士課程 5 名（越智昭仁、高場啓之、冨田和沙、森田大輔、森本絢子)、博士課程編入 1 名（福井一)、また医学研究科より博士課程 1 名（大塚篤司）の計 7 名が加わり、研究指導という点では慌ただしい 1 年であった。4 月中は、学生を 2 班に分け、Ｔ細胞や樹状細胞を中心とした細胞培養、脂質の精製や薄層クロマトグラフィー、FACS や蛍光顕微鏡解析などラボの基本的手技について初期トレーニングメニューを設定し実践した。6 月までに個々の研究プロジェクトを決定し、その後は個別ミーティング、グループミーティング、ラボミーティングを頻回に開催し、議論を重ねた。厳しい指導に対し学生からは時として苦情も聞こえてきたが、少なくとも「学生実習」とは異質の「研究」の有り様を実感してくれたと思う。その過程で、最初は頼りなかった学生が、脂質の精製において天才的と思えるような才能を発揮したり、ひとつの小さな発見をきっかけにして突如として研究への意欲を格段に高めていく姿など、若い研究者の潜在的な能力を改めて実感した 1 年でもあった。

「脂質免疫応答」という新しい切り口から感染防御機構を解明しようとする私たちの取り組みは、*Mycobacterium avium* complex (MAC)という非定型（非結核性）抗酸菌に対する宿主免疫応答を詳細に観察することにより、大きな進展を見た。MAC 感染モルモットにおいて、主たる免疫標的となる MAC 細胞壁脂質を単離・同定し、その抗原に対するメモリー応答の成立を初めて実証することができた。さらにそのメモリー応答を基盤として誘発される遅延型アレルギー反応の本態が、蛋白抗原に対する免疫応答をもとにして確立されたこれまでの教科書的な常識とは全く異質のものであることを見出した。その発見の普遍性と分子基盤について、今年度作製を完了した CD1a、CD1b、CD1c トランスジェニックマウスを用い、検証を進めている。

一方、「脂質免疫応答」のウインドウを広げ、「ウイルス感染」「がん免疫」「アレルギー・自己免疫」の新しい理解を目指した研究を展開している。まだこの紙面に特記できるだけの成果はほとんどないが、本学農学研究科の森直樹博士との共同研究として行ったダニ由来脂質アレルゲンの同定とその生化学的・免疫学的解析はほぼ完結した。

免疫学と脂質生化学の融合をもとに私たちが開拓してきた新領域の研究が、ようやく目に見える形となってきた印象である。

ＩＩ．村上グループ

２００７年３月に生命科学研究科博士後期課程の加藤が博士を取得し、日本学術振興会特別研究員として島根大学生物資源学部に巣立っていった。島根大から博士後期課程に入学して以来５年をかけての博士取得であったが、最後に RNAi に依存するヘテロクロマチン合成システムにおける RNA ポリメラーゼ II の機能を示すという重要な発見をおこない、特別研究員の中でも SPD という数少ない地位を得たことはまことに喜ばしいことであった。彼の地道な努力が花開いたもので、後輩達の励みにもなっている。島根大で本来の研究課題の他に我々との共同研究を続けており良いパートナーとなっている。

一方、４月からは生命科学研究科の大学院生として修士１年に甲南大から常峰、博士後期課程一年に筑波大から仲間、生命科学研究科の統合生命科学専攻から島田、の３人が加わった。それぞれ、個性的な面々で小世帯の研究室に活気を与えてくれている。常峰は加藤の仕事の延長で、RNA ポリメラーゼ II の新たな変異の単離をおこない、さらに得た変異を脊椎動物細胞に導入しその影響を調べることを計画している。仲間は RNAi 依存的ヘテロクロマチン系で重要な non-coding RNA の動態を特にクロマチン結合の側面から解析を進め、興味深い知見を得ている。また、島田は RNAi 依存的ヘテロクロマチン形成に関わる新たな変異の単離を試み、重要と思われるヘテロクロマチン関連因子を見つけつつある。特に RNA の 5’キャップ構造を修飾し RNA 局在に関わる因子がヘテロクロマチン形成に関与すると言う知見は、non-coding RNA の運命決定機構の理解につながる重要な発見ではないかと考えている。

博士課程３年の道家は、ヘテロクロマチンの維持機構について解析を続けている。これはクロマチン構造によるエピジェネティックな遺伝子発現制御を考える上で非常に重要でありながら未だに良く理解されていない問題である。道家は CAF1 と呼ばれる DNA 複製依存的クロマチンアセンブリー因子に着目して解析を進め、この因子がヘテロクロマチン維持に実際に関わることを示し、現在はその分子機構に迫ろうとしている。横山は埼玉大学在学中に解析していたアカパンカビの DNA 損傷修復に関わる遺伝子 mus-7 の分裂酵母ホモログ *mus7* の解析を進めてきた。詳細な遺伝解析の結果 DNA 複製時に生じる二本鎖切断修復の修復経路のうち Mus7 は相同組換えを使って修復する経路で機能することがわかった。DNA 複製時の損傷修復はゲノム安定維持に重要であるがその全貌はあきらかでなく、この知見はその理解に貢献する物であろう。

ポストドクターの神崎は DNA 複製開始制御における転写因子の役割を中心に研究を進めてきた。出芽酵母を使った解析から、複製開始制御における転写因子によるクロマチン構造変換の重要性を示す結果を得てそれをまとめようとしている。一方でショウジョウバ

エの発生時期・組織特異的なコリオン遺伝子増幅に着目しその制御機構の解析を、京都工芸繊維大学の山口政光研究室、生命科学研究科の上村匡研究室、さらにノースカロライナ大学の浅野摩樹研究室の助力を得ながらおこない、成果を上げつつある。