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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims 1-17 and 19-29 are pending in the application.

This action is in response to applicants' amendment dated February 21, 2020. Claims 1, 2, 4-13, 15, 16 and 19 have been amended, claim 18 has been canceled and claims 21-29 are newly added.

Response to Amendment

Applicant's arguments filed February 21, 2020 have been fully considered with the following effect:

1. With regards to the 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph rejection, labeled paragraph 2) in the last office action, the applicant's arguments have been fully considered, however they were not found persuasive.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The scope of the method claims are not adequately enabled solely based on its inhibitory effect of TRPC6 provided in the specification.

The treatment of cancer generally cannot possibly be considered enabled.

As a general rule, enablement must be commensurate with the scope of claim language. MPEP 2164.08 states, "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)" (emphasis added). The "make and use the full scope of the invention without undue experimentation" language was repeated in 2005 in *Warner-Lambert Co. v. Teva Pharmaceuticals USA Inc.*, 75 USPQ2d 1865, and *Scripps Research Institute v. Nemerson*, 78

USPQ2d 1019 asserts: “A lack of enablement for the full scope of a claim, however, is a legitimate rejection.” The principle was explicitly affirmed most recently in *Liebel-Flarsheim Co. v. Medrad, Inc.* 481 F.3d 1371, 82 USPQ2d 1113; *Auto. Tech. Int’l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 84 USPQ2d 1108 (Fed. Cir. 2007), *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 84 U.S.P.Q.2d 1705 (Fed. Cir. 2007), and *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 85 USPQ2d 1826 (Fed. Cir. 2008).

By way of background, four cases are of particular relevance to the question of enablement of a method of treating cancers broadly or even generally:

In *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, the claim was drawn to “The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas, adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors” using a small genus of compounds. The Court decided that human testing “limited to one compound and two types of cancer” was not “commensurate with the broad scope of utility asserted and claimed”.

In *Ex parte Jovanovics*, 211 USPQ 907 the claims were drawn to “the treatment of certain specified cancers in humans” by the use of a genus of exactly two compounds, the N-formyl or N-desmethyl derivative of leucosine. Applicants submitted “affidavits, publications and data” for one of the compounds, and a dependent claim drawn to the use of that species was allowed. For the other, no data was presented, applicants said only that the other derivative would be expected to be less effective; claims to the genus were refused.

In *Ex parte Busse*, et al., 1 USPQ2d 1908, claims were drawn to “A therapeutic method for reducing metastasis and neoplastic growth in a mammal” using a single species. The decision notes that such utility “is no longer considered to be “incredible”, but that “the utility in question is sufficiently unusual to justify the examiner’s requirement for substantiating evidence. Note also that there is also a dependent claim 5 which specified “wherein metastasis and neoplastic growth is adenocarcinoma, squamous cell carcinoma, melanoma, cell small lung or

glioma.” The decision notes that “even within the specific group recited in claim 5 some of the individual terms used actually encompass a relatively broad class of specific types of cancer, which specific types are known to respond quite differently to various modes of therapy.”

In *Ex parte Stevens*, 16 USPQ2d 1379 a claim to “A method for therapeutic or prophylactic treatment of cancer in mammalian hosts” was refused because there was “no actual evidence of the effectiveness of the claimed composition and process in achieving that utility.”

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds.

(b) Scope of the diseases covered. Cancer is not a single disease, or cluster of closely related disorders. There are hundreds of cancers, which have in common only some loss of controlled cell growth. Cancers are highly heterogeneous at both the molecular and clinical level, something seen especially in, for example, the cancers of the breast, brain and salivary glands. They can occur in pretty much every part of the body. Here are some assorted categories:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories.

There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of

primary brain tumors, most of which are aggressive, highly invasive, and neurologically destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of glial differentiation. These fall mostly into five categories. There are the astrocytic tumors (astrocytomas): pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric optic nerve glioma) diffuse astrocytomas (including fibrillary astrocytomas, protoplasmic astrocytomas and gemistocytic astrocytomas), anaplastic astrocytomas (including adult optic nerve glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but GBM is considered to be one clinical entity. Second, there are the oligodendroglial tumors (oligodendrogliomas): low grade oligodendroglioma and anaplastic oligodendroglioma. Third, there is oligoastrocytomas ("mixed glioma"), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the ependymomas, which are intracranial gliomas, including papillary ependymoma, myxopapillary ependymoma, tanycytic ependymoma, anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is the gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, pineal ganglioglioma, hypothalamic ganglioglioma, cerebellar ganglioglioma, ganglioglioma of the right optic tract, rosetted glioneuronal tumor ("glioneurocytic tumor with neuropil rosettes"), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG) and non- infantile), angioganglioglioma, and others. There are also some glial tumors which do not comfortably fit into these five categories, notably astroblastoma, gliomatosis cerebri, and chordoid glioma, which are found solely in the

hypothalamus and anterior third ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(choroid plexus papilloma, choroid plexus carcinoma), assorted neuronal and neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, olfactory neuroblastoma, olfactory neuroepithelioma, and neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, ependymblastoma, atypical teratoid/rhabdoid tumor, desmoplastic medulloblastoma, large cell medulloblastoma, medullomyoblastoma, and melanotic medulloblastoma) and others such as polar spongioblastoma and gliomatosis cerebri. A second Division is tumors of the meninges. this includes tumors of the meningotheial cells, including meningiomas (meningotheial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, metaplastic, clear cell, chordoid, atypical, papillary, rhabdoid, anaplastic meningioma) and the non- meningioma tumors of the meningotheial cells (malignant fibrous histiocytoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, chondroma, chondrosarcoma, osteoma, osteosarcoma, osteochondroma, haemangioma, epithelioid haemangioendothelioma, haemangiopericytoma, angiosarcoma, kaposi sarcoma). There are also mesenchymal, non-meningotheial tumors (liposarcoma, (intracranial) solitary fibrous tumor, and fibrosarcoma) as well as primary melanocytic lesions (diffuse melanocytosis, melanocytoma, malignant melanoma, and meningeal melanomatosis). A third division are the tumors of cranial and spinal nerves. This includes cellular schwannomas, plexiform schwannomas and the melanotic schwannomas (e.g. psammomatous melanotic schwannoma , neuro-axial melanotic schwannoma, dorsal dumb-bell melanotic schwannoma). There is also Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor

(MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, and MPNST with epithelial differentiation. A fourth division are germ cell tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (mature teratoma, immature teratoma, and teratoma with malignant transformation). A fifth division are the tumors of the sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (adamantinomatous and papillary). Yet another division are local extensions from regional tumors, including paraganglioma, chondroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas. Primary central nervous system lymphoma (PCNSL), including Primary ocular lymphoma, is a form of extranodal high-grade non-Hodgkin B-cell neoplasm, usually large cell or immunoblastic type. Secondary central nervous system lymphoma (SCNSL) is most commonly from Burkitt's lymphoma and lymphoblastic lymphoma. There is also Meningeal Carcinomatosis, plasmacytoma, and granulocytic sarcoma. And there are many, many others.

B. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These include viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic Lymphoid leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma (ATLL), and T-cell

granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias (undifferentiated AML, acute myeloblastic, acute myelomonocytic leukemia, acute monocytic leukemias, acute monoblastic, acute megakaryoblastic (AmegL), acute promyelocytic leukemia (APL), and erythroleukemia). There is also lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, and acute basophilic leukemia. Chronic leukemias include chronic lymphocytic leukemia (CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia (PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia (CEL), and many others.

C. Carcinomas of the Liver include hepatocellular carcinoma, combined hepatocellular cholangiocarcinoma, cholangiocarcinoma (intrahepatic), bile duct cystadenocarcinoma and undifferentiated carcinoma of the liver. There is also cancer of the blood vessels in the liver (hemangioendothelioma), primary non-hodgkin's lymphoma of the liver, undifferentiated liver sarcoma (also known as undifferentiated embryonal sarcoma), primary pleomorphic liver sarcoma, angiosarcoma of the liver, and primary malignant melanoma of the liver. Most liver cancers are secondary, especially those originating in the breast, lung, or gallbladder, as well as both Hodgkin's or non-Hodgkin's lymphoma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinomas, bronchioloalveolar carcinomas (nonmucinous, mucinous, and mixed mucinous and nonmucinous or indeterminate cell type), acinar, papillary carcinoma, solid adenocarcinoma with mucin, adenocarcinoma with mixed subtypes, well-differentiated fetal adenocarcinoma, mucinous (colloid) adenocarcinoma, mucinous cystadenocarcinoma, signet ring adenocarcinoma, and clear cell adenocarcinoma), squamous cell (papillary, clear cell, small cell and basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and large cell carcinoma (which include large-cell neuroendocrine carcinoma,

combined large-cell neuroendocrine carcinoma, basaloid carcinoma, clear cell carcinoma lymphoepithelioma-like carcinoma, and large-cell carcinoma with rhabdoid phenotype). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including carcinomas with spindle and/or giant cells, spindle cell carcinoma, carcinosarcoma and pulmonary blastoma. The non-small cell lung carcinomas also include adenosquamous carcinoma, the carcinoid tumor (both typical carcinoid and atypical carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma (which occurs three fairly different sub-types); chondroma; calcifying fibrous pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (e.g. adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There are some papillomas, including squamous cell papilloma and glandular papilloma. There is also melanoma of the lung, cylindroma (cylindroadenoma), some germ cell tumors, thymoma and sclerosing haemangioma and many others as well. Lung cancers are quite diverse. Thus, for example, oat cell carcinoma, Signet ring adenocarcinoma, pleuropulmonary blastoma, cylindroma, and malignant mesothelioma really have very little in common, other than being cancers of the lung.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Cancer of the skin cells is melanoma. Malignant melanomas come in four fundamental forms: superficial spreading melanoma, nodular melanoma (including its variant, Polypoid melanoma), lentigo maligna melanoma and acral melanoma. Mucosal melanomas are sometimes malignant. These sometime occur in amelanotic form, such as in desmoplastic

melanoma.

G. Non-melanoma skin cancers are quite varied. There is a very wide range of carcinomas of the skin, most notably the basal cell carcinomas (BCC), including superficial BCC, nodular BCC (solid, adenoid cystic), infiltrating BCC, sclerosing BCC (desmoplastic, morpheic), fibroepithelial BCC, BCC with adnexal differentiation, follicular BCC, eccrine BCC, basosquamous carcinoma, keratotic BCC, pigmented BCC, BCC in basal cell nevus syndrome, micronodular BCC.

Another important family is the squamous cell carcinomas (SCC) which include spindle cell (sarcomatoid) SCC, acantholytic SCC, verrucous SCC, SCC with horn formation, and lymphoepithelial SCC, along with less well classified SCCs such as papillary SCC, clear cell SCC, small cell SCC, posttraumatic (e.g., Marjolin ulcer) and metaplastic (carcinosarcomatous) SCC. Another family is the eccrine carcinomas including sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal carcinoma), malignant mixed tumor of the skin (malignant chondroid syringoma), porocarcinoma, malignant nodular hidradenoma, malignant eccrine spiradenoma, mucinous eccrine carcinoma, adenoid cystic eccrine carcinoma, and aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include epidermal carcinomas, Paget disease, mammary Paget disease, merkel cell carcinoma (neuroendocrine cancer of the skin), extramammary paget disease adnexal carcinomas, apocrine carcinoma, sebaceous carcinoma, tricholemmocarcinoma and malignant pilomatricoma (matrical carcinoma). There are also skin sarcoma's, most notably Kaposi's sarcoma, but also granulocytic sarcoma of the skin, hemangiopericytoma (HPC), fibroblastic/myofibroblastic sarcoma of the skin, primary extraosseous Ewing's sarcoma of the skin. Cutaneous lymphomas come in four categories. A) Primary Cutaneous T-cell lymphomas come in numerous forms: Mycosis fungoides, Pagetoid reticulosis, Sézary syndrome, Granulomatous slack skin, Lymphomatoid papulosis, Pityriasis lichenoides chronica, Pityriasis lichenoides et varioliformis acuta, CD30+ cutaneous T-cell lymphoma, Secondary cutaneous CD30+ large cell lymphoma, Non-mycosis fungoides CD30- cutaneous large T-cell lymphoma,

Pleomorphic T-cell lymphoma, Lennert lymphoma, Subcutaneous T-cell lymphoma, Angiocentric lymphoma, and Blastic NK-cell lymphoma. B) There is also secondary cutaneous peripheral T-cell lymphoma, including secondary cutaneous peripheral T-cell lymphoma. C) Primary Cutaneous B-Cell Lymphoma comes in several forms. There is Primary cutaneous marginal zone B-cell lymphoma (MALT-type), which comes in some variant forms, including Immunocytoma and Primary cutaneous plasmacytoma; Primary cutaneous follicle center lymphoma, which comes in variant forms including Follicular, Follicular and diffuse, and Diffuse; and Primary cutaneous diffuse large B-cell Lymphoma. D) Finally, there is secondary Cutaneous B-Cell Lymphoma. This is commonly from Intravascular large B-cell lymphoma (IVLBL), or Lymphomatoid granulomatosis, but can also come from Mantle cell lymphoma, Burkitt lymphoma, and Hodgkin Lymphoma. In addition to that secondary form of cutaneous Hodgkin's Lymphoma, there is also a primary cutaneous Hodgkin's Lymphoma. Also there is Granular cell tumor (Abrikossoff's tumor, Granular cell myoblastoma, Granular cell nerve sheath tumor, Granular cell schwannoma) all of neural derivation; these are sometimes malignant and have no pharmacological treatment, only surgical. There is also Leukemia cutis, infiltration of leukemia cells into the skin, usually from acute myeloid leukemia, but also from acute lymphoblastic leukemia, Chronic lymphocytic leukemia, and some other forms. There is also neuroma cutis.

