Basal cell carcinoma (BCC)

Definition
BCC is a malignant tumour of the **pluripotential epithelial** cells of the epidermis and hair follicles; not from the basal cells (*cf* SCC in the next section)

Epidemiology
BCC is the **most common tumour of humans**, accounting for more than 50% of all the tumours removed (More than 1,3 million per annum in the USA alone). Despite this incidence, these tumours account for <0.1% of all cancer deaths in humans. BCC is at least 3 times more common than SCC in non-immunocompromised patients.

BCC occurs on sun-exposed areas of light-skinned patients. BCC has been described in negroid patients, but is exceptionally rare (I have seen it though!). This is a disease of advancing age and is most common in the 50+ age group. Men are affected slightly more than women, reflecting a past bias in outdoor labour activities.

Etiology
The etiology of both BCC and SCC can be logically divided into **environmental factors** and **host (patient) factors** (See table). Interestingly, BCC has not been generated experimentally by UV radiation alone, suggesting an interplay between factors.

A. Environmental factors
1. Non-Ionizing Radiation – Ultraviolet (UVA & UVB)
Two wavelength "types" of UV reach the earth's surface – UVA (320-400nm) and UVB (290-320nm). Most of the UVB and all UVC are filtered by stratospheric ozone. UVA was initially thought to be non-carcinogenic, but is now thought to be a **potent** co-carcinogen with **UVB**. Recently**, high dose UVA** (as found in tanning beds) has been shown to be **carcinogenic in its own right**. The carcinogenic effect of sunlight is both as an initiator and promoter of tumors. UV energy is **absorbed by DNA**, causing DNA methylation, double strand breaks and the formation of thymidine dimers (**photochemical damage**), which prevent accurate DNA transcription during mitosis **leading to mutations**.

The amount of UV reaching the surface is dependant on several factors : weather conditions, season, time of day, latitude and ozone depletion. Interestingly, **infra-red (heat)** has been shown to be a **co-factor** in accelerating the carcinogenic effect of UV radiation.

2. Ionizing Radiation
The carcinogenic effect of radiation in the generation of both BCC and SCC has been known for over 100 years. Accidental and war-related expose is fortunately rare. **Occupational exposure** plays an important risk in airline pilots, medical staff, and uranium miners. **Therapeutic exposure to radiation** is often underappreciated and in certain disorders may be contra-indicated (such as in Gorlin's syndrome).

3. Chemicals
As early as 1775, the carcinogenic effect of hydrocarbons was identified in chimney sweeps. Occupational exposure to **polycyclic hydrocarbons** is found in wood preservative, fuel oils, die mold lubricant and roofing industries. **Arsenic** was formerly used to treat syphilis, as well as for skin lightening and its use is rare today. The pollutant, **dimethyl benzanthracene** is found where incomplete combustion of organic hydrocarbons occurs, both in the atmosphere and in **tobacco smoke (**much higher concentration !).

B. Host Factors
1. Skin Phenotype – Fitzpatrick Classification
The effects of DNA damage are modified by the amount of melanin, which absorbs UV radiation. Although skin colour is genetically determined, it is more useful to describe the actual phenotype. Fitzpatrick has classified skin colour into 6 types based on the **colour** and the **reaction** to the first summer exposure – it is VERY important to note that he did not distinguish any specific racial groups. **The higher**

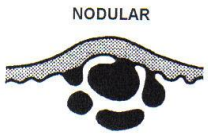
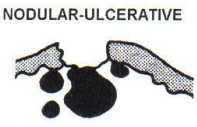
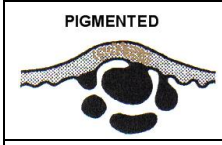
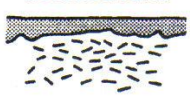
the Fitzpatrick type, the less likely the individuals' risk of skin cancer. (Remember, even type VI patients can get skin cancer!)

TYPE	COLOUR	REACTION TO FIRST EXPOSURE
I	White	Always burns, never tans
II	White	Usually burns, tans with difficulty
III	White	Sometimes burns, average tan
IV	Light Brown	Rarely burns, tans with ease
V	Dark Brown	Very rarely burns, tans very easily
VI	Black	Never burns, always tans

2. Genetic Syndromes and Predisposing Lesions
The conditions associated with BCCs are : **Gorlin's Syndrome**, Basex Syndrome, Rombo Syndrome, Unilateral basal cell nevus Syndrome and **Nevus Sebaceous of Jadassohn**.