H. There are many types of colorectal cancers. The carcinomas include adenocarcinoma; mucinous adenocarcinoma; signet-ring cell carcinoma; small cell carcinoma; adenosquamous carcinoma; medullary carcinoma; choriocarcinoma; and undifferentiated carcinoma. The malignant lymphomas include marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type; mantle cell lymphoma; Diffuse large B-cell lymphoma; Burkitt lymphoma; and Burkitt-like/atypical Burkitt lymphoma. There are also some carcinoid tumors, sarcomas (including GISTs, leiomyosarcoma, hemangiosarcoma, angiosarcoma, Kaposi sarcoma, fibrosarcoma, neurofibrosarcoma and Leiomyosarcoma), primary plasmacytoma of

the colon and primary malignant melanoma of the colon. A wide variety of cancers are secondary to the colon, e.g. ovarian carcinoma.

I. Renal carcinomas comprise the papillary renal cell carcinoma (which has two subtypes, type 1 and type 2, with very different prognostic values), clear cell renal carcinoma, chromophobe renal carcinoma, collecting duct renal carcinoma, and some unclassified carcinomas. Renal sarcomas include leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, liposarcoma of the kidney, malignant hemangiopericytoma, angiosarcoma of the kidney, osteosarcoma, synovial sarcoma, chondrosarcoma of the kidney, malignant mesenchymoma, and clear cell sarcoma of the kidney. Lymphomas include Primary Renal Non-Hodgkin's Lymphoma, primary renal MALT lymphoma, primary renal Hodgkin's lymphoma, and secondary renal lymphomas, which can be of either Hodgkin's or Non-Hodgkin's type. Other kidney cancers include transitional cell carcinoma, Wilms Tumor, malignant rhabdoid tumor of the kidney, renal melanoma, primitive neuroectodermal tumor of the kidney, neuroepithelial tumor of the kidney, and congenital mesoblastic nephroma, some renal adenomas, and oncocytomas.

J. Prostate Cancer is not a single disease or group of very closely related disorders, but ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including prostatic ductal adenocarcinoma, adenocarcinoma with paneth-like cells, clear cell adenocarcinoma, foamy gland adenocarcinoma, adenocarcinoma of Cowper's glands, and atrophic adenocarcinoma. It includes a huge variety of carcinomas, including mucinous carcinomas of the prostate, prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, adenosquamous and squamous cell carcinomas, basaloid and adenoid cystic carcinoma, sarcomatoid carcinoma of the prostate, lymphoepithelioma-like carcinoma of the prostate, urothelial (transitional cell) carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), basaloid carcinoma,

pseudohyperplastic carcinoma, and primary carcinoma of the seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), phyllodes tumor of the prostate, primitive peripheral neuroectodermal tumor (PNET) and malignant fibrous histiocytoma. There are also lymphomas, which are usually secondary, but primary ones include diffuse large B-cell lymphoma. The great majority of this list are not treatable with pharmaceuticals.

K. The carcinomas of the bile ducts are of numerous types, including carcinoma in situ, adenocarcinoma, papillary adenocarcinoma, adenocarcinoma (intestinal-type), mucinous adenocarcinoma, clear cell adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma, small cell carcinoma (oat cell carcinoma), Cholangiocarcinoma and undifferentiated carcinoma of the bile ducts. There is also a primary malignant melanoma of the bile duct, a carcinoid tumor, as well as myeloid, nonleukemic granulocytic, and botryoid sarcomas of the bile ducts. There is also primary non-Hodgkin's lymphoma, diffuse large B cell lymphoma, and follicular lymphoma of the bile ducts.

L. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers. These come in an assortment of types. Presently, these are divided into the following categories: intraductal (in situ); invasive with predominant intraductal component; invasive, NOS; Comedo; Inflammatory (IBC); medullary with lymphocytic infiltrate; mucinous carcinoma (colloid carcinoma); papillary carcinoma; scirrhous; tubular; and other. Another category is the Lobular breast cancers, which can be in situ, Invasive with predominant in situ component, and Invasive. There is Paget's disease of the nipple, which can be also with intraductal carcinoma or with invasive ductal carcinoma. There is adenomyoepithelioma, a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and

Hodgkin's disease of the breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, angiosarcoma of the breast, cystosarcoma phylloides, and liposarcoma of the breast. There are carcinoid tumors which can be primary carcinoid tumors of the breast, or can arise from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma, oncocytic carcinoma (mammary epithelial oncocytoma), and mucoepidermoid carcinoma. Other rare carcinomas include spindle cell carcinoma of the breast, squamous cell carcinoma of the breast, secretory carcinoma of the breast (juvenile secretory carcinoma), metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), invasive micropapillary carcinoma of the breast, adenoid cystic carcinoma of the breast, cribriform carcinoma, myofibroblastoma of the breast (benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas, and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus, and colon). Complicating the treatment of breast carcinomas is the fact that a significant proportion of mammary carcinomas are not monoclonal.

M. Ovarian cancers are a heterogeneous group of tumors. The most important are the epithelial tumors. These are themselves fairly diverse, the categories being serous cystomas (serous benign cystadenomas, serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth and serous cystadenocarcinomas); mucinous cystomas (divided the same three ways); clear cell tumors (mesonephroid tumors, again divided the same way), endometrioid tumors (similar to adenocarcinomas in the endometrium: endometrioid benign cysts, endometrioid tumors with proliferating activity of the epithelial cells and endometrioid adenocarcinomas), mixed

mesodermal (now considered to be carcinomas with areas of sarcomatous differentiation), transitional cell carcinoma, the Brenner tumor, and mixed epithelials. Second, there are the granulosa-stromal cell tumors. These include the granulosa cell tumor (which exists in juvenile and adult forms) and the tumors in the thecoma-fibroma sub-group. This sub-group also includes thecoma-fibroma group typical: thecoma and luteinized thecoma, as well as fibroma, cellular fibroma, fibrosarcoma, stromal tumor with minor sex cord elements, sclerosing stromal tumor, signet ring cell stromal tumor and others. Third, there are the Sertoli stromal cell tumors: Sertoli-Leydig cell tumor of the ovary (which comes in three different levels of differentiation, as well as a retiform version); Sertoli cell tumor (tubular androblastoma), and Stromal- Leydig cell tumor. Fourth are the Sex cord-stromal tumors of mixed or unclassified cell types: sex cord tumor with annular tubules, gynandroblastoma of the ovary (composed of sex cord and stromal cells of both ovarian and testicular types), and sex cord-stromal tumor NOS. Fifth, there are the steroid cell tumors: Ovarian Leydig cell tumor, which comes in hilus and non-hilar types, Stromal luteoma, and steroid cell tumor, NOS. Sixth, there is an assortment of Germ Cell Tumors. These include dysgerminoma; yolk sac tumors (endodermal sinus tumor, and polyvesicular vitelline tumor, hepatoid and others); embryonal carcinoma; polyembryoma; choriocarcinoma, gonadoblastoma and a wide variety of teratomas. These tetromas include immature, cystic (dermoid cyst), retiform (homunculus), and Monodermal, including struma ovarii, carcinoid (insular and trabecular), struma carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors and others. There are also the teratocarcinomas which come in many mixture types. Finally, there are an assortment of other tumors which do not fit into the above categories. There is Tumors of Rete Ovarii (which can be adenomatoid tumor or a mesothelioma). There are some tumors of uncertain origin, including small cell carcinoma, tumors of probable wolffian origin, a hepatoid carcinoma and oncocyoma. There are some soft tissue tumors not specific to ovary, and there are assorted malignant lymphomas and leukemias which land up in the ovaries.