3. Immunological Factors
The most important defense against tumours is **cell-mediated immunity**. T-Cell (CD4+), Natural Killer (NK) cells, Langerhans cells and lymphocytes are the most important components. A decrease in CD4+ numbers is associated with a decreased stimulation of NK cells and tumour proliferation. Factors which affect the immune function include chronic UV radiation (sub-carcinogenic doses), HIV, transplant immune-suppression, occult malignancy, and anti-neoplastic chemotherapy.

Diagnosis
Although there are many different clinical presentations for basal cell carcinoma, the most characteristic types of BCC include : Superficial, Nodular, Ulcerative, Invasive, Pigmented and Morpheaform. Generally, BCC has a tendency to be locally destructive.

	Superficial BCC lies within the dermis and has no dermal invasion. Clinically, the lesion is erythematous with a thread-like border and may have superficial ulceration or crusting. It is often confused with eczema.
	Nodular BCC is flesh-coloured nodule, elevated from the surrounding skin and has a pearly quality and contains telangiectatic vessels. This is the **"classical" appearance of BCC.**
	Ulcerative BCC is classically a deep seated ulcerative lesion with rolled pearly edges – the so-called "Rodent Ulcer".
	Infiltrative BCC often has an intact epidermis and may be heralded by a plaque like firmness, with deep extension. Generally though, ulcerative lesions are more aggressive than infiltrative ones.
	Pigmented BCC is similar to nodular form, except that it is pigmented brown, sometimes so intensely that it is blue-black and may be confused with melanoma.
	Morpheaform BCC presents as a firm, ill-defined white or yellow plaque. It is classically described as an "enlarging scar" with no prior traumatic history. The ability of this type to produce **collagenase-4** and the stimulation of surrounding fibroblasts to produce collagen (hence the scar-like quality) accounts for the diffuse invasion and aggressive nature of this sub-type.

Cellular Classification

Ultimately, the diagnosis is made by **histological examination**. Histologically, more than 26 sub-types are described (and are of great interest to pathologists, but few others!). Sometimes the pathologist is uncertain about the cell type and the diagnosis proffered is the controversial **baso-squamous carcinoma** – these often turn out to be small cell SCC.

Treatment

The overall cure rate for basal cell carcinoma and squamous cell carcinoma is directly **related to the stage** of the disease and the **type of treatment** used. Since neither basal cell carcinoma nor squamous cell carcinoma are reportable diseases (although many pathologists in South Africa do report such cases to the National Cancer Registry), precise 5-year cure rates are known. Basal cell carcinoma rarely metastasizes, and thus a metastatic work-up is usually not necessary.

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to stage **both BCC and SCC**. A recent update (the 7th Edition, published in 2010) has made the classification of all non-melanoma cutaneous carcinoma MUCH more complex. Several important controversies have also evolved from the new classification.

TNM definitions

"OLD" Classification	*"New" 2010 Classification*
• **Primary tumor (T)** TX: Primary tumor cannot be assessed T0: No evidence of primary tumor Tis: Carcinoma in situ T1: Tumor ≤2 cm in greatest dimension T2: Tumor >2 cm but ≤5 cm in greatest dimension T3: Tumor >5 cm in greatest dimension T4: Tumor invades deep extra-dermal structures (e.g., cartilage, skeletal muscle, or bone) *[Note: In multiple simultaneous tumors, the tumor with the highest T category will be classified, and the number of separate tumors will be indicated in parentheses, e.g., T2 (5).]*	• **Primary tumor (T)** TX: Primary tumor cannot be assessed T0: No evidence of primary tumor Tis: Carcinoma in situ T1: Tumor ≤2 cm in greatest dimension, **with less than 2 high risk features.** T2: Tumor >2 cm **OR >2 high risk features.** T3: Tumor **with invasion of maxilla, mandible, orbit or temporal bone.** T4: Tumor invades **skeleton (axial or appendicular) or perineural invasion of the skull base.**
• **Regional lymph nodes (N)** NX: Regional lymph nodes cannot be assessed N0: No regional lymph node metastasis N1: Regional lymph node metastasis	• **Regional lymph nodes (N)** NX: Regional lymph nodes cannot be assessed N0: No regional lymph node metastasis **N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension.** **N2a: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension.** **N2b: Metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension.** **N2c: Metastases in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension.** **N3: Metastasis in a lymph node, >6 cm in greatest dimension.**
• **Distant metastasis (M)** MX: Distant metastasis cannot be assessed M0: No distant metastasis M1: Distant metastasis	• **Distant metastasis (M)** MX: Distant metastasis cannot be assessed M0: No distant metastasis M1: Distant metastasis

High-Risk Features for Primary Tumor (T) Staging	
Depth/invasion	>2 mm thickness.
	Clark level ≥IV.
	Peri-neural invasion.
Anatomic	Primary site ear.
Location	Primary site non hair-bearing lip.
Differentiation	Poorly differentiated or undifferentiated.

Visual AJCC Stages

	T1	T2	T3	T4
NO	I	II	II	III
N1	III	III	III	III
N2	IV	IV	IV	IV
N3				
M1				

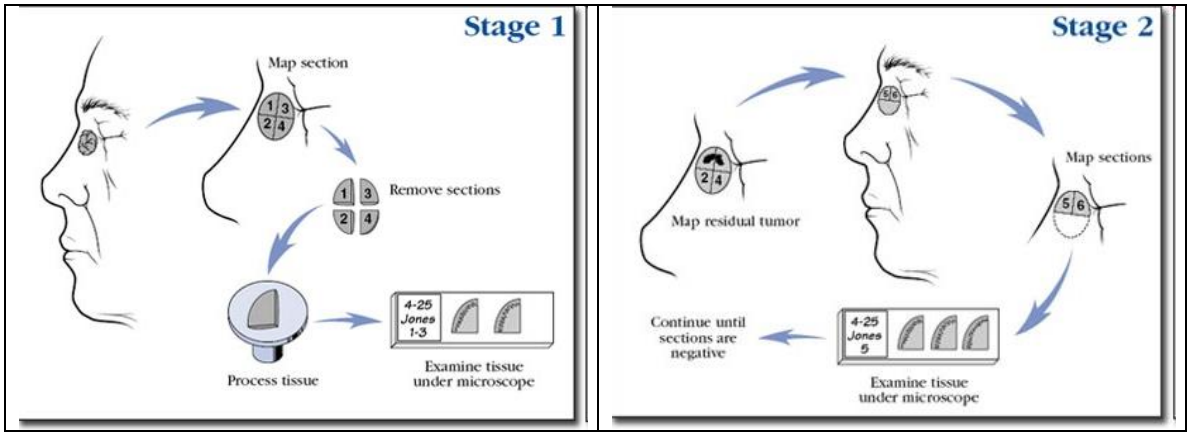
INTERESTING NOTE : From the above amended classification it can be seen that no tumour from the neck down could ever be classified as a T3 (see the definition above). This is a most controversial problem and is, in my opinion, very likely to be changed at the next AJCC update.

Treatment Overview

The traditional methods of treatment involve the use of cryosurgery, radiation therapy, electrodesiccation and curettage, and simple excision. Each of these methods is useful in **specific clinical situations**. Depending on case selection, these methods have cure rates ranging from 85% to 95%.

1. Mohs micrographic surgery

Although this method is complicated and requires special training, it has the highest cure rate of all surgical treatments because the tumor is microscopically delineated until it is completely removed. Mohs is very rarely offered in South Africa, as specially trained team of surgeon, pathologist and support staff are required. Very briefly, the specimen is curetted and the now ulcerative "rim" is excised as an *en bloc* specimen. The specimen is flattened and then sectioned transversely (as opposed to the standard vertical sectioning technique). This yields a specimen with a 360^{o} representation of the tumour margin. Special dyes are used to map the various quadrants for orientation.



2. Simple excision (with frozen or permanent sectioning for margin evaluation).
This traditional surgical treatment usually relies on surgical margins ranging from **4 mm to 10 mm**, depending on the diameter of the tumor *[I use 5mm margins for "simple" lesions and 10mm margins for lesions having any high risk criteria]*. Tumor recurrence may occur because only a small fraction of the total tumor margin is examined pathologically (see why Moh's is better above). Recurrence rate for tumours larger than 3cm is increased. Primary tumors of the lips, ears, eyes, scalp, and nose are characteristically more aggressive – this is borne out by the additional "high risk" table in the present classification.