N. Testicular cancers. All of the germ cell tumors listed above except for dysgerminoma also appear as cancers of the testis. In addition, seminoma itself as well as spermatocytic seminoma and choriocarcinoma of the testis are germ cell cancers of the testis. There are both juvenile and adult forms of the Granulosa cell tumor, as well as other cancers of the gonadal stroma, including leiomyomas, and neurofibromas. In addition to the germ cell cancers, there are the Sex cord-gonadal stromal tumors, including Sertoli cell tumor, Leydig cell tumor, and mixed form called Sertoli-Leydig cell tumor, and Gynandroblastoma of the testis. There are both adenomas and adenocarcinomas of collecting ducts and rete testis. There is Primary malignant melanoma of testis. There are a range of secondary tumors of the testis, most commonly Lymphomas, but also leukemic infiltration of the Testis, malignant melanoma metastatic to the testis, and metastatic cancers from the prostate or lung.

O. Paratesticular cancers (cancers of the spermatic cord, epididymis, vestigial remnants, and tunica vaginalis) are commonly classified separately from testicular cancers, and are rather varied. These include rhabdomyosarcoma of the spermatic cord (which can occur in embryonal, alveolar, and pleomorphic subtypes), liposarcomas, leiomyosarcomas, ovarian-type epithelial tumors, the desmoplastic small round cell tumor, the melanotic neuroectodermal tumor of infancy, primary paratesticular neuroblastoma, primary hematopoietic tumors of the paratesticular structures, plasmacytoma and granulocytic sarcoma of the paratestis, malignant schwannoma, malignant fibrous histiocytoma, malignant spermatic cord fibrosarcoma, and pleomorphic hyalinizing angiectatic tumor. There are also an assortment of secondary tumors, especially from the prostate, testis, kidney, and stomach, and malignant melanoma.

P. Cancers of the vulva are mostly squamous carcinoma, but these also include melanoma, Bartholin's Adenocarcinoma, basal cell carcinoma and some sarcomas.

Q. Vaginal cancers are primarily squamous carcinoma, but some are adenocarcinoma, melanoma of the vagina; sarcoma of the vagina, bowen's disease and germ cell tumors. There is also primary malignant melanoma of the vagina.

R. The most important of the cancers of the uterus are the Endometrial Carcinomas. The great majority of these are endometrioid; others include uterine papillary serous tumor (upst), clear cell carcinoma, mucinous and squamous. There is also plexiform tumorlet, Intravenous leiomyomatosis, benign metastasizing leiomyoma, leiomyomatosis peritonealis disseminate and leiomyosarcoma. Endometrial Tumors include endometrial stromal nodule, endolymphatic stromal myosis, and endometrial stromal sarcoma. There are the mixed tumors: Müllerian adenosarcoma and Malignant mixed mesodermal tumors (MMMT). Other sarcomas are rhabdosarcoma, osteosarcoma, chondrosarcoma and hemangiopericytoma. Some uterine cancers are secondary, starting in e.g. the tissue that begins to develop immediately after conception: epithelioid trophoblastic tumor, choriocarcinoma, and placental site trophoblastic tumors (PSTT).

S. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are found in the wall of the stomach. These come in two main categories. One is the Non-Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large Cell Lymphoma of the Stomach such as anaplastic Ki-1 (CD30) positive large cell lymphoma. The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison syndrome [ZES] tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) There is a primary malignant melanoma of

the stomach (6) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach.

T. Cancer of the esophagus is most commonly a squamous cell carcinoma or an adenocarcinoma. However, malignant melanomas, both primary and secondary can occur, and spindle cell carcinoma and Kaposi's sarcoma can also occur in the esophagus. There is also primary oat cell carcinoma of the esophagus, choriocarcinoma of the esophagus, carcinoid tumor of the esophagus, adenosquamous carcinoma of the esophagus and the related mucoepidermoid carcinoma of the esophagus, and cylindroma of the esophagus. In addition, verrucous carcinomas and pseudosarcomas of the esophagus have been reported.

U. Cancers of the spleen which are primary are commonly divided into vascular, lymphoid and non-lymphoid. Vascular tumors include hemangiosarcoma, lymphangiosarcoma, hemangioendothelial sarcoma and malignant hemangiopericytoma of the spleen, all of which are considered malignant. Lymphoid tumors include both Hodgkin's and Non-Hodgkin's lymphoma, plasmacytoma and Castleman's tumor. Nonlymphoid tumors are more diverse, and include malignant fibrous histiocytoma, fibrosarcomas, leiomyosarcomas, malignant teratomas, and Kaposi's sarcoma of the spleen. There are also metastatic tumors, secondary to tumors most typically from the lung, stomach, pancreas, liver, breast and colon. These are typically adenocarcinomas or squamous cell carcinomas, but large cell carcinoma, small cell carcinoma, hepatocellular carcinoma, melanoma, mesothelioma and choriocarcinoma are known as well.

V. Salivary gland carcinomas arguably represent the most heterogeneous group of tumors of any tissue in the body. The main four histopathologic types are: (1) mucoepidermoid carcinoma (2) adenoid cystic carcinoma (which has three histologic types: cribriform, tubular, and solid), (3) adenocarcinoma which includes acinic cell carcinoma, polymorphous low-grade adenocarcinoma, Sebaceous Lymphadenocarcinoma, adenocarcinoma not otherwise specified (NOS), Mucinous adenocarcinoma, and cystadenocarcinoma; (4) salivary duct carcinoma. In addition, there is an adenosquamous carcinoma, lymphoepithelial carcinoma, epithelial-myoeipithelial carcinoma, basal cell adenocarcinoma, sebaceous carcinoma, oncocytic

carcinoma, myoepithelial carcinoma, and clear cell carcinoma of the salivary glands NOS (hyalinizing clear cell carcinoma). In addition to the carcinomas, there are some adenomas, including carcinoma ex-pleomorphic adenoma, pleomorphic salivary adenoma, canalicular adenoma, oxyphilic adenoma, papillary cystadenoma, lymphadenoma, sebaceous adenoma, basal cell adenoma, and ductal cystadenoma. There are two ductal papillomas: inverted ductal papilloma and intraductal papilloma. There is also an assortment of perinatal salivary gland tumors. There are a group of haematolymphoid salivary Tumors: Hodgkin lymphoma, Diffuse large B-cell lymphoma and extranodal marginal zone B-cell lymphoma. In addition, there is a salivary haemangioma, warthin tumor, salivary carcinosarcoma, sialadenoma papilliferum, oncocytoma, and myoepithelioma of the salivary glands, Low-Grade Cribriform Cystadenocarcinoma (LGCCC), and sialoblastoma.