3. Electrodesiccation and curettage.
Although it is a quick method for destroying the tumor, adequacy of treatment cannot be assessed immediately since the surgeon cannot visually detect the depth of microscopic tumor invasion. Tumors >3 cm have a very high recurrence rate and should not be treated by this method. Although I have the equipment for this, I personally don't employ this method as the scarring is particularly unattractive.

4. Cryosurgery.
Cryosurgery may be considered for patients with small, clinically well-defined primary tumors. It is especially useful for debilitated patients with medical conditions that preclude other types of surgery. Absolute contraindications for cryosurgery include abnormal cold tolerance, cryoglobulinemia, cryofibrinogenemia, Raynaud's disease and platelet deficiency disorders. Morphea or sclerosing basal cell carcinoma should not be treated by cryosurgery. Oedema is common following treatment, followed by an **eschar** which usually resolves in 1-4 weeks [1 week = gentle, 4 weeks = vicious!]. **Permanent pigment loss at the treatment site is unavoidable** and it should thus only be used for Caucasians.

5. Radiation therapy.
Radiation therapy is a logical treatment choice, particularly for patients with primary lesions requiring difficult or extensive surgery (e.g., eyelids, nose, or ears). It eliminates the need for skin grafting when surgery would result in an extensive defect. Cosmetic results are generally good to excellent with a small amount of hypopigmentation or telangiectasia in the treatment port. Radiation therapy can also be used for lesions that recur after a primary surgical approach. **Radiation therapy is contraindicated** for patients with xeroderma pigmentosum, epidermodysplasia verruciformis, or the basal cell nevus syndrome (Gorlin's Syndrome) because it may **induce more tumors in the treatment area**. It must be remembered that this is a financially costly option, and may preclude or complicate future surgery.

6. Carbon dioxide laser.
This method is best applied to the superficial type of basal cell carcinoma. It may be considered when a bleeding diathesis is present, since bleeding is unusual when this laser is used. A more useful option may be to resurface severely damaged skin in high risk individuals, as a prophylactic measure, rather than a treatment, *per se*.

7. Topical fluorouracil (5-FU / Efudex).
This method may be helpful in the management of selected patients with superficial basal cell carcinomas. Careful and prolonged follow-up is required, since deep follicular portions of the tumor may escape treatment and result in future tumor recurrence. A **5% topical ointment** is applied daily to the affected area, and the total surface area should be limited to 1-2% of TBSA. Intense erythema and weeping occurs after about 6 weeks and represents this represents the clinical end-point of treatment.

8. Interferon alfa.
Several early studies have shown variable responses of basal cell carcinoma to intralesional interferon alfa. Further reports are awaited until this treatment may be recommended for routine clinical practice. I have used this modality with excellent results on superficial BCC. It is supplied in pre-measured sachets (able to treat about 1% TBSA) in a so called "24 Pack". Drug holidays are advised – my usual protocol is daily application Monday to Friday for 5 weeks. It is a rather expensive option.

9. Photodynamic therapy (PDT).
Photodynamic therapy treats affected areas with a photosensitizer drug (applied topically as a cream) and then exposing the area to far blue light which "activates" the drug and results in cell death. It may be effective treatment for patients with superficial epithelial skin tumors.

[My personal treatment protocol is simple excision for aggressive appearing lesions and cryotherapy for less impressive lesions. I always use intra-operative pathology for any lesion requiring flap reconstruction – It is more readily available in private practice. I use Efudex (5-FU) or Aldara (5% imiquimod) for extensive actinic keratosis, but I am cautious when dealing with established BCC. Aldara is more patient friendly but costs about 5 times more for a treatment course – about R2500.00 for a "24 Pack"]

Follow-up
Following treatment for basal cell carcinoma, patients should be clinically examined every 6 months for 5 years. Thereafter, patients should be examined for recurrent tumors or new primary tumors at yearly intervals.

Prognosis
Generally the prognosis is excellent. Neglected lesions with extensive infiltration may require radical ablative surgery, or may be irresectable.