W. Cancers of the Heart (including pericardium, valves, etc.) include a wide range of primary cardiac sarcomas, including angiosarcomas, undifferentiated sarcomas, osteosarcomas, fibrosarcomas, malignant fibrous sarcomas, histiocytomas, leiomyosarcomas, myxosarcomas, synovial sarcomas, neurofibrosarcomas, rhabdomyosarcomas, reticulum cell sarcomas, desmoplastic small round cell tumors, and liposarcomas. Primary heart tumors also include melanoma, atrial myxoma, rhabdomyoma, papillary fibroelastoma of the endocardium, and teratoma. There is also Purkinje cell hamartoma of the conduction tissue. In the Pericardium, there is also malignant schwannoma, aberrant synoviosarcoma, neurofibroma and thymomas (invasive and non-invasive). Secondary tumors of the heart are more common, and can arrive by many pathways. For example, bronchogenic carcinoma can arrive by direct extension or by a combination of lymphatic and hematogenous dissemination. breast, lung and esophagus carcinomas, Hodgkin and non-Hodgkin lymphomas, melanomas, mesothelioma, renal cell carcinoma, leukemias, Kaposi sarcoma and osteosarcomas are the most common forms, but there are many more.

X. Odontogenic tumors are cancers of the jaw derived from primordial tooth-forming tissues.

The epithelial tumors include squamous odontogenic tumor, adenomatoid odontogenic tumor, calcifying epithelial odontogenic tumor (Pindborg tumor), and ameloblastoma. And adamantinoma and adamantinomatous craniopharyngioma are included here as well. The mixed odontogenic tumors include ameloblastic fibro-odontoma, and ameloblastic fibroma. The mesenchymal odontogenic tumors include cementoblastoma, and odontogenic myxoma. There is also ameloblastic fibrosarcoma, granular cell ameloblastic fibroma, ameloblastic sarcoma, malignant ameloblastoma, ameloblastic carcinoma, clear cell odontogenic carcinoma, odontoameloblastoma and squamous odontogenic tumors.

Y. Cancers of the oral cavity and oropharynx, including the tongue is most commonly squamous cell carcinoma and Verrucous carcinoma. There are also lymphomas of the tonsils and base of the tongue, Nasopharyngeal carcinoma (which exists in three subtypes), as well as neurofibroma, schwannoma and rhabdomyoma of the mouth, and primary melanoma melanoma of the oral cavity. In addition, HPV-positive oropharyngeal cancer is now considered a distinct disease entity. Salivary gland cancers and odontogenic tumors are discussed separately above.

Z. Cancers of the lymph glands are of course the lymphomas. There are also carcinomas of the lymph nodes, including large cell carcinoma of the lymph nodes, metastatic squamous cell carcinoma of the lymph nodes, primary neuroendocrine carcinoma of the lymph nodes and Merkel cell carcinoma of the lymph nodes. There is also generalized reticulum cell sarcoma of the lymph nodes, Kaposi's sarcoma of the lymph nodes and lymph node melanoma.

AA. Cancers of the adrenal glands include adrenocortical carcinoma, pheochromocytoma, adrenal neuroblastoma, and adrenal ganglioneuroma.

AB. Cancer of the eye is a very loose category, as the set of cancers involved depends very much on which structure of the eye or its adnexa is involved. Choroidal tumors include choroidal melanoma, ciliary body melanoma choroidal osteoma and metastatic choroidal tumors, including tumors from the lung, breast, prostate, kidney, thyroid and blood. Eyelid tumors include basal cell carcinoma, malignant melanoma of the eyelid, sebaceous carcinoma

of the eyelid and squamous carcinoma of the eyelid. Iris tumors include iris melanoma, malignant iris melanocytoma, and anterior uveal metastasis, most commonly from breast, lung, prostate, skin, kidney, colon and thyroid. Optic nerve tumors include juxtapapillary choroidal melanoma (choroidal melanoma affecting the optic nerve), circumpapillary metastasis with optic neuropathy, and optic nerve melanocytoma. Retinal tumors include retinal pigment epithelium tumors, and retinoblastoma. Conjunctival tumors are quite varied, and include conjunctival kaposi's sarcoma, epibulbar dermoid, lymphoma of the conjunctiva, pigmented conjunctival tumors (a malignant melanoma), and squamous carcinoma (including intraepithelial neoplasia of the conjunctiva). Infiltrative intraocular tumors include chronic lymphocytic leukemia, infiltrative choroidopathy and intraocular lymphoma. Orbital tumors include adenoid cystic carcinoma of the lacrimal gland, lymphangioma of the orbit, orbital pseudotumor, and orbital rhabdomyosarcoma. Optic nerve gliomas are mentioned above in cancers of the brain.

AC. Cervical cancers. There are many different categories and sub-categories of cervical cancers. The majority of cervical cancers are Squamous Cell Carcinomas. These come in numerous types: large cell nonkeratinizing type; large cell keratinizing type; basaloid; verrucous; warty; papillary; lymphoepithelioma-like; and squamotransitional, Early invasive (microinvasive) squamous cell carcinoma; Squamous intraepithelial neoplasia (including Cervical intraepithelial neoplasia and Squamous cell carcinoma in situ). There are also a variety of adenocarcinomas, the most important of which are the mucinous adenocarcinoma, which include the endocervical, intestinal, signet-ring cell, minimal deviation, and villoglandular. There is also endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, mesonephric adenocarcinoma, Early invasive adenocarcinoma, and adenocarcinoma in situ. In addition, there are neuroendocrine carcinomas, divided into Small Cell, large cell, classical carcinoid and atypical carcinoid. Other epithelial tumors include adenosquamous carcinoma, mixed adenosquamous carcinomas, which can be either well-differentiated or poorly differentiated, the latter including glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma and

undifferentiated carcinoma. There are also some mixed carcinoma with signet-ring cells, and other types of other poorly differentiated mixed carcinomas. This group includes tumors sometimes called apudomas or argyrophil cell carcinomas. There are also an assortment of mesenchymal tumors of the cervix, including leiomyosarcoma; endometrioid stromal sarcoma, low grade; undifferentiated endocervical sarcoma; sarcoma botryoides; alveolar soft part sarcoma, angiosarcoma of the cervix, malignant peripheral nerve sheath tumor of the cervix; cervical leiomyoma; and rhabdomyoma of the cervix. There are also some mixed epithelial and mesenchymal tumors, including carcinosarcoma (malignant müllerian mixed tumor), adenosarcoma, Wilms tumor, typical and atypical polypoid adenomyoma, and papillary adenofibroma of the cervix. There are also melanocytic tumors, including primary malignant melanoma of the cervix and blue naevus of the cervix. There are also germ cell type tumors, including yolk sac tumor, dermoid cyst, and mature cystic teratoma of the cervix. There is also primary choriocarcinoma of the cervix, which does not fit well into any category. There are also numerous cancers secondary to the cervix.