Of the patients who develop a basal cell carcinoma, 35% will develop a second primary basal cell carcinoma within the next 3 years and 50% at 5 years, due to the "**field cancerization effect**". The new lesions are typically identical to the prior lesion. Recurrence is a marker of significant epidermal damage and is a **risk factor for both future SCC and melanoma**.

BCC metastasizes very, very infrequently – only 175 cases have ever been described (and there are 1.3 million cases in the USA per year !). These metastatic lesions may be attributed to the baso-squamous variants, but conclusive evidence is lacking.

Squamous Carcinoma of the Skin (SCC)

Definition
Malignant tumours of the **malpighian or basal layer** of the epidermis (Cross reference this with BCC above). The tumour biology of SCC indicates a more rapid cell doubling time than BCC, but the clinical growth of the lesion may also be slow, as not all cells in the tumour mass are dividing.

Epidemiology
This is the second most common type of cancer in humans, but is 3 times less prevalent than BCC. There is a stronger association between UV radiation and SCC, and thus climate and lifestyle have an important bearing on the epidemiology of SCC.

Etiology
The etiology of both BCC and SCC can be divided into environmental factors and host (patient) factors, as described above for BCC. Additional etiology includes:

A. Infective Agents
Current classification of **Human Paillioma Virus (HPV)** infections describes 3 groups : anogenital/mucosal, non-genital cutaneous and Epidermodysplasia Verruciformis (EV). **Type 8 and 38** seropositivity is associated with the highest risk (RR= 14.7 and 3.0)

B. Genetic Syndromes and Predisposing Lesions
The conditions associated with SCC are : **Xeroderma Pigmentosum**, **Albanism**, Epidermodysplasia Verruciformis, Epidermolysis Bullosa, Rothmund-Thompson Syndrome, KID Syndrome, Werner Syndrome, **Fanconi Anaemia** and Ferguson-Smith Syndrome.

Diagnosis
The clinical features of SCC are varied, from erythematous plaques to papules, ulcerative lesions, inflammatory masses and verrucous lesions, but do not have the classical pearly edges of BCC. Ultimately, as the presentation may be similar, **biopsy is required**.

Cellular Classification
All SCCs are histologically similar, consisting of irregular masses of neoplastic epithelium proliferating into the dermis. Keratin may be present. The grade of the tumour may be classified by the system of **Broders**, taking into account differentiation, nuclear hyperchromasia, cellular atypia and architecture :
Grade 1 to 4 (> 75 %, > 50 %, > 25 % and < 25 % of the cells differentiated, respectively). Anaplastic varients may be impossible to classify by light microscopy and cytokeratin and S-100 stains are used.

Treatment
The AJCC classification is also used for SCC. The treatments for SCC are analogous to those for BCC, but consideration must be given to the more aggressive nature of SCC, as well as the increased risk of metastatic disease. **Radiation for verrucous SCC has been associated with anaplastic change and is not recommended.**

1. Mohs micrographic surgery.

2. Simple excision with sectioning for margin evaluation.

3. Electrodesiccation and curettage.
It should be reserved for very small primary tumors since this disease has metastatic potential.

4. Cryosurgery.
Same caveat as above.

5. Radiation therapy.
Radiation therapy is **contraindicated** for patients with xeroderma pigmentosum, epidermodysplasia verruciformis, or verrucous carcinoma. Note that the use of **diagnostic radiology** (especially CT Scans !) in these conditions may also cause the development of new lesions – due caution should be exercised by referring doctors!

6. Topical fluorouracil (5-FU).
This method may be helpful in the management of selected in situ squamous cell carcinomas (Bowen's disease).

7. Carbon dioxide laser.
This method may be helpful in the management of selected squamous cell carcinoma in situ. It may be considered when a bleeding diathesis is present, since bleeding is unusual when this laser is used.

8. Interferon alfa.
Clinical trials are ongoing but show the combination of interferon alfa and retinoids is effective treatment for squamous cell carcinoma. This is however still experimental.

Follow-up
Since squamous cell carcinomas have definite metastatic potential, patients should be re-examined every 3 months for the first several years and then followed indefinitely at 6-month intervals. **Incompletely excised SCC should be re-excised** – There is NO PLACE for expectant management in these cases.