AD. Gestational Trophoblastic Neoplasia is cancer of the placenta; it actually derives from the conceptus rather than from the pregnant woman. It has three different forms: choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor

AE. Cancer of the throat is a loose term, depending on the particular structure. Cancers of the oropharynx are discussed above in cancers of the oral cavity. Hypopharyngeal cancer is usually a form of squamous cell carcinoma, including basaloid squamous cell carcinoma, superficial spreading cancer, sebaceous cancer, adenosquamous cancer, and signet-ring and verrucous types. Less common forms of hypopharyngeal cancer include adenocarcinoma, lymphoma, and sarcoma. Nasopharyngeal cancer is usually a carcinoma, and is commonly divided into three types: keratinizing squamous cell carcinoma, non-keratinizing carcinoma, and undifferentiated carcinoma. There are also rhabdomyosarcomas and lymphomas as well.

AF. Cancer of the thymus is normally a carcinoma, called thymoma, including Type C, also

called thymic carcinoma, and a clear cell carcinoma of the thymus. There are also a series of germ cell tumors of the thymus as well as both Hodgkin and non-Hodgkin lymphomas. There are also carcinoid tumors of the Kulchitsky cells.

AG. Fallopian Tube Cancer most commonly takes the form of a papillary serous adenocarcinoma. There are also leiomyosarcomas (arising from smooth muscle in the fallopian tubes), squamous cell carcinoma, choriocarcinoma, and transitional cell carcinomas. Secondary cancers are more common, and come from the ovaries, the endometrium, the GI tract, the peritoneum, and the breast.

AH. Bladder cancers. Most cases of bladder cancers are transitional cell (urothelial) carcinoma, which includes non-invasive papillary urothelial carcinoma, flat urothelial carcinoma in situ (CIS), superficially invasive urothelial carcinoma, and muscle invasive tumors. Adenocarcinomas of the bladder include Primary Adenocarcinoma (urachal and non-urachal), Prostatic adenocarcinoma, Gastro-intestinal adenocarcinomas and Clear cell carcinoma. Squamous cell carcinomas include Verrucous carcinomas, and a secondary squamous cell carcinoma of the bladder, from the cervix. Small cell carcinomas include Primary small cell carcinoma of the bladder and the secondary small cell carcinoma ('reserve cell carcinoma') of the lung.

Lymphomas include the primary lymphomas (Low grade B-cell lymphoma of MALT type, High grade B-cell lymphoma, and T-cell lymphoma), as well as secondary lymphomas, including mantle cell lymphomas. Melanomas include Primary malignant melanoma of the bladder, and secondary ones. The sarcomas of the bladder are leiomyosarcoma, osteosarcoma and rhabdomyosarcoma. There is also a primary primitive neuroectodermal tumor (PNET) of the bladder, Paraganglioma (which can metastasize), nephrogenic adenoma, metastatic renal cell carcinoma of the bladder, and both primary and secondary (from the uterus) choriocarcinoma of the bladder.

AI. Cancers of the gallbladder are most commonly adenocarcinomas, including non-papillary adenocarcinoma, papillary adenocarcinoma, and mucinous adenocarcinoma. There is also

squamous cell, adenosquamous, and oat cell carcinoma, of the gallbladder. Primary non-Hodgkin's lymphoma of the gallbladder, exists in both MALT and non-MALT forms. Primary neuroendocrine tumors (NETs) of the gallbladder can be of either large-cell or small-cell type. Primary gallbladder sarcoma includes leiomyosarcomas, myxofibrosarcomas, epithelioid angiosarcomas, and botryoid embryonal rhabdomyosarcomas. There is also primary malignant melanoma of the gall bladder, although secondary melanoma of the gallbladder is much more common.

AJ. Cancers of the paranasal sinus and nasal cavity are most commonly squamous cell carcinoma, but other primary forms include adenocarcinoma, malignant lymphoma, malignant melanoma (including primary melanoma of the sphenoid sinus), esthesioneuroblastomas (olfactory neuroblastoma, which occurs in the upper cribriform region of the nasal cavity) and lethal midline granuloma (malignant granuloma). There are also tumors secondary to this area, especially from bone and cartilage.

AK. In the spinal cord (including the covering), intramedullary tumors are most commonly astrocytomas and ependymomas, while meningiomas and nerve-sheath tumors are the most common types of intradural extramedullary spinal tumor. There is a primary malignant melanoma of the leptomeninges. Extradural spinal tumors arise in the bones of the spine and include chordomas, osteosarcomas, chondrosarcomas and fibrosarcomas.

AL. Penile carcinoma is usually a squamous cell carcinoma (including carcinoma in situ or Bowen disease), but there is also primary melanoma of the penis, penile clear cell carcinoma, and sarcomatoid carcinoma. There is also primary reticulum cell sarcoma of the penis, Kaposi sarcoma of the penis, and Paget disease of the Penis.

AM. Primary cancers of the bone itself are of eight types. Osteosarcoma (Osteogenic Sarcoma), Chondrosarcoma (which actually develops in the cartilage tissue), Ewing's Sarcoma, Malignant fibrous histiocytoma, Fibrosarcoma, Giant cell tumor of the bone (Osteoclastoma), Adamantinoma (which develops almost exclusively in the long bones, and occurs in two forms,

classic and differentiated) and Chordoma. Secondary bone cancers can come from a wide variety of sources, but most commonly arise in the breast, prostate, lung, kidney and thyroid.

AN. The Non-Hodgkin lymphomas fall into four categories. The first is the Precursor B-cell tumor, i.e. Precursor B-lymphoblastic leukemia/lymphoma. The second are the mature B-cell neoplasms: Chronic lymphocytic leukemia/small lymphocytic lymphoma; B-cell prolymphocytic leukemia; Splenic marginal zone lymphoma; Hairy cell leukemia; Splenic lymphoma/leukemia, unclassifiable (including Splenic diffuse red pulp small B-cell lymphoma and Hairy cell leukemia-variant); Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia); the Heavy chain diseases (Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease); Plasma cell myeloma; Solitary plasmacytoma of bone; Extraosseous plasmacytoma; Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma); Nodal marginal zone B-cell lymphoma (MZL, including Pediatric type nodal MZL); Follicular lymphoma (including Pediatric type follicular lymphoma); Primary cutaneous follicle center lymphoma; Mantle cell lymphoma; Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (including T cell/histiocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation, and Epstein-Barr virus DLBCL of the elderly); Lymphomatoid granulomatosis; Primary mediastinal (thymic) large B-cell lymphoma; Intravascular large B-cell lymphoma; Primary cutaneous DLBCL, leg type; ALK+ large B-cell lymphoma; Plasmablastic lymphoma; Primary effusion lymphoma; Large B-cell lymphoma arising in HHV8-associated multicentric (including Castleman disease); Burkitt lymphoma; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma; and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. The third is Precursor T-cell tumor, i.e. Precursor T-lymphoblastic lymphoma/leukemia. The fourth category is the mature T-cell and NK-cell neoplasms: T-cell prolymphocytic leukemia; T-cell large granular lymphocytic leukemia; Chronic lymphoproliferative disorder of NK-cells; Aggressive NK cell leukemia; Systemic EBV+