Keratoacanthoma (KA)

Definition
A cutaneous lesion characterised by rolled edges and a central keratin plug and is histologically almost indistinguishable from SCC – indeed, many pathologists consider KA to be an extremely well differentiated SCC.

Incidence
This lesion is common in sun-exposed areas of middle aged, fair skinned patients. Males are affected more than females and the general incidence is 1:1000. There is a greater incidence in immuno-suppressed patients, and in those exposed to polycyclic hydrocarbons (Tar workers).

Aetiology
The aetiology is controversial. Some believe that it is a low-grade SCC which frequently undergoes regression, other believe that it is strictly benign. A viral aetiology is suggested but not proven. There is evidence that it originates from the hair follicles.

Clinical Features
The tumour occurs on the sun-exposed areas of face, pinna and dorsum of the hands. Occasionally it may be subungual, where bony erosion may occur. It goes through 3 clinical phases (analogous to hair growth) :

1. **Proliferation :** The lesion appears as a red macule or papule and grows rapidly for 2 – 4 weeks reaching sizes of up to 2 cm
2. **Maturation :** For several months the appearance remains unchanged ; an erythematous dome shaped lesion with a firmly embedded central keratin plug.
3. **Involution :** The central plug is expelled and the lesion regresses completely, leaving a depressed, hypopigmented scar.

Histologically there are 2 sub-types : Follicular (common) and non-follicular (such as subungual types). Metastatic spread has been described as has aggressive perineural invasion. This lends credence to the consideration of KA as a well differentiated SCC, but the debate continues.

The Differences between Keratoacanthoma and SCC

FACTOR	**KERATOACANTHOMA**	**SCC**
Growth Rate	Very Rapid	Usually Slow
Course	Rapid growth, static phase and involution within 6/12	Slow indefinite progression with local destruction
Natural history	Usually complete regression	Usually progressive
Age of onset	50s	70s
Character	Central keratotic plug	Central ulceration (crusting)
Shape	Crateriform	Irregular
Borders	Well defined	Poorly defined
Metastatic potential	Very Rare	Yes
Mucosal origin	Very Rare	Yes

Treatment
Malignant transformation may occur in up to 25 % of cases. Although watchful waiting is accepted, most will suggest some form of treatment. Surgical excision is the gold standard, as it provides histological evidence of complete removal. Margins of 2-3 mm are suggested.

Other invasive modalities are : Carbon dioxide laser, curettage and electrodessication and cryosurgery.

Medical therapies are : 5-FU (topically or intralesional), Imiquimod topically, and intralesional bleomycin, interferon and methotrexate.

Table : Causes of Non-Melanoma Skin Tumours

Host Factors	Environmental Factors
Phenotype *Fitzpatrick Skin Type* **Genetic Predisposition** *Xeroderma Pigmentosum* *Albanism* *Epidermodysplasia Verruciformis* *Epidermolysis Bullosa* *Rothmund-Thompson Syndrome* *KID Syndrome* *Werner Syndrome* *Fanconi Anaemia* *Ferguson-Smith Syndrome* *Gorlin's Syndrome (Naevoid BCC)* *Bazex Syndrome / Rombo Syndrome* **Predisposing Lesions** *Naevus Sebaceous of Jadassohn* *Dermatofibromas* *Linear Basal Cell Naevus* *Bowen's Disease* *Actinic Keratosis* *Cutaneous Horns* *Keratoacanthoma* *Leukoplakia* *Scarring Dermatoses (Marjolin)* **Immunological Factors** *Chronic UV exposure* *Transplant Immuno-suppression* *Chemotherapy* *HIV* *Occult Malignancy*	**Non-Ionizing Radiation** *Ultraviolet Irradiation (UVA/UVB)* *Infrared (Co-factor)* **Ionizing Radiation** *Accidental* *Occupational* *Therapeutic* **Chemicals** *Arsenic* *Tobacco Use* *Pollutants* *Polycyclic Hydrocarbons (phenols, cresols, xylenols)* *Benzanthracene* *Therapeutic* *Nitrogen mustards* *Nitrosurea* *Psoralens* **Infective Causes** *HIV* *Human Papilloma Virus*

Blue = BCC
Red = SCC
Purple = Both SCC and BCC