T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection); Hydroa vacciniforme-like lymphoma; Adult T-cell leukemia/ lymphoma; Extranodal NK/T cell lymphoma, nasal type; Enteropathy-associated T-cell lymphoma; Hepatosplenic T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Mycosis fungoides; Sézary syndrome; Primary cutaneous CD30+ T-cell lymphoproliferative disorder (including Lymphomatoid papulosis and Primary cutaneous anaplastic large-cell lymphoma); Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma; Primary cutaneous gamma-delta T-cell lymphoma; Primary cutaneous small/medium CD4+ T-cell lymphoma; Peripheral T-cell lymphoma, not otherwise specified; Angioimmunoblastic T-cell lymphoma; Anaplastic large cell lymphoma (ALCL), ALK+; and Anaplastic large cell lymphoma (ALCL), ALK-. Note that this category overlaps to some degree with the leukemias, and also includes all of the cutaneous lymphomas listed above under non-melanoma cancers of the skin, except for primary and secondary cutaneous Hodgkin's Lymphoma.

AO. Classical Hodgkin's lymphoma comes in four forms: Nodular sclerosis classical Hodgkin lymphoma; Lymphocyte-rich classical Hodgkin lymphoma; Mixed cellularity classical Hodgkin lymphoma; and Lymphocyte-depleted classical Hodgkin lymphoma. Nodular lymphocyte-predominant Hodgkin lymphoma is also considered to be a subtype of Hodgkin lymphoma.

AP. Cancer of the Pancreas. These cancers are primarily carcinomas. There is duct cell carcinoma, acinar cell carcinoma, papillary mucinous carcinoma, signet ring carcinoma, medullary carcinoma, squamous carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, colloid carcinoma (mucinous carcinoma or mucinous non-cystic carcinoma), giant cell carcinoma, and small cell carcinoma. Cancers of the endocrine part of the pancreas (islet cell tumors) include insulinoma, glucagonoma, somatostatinoma, gastrinoma, VIPoma, carcinoid, ACTHoma, GRFoma, PTF-like-oma, neurotensinoma, and Multiple Endocrine Neoplasia Type 1 (MEN1). Neurofibromatosis (NF) Type 1 is usually included with this category. There are mixed types, notably pancreatoblastoma, as well as ductal-endocrine or acinar-

endocrine types. There is also cystadenocarcinoma which comes in serous and mucinous types, pancreatic lymphoma, pseudopapillary solid tumor of the pancreas (Frantz's tumor) and mucinous cystic tumor with dysplasia.

AQ. Cancers of the ear, including the temporal bone, are most commonly skin cancers of the outer ear, but there is also nonmelanoma skin cancer (NMSC) of the ear. There is also squamous cell carcinoma of the ear, adenoid cystic carcinoma of the ear, and ceruminomatous adenoid cystic carcinoma of the ear. Other cancers of the ear may arise from invasion from adjacent structures such as the parotid gland. Glomus tumours, which arise from the outer layers of the blood vessels in the middle ear, are sometimes malignant.

AR. Cancer of the small bowel. Adenocarcinoma, usually divided into non-ampullary and ampullary, is the most common type, and usually occurs in the duodenum. One variant of this is a small cell carcinoma. Sarcomas include both the gastrointestinal stromal tumor, as well as assorted non-GIST sarcomas, including leiomyosarcomas, angiosarcomas, and malignant fibrous histiocytomas. The neuroendocrine tumors of the small bowel are usually carcinoid tumors and are typically seen in the ileum; gastrin G-cell tumors account for a majority of the duodenal carcinoids. Lymphomas are most commonly diffuse large B-cell lymphomas, and there is a T-cell type sometimes seen in patients with celiac disease, and MALT lymphoma can arise in the ileum, as well as Mediterranean lymphoma (IPSID, sometimes considered a form of MALT lymphoma), centrocytic Malignant lymphoma, and Burkitt-like lymphoma. In terms of secondary cancers, cancer arising from the breast, lung and especially melanomas metastasize to the small bowel hematogenously. Primary tumors of the colon, ovary, uterus and stomach usually enter the small bowel either by direct invasion or by intraperitoneal spread.

AS. Metastatic umbilical cancer sometimes goes by the name of "Sister Mary Joseph's nodule", and is usually an adenocarcinoma. These arise from the stomach, colon or ovary. There is also primary malignant melanoma of the umbilicus and a primary basal cell carcinoma of the umbilicus.

(2) The nature of the invention and predictability in the art: With specific reference to cancer, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the “general unpredictability of the field [of] ...anti-cancer treatment.” *In re Application of Hozumi et al.*, 226 USPQ 353 notes the “fact that the art of cancer chemotherapy is highly unpredictable”. More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

In terms of specific cancers, brain, breast, kidney, cervix, prostate, gastrointestinal tract, (e.g., gastric cancer or stomach cancer), skin, and epithelia.

(4) State of the Prior Art: The claimed compounds are substituted pyridazines. So far as the examiner is aware pyridazines have not been successfully used as anticancer agents.

(5) Working Examples: There are 95 examples of which there are variable levels of inhibition.

(6) Skill of those in the art: Many, many mechanisms have been proposed over the decades as methods of treating the assorted cancers generally. Cytotoxic agents could be applied directly to the tumors cells, directly killing them. Immunotherapy involves stimulating the patient's immune system to attack cancer cells generally, either by immunization of the patient, in which case the patient's own immune system is trained to recognize tumor cells as targets, or by the administration of therapeutic antibodies as drugs, so the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies. Another approach would be to increase the amount or activity of the body's tumor suppressor genes, e.g. p53, PTEN, APC and CD95, which can for example activate DNA repair proteins, suppress the Akt/PKB signaling pathway, or initiate apoptosis of cancer cells. The angiogenesis inhibitor strategy was based on cutting off

the blood supply that growing tumors need by shutting off the growth of new blood vessels by, for example, suppressing proliferation of endothelial cells or inducing apoptosis of endothelial cells. There is also the cancer stem cell paradigm, which hypothesizes that cancer could be treated generally, either by targeting the cancer stem cells themselves, or by targeting the epithelial-to-mesenchymal transition which supposedly generates the cancer stem cells. Yet another approach is to inhibit one or more of the assorted HSP90 proteins, which will supposedly disrupt the proper folding of signaling proteins that all cancers rely on. Inhibiting telomerase was said to be able to be able to simply stop cancer cells generally from being able to proliferate. Many of these approaches --- and there have been others as well --- have produced anti-cancer drugs. However, despite high hopes for success, and a plausible theory why these should work for cancers generally, none of these approaches have ever produced a drug which come remotely near such a goal.

Specifically, the prior art knows that there never has been a compound capable of treating cancers generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally."

(<<http://www.uspto.gov/web/offices/pac/dapp/lpecha.htm#7>> ENABLEMENT DECISION TREE, Example F, situation 1). A similar statement appears at *In re Application of Hozumi et al.*, 226 USPQ 353: "In spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cancer. Cancer is not a simple disease, nor is it even a single disease, but a complex of a multitude of different entities, each behaving in a different way". There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers.

The attempts to find compounds to treat the various cancers arguably constitute the single most massive enterprise in all of pharmacology. This has not resulted in finding any treatment for tumors generally. Indeed, the existence of such a "silver bullet" is contrary to our

present understanding in oncology. This is because it is now understood that there is no “master switch” for cancers generally; cancers arise from a bewildering variety of differing mechanisms. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, primarily a wide variety of failures of the body's cell growth regulatory mechanisms, but also such external factors such as viruses (an estimated at least 20% are of viral origin e.g. Human papillomavirus, EBV, Hepatitis B and C, HHV-8, HTLV-1 and other retroviruses, and quite possibly Merkel cell polyomavirus, and there is some evidence that CMV is a causative agent in glioblastoma), exposure to chemicals such as tobacco tars, excess alcohol consumption (which causes hepatic cirrhosis, an important cause of HCC), ionizing radiation, and unknown environment factors.

Accordingly, there is substantive “reason for one skilled in the art to question the objective truth of the statement of utility or its scope” (*In re Langer*, 183 USPQ 288, 297), specifically, the scope of covering cancer generally.

Similarly, *In re Novak*, 134 USPQ 335, 337-338, says “unless one with ordinary skill in the art would accept those allegations as obviously valid and correct, it is proper for the examiner to ask for evidence which substantiates them.” There is no such evidence in this case. Likewise, *In re Cortright*, 49 USPQ2d 1464, states: “Moreover, we have not been shown that one of ordinary skill would necessarily conclude from the information expressly disclosed by the written description that the active ingredient” does what the specification surmises that it does. That is exactly the case here. Moreover, even if applicants’ assertion that cancer in general could be treated with these compounds were plausible --- which it is not ---, that “plausible” would not suffice, as was stated in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1301: “If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to “inventions” consisting of little more than respectable guesses as to the likelihood of their success.”

Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. The skill thus depends on the particular cancer involved. There are some cancers where the chemotherapy skill level is high and there are multiple successful chemotherapeutic treatments. The mechanism in these situations, however, is not necessarily the same as is alleged for these compounds.

One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. pilocytic astrocytoma and diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs.

Cartilage tumors do not respond to chemotherapy, nor, generally, do cancerous teratomas.

Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones.

Lymphomas of the stomach are not commonly treated with anti-cancer agents per se, but instead, surgery or radiation and antibiotic therapy (e.g. amoxicillin, metronidazole, bismuth,

omeprazole) are the primary treatments.

Neuroendocrine tumors of the cervix generally do not respond to chemotherapy.

A number of sarcomas, including alveolar soft part sarcoma (ASPS), retroperitoneal sarcoma, most liposarcomas, and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no chemotherapeutic agent has been established as effective.

Aggressive NK cell leukemia is considered to be untreatable with pharmaceuticals.

Myxoma of the heart (atrial myxoma) is the most common primary cardiac tumor and has no chemotherapy; excision is the only treatment.

Chemotherapy of spleen tumors is rarely even attempted, and no drug has been established as effective for any primary or secondary splenic tumor types.

Many cerebral metastases, such as those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy.

Cancers of the ear canal, middle ear and temporal bone have no established effective chemotherapy. Treatment is via surgery, sometimes combined with radiation. Skin cancers of the outer ear are treated with surgery, sometimes requiring total pinnectomy.

Hepatocellular Carcinoma (HCC or hepatoma) is, in humans, possibly the most prevalent solid tumor and in certain parts of the world is the most common cancer; it has long been understood as a chemotherapy-resistant tumor, with only very recently, some success seen with the Tyrosine protein kinase inhibitor Sorafenib.

Metastatic esophageal cancer, and malignant melanoma of the esophagus do not respond to chemotherapy; there is no chemotherapy for subungual melanoma, which can be treated only with surgery. Indeed, metastatic melanomas as a group are largely unresponsive to chemotherapy; only one drug (dacarbazine, an alkylating agent, approved by the FDA in 1975) has been shown effective, although response rates are fairly modest.

Adamantinomas have no chemotherapy. No effective chemotherapy regimens are available for either intraocular or metastatic uveal melanoma.

It is important to note that tumors can need to be treated quite differently even though they are tumors of the same organ. For example, the drugs used most often to treat Wilms tumor, the most common malignant tumor of the kidneys in children, are actinomycin D and vincristine. Such drugs are never used with clear cell renal carcinoma, which is treated, although without much success, with immunotherapy using the cytokines interleukin-2 and interferon-alpha. However, such immunotherapy has never been established as effective in non-clear cell RCC forms such as papillary renal cell carcinoma. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer. Cancers of the stomach can be lymphomas, GISTs, carcinoid tumors, carcinomas, or soft tissue sarcomas, and for a single agent to be effective against all or even most of these categories would be contrary to what is known in oncology.

(7) The quantity of experimentation needed: Given the fact that, historically, the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 4 and 6, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim 19 is rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and stated above.

2. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph rejections, labeled paragraph 3a), b), c), d), e), f), g), h), i), j), k), l), m), n), o), p) and q) in the last office action, which are hereby **withdrawn**.

3. With regards to the provisional nonstatutory double patenting rejection of claims 1-7 and 17-19, labeled paragraph 4) over copending Application No. 16/170,178 in the last office action, the applicants requested that this rejection be deferred until the claims of this application are otherwise in condition for allowance.

Claims 1-7, 17 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 and 12-29 of copending Application No. 16/170,178 (reference application), for reasons of record and stated above.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

In view of the amendment dated February 21, 2020, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6, 7, 19 and 29 rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claims 1, 2 and 4 where the definition of R³ and R⁴ is amended to include the following moieties together with the atom to which they are attached may join to form a 3- to **7-membered** carbocyclyl ring is not described in the specification with respect to the compounds of Formula (I).

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2 and 4 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The following reasons apply:

- a. Claim 2 is vague and indefinite in that it is not known what is meant by the definition of R³, R⁴ and R⁵ which is not stated in the form of a proper Markush grouping, it is believed that the Applicants meant to place and or after the definition of R⁵ is H.
- b. Claims 2 and 4 recite the limitation "carbocyclyl" in the definition of R³ and R⁵ together. There is insufficient antecedent basis for this limitation in the claim.

- c. Claim 4 is vague and indefinite in that it is not known what is meant by the definition of R³ which is not stated in the form of a proper Markush grouping.

Claim Objections

6. Claims 8-16 and 20-22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter

7. Claims 23-28 are allowed. None of the prior art of record nor a search in the pertinent art area teaches the specific compounds as claimed herein.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRENDA L COLEMAN whose telephone number is (571)272-0665. The examiner can normally be reached on Mon-Fri 10-6 (flex).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRENDA L COLEMAN/
Primary Examiner, Art Unit 1